NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

May 27, 2008

The 159th meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Tuesday, May 27, 2008, 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 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. Ann Arvin
Dr. Barbara Baird
Dr. Carol Carter
Dr. Satya Dandekar
Dr. Richard Insel
Dr. Shelley Payne
Dr. Louis Picker
Dr. Martin Rosenberg
Dr. Marc Rothenberg
Dr. Gary Schoolnik
Dr. Christel Uittenbogaart
Dr. David Wilkes

***Ex Officio* Members Present:**

Dr. Mitch Cohen
Dr. Anthony Fauci
Dr. Ronald Valdiserri

Council Members Absent:

Dr. Robert Brooks
Dr. Kathryn Edwards
Dr. Sharon Kiely
Dr. Martin Myers
Dr. Regina Rabinovich
Dr. Megan Sykes

***Ex Officio* Members Absent:**

Major General George Weightman

***Ad Hoc* Members:**

Dr. Mark Davis
Dr. Patrick Wilson

NIAID Senior Staff:

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 2,457 research and training applications with primary assignment to NIAID for a requested amount of $604,207,821 in first-year direct costs and recommended approval of 345 applications for $98,009,645 in first-year direct costs. Fourteen 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 and noting that Drs. Brooks, Edwards, Kiely, Myers, Rabinovich, and Sykes would be absent. Also, one *ex officio* member, Major General George Weightman, was unable to attend. He introduced two *ad hoc* Council members: Dr. Mark Davis, Stanford University School of Medicine and Dr. Patrick Wilson, Oklahoma Medical Research Foundation.

Consideration of Minutes of Previous Meeting

The minutes of the January 28, 2008, meeting were considered and approved as written.

Staff and Organizational Changes

Several staff changes have taken place since the last Council meeting. Dr. Fauci announced the official appointment of Dr. Carl Dieffenbach as the director of NIAID's Division of AIDS. Also in the Division of AIDS, Dr. Roberta Black has been appointed chief of the Microbicide Research Branch, and Dr. David Burns was named chief of the Prevention Research Branch. Both of these Branches are within the Prevention Sciences Program.

In the Office of the Director, Division of Microbiology and Infectious Diseases, Dr. Richard Gorman was appointed associate director for clinical research.

Dr. James Lawler has been appointed chief medical officer of NIAID's Integrated Research Facility at Fort Detrick.

Dr. Fauci announced several staff changes in key administrative positions. Manizhe Payton was named director of the Office of Clinical Site Oversight in the Division of AIDS. In the Office of Communications and Government Relations, Cynthia Fabry has been appointed deputy director. Sarah Landry has returned to NIAID as the director of the Office of Program Operations and Scientific Information in the Division of Allergy, Immunology, and Transplantation.

Tributes and Awards

Dr. Fauci paid tribute to Dr. William Jordan who recently passed away. Dr. Jordan served as the first director of the Division of Microbiology and Infectious Diseases. He created an annual report to review progress in vaccine research, which is now known as *The Jordan Report*.

Gregg Gonsalves, an AIDS advocate and activist whose ideas have contributed to the NIAID AIDS research program over many years, received the first John M. Lloyd Foundation AIDS Leadership Award.

Budget Update

The President's FY 2009 budget request for NIH is $29.2 billion, virtually the same as the level in FY 2008. NIAID's allocation is approximately $4.6 billion, an increase of 0.2 percent over FY 2008. The total FY 2009 increase for NIAID is $8 million. Of the $8 million, $5 million is slated for the Global Fund to fight AIDS, TB, and malaria. After accounting for the Global Fund, the actual increase for the Institute is $3 million or 0.1 percent.

If the requested budget level stands, this would be the fourth consecutive year in which NIAID will operate with a flat budget.

Legislative Update

In March, Dr. Zerhouni presented the FY 2009 NIH budget request before the House Appropriations Subcommittee on Labor, Health and Human Services, and Education. The Senate appropriations hearing on the NIH budget was canceled and has not been rescheduled.

At a hearing of the Senate Committee on Health, Education, Labor, and Pensions Subcommittee on Children and Families, Dr. Fauci testified about food allergies in children.

Dr. Fauci gave a brief update on two bills of interest to NIH and NIAID. President Bush signed the Genetic Information Nondiscrimination Act (GINA), which prohibits health insurance companies and employers from discriminating based on genetic information. The House of Representatives introduced a bill that would reauthorize the PEPFAR programs. It still needs to be considered by the full Senate.

Dr. Fauci thanked NIAID staff for their assistance preparing for and participating in trips to NIH and CDC program sites in Uganda and South Africa. Dr. Tom Quinn accompanied the Senate appropriations staff delegation to Uganda, and Gray Handley accompanied the group during its visit to South Africa. Dr. Fauci thanked Dr. Dieffenbach for participating in a congressional briefing on HIV prevention.

Other Information Items

The Rocky Mountain Laboratories Integrated Research Facility is substantially completed and occupancy has started.

In May, the Institute Pasteur held a high profile HIV meeting, "25 years of HIV." The meeting coincided with the discovery of HIV in May of 1983 and celebrated scientific progress in the field. On March 25, NIAID held a successful Summit on HIV Vaccine Research and Development. Dr. Fauci summarized accomplishments, challenges, and the direction the Institute is headed in the field of HIV research.

Dr. Fauci gave a brief update on the problems encountered during the 2007-2008 influenza season and noted that the influenza vaccine composition for the upcoming season will have an unprecedented three-strain change. He also reported on the Institute's research agendas and activities in malaria, tuberculosis, antimicrobial resistance, and food allergies.

III. GUEST SPEAKER – Gary Nabel, M.D., Ph.D., Director, NIAID Vaccine Research Center

Like the rest of NIH, Vaccine Research Center (VRC) funding has leveled off. Funding the VRC receives is divided between non-biodefense, mostly HIV, and biodefense, which includes Ebola, Marburg, and influenza. The VRC has developed vaccines for Ebola and influenza that have gone into human trials. The Center has completed phase I studies showing good immunogenicity for both West Nile Virus and SARS, but for various reasons will not pursue these into advanced development. Since Marburg is a cousin of the Ebola virus and outbreaks continue to occur, the VRC is continuing to develop this vaccine.

Dr. Nabel summarized the outcome of Merck's HIV vaccine trial. He noted that researchers in the field are trying to sort out what the risk is and if there is a safe way to proceed with vaccines that contain adenovirus in Ad seropositive individuals.

VRC's HIV vaccine candidate differs substantially from the Merck vaccine. The VRC vaccine has completed phase II testing, with more than 900 person years of safety data and very good immunogenicity data in Africa and the U.S.

Another virus of concern is Chikungunya. It was originally discovered in equatorial Africa and has spread into the tropical regions. The VRC is developing and testing in animals DNA and viral-like proteins that have considerable promise for vaccination.

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

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

STAFFING/ORGANIZATIONAL CHANGES

Sarah Landry, M.A. Ms Landry joined the Office of Program Planning Operations and Scientific Information in April as Director. She received her bachelor's in Zoology from the University of Maryland and an MFA in Science Writing from Johns Hopkins University. Ms. Landry joined NIAID after working as Director of Public Policy for Vaccines at GlaxoSmithKline. Prior to that she served as the Associate Director for Policy and Communications in the National Vaccine Program Office and was instrumental in the development of the National Pandemic Influenza Plan. Ms. Landry previously worked in communication and science policy at NIAID for twelve years and gained experience in HIV/AIDS, global health, vaccine safety, emerging infectious diseases and biodefense research. In addition, Ms. Landry was the editor of the 20th edition of the Jordan Report, which is recognized as the authoritative guide on the state of vaccine research.

Wolfgang Leitner, Ph.D. Dr. Leitner joined the division in April 2008 as a Program Officer in the Innate Immunity Section, Basic Immunology Branch. He received his M.S. and Ph.D. from the University of Salzburg/Austria and did his postdoctoral training at the Walter Reed Army Institute of Research in Washington, DC on malaria vaccine development and malaria escape mechanisms. He then joined the Surgery Branch of the National Cancer Institute to work on Melanoma vaccines with Dr. Nicholas Restifo. For the last 6 years, he worked as a staff scientist in the Dermatology Branch of the NCI on the development of a lymphoma vaccine and basic tumor immune mechanisms.

Stacy Ferguson, Ph.D. Dr. Ferguson joined the divison in May 2008 as a Program Officer in the Immunoregulation Section, Basic Immunology Branch. She received her Ph.D. from the University of

Massachusetts and conducted postdoctoral work with Dr. Michael Cancro at the University of Pennsylvania and Dr. Craig Thompson at the University of Chicago. She then worked in the biotechnology industry at Hematech, LLC. Prior to joining DAIT, she was the Associate Director of Immunology at Macrogenics, Inc. in Rockville, MD.

SCIENTIFIC INITIATIVES

Request for Information (RFI): State-of-the-Science Evidence-Based Review of the Diagnosis and Management of Food Allergy (NIH-NIAID-DAIT-EBRN-01): To determine the availability of qualified contractors to produce an evidence-based literature report that will summarize the state of the science for definition, diagnosis, and management of food allergy.

Autoimmunity Centers of Excellence (U19) (RFA-08-010): The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) the National Institute of Neurological Disorders and Stroke (NINDS), and the Office of Research on Women's Health (ORWH) invite applications from institutions that propose to accelerate the discovery and development of therapies for autoimmune diseases through their participation in the Autoimmunity Centers of Excellence (ACE) program. The ACE network of biomedical research centers will foster collaborations among basic and clinical scientists and facilitate cooperative clinical trials in autoimmune diseases. Each application in response to this FOA must include: (1) a clinical component, (2) a research component, (3) a pilot research project, and (4) cores that participate in cooperative and collaborative projects within each Center and among the Centers.

Rejuvenating the Aged Immune System (R01) (RFA-AI-08-012): The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute on Aging (NIA), National Institutes of Health, invite Research Project Grant (R01) applications from institutions/ organizations that propose to study the biology of thymic involution and the decline of T cell production, differentiation, and function in the aged population (defined as individuals over 50 years of age, for the purpose of this FOA). This Funding Opportunity Announcement (FOA) will support basic and applied research projects that utilize appropriate animal models and/or in vitro human cells/tissues to understand the mechanisms responsible for thymic involution and decreased T cell production and function, or to analyze the functional activity of the T cells, beneficial or detrimental, generated from experimental or clinical approaches to reverse or prevent thymic involution and increase T cell output in patients exhibiting immune senescence.

Cooperative Centers for Translational Research on Human Immunology and Biodefense (U19) (RFA-AI-08-014): The National Institute of Allergy and Infectious Diseases (NIAID) invites new or competing renewal applications from institutions with multi-disciplinary investigator teams to participate in the Cooperative Centers for Translational Research on Human Immunology and Biodefense (CCHI) program. The goal of this Funding Opportunity Announcement (FOA) is to support research on human immunology as it applies to potential agents of bioterrorism or emerging/re-emerging infectious diseases. The immediate objectives are to support basic and translational research on human immunological responses to NIAID Category A, B, or C Priority Pathogens, their toxins, or other emerging and re-emerging diseases; and to create the stable, flexible, and centralized infrastructure needed to promote and coordinate multi-disciplinary research in human immunology as it relates to defense against these agents. This research program was originally established by NIAID in fiscal year 2003, and is now being renewed through open competition. All

qualified investigators are invited to apply; prior funding under this program or through NIAID or NIH is not required.

Immune Mechanisms of Virus Control (U01/U19) (RFA-AI-08-013): The National Institute of Allergy and Infectious Diseases (NIAID) invite new applications from single institutions and consortia of institutions to participate in the "Immune Mechanisms of Virus Control" program. The goals of this initiative are to: 1) establish a network of synergistic research teams focused on basic immunological parameters of virus infection, mechanisms of virus-induced inflammation, and protective vaccination; and 2) to discover and define novel basic immune mechanisms for controlling virus infections that will lead to new potential targets for developing future vaccines and therapeutics.

DIVISION ACTIVITIES

Predicting Individual Radiation Sensitivity: Current and Evolving Technologies: On March 17-18, 2008, NIAID sponsored a two-day meeting at Columbia University, New York. In recent years, there have been exciting genomic and proteomic biomarker studies to predict acute and long-term normal tissue injury based on individual radiation sensitivity. The focus of this workshop was to understand ongoing research and challenges in predicting acute and long-term radiation injury based on individual radiation sensitivity. Also discussed was the need to develop new biodosimetry/biomarker technologies for triage and treatment following radiological/nuclear attacks or accidents.

Regulatory T Cells in Immune-Mediated Diseases As part of the annual meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI): On March 14, 2008, the NIAID organized a symposium entitled "NIAID Morning Symposium: Regulatory T Cells in Immune-Mediated Diseases." Six experts in the field presented lectures on the role of regulatory T cells in immune-mediated diseases including asthma and allergy, including mechanisms by which these cells participate in development of immunologic tolerance.

Atopy, Immune Regulation and Infectious Diseases: As part of the annual meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI) on March 14, 2008, the NIAID organized a symposium entitled "NIAID Afternoon Symposium: Atopy, Immune Regulation and Infectious Diseases." Six experts discussed the interactions between atopic diseases and infection, including alterations in susceptibility to infection with specific agents, and possible mechanisms underlying these clinical observations.

Formula for Success: Connecting with NIH Program Officers: As part of the annual meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI) on March 17, 2008, the NIAID organized the seminar "Formula for Success: Connecting with NIH Program Officers." The purpose of the seminar was to familiarize the research community with NIAID funding opportunities and applications. Discussions covered the use of various instruments/tools, the new electronic grant SF424 submission format, the optimal use of Program Officers as resources, and guidance on what to do and what to avoid in the grant writing/application process.

New Developments in Inner City Asthma: Identifying Risk Factors and Designing Preventive Strategies: As part of the annual meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI) on March 17, 2008, results from the NIAID-sponsored studies in the Inner City Asthma Consortium were presented in a session entitled "New Developments in Inner City Asthma: Identifying Risk Factors and Designing Preventive Strategies." Presentations from three investigators discussed alterations in the pattern of immune development in babies in urban environments, obesity in

inner city populations and its possible relationship to asthma and the relationship between allergen specific IgE and asthma severity in urban children.

American Association of Immunologists (AAI) Annual Meeting: The twenty-fourth annual Symposium on Contemporary Topics in Immunology, cosponsored by the NIAID and the AAI, was held as part of the Annual AAI Meeting that convened in San Diego, CA on April 5-9, 2008. At the same conference, the NIAID also sponsored a workshop on NIAID Pay lines and Funding Opportunities; and the NIAID and the Office of AIDS Research cosponsored a workshop on basic B cell immunology and the development of a neutralizing HIV vaccine.

NIAID Workshop - Immune Cell Representation in the Cell Ontology: The Cell Ontology (current version available at http://obofoundry.org/; click on the cell.obo link) includes many cells of interest to the immunology community. The original representations of immune cells were useful, but required input from the broader immunology community to incorporate current knowledge of immune cell ontogeny and subsets. On May 13-14, 2008, NIAID program staff, representatives from the GO Immune Ontology and the CL Ontology, and other immunologists participated in an NIAID-sponsored "hands-on" workshop to further enhance the representation of several immune cell populations in the CL, including B cells, dendritic cells, macrophages, and T cells. The updated representations are being incorporated into the CL and made available to the research community.

NIAID Workshop - Systems Biology: The first annual meeting of the NIAID Systems Approach to Immunity and Inflammation Program was held on May 19, 2008 in Bethesda, MD. Investigators funded under this program presented recent results from screens of ENU mutagenized mice to identify genes regulating innate and adaptive immune responses to TLR agonists, pox virus, influenza virus, and cytomegalovirus; as well as progress in utilizing genomics, proteomics, and mathematical computation to define signaling and gene regulatory networks underlying responses to a variety of infectious pathogens. Additional information on this program is available at http://www.innateimmunity-systemsbiology.org.

DIVISION ADVISORY COUNCIL PRESENTATION

Update on Technical Advances from the Human Immunology Center Program

A programmatic presentation was given by Helen Quill, Ph.D., Chief, Basic Immunology Branch in which she discussed an **Update on Technical Advances from the Human Immunology Center**. This was followed by Mark M. Davis, Ph.D., Director of the Institute for Immunity Transplantation and Infection, Stanford University discussing **Monitoring the Human Immune System: Problems and Prospects.** Finally, Patrick C. Wilson, Ph.D., Adjunct Assistant Professor, Oklahoma Medical Research Foundation discussed **Rapid Cloning of High Affinity Human Monoclonal Antibodies.**

CONCEPT REVIEW

All concepts were presented and approved.

Biomarkers and Biodosimetry for Radiation Exposure
develop rapid, reliable, inexpensive and easy-to-use devices with long shelf lives to be used to measure civilian radiation doses post-exposure, for both emergency triage and to inform medical treatment decisions.

This program will support cooperative agreement grants on basic, applied or translational research to identify novel methods for post-exposure radiation dose measurement in all segments of the civilian population. Biologically-based systems will be developed for this purpose, and may be founded on patterns of biomarker expression or other physiological changes that correlate well with the particular dose of radiation received. Dose determination may be performed for defined threshold levels for use in emergency triage, or may be finely tuned to provide more accurate dose measurements to assist in specific medical treatment decisions. Dynamic considerations will be incorporated into these studies, as well as assessment of variance with age, gender, ethnicity, and underlying health conditions.

Development of an Oral Radionuclide Decorporation Agents for Use in Radionuclide Decorporation in Radiological Emergencies (N01)
The objective is to provide additional funds to continue and expand non-clinical efforts for product development of oral decorporation agents effective for a broad range of radionuclides for inclusion in the Strategic National Stockpile for use during a radiological emergency.

This program will support N01 contracts to support specific IND-enabling product development activities leading to an IND submission package to be submitted to FDA. The IND-enabling activities will include decorporation efficacy studies to optimize formulation, dose, and dose schedule, drug product stability studies, drug product GMP manufacturing scale-up, GLP toxicology and pharmacology safety studies, pharmacokinetic and metabolism studies, development of GLP analytical methods for efficacy studies and radiation committed dose assessments, and completion of IND package for FDA submission. The product development efforts will advance the new radionuclide decorporation agents towards phase I clinical safety studies, GLP animal pivotal efficacy studies, and licensure.

Development of an Oral Form of Diethylenetriaminepentaacetate (DTPA) for Use in Radionuclide Decorporation in Radiological Emergencies (N01)
The objective is to provide additional funds to continue and expand non-clinical efforts for product development of an oral form of DTPA to decorporate radionuclides for inclusion in the Strategic National Stockpile for use during a radiological emergency.

This program will support N01 contracts to support specific IND-enabling product development activities leading to an IND submission package to be submitted to FDA. The IND-enabling activities will include decorporation efficacy studies to optimize formulation, dose, and dose schedule, drug product stability studies, drug product GMP manufacturing scale-up, GLP toxicology and pharmacology safety studies, pharmacokinetic and metabolism studies, development of GLP analytical methods for efficacy studies and radiation committed dose assessments, and completion of IND package for FDA submission. The product development efforts will advance the oral DTPA radionuclide decorporation agents towards phase I clinical safety studies, GLP animal pivotal efficacy studies, and licensure.

Investigations on Immunodeficiency Diseases (R01)
The objective is to encourage Research Project Grant (R01) applications that propose investigations in primary immunodeficiency diseases focusing on ex vivo studies with human specimens and on studies with current or new animal models including novel clinical strategies for detecting, identifying the molecular basis of, or developing innovative therapies for primary immunodeficiency diseases. The Jeffrey Modell Foundation has committed funding over 5 years to fund applications which do not receive funding under this solicitation.

This is a new solicitation which seeks R01 applications in primary immunodeficiency disease research.

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

Dr. Carole Heilman, Director of the Division of Microbiology and Infectious Diseases (DMID), chaired the May 27, 2008 NAAID Microbiology and Infectious Diseases Subcommittee meeting.
She informed the Subcommittee that Dr. Richard Gorman has officially been appointed Associate Director for Clinical Research in DMID; Dr. Heilman then referred to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their respective new hires.

Dr. Heilman noted that in response to the large influx of biodefense funding the Institute received in 2003, DMID rapidly initiated several preclinical activities to assist the research community in developing products. Many of these programs will expire in 2010, and DMID has been considering how best to address the needs filled by these programs in the coming years. Over the past year and a half, DMID has held numerous internal planning meetings in an effort to ensure that DMID provides a full spectrum of preclinical services that is both effective and efficient, given the current fiscal restraints the Institute is operating under.

One of the major components of DMID's scientific portfolio considered were those activities deemed critical infrastructure, which Dr. Heilman defined as those research programs and services that support the institute's core mission and lead to the development of new and improved public health products and tools. Dr. Heilman discussed DMID's efforts over the past several years that have helped to expand the division's critical infrastructure activities and make them available to the research community. Dr. Heilman noted that DMID is planning to consolidate multiple, disparate critical infrastructure programs into a comprehensive, coordinated program to conveniently serve the research community and provide the flexibility needed to respond to changing priorities in infectious diseases.

Following Dr. Heilman's remarks, Dr. Michael Kurilla, Director of DMID's Office of Biodefense Research Affairs, described several recent DMID research accomplishments achieved within existing critical infrastructure programs, which span the product development spectrum. He then further described DMID's plans, as outlined by Dr. Heilman, to consolidate currently active, pathogen-specific resources into four broad research initiatives, three of which were subsequently presented for Council approval. Those three initiatives focus on: *in vitro* assessment, animal models, and biological resource centers. A fourth, focused on vaccine and therapeutic development services, will be put forward as a Fiscal Year 2011 concept. The four concepts together will comprise the foundation of DMID's critical infrastructure program, and will provide maximal flexibility so that DMID can respond rapidly to new scientific opportunities, as well as to emerging threats, in its broad infectious diseases research portfolio.

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

***In Vitro* Assessments for Antimicrobial Activity** – This initiative is a renewal of several existing initiatives (viral, bacterial, mycobacterial) and an expansion into new areas (fungal, parasitic). The Subcommittee was enthusiastic about the potential efficiencies of a DMID-wide approach to providing low-to-medium throughput screening. The Subcommittee felt that this contract provides a valuable resource and an important infrastructure for the infectious disease research community. The Subcommittee unanimously approved the initiative.

Animal Models of Infectious Disease – This initiative is a renewal of a number of existing, pathogen-specific initiatives into one consolidated program. The new awards will provide DMID with a number of animal model resources that can be tasked to flexibly respond to current and emerging infectious disease animal model priorities. The Subcommittee felt that these contracts provide a valuable resource and an important infrastructure for the infectious disease research community as well as the product development community. The Subcommittee unanimously approved the initiative.

Microbiology and Infectious Diseases Biological Resource Repository -- This initiative is a renewal of a number of existing, pathogen-specific initiatives. The new awards will be made as a consolidated program with two parts. The Biological Resource Repository will be the main repository and will assume as many functions as possible, including all the general tasks repositories typically perform. The Specialized Biological Resources will be awarded in areas where a pathogen requires special expertise or infrastructure, such as the growing of fastidious pathogens in animals or under the highest biosafety containment levels. The Subcommittee felt that these contracts provide a valuable resource and an important infrastructure to stimulate and advance research in infectious diseases. The Subcommittee unanimously approved the initiative.

Microbiology and Infectious Diseases Specialized Biological Resources – This initiative is a renewal of a number of existing, pathogen-specific initiatives. The new awards will be made as a consolidated program with two parts. The Biological Resource Repository will be the main repository and will assume as many functions as possible, including all the general tasks repositories typically perform. The Specialized Biological Resources will be awarded in areas where a pathogen requires special expertise or infrastructure, such as the growing of fastidious pathogens in animals or under the highest biosafety containment levels. The Subcommittee felt that these contracts provide a valuable resource and an important infrastructure to stimulate and advance research in infectious diseases. The Subcommittee unanimously approved the initiative.

DMID Clinical Research Operations and Support – This initiative is a renewal of an existing contract that provides clinical research support, including clinical site monitoring, safety data monitoring, site quality management, protocol development, and research information tracking databases and other operational, administrative, and logistical support. The Subcommittee felt that this contract provides a valuable resource and an important infrastructure for the clinical research community. The Subcommittee unanimously approved the initiative.

Innovative Approaches to Target Identification and Assay Development for Fungal Diagnosis – This initiative is a new solicitation for grants that will foster collaborative efforts between the mycology research community and technology-based entities to explore emerging and innovative technologies for diagnostic target identification. The new award will build on resources from an expiring contract. The Subcommittee felt that this initiative addresses a critical need and unanimously approved the initiative.

Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance -- This 2010 initiative is similar to an initiative released for Fiscal Year 2009 funding focused on the use of innovative, strategy-based designs in the conduct of clinical trials aimed at reducing the risk of antimicrobial resistance. The new initiative provides the opportunity to address strategies and/or disease areas not covered in the 2009 initiative. The Subcommittee unanimously approved the initiative.

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

Dr. Wafaa El-Sadr, Chair of the ARAC, welcomed ARAC members, DAIDS representatives, and guests.

DIRECTOR'S REPORT
Carl W. Dieffenbach, Ph.D., Director, DAIDS

New ARAC Members: Dr. Dieffenbach welcomed new ARAC member Christel Uittenbogaart, who was attending her first meeting. He announced two new *ex officio* members—Dr. Alan Bernstein, executive director of the Global Vaccine Enterprise, and Dr. Paul Volberding, the Office of AIDS Research Advisory Committee liaison, both of whom were unable to attend the meeting. Dr. Bernstein is its first executive director of the Global Vaccine Enterprise, an international alliance of researchers, funders, and advocates that supports the development of an HIV vaccine. Dr. Volberding is chief of the Medical Service at the San Francisco Veterans Affairs Medical Center and co-director of the University of California, San Francisco's Center for AIDS Research.

DAIDS Staff Updates: Dr. Dieffenbach announced that Manizhe Payton recently joined DAIDS as director of the Office of Clinical Site Oversight. Ms. Payton was previously director of Trial Management and Operations at the Immune Tolerance Network. Roberta Black, Ph.D., was selected as chief of the Microbicide Research Branch in DAIDS' Prevention Sciences Program. Dr. Black has extensive experience. She started out in the Developmental Therapeutics Branch of the DAIDS Basic Sciences Program and then moved into prevention, where she has played a pioneering role in the field of microbicides. David Burns, M.D., was named chief of the Prevention Research Branch in the DAIDS Prevention Sciences Program, where he most recently served as a medical officer. Prior to that, he served as director of infectious diseases and public health programs for the Abt/USAID-funded ZdravPlus Program for Central Asia.

Dr. Dieffenbach noted that Matthew Murguia, former director of the Office of Program Operations and Scientific Information, left DAIDS in April to become associate director of NIAID's Office of Ethics. Mary Owens was asked to serve as acting director of the Office.

Budget Update: Dr. Dieffenbach reviewed increases in the NIAID budget during the past 20 years, which reflect growth in programs for HIV/AIDS, biodefense, and emerging infectious diseases. However, the President's FY 2009 budget request for NIH is $29.2 billion, which represents a zero-percent increase over the FY 2008 amount. The NIAID allocation in the FY 2009 is $4,568,778,000, an increase of 0.2 percent over FY 2008. Of the $8 million increase in proposed budget for NIAID, $5million is slated for the Global Fund. Thus, the remaining $3 million (representing a 0.1 percent increase over FY 2008) would be available for funding research.

Scientific Updates: In July 2007, the NIAID initiated the PreExposure Prophylaxis Initiative, or IPrEX study. IPrEX is a phase IIB proof-of-concept study to examine if Truvada is effective in preventing HIV infection when combined with safe-sex counseling and condom use for men who have sex with men. With support from the Gates Foundation the study is expanding from the initial 4 Andean sites to 7 additional sites in the United States, Brazil, South Africa and Thailand. With the new sites, the study will enroll about 3,000 participants.

Dr. Dieffenbach concluded with his report with an overview of the clinical trials development process as a context for the concepts that will be presented to the committee for approval.

CONCEPT REVIEWS: OFFICE OF POLICY AND CLINICAL RESEARCH OPERATIONS
Carl W. Dieffenbach, Ph.D., Director, DAIDS

DAIDS Clinical Site and Study Monitoring Contract
This contract, using an N01 mechanism, is a renewal with a total first-year cost of $22 million and duration of 7 years. There will be one award. Site monitoring is an integral component of trial oversight, verifying the well-being of study participants, accuracy and completeness of data, and compliance with the protocol, general practices, and regulatory requirements. The contractor will provide qualified monitors, a training program for them, and evaluation of that training. It will perform GCP/ICH monitoring of sites and pharmacies, report the results (including recommendations for actions), and develop standard operating procedures, templates, assignments, and tracking systems for site monitoring. The contractor will also work to control costs by adjusting site assignments. The monitoring contractor will be audited by an independent contractor (see next concept).

The reviewers wanted to be sure that sites are not overly taxed when monitors find minor issues that do not have an overall impact on the rigor of the research. It was also noted that a site's degree of community engagement in the clinical trials process is not part of the monitoring process, but is incorporated into the evaluation done by the Networks. Additional discussion of the concept focused on: the need to ensure coordination between the monitoring and auditing contracts, which are now being competed separately; the need to facilitate communication between the protocol team, the Division and all sites participating in a given protocol as soon as issues are identified as these may have relevance to other sites; and the suggestion that site investigators and Network Evaluation Committee members provide input for optimizing the monitoring system.
The committee voted to approve the concept for this initiative.

Clinical Research Auditing
This contract, using an N01 mechanism, is new, with a total first year cost of $2 million and a duration of 7 years. There will be one award. Activities will include independent quality-assurance auditing of the site-monitoring process to consider trial conduct. Auditors will evaluate the consistency and quality of site monitoring to identify deficiencies and strategies for increasing performance and efficiency. The contractor will audit both DAIDS and non-DAIDS site monitoring—covering up to 10 percent of all monitoring. High-risk studies will receive particular attention. The contractor will develop templates, standard operating procedures, and training for auditing.

The reviewers of the concept supported approval. They asked for clarification on the need for auditing in addition to the monitoring. It was clarified that the auditing will not focus on details of the monitoring but will determine whether the monitoring properly addresses the larger issues and will focus on "highest risk" studies. Project officers will facilitate communications between the monitoring and auditing functions. The committee asked how "highest risk" would be defined for auditing purposes and recommended that an external advisory body be established to advise on the infrastructure for and implementation of the auditing process. The committee was supportive of this approach without making it a stipulation of approval, and voted to approve the concept for this initiative.

Regulatory Support Center
This contract, using an N01 mechanism, is a renewal and expansion, with a total first year cost of $9.3 million and a duration of 7 years. There will be one award. The contractor will support: the preparation and filing of new INDs and amendments, related submissions, and annual report; regulatory assessments of informed consent; DAIDS Scientific Review Committees; and provide documentation and tracking for negotiations for clinical trials agreements. This contract is the key to maintaining the clinical trials infrastructure and facilitates protocol registration, safety reporting, and the distribution of safety information. The contractor will respond to new changes in safety rules and procedures and will create a Protocol Information Office (PIO), which will consolidate protocol activities.

The reviewers of this concept supported approval. Committee members noted the importance of this contract for ensuring participant safety and recognized the increased burden on regulatory activities given the growth of the number of DAIDS-supported sites, particularly international sites. Questions focused on differences between this contract and the current regulatory contract, and how performance would be evaluated. Also, if a new contractor is selected, the committee noted the importance of ensuring a smooth transition. Dr. Jonathan Kagan stated that

DAIDS has been developing its own data system, which will allow for a smoother transition from one contractor to another and eliminate DAIDS' dependence on any specific contractor's data. The committee voted to approve the concept for this initiative.

HIV Clinical Research Support Contract (CRS)
This contract, using an N01 mechanism, is a renewal, with a total first year cost of $16.2 million and a duration of 7 years. There will be one award. This contract helps fill gaps, facilitates changes in studies to meet new scientific opportunities and challenges, assists with international infrastructure development, strengthens non-network studies, and provides support services not provided by other contracts. Basic objectives are to facilitate research program management, clinical site and laboratory support, clinical trial support, and GCP/GCLP and regulatory compliance. Program management will include developing subcontracts for activities that are not otherwise supported. Site and laboratory support will include aiding the assessment and auditing activities. Clinical trial support includes facilitating Data and Safety Monitoring Board (DSMB) meetings and biostatistical activities. Finally, the contractor will support training for GCP/GCLP and regulatory compliance.

In discussion, the role of this contract vis a vis the other contracts was clarified. It was emphasized that the CRS supports a variety of cross-network activities, including many HANC related cross-network activities that are critical for harmonization and collaboration. DAIDS pointed out that it has also developed a mechanism to approve large expenditures of this contract and has been very prudent to date. The committee voted to approve the concept for this initiative.

UPDATE: STRATEGIC WORKING GROUP
David Margolis, M.D., University of North Carolina at Chapel Hill

Dr. David Margolis reviewed the May 19–20, 2008 meeting of the Strategic Working Group (SWG), which provides the division with external expert advice on the efforts of the clinical trials networks. The meeting focused on four topics: the PROMISE trial, the HIV Vaccine Trials Network (HVTN) strategic update, the PAVE 100A trial, and the HIV Prevention Trials Network's (HPTN) domestic research agenda.

The International Maternal Pediatric Adolescent AIDS Trials (IMPAACT) network proposed a large trial to address multiple questions about how to best prevent mother to child transmission (MTCT) of HIV, ensure the health of the infant throughout breastfeeding and beyond, and determine what treatment is most appropriate for the women who begin therapy solely for the purpose of preventing MTCT. The proposed PROMISE trial will be large and complex, requiring an estimated 5,950 mother-infant pairs, 2,000 additional mothers, and four sequential randomizations. The SWG strongly supported PROMISE although concerns were raised about the complexity of the study. There was also some discussion over the domestic component of the study that addresses the question of "when to start or stop" antiretroviral therapy. The total cost of the trial was estimated at approximately $141 million, of which DAIDS would need to fund an additional $11 million each year. Dr. Dieffenbach stated that the division would seek to shift funds from other areas and obtain contributions from outside partners. It was suggested that programs such as PEPFAR program, might be able to offer infrastructure support. Dr. Andrea Kovacs also noted that the PROMISE trial would allow for many nested studies. The cost of the study is being re-calculated so all the funding issues can be more carefully considered.

The HVTN presented a revised scientific agenda, which included plans to garner as much information as possible from STEP samples and follow-up. The SWG appreciated the efforts and plans that have been made following the STEP and Phambili trials. The HVTN also presented the PAVE 100A study, which is a phase IIB test of concept study of the Vaccine Research Center's (VRC) multiclade DNA vaccine followed by a multiclade recombinant adenoviral vector vaccine. The vaccine and the regimen differ from those used in STEP and to further address any safety concerns posed by the STEP study, PAVE 100A would only enroll circumcised men who are adenovirus serotype 5 negative in the US. The SWG deferred its comments about PAVE 100A until after the AIDS Vaccine Research Subcommittee (AVRS) meeting.

The HPTN presented its domestic research agenda, which includes a study of seroincidence in women in the rural Southeast (HPTN 064), and a feasibility study of a community-level multi-component intervention in Black MSMs

(HPTN 061). The SWG was impressed with the HPTN's progress in formulating its agenda and supportive of both of the studies presented. The SWG strongly recommended moving this forward now, and requested an update on implementation at the September meeting.

Dr. Margolis stated that the September meeting of the SWG would feature presentations and discussions of the AIDS Clinical Trials Group, the Office of Clinical Site Oversight, and top priorities.

UPDATE: HIV VACCINE SUMMIT AND NEXT STEPS
Carl W. Dieffenbach, Ph.D., Director, DAIDS

Dr. Dieffenbach reported on the NIAID Summit for HIV Vaccine Research and Development Summit, which took place on March 25, 2008. Discussions focused on vaccine-related basic research, discovery and development; animal model development and utilization; and clinical research and trials. Summit participants discussed the need for balancing discovery research and developmental research, how to foster innovative research proposals, and how to attract new investigators to the field. One result of the summit was a consensus in supporting the concept of a new basic vaccine discovery research program (see below).

CONCEPT REVIEW: VACCINE RESEARCH PROGRAM
Jorge E. Flores, M.D., Deputy Director, Vaccine Research Program, DAIDS

Dr. Jorge Flores presented the concept for the Basic HIV Vaccine Discovery Research initiative, which has a goal of accelerating HIV vaccine discovery by supporting a new generation of knowledge that can inform new conceptual approaches. This is a new concept, using the R01 mechanism, with a total first year cost of $10 million. The initiative will span FY 2009 and FY 2010.

At the vaccine summit, participants stressed NIAID's commitment to discovery research and to an R01 program that will emphasize discovery, fundamental research, and flexibility. The RFA for the program will be informed by input from investigators and will help address many of the issues that have been raised to date, including the need to: invigorate the field, attract new, young investigators; and use technologies from the vaccine area and related fields. The program will support research that is hypothesis-driven, that links directly to HIV vaccine design, that includes other related fields, and that promises preliminary data and rationale for biological plausibility. In most cases, each awardee will receive less than $500,000 per year.

Dr. Flores listed types of research that the program might foster, including mechanisms of vaccine-induced protection, early events in HIV/SIV infection, the role of innate and mucosal immunity in control of infection, broadly reactive neutralizing antibodies, mechanisms of control of HIV/SIV, non-pathogenic models of SIV infection, and structural biology of the HIV envelope. Non-responsive research may include human clinical trials, studies of incremental improvement of approaches already in development, research strategies previously proposed for ongoing solicitations, and purely descriptive basic research. DAIDS will encourage cross-disciplinary collaborations, provide review by a senior special review panel, and establish a cross-program management team.

The ARAC reviewers suggested that the concept highlight what would be considered non-responsive research; encourage research in additional areas such as mucosal immunology and HIV pathogenesis; exclude mouse-model studies that do not indicate how aims will have an impact on vaccine design; use open-minded, experienced reviewers, including persons outside the HIV field who are experienced in immunology; and consider incentives for young investigators but do not discourage senior scientists. There was additional discussion about these suggestions, including whether a differential payline strategy and/or the opportunity for smaller projects could help attract young investigators. The ARAC members voted to approve the concept for this initiative.

VII. ADJOURNMENT

The meeting of the Council was adjourned at 4:10 p.m., on Tuesday, May 27, 2008.

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

_____-s-_____ **_07/11/2008_____**
Anthony S. Fauci, M.D. Date
Chairman, National Advisory Allergy
and Infectious Diseases Council
Director, National Institute of Allergy
and Infectious Diseases

_____-s-_____ **_07/02/2008_____**
Marvin R. Kalt, Ph.D. Date
Executive Secretary
National Advisory Allergy and Infectious
Diseases Council
Director, Division of Extramural Activities
National Institute of Allergy and Infectious
Diseases

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