Board of Scientific Advisors

Meeting Minutes

November 8, 1999

Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI) convened for its 12th regular meeting at 8:30 a.m. on Monday, November 8, 1999, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. David Livingston, Professor of Medicine and Genetics, Dana-Farber Cancer Institute, presided as Chair.

The meeting was open to the public from 8:30 a.m. until adjournment for introductory remarks from the Chair; ongoing and new business; an award presentation; an ethics overview for government employees; and presentations and discussion on the status of the NCI budget and paylines, the Program for Assessment of Clinical Cancer Tests, the Nutrition Implementation Group report, establishing subgroups to monitor large-scale initiatives, outcomes research, the Chemoprevention Implementation Group report, the Developmental Therapeutics Program AIDS Review Group report, and concepts for Requests for Applications (RFAs) and a Request for Proposals (RFPs).

BSA members present:
Dr. David M. Livingston (Chair)
Dr. David B. Abrams
Dr. David S. Alberts
Dr. Hoda Anton-Culver
Dr. Frederick R. Appelbaum
Dr. Joan Brugge
Dr. Esther H. Chang
Dr. Mary Beryl Daly
Dr. Waun Ki Hong
Dr. Susan B. Horwitz
Dr. E. Tyler Jacks
Dr. Kenneth W. Kinzler
Dr. Herbert Y. Kressel
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Dr. Joan Massague
Dr. W. Gillies McKenna
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Franklyn G. Prendergast
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal
Dr. Joseph V. Simone
Dr. Louise Strong
Dr. Peter K. Vogt
Dr. Daniel D. Von Hoff
Dr. Barbara L. Weber
Dr. Alice S. Whittemore
Dr. William C. Wood
Dr. Robert C. Young
Dr. Elias Zerhouni

BSA members absent:
Dr. Virginia L. Ernster
Dr. Suzanne W. Fletcher
Ms. Deborah K. Mayer
Dr. Allen I. Oliff

NCAB liaison:
Dr. Philip A. Schein (absent)

Others present included: Members of NCI's Executive Committee (EC), NCI Staff, Members of the Extramural Community, and Press Representatives.

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I. CALL TO ORDER AND OPENING REMARKS - DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 13th regular meeting of

the Board of Scientific Advisors (BSA or Board) and welcomed members of the Board, National Institutes of Health (NIH), and National Cancer Institute (NCI) staff, guests, and members of the public. Dr. Livingston introduced and welcomed new members to the Board: Dr. David Abrams, Professor and Director, Center for Behavioral and Preventive Medicine, Brown University School of Medicine; Dr. David Alberts, Professor of Medicine, Pharmacology, and Public Health and Associate Dean for Research, University of Arizona College of Medicine; Dr. Hoda Anton-Culver, Professor and Chief, Epidemiology Division, University of California School of Medicine at Irvine; Dr. Esther H. Chang, Professor, Departments of Oncology and Otolaryngology, Georgetown University Medical Center and Lombardi Cancer Center; Dr. Susan Horwitz, Falkenstein Professor of Cancer Research, Albert Einstein College of Medicine; Dr. Kenneth Kinzler, Professor of Oncology, Johns Hopkins Oncology Center; and Dr. Richard Schilsky, Professor of Medicine and Associate Dean for Clinical Research, University of Chicago Pritzker School of Medicine.

As far as future BSA meeting dates, a potential conflict with the June 2000 meeting of the NCI/European Organization for Research on Treatment for Cancer was noted. Members should review confirmed dates through November 2001 and report conflicts to the Executive Secretary.

CONSIDERATION OF 23 JUNE 1999 MEETING MINUTES - DR. DAVID LIVINGSTON

Motion: The minutes of the 23 June 1999 BSA meeting were unanimously approved.

REPORT OF THE DIRECTOR, NCI - DR. RICHARD KLAUSNER

Dr. Richard Klausner, Director, NCI, discussed recent NCI personnel changes, aspects of the FY2000 budget, issues related to implementing recommendations in the Biomedical Information Science and Technology Initiative (BISTI) report, progress and new initiatives in the Cancer Genome Anatomy Project (CGAP), and Phase III clinical trials restructuring.

NCI Personnel Changes. Dr. Klausner reported that Dr. George Vande Woude, former Director, Division of Basic Sciences (DBS), had assumed leadership of the Van Andel Research Institute in Chicago. Dr. Dinah Singer, former Science Administrator, Howard Hughes Medical Institute, had assumed the position of Director, Division of Cancer Biology (DCB). Dr. Klausner announced the death of Mrs. Eleanor Nealon, Director, Office of Liaison Activities, and acknowledged her important contributions to the NCI and to the development of the Director's Consumer Liaison Group.

Budget and Research Project Grant (RPG) Pool Update. Dr. Klausner informed members that the NCI was currently operating under a continuing resolution pending enactment of the Labor and Health and Human Services (HHS) FY2000 appropriations. In the conference bill, the NCI appropriation would be $3.332B, an increase of $438M (15 percent) over FY99. Other conference bill provisions with the potential to impact the NCI budget include a government-wide across the board cut of 0.97 percent (approximately $33M for the NCI), a provision to delay the obligation of $7.5B of NIH's proposed $17.9B budget until the final 48 hours of the fiscal year. A new cap for salary support through extramural grants not to exceed Level 2 of the executive schedule ($125K- $136K) was included in the bill. Dr. Klausner projected that if the 14 percent increase in the conference mark becomes a reality, the RPG pool would increase proportionately; however, an RPG pool increase of 25 percent would be needed to maintain the payline at the 24th percentile. This increase would be due to the outyear commitment for noncompeting funds and pressure from new and competing investigator-initiated grants (R01s) due to an increase in the number of applications received and the increased average cost requested. Other pressures on the RPG budget line include increases in RFA funded grants and the new Phased Innovation Awards, as well as the dollars requested in program project (P01s) grant competing renewals.

He reported that: (1) total grants awarded had increased from 3,958 in FY98 to approximately 4,855 in FY 2000, and total applications over the same period increased from 3,196 in FY 98 to almost 4,400 in FY 2000; (2) grants awarded under the new career training mechanisms, which includes the K22 transition award and the K23/ K24 clinical awards are projected to increase from 241 to 300 or

more; (3) the announced extension of the Special Programs of Research Excellence (SPOREs) is expected to result in increased funding for the program; and (4) a significant increase is projected to address clinical trials, informatics, and technologic needs in the cancer centers program.

Biomedical Information Science and Technology Initiative. Dr. Klausner reminded members that a group, established by the Advisory Committee to the Director, NIH, and co-chaired by Drs. Larry Smarr and David Botstein had been convened to address issues related to NIH's investments in biomedical information science and technology. The group's discussions resulted in a report entitled "Biomedical Information Science and Technology Initiative". BISTI recommendations were to: (1) establish National Programs of Excellence or Centers in biomedical computing; (2) establish a new program directed toward the principles and practice of information storage, curation, analysis, and retrieval (ISCAR); (3) provide more resources and incentives for basic research to adequately support those who are inventing, refining and applying the tools of biomedical computing; and (4) foster a national computing infrastructure with appropriate resources to increase computing capacity.

Dr. Klausner reported that a trans-NIH committee, which he chairs, has been formed to develop BISTI implementation plans. In a summary of early deliberations, he indicated that implementation approaches being considered are: (1) establishing NIH-wide planning grants to identify areas to be addressed that are linked to major problems before attempting to establish centers; (2) establishing an NIH-wide forum for ISCAR representatives, accessible on the Web, to share best practice information, and an annual informatics technology fair; and (3) using the NCI Phased Innovation Award as a model in developing an appropriate award mechanism.

BSA members were asked to comment on plans for informatics initiatives related to the NIH-wide BISTI, i.e., programs of excellence and development of appropriate awareness mechanism (s). Comments should be sent to Drs. Klausner or Carol Dahl.

Cancer Genome Anatomy Project Update. In discussing efforts to strengthen the informatics support structure for the Cancer Genome Anatomy Project (CGAP), particularly the interface with

Director's Challenge grantees, Dr. Klausner reported that gene discovery in the CGAP program continues at a rapid pace, with an expansion of high-quality libraries and several initiatives designed to make the products of CGAP accessible and useful. A progress report on the mammalian gene project will be presented at a future meeting.

Dr. Klausner stated that the research on molecular targets being conducted through the Director's Challenge and the strengthening of technology for programs, such as CGAP, will produce rapid changes in disease classification, diagnosis, prognosis, and treatment choice. The challenge for the NCI will be to develop a mechanism(s) to fund the rapid expansion of such studies.

Phase III Clinical Trials Restructuring Update. Dr. Klausner announced that a contract had been awarded to Westat and two subcontractors to create a Clinical Trials Support Unit (CTSU), a critical component in the experiment to test the redesigned Phase III clinical trials system. The CTSU will provide cost-effective and Web-based access to clinical trials for patients, physicians, and investigators. The CTSU also will be responsible for credentialing investigators, auditing, providing quality assurance, compiling reports, managing finances, educating and training, and addressing regulatory issues. Board members were informed that the organizational phase of this experiment will require a year or two, but that the process has been going well, thanks to multiple collaborations with the cooperative groups. He noted that key to the issue of curing cancer will be the linkage through a variety of communications tools and media to NCI's redesigned clinical trials information systems, notably the newly redesigned CancerNet Web site. Ms. Susan Hubbard, Ms. Mary McCabe, and staff in the NCI Office of Cancer Information, Education, and Communication were commended for the successful redesign. Dr. Klausner emphasized that improving NCI's large-scale clinical trials system is a high priority in terms of providing innovative grant mechanisms and support infrastructure, especially as ideas for cancer prevention and treatment emerge from new BSA approved programs.

In discussion and in response to questions, the following point was made:

- NCI staff were commended for the outstanding state-of-the-science meeting on small cell lung cancer, the results of

which are available on an interactive Web site.

ONGOING AND NEW BUSINESS - DR. DAVID LIVINGSTON

BSA at National Meetings

American Society of Hematology (ASH). Dr. Frederick Appelbaum reported that no BSA "NCI Listens" session was held at the 1999 meeting because Dr. Klausner spoke. The ASH 2000 meeting will include a major NCI session.

American Society of Clinical Oncology (ASCO). Dr. Robert Young reported that ASCO leadership has expressed satisfaction with it's access to Dr. Klausner and NCI leadership and questions the need for "NCI Listens" sessions in the usual format. Moreover, the results of interactions between NCI and ASCO leadership are rapidly imparted to most of the active clinical researchers in ASCO. Additionally, ASCO leadership has solicited suggestions and help from NCI staff in developing scientific sessions for the annual meeting, and most of NCI's suggestions were accepted. After a brief discussion, the consensus of the Board was that there would not be a "NCI Listens" session at this years ASCO meeting.

American Society of Preventive Oncology (ASPO). Dr. Mary Daly reported that her meeting with the President of ASPO revealed a lack of interest in having an "NCI Listens" session and offered to query the leadership about selected topics for NCI to address. Dr. Daly commented on the possibility of placing the focus this year on involving junior members who are forming a special group within ASPO. There will not be a "NCI Listens" session at ASPO this year.

American Society for Therapeutic Radiology and Oncology (ASTRO). Dr. Gillies McKenna reported that ASTRO leadership strongly favors having an "NCI Listens" session at the October 2000 meeting in Boston. Dr. McKenna noted that ASTRO leaders recently met with Dr. Klausner to discuss issues of particular

concern. Participants at the 22-26 October 2000 ASTRO meeting will be Drs. McKenna (Chair), Klausner and Robert Wittes.

Cold Spring Harbor Laboratory (CSHL) Symposium. Dr. Livingston reported that the "NCI Listens" session at the 1998 meeting on Cancer Genetics and Tumor Suppressor Genes was well attended and well received. BSA "NCI Listens" session participants at the CSHL meeting in 2000 will be Drs. Tyler Jacks (Chair), Joan Brugge, and Louise Strong.

American Association of Cancer Research (AACR). BSA participants at the "NCI Listens" session at the 1-5 April 2000 AACR meeting will be Drs. Louise Strong (Chair), Enrico Mihich, Alice Whittemore, and Nancy Mueller.

Oncology Nursing Society (ONS). BSA participants at the ONS "NCI Listens"session 11-14 May 2000 will be identified at the next BSA meeting. The Chair will be Ms. Deborah Mayer.

ETHICS OVERVIEW - DR. MAUREEN WILSON

Dr. Maureen Wilson, NCI Ethics Counselor, reviewed the procedural code of operation and administration for federal advisory committees as set forth in the Federal Advisory Committee Act (FACA) (P.L. 92-463). Since the BSA is a FACA committee, members are special government employees for the period during which they serve and must assure that their deliberations are free from real or apparent conflict of interest. Examples of activities that are and are not permitted under each statute were presented. Lobbying Congress and concept review issues were clarified.

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AWARD PRESENTATION - DR. RICHARD KLAUSNER

On behalf of the NCI, Dr. Klausner presented retiring BSA Chair Dr. David Livingston with a special Director's Service Certificate "in recognition of exemplary leadership as the first Chair of the Board of Scientific Advisors and for overall contributions to the restructuring of the National Cancer Institute and the National Cancer Program from 1996 to 1999".

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PROGRAM FOR ASSESSMENT OF CLINICAL CANCER TESTS (PACCT) - DRS. ROBERT WITTES AND SHEILA TAUBE

As background, Dr. Robert Wittes, Deputy Director for Extramural Science and Director, Division of Cancer Treatment and Diagnosis (DCTD), reminded members that defining the signatures of cancer cells for early detection and diagnosis was one of the extraordinary scientific opportunities included in the FY 2000 Bypass Budget. Dr. Wittes noted that the challenge for the NCI will be to develop programs to ensure that scientific breakthroughs from these and other gene discovery initiatives result in clinically useful tools for healthcare delivery in cancer medicine. To that end, NCI staff have started planning a Program for Assessment of Clinical Cancer Tests (PACCT).

Dr. Sheila Taube, Associate Director, Cancer Diagnosis Program (CDP), DCTD, reviewed the development process for clinical laboratory tests, identified barriers to progress, and proposed solutions to address some of the issues. The three phases in the development process, as analyzed, are: (1) recognition of a clinical need and/or identification of a potentially useful marker or technology; (2) development of an assay method; and (3) development of a standardized assay system and evaluation of clinical usefulness.

Major barriers to progress were: (1) the profusion of small studies that appear in the literature in the early phases of development, often with conflicting results, and techniques and data that cannot be compared; (2) the lack of access to statistical collaborators, resulting in studies that often are not designed to have the power to

answer all questions posed; (3) the need for large numbers of well-defined and annotated cases or specimens, as well as specimens with long periods of follow-up; (4) the need for standardization of reagents and assay procedures to facilitate comparison of data from multiple studies; and (5) intellectual property issues that could complicate the development of assays and tests that can be performed for acceptable costs.

Proposed solutions: (1) convene a strategy group with relevant expertise from academia, industry, and the NCI; (2) form a statistical consulting group based on identified needs to assist investigators in developing efficient, innovative study designs that adapt existing statistical approaches to new types of analyses; (3) develop a tissue expediter program, an expanded Web site, shared pathology informatics network, and tissue micro-arrays; (4) prepare and supply probes or antibodies and control materials, and evaluate standardized assay protocols; and (5) no solution proposed.

Members were informed of the rationale behind the proposed solutions and some activities under discussion, and they were asked to comment on whether planning for the PACCT had: (1) adequately identified the major barriers; (2) proposed logical solutions that addressed the barriers; and (3) provided alternative solutions to facilitate translation research.

In discussion, the following comments were made:

- Information on assays and associated clinical data included in the literature should be incorporated into the Internet-accessible database, and investigators should be encouraged to submit their data. A group could be convened to discuss this issue.

- MedLine references should contain a tag to facilitate searching. Staff indicated that this topic should be discussed by the Specimen Resources Committee.

- The proposed strategy group should work on a theory-driven way to identify new markers.

- Specimen from cooperative group patients on protocol are an underutilized resource.

- Clinical epidemiologists should be considered for strategy group membership.

- Intellectual property issues have the potential for inhibiting the use of proposed methodologies for nonprofit research, and must be addressed.

- A compromise is needed between allowing a recovery of research expense and the barriers to research created by the practice of granting patents for discoveries.

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NUTRITION IMPLEMENTATION GROUP REPORT - DRS. PETER GREENWALD AND VERNON YOUNG

Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), informed members that the Nutrition Implementation Group (NutrIG) report was a follow-up to the 1997 review of NCI's Cancer Prevention Program Review Group (CPPRG) report. Dr. Vernon Young, Professor, Nutritional Biochemistry, and Chair, NutrIG, noted that the CPPRG identified diet and nutrition as one of the two priority areas with respect to reducing cancer incidence at various organ sites.

Dr. Young stated that the charge to the NutrIG was to outline an invigorated, leading-edge nutrition research effort designed to improve the precision with which the impact of diet and its complex chemical makeup could be predicted. The NutrIG report recommendations were: (1) create a trans-NCI coordinating committee on nutrition and cancer led by the DCP; (2) establish a number of programs of excellence in nutritional science and cancer prevention, including several at existing cancer centers; (3) provide developmental funds to encourage nutritional science-related projects in existing cancer centers; (4) hold interdisciplinary workshops linking basic areas of biology and nutritional sciences with cancer etiology and pathogenesis; (5) enhance training and career development in the nutritional sciences aspects of cancer research; (6) assure an appropriate mix of reviewers for diet and

cancer research grant applications; and (7) invite nutritional scientists to join the BSA. Dr. Young further recommended that nutritional sciences be represented in future bypass budgets and that nutrition professional societies be encouraged to schedule "NCI Listens" sessions.

In discussion and in response to questions, the following comment(s) was made:

- Industry has an important role to play in terms of translating new nutritional science knowledge into the context of improving the nation's health with respect to cancer prevention. Collaborations may develop as research ideas are implemented in an action plan
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WORKING LUNCH - DR. DAVID LIVINGSTON

Establishing Subgroups to Monitor Large-Scale Initiatives

As background for new BSA members, Dr. Wittes explained that oversight of NCI programs is an important BSA function, exercised principally through prospective review of concepts for new initiatives and retrospective review of extramural programs to be conducted once every 6 years. In addition, the BSA will provide ongoing surveillance of new, high-profile NCI initiatives. The proposed process outlined how programs could be selected for review, the nature of the oversight, products of the oversight, and a tentative list of initiatives for review. Details related to advance preparations, presentation format, and a review calendar were presented.

In subsequent discussion, the following points were made:

- Provide frequent and informal feedback on BSA approved concept initiatives.

- A BSA subgroup will be formed for the preliminary review of the clinical trials restructuring initiative. Materials will be sent to all BSA members prior to a discussion during the open session at the March 2000 meeting.

Motion: A motion to implement the Institute's plan (based on the model used for concept review) to establish subgroups for BSA ongoing surveillance of large NCI programs was unanimously approved; the first will be a review of clinical trials restructuring. The process should be evaluated and modified as necessary.

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UPDATE ON OUTCOMES RESEARCH - DRS. ROBERT HIATT, MARTIN BROWN, AND JOSEPH LIPSCOMB

Dr. Robert Hiatt, Deputy Director, Division of Cancer Control and Population Sciences (DCCPS), reminded members that the update on NCI's outcomes research agenda was requested as a follow-up to the Surveillance Research Implementation Plan presented to the Board in March 1999. For the benefit of new members, Dr. Hiatt outlined events since then, including the organization of the Applied Research Program and Outcomes Research Branch; the complementary reports of the Institute of Medicine (IOM), National Cancer Policy Board (NCPB), and President's Cancer Panel; the development of NCI's response to the IOM-NCPB report; and the formation of NCI's Quality of Cancer Care Committee (QCCC).

Dr. Martin Brown, Chief, Health Services and Economics Branch, DCCPS, reviewed the history of NCI's research in this area, noting that the outcomes research agenda has evolved from descriptive studies, such as patterns of care and variation studies, to studies that are more evaluative in nature, using longitudinal cohorts and collecting data on treatment effects and quality of life. NCI's preventive services patterns of care research began in 1991 with the Surveillance Epidemiology End Results (SEER) pilot studies for the Breast Cancer Surveillance Consortium. The treatment patterns of care research began in 1987 with the SEER-Community Clinical

Oncology Program (SEER-CCOP) Patterns of Care studies. The Surveillance Implementation Group (SIG) recommended supporting more studies like Prostate Cancer Outcomes Study (PCOS) to determine the best measures of patterns of care, morbidity, quality of life, etc. Responsibility for implementing the recommendations will reside in the newly organized Outcomes Research Branch.

Dr. Joseph Lipscomb, Chief, Outcomes Research Branch, DCCPS, informed members that the major intent of the quality of cancer care initiative is to review, evaluate, and ultimately foster improvement in the field of cancer outcomes. The intent is to go beyond traditional measures of survival and clinical change to new forms of endpoints focusing on quality of life, patient satisfaction, cost burden to the patient and family. The objective is to enhance the state of the science for defining, monitoring, and improving the quality of cancer care, with the ultimate goal of ensuring that all Americans receive the highest quality of cancer services across the continuum of care. Dr. Lipscomb reviewed the elements of consensus that have emerged from the IOM-NCPB, President's Cancer Panel, and SIG reports, as well as from the 2001 Bypass Budget: (1) develop a core set of outcomes measures that are valid, patient-centered, acceptable to providers, and that span the continuum of care; (2) intensify efforts to understand the effect of interventions on cancer outcomes by strengthening the methodological and empirical research base for quality assessment in cancer; (3) restructure the NCI clinical trials program; and (4) improve communications across the spectrum. These consensus issues constitute the objectives of NCI's quality of care research plan, which will be carried out through the Outcomes Research Branch in partnership with the Secretary's Quality Improvement Initiative (QII) and in cooperation with other DHHS agencies, the Veterans' Administration (VA), and the Department of Defense (DoD). Board members were given a brief description of ongoing and planned activities to implement each of the objectives.

Dr. Lipscomb also described the QCCC as NCI's organizational mechanism to move the quality of care research plan forward. The QCCC will be linked directly to the Federal Quality Interagency Coordinating (QuIC) Task Force, have subcommittees for Research and Care Delivery, and report to the Secretary, QuIC, BSA, National Cancer Advisory Board (NCAB), and NCPB. The end of FY 2000 is the target date for completing an action plan.

In discussion and in response to questions, the following points were made:

- Members requested a report on how the plan's broad elements would be prioritized in the near and long term, and an indication of the estimated budget. For example, one issue to be resolved in regard to expanding the SEER program is the tension between gathering additional information from the sites already covered versus expanding the number of sites. Staff noted that work on core outcome measures, clinical trials, and communications is already ongoing, the latter two with other NCI resources.

- A RFA proposal for the "National Consortium of Research Team for Outcomes Research" will be presented at a future meeting.

Members were asked to e-mail their views of the evolving outcomes research agenda and of initiatives related to improving the quality of care in cancer to Drs. Brown and Lipscomb.

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RFA-COOPERATIVE AGREEMENT CONCEPTS - PRESENTED BY NCI STAFF

Division of Cancer Treatment and Diagnosis and Division of Cancer Prevention

Image Database Resources for Image Processing Research (RFA-Coop. Agr.) - Dr. Daniel Sullivan, Associate Director, Diagnostic Imaging Program, DCTD, stated that the proposed RFA responds to a need for medical image databases as research resources for medical image processing, which was identified as having a high priority in various NCI/NIH workshops and by the Radiological Society of North America (RSNA). Specific needs include data sets for image processing research, a consortium to develop standardized methods for database generation and evaluation of

image processing techniques, and internet access by investigators. The intent of this initiative is to support a consortium of institutions to develop the necessary consensus and standards for a lung computed tomography (CT) image database resource, and to construct a database of spiral CT lung images. As proposed, the consortium would create a consensus on image acquisition parameters and metrics for software evaluation. It is focused on one organ system and one modality. The intent is to develop a process that would serve as a model for other groups to develop additional image database resources.

It was estimated that U01s would be awarded to five individual academic sites from a set-aside of $0.8M for the first year, with a total estimated cost of $4.4M for the 5-year project period.

In discussion and in response to questions, the following points were made:

- The image database to be acquired should have state-of-the-art scanners, especially multi-detector array CT scanners with provisions for storing raw data (e.g., clinical data and an agreed-upon set of clinical data points for correlation studies). In addition, initial planning should include a method for updating the images as technology improves.

- It is important that some method to assure the review and overall quality of the pathology that is leading to the inaccurate diagnosis in these cases be developed. There should be similar pathology standards for the number of sites accruing patients.

- The budget may be too low to address longitudinal studies and raw data storage issues.

Motion: A motion to approve the RFA/Cooperative Agreement concept entitled "Image Database Resources for Image Processing Research" was unanimously approved. NCI leadership was asked to reconsider the proposed budget and decide on an appropriate increase, not to exceed 75 percent of the proposed budget.

Cancer Vaccine Studies Consortium (Coop. Agr.) - Dr.

Michaele Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), DCTD, stated that the proposed project is intended as part of NCI's effort to restructure the early clinical trials program. Vaccines were identified as an area to address because of the demonstrated potential for both preventive and therapeutic applications, and because scientific advances have brought many promising vaccine approaches to the point of clinical development. The goals of the proposed Cancer Vaccine Studies Consortium (CVSC) would be to bring basic and clinical expertise together to: (1) address critical development questions (e.g., optimal vaccine approaches, more efficient clinical trial designs); (2) provide a reliable resource with state-of-the-art immunologic monitoring to evaluate new agents and approaches; and (3) advance the most promising approaches through multi-institutional participation and a logical sequence of studies. As planned, 6-7 clinical trial members would be selected by peer review and assembled into a consortium. Basic science expertise would be leveraged to address the practical problems of vaccine development; clinical expertise would be available to conduct 8-10 trials per year with accruals of 240-300 patients; and the clinical trials members would have the ability to perform state-of-the-art immunologic monitoring techniques. Other features in the organization and structure of the CVSC would be a steering committee, a separately funded central headquarters, flexible funding, and a laboratory oversight committee.

The estimated set aside for the first year is $3M for 7-8 awards, and the estimated total for the 4-year project period is $15M.

In discussion and in response to questions, the following points were made:

- Although the need has been established for well coordinated and standardized clinical trials to test candidate vaccines, the budget estimation of $200,000 for each trial member may be inadequate; hidden costs could be sizeable. Staff noted that a variety of NCI mechanisms would be used to bring production into the Institute.

- Other issues to be addressed include the insufficiency of monitoring assays and the need for additional biologic research, for example, to be able to identify specific tumor antigens in the adult that are beyond the developmental

stage. Collaborations should be sought with immunologists who work in transplantation tolerance.

The concept was withdrawn by staff.

Office of the Deputy Director for Extramural Science

Minority Institution Cancer Center Partnership (RFA-Coop Agr.) - Dr. Sanya Springfield, Chief, Comprehensive Minority Medical Branch, Office of Centers, Training and Resources, Office of the Deputy Director for Extramural Science (ODDES), stated that the Minority Institution Cancer Center Partnership (MICCP), if approved, would mark the establishment of long-term collaborations between the NCI and NIH Office of Research on Minority Health (ORMH) to fund, support, and manage the proposed partnerships to successful conclusions. The goal is to devise methods with greater impact on reducing cancer incidence, mortality, and morbidity in ethnic minority populations. Partnerships would be formed between minority-serving institutions (MSIs) and NCI-designated cancer centers to develop cancer programs in research, research training, education, and outreach. MICCP objectives are to: (1) create stable, long-term collaborations that focus on issues relevant to cancer burden; (2) build and stabilize competitive research and research training at MSIs; (3) improve the effectiveness of research, education, and outreach programs to minority communities at the cancer centers; and (4) export successful approaches and models to other NCI-funded cancer centers, minority institutions, and networks.

Funding would be awarded through either planning grants (P20s) or specialized center-cooperative agreements (U54s). The P20 set-aside in the first year was estimated at $5M for 6 awards and 12 awards over the 5-year project period at an estimated $40M. It was anticipated that one U54 will be awarded each year for an estimated $2.5M in the first year and a total of $37.5M.

In discussion and in response to questions, the following points were made:

- The RFA should: (1) include specific examples of the nature of the projects to be considered, types of activities that

would be covered by the award, defined outcome measures, and well-developed and articulated principles of accountability; (2) involve in the planning stage all constituencies necessary to ensure identification of the best areas of opportunity; and (3) include concrete education outcomes.

- Staff should consider: (1) conducting a pilot project first; and (2) opening the program to institutions that are not designated cancer centers.

Motion: A motion to approve the RFA/Cooperative Agreement concept entitled "Minority Institution Cancer Center Partnership" was unanimously approved. Concerns relating to the need for specificity should be addressed in developing the narrative and during the evaluation.

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CHEMOPREVENTION IMPLEMENTATION GROUP REPORT - DRS. PETER GREENWALD AND DAVID ALBERTS

Dr. David Alberts, Associate Dean for Research, Arizona Cancer Center, College of Medicine, University of Arizona, and Chair, Chemoprevention Implementation Group (CIG), reminded members that the cross-disciplinary CIG was organized in 1998 to implement recommendations of the Cancer Prevention Program Review Group report. Originally, CIG functions were to set priorities for agents to be evaluated in chemoprevention clinical trials, identify research opportunities, and develop strategies for advancing the field, especially the basic science aspects. Subsequent changes in the structure and function of the chemoprevention program, which reflect CIG recommendations, included a revised set of challenges: (1) build basic science programs within cancer prevention; (2) strengthen the chemopreventive agent development effort; (3) establish an infrastructure and planning process for chemoprevention trials; and (4) develop expertise in the research community. In January 1999, the Basic Science Implementation Subcommittee (BSIS) of the

CIG met to begin formulation of specific recommendations for enhancing the basic science component of cancer prevention within the DCP. The CIG recommendations provided advice in four areas: (1) building an infrastructure to enhance the basic science component in cancer prevention research; (2) strengthening genetics, molecular biology, and biomarkers research; (3) strengthening basic nutrition science and cancer prevention research; and (4) strengthening cancer prevention basic science at cancer centers.

Dr. Alberts then briefly reviewed DCP's new matrix structure, which was organized according to CIG recommendations. Organ system research groups make up one axis of the matrix, and prevention research groups the other. Four research groups, basic prevention science, cancer biomarkers, nutrition, and early detection, have been formed to focus on expanding the basic science component. New programs for chemopreventive agent development include providing access to resources for early agent development; developing new preclinical models for evaluating chemopreventive efficacy; incorporating new technology into discovery and characterization; and validating surrogate endpoints for cancer incidence. Two new programs developed collaboratively by DCP and DCTD are molecular target drug discovery grants and the new centers of excellence. These programs have the ultimate goal of encouraging and realizing the full potential of chemoprevention studies as well as fostering the growth of the chemoprevention research community. He also gave: (1) an overview of the proposed decision process for developing and prioritizing prevention clinical trials; (2) a summary of essential review elements for large cancer prevention trials; and (3) recommendations for developing chemopreventive expertise in the research community.

In discussion and in response to questions, the following points were made:

- Areas needing urgent attention are the development of new agents and novel drug delivery techniques. Other areas to address are: (1) linkages with behavioral science expertise to meet the challenges of improving accrual, compliance, and retention; (2) how to engage the non-oncology medical community for these studies; (3) financial implications of mounting large prevention programs; (4) collaborations with

MICCP grantees to enhance accrual of minorities and the underserved to clinical trials; (5) changing the terminology to reflect that preventive therapy is actually treatment of precancerous lesions; and (6) coordination between cancer therapeutics and cancer prevention researchers and programs.

- Scientific areas that should be encouraged are: (1) chemopreventive agents delivered locally with the help of image guidance systems; (2) preventive ablation (chemical or physical) for patients at high risk; and (3) discovery and validation of surrogate markers.

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NCI DEVELOPMENTAL THERAPEUTICS PROGRAM AIDS REVIEW GROUP REPORT - DRS. DOUGLAS EDWARDS, ELLEN FEIGAL, AND KARL DIEFFENBACH

Dr. Douglas Edwards, Chief of Infectious Diseases, University of California at Los Angeles, and Chair of the Developmental Therapeutics Program (DTP) Acquired Immune Deficiency Syndrome (AIDS) Review Group, presented the DTP AIDS Review Group report. Dr. Edwards stated that the NCI AIDS research effort began in 1986 with the discovery program for AIDS therapeutics. A trans-NIH review by the Levine Committee of the entire AIDS portfolio in 1997 produced the recommendation to reorganize the DTP AIDS therapeutics screening program to focus on target-based assays rather than the cell-based non-selective assay, a recommendation that was reinforced by the DTP Program Review Group (PRG) in 1998. The charge to the DTP AIDS Review Group was to review changes resulting from the Levine review and define NCI's future role in discovery of agents for HIV/AIDS/opportunistic infections (OI). The DTP AIDS Review Group recommended that the DTP should: (1) establish a single scientific review and oversight advisory board; (2) develop non-cell-based, high-throughput, target-based assays in collaboration with academia, emphasizing targets not actively pursued by industry; (3) continue cell-based assays as secondary assays for confirmation of leads from molecular and biochemical assays and, on a limited

basis, for use as primary screening of synthetic compound libraries and purified natural products; (4) maintain, replenish, and expand the natural products repository and acquire/build combinatorial small molecule chemical libraries for use in mechanism- and cell-based screening for AIDS therapeutics; (5) use advisory groups of experts to address issues related to chemical diversity, prioritization of compounds for screening, and supervision of natural products libraries and combinatorial small molecule chemical libraries; (6) develop state-of-the-art methods for data management of compound libraries and implement improved access by the extramural community to DTP resources; (7) establish medicinal chemistry capability to optimize leads generated by screening and play a translational role in identifying industrial partners to move forward the leads; (8) make DTP-supported lead optimization and preclinical activities available to both extra- and intramural investigators and establish an NCI HIV-AIDS Research Office; (9) become a member of the Inter-Company Collaboration for AIDS Drug Development; and (10) receive a budget increase to a level compatible with the perceived needs for development of AIDS therapeutic agents for the treatment of AIDS. In summary, the DTP ARG considered the DTP AIDS program to be of high value and worthy of expansion in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and other Institutes in working on AIDS problems of global concern.

Asked to comment as a member of the DTP AIDS Review Group, Dr. Elliott Kieff, Professor of Microbiology and Molecular Genetics and Medicine, Harvard University, enumerated DTP's significant strengths and those of the new HIV program. Dr. Kieff noted, however, that there is a need for building long-term strategic planning activities into the process.

Dr. Ellen Feigal, Deputy Director, DCTD, reported that a plan of action to address the DTP AIDS Review Group recommendations is to work with the NIAID to develop an integrated NIH plan on AIDS and AIDS-related complications. NCI's DTP and NIAID's Basic Science Program (BSP) staff met to discuss respective grant portfolios and contract resources to identify strengths, weaknesses, and gaps in the spectrum of both their activities and to formulate an integrated plan. The plan has since been presented to the NIH Office of AIDS Research (OAR) and its advisory group. Following review and comment by the BSA, the plan will be returned to the OAR for the allocation of funds.

Dr. Carl Dieffenbach, Associate Director, BSP, NIAID, presented the integrated trans-NIH AIDS Drug Discovery and Development Plan, beginning with a brief historical overview of AIDS therapeutics research in NIAID and NCI since 1985. Dr. Dieffenbach described the collaborations that had developed and acknowledged NIAID strengths (developing new concepts for therapeutics and in Phase III clinical trials, both adult and pediatric) and NCI's strengths (medicinal chemistry and synthesis, pharmacology, and toxicology) in areas needed to move agents into Phase I/II testing. He stated that the objective of the new plan is to optimize the utilization of all NIH resources for the rapid discovery and development of new and improved therapeutics and microbicides for HIV disease and the associated OIs. The plan represents the formalization of a collaborative process embraced by NCI and NIAID over the years to address development questions on a compound-by-compound basis. The plan also furthers the development of a trans-NIH process and establishes a management structure for utilization of the tremendous resources that exist throughout the NIH for drug discovery, preclinical development, and clinical trials. The responsibility of NIH priority-setting for AIDS and AIDS-related research will continue to reside with the OAR; established priorities will be utilized to examine requests for the use of resources and make allocations. The results will be reviewed by the OAR and extramural advisory committees, such as the BSA, based on established review criteria that have been published on the NIAID Web Site.

In discussion and in response to questions, the following points were made:

- In general, the practice in NIAID has been to move agents along intramurally until they are ready for licensing to industry; however, gaps have been identified in industry's research, for example, microbicides and therapeutics for tuberculosis and other OIs.

- NCI's participation in the AIDS drug discovery and development program is important and constructive, and the plan could serve as a model for future inter-Institute cooperation.

RFA-COOPERATIVE AGREEMENT/RFP CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis

Shared Pathology Informatics Network (RFA-Coop. Agr.) - Dr. Sheila Taube, Associate Director, CDP, DCTD, stated that the overall goal of the proposed Shared Pathology Informatics Network is to create and test a Web-based model system that can request and receive data from existing medical databases at multiple institutions. The initiative represents another step toward the long-term goal of developing informatics systems to support NCI efforts to improve researchers' access to pathology and other clinical information that is linked to tissue specimens. Activities to be undertaken in this initiative are: (1) developing standard data elements and rules for converting free-text pathology reports into data elements; (2) selecting and implementing Internet search software and adapting the software at each member institution; (3) developing procedures for protecting patient confidentiality and obtaining IRB approval; and (4) testing and validating the system. Dr. Jules Berman, Pathologist, Resources Development Branch, CDP, presented evidence that institutions have pathology reports in electronic form and the needed informatics infrastructures and are willing to participate in research that utilizes their data. Evidence was also presented to demonstrate that Internet technology, standardized network query protocols, common medical terminologies, secure encryption capabilities, and standardized pathology report formats are already available to make this initiative feasible.

It is anticipated that awards would be made to 7-10 institutions with a first year set aside of $2.75M and an estimated cost for the 5-year project period of $13.75M.

In discussion and in response to questions, the following points were made:

- Researchers will need access to large numbers of specimens for marker and validation studies.

- The success of the proposed Network will be to ensure that pathology departments at participating institutions receive advance notice and agree to participate, obtaining institutional commitment (in writing, if possible), and enlisting the help of the American Academy of Pathology. Final deliverable descriptions should be minimum requirements.

- Issues to consider in preparing the RFA are: (1) how the specimens will be released; (2) standardization of specimen preparation and storage; (3) the possibility of linking with registries in institutions rather than pathology departments; (4) potential difficulties in linking with legacy information systems in the various institutions; and (5) the need to understand the nomenclature in free-text searches.

Motion: A motion to approve the RFA/Cooperative Agreement concept entitled "Shared Pathology Informatics Network" was approved with one abstention. The concept should be written as Phase I based on input and comments from Drs. Minna, Zerhouni, Schilsky, Anton-Culver, and Alberts.

Ultrasound Research Interface (RFP) - Dr. Daniel Sullivan, Associate Director, Diagnostic Imaging Program, DCTD, presented the concept for the development of an ultrasound research interface with the intent of creating these interfaces as a resource for the research community. The specific contract deliverable would be control software that gives investigators experimental access to, and control over, the raw signals going into ultrasound transducers or the signals coming back. It was noted that the absence of ultrasound research interfaces is a barrier to research on new ultrasound techniques, quantitative image reconstruction, and analysis or interpretation. Examples were given of ultrasound research that would benefit, including high spatial resolution imaging, quantitative flow imaging, molecular imaging, and ultrasound-guided surgery and microsurgery. Improved localization of drug delivery and the combination of ultrasound with other technologies, particularly optical technologies, to maintain and maximize spatial resolution of deep tissue images were cited as

potential applications of ultrasound research made possible by the interface software. Originally, the concept proposed two awards from a first year set aside of $2.4M and a total cost of $3.8M for the 2-year project period. Based on a suggestion from Drs. Kressel and Zerhouni, the concept was modified to propose one demonstration award of $1M in the first year and $0.5M in the second year. The single project would be illustrative of a government-industry-academic partnership and would include both the basic and advanced specifications.

In discussion, the following points were made:

- Consideration should be given to a single demonstration project which would be illustrative of government-industry-academic partnership, a single contract to include both basic and advanced specifications up to one million in year one and a half million in year two. This should be on a contract competitive basis so the low bid might come in significantly less than the specified amounts. Two demonstration projects are also acceptable.

- The awardee should agree to provide ongoing support for the interface. Staff thought this was a good suggestion because it would essentially force some cost sharing by industry.

- The promises of the ultrasound are real, and research interfaces have become essential for advancing novel research fields, as well as for cancer surgery.

Motion: A motion to approve the RFP concept entitled "Ultrasound Research" was unanimous.

Adjournment: The meeting was adjourned at 12:05 p.m. on Tuesday, November 9, 1999.