

Board of Scientific Advisors

Meeting Minutes

March 2-3 ,1998

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 7th regular meeting at 9:20 a.m. on Monday, March 2, 1998, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. David Livingston, Professor of Medicine, Dana-Farber Cancer Institute, presided as Chair.

The meeting was open to the public from 9:20 a.m. until adjournment on Tuesday, March 3, for introductory remarks from the Chair; discussion of procedural matters and future meeting dates; ongoing and new business; and presentations and discussion on the status of the NCI budget and paylines, Request for Application (RFA) concepts, implementation of Program Review Group recommendations, the new Division of Cancer Control and Population Sciences, Rapid Access Intervention Development program, clinical oncology study section negotiations, guidelines for BSA review of extramural programs, and NCI informatics systems.

BSA members present:

Dr. David Livingston (Chair)

Dr. Frederick R. Appelbaum

Dr. Joan Brugge

Dr. Mary Beryl Daly

Dr. Virginia Ernster

Dr. Eric R. Fearon

Dr. Suzanne W. Fletcher

Dr. E. Robert Greenberg

Dr. Waun Ki Hong
Dr. Tyler Jacks
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Ms. Deborah Mayer
Dr. W. Gillies McKenna
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Sharon B. Murphy
Dr. Allen I. Oliff
Dr. Franklyn G. Prendergast
Dr. Louise C. Strong
Dr. Peter K. Vogt
Dr. Barbara L. Weber
Dr. Daniel D. Von Hoff
Dr. Alice S. Whittemore
Dr. William C. Wood

BSA members absent:

Dr. E. Robert Greenberg
Dr. David D. Ho
Dr. Joan Massague
Dr. Stuart L. Schreiber
Dr. Joseph V. Simone
Dr. Robert C. Young

NCAB liaison:

Dr. Philip 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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CALL TO ORDER AND OPENING REMARKS - DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 7th 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 discussed upcoming BSA meeting dates and asked that potential conflicts with the proposed dates be reported as soon as possible.

CONSIDERATION OF NOVEMBER 1997 MEETING MINUTES - DR. DAVID LIVINGSTON

A motion was made to approve the minutes of the 6th meeting of the Board of Scientific Advisors, which was held on 13-14 November 1997. The motion was seconded and unanimously approved.

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NCI/CONGRESSIONAL RELATIONS - MS. DOROTHY FOELLMER

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities, reported on the status of appropriation hearings on the President's Budget for FY99, staff changes in the Senate and House of Representatives Subcommittees for Labor, Health and Human Services, and Education, and congressional briefings involving NCI and NIH staff. Members were informed that several resolutions introduced in the House and Senate support funding increases for the NIH over a number of years. Provisions in and status of legislation in the House and Senate were

summarized.

In response to questions, the following additional information was provided:

- To counteract movements in the area of health information legislation that could adversely affect certain kinds of research, an interinstitute group is developing a series of formal recommendations to the Secretary of Health and Human Services. NCI is also preparing a position statement of the issues and consequences for various kinds of research, together with suggestions about how privacy and confidentiality issues can be addressed.

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ONGOING AND NEW BUSINESS - DR. DAVID LIVINGSTON

BSA at National Meetings: Status Report - The Chair displayed a sample of the identification ribbons that will be worn by BSA members and NCI staff during "NCI Listens" sessions at the annual meetings of professional associations. A list of questions was received from the American Society of Preventive Oncology (ASPO) to be discussed during the "NCI Listens" session at the March 5 meeting in Bethesda.

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PRESENT STATUS OF PAYLINES ON NCI FUNDING POLICY - MR. STEPHEN M. HAZEN

Mr. Stephen M. Hazen, Chief, Extramural Financial Data Branch, presented an update on paylines for major Research

Project Grant (RPG) mechanisms and the annual report on funding for career and training awards made in FY97. Mr. Hazen reported that the payline for investigator-initiated (R01) grants has been set at the 24th percentile for FY98 compared with the 23rd percentile at the end of FY97. He explained that the effect of using a percentiling method for setting the payline and ranking applications is that the number of awards falling within a specific payline will increase in proportion to the increase in the total number of applications received. Therefore, the NCI would be awarding more grants in FY98 even if the payline continues at the 23rd percentile. The payline for FIRST (R29) grants remains unchanged at the 30th percentile, and the payline for program project (P01) grants is set at 135 compared with 140 at the conclusion of FY97.

In discussion, the following points were made:

- The NCI will provide information on whether the increase in the number of grants awarded is due to new investigators being funded or multiple awards to currently funded investigators.
- A report will be presented on training proposals to be developed throughout the NCI and across Divisions at the June meeting.

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**INTERIM REPORTS FROM PROGRAM REVIEW
IMPLEMENTATION GROUPS - DRS. ROBERT WITTES,
PETER GREENWALD, MICHAELE C. CHRISTIAN, AND
BARNETT KRAMER**

Dr. Robert Wittes, Deputy Director for Extramural Science, informed members of actions taken to address implementing the recommendations of the Cancer Prevention, Clinical Trials, and Cancer Control Program Review Groups. Dr. Wittes stated that because of the complexity of these

programs and their transdivisional nature and the varying degrees of specificity of the recommendations, the NCI has instituted an organized process by which models for action would be developed interactively with experts from the extramural community. He noted that interim implementation reports would be given by staff.

Chemoprevention Response Implementation Committee - Dr. Peter Greenwald

Dr. Peter Greenwald, Acting Director, Division of Cancer Prevention (DCP), reported that the general approach to implementation in the area of chemoprevention and nutrition is to establish a more formal decisionmaking advisory structure, i.e., on an ad hoc preliminary basis, for developing large-scale prevention trials. Two-thirds of the members will be extramural scientists and one-third of the members being NCI staff. The intent is to ask the broad committee to consider the process, then to recommend clinical development for five agents or situations. The same committee would be asked to critique and refine the process on the basis of these five test situations before establishing the permanent advisory process for receiving and reviewing proposals for large-scale prevention trials. He stated that selective cyclooxygenase 2 (COX2) inhibitors, selective estrogen receptor modulators (SERMs), and selenium compounds were chosen for the first three agents for the tests. He presented results from epidemiological, preclinical, and early clinical studies, which formed the basis for selecting these agents as priorities. Dr. David Alberts, University of Arizona in Tucson, has agreed to serve as chair. Dr. Greenwald reported that the redesigned PDQ database and DCP's Human Intervention Studies (HINTS) computerized data system, with enhancements, will be the major databases for chemoprevention trials.

Nutrition Response Implementation Committee - Dr. Peter Greenwald

Dr. Greenwald reported that the Nutrition Response Implementation Committee held an NCI-wide planning

meeting. Because response to nutrition issues extends beyond the NCI, plans are to form an advisory group that includes representatives from the Food and Drug Administration (FDA), other federal agencies and institutes as appropriate, and the extramural community. This group would work with the NCI to establish directions for nutrition research.

In discussion, the following points were made:

- A question was asked about the envisioned interaction between the BSA and the proposed advisory committees, respective responsibilities, and response to the interim report expected from members at this meeting. It was noted that developing a peer-review decision making process for large-scale prevention trials, Chemoprevention, and other areas was the leading recommendation from the BSA's Cancer Prevention Program Review Group. The special advisory committees that are being developed in response include BSA members and will report to the BSA periodically. The BSA was described as having broad oversight responsibility and the advisory committees as providing a closer degree of interaction on operational issues such as decision making about specific drugs, programs, and protocols. The BSA will be kept informed of the progress in implementing the recommendations from the BSA's Program Review Groups and will have an opportunity to act on specific programs or activities as part of its responsibility for concept review.
- Identification of surrogate markers would be part of the Chemoprevention trials research effort. There is no specific plan for research that would provide information on the sensitivity, specificity, and predictive value of the 75 or more biomarkers that have been identified; however, this type of information is encouraged in the context of clinical trials, and consideration has been given to requesting such information in grant applications.

Clinical Trials Report Implementation Committee - Dr. Michael C. Christian

Dr. Michael C. Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), stated that the charge to this 37-member committee of intramural and extramural experts was to think broadly about the design of an optimal clinical trials program, using the report of the Clinical Trials Program Review Group (CTPRG) as a starting point. With Dr. John Glick, University of Pennsylvania Cancer Center, as Chair, the committee has structured its deliberations into 13 major focus areas, which encompass the CTPRG recommendations. Since December, the committee has met monthly, developed a three-point common functional vision for the clinical trials program, and reviewed ongoing NCI initiatives that address some of the major focus areas. Two subcommittees were created to review established models. One subcommittee will address accrual and access issues; the other subcommittee will address idea generation, prioritization, and concept review. Two working groups also were formed to work with staff on the development of models for the peer review system and early clinical trials system. Monthly meetings will continue until the completion date in June. The goal is to present the report and recommendations to the BSA in June and the National Cancer Advisory Board (NCAB) in May.

In discussion, the following points were made:

- One member asked whether the implementation committee would address ways to help make the existing clinical trials machine more efficient and productive rather than creating a new approach to clinical trials. Dr. Christian stated that the committee recognizes the accomplishments of the current system and is balancing that recognition with the advice from the BSA and NCAB, and considering ways to address areas that need revision yet retain what has been good and productive. Broad representation on the committee, frequent meetings, and input from CCOP investigators and cooperative

group chairs are included in the process.

- To address the issue of how clinical trials are to be reviewed to ensure the promotion of the best ideas without creating additional review hurdles for clinical investigators, the committee will develop specific proposals about peer review of the science that goes forward into Phase III trials.

Early Detection Response Implementation Committee - Dr. Barnett Kramer

Dr. Barnett Kramer, Deputy Director, DCP, stated that the early detection and screening recommendations to be addressed were taken from the reports of the Cancer Prevention and Cancer Control Program Review Groups. In preliminary NCI staff meetings, recommendations from these reports were classified into the following categories to be addressed by the Early Detection Response Implementation Committee: (1) advisory process, resources, and prioritization; (2) screening studies; and (3) molecular early detection and exposure or risk markers. Other recommendations from these reports will be addressed by the Cancer Control Response Implementation Committee. Dr. Kramer stated that a series of questions have been compiled from the recommendations and will be sent as part of the information package to the full committee prior to the first meeting. This committee, like the others, includes a broadly representative group of experts from the extramural community and from across the Institute, with Dr. Bernard Levine, Vice President for Prevention, M.D. Anderson Cancer Center, and Dr. Kramer as co-chairs.

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Dr. Barbara Rimer, Director, DCCPS, stated that the recommendations in the Cancer Control and Cancer Prevention Program Review Group reports have been used in organizing the new division. She described the DCCPS as embodying a rational structure for cancer control, with the Office of Cancer Survivorship operating out of the Office of the Director and three organizational components headed by associate directors in the following program areas: Epidemiology and Genetics Research, with two branches; Behavioral Research, with six branches; and Surveillance Research, with two branches and four sections. Dr. Rimer listed review group recommendations that have already been or are being implemented in developing the infrastructure and in program initiatives already issued or pending review as RFAs. Plans were described for other recommendations that will be implemented when the infrastructure is in place or the science base is better understood.

Dr. Rimer discussed research directions and process issues in each program area, highlighting some of the specific initiatives. Short-term implementation groups will be convened in the area of surveillance and tobacco research to address specific questions about surveillance, the future of surveillance at the NCI, and the development of a tobacco research process plan. Additionally, *ad hoc* groups will be convened to advise about various aspects of behavioral research, toward the goal of balancing the research portfolio of the Behavioral Research Program. Additional information about DCCPS genetics and epidemiology initiatives will be presented at the June BSA meeting.

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

- The DCCPS has taken steps to formalize interactions with other institutes with initiatives in the areas of tobacco, as it plans a tobacco research process and will do the same when diet and physical activity initiatives are addressed at a later date.
- The tobacco research implementation group will address both basic tobacco research and tobacco

policy research, the latter in conjunction with the Agency for Health Care Policy Research (AHCPR).

- Organizational locations in the NCI for intramural behavioral research, if undertaken, and studies of palliative and other types of supportive care have not yet been identified. In accord with the Bishop-Calabresi Report, intramural behavioral research would be part of the Intramural Research Program and would fall within the purview of another division.
- The proposed colorectal screening and surveillance program will be modeled after the Breast Cancer Screening Consortium. Plans are to present to concept initiatives at the June BSA meeting.

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RAPID ACCESS TO INTERVENTION DEVELOPMENT - DR. ROBERT WITTES

Dr. Wittes requested BSA approval of a new program entitled "Rapid Access to Intervention Development" (RAID) for BSA approval. RAID is a program that would bring some of the NCI's existing resources for developing large and small molecules to the service of academically based drug discovery on a competitive basis. The program would enable the transition of small or large molecules through preclinical development to the clinic for proof-of-principle clinical trials. Dr. Wittes stated that, although details have not been worked out, the intent would be to advertise the existence of this program twice a year, and impanel a group of extramural experts and NCI staff to evaluate incoming proposals according to established criteria. The number of projects to be supported in any review cycle would be a function of the level of merit and availability of funds. Strength of hypothesis and scientific novelty would be important criteria in establishing merit. Metrics have been suggested by which RAID could be evaluated after several cycles of review. Dr. Wittes stated that the next step, if the proposal is approved in concept by the BSA, would be public

announcement as soon as a review panel and review procedures have been established.

Motion: A motion was made to approve the RAID program, with the provision that metrics for the evaluation of funding and scientific progress be developed and presented for BSA review in 1 year and at subsequent intervals. The motion was seconded and unanimously approved.

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BSA WORKING LUNCH - DR. DAVID LIVINGSTON

The BSA lunch discussion was devoted to reports on metrics for the SPORE program, Data Safety Monitoring Boards for NCI-Sponsored Clinical Trials, and program project (P01) grant review issues.

Interim Reports: Metrics for the Spore Program - Dr. Franklyn G. Prendergast, acting for Dr. Robert C. Young, reminded the Board that the objective of the *ad hoc* committee meetings was to develop criteria or metrics for evaluating SPORE programs and their progress. Dr. Prendergast noted that the committee worked to attach specific measures to assessment issues that have already been identified as important and is reevaluating the priorities among the criteria. Principal criteria in order of importance were: (1) the program should exhibit significant (and substantial) advances toward the diagnosis, prevention, or treatment of cancer; (2) the research should be definitively and totally translational in nature and include a population science component; (3) the research program should be scientifically novel, intrinsically and for the particular institution; (4) the program should promote collaboration to develop interdisciplinary or multidisciplinary approaches; and (5) value should be added by the SPORE program in a particular institution. Dr. Prendergast stated that issues yet to be addressed are: makeup of the evaluation committee; the timetable for the

review; consequences of the evaluation; and optimal size of the SPORE program. The final report of the BSA Subcommittee charged with developing metrics for evaluating the SPORE program will be presented at the June BSA meeting. If possible, materials for the report on "Metrics for the SPORE Program" would be provided to the BSA prior to the June meeting.

Data Safety Monitoring Boards (DSMB) for NCI-Sponsored Clinical Trials - Dr. Christian reminded the Board that an *ad hoc* task force had been formed to coordinate the development of a workshop on the issue of whether disease committee chairs should have routine access to interim data for ongoing clinical trials as they plan subsequent studies. She reported that a DSMB workshop has been planned in conjunction with the June 11 meeting of clinical trials cooperative group chairs. Data from Cooperative Group reports received prior to the June 1998 Data Safety Monitoring Boards (DSMB) workshop for NCI-sponsored clinical trials should be sent to all meeting participants. The planned DSMB meeting should be announced during the BSA "NCI Listens" session at the upcoming ASCO meeting. Cooperative Groups and consumer advocates should also be informed.

Final Report: Program Projects (P01s) Review Issues - Dr. Livingston reminded members that the BSA had recommended, as the result of a vote in November, that the second-level review of P01 applications by the NCI-IRG Parent Subcommittee(s) be eliminated in favor of a more streamlined process. Dr. Marvin Kalt reported that information-gathering discussions or interviews had been held with all constituencies, including the Extramural Advisory Board, current free-standing P01 review committees, program and review staff, applicants, the NCAB, and the Executive Committee. He stated that, at the present time, the prevailing message was to keep the current two-tier review, and the NCAB recommended that the Executive Committee consider the best way to review P01s from their perspective. Dr. Kalt presented the rationale for this decision and briefly described a "hybrid review" model.

He noted that the model had been developed and is available to consider as an option in the future if resources for peer review should become limiting or other factors intervene.

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STATUS REPORT: CLINICAL ONCOLOGY STUDY SECTION NEGOTIATIONS - DR. ELVERA EHRENFELD

Dr. Elvera Ehrenfeld, Director, Center for Scientific Review (CSR), NIH, presented an update on the CSR plans for reorganizing the NIH clinical research review processes. The reorganization was undertaken to address concerns of the clinical research community and within the CSR, implement the NIH commitment to take advantage of current opportunities to translate scientific discoveries into solutions to human health problems, and ensure that all fields of biomedical research get a fair and high-quality review in the CSR. Dr. Ehrenfeld reported that Dr. Michael Simmons, University of North Carolina, was recruited to work part-time on the design of the new process and as liaison with the clinical research community. CSR staff, with the help of Dr. Simmons, have formulated a set of proposals for changes in the CSR review of clinical research applications. Members were informed that CSR staff approached the task by proposing cardiovascular and clinical oncology research as two scientific area clusters where about one-half of the problem clinical research applications might readily be organized. A reorganization plan for these cluster review groups to create a new venue for the exclusive review of patient-oriented translational and small clinical experiment research. Another set of possible solutions has been developed to handle the half of clinical research applications that are too diverse to be clustered. Dr. Ehrenfeld noted that proposals for change will be implemented slowly and with sensitivity. The CSR recognizes the importance of defining objectives and goals from the outset to be used later in evaluating the new review organization and processes and is setting up an Evaluation Office within the CSR. Suggestions for evaluation metrics

and continued dialogue with and input from BSA members as the CSR continues to analyze review patterns and formulate proposals are welcomed. Members were informed that the CSR plans to join with some of the institutes in the coming year to explore the timeliness and desirability of establishing an infrastructure within the CSR for the review of some of the larger multicenter clinical trials, including outcomes and health services research.

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

- The intent in implementing the reorganization and new review processes is to move the clinically focused portion of clinical oncology review into a new venue where a rigorous but fair review is accorded to all grants, without regard to workload. Study sections will be constituted with the appropriate proportions of core and ad hoc members needed to look at the science that is being reviewed at any given time.
- Members were asked to suggest metrics to evaluate the new CSR organization and process for grant review and for potential study section nominees, particularly epidemiologists.
- The CSR is establishing extensive training efforts for CSR staff, study section chairs, and reviewers. The subject of grading study section performance, but not individual reviewers, is under discussion. Scientific opportunities that are propelling science into new and different areas underscores the need for a change in mindset in the biomedical research enterprise, which can only occur with time and through the accumulated efforts of a large number of activities (e. g., the recently implemented changes in NIH's review criteria).
- BSA representatives to the ASCO need information on clinical translational research review prior to that meeting.

- BSA representatives to the ASPO meeting need information on the review by Epidemiologic and Disease Committee 2 (EDC-2) of epidemiologic and prevention grants and what the NIH is doing in these areas. BSA representatives also need information on how blue ribbon panels are constituted.
- Once the new clinical research study section is implemented, the number of applications received and funded should be tracked.

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GUIDELINES FOR BSA REVIEW OF EXTRAMURAL PROGRAMS - DR. ROBERT WITTES

Dr. Wittes presented for Board consideration a draft of "Guidelines for Review of the Extramural Activities of the NCI," explaining that the document attempts to outline a philosophy for review, the kinds of responsibilities NCI staff should have, and the kinds of accountability NCI's extramural programs should have to the communities they serve. He emphasized the rigor that is expected of the reviews and the fact that they will be program centered, with the purpose of ensuring that the programs are responsive to the scientific, medical, and population needs at any given time. Dr. Wittes stated that the attempt in developing this document was to stipulate general guidelines that reviews should follow, recognizing the diversity of the extramural programs and the variety of activities that program staff accomplish. He pointed out that the quadrennial review cycle was replaced by a more feasible 6-year cycle, in which two reviews would be scheduled each year.

In the discussion, the following comments and suggestions were made:

- One member commented on the difficulty of reviewing the research component of an extramural

program because of the need to avoid even the appearance of conflict of interest. Another member suggested the need to include in the pre-review materials the rationale and justification for a research component as opposed to using the more traditional academic approach.

- Others commented that there should be at least two BSA members on the review committee, and the stipulation that members of the review committee cannot have coauthored a publication with any member of the unit being reviewed within 5 years should be reinterpreted because of the proliferation of consortia and networks being developed.
- A member emphasized the need to consider how the review committee would evaluate the quality of counseling for applicants on the submission of amended applications and whether attention is being given to first-time applicants, new and minority investigators.
- Another member emphasized the need to stipulate a specific format and content of the narrative of pre-review documentation. It was suggested that directors of the divisions under review would prepare a draft for the BSA review committee of what is appropriate to be included in the review.

Motion: A motion was made to support the "Guidelines for BSA Review of the Extramural ProgramsI" with modification of the guidelines with regard to specific format and context of review documents prepared and submitted by program staff; documentation should be standardized, high-quality data. The motion was seconded and approved unanimously. In conjunction with the Division Directors and Deputy Director, DDES, an ad hoc subcommittee was formed, Drs. Vogt (Chair), Appelbaum, Murphy and Hong, to help draft a standardized report format to be used during BSA reviews of NCI extramural programs/activities. The subcommittee will report back to the Board in June or November. The Executive Secretary is Dr. Gray. (**Note: Dr. Austin will do the first draft.**)

RFA/RFP CONCEPTS: PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Control and Population Sciences

Basic Biobehavioral Research on Cancer-Related

Behaviors (RFA) - Dr. Barbara Rimer, Director, DCCPS, stated that the intent of this RFA is to promote research on the biobehavioral basis of cancer-related behaviors, research that elucidates how biology, behavior, and environment are linked to cancer-related behavior. Preintervention designs are being sought, which can include analogue or laboratory research. She noted that, whereas, the previous cancer control paradigm placed emphasis on intervention research, the Prevention and Cancer Control Working Groups, as well as the Working Group on Behavioral Research in Cancer Control, have recommended the change in course to basic behavioral research as the necessary research and development step toward more effective interventions. In a portfolio analysis, this area of research was found to be more or less unfunded by the NCI and NIH and has been largely ignored by population scientists. Dr. Rimer presented rationale for choosing the RFA as the best mechanism to stimulate the critical mass of research needed to move the field forward.

Approximately 10 R21 (exploratory/development) awards, each for approximately \$100K per year in direct costs for 1 to 2 years duration are anticipated.

In discussion, the following points were made:

- One important end result of this type of research is the possibility that it might lead to sophisticated treatment matching such as tailoring interventions to individual biological differences for greatest

efficacy.

- The concept narrative should be modified to reflect the role of socioeconomic and cultural determinants in large-scale cancer control intervention trials and to clarify the need for understanding mechanisms. The definition of cancer control also should include genetic interaction. Language should be included to encourage pediatric investigators to apply.
- Some milestones to measure the success of this mechanism might be the number of new investigators brought in, the number of R01s funded, and the number of papers published. Creating a cohort of new investigators is the subtext for increasing the knowledge base in areas where knowledge is limiting the ability to craft better interventions.

Motion: A motion was made to approve the DCCPS concept for the RFA entitled "Basic Bio-behavioral Research on Cancer-Related Behaviors," with revisions to the Background and Objectives Section as recommended by BSA members. The motion was seconded and unanimously approved.

Health Communications in Cancer Control (RFA) - Dr. Sherry Mills, Acting Branch Chief, Cancer Control Research Branch, stated that the purpose of this proposed project is to stimulate research on the use of new communications technology, such as the World Wide Web, interactive kiosks, and voice response systems, for preventing and controlling cancer as well as for refining and evaluating systems to deliver cancer-related information. Another objective would be to develop optimal communication strategies to reach underserved populations, the elderly, ethnic minorities, and rural and low-literacy populations. Research envisioned for support under this RFA would refine the technology and message content. Dr. Mills stated that an analysis of the current NCI portfolio revealed few grants that focus major attention on health communications. She presented rationale for using the RFA

mechanism, noting that the research envisioned is inherently multidisciplinary, and many of the disciplines have not focused on cancer control problems in the past.

This concept for a nonrenewable RFA proposes 8 to 10 R01 awards for up to 4 years each, with a set-aside in year 1 of \$2.5M in direct costs.

In the discussion, the following suggestion was made:

- Because of the broad dimensions of this research, the narrative introduction should include an emphasis on the theoretical aspects of the communications process and background on tailored health studies.

Motion: A motion was made to approve the DCCPS concept for the RFA entitled "Health Communications in Cancer." The motion was seconded and approved with one abstention.

Division of Cancer Treatment and Diagnosis

In Vivo Efficacy in Disease-Related Models (RFP) - Dr. Edward Sausville, Associate Director, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis (DCTD), stated that the goal of this proposed request for proposals (RFP) would be to establish a master agreement that would provide a venue for examining candidate agents or biological constructs for evidence of in vivo activity. This proposal would define a means for a compound to be shown as affecting a molecular process in vivo rather than merely demonstrating empirical antitumor activity. Relevant targets would be apoptosis, hormone receptors, transcription factors, angiogenesis, and metastasis. Successful offerors would demonstrate facility in immunochemistry, gene expression, and physiologic measures. Other criteria for selection are prior experience and demonstrated accomplishment in the target molecule, process, or disease site and the ability to define drugs that target particular molecules, not simply affect tumor growth. This RFP would seek to form an alliance with scientists who already have an independent research program in the area of

interest. An important characteristic of the master agreement is that the mechanism would be activated only for a particular question and more than one agreement holder then could be used.

The requested funding levels (up to 10 awards of \$50K per year) are anticipated to be sufficient for evaluation of 10 different compound/molecular target pairs per year.

In discussion, the following points were made:

- The Developmental Therapeutics Program Review Group is in the process of trying to define a better algorithm for junior compounds to go into the clinic. This proposal promises to provide more information on novel mechanisms and animal model systems.
- When asked whether the work envisioned under this RFP would be restricted to molecular targets or could include developing models such as the SCID mouse, which has an immunological connotation, Dr. Sausville stated that the narrative could be written to be as inclusive as possible.

Motion: A motion was made to approve the DCTD concept for the RFP entitled "In Vivo Efficacy in Disease-Related Models." The motion was seconded and approved with two opposing votes.

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INFORMATICS AND THE NCI - DR. JOHN SILVA, DR. MICHAELE CHRISTIAN and MS. NANCY SEYBOLD

Clinical Trials Informatics: Dr. John Silva, Program Manager, Defense Advance Research Projects Agency (DARPA), and part-time NCI communications expert, presented an update of progress in developing Clinical

Trials Informatics, an initiative recommended in the report of the Clinical Trials Program Review Group. Dr. Silva stated that the goals are to create an approach to clinical trials that capitalizes on technologies already in use in the business community, develop usable standards that could simplify trials significantly, and provide secure cancer information on a need-to-know basis to exploit the most promising discoveries. Core principles for the clinical trials enterprise are that it be user focused, simple, private, standardized, and of value to the prospective users. A public-private partnership that engages the entire cancer community is envisioned to develop the national-scale blueprint. He described how the clinical trials repository of agreed-upon standards will be used to conduct and manage the clinical trials of the future using the national infrastructure of information superhighways. Products scheduled for completion in 1998-1999 include breast and prostate data models. Pilot sites have been chosen to test the models in actual clinical settings, and a long-range planning committee is being established.

CTEP Information Management Initiatives: Dr. Michael C. Christian, Associate Director, CTEP, reported on how the clinical informatics initiative will be applied in discharging CTEP's responsibility for supporting and coordinating clinical trials to evaluate anticancer therapies. Dr. Christian stated that this function involves responsibility for disease-oriented treatment development, clinical development of new anticancer treatments, drug distribution, responding to multiple regulatory requirements, and quality assurance. The inefficiencies of previous paper-based reporting systems, redundancy and duplication of data requests, problems with incompatible databases within CTEP, across the Institute, and with collaborators, and the need to balance the administrative burden of these medical and scientific objectives were described. She reported that the CTEP initiative to address these problems began with a needs assessment in 1995 and working groups organized in 1996 to develop implementation approaches. In 1997, the Clinical Data Update System (CDUS), Adverse Event Report System (AERS), computer support for reporting and revising Common Toxicity Criteria (CTC), and CTEP informatics infrastructure were developed. The information

management process in the areas of standards development, dictionaries, and coding has been integrated within the Institute and NIH, and with DHHS, FDA, industry, cancer centers, cooperative groups, and international participants. All systems developed to date have been translated and coded into the international medical terminology, which was developed by the International Committee for Harmonization. An extensive training program is planned for CDUS and AERS users nationwide. Dr. Christian called attention to the timeline for CTEP Information Management Initiative projects, approximate times for completion, and ongoing project tasks so that individuals in the cancer research community can appreciate where opportunities for interaction may exist. This information will be available on the CTEP Web site. An online demonstration of the Web-based Clinical Data Update System concluded the presentation.

Clinical Trials Web Site: Ms. Nancy Seybold, Office of Clinical Research Promotion, ODDES, stated that the Clinical Trials Web site, as planned, is intended to raise the profile of cancer treatment trials within the cancer community and with the general public and to address some of the perceived barriers to participation in trials. Primary audiences being targeted are cancer patients and their families, at-risk individuals, and the entire spectrum of health care professionals that comprise the gateway to cancer care decisions. Secondary audiences are NCI partners, cancer-related organizations, health plans and the payer community, and information providers. Ms. Seybold explained that the Web site is intended to accomplish the separate but interlinking tasks of delivering information and communicating the proactive message that clinical research is a crucial means of advancing cancer care, often provide the best available care, and should be considered as part of cancer care decisions. She noted that the site is being designed to complement the NCI's existing pool of trials information, such as the Physicians Data Query (PDQ), and to extend the reach and usefulness of those resources by providing a comprehensive pool of trials information together with the tools for accessing that information and using it to make decisions about participation. Ms. Seybold

reported that a Web Site Working Group has been formed to assist in navigating the abundance of clinical trials information that is available from different parts of the Institute and to serve as liaisons to their respective areas within the Institute. The initial launch of the Web site is planned for the May American Society of Clinical Oncology (ASCO) meeting. In conclusion, a list of Web site contents planned to date and demonstrated features of the Web site interface were presented.

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

- One member suggested the need for planning for evaluation to find out how many people use the Clinical Trials Web site and, importantly, how many were accrued to clinical trials as a result of Web site usage.
- Cancer centers and other collaborating institutions need to know the rating requirements for the Clinical Trials Enterprise as rapidly as possible so that integrated systems can be developed. Payers, managed care organizations, state health departments, regulatory agencies, and primary care physicians also should be consulted.
- The explosion of biologic information about cancer, correlative science, and outcomes research must be accounted for in the effort to simplify and create minimum datasets. Clinical research assistants responsible for entering data from primary patient records in the centers and cooperative groups, will need training on the new hardware platforms.
- One member suggested the need for proactive steps to ensure that paperless, Web-based medical records developed by independent institutions are compatible with the format of the CTEP Clinical Trials Enterprise.

CRITICAL ISSUE: INFORMATICS SYSTEMS FOR CANCER RESEARCH - DR. SHEILA TAUBE

Dr. Sheila Taube, Chief, Cancer Control Research Branch, discussed informatics problems related to the Institute's goal of ensuring that there is an infrastructure that can make a broad spectrum of human specimens with associated clinical and outcome data available for research. Some of the initiatives undertaken to address technical, ethical, social, and legal deterrents were described. Dr. Taube stated that current climate supports the notion that explicit informed consent should be obtained for the collection, storage, and research use of tissue, even specimens that would otherwise be discarded, and that current general practice does not include explicit consent. She presented, as one possible means to address this problem, the model consent form developed by the Ethical Issues Subcommittee of the Biological Resources Working Group of the National Action Plan on Breast Cancer.

Dr. Taube addressed the legal issues surrounding the use of specimens, legislative activity at the state level and the differences in the laws that have the potential to affect the ability to do multiinstitutional research, and the technical issues surrounding access to human specimens and the associated clinical information. She stated that the next steps are to integrate pathological data information needs with ongoing data definition informatics efforts and develop informatics systems that can implement the one-way flow of information. Members were told that a series of concepts to address these informatics challenges will be presented for BSA consideration in the coming year. Dr. Taube stated that the NCI seeks to implement some technological responses that will protect patient information on the theory that, with an effective system for encryption, research on specimens could be considered minimal risk under the new Office of Prevention from Research Risks (OPRR) regulations, and there could be a waiver of need for informed consent.

In the discussion, the following key points were made:

- BSA members expressed concern about: (1) the apparent trend toward requiring a consent form specifically for tissue research because of the affect to population-based studies where a good response rate is needed; (2) the added hurdle to researchers and added burden to the patient; and (3) how informed consent is envisioned for past specimens (legacy databases) and how consent is to be obtained on current specimens. In the ensuing discussion about who will be making these decisions, it was noted that the National Bioethics Advisory Commission (NBAC) will be issuing a judgment on these issues in its next session, which will influence the actions of institutional review boards, OPRR, and Congress. NBAC discussions will be available on a Web site and open for public comment for a short period. At that time, it will be important that the implications for research are articulated, especially retrospective research, together with the concern for patient privacy and confidentiality issues.

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**RFA CONCEPTS: PRESENTED BY NCI PROGRAM STAFF
(cont'd)**

Division of Cancer Treatment and Diagnosis (cont'd)

Image-Guidance for Radiation Therapy Planning (RFA) - Dr. Daniel Sullivan, Associate Director, Diagnostic Imaging Program, DCTD, presented the concept for Image-Guidance for Radiation Therapy Planning on behalf of both the Diagnostic Imaging Program and Radiation Research Program. Dr. Sullivan stated that the RFA is in response to the need to improve the precision and standardization of target definition and to incorporate anatomic and functional imaging data in the planning for radiation therapy using the sophisticated new 3-D conformal radiation therapy (3DCRT)

machines. The clinical goals of improved tumor definition would be to increase the dose to the tumor and reduce the dose to normal tissue. NCI workshops in 1994 and 1997 identified the need for research on the development of technologies to reduce the uncertainties of dose delivery to target tissues and surrounding structures. As justification for use of the RFA, he cited the paucity of investigations currently in the NCI and NIH portfolios, logistic hurdles in terms of validation issues, and the need for interaction among relevant clinicians, mathematicians, and computer and image-processing scientists. The concept, if approved, would be advertised through mechanisms that would target applied mathematicians.

A set aside of \$1.8M per year for 5 years is requested based on funding six grants at approximately \$300K per year each. The total for 5 years would be \$9M.

In discussion, the following key points were made:

- The important problem related to validation was not addressed in the RFA. It was noted that the issue of precision was already being addressed in other grants.

Note: Staff withdrew the concept.

Office of the Deputy Director for Extramural Science

Mouse Models for Human Cancers Consortium (Cooperative Agreement) - Dr. Cheryl Marks, Program Director, Cancer Biology Branch, Division of Cancer Biology, stated that the basis for this concept was a recommendation of the Mouse Models Subgroup of the Preclinical Models for Cancer Working Group for a more coordinated effort in the area of mouse model development. The purpose would be to create a consortium of scientific laboratories and teams of scientists dedicated to the development, validation, and characterization of mouse models for human cancers. The initiative as proposed would provide each individual laboratory the flexibility to explore innovative, new technologies and would promote interaction and information exchange between the participating

laboratories and with the NCI and key research communities and networks. Dr. Marks briefly described plans for implementing the Mouse Models Consortium, which included an oversight group composed of NCI staff, the leadership of each cooperative agreement, and additional scientific expertise as needed from the Working Group and extramural community. She stated that mouse models deemed ready for dissemination would be released to the scientific community through a distribution resource that would be developed.

A total of six cooperative agreements (U01s) is estimated, each with a cap of \$500K per year in direct costs. The amount of the set aside for year 1 is \$4.5M, and the estimated cost for the 5-year project period is \$22.5M.

In the discussion, the following key points were made:

- In the planning process, discussions have already focused on broadening the scope of the development effort to include as many different types of organ sites as possible and on the need of the cooperative group to include people familiar with the histopathology and molecular genetics of the relevant human cancers.
- It was emphasized that models developed, validated, and characterized by the Consortium would be made available immediately to the scientific community. It was noted that the intellectual property issues surrounding the free dissemination and use of existing models has been a deterrent in the development of therapeutics.

Motion: A motion was made to approve the Cooperative Agreement entitled "Mouse Models for Human Cancers Consortium." The motion was seconded and approved with one abstention.

Adjournment: The meeting was adjourned at 12:13 p.m., March 3, 1998.