NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

September 15, 2008

The 160th meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, September 15, 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 4:30 p.m. The meeting was closed to the public from 8:30 a.m. to 10:00 a.m. and from 11:40 a.m. to 12:00 p.m. for review and consideration of individual grant applications. Notice of the meeting was published in the *Federal Register*.

Council Members Present:

Dr. Ann Arvin
Dr. Barbara Baird
Dr. Robert Brooks
Dr. Carol Carter
Dr. Satya Dandekar
Dr. Kathryn Edwards
Dr. Richard Insel
Dr. Sharon Kiely
Dr. Martin Myers
Dr. Louis Picker
Dr. Regina Rabinovich
Dr. Martin Rosenberg
Dr. Marc Rothenberg
Dr. Gary Schoolnik
Dr. Megan Sykes
Dr. Christel Uittenbogaart
Dr. David Wilkes

Council Members Absent:

Dr. Shelley Payne

***Ad Hoc* Member:**

Dr. Jenny Ting

NIAID Senior Staff:

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

***Ex Officio* Members Present:**

Dr. Mitchell Cohen
Dr. Anthony Fauci
Dr. Ronald Valdiserri
Major General George Weightman

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 2,128 research and training applications with primary assignment to NIAID for a requested amount of $481,663,040 in first-year direct costs and recommended approval of 444 applications for $68,492,779 in first-year direct costs. Five 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 introducing ad hoc Council member Dr. Jenny Ting, University of North Carolina at Chapel Hill. He also welcomed Major General George Weightman who replaced Brigadier General Eric Schoomaker as the *ex officio* representative from the Department of Defense. MG Weightman is Commanding General, U.S. Army Medical Research and Materiel Command. Dr. Shelley Payne, a retiring Council member, was unable to attend the meeting.

Dr. Fauci acknowledged the contributions of three other retiring members, Dr. Richard Insel, Dr. Martin Myers, and Dr. Gary Schoolnik, and presented them with plaques.

Consideration of Minutes of Previous Meeting

The minutes of the May 27, 2008, meeting were considered and approved as written.

Staff and Organizational Changes

Dr. Fauci began by announcing new scientific staff in the Institute. Last month, Dr. Heinz Feldmann began his tenure as chief of the new Laboratory of Virology in the Integrated Research Facility at the Rocky Mountain Laboratories in Hamilton, Montana. Dr. Richard Schwartz was appointed director of the Vaccine Production Program at the Vaccine Research Center.

Dr. Fauci announced appointments for two new positions in the Division of Extramural Activities. Dr. Patricia Haggerty is Associate Director for Operational Infrastructure, and Dr. Anna Ramsey-Ewing is Associate Director for Extramural Science Policy.

In the Office of Strategic Planning and Financial Management (OSPFM), there have been several new appointments. Jane Lockmuller is chief of the Strategic Planning and Evaluation Branch. Mei-Wan Hoh was promoted to chief of the Referral and Program Analysis Branch. Dr. Lawrence Yager accepted the position as director of the Office of Initiative Development. Marie Parker is now the deputy director of OSPFM.

Tributes and Awards

Dr. Fauci recognized Dr. Rose Mage from the Division of Intramural Research for being named NIH Scientist Emeritus. For the past 20 years, Dr. Mage has served as chief of the Laboratory of Immunology's Molecular Immunogenetics Section.

Budget Update

The president's FY 2009 budget request for NIH is $29.2 billion, virtually the same as the level for FY 2008. The NIAID proposed allocation is approximately $4.6 billion, an increase of $8 million over the FY 2008 appropriated level. Of the $8 million, $5 million is slated for the Global Fund. After accounting for the Global Fund increase, NIAID's actual increase is $3 million or 0.1 percent. This increase is comparable to that of most other NIH ICs.

The House and Senate have both passed their own versions of an FY 2009 appropriation for NIH, which includes more money than the president's request. The president has threatened to veto the bills if they are submitted to him. Until the FY 2009 appropriations bills are signed, NIAID will be operating under a continuing resolution. The FY 2009 provisional payline for R01 research project grants is the 10.0 percentile.

Dr. Fauci presented a couple of updates to the FY 2008 budget. First, NIH set aside about $90 million to support an NIH-wide bridge program. NIAID's extramural investigators received 22 NIH bridge awards totaling more than $10 million. These additional funds will support NIAID investigators beyond our own budget. Second, the Supplemental Appropriations Act of 2008, signed into law on June 30, 2008, provided $150 million of supplemental funds to NIH for FY 2008 only. NIAID received $22.7 million of that amount.

Legislative Update

On July 16, 2008, Dr. Fauci accompanied Dr. Zerhouni as he presented the FY 2009 NIH budget to the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education. On July 30, the president signed into law the Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008. This law reauthorizes PEPFAR and authorizes up to $48 billion to fight HIV/AIDS, tuberculosis, and malaria.

Also in July, Dr. Michael Kurilla represented NIAID at a hearing to examine the status of public health preparedness to deal with emerging biological threats. Additionally, Congressional staff visited NIAID's Integrated Research Facility at Fort Detrick. The visit included a tour and briefing on research activities planned for the facility.

Dr. Fauci spoke at the Center for Strategic and International Studies for HIV/AIDS Conference on July 14, presenting scientific and technological advances and challenges in the field. In early August, Dr. Fauci welcomed Senator Benjamin Cardin to NIH on behalf of Dr. Zerhouni. During the visit, Senator Cardin received an overview of the NIH and NIAID missions and met with other institute directors.

Other Information Items

HHS requested that NIH become more involved in addressing the issue of vaccine safety. In response, NIAID developed a plan that includes an interagency working group to disseminate information on basic research in vaccine safety, subject matter experts at NIH who can assist CDC when vaccine safety concerns occur, and a program announcement for vaccine safety research.

In June 2008, Dr. Fauci addressed the United Nations General Assembly to discuss global health and HIV/AIDS. He reviewed areas in HIV/AIDS research where significant progress has been made but noted there is much work to be done.

Dr. Fauci talked about the decision NIAID made not to proceed with the PAVE 100 trial. He also outlined the priorities identified at the NIAID HIV Vaccine Summit held in March 2008, and noted that NIAID has created an HIV Vaccine Discovery Branch. He gave an overview of his presentation at the 17th International AIDS Conference held in Mexico City in August and concluded with updates on seasonal and pandemic influenza and Institute activities in the area of food allergies.

III. GUEST SPEAKER – Kathryn Zoon, Ph.D., Scientific Director, NIAID Division of Intramural Research

Two major changes are taking place in the Division of Intramural Research (DIR). The first is the creation of a new laboratory within the Malaria Vaccine Development Branch, the Laboratory of Malaria Immunology and Vaccinology. The second is the recruitment of Dr. Heinz Feldmann to lead the new Laboratory of Virology in the Integrated Research Facility at the Rocky Mountain Laboratories.

Dr. Kathryn Zoon discussed some of the difficult issues the Division is facing since DIR's budget has decreased by eight percent over the past two years. She presented priorities for the science programs in DIR which include emerging infectious disease and biodefense initiatives, with particular emphasis on influenza and drug-resistant TB.

Dr. Zoon announced new hires, retirements, and distinguished honors and awards received by DIR staff. Five DIR scientists, Drs. Bernard Moss, Bill Paul, Bob Purcell, Malcolm Martin, and Lou Miller, were selected as NIH distinguished scientists.

In other areas, Dr. Zoon gave updates on new DIR facilities, new initiatives, the clinical research transition program, the independent scholars program, the infection biology training program, and the International Centers of Excellence in Research program.

The Board of Scientific Counselors conducted its periodic review of DIR laboratories and programs. Almost all the labs reviewed received outstanding or excellent reviews. Tenure track investigators who received their midpoint and final reviews all did well. Dr. Zoon concluded by highlighting advances in selected scientific areas and product development.

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

Dr. Rotrosen welcomed the Council members to the 159th meeting of the National Advisory Allergy and Infectious Diseases Council. Dr. Rotrosen began his presentation by announcing new staff members: Ms. Adeline Bartels who joined the Office of Regulatory Affairs as a Program Specialist; Dr. Mercy PrabhuDas has joined the Basic Immunology Branch as a Program Officer; and Ms. Mai-Kim Norman joined the Radiation/Nuclear Program as a Health Specialist.

Dr. Rotrosen mentioned to the committee members that the division had released several scientific initiatives in the area of Immune Defense and Innate Immune Receptors and Adjuvant Discovery.

Dr. Rotrosen concluded his remarks by noting that members of the division's branches and offices had participated in a number of workshops, symposiums and meetings.

As a means of continued scientific interchange between the division's staff and Council members the division presented an update on DAIT Adjuvant 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 Centers. 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 REVIEWS
There were several concepts presented for the Subcommittee's consideration:

Maintenance of the NIAID Specific Pathogen-Free (SPF) Macaque Breeding Colonies: The contract will support high-quality maintenance of the colonies including housing, medical care, breeding, detailed pedigree and health records, and derivation of SPF research animals. In addition, the contract will meet the special requirements of the investigators and NIAID by facilitating MHC typing, establishing directed breeding groups, culling non-SPF, aged, and unsuitable animals, analyzing and maintaining genetic diversity, and providing enhanced colony database capabilities. The Subcommittee felt that this contract provides a valuable resource and an important infrastructure to stimulate and advance research. The Subcommittee unanimously approved the initiative.

Data Coordinating Center for Transplantation Clinical Trials (DCC): The DCC will provide statistical and clinical trial design expertise, data management, site monitoring, regulatory support, adverse event reporting, specimen tracking, drug distribution, support for the NIAID Transplant DSMB, and medical writing. The DCC for Transplantation Clinical Trials will continue to support those clinical trials already underway at the time of award as well as any new clinical trials developed by Clinical Trials in Organ Transplantation (CTOT) and Clinical Trials in Organ Transplantation in Children (CTOT-C). The Subcommittee unanimously approved the initiative.

The Primary Immunodeficiency Disease Registry/Repository: This project will develop resources to encourage and promote research in primary immunodeficiency diseases. The project will renew a portion of the work currently being conducted by the NIAID-funded Primary Immunodeficiency Disease Consortium. This initiative is to provide resources to encourage research in primary immunodeficiency disease. The Subcommittee unanimously approved the initiative.

Consortium of Food Allergy Research (CoFAR) Statistical and Clinical Coordinating Center (SCCC): This initiative is to support basic and clinical research to develop new approaches to prevent and treat food allergy, including studies of food allergy-associated anaphylaxis. This initiative will also support a Statistical and Clinical Coordinating Center (SCCC) for the CoFAR. The SCCC will provide support for the clinical research studies performed in CoFAR. The Subcommittee felt that this contract provides a valuable resource and an important infrastructure. The Subcommittee unanimously approved the initiative.

Exploratory Mechanisms in Food Allergy: This initiative will support *ex vivo* studies with human specimens and studies with current or new animal models of food allergy. Areas for research focus may include: pathogenesis, biomarkers and genetic components of food allergy and severe food

allergy; food allergens and their epitopes including molecular characteristics; and pathogenesis, biomarkers, genetics, mechanistic studies, and risk assessment in animal models. The Subcommittee unanimously approved the initiative.

Atopic Dermatitis Network: Clinical and Animal Studies: This initiative will continue to support the development of diagnostic tools and biomarkers/surrogate markers to identify subjects with AD who are at risk for EV and other disseminated cutaneous viral infections. This initiative also supports animal models of AD in projects that will be closely integrated with human studies. The subcommittee felt that this initiative addresses a critical need. The Subcommittee felt that this initiative addressed a critical need and approved the initiative.

Atopic Dermatitis Research Network: Statistical and Clinical Coordinating Center (SDCC): The Statistical and Data Coordinating Center (SDCC) provides statistical leadership, Web site management, and logistics management for the entire Network and is focused on assistance with the clinical activities. The SDCC activities include: statistical and clinical leadership needed for study design and protocol development, data collection and quality assurance, clinical site training and monitoring, and regulatory and other support for applications for investigational new drugs. The Subcommittee felt that this contract provides a valuable resource and an important infrastructure. The Subcommittee unanimously approved the initiative.

Modeling Immunity for Biodefense: This renewal contract will support multi-disciplinary Centers focused on developing a mathematical modeling package that provides tools for high (whole organism or system), intermediate (tissue or organ), or fine (single cell) resolution modeling of host immune responses to infection and vaccines, with an emphasis on NIAID Category A-C pathogens. Each Center will have strong bioinformatics and training components. The training component can also support internal programs that provide trainees with an understanding of the power of applying mathematical principles to biological phenomena in immunology; drawing from other fields, such as population genetics, ecology, and epidemiology; and may develop teaching tools based on simulations of immune function. The subcommittee felt that this initiative addresses a critical need and unanimously approved the initiative.

Population Genetics Analysis Program: This program will support studies on the association of genetic polymorphisms with host immune responsiveness to infections and vaccination. The focus will be on NIAID Category A-C agents of bioterrorism and emerging/reemerging infectious diseases. Interdisciplinary teams that combine diverse scientific expertise (e.g., microbiology, immunology, genetics, mathematics, computer science) will be encouraged. The Subcommittee unanimously approved the initiative.

NIAID Radiological/Nuclear Medical Countermeasure Product Development Program: This program will fund small business R43/44 grants (Phase I, Phase II, and Phase II competing continuations) to support specific IND/IDE-enabling product development activities leading to an IND or IDE submission packages to be submitted to FDA. The product development efforts will advance the new medical countermeasures towards phase I clinical safety studies, GLP animal pivotal efficacy studies, and licensure. The Subcommittee unanimously approved the initiative.

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

Dr. Heilman acknowledged the retirement of three current Council members -- Gary Schoolnik, Marty Myers and Shelley Payne -- and expressed her sincere appreciation for the many contributions they have

made during their service on the NIAID Advisory Council. Dr. Heilman then referred to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their respective new hires.

Following Dr. Heilman's remarks, Dr. Michael Schaefer provided a brief overview of the DMID partnerships program. The program has been active since 2002 and encourages collaborative research projects centered on multidisciplinary approaches to develop vaccines, vaccine technologies, therapeutics, immunotherapeutics, adjuvants and medical diagnostics for NIAID Category A, B, and C priority pathogens and toxins. DMID staff have proposed three biodefense-related partnership concepts for the Subcommittee's clearance, which were presented immediately following Dr. Schaefer's remarks. Several other concepts were also presented for the Subcommittee's consideration:

2010 DMID Concepts Presented:

Cooperative Research Partnerships for Development of Antimicrobials and Diagnostics for Drug-Resistant Bacteria and Parasites

This program supports translational research on select drug-resistant bacterial and parasitic diseases, and focuses primarily on the development of novel diagnostic and therapeutic approaches.

This specific initiative will support collaborative, multidisciplinary projects that seek to develop new therapeutics and/or diagnostics for select infectious diseases. Projects that characterize novel therapeutic or diagnostic targets are encouraged provided they focus on product discovery and include downstream product development steps. Research on broad-spectrum antimicrobials, platform diagnostics, and truly novel drug classes is particularly encouraged.

Projects should focus on NIAID Category A, B, or C bacterial pathogens and/or other bacteria or parasites where drug resistance is a significant and/or rapidly growing clinical problem. Projects addressing eligible drug-resistant pathogens for which limited therapeutic options are available are also encouraged. Examples of eligible non-category A, B, or C pathogens include but are not strictly limited to Clostridium difficile, Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter spp.

Antimicrobial Drugs: This initiative will support projects focused on discovery and early development of new or improved antimicrobial agents, including small molecule inhibitors, therapeutic antibodies, and peptides. Broad-spectrum drugs and/or drugs targeting novel mechanisms are encouraged.

Adjunctive Therapeutics: Projects seeking to develop adjunctive pharmacologic approaches to specifically target and prevent drug resistance during therapy are encouraged. Such approaches need not be geared to a specific pathogen, but rather should directly target known mechanisms of resistance in order to extend the clinical utility of existing antimicrobials.

Diagnostics: This initiative will support development of rapid point-of-care diagnostics to quickly identify pathogens and their resistance profiles. Multiplexed diagnostics, as well as those able to provide diagnostic information on potential presymptomatic carriers are particularly encouraged.

The subcommittee was highly supportive of the initiative and recognized the need for bedside treatments and point-of care diagnostics. The inclusion of screening for pre-symptomatic individuals was especially commended. Council members suggested including elements of state-of-the-art metabolomics technologies (genomics, proteomics and bioinformatics) explicitly in the announcement. Council members also asked whether the effort could extend to research on environmental samples. Dr. Heilman indicated that environmental detection is handled by the CDC in accordance with a previous agreement

between our two agencies. Council members also recommended fostering greater collaboration between scientific experts in basic research and translational and clinical aspects to maximize progress in developing these tools. It was also noted that because some of the pathogens in question are difficult to detect, the sensitivity of a proposed diagnostic must be taken into consideration. The subcommittee unanimously approved the initiative.

Cooperative Research Partnerships for Biodefense Food- and Water-borne Diseases

This program will support translational research on food- and water-borne diseases, focusing primarily on the development of broad spectrum therapeutics and diagnostics.

This initiative will support collaborative, multidisciplinary projects that utilize broad spectrum approaches to design and develop products to diagnose or treat multiple diseases caused by NIAID Category A, B, or C food- and water-borne prokaryotic or eukaryotic pathogens or toxins. NIAID has identified three key strategies (broad spectrum activity, broad spectrum technology, and broad spectrum platforms) for biodefense research; thus, this program promotes the development of multiplex diagnostics and broad spectrum drugs. Partnerships between researchers from different disciplines and industrial laboratories will be strongly encouraged to facilitate discovery, design, and/or development of new products. Clinical trials will not be supported by this program.

This program calls for the design and development of rapid, sensitive multiplex diagnostics that can differentiate diarrheal pathogens in a single clinical specimen. The focus may be on either previously identified pathogen- or host-specific targets or novel approaches to identify and validate new targets, technologies, or multiplex platforms amenable to large-scale production and validation for clinical diagnosis and point-of-care use. Diagnostics for the protozoan pathogen, Toxoplasma gondii, are not part of this program.

Therapeutics and Immunotherapeutics: The development of new or improved therapeutics may focus on known targets (including antimicrobial resistance mechanisms) or the identification of new targets based on, for example, microbial physiology, immune responses, genomic/proteomic approaches, structural characterization, and components or pathways common to the targeted pathogens. The design of novel drugs or immunotherapies should include lead compound identification and optimization and pre-clinical efficacy testing in animal models. Emphasis will be placed on projects that focus on development of broad-spectrum therapeutics or platforms for discovery of novel targets.

The subcommittee commented that this initiative is intended to promote the development of therapeutics and diagnostics, with a minor focus on broad, cross protective vaccines, for NIAID high priority food- and water-borne pathogens and toxins. It received minimal comments, and no questions were raised about this program. One Council member cited the importance of including detection and surveillance of these pathogens in the environment and in animals; however, it was noted that environmental detection and surveillance fall under the purview of the CDC. The Subcommittee underscored the need to communicate with the CDC on these issues and staff acknowledged that these types of communications are ongoing. The only other comment touched on the fact that current diagnostics require up to 15 days to definitively identify subtypes or fingerprints of outbreak strains, and the Subcommittee member's hope that, under this program, new diagnostics might be developed that would shorten this timeframe. The subcommittee unanimously approved the initiative.

Cooperative Research Partnerships for Biodefense Viral Pathogens

This program will support translational research on NIAID Category A, B, or C viral pathogens, focusing primarily on the development of broad spectrum therapeutics and diagnostics.

This initiative will support collaborative, multidisciplinary projects that utilize broad spectrum approaches to design and develop products to diagnose or treat multiple diseases caused by NIAID Category A, B, or C viral pathogens. NIAID has identified three key strategies (broad spectrum activity, broad spectrum technology, and broad spectrum platforms) for biodefense research; thus, this program promotes the development of multiplex diagnostics and broad spectrum drugs. Partnerships between researchers from different disciplines and industrial laboratories will be strongly encouraged to facilitate discovery, design, and/or development of new products. Clinical trials will not be supported by this program.

This program calls for the design and development of rapid, sensitive, and specific diagnostics which may focus on previously identified pathogen- or host-specific targets or novel approaches to identify and validate new targets. Emphasis will be placed on technologies or multiplex platforms amenable to large-scale production and validation for clinical diagnosis and point-of-care use.

Therapeutics and Immunotherapeutics: The development of new or improved therapeutics should focus on known targets or the identification of new targets based on viral biology, immune responses, genomic/proteomic approaches, structural characterization, etc. The design of novel drugs or immunotherapies should include lead compound identification and optimization and pre-clinical efficacy testing in animal models. Emphasis will be placed on therapeutics for viral hemorrhagic fevers and encephalitides and on drugs which have broad-spectrum activity arising from novel target/mechanisms and broad-spectrum platforms.

The Subcommittee supported the proposed emphasis on validation of diagnostic assays with clinical samples, but was concerned that some investigators may have trouble obtaining such samples and wondered if NIAID maintained repositories of clinical samples that could be made available. It was noted that NIAID does not have such a repository, but that program officers try hard to connect investigators in need of clinical specimens with those who have them, and that this approach has worked well in the past. The Subcommittee suggested that inasmuch as a large percentage of encephalitis cases appear to be caused by unknown viruses, virus discovery could be part of the diagnostic component of the initiative. The Subcommittee supported the emphasis on broad-spectrum therapeutics, but agreed that in the case of viral therapeutics broad-spectrum activity may be difficult to achieve. The subcommittee unanimously approved the initiative.

Partnerships for Development of Vaccines for Selected Pathogens

This partnership would engage academia and industry in the development of vaccines against select non-biodefense pathogens (cytomegalovirus, respiratory syncytial virus, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Clostridium difficile*) that have a significant impact on public health.

This new initiative will advance vaccine development by supporting:

- Improvement of existing candidates - alternate formulation; stabilization; immunopotentiation, through regimen optimization and novel adjuvants.
- Evaluation of novel vaccine strategies - recombinant DNA; reverse genetics leading to live attenuated strains and vectors; chimeras and mono- or multi-valent subunits.

- Advanced preclinical studies - safety and host response; efficacy in animal models; toxicology studies; correlates of immunity and surrogate endpoints (e.g., protection of the fetus for CMV).

The Subcommittee raised concerns regarding the breadth and scope of this initiative and recommended careful consideration of the state of development at which a product must be eligible for support. They also recommended further consideration of the target populations for the products being developed and vehicles for vaccine delivery. The Subcommittee also recommended consideration of a short term therapeutic approach as another strategy to limit disease for some of these pathogens. The subcommittee unanimously approved the initiative.

Development of Therapeutics for Biodefense

The project would evaluate platform technologies, as they are applied to the development of therapeutic countermeasures for biodefense, for their capability to provide broad advances in technologies that may be widely applicable to drug development.

This initiative is designed to advance high priority promising candidate therapeutics toward the product stage by a focused, development-based approach that is consistent with all applicable federal regulations and guidelines for the conduct and oversight of developing therapeutics to be tested in human subjects. The government is particularly interested in supporting the development and evaluation of treatments with broad spectrum activity, broad spectrum technologies, and broad spectrum development platforms.

The types of activities that are envisioned to be funded may include the following:

1. Non-clinical research and development;
2. Lead optimization;
3. Development of manufacturing processes, manufacturing/synthesis of cGMP pilot lots, and conduct of extended product stability studies;
4. Preparation and submission to the FDA of investigational new drug (IND) applications and conduct of a Phase 1 clinical trial; and
5. Post-Phase I Biological License Application (BLA) or new drug application (NDA) enabling activities.

The Subcommittee members requested additional information about the role that program staff plays in the review of completed milestones, and the approval to transition to the next stage of the project. Program staff described the formality of the process that is also part of the solicitation. Awardees are required to submit Change/Deviation Requests, Decision Gate Reports, and updated Strategic Staged Product Development Plans for review and approval by the DMID Project Team. The subcommittee recommended caution regarding the cost of development of these products and requested information about communication between the federal agencies that fund related therapeutic development activities. Program staff indicated that a formal Memorandum of Understanding exists between NIAID and Biomedical Advanced Research and Development Authority (BARDA), its partner in these product development activities, that explicitly defines the roles and responsibilities of each agency during all phases of the project, and it provides plans for program coordination and elimination of funding overlap. In addition, Program staff meet regularly with staff from the Department of Defense and the Defense Threat Reduction Agency to review and coordinate programs and identify overlap prior to award of these

contracts. Subcommittee members were very supportive of these efforts and unanimously approved the initiative.

Hepatitis C Cooperative Research Centers

Applicants for this project would perform clinically-relevant research to elucidate the mechanisms involved in spontaneous clearance of acute hepatitis C virus (HCV) infection, and the frequent progression to chronic persistence; and, thereby, to provide the rationale for immunotherapeutic strategies against HCV.

Previous research has provided insights into host immunological responses to HCV infection and described some of the important differences between clearance of acute infection and chronic persistence. However, this has not been sufficient to allow the development of successful therapy against HCV suggesting that many of these differences are only markers of a given clinical outcome and that true effectors remain undiscovered.

This project is intended to stimulate the field into developing innovative ideas that would cast fresh light on the capability of the immune system to eliminate HCV infection. This includes elucidating key molecular pathways involved in cellular immunity, clarifying the role of the antibody response, and addressing the neglected question of how the adaptive responses are integrated with the innate immune responses.

The clinical outcome of HCV infection is also affected by factors such as race, virus genotype, mode of infection, and co-infection with HIV or liver parasites. A proper understanding of virus clearance or persistence will require the study of different infected population groups. Therefore, this project will require that the significance and clinical relevance of laboratory observations be determined in the appropriate cohorts of humans infected with HCV.

The subcommittee was very enthusiastic about DMID's plans to renew the Hepatitis C Cooperative Research Centers. The subcommittee unanimously approved the initiative.

NIAID Partnerships with Product Development Public- Private Partnerships (PPPs)

The project would establish collaborative relationships with Public-Private Partnerships (PPPs) so that NIAID and PPPs, acting in concert, can accelerate research and development of new diagnostic, preventive, therapeutic, and control strategies for high-priority infectious diseases of global importance for which commercial markets currently provide insufficient incentive for corporate investment.

This initiative seeks to build on NIAID's investments in various emerging and re-emerging diseases, malaria, tuberculosis, dengue, sexually transmitted infections, parasitic diseases, diarrheal diseases, or other diseases that predominantly affect the poor and disenfranchised, and may also be termed "neglected diseases." NIAID will enter into cooperative agreements with PPPs to support projects on various aspects of preclinical development (e.g., target validation, process development, formulation, toxicology, etc.) and targeted aspects that would facilitate or enhance clinical development (e.g., diagnostics, pretrial infrastructure assessment and development, epidemiologic surveillance in anticipation of clinical trials, trial monitoring, etc.).

The Subcommittee noted that the Institute's interest in the initiative might need to continue further into product development than preclinical development and targeted aspects that would facilitate or enhance clinical development. The Subcommittee recommended that the activities undertaken in this initiative be considered as a first step in a continuum of collaborations linking academia, industry, and the Federal Government. The subcommittee unanimously approved the initiative.

DMID Services for Researchers

Following the concept presentations, Dr. Irene Glowinski, Deputy Director of DMID, reported on recent efforts to inform the infectious diseases research community about the availability of DMID-supported preclinical resources and services to assist with product development activities. At a previous Council meeting, the Subcommittee had encouraged DMID to ensure a wider dissemination of this information to the research community. Dr. Glowinski shared screen shots of the recently-created DMID web portal (http://www3.niaid.nih.gov/research/resources/dmid/), which lists all available services and key information for each in a user-friendly format. She noted that efforts will be made to evaluate the effectiveness of these activities to ensure maximum benefit for the research community. Dr. Glowinski encouraged the Subcommittee to visit the website and provide feedback on the site. Council members were pleased to hear about these efforts.

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

Wafaa El-Sadr, M.D., M.P.H., M.P.A., Chair of the ARAC, welcomed the ARAC members, DAIDS staff, and guests. She presented the minutes of the May 2008 ARAC meeting, and the members approved them with a show of hands.

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

New ARAC Members

Dr. Dieffenbach welcomed two new ex-officio members to the ARAC: Paul Volberding, M.D., Chief of the Medical Service at the San Francisco Veterans Affairs Medical Center and Co-Director of UCSF's Center for AIDS Research; and Dr. Alan Bernstein, Ph.D., O.C., Executive Director of the Global Vaccine Enterprise. He also recognized three ARAC members who were attending their final meeting—Susan Buchbinder, Jeffrey Lennox, and David Margolis—and thanked them for their service during the last 4 years by presenting them with certificates of recognition.

Organizational Update

Dr. Dieffenbach announced that the Division recently established the Vaccine Discovery Branch within the Vaccine Research Program. The new branch will monitor scientific developments related to HIV vaccine discovery, build bridges between basic researchers and HIV vaccine designers, identify gaps in knowledge and promote research to address them, and finally, oversee the Center for HIV/AIDS Vaccine Immunology. Jorge Flores, M.D., is serving as Acting Branch Chief.

President Bush's FY 2009 budget for the NIH of $28 billion is nearly unchanged from the previous year. The NIAID would receive an $8 million increase to about $4,568,778,000 (an increase of 0.2 percent). The Senate and House have their own versions, which the President has promised to veto if they differ from his. Because of the impasse, the NIH will operate under a continuing resolution into next year. The FY 2009 budget request calls for a $5 million increase in NIAID's contribution to the Global Fund.

The NIH set aside about $90 million in FY 2008 to support the Bridge Award program for investigators who are just outside the payline. Twenty-two NIAID extramural researchers received these awards, for a total of $10 million beyond the NIAID budget. In June 2008, the President signed the Supplemental Appropriations Act, with the NIH receiving $150 million, $22.7 million of which went to the NIAID. NIH Director Elias Zerhouni requested that each Institute and Center use at least 50 percent of the supplemental funds to support research project grants (RPGs).

Scientific Update

In order to lay the groundwork for talking about future directions and new initiatives, Dr. Dieffenbach provided some background about recent HIV vaccine trials, focusing on the STEP and Phambili trials, which were stopped prematurely last year. Immunizations were discontinued because the vaccine did not protect against infection and did not lower the viral set point. There were also more infections in a subset of people who received the vaccine compared to those who received placebo. Nevertheless, the STEP trial demonstrated the usefulness of a test-of-concept trial in defining vaccine efficacy and it helped recalibrate the nonhuman primate model. The STEP trial also demonstrated the need to evaluate vector-induced immunity in vaccine development.

In the aftermath of STEP, NIAID is charting a new course in HIV vaccine research, with an increased emphasis on basic science. In March 2008, NIAID convened a Summit on Vaccine Research to solicit input on the balance between basic vaccine research and product development. Other smaller meetings and consultations have taken place as well. As a result, NIAID determined there is a consensus to adjust the balance between product development and discovery of innovative vaccine concepts and to ensure flexibility and streamlining for discovery research. There was also agreement that NIAID should be more selective in moving candidate vaccines into clinical trials and that non-human primate studies should be performed in parallel with human studies to determine whether a vaccine candidate should be developed.

The NIAID will not move forward with the PAVE 100 trial. However, because its regimen is still scientifically intriguing, a smaller focused trial will be considered. This revised trial will focus on whether or not there is an impact on viral load.

Dr. Dieffenbach closed by noting the basic vaccine research efforts that are already underway, while others will be presented during the meeting. In addition, the Basic Sciences Program will outline approaches and initiatives that will help to support this focus.

BASIC SCIENCES OVERVIEW

Susan F. Plaeger, Ph.D., Acting Director, Basic Sciences Program, presented an overview of the program, which has a goal of discovering and exploring fundamental mechanisms that govern the acquisition and progression of HIV disease. The program supports studies of the biology of HIV and its interactions with the human host, studies of populations, and efforts to move basic discovery to the development of targets for intervention. It is supporting the back-to-basics initiative of the Division.

Dr. Plaeger presented three concepts for review:

- Dissecting the HIV Immune Response: A Systems Biology Approach
- *In Vivo* Imaging of HIV Pathogenesis
- NIH Centers for AIDS Research (CFAR)

Dissecting the HIV Immune Response: A Systems Biology Approach

This first concept was for a new program, using a P50 funding mechanism, lasting for 5 years, with a first-year cost of $4 million. The objective is to support integrated teams of HIV biologists, immunologists, and computational biologists and apply a systems biology approach to better understand the complex interactions of HIV with the immune system. The goal is to integrate teams and technologies, and analyze and predict effects of HIV acquisition and disease progression. The concept's ARAC reviewers called this an important, unique, and timely initiative. They saw a need to specify essential scientific expertise but limit it, and to focus on the most important areas of HIV research but again not to be too restrictive. Questions were raised about the review process, how models would be evaluated and funding. Although it was assumed that 2 awards would potentially be made within the $4 million budget, the committee voted to approve the concept with the modification that the level of funding is flexible to allow for funding of one or more larger projects depending on merit and availability of funds.

In Vivo Imaging of HIV Pathogenesis

This second concept was for a new program, using a P01 funding mechanism, lasting 5 years, with a first-year cost of $1 million. The objective is to promote collaboration among multidisciplinary teams of immunologists, virologists, and *in vivo* microscopists to conduct real-time visualization of the dynamic interaction between immune cells and HIV in human and primate tissues and humanized mice. The ARAC reviewers felt that the concept was important in addressing fundamental questions about transmission and pathogenesis. They cited a need to include tracking post-infection and a need for greater funding. Committee members concurred with the importance of this effort recognizing that it is an understudied area of HIV research but also noted that it is an expensive area of research given the need for a multidisciplinary team and large imaging facilities. Given the expense involved, they were concerned about attracting researchers to apply. The committee voted to approve the concept with the modification that this initiative use a P01mechanism, funding one award up to $1 million and funding additional awards if funds are available. They added that the solicitation should be repeated in subsequent years, with revisions of funding levels and award requirements as needed.

Centers for AIDS Research (CFAR)

The third concept was for the renewal of the Centers for AIDS Research (CFAR), using a P30 funding mechanism, lasting 5 years, with a first-year cost of $37.5 million. (This includes the total cost for all participating Institutes and Centers; NIAID's contribution is $22.5 million) The objective is to foster high-quality AIDS research by increasing multidisciplinary collaborations within an institution and between institutions and by enhancing the translation of basic research findings into vaccine and therapeutic concepts in a synergistic and cost-effective manner. CFAR supports HIV/AIDS research through scientific leadership, infrastructure, and core services that are not available through other mechanisms. NIAID is the main supporter of the program, which also derives support from five other institutes of the NIH. The reviewers stated the need for continuing the CFAR because it provides valuable resources that aren't available through other means. They suggested expanding funding for pilot studies, new investigators, and emerging areas of research. They encouraged the CFARs to continue leveraging resources of other NIH institutes and centers and to disseminate information about supplements and workshops. In discussion, Dr. Plaeger noted that the program features a steady state, with turnover, of 18 to 20 centers. Dr. Volberding praised the program's organic linkage with the Clinical and Translational Science Awards (CTSA) program (former GCRCs) and others noted its value for pilot studies that can be done by young investigators and the administrative core for larger clinical trials. The

difference between a full and developmental CFAR was also clarified in discussion: the developmental CFAR is for institutions that have a nucleus of HIV/AIDS researchers but do not have the critical mass to provide the structure for a full CFAR. Thus, it allows new institutions funding to build their program so that they will be competitive for a full CFAR. It was also noted in discussion that funding for the CFARs is level and that the NIH has capped all centers programs agency-wide. So, there is no opportunity for expansion. The ARAC members approved the concept as presented.

VACCINE OVERVIEW

Margaret (Peggy) Johnston, Ph.D., Director of the DAIDS Vaccine Research Program, reviewed activities and plans for the program. She noted again the work that's underway to better understand the results of the STEP study, the pause and then eventual decision to not initiate the PAVE 100 trial, and current discussions for a smaller focused study of the VRC's candidate vaccine. Dr. Johnston also delineated the research priorities that emanated from the March summit including:

- Early events
- Adaptive and innate immune responses
- 3D structure of HIV envelope trimmer
- Neutralizing antibodies
- Animal models
- Correlates of vaccine-induced immune protection
- An emphasis on new and young investigators

Dr. Johnston highlighted new initiatives to bolster HIV vaccine discovery research. The Basic Vaccine Discovery RFA, which was previously approved by ARAC, has an objective of accelerating vaccine discovery efforts by generating new knowledge to inform new conceptual approaches to vaccine design. The Highly Innovative Technologies to Interrupt Transmission of HIV (HIT-IT) RFA has an objective of stimulating novel, unconventional, high-risk, high-impact approaches. Awards for both initiatives are expected to be made in July 2009.

Building on the announcement this spring of a program to bridge B-cell biology and HIV vaccine discovery, there is a new concept for an initiative to expand this effort and create a program that will foster cross fertilization between B-cell immunologists and HIV vaccinologists. Dr. Johnston talked about the importance of innovation, highlighted specific innovative studies that DAIDS has supported, and noted that the Phased Innovation Award program that the committee will review later in the day, is designed foster investigator-initiated AIDS vaccine discovery research at the earliest stages of concept genesis and evaluation.

Dr. Johnston also reviewed approaches that guide efforts to advance the induction of broadly neutralizing monoclonal antibodies and the role of the HIV Vaccine Research and Design (HIVRAD) program in supporting multidisciplinary HIV vaccine discovery-related preclinical research, including animal model development, immunogen design, structure, evaluation, and mechanism of action. In addition, the Non-Human Primate (NHP) Core Laboratory Support provides core immunology and virology support for NIAID's Simian Vaccine Evaluation Unit contracts and extramural researchers and ensures standardization and comparability. Dr. Johnston described ongoing NHP activities and plans, as well as the many activities in the NIAID clinical agenda, such as development of new assays, increasing the breadth and efficacy of T-cell responses, and studying polyvalent "mosaic" vaccines.

Vaccine Concepts

The External Quality Assurance Program Oversight Laboratory (EQAPOL)

The External Quality Assurance Program Oversight Laboratory (EQAPOL) has the objective of creating a facility to develop, implement, and oversee external quality assurance programs for immune monitoring assays, including vaccine vectors and novel diagnostic tests. This initiative is a renewal and expansion that will make one award using the N01 mechanism. The award is for 7 years, with a first-year cost of $3 million. The ARAC reviewers considered this program a critical part of the DAIDS quality assurance portfolio. They called it to make efficient use of resources and encouraged it to avoid duplicating other assay validation programs. Reviewers had asked about support of non-vaccine work; EQUAPOL is intended only for NIAID HIV vaccine work but could be expanded if additional funds were available. In discussion, it was suggested that assay validation efforts be minimized until a true immune correlate of protection is identified and that oversight does not use up too much of the funding. The validity of data and the level of funding were also raised. To clarify, Dr. Johnston noted that through the Partnership for AIDS Vaccine Enterprise (PAVE), the HIV Vaccine Trials Network, the Department of Defense, NIAID and others have come up with methodologies to ensure that collected cells are both viable and functional. While funding is less than in previous years, it is enough for the most critical activities. The ARAC members voted to approve the concept.

B-Cell Biology Network for HIV-1 Vaccine Development

The B-Cell Biology Network for HIV-1 Vaccine Development has the objective of cross-fertilizing the work of B-cell immunologists and HIV vaccinologists to inform vaccine discovery and immunization strategies for eliciting broadly protective HIV-1 antibodies. This is a new concept, funding two to four research teams under the U19 mechanism. Each award will be for 5 years, with a first-year program cost of $3.5 million. The ARAC reviewers had stated that the concept addresses basic discovery research that explores mechanisms for inducing protective neutralizing antibody. They encouraged the program to include B-cell immunology teams outside the field of HIV and to emphasize human immunology and translational studies using humanized mouse and nonhuman primate models. The program should define primary data requirements and provide guidance on suitable international and industry partners. The ARAC members suggested developing ways to make the data available and to encourage its dissemination within and outside of the network. The need for an exchange of reagents and the importance of encouraging applications from B-cell immunologists who are not working in HIV were also discussed. The ARAC voted to approve the concept.

The HIV Vaccine Research and Design (HIVRAD)

The HIV Vaccine Research and Design (HIVRAD) initiative has the objective of addressing important scientific questions relevant to AIDS prophylactic vaccine discovery research. This is a renewal, funded by the P01 mechanism, and it will make one or two awards. The award is for 5 years, and the first-year program cost will be $4.5 million. The ARAC reviewers had described this as an outstanding program that has stimulated strong, collaborative, innovative, and timely work building the foundation for HIV vaccine research. The reviewers suggested increasing the funding, stressing new and young investigators, and encouraging communication among the HIVRAD projects. The ARAC voted to approve the concept.

Phased Innovation Award (PIA)

The Phased Innovation Award (PIA) program has the objective of fostering investigator-initiated AIDS vaccine discovery research at the earliest stages of concept genesis and evaluation, stressing high-risk, high-impact studies. This is a renewal, funded by the R21/R33 mechanisms, offering seven to 10 awards. The award is for 2 to 5 years, with a first-year program cost of $2 million. The ARAC reviewers stated that the program fills a crucial niche in the NIAID AIDS vaccine research portfolio, in part by supporting high-risk, high-gain research. They suggested increasing the funding for the R21 phase because of the high costs of nonhuman primate studies. Dr. Johnston reminded the ARAC members that the amount of funding rises as an awardee moves into years 3, 4, and 5. After discussion focusing primarily on funding and previous accomplishments, the ARAC members voted to approve the concept.

Preclinical Master Contract

The Preclinical Master Contract award has an objective of advancing clinical research reagents and promising HIV prophylactic vaccine candidates into human clinical trials by supporting gap-filling activities through contractors. It is a renewal/expansion, funded by the N01 mechanism, offering a single 7-year award. The first-year cost is $4.25 million. This is a reduction in the previous award of $11 million. The awardee operates by subcontracting to other contractors as program needs arise. The ARAC reviewers were highly supportive. The initiative is necessary for developing clinical research reagents for use in clinical trials as part of the vaccine discovery process. The reviewers cited the importance of emphasizing the success of the current PCMC mechanism and the fact that the contract will be funded and utilized on an as-needed basis with rapid response. The ARAC members recognized that this contract is important for jump-starting work and filling gaps in the portfolio. It provides the program with flexibility and will support a shift toward basic vaccine discovery. The ARAC members voted to approve the concept.

Nonhuman Primate Core Immunology and Virology Laboratories

The Nonhuman Primate Core Immunology and Virology Laboratories have the objective of ensuring standardization and comparability of assays for preclinical studies. They provide a common basis for assessment of the immunogenicity and efficacy of candidate HIV and SIV vaccines. This is a renewal, funded by the N01 mechanism, offering one to three awards for 7 years. The first-year program cost is $4.5 million. The ARAC reviewers described this as an important resource used by all investigators to standardize viral quantitation and humoral immune responses across trials. This will allow eventual comparisons between nonhuman primate studies and clinical trial data. The reviewers supported continuation of all three components of the program—cellular immune responses in immunized and infected macaques, anti-HIV- and anti-SIV-neutralizing antibodies, and viral RNA levels in plasman and tissues of infected macaques. It was also suggested that the contracts only focus on existing assays rather than develop new ones and this is indeed the current practice. In response to a question about the extent of the use of standard assays in the field, it was noted that the neutralizing antibody assay laboratory uses standardized assays. With regard to cellular immune studies, while investigators are encouraged to have our laboratories conduct assays, some use their own lab. This is also true of reagents. The ARAC members voted to approve the concept.

Dr. El-Sadr stated the next ARAC meeting will take place January 26, 2009. Potential topics for the next meeting include a program update/overview from the therapeutics program, including the ESPRIT study that will be closing in the fall, to the extent more is needed, an update from the basic sciences, and an update on microbicides especially since a large trial of PRO200 and BufferGel will be closing this fall.

VII. ADJOURNMENT

The meeting of the Council was adjourned at 4:30 p.m., on Monday, September 15, 2008.

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

_____-s-_____ **_11/21/2008_____**
Anthony S. Fauci, M.D. Date
Chairman, National Advisory Allergy
and Infectious Diseases Council
Director, National Institute of Allergy
and Infectious Diseases

_____-s-_____ **_11/06/2008_____**
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.