Board of Scientific Advisors

Meeting Minutes

November 12,1998

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

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI) convened for its 10th regular meeting at 8:30 a.m. on Thursday, November 12, 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 8:30 a.m. until adjournment on Friday, 13 November, for introductory remarks from the Chair; discussion of procedural matters and future meeting dates; ongoing and new business; presentations and discussion of the status of NCI's budget and paylines, Request for Application (RFA) concepts, reports of the Breast and Prostate Cancer Progress Review Groups, the Rapid Access to Intervention Development (RAID) program, Early Detection Implementation Group Report, how NCI communicates the National Cancer Program, accelerated review of amended program project grants, consumers in peer review, and sexennial reviews of the NCI extramural program.

BSA members present:
Dr. David Livingston (Chair)
Dr. Joan Brugge
Dr. Mary Beryl Daly
Dr. Virginia Ernster
Dr. Suzanne W. Fletcher
Dr. E. Robert Greenberg
Dr. Waun Ki Hong
Dr. Herbert Y. Kressel
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Dr. Joan Massague
Dr. Enrico Mihich
Dr. John D. Minna
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. Alice S. Whittemore
Dr. Robert C. Young
Dr. Elias A. Zerhouni

BSA members absent:
Dr. Frederick R. Appelbaum
Dr. Eric R. Fearon
Dr. David D. Ho
Dr. Tyler Jacks
Ms. Deborah Mayer
Dr. W. Gillies McKenna
Dr. Nancy E. Mueller
Dr. Stuart L Schreiber
Dr. Joseph V. Simone
Dr. Daniel D. Von Hoff
Dr. William C. Wood

NCAB liaison:
Dr. Philip A. Schein

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 10th regular meeting of the Board of Scientific Advisors 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 newly appointed Board member Dr. Herbert Y. Kressler, President and CEO, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

CONSIDERATION OF SEPTEMBER 22-23, 1998 MEETING MINUTES - DR. DAVID LIVINGSTON

Motion: A motion was made to approve the minutes of the Special Session and 9th meeting of the Board of Scientific Advisors, which was held on September 22-23,1998. The motion was seconded and unanimously approved.

BREAST AND PROSTATE CANCER PROGRESS REVIEW GROUP REPORTS - DR. ROBERT WITTES

Dr. Robert Wittes, Deputy Director for Extramural Science (DDES) and Director, Division of Cancer Treatment and Diagnosis (DCTD), reported on the NCI's progress in implementing the Breast Cancer Progress Review Group (BCPRG) and Prostate Cancer Progress Review Groups (PCPRG) recommendations. Progress Review Groups were instituted by the NCI Executive Committee (EC) to measure systematically the progress of NCI's programs toward addressing current research opportunities in prevention, early detection, and treatment in particular disease sites, beginning with breast and prostate cancer. Board members were informed that although many recommendations were highly specific to breast or prostate cancer, the processes of the BCPRG and PCPRG produced similar recommendations, e.g., both recommended increased attention to the biology of the organ from which the cancers arise; similar processes were recommended for outlining the steps in carcinogenesis; both reports identified the need for better markers for risk, early detection, and prognosis; and both recognized the need for better infrastructures and procedures for clinical trials and the need for more training. Dr. Wittes stated that the NCI is analyzing the reports and that NCI responses to the reports will be discussed at a January PRG meeting.

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

- Progress in other disease sites will probably be assessed in

the future, although the precise process and methodology for conducting the reviews remains to be decided.

- A report, matrix, and progress map on the plans that will be implemented as a result of the Breast Cancer and Prostate Cancer Progress Review Group Reports should be given at a future meeting.

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ONGOING AND NEW BUSINESS - DR. DAVID LIVINGSTON

BSA at National Meetings

Cold Spring Harbor Symposium (CSHS) Report - BSA members at the CSHS NCI Listens session reported good attendance and vigorous discussion among the attendees. Questions centered around the peer review and appeals process, clarification of grants mechanisms, triage, funding decisions, issues related to encouraging graduate students to enter the oncology research field, transition support between the end of the postdoctoral fellowship and beginning of an academic post, funding for informatics, and problems with the NCI Web site. The consensus of BSA members was that the CSHS session was constructive and should be repeated at the next biennial symposium, as requested by the leadership.

Subcommittee Report: Discussions with American Association of Clinical Oncology (ASCO) - Dr. Barbara Weber, ad hoc subcommittee Chair, reported on discussions with Dr. Alan Lichter, President, ASCO Board of Directors, regarding plans for increasing the involvement of ASCO members in the "NCI Listens" sessions. Dr. Weber stated that although ASCO represents mostly academic clinical researchers, the majority of the vast, international membership are private practitioners who may not have many issues with the NCI. However, ASCO has offered to conduct a survey in the late fall or early winter using its Web site Bulletin Board to identify membership issues/concerns. It was

recommended that the BSA not hold a formal "NCI Listens" session at the May 1999 meeting since Dr. Richard Klausner, NCI Director, will speak. Questions and concerns identified in the survey will be given to Dr. Klausner to be addressed as part of the formal presentation. BSA members concurred with the proposal as presented. Dr. Weber agreed to obtain information on the makeup of the ASCO membership, in particular, the percentage of clinical investigators versus private practitioners.

1999 Schedule - Dr. Paulette Gray, Deputy Director, Division of Extramural Activities (DEA), confirmed BSA representation at the 1999 meetings: *American Association for Cancer Research* (April, Philadelphia, PA) - Drs. Mihich, Weber, Ernster, Strong, and Oliff; *American Society of Preventive Oncology* (March, Houston, TX) - Drs. Daly, Lerman, and Strong; *Oncology Nursing Society* (April, Atlanta, GA) - Ms. Mayer.

In subsequent discussion, the following points were made:

- Members emphasized the important role of primary care physicians in future clinical translation efforts and the need to continue efforts to find a suitable forum for interactions with ASCO and to involve the large ASCO contingent in a coordinated effort with the academic clinical researchers beyond 1999.

- A member suggested that NCI should consider establishing formal relationships with several major primary care societies (e.g., the American College of Physicians, American Academy of Family Practice, and the Society of General Internal Medicine) in order to translate what is learned quickly into patient care, especially at the end of prevention and early detection trials.

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SPECIAL ISSUE: RAPID (RAPID ACCESS TO PREVENTIVE INTERVENTION DEVELOPMENT) - DRS. PETER GREENWALD AND JAMES CROWELL

Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), reminded Board members that the Cancer Prevention Program Review Group recommendations were addressed by the NCI through the Chemoprevention Implementation Committee. One major recommendation was to develop a system for promoting prevention intervention development patterned after RAID (Rapid Access to Intervention Development), the treatment development initiative being tested by the DCTD. Dr. James Crowell, Program Director, DCP, reported that the RAPID initiative will support: 1) *in vitro* and *in vivo* preclinical pharmacology and efficacy studies; 2) development of analytical methods for agents in plasma and tissue; 3) acquisition of bulk drug substance; 4) scale up production from laboratory to clinical trial lots; 5) development of suitable formulations; 6) production of dosage forms; 7) stability testing programs for dosage forms; 8) Investigational New Drug (IND)-directed toxicology studies; 9) consultation for clinical trials planning of and for regulatory affairs and IND submission; and 10) early Phase I pharmacokinetics and safety clinical studies in healthy volunteers. The RAPID initiative will be supported from the master agreement contract pool (for *in vitro* and *in vivo* screening, efficacy studies in animal models, preclinical toxicology, and Phase I clinical studies) and support contract pool. While RAPID is primarily intended for academic discovery laboratories, early Phase I studies in healthy volunteers to obtain pharmacologic and safety data would be considered for support. The process and timelines for receiving RAPID proposals, conducting peer review, and initiating work were reviewed.

In the discussion, the following points were made:

- A report should be given at a future meeting on the number and cost of projects funded through RAID after the second round of applications has been processed. A status report, along with budgeted funding, on projects initiated under the new RAPID program, should also be given at a future meeting.

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REPORT OF THE DIRECTOR, NCI - DR. RICHARD KLAUSNER

Dr. Klausner reported on the fiscal year (FY) 1999 budget legislative issues, the expectations for NCI included in the language accompanying the congressional appropriation, the status of the NCI's FY 1999 budget distribution plan, and the process for making distribution decisions.

FY 1999 NCI Budget: Dr. Klausner reported that the NIH budget passed by Congress in the FY 1999 omnibus bill included a 14.5 percent increase or approximately $2B in new funding. The NCI appropriation of $2.3B represented a 15.1 percent increase or approximately $375.8M in new dollars over FY 1998. Board members were reminded that distribution of the NCI budget begins with the research projects grant (RPG) pool and proceeds to other nonRPG needs, requirements, commitments, and intramural costs associated with administering and monitoring the NCI research program. The competing grant pool, without RFAs, will receive a 28.4 percent increase in dollars. However, the payline for R01s approved in the initial policy setting by the Executive Committee (EC) is expected to continue at the 24th percentile for FY 1999, with a 2 percent decrease in downward negotiation. This payline is based on an anticipated 15-20 percent increase in R01 applications and an increase in the average cost per grant. The total number of grants funded is expected to be over 800 (compared with 736 new or competing grants in FY 1998), with a significant increase in dollars per grant. Similarly, although the dollars allocated to program project grants (P01s) will increase by 15 percent in FY 1999, the payline is expected to remain at 135. Average cost per grant will be $1.6M compared with $1.2M in FY 1998. Other RPG mechanisms and initiatives that contribute to the inability to increase the payline in FY 1999 include: 1) the special R01s for new grantees with a guaranteed success rate; 2) new R21/R33 phased innovation awards; 3) accelerated executive review (AER) up to the 35th percentile for patient-oriented research applications and 30th percentile for all R01s; 4) an increased commitment base; 5) exception funding based on Institute priorities; and 6) the new NCI policy on Program Announcements (PAs). Board members were asked in their capacity as advisors and representatives to the community to assist the NCI in answering questions about the payline, dollars, and numbers of grants.

Board members were informed that the approximately $290M in new dollars that remains after the RPG commitment is subtracted will be distributed among approximately 40 other budget lines, including the $8.3M mandated for the Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) awards, the mandated 25 percent increase in National Research Service Award (NRSA) stipends, $22M in RFAs for Specialized Programs of Research Excellence (SPOREs) and new initiatives in cancer control and prevention, funding for the Intramural Research Program (IRP), a 25 percent increase in funding for the clinical trials program, and a 25 percent increase for new training programs that span the continuum of training and career development. Details on funding allocations to NCI programs will be provided after the distribution plan for FY 1999 has been completed. Board members were informed that a series of short-term, one-time funding initiatives are being planned to stimulate research in interesting new areas of opportunity without incurring sizeable out year commitments of funding. These initiatives will be brought to the Board for a discussion on the effectiveness of this activity.

Provisions of the FY 1999 Appropriations Legislation/Impact on the NCI: Dr. Klausner reminded Board members that provisions in the House and Senate bills and the Conference Report, which represent areas of Congressional interest or concern, are taken into account in planning National Cancer Program (NCP) initiatives. Recommendations included in the FY 1999 bill were: 1) expansion of NCI's tobacco-related research portfolio with greater emphasis on behavioral, community, and state intervention research; 2) increased funding for a comprehensive breast cancer research initiative to assist in cancer control, prevention, and treatment in minority populations; 3) initiatives to address concerns of the Inspector General (IG) concerning the Cancer Information Service (CIS); 4) greater emphasis on funding clinical trials; 5) development of a plan to manage a large-scale trial to evaluate digital mammography to be presented during the FY 2000 budget hearings; 6) expansion of research on the basis for skeletal metastasis of malignancies; and 7) participation in research on hepatitis C virus. Reports were also requested for FY 2000 budget hearings on the barriers and impediments to clinical testing of new technologies and prostate cancer research over the next 5 years.

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

- Copies of the Office of the Inspector General's (OIG) report on the Cancer Information System (CIS) as well as CIS's response to the OIG recommendations should be sent to members. Focus group reports from meetings that were conducted around the country on communication, CIS, and PDQ should also be sent to members.

- The 5-year plan for space, budget, and recruitment across the intramural program will be presented at a later BSA meeting. The report will include specifics on the clinical program and the new Clinical Center.

- An *ad hoc* subcommittee (Drs. Murphy, Daly, Weber, and Zerhouni) will work with the Office of the Deputy Director for Extramural Science (ODDES) on the development of an evaluation plan for the Clinical Trials Implementation reengineering initiative. The ODDES will report to the BSA at the March 1999 meeting. Dr. Appelbaum will be asked to participate.

- Progress in the Cancer Genome Anatomy Project (CGAP) includes breakthroughs in the production of tissue libraries that have led to a significant increase in the gene discovery rate, work to make the CGAP Web site more user friendly, planning for an initiative to get 20,000 full-length cDNAs sequenced, planning for a funded initiative (i.e., Director's Challenge) to challenge the research community to use the CGAP data in developing comprehensive molecular classification schemes for cancer, and planning for short-term initiatives to ensure that the information from CGAP is used to raise the level of clinical discovery.

- A mechanism is needed for uniform distribution of CGAP-related technology to cancer centers nationwide. A funding mechanism is also needed for the broad distribution of knowledge and information from experiments in the intramural's Center for Advanced Technology, for example, on the methodology for using high-throughput analysis. The importance of linking CGAP and other advanced technology

and information back to people with cancer or at high risk for developing cancer was discussed. The NCI will prepare a report on advances being made in the development of technology for CGAP.

- Within the next year, the NCI will report to the BSA on how peer review of the Cancer Center Support Grants (CCSG) is working under the new guidelines. Technology development and dissemination as they relate to the cancer centers and the CCSG is currently being addressed.

- Additional NCI program funding allocation details should be presented to the Board following completion of the FY99 distribution plan.

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WORKING LUNCH

How NCI Communicates the National Cancer Program: Board members were reminded that this agenda item resulted from a discussion at the September meeting about the need both to inform potential applicants about the many initiatives and resources already in place at the NCI and to communicate to the general public the complete national research program in cancer. Dr. Klausner described the newly proposed "Communicating NCI's Initiatives" targeted primarily to the extramural scientific community. A print-version prototype of the communication materials was presented for Board comment. Topics included in the prototype were CGAP, Access to Extramural Funding Initiatives for Technology Development, Cancer Genetics Network, Human Specimens for Research, and Phased Innovation Awards. The 40 or more initiatives that link to the extraordinary opportunities in the bypass budget will be included in the final product. If the pilot testing demonstrates that the print version is useful, a Web version with hyperlinks to PAs, review group reports, and NCI databases will be developed. A series of slides will also be developed to be used for presentations in other venues by members of the BSA and Board of Scientific Counselors (BSC).

In subsequent discussion, the following points were made:

- BSA members should e-mail Dr. Joe Harford comments on the proposed format for "Communicating NCI's Initiatives." Drafts of the new communication materials that will describe the clinical trials system will be sent to members prior to the March meeting. The BSA will revisit this subject in approximately 6 or 9 months.

- Other avenues of communication suggested by members were: 1) distribution of a well-designed poster listing the initiatives, and 2) working with young investigators through the American Association of Cancer Research Associates Program and NCI training programs.

- New print and electronic communication materials also are being developed to describe the clinical trials system. A draft of these materials will be distributed to members.

- BSA members supported dissemination of the new communication materials to the general public as well as the extramural scientific community.

- A progress report on "Communicating NCI Initiatives" should be given at a future BSA meeting.

Accelerated Review of Amended Program Project Grants: Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), described the current NCI procedure for accelerated peer re-review (APR) of P01 grant applications. The new process applies to applications that are rated highly meritorious but fall beyond the current payline. APR involves an expedited re-review by the parent committee of salient changes in the application made in response to a summary statement. Objectives are to shorten the time for consideration of an amended application and reduce the amount of paperwork. The first applications eligible for this process will be reviewed in December 1998 and considered by the National Cancer Advisory Board (NCAB) at the February 1999 meeting. In the ensuing discussion, Board members received clarification of issues relating to the expedited return of summary statements to eligible

applicants, the status of standing study sections of the parent committees, and efforts to recalibrate P01 review committees with the intent of spreading priority scores to distinguish differences in scientific merit.

Consumers in Peer Review: Dr. Kalt reminded members of the President's and Vice President's commitment of having consumer participation at every level in NCI activities. Members were informed that NCI actions to date are the installation of consumer representation on every NCI advisory board, inclusion on several types of peer review committees, and the involvement of the recently chartered Director's Consumer Liaison Group (DCLG). Working with the Office of Liaison Activities, the DEA has developed a process by which to identify consumer reviewers. Established criteria for eligibility are: 1) involvement in the cancer experience; 2) cancer advocacy experience; and 3) the ability to communicate and advocate a position effectively, think globally, and work well in groups. Recruitment of potential advocates will be paced to match expected use. Specific review and orientation materials have been created for consumer advocates who serve as reviewers; materials have also been created for NCI staff and for members of study sections who interact with consumers.

In discussion, the following points were made:

- Guidelines should be developed to help investigators as they respond to mandates to involve the public, for example, in data and safety monitoring and concept review.

- Support of consumer advocate participation in peer review was indicated with the caveat that the process and selection be as rigorous as that used to select scientists and that the experience of the Department of Defense (DoD) be studied.

- BSA members were asked to recommend consumer advocate candidates for NCI peer review committees.

Sexennial Reviews: Dr. Wittes informed members that the major changes incorporated in the draft document entitled "Guidelines for Review of the Extramural Activities of the National Cancer Institute" as previously recommended by the Board review were: 1)

a 6 year review cycle; 2) revised format to eliminate excessive variation from review to review; and 3) identification of sections to be included in the NCI unit's review document. The sexennial reviews will evaluate whether programs are aligned with the direction of science and whether they function optimally in creating opportunities for research consistent with a successful program. In discussion, Board members debated the merit and drawbacks of the longer review interval and the need for more frequent review of research conducted by individuals in extramural programs. A request was made that budget breakdowns and funding mechanisms for the functional and scientific components of the extramural programs be included in the review documents.

In discussion, the following point was made:

- A timeline (proposed calendar) for BSA sexennial reviews will be reviewed at the March or June 1999 BSA meeting.

Motion: A motion to approve the "Guidelines for Review of the Extramural Activities of the National Cancer Institute" with the understanding that the BSA can accelerate the review schedule for specific activities as deemed necessary. The motion was seconded and unanimously approved.

RFA CONCEPTS: PRESENTED BY NCI PROGRAM STAFF

Office of Special Populations Research

Leadership Initiatives on Cancer (RFA/Coop. Agr.) - Dr. Otis Brawley, Associate Director, Office of Special Populations Research (OSPR), informed Board members that this concept draws upon a series of Leadership Initiatives launched in 1989 and funded through the cooperative agreement grant mechanism. The National Black Leadership Initiative on Cancer (NBLIC), Appalachian Leadership Initiative on Cancer (ALIC), and National Hispanic Leadership Initiative on Cancer (NHLIC) have been successful over the 10-year period in establishing a structure for information dissemination in those specific populations, increasing outreach and cancer awareness, and training community volunteers. Cooperative agreements currently funding these initiatives will end in FY 1999. Strengths and weaknesses identified in the first Initiatives have been addressed in the proposed followup

"Leadership Initiatives on Cancer," which would have major goals of: 1) building relationships between minority leaders and communities, the NCI, other NIH Institutes and Centers, and other federal agencies; and 2) building the capacity within minority and special populations communities to conduct research. Objectives would be to establish academic partnerships with major cancer centers and cooperative groups, plan and institute collaborative developmental research projects, and catalyze investigator-initiated research projects focusing on minority issues. Some features of the proposed schema are a Cancer Control Academy to plan for cancer control research, an annual summit of Initiative leadership, and mini-sabbaticals. Evaluation criteria as proposed would be: 1) structure and function of the network; 2) number of partnerships developed; 3) quality of developmental projects; and 4) number of grant applications produced. Enhanced accrual of minorities and special populations to clinical trials would also be tracked, as well as increases in the number of minority science and cancer research careers.

Six to eight awards are envisioned, each having three phases of operation: Phase I would center primarily on information dissemination and cancer awareness activities; Phase II would establish and maintain partnerships; and Phase 3 would focus on developing grant applications and conducting research. Activities begun in each phase would continue throughout the grant award period. A 5-year award is proposed, with a set aside of $6M for the first year. The anticipated cost for the project period is $30M.

In discussion, the following points were made:

- Strategies found to be effective in the first Leadership Initiatives have been incorporated in the proposed RFA, specifically, the strong linkage needed between the new Initiatives and the NCI Cancer Information Service. In addition, the first series of initiatives taught that professional educators are needed for effective information dissemination.

- Statistics on the utilization of the CIS by minorities indicate good usage from certain groups; some of the success is directly related to the first Leadership Initiatives.

- Educational and research objectives will focus primarily on cancer prevention and control, the latter in the broadest sense to include accrual to treatment trials.

- The language of the RFA should be highly focused to engender the appropriate measures of interest, participation, and commitment necessary to produce meaningful results. External advisory committees should be a requirement. An attempt should be made to link this leadership initiative with existing trans-NIH minority initiatives into a construct that will maximize efficiency and utilization of resources. Educational materials that are developed should be culturally sensitive to reach the many different societies. The RFA language also should ensure that investigators consider projects that interface with other new NCI initiatives, such as the Cancer Genetics Network.

- Baseline measures for minority and subpopulation scientists, patient accrual, and cancer awareness for the nation as a whole would be needed for use as benchmarks to gauge the success of this leadership initiative.

Motion: A motion was made to approved the RFA/Cooperative Agreement concept entitled "Leadership Initiatives on Cancer." The motion was seconded and approved with one vote in opposition.

Division of Cancer Control and Population Sciences

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences (DCCPS), reviewed the Tobacco Research Implementation Group (TRIG) recommendations in the recently completed Tobacco Research Implementation Plan (TRIP) as background information for two DCCPS RFA concepts. Dr. Rimer stated that the purpose of the TRIP was to examine the NCI's research portfolio in tobacco and determine priorities for tobacco-related research for the next 5 to 7 years. TRIG members concluded that an unequivocal commitment of the NCI to a comprehensive, focused program of research on tobacco use can help to reverse the existing epidemic of tobacco-related cancers. Board members were given a summary of NCI plans for addressing the recommendations, including initiatives that have already been

advertised through RFAs and PAs. The proposed RFAs entitled "Research in State and Community Tobacco Control Interventions" and "Transdisciplinary Tobacco Research Centers" were developed in response to two other recommendations in the TRIP. Board members were informed that the report from the Surveillance Implementation Group (SIG) will be presented at the next BSA meeting, and that recommendations in the area of tobacco research will be coordinated with those of the TRIG.

Research in State and Community Tobacco Control Interventions (RFA) - Dr. Marc Manley, Chief, Public Health Applications Branch, DCCPS, stated that the RFA concept entitled "Research in State and Community Tobacco Control Interventions" would support research on tobacco control interventions that are currently being used by states and communities. The results of this research would be applied to make tobacco control programs more effective in all 50 states and would provide information to strengthen the Nation's investment in tobacco control. BSA members were given background information on existing state tobacco control programs as a basis for understanding the information needs related to mass media campaigns and to develop state policy that has the potential to influence smoking behavior. Tobacco causes at least 30 percent of all cancer deaths. States fund the largest tobacco control programs and are the loci of most of the decisions about investment in this problem. These decisions, however, can rarely be based on rigorous research results. New and expanded state programs present an enormous need and an unprecedented opportunity for the research proposed in this concept, which would study the impact of mass media efforts for tobacco control and the impact on smoking rates of public and private policies (e.g., advertising restrictions, clean indoor air policies, youth access restrictions, and product regulation). The list of proposed research questions that would be included in the RFA announcement was developed from questions provided to the NCI by the people who administer the state tobacco control programs in all 50 states. Collaboration across studies initiated would be fostered. In discussions with other Institutes, DCCPS is exploring the possibility of obtaining additional funding for this initiative.

This concept proposes an RFA for R01 grants. Awards would begin in FY 2000. The proposed budget is $18M per year for a period of 4 years.

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

- The language of the RFA announcement should suggest more strongly: 1) that collaborations with state or community groups should be formed, and 2) that collaborative research is important, particularly if the proposed research is studying the effect of policy. A workshop should be held to provide applicants an opportunity to explore the possibilities for coordinating their research efforts. Individuals responsible for state tobacco control programs could be invited to help forge linkages with the research community.

- Experience from breast cancer control and wellness programs indicates that customized approaches are necessary to reach the diverse populations and that community leaders can play an influential role in outreach efforts. Issues related to affordability of and access to appropriate wellness services should be addressed at the outset.

- The NCI will work closely with the Centers for Disease Control and Prevention (CDC) throughout the project period toward the future transition from research status to a nationwide intervention effort.

- A bimodal budget distribution is anticipated, with some grants that may be in the $1M range and others in the range of $300K to $400K per year. The coordinating center would provide the resources needed for cross-project collaborations and ensure that results of the research are disseminated rapidly and broadly to the end users in the state health departments.

- The DCCPS Web site will be expanded over the coming year to include examples of research synthesis that more graphically convey the lessons learned in the various aspects of cancer control.

Motion: A motion was made to approve the RFA concept entitled "Research in State and Community Tobacco Control

Interventions." The motion was seconded and unanimously approved.

Transdisciplinary Tobacco Research Centers (RFA) - Dr. Robert Croyle, Associate Director, Behavioral Research Program, DCCPS, stated that the intent of the RFA concept for the development of Transdisciplinary Tobacco Research Centers (TTRCs) is to integrate, synthesize, and invigorate basic to applied translational research on tobacco use. The project would seek to overcome barriers to progress in this research area. Transdisciplinary was defined as the development and application of a shared integrative conceptual framework based on discipline-specific theories, concepts, and methods. Instead of working in parallel, investigators collaborate across levels of analysis and intervention to develop a comprehensive understanding of tobacco use. The creation of TTRCs was a high priority of the NCI TRIG. Moreover, the need for transdisciplinary research was highlighted in the Robert Woods Johnson Foundation (RWJF) Youth Tobacco Prevention Initiative. TTRCs as proposed in this concept would address research gaps in this area by: 1) creating a critical mass of investigators at the different center sites; 2) encouraging transdisciplinary collaboration within and across centers; 3) creating a unique context for training; 4) supporting pilot projects to rapidly pursue new research opportunities; and 5) providing shared resources for greater efficiency. Required features in the RFA would be at least three projects related to a theme, research that bridges disciplines and levels of analysis, and an interactive organization that promotes cross-fertilization and synergy within and across centers.

Set aside funding for the year 01 is estimated at $10M for 4-5 awards; $50M is the estimated cost for the 5-year project period. Additional funding of $4M per year would be provided by the National Institute on Drug Abuse (NIDA), and NIDA would collaborate in all phases of the TTRCs, including the project management and evaluation processes. In addition, the RWJF has expressed interest in supporting policy research and some forms of information dissemination efforts.

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

- Strengths of the proposed RFA are: 1) the use of the P50 funding mechanism to stimulate collaborations that will position the tobacco research community to respond to RFAs that will be initiated in response to other TRIG recommendations; 2) the training component; 3) collaboration with NIDA that promises to synergize the extramural programs of both NIDA and NCI and open channels to different professional organizations; and 4) the potential for synergism with NCI programs such as the Cancer Genome Anatomy Project (CGAP) and mouse model development to stimulate neuroscience research.

- In response to concerns about the possibility of overlapping research, it was noted that this concept is intended to integrate components of research already under way to develop a comprehensive conceptual model focusing on tobacco research that involves biological, psychological, and sociological levels of analysis.

- The announcement should clearly state that the RFA calls for projects focused on tobacco use, not tobacco consequences.

- Cycles of BSA review should be established for both the "Research in State and Community Tobacco Control Interventions" and the "TTRCs" as the programs are funded and progress.

Motion: A motion was made to approve the RFA concept entitled "NCI-NIDA Transdisciplinary Tobacco Research Centers." The motion was seconded and approved, with one abstention.

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EARLY DETECTION IMPLEMENTATION GROUP REPORT - DR. BARNETT KRAMER

Dr. Barnett Kramer, Deputy Director, Division of Cancer Prevention (DCP), reminded Board members that the Early

Detection Implementation Group (EDIG), co-chaired by Drs. Kramer and Bernard Levin, M.D. Anderson, was formed to develop the NCI's response to the Cancer Prevention and Cancer Control Program Review Groups' (CPPRG and CCPRG, respectively) recommendations. Specific recommendations were related to: 1) developing and expanding biorepositories with appropriate consent for testing of molecular detection strategies; 2) developing and validating intermediate biomarkers for exposure and biological effects; 3) developing new molecular markers for early detection and high-throughput assays for clinical and population-based tests of promising molecular diagnostic approaches; 4) developing databases of clinical cancer prevention trials and associated tissue resources; 5) working with the Food and Drug Administration (FDA) on matters affecting prevention; and 6) conducting comprehensive trials in high-risk populations to validate and integrate novel prevention and detection strategies and randomized clinical trials in prevention. Dr. Levin continued the presentation of the EDIG report with a review of the questions developed from the CCPRG and CPPRG recommendations, which became the charge to the EDIG, and a brief summary of EDIG recommendations for action as included in the report. The RFA to create an Early Detection Research Network was developed in response to one of these recommendations.

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RFA CONCEPTS: PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Prevention

Early Detection Research Network (RFA/ Coop. Agr.) - Dr. Levin stated that the concept entitled "Early Detection Research Network" was an infrastructure for supporting collaborative research on molecular, genetic, and other biomarkers in human cancer detection and risk assessment. The concept for this network was derived from the CPPRG, Chemoprevention Implementation Group, Breast Cancer Progress Review Group, and Prostate Cancer Progress Review Group in addition to the EDIG recommendations. Stated goals are: 1) establish a stable connection between basic

laboratory research and facilitate rapid clinical applications; 2) provide multidisciplinary expertise and multiinstitutional resources for integrated biomarker evaluation; 3) provide access for industry to academia and to various populations for clinical investigation; 4) develop and institute quality assurance for biomarker testing and evaluation; 5) establish decision criteria for the development of biomarkers; and 6) foster interaction among academic, clinical, and industrial leaders for the development of high-throughput, sensitive assays for biomarkers for cancer detection, risk assessment, and prevention. The consortium would be guided by a steering committee, an independent scientific oversight review group, and a data management and coordinating center. The envisioned consortium process would be flexible, interdisciplinary, and have the ability to foster translational research and forge collaborations with NCI-funded entities and with the extramural research community nationwide and worldwide. Board members were then given a description of how the biomarker research would flow from discovery to laboratory validation to clinical validation. Network progress would be monitored by the advisory committee through workshops and in consultations with members of the BSA and NCAB. Biennial progress reports would be presented to the BSA.

The proposed funding mechanism would be the cooperative agreement. The amount of the set aside in year 01 would be $3M for an anticipated 10-12 awards. Anticipated cost for the 6-year project period is $61M.

In discussion, the following points were made:

- Strengths of the proposed program are: 1) its response to the need for validated biomarkers that could make an impact on survival rates; 2) its potential for validating the large number of candidates for early markers that could result from initiatives like the CGAP and Cancer Genetics Network; 3) a good organizational structure and solid criteria for evaluation; 4) the emphasis on collaboration; 5) the involvement of industry; and 6) the provisions for informed consent related to future projects.

- Suggestions for strengthening the proposed project are: 1) careful definition of the roles and responsibilities of the steering committee; 2) including consumers on the steering committee; 3) including clinical cooperative groups in the

list of potential collaborators in the RFA announcement; and 4) the need to integrate the discovery of new markers with behavioral research to deal with psychosocial implications to patients.

Motion: A motion was made to approve the RFA/Cooperative Agreement concept entitled "Early Detection Research Network." The motion was seconded and approved unanimously.

Division of Cancer Treatment and Diagnosis

Multidisciplinary Functional Imaging Programs (RFA/Coop. Agr.) - Dr. Daniel Sullivan, Associate Director, Diagnostic Imaging Program, stated that the proposed RFA to establish Multidisciplinary Functional Imaging Programs (MFIPS) was developed in response to a major recommendation of the In Vivo Molecular Imaging Subgroup of the Imaging Sciences Working Group. Its purpose is to bridge the scientific gulf between basic sciences (especially genomics and intracellular pathways) and imaging sciences. Rationale for the MFIPs included the need to bring multidisciplinary investigators into close physical proximity and to provide funds for infrastructure for both research and training. As proposed, the RFA would support both P20 planning grants to establish organizational structure and perform pilot projects and P50 center grants similar to the SPORE mechanism. Developments in the field that support the initiation of MFIPs at this time demonstrate significant progress in technology that has the potential to enable specific targeted imaging for early detection of small metastases that cannot be detected by other technologies as well as targeted imaging for administration of specific therapy.

The proposed schedule for the P20 grants would feature a single receipt date, a 3-year project period at $400K per year for 6 awards. The first year commitment would be $2.4M, and the total 5-year commitment would be $7.2M. For the P50 grants, the proposed schedule includes four receipt dates , a 5-year project period at $2M per year for eight awards (two for each offering), a first year commitment of $4M, and a total commitment of $48M.

In discussion, the following points were made:

- The term "functional" in the title should be changed to encompass the concept of "subcellular function" and the language of the announcement should specifically define the scope of the proposed RFA and what is meant by "molecular imaging". The final document also should encourage institutions to commit to the formation of dedicated *in vivo* molecular and physiologic tumor imaging centers for tumors to ensure the co-localization of investigators with the appropriate disciplines.

Motion: A motion was made to approved the RFA/Cooperative Agreement concept entitled "Multidisciplinary Functional Imaging Programs (MFIPs)." The motion was seconded and unanimously approved.

Director's Challenge: Toward a Molecular Classification of Tumors (RFA) - Dr. James Jacobson, Chief, Technology Development Branch, DCTD, stated that, in introducing this concept, the NCI is issuing a challenge to the cancer research community to demonstrate the power of comprehensive molecular technologies by developing profiles of molecular alterations in tumors. The purpose of the proposed concept is to lay the groundwork for changing the language of tumor classification from tumor morphology to molecular profiles. The five-year goal is to establish robust and reproducible molecular profiles that will form the basis for new tumor classification schemes. Specific goals are: 1) establish patterns of molecular alterations that are ready for validation as the basis for tumor classification schemes; 2) establish organ-specific molecular profiles that will help identify the origin of metastatic tumors of unknown primary site; and 3) develop and execute a plan for making molecular profile data publicly available. To accomplish these goals, the proposed RFA would lead to the establishment of National Cooperative Tumor Signature Groups (NCTSGs) consisting of technology developers, engineers, basic cancer biologists, oncologists, pathologists, statisticians, and experts in bioinformatics. Collaboration between investigators from academia and industry would be encouraged. BSA members were given a brief summary of how the NCTSGs would function in relation to the application of technologies to tumor specimens, specimen selection, studies of tumors of unknown origin, access to specimens, development and use of bioinformatics and statistical tools, and public release of data. Applicants would be required to

demonstrate that collaborating institutions have considered intellectual property issues. Use of the cooperative agreement mechanisms U01 and U19 was proposed to facilitate the eventual linkage of investigators to resources that are available in other NCI-funded entities, coordinate public data release, and bring investigators together for an annual meeting.

Two receipt dates are envisioned for applications in response to this initiative, with funding in FY 1999 for awards in the first round of applications. Five years of funding is proposed for an estimated 8-10 awards. The amount of the set aside for year 01 is $10M; estimated cost for the project period is $50M.

In the discussion, the following points were made:

- NCI staff will work with the investigator community as needed to try to reach reasonable budget agreements based on size and complexity of the research endeavor.

- The research proposed in this initiative relates to and overlaps with the work of the Early Detection Research Network; therefore, good lines of communication should be established.

- A presentation on the legal issues associated with intellectual property rights and their ramifications on the scientific community should be given at the March or June 1999 meeting. [Note: The Technology Transfer Office should be consulted in preparing for this presentation.]

- The language of the RFA announcement should emphasize the dynamic nature of tissue characterization because of the therapeutic implications of knowing how a single tumor progresses over its lifetime.

- A nationally coordinated effort should be considered that would involve consumer and patient communities in the development of tissue resources.

Motion: A motion was made to approve the RFA concept entitled "Director's Challenge: Toward a Molecular Classification of Tumors." The motion was seconded and unanimously approved.

Adjournment: The 10th regular meeting of the Board of Scientific Advisors was adjourned at 11:41 a.m. on Friday, November 13, 1998.

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