Board of Scientific Advisors

Meeting Minutes

March 8,1999

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

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI) convened for its 11th regular meeting at 9:45 a.m. on Monday, March 8, 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 9:45 a.m. until adjournment on Monday, March 8, for introductory remarks from the Chair; confirmation of future meeting dates; ongoing and new business; and presentations and discussion on the status of the NCI budget and paylines, the Cancer Genome Anatomy Project, Surveillance Implementation Group Report, a subcommittee structure for new large initiatives, BSA sexennial reviews, clinical trials restructuring project, plans for drug discovery and early clinical trials, Request for Applications (RFA) concepts, and improving access to human specimen resources.

BSA members present:
Dr. David Livingston (Chair)
Dr. Frederick R. Appelbaum
Dr. Joan Brugge
Dr. Mary Beryl Daly
Dr. Virginia Ernster
Dr. Waun Ki Hong
Dr. E. Tyler Jacks
Dr. Herbert Y. Kressel
Ms. Deborah K. Mayer
Dr. W. Gilles McKenna
Dr. Enrico Mihich
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

BSA members absent:
Dr. Eric R. Fearon
Dr. Suzanne W. Fletcher
Dr. E. Robert Greenberg

Dr. John D. Minna
Dr. Sharon B. Murphy
Dr. Allen I. Oliff
Dr. Franklyn G. Prendergast
Dr. Ellen V. Sigal
Dr. Joseph V. Simone
Dr. Louise C. Strong
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Dr. Joan Massague
Dr. Stuart L Schreiber

NCAB liaison:
Dr. Philip A. Schein

Others present included: Members of NCI's Executive Committee (EC), NCI staff, members of the extramural community, and press representatives.

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Update: Improving Access to Human Specimen Resources - Dr. Sheila Taube

CALL TO ORDER AND OPENING REMARKS - DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 11th regular meeting of the Board of Scientific Advisors (BSA or Board) and welcomed members of the Board, National Institutes of Health (NIH) and National Cancer Institute (NCI) staff, guests, and members of the public. Dr. Livingston introduced Dr. Ellen Sigal, President, SIGAL Environmental, Inc. and Dr. Jerome E. Groopman, Professor of Medicine, Harvard Medical School, as newly appointed BSA members. Board members were asked to review the tentative meeting 2001 dates and report any conflicts.

CONSIDERATION OF NOVEMBER 12-13, 1998 MEETING MINUTES - DR. DAVID LIVINGSTON

Motion: A motion was made to accept the minutes of the November 12-13, 1998 BSA meeting. The motion was seconded and unanimously approved.

ONGOING AND NEW BUSINESS - DR. DAVID LIVINGSTON

BSA at National Meetings: Dr. Livingston announced the following BSA representation at NCI Listens Sessions at 1999 annual national meetings: American Society of Preventive Oncology (ASPO), March 14-16, Houston, TX, Drs. Daly (Chair), Hong, and Lerman; American Association for Cancer Research (AACR), April 10-14, 1999, Philadelphia, PA, Drs. Ernster (Chair), Mihich, Minna, Mueller, and Strong; and the Oncology Nursing Society (ONS), April 27-May 1, Atlanta, GA, Ms. Mayer (Chair). Drs. Minna and Appelbaum will report in June on the possibility of an "NCI Listens Session" at the American Society of Hematology (ASH) meeting in 2000.

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

Mr. Stephen M. Hazen, Chief, Extramural Financial Data Branch, presented an update on paylines for major Research Project Grant (RPG) mechanisms and the annual report on funding for career and training awards made in FY98. No change was reported in the payline for investigator- initiated (R01) grants, which has been set at the 24th percentile since the end of FY98. The payline for program project (P01) grants remained unchanged at a priority score of 135. Initial paylines for the National Research Service Awards (NRSA) have been set at 192 for the fellowship program (F32/F33) and 145 for institutional awards (T32). The final paylines will be contingent on actions in the third round of applications. Paylines for the Community Clinical Oncology Program (CCOP-U10) will be set when the full year's priority scores have been received.

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

- To address the potential problems in meeting obligations in noncompeting grant years and maintain its commitment base, the NCI uses a series of programs to model for outyear costs of grants and the effect of NCI budget increases or decreases on the paylines for RPG mechanisms. Major variables in the projection models are average cost per year for competing grants, based on cost-of-living allowances and success rates, and annual growth in applications received. Current projections are that the total budget percentage that goes into the RPG pool will not change because of high priority surveillance, cancer control, clinical trials, cancer centers, and translational research programs. The uncertainty of receiving continued budget increases is recognized and is being addressed.

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PROGRESS REPORT: CANCER GENOME ANATOMY PROJECT (CGAP) - DRS. ROBERT SYRAUSBERG AND KENNETH BUETOW

Dr. Robert Strausberg, Project Manager, CGAP Tumor Gene Index, stated that the overall goals of the CGAP are to enhance the discovery of acquired and inherited molecular changes involved in cancer and to apply those discoveries in the clinical arena through creation and dissemination of information and technologies. Dr. Strausberg emphasized that CGAP is a technology and information infrastructure project designed to build an interface of genomics and cancer research for the entire community. Current components are the Human Tumor Gene Index, Mouse Tumor Gene Index, Cancer Chromosome Aberration Project , and Genetic Annotation Initiative.

Human Tumor Gene Index (TGI). The TGI was designed to enhance the discovery of human genes through expressed sequence tag (EST) sequencing. Technology to better interface laser capture microdissection (LCM) gene discovery in the context of the development of cancer is being developed. CGAP investigators have also been exploring other gene expression technologies such as SAGE and DNA arrays. When the TGI was initiated in 1997, the implementation plan was designed to focus on five tumor sites (breast, prostate, colon, lung, ovary) and some other tissues to drive the process of gene discovery. Planned approaches to building cDNA libraries included starting from bulk tissue as well as from microdissected tissue and then building both normalized and subtracted libraries to help drive the process of discovery. Progress in human gene discovery is updated weekly and reported on the NCI CGAP Web site, based on the UniGene database maintained by the National Center for Biotechnology Information (NCBI). To date, more than 500,000 human cDNA sequences have been discovered and 20,000 UniGene clusters (each of which represents a unique human gene) have been categorized as new human expressed genes, a discovery rate for CGAP of about 4 percent. CGAP's record of gene discovery by organ site includes more than 1,200 expressed in the kidney and nearly 800 expressed in the brain. In a comparison with the totals of genes discovered through non-CGAP research, CGAP has made major contributions in identifying genes expressed in the colon, lung, and ovary and has discovered essentially all of the genes expressed in the breast and

prostate. Weekly progress reports on all the libraries produced drive the CGAP process of gene discovery. These reports indicate the characteristics of the libraries (including the number of sequences discovered and a sense of the diversity of the genes) and present algorithms to help predict future gene discovery. This information is helpful in setting priorities based on biological interest.

Board members were then given a brief summary of: 1) CGAP approaches to building specialized libraries, both normalized and subtracted, and their potential importance to furthering gene discovery over the next year; 2) statistically significant differences among the findings from the CGAP libraries; and 3) tools that have been developed to help researchers analyze CGAP data including digital differential display and informatics technologies.

Mouse CGAP TGI. Overall goals of the Mouse TGI are to 1) provide for comparative assessment of mouse cancer stages with those of cognate human cancers, both to validate the mouse models and to promote crossfeeding in the identification of genes that characterize those cancers; and 2) promote the discovery of new genes and gene pathways involved in the stages of carcinogenesis. To date, about 15,000 mouse gene clusters have been identified, compared with the more than 62,000 known human gene clusters. The emphasis now is on equalizing the number of known mouse and human clusters so that investigators can make ultimate use of the mouse. Board members were told that the NIH is beginning a full-length cDNA project in collaboration with the NCI and National Human Genome Research Institute (NHGRI). A clone repository will be built for the enriched and full-length cDNA libraries, and a sequencing pipeline is planned, with the goal of sequencing 20,000 or more full-length mammalian cDNAs per year.

Cancer Chromosome Aberration Project (cCAP). The cCAP is an initiative designed to build an interface between the cytogenetic and physical maps of the human genome. A clone repository of genetically and physically mapped sequence-ready bacterial artificial clones (BAC) will be generated and made available to the research community through an accessible, user- friendly database. This database will provide a platform for correlation with parallel databases of cancer-associated chromosome aberrations and clinical, histopathologic information.

Genetic Annotation Initiative (GAI). Dr. Kenneth Buetow, Project Leader, GAI, stated that the GAI, is an initiative designed to expand the utility of the particular reagents that are being developed within CGAP. GAI goals are to identify polymorphisms or genetic information that will enable investigators to track the transmission of traits in families or identify significant differences in the distribution of variation in populations. This project takes advantage of CGAP cancer gene identification and differential expression efforts to systematically look for variation in formation or polymorphism information in the collections of genes that are being identified. Such information is needed to conduct genetic analysis through family studies, pathway dissection, and genome-wide association studies. A broad consortium of experts has been assembled, which includes scientific investigators and technology development experts from the NCI, NCBI, extramural research community, and industry. Within this consortium, the decision was made to perform genetic annotation of CGAP sequences through two approaches, by tagging the genes with anonymous polymorphic tags and by looking for variation in coding regions. Members were given a brief overview of the large-scale resequencing effort occurring in the first approach, in which a collection of approximately 500 genes are systematically being resequenced in a relatively small number of individuals .

Complementing the resequencing effort is an informatically intensive data-mining exercise, which takes advantage of the 50,000 genes and 1 million sequences represented in databases in the public domain. Informatics tools are being assembled to harvest the sequence or variation information that is already present in the genome. Board members were given an illustration of single nuclear polymorphism (SNP) discovery achieved in a pilot project using GAI informatics tools. Members were told that pilot projects using a variety of molecular methods have been conducted on almost 500 of these high-confidence sequences to validate the outcomes of the predictions. Dr. Buetow estimated that, if these preliminary success rates hold, 5,000 targets could be screened by the end of the year, with the potential for delivering 3,000 to 4,000 new gene base variants within the GAI.

In addition to these specific experiments, work is ongoing with extramural and corporate groups to develop the technology for high-throughput assays needed to reduce the labor intensiveness

and expense of resequencing. GAI products are also being distributed through the GAI home page, which is linked to the CGAP Web site, and through all major public resources.

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

- All CGAP data become part of the larger set of databases, which include a gene map of the human genome that is searchable. Specific resources are also being developed that could facilitate genetic and linkage analysis. Because informatics present the greatest future challenge to all CGAP components, the goal is to develop standard ways of cataloguing all data in the various databases and then to link the databases with clinical data.

- A systematic effort focusing on promoters has not been part of the current GAI research but would be a logical extension of the project in the future. The next steps will be to enlist the help of the research community in validating the annotation of gene expression through a variety of NCI initiatives. Projects to develop stage-, tissue-, and tumor development- specific promoters, which could be funded through mechanisms such as the Phased Innovation Awards would follow. NCI investigators will continue to annotate all CGAP data through microarrays and seek assistance from the extramural community in projects to enhance the quality of the annotation.

- Ultimately, reconstruction experiments across regions that are known to be rich in SNPs in which linkage already has been established in families (e.g., the Li-Fraumeni family) will demonstrate proof of concept. Efforts also are under way to sample additional ethnic and clinically defined populations for inclusion in the polymorphisms database of, but the logistics of the task, at present, are a limiting factor.

- Data-mining procedures are drawing from a centralized data resource, and search engines are being shared through the GAI Web-based interface. The NCI is working to accelerate the development of technologic tools needed by all laboratories to deal with the huge amount of genetic

information that is being generated. One challenge in building the interface is the difficulty in framing questions on which to build the search engines.

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SURVEILLANCE IMPLEMENTATION GROUP REPORT - DRS. BARBARA RIMER AND ROBERT HIATT

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences (DCCPS), reminded Board members of the importance of surveillance as a function of the NCI, both because of the legislative mandate and because the trend data produced is used to improve the public health. Although the Cancer Surveillance Research Program (CSRP) is the organizational locus, NCI's surveillance activities cut across all divisions and deal with most of the important questions asked at the Institute.

Dr. Robert Hiatt, Deputy Director, DCCPS, presented the Surveillance Implementation Group (SIG) report, NCI's response to the 1997 Cancer Control Program Review Group's (CCPRG) surveillance recommendations. Dr. Hiatt stated that the CCPRG recognized that NCI's CSRP performed high-quality data collection and applied research and was responsive to the reporting requirements of the National Cancer Act of 1971. The CCPRG also noted that "additional measures of the total cancer burden are needed (building on existing infrastructure) to measure progress in reducing this burden and to allow NCI to properly plan and evaluate its research agenda." Two basic recommendations were: 1) to expand the Surveillance, Epidemiology, and End Results (SEER) program (taken to mean the full surveillance program) to include additional populations, more patient data, and population data from the SEER regions to monitor individual and societal mediators of cancer; and 2) use the SEER expanded data and expertise to produce a timely report card on the cancer burden. The multi-disciplinary and multi-institutional Surveillance Implementation Group was organized and charged with developing NCI's response. After extensive research and debate, the SIG reached consensus on a broad vision statement based on the CSRP's record. To implement this vision, the SIG made 12 specific

recommendations, which they categorized into five priority areas: 1) expand the scope of surveillance research through additional data collection and methods development; 2) expand the scope of surveillance to improve the representativeness of burden estimates; 3) produce a national report card; 4) support molecular and genetic research; and 5) develop a strategy for training cancer prevention and control scientists.

Board members were given an overview of the implementation plan and a description of research opportunities presented by each priority area. Dr. Hiatt indicated that the NCI will work with its partners to effect a National Cancer Surveillance Plan through the National Coordinating Council for Cancer Surveillance. A summary of specific SIG implementation initiatives and an initiation timetable for each was presented. Board members were asked for comment and suggestions on the SIG report in terms of how the areas of investment chosen therein and the proposed funding and timelines would meet the challenge of explaining national cancer trends and understanding differential cancer burden.

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

- Plans for implementing the CSRP recommendation to expand surveillance research to include data on quality of cancer care include: 1) an approach similar to that taken in the Prostate Cancer Outcome Studies; 2) selective sampling of subsets of cases to augment the information that is routinely collected; 3) more in-depth, longitudinal studies that link SEER data with other existing data systems, such as the National Cancer Data Base and Medicare; and 4) exploring methodology to link SEER population-based data to clinical trials data.

- The SIG recognized the critical need to understand patterns of care and quality of care issues. At this time, the Group sees population-based assessment of outcomes of care within incidence-based cohorts as the best way to proceed with surveillance research for the large and most common cancers. Ways of understanding what are the best measures of quality and patterns of care over time or in the future may be incorporated in routine surveillance, with some

additional funding.

- Although it is not presently feasible for the SEER program to routinely capture outcome data, the NCI remains committed to finding alternative and appropriate methodologies, some of which may be linked to SEER.

- The problems encountered in obtaining archived tissue from pathologists will need to be addressed to realize the goal of expanding the population-based efforts to include molecular and genetics research. Recognizing this, the SIG is proposing feasibility studies to look at various models for capturing specimens.

- Data collected in the SEER registries can be pooled with data collected in emerging state- based registries; however, it depends on the comparability of data elements, data quality, and data standards. The speed with which efforts toward achieving poolable data can evolve will depend on the amount of state and federal funding available and technical contributions made by SEER staff work with others. SEER program staff also are examining profiles of the characteristics of populations covered by the different registries to identify potential sources of data on geographic areas and populations that are not being collected by the SEER registries.

- At the November 1999 meeting, the BSA will revisit the progress being made toward expanding surveillance research to include clinical outcomes questions. Data from the Prostate Cancer Outcomes Study and recent DCCPS studies of Medicare data on inpatient and outpatient breast cancer treatment procedures will also be presented.

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WORKING LUNCH - DR. DAVID LIVINGSTON

Subcommittee Structure for New Large Initiatives: CGAP, Tumor Markers, Tobacco, Imaging, Clinical Trials:

Board members were asked to consider how they propose to carry out the BSA's responsibility for oversight of large initiatives. The goal is to ensure that a core of members follow the operation of each initiative and perform continuous oversight. Discussion focused on the need to develop prospective measures for success or failure, develop criteria for choosing the projects for oversight, derive evaluation metrics with reference to the implementation reports and with the help of the people who develop the major program, and enlist the help of one or two ad hoc experts. Several BSA subgroups will be formed to work with staff towards implementing the NCI's six to eight new large initiatives (developmental therapeutics, clinical trials, surveillance chemoprevention, cancer control, tobacco, early detection, etc.). BSA members' rotation dates should be considered when constituting the subgroups. Subgroup assignments will be presented at the June 1999 meeting.

STATUS REPORT: TIMELINE FOR BSA SEXENNIAL REVIEWS - DR. ROBERT WITTES

Dr. Wittes presented a proposed schedule for beginning BSA sexennial reviews of extramural programs. The propose sexennial review schedule was divided into units that could be encompassed in a single session or series of sessions over a 1- or 2-day period, beginning in 2000 with two units that have not had a PRG review. A copy of the previously approved sexennial review guidelines should be sent to BSA members.

Motion: A motion was made to approve the proposed 13-unit Sexennial Review Schedule. The motion was seconded and unanimously approved.

STATUS REPORT: EVALUATION OF THE CLINICAL TRIALS RESTRUCTURING PROJECT - DR. JEFFREY ABRAMS

Dr. Jeffrey Abrams, Medical Officer, Clinical Investigations Branch, Cancer Therapy Evaluation Program (CTEP), Division of

Cancer Treatment and Diagnosis (DCTD), presented a status report on the development of metrics to evaluate NCI's restructured clinical trials process. Board members were reminded of the key aspects of the restructuring: 1) better trials and science; 2) broader pool of trial concepts; 3) concept evaluation panels; 4) state-of-the-art meetings; 5) uniform informatics and a Cancer Trials Support Unit (CTSU) to reduce burdens on investigators in the field; 6) an open menu of trials with cross-group registrations to broaden access, increase accrual and the rate of accrual, and involve new physicians; and 7) adequate compensation for all physicians involved. The pilot project to be evaluated would have four components: 1) idea generators (cooperative groups, cancer centers, community practitioners, independent investigators); 2) a scientific panel composed of CTEP staff and extramural individuals to achieve broader review of concepts; 3) state-of-the-science meetings to stimulate new ideas and bring translational ideas into Phase III clinical trials; and 4) a network of cooperative group and nongroup investigators to enroll patients on NCI-sponsored trials. Diseases to be addressed in the pilot are GU and lung tumors. State-of-the-science meetings for the pilot, which are to be conducted by the cooperative group chairs, are leukemia and gastrointestinal (GI) and breast cancers. Dr. Abrams also reviewed the draft evaluation plan for the state-of-the science meetings, concept evaluation panels, CTSU and network concept.

Members were told that the Clinical Investigations Branch will continue to work on the draft evaluation plan, with the help of staff from other divisions. A follow-up report to the Board will include actual timelines for reporting the metrics. BSA members emphasized the importance of supporting the new directions for clinical trials and the need for checkpoints along the way to make certain that appropriate progress is being made. Members also requested that updates of the projects relating to clinical trials restructuring be presented at a future BSA meeting.

PLANS FOR DRUG DISCOVERY AND EARLY CLINICAL TRIALS - DRS. ELLEN FEIGAL, EDWARD SAUSVILLE, SUSAN ARBUCK, AND ROBERT WITTES

Dr. Ellen Feigal, Deputy Director, DCTD, reviewed the charge to and recommendations of the Developmental Therapeutics (DTPRG) and Clinical Trials (CTPRG) Program Review Groups,

which led to the development of NCI's action plan for integrating drug discovery and the early clinical trials system. The plan was developed by NCI staff with input from academic investigators, industry, and patient advocacy groups. Goals of the NCI plan are to: 1) make the emerging knowledge of cancer biology the basis for drug discovery, drug development, and clinical testing; and 2) understand why a therapeutic intervention leads to a response or no response. Objectives are to: 1) provide a clear path from discovery and development of compounds to clinical testing and 2) create an integrated drug discovery and development program and early clinical trials system founded on mechanism-based approaches. Board members were given a review of the phases that comprise the continuum from drug discovery to clinical practice, the conventional funding mechanisms, and recent initiatives in each phase of the continuum. Dr. Feigal stated that the plan will be presented in greater detail at a future or BSA meeting.

Drug Discovery: Dr. Edward Sausville, Associate Director, Developmental Therapeutics Program (DTP), DCTD, stated that the goals of the plan are to create a new national capability to harness biological and technological advances for target-based drug discovery and to refine understanding of those potential therapeutic targets and develop usable tools for effective translation into clinical trials. Two new mechanisms being considered to implement the plan are the Molecular Target Discovery Program and Centers of Excellence. Board members were given an overview of how these mechanisms would function. In the Molecular Target Discovery Program, target identification would be accomplished through grants awarded to extramural principal investigators (PI), with the potential for structure and production supplements. Lead structures could be licensed to industry, developed autonomously by the PI through NCI's Rapid Access to Intervention Development (RAID) program, or reviewed for conversion to high-throughput screening by a compound decision group and developed in conjunction with the NCI through the proposed, grant-funded Centers of Excellence. The PI would have access to contract research resources for screening and lead optimization and would co-direct optimization strategy. As envisioned, the Centers of Excellence would be multiinstitutional collaborations with a mechanism- based focus and appropriate component programs. NCI's role in the new proposed programs would be as coordinator, catalyst, center for informatics resources, and central repository of libraries and natural product extracts.

Early Clinical Trials: Dr. Susan Arbuck, Head, Developmental Chemotherapy Section, Investigational Drug Branch, Cancer Therapy Evaluation Program (CTEP), informed members that the objectives of proposed initiatives for early clinical trials was to exploit new scientific opportunities by instituting flexible and responsive clinical trials mechanisms, change the conduct of early trials to emphasize proof of principle and target assessment as critical endpoints, and increase speed and efficiency in the early trials of NCI compounds. The major components of the proposed plan for enhancing early therapeutics development are: 1) QuickTrials, a new grant program for investigator-initiated trials with important agents; 2) flexible resources, DCTD contracts for development of critical resources; 3) early therapeutics development contracts or cooperative agreements; 4) the new Centers of Excellence; and 5) Therapeutics Working Group for Novel Targets, consisting of intra- and extramural laboratory and clinical scientists. Ongoing NCI initiatives designed to increase efficiency and promote collaboration also were reviewed. A report on the establishment of the "Quick Trial" mechanism will be given at a future BSA meeting.

Decision-Making and Governance: Dr. Robert Wittes, Deputy Director for Extramural Science, Office of the Director, and Director, DCTD, described how the plans for drug discovery and early clinical trials initiatives will be synthesized and integrated at the divisional level. Dr. Wittes stated that the two-part action plan is an attempt to: 1) harness the immense amount of discovery in academia in the area of cancer biology in the service of drug discovery, and 2) provide an infrastructure with the tools to make target-based early clinical trials a reality. Elements in the plan are a Biologics Group which would consist of internal and external experts in appropriate scientific disciplines to govern access to NCI's synthesis facilities at the Frederick Cancer Research and Development Center (FCRDC), a Compound Decision Group comprised of NCI staff and expert reviewers external to the NCI, and a "Big Questions" Group comprised of NCI staff, BSA members, and external experts to provide overall scientific direction, target emphasis and prioritization, and ongoing portfolio review. An overview of how each group would be organized and operate was also given.

In discussion and in response to questions, the following points

were made:

- As envisioned, the Centers of Excellence would be funded in a manner similar to Specialized Programs of Research Excellence (SPOREs), but with mechanism as a research focus. Supplements would be available as a catalyst to scientific collaborations.

- The National Cooperative Drug Discovery Groups (NCDDGs) differ from the proposed Centers of Excellence in that their work ends at the filing point of the Investigational New Drug (IND). The Centers, as planned, would focus on developing the tools necessary to translate the target-based agents from laboratory to clinic.

- Recommendations of the DTPRG regarding the need for more flexible budgetary mechanisms were considered in developing the action plan. Strategies to address this include the use of NCI contracts for both preclinical and clinical aspects of the proposed program and the quick turn-around from submission to award envisioned with the QuickTrials mechanism for proof-of-principle clinical studies.

- A significant challenge to the BSA and all involved will be promoting the best therapeutic interventions for the biologic targets that are discovered (i.e., lead identification and optimization). One consideration in this regard is how to enhance interaction between pharmaceutical companies and academic institutions to ensure that the cancer biology targets are exposed to the highest quality compounds. Another aspect to address is the type of funding that will be required to establish and maintain in academia the core facilities needed for the higher throughput biologic technologies and research.

- Concepts relating to a previous presentation on "Molecular Targets and Clinical Trials" will be given at the June 1999 meeting.

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RFA CONCEPTS: PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis

National Network for Research on Causes of Cancer in Children (Coop. Agr.) - Dr. Malcolm Smith, Head, Pediatrics Section, Clinical Investigations Branch, DCTD, informed members that one impetus for the initiative was the President's Executive Order (E.O. 13045) on Protection of Children from Environmental Health Risks and Safety Risks. To respond, the Childhood Cancer Working Group was convened, with representatives from the NCI, Center for Disease Control and Prevention (CDC), Environmental Protection Agency (EPA), Agency for Toxic Substances and Disease Registry (ATSDR), and National Institute for Environmental Health Sciences (NIEHS). The proposed National Network would comprise a U.S.-wide registry of childhood cancer cases and a national tissue bank as a resource for researchers studying the causes of cancer in children. Following endorsement of the proposed National Network by the Secretary of Health and Human Services (HHS) and the Directors of EPA and NCI, the NCI, as lead institute, formed the multidivisional National Network Internal Working Group to develop the concept.

This concept proposes the establishment of a National Network as a resource cooperative agreement (U24). The Network would include a registry of children with cancer from throughout the United States; utilize physician-based identification to report cases; identify children at the time of diagnosis to allow collection of tumor specimens before treatment initiation; and support and facilitate high-quality scientific studies by the most qualified U.S. investigators. Dr. Smith stated that the justification for identifying causes of cancer in children includes: 1) the scientific opportunities inherent in the technologic and scientific advances of the past decade; 2) the possibility that lessons learned from childhood cancers may provide insight that apply also for adults with cancer; and 3) the possibility that the more limited duration of environmental exposures for children might facilitate the identification of important and potentially generalizable associations between genetic and environmental factors in cancer risk. Evaluation criteria to determine the effectiveness and success

of the proposed National Network have been formulated. Additionally, the NCI and NIEHS are co-sponsoring a workshop to identify areas of research opportunity relating to environmental causes of cancer in children, with a specific focus on the leukemias and brain cancer.

The proposed length of award is 5 years with a set-aside in the first year of $2M direct costs and a total cost for the project of approximately $14.8M.

In discussion, the following points were made:

- A unique focus should be defined for this project to avoid duplication of or redundance with other NCI-funded resources, for example the recently approved Pediatric Brain Tumor Clinical Trials Consortium, National Wilm's Tumor Study Group, extension of CGAP research to include childhood cancers, and SEER cancer surveillance objectives in defined populations.

- The National Network, as envisioned, would serve to organize, not duplicate, existing structures and would be a tool for epidemiologic research inasmuch as a complete ascertainment of cases from throughout the United States is being sought to study causation, not treatment. Inherent in the award would be the requirement to establish a working relationship with existing structures.

- Childhood cancer cases are so few in number that an adequate basis for epidemiological studies would not be available. This may not be a suitable vehicle for identifying every pediatric case in the nation or for contributing to an understanding of important distinctions in childhood leukemia. Moreover, little evidence exists for any environmental factor as a causative agent in childhood cancers.

- The National Network as proposed would be a unique resource because of the universal coverage envisioned for the registry of childhood cancer cases and because of the provision for tissue banking. Success would be contingent on enlisting all state registries and programs and all federal

agencies to ensure universal registration of cases and to provide adequate funding, policy, and programmatic support.

- A concern is to the variations among state registries in terms of completeness and speed with which cases are reported and the need for rapid diagnosis and case reporting for children. Moreover, comparison groups of children will be needed to study environmental exposures, in utero exposures, or genetic polymorphisms, and there is difficulty in identifying children in a population base and obtaining cell and DNA specimens on a national level.

The concept proposal to establish a National Network for Research on Causes of Cancer in Children was withdrawn from consideration. Board members and NCI staff will develop a plan for reviewing and responding to the issues surrounding the Executive Order requiring the establishment of a National Network for Research on Causes of Cancer in Children.

Cooperative Prostate Cancer Tissue Resource (Coop. Agr.) - Dr. Roger Aamodt, Chief, Resources Development Branch, Cancer Diagnosis Program, DCTD, presented for Board consideration a concept to create a national prostate cancer tissue resource complete with clinical and outcome data. NCI metrics for the development and evaluation of tissue resources would apply. The bank would have formalin-fixed paraffin-imbedded archival tissues, fresh frozen tissue, and informatics support. As proposed, the archival resource, operating policies, and the database would be developed and data centralized during the first year. During the second year, the resource would begin procurement of fresh tissue which would be made available to the research community. Tissue in excess of current needs would be banked and the clinical and outcome data entered into the central database as it becomes available. Informatics support would come from the NCI in the form of access to data contractors who can assist in the rapid development of the database and a resource website. Results of NCI's major informatics initiatives also would be made available to the resource. The need for this resource was raised repeatedly in requests from the research community, by the Prostate Cancer Progress Review Group, and in meeting reports. As envisioned, the prostate cancer tissue resource would be developed as a virtual

bank, on the model of the Cooperative Breast Cancer Tissue Resource (CBCTR). Tissue specimens would be identified at each of several cooperating institutions and remain there, and clinical and outcomes data would be collected and stored in a central database, with a single point of contact for information and to request specimens. The coordinating committee would consist of the PIs and an NCI representative. A research evaluation panel would be responsible for scientific review and prioritization of applications for use of the resource. A pilot project has begun to define common data elements for prostate cancer that will be consistent with those defined by NCI's informatics initiatives.

This concept is for approximately 3-5 U01 awards for 5 years with a set-aside in year 1 of $1.5M direct costs and a total cost for the project period of $11.1M.

In discussion, the following points were made:

- Consideration should be given to integrating benign specimens being collected in the Proscar trial for use as control specimens for prostate cancer studies. The collection of epidemiologic data and blood specimens also should be considered because of their potential value for subsequent genetic epidemiology studies and serologic risk factor detection. The collection of post-treatment specimens, if feasible, would provide a valuable resource for molecular analysis.

- Currently, the demand for prostate specimens has out-stripped the ability of the best high throughput tissue resource to supply it. PCPRG discussions indicated that a large number of markers will be needing further development. Prostate cancer lesions are getting smaller at diagnosis at a time when there is increased interest in studying this disease at the molecular level. Obtaining sufficient tissue to do a meaningful analysis on a number of samples could become increasingly difficult without a centralized resource.

Motion: A motion was made to approve the concept for an RFA entitled "Cooperative Prostate Cancer Tissue Resource." The motion was seconded and approved unanimously.

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UPDATE: IMPROVING ACCESS TO HUMAN SPECIMEN RESOURCES - DR. SHEILA TAUBE

Dr. Sheila Taube, Associate Director, Cancer Diagnosis Program, DCTD, presented the annual update on NCI's comprehensive approach to developing a human specimen resources program. Efforts to ensure that specimens needed for both basic and translational research will be available to the research community the near term and future include: 1) extensive and detailed cataloging from all NCI-supported public resources and specific extramural and intramural programs, as well as commercially available and foreign sources; 2) establishing a standing committee, the Specimen Resources Committee, to develop a rational process for addressing research needs; 3) preparing to act on the concept just approved by the BSA to establish a new national prostate cancer repository; and 4) dealing with the ethical and legal issues associated with the use of human specimens in research. Efforts to ensure that researchers will be able to find the needed specimens include: 1) developing the Tissue Expediter Program as a central information point for investigators; 2) advertising regularly in major scientific journals; 3) distributing tools such as the Tissue Expediter card and a new NCI Cooperative Breast Cancer Tissue Resource (CBCTR) bookmark at major scientific meetings and all small meetings; 4) marketing at major meetings, using well-designed traveling exhibits; and 5) developing new Cancer Diagnosis Program Web sites with regularly updated links to resource Web sites and user-friendly search engines.

Adjournment: The meeting was adjourned at 4:45 p.m. on Monday, March 8, 1999.

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