DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CENTER FOR RESEARCH RESOURCES

NATIONAL ADVISORY RESEARCH RESOURCES COUNCIL
MINUTES OF MEETING
JANUARY 27, 2000

The National Advisory Research Resources Council (NARRC) convened for its 114th session at 9:00 a.m. on Thursday, January 27, 2000, in Conference Room 10, Building 31, and adjourned at 3:45 p.m. Dr. Judith L. Vaitukaitis, Director, National Center for Research Resources (NCRR), National Institutes of Health (NIH), presided as Chair. The meeting was open to the public until 2:00 p.m, at which time it was closed to the public for the review, discussion, and evaluation of grant applications as provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of Public Law 92-463.[1]

COUNCIL MEMBERS PRESENT

Dr. Joseph Andrade
Dr. Kenneth I. Berns
Dr. Delwood C. Collins
Dr. Muriel T. Davisson
Dr. Chien Ho
Dr. Keith O. Hodgson
Dr. Michael M.E. Johns
Dr. Peter G. Katona
Dr. Peter O. Kohler
Dr. Norman I. Maldonado
Dr. Daniel E. Morse
Dr. Maria I. New
Dr. James H. Wyche
Ms. Sheila C. Zimmet, Esq.
Capt. Craig Hyams
Ex-Officio, DOD
Dr. William W. King
Ex-Officio, VA
Dr. Machi F. Dilworth
Liaison Member, NSF
Dr. Roland F. Hirsch
Liaison Member, DOE

COUNCIL MEMBERS ABSENT

Dr. Evangelia G. Kranias
Dr. Judith L. Swain
Dr. Burton A. Weisbrod
Dr. Donald E. Wilson

[1]For the record, it is noted that to avoid a conflict of interest, Council members absent themselves from the room when the Council discusses grant applications from their respective institutions or when a conflict of interest (COI) may occur. Members are asked to sign COI statements. This does not apply to "en bloc" actions.

SPECIAL INVITED GUESTS FOR OPEN SESSION:

Dr. Kristina Borror, Office of the Director, NIH
Dr. James Kushner, Professor of Medicine, University of Utah Medical Center, Salt Lake City, Utah
Dr. C. Max Lang, George T. Harrell Professor and Chairman, Department of Comparative Medicine, The Milton S. Hershey Medical Center, Hershey, Pennsylvania
Dr. Keith G. Mansfield, Chairman, Primate Resources, New England Regional Primate Resources Center, Harvard Medical School, Southborough, Massachusetts
Dr. Roger E. Meyer, Senior Consultant on Clinical Research, Association of American Medical Colleges and Clinical Professor of Psychology, Georgetown University, Washington, DC
Dr. Earl D. Mitchell, Associate Vice President for Multicultural Affairs, Oklahoma State University, Stillwater, Oklahoma
Dr. Pamela H. Mitchell, Elizabeth S. Soule Professor, Department of Biobehavioral Nursing and Health Systems, University of Washington
Dr. William R. Morton, Director, Regional Primate Research Center, Department of Comparative Medicine, University of Washington, Seattle, Washington
Dr. Inder Verma, Professor, Laboratory of Genetics, The Salk Institute, La Jolla, California

STAFF OF OTHER NIH ATTENDEES:

Dr. Sally Amero, CSR/NIH
Dr. Houston Baker, CSR/NIH
Dr. Eileen Bradley, CSR/NIH
Dr. Nelson Garnett, OER/OD/NIH
Dr. Stephen Groft, OD/NIH
Dr. Nancy Lamontagne, CSR/NIH
Dr. Heather Miller, OER/NIH
Dr. Arnold Revsin, CSR/NIH
Dr. Dick Swaja, OER/OD/NIH

OTHERS PRESENT:

Mr. Bruce Agnew, *Washington Fax*, Washington, DC
Mr. Steve Heinig, Association of American Medical Colleges,Washington, DC
Ms. Pamela Moore, *Capital Publications*, Alexandria, Virginia
Ms. Rebecca Spieler, *The Blue Sheet*, Chevy Chase, Maryland

I. Call to Order
Dr. Judith Vaitukaitis, Director, NCRR

Dr. Vaitukaitis welcomed NARRC members and guests to the 114th meeting of the Council. She announced that the following Council members would be unable to attend: Drs. Evangelia Kranias, Judith Swain, Burton Weisbrod, and Donald Wilson. She introduced a new Council member from the Department of Veterans Affairs, Dr. William W. King, Director and Veterinary Medical Officer of the Veterinary Medical Unit at the Hines VA Hospital in Hines, Illinois. She then introduced the invited guests.

II. Consideration of Minutes

The minutes of the September 9, 1999, NARRC meeting were approved as written.

III. Future Meeting Dates

Dr. Vaitukaitis announced that the next NARRC meeting will be held on Thursday and Friday, May 18 and 19, 2000. A one-day meeting will be considered, and Council members will be notified when a decision is made.

IV. Personnel Update

Dr. Vaitukaitis announced that Dr. Varmus appointed Dr. Stephen E. Straus as Director of the National Institutes of Health (NIH) National Center for Complimentary and Alternative Medicine. Dr. Phillip Gorden, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) stepped down to resume scientific research. Dr. Gorden is succeeded by Dr. Allen M. Spiegel, who previously headed the Metabolic Diseases Branch at NIDDK. Dr. Harold Varmus resigned as the Director of NIH on December 31, 1999, to accept a position as President and Chief Executive Officer of the Memorial Sloan-Kettering Cancer Center. Dr. Ruth Kirschstein was appointed Acting NIH Director on January 1, 2000.

Dr. Vaitukaitis also announced recent NCRR personnel actions as follows: Dr. Leo Whitehair, former Director of NCRR's Comparative Medicine area and Dr. Bela Gulyas, Director of NCRR's Office of Review retired January 1, 2000. Dr. Gulyas is succeeded by Dr. Charles Hollingsworth, who previously served as Deputy Director in the Office of Review. Dr. Sidney McNairy was selected as NCRR's first Associate Director for Research Infrastructure. Dr. Michael Marron was selected as Associate Director for Biomedical Technology. Dr. Amy Swain, a Health Scientist Administrator, joined NCRR's Biomedical Technology area. Dr. John Meyer was selected as Deputy Director of the Office of Review. NCRR has three new Scientific Review Administrators: Drs. C. William Angus, Camille M. King, and Sybil A. Wellstood.

V. Legislative Update

Dr. Vaitukaitis directed the Council's attention to a summary of recent Federal legislative activities.

VI. Budget Update

Dr. Vaitukaitis reported that the Presidents's Fiscal Year (FY) 2000 budget request was submitted to Congress in early February 1999. She described the House and Senate proposals for NIH and NCRR funding levels, including specific NCRR programs targeted for increases. She reported that the final FY 2000 NIH appropriation is $17.9 billion, a 14.7 percent increase over FY 1999. NCRR's FY 2000 appropriation was $680.2 million, a 22.6 percent increase. But, an across-the-board rescission reduced this level for NCRR to $676.6 million, which includes $72.5 million for the facilities construction program, $39.5 million for Institutional Development Awards, and $14.5 million for the Science Education Partnership Awards (SEPA) Program. This increase in the SEPA Program will allow NCRR, which has been urged by Congress to increase the public's understanding of health and medical sciences, to emphasize awards to science centers and museums nationwide. The remainder of NCRR's budget increase will be distributed among its other programs.

VII. Update on NIH Chimpanzee Management Program (CHiMP) Activities Dr. Ray O'Neill, Comparative Medicine, NCRR

Dr. O'Neill provided a brief history of chimpanzees in biomedical research and then described the NIH Chimpanzee Management Program (CHiMP). In 1986, researchers considered chimpanzees to be a critical animal model to study HIV. Therefore, NCRR established a breeding program to provide animals that could be used in HIV-1 virus research. The breeding program was very productive, but the combination of an increase in chimpanzees and less-extensive research use than expected, created a surplus of chimpanzees, and a substantial management problem. To address the management problem, in 1994 NIH requested advice from the National Research Council (NRC), an arm of the National Academy of Sciences. In 1997, the NRC published a report entitled, *Chimpanzees in Research: Strategies for Their Ethical Care, Management and Use*. This report formed the basis of the NIH CHiMP, which NCRR administers. In 1998, NCRR published the NIH CHiMP plan. Dr. O'Neill updated Council on eight major elements of this plan: (1) Develop, implement, and administer the ChiMP; (2) Consolidate the preexisting facilities; (3) Establish a Working Group of nongovernment experts of the National Advisory Research Resources Council; (4) Impose a breeding moratorium at the NCRR-supported CHiMP facilities; (5) Improve the database that contains pertinent data on chimpanzees in U.S. biomedical research; **(**6) Receive support from

multi-NIH components for the ChiMP; (7) Determine the number of chimpanzees in U.S. biomedical research; and (8) Assess the physical capacity of existing and future research facilities.

Dr. O'Neill said that in addition to efforts by NIH and other Federal agencies to manage chimpanzees in biomedical research, Representative James Greenwood (R-PA) has introduced H.R. 3514 to relocate some chimpanzees to sanctuaries. If passed, the Bill would provide Federal funding for maintenance of chimpanzees deemed as "surplus" in terms of their future use in breeding or research. Hearings are expected on this Bill in early 2000.

VIII. Concept Clearance: Research Centers in Minority Institutions (RCMI) Medical Student and Clinical Research Scholars Programs
Dr. Sidney McNairy, Associate Director, Research Infrastructure, NCRR

NCRR provided two concept clearances for Council's recommendation: (1) The RCMI Mentored Medical and Veterinary Student (RMMVS) Program, which would be a one-year program for medical and veterinary students to mentor clinical research at RCMI-Clinical Research Centers, General Clinical Research Centers, or additional appropriate settings for veterinary students. The program director and a clinical investigator would serve as student mentors. (2) The RCMI Clinical Research Scholars (RCRS) Program would be a one-year or two-year program for candidates with an M.D., D.V.M., Ph.D., or D.D.S., with potential to fulfill requirements for a M.S. or M.P.H. An investigator will serve as mentor and will be required to work closely with the awardee to define and oversee career development. Council endorsed both concepts.

IX. Recommendations from the Bioinformatics in Clinical Research Meeting
Dr. James Kushner, Professor of Medicine, University of Utah Medical Center, Salt Lake City, Utah

Dr. Kushner provided highlights from the November 7-9, 1999, General Clinical Research Centers Bioinformatics Conference. Dr. Kushner said that 182 individuals, including 46 clinical investigators, attended the conference. The conference included general session presentations; working group sessions; reports from the working groups; and a steering committee report. Working group topics included training and education; standards for data collection and management; incorporation of informatics in protocol development; and development of new technologies. Recommendations from the working groups included the definition of informatics versus bioinformatics; protocol development (data management plan); a common data dictionary for GCRCs; data security and encryption; advisory committee review of protocol data plans (similar to biostatistical review); additional FTEs for data management planning, database development, and technology development; and a Web site for GCRC resources (hardware, software, expertise). Three key recommendations were the need for a data management plan in

protocol development; common data dictionary; and multi-center research data transfer, confidentiality and encryption. The conference had two target audiences: (1) informatics core managers and biostatisticians; and (2) clinical investigators. The working groups' recommendations included expanding the size of the meeting; conducting simultaneous working sessions and general sessions; promoting practical training for both audiences; and endorsing the recommendations of the working groups.

X. National Gene Vector Laboratories (NGVL) Advisory Panel Recommendations
Dr. Inder Verma, Professor, The Salk Institute, LaJolla, California

Dr. Inder Verma summarized the findings of an ad hoc panel that convened October 26 and 27, 1999, in Bethesda, Maryland, to assess the success and limitations of the NIH NGVL Program and to develop guidelines for the program's future. The panel, comprised of nine gene therapy and biological therapeutics experts, heard a series of presentations from current NGVL directors and researchers who have used NGVL facilities for vector production, researchers affiliated with non-NGVL facilities that produce clinical-grade gene vectors, and experts in related fields.

Dr. Verma prefaced his report by explaining that the production of effective gene-delivery systems remains a roadblock to successful gene therapy. He said that in 1994, the United States had one contract manufacturer of clinical-grade vectors and one academic producer at the University of Michigan. So in l995, through a competitive grant process, NIH established three NGVL's: Indiana University (retroviral vectors), the University of Michigan (nonviral vectors), and the University of Pennsylvania (adenoviral and adeno-associated viral vectors). Since the NGVL Program was launched, a number of additional facilities for clinical gene vector production have been established nationwide, in both industrial and academic institutions.

The NGVL ad hoc panel found that the current NGVL facilities have generally fulfilled their mission. Moreoever, since the clinical vector production infrastrucuture is already in place at a number of other institutions, there is an exceptional opportunity for building a strong national network that will promote scientific sharing and widespread use of these valuable gene vector facilities. Dr. Verma presented the following six broad areas where the NGVL Program could be modified to better meet the needs of the biomedical research community: (1) Expand the number of gene vector laboratories in the NGVL Program to six or eight production facilities at institutions that have General Clinical Research Centers. (2) Modify the composition of the NGVL Steering Committee to include representatives of the Food and Drug Administration (FDA), and to exclude NGVL directors as voting members. (3) Add a safety assessment, with FDA input, to the comprehensive NGVL proposal review process. Early input from FDA would streamline the approval process for moving vectors to clinical trials. (4) Encourage NIH grantees to utilize NGVL resources. The more the NGVLs are utilized, the more valuable they become as a centralized source of information and expertise. (5) Expand the scope of the NGVL

Coordinating Center to enhance outreach to the user community and to provide centralized services and information, such as a repository of reagents, distribution of Standard Operating Procedures, etc. (6) Ensure that adequate funding is available for services and resources that enable vector production, such as process development, quality-assurance, quality control assays, production of novel vectors, drug master files, and follow-up monitoring of clinical trials--all critical elements to the functioning of a clinical gene vector facility.

XI. Update of *Cost Analysis and Rate Setting (CARS) Manual* and Impact of Re-Interpretation of Circular A21 on Animal Research Facilities
Dr. C. Max Lang, The Milton S. Hershey Medical Center, Pennsylvania

Dr. Lang discussed the actions taken by the Committee on Revision of the Cost Accounting and Rate Setting (CARS) Manual. He identified several problems, including the need to remove animal resource centers from the category of specialized service facility, and the need to clarify terminologies, such as vivarium and animal-holding rooms. The manual clarifies the differences between per-diem rates versus rate schedule, cost versus charge, and load versus no-load. The CARS proposes three categories of costs: (1) facilities and administration (indirect) costs; (2) animal research facility direct costs; and (3) animal research facility internal support costs. The facilities and administration (indirect) costs would include depreciation of physical plant and fixed equipment, general administration, operations and maintenance of physical plant, procurement, and regulatory compliance. Animal research facility direct costs would include procurement processing, husbandry, and research technical services. Animal research facility internal support costs would include animal health care, cage washing, facility administration, maintenance and repair of movable equipment, and transportation. The outcomes of these changes will not be automatic because more detailed cost recording is needed, along with a space survey according to research activity. More interaction between the facility director and administration may also be required. However, this will result in consistency in the support of research, investigators knowing what they are paying for, and minimum increase in the cost to the government.

XII. NIH Human Pluripotent Stem Cell Guidelines
Dr. Kristina Borror, Office of the Director, NIH

Dr. Borror reported that the NIH Draft Guidelines on Research Using Human Pluripotent Stem Cells (hPSCs) was published in the Federal Register on December 2, 1999, and will be open for public comment for 60 days. These draft guidelines represent a continuation of the public consultation process concerning future directions of research utilizing hPSCs.

To ensure that research utilizing hPSCs is appropriately and carefully conducted, the NIH convened a Working Group of the Advisory Committee to the NIH Director. The working group was comprised of scientists, patients, patient advocates, ethicists, clinicians, and lawyers.

After reviewing and considering public comments, NIH will revise the NIH Draft Guidelines on Research Using hPSCs and will publish the final guidelines in the Federal Register. Until the final guidelines and the oversight process are completed, the NIH will not fund research using hPSCs derived from either human embryos or fetal tissue.

Research using hPSCs derived from early human embryos will be considered for funding only if investigators use cells derived from frozen embryos created for the purpose of infertility treatment and were in excess of clinical need. In addition, the investigator can offer no inducements, monetary or otherwise, for donated embryos. There must be a clear separation between the infertility treatment and the decision to donate embryos.

The draft guidelines specify what should be contained in the informed consent document for the donation of human embryos or human fetal tissue. In submitting an application or proposal for funding, investigators will be required to provide documentation showing compliance with the guidelines. This documentation will be submitted to a newly established Human Pluripotent Stem Cell Review Group (HPSCRG). The HPSCRG will hold public meetings when a funding request proposes the use of a newly derived line of human pluripotent stem cells. The HPSCRG will also compile an annual report, which will include the number of applications reviewed and the titles of all awarded applications.

The draft guidelines state that no NIH funds may be used to derive pluriptotent stem cells from human embryos. The draft guidelines also address other areas of research that are ineligible for funding, including studies in which human pluripotent stem cells are: (1) utilized to create or contribute to a human embryo; (2) combined with an animal embryo, used for reproductive cloning of a human; (3) derived using somatic cell nuclear transfer into a human or animal egg; (4) derived using somatic cell nuclear transfer into a human or animal egg; and (5) derived from human embryos created for research purposes.

XIII. Council Operating Procedures and Possible Expedited Review
Dr. Louise Ramm, NCRR

Dr. Ramm reported that NCRR is required to review Council Operating Procedures in February of each year. Council members received a copy of the Operating Procedures prior to this meeting, but no changes were suggested.

Dr. Ramm proposed an expedited, streamlined, en bloc concurrence for some of the applications that NCRR anticipates funding. This proposal will expedite the awards process and will be included in the Council Operating Procedures. NCRR's proposal would have the Chair of the Council select a few Council members who would provide the en bloc concurrence for certain grant applications. All Council members will be alerted by e-mail that a cohort of applications are ready for review; however, only the preselected Council members will be

required to concur with the Initial Review Groups' recommendations. These Council members would notify the Executive Secretary of the Council of their review results within two weeks. Dr. Ramm noted that any Council member could request that an application get full Council discussion. These applications would be removed from the en bloc process. The following applications will continue to be reviewed by the full Council: Center grant applications; human subject, animal, or biohazard concerns; applications from foreign institutions; issues regarding recruitment of women and minorities; anything identified as a special concern; any application with special policy issues; any application previously deferred by Council for additional information or re-review; and applications identified by NCRR staff as requiring special consideration or discussion by Council–such as high program priority, applications with high costs, and restoration of time. The Council agreed to try this pilot proposal for one year with six members of Council. The six members will rotate with each Council cycle.

XIV. Regional Support Laboratories and Waiver for Animal Facility Improvement Grant Applications
Dr. John Strandberg, Associate Director, Comparative Medicine, NCRR

Dr. Strandberg presented two concept clearances for Council's endorsement. (1) Establish a regional network of comparative medicine and integrative biology core labs to enhance the ability of researchers to conduct animal-based research. Grants would be awarded to institutions that have at least five NIH awards and they would be divided into modules that would each provide shared lab services such as necropsy, histology, histochemistry, and immunology. (2) Waive the requirement for the consolidated chimpanzee centers to have matching funds in order to obtain facility improvement grants. He said this waiver would facilitate essential facility upgrades. Both concept clearances were approved by Council.

XV. The Clinical Research Summit and its Recommendations
Dr. Roger E. Meyer, Senior Consultant on Clinical Research, Association of American Medical Colleges and Clinical Professor of Psychology, Georgetown University, Washington, D.C.

Dr. Meyer shared recommendations the Clinical Research Task Force established to assess the opportunities and challenges facing clinical research in U.S. medical schools and teaching hospitals. The Task Force was comprised of members of the Council of Deans, the Council of Teaching Hospitals, the Council of Academic Societies, as well as representatives of some Federal government agencies. The Task Force divided its effort into four separate, but related analyses.

First, to improve the current state of clinical research education in medical schools and teaching hospitals, the Task Force recommended that: clinical research training programs must define a rigorous set of competencies, skills, and knowledge-based requirements for their program

graduates; programs should strive to develop and maintain a demographically diverse cadre of trainees and faculty mentors; programs should plan for long-term funding of trainees and a stable, long-term funding base; systematic outcomes data on early career choices and opportunities must be collected and analyzed; and medical schools and teaching hospitals should develop model training programs and credentialing for clinicians who wish to participate as investigators in clinical trials.

Second, to optimize clinical research infrastructure, the Task Force recommended that medical schools and teaching hospitals engage in clinical research strategic planning; develop an effective, efficient, and responsive human subjects protection and compliance process; identify ways to develop and support specific clinical research infrastructure; and explore emerging technologies and computerized clinical information systems. To support this effort, the American Association of Medical Colleges needs to improve its support to enhance member institutions' clinical research programs.

Third, to organize and administer clinical trials, the Task Force recommended that medical schools and teaching hospitals expand their sponsored clinical trials programs, engage senior investigators in clinical research strategic planning, assess the effectiveness of its clinical research initiatives over time, and make necessary changes.

Last, to interface with evolving clinical delivery systems, the Task Force recommended that medical schools and teaching hospitals invest in health services research, explore better ways to collaborate on clinical research, and share costs and benefits of clinical research.

XVI. Adjournment

The Council met in closed session on Thursday, January 27, 2000, from 2:00 p.m. until 3:45 p.m., to review grant applications. The Council adjourned at 3:45 p.m.

XVII. Application Review

Council considered 355 applications and concurred with the recommendations of 353. Council also considered and concurred with the recommendations of 166 dual applications.

Attachments:
A. Council Roster
B. Competing Grants: Summary of Council Recommendations

NOTE: Open Session materials are available from the Executive Secretary or the Committee Management Office, NCRR.

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

/ S/ 2/25/00

Judith L. Vaitukaitis, M.D. Date
Chair, National Advisory Research Resources Council
and Director, National Center for Research Resources

/S/ 2/25/00

Louise E. Ramm, Ph.D. Date
Executive Secretary, National Advisory Research Resources Council
and
Deputy Director, National Center for Research Resources

Mrs. Cheryl A. Fee
Committee Management Officer
and
Ms. Sheryl P. Lane
Committee Management Assistant

These minutes will be formally considered by the Council at its next meeting; corrections or notations will be incorporated into the minutes of that meeting.