NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

May 21, 2007

The 156th meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, May 21, 2007, in Conference Room E1/E2, Building 45, National Institutes of Health. Dr. Anthony S. Fauci, director, National Institute of Allergy and Infectious Diseases (NIAID) presided as chair.

In accordance with the provisions of Public Law 92-463, the meeting was open to the public from 10:30 a.m. to 11:40 a.m. and from 1:00 p.m. to 5:00 p.m. The meeting was closed to the public from 8:30 a.m. to 10:00 a.m. and from 11:40 a.m. to 12:00 p.m. for review and consideration of individual grant applications. Notice of the meeting was published in the *Federal Register.*

Council Members Present:

Dr. Robert Brooks
Dr. Barbara Baird
Dr. Stanley Chapman
Dr. Satya Dandekar
Dr. Kathryn Edwards
Dr. Richard Insel
Dr. J. Brooks Jackson
Dr. Sharon Kiely
Dr. Martin Myers
Dr. Marc Rothenberg
Dr. Ruth Ruprecht
Dr. Nathan Thielman
Dr. Gail Wertz

***Ex Officio* Members Present:**

Dr. Anthony Fauci

Council Members Absent:

Dr. Shelley Payne
Dr. Martin Rosenberg
Dr. Gary Schoolnik
Dr. Megan Sykes
Dr. David Wilkes

***Ex Officio* Members Absent:**

Dr. Mitchell Cohen
Major General Eric Schoomaker
Dr. Ronald Valdiserri

***Ad Hoc* Members:**

Dr. George Drusano
Dr. Marie Freire
Dr. Donald Leung

NIAID Senior Staff:

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

I. REVIEW OF GRANT APPLICATIONS

The National Advisory Allergy and Infectious Diseases Council convened in closed session to consider applications in the areas of allergy and immunology, microbiology and infectious diseases, and AIDS.

Funding Actions: The Council reviewed 2,526 research and training applications with primary assignment to NIAID for a requested amount of $681,328,130 in first-year direct costs. The Council recommended approval of 481 applications for $175,636,627 in first-year direct costs. Five Method to Extend Research in Time (MERIT) award were recommended for approval.

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

Dr. Fauci opened the Council session by welcoming visitors to the meeting and noting that Drs. Payne, Rosenberg, Schoolnik, Sykes, and Wilkes would be absent. Also, the three *ex officio* members, Dr. Mitch Cohen, Major General Eric Schoomaker, and Dr. Ronald Valdiserri were unable to attend. He introduced three *ad hoc* Council members: Dr. George Drusano, Albany Medical College of Union University; Dr. Marie Freire, Global Alliance for TB Drug Development; and Dr. Donald Leung, National Jewish Medical and Research Center in Denver.

Dr. Fauci congratulated two current Council members and one former member for major accomplishments. Major General Schoomaker was appointed the Commanding General of the North Atlantic Regional Medical Command and Walter Reed Army Medical Center. Dr. Marc Rothenberg received the E. Mead Johnson Award for research in pediatrics. Former Council member Kim Bottomly was recently named Wellesley College's 13th president.

Consideration of Minutes of Previous Meeting

The minutes of the January 29, 2007, meeting were considered and approved as written.

Staff and Organizational Changes

Several staff changes in administrative positions have taken place, primarily related to the reorganization of the Office of the Director. Kevin Callahan has been appointed director of NIAID's Office of Strategic Planning and Financial Management. The new director of the Office of Communications and Government Relations is Courtney Billet. William Gillen is the new special assistant to Dr. McGowan, NIAID deputy director for Science Management. The chief of the Workforce Management Resources Branch in the Office of Workforce Effectiveness and Resources is now Mildred Allen.

In the Division of AIDS, Edward Handelsman was named chief of the Pediatric Medicine Branch.

Dr. Fauci announced that Dr. Tom Wellems, chief of the Malaria Section of the Laboratory of Malaria Research in the Division of Intramural Research, has been elected as a member of the National Academy of Sciences.

Budget Update

The President's FY 2008 budget request for NIH is $28.8 billion, a 0.8 percent increase over the FY 2007 budget. NIAID's allocation is approximately $4.6 billion, an increase of $210 million over FY 2007. Of the $210 million, $201 million is slated for the Global Fund to fight AIDS, TB, and malaria. After accounting for the Global Fund increase, the actual increase for the Institute is $9 million or 0.2 percent.

Dr. Fauci described two NIH programs that are subsidized by the Common Fund: the Bridge Awards program and the NIH Roadmap. He reviewed the criteria used to consider applications for bridge awards and outlined the differences between the NIH and NIAID bridge awards programs.

NIAID played a leadership role in the most recent Roadmap activities, called Roadmap 1.5. Dr. Fauci briefly described the top five topics selected by the institute and center directors for consideration of Roadmap 1.5 funding for 2008.

Legislative Update

In March, Dr. Fauci accompanied Dr. Zerhouni as he testified on the FY 2008 NIH budget before the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies.

Dr. Fauci testified at congressional hearings on emergency preparedness activities within the Department of Health and Human Services and on Project Bioshield.

In April, NIAID hosted two congressional visits. Rep. Dave Weldon toured the Vaccine Research Center, and Senator John Tester visited the Rocky Mountain Laboratories and toured the new integrated research facility.

Dr. Fauci is serving on an *ad hoc* working group of NIH's steering committee for implementing the NIH Reform Act of 2006. He is co-chair of the subgroup that is reviewing provisions that affect peer review, demonstration projects, and research training authority. The only major change for peer review is the requirement that all grant applications, even those under $50,000, must be considered by Council.

Other Information Items

On February 23, 2007, a retirement gala was held at the Cloisters for former NIAID Director, Dr. Richard Krause.

The latest version of the Jordan Report was published online on May 21. This report describes NIAID's vaccine activities.

Dr. Fauci gave an update on some of the Institute's international activities. An NIAID delegation met with the leadership of the Chinese National Academy of Medical Science to reaffirm collaborations, and NIAID renewed the Indo-U.S. Vaccine Action Program.

Our grantees finished the genomic sequencing of *Aedes aegypti*, which is a major arbovirus vector. Other areas that NIAID continues to focus on are emerging diseases, malaria, tuberculosis, and immunology. Researchers are making advances in AIDS with new drugs and new prevention measures.

Dr. Fauci gave an update on influenza. The FDA approved the first U.S. vaccine for humans against the avian flu. The first human trial of a DNA vaccine to prevent H5N1 avian influenza infection began in December 2006. NIAID began funding a program to establish six Centers of Excellence for influenza research and surveillance.

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

The Vaccine Research Center (VRC) opened a pilot plant to manufacture vaccines and a clinical immunology lab in collaboration with the Division of AIDS to perform validated T-cell assays. The number of staff at the Center has increased based on these two new activities.

Dr. Nabel gave an update on the status of several vaccines that the VRC has been working on including vaccines for SARS, West Nile Virus, Ebola, Marburg, and influenza.

The main focus of the Center is HIV vaccines. Since the VRC began six years ago, it has created 12 HIV vaccine products and 11 other vaccine targets. It has conducted 30 trials, 21 related to HIV, and 9 in non-HIV targets.

Dr. Nabel reviewed in detail the VRC multiclade AIDS vaccine candidate that is progressing into clinical trials later this year. This trial will be done under the auspices of the Partners in AIDS Vaccine Evaluation with an anticipated start time of late summer or early fall. The double-blind placebo controlled trial is looking at whether the vaccine will prevent infection or affect $CD4^+$ T-cells and viral loads in people who become infected after receiving the vaccine. Dr. Nabel also reviewed the potential outcomes of the trial.

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

Ms. Peggy (Margaret) Lund Fitzgibbon, RN Ms. Fitzgibbon joined the Office of Project Management in February 2007 as a Project Manager. She received her bachelor's degree in nursing from Morris County College in New Jersey. Ms. Fitzgibbon has 10 years of clinical trial experience at Merck, where she developed an expertise in managing Phase III and IV clinical trials. In addition, she has extensive knowledge of the health authority requirements abroad resulting from her work with international trials.

SCIENTIFIC INITIATIVES

NIH Tetramer Facility (RFP-NIH-NIAID-DAIT-08-13): To support the operation of the NIH MHC Tetramer Facility, which provides synthesis and distribution of soluble MHC-peptide tetramers and related reagents to the scientific research community. Reagents include mouse, non-human primate, and human MHC class I monomers and tetramers; custom-made mouse, non-human primate, and human class II tetramers; non-classical MHC TL, Qa-1, and mouse and human CD1 monomers and tetramers; CD1d and other MHC ligands; and fluorophores for tetramer detection. This is a recompetition of the current Tetramer Facility contact held by Emory University.

Exploratory Investigations in Food Allergy (NOT-AI-07-023): To support innovative exploratory and developmental investigations to determine the mechanisms underlying food allergy, focusing on ex vivo studies with human specimens, and on studies with current or new animal models of human food allergy.

Request for Information (RFI): GLP Radionuclide Testing Facilities (NOT-AI-07-028): To obtain information on the status of existing Good Laboratory Practice (GLP) radionuclide testing facilities to support NIH's development of medical countermeasures against radiation injury. These facilities are

needed to evaluate potential drug candidates, and to perform GLP studies to support licensure of new medical countermeasures.

Clinical Trials in Organ Transplantation in Children (U01) (RFA-AI-07-006): NIAID and the National Heart, Lung, and Blood Institute (NHLBI) invite new and/or competing continuation applications from teams of institutions to participate in a clinical trials program to improve graft acceptance and patient/graft survival in pediatric organ transplant recipients, i.e., children up to 20 years of age, who have undergone heart, lung, liver, kidney or intestinal transplantation.

B Cell Immunology for Protective HIV-1 Vaccines (R21) (RFA-AI-07-015) and **(U01) (**RFA-AI-07-014): To support high impact basic immunology studies and innovative methods that may lead to induction of broadly reactive, neutralizing antibodies that can prevent infection by a wide spectrum of clinically relevant HIV-1 strains. Identification of approaches that induce effective and broadly neutralizing antibodies is a priority of the Global HIV/AIDS Vaccine Enterprise.

DIVISION ACTIVITIES

Special Topic Meeting: Medical Countermeasures for Radiation Combined Injury (RCI): Radiation with Burn, Blast, Trauma and/or Sepsis: On March 26-27, 2007 NIAID sponsored a two day meeting in Washington, DC to bring together experts in the areas of radiation, burn, blast, trauma (e.g. wound, head injury) and sepsis in order to address complications that arise when radiation exposure is combined with other types of injury. Speakers and participants were asked to help determine the state of science, identify gaps, and define future research directions for the development of medical countermeasures to treat RCI. The group identified several combined injury scenarios, optimal animal models, and techniques, assays and potential endpoints relevant for pivotal animal efficacy studies. Attendees included researchers from the Centers for Medical Countermeasures against Radiation (CMCR) program, and local NIH, Department of Defense and Food and Drug Administrative representatives. Access to slides presented at the meeting can be found at the following website: http://www3.niaid.nih.gov/research/topics/radnuc/Meeting_Slides.htm

Meeting on World Health Organization Strategic Stockpile Development: On February 14-16, 2007, the NIAID co-sponsored an expert consultation meeting in Geneva, Switzerland on the stockpile development for radiation environmental emergencies. The World Health Organization has in place logistics mechanisms and storage facilities to bring essential medical supplies to areas of health emergencies around the globe (e.g. natural disasters, conflicts, disease outbreaks). WHO intends to further expand the existing stockpiles to address radiation emergency needs. The objectives of the meeting were to identify and justify the type and quantity of supplies for a radiation emergency stockpile, to develop recommendations for use; establish procedures for acquisition, release, refill and disposal of these supplies; and to develop a concept-of-operations paper to be applied to radiation emergency stockpile set up. The NIAID was represented at the meeting by DAIT Radiation/Nuclear Program staff.

NIAID Morning Symposium: Dendritic Cells: On February 23, 2007 at the American Academy of Allergy, Asthma and Immunology (AAAAI), NIAID held a symposium entitled "NIAID Morning Symposium: Dendritic Cells." Five experts in the field presented lectures on the function of dendritic cells in the presentation of antigens and the subsequent development of the adaptive immune response, including different functional roles played by distinct subpopulations of dendritic cells.

NIAID Afternoon Symposium: Immunologic Basis of Food Allergy: On February 23, 2007, as part of the annual meeting of the AAAAI the NIAID held a symposium entitled "NIAID Afternoon Symposium: Immunologic Basis of Food Allergy." The panelists discussed the pathophysiology of food allergy and

anaphylaxis due to food allergy, including the role of allergen structure and genetics, and identified potential new therapeutic allergen-specific approaches to prevent and treat food allergy.

Formula for Success: Connecting with NIH Program Officers: On February 26, 2007, as part of the annual meeting of the AAAAI the NIAID held the seminar "Formula for Success: Connecting with NIH Program Officers." The purpose of the seminar was to familiarize the research community with NIAID funding opportunities and mechanisms. Discussions covered the use of various funding, the new electronic grant SF424 submission format, the optimal use of Program Officers as resources, and guidance on what to do and what to avoid in the grant writing/application process.

Inner City Asthma Consortium (ICAC) Presentations: On May 23, 2007, as part of the annual American Thoracic Society (ATS) meeting the first public presentation of results from the Asthma Control Evaluation (ACE) ICAC Protocols-01/2 will occur. ACE is a randomized clinical trial evaluating the use of a biomarker eNO to improve the management of children residing in inner cities. Three lectures will be given during this DAIT-sponsored session: 1) Baseline characteristics of the ACE population and a computerized treatment algorithm for childhood asthma; 2) relationship of eNO to allergy and other biomarkers; and 3) results of a randomized, double-blind, placebo controlled trial of a biomarker (eNO) as a guide for the treatment of childhood asthma.

American Association of Immunologists (AAI) Annual Meeting: On May 18-22, 2007, the twenty-third annual Symposium on Contemporary Topics in Immunology, cosponsored by the NIAID and the AAI, was held as part of the annual AAI meeting. At the same conference, the NIAID also sponsored a symposium on Immunology Ontology; the NIAID and the Office of AIDS Research cosponsored a workshop on basic B cell immunology and the development of a neutralizing HIV vaccine; and the NIAID sponsored a focus group meeting to discuss NIAID/NIH policies and issues of concern to basic and clinical research extramural investigators.

Annual Meeting of the Cooperative Centers for Translational Research on Human Immunology and Biodefense: On May 2-3, 2007 the fourth annual meeting of this cooperative research program was held at Stanford University, in conjunction with a scientific symposium focused on human immunology. Members of the Centers program presented their latest research results and discussed future plans.

DIVISION ADVISORY COUNCIL PRESENTATION

NIAID Overview of the Atopic Dermatitis and Vaccinia Network

The following programmatic presentation was given by division staff and guest: Marshall Plaut, M.D. Chief, Allergic Mechanisms Section, Asthma, Allergy and Inflammation Branch discussed an **Overview of the Division's Atopic Dermatitis and Vaccinia Network Program**; and Donald Y.M. Leung, M.D., Ph.D., Head, Division of Pediatric Allergy and Immunology, National Jewish Research and Medical Center presented a general **Update on the Atopic Dermatitis and Vaccinia Network.**

CONCEPT REVIEW

A single concept was presented and approved.

Exploratory Investigations in Food Allergy: This initiative will support novel mechanistic studies in food allergy using human specimens or animal studies using models of human food allergy. Research may focus on the recommendations of the NIH Expert Panel on Food Allergy Research, including:

biomarkers and genetic components of food allergy and severe food allergy; food allergens epitopes and novel food allergens; and biomarkers, genetics, and mechanistic studies in animal models.

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

Dr. Carole Heilman, Director of the Division of Microbiology and Infectious Diseases (DMID), chaired the Subcommittee meeting. She introduced Dr. George Drusano and Dr. Maria Freire, who joined the meeting as *ad hoc* members of the Subcommittee. Dr. Drusano is an infectious diseases physician based at Ordway Research Institute in Albany, New York, and Dr. Freire is the President and CEO of the Global Alliance for TB Drug Development based in New York City. She then referred to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their respective new hires.

Dr. Heilman noted that there were no concepts to present to the Subcommittee for approval at this meeting, but that several programmatic updates would be provided. She also mentioned that following this session, the DMID Subcommittee would join the Division of AIDS council subcommittee to discuss TB and the interactions of HIV/TB, and consider a research strategy that DMID and DAIDS have drafted on the topic.

She began by presenting information on a new Presidential directive, Homeland Security Presidential Directive (HSPD)-18, released in January 2007. Under this directive, biological threats are now considered in four distinct categories, each of which presents unique challenges and significant opportunities for developing medical countermeasures. The four categories include traditional agents, emerging agents (e.g., previously unrecognized pathogens such as SARS), as well as enhanced and advanced agents (e.g., those that have been modified or artificially engineered).

In keeping with this new directive, Dr. Heilman reported that while the Institute will continue to focus on specific countermeasures for specific pathogens that are of greatest threat, DMID is also pursuing new, broad-based approaches to product development by supporting research on products that are applicable to broad classes of threats, host-directed interventions, and new technological strategies, such as temperature stabilization, alternative delivery devices, and vaccine adjuvants.

Dr. Heilman pointed out that this directive dovetails with the Department's ongoing efforts to develop a strategy and implementation plan for the advanced development and procurement of medical countermeasures for chemical, biological, radiological and nuclear threats. At present, the implementation plan is out for public comment and Dr. Heilman encouraged the Subcommittee to review the Plan at the link provided and comment if they were so inclined.

Dr. Heilman introduced Dr. Dennis Dixon, who serves as the Chief of DMID's Bacteriology and Mycology Branch. Dr. Dixon updated the Subcommittee on the National Science Advisory Board for Biosecurity (NSABB), which recently released recommendations that will inform the development of federal guidelines for the evaluation and review of dual use research. Dr. Dixon is a NIAID representative on the NSABB.

Dr. Dixon then provided the Subcommittee with an update on DMID's antimicrobial resistance research program. He reported on research activities DMID has pursued in recent years to address the growing problem of resistance, noting several research initiatives designed to address specific needs, for example the development of new diagnostics and the support of clinical trials. He also reported on recent activities of the Interagency Task Force for Antimicrobial Resistance, which NIH co-chairs with the Centers for Disease Control and Prevention and the Food and Drug Administration.

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

Participating ARAC members included: Drs. Wafaa El-Sadr (chair), Debbie Birx (ex officio), Robert Brooks, Susan Buchbinder, Satya Dandekar, Kathryn Edwards, Brooks Jackson, Andrea Kovacs, Jeffrey Lennox, David Margolis, Henry Masur (ex officio), Ruth Ruprecht, and Nathan Thielman. Participating NIAID staff included: Drs. Carl Dieffenbach, Peggy Johnston, Sandra Lehrman, Richard Hafner, Jonathan Kagan, and Mr. Matthew Murguia, Ms. Madelon Halula and Ms. Rona Siskind (Executive Secretary).

Dr. El-Sadr called the meeting to order at 1:00 p.m. The minutes of the previous meeting were approved unanimously.

Director's Report – *Carl Dieffenbach, Ph.D.*

Carl Dieffenbach, Acting Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), welcomed everyone to the meeting and introduced invited guests who would be participating in the joint meeting with the NIAID Council Subcommittee later in the afternoon. He also announced the appointment of Dr. Ed Handlesman as Chief of the Pediatric Medicine Branch in the Therapeutics Research Program.

With regard to scientific and program highlights, Dr. Dieffenbach noted the launch of HVTN 503 or the Phambili Trial, a Phase 2B vaccine trial that will test the Merck Ad5 HIV-1 (gag/pol/nef) candidate in 3,000 volunteers in South Africa. He also reported that the vast majority of Clinical Trial Units (CTUs) have been awarded. A press release was issued on March 12, 2007 for 64 CTUs (9 more are anticipated) and 121 Clinical Research Sites (22 more are anticipated), including sites in 20 U.S. states and 19 foreign countries. When all the awards are made, NIAID will have sites in a total of 24 U.S. states and 26 countries.

The President's budget for FY2008 includes $4.6 billion for NIAID, a 4.8 percent increase from FY2007, making NIAID the second largest among the NIH institutes and centers. This total includes $201 million for the Global Fund (a 200 percent increase over FY 2007) and $9 million to support unsolicited Research Project Grants (RPGs) for new investigators. The DAIDS portion of this budget is just under $3 billion and has been flat or declining for the past three years.

The success rate for DAIDS proposals is 23 percent, slightly higher than the 21 percent for NIAID and in the middle range for NIH overall. Beginning in 2006, a differential payline for new investigators was added. This was continued in 2007 and will be continued again into 2008. For NIAID, the total number of research project grants has increased relatively steadily to 2006, and in 2007 there was a large jump in terms of numbers of applications. This will have a profound impact on the success rate because even if the same numbers of grants are funded, the success rate will drop significantly. The number of K award applications DAIDS has received nearly doubled between 2005 and 2007, but the number that can supported has fallen, and will likely continue to do so.

In response to questions, Dr. Dieffenbach said that the success rates he presented included resubmissions, and that all clinical proposals to DAIDS are classified as "solicited." The committee expressed concern that peer reviewers are becoming more conservative and demanding more preliminary data. Dr. Dieffenbach noted that the Center for Scientific Review will be holding an "open house" on June 29, during which they will be welcoming comments on peer review. The goal is to identity better ways to

deal with innovation, and shorten the application process – essentially making it a kinder, gentler application process.

Update: AIDS Vaccine Research Working Group—*Susan Buchbinder, M.D.*

Dr. Buchbinder reported that the AIDS Vaccine Working Group (AVRWG) has four new members (Kevin Fischer, Bruce Walker, Louis Picker, and Jeffrey Lifson) to replace three that rotated off (David Watkins, Scott Hammer, and Steve Wakefield) Dr. Eric Hunter is the new chair of the working group. The last meeting (Jan 30-31) focused on adenovirus (Ad)-based vaccines. Day 1 of that meeting was a workshop to discuss AIDS vaccines based on novel recombinant adenovirus vectors. Day 2 was a discussion of a planned Phase IIB trial (PAVE 100) testing the VRC's DNA/rAd5 vector vaccine. There is considerable interest in recombinant adenovirus vaccines due to their ability in animal challenge studies to maintain CD4+ counts and control viral replication; the latter a predictor of slow progression in humans. Ad5, in particular, evokes a good immune response in humans, but unfortunately between 65 and 75 percent of some subpopulations in sub-Saharan Africa and Thailand have preexisting immunities to Ad5 that theoretically may attenuate that response. This may be addressed through different products (as discussed in the Day 1 workshop) and dosing. Further information on the impact of preexisting immunity to Ad5 to immune response elicted to rAd5 vectors will be derived from the PAVE 100 protocol.

The AVRWG meeting on May 22-23 will include an annual report from the Center for HIV/AIDS Vaccine Immunology (CHAVI) and a review of the DAIDS HIV Vaccine Research and Design Program (HIVRAD).

Concept Review: HIV/AIDS Scientific and Operations Support – *Madelon Halula*

Dr. Madelon Halula described the concept underlying the HIV/AIDS Scientific and Operations Support (HASOS) contract, which allows NIAID to hire contract employees to maintain or increase capacity in a flexible manner. The contract will have a projected budget of $15.6 million in year 1. The award will have an initial two-year base period, with the option to renew/expand for a total of seven years. Much of the award will focus on support of clinical research activities including protocol development, collaborative partnerships, training, and operations (portfolio tracking, data management, and outreach). Currently, these services are provided through a cooperative agreement with the Henry M. Jackson Foundation. The new contract represents a formal competition of an existing function that has not kept pace with growing workloads. The future contract will formalize limits on what contractors "can and can't do." Federal employees will continue to be responsible for "inherently governmental activities" such as making policy decisions, overseeing extramural awards, committing funds, and representing the government. Comparisons with other institutes or private industry are difficult to make, but the scope and cost of this approach are considered to be roughly comparable.

In response to questions, Ms. Halula said that this contract would not involve a new expenditure of funds, but represents use of a different mechanism for an existing expense. The reviewers commented favorably on the expansion feature, which gives DAIDS the flexibility it needs to ramp up support for international clinical trial initiatives, including the possible expansion to accommodate Phase 3 trials when a successful vaccine candidate emerges. Such expansion would require new money.

The committee voted to approve the concept.

Following a short break, the ARAC reconvened at 3:00 p.m. in joint session with the NIAID Microbiology and Infectious Diseases Council Subcommittee for a discussion of research on Tuberculosis (TB) and HIV/TB.

VII. JOINT MEETING ON TUBERCULOSIS AND HIV-TUBERCULOSIS

Dr. El-Sadr called the meeting to order at 3:00 p.m. and announced that this was the first joint meeting of the two committees. She expressed hope that it would generate ideas and recommendations toward a joint HIV/TB research agenda.

Overview – *Barbara Laughon, Ph.D.*

Barbara Laughon, Chief, Complications and Co-infections Branch, DAIDS, NIAID, reported that joint HIV/TB programs have taken on new importance since the first reports of a rapidly lethal, extensively drug-resistant (XDR) form of tuberculosis (TB) in HIV infected persons at Tugela Ferry, South Africa, in 2006. Evidence suggests that 1) the existing directly observed therapy, short course (DOTS) regime has not assured complete treatment and may be contributing to the development of drug resistant TB; 2) HIV/TB co-infection may have accelerated the selection for drug resistance in TB, and transmission of already drug resistant strains of Mtb to HIV infected individuals is occurring, and 3) XDR-TB cases in the Tugela Ferry area in South Africa appear to be primarily nosocomially transmitted affecting HIV-infected patients and health workers alike. Cases of XDR-TB have now been reported in 37 countries, including the United States.

NIH conducts TB research in five different institutes and centers, and research programs are coordinated as part of several joint research and working groups. However, increased partnerships between the public and private sectors will be needed to bring new drugs to market. The global market for first-line TB drugs is estimated at $320 million/year. The pharmaceutical industry reports that it will cost $800 million to develop a new drug for XDR-TB, while the World Health Organization estimates that $4.8 billion will be needed to develop and adopt such a drug.

The objective of this joint council meeting is to share information among key experts in TB and HIV/AIDS research, to explore opportunities to coordinate current activities, to discuss the current draft of NIAID's research agenda for Multi-drug resistant (MDR) and XDR-TB, and to generate recommendations that will strengthen these activities and plans.

Perspective on Intersecting Epidemics – *Mark Harrington*

Mark Harrington, Executive Director of the Treatment Action Group, noted that May 21 is the 17th anniversary of the ACT-UP "Storm the NIH" demonstration. He went on to say that while the community now faces these two "intersecting epidemics" – that of HIV and TB – it is not the same TB the world was facing 40 years ago, or even 17 years ago. In Tugela Ferry, South Africa, 50 percent of XDR-TB patients died within 300 days of diagnosis, and throughout sub-Saharan Africa, 50 percent of autopsies show disseminated TB that has never been diagnosed or treated, pointing to the importance of developing strategies to more rapidly diagnose all forms of TB. XDR-TB is particularly detrimental to HIV-infected populations, causing great mortality even in patients receiving antiretroviral treatment (ART).

NIAID is already funding two-thirds of global TB drug research, with funds also spent on basic research, diagnostics and vaccine development. However this investment is dwarfed by its AIDS budget which is currently 20 times that of TB. He urged that ways to advocate for a general increase in NIH funding, and

particularly an increase in spending on TB are needed, and that the Seven-Point XDR-TB Action Plan that was developed as part of a WHO co-sponsored expert consultation in September 2006 (http://www.who.int/tb/kg1/en/) provides a good basis for the research agenda. This Action Plan calls for increased research support to develop rapid diagnostic tests, as well as anti-TB drugs, with an emphasis on implementing rapid drug resistance surveys and improved control programs for drug resistant TB. Mr. Harrington encouraged the establishment of a presidential initiative for TB, similar to the program created for AIDS.

Improving Diagnostics: Identification of TB and MDR-TB in HIV-Infected Patients—*Mark Perkins, M.D.*

Dr. Mark Perkins, with the Foundation for Innovative New Diagnostics (FIND), noted that sputum smear microscopy is still the principal tool for diagnosing TB today, just as it was 120 years ago. Globally, however, microscopy identifies only a small number of new cases of TB since not all patients carry sufficient quantities of Mtb in sputum to be detected by microscopy (i.e. HIV co-infected persons, young children). Furthermore, current delays in diagnosis and treatment greatly increase the burden of morbidity, mortality and transmission. Consequently, development of improved diagnostics must be considered one of the cornerstones for improved TB control, especially in an era of increasing co-infection with HIV and the inadequacies of current diagnostic tests for rapid identification of TB in these co-infected persons. FIND is pursuing the development of new TB diagnostic tools at several levels, with the goal of producing tests that are as affordable, fast and reliable as pregnancy or blood glucose testing is today. To do this, however, systematic research on TB biomarkers is needed to identify molecular and clinical targets that can be translated into new diagnostic strategies to fill the developmental pipeline. To this end, Dr. Perkins encouraged researchers to focus their efforts on identifying the most promising antigens for a serological TB diagnostic test.

New Drugs for Treatment of TB and MDR-TB – *William Burman, M.D.*

Dr. William Burman, Denver Public Health, reported that only one new drug for TB has been introduced since 1968. While TB drugs are available, numbers of TB cases have continued to increase worldwide, partially fueled by the HIV co-epidemic. According to Burman, this continued rise is an indication that the current TB control programs are inadequate, and the emergence of MDR and XDR-TB does not come as a surprise. Three new classes of drugs, now being tested in mice, promise to be more effective, particularly in combination. If the development of these new drugs proceeds successfully, an improved regimen may be available by 2015. But success is not guaranteed and there are serious challenges to developing new TB combination regimens, not least of which is the currently small number of drug candidates in the development pipeline - a stark contrast to the drug pipeline for HIV.

Dr. Burman emphasized the need for HIV researchers to get involved in TB research, bringing with them the research tools and methodologies that have been developed for HIV. He noted that one important area of HIV/TB research will be the development of clinical trial protocols to evaluate therapies for co-infected patients.

Global funding for TB trials is estimated to be $43 million per year, compared with over $1.1 billion for HIV. Any clinical trial for MDR or XDR-TB will by necessity be large and long-term, will include special populations and will require a significant number of ancillary studies. Dr. Burman identified the following clinical research needs:

- Pharmacokinetic studies of new and existing TB drug regimens, alone and in various combinations to identity the most active comparison drugs.
- Development and maintenance of laboratory and X-ray capacity to facilitate patient enrollment and follow-up.
- Improved integration of research and treatment programs to provide the foundation for high quality clinical trials and studies.
- Identification of clinical research/trial sites that have the ability to design clinical studies that may change TB control strategies.
- Inclusion of biomarker studies in clinical trials.
- Development of patient surveys to increase awareness of and stimulate integration of HIV/TB control programs.

Immune Response in Patients with HIV-TB – *Henry Boom, M.D.*

Dr. Henry Boom, Case Western Reserve University and University Hospitals of Cleveland, reported that in Kampala, Uganda, 46 percent of TB patients are also HIV-infected, and the two diseases affect each other's progression– HIV increases susceptibility to and development of active TB, while TB accelerates disease progression in HIV. Better screening to identify patients early and availability of more effective and easier to complete treatment regimens are urgently needed, as are TB drug combinations that do not negatively interact with antiretrovirals (ARVs). According to Dr. Boom, basic research to support these efforts should include studies to identify biomarkers and to define host genetics of susceptibility to TB, HIV and co-infection. He also suggested that, in settings where TB and AIDS are both endemic, close integration of screening and treatment programs for the two diseases are warranted.

Draft NIAID Research Agenda for MDR (XDR)-TB – *Christine Sizemore, Ph.D.*

Christine Sizemore, acting Chief of the TB, Leprosy and other Mycobacterial Disease Section in DMID, NIAID, outlined a research agenda for MDR/XDR-TB that includes basic, translational and clinical research and research support in the following priority areas:

- Diagnostics – Develop reliable technologies to rapidly diagnose TB, MDR and XDR in the general population.
- Drugs – Evaluate utility of existing drugs for TB, and accelerate the development of new drugs.
- Basic studies – Improve understanding of the biology, immunology and epidemiology of drug-resistant TB strains in HIV-infected and uninfected populations.
- HIV/AIDS – Improve understanding of the effect of HIV co-infection on the development of drug resistance in TB.
- Prevention – Develop new and more effective vaccines and chemoprevention strategies for all forms of TB.

Feedback from extramural reviewers of the draft research agenda for MDR/XDR-TB has emphasized the importance of paying attention to special populations, diagnostics, biomarkers, and collaboration among TB and HIV researchers. Dr. Sizemore invited ARAC members to send their own comments and suggestions for inclusion in the next draft of this research agenda.

Discussion

Dr. El-Sadr invited comments from the presenters and invited discussants as well as committee members, asking them to focus on research priorities for NIAID.

At the beginning of the discussion it was reiterated that the research agenda should be written in a tone that reflects the urgency of the situation, with an emphasis on establishing goals that can be completed in the short term to facilitate immediate action. This "near-term" response would have to be crafted in a way where it would provide the foundation on which additional long-term programs could be built. There was agreement that a better understanding of transmission and latency is urgently needed. Improved communication and coordination of resources among current researchers in all areas of HIV and TB research – diagnostics, drug development, treatment – is also encouraged to ensure that scientific progress in translational research can be expected within the current NIAID budget. This will ensure that the community is well poised to expand coordinated and well integrated research programs if additional funds become available. It was also argued by some participants that progress will not come without political leadership and they encouraged communities and advocates to discuss needs for expanded TB and HIV/TB research.

Overall comments and suggestions are outlined below.

1. *Knowledge gaps in current approaches to new diagnostics*

- Diagnostic research is not an area that is fully embraced by the scientific community and despite open initiatives for diagnostic research and development, few academic labs are participating.
- There is a need for better diagnostics to develop epidemiological statistics.
- Better diagnostics are also needed to identify drug resistance and inform response to therapeutics.
- Centers of excellence in laboratory diagnosis may be one way to increase interest in the community to engage in diagnostic research and development.
- The use of systems approaches that integrate genomics, instrumentation, analytics, etc. should be encouraged.
- TB grantees should be encouraged to collaborate with investigators who have expertise in genomics, immunology and/or microchip technology on diagnostics efforts.

2. *New drugs in the pipeline and path to approval*

- There is a clear and unmet need for new second-line medications.
- NIAID should consider convening a panel to discuss new approaches, including a re-assessment of the pharmacology of current drugs, to developing shortened regimens for treatment of TB to facilitate adherence and reduce the risk of development of drug resistant TB.
- A major new global investment is needed for drug development.
- NIAID should ensure that particular attention is given to drug-drug interactions with ARVs, which may be a contributing factor in the development of drug resistance in TB and HIV/TB treatment.

3. *Novel clinical trial designs for HIV/TB and MDR-TB*

- NIAID funded investigators should leverage existing clinical trials infrastructure for HIV to facilitate studies in TB/HIV.

- The newly funded HIV/AIDS clinical trials networks should consider prioritizing HIV/TB research with special attention to pediatric populations, when designing studies to be undertaken during the current funding period.
- Clinical trials comparing Optimized Background Therapy [OBT] versus OBT-plus-study-drug for MDR-TB, similar to studies done in extensively drug-experienced patients with HIV, should be encouraged to benefit from lessons learned in HIV therapeutic trials.
- Apply new designs and methodologies such as Bayesian and stochastic designs to conduct high quality clinical trials with fewer patients and at lower costs.

Dr. El-Sadr summarized the discussion as follows:

- The MDR/XDR-TB situation is urgent and requires a new approach to facilitate a rapid response.
- The draft research agenda needs to reflect this urgency by clearly articulating the most urgent research priorities.
- The research priority areas identified during this meeting, and already contained in the research agenda, include:
    - Diagnostics
    - Biomarkers
    - Drug Development
    - Transmission and infection control
- Research in HIV/TB, including drug resistant forms of TB should be encouraged within the HIV/AIDS clinical trials networks, along with an emphasis on special populations, i.e., pediatrics.
- Coordination of research responses between US and international agencies and other government programs that are implementing treatment and research programs, e.g. PEPFAR, should be strengthened to leverage existing and future funding and infrastructure provided by public and private agencies.
- Program Announcements that re-articulate NIAID's TB program goals would be a good vehicle to encourage investigators to focus on research questions identified in the research agenda; NIAID is encouraged to revisit two previously proposed concepts that were supported by ARAC regarding HIV/TB and re-evaluate them in the context of the overall extramural NIAID TB program infrastructure.
- ARAC as well as the MID Council Subcommittee request regular updates on this topic at their upcoming meetings.

VII. ADJOURNMENT

The meeting of the Council was adjourned at 5:30 p.m., on Monday, May 21, 2007.

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

_____-s-_____ **__7/26/07_____**

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

_____-s-_____ **__7/22/07_ ___**

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.