Board of Scientific Advisors

Meeting Minutes

June 23, 1999

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

Quick Links

Members

Agenda & Future Meetings

Meeting Minutes

BSA: Page 1

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI) convened for its 12th regular meeting at 8:00 a.m. on Wednesday, June 23, 1999, 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 8:00 a.m. until adjournment at 5:15 p.m. on 23 June for introductory remarks from the Chair; ongoing and new business; award presentations; and presentations and discussion on the status of the NCI budget and paylines, the Developmental Therapeutics Program Review response, NCI's update on its response to the Cancer Centers Program Review Report, the National Pediatric Cancer Network, metrics for clinical trials restructuring, establishing subgroups to monitor large-scale initiatives, and concepts for Requests for Applications (RFAs) and a Request for Proposals (RFP).

BSA members present:
Dr. David Livingston (Chair)
Dr. Frederick R. Appelbaum
Dr. Joan Brugge
Dr. Mary Beryl Daly
Dr. Virginia Ernster
Dr. Suzanne W. Fletcher
Dr. E. Robert Greenberg
Dr. Waun Ki Hong
Dr. E. Tyler Jacks
Dr. Herbert Y. Kressel
Dr. Allen I. Oliff
Dr. Stuart L Schreiber
Dr. Ellen V. Sigal
Dr. Joseph V. Simone
Dr. Louise Strong
Dr. Peter K. Vogt
Dr. Barbara L. Weber Dr. William C. Wood
Dr. Robert C. Young
Dr. Elias Zerhouni

BSA members absent:

Ms. Amy S. Langer
Dr. Caryn E. Lerman
Dr. Joan Massague
Ms. Deborah K. Mayer
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Sharon B. Murphy
Dr. Eric R. Fearon
Dr. W. Gilles McKenna
Dr. Franklyn G. Prendergast
Dr. Daniel D. Von Hoff
Dr. Alice S. Whittemore

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

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

TABLE OF CONTENTS

Early Detection - Members

RFA Concepts: Presented by NCI Program Staff

Division of Cancer Treatment and Diagnosis:

-Imaging Techniques for Early Prostate Cancer (RFA) - Dr. Daniel Sullivan

Division of Cancer Control and Population Sciences:

-Cancer Intervention and Surveillance Modeling Network (Coop. Agr.) - Dr. Eric Feuer

Division of Cancer Treatment and Diagnosis & Division of Cancer Prevention:

-Modular Target Drug Discovery Grants (Coop. Agr.) - Dr. Edward Sausville

-Centers of Excellence in Interventions Directed at Molecular Targets (Coop. Agr.) - Dr. Michaele Christian

Division of Cancer Treatment and Diagnosis:

-Early Therapeutics Development with Phase II Emphasis (RFP) - Dr. Michaele Christian

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CALL TO ORDER AND OPENING REMARKS - DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 12th regular meeting of the Board of Scientific Advisors (BSA or Board) and welcomed members of the Board, National Institutes of Health (NIH) and National Cancer Institute (NCI) staff, guests, and members of the public.

In discussing future BSA meeting dates, a conflict with the March 2000 American Society of Preventive Oncology meeting was noted. Members were asked to review the proposed change of dates from 7-8 March to 23-24 March and report conflicts to the executive secretary.

CONSIDERATION OF MARCH 8, 1999 MEETING MINUTES - DR. DAVID LIVINGSTON

Motion. The minutes of the 8 March 1999 BSA meeting were unanimously approved.

top

REPORT OF THE DIRECTOR, NCI - DR. RICHARD KLAUSNER

Dr. Richard Klausner, Director, NCI, discussed aspects of the FY99 budget, provided an update on new programs, NCI communications, the Cancer Genome Anatomy Project (CGAP), and an overview of legislative activities.

Budget and Research Project Grant (RPG) Pool Update: Dr. Klausner projected that 4,419 grants will be awarded in FY99 by all mechanisms, for a total of approximately $1.367B (compared with 3,950 and $1.231B in FY98). Based on current projections, new and competing traditional research grants (R01s) will total 2,800, a 23 percent increase over FY98, a success rate of 32.8 percent. Program projects (P01s) are projected to increase by 15 percent to a total of 175, with 45 new and competing grants. He reported that a large number of excellent applications had been received in response to the new Phased Innovation Awards (R21/ R33) announcements, with projections that 118 new and competing grants will be awarded, raising the total to 156 (for $22.6M) since initiation of the mechanism. An expansion of this mechanism beyond the molecular technologies to include other programmatic aspects of the Institute is anticipated. Applications for Accelerated Executive Review (AER) increased from 61 in FY98 to 112 in FY99, requiring an increase in dollars from $8M to approximately $20M. The FY99 success rate for AER awards is projected at 68 percent.

Update on major Requests for Applications (RFAs): Dr. Klausner presented preliminary data on the level of response to RFAs for high-priority NCI programs, which represent an articulation of NCI's new approaches and directions that have emerged from extensive planning processes. In comparing the number of applications or the letters of intent received for recent RFAs and the indirect cost dollars requested with the size of the set-aside, several examples were cited. Such as, 1) Mouse Models for

Human Cancer Consortia - 31 consortia have been assembled requesting about $25M for a set-aside of $5M; 2) Director's Challenge - 38 responses were received for $50M with a set-aside of 10M; 3) requests for array facilities totaled about $11M in direct costs for a set-aside of $2.5M; 3) Early Detection Research Network - 18 groups were reviewed as excellent to outstanding of the 45 groups that applied requesting more than $20M in funding for a $3M set-aside; 4) Small Animal Imaging Research Programs - 29 applications requested a total of $51M for a set-aside of $4.5M; 5) Transdisciplinary Tobacco Use Research Centers - 25 applications requested about $50M for a $10M set-aside; 6) Special Populations Networks for Cancer Awareness Research and Training - 64 letters of intent were received for a set-aside of $6M, which would potentially fund six to eight or possibly 10; and 7) In vivo Cell and Molecular Imaging Centers - 20 letters of intent had been received for a set-aside of $6.4M. Dr. Klausner stated that the underfunding of these major priority programs would be an issue to address in working with the as-yet unknown future budget appropriations.

Update on New Programs: Dr. Klausner reviewed progress in implementing the new **Rapid Access to Intervention Development (RAID)** program, which provides support through NCI resources for compound development from the laboratory to the point of Phase I to early clinical trials. Approximately 25 applications were approved of the 80 received in the first two rounds; the investigators and their approved compounds are described on the NCI Web Site.

An update on the **Unconventional Innovations Program**, which is currently aimed at developing the technologies necessary to identify molecular changes within the human body and link that information to cancer imaging, diagnosis, and, ultimately, delivery of therapy was given. Dr. Klausner reported that the tremendous response to this contract solicitation included a diversity of ideas and applicants. Negotiations to create the single program from the many components will begin following completion of the review. The NCI is partnering with the Defense Advanced Research Projects Agency (DARPA) on this initial project and has supplemented some projects in the DARPA Unconventional Pathogen Counter Measures Program. Discussions are also underway with the National Aeronautics and Space Administration (NASA) and CalTech to explore the overlap in unconventional

technologies of interest to each institution and how the individual programs intersect and can be linked. An Unconventional Innovations Program update will be presented at a future meeting.

NCI Communications: Board members were reminded of the vital role played by communication in launching the 22 new initiatives. Dr. Klausner reported that the NCI Web Site is undergoing a redesign, which is scheduled for completion in coming months and could be ready for demonstration at the November BSA meeting. He then presented an update on the 1) characteristics and customer usage of CancerNet and CancerTrials, and 2) the Physicians' Data Query (PDQ)/CancerNet redesign. He noted that the PDQ/ CancerNet redesign will be integrated with the redesign of the overall NCI Web Site, and will be a model for NIH clinical trials registries, toward the mandated goal of creating a single gateway for all NIH clinical trials.

Another aspect of communications that is currently being addressed relates to how the NCI portfolio can be viewed. Dr. Klausner reported that a Common Scientific Outline (CSO) has been developed jointly by expert groups, internal task forces, and the Progress Review Groups operating under the leadership of the NCI Office of Scientific Policy (OSP). The CSO has been used to code all extramural projects and grants funded since 1997; intramural projects will be added later in the year; and future projects will be coded on an annual basis. Board members were given an overview of the CSO structure and how portfolio components are coded to facilitate online searches. This information will be made publically available on the Web for searching according to general and specific scientific areas, organ site, and specific cancer, with the added help of a series of special interest codes. Dr. Klausner announced that the Department of Defense (DoD) entered into an interagency agreement to review and code its entire portfolio according to the CSO. Discussions also are under way with the American Cancer Society, the state of California, and others to make the software available to them in the interest of coordinating research across cancer-funding organizations to identify gaps, redundancies, and areas where synergy can be developed.

Dr. Klausner called attention to the recommendations contained in the Report to the Advisory Committee to the Director, NIH, from the Office for Protection from Research Risks (OPRR).

Update on the Cancer Genome Anatomy Project (CGAP): Dr. Klausner briefly reviewed progress in several CGAP components noting that: 1) the rate of discovery in the Tumor Gene Index (TGI) continues to expand the number of known genes, currently between 72,000 and 73,000; requests for clones and reagents are increasing for molecular diagnostics, and early detection research has expanded; 2) the Cancer Chromosome Aberration Project now includes 22,000 searchable recurrent chromosomal anomalies from the Mittleman database, and the goal is to fill out the entire genome with clones available for mapping aberrations, abnormalities, or loci of interest to the physical genetic and chromosomal map by high resolution fluorescent in situ hybridization; and 3) the Genetic Annotation Initiative (GAI) was initiated with the goal of discovering common variations that underlie cancer initiation and progression. Dr. Klausner reported that the GAI database recently became available for searching at the CGAP Web site. Board members were given a demonstration of the CGAP-GAI Web site and how the SNP index might be used for a molecular epidemiology study.

Dr. Klausner reported that the NCI and the National Human Genome Research Institute (NHGRI) are the lead organizations in the NIH Mammalian Full-length cDNA Project based on the CGAP model. Scientific goals of the project are to develop a national production infrastructure for cDNA libraries and clones, clone repositories and distribution centers, and cDNA sequencing, informatics, and technology development. Board members were given a preview of how the libraries are being constructed.

Legislative Update: Dr. Klausner reminded Board members that the 1996 Health Insurance and Portability Act mandated that Congress enact a law by August 1999 that would protect the privacy of health information. Without such action or an extension of the deadline, the Secretary, Department of Health and Human Services (DHHS), would be required to promulgate regulations for protecting medical privacy by February 2000. Because of the potential impact on the interface between medical information/ medical records and different aspects of research, NCI staff has prepared and posted a White Paper on the NCI Web Site which outlines major confidentiality issues as they relate to surveillance, epidemiologic, genetic, and clinical trials research. Board members were informed that a fall meeting with members of NCI's research

communities is planned to discuss these issues.

In discussion, the following points were made:

- Constructs or compounds submitted for development under the RAID program are subject to peer review by a committee of extramural experts.
- The level of funding in the unrestricted RPG pool might be eroded with the expansion of research opportunities presented by RFA initiatives.

ONGOING AND NEW BUSINESS - DR. DAVID LIVINGSTON

BSA at National Meetings: Status Reports

American Society of Preventive Oncology (ASPO): Dr. Mary Daly reported good attendance at the ASPO "NCI Listens" session. Following NCI staff informational presentations, members' questions focused on ramifications of the new Center for Scientific Review (CSR) study section organizational impact on prevention and control research and on issues relating to the Freedom of Information Act. Members suggested that Dr. Daly discuss with the ASPO leadership the possibility of organizing a set of specific topics to be addressed at the next session.

American Association for Cancer Research (AACR): Dr. Virginia Ernster reported good attendance and a good discussion covering a wide range of topics. NCI staff actions taken in response to questions and comments (e.g., actions to improve interactions between grantees and NCI grants management staff) will be reported at next year's session.

Oncology Nursing Society (ONS): Ms. Deborah Mayer reported that the ONS membership was satisfied that most issues raised at the 1998 session had been implemented or addressed by the NCI. There was consensus that "NCI Listens" sessions at future ONS meetings should be continued. Major discussions focused on the design of a clinical trials nurse training program and how to increase the number of nursing applications to NCI, particularly for career development awards.

American Association of Hematology (ASH): There was no "NCI Listens" session at the 1998 ASH meeting because of the scheduled address by Dr. Klausner. Dr. Frederick Appelbaum reported that ASH leadership has been contacted about scheduling an "NCI Listens" session at the next meeting in a better time slot than the previous two sessions.

American Society for Therapeutic Radiology and Oncology (ASTRO): The Chair reported that the ASTRO leadership had indicated an interest in having an "NCI Listens" session at their fall 1999 meeting. Dr. McKenna will coordinate this activity with the ASTRO leadership.

American Society of Clinical Oncology (ASCO): Because of the scheduled presentation by Dr. Klausner, the ASCO meeting did not include an "NCI Listens" session. An ad hoc subcommittee composed of Ms. Langer and Drs. Weber, Young, and Wood will discuss with the ASCO leadership prospects for "NCI Listens" sessions at future meetings, as well as a more creative format for the sessions.

top

DEVELOPMENTAL THERAPEUTICS PROGRAM REVIEW RESPONSE-DR. EDWARD SAUSVILLE

Dr. Edward Sausville, Director, Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), reviewed the Developmental Therapeutics Program Review Group (DTPRG) recommendations and outlined initial DTP actions in response to each, together with a projected implementation timeline. Dr. Sausville stated that the report was the product of the DTPRG review which began in October 1997 and was presented to and accepted by the BSA at its October 1998 meeting.

Restructuring Decision-making and Oversight. The threefold DTP response included: 1) establishing a new senior-level Compound Decision Group to identify opportunities, challenges,

and needs, and assist in planning related to the use of NCI's preclinical contract resources (December 1999); 2) establishing a new Biological Resources Branch (BRB) Advisory Group to oversee governance of the Monoclonal and Recombinant Protein Facility (MARP) at the Frederick Cancer Research and Development Center (FCRDC) (August 1999); and 3) restructuring the Decision Network to include extramural participation in the process for selecting candidates for development using contract research resources for pharmacology, toxicology, and initial Investigational New Drug (IND) filing (January 2000).

Chemical Diversity. To increase the sources of diversity available to the community, NCI's repository has been opened for the distribution of pure compounds and extracts, as well as natural products. In addition, a program is planned in which the NCI will broker the distribution of libraries produced by industrial or academic sources to other extramural screening laboratories through appropriate materials transfer agreements (MTAs). Related to this effort are the proposed new RFAs for a Molecular Target Drug Discovery (MTDD) Program and the recompetition of the chemistry and biology program project grants (P01s) to establish a network of extramural sites for the development and deployment of novel screens. Board members were informed that the NCI also has reduced the scope of the 60-cell-line antiproliferative initial screen to a 3-cell pre-screen composed of the NCI H460 lung cancer, MCF7 breast cancer, and glioma cell lines.

Structure. The DTPRG recommendation calling for a determination of the three-dimensional (3D) structure for all cancer-relevant proteins is being addressed by co-funding with the National Institute of General Medical Science (NIGMS) a dedicated beam time relevant for cancer targets at three beam line centers across the nation. In addition, the NIH has agreed to co-fund the upgrading of the energy sources at the three centers, and a proposed joint NCI and NIGMS initiative is to build a dedicated center at Argonne's Advanced Photon Source (APS). The recommendation to promote research into ligand-receptor interactions will be addressed as grant applications are submitted in response to MTDD solicitations following concept approval.

Developmental Aspects of Drug Discovery. Plans for responding to the recommendation for centers of excellence in pharmacology, toxicology, and metabolism are linked to a new RFA concept

entitled "Centers of Excellence (COEs) in Interventions Directed at Molecular Targets". (scheduled for review and approval later in the meeting). The recommended state-of-the-science meetings for toxicology, pharmacology, metabolism, and delivery will include workshops on the pharmacology and toxicology of cancer-directed therapeutics at the AACR and European Organization for Research on Treatment for Cancer (EORTC) fall meetings and a meeting of formulation scientists in mid-2000 with the Control Release Society. Integration of in-house extramural efforts is envisioned through the RAID program and proposed COEs.

Scope of the Biological Resources Branch (BRB). The recommendations to expand the BRB's scope to include technology development capability were addressed by training staff in vector and other technologies, outsourcing RAID projects to extramural contractor sites, and recruiting additional staff with vector expertise to increase the capability for generating recombinant vectors and protein-based therapeutics for the extramural community. Governance and coordination of these efforts rests with the BRB Advisory Group, which also will address questions such as those relating to cost sharing and royalty collection for successful reagents. Other DTP responses to recommendations include the following: 1) the National Cooperative Drug Discovery Group (NCDDG) concept was expanded to address biologics in the most recent competitions of the NCDDGs; 2) the proposed COEs, if approved, would respond to the question of creating biologic SPOREs; 3) with the February and August solicitations, the RAID mechanism was modified to include industrial participants and broader access to reagents in the industrial sector; and 4) the NCI is actively seeking to network successful RAID participants with the business community.

Public Access Databases/Resources. Board members were informed that DTP has made its screening and structural data for more than 40,000 compounds, 60 cell lines, and chemical and biological data available at the http://dtp.nci.nih.gov web site. Molecularly defined mouse models will be available through the FCRDC as they are produced in the extramural community under a mechanism to be discussed with the Compound Decision Group. As mentioned earlier, sources of chemical diversity have been increased through DTP's open compounds and natural products libraries. The recommendations for generating engineered cell lines and making microarrays available are topics of continuing

discussion.

Administrative and Fiscal Management. Board members were reminded that the RAID program was the initial response to the identified need for rapid response mechanism to coordinate different types of laboratory proposals. The proposed MTDD program, if approved, would move that general concept forward to create opportunities for grantees to interact with NCI staff and contractors. The Compound Decision, Drug Development, and BRB Advisory Groups would provide flexible and rapid mechanisms for evaluating proposals. The aggregate of intramural and contractor resources has been adjusted to more closely approximate extramural program expenditures, as recommended by the DTPRG.

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

- The Compound Decision Group will oversee the entire spectrum of drug discovery, development, and clinical testing. Consideration also is being given to including chemopreventive agents in the committee's area of responsibility.

- Members of the DTPRG, recognizing that the initial response would attempt to address the concerns of all of the diverse interests represented on the committee, recommended that the program be evaluated as it moves forward and that resource allocations be adjusted to reflect the success or failure of the individual components.

- The Compound Decision Group, in principle, has the authority and responsibility to establish priorities for the entire drug discovery and development effort.

- The NCI's role in moving compounds out of the laboratory toward the clinic was confirmed by the DTPRG; moreover, molecular targets for intervention was one of three new extraordinary opportunities in the rewritten Bypass Budget.

top

AWARD PRESENTATIONS - DR. RICHARD KLAUSNER

Dr. Klausner recognized the contributions of Drs. Sharon Murphy, Stuart Schreiber, and E. Robert Greenberg, whose terms of office expired following the current meeting. He thanked them, on behalf of the Institute, for contributing greatly to the restructuring that the Institute has been undergoing in recent years.

UPDATE: NCI'S RESPONSE TO THE CANCER CENTERS PROGRAM REVIEW REPORT - DRS. ROBERT WITTES, MARGARET HOLMES, DAVID MASLOW & JOSEPH SIMONE

Dr. Robert Wittes, Director, Division of Cancer Treatment and Diagnosis, and Deputy Director for Extramural Science (DDES), reminded BSA members that the guidelines for the Cancer Centers Program were revised according to the recommendations of the Cancer Centers Program Review Group (CCPRG), the first group to conduct a major review of NCI programs. Dr. Wittes informed members that status reports on NCI's response to the CCPRG report would be given from the perspectives of the Cancer Centers Branch (CCB), ODDES, Grants Review Branch (GRB) of the Division of Extramural Activities (DEA), and cancer center directors.

Cancer Centers Branch, ODDES. Dr. Margaret Holmes, Chief, CCB, ODDES, reported that as of April 1997, 29 applications had been reviewed using the revised "Policies and Guidelines Relating to the Cancer-Center Support Grant (CCSG)", and that 22 have been funded. Seven from the October 1998 round of applications are still in the process of review. The goals of the revised guidelines were to achieve a greater emphasis in the review on the quality of the science and to assess the quality and value added by the presence of the cancer center. Two main issues in the review are the quality and completeness of the application and the subjectivity of any assessment of value added. Conclusions drawn from this early experience were that applications can be prepared from the new guidelines; the review can be completed in 1.5 days on site if the applications are well prepared and complete; and

centers can be reviewed on the basis of the quality of their science and the value added. Board members were informed of several mid-course corrections to the guidelines which were made in response to either applicant comments or review needs. Proposed changes were shared with cancer center directors and reviewed and approved by the National Cancer Advisory Board (NCAB) Subcommittee on Cancer Centers before implementation. Dr. Holmes noted that additional guideline revisions will be made annually as the learning process continues. Areas under consideration in the near term are technology resources and center relationships with industry.

Grants Review Branch, DEA. Dr. David E. Maslow, Scientific Review Administrator, NCI Initial Review Group, Subcommittee A, reviewed for the Board the measures undertaken by GRB staff to prepare for the peer evaluation. These activities had the goal of assuring a fair review consistent with the spirit of the CCPRG report and recommendations, as well as the review criteria of the new CCSG guidelines. He emphasized that the quality of the review is dependent on GRB's success in recruiting reviewers with recognized broad scientific expertise and an understanding of cancer centers. Dr. Maslow welcomed BSA members' assistance in encouraging senior leaders of the cancer research and cancer center communities to participate in these reviews. Dr. Maslow concluded by reporting that more than 30 applications have been reviewed under the new guidelines and the assessment is that the GRB has been successful in reinvigorating cancer center reviews and increasing their focus on scientific merit as called for in the CCPRG report and incorporated into the new guidelines.

Cancer Centers Directors. Dr. Joseph Simone, Medical Director, Huntsman Cancer Foundation and Institute, University of Utah, and Chair, CCPRG, reported on the results of his request for comments from cancer center directors that had been reviewed under the new guidelines, specifically focusing on the preparation of the grant application and conduct of the site visit. A summary of the 13 responses received indicated that the directors perceived positive changes in the scientific focus of the review and in the organizational and financial flexibility that was made available and improvement in the oversight and helpfulness of program staff. Process elements perceived as showing no change were the time and personnel needed to prepare the grant. Other comments focused on the need for new reviewers and on the large volume of

information often requested on the evening before the site visit.

In discussion, the following points were made:

- Several BSA members stated that minimal change was seen in the ratio of time spent on science during the site visit versus governance and structure. The time needed to prepare the grant application continued to occupy about a year of effort by many individuals and, although the preparation was straight forward and primarily focused on the science, the site visit, however, focused neither on science nor process. However, several members indicated that there indeed appeared to be a movement toward increasing the scientific focus of both the application and the site visit.

- Members were informed that specific discussions at the time of the site visit are not necessary if the application is well-written and complete, presentations are clear, and scientific expertise and program members' track records are well known to the review committee. Staff suggested that the culture change implicit in the revised guidelines will need a period of many cycles to become established. The preparation time and the amount of paperwork involved, however, will require continued work to reach a reasonable compromise in relation to the amount of detail needed to justify the award of from $1M to $6M of the public's funds. Assistance is needed from those individuals who can see both sides of the issue based on experience both as applicants and reviewers.

- Members suggested that a process be developed for identifying reviewers, involving them in an educational process, and ensuring a more rapid turnover of the group. In addition, the expanded definition of cancer research to include areas without direct cancer relevance, such as fundamental cell biology, mathematics or engineering, still needs to be applied to the cancer centers review. Also needed is more explicit information on the budget process, especially as it relates to reductions made at the time of the grant award.

- The guidelines were revised according to the CCPRG's

mandate that there should be no unpublished guidelines but, at the same time, allow applicant flexibility to address specific circumstances that may exist at a given cancer center. These conflicting mandates create a level of tension in practice. A suggestion was that the uncertainty over the level of detail to be provided in the application to support a budget request for shared resources, for example, might be addressed by developing a list of frequently asked questions and providing best practices statements about how to approach the issue. BSA members suggested also that the top tier grants be made available after funding as a training tool and that specific reviewer guidelines be developed.

top

WORKING LUNCH - DR. DAVID LIVINGSTON

National Pediatric Cancer Network

Dr. Malcolm Smith, Head, Pediatrics Section, Clinical Investigations Branch, DCTD, presented a follow-up on the March BSA discussion of the proposed National Network for Research on Causes of Cancer in Children concept, which was withdrawn from consideration. Dr. Smith discussed plans for proceeding with the feasibility phase of a national network that had been developed after extensive discussions with Board members and group investigators to address concerns expressed at the March meeting which were related to: 1) coordination of existing activities and, at a national level, with state population-based cancer registries and 2) the contribution of environmental factors to childhood cancer etiology. In regard to the latter, Dr. Smith presented justification of the need for understanding the etiology of all childhood cancers, for identifying risk factors other than ionizing radiation and genetic syndromes, for identifying potential protection factors, and for evaluating the role of gene-environment interactions.

Dr. Smith described the proposed national resource as a registry of children with cancer and their families who have consented to or will consider participation in future research activities. Board

members were given a demonstration of how researchers' access to this national resource is envisioned. As proposed, the national network would build upon the NCI-sponsored Children's Oncology Group (COG), a single nationwide structure involving most of the institutions that treat childhood cancer. Registration procedures would be coordinated with existing population-based registries through the use of standard cancer registration coding conventions and by establishing data exchange. Other research opportunities presented by a national network include enhancing surveillance activities by state and regional population-based registries, supporting outcomes research and monitoring survival rates for all children at COG institutions, evaluating nationwide patterns of care for children with cancer, and facilitating long-term follow-up and childhood cancer survivor research. Dr. Smith emphasized that the national network would be a substantial extension of what the pediatric cooperative groups are funded to do. Extending their capabilities would involve additional support to identify and enlist the participation of non-treatment protocol patients in the registry, enhance statistical center activities, and collect the requisite tumor and normal tissue specimens.

He stated, as noted by BSA members, the challenges to be addressed were: 1) determining the proportion of children with cancer who actually present to COG member institutions and the ability to recruit these children to participate in a national cohort; 2) collecting tissue specimens; 3) developing acceptable and efficient registration and informed consent processes; and 4) establishing data exchange with state and regional registries. Progress in addressing the challenges included a coordinated effort by the NCI SEER program and Centers for Disease Control and Prevention (CDC) to support studies to compare the patients identified at pediatric cooperative group institutions with those identified with the selected state cancer registries. One result of this effort is expected to be greater certainty as to the proportion of patients seen at COG member institutions. Additionally, COG investigators are developing the registration protocol and informed consent document for pilot testing. Plans for enhancing resources for etiologic studies include supplemental funds for COG epidemiological research and working with COG investigators over the coming year to address feasibility issues related to registration and informed consent procedures, tissue specimen and data collection, and interactions with population-based registries.

In discussion, the following points were made:

- The pilot as presented provides an opportunity to plan for and test the feasibility of several of the elements (e.g., the collection of requisite tumor tissues and coordination with state central cancer registries) before a larger project is implemented. The experiences and lessons learned in the 12 extant family registries should be applied in the planning.
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- Although there were reservations about the potential yield in terms of environmental causation of childhood cancer, it was noted that the ability to study trends of childhood cancers could be very valuable.
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- Multidisciplinary expertise and wide support will be necessary to ensure the success of the proposed national resource. As envisioned, the national network would be accessible by all epidemiologists through review and solicitation mechanisms that would reach out to investigators outside the cooperative groups.
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- A report on the progress in implementing the pilot feasibility project for the National Pediatric Cancer Network will be presented in the next year.

Metrics: Clinical Trials Restructuring

Dr. Jeffrey Abrams, Medical Officer, Clinical Investigations Branch, Cancer Therapy Evaluation Program (CTEP), DCTD, reviewed the organization of the proposed pilot projects that resulted from the recent restructuring of NCI's clinical cooperative group program. Metrics for evaluating each new component, i.e., the new state-of-the-science meetings, disease-specific concept evaluation panels (CEPs), Clinical Trials Support Unit (CTSU), and the network of NCI-sponsored clinical investigators, were presented.

As planned, the **state-of-the-science meetings** will be evaluated for the breadth and expertise of the participants, contribution to all phases of clinical trials, satisfaction of participants, number of times the results of the meetings are accessed on the Web site, and formation of new scientific collaborations. The first meetings on

targeted therapies for small cell lung cancer and prostate cancer will be held in September and November, respectively, and the evaluation plan will be implemented in the fall.

Metrics for evaluating the CEPs will include the qualifications and range of competencies of the panel members, ratings of concepts over time, rating trends, effectiveness of the Internet-assisted teleconference, backgrounds of investigators submitting concepts, and scientific quality over time as reflected in publications and national meeting presentations. Dr. Abrams noted that the panels have been assembled and trained in the use of the teleconferencing system and that monitoring their progress will begin in the fall.

The CTSU will be evaluated on the commonality of forms and eligibility criteria for the national menu of studies, ability to perform single site audits, timeliness and quality of operations of the CTSU, and the timing and efficiency of execution from concept to protocol activation. Related NCI initiatives are addressing institutional review board (IRB) and compliance issues. The model for a national IRB format is being developed in collaboration with the cooperative groups, non-group physicians interested in participating in the national trials, health maintenance organizations, and the OPRR, NIH. The CTSU, which is currently being competed, is expected to be funded by September 1999 and begin enrolling patients between April and June 2000.

Evaluation of the network of NCI-sponsored clinical investigators will assess how many sites open trial menus, measure targeted vs. actual accrual rates and cross-/non-group accruals, and compare the data with pre-pilot statistics. Data from the CTSU will accrue beginning in the fall, and a large enough body of data is expected midway through 2001 for a report on progress in achieving the goals for the pilots.

Establishing Subgroups: Developmental Therapeutics, Cancer Control, Clinical Trials, Surveillance, Chemoprevention, Tobacco, and Early Detection

Dr. Klausner presented an alternative solution to the formal standing subcommittee structure for continuous oversight of NCI's new large initiatives (e.g., developmental therapeutics, cancer

control, clinical trials, surveillance, chemoprevention, tobacco, early detection, etc.) proposed at the March 1999 BSA meeting. In the suggested format, division directors and/or the Board would identify specific initiatives to be monitored; division directors, their staff, and BSA members who are expert or interested in the particular research area(s) would then develop a set of parameters (e.g., process issues in the short term, content and outcome over time) designed specifically for each initiative chosen and plans for reporting to the Board. The Board as a committee of the whole would comment definitively on the progress reported or lack thereof. The review and reporting process would be similar to that employed for RFA concept reviews. After a brief discussion in which aspects of the proposed alternative were clarified, staff indicated that a plan for establishing BSA ongoing oversight of large NCI programs (based on the model used for concept reviews) will be presented at the next BSA meeting. The plan will include a proposed set of parameters, how subgroups would be formed and operate, and how they would interact with program staff and report to the BSA as a whole.

Members requested an annual listing of new NCI programs awarded through the RFA mechanism, dates or projected dates of initiation, and a glossary of acronyms.

top

RFA CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis

Imaging Techniques for Early Prostate Cancer (RFA) - Dr. Dan Sullivan, Associate Director, Diagnostic Imaging Program, DCTD, stated that the purpose of this initiative is to stimulate research in the development and application of improved imaging methods for the localization, biopsy, and minimally invasive delivery of therapy for prostate cancer. The need for this initiative was identified by the Prostate Cancer Clinical Guidelines Panel of the American Urological Association, NCI Prostate Cancer Progress Review

Group, NCI Imaging Science Working Group, and several workshops on prostate cancer and other more generic topics. Specific goals are to improve measurement of the local extent of disease using anatomic, metabolic, or alternative novel imaging methods; improve image-guided biopsy, staging, and identification of aggressive cancers by metabolic or alternative novel imaging systems; and improve the navigation and control of image-guided therapy and measures of early biological effects. Dr. Sullivan stated that the proposed grant program could serve: 1) to signal NCI's interest and focus research in the field and 2) act as a catalyst to bring about the integration, through academic bioengineering centers, of pieces of the systems that are being developed by various device companies.

The proposed length of award is 4 years with a first year set-aside of $1.6M and a total cost of $13.6M for an estimated 8 R/21/R33 awards.

In discussion, the following points were made:

- The RFA should be expanded to include: 1) the development of more innovative biopsy techniques; 2) the monitoring of image response to therapy to study the effect of signal intensity or spectroscopy that is supportive of a good or bad response; and 3) the requirement for reducing operator dependence in the development of the technologies.

Motion: A motion to approve the RFA concept for "Imaging Techniques for Early Prostate Cancer" was seconded and unanimously approved with the modification that innovative tissue sampling methods should be added to the RFA narrative.

Division of Cancer Control and Population Sciences

Cancer Intervention and Surveillance Modeling Network (CISNET) (Coop. Agr.) - Dr. Eric Feuer, Cancer Surveillance Research Program (CSRP), Division of Cancer Control and Population Sciences (DCCPS), stated that the concept has as its focus the use of modeling to study the impact of interventions (treatment, screening, and primary prevention) on population

trends. The concept for the CISNET has been endorsed by the Surveillance Implementation Group and submitted as part of a prostate cancer 5-year research plan. Its purpose is to stimulate the development of models that describe the impact of cancer intervention on national surveillance trends. Types of studies anticipated are: 1) modeling dissemination patterns; 2) modeling the impact of interventions on observed national trends; 3) predicting the impact of new interventions on national trends; and 4) determining the impact of targeted cancer control interventions on population outcome. As proposed, site-specific working groups and a working group on methods would be formed, together with a technical advisory group drawn from NCI staff. The strength of these collaborations would be the sharing of methods and jointly developed data resources, as well as a joint effort to decide directions.

A two-part solicitation was proposed with a first round budget of $1.5M per year for 6 awards for 4 years, and a second round to begin at year 3 with a budget of $1.25M per year for an anticipated 5 awards for 4 years. The estimated cost for the 6-year project period is $11M. Submissions in the first round would be limited to breast, prostate, and colorectal cancers; new sites, especially tobacco-related cancers, would be added for the second round.

In discussion, the following points were made:

- It was suggested that the announcement include: 1) the need within any group of responders to include experts from other disciplines, for example, epidemiologists and clinicians; and 2) the need to answer the "why not" question when the models do not fit with anticipated outcomes. It also was suggested that this effort should include people knowledgeable in the predicted effects of treatment as well as the predictive effects of screening and risk factors.

Motion: A motion to approve the RFA/Coop. Agr. concept for a "Cancer Intervention and Surveillance Modeling Network (CISNET) was seconded and unanimously approved.

Division of Cancer Treatment and Diagnosis
Division of Cancer Prevention

Molecular Target Drug Discovery (MTDD) Grants (Coop. Agr.) - Dr. Edward Sausville, Associate Director, DTP, DCTD, stated that the concept for the MTDD program is a specific effort to implement the early therapeutics development plan outlined earlier in the meeting. It is envisioned as a grant to extramural principal investigators that would allow the translation of cancer biology discoveries to be validated and brought forward as potential useful targets. The grant also would provide the means of defining potential lead structures against these targets. The difference in this program from the traditional R01 or any other program now in place is that funding is to be built in for supplements to elucidate structure and/or produce large amounts of compounds that might be needed for screening or for structure determination. The program would be interactive with the Compound Decision Group and NCI staff so that additional resources could be provided through contracts managed in concert with the prinicpal investigators. This would allow conversion of appropriately vetted targets to high throughput screens for the purpose of generating lead structures against novel targets. Goals of the MTDD program are to: 1) bring academics with "state-of-the-art" science capabilities but without chemistry, screening, and pharmacology resources to drug discovery research; and 2) define drugs that are truly novel in their application and the target they utilize. A review of the NCI grant portfolio indicated that a significant proportion of the traditional R01s reflects work on standard agents and analogs.

The proposed 10 awards are for 4 years at approximately $300K direct costs, for a total of $12M. Structure and screening supplements ($1M and $2M, respectively) would be built in the third and fourth years, as well as a $1.6M supplement for chip production. Anticipated total cost for 4 years is $16.6M.

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

- Consideration should be given to using the Program Announcement (PA) mechanism in subsequent years. Because the MTDD program as proposed is applicable to the needs of both treatment and prevention research, it may be necessary in time to consider increasing the budget.

- A future direction of this research should be to emphasize

the chemistry (small molecule-based) approach by screening for pathways and processes relevant to cancer to define new targets.

- The RFA should clarify that potential targets should be supported by some level of evidence to provide peer reviewers with more than first principles on which to base their decisions.

Motion: A motion was made to approve the RFA/Coop. Agr. concept for "Molecular Target Drug Discovery Grants". The motion was seconded and unanimously approved.

Centers of Excellence in Interventions Directed at Molecular Targets (Coop. Agr.) - Dr. Michaele Christian, Associate Director, CTEP, DCTD, stated that the concept for the COEs represented the second part of the NCI approach to designing more molecularly targeted early therapeutics development programs. The goals are to bridge the gap between target-based drug discovery and mechanism-based clinical testing and to provide clinically useful assays and tools to make translational research a reality in the areas of cancer prevention and treatment. The proposed program would develop multidisciplinary translational research teams with broad basic and clinical expertise focused on high priority targets or families of biological mechanisms. These teams would be virtual centers with collaborators drawn from one or more institutions (e. g., academic, industry, government), which would have access to agents from any source for developing and validating assays and tools needed for mechanism assessment. The COEs are envisioned as a national resource to provide scientific leadership through extensive collaborations with other groups of investigators.

The intent is to fund 4-6 centers for 5 years in the first issuance and another 4-6 in the third year. An estimated set-aside in the first year is $7.98M at an anticipated total cost of $64M for the project period.

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

- It was recommended that: 1) the name for the proposed

program be changed to more clearly reflect the scientific question; and 2) the language of RFA narrative should be less directed and more generic.

Motion: A motion to approve the concept for "Centers of Excellence in Interventions Directed at Molecular Targets" for the first issuance of the RFA/Coop. Agr. with a proposed funding of $32M for 4-6 grants was approved, with 20 for and 6 opposed. BSA approval would be required for a second issuance in year 3 of the first awards.

top

Division of Cancer Treatment and Diagnosis

Early Therapeutics Development with Phase II Emphasis (RFP) - Dr. Christian stated that the proposed request for proposals (RFP) would continue the 30-year program to address the needs in CTEP's early clinical therapeutics development program for: 1) an efficient mechanism to evaluate a large number of agents for clinical activity and to assess and correlate drug effects at the putative target; and 2) new insights into drug mechanism and determinants of response for those drugs. The contracts to be awarded would be a major mechanism for the conduct of NCI-sponsored Phase II trials by expert investigator teams in institutions where there is a commitment to study molecular endpoints. The contracts would provide flexibility in testing new approaches and paradigms for clinical trials methodology, with rapid accrual and completion of trials as a requirement. As planned, the contracts would fund eight consortia or institutions with capacity to accrue 100 - 200 patients per year and the ability to implement approved protocols rapidly. New to this solicitation would be the proposal for a Translational Research Fund (TRF) to support real-time correlative laboratory studies in the context of the trials and to facilitate incorporation of the best correlative studies from any site into clinical trials. Supplemental funding for correlative studies would be based on a detailed correlative study plan, rationale, analysis plan, and budget, with external review of the proposals and quarterly progress reports of protocol accrual and response data

via the CTEP Clinical Data Update System. Metrics were presented for evaluating both components of the proposed program.

Total funding for the eight Phase II contracts was estimated at approximately $7.6M in direct costs per year for 5 years. TRF funding was estimated at $6.3M per year.

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

- Members expressed concern that the proposed program may fail to accelerate accrual because of: 1) the need for new organizational skills to conduct the trials by a consortium; 2) competition from contract research organizations and insurance coverage problems related to Phase II trials; 3) the restricted amount of time physicians have to devote to the informed consent process; and 4) delays in accrual caused by the addition of multiple intermediate markers or complex technology.

Motion: A motion for approval of the RFP concept entitled "Early Therapeutics Development with Phase II Emphasis" was seconded and unanimously approved.

Adjournment: The meeting was adjourned at 5:15 p.m. on Wednesday, June 23, 1999.