NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

September 26, 2005

The 151st meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, September 26, 2005, in Conference Room E1/E2, Building 45, National Institutes of Health. Dr. Anthony S. Fauci, Director, National Institute of Allergy and Infectious Diseases (NIAID) presided as Chairman.

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 10:30 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. Stanley Chapman
Dr. Charles Davis
Dr. Luis Diaz
Dr. Richard Insel
Dr. J. Brooks Jackson
Dr. Margaret Liu
Dr. Richard Locksley
Ms. Anne Munoz-Furlong
Dr. Martin Myers
Rev. Raymond O'Brien
Dr. Shelley Payne
Dr. Anjana Rao
Dr. Ruth Ruprecht
Dr. Gary Schoolnik
Dr. Nathan Thielman
Dr. Gail Wertz

***Ex Officio* Members Present:**

Dr. Lawrence Deyton
Dr. Anthony Fauci
Brig. Gen. Eric Schoomaker

Council Members Absent:

Dr. Anthony D'Alessandro
Dr. Dorothy Lewis

***Ex Officio* Members Absent:**

Dr. Mitchell Cohen

***Ad Hoc* Members:**

Dr. Martin Rosenberg

NIAID Senior Staff:

Dr. John McGowan
Dr. Carol Heilman
Dr. Daniel Rotrosen
Dr. Ed Tramont

Others Present:

Dr. Kathryn Zoon

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 2,524 research and training applications with primary assignment to NIAID for a requested amount of $974,720,293 in first-year direct costs and recommended approval of 748 applications for $490,744,128 in first-year direct costs. One Method to Extend Research in Time (MERIT) award was recommended for approval.

II. REMARKS OF THE DIRECTOR, NIAID - Anthony S. Fauci, M.D.

Dr. Fauci opened the Council session by welcoming visitors to the meeting and introducing ad hoc Council member, Dr. Martin Rosenberg. He also welcomed a new ex-officio member, Brigadier General Eric Schoomaker, who is currently the Commanding General of the United States Army Medical Research and Materiel Command. Ex-officio member Dr. Mitchell Cohen was unable to attend.

Dr. Fauci acknowledged the contributions of three retiring members, Dr. Luis Diaz, Dr. Margaret Liu, and Dr. Richard Locksley and presented them with plaques.

Consideration of Minutes of Previous Meeting
The minutes of the May 23, 2005, meeting were considered and approved as written.

Staff and Organizational Changes
Dr. Fauci announced new appointments in the Institute. Three new staff have joined the Division of Allergy, Immunology, and Transplantation. Dr. Matthew Fenton is the new chief of the Asthma, Allergy, and Inflammation Branch. He replaces Dr. Chuck Hackett who was recently promoted to be deputy director of DAIT. Dr. Richard Hatchett is the new associate director for Radiation Countermeasures Research and Emergency Preparedness, and Dr. Bert Maidment is the associate director for Product Development.

There have been three key promotions in the Division of Intramural Research. Dr. Tom Wellems has been promoted to chief of the Laboratory of Malaria and Vector Research. Dr. Alan Sher is now the chief of the Laboratory of Parasitic Diseases. And Dr. Tom Schwan has been promoted to chief of the newly established Laboratory of Zoonotic Pathogens.

Budget Update
Until the FY 2006 budget is signed, NIAID is operating under a continuing resolution. In his budget update, Dr. Fauci provided an overview of the President's FY 2006 budget, which includes an NIH increase of $146,000,000 or 0.5 percent compared to FY 2005.

NIAID's FY 2006 increase of $55,000,000 or 1.3 percent is better than the 0.5 percent average increase of the NIH. For NIAID, the FY 2006 President's budget requests an increase of $34,000,000 for the Center for HIV/AIDS Vaccine Immunology (CHAVI). In addition, NIAID received a general increase of about 0.5 percent for their remaining research programs.

Legislative Update

Dr. Fauci and other NIAID staff members were invited to testify at a number of House and Senate committee hearings over the summer. These hearings were focused largely on biodefense, pandemic flu, HIV/AIDS, and the intense effort to develop an effective HIV vaccine.

In addition to congressional hearings Dr. Fauci and other NIAID staff members have briefed the President, members of the administration, and members of Congress and their staff on a variety of topics including pandemic influenza, biodefense preparedness, and HIV/AIDS.

NIH hosted a visit from Michael Gerson, assistant to the President for Policy and Strategic Planning, and several of his guests. Dr. Cliff Lane and Dr. Fauci briefed them on AIDS related issues. Dr. Tom Wellems provided an overview of our malaria research, including a tour of the insectiary in Building 4.

Other Information Items

Dr. Fauci described a newly formed working group of the NIAID Advisory Council referred to as the Sullivan Committee. Dr. Louis Sullivan, former secretary of HHS, is chairing the working group whose charge is to review and evaluate regulatory activities in the Division of AIDS. The group will report their findings to Dr. Fauci and the advisory Council.

NIH was part of the HHS-wide response to the disaster caused by Hurricane Katrina. NIH mobilized the national armed corps volunteer medical network which provides round-the-clock medical consultation services for health care professionals, information about clinical trials regarding alternative sites, and information for patients affected by the hurricane.

NIAID is involved in a very intense effort to prepare for pandemic influenza and seasonal influenza. The Institute has been involved in testing and clinical trials of an H5N1 vaccine. Also on the influenza front, the Department is actively addressing the issue of stockpiling vaccine and antivirals.

Dr. Fauci gave brief updates on biodefense, the development of a universal group B streptococcal vaccine, and HIV vaccine development.

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

Dr. Kathryn Zoon gave an overview of the facilities and branches that make-up the Division of Intramural Research (DIR). DIR has a wide variety of labs that focus mostly on immunology and infectious diseases. Recently the laboratories have undergone some restructuring which has led to the creation of some new labs and staff changes. Among its staff, DIR has 94 tenured scientists and 23 tenure-track scientists.

The Board of Scientific Counselors (BSC) conducts periodic reviews of DIR laboratories and programs. For FY 2005 the BSC reviews included the Laboratory of Infectious Diseases, the Molecular Vaccine Development Branch, the Laboratory of Malaria and Vector Research, and the Laboratory of Parasitic Diseases. All of the reviews went very well.

Dr. Zoon gave an update on NIAID's containment laboratories. Building 33 on the NIH campus in Bethesda is scheduled for completion at the end of 2005, with occupancy expected in the spring of 2006. The Rocky Mountain integrated laboratories in Montana is currently under construction, with completion expected in the second quarter of 2006 and occupancy beginning at the end of the year. Construction of

the NIAID Integrated Research Facility at Fort Detrick has officially begun. Completion is expected in the second quarter of 2008 and occupancy later that year.

Dr. Zoon highlighted some of DIR's top research advances during the past year including identification of a promising candidate for a new respiratory syncytial virus vaccine, development of potent monoclonal antibodies against anthrax-protected antigen, a study on IL-2 which has the potential to improve the outcome and immune response of patients with HIV, discovery of how hemoglobin C protects against malaria, and discovery of an enzyme that is critical for HIV replication.

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

Susan Cooper, M.Sc. Ms. Cooper joined the Office of Program Planning, Operations, and Scientific Information in June 2005 as a Health Science Specialist. Ms. Cooper received her bachelor's degree in biochemistry from Glasgow University, UK and her master's degree in steroid endocrinology from Leeds University, UK. Ms. Cooper has worked extensively in academia, industry, and government. Prior to joining the Division, she was a Technology Coordinator in the Office of Cancer Genomics, at the National Cancer Institute.

Matthew J. Fenton, Ph.D. Dr. Fenton joined the Asthma, Allergy, and Inflammation Branch in June 2005 as Chief. He received his doctoral degree in biochemistry from Boston University and completed post-doctoral studies in immunology at the Massachusetts Institute of Technology. Prior to joining the Division, he was a Professor of Medicine and Director of Pulmonary Research at the University of Maryland, School of Medicine. Previously, he was a Professor of Medicine at the Boston University School of Medicine. Dr. Fenton also served as a member of the Experimental Immunology Study Section, and later, as Chair of the Innate Immunity Study Section.

Donna Jo McCloskey, Ph.D., R.N. Dr. McCloskey joined the Clinical Immunology Branch in July 2005 as a Nurse Consultant. Dr. McCloskey received her bachelor's degree in nursing from Marymount University, and her doctorate in nursing from George Mason University. Prior to joining the Division, she was a Nurse Research Specialist with the Department of Laboratory Medicine at the Clinical Center.

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Rebecca Mitchell, M.S. Ms Mitchell joined the Clinical Immunology Branch in June 2005 as a Health Specialist. She received her master's degree in biotechnology from Johns Hopkins University. Prior to joining the Division, she was a Lab Technician at Johns Hopkins University working in the area of genetics in prostate cancer research.

John Peyman, Ph.D. Dr. Peyman joined the Clinical Immunology Branch in July 2005 as a Program Officer. He received his doctoral degree in experimental medicine from McGill University in Montreal and completed post-doctoral studies in the Department of Cell Biology at Yale University. Prior to joining the Division, he was a Senior Research Scientist and Collaboration Coordinator at CuraGen Corporation.

Richard Hatchett, M.D. Dr. Hatchett joined the Office of the Director in July 2005 as Associate Director for Radiation Countermeasures Research and Emergency Preparedness. He received his medical

degree from Vanderbilt University and completed postgraduate training in internal medicine at New York Weill Cornell Medical Center and medical oncology at Duke University Medical Center. Prior to joining the Division, he served as Senior Medical Adviser in the DHHS Office of Public Health Emergency Preparedness.

SCIENTIFIC INITIATIVES

Asthma and Allergic Diseases Cooperative Research Centers RFA-AI-05-027: The National Institute of Allergy and Infectious Diseases (NIAID) invite applications from single institutions and consortia of institutions to participate in the Asthma and Allergic Diseases Cooperative Research Centers (AADCRC) program. The purpose of this RFA is to support basic and clinical research on the immunological basis, pathobiology, diagnosis, treatment and prevention of asthma and allergic diseases and to accelerate the application of fundamental knowledge of immune function to the investigation, prevention, and treatment of asthma and allergic diseases.

Amendment to RFA-AI-05-027 "Asthma and Allergic Diseases Cooperative Research Centers" - NOT-AI-05-047: The National Institute of Allergy and Infectious Diseases will not award more than one AADCRC grant to an applicant institution nor to an institution, which is currently funded under the previous RFA-AI-02-007. The PI of a grant currently funded under RFA-AI-02-007, or of an application submitted in response to this RFA, may serve as a project leader in a multi-project application submitted by other institutions if there is no scientific overlap.

Hyperaccelerated Award/Mechanisms in Immunomodulation Trials RFA-AI-05-028: This RFA invites R01 applications for mechanistic studies in clinical trials of immunomodulatory interventions for immune system mediated diseases, including, but not limited to asthma and allergic diseases; graft failure in solid organ, cell, tissue and stem cell transplantation; and chronic inflammatory, autoimmune, and immunodeficiency diseases; preventative and therapeutic, vaccines for non-HIV/AIDS infectious diseases, including NIAID Category A, B, and C agents of bioterrorism and emerging/re-emerging infectious diseases.

Innate Immunity to NIAID Category B Protozoa RFA-AI-05-042: This RFA invites applications for research projects to discover the cellular/molecular/biochemical mechanisms by which the mammalian innate immune system responds to the food and waterborne protozoa classified as NIAID Category B Priority Pathogens http://www2.niaid.nih.gov/Biodefense/bandc_priority.htm (Cryptosporidium parvum, Cyclospora cayetanensis, Giardia lamblia, Entamoeba histolytica, Toxoplasma, and Microsporidia). The rational development of adjuvants and immunotherapeutics to eukaryotic diseases will require a basic understanding of the underlying novel innate immune responses to these complex pathogens. This RFA will advance our understanding of the mechanisms of action by which the mammalian innate immune system reacts to eukaryotic pathogens and produces a protective response.

Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D) and its Complications - RFA-DK-05-010: The National Institute of Diabetes, Digestive and Kidney diseases (NIDDK), National Eye Institute (NEI), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Child Health and Human development (NICHD) invite the small business community to apply cutting edge technology to investigate the development of new approaches to predict, prevent, treat, and cure type 1 Diabetes (T1D) and its complications.

Biology of RNA Interference: Stability, Delivery and Processing by Tissues - RFA-HL-05-019: The purpose of this RFA is to stimulate research towards (1) understanding uptake and processing of RNAi by target tissues, (2) assessing stability, half-life and off-target effects in target tissues, and (3) determining optimal delivery methods for uptake by the target tissues.

Short-Term Courses In Human Embryonic Stem Cell Culture Techniques PAR-05-133: The National Institutes of Health (NIH) invites applications for grants to develop and conduct short-term continuing education programs on laboratory research techniques for human embryonic stem cell (hESC) lines, and to disseminate course materials and instructional experience to the scientific community. The program should include laboratory and didactic experiences to improve the knowledge and skills of biomedical researchers, and to enable them to maintain, characterize, and utilize hESC lines in basic research projects. Programs will be made available to investigators in research areas of interest to all of the Institutes and Centers of the NIH.

Cooperative Study Group for Autoimmune Disease Prevention RFA-AI-05-026: The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institute of Environmental Health Sciences (NIEHS), and the Juvenile Diabetes Research Foundation International (JDRFI) invite applications to participate in the Cooperative Study Group for Autoimmune Disease Prevention. This group is a unique multi-center cooperative program established in 2001 as a collaborative network of investigators, with a focus on autoimmune disease prevention and an emphasis on type 1 diabetes. The goals of this group include understanding the immune mechanisms that underlie autoimmunity and autoimmune disease, and the mechanisms and consequences of manipulation of the immune response in autoimmunity, as well as applying this information to the prevention of autoimmune diseases in humans. The long-term goal of this program is to develop the knowledge base necessary to design interventions for the prevention of autoimmune disease that could be administered efficiently and safely to individuals at risk or to the general population.

DIVISION ACTIVITIES

Asthma Monitoring, Allergen Standardization, and Lasting Effects of an Asthma Intervention: Results from NIAID Sponsored Inner City Asthma Studies**:** On May 25, 2005, NIAID-sponsored a clinical workshop at the American Thoracic Society Meeting, in San Diego, CA. The workshop focused on novel approaches to prevent asthma in minority populations. Topics presented included exhaled breath condensate in asthma, standardizing cockroach allergen, and the potential for cockroach allergen immunotherapy for asthma, and lasting impact of asthma counselor intervention.

Second Symposium on the Definition and Management of Anaphylaxis: On July 26-27, 2005, a symposium was held in Bethesda, MD to review the current definition, diagnosis, and management of anaphylaxis, as well as to assess future anaphylaxis research needs. This Symposium was jointly sponsored by NIAID and the Food Allergy and Anaphylaxis Network (FAAN).

NIAID Workshop on Humanized Mice: On June 13-14, 2005, the NIAID convened a biodefense workshop on humanized mouse models in Bethesda, MD. While mouse models have been invaluable in understanding human physiology, especially the human immune system, the differences between human and mouse are significant enough to warrant the creation of chimeric mouse models bearing partial or intact human physiological systems. This is accomplished by engrafting human cells and/or human tissues into immunodeficient mouse strains incapable of rejecting these xenogeneic grafts. Workshop participants presented research findings, discussed the current state of research and made recommendations on the potential use of humanized mouse models for human biomedical research.

Topics included the development and use of humanized mice as models for immune system reconstitution, autoimmunity, microbial infection, vaccine and antimicrobial drug optimization, and transplantation tolerance.

Annual U.S. Japan Immunology Board Joint Meeting: The twenty-third annual joint meeting of the U.S. and Japanese Immunology Boards of the U.S.-Japan Cooperative Medical Sciences Program convened in Seattle, WA, on July 26-27, 2005. This meeting included scientific presentations by members of the U.S and Japanese Boards, as well as invited speakers from the University of Washington, the Benaroya Research Institute and the Institute for Systems Biology. In addition, a half-day workshop was convened on July 27, 2005, in Seattle to address tuberculosis and other mycobacterial diseases. This workshop was co-organized by the Immunology Board and the US-Japan TB/Leprosy Panel to discuss immune parameters of vaccine development for mycobacterial diseases.

CONCEPT REVIEW

All concepts were presented and approved.

Allergen and T Cell Reagent Resources for the Study of Allergic Diseases: This initiative supports two distinct objectives. The first objective is to support core facilities that will use innovative isolation and purification techniques to identify novel allergens from various sources. The second objective is to identify and characterize peptides containing T cell epitopes that induce anergy in allergen-specific effector T cells, or activate allergen-specific regulatory T cells. The major goals of this initiative are to identify novel allergens using innovative purification methods, and to generate a set of defined peptides that regulate the function of allergen-specific effector and regulatory T cells.

NIH Tetramer Facility: The goal of this initiative is to support the continuation of a reagent resource, which provides custom-made MHC class I, MHC class I-like, and MHC class II tetramers to the research community. The NIH Tetramer Facility provides custom synthesis and distribution of soluble major histocompatibility complex (MHC)-peptide tetramer reagents that can be used to detect antigen-specific T cells. These reagents are provided to approved investigators, who supply the purified peptides and cover the cost of shipping these peptides and the synthesized tetramer reagents. The Tetramer Facility contract covers the cost of tetramer production and validation/quality control. The Facility has two main functions: 1. a tetramer production facility; and 2. research and development facility for generation of novel tetramer reagents.

Systems Approach to Immunity and Inflammation: The primary objective of the program is to develop an encyclopedia of innate and adaptive immune responses to microbial infection, with a focus on NIAID Category A-C priority pathogens. Development of the “encyclopedia” will be based on genome-wide screens of mutant mice for identification of key regulatory immune response genes. Random mutagenesis approaches are preferred (e.g., use of ethylnitrosourea (ENU)), although more targeted high-throughput methods may be utilized, with adequate justification. Research teams will be required to meld genomics, proteomics, immunology, and bioinformatics into a “systems biology” approach.

Non-Human Primate Transplantation Cooperative Study Group (NHPCSG): The goal of the Non-Human Primate Transplantation Cooperative Study Group is to evaluate the safety and efficacy of existing and novel tolerance-induction therapies in non-human primate (NHP) models of kidney and islet transplantation. In addition, research into the immunological mechanisms of tolerance induction and development of surrogate markers for induction, maintenance, and loss of tolerance is supported through the program.

Allogeneic Hematopoietic Stem Cell Transplantation for Autoimmune Disease – A Pilot Study: This initiative will investigate effectiveness of allogeneic hematopoietic cell transplantation (alloHCT) to halt progression or effect clinical cure in patients with autoimmune diseases, and to utilize outcome data in re-evaluation of pathophysiologic mechanisms of disease. Diseases and patient populations that may benefit from alloHCT in particular will be determined in consideration of currently available treatment regimens. For example, patients with diseases that are sensitive to high dose immunosuppressive therapy (HDIT), but excluded from autologous HCT (autoHCT) protocols due to major organ dysfunction, may be eligible for nonmyeloablative regimens utilizing chemoradiation that is less severe.

High Dose Immunosuppressive Therapy with Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases: The goal of this program is to provide additional funding to complete three ongoing multicenter clinical trials in high dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (HCT) in autoimmune diseases funded by DAIT, NIAID contracts. These include 1) a pivotal clinical trial in scleroderma (SSc), 2) a phase II clinical trial in systemic lupus erythematosus (SLE), and 3) a phase I/II clinical trial in multiple sclerosis (MS).

Immune Tolerance Network: This initiative will renew NIAID's successful Immune Tolerance Network (ITN), a consortium of basic and clinical scientists that: (1) develops a scientific agenda for clinical trials and mechanistic studies of various approaches to tolerance induction; (2) develops, tests and validates assays to measure the induction, maintenance and loss of immune tolerance in humans; (3) designs and conducts clinical trials at all phases to determine the feasibility, safety, toxicity and efficacy of tolerogenic intervention strategies for multiple immune system diseases; and (4) designs and conducts research to delineate the underlying mechanisms of immune tolerance in conjunction with clinical trials undertaken by the ITN as well as clinical trials sponsored by other Federal and private sector organizations and companies.

For this initiative, tolerance is broadly defined as specific lack of an immune response to targeted antigens (e.g. alloantigens, autoantigens, or allergens) by any of a variety of approaches including deletion, induction of anergy, immune deviation, sequestration, or suppression. Approaches may target antigen specific receptors, molecules of the co-stimulation pathways, homing molecules, or other relevant approaches; and may use any of a variety of agents including antigen, peptides, altered peptides, monoclonal antibody blockade, cytokines, molecularly engineered cells or tissues, DNA vectors, or other relevant molecules.

NIAID-Taconic Mouse Exchange: This initiative is to foster increased availability to the scientific community of immunologically-related, gene-targeted mouse strains.

Sarcoidosis: Research into the Cause of Multi-Organ Disease and Clinical Strategies for Therapy: The goal of this program is to delineate possible causes and phenotypic host characteristics in susceptible individuals and devise approaches for prevention, early diagnosis and treatment of sarcoidosis.

V. JOINT MEETING OF THE AIDS SUBCOMMITTEE, NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL AND AIDS RESEARCH ADVISORY COMMITTEE - Ed Tramont, M.D., Director, DAIDS

Director's Report—*Edmund Tramont, M.D.*

Dr. Tramont welcomed new members Ms. Brenda Lein from Project Inform and Dr. Wafaa El-Sadr, who was not able to attend this meeting. He thanked outgoing members Dr. Dorothy Lewis, who was also unable to attend due to Hurricane Rita, and Dr. Janet Collins, who has moved on to a new position at CDC.

Dr. Tramont outlined Dr. Zerhouni's 5 priorities for FY2006: HIV vaccine development, research project grants, a roadmap for medical research, biodefense research, and a neuroscience blueprint. Dr. Tramont also reviewed FY06 budget projections, and it is expected that NIAID's budget of $4.4 billion will stay level. The FY06 budgets submitted by the President, the House and the Senate are all in that range and each includes $49 million of new money for the Center for HIV/AIDS Vaccine Immunology (CHAVI). CHAVI was awarded this past July to address key immunological roadblocks to the discovery and development of a safe and effective HIV vaccine as defined by NIAID and as identified by the Global HIV Vaccine Enterprise, a virtual consortium of independent organizations committed to the discovery of a vaccine. Dr. Barton Haynes was selected to lead the consortium, which will receive $15 million in its first year, and $49 million in subsequent years for 7 years. CHAVI goals include studying people before they seroconvert, and determining correlates of SIV immune protection. More information about CHAVI can be found at www.chavi.com.

Updates

Microbicides. An international trial of 2 microbicides began recently, with one site in the United States and several in Africa and India.

Circumcision Trials. The first of the 3 trials examining whether circumcised men are better protected against sexually transmitted infections (STI) has been completed, and found a 65% reduction of incidence of HIV infection. That trial, conducted by French and South African investigators at Orange Farm, SA has ended. NIAID's two trials are still underway.

CRS Contract. The HIV Clinical Research Management Support Contract (CRS) was awarded to PPD in July 2005 for five years. First year costs are $24 million.

Public-Private Partnerships. The HVTN began enrolling volunteers (1500 men and women at risk) in a vaccine trial in collaboration with Merck. HVTN 502/Merck 023 is a phase IIb (proof-of-concept) trial involving an adenovirus type 5 vector expressing 3 HIV genes, gGag, poL, and nef. $818 million worth of drugs has been donated for ongoing DAIDS studies (2006).

PEPFAR. Progress for 2005 has exceeded the January 2004 goal to support treatment of 200,000 people by June 2005.

Hurricane Katrina. NIH responded to the disaster by setting up Medical Consultation Services; deploying advance and medical teams to a field hospital in Meridian, Mississippi; and making available at the Clinical Center 100 beds for patients.

Prevention of Mother to Child Transmission. The Institute of Medicine completed its review of HIVNET 012 and found that, despite some concerns, the results of the study are valid. (The report is available through the Institute of Medicine at http://www.iom.edu/report.asp?id=26287)

Working Group on DAIDS Regulatory Activities in DAIDS—*Cliff Lane, M.D.*

Dr. Lane reported that the NIAID Council has convened a working group to evaluate the regulatory functions at DAIDS. The panel will examine current organization, operating procedures, formal and informal channels of communication, and timeliness of completing critical functions as they relate to regulatory affairs. It should be noted that the panel will not review NIH–FDA interactions, or NIH regulatory activities overall. Rather it will examine only DAIDS regulatory systems, policies and procedures and identify potential opportunities for the Division to most effectively meet its regulatory and clinical research oversight responsibilities.

The panel, known as the "Sullivan Committee" since it will be chaired by Louis Sullivan, is comprised of leading experts from a variety of disciplines; these include: John Arras, Gail Cassell, Susan Ellenberg, Maria Freire, Peter Hutt, and Gary Schoolnik. Michael Calhoun is a senior consultant who will be responsible for fact-finding for the panel, managing the agenda and facilitating meetings, assisting the working group with deliberations, and drafting the final report. Investigators are encouraged to contact Mr. Calhoun with any thoughts they would like to share with the panel. Dr. Lane expects a report to be completed in 3 to 6 months.

CONCEPT REVIEWS

Basic Sciences Program—*Carl Dieffenbach, Ph.D.*

Resources for AIDS Therapeutics Development (FY07). The concept for this initiative consists of 2 parts – Part A will support confirmatory *in vitro* evaluations of HIV therapeutics and Part B will support specialized *in vitro* virological assays. The concept is for a 7-year contract resource with first year costs for Part A and B together totaling $1 million. As in the past, the primary activity of both contracts will be the *in vitro* evaluation of potential HIV therapeutics and topical microbicides to determine efficacy and toxicity in specialized cell or target-based assays. To date, there have been 2 contracts, one providing evaluation of compounds in cell-based assays and one providing specialized assays. This initiative will provide for the continuation of these activities. Model and assay development will continue to be an important part of the contracts. New activities include the implementation of an explant model(s) for evaluating transmission inhibitors and the development and implementation of high throughput screens for inhibitors of newly discovered targets and/or existing targets that have not been sufficiently studied (for example HIV regulatory proteins and integrase). Offerors will have the possibility of applying for Part A, Part B, or Parts A and B. Compounds submitted for *in vitro* evaluation have been from academia (20%), from small biotechnology or pharmaceutical companies (40%), and from government sources (40%).

Reviewers (Drs. Margolis and Jackson) thought this a highly significant and needed activity and they recommend acceptance. It was unanimously approved.

Tissue-based Small Animal Model for HIV Drug Discovery (FY07). This concept is for a 7-year contract resource with $1.1 first year costs. It will support DAIDS drug discovery and evaluation programs by evaluating potential HIV therapeutics in a tissue-based small animal model. The animal model being

solicited in this initiative is an immunodeficient (SCID) mouse engrafted with human fetal thymus and liver and infected with well-characterized clinical isolates of HIV-1. Types of therapies to be evaluated include antiviral regimens, biologics (e.g. cytokines and growth factors), engineered viruses, and agents that affect thymus function. Studies will include determination of efficacy, toxicity, and limited pharmacokinetics. Model development will continue to be an integral part of this program. Reviewers (Drs. Margolis and Jackson) think the money is well spent and recommended approval. The concept was unanimously approved.

Therapeutic Research Program— *Sandra Lehrman, M.D.*

Preclinical Development Resources
The following 3 concepts for initiatives were presented together -- Pharmaceutical and Chemical Resources for AIDS Therapeutics Development, Safety Evaluation of Anti-Infective Agents, and Management of Information Resources for AIDS Drugs.

Pharmaceutical and Chemical Resources for AIDS Therapeutics Development (FY07). This concept is for a 7-year contract that would provide resources to facilitate the advanced development of promising compounds. It would provide quantitative analytical chemistry detection of drug substances and dosage formulations, as well as small-scale manufacture of clinical supplies. First year costs are $700,000. First competed in 1990, the contract has produced 13 drugs manufactured for clinical trials, with 2- to 4-year stability studies conducted on each. They are developing a generic microbicide formulation, a condom-burst test protocol, and methods to establish the identity and purity of newly synthesized drugs and to assess molecular weight. Reviewers (Drs. Ruprecht and Kanki) noted that, as in the past, this resource continues to fill a critical gap.

Safety Evaluation of Anti-Infective Agents (FY07). This concept is for a contract that would provide preclinical safety and pharmacokinetic assessment of anti-AIDS therapies, including GLP and non-GLP toxicity and pharmacological studies. The contract was first competed in 1990 and the renewal cost is at the same level as that of the expiring contract -- $1.9 million in year 1. The contract would continue to provide the GLP toxicity/pharmacokinetics of therapeutic vaccines. Recently, the current contractor studied the vaginal irritation of 5 drugs, and is currently developing screening models for rectal irritation and neurotoxicity. The concept had the full support of its reviewers (Drs. Kanki and Ruprecht).

Management of Information Resources for AIDS Drugs (FY07). The concept for this initiative provides computerized chemical and biological databases, which serve as tools for the rational selection and discovery of potential therapies for HIV and a variety of opportunistic pathogens (see http:chemdb.niaid.nih.gov). The database was first established through a contract in 1990 and now contains more than 120,000 chemical structures with associated biological data. It provides for consolidation and standardization of biological data from multiple DAIDS testing contracts and contains virtually all that is known about the structure, including *in vitro* testing, animal models, and pharmacokinetics. The reviewers (Drs. Ruprecht and Kanki) considered this to be an important information tool.

After discussion, all 3 concepts were unanimously approved.

International Pharmacology Capacity and Quality Assurance (FY07). This concept seeks to establish a clinical pharmaceutical quality assurance (PQA) and quality control (QC) program that will support DAIDS-sponsored clinical trials. The concept is for a 7-year contract, with first year costs of $1 million. The PQA would include pharmacological proficiency testing, providing assistance and training to lab

staff, developing guidance documents, providing technical and resource assistance to allow labs to validate existing assays, and facilitating the development and validation of novel pharmacological assays that would comply with FDA guidelines. Reviewers (Drs. Buchbinder and Margolis) recommended that microbicides and possibly vaccine reagents be added to the purview of the PQA program. In discussion it was noted that the infrastructure at the international level, which is important given the number of locations where drugs might be made, was well-suited to generics as well as pediatric formulations.

The concept was unanimously approved.

Vaccine and Prevention Research Program—*Peggy Johnston, Ph.D.*

From 2005 to 2006, the key scientific challenge remains to elicit broadly neutralizing antibodies, identify relationships of structure and immunogenicity, induce cellular responses capable of preventing escape, explore novel approaches, elicit durable responses and mucosal responses, identify and advance the most promising candidates into efficacy trials, and evaluate potential immune correlates. Dr. Johnston noted two important studies that are currently underway. One is a phase IIb (proof-of-concept) trial being conducted by the HIV Vaccine Trials Network (HVTN) in conjunction with Merck. This study, HVTN 502/Merck 023, opened in December 2004 and is the first NIAID trial of an HIV vaccine that stimulates primarily cellular immunity. The trial is designed to detect a "minimal" level of efficacy of adenovirus vectors expressing *gag*, *pol*, and *nef* and is being conducted in the US, Canada, Peru, Puerto Rico, Dominican Republic, Haiti, and Australia. Another candidate vaccine developed by NIAID's Vaccine Research Center — a multiclade, multigene DNA plasmid vector prime and adenoviral boost is being evaluated in a phase II trial being conducted by the HVTN. This study is harmonized with two similar studies being conducted by IAVI and the Department of Defense.

HIV Vaccine Research and Design Program (HIVRAD) (FY06). The concept for this initiative is designed to evaluate promising preventive HIV-1 vaccine design concepts. This is a 5 year program with first year costs of $3.4 million. HIVRAD addresses the need for private industry participation and innovation in HIV/AIDS by supporting consortia of academic and industrial scientists. Started in 1997, 20 grants have been awarded, of which 10 are active. Reviewers (Drs. Buchbinder, Ruprecht, and Margolis) concurred that the program is highly significant and should be continued. In discussing the need for close monitoring, it was noted that negotiated milestones and annual site visits will be an essential part of the program. The concept was unanimously approved.

Integrated Pre-Clinical/Clinical AIDS Vaccine Development Program (IPCAVD). (FY06). This concept overlaps with HIVRAD by taking advanced promising vaccine candidates into an initial human trial and encourages applicants to collaborate with HVTN for the conduct of clinical trials. The concept is for a 5-year initiative that would support 1 or 2 awards per year, with first year costs at $4 million. Launched in 1998, 10 grants have been awarded, 5 are currently active. Each IPCAVD has an external advisory committee that helps NIAID evaluate it; HVTN members are usually directly involved or serve as external advisers. Reviewers (Drs. Margolis, Ruprecht, and Buchbinder) concurred that this is important and should be continued. A suggestion to hold an annual HIVRAD-IPCAVD meeting to facilitate collaboration will be explored further. The concept was unanimously approved.

Innovation Grant Program (FY06) (for information only). The concept for this imitative was approved at the January 2005 ARAC meeting. However, in response to a gap identified by the AIDS Vaccine Research Working Group (AVRWG) a change in the mechanism is being made, such that awards will be made as R21/R33 grants. It was noted that successful R21 grantees with promising applied or empirical data were having difficulty getting to the next stage of research because they could not obtain the

preliminary data they needed within the required 2 years to compete for an RO1 and they were not yet ready for a HIVRAD program grant. At NCI, an R21 award is combined with an R33, which extends the time allowed for preliminary data from 2 to 5 years. The idea is to keep the R21 milestone-driven innovative research, and allow for the possibility of an R33. Thus, the funding mechanism for this initiative is being change to help move successful preliminary work into development more quickly.

Prevention Sciences Branch—*Mary Fanning, M.D.*

When the Transition Office of International Research Integration was established, it brought the Prevention Sciences Branch and DAIDS International Research Branch under one umbrella, with Dr. Mary Fanning as the director. Dr. Fanning is trying to optimize the functioning of the 2 branches.

Microbicide Design and Development Teams (FY07). The concept for this initiative spans the period from clinical development to clinical trials. The objective is to advance microbicide concepts into phase I trials via a focused, development-based approach with an NO1 mechanism. It is a 5-year program, with costs of $4.8 million in year 1. The goals are to develop a vaginal and rectal microbicide under GMP conditions and initiate phase I testing. Large pharmaceutical companies would be engaged in milestone-driven microbicide R&D, including novel microbicides and under-explored combinations. Reviewers (Drs. El-Sadr and Howell) thought this program would address a critical gap in microbicide research and encouraged DAIDS to continue to address the gaps industry cannot fill; they recommended approval. The vote was unanimously in favor.

Microbicide-specific Innovation Program (FY06). This concept is for a trans-NIH initiative developed by the Office of AIDS Research to support novel and under-explored projects that have potential to advance the field. This is a 2 to 5 year program, with first year costs of $3 million. Milestone achievements would be assessed by a standing NIAID Topical Microbicide Team. The program will focus on discovery and exploration of microbicides (singly or in combination) directed against HIV and sexually transmitted infections (STI) linked to HIV acquisition, emerging technologies or models that contribute to the development of new and more efficient ways of assessing microbicide safety, efficacy and acceptability and exploration of complex prevention strategies that incorporate vaginally and/or rectally applied microbicides in the context of oral prophylaxis and mucosal vaccines.

Reviewers (Drs. Jackson and Margolis) asked for clarification of the behavioral tools for the clinical trials and the role of other institutes, e.g., National Institute of Mental Health.

Both concepts were discussed and it was questioned whether the focus of the initiative should be on vaginal and rectal microbicides (i.e., women and gay men) because they represent the context of HIV and sexually transmitted diseases only in the United States and other developed countries. The driving force behind the concept was that women need a microbicide they can control; moving to rectal microbicide will take place automatically after the proof of concept has been established. It was agreed that the MDDT should not be modified but Drs. Margolis and Holmes suggested approval of the MIP concept with the modification that the initiative focus on vaginal microbicides, but also encourage applications for rectal and/or penile use. All voted in favor of the initiative with the modification.

External Scientific Review for Future HIV/AIDS Clinical Trials Networks— *Jonathan Kagan, Ph.D.*

In follow-up of previous discussions, Dr. Kagan, presented ideas for how external scientific reviews could be conducted once the future HIV/AIDS Clinical Trials Networks are established in 2006. He reminded

the ARAC that the reviews would differ in purpose and scope from the annual Network evaluation process and would help ensure that the highest-priority science drives the future networks for HIV/AIDS clinical trials,

Drs. Margolis and Davis and Ms. Brenda Lein met with DAIDS staff via conference call on several occasions prior to the ARAC meeting to discuss what these external reviews might consist of and they supported the ideas presented at the meeting.

It is proposed that the external scientific reviews take place every 2 or 3 years, allowing time for the Networks to establish themselves, for studies to be initiated and for data to be collected. A Working Group, under the auspices of ARAC, could be convened for each scientific review, and focus on Network(s) progress toward achieving specific scientific goals. In addition, Working Groups would be convened when needed to review selected, high-resource, high-impact clinical trials to provide advice and guidance in setting priorities for limited resources. None of these would be standing Working Groups; rather they would be convened as needed and their composition would be based on scientific needs and individual expertise. As a Working Group of ARAC, each would include ARAC members as appropriate.

In contrast to the annual Network evaluation program, which will use objective measures, established criteria, and involve network leadership, the scientific reviews will be conducted every 2 or 3 years using subjective and objective measures of progress and may encompass one or more Networks. The scientific review would be based on a specific aspect of a scientific priority (treatment, microbicides, mother-to-child transmission, vaccines, optimization, prevention), and would use data from the network evaluation program as appropriate. Possible outcomes of the review would be recommendations and proposed adjustments to network research plans, greater collaboration, shifting of resources, and advisory guidance on priorities for high-resource, high-impact clinical trials. Only a select number of clinical trials would be reviewed at early phases of development; not all trials would be effected.

The AIDS Vaccine Research Working Group (AVRWG), which has a standing role and mission might be able to conduct the scientific reviews for vaccine research efforts, but that would need to be explored further to ensure that the composition of the AVRWG is appropriate.

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

Director's Report

Dr. Heilman introduced the new *ex officio* member of the Subcommittee, Dr. Eric Schoomaker, who was recently appointed as the new Commander of Fort Detrick and the US Army Medical Research and Materiel Command. She also introduced *ad hoc* member Dr. Marty Rosenberg, who is currently the Chief Scientific Officer with Promega Corporation. He retired from GlaxoSmithKline in 2001, where he served as the Senior Vice President for Anti-Infectives, Drug Discovery and Development. Dr. Heilman then thanked Dr. Margaret Liu for her service to the Subcommittee; today is her last day as a member of the NIAID Council. Dr. Heilman then turned to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their own respective new hires.

Dr. Heilman presented several slides summarizing DMID's broad research mandate and reported on the top scientific advances stemming from DMID-supported programs over the past year. Several of these advances cut across multiple categories, e.g., biodefense, vaccine development and global health.

Following her remarks, the following concepts were presented for consideration by the Subcommittee:

NIAID Partnerships with Public-Private Partnerships (PPPs) -- This initiative seeks to build on NIAID's investments in various emerging and re-emerging diseases, such as malaria, tuberculosis, dengue, sexually transmitted infections, parasitic diseases, and diarrheal diseases. Under this initiative, NIAID would 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., pretrial infrastructure assessment and development, epidemiologic surveillance in anticipation of clinical trials, trial monitoring, etc.). The Subcommittee unanimously approved the initiative.

Tropical Medicine Research Centers -- This initiative seeks to advance tropical medicine research in endemic areas, and, in keeping with the "Guiding Principles for NIAID Global Health Research," to "build and sustain research capacity in-country" by awarding funds directly to foreign institutions in endemic areas. The TMRC program, initiated in 1991, consists of Center Awards made directly to foreign institutions for the purposes of conducting and supporting research in the causes, diagnosis, prevention, and cure of tropical parasitic diseases in endemic areas. Research is multidisciplinary but focused on a single pathogen or disease entity. The Subcommittee unanimously approved the initiative.

Production of Monoclonal Antibody-Based Therapeutics for Botulinum Neurotoxin Serotype B -- This initiative will provide contract resources for the development and manufacture of candidate MAbs against BoNT serotype B. The Subcommittee unanimously approved the initiative.

Development of Therapeutic Agents for Selected Viral Diseases -- This effort will support the development of promising therapeutic candidates against selected viral diseases through a well-defined product development path that includes completion of a Phase 1 clinical trial within the 5 year contract period. The Subcommittee unanimously approved the initiative.

Development of Medical Interventions to Diagnose or Treat Underserved Health Care Associated Drug-Resistant Infections -- The goal of this initiative is to stimulate the development of new treatment strategies that include either exploration of novel compounds or approaches, or novel means to determine antimicrobial susceptibility so as to guide therapy. After much discussion, the subcommittee approved the initiative and requested consideration of the addition of tools to prevent the spread of antibiotic-resistant nosocomial pathogens.

Partnerships for Influenza Therapeutics and Diagnostics -- This initiative will support the development of next generation clinical point of care diagnostics and the development of new antiviral agents for influenza. The Subcommittee unanimously approved the initiative.

Non-Antibiotic Selectable Markers for Biodefense -- This initiative will support research leading to the development of non-antibiotic selectable genetic markers for category A-C bacterial pathogens. Non-antibiotic selectable markers have been developed for plants and fungal pathogens, suggesting that similar approaches should be applicable to bacteria. Priority will be given to projects leading to development of non-antibiotic selectable markers for those category A-C pathogens lacking readily available vaccines and/or subject to few selectable marker options The Subcommittee unanimously approved the Initiative.

Topical Microbicide Safety and Efficacy Evaluation in Nonhuman Primates – The Subcommittee discussed and approved this initiative to recompete this contract, and agreed to a revision to the current scope of work to include efficacy testing for additional infections beyond the current capability to test for

efficacy against chlamydial infection. This resource will provide testing capacity which is integral to the Institute's Topical Microbicide development program. As outlined in the NIAID Topical Microbicide Strategic Plan, the evaluation of products in nonhuman primates is a critical path component of the product development algorithm. The Subcommittee unanimously approved the initiative

VII. ADJOURNMENT

The meeting of the Council was adjourned at 5:00 p.m., on Monday, September 26, 2005.

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

_-s-_ **12/19/2005**
Anthony S. Fauci, M.D. Date
Chairman, National Advisory Allergy
and Infectious Diseases Council
Director, National Institute of Allergy
and Infectious Diseases

_-s-_ **12/16/2005**
John J. McGowan, 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.