Board of Scientific Advisors

Meeting Minutes

November 13-14, 2001

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

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Meeting Minutes

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI), convened for its 19th regular meeting on Tuesday, November 13, 2001, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Frederick Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, presided as Chair.

The meeting was open to the public from 8:30 a.m. until adjournment on 14 November for opening remarks from the Chair; the Acting Director's and NCI's Deputy Director for Extramural Science reports; the NCI/Congressional Relations report; the Annual Ethics Overview; ongoing and new business; the Molecular Profiling of Breast Cancer presentation; and concepts for Request for Applications (RFA) and Request for Proposals (RFP) presentations

Board Members present:
Dr. Frederick R. Appelbaum (Chair)
Dr. David B. Abrams
Dr. Hoda Anton-Culver
Dr. Esther H. Chang
Dr. Thomas Curran
Dr. Mary Beryl Daly
Dr. Waun Ki Hong
Dr. Susan B. Horwitz
Dr. William G. Kaelin, Jr.
Dr. Kenneth W. Kinzler
Dr. Herbert Y. Kressel
Dr. Caryn E. Lerman
Dr. Louise C. Strong
Dr. Peter K. Vogt
Dr. Daniel D.Von Hoff
Dr. Barbara L. Weber
Dr. Alice S. Whittemore
Dr. William C. Wood
Dr. Robert C. Young
Dr. Elias A. Zerhouni

Board Members absent:
Dr. David S. Alberts
Dr. Neil J. Clendeninn
Dr. Suzanne W. Fletcher
Dr. Tyler Jacks

Dr. W. Gillies McKenna
Dr. Christine A. Miaskowski
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal
Dr. Joseph V. Simone
Ms. Amy S. Langer
Dr. Franklyn G. Prendergast

NCAB Liaison:
TBN

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

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- Chemoprevention of Estrogen Receptor-Negative Breast Cancer: Clinical Studies (RFA/Coop. Agr.); Dr. Worta McCaskill-Stevens

Division of Cancer Control and Population Sciences
- Centers for Population Health and Cancer (RFA); Dr. Robert Hiatt

Division of Cancer Prevention and Division of Cancer Treatment and Diagnosis
- Spiral CT Lung Cancer Screening Trial (RFP); Drs. Peter Greenwald, Ellen Feigal, John Gohagan, Daniel Sullivan, and Robert Wittes

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I. CALL TO ORDER AND OPENING REMARKS - DR. FREDERICK APPELBAUM

Dr. Appelbaum called to order the 19th regular meeting of the BSA and welcomed members of the Board, National Institutes of Health (NIH) and NCI staff, guests, and members of the public. Members were reminded of their responsibilities regarding conflict-of-interest issues.

II. CONSIDERATION OF 25-26 JUNE 2001 MEETING MINUTES - DR. FREDERICK APPELBAUM

Motion: The minutes of the 25-26 June 2001 BSA meeting were unanimously approved.

III. REPORT OF THE ACTING DIRECTOR, NCI - DR. ALAN RABSON

Dr. Alan Rabson, Acting Director, observed that he has worked for

eight different NCI Directors during his career at the Institute. Dr. Rabson gave a brief overview of NCI's history and the status of the current search for a new Director. Specifically, members were told that in 1971, when the National Cancer Act was passed, the original intent of the legislation was to remove the NCI from NIH and create a separate program that reported directly to the President. The scientific community expressed many concerns about the impact of this change on biomedical research, in general, and cancer research, in particular. A compromise left the NCI within NIH but also gave the Institute special privileges. Those privileges included Presidential appointment of the Director, the establishment of special advisory Panels, the National Cancer Advisory Board (NCAB) and the President's Cancer Panel (PCP), and power to develop a Bypass Budget which would be delivered directly to the President. To ensure that the NIH Director had a higher status than the NCI Director, it was also decided that the NIH Director would be a Presidential appointee with Senate confirmation.

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IV. REPORT OF THE NCI DEPUTY DIRECTOR FOR EXTRAMURAL SCIENCE - DR. ROBERT WITTES

NCI Personnel Changes. Dr. Wittes reviewed recent NCI personnel changes: 1) departure of the former NCI Director, Dr. Richard D. Klausner; resignation of Dr. Susan Seiber as Director, Office of Communications (OC) and the selection of Ms. Mary McCabe as Acting Director of the OC; departure of Dr. Carol Dahl, Director of NCI's Office of Technology and Industrial Relations (OTIR); Ms. Diane Bronzert, appointed as Associate Director for Review and Program Coordination within the Division of Extramural Activities (DEA).

Budget Levels. Dr. Wittes reported that NCI obligated $3.754B in fiscal year (FY) 2001 representing a 13.8 percent increase over the previous year. Research Project Grants (RPGs) totaled $1.7B, approximatly 45 percent of the budget. He noted that this included 1) $417M for 1,100 competing awards; RFAs at approximately $29M, or about 7 percent of the competing pool; Cancer Centers,

approximately $34M, or about 17 percent; and Specialized Programs of Research Excellence (SPOREs), approximately $77M, nearly a third more than in FY 2000. Intramural research, at $15.1M, continued to decline as a percentage of the total budget.

Dr. Wittes informed members that pending approval of the FY 2002 budget, the NCI is operating under a continuing resolution and spending is limited to FY 2001 levels. The President's FY 2002 budget request includes $4.177B for the NCI, increasing the budget by 11 percent. He stated that funding approved by the House of Representatives is close to that amount and the Senate's proposed figure is approximately $80M higher.

RPG Pool: The NCI's objectives for the Research Project (RPG) pool are to 1) fund approximately the same number of new and recompeting awards as last year, 2) continue using the exceptions pool, and 3) continue the Accelerated Executive Review (AER) program. The Institute will fund applications of high priority that fall below the payline, including the R01 Star awards, certain priorities articulated in the Bypass Budget, and the recommendations of various Progress Review Groups. He noted that the Institute is approaching cost control in several ways: 1) capping allowable increases in major RPG mechanisms; 2) controlling the rising average cost of awards; 3) continuing downward negotiation; and 4) restraining the growth of the RFA line.

Dr. Wittes explained that Type 5 RPG commitments, which are noncompeting continuations, will require an increase of $170M, representing a substantial portion of the Institute's expected budget increase. Members were told that the NCI anticipates an increase of 4 to 8 percent in the number of R01 applications received, continuing a trend over the past several years. In order to maintain the same success rate as 2001, the payline may have to drop slightly. The recent restrictions placed on large grant submissions seems to have had an effect on the average cost of grants; if this trend continues, Dr. Wittes observed, the Institute may be able to fund competing R01s at levels closer to those recommended by study sections. The 20 percent cap on Type 2 R01 and P01 applications will continue; and exceptions will be infrequent. Because applications that request increases greater than 20 percent are not always identified upon submission, some will require downward negotiation after they have received a fundable score.

The increase in P01 applications and the cost of Type 2 renewals of large grants may require a reduction in the success rate for P01s.

Dr. Wittes reported that the NCI intends to keep funds allocated to RFAs at around 7 percent of the total competing budget, which is close to last year's level. This may require delaying the funding or supplementation of some worthy initiatives, as well as the possibility of deferring the publication of some BSA approved concepts. Part of the rationale for caution in issuing new initiatives, he stated, is the need to ensure adequate continued support for existing initiatives.

President's Budget: The President's budget reflects an estimated 12 to 13 percent increase for Centers and SPOREs. While the NCI feels that the SPOREs program should continue its recent growth, Dr. Wittes acknowledged that, if additional funds are not forthcoming, that growth may have to be constrained. The President's budget also contains an estimated 11 percent increase in the Careers Program and a 12 percent increase for Prevention and Control.

Dr. Wittes reminded the Board that the NCI budget, like those of other NIH components, is subject to "taps" at the NIH level to support agencywide needs, such as information technology and business systems. Security has been a significantly greater concern for the NIH since September 11, and is likely to result in additional taps that will affect the NCI budget.

ByPass Budget & Progress Review Groups: Dr. Wittes reported that the current format for the ByPass Budget, as envisioned and implemented by former NCI Director, Dr. Richard Klausner, remains a clear articulation of NCI's priorities and that the document should continue to provide a visionary statement of the NCI's best professional need judgment. While Extraordinary Opportunities (EOs) within the Bypass Budget should be subject to revision, there should not be a great deal of turnover among the concepts.

Ideas that are suggested to the NCI as potential EOs may be viewed by the Executive Committee (EC) as being extraordinarily important without meeting the criteria used to define EOs for the purposes of the Bypass Budget. One source of such ideas, Dr.

Wittes noted, is the series of Progress Review Groups (PRGs) that have convened experts to assess progress in the fight against particular diseases and offer recommendations for action. He informed members that the NCI faces a challenge in responding to these recommendations within its budget constraints. In light of the large investment of staff time and resources required to respond to existing PRG reports, Dr. Wittes continued, the NCI has decided to temporarily suspend the creation of new PRGs to assure the Institute can adequately support what has already been initiated. The NCI also wants to rethink aspects of the PRG process to make the initial stages less labor-intensive (both for NCI staff and for external experts) and to maintain a continuous dialog with the communities with which interactions have been established through the PRG process.

Partnerships through the PRG Process: As an example of a partnership created through the PRG process, Dr. Wittes stated that the Avon Foundation had approached the NCI to explore collaboration on breast cancer research. The Foundation has recently awarded three NCI Cancer Centers $10M each, with a commitment of an additional $20M over a 5- or 6-year period to support translational research in breast cancer at Cancer Centers and in SPOREs. The NCI will establish and coordinate an expedited peer-review process in which awards will be made within 75 or 80 days of receipt of application. Funds will be transferred directly from the Foundation to the awardees, rather than routed through the NCI. A report will on the status of this collaboration will be given periodically to the BSA.

The NCI is also considering partnerships in the area of Palliative Care and recently began to discuss a response to recommendations in the recent Institute of Medicine (IOM) Palliative Care report. A workshop involving experts and funders in this area, including the Robert Wood Johnson Foundation and the American Society of Clinical Oncologists (ASCO), will be convened next year prior to formulating new initiatives in response to the IOM report.

In discussion, the following points were made:

- The issue of reconsidering the modular funding structure for R01s or analyzing its impact has been brought before the NIH for discussion. However, there does not seem to be any sentiment at NIH for changing the system. It was noted that

while this funding method has led to some increases in expenditures, modular grants provide longer-term savings because budgets remain flat in noncompeting years.

- The Director's Reserve, a part of the budget that in past years was used in part for NIH taps as well as for operational needs and special NCI initiatives may now be tapped by for NIH infrastructure, including security, and the Secretary's 1-percent transfer authority to help meet the needs of other DHHS agencies. Therefore, a smaller amount of this reserve may be available for NCI programs.

- Review costs for the NCI/Avon Foundation project will be covered by the NCI, whereas the administrative costs associated with the grants will be covered by the Foundation. Review will probably be performed by an ad hoc panel that is likely to include both outside experts and NCI staff. The Foundation's Board will then make its decisions, taking the review panel's rankings into consideration.

- One problem in including cancer-related research supported by outside entities (e.g., the Department of Defense (DoD), the Komen Foundation, and various states) in assessing needs and making decisions has been the lack of an accurate portfolio analysis of research being done by the various entities.

- The NCI postponed publication of a concept previously approved by the BSA to create tissue banks dedicated to specific cancer sites. Cost was a fundamental issue, combined with concerns that tissue banks linked to cooperative groups or SPOREs may be underutilized. If issued, the concept will be in a somewhat altered form. Regulations that would require epidemiology studies to submit paraffin blocks to a central repository rather than discard them should be established.

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V. NCI/CONGRESSIONAL RELATIONS - MS. DOROTHY FOELLMER

Ms. Dorothy Foellmer, Director, Office of Legislative and Congressional Activities, presented an overview of the recommendations included in the report prepared by the National Cancer Legislation Advisory Committee (NCLAC) for Congress and the President. She noted that the Committee was appointed by Senator Diane Feinstein (D-CA) to assess the progress in cancer research and care, develop recommendations, and determine whether to update the National Cancer Act of 1971.

In discussion, the following points were made:

- Copies of the NCLAC report should be sent to BSA members.

- Research on how to develop cancer patient-centered information systems, such as electronic patient records that integrate and standardize the data from different sources, is needed. Existing information systems are fragmented and are claims-based.

- The American Cancer Society, the Centers for Disease Control and Prevention (CDC), and NCI are collaborating on comprehensive cancer control leadership institutes, which are related to the state cancer control planning process

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VI. ANNUAL ETHICS OVERVIEW - DR. MAUREEN WILSON

Dr. Maureen Wilson, Deputy Ethics Counselor, informed Board members that for the purposes of Federal laws and regulations, they are special government employees (SGEs) of the Executive Branch, performing temporary duties. Ethics laws and regulations

affecting Board members in this capacity include: the requirement to file and update financial disclosure; prohibitions against accepting anything of value to perform or not perform an official duty; prohibitions against representing individuals or organizations before the Federal Government in matters in which the Board members had substantial involvement; and prohibitions against participating in matters that involve conflicts of interest. Dr. Wilson noted that the latter may involve a member's financial interests and those of family members, a general partner or an organization in which the member is an officer, director, partner, or employee; or an organization with which the member is negotiating or has arranged for employment. embers are also prohibited from speaking, teaching, or writing for compensation about matters related to Board deliberations.

These restrictions generally apply to specific matters involving particular institutions and issues before the Board. Dr. Wilson told members that most of the matters that come before the BSA are general matters involving classes of institutions for which there are statutory waivers from ethics laws, except for those involving financial interests. Exemptions also apply to a member's employing institution, diversified mutual funds, unit investment trusts, and pension plans.

Dr. Wilson informed members that other areas affected by ethics laws and regulations include limitations on charitable fund raising, restrictions on serving as an expert witness, prohibitions against use of public office for private gain, limitations on the use of government property, and prohibitions against employment by foreign governments. She stated that the latter situation applies to many foreign universities, and Board members can not accept a title, compensation, or gift from agencies of foreign governments while serving as SGEs. Additionally, Board members are prohibited from lobbying Congress in their official capacities as SGEs, but may engage in educational activities related to proposed legislation and may lobby as private citizens.

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VII. ONGOING AND NEW BUSINESS - DR. FREDERICK

APPELBAUM

BSA at National Meetings

Members representing the BSA during "NCI Listens" sessions at annual national meetings are: American Society of Preventive Oncology (ASPO), March 10-12, 2002, Bethesda, MD - Drs. Daly (Chair), Lerman and Mueller; American Association for Cancer Research (AACR) April 6-10, 2002, San Francisco, CA -- Drs. Mihich (Chair), Anton-Culver and Strong; Oncology Nursing Society (ONS), April 18-21, 2002, Washington, DC., Dr. Miaskowski (Chair); Cold Spring Harbor Laboratories (CHL), August 14-18, 2002, Cold Spring Harbor, NY -- Drs. Jacks (Chair) and Kaelin; and American Society for Therapeutic Radiology and Oncology (ASTRO), October 6-9, 2002, New Orleans, LA, Dr. McKenna (Chair).

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VIII. MOLECULAR PROFILING OF BREAST CANCER - DR. JEFFREY TRENT

Dr. Jeffrey Trent, Director, Division of Intramural Research and Chief, Cancer Genetics Branch, Division of Cancer Biology (DCB), discussed different approaches to gene-expression profiling being used to study breast cancer. Dr. Trent addressed the basic question of whether cancer can be classified using gene-expression signatures by reviewing recent studies researching the specific questions: What genes are associated with hereditary disease? What genes other than the estrogen receptor (ER) gene are associated with ER-positive and ER-negative cancers? What genes are associated with hormones and growth-factor signaling? The results of studies in which he has been involved that demonstrate the usefulness of gene-expression profiling were outlined.

Dr. Trent explained that his latest efforts in breast cancer gene profiling revolve around identifying those genes most critical for classifying the disease. This endeavor involves identifying common chromosomal regions of loss, as well as suspect gene

expression. He stated that BRCAx represents hereditary breast cancer not associated with BRCA1 or BRCA2 mutations. Profiling results from a BRCAx individual confirms findings by other investigators that chromosome 13 may be a source of absent gene (s). Dr. Trent called this the "chromosome 13 bias." Finally, Dr. Trent described the strategy of characterizing gene-expression changes in cell lines

responding to growth regulators. He noted that a series of agonists and antagonists being studied by Dr. Paul Meltzer are to compare gene activation profiles and, ultimately, to help in developing molecular targets.

In discussion, the following points were made:

- Research suggests that ER-negative and ER-positive tumors arise from different progenitor cells or, alternatively, from cells originating from a very early branch point in a common progenitor lineage.

- A difference in the molecular signature of lymphocytes taken from patients with BRCA1 mutations versus those taken from patients with BRCA2 mutations is anticipated. Normal tissue from breast cancer patients may also reveal a molecular signature different from that of tissue in patients with low risk for breast cancer.

- Gene-expression profiling has revealed significant differences among breast cancer cell lines and the tumors themselves; however, there are shared components of the expression patterns.

- Comparison of array studies can be accomplished with the appropriate statistical tools. Validation, particularly via tissue arrays, is extremely important.

- Other genes besides BRCA1 and BRCA2 influence breast cancer, and population-based research efforts involving large families will be useful in identifying these genes.

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IX. WORKING LUNCH

RFA Annual Report

Dr. Paulette Gray, Executive Secretary, BSA, described for Board members the contents of the BSA Concepts Review Report, November 1996-June 2001. Dr. Gray stated that the report included a listing of all RFA concepts acted on by the Board according to date of consideration. The report includes the number of reissues approved; total dollars and number of years approved; total number of applications submitted and funded; the first year and total amount funded (i.e., paid to date plus future commitments); period of funding; and whether the RFA was in response to an EO. Members were informed that information on whether a concept was deferred or withdrawn was also featured and that RFP concepts were listed in chronological order of Board consideration. A listing of reissued RFAs and abstracts of funded grants were also included.

RFA Reissuance Report

Dr. Wittes informed the Board that decisions regarding reissuance of RFAs are among the most serious decisions the Executive Committee must make. In general, NCI Divisions and the Executive Committee look for definite signs of tangible progress in recent years of funding before reissuing an RFA. In some cases, an initial RFA might be very successful and, thus, clearly worth repeating. In other cases, an RFA might be reissued even when success in the first award is not apparent, but some scientific progress is being made and the research area remains an NCI priority. Examples of grants in this category may include those with complex logistics and/or collaborations that may develop at a slower pace than anticipated.

Emergency Alterations in Review

Dr. Marvin Kalt, Director, Division of Extramural Activities, explained that 15 program project applications had site visits or face-to-face interviews scheduled for the period between

September 11 and the first week of October 2001. Due to the events of September 11, the availability of air transportation and the willingness of reviewers to travel during that time were not known. The decision was made to suspend site visits for all P01 applications scheduled for that round of review and substitute "virtual" site visits made up of three teleconference calls: standard night meeting before the site visit, applicant interview, and completion of site-visit evaluation. On short notice, DEA's Applied Information Systems Branch set up a Web site to receive the additional information from applicants that would otherwise have been distributed at the site visit. Information was also provided to the reviewers via hard copy, e-mail, and Web communications. The process was not optimal, but it provided the means to discern the true merit of all the projects. He noted that staff have been vigilant in determining situations in which the Committee chair or the members believe that more communication is necessary.

In subsequent discussion, the following points were made:

- A pie chart should be added to the BSA Concepts Review Report that would include the spending on RFA-directed research as a percentage of the overall NCI research budget. The inclusion of a table showing the distribution of total funds by meaningful categories (e.g., chemo-prevention, tobacco, etc.) should also be considered.

- A broad evaluation of RFAs should be completed. Three groups of BSA members (three members in each group) should each screen 10 RFAs. If issues result, the BSA should select a few and revisit the status of those RFAs. The first RFA group should be those approved from 1996 to 1999. The Board would review remaining RFAs on a yearly basis.

- The emergency alterations in review resulted in project reviews that were less rigorous than the usual site visits. Thus, the grants that underwent this process should be closely monitored.

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X. PROPOSED RFA, RFA/COOPERATIVE AGREEMENT, AND RFP CONCEPTS - PRESENTED BY NCI STAFF

Division of Cancer Treatment and Diagnosis

Network for Translational Research in Optical Imaging (NTROI) (RFA). Dr. Laurence P. Clarke, Chief, Imaging Development Program, indicated that optical techniques offer unique advantages over other modalities for in vivo molecular imaging and spectroscopy. For example, smart optical contrast agents, selectively activated at target sites, have the potential to improve sensitivity and specificity for cancer detection and classification. Optical tomography, combined with optical contrast agents, can improve penetration depth for small-organ imaging. Miniaturized detectors represent a new generation of optical sensors that are capable of producing two- and three-dimensional images and can potentially improve target sampling.

Dr. Clarke noted that there are several obstacles to full optimization of optical systems for cancer applications: a lack of communication between optical scientists and clinical end-users; slow progress in translational research because of the complexity of optical methods; and a lack of consensus on validation methods. Moreover, much of the development of new optical systems is taking place in the small business sector, which has little contact with the medical community. This RFA concept would support the establishment of a multi-institutional network of three interdisciplinary teams from academic, industrial, and national laboratories. These teams of preformed consortia would conduct translational cancer research in the validation of optical signatures, development and validation of contrast agents, and system integration and optimization of optical devices. Inter- and intra-team collaborations would be encouraged. The project's goals would be to optimize optical systems and their validation for cancer applications; identify common research elements and develop and share validation methods; and identify and prioritize promising cancer-specific applications. The network would be coordinated by a steering committee.

The estimated set-aside for the first year is $4.95M for three awards, and the estimated total for the 5-year project and one-time solicitation is $30M. Funding would be through the cooperative

agreement mechanism (U54).

In subsequent discussion, the following points were made:

- The complex arrangement of the three teams and their potential partnerships with industry might lead to conflicts regarding intellectual property issues. These issues should be addressed.

- A strength of the proposed concept is its attempt to integrate the biology, engineering and physics communities to validate a cancer application for the clinical setting.

- Project data and validation methods should be standardized and shared. Data and analytical tools-sharing should occur when collaborators develop relationships. The need for a centralized data management component is not crucial.

- The multi-institutional team structure may be too rigid. It might be possible for a single institution to have all the required capabilities and therefore, could constitute its own team and would not require outside collaborators.

Motion: A motion to approve the RFA concept entitled "Network for Translational Research in Optical Imaging (NTROI)" was approved with 1 abstention.

Division of Cancer Prevention

Molecular Targets for Nutrients in Prostate Cancer Prevention (RFA). Dr. Young S. Kim, Special Expert, Nutritional Science Research Group, noted that clinical studies provide evidence that selenium, vitamin D, and vitamin E are likely inhibitors of prostate cancer. Other nutrients, such as vitamin A and genistein, have been shown to suppress prostate cancer cell growth in model systems. However, molecular targets for these nutrients have not been defined. The intent of the proposed concept would promote genetic and epigenetic research to define molecular targets for nutrients in prostate cancer prevention. Such targets should be closely linked to a significant proportion of prostate tumors and should be specific for prostate cancer across various genetic backgrounds; modifications should influence tumor risk and/or behavior.

Evidence already exists that nutrients can modulate various cellular processes, including carcinogen metabolism, cell signaling, and apoptosis. Various animal models, including chemically induced rats and transgenic mice as well as cultured tumor cells, have been used to demonstrate the modulatory role of nutrients in different genetic events. These models should be used to determine the impact of nutrients on molecular targets with different levels of expression. It should be possible to determine whether nutrients interact directly with a specific process, such as apoptosis; whether nutrients modulate a specific pathway that has a secondary effect on a gene; or whether nutrients directly interact with a common target and thus bring about changes in multiple cancer processes. This concept is a recommendation from the NCI Prostate Cancer PRG, and also represents an EO in the NCI 2002 ByPass Budget.

The estimated set-aside for the first year is $1.5M for four to six awards, and the estimated total cost for the 3 year project is $4.65M

In subsequent discussion, the following points were made:

- Responses to the RFA should incorporate state-of-the-art techniques for target identification, molecular targeting methodologies, and studies of small molecules that have phenotypic effects in those cases where the mechanism of action is unknown.

- This concept provides a good opportunity for collaborative work between members of the Mouse Models for Human Cancer Consortium (MMHCC) and investigators conducting human prostate cancer studies, particularly those studies involving nutritional science at a molecular level.

- This concept is overambitious in proportion to the funding level and duration of award. The funding level and duration should be increased to $2.5M per year and 5 years, respectfully.

Motion: A motion to approve the RFA concept entitled "Molecular Targets for Nutrients in Prostate Cancer Prevention" with the amendment to increase both the funding period to 5 years and the funding level to $2.5M was approved; 26 in favor and 1 opposed.

Chemoprevention of Estrogen Receptor-Negative Cancers in Women at High Risk: Preclinical Studies (RFA). Dr. Vernon E. Steele, Program Director and Estrogen Receptor-Negative Breast Cancer Project Team Leader, Division of Cancer Prevention (DCP), stated that the purpose of this initiative is to stimulate preclinical research aimed at reducing the risk of ER-negative breast cancer and to identify agents and potential surrogate endpoints that could be translated from the preclinical into the clinical setting. The goal is to address the nonhormonally responsive subset of mammary tumors, since these are not as well characterized as ER-positive tumors, and they may represent a separate disease. The American Cancer Society estimates that 25 to 30 percent of breast cancers are ER-negative, and these cancers account for a slightly higher percentage of all cancer-related deaths. The intent it is to identify a preclinical model that develops hormonally nonresponsive mammary cancer; exam known genes or proteins in human samples and their comparison with animal data; identify potential molecular targets; and identify and validate surrogate endpoints with agents that prevent ER-negative breast cancer. Strategies for chemopreventive drug development would include both investigator-initiated research and collaborative work, with the Mouse Models for Human Cancer Consortium (MMHCC) for development and validation of mouse models, and the EDRN for identification of biomarkers specific to ER-negative breast cancer. Currently, there are five grants, totalling $1.1M, that focus on ER-negative breast cancer as a separate entity from ER-positive breast cancer.

The estimated set-aside for the first year is $3M for six to eight awards, and the estimated total for the 3-year project is $9.4M.

In discussion, the following points were made:

- It is important to identify new agents that target ER-negative tumors, since tamoxifen has no effect on these tumors. Screening advances made through preclinical animal models could have an impact on patients with ER-negative breast cancer.

- There has been much emphasis on separating ER-negative and ER-positive tumors, but tumors that change from

positive to negative should not be ignored.

- The breast SPORE is another resource for applicants of this concept. Investigators from that program should be encouraged to apply for an R01 or supplements.

- The inclusion of the term "high risk" in the RFA title may have the effect of limiting the preclinical studies to perfect models of inherited predisposition in high-risk women.

- There is some ambiguity to the phrase "prevention of ER-negative breast cancer." The intent is to indicate that effective agents for the prevention of nonhormonally responsive breast tumors will be used because these drugs may include hormonal agents that may affect ER-negative tumors. The title of the RFA may require revision.

- A broad definition of animal models should be utilized and investigators should be encouraged to justify the use and significance of a particular model.

- The concept should be revised to state more clearly that the endpoints used in the animal models should be translatable to a clinical situation.

Motion: A motion to approve the RFA concept entitled "Chemoprevention of ER- Cancers in Women at High Risk: Preclinical Studies" was unanimous.

Chemoprevention of Estrogen Receptor-Negative Breast Cancer: Clinical Studies (RFA/Cooperative Agreement). Dr. Worta McCaskill-Stevens, Project Team Clinical Section Leader, DCP, stated that the purpose of this initiative is to stimulate clinical research aimed at reducing the risk of ER-negative breast cancer. The intent of the study is to identify and validate potential biomarkers of ER-negative breast cancer and demonstrate the modulation of these biomarkers by chemopreventive agents. Approximately 20 to 30 percent of new breast cancer cases are ER-negative, with African-American women, women under the age of 50, and carriers of a BRCA1 mutation most at risk. Because antineoplastic compounds targeted at ER-positive tumors do not affect ER-negative tumors, there is a need to identify agents

specific to ER-negative tumors. Several targets that are good candidates for clinical studies are: elements of the EGF and HER2/neu signaling pathways, cyclooxygenases, retinoid receptors, orphan receptors, neovasculature modulators, and farnesyl transferases. Both short-term Phase I and Phase II clinical studies and translational studies will be incorporated in the RFA. There are no plans for to fund Phase III clinical trials. A cooperative agreement is being sought as the funding mechanism because of the need for regulatory and licensing support, protocol review, and drug supply. A supportive infrastructure is available through the Early Detection Research Network (EDRN) and SPOREs.

The estimated set-aside for the first year is $2.5M for four to six awards, and the estimated total for the 5 year project is $15.5M. Two reissuances are expected.

In discussion, the following points were made:

- Patient care costs, in terms of healthy people participating in the clinical studies and undergoing diagnostic and other types of procedures, have not been adequately factored into the total costs of the award.

- There may be intellectual property issues when testing combination therapies if the agents have not been marketed and they belong to two different pharmaceutical companies.

- Proposals submitted in response to this RFA should include mechanistic or correlative studies and intermediate endpoints.

- Only a few of the agents proposed as candidates for clinical chemoprevention are specific for breast cancer. In addition, the toxicity of these agents is not well understood, so their administration to healthy individuals as chemopreventive agents may be an issue. Focus should be on the preclinical development of chemopreventive agents that could subsequently be used in clinical studies.

- Pharmaceutical companies are already pursuing the development of relevant biomarkers for multiple indications, so it is difficult to understand how this concept

fulfills an unmet need in this area of research. Pharmaceutical companies are already pursuing the development of relevant biomarkers for multiple indications, so it is difficult to understand how this concept fulfills an unmet need in this area of research.
Pharmaceutical companies are already pursuing the development of relevant biomarkers for multiple indications, so it is difficult to understand how this concept fulfills an unmet need in this area of research.

- Certain regulatory issues may arise when a drug approved as a chemotherapeutic agent is used as a chemopreventive drug or when the drug is used for an indication other than the one approved by the FDA.

- The short-term Phase I/II studies may not yield sufficient data to establish a good model of prevention. Prevention agents may only delay the onset of cancer by 5 years. If the trials are shorter than that, it is difficult to ascertain whether the agent is really preventing oncogenesis or merely delaying it.

- A long-term multicenter prevention study with tumor incidence as an endpoint is not proposed. However, the identification and validation of intermediate markers that could be applied to larger trials is proposed. The question is whether there is a need for such proposals to address the biology specific to ER-negative breast cancer.

Motion: A motion to approve the RFA/Coop. Agr. concept entitled "Chemoprevention of Estrogen Receptor Negative Breast Cancer: Clinical Studies" was defeated; 10 in favor, 12 opposed, and 3 abstentions.

Division of Cancer Control and Population Sciences

Centers for Population Health and Cancer (CPHC) (RFA). Dr. Robert Hiatt, Deputy Director, Division of Cancer Control and Population Sciences (DCCPS), reminded Board members that persistent and marked disparities in cancer incidence and outcomes exist among racial and ethnic groups. However, to understand these disparities it is necessary to go beyond race and ethnicity and

analyze such factors as socioeconomic status, culture, and environment.

The proposed concept has three goals: 1) catalyze interdisciplinary research to determine the nature and impact of social determinants on cancer; 2) integrate research from multiple areas, such as geography, health economics, and anthropology and other social sciences; and 3) support development and implementation of interventions to reduce the overall cancer burden and disparities in cancer incidence and outcomes. Three or more hypothesis-driven research projects linked by a thematic emphasis, pilot funding to attract multidisciplinary researchers, the creation of an environment for interdisciplinary interaction, career development and training, and interaction with other Centers and NCI are needed. Data generated from this project would include the examination and description of the cancer burden and disparities in terms of socioeconomic, cultural, and environmental factors.

Dr. Hiatt informed members that the DCCPS grant portfolio consists of 30 grants with some emphasis on social alternatives. Twelve of those, representing $10M, deal with tobacco issues. Eight grants in other NCI Divisions deal with social determinants, but few have an interdisciplinary approach.

Discussions to establish collaborative relationships with the National Institute of Environmental Health Sciences (NIEHS) and the National Heart, Lung, and Blood Institute (NHLBI) on this project appears likely.

The estimated set-aside for the first year is $8M for 4-5 awards, and the estimated total for the 5 year project period is $40M. No reissuances are requested.

In further discussion, the following points were made:

- Linking the Centers' research projects to specific diseases might provide additional focus.

- Transdisciplinary research is required to identify nested contextual factors. This RFA represents aan opportunity to study transdisciplinary interactions and perform multilevel analyses.

- This concept is a new way of looking at large populations and a departure from the usual classifications that have been used for decades in epidemiology and behavioral medicine.

- The concept is a long-term investment for science in the 21st century, combining population medicine with biologic medicine.

Motion: A motion to approve the RFA concept entitled "Centers for Population Health and Cancer" was approved; 14 in favor, 9 opposed, and 3 abstentions.

Division of Cancer Prevention and Division of Cancer Treatment and Diagnosis

Spiral CT Lung Cancer Screening Trial (RFP). Dr. John Gohagan, Chief, Early Detection Research Group, DCP, NCI, stated that the revised Lung Screening Study II (LSS II) RFP reflected concerns expressed by Board members when the concept was initially presented at the June 2001 BSA meeting. The primary goals of this definitive trial are to determine: 1) whether lung cancer mortality is reduced by spiral computed tomography (SCT) compared to chest x-ray (CXR) screening, and 2) the risk/benefit ratio. Secondary goals would include determining the sensitivity, specificity, predictive value, and cost-effectiveness of SCT, along with its value in nodule management, improvement in quality of life, and identification of biomarkers. The design of the 8-year trial calls for randomization of 50,000 participants on a one-to-one basis to either SCT or CXR over a 2-year period. About 40,000 participants would be accrued to the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, and 10,000 participants would be accrued to the American College of Radiology Imaging Network (ACRIN) sites. Participants will undergo an initial and two subsequent annual screens.

According to preliminary studies, SCT is the most likely screening modality for early detection of cancers among current and former smokers, the groups at highest risk for lung cancer. Therapies currently in use have had only a modest effect on patient outcomes, and considerable research remains to be done on the molecular underpinnings of the development of lung cancer. Tobacco control may ameliorate the problem, but it will not likely eliminate it in the

near term. Thus, effective screening technologies are needed.

The trial organization would include an Executive Committee with NCI oversight, a Data and Safety Monitoring Board, Steering Committees for LSS II and ACRIN, an LSS II Data Management and Coordination Center (CC), and an ACRIN Statistical Unit and CC. The CCs would provide overall quality assurance, data preparation, and operational oversight.

The proposed budget of approximately $197M over 8 years is significantly greater than the budget presented at the June 2001 BSA meeting. Dr. Gohagan informed members that ancillary studies and outside collaborations could be conducted on such issues as smoking cessation, quality of life, statistical modeling, and biomarkers, but such studies would add to the total cost.

Dr. Ellen Feigal, Deputy Director, DCTD, NCI, outlined the current distribution of NCI funds for lung cancer, early detection, and smoking prevention and cessation. Dr. Feigal also described NCI efforts to actively seek partners to alleviate some of costs by promoting interest in this trial with researchers in Europe and Israel, from device manufacturers, and from the American Legacy Fund. While the proposed trial has generated great interest, both nationally and internationally, no collaborative funds have been secured to date.

Dr. William Wood, Chair of the BSA ad hoc subcommittee appointed to work with NCI programmatic staff in refining the LSS II RFP concept, stated that the major issues considered by the subcommittee in revising the RFP concept were the: 1) overall cost and the impact the study would have on the NCI budget relative to competing funding requests; 2) message that a negative screening result might give smokers a false sense of security, deterring them from participating in smoking cessation programs; 3) heterogeneity of treatments following screening and detection of a radiographic abnormality; and 4) need for the LSS II and ACRIN studies to function in unison, with a single Data Safety and Monitoring Board, coordinated eligibility criteria, and monitoring standards, among other organizational components.

In subsequent discussion, the following points were raised:

- A project of this magnitude will have an effect on the flexibility of a number of NCI funding mechanisms. A possibility would be to fund the LSS across targeted areas of Institute investment rather than from the research grants pool only.

- The proposed study as revised is scientifically very well designed.

- The high cost of the project represents "lost opportunity" costs. Such opportunities include better smoking prevention and cessation programs and improved treatment modalities. A concern is that the proposed budget will have a negative impact on investigator-initiated grants (R01s and P01s).

- The Data Safety and Monitoring Board must perform its review function aggressively. With early-stopping rules and clear-cut progress reviews in place, the trial could be ended early if the results are strongly positive or strongly negative, thus reducing the cost.

- Health care insurance companies should be likely candidates for partnerships. If SCT is effective as a screening device, it should be covered by insurers because early detection is cheaper than late-stage treatment; if it is not effective, coverage should not be provided. With its increasing popularity, SCT might become the standard of care and would be covered by insurers regardless of whether it is effective.

- Screening technology may change over the 10-year period of the study. Such changes should not invalidate the study's findings, because researchers will have the opportunity to identify key features of early detection.

- The trial could have a direct positive impact on NCI's mission of reducing the cancer burden in the United States and improving the health status of the population.

- LSS II and ACRIN, should be compatible in all their components, including protocol development, quality assurance, instrumentation, eligibility requirements, etc.

- Since the trial does not call for uniform treatment options following a positive screening result, some treatments may obscure SCT's impact on mortality, the study endpoint.

- The possibility of early detection of lung cancer may remove some motivation for smoking cessation. However, social scientists are working on message-framing techniques to motivate smokers to quit despite the existence of early detection methods.

- More effort should be devoted to finding partners for cost-sharing. Consideration should be given to approaching the DoD since smoking has been a problem among veterans.

- Progress has been made in understanding the interactions between carcinogens and genes, and this knowledge may produce a risk model for lung cancer. Such a model may help to identify high-risk individuals for SCT, and surgical cure rates could potentially be improved by as much as 80 percent.

- The trial appears to be cost-effective in terms of projected dollars per years of life saved.

- The project should not be viewed as an "either/or" supporting decision between tobacco control and behavioral science on the upstream side, and early detection and other therapeutic and diagnostic interventions on the downstream side. All of these approaches are needed to reduce the burden of lung cancer.

Motion: A motion to approve the RFP concept entitled "Spiral CT Lung Cancer Screening Trial" with an amendment to continue efforts to seek funding partners (with periodic updates to the BSA) and to have the Data Safety and Monitoring Board aggressively monitor the trial from its commencement and consider stopping the trial early if warranted, was approved. The vote was 17 in favor, 8 opposed, and 1 abstention.

Adjournment: The meeting adjourned at 12:15 p.m. on Wednesday, 14 November 2001.