Board of Scientific Advisors

Meeting Minutes

November 13-14 ,1997

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

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI) convened for its 6thregular meeting at 8:00 a.m. on Thursday, November 13, 1997, 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. on Thursday, 13 November, until adjournment on Friday, 14 November, for introductory remarks from the Chair; discussion of procedural matters and future meeting dates; ongoing and new business; and presentations and discussion on the present status of the NCI budget and paylines, Request for Application (RFA) concepts, BSA at national meetings, reports of the Clinical Trials and Cancer Control Program Review Groups, the Human Genome Project, and the NCI HIV and SPORE programs.

BSA members present:
Dr. David Livingston
Dr. Frederick R. Appelbaum
Dr. Joan Brugge
Dr. Mary Beryl Daly
Dr. Virginia Ernster
Dr. Eric R. Fearon
Dr. David D. Ho
Dr. Waun Ki Hong
Dr. Tyler Jacks
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Dr. Franklyn G. Prendergast
Dr. Joseph V. Simone
Dr. Louise C. Strong
Dr. Daniel D. Von Hoff
Dr. Alice S. Whittemore
Dr. Robert C. Young

BSA members absent:
Dr. Suzanne W. Fletcher
Dr. E. Robert Greenberg
Dr. Stuart L Schreiber
Dr. Peter K. Vogt

Dr. Joan Massague
Ms. Deborah Mayer
Dr. W. Gillies McKenna
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Sharon B. Murphy
Dr. Allen I. Oliff
Dr. Barbara L. Weber
Dr. William C. Wood

NCAB liaison:
Ms. Zora Brown (absent)

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

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CALL TO ORDER AND OPENING REMARKS - DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 6th regular meeting of the Board of Scientific Advisors (BSA or Board) and welcomed members of the Board, National Institutes of Health (NIH) and National Cancer Institute (NCI) staff, guests, and members of the public.

Dr. Livingston discussed upcoming BSA meeting dates and asked that potential conflicts with the proposed dates be reported as soon as possible.

CONSIDERATION OF JUNE MEETING MINUTES - DR. DAVID LIVINGSTON

The minutes of the 19-20 June BSA meeting were approved.

REPORT OF THE DIRECTOR, NCI - DR. RICHARD KLAUSNER

Dr. Richard Klausner discussed aspects of the FY97 budget, progress in the development of the FY 98 budget, and progress in

implementing working group recommendations.

Budget: Although the legislation has not yet been signed, a House and Senate agreement on the NIH budget for FY98 includes an increase for NIH of 7.1 percent over FY97. The NCI budget will be approximately $2.5B, an increase of 6.97 percent. An R01 payline beginning at the 24th percentile is proposed. Dr. Klausner then presented highlights of the FY97 budget by mechanism.

Research Project Grants (RPG) Pool: In FY97, the NCI was able to maintain the R01 payline at the 23rd percentile. About 675 recompeting and 374 new R01s were funded, a 33 percent increase in investigator-initiated research during a 2-year period when the overall NCI budget increased only by 12 percent. Total funding was approximately $580M for almost 2,200 NCI R01s, an increase of 14 percent in FY97 over FY96 compared with the 6.5 percent increase in the NCI budget for that same time period. P01s (program project grants) were funded in FY97 to a priority score of 140, increasing the overall funding level by about 10 percent or more than $200M for this mechanism between FY96 and FY97. Approximately 10 percent of the RPG dollars in the new and competing line are allocated for interim support, bridge funding, supplemental support, AER (Accelerated Executive Review), and exceptions. About 54 percent of the applications that came in for AER in FY97 were funded. In FY98, paylines for patient- and nonpatient-oriented R01 grants receiving AER will be the 34th and 29th percentile, respectively, based on a payline at the 24th percentile as proposed. The NCI funded R29s (FIRST Awards) to the 30th percentile, resulting in a 10 percent increase over FY96 in the number of competing awards funded.

Training: In FY98, the NCI intends to increase the overall training program by an amount commensurate with the total increase of the NCI budget and to target the increase to specific areas, such as clinical research. In response to recommendations from many of the Program Review Groups, NCI increased funding for cancer education programs by 12 percent. In addition, the National Research Service Award (NRSA) received an 8 percent funding increase. Two other training initiatives directed at multidisciplinary areas were an institutional career award in AIDS oncology and a program announcement (PA) in the area of genetic epidemiology. A sum of $10M added to the Minority Mentored Career Development Award provided transition funding to 10 young

cancer researchers who had been recipients of Minority Supplement Research Project Awards.

Bypass Budget: Dr. Klausner reported that the NCI Bypass Budget for FY99 has been sent to the President and Congress after review by the Director, NIH, and Secretary, Department of Health and Human Services (DHHS). In its new format, a third section, entitled the NCI Challenge, is an attempt to bridge an increasing gap between extraordinary scientific possibilities and the ability to translate them into changing public health practice and reducing the cancer burden to individuals at risk for and with cancer. The Board was asked to comment on the seven areas of challenge included in the Bypass Budget.

Board members were told that Working Groups have been convened to begin articulating the four extraordinary opportunities listed in the Bypass Budget. Recommendations from the Developmental Diagnostics Working Group (DDWG) led to the initiation of the Cancer Genome Anatomy Project (CGAP). The Preclinical Models Working Group has been developing recommendations for initiatives related to problems with access to and availability of models. An early initiative for the Cancer Genetics Working Group will be to develop a common lexicon for susceptibility gene discovery that lays out the challenge of cancer genetics from multiple disciplines. Implementation of the Group's recommendations will require new study designs and resources.

NCI Reorganization: Dr. Klausner informed members of the recent establishment of the position of Deputy Director for Extramural Science (DDES) within the Office of the Director (OD), NCI, and the appointment of Dr. Robert Wittes to that position. The Office of the DDES (ODDES) will coordinate communication and activities across the extramural divisions, serve as the center for core functions, and coordinate implementation of recommendations emanating from NCI's three major planning processes as they relate to the extramural program.

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

Dr. Wittes reviewed the organizational structure within the ODDES and highlighted several features and current activities of the components. Specifically, with the transfer of the Minority Training Program from the Division of Extramural Activities (DEA) to the **Office of Centers, Training and Resources (OCTR)**, all NCI extramural training programs have been integrated. The **Office of Cancer Information, Communication, and Education (OCICE)** combines the functions of the former International Cancer Information Center (ICIC) and the Office of Cancer Communication (OCC) to form an integrated structure for information dissemination to the general public. An **Office of Information Architecture (OIA)** is responsible for conceptualizing and actuating the informatics infrastructure for the National Cancer Program. The **Office of Clinical Research Promotion (OCRP)** responsibilities include negotiating and concluding agreements with other federal agencies and with health care providers and payers relating to support for the clinical research enterprise. An **Office of Industrial Relations** is under consideration. This office would serve as a point of entry to the NCI, providing orientation and education for companies wanting to do business with the NCI. The Board was asked to comment and provide review concerning the opportunities, or lack of, for the establishment of an Industrial Relations Branch.

Dr. Wittes briefly reviewed the new organizational structure of the NCI Extramural Research Program (ERP) which includes: the Division of Cancer Biology (DCB), Division of Cancer Treatment and Diagnosis (DCTD), and the Divisions of Cancer Prevention (DCP) and Cancer Control and Population Science (DCCPS). Changes reflected in this configuration are the creation of the two new divisions (DCP and DCCPS) from the former Division of Cancer Prevention and Control (DCPC) and the transfer of the Centers, Training, and Resources Program from the former Division of Cancer Treatment, Diagnosis, and Centers (DCTDC) to the new ODDES.

In response to questions, the following points were made:

- The Office of Cancer Survivorship has been moved to the OD, DCCPS, but the final disposition of the supportive care

portfolio has not been decided.

- Guidelines to assist the BSA in its quadrennial review of the NCI Extramural Divisions and Division Directors should be developed. The guidelines should include how research is to be reviewed by the BSA and should be tailored to the individual programs. Draft Quadrennial Review Guidelines will be sent to members prior to the next meeting.

- A priority for the extramural programs is to implement simultaneously received recommendations affecting major NCI programs, namely clinical trials, cancer control, and cancer prevention. The need for an integrated process was recognized, and a tentative decision is to create internal work groups to consider the recommendations of each Program Review Group and develop various solution models that will be responsive to the needs articulated in the reports. The BSA will receive periodic updates on the status of the various internal or external groups.

- The Cancer Training Branch is conducting a strategic review of the NCI training program as a whole in the context of recent scientific advances and current needs. The Branch is in the process of outlining major issues and plans to engage the BSA either as a committee of the whole or through a subcommittee. The Board was asked to consider establishing a BSA subcommittee to review NCI's consolidation plans for training and education workshops and seminars.

The issue of developing new types of cancer research consortia as a topic for a general discussion by the BSA was raised. Members were asked to focus on the goal of creating a flexible organizational framework for the national research effort in any disease that reaches across institutions and uses funding mechanisms that could be administered flexibly.

Following a brief discussion, the following points were made:

- The National Cooperative Drug Discovery Groups (NCDDGs) and the natural products NCDDGs were consortia of academic institutions, industry, and the

government funded by cooperative agreements. Although successful in generating many products that have gone into the clinic, NCDDGs were more restricted and less comprehensive in scope than proposed new models.

- Several issues identified for consideration were the perception of risk by the individual investigator in regard to being rewarded at the institutional level; the review process; the need for commitment of larger amounts of money than ever before considered; the need to develop a mechanism for the timely disbanding of consortia to ensure optimal use of finite resources; and that the concept and structure of academic research are counter to the idea of consortia.

- A formalized training component should be considered for the consortia to train young investigators to be more collaborative. Although the funding mechanism for consortia should not be limited to already funded investigators, there is merit in the idea of leveraging existing structures and investments if the mechanism can be developed for retaining flexibility.

- The ability to link with peer-reviewed, funded grants in an institution would be a strength of the consortia, and potential problems, such as overlaps in funding for R01 or P01 grants in institutions and consortium funding and the need for the individual to receive credit for participating, should be resolved.

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NCI/CONGRESSIONAL RELATIONS - MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, Director, Office of Legislation and Congressional Activities, informed members of the report language that accompanied the FY98 legislation for the President's signature. Ms. Tisevich reported that the Human Research Protection Act of 1997, which was introduced in January 1997, had been referred to

the Senate Committee on Labor and Human Resources. Research requirements covered in Title I and Title II were reviewed.

In response to questions about the implications for cancer research if this legislation is enacted, the following point were made:

- In its current form, the bill does not appear to have major implications for NIH-funded institutions. The provision to relocate the NIH Office of Protection from Research Risks (OPRR) to the Office of the Secretary, DHHS, would make it somewhat less accessible.

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ONGOING AND NEW BUSINESS - DR. DAVID LIVINGSTON

BSA at National Meetings: Status Report. The Chair asked for resolution of the tentative plan for BSA members to continue as participants in the BSA NCI Listens project. Following a lengthy discussion, a consensus was reached that the project should be continued in 1998. Staff responses to comments received at "future" sessions should be sent to the BSA for review. Following BSA review, the NCI should send the responses to the appropriate associations for inclusion in their publications. Prior to upcoming NCI Listens sessions, one or two questions should be obtained from the society's leadership. NCI responses to those questions should be sent to the full BSA so that the designated participants will have the information prior to the sessions. The remainder of the session will be dedicated to questions from the rank and file association membership. Extra measures will not be taken to invite the press. All BSA members attending the association meetings should have some form of ribbon or badge indicating that they are BSA members representing the NCI.

Members representing the BSA during "NCI Listens" sessions at annual national meetings are : American Society of Clinical Oncology (ASCO) meeting, May 16, 1998, Los Angeles, CA -- Drs. Appelbaum (Chair), Minna and Ms. Langer; American Society

of Preventive Oncology (ASPO) meeting, March 5, 1998, Bethesda, MD -- Drs. Daly (Chair), Lerman and Ernster; American Association for Cancer Research (AACR) meeting, March 30, 1998, New Orleans, LA -- Drs. McKenna (Chair), Mihich, Strong, and Whittemore; Oncology Nursing Society (ONS) meeting, May 6-10, 1998, San Francisco, CA -- Ms. Mayer (Chair); and Cold Spring Harbor meeting, August 1998 -- Drs. Livingston (Chair), Fearon, Strong, and Jacks.

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RFA CONCEPTS: PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Biology

Generation of a Resource of Arrayed BAC Clones for FISH Mapping of Human Genes (Coop. Agr.) - Dr. Grace Shen, Cancer Genetics Branch, DCB, informed the Board that the goal of this concept is to generate a resource of 3,000-5,000 arrayed human bacterial artificial chromosome (BAC) clones across the whole genome, at 1 megabase intervals, for fluorescence *in situ* hybridization (FISH) analysis and cloning projects. This proposed project recognizes that genes disrupted in microscopically discernable chromosome aberrations frequently are found to contribute to malignancies and seeks to develop a resource that will facilitate identification of disrupted genes and provide reference points for the development of a "cancer chromosome aberrations" database. A steering committee of extramural and intramural scientists will collaborate in developing a publicly available database using this resource.

The proposed budget is $500K for the first year, with the anticipated cost of $750K for the 2 year project period. The award mechanism will be the U24. One to three awards are anticipated.

In response to questions, the following points were made:

- Two intramural investigators (NCI and National Human

Genome Research Institute (NHGRI)) will perform all of the FISH mapping in a single laboratory and work directly with the National Library of Medicine (NLM) to transfer the results to the database. A steering committee formed by the NCI, NHGRI, and NLM will work with the cytogenetic community to develop a standardized protocol for cytogenetic identification and statistical analysis. Distinguishing causal abnormalities from random noise should then be possible by looking for precisely defined, recurrent changes using the database.

- Plans are to link the chromosome abnormalities database to the Cancer Genome Anatomy Project (CGAP) so that it will be Web-based and open to public access as the data emerges.

Motion: A motion was made to approve the concept. The motion was seconded and approved unanimously.

Division of Cancer Treatment and Diagnosis

Supplements for Consortia To Access Comprehensive Expression Analysis Technology - Dr. James W. Jacobson, Diagnosis Branch, DCTD, stated that the original intent was to present this RFA concept as an initiative to enhance access to this technology through competitive supplements to consortia of NCI-supported investigators. However, rapid changes in the market are making expression arrays available more rapidly than anticipated. Thus, this initiative is being presented as a case study of the issues that surround the Institute's attempts to respond to the needs of the cancer research community by making these and other novel emerging technologies as widely available as possible. Following a brief description of NCI's efforts in developing this concept, members were asked to discuss what the NCI could do to 1) take advantage of the scientific opportunities that availability of these technologies present; (2) facilitate their continued development; (3) increase the rate of progress in cancer research by the application of these technologies; and (4) ensure the pursuit of as many good ideas as possible in the community. Specifically, suggestions that would enable the NCI to speed up technical development and distribution of new technology to the cancer research community and to establish effective methods of measuring and monitoring

new and developing technology.

In subsequent discussion, the following points were made:

- This area of research follows the CGAP with regard to pathogenesis, diagnostics, and prognosis and would be valuable. A more useful approach than an RFA, which focused more on methodologic issues than access, would be a range of proposals that addressed both methodologic issues and application of the technology at an early stage to address scientific principles. Because the market is in flux, the difficulty is in choosing the system most likely to advance. For this reason, the NCI approach, to get as many technologies as possible into the hands of investigators so that they can be evaluated in real time, is a good one.

- Because information exchange and funding are important issues, the idea of an NCI Web page providing analysis of the available technologies has merit. In addition to making information available, the NCI could play a role by evaluating the utility of a particular technology.

- The suggestion was made to generate a broad omnibus technology structure that could be approved by the BSA and would grant discretionary authority for the NCI to use any of the various grant support mechanisms as the opportunity arises, with a defined dollar constraint, to facilitate technologic advancement in any area applicable to cancer research.

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BSA WORKING LUNCH - DR. DAVID LIVINGSTON

The BSA lunch session was devoted to a discussion of the BSA proposal regarding the Center for Scientific Review (CSR) review of R01 grants, a report of the ad hoc subcommittee instituted to study procedures of Data Safety Monitoring Committees (DSMCs) for NCI- sponsored clinical trials, and consideration of review

issues related to P01 grant applications.

Follow up of BSA Proposal: CSR Review of R01 Grants - Dr. Livingston opened the discussion by reminding the Board of the substance of the proposal to encourage creation of a CSR study section to deal with investigator-initiated clinical research. After considerable discussion, members agreed that the Chair and the Director, NCI should meet with the Director, CSR. An ad hoc Clinical Oncology Subcommittee (Drs. Simone (Chair), Von Hoff, McKenna, Daly, Wood, and Ms. Langer) should also meet with the Director, CSR, to discuss the complexity of establishing an R01 Clinical Oncology Study Section. An informational packet of CSR study section activities will be developed by NCI staff and sent to all BSA members. A report of the status of discussions with CSR should be given at the March 1998 BSA meeting. [Dr. Marvin Kalt was subsequently assigned as the Executive Secretary.]

Members requested that a copy of the letter from sent to the Director, CSR, concerning the Clinical Oncology Study Section should be distributed to BSA members. [Note: The letter was distributed at the November 1997 BSA meeting.]

Status Report: Data Monitoring Committees for NCI-Sponsored Clinical Trials - Dr. Sharon Murphy briefly described the process ad hoc subcommittee used to address the issue of access to clinical trials data by disease committee chairs in the cooperative groups. It was noted that the cooperative group leadership has had an ongoing concern with accessing trial results, particularly toxicity or feasibility data needed to plan future studies. Dr. Appelbaum summarized the committees conference call discussion and noted that the issue remained unresolved and that a process was needed to continue the work toward a solution.

Following a lengthy discussion, the NCI, with input and guidance from the BSA, will develop a workshop that includes patient advocates, ethicists, and clinical trialists to review the question of access to data currently available only to DSMB's for the purpose of planning future studies. A BSA task force consisting of Drs. Appelbaum and Christian (co-chairs), Murphy and Ms. Langer will coordinate the workshop and report back to the BSA. A status report should be given at the March 1998 meeting.

Program Project Grants (P01s): Review Issues - Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), reviewed the current two-tier process for reviewing approximately 100 P01 applications received annually by the NCI. Information was presented on the advantages and disadvantages of returning to a one-step initial scientific review of P01s, which would eliminate the second-tier review by the NCI-IRG Parent Committee of the Site Visit Panel's report. He asked for Board discussion as to whether an experiment to evaluate a return to the one-tier review should be proposed for consideration by NCI's Executive Committee.

Following a brief discussion, members stated that the NCI needs to ensure that all constituents, including patient advocates, payors, and providers, are involved in the peer-review process, particularly in regard to the study section now being considered for clinical oncology.

Motion: A motion was made to delete the Program Project (P01) parent committee(s) from the review process. Ad hoc site visit peer review will be tailored to the individual grants. The motion was seconded and approved with 20 in favor and 4 opposed. [Note: Additional advice and comments will be requested from other advisory boards and the parent committee(s).]

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CLINICAL TRIALS PROGRAM REVIEW GROUP REPORT - DR. JAMES O. ARMITAGE

The Clinical Trials Program Review Group (CTPRG) Chair, Dr. James Armitage, Henry J. Lehnhoff Professor and Chairman, Department of Internal Medicine, University of Nebraska Medical Center, informed members that the clinical trials program, particularly the clinical cooperative groups and cancer centers, constitutes the Nation's laboratory for clinical science, provides support for clinical scientists, facilitates translational research, and provides a way to focus the expertise and efforts of clinical

scientists on problems of translation. Dr. Armitage stated that the challenge to the CTPRG was to determine whether the clinical trials establishment had consolidated to the extent that bureaucratic problems were slowing the process of translational science, and if so, how to invigorate the program.

Dr. Armitage briefly reviewed the charge to the CTPRG and the process established for gathering information and considering the broad issues implicit in the charge questions. He summarized the recommendations for special emphasis, specifically those to establish a patient-oriented clinical research study section and to increase funding for the cooperative groups to recommended levels produced the strongest consensus among members. Other major recommendations were: 1) a reduction in the amount of information accrued; 2) uniformity in the data collection process; 3) development of uniform standards and reporting requirements; 4) data transfer and access to relevant electronic databases; 5) reduction in bureaucratic obstacles; 6) integration of representatives of patients and high-risk communities into the decisionmaking process; 7) transfer of CCOP therapeutic trials to the DCTD; 8) increased training opportunities for new and midcareer investigators; and 9) development of strategies to convince payers that clinical trials are the preferred way to manage cancer patients.

Dr. Armitage noted that the questions about the number and configuration of groups in the clinical trials system were not addressed in the CTPRG report. The experience of the Group in attempting to reach a consensus on this issue suggested that recommendations about the optimal number of cooperative study groups will be achieved only by appointing a small committee of individuals with no vested interest in the existing groups. The charge to that committee should be to review numbers and performance of existing groups and base recommendations on issues of quality not process, emphasizing the goals and values desired in the clinical trials program.

NCI Response: Dr. Wittes outlined NCI plans for implementing the recommendations in this and the parallel Program Review Group reports. Suggestions for action will be reviewed by the BSA and NCAB and an iterative process adopted until solutions are found. An update is to be given at the next BSA meeting on the status of the groups formed to develop implementation plans for

the various reviews. Updates on the status of all review group implementation plans will be given at future BSA meetings.

In discussion of the CTPRG report, the following points were made:

- The current Internet and interactive television in the future are technologies that should be exploited to increase access to clinical trials information. An example is the University of Michigan Cancer Center's demonstration cancer prevention and control project using highly interactive television kiosks.

- Tissue specimens are a valuable resource to members of cooperative groups, and the recommendation to have the coordinating group store all specimens for an intergroup study would be a strong disincentive to participation.

- The difficulty in obtaining clinical-grade molecules or antibodies needed for specific studies was identified as one barrier to moving ideas from the laboratory to the clinic.

- Alternatives to the cooperative groups for doing clinical trials (e.g., regional networks, health care systems) were not been addressed in the CTPRG report. Although implementation of the recommendations will optimize the current system, cooperative groups will continue to be ponderous in their decisionmaking, expensive, and consensual in their decisions about clinical trial design.

- These reports should be viewed only as a first step in a process to review the entire clinical trials system, which is currently based on the chemotherapy model but should reflect recent scientific discoveries and the epidemiologic and population sciences. Other important considerations are: (1) how to translate advances in treatment to community settings where the majority of people are treated, and (2) the need to include the patient perspective in the design process to ensure that issues important to cancer patients are addressed and that the trials are easily accessible.

- The NCI, cooperative groups, cancer centers, networks, and

CCOP physicians must work collaboratively to develop payer/provider clinical trials participation models.

- A more in-depth discussion by the BSA of how peer review can change to involve both protocol and science constituencies and how peer review could result in the optimal number of cooperative groups is needed. Other questions to be discussed are: (1) how the BSA should exercise its oversight responsibility in evaluating the success or failure of new experiments in terms of budget allocations, and (2) how to protect human subjects and comply with all of the federal regulations for NCI-sponsored work.

- The BSA should continue to ask questions and press for a reexamination and restructuring of the clinical trials system to meet the challenge of having increasingly broad biological information to test in a time of decreasing resources and to position the system for the future.

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STATUS REPORT: THE HUMAN GENOME PROJECT AND ITS RELATIONSHIP TO NCI - DR. FRANCIS COLLINS

Dr. Francis Collins, Director, NHGRI, presented a status report on the Human Genome Project, interactions between the NCI and NHGRI on various initiatives in this collaborative project, and the process for defining the next 5-year plan in the 15-year project. Dr. Collins stated that from its beginning in 1990, the project had specific goals and milestones for the development of genetic and physical maps and for the DNA sequencing effort. New initiatives are planned as a need for resources is identified in the cancer genetics community and other sectors of the scientific community that use genetics to understand their disorders.

Dr. Collins informed members that the goal of having 1,500 microsatellite markers in 5 years was achieved in 3 years, and the total at the halfway point in the project is about 20,000. The

physical maps, collections of overlapping clones spanning the genome and anchored by sequence tag sites (STSs) about every 100 kilobases, were the second goal of the Human Genome Project and have almost been completed. Dr. Collins demonstrated the use of the web site that reflects the recent publication of the first gene map of the human genome, a joint effort of a large number of genome centers worldwide.

He noted that the goal of DNA sequencing is to sequence 3 billion base pairs by the year 2005. Only about 2 percent of the human genome has been sequenced in large-scale sequencing enterprises, but scientists nationwide are building technologic experience on model organisms. The NCI Preclinical Models Working Group has been instrumental in bringing groups together to discuss the mouse genome project, and a joint workshop with NCI and the Office of the Director, NIH is planned for February to define ways to accelerate the mouse genome project as a basis for comparison with the human genome.

As far as long-range planning, the first 5-year plan, begun in 1990, was revised in 1993 to reflect technologic advances and will end in October 1998. Specific milestones of the plan have been met or exceeded. A subcommittee of the NHGRI advisory council has been convened to review a broad range of issues related to designing the next plan.

Dr. Collins described sequence variation as a topic of great interest with major consequences for understanding the genetics of cancer, particularly for identifying weaker influences that may, in aggregate, be more important than the high penetrance alleles. He told members that an RFA will be issued jointly by 18 Institutes, including the NHGRI and NCI. The RFA will promote research to discover the multitudes of single nucleotide polymorphisms needed as infrastructure for conducting whole-genome association studies as an alternative to traditional pedigree linkage analysis to identify genetic predispositions to disease.

Dr. Collins emphasized the importance of promoting the ELSI agenda, which includes promoting the privacy, fair use, and clinical integrity of genetic information. The NHGRI and NCI have been in the forefront of efforts against insurance discrimination so that otherwise beneficial genetic tests are not used against individuals.

In response to questions, the following points were made:

- After libraries of full-length cDNAs are developed, they will probably be transferred to a commercial enterprise for distribution, with adequate safeguards.

- The technology for developing high-quality and affordable genetic tests is moving forward, but the complexities are not to be underestimated. The cost of the BRCA-1, BRCA-2, and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) tests are still relatively prohibitive, but other technologies are expected to mature within the next 3 or 4 years to reduce the cost.

- The Kennedy-Kassebaum law, which took effect July 1, 1997, applies across the Nation and prohibits an insurance company from using genetic information to deny coverage or set higher premiums for any member in a group health policy. Current efforts are aimed at plugging loopholes and making the same rules apply to policies for individuals.

- The Animal Models Working Group is considering a mouse CGAP project. The Group has expressed interest in using the technological improvements realized in CGAP as part of the validation protocol for the mouse models. Also, the Group has been asked to come to an agreement on a set of decisionmaking criteria as a step toward building the mouse libraries and linking them to the CGAP.

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

Division of Cancer Treatment and Diagnosis

Pediatric Brain Tumor Clinical Trials Consortium (Coop. Agr.) - Dr. Malcolm Smith, Chief, Pediatric Section, introduced

this revised concept to establish a multidisciplinary network of highly specialized investigators to efficiently evaluate technically challenging innovative treatment approaches for children with brain tumors. As a result of those comments, Dr. Smith informed members that program staff conducted an extensive review of the NIH-supported childhood brain tumor research portfolio and found that new ideas are being generated through a variety of research projects sponsored by the NIH and through the biotechnology and pharmaceutical sectors. However, he noted that a difficulty in transforming these ideas to therapeutic benefit is that no single institution sees sufficient children with brain tumors to pilot test these innovative and technically challenging approaches. The proposed concept will address the need for Phase I testing by establishing a consortium of institutions with the requisite multimodality and research expertise to rapidly conduct the initial clinical trials of novel treatment approaches for children with brain tumors, prior to definitive evaluations of these approaches by the pediatric cooperative groups. Effective mechanisms for communication will be built to facilitate the transition from Phase I testing in the consortium to Phase II and Phase III testing in the cooperative groups.

Requested support for the pediatric CNS clinical trials consortium is for 8 institutions at $125K each, an operations center at $500K, and 100 patients at $55K each for 3-4 clinical trials. The estimated total for the first year is $2M for 10 awards. Anticipated cost for the 5-year project period is $10M.

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

- When asked whether members of the adult consortium would be eligible to apply and whether consideration had been given to mechanisms for enlarging the pool of potential investigators in what is a relatively small field, program staff indicated that members of the adult consortium would be eligible to apply and that the institutions to receive awards will be selected by peer review. At the end of the award period, a decision would be made about continuing the experiment for another 5-year period.

- In response to the suggestion that a permanent structure

might be created for what is hoped to be a constantly changing set of novel ideas requiring changing expertise, program staff explained that the consortium would not be permanent in the sense that new institutions could apply at the recompetition.

- Parent/patient constituency groups such as the North American Brain Tumor Association will be solicited for input.

Motion: A motion was made to approve the DCTD concept "Pediatric Brain Tumor Clinical Trials Consortium" (Cooperative Agreement). The motion carried with 22 for and 1 abstension.

Advanced Technology Radiation Therapy Clinical Trials Support (Coop. Agr.) - Dr. Richard Cumberlin, Acting Associate Director, Radiation Research Program, stated that the intent of the concept is to establish a quality assurance center for ongoing and pending NCI- sponsored clinical trials using advanced technology radiation therapy. The areas of support that are envisioned are quality assurance through the central review and verification of CRT or brachytherapy plans and database maintenance. The database will collect treatment planning CT scans done on patients entered in clinical trials to record normal tissue dose-volume relationships and related toxic effects. This cooperative agreement is modeled after the 3D- CRT QA center for a prostate study that will expire in March 1998, and is intended to be a successor agreement. The scope will be expanded to include all clinical trials using all forms of advanced technology radiation therapy.

One or two awards are anticipated, with a first-year funding of $1M. The anticipated cost for the 3-year project period is $3.1M.

In discussion of the concept, the following point was made:

- This project has the potential to advance the current state of the art in radiotherapy by gathering important data and providing access to treatment plans that are necessary to increase the dosage of radiation and increase cure rates.

Motion: A motion was made to approve the revised concept. The

motion was seconded and approved unanimously.

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CANCER CONTROL PROGRAM REVIEW GROUP (CCPRG) REPORT - DR. DAVID ABRAMS

The Chair of the Cancer Control Prgram Review Group (CCPRG), Dr. David Abrams, Professor and Director, Center for Behavioral and Preventive Medicine, Brown University of Medicine, informed members that the CCPRG addressed problems in defining cancer prevention and control, reviewed the status of today's biomedical and sociobehaviorial paradigms, and considered new directions. Dr. Abrams stated that the CCPRG concluded that breakthroughs in genetics, informatics and communications, biomedicine, and behavioral and public health science afford a unique opportunity to reduce the absolute cancer burden by more than one- half through environmental, population, and public health interventions, if they are disseminated to every level of society. He noted that this would require a behavioral, social, and population science research arm in the NCI to parallel the powerful and successful biomedical research arm, which has led to the medical breakthroughs of the 20th century.

A summary of the major recommendations is as follows: 1) create a unit focused on basic behavioral and social research in cancer control; 2) create a research focus in informatics and communication; 3) establish programs that recognize the role of behavioral prevention across the lifespan; 4) increase integration of and support for cancer screening research; 5) create a research focus on rehabilitation and survivorship; 6) establish research links to various health care delivery systems; 7) expand cancer surveillance and produce a "cancer report card;" 8) maintain strong support of biometry and applied research; 9) focus research efforts on underserved populations and those with a disproportionate cancer burden; and 10) expand training in cancer control research. Two general recommendations addressed parameters for conducting large-scale cancer control trials and delegation of responsibility for transferring innovative, proven interventions to ensure their proper dissemination to society.

In response to questions, the following points were made:

- A member stated that the Surveillance Epidemiology and End Results (SEER) program database should be kept simple, complete, and standard but suggested encouraging development of an infrastructure to permit use of the SEER registries for analytic studies, for example, by incorporating rapid case identification units so that population- based, case control studies can be mounted. Dr. Abrams responded that changes to the SEER database envisioned by the CCPRG were better linkages with tissue data or a model similar to the Health Plan Employer Data and Information Set (HEDIS) report card that Health Maintenance Organizations (HMOs) are using to improve the quality of patient care delivery.

- When queried as to whether the CCPRG had considered a possible strategy for implementing recommendations that infer an expanded intramural research component for an extramural program and how the BSA would exercise oversight, Dr. Abrams stated that a modest extramural basic science program was envisioned at first, to drive and inform some of the recommended innovations.

- It was suggested that former smokers should be targeted in future research because about one-half of the new cases of lung cancer in America were diagnosed in former smokers who have been found to have clonal genetic abnormalities.

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Dr. Klausner reminded BSA members that the NCI AIDS program has been reorganized and restructured during the past 2 years to articulate areas of scientific emphasis and to correct an imbalance between funding for extramural science supported through the RPG pool and funding for the intramural program. The overall goal of the restructuring is to promote the systematic development of the emerging field of viral or cellular evolution and resistance biology, both conceptually and technologically. Through the reorganization,

the NCI has attempted to capitalize on the strengths of the intramural program by creating an interactive community within the NCI to share infrastructure in three new programs, the HIV Drug Resistance Program, the AIDS-related Malignancy Program, and AIDS Vaccine Development Program. Progress reports on two of the programs were presented.

HIV Drug Resistance Program (HDRP) - Dr. John Coffin

The Head of the HDRP, Dr. John Coffin, Professor of Biology and Microbiology at Tufts University Medical School and part-time staff at the NCI, explained that a new HIV initiative will create a center for retrovirology research, with emphasis on basic and translational research related to viral evolution and resistance biology. Scientific issues to be addressed in solving the problem of HIV drug resistance will require the coordinated efforts of experts in structural biology and biochemistry, molecular and clinical or in vivo virology, epidemiology, and chemistry. The new program also will include animal model studies of population dynamics and population genetics of HIV, mathematical modeling of virus populations and evolution, and, ultimately, translation of the findings into drug development.

The HIV drug resistance program will operate out of the OD, NCI, but will cut across all divisions and involve major contractors. The program will be centered in laboratories at the Frederick Cancer Research and Development Center (FCRDC) and will involve existing programs, an internal grant mechanism, and newly recruited groups. An advisory committee of intramural and extramural experts representing major research areas is being assembled, and conferences on virus diversity and resistance will be sponsored.

In response to questions, the following points were made:

- The goal of this basic research program is to develop and eventually translate fundamental information on issues into strategies for drug development and therapeutics. About $5M is envisioned as the initial budget to fund at least six research groups, engage much of the ongoing HIV research activity in the NCI, and convene extramural and intramural scientists to promote collaboration on HIV and retroviral

research issues.

AIDS Malignancy Program (AMP) - Dr. Ellen Feigal

Dr. Ellen Feigal, Deputy Director, DCTD, explained that the AIDS Malignancy Program was initiated in the DCTD but crosses multiple branches, divisions, and institutes. The overall goal of the AIDS Malignancy Program is to provide opportunities for an integrated, multidisciplinary research program in virology, epidemiology, immunology, and basic biology. NCI's involvement in extramural clinical trials began in 1992 with the AIDS Lymphoma Network of 12 R01-funded investigators and CTEP liaison with the National Institute of Allergies and Infectious Diseases (NIAID) for a joint review of HIV-oncology protocols. Other initiatives since 1992 were the National Task Force on AIDS malignancies; an RFA for small clinical trials in AIDS malignancies; set-aside funding within the clinical trials cooperative groups for AIDS malignancies and the AIDS Malignancy Tissue Bank; an RFA to establish the AIDS Malignancy Consortium; and the AIDS Malignancy Working Group of intramural and extramural scientists, patients, and patient advocates. Initiatives recommended by the Working Group that have already been implemented are the NCI *Handbook on Resources in AIDS and AIDS Malignancies*; supplements for cancer centers to encourage collaborations of researchers in cancer and AIDS; the National AIDS Malignancy Conference; and an RFA for AIDS/oncology clinical research training.

Short- and long-term goals have been established for each undertaking of the AMP to assess progress and ensure that components and mechanisms are adaptable to changing research opportunities. The program has worked at fostering collaborations among basic scientists in AIDS and oncology across a spectrum of disciplines in the NIH and extramural scientific community. Including industry and the Food and Drug Administration.

In response to questions, the following information was provided:

- The extramural divisions support about $90-95M of basic research, predominantly in the areas of virology, immunology, and epidemiology. The Biological

Carcinogenesis Branch, alone, has funded about 25 new grants (totaling about $7M) during the past 2 years, many of them dealing with the role of EBV and HTLV in AIDS malignancies. Currently, that branch is supporting about $20M in basic virology research in the areas of AIDS and AIDS malignancies.

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PROGRESS OF THE SPORE PROGRAM - DR. ROBERT WITTES & DR. BRIAN KIMES

In introducing this topic, Dr. Wittes reminded BSA members that the Cancer Center Program Review Group had recommended periodic formal review of the Specialized Programs of Research Excellence (SPORE). As part of the response to this recommendation, an evaluation was conducted by NCI staff for BSA consideration and help in deciding future directions for this experimental program. To provide an information base for the BSA discussion, Dr. Brian Kimes, Chief, Centers, Training, and Resources Program, briefly described the background and context for the SPORE program, the issues and strategies involved in NCI's implementation of the program, expectations for the program, achievements of the SPORE grantees, and NCI observations comparing expectations as outlined in the RFAs to the productivity. The SPORE program was initiated in 1992 with $20M in newly appropriated funding as a disease-focused research approach to stimulate better collaboration among basic, clinical, and prevention and control population scientists. Currently the program consists of 14 SPOREs conducting translational research in breast, lung, prostate, and gastrointestinatal cancers, each with a $1.5M direct cost cap, for a total of about $28M.

Dr. Kimes stated that the progress report is based on NCI observations of the program (in peer review, annual reports and workshops, working groups, interactions) and on scientific achievements and responses to the above expectations as reported by each SPORE applicant. He briefly reviewed the scientific highlights of the SPOREs, consortia activities, and other grant funding generated as a spinoff of SPORE activities.

In discussion, the following points were made:

- Evidence is needed to show that the translated research and positive outcomes in studies reported in the publication lists are linked to the SPORE. Relevant issues to assess are whether: 1) SPORE funding itself has produced important research without the spinoff; 2) evidence of spinoff is needed for the SPORE to be an important mechanism for supporting research; and 3) separating the SPORE funding from the RPG pool is necessary to get the same result.

- The BSA should first decide what grading scale or report card should be used to determine whether translational research has been accomplished and how good it is. Several suggested benchmarks were: (1) the extent to which new fellows and established basic scientists enter this research area with the help of the developmental funds, (2) the increased involvement of advocates, (3) therapeutics produced, (4) scientific accomplishments from studies that would not have been funded through traditional sources, and (5) unique collaborations that have been established.

- Although SPORES promise to be successful at contributing to advances in translational research, the short-term evaluation should focus on the quality of the science accomplished. The crux of the issue was to determine the best use of limited resources by evaluating whether the research conducted by the SPOREs is better and fundamentally different than what would have resulted from an investment of the same number of dollars in something other than the SPOREs.

- One member asked for a discussion by the BSA or program staff as to how the SPOREs might eventually integrate into the networks or consortia as a basis for determining how to develop solution models for testing all translational research discoveries.

Program staff noted that the NCI is looking for guidance as to a procedure for deciding what added value is realized from the funding currently allocated to the SPOREs. The purpose of this

presentation was to ask what kind of evaluation the BSA would recommend. In assisting in the development of an evaluative mechanism for this type of multicollaborative and translational research effort, the BSA also would be contributing to the development of parameters for the consortial mechanisms and other innovative approaches being considered for conducting clinical and translational research. These parameters developed at the outset could then be used for the subsequent evaluation of these types of experimental programs.

NCI staff (Dr. Andrew Chiarodo et al) working with an ad hoc committee of the BSA, consisting of Drs. Young (Chair), Pendergast, Vogt, Mueller, Brugge, Daly, and Minna (a member of a SPORE recipient institute), will develop metrics to evaluate SPORE programs and their progress. [Note: Msss. Amy Langer (BSA member) and Debra Collyar (consumer advocate) have been added to this subcommittee. The Executive Secretary is Dr. Gray.]

Adjournment: The meeting was adjourned at 11:54 a.m. on Friday, 14 November 1997.

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