NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

January 28, 2008

The 158th meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, January 28, 2008, 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. Ann Arvin
Dr. Barbara Baird
Dr. Robert Brooks
Dr. Carol Carter
Dr. Satya Dandekar
Dr. Kathryn Edwards
Dr. Sharon Kiely
Dr. Martin Myers
Dr. Shelley Payne
Dr. Louis Picker
Dr. Regina Rabinovich
Dr. Marc Rothenberg
Dr. Gary Schoolnik
Dr. Megan Sykes
Dr. David Wilkes

***Ex Officio* Members Present:**

Dr. Anthony Fauci
Dr. Ronald Valdiserri
Major General George Weightman
(On behalf of Lieutenant General Eric Schoomaker)

Council Members Absent:

Dr. Richard Insel
Dr. Martin Rosenberg
Dr. Christel Uittenbogaart

***Ex Officio* Members Absent:**

Dr. Mitch Cohen
Lieutenant General Eric Schoomaker

***Ad Hoc* Members:**

Dr. Beth Bell
Dr. Thomas Platts-Mills

NIAID Senior Staff:

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

I. REVIEW OF GRANT APPLICATIONS

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

Funding Actions: The Council reviewed 2,288 research and training applications with primary assignment to NIAID for a requested amount of $778,179,089 in first-year direct costs and recommended approval of 318 applications for $169,472,842 in first-year direct costs. Five Method to Extend Research in Time (MERIT) awards were recommended for approval.

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

Dr. Fauci opened the Council session by welcoming visitors to the meeting. He announced the appointment of five new Council members: Dr. Ann Arvin, Stanford University; Dr. Carol Carter, State University of New York at Stony Brook; Dr. Louis Picker, Oregon Health Sciences University; Dr. Regina Rabinovich, Bill & Melinda Gates Foundation; and Dr. Christel Uittenbogaart, University of California, Los Angeles. Council members Drs. Uittenbogaart, Rosenberg, and Insel and, *ex officio* members, Dr. Mitchell Cohen and Lieutenant General Eric Schoomaker were unable to attend the meeting. Major General George Weightman attended on behalf of LG Schoomaker.

Dr. Fauci introduced two *ad hoc* Council members, Dr. Beth Bell, Centers for Disease Control and Prevention, and Dr. Thomas Platts-Mill, University of Virginia.

Dr. Fauci offered congratulations to Lieutenant General Eric Schoomaker on his appointment as Surgeon General and Commander of the U.S. Army Medical Command.

Consideration of Minutes of Previous Meeting
The minutes of the September 27, 2007, meeting were considered and approved as written.

Consideration of Operating Procedures
The 2008 Council operating procedures were considered and approved.

Staff and Organizational Changes
In the Division of Microbiology and Infectious Diseases, Dr. Shy Shorer has been appointed director of the Office of Clinical Research Affairs, and Dr. Barbara Mulach is now the director of the Office of Scientific Coordination and Program Operations.

Three appointments have been made in the Office of Communications and Government Relations. Dr. Jill Harper is now chief of the Legislative Affairs and Correspondence Management Branch. Tori Matthews has been selected as chief of the Digital Policy and Information Office. Marg Moore has been named chief of the Freedom of Information Office.

In the Office of Technology Development, three appointments have been made. Dr. Vince Feliccia has been appointed chief of the Inventions Branch, Dr. Mukul Ranjan is now the chief of the Intramural Agreements Branch, and Cindy Fuchs has been selected as chief of the Extramural Agreements Branch.

In the Office of Ethics, Leonard Ross has been named chief of the Conflicts of Interest Analysis Team, and Shareece Gantt has been appointed chief of the Financial Disclosure Team.

Steven Smith has joined NIAID as director of the Office of Global Research. In the Office of Administrative Services, Marie Hirsch has been selected as chief of the Vaccine Research Center Administrative Management Branch.

Tributes and Awards

Several NIAID scientists were recognized for recent honors and awards they have received. Dr. Thomas Quinn was elected a Fellow of the American Association for the Advancement of Science. Two NIAID intramural scientists were named NIH senior investigators: Dr. Lou Miller and Dr. Malcolm Martin.

Dr. Fauci congratulated Drs. Richard Koup and Daniel Douek of the NIAID Vaccine Research Center for receiving the 2007 World AIDS Day Award.

Budget Update

On December 26, 2007, President Bush signed into law the Consolidated Appropriations Act of 2008, which includes the FY 2008 budget for NIH. NIH received a total of $29.2 billion, a 1.1 percent budget increase over FY 2007. NIAID received $4.6 billion, an increase of $193 million or 4.4 percent over FY 2007. NIAID is required to contribute $196 million over the FY 2007 amount to the Global Fund to Fight AIDS, Tuberculosis, and Malaria. After accounting for the Global Fund increase, the NIAID FY 2008 research budget is $2.8 million below the FY 2007 level.

NIAID has taken steps to reduce any negative impact the budget will have on investigators and the payline for investigator-initiated research. The Institute is providing additional support for new investigators by setting their payline for unsolicited R01s at two percentile points above our traditional payline.

Legislative Update

On September 20, 2007, Dr. Fauci briefed members of the HHS pandemic influenza contract steering committee about various strategies to develop influenza vaccines. On December 5, 2007, he participated in a briefing on NIH activities that relate to the President's Emergency Plan for AIDS Research. Dr. Carl Dieffenbach and Dr. Peggy Johnston briefed the staff of the Committee on Oversight and Government Reform in the House of Representatives on the status of the HVTN 502 (STEP) HIV vaccine study.

Recent congressional interest in biodefense and related programs prompted several hearings. Dr. Hugh Auchincloss testified at a hearing entitled "Germs, Viruses, and Secrets: The Silent Proliferation of Bio-Laboratories in the United States." Dr. Richard Hatchett and Dr. David Yeskey, HHS deputy assistant secretary for preparedness and response, testified at a congressional hearing and responded to questions regarding NIH on medical countermeasures against radiological and nuclear attacks.

Dr. Fauci thanked NIAID staff for their assistance with congressional briefings. In December and January, Dr. Richard Hatchett, Dr. Michael Kurilla, and Deborah Katz participated in three congressional briefings related to biodefense issues.

Other Information Items

Dr. Fauci gave an overview of recent developments in the area of emerging and re-emerging infectious diseases, with a major focus on antimicrobial resistance. NIH is working with other agencies to update a Public Health Action Plan to Combat Antimicrobial Resistance. The Research Agenda of the National Institute of Allergy and Infectious Diseases in Antimicrobial Resistance is in press in the Journal of Infectious Diseases and will be released soon.

Dr. Fauci recognized the passing of Merle Sande, a respected figure in the history of HIV/AIDS, who was the chief of medicine at San Francisco General Hospital when the first cases of HIV were discovered.

Two of the top three medical breakthroughs of 2007 were funded by NIAID. At the top was medically supervised adult male circumcision, which can protect men from HIV infection, and number three was development and licensure of the first human vaccine against H5N1 avian influenza.

On March 25, 2008, NIAID will hold a summit on HIV vaccine research to reexamine the HIV vaccine research portfolio with an emphasis on attaining the appropriate balance between discovery and development.

Dr. Fauci also reported on activities in malaria, tuberculosis, influenza, and allergy, immunology, and transplantation.

III. GUEST SPEAKER – Henry Masur, M.D., Chief, Critical Care Medicine Department, Warren Grant Magnuson Clinical Center, NIH - MRSA: Current Status in the United States

Dr. Masur summarized the scope of the problem, clinical implications, and how to approach threat reduction to methicillin-resistant *Staphylococcus aureus* (MRSA).

Statistics show that a substantial number of people in the U.S. are colonized with MRSA, which creates a reservoir for potential transmission and the development of invasive disease in the hosts. Dr. Masur presented the differences in the types of diseases caused by community-associated versus hospital-acquired strains of MRSA and noted that the hospital-acquired strains are more invasive.

Dr. Masur discussed factors that contribute to the spread of MRSA. Areas where we need better information include host and microbial factors that cause invasive disease, threat reduction, rapid screening tests, behavior modification, and antimicrobial management.

It is important to increase the investment in antibiotic research as organisms continue to develop drug resistance.

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

Thomas Palker, Ph.D. Dr. Palker joined the Basic Immunology Branch in December 2007 as a Program Officer. He received his bachelor's and doctorate degrees from the University of Connecticut. At Duke University Dr. Palker did his post doctoral fellowship and began a research career with Dr. Barton Haynes. He then remained on Duke's faculty and held a joint appointment as an Associate Research Professor in the Department of Medicine and an Assistant Professor in the Department of Immunology. He worked at Merck & Co. for a number of years and was a scientific review administrator with NIAID's Scientific Review Program prior to joining DAIT.

SCIENTIFIC INITIATIVES

Request for Information (RFI): Registry and Repository for Primary Immunodeficiency Diseases (NOT-AI-07-047): To develop a portfolio of basic and preclinical research projects, create an educational and mentoring program in primary immunodeficiency diseases, maintain and modify the existing registry for primary immunodeficiency diseases, and create a repository for PID samples.

Medical Countermeasures to Enhance Platelet Regeneration and Increase Survival Following Radiation Exposure (RC1) (RFA-AI-07-036): To accelerate the development of safe and effective medical products to mitigate and treat thrombocytopenia and to enhance platelet regeneration after radiation exposure from radiological and nuclear terrorist attacks. Specifically, this new initiative will support research and development of promising new approaches and medical products to enhance platelet regeneration and yield improved survival.

BARDA/NIAID Medical Countermeasures to Mitigate and/or Treat Ionizing Radiation-Induced Cutaneous Injury: Project Bioshield (RC1) (RFA-AI-07-037): To accelerate the development of safe and effective medical products (including but not limited to devices, materials, drugs, neutraceuticals, cytokines or cytokine inhibitors, free radical scavengers, anti-inflammatory agents, cellular therapy, etc.) to mitigate or to treat cutaneous injury arising from accidental or intentional exposure to ionizing radiation. Specifically, this new initiative will support research and development of the most promising new approaches and medical products to mitigate and/or treat radiation-induced cutaneous injury.

Radiation Combined Injury: Radiation Exposure in Combination with Burn, Wound, Trauma or Infection (Phased Innovation Award [R21/R33]) (RFA-AI-07-038): To support research into the mechanisms and biological effects of radiation exposure combined with other injuries such as burn, wound, trauma or infection, and development of safe and effective countermeasures for radiation combined injuries.

Mechanisms, Diagnosis and Treatment of Radiation Injury from a Nuclear Accident or Terrorist Attack (R01) (RFA-AI-07-039): To support research on: 1) establishment of mechanisms of radiation damage to cells and tissues; 2) identification of radiation exposure-specific biomarkers; 3) development of biodosimetry methods and devices for triage of large populations in the wake of a nuclear or radiological event; and/or 4) development of medical countermeasures to mitigate and/or treat radiation injury.

BARDA/NIAID Medical Countermeasures to Mitigate and/or Treat Ionizing Radiation-Induced Pulmonary Injury: Project Bioshield (RC1) (RFA-AI-07-040): To accelerate the development of safe and effective medical products (including but not limited to devices, materials, drugs, neutraceuticals, cytokines, free radical scavengers, anti-inflammatory agents, cellular therapy, antifibrotics, etc) to mitigate or to treat pulmonary injury arising from intentional or accidental exposure to ionizing radiation Specifically, this new initiative will support research and development of the most promising new approaches and medical products to mitigate and/or treat radiation-induced pulmonary injury.

Adjuvant Development Program (RFP-BAA-NIH-NIAID-DAIT-08-11): To further develop promising vaccine adjuvant candidates known to function by signaling through receptors of the innate immune system.

Exploratory/Developmental Investigations on Primary Immunodeficiency Diseases (R03) (PAR-07-447): To support small grants in primary immunodeficiency diseases focusing on ex vivo studies with human specimens and on studies with current or new animal models, including novel clinical strategies for detecting, identifying the molecular basis of, or developing innovative therapies for primary immunodeficiency diseases.

Exploratory/Developmental Investigations on Primary Immunodeficiency Diseases (R21) (PAR-07-446): To support innovative exploratory/developmental investigations in primary immunodeficiency diseases focusing on ex vivo studies with human specimens and on studies with current or new animal models including novel clinical strategies for detecting, identifying the molecular basis of, or developing innovative therapies for primary immunodeficiency diseases.

DIVISION ACTIVITIES

Medical Countermeasures against Nuclear Threats: Decorporation Agents Workshop: On September 17-18, 2007, NIAID sponsored a two day meeting to discuss the research and development of new radionuclide decorporation agents to facilitate the elimination of internal radionuclide contamination in a mass casualty radiological event. The workshop agenda included a summary of the available historical data and information, a discussion of the future research and development pathways and requirements for FDA licensure of decorporating agents. Participants included staff from several government agencies, such as NIH, FDA, DHS, DHHS, FDA, and representatives from academic institutions throughout the US.

Grants Awarded: Medical Countermeasures to Restore Gastrointestinal Function after Radiation Exposure: Under Project Bioshield (RC1) (RFA-AI-07-013) ten 18-month grants were awarded in August and September 2007 totaling $8 million. To accelerate the development of safe and effective medical products to prevent, mitigate and treat the gastrointestinal injury and to restore gastrointestinal function after radiation exposure from radiological and nuclear terrorist attacks. The following institutions/companies are recipients of this grant funding: Children's Hospital and Research Center at Oakland, Duke University, RxBio, Inc., University of Medicine and Dentistry of New Jersey (2 awards), Fred Hutchinson Cancer Research Center, University of Arkansas for Medical Sciences, University of Rochester, University of Maryland at Baltimore, and University of Tennessee Health Science Center.

Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases: This Broad Agency Announcement (RFP-BAA-NIH-NIAID-DAIT-07-34) solicited proposals 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. Contracts were awarded to the Benaroya Research Institute at Virginia Mason and the La Jolla Institute for Allergy and Immunology on September 26, 2007. A contract kick-off meeting was held with the investigators on December 7, 2007 to launch the studies and establish shared methods for laboratory analysis and clinical data collection.

2007 Annual Asthma and Allergic Disease Cooperative Research Center (AADCRC) Meeting: On September 18-19, 2007, the NIAID sponsored a one and a half day meeting to assemble investigators from the 15 NIAID-funded Centers and provide a forum for the AADCRC researchers to present data from the first year of the program. This meeting included co-investigators and students as well as the Centers' Principal Investigators, and incorporated a poster session to promote increased data-sharing and collaboration among the Centers.

NIAID New Investigator Workshop: On October 15-16, 2007, the three extramural divisions of the NIAID organized a two day meeting for first-time R01 and R21 grantees. The goal of this workshop was to provide new investigators with the skills and tools they need to prosper as independent scientists and to compete successfully for future NIH grants. Discussion topics included time, personnel and financial management, as well as strategies for career advancement and accessing NIH resources. Division-specific breakout sessions that gave these new investigators the opportunity meet informally with their NIAID Program Officers were also held.

Systems Biology Approach to Immunity and Inflammation: NIAID awarded a five-year contract to support a systems biology approach to immunity to The Scripps Research Institute in collaboration with the Institute for Systems Biology (Seattle, WA), Stanford University (Palo Alto, CA), and Australian National University (Canberra, Australia). High though-put mouse models in conjunction with genomics and proteomics approaches will be used to study immune responses to infection with NIAID Category A, B, and C priority pathogens. This research builds on a highly successful cooperative agreement funded by NIAID in 2003 to The Scripps Research Institute. The systems biology analysis is based on high-throughput screening of novel mouse models for identification of key regulatory genes. The current studies are supported by detailed genomics, proteomics, computational biology and bioinformatics that focus on transcriptional regulation and complemented by novel signaling assays. Human correlation studies will be done to analyze a subset of the immune regulatory genes identified in the mouse using human cells. This collaboration will lead to an understanding of novel gene products' functions in the innate and adaptive immunity to infection.

Population Genetics Analysis Program: The annual meeting of this NIAID biodefense program was held on October 22-23, 2007. Highlighting progress in identifying associations between immune response gene polymorphisms and outcomes of infection or vaccination was discussed. Areas of research include smallpox, influenza, tuberculosis, West Nile virus, and anthrax.

Immune Epitope Database and Discovery Contracts: The fourth Annual Immune Epitope Database and Discovery annual meeting was held on November 14-15, 2007. The meeting provided an opportunity for the contractors of the Immune Epitope Database and Analysis Resource (IEDB) and the Large Scale Antibody and T Cell Epitope Discovery programs to present their research and discuss future plans and collaborative efforts. Significant progress was achieved by many of the contractors. For example, the IEDB completed curation of the relevant epitope references for NIAID Category A-C priority pathogens and emerging/re-emerging infectious diseases. In terms of epitope discovery, novel T cell epitopes were identified for Mycobacterium tuberculosis, Influenza A, vaccinia virus, and several arenaviruses; and improvements to MHC class I epitope prediction algorithms were reported.

Immune Mechanisms of Viral Control Program Kick-Off Meeting: On November 27-28, 2007, the NIAID convened a meeting to bring together the researchers recently funded under the new Immune Mechanisms of Viral Control Program. The session topics were predominately divided by the type of organism involved in the project. Each investigator participating in the meeting presented an overview of the project and answered questions regarding the research plan. The intent of the meeting was to provide a "big picture" view of the program to NIAID staff as well as facilitate future collaborations among this group of researchers.

Financial Solvency & Writing a Successful NIH Grant: On November 9, 2007 a mentoring session was held for young investigators during the annual scientific meeting of the American College of Rheumatology in Boston, Massachusetts. Branch staff presented information on NIH loan repayment programs and on grantsmanship. The presentation was paired with a talk on "Balancing Family and

Career" given by a successful, young, academic clinician who is also a researcher, wife and mother. Attendees were guided to numerous grant-writing resources on the NIAID website and the response was enthusiastic from this group of up-and-coming medical researchers.

DIVISION ADVISORY COUNCIL PRESENTATION

Overview on the NIAID Asthma and Allergic Diseases Cooperative Research Centers

A programmatic presentation was given by Matthew Fenton, Ph.D., Chief, Asthma, Allergy and Inflammation Branch in which he discussed a **General Overview of NIAID Asthma and Allergic Diseases Cooperative Research Centers.** This was followed by Thomas A. Platt-Mills, M.D., Ph.D., Professor, Asthma and Allergic Diseases Center, University of Virginia who presented an **Update on the NIAID Asthma and Allergic Diseases Cooperative Research Centers.**

CONCEPT REVIEW

All concepts were presented and approved.

Ancillary Studies in Immunomodulation Clinical Trials

The objective is to incorporate immune mechanistic studies in clinical trials of immunomodulatory interventions for immune-mediated diseases, including, but not limited to: asthma and allergic diseases, autoimmune disorders, graft failure and graft-versus-host disease in transplantation, and clinical vaccine trials for infectious diseases. The renewal of this program will incorporate the same elements pioneered by the NIAID in FY 1999 to facilitate submission, peer review, and award of successful applications including expedited council approval. This renewal will also incorporate all aspects of RFA AI-05-028, released June 2005. Studies will focus on the inclusion of patients and utilization of patient samples for:

- evaluation of immunologic and other relevant parameters to facilitate the study and definition of immunological mechanisms underlying the intervention;
- definition and characterization of the mechanisms of disease pathogenesis;
- definition of surrogate/biomarkers of disease stage, activity, and therapeutic effect;
- definition and characterization of the human immune system; and
- evaluation of the underlying immune mechanisms of effective responses to candidate vaccines.

Proposed mechanistic studies associated with clinical trials supported by industry are particularly encouraged; however, clinical trials supported by any source, public or private, are eligible.

Immune Defense Mechanisms at the Mucosa

The objective is to support basic research projects on immune defense mechanisms and immune regulation at respiratory, gastrointestinal, and urogenital tract mucosal surfaces. This program will solicit innovative basic research applications with the potential to increase understanding of immunity at mucosal surfaces. The goal is to gain new insights that will facilitate future development of vaccines and immunotherapies to protect mucosal surfaces from infection and inflammation. Research areas to be supported would include, but are not limited to:

- Antigen sampling across mucosal epithelial barriers
- Role of the mucosal epithelium in innate immune signaling and antigen presentation
- Host immune mechanisms discriminating pathogens from commensals
- Function of specialized cells (e.g. Paneth cells, M cells) and structures (e.g. lymphoid follicles) in promoting mucosal immunity versus tolerance
- Immunoregulation at mucosal surfaces

Non-human Primate Reagent Resource
The objective is to competitively renew support of the Non-human Primate Reagent Resource. This Resource will accelerate immunological research in non-human primate (NHP) models of vaccine and adjuvant development, infectious and immune-mediated diseases, and transplantation by developing and providing reagents and technologies for (1) monitoring immune parameters, (2) *in vivo* modulation of the immune response, and (3) conducting immune-based mechanistic studies in NHPs. This Resource develops, evaluates, produces, and distributes a wide variety of new or improved reagents, including novel immune-based therapeutics, for use in NHP immune-mediated and infectious disease research. The Resource develops and distributes reagents that are not commercially available or, if commercially available, are not formulated for optimum use in NHPs. The Resource provides reagents for research use only and recovers production costs for supply of significant quantities of reagents. The NIAID designates the reagents for development and distribution based on the recommendations of an NIAID-appointed Scientific Advisory Committee. The NHP Reagent Resource also maintains a website and online database resource for the NHP community.

Clinical Trials in Organ Transplantation (CTOT)
The objective is to support a competing renewal of multi-center cooperative clinical trials evaluating modified or new therapeutic regimens in kidney, liver, and heart transplantation and the underlying immune mechanisms of graft acceptance or rejection. These trials will build upon new findings that become available as a result of work done in the first funding cycle, in the area of noninvasive predictors of rejection and immune quiescence. Equal emphasis will be given to increasing what is known about human transplant immunology and to the application of that knowledge in the clinical setting.

During the first funding cycle of CTOT, a number of clinical trials were developed and implemented to study: (1) non-invasive predictors of rejection or immune quiescence, based on gene expression profiles; (2) incidence, impact and treatment of de novo anti-HLA antibody production after kidney transplantation; and (3) the relationship between early and late immunologic events in liver, lung, and heart transplantation. In the proposed second funding cycle, investigators will build upon these results to evaluate novel and innovative therapeutic approaches for improving the outcome of solid organ or tissue transplantation in patients with end-stage organ disease. Examples of trials to be supported include, but are not limited to: (1) proactive, individualized immune modulation strategies based upon noninvasive immunologic profiles; (2) drug minimization protocols; (3) early phase evaluation of new pharmacologic agents that target known or newly discovered immune mechanisms; (4) definitive phase III clinical trials of immunomodulatory agents for organ or tissue transplantation. Multi-center studies will be designed and implemented using rigorous standards. A data and safety monitoring board will review the clinical protocols and adjunct studies.

Statistical and Clinical Coordinating Center for Autoimmune Disease Clinical Trials (SACCC-ADCT)
The objective is to recompete the biostatistical, data management and clinical trial operations contract that supports clinical trials of autoimmune disease. The Statistical and Clinical Coordinating Center for Autoimmune Disease Clinical Trials (SACCC-ADCT) provides complete biostatistical and operational support for clinical trials in the area of autoimmune diseases. Studies currently being supported include multiple autoimmune disease clinical protocols sponsored by the Autoimmunity Centers of Excellence (ACEs), as well as autologous stem cell transplantation for autoimmune disease. Support for these and other studies in autoimmunity will include: 1) statistical leadership for the design and analysis of clinical trials, including periodic safety and administrative reports, Data Safety Monitoring Board reports and final analyses; 2) clinical site monitoring and training; 3) data collection, management and quality

assurance programs; 4) regulatory support for IND and associated regulatory submissions, including serious adverse event data collection, evaluation and report preparation; 5) distribution and quality control of study products; and 6) support for technical and administrative functions of the clinical trial consortiums.

Reagent Development for Toll-Like and other Innate Immune Receptors
The objective is to support multi-disciplinary projects focusing on the development of specific reagents including, but not limited to, antibodies, small molecules, and fusion proteins to study the expression and physiological function of human Toll-Like Receptors (TLRs) and other innate immune receptors. Currently, there are few reagents available to study the expression and function of these receptors. Therefore, novel reagents developed under this solicitation will help researchers to study the patterns and kinetics of the expression and functional mechanisms of these important immune receptors both *in vitro* and *in vivo*.

This program will support multi-disciplinary projects focused on: (1) development of specific reagents for human TLRs and other innate immune receptors, such as NLR and RIG-1; and (2) study of the specificity and functions of these reagents. Investigators may choose to focus on the generation of natural or designer antibodies, small molecules, fusion proteins, or natural or synthetic compounds that specifically recognize and bind to human TLRs or other innate immune receptors. The goal is to develop reagents that can be used as specific tracers/markers with or without agonistic/antagonistic activities.

Rejuvenating the Aged Immune System
The objective is to support research projects that will focus on at least one of the following research areas:
1. the mechanisms underlying age-related deficiencies in bone marrow function and development of methods to correct such defects;
2. the mechanisms underlying age-related deficiencies in germinal center formation and activity, and development of methods to correct such defects; and
3. the mechanisms underlying thymic involution related to aging and development of methods to reconstitute normal thymic output of T cells.

This program will support basic and applied research to prevent or reverse the decline of naïve immune cell production and differentiation, including both adaptive and innate immunity, in the aged population. Research will incorporate the use of appropriate animal models and/or *in vitro* human cell/tissue cultures to understand the mechanisms related to decreased immune cell output and function in the elderly human population. An understanding of these mechanisms will be applied to the development of methods to reverse or prevent immune defects in the elderly.

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

Dr. Heilman welcomed the Subcommittee's three new members: 1) Dr. Ann Arvin, a professor of pediatrics, and microbiology and immunology at Stanford University School of Medicine, who also serves as Vice Provost and Dean of Research at Stanford University (Dr. Arvin's principal research interests include the human herpesviruses and childhood viral diseases and vaccines); 2) Dr. Regina Rabinovich, who was with DMID during the 1990s as Chief of DMID's Clinical and Regulatory Affairs group, and is currently with the Bill & Melinda Gates Foundation, where she leads their global health initiative; and 3) Major General George Weightman, who is the commanding general at the U.S. Army Medical Research and Materiel Command at Ft. Detrick. Dr. Heilman also introduced Dr. Beth Bell, who

joined the meeting as an *ad hoc* member of the Subcommittee. Dr. Bell is the Associate Director for Epidemiologic Research at CDC's National Center for Immunization and Respiratory Diseases.

She then informed the Subcommittee of several recent senior level appointments in DMID, including: Dr. Richard Gorman, appointed as the Acting Associate Director for Clinical Research in DMID; Dr. Shy Shorer, appointed Director of the Office of Clinical Research Affairs; Dr. Barbara Mulach, appointed Director of the Office of Scientific Coordination and Program Operations; and Dr. Barbara Laughon, who comes to DMID from the Division of AIDS and serves as the NIAID liaison to the Eli Lilly Not-For-Profit Partnership for TB Early Phase Drug Discovery. Dr. Heilman then referred to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their respective new hires.

Following Dr. Heilman's introductory remarks, Dr. Maria Giovanni, Assistant Director for Microbial Genomics and Advanced Technologies, briefly updated the Subcommittee on the NIH Human Microbiome Project, a new NIH Roadmap initiative started in 2007. The goal of this initiative is to characterize the human microbiome and study its influence on health and disease.

Dr. Carolyn Deal, Chief of the Sexually Transmitted Infections (STI) Branch, provided the Subcommittee with an update on DMID's STI program. She discussed the scope of the STI problem worldwide, and described current DMID STI research activities, spanning basic through clinical research, aimed at improving efforts to diagnose, prevent and treat STI infections.

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

Sexually Transmitted Infections (STI) Cooperative Research Centers
This initiative is a renewal of an existing cooperative agreement. The multidisciplinary, collaborative nature of the center program was viewed as an effective mechanism for developing tools and strategies for the control and prevention of STIs. This synergistic approach results in the ability of Center investigators to share knowledge and leverage resources, such as reagents and core testing capabilities. The Development Awards Program was viewed as an important training and mentoring component provided through the Center funding mechanism. As a group, the Centers provided service and leadership to the STI field. The Subcommittee unanimously approved the initiative.

Partnership for Point of Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings
This is a new initiative to stimulate product development for point of care diagnostic technologies for infectious disease-causing pathogens and toxins to be utilized in nontraditional health care settings. The requirement for industry participation was viewed as an appropriate stimulus for the creation of partnerships between infectious disease experts and bioengineers developing appropriate POC diagnostic technologies. The Subcommittee felt that projects funded through this initiative will benefit from NIAID staff input and oversight, which are required as part of this milestone-driven Cooperative Agreement funding mechanism. The subcommittee unanimously approved the initiative.

Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance
The concept is a new initiative that seeks to address the public health need to reduce antimicrobial resistance. The solicitation targets infectious diseases where improved treatment strategies could reduce the risk of antimicrobial resistance and preserve the effectiveness of existing antimicrobials. The subcommittee felt that this initiative is timely and vital to fill the gaps in the scientific community. The subcommittee unanimously approved the initiative.

Consortium for TB Diagnostics Tools and Strategies
This new initiative will establish a consortium of clinical research sites in TB endemic countries, using existing clinical infrastructure, to conduct clinical studies to evaluate new TB diagnostics. The Subcommittee felt that this contract addresses an important gap in TB diagnostic research and provides a valuable resource to the TB research community. The Subcommittee unanimously approved the initiative.

Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors
This new initiative addresses an important gap in the research and development pipeline for malaria, neglected tropical diseases, and their vectors. The Subcommittee felt that this initiative, which focuses on translational aspects, will stimulate appropriate research in the targeted areas. While it was noted that the scope of the concept is broad, it was also noted that only some diseases and vectors included in the initiative are mature enough for translational studies, the focus of this initiative. The Subcommittee unanimously approved the initiative.

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

Wafaa El-Sadr, M.D., M.P.H., M.P.A., Chair of the ARAC, welcomed the ARAC members, DAIDS representatives, and invited guests.

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

Dr. Dieffenbach welcomed three new ARAC members—Carol Carter, Ph.D., of the State University of New York at Stony Brook; Louis Picker, M.D., of Oregon Health and Science University; and Christel Uittenbogaart, M.D., University of California, Los Angeles (who was unable to attend). He also introduced two invited participants – Eric Hunter, Ph.D., of the Emory Vaccine Research Center; and Kevin Fisher, J.D., M.Sc., of the AIDS Vaccine Advocacy Coalition. Dr. Dieffenbach announced the recent death of Merle Sande, a former member of the ARAC.

Dr. Dieffenbach reported on the 2008 NIAID budget, which for the fifth straight year will be at level funding. Although NIAID received an increase of 4.4 percent over FY 2007, a required allocation to the Global Fund will result in an overall 0.1 percent decrease for the Institute.

The payline for R01s has eroded slightly in the past 4 years, but the Institute will continue to support a 2-percent differential payline for first-time grantees. NIAID continues to take steps to stabilize the payline by realigning funds from research contracts, intramural research, the Centers programs, and solicited research programs. Dr. Dieffenbach also presented success rates: in FY 2007 AIDS RPGs had a success rate of 35 percent compared to 23 percent in 2006; AIDS R01s had a steady success rate of 25 percent. DAIDS hopes to maintain success rate levels in the mid 20s for 2008.

Dr. Dieffenbach noted that the focus of today's meeting will be on HIV vaccine research – with an update on the results of the STEP trial and discussions that have taken place with the AIDS Vaccine Research Subcommittee, as well as a discussion of future plans in vaccine research.

VACCINE RESEARCH – UPDATE AND DISCUSSION

STEP Trial Results

Susan Buchbinder, M.D., Director, San Francisco Department of Health

Dr. Buchbinder reported on the status of the STEP trial (HVTN 502), a test-of-concept of the Merck trivalent HIV vaccine (MRK Ad5). The trial studied an admixture of three Ad 5 vectors in 3,000 volunteers in clade B regions. The study was designed to determine if the vaccine would, in persons with low levels of Ad 5 antibodies, either reduce HIV acquisition or lower the viral set point measured 3 months post-diagnosis. A second hypothesis was that the vaccine would reduce risk of acquisition or lower the viral set point for the whole population. Study participants include both men and women who were at high-risk of acquiring HIV in Australia, Brazil, Canada, the Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico and the United States.

On September 18, 2007, an independent Data and Safety Monitoring Board (DSMB) met to review interim data obtained from the volunteers who had low antibody levels against Ad 5 at the time of enrollment. The DSMB recommended that the trial as originally designed should be discontinued because the trial would not meet its efficacy endpoints. As a result of the DSMB review, NIAID, Merck and the HVTN agreed to cease immunizations with the investigational vaccine and continue scheduled follow-up site visits with all volunteers until the data could be more thoroughly evaluated and a course of action developed.

On November 7, 2007, additional analyses of the STEP data were presented at an open scientific meeting in Seattle. These analyses suggested that those study participants who received the vaccine may get infected with HIV more easily if they are exposed to the virus. This trend was more evident among those volunteers with higher levels of pre-existing immunity (antibodies) to Ad5 because of prior natural exposure to that particular type of cold virus. The HIV infections were mostly among men who have sex with men. Only one woman became infected with HIV during the trial, and only one heterosexual man acquired HIV. Therefore, there is little information about the effects of the vaccine in women or in heterosexual men.

A multivariate analysis of the STEP data assessing the potential influence of certain confounding factors, such as baseline Ad5 antibody levels, circumcision status, region of enrollment, age and reported risk behavior, on the potential for developing HIV infection was to be presented at the February 2008 Conference on Retroviruses and Opportunistic Infections. That analysis confirmed that, overall, male study volunteers who received the vaccine were approximately 1.6 times more likely to develop HIV infection than those who received placebo, although the reason for this unexpected outcome remains unclear.

The same Merck candidate HIV vaccine was also being tested in South Africa by the HVTN and the South African AIDS Vaccine Initiative in a separate NIAID-sponsored clinical trial known as HVTN 503 or the “Phambili” study. In contrast to the STEP study where the interim analysis was almost exclusively based on results in volunteers who were men who have sex with men, the Phambili study has primarily enrolled heterosexuals at high risk for HIV. The independent DSMB that oversees the Phambili trial met to review all available HVTN 503 and STEP interim findings and recommended that that trial also be stopped.

In discussion, the ARAC members suggested the possibility that other research on the effect of Ad 5 infection in the context of other conditions or vaccination could shed light on the STEP results. They encouraged the investigators to search for any factors that might have affected the outcome including circumcision (or lack of), condom use, and the possibility that unblinding of vaccine vs. placebo status by

the volunteers that might have been associated with changes in sexual risk behavior. In response to a question, Dr. Buchbinder noted that comparisons of viral load set point in men and women are difficult to make because only one woman in the trial became infected.

AIDS Vaccine Research Subcommittee (AVRS) Update
Susan Buchbinder, M.D., Director, San Francisco Department of Health

Dr. Buchbinder reported that the AVRS met on December 7, 2007, to discuss the STEP trial and future efforts. It posed the following questions:

- What are the implications of STEP for future NIH vaccine development?
- Is the process for establishing scientific priorities and access to STEP trial specimens adequate? Are the timelines acceptable?
- (For the future) From an efficacy perspective, is the candidate sufficiently different from other vaccine candidates and promising for further investigation?
- (For the future) Is there equipoise for proceeding with a Phase 2 test-of-concept trial with a vaccine regimen in Ad 5 seronegative individuals?

The AVRS members discussed implications for the vaccine field, considering STEP to be a failure of product. It considered many recommended analyses of the STEP results, such as studies of genome-wide associations and various parameters. Are the antibodies markers for another factor (s) that actually defines susceptibility? What are the differences in vaccine response in persons Ad 5 positive vs. negative? The AVRS considered the process and timeline for future laboratory studies. They discussed the substantial differences between the Merck and the VRC Ad 5 approaches, including differing Ad 5 backbones, inserts and CD8 responses.

The AVRS members discussed reasons for proceeding with the PAVE 100 test-of-concept trial and agreed that, in general, the DNA prime Ad 5 boost is sufficiently promising to warrant further study. They expressed concerns about the breadth of the response and suggested various ways to explore it. A meeting to review the redesigned PAVE trial is scheduled for March 3.

In discussion, the ARAC members wondered whether the revised PAVE trial would address safety and efficacy. Dr. Buchbinder stated that the PAVE planners likely will consider the STEP analyses in identifying subpopulations to include. She noted that persons investigating the STEP results will consider differences in polyfunctional cell response in the Merck and VRC methods. One ARAC member suggested examining behavior (e.g., immune response) in the mucosa in addition to the blood. Dr. Buchbinder suggested that important information about infection rates likely will have to come from non-clade B regions.

Next Steps
Margaret Johnston, Ph.D., Director, DAIDS Vaccine Research Program (VRP)

Dr. Johnston reviewed ongoing work and plans in terms of HIV vaccine research. In light of the STEP results, the DAIDS Vaccine Research Program (VRP) is monitoring other ongoing trials taking safety precautions where necessary and offering counseling to trial participants. Additional analyses of the STEP results are under way. A challenge for future plans is to ensure that the high-priority questions are answered.

The VRP is moving forward with simian vaccine studies to learn whether the potential for increased acquisition can be modeled in the SIV system. A meeting planned in spring 2008 will help further evaluate revised PAVE 100 trial plans. In addition, on March 25, NIAID will convene an HIV Vaccine Summit to obtain input from stakeholders about the HIV vaccine research portfolio; the Summit will feature panels on preclinical discovery and development, animal models, and clinical research.

Other groups are also convening meetings related to future vaccine research efforts: the AIDS Vaccine Advocacy Coalition (AVAC) will host a meeting at the February CROI meeting and the International AIDS Vaccine Initiative (IAVI) plans to hold a retreat to consider its agenda. In addition, DAIDS has been invited to participate in the UNAIDS Vaccine Advisory Committee meeting to be held in March in Bangkok and the NIAID Strategic Working Group will review the HIV Trials Network research agenda. DAIDS may also present at an FDA advisory committee meeting later this year. Finally, the Global HIV Vaccine Enterprise plans to hold a consultation on future directions.

Dr. Johnston indicated that DAIDS will listen to input from all of these groups, digest the information, and develop new programs targeting the most important scientific questions.

In discussion, the ARAC members queried DAIDS as to how trials of other adenovirus vaccines, for example, malaria vaccines, might progress in populations also at risk for HIV. Dr. Johnston suggested that until animal studies or additional human studies offer relevant mechanistic information, the safest approach was to confine adenovector trials those without pre-existing immunity to adenovirus. Dr. El-Sadr noted that by narrowing a study population, of course, reduces the generalizability of results. One question about the trial population is whether the participants who are adenovirus seronegative remain seronegative, and if not, what are the implications for those who seroconvert their adenovirus status during their study participation.

Dr. Picker raised the concern that the NIH grant program has a tendency to focus on seeking a product, such as a vaccine. Failed experiments can, in some cases, produce good new knowledge that can inspire pursuit of new avenues of research. Still, should the NIH/NIAID consider a shift in its funding philosophy to allow for more innovative but risky research that might end up with a negative result while producing helpful knowledge? Such a discussion would have to involve the Center for Scientific Review.

ARAC members also suggested that behavioral scientists be involved in trials and analysis, as in the case of STEP.

CONCEPT REVIEWS

Highly Innovative Technologies to Interrupt Transmission of HIV
Margaret Johnston, Ph.D., VRP, DAIDS

Dr. Johnston described this program to stimulate research on novel, high-risk, potentially high-impact approaches the might provide long-term safe protection from HIV acquisition. This new R01 initiative would have a first-year of $5.6 million (in one scenario), with 5–15 projects awarded. The award duration will be 3–4 years. The applications will be brief, featuring a research plan with no appendices and no preliminary data. Dr. Johnston provided examples of research topics the program would foster, such as the role of host proteins as immunogens and previously unexplored HIV encoded targets. The reviewers praised the program's emphasis on novel ideas, noting that it will encourage cross-discipline collaborations. They encouraged the program to include basic research that could link to intervention hypotheses.

The ARAC voted to approve the concept for this initiative with the modification that it not exclusively focus on the prevention of HIV acquisition; methods to prevent disease progression should also be included. Suggestions were made to change the title of the concept because "technologies" has a product connotation, but it was agreed that it would left to program staff to determine.

Rapid Virological Tests
Patricia D'Souza, Ph.D., DAIDS

Dr. Patricia D'Souza described this program to develop fully functional, FDA-approvable and licensable low-cost rapid point-of-care diagnostic device for identifying HIV-infected individuals in the presence of vaccine-induced HIV-1 specific antibody responses. It is a new concept using an N01 mechanism that would be solicited with a broad agency announcement. The first-year program cost will be $1.5 million (total program cost of $7.5 million), and the awards will be for 5 years. Dr. D'Souza indicated that the emphasis would be on making this diagnostic device appropriate for resource-limited settings. Goals of the program will be to develop systems that, at a minimum, are simple, detect fewer than 1,000 copies/ml, and have sensitivity greater than 90 percent and specificity greater than 99.5 percent. The reviewers stated that this concept will bridge a critical gap in the field but asked how the program will select test specifications. They questioned whether there would be sufficient funding to ensure the success of a lead candidate.

The ARAC members noted that some rapid tests are used overseas and that perhaps "point-of care" facilities should be defined better. Dr. D'Souza noted that there are no licensed rapid tests for nucleic acids and that this device was not intended to replace existing, FDA-licensed, nucleic acid tests, but rather to simplify future diagnostic algorithms. The group noted that the volume of blood used in testing will be an important factor, especially for children. The ARAC members approved the concept.

HIV Vaccine Design and Development Teams
James Bradac, Ph.D., DAIDS

Dr. James Bradac described this program to advance the development of promising novel-candidate preventive vaccines into human testing. The concept is a renewal with an N01 mechanism to be solicited with a broad agency announcement. The first-year program cost would be $5 million (total program cost of $29.6 million), and the awards would be for 5–7 years. The projects would feature consortia of academic and industrial scientists working and offerers would be encouraged to conduct clinical studies with NIAID-supported clinical networks. Dr. Bradac cited a need to move from studies of cellular response to studies of, for example, neutralizing antibodies. He reviewed the key resources and activities that the offerers would be required to consider. The reviewers characterized this as a successful program and a key element in the vaccine development strategy. They encouraged the program to ensure that coordination in non-human primate studies be extended to these studies to create consistency in immunogenicity and challenge models.

The ARAC members questioned the use of this concept strategy in light of other efforts and debated the concept of testing a "vaccine in a bottle." Dr. Bradac stated that this strategy would proceed only when the vaccine shows promise. Dr. Johnston added that DAIDS has discussed the program and established that the work must be unique. Dr. Picker proposed that the program be reconsidered after the upcoming HIV Summit meeting. Dr. Michael noted that this raises an old debate, basic research versus the development of "vaccine in a bottle." The ARAC members voted to defer their vote on this concept until

additional information is obtained from the HIV Summit meeting as well as other consultations on HIV vaccine research that are being planned.

Multicenter AIDS Cohort Study
Carl Dieffenbach, Ph.D., DAIDS

Dr. Dieffenbach described this ongoing cohort study to investigate the natural and treated history of HIV-1 infection in homosexual and bisexual men. The concept is a limited renewal and a U01 cooperative agreement mechanism solicited with RFAs. The first-year program cost would be $10 million (total program cost of $50 million), and the awards would be for 5 years. Dr. Dieffenbach noted that the program has been successful in revealing patterns of disease and has, for example, demonstrated the impact of HAART. He presented numbers for enrollment in the MACS cohort and noted areas of research being conducted or conducted in past years. The cohort includes HIV positive and HIV seronegative men, patients with varying duration of infection and treatment, and patients with heterogeneous treatment. The MACS is a phenotypically well-characterized cohort. Other institutes have issued RFAs that use MACS data.

Some ARAC members noted that the cohort size has been decreasing primarily because it is a closed cohort; but Dr. Buchbinder noted that new investigators have used the MACS cohort data to develop preliminary data for R01 applications and highlighted its value. The ARAC members approved the concept.

Methods for Prevention Packages Program
David Burns, M.D., M.P.H., DAIDS

Dr. David Burns described this program to develop new research strategies that will facilitate the design and testing of combination interventions to reduce HIV incidence in the near term. It is a new concept, using an R01 mechanism and would be solicited by RFA. The first-year program cost would be $4 million (total program cost of $16 million). Dr. Burns noted that the initiative will support collaborations between behavioral and biomedical clinical scientists, epidemiologists, mathematical modelers, and clinical trial design specialists. It will seek methodologies that enable us to determine the optimal combination of prevention interventions for a given population (“prevention packages”). The reviewers stated that the program can fill a critical gap by bringing together experts in various disciplines, but noted that the requirement of the use of mathematical modeling to devise prevention packages would increase the cost and complexity of projects. Coverage of high-priority populations should be maximized.

The ARAC members questioned the mathematical modeling component of the concept, proposing that it be encouraged but not required. Dr. Dieffenbach noted that this concept will allow for new approaches that tailor multidisciplinary interventions to target populations. Dr. Burns also noted that the projects could include international components. The ARAC members approved the concept with the modification that mathematical modeling not be required.

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

Dr. Margolis reported on the recent activities of the Strategic Working Group (SWG), whose purpose is to provide expert advice on strategic questions and scientific priorities for the clinical trials networks. Ambassador Mark Dybul provided an update on the President’s Emergency Plan for AIDS Relief (PEPFAR) program, and described some of the program’s accomplishments and the need for increased

interactions between the clinical trials networks and in-country PEPFAR teams to improve implementation activities. The SWG received a strategic update from the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) program. In addition, the HIV Prevention Trials Network (HPTN) described their proposed domestic research agenda and presented an international concept (HPTN 060) for review. Dr. Margolis reported that the next SWG meeting, in May 2008, will feature the presentation of an IMPAACT concept, a discussion surrounding the structure of future vaccine studies and a strategic update from the HIV Vaccine Trials Network (HVTN).

VII. ADJOURNMENT

The meeting of the Council was adjourned at 5:15 p.m., on Monday, January 28, 2008.

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

_-s-_ **3/10/2008**

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

Date

_-s-_ **3/7/2008**

Marvin R. Kalt, Ph.D.
Executive Secretary
National Advisory Allergy and Infectious Diseases Council
Director, Division of Extramural Activities
National Institute of Allergy and Infectious Diseases

Date

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