Board of Scientific Advisors

Meeting Minutes

March 7-8, 2005

Building 31C, Conference Room 10
Bethesda, Maryland

Quick Links

Members

Agenda & Future Meetings

Meeting Minutes

BSA: Page 1

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 30th meeting on Monday, 7 March, 2005, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert Young, President, Fox Chase Cancer Center, presided as Chair.

The meeting was open to the public from 11:00 a.m. until 5:35 p.m. on 7 March for the NCI Director's report and budget overview, an update on the National Lung Screening Trial (NLST), a report on the NCI and Congress, special recognition for a retiring BSA member, an update on the U.S. Food and Drug Administration (FDA)/NCI Interagency Oncology Task Force (IOTF), ongoing and new business, reissuances of Requests for Applications (RFAs)/ Cooperative Agreements, and a mini-symposium on the current state of cancer proteomics. On Tuesday, 8 March, the meeting was open to the public and lasted from 8:30 a.m. until adjournment at 12 noon. Presentations included new RFAs and Requests for Proposals (RFPs), bioethics and the future of biorepositories, and a report from the Clinical Trials Working Group (CTWG).

Board Members Present:
Dr. Robert Young (Chair)
Dr. David B. Abrams
Dr. David S. Alberts
Dr. Hoda Anton-Culver
Dr. Kirby I Bland
Dr. Neil J. Clendeninn
Dr. Thomas Curran
Dr. Raymond N. DuBois, Jr.
Dr. H. Shelton Earp III
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Patricia A. Ganz
Dr. Joe W. Gray
Dr. William N. Hait
Dr. Mary J.C. Hendrix
Dr. Susan B. Horwitz
Dr. Eric Hunter
Dr. William G. Kaelin, Jr.
Ms. Paula Kim

Board Members Present:
Dr. Michael P. Link
Dr. Christopher J. Logothetis
Dr. Lynn M. Matrisian
Dr. Edith Perez
Dr. John Potter
Dr. Mack Roach III
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal
Dr. Margaret R. Spitz
Dr. Jane Weeks

Board Members Absent:
Dr. Esther Chang
Dr. Leroy Hood
Dr. Hedvig Hricak
Dr. Kenneth W. Kinzler
Dr. Christine A. Miaskowski

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

TABLE OF CONTENTS

Division of Cancer Treatment and Diagnosis (DCTD)

Blood and Marrow Transplant Clinical Trials Network (RFA Re-Issuance)

Division of Cancer Control and Population Sciences (DCCPS)

Breast Cancer Family Registries (RFA Re-Issuance)

X. Mini-Symposium: The Current State of Cancer Proteomics; Dr. Anna Barker

Overview; Dr. Leland Hartwell

Proteomic Analysis in Cancer Research; Dr. Richard Caprioli

Advances in Mass Spectrometry in Serum-Basedd Proteomics; Dr. Richard Smith

Platform Technologies in Affinity Methodologies; Dr. Johusa LeBaer

Considerations for Study Design and Technology Evaluation; Dr. David Ransohoff

XI. RFA/RFP Concepts; Presented by NCI Program Staff

Office of the Director (OD)

Clinical Proteomic Technologies Consortia (RFA & RFP)

XII. Report Update: Clinical Trials Working Group; Dr. James Doroshow

XIII. Bioethics and the Future of Biorepositories; Dr. Arthur Caplan

XIV. Adjournment; Dr. Robert Young

I. CALL TO ORDER AND OPENING REMARKS—DR. ROBERT YOUNG

Dr. Young called to order the 30th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. Board members were reminded of the conflict-of-interest guidelines, and attention was directed to confirmed meeting dates through November 2006 and dates to be confirmed through 2007. Dr. Young then invited the public to submit to Dr. Paulette Gray, Board Executive Secretary and Acting Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the

meeting.

top

II. CONSIDERATION OF THE 8-9 NOVEMBER 2004 MEETING MINUTES — DR. ROBERT YOUNG

Motion: The minutes of the 8-9 November 2004 meeting were approved unanimously.

top

III. REPORT OF THE DIRECTOR, NCI—DR. ANDREW von ESCHENBACH

Dr. Andrew von Eschenbach, Director, NCI, reviewed the overarching philosophies continuing to drive NCI leadership and management in the face of important opportunities and challenges that lie ahead for the National Cancer Program. Dr. von Eschenback informed members that the NCI will continue to strategically grow the programs and initiatives that are essential to maintaining progress across the cancer Discovery, Development, and Delivery continuum to meet the 2015 goal of eliminating the suffering and death due to cancer. He asked that the BSA, in its review of the initiatives that are being developed and will need to be implemented, take the opportunity to view them from the perspective of helping NCI leadership critically assess their scientific impact. At the same time, it must be recognized that approval of any new initiative means redeployment of funds. The choices to be made will be driven not only by the inherent value of the initiative, but also by the value that the initiative has in the entire mix of the portfolio.

Dr. von Eschenbach stated that mechanisms are being developed to examine and assess the overall NCI portfolio to make much finer and more discriminating decisions about priorities. The probable budget trajectory for the next few years dictates a longer range planning process to prepare for redeployment and the de-emphasis of programs. A critical factor in decisions that are made is the risk of losing significant assets and infrastructure if decisions are made

precipitously. Dr. von Eschenbach emphasized that decisions will be made in a deliberative way, using tools that will enable a longer range management of the portfolio. The theme will be differentiation within the portfolio so that initiatives will have great scientific merit, value, and worth both as individual programs and as they relate to adding value to the entire enterprise.

Budget Update. Members were reminded that Fiscal Year (FY) 2006 budget hearings are underway in Congress. Dr. von Eschenbach noted that the principles guiding the FY 2006 budget were established at the level of the NIH. For example, the NCI has been operating under the NIH policy that committed cost-of-living increases in out years will be paid; this will create a challenge to the NCI due to significant out-year commitments. Dr. von Eschenbach noted that this principle applies to the FY 2006 budget, but it is probable that there will not be inflationary increases for noncompeting Research Project Grants (RPGs) in FY 2006, and the average cost of competing RPGs in FY 2006 will be the same as in FY 2005. The NCI will be unable to maintain the payline at 20 percent as was the case in FY 2004, and the FY 2006 payline may be approximately 16 percent. However, mechanisms and processes have been put in place to allow Division heads to fund below the line with exceptions funding so that the overall success rate is expected to be in the low 20s (this will depend on the number of applications received). Dr. von Eschenbach emphasized that the NCI remains committed to placing a high priority on young investigators and first-time R01s and maintaining a critical mass of first-time investigators. The intramural component will continue to be managed aggressively so that seamless interactions between the intramural and extramural community are created and the intramural program will be so unique and distinctive that it adds value to what is occurring in the extramural portfolio.

top

IV. UPDATE: NATIONAL LUNG SCREENING TRIAL—DRS. CHRISTINE BERG AND DENISE ABERLE

Dr. Christine Berg, Project Officer, Lung Screening Study (LSS), NLST, Division of Cancer Prevention (DCP), reminded members that the NLST was initiated to address the high mortality rate of patients with lung cancer by identifying a screening mechanism to

detect early stage disease. At the time, low-dose helical computed tomography (spiral CT) was being promulgated to effect lung cancer mortality reductions of 50 percent or more. Problems associated with that screening tool include the difficulty of distinguishing bias from benefit and prolonged survival from mortality advantage. Dr. Berg noted that CT observational trials contributed substantially to the body of literature about spiral CT and moved imaging science forward.

One prerequisite to the launching of a large-scale national trial was the LSS, a feasibility study coordniated by Dr. John Gohagan, then-DCP Project Officer. The LSS was a 12-month special project conducted within the Prostate, Lung, Colorectal and Ovarian Study (PLCO) sites to which 3,318 at-risk individuals (ages 55-75) were enrolled and randomized to chest x-ray (CXR) or CT screening. The LSS showed that individuals in this age group with substantial smoking history would participate in a large study and that there was an increase in incidents of positive CT screens versus CXR. An increased detection of lung cancer in the spiral CT arm also was seen but not with as much disparity as previously reported. The NLST was launched from the White House in September 2002. A total accrual of 53,477 was completed in 20 months (on April 30, 2004) at 23 participating sites of the American College of Radiology Imaging Network (ACRIN) and 10 original PLCO sites plus 19 satellites.

In response to a BSA request, Dr. Berg discussed problems encountered in the study. She noted that the Data and Safety Monitoring Board (DSMB) resigned in March 2004 because of liability concerns and was reconstituted with an interim chair under coverage through Westat, an NLST contractor, until 30 April of this year. Options for coverage beginning in May include a special government employee, a special volunteer, or coverage through a home institution. The Executive Committee meets monthly to discuss DSMB liability, media, and communication issues. Publication policies and procedures ensure the timely flow of information from this trial. The Oversight Committee, with Dr. Young as Chair, meets 6-8 weeks after the DSMB to review that Board’s findings. A variety of subcommittees address data elements on the case report forms, joint preparation of DSMB reports, and the interim analysis plan.

Dr. Berg explained that a great deal of effort went into harmonizing

the critical trial elements of the LSS and ACRIN, including trial design, eligibility criteria, image acquisition protocols, interpretation of imaging, and critical outcomes collection on positive screens. Common endpoints were established that include lung cancer-specific mortality, lung cancer incidence, stage distribution, screening test performance, and medical resource utilization for positive screens. The NLST was designed to observe a 20 percent difference between CXR and CT arms, with 90 percent power

Dr. Berg informed members that the endpoint verification process is critical because the NLST is a study with lung cancer mortality as the primary outcome. Death certificates and medical documentation are collected, ICD10 codes are assigned, all work is compliant with patient privacy issues covered in the Health Insurance Portability and Accountability Act, and documents (not death certificates) are sent to the Endpoint Verification Committee for blinded determination. A compilation of recruitment data shows a population that is 59 percent male and an even distribution between current and former smokers. Current smokers are given information on how to quit smoking. Approximately 70 percent of the study subjects had levels of education above high school.

Dr. Denise Aberle, National Principal Investigator (PI), ACRIN-NLST, continued the update with responses to BSA questions related to the NLST. In the area of focused recruitment efforts of special populations, Dr. Aberle reported that eight NLST sites had dedicated recruitment of special populations in conjunction with both the NCI Office of Communications and American Cancer Society (ACS). This involved translating consent forms into Spanish and Asian dialects; hiring targeted minority research staff; mass mailings to areas populated by target minority groups; targeting through ethnic radio, television, or print media; and enlisting individuals representing the targeted populations to be part of the clinical trial groups. Dr. Aberle presented minority accrual figures as of 30 July 2004 to show that the dedicated efforts across all sites, especially through the eight targeting sites, were relatively successful. In addition to the common endpoints listed above, the ACRIN sites have other research objectives, th most important being the development of the specimen biorepository with the annual collection of blood, urine, and sputum specimens. The biorepository is located at the University of Colorado Health Sciences Center. Dr. Aberle noted that, because the ACRIN

initiative originally was undertaken as an imaging-based trial looking at early detection and mortality reduction, followup steps for the biorepository were not conceived, nor did the means exist to carry them out. To ensure a return on the original investment, next steps for the biorepository include standardization through the Cancer Bioinformatics Grid (caBIG) and dissemination of the specimens to investigators in the scientific community. In addition to the blood, urine, and sputum specimens, remnant tissue from resected lung cancers will be collected, with de-identified links to participant data.

Part of the return on investment is the potential to leverage this rich repository with repositories in the Cooperative Groups and those that are part of the larger PLCO, lung Specialized Programs of Research Excellence, and Early Detection Research Network (EDRN). The biorepository's organizational structure includes the ACRIN-NLST Executive Committee, a Biomarker Advisory Committee,, and a Research Evaluation Panel is planned. The Panel will have responsibility for strategic marketing of the inventory, prioritizing uses of the data archive, standardizing the review process, and developing policies for distribution of the specimens to the scientific community.

The NLST Image Management component was described as another major repository and source of scientific leverage, establishing the standard for imaging-based trials. Dr. Aberle stated that there had been extensive harmonization between the LSS and ACRIN in setting standards for consistency and QC in the NLST component. The process for controlling the quality of NLST CT and CXR data across all sites, how and where CT and CXR data are archived, and the role of the Physicians QC Committee was explained.

Dr. Aberle reported that, in response to the NCI recommendation to accelerate accrual, ACRIN-NLST identified additional recruitment sites and accrual was completed ahead of schedule. The result was that ACRIN-NLST realized a 10 percent net cost savings ($5.9 M) for this time period and from 2005 to 2010 and LSS-NLST realized 20 percent net savings ($12.4 M) for the same period. Next steps for the NLST will be the completion of T2 screening in late 2006, an interim analysis plan that will be reviewed at the next DSMB meeting, execution of plans for critical retention and followup activities to be conducted both collectively and independently, and

publication of valid results when they emerge. With regard to the latter, an initial omnibus paper on the NLST and its trial design is planned for release in mid-2005, and the results on the prevalence paper may be published within the next several months.

In discussion, the following points were made:

- The NLST continues to explore with the ACS, industry, and philanthropic organizations avenues for broadening support and funding for the study.
- Despite dedicated minority recruitment efforts, the rate of accrual of minorities was not very high.
- Screening will be completed in the next year and software packages for image interpretation will be evaluated continually for necessary changes.

top

V. ONGOING AND NEW BUSINESS: BSA AT NATIONAL MEETINGS—BSA MEMBERS

Ms. Susan Erickson, Director, Office of Policy Analysis and Response reminded members that the President's budget was announced February 7 and includes $28.8 B for the NIH and $4.8 B for the NCI. Preliminary information on the hearing format and schedule indicates that there will be a 1-day hearing for all of the NIH in both the House and Senate: in the House on March 9, in the Senate on April 6. The House will hold a number of theme hearings, but none that will involve the NCI. Dr. Elias Zerhouni, Director, NIH, will be the principal witness, and all Institute and Center Directors will attend, provide written statements, and be available to answer questions. Ms. Erickson also reported on the outlook for the 109th Congress, i.e., the appointment of new Chairs and finalization of the overall subcommittee structure. She also reported that Dr. Zerhouni had been invited to testify at an NIH reauthorization hearing that is likely to be held later in the month.

In discussion, the following points were made:

- The BSA will be kept informed of any movement toward reauthorization hearings. Dr. Young will work with Dr.

Gray to draft a letter from the BSA expressing interest in reauthorization proceedings. The draft will be circulated to all members for comment.

- The Chair should draft a letter expressing the Board's interest in the NIH reauthorization to be legislated in both houses of Congress. It should be circulated to members for comment.

top

VI. SPECIAL RECOGNITION FOR A RETIRING BSA MEMBER—DRS. ANDREW von ESCHENBACH AND ROBERT YOUNG

Dr. von Eschenbach announced that Dr. David Abrams, Professor and Director, Brown University Center for Behavioral and Preventive Medicine, will be retiring from the Board to assume the position of Associate Director for Behavioral and Social Sciences Research, and Director, Office of Behavioral and Social Sciences Research, NIH. On behalf of the BSA, Dr. Young presented Dr. Abrams the Director's Service Award, which was inscribed with the message: "With gratitude for outstanding and dedicated service to the Institute and the BSA, 1999-2005."

top

VII. FDA/NCI TASK FORCE UPDATE—DR. ANNA BARKER

Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, Office of the Director (OD), NCI, briefly reviewed the origins of the FDA/NCI Interagency Oncology Task Force (IOTF). Dr. Barker informed members that the IOTF was created in May 2003 with the objective of increasing the efficiency of, accelerating the process for, and reducing the cost of developing new agents for cancer by more closely integrating the science and the regulatory requirements. The Task Force has grown to include more than 100 individuals. The IOTF subcommittees or subgroups, which reflect the process of drug discovery and development, are the Process, Markers of Clinical Benefit, Joint Training and

Collaborative Program, Bioinformatics, Advanced Technologies, and Chemoprevention Subgroups. Dr. Barker and the co-chairs presented a snapshot of each Subgroup.

Process Subgroup. The objective of this Subgroup is to identify and implement mechanisms for improving the process of drug development. Three initiatives are planned or underway. The first is the creation and pilot testing of the Senior Leadership Team, from which NCI-funded investigators can seek help in resolving problems associated with navigating the regulatory process. Triage and feedback will be part of the process. The official start of the initiative will be announced later in the month. The second initiative is the development of several FDA Guidances, one for investigators to conduct proof-of-concept or exploratory investigational new drug (IND) studies. This Guidance is expected to be ready for release soon and is expected to have an impact beyond cancer. A second FDA Guidance that is nearing completion will address manufacturing criteria early in the process for developing chemical agents and biologics. In preparation for a third Guidance, a White Paper has been completed and circulated on the issue of evaluating potential toxicity in new cancer agents. The goal is to accelerate the development process while maintaining FDA's mission to protect the patient. A fourth Guidance being considered would address combination therapies.

Joint Training and Collaborative Program Subgroup. At the February 2005 National Cancer Advisory Board (NCAB) meeting, the new Research and Regulatory Review Fellowship Program was announced and posted on the Internet (http://iotftraining.nci.nih.gov). Through this program, the FDA and NCI are offering fellowship training in cancer-related scientific research and research-related regulatory review. The objective is to train a cadre of scientists who can help to develop a skill set that can bridge these two processes. An ongoing evaluation process for both the fellow and mentor will be implemented to monitor program outcomes, and biannual training plan updates will be executed in a collaboration between the fellow and mentor. Fellows will be tracked as they finish the program to determine where they transition after graduation. Exit interviews will help the Subgroup understand whether new mechanisms can be put in place to improve the program. Benchmarks will include coursework requirements by the FDA and a minimum skill set as determined by the course examination at the FDA and a review of an IND

exemption. In discussion following this presentation, BSA members emphasized the need for this type of training and for consideration of ways to expand its influence.

Bioinformatics Subgroup. In addition to being actively engaged in caBIG planning and implementation, the FDA/NCI IOTF is undertaking another bioinformatics initiative to move clinical trials reporting to electronic submission for regulatory review. The Clinical Research Information Exchange (CRIX) is being built by the NCI/FDA partnership and in a collaboration that includes representatives from government, industry, and academia. The objective is to build an information Technology infrastructure to facilitate the life cycle of regulatory submissions. Due to the complexity of the regulatory submissions process, the strategy will be to construct the system sequentially and incrementally, beginning with the more easily defined investigator registry resource and building out the rest of the life cycle submission components. Ultimately, the CRIX will involve the technical and operational development of individual pieces, an expanding production infrastructure, and business models for supporting this complex infrastructure and bringing in additional funding partners. The first component of this initiative, the Federal Investigator Registry for Biomedical Informatics Research Data (Project FIREBIRD) is geared to automate and centralize the registration process. Investigators will be able to register online with the NCI and other sponsors. It is a universal, open repository, but because of FDA and pharmaceutical requirements, appropriate authentication and authorization infrastructure will be in place. Individuals using this infrastructure to process documents will use digital signatures that are enforceable and state-of-the-art measures for controlling access to information and determining how information ultimately will be signed and recorded. These are open infrastructures and Board members were invited to use them and were encouraged to provide input and comment.

Markers of Clinical Benefit Subgroup. This Subgroup is attempting to empower a process to identify a roadmap for biomarkers of the future that will enable the science and, at the same time, integrate the science with the FDA Critical Path Initiative. The use of imaging as an endpoint in clinical cancer management was chosen as an initial focus for the IOTF because it could serve to substantiate drug development and proof-of-clinical-effectiveness of oncologic drugs. Three areas have been identified

for the first year's effort: 1) fluorodeoxyglucose positron emission tomography (PET) imaging in clinical oncology, 2) the science of imaging probe development, and 3) anatomical imaging for managing cancer patients and in oncologic drug development. A White Paper is nearing completion summarizing the extant information from the literature that gives credence to PET imaging technology from cell and molecular biology perspectives. The White Paper also will summarize the fairly direct and definable critical path to move from the science to augmenting oncologic drug development in both preclinical science and early and late-stage Phase III pivotal trials. In the area of imaging probe development, a document is being written that will, by case study method, illustrate which imaging probes are available, their stage of development, a definition of the hurdles to be surmounted to get to first-in-man studies, and their promise. Work also has started on a White Paper that defines the critical pathway for moving from unidimensional to biometric or volumetric imaging. It addresses issues such as software algorithm development for different cancers and developing the needed knowledge base.

Nanotechnology Subcommittee. Dr. Gregory Downing, Director, Office of Technologies and Industrial Relations, informed members that the bulk of the Nanotechnology Subcommittee's activities involves the Nanocharacterization Laboratory (NCL), which was established to help develop the knowledge base and information for the research community. Setting up multifunctional nanoparticles for INDs is an issue for a number of NCI programs because the nanoparticles have imaging, targeting, and drug delivery components. To begin to address this, the FDA, National Institute for Standards and Technology, and the NCI formulated an agreement to help develop analytical cascades and public databases of standard nanoparticles with both physical & chemical characterizations and biological interactions. The NCL was established in September 2004 and currently has three base nanoparticles in the cascade. Three activities of the Nanotechnology Subcommittee are the: 1) creation of an NCL business plan to address the issue of a trans-FDA clearance of some issues necessary for developing the analytical cascade; 2) development of the science in close collaboration with the National Institute for Occupational Safety and Health, U.S. Environmental Protection Agency, and U.S. Department of Energy (DOE); and 3) planning for a joint NCI/FDA summer workshop on analytical cascades and the information, such as review criteria, that is

necessary in conducting the preclinical studies leading up to holding INDs for the new applications.

Dr. Barker concluded the update by noting that information on IOTF's Chemoprevention Subcommittee will be presented at a future BSA meeting. She thanked the FDA Commissioner, Drs. Theresa Mullen and Janet Woodcock, and all Subgroup heads for their contributions to the IOTF mission.

In discussion, the following points were raised:

- All IOTF initiatives are strategically linked to other parts of the NCI research portfolio so that both safety and efficacy issues related to any new drug or application are addressed. In addition, opportunities in emerging areas (e.g., genomics, proteomics, and biomarker development) are being pursued to help understand the individual patient with regard to risk and safety issues. The NCI is partnering with other Institutes in efforts to understand biomarkers; for example, those related to liver and cardiovascular toxicity.

top

VIII. ONGOING AND NEW BUSINESS: BSA AT NATIONAL MEETINGS—BSA MEMBERS

American Society of Therapeutic Radiology and Oncology (ASTRO). Dr. Mack Roach, III, Professor Department of Radiation Oncology, University of California, San Francisco, presented the report of the "NCI Listens" session at the ASTRO meeting held October 3-7, 2004, in Atlanta, GA. Topics covered during the session included the NCI budget and future funding, funding for radiation research as it relates to homeland security, study section changes and other radiation grant review issues, health care disparities, and the potential for delays in the funding timeline.

Dr. Young informed members of upcoming NCI Sessions:

- Society of Behavioral Medicine (SBM). March 13-16, Boston, MA; Drs. Jane Weeks (Chair), Robert Croyle, and Paulette Gray.

- American Association for Cancer Research (AACR). April 16-20, Anaheim, CA; Drs. William Hait (Chair), Suresh Mohla (Presenter), Esther Chang, James Doroshow, Paulette Gray, Susan Horwitz, Ellen Sigal, and Carolyn Strete.

top

IX. RFA/COOPERATIVE AGREEMENT AND RFP CONCEPTS—PRESENTED BY NCI STAFF

Division of Cancer Treatment and Diagnosis (DCTD)

Blood and Marrow Transplant Clinical Trials Network (BMT CTN) (RFA Re-Issuance) Dr. LeeAnn Jensen, Program Director, Clinical Grants and Contracts Branch, Cancer Therapy Evaluation Program, DCTD, reminded members that under the original RFA, the NCI and National Heart Lung and Blood Institute (NHLBI) jointly established the BMT CTN. It was co-funded in September 2001 at a total cost of $43.4 M, with NCI contributing about one-third of that amount. The mission of the BMT CTN was to accelerate research in blood and marrow transplantation and improve outcomes by comparing novel existing treatment strategies. Key features of the Network were that it would be open and nonexclusive; leverage existing resources; achieve timely accrual; address important scientific questions; and partner with stakeholders including industry, patients, and payers. The original Network, comprising a Data Coordinating Center (DCC) and 16 Clinical Core Centers, has expanded over the 5 years to include 30 Core-affiliated and 23 non-Core Centers. The BMT CTN is managed by the Steering Committee, which includes the Core Center and DCC PIs, NHLBI and NCI staff, and Cooperative Group Transplant Chairs through biannual meetings and conference calls, as needed. Of a total of 33 concepts that have been approved, 10 protocols have been written and are in various stages of implementation. Priority areas are source of stem cells, grant versus host disease, infections, relapse after auto transplant, relapse after allo transplant, immune reconstitution, late complications, and quality of life. The status of BMT CTN protocols is as follows: four Phase III trials are open and

enrollment is ahead of projection in the first two, two Phase II exploratory trials are in final preparation, two Phase III trials are awaiting Institutional Review Board approval, one Phase II trial is awaiting DSMB review, and one Phase II/III trial is in protocol development. Anticipated enrollment to the four open protocols and six pending protocols is approximately 3,000 patients. More than 500 patients were enrolled in the first 14 months. The renewal timeline calls for notice of limited competition to be published in the June NIH Guide and for applications to be received in September 2005 for awards to be made in September 2006.

Questions raised by the BSA after the presentation were: (1) whether the BMT CTN mission is distinct from that of other groups that conduct BMT trials; (2) what the BMT CTN's level of productivity is to date, and what has been learned to facilitate more rapid protocol development; and (3) whether future plans for the Network could be articulated to a fuller extent. Additional questions in the discussion related to the level of cross communication among the 16 Core Centers, examples of collaborations to develop a trial, and the proportions of the funding used for infrastructure and trials.

NCI funding requested for the 5-year project period is $15.6 M (of the total $49 M), or $3.2 M per year.

Motion: A motion to concur in the reissuance of the Division of Cancer Treatment and Diagnosis RFA entitled "Blood and Marrow Transplant Clinical Trials Network (BMTCTN)" was approved with 11 votes in favor, 9 against, and 6 abstentions.

Division of Cancer Control and Population Sciences (DCCPS)

Breast Cancer Family Registries (B-CFR) (RFA Re-Issuance)
Dr. Daniela Seminara, Program Director, Epidemiology and Genetics Research Program, DCCPS, reviewed programmatic goals for the past funding period and progress made toward meeting them, commenting specifically on the identification, accrual, and characterization of populations at genetic risk for breast or ovarian cancer, and the implementation of the "Minority Project." Dr. Seminara informed members that the cumulative

accrual projected through November 2005 is more than 7,500 population-based families with the full spectrum of risk; more than 3,100 population-based controls, and more than 3,300 clinic-based families at higher risk. Dr. Seminara described the B-CFR review process, which features an external advisory committee review of applications for their scientific merit. She noted that the approval rate for research projects relying on the B-CFR infrastructure is 88 percent, and 78 of the 134 currently approved applications are from investigators external to the CFR institution. Dr. Seminara reviewed key findings from B-CFR-based studies as well as response rates for the population-based pilot data and clinic-based sites.

Dr. Seminara noted that after considering the potential consequences of terminating or reducing the infrastructure, the working group recommended maintaining and restructuring the B-CFR; specifically, to adapt the B-CFR to evolving scientific needs and enable answers to key questions in breast cancer research and to achieve increased efficiency and higher quality. Objectives of the competitive renewal are to maintain and restructure the B-CFR into eight core platforms, develop the infrastructure to facilitate collaborative research on four main research themes, and maintain open access to the B-CFR infrastructure for interdisciplinary teams of researchers. The main research themes will be behavioral response to risk, environmental modifiers, identification of genetic modifiers, and translational studies.

Estimated funding is $7.4 M per year plus interim funding of $3 M to cover the 5-month period between the expiration of the current funding period and earliest expected date of award. The total cost estimated for the 5-year project period is $40 M.

In discussion, the following points were made:

- A list of publicly available specimens and their characteristics should be included on the B-CFR Web Site.
- Core staffing needs at each of the six sites should be clarified, and more detail should be included in the budget regarding the scope of work at each site (e.g., numbers of patients, individual probands, and families the site is following) and the amount that they get paid.

Motion. A motion was made to concur in the reissuance of the Division of Cancer Control and Population Sciences RFA entitled "Breast/Ovarian Cancer Family Registries (B-CFR)" with the request that the budget issues that were raised in discussion be addressed. The motion was approved with 21 votes in favor, 2 against, and 4 abstentions.

top

X. MINI-SYMPOSIUM: THE CURRENT STATE OF CANCER PROTEOMICS— DRS. ANNA BARKER, LELAND HARTWELL, RICHARD CAPRIOLI, RICHARD SMITH, JOSHUA LABAER, AND DAVID RANSOHOFF

Dr. Barker reminded Board members that the NCI has been examining issues related to biomarker discovery, specifically as it might underpin early diagnosis of cancer, more informed development of targeted therapeutics, and ultimately, rational prevention. With the help of Dr. Leland Hartwell, Nobel Laureate and Director of the Fred Hutchinson Cancer Research Center, the NCI has been exploring the issue of early diagnosis and how to build some of the infrastructure that will be needed to inform the development of a new area of rational diagnosis of cancer. She noted that the objective of this mini-symposium was to consider the science of proteomics as a prelude to the NCI concept initiative to be presented later during the meeting. To facilitate the decisionmakeing process, Dr. Young asked that the presentations also address obstacles that have been perceived from the initial efforts in clinical applications of proteomics; namely, the issues of reproducibility of the applications of proteomics techniques, statistical overfitting, and observational bias.

Overview: Dr. Hartwell noted that the demand for better biomarkers is very great and that there is universal recognition that applying science to clinical problems requires a different magnitude of activity than fundamental discovery science and that the community is ready for a more comprehensive approach to some of the problems. He suggested that the first applications of new biomarkers will be in the stratification of patients for treatment, for monitoring therapeutic response with the more targeted therapies, and for early detection of disease recurrence in high-risk patients. Screening of total populations for early detection

will be the last of its applications. Dr. Hartwell reminded members that the success of the very targeted drug Gleevec against chronic myelogenous leukemia depended on DNA biomarkers to select the right disease and protein biomarkers to decide the level of treatment. This is the example to bring to all cancers. Although protein biomarkers are believed to be more informative because they are more numerous and closer to the function of biological systems, the limiting factor is their discovery. Dr. Hartwell expressed the view that the existing technology capable of analyzing proteins in the proper scale has not been applied and what is needed is a systematic, comprehensive, coordinated effort that imposes QC standards. He noted that the main elements in the initiative to be proposed that could change the success rate for discovering protein biomarkers are perhaps the following: 1) Discovery will take place first at the tissue level, and the existing technology is adequate for this purpose; more sensitive techniques in the future will be needed to identify biomarkers in serum; 2) The protein that is the biomarker will have to be identified and quantitated, and QC issues will have to be addressed to ensure reproducibility; 3) This is “big science” and will require the cooperation of many institutions; 4) Informatics will be needed to standardize and aggregate data across platforms and with standard algorithms; this currently is being addressed in a funded RFP for two groups working on mouse proteomics; and 5) Reagents will increase the rate of discovery, and standardized reagents for thousands of proteins known to be involved in cancer should be supplied to empower testing by the entire community.

Dr. Hartwell emphasized that although this project is about empowering existing technology, it is important to continue to move the technology forward. He asserted that this “big science” is an international problem. Efforts to put together teams in Korea, Taiwan, Australia, and France, with many other countries expressing interest as well, were described.

Proteomic Analysis in Cancer Research: Dr. Richard Caprioli, Stanley Cohen Professor of Biochemistry and Director of Mass Spectrometry Research Center, Vanderbilt University, listed and briefly described four of the current core proteomics technologies and platforms used in tissue/protein extract analysis, which have demonstrated proof of concept. Dr. Caorioli stated that the promise of proteomics lies in the potential for better survival prediction, tissue/serum multiprotein profiles, markers of preneoplasia, timely

assessment of response, and potential new therapeutic targets.

He described several proteomics platforms, such as 2D gel-based analysis, “shotgun” analysis, direct tissue profiling/imaging, and chip/array. In greater detail, he described studies in his laboratory working with direct tissue analysis to illustrate the types of investigation that would support the promise of proteomics and are possible with current technologies and tools. Dr. Caprioli described the approach used in the mass spectrometer (MS) analysis of tumor tissues, the product of which is diagnostic protein candidates or biomarkers that can be used in the identification of proteins or to correlate with a clinical outcome. Ongoing research in his laboratory on the profiling and imaging of drugs not only to assess the relative distribution of drugs in tissues, but also to measure the protein changes that occur at the point of drug arrival was also described. A brief summary of technology challenges yet to be addressed in areas such as sensitivity, identification, quantitation, resolution, and validation were presented.

Advances in Mass Spectrometry in Serum-Based Proteomics: Dr. Richard Smith, Battelle Fellow, William R. Wiley Environmental Molecular Sciences Laboratory, informed members that his approach was funded through an Innovative Molecular Analysis Technology (IMAT) grant in 1998, and the large proteomics center at the Laboratory was funded by the DOE to meet longer range Department of Energy (DOE) interests in a systems biology approach in which proteomics plays a large role. Additional funding was provided to advance the technology by putting it into a high throughput environment to address a large quantity of samples being provided through a number of different laboratories (i.e., a large science environment). Funding from the National Center for Research Resources has been used to advance the technology for use in mammalian proteomics. Among the large issues emerging from that work, the following challenges for cancer protein biomarker development were identified: (1) the need for statistically sound approaches and quality clinical specimens; (2) informatics capabilities to handle and manage very large data sets; (3) technologies providing high depth of proteome coverage with quantitative and reproducible measurements; (4) throughput for cost-effective studies of large sample numbers; and (5) effective management, interaction, and data exchange among laboratories, teams, and investigators. For these reasons, large and well-coordinated efforts are needed.

Dr. Smith explained that their approaches to global proteome measurements require the use of a cutting-edge mass spectrometer (MS) with greater depth and sensitivity such that one measurement can cover 3-4 orders of magnitude of dynamic range. These measurements can cover the spectrum of proteins to be detected more broadly by a technique that "divides and conquers," producing an effective dynamic range of 6-7 orders of magnitude for one of these measurements. To delve deeper into the subproteome, affinity reagents, fractionation, or other approaches are needed. The need for high throughput is magnified when the investigation extends to biofluids, blood plasma, and serum. He informed members that the high throughput approach is most useful in the discovery mode, in which the search is for useful characteristic changes.

In summary, Dr. Smith noted that new technologies allow high-sensitivity proteome measurements with much greater throughput than previously was feasible. Approaches to working with blood plasma or serum in a discovery mode will be applied most effectively in conjunction with fractionation approaches, and well-organized, multi-institutional efforts will be needed to cover a range of plasma subproteomes in sufficient depth. In addition, there are significant opportunities for further advances in technology, particularly using gas-phase ion mobility separations with MS for greater throughput with the potential for broad clinical use. Although improvements are inevitable over the next few years, the technology is good enough now for the NCI program under consideration. However, if the raw capability represented by the improving technologies, tools, and informatics is to be harnessed and used effectively, it must be in the context of a program that coordinates the technology with the right biology, statistically sound studies, and proper management.

Platform Technologies in Affinity Methodologies: Dr. Joshua LaBaer, Founder and Director, Institute of Proteomics, Harvard School of Medicine, presented an update on the current state of cancer proteomics that does not involve MS but is also a direction of future research, in terms of both biomarker discovery and validation. Dr. LaBaer reviewed the two types of approaches to protein-based biomarker discovery. The first is through the study of peptide antigens, which are proteins shed by tumors or produced in the cancer process and are present in the bloodstream, and their

identification as markers for disease. This approach already is used clinically in the form of blood tests for prostate-specific antigen and CA-125. The second approach is by studying antibody responses to the peptides, which have been used for years as biomarkers of infection and for autoimmune disease. Dr. LaBaer noted that an emerging concept in proteomics is the idea that measuring multiple proteins or antibodies at the same time would produce more information than measuring them singly. He then described new platforms for measuring the presence of peptides, which begins to address multiplexing (i.e., abundance-based protein microarrays). The advantages and challenges to both microarray approaches that measure the proteins themselves were briefly presented.

Next, Dr. LaBaer discussed approaches that involve looking at antibodies to the proteins, known as autoantibodies. Members were reminded that autoantibodies against tumor antigens are produced spontaneously by cancer patients because tumor antigens are proteins not usually encountered by the immune system. Autoantibodies can predate cancer presentation by years, and could be ideal as early detection markers. Advantages to studying autoantibodies over the antigens themselves are that they: 1) persist long after the triggering antigen is gone; 2) have a half-life greater than 7 days and do not fluctuate; 3) are very stable in the serum sample; and 4) have excellent detection reagents already available. Challenges to using this approach are twofold: the complexity of the cancer and the different responses in each patient; and the fact that responses to a particular antigen are highly specific but have low sensitivity. Dr. LaBaer noted that multiplexing the antigens would improve both sensitivity and specificity, but platform technologies are needed that would allow the testing of multiple tumor antigens simultaneously. Also needed are appropriate antigens to test. He stated that two protein microarray technologies are currently available that can be used for autoantibody detection. The first is the reverse-phase protein blot, which can be used primarily for discovery and has disadvantages related to difficulty and bias. The second is the target protein microarray, which can be used for both discovery and validation. Dr. LaBaer described this emerging approach, which consists of micro-enzyme-linked immunosorbent assays (ELISA) on protein microarrays. Antigens specific to patient sera can be identified, and validation and discovery can be achieved in one step. Although early approaches to building target protein arrays have been successful, challenges

yet to be addressed relate to the difficulty of expressing and purifying proteins, array shelf life, and mammalian context.

In closing, Dr. LaBaer summarized what is needed for the array platforms: 1) more content, cloned and validated genes in expression-ready format, and purified proteins; 2) continued investment in new technologies; 3) access to well-annotated clinical samples; and 4) support with biostatistical design and analysis.

Considerations for Study Design and Technology Evaluation: Dr. David Ransohoff, Professor of Medicine and Epidemiology, University of North Carolina at Chapel Hill, called attention to articles in recent publications as a reminder that in considering study design and evaluation, the promise of breakthrough science can be accompanied by problems that are important enough to be reported in the New York Times. To consider reasons for the problems and lessons for the future, he first reviewed the history of claims for cancer markers for the lessons it provides. He cited the carcinoembryonic antigen (CEA) experience in which nearly 100 percent sensitivity and specificity for colon cancer was reported, creating high expectations that were followed by disappointment. The CEA experience led to the development of the first rules of evidence to evaluate studies of diagnostic tests, rules about bias, and other problems. Dr. Ransohoff noted that cancer markers have become promising because new knowledge about molecular biology provides many targets to measure and multidimensional assays can measure any target through the use of powerful technology. New reductionist methods result in more data, but not necessarily more knowledge, and the rules of evidence have not changed. The task, therefore, is to explore new technologies and fields efficiently, avoid predictable mistakes and inflated expectations, and ensure that exploration is interdisciplinary and translational. He then discussed the implications of two critical threats to validity, chance and bias, how to avoid them, and their status in proteomics research today. He suggested that chance can be avoided by showing that the model discriminates in an independent group; however, independent groups rarely are used and many published results are no better than chance. The process of avoiding biased conclusions requires a detailed and explicit process in the design, conduct, and reporting of research, which in proteomics research is widely unappreciated. He recommended learning about effective processes to deal with bias by looking at

the process developed in clinical trials to address the bias of baseline inequality.

In terms of the present and lessons to be learned, Dr. Ransohoff explored the strong, widely published claims that serum proteomics can diagnose multiple cancers with very high sensitivity and specificity. The claims were followed by plans for a commercial test, Ovacheck, in 2003, but the plans were delayed by the FDA. Researchers subsequently were led to redirect their efforts and grant proposals. In response to the question of whether serum proteomics can diagnose cancer, Dr. Ransohoff expressed his view that proof of principle has not been demonstrated, but the Zhang ovarian cancer study, which reported 74 percent sensitivity and 97 percent specificity, may come the closest. He acknowledged that stronger data might exist that are not published.

In terms of the future and how to avoid pitfalls to explore the "omics" fields efficiently and successfully, Dr. Ransohoff expressed the view that translational research requires communication among the technology, biology, clinical epidemiology, and biostatistics disciplines. He acknowledged, however, that effective communication can be hindered by "culture clash" in that investigators, reviewers, and editors may not be comfortable at the interface of disciplines. Small studies were cited as another strategy that may be useful for serum proteomics research, with the caveat that they must be reliable to serve as a building block for other research. Dr. Ransohoff stated that small studies can be carried out to avoid chance and bias or, at the least, be totally forthright and candid in the analysis and discussion section. Small studies can be used to avoid inefficient application of resources in bigger studies, and standardization will be critical for certain purposes. In development of the technology, the question to be considered is when standardization should be done and what kind is needed.

In conclusion, Dr. Ransohoff summarized the challenges and opportunities related to proteomics research, noting once again that this is an exciting era because so much biology is known and powerful tools are available. The rules of evidence about validity have not changed, however, and such rules (i.e., within clinical epidemiology) will be critically useful. He suggested that expectations in 2005 are greater than results will support and that disappointments could occur; however, the task ahead is to develop

a process to generate useful knowledge about new markers, and in doing so, avoid predictable disappointment and wasted effort.

top

XI. RFA/RFP CONCEPTS—PRESENTED BY NCI PROGRAM STAFF

Office of the Director (OD)

Clinical Proteomic Technologies Consortia (RFAs and RFP)
Dr. Barker presented in place of Dr. Hartwell, who was unable to attend this portion of the meeting. She expressed her appreciation for his work over the last 2.5 years on this issue. The Consortia hopes to develop a transparent, flexible, systems approach program that is rigorous and ultimately will prioritize research and infrastructure to best advance proteomic technologies. The planning process began with an evaluation of proteomics literature. Dr. Barker reminded members that the inability of investigators to reproduce data is a critical issue. A portfolio analysis of current NCI and other research and development proteomics programs was conducted. The analysis included national and international proteomics projects as well as an evaluation of resources and capabilities available to the Consortia. Other disease models also were considered. The planning process included discussions with or responses from more than 1,000 investigators. From the planning process, the Consortia learned that using a systematic approach with proteomic technologies provides opportunities for early detection, molecular imaging probe and sensor development, discovery of targeted drugs, and rationally developed clinical trials.

Dr. Downing described the steps in the proteomic initiative, which include identifying exactly what is being measured, developing the capability to quantify the measurements, and having the ability to reproduce the data. There are, however, technology and systems barriers such as limited interoperability across instruments and platforms, difficulty in measuring and analyzing large numbers of features simultaneously, insufficient capability for developing and characterizing high-quality reagents, and a lack of standards and

protocols. He also presented an overview of the five proposed funding initiatives, which include: (1) Clinical Proteomic Technology Assessment Cores, (2) Clinical Proteomic Reagents Core, (3) Clinical Specimen and Data Collection for Technology Application, (4) Clinical Proteomic Data Analysis and Computational Resources, and (5) Clinical Proteomic Technology Development. A program coordination and management council is included as a sixth element of the initiative. The Council is intended to function as a shared governance model and is expected to monitor performance and integration across all program components and will report annually to the NCAB and BSA.

Dr. Downing noted that there are several expected returns on investment, including a system to support reliable protein identification and measurement; broadly available, optimized MS and affinity technology platforms; innovative technologies to support more rapid and specific proteomic analysis; standard proteomic databases; and high-quality biospecimen, antibody, and other reagents to support investigator-initiated proteomics research.

In discussion, the following points were raised:

- The creation of a biorepository specifically for proteomics, although highly focused and specific in terms of application, will not occur in a vacuum. The NCI currently is funding the creation and support of biorepositories in various initiatives with the goal of establishing quality standards for all repositories. The goal of the Consortia is to create a state-of-the-art proteomic biorepository that will drive the standards for all others.
- This is an infrastructure proposal to develop the capability to achieve precise and early diagnosis and to better inform drug discovery. It is hoped that proteomics technology also will enable improved monitoring of therapeutic interventions.
- The term “biorepository” as used by the Consortia is conceptually very different than the way it currently is used within the research community. A recommendation was made to find a new word or term that better and more clearly defines the particular technology being used in the proteomic initiative.
- The proteomics program should be integrated with other ongoing and planned NCI initiatives. Established milestones

should satisfy concerns that there is a clear sense of direction for the program and that specific goals have been created. Efforts should be made to integrate genomic approaches based on RNA and DNA with proteomic approaches to identify markers that may be very specific for unique cancer types.

- Informatics standards need to be developed and approaches that work across platforms are needed.
- The proteomics initiative needs strong management with clinicians involved throughout the entire process. The NCI should assume a leadership position within the proteomics program and offer robust support for standardization, integration, and focus.
- Controlled experiments in animal model systems should be carried out to test the underlying proof of principle. Animal model approaches could explore clinical specimen reproducibility issues that might be incorporated into the proteomic program as it moves ahead.
- The proposed initiative should link to activities within the EDRN and SPORE programs and also be embedded into NCI's larger portfolio of investments.

Motion:A motion was made to approve the RFA/RFP/SBIR/STTR concepts proposed by the Office of the Director (OD) for a Clinical Proteomic Technologies Consortia with the exception of the biorepository component entitled "Clinical Specimen and Data Collection for Technology Application (Coop. Agr.)." The motion was not approved, with 13 votes against, 9 in favor, and 1 abstention.

Motion: A motion was made to defer approval of the OD concepts for Clinical Proteomic Technologies Consortia with a request that the proposed concepts be recrafted to address issues raised in the discussion, including a stronger animal model focus to establish proof of principle; data reproducibility; clarification of goals and framing; and integration across NCI-sponsored structures such as the Cancer Centers, Specialized Programs of Research Excellence, and Early Detection Research Network. Staff were also encouraged to work with the subcommittee in the rewrite. The motion was approved with a vote of 12 in favor, 10 against, and 1 abstention.

top

XII. REPORT UPDATE: CLINICAL TRIALS WORKING GROUP— DR. JAMES DOROSHOW

Dr. James Doroshow, Director, DCTD, presented the CTWG's Draft NCAB Recommendations to the BSA. Dr. Doroshow informed members that advances in molecular medicine make it imperative that clinical trials practices improve. A more coordinated process is required to successfully address compelling issues and to enhance interdisciplinary, scientifically driven clinical trials. The CTWG recognizes the urgent need to integrate successful but functionally diverse elements of the current clinical trials system to enhance the timeliness of clinical trials accrual; increase efficiency by improving the scientific and bioinformatic infrastructure for clinical studies; and expand the involvement of all stakeholders in clinical trial development, prioritization, and completion activities.

The CTWG's purpose is to advise the NCAB and its Clinical Investigations Subcommittee about the development, conduct, infrastructure, support, and coordination of cancer clinical trials across the NCI. Six CTWG subcommittees were formed to assess what were thought to be the most pressing issues in cancer clinical trials research. The subcommittees and their chairs are as follows: (1) Patient Accrual, Dr. Richard Schilsky; (2) Enhancing Regulatory Affairs, Dr. Steven Averbuch; (3) Core Research Services, Dr. Fred Applebaum; (4) Standardization and Infrastructure for Clinical Trials, Dr. David Parkinson; (5) Coordination of Trials Across Venues, Dr. David Alberts; and (6) Improving the Protocol Prioritization Process, Dr. James Abbruzzese. He noted that each subcommittee developed a series of proposed recommendations to improve the conduct of cancer clinical trials.

Members were told that each subcommittee developed a series of questions that were displayed on the CTWG Web Site from 29 November through mid-January. Numerous e-mails were sent out to clinical trialists requesting input; 2,228 responses were obtained. A summary of these responses is available on the Internet at http://integratedtrials.nci.nih.gov. The subcommittee chairs incorporated this input into the recommendations as they were developed and drafted. Dr. Doroshow briefly summarized the activities and recommendations of each subcommittee.

Patient Accrual Subcommittee. The goals of this Subcommittee are to: (1) increase the rate of patient accrual to cancer clinical trials, and (2) increase the accrual of under-represented segments of the population to clinical trials. The Patient Accrual Subcommittee recommended the development of standardized materials and/or other resources to help sites plan, staff, implement, and manage clinical trials. The Subcommittee also recommends increasing public visibility of NCI's clinical trials program. The following needs were identified: (1) develop promotional and marketing programs for high-priority studies; (2) partner with community groups, consumer media, and physicians to communicate patient benefits of trial participation; and (3) create tailored programs and community partnerships to engage minorities and special populations to help community sites enhance their rate of accrual to the wide array of available trials.

Dr. Doroshow suggested that perhaps one of the most important recommendations is to develop and provide incentives that encourage community oncologists and patients to participate in the clinical trials process. These incentives may include: (1) developing an NCI certification program for clinical oncologists; (2) educating patients about the unique qualifications of an NCI-certified investigator; (3) seeking reimbursement for clinical care within qualified clinical trials, including counseling and education; and (4) communicating trial results to patients and emphasizing their contribution to the care of future patients.

In addition, the Subcommittee suggested that improvement is needed in terms of access to clinical trials. This could be accomplished by: (1) developing Community Clinical Oncology Program (CCOP) mentoring programs for community oncologists (especially those serving minority populations); (2) expanding the use of community-based regional IRBs to decrease lead time and conserve resources; (3) improving the awareness and utilization of the Cancer Trials Support Unit; and (4) creating multiple user-friendly channels including comprehensive Web sites to enable patients and physicians to find information pertaining to cancer clinical trials.

Regulatory Affairs Subcommittee. Regulatory affairs was identified as a major issue that impaired the speedy and efficient conduct of cancer clinical trials. The goals of the Regulatory

Affairs Subcommittee are to: (1) enhance cooperation among federal agencies, industry, and other key stakeholders to reduce regulatory burdens and accelerate drug and device development; and (2) develop approaches for increasing involvement of industry, the Centers for Medicare and Medicaid Services, and other payers in the NCI cancer clinical trials enterprise. The subcommittee's recommendations are to: 1) develop guidelines/procedures for joint participation of the NCI, FDA, and industry concerning new agents and diagnostics early in the process to coordinate and accelerate drug and device development; 2) develop an infrastructure by coordinating the requirements of the NCI, FDA, and Office for Human Research Protections to reduce the auditing, monitoring, and regulatory burdens that plague clinical trials; 3) establish a robust and transparent process for identifying clinical studies that would warrant reimbursement of appropriate clinical trial and investigational costs;and 4) support training programs, in conjunction with the FDA, American Society of Clinical Oncology, American Association for Cancer Research, and the NCI that are designed to increase the number of cancer investigators who are qualified to guide new agents and devices through the development and regulatory process.

Core Research Services Subcommittee. The CTWG unanimously agreed that there are insufficient resources to support the translation of new discoveries from correlative science studies into clinical practice. Dr. Doroshow also emphasized that there are insufficient funds for early phase studies. There is no facile way to obtain grant funds for these types of studies, and yet they can completely change a clinical practice. The goals of the Core Research Services Subcommittee are to: (1) enhance access to the scientific infrastructure necessary to facilitate the conduct of high-priority, high-quality correlative science studies to translate new discoveries into clinical practice; and (2) integrate, in an efficient and timely manner, a strong scientific review of correlative studies with the development and review of clinical protocols. The intent is to 1) develop an efficient process for the review of correlative studies and determine how best to provide the resources for those correlative studies that would allow these essential activities to proceed in the context of a large practice-changing cooperative study; and 2) establish annual budgets for studies ancillary to clinical trials, including correlative science, health economics, and quality-of-life investigations that can be accessed on a protocol-by-protocol basis.

Standards and Infrastructure Subcommittee. The goals of the Standards and Infrastructure Subcommittee are to: (1) improve efficiency, reduce duplication of effort, and achieve cost savings; (2) facilitate innovation and promote integration across trials; (3) facilitate data interpretation and data comparison across trials; (4) allow for closer integration of biological measurements and clinical trial findings. The Subcommittee focused on means to enable clinical trialists to be actively engaged in the development of the infrastructure that is going to be constructed for caBIG; and 5); encourage FDA and industry develop well-defined electronic case forms and the infrastructure associated with these forms to establish a core set of data elements that are common to all clinical trials and used across the NCI, FDA, and industry partners; and 6) develop official credentialing process (not certification) to create a national, central database of credentialed investigators and sites; and that correlative science studies be performed according to standard protocols in credentialed reference laboratories.

Coordination Subcommittee. This subcommittee focused on the coordination of information and the provision of better information on ongoing trials to investigators and the clinical trials, advocacy, and patient communities. Specifically, the goals of the Subcommittee recommendations are to: (1) promote and reward team science and collaborative clinical trials participation; (2) facilitate information exchange and collaboration among clinical investigators; (3) enhance the design and planning of new clinical trials by providing investigators with access to comprehensive, up-to-date information on ongoing and completed studies; and (4) enable patients and community oncologists to make better decisions about cancer care by providing access to comprehensive, up-to-date clinical trial information; 5) establish a comprehensive database across the NCI and its venues that includes active, up-to-date information about ongoing trials and their accrual; 6) establish a process and change guidelines so that trials that are supported also are reported; 7) develop incentives and rewards to promote collaborative team science and clinical trials cooperation.

Group-Wide Recommendations. The CTWG unanimously agrees that there needs to be a permanent Clinical Trials Subcommittee with broad representation from the extramural community, including regulatory, industry, and patient advocacy groups to examine the implementation recommendations and begin the

implementation process. An ad hoc, intermittent group cannot deal with critical issues as they arise. Finally, there is a need to develop the necessary organizational structure within the NCI to coordinate the clinical trials enterprise supported by the Institute, including the intramural clinical trials program.

In discussion, the following points were raised:

- The clinical trials process is desperately in need of an overhaul. This will be a long-term process, but it will benefit the NCI to have a coordinated effort and to rethink how clinical trials are carried out.
- The two greatest impediments to bringing an individual to a clinical trial may be: (1) the functionality of the IRB at institutions, universities, clinical sites, or CCOPs; and (2) informed consent. In general, the CTWG is very supportive of the continued expansion of the NCI Central IRB, and is looking at suggestions that would simplify the IRB process. Examples might include incentives for an institution to include a number of other institutions in the region under their federal-wide assurance. Effectively, then, one IRB would serve as the IRB of record for many practice sites in the community. Once the protocol is approved at one IRB, it would cover multiple venues.

top

XIII. BIOETHICS AND THE FUTURE OF BIOREPOSITORIES—DR. ARTHUR CAPLAN

Dr. Arthur Caplan, Emanuel and Robert Hart Professor of Bioethics and Chair of the Department of Biomedical Ethics in the Center for Bioethics at the University of Pennsylvania, began by acknowledging his colleague, Dr. Bernice Elger, a visiting scholar from the University of Bern, Switzerland, for her contributions to his presentation. Dr. Caplan defined biobanking and biorepositories as the storage of biological samples or data created from biological samples for diagnostic, therapeutic, or research purposes. He noted that there are numerous ways in which to create a biorepository that could be mined for genetic information. Currently, there are policies in place related to biorepositories for tissue procurement,

tissue storage, and the distribution of organs and tissues for transplant as well as for research. However, there has not been a concerted effort to address the collection of information from a variety of human tissues and remains for many other purposes. A consensus is needed regarding how to operate the banks and how to use them for multiple purposes.

Dr. Caplan described the key goals for biobanking: 1) promoting respect for autonomy/dignity, 2) advancing public health, 3) developing new treatments, 4) advancing future research, 5) doing no harm to persons or groups, and 6) promoting efficiency. He emphasized that in the United States and Europe, biobanks are run by both government agencies and private interests. These organizations have many different characteristics, including whether or not they operate for profit. Dr. Caplan also presented some of the challenges related to collecting biological specimens. He noted that at the present time, there are no national or international standards for tissue repositories that collect and store specimens for use in research. There are no standardized procedures for informed consent, to ensure privacy, to determine access to materials, or to control the resale of materials.

Individuals worry about privacy and confidentiality and the issue of whether or not these are linked to specific consequences. Individuals do not want their contributions of biological materials to lead to difficulties securing employment or health, disability, or life insurance. Some groups are concerned that they may be stigmatized or face discrimination based on their ethnicity. Exploitation is a prime concern. Fair access to data and to products derived from those data also is of importance to the public. Fighting over access to materials, which in Dr. Caplan's experience is widespread, negatively impacts the spirit of contributing to biobanks. Since samples might be obtained from both living and dead individuals, this raises issues about how and when to approach individuals for permission to obtain materials.

Many organizations are based in one country but collect biospecimens from all over the world. Other problems include offering high rates of payment for specimens that are not consistent with the work being done to obtain them. He posed the following questions: (1) What is reasonable reimbursement in the collection area? (2) How do you standardize the collection process? (3) How do you qualify collectors? (4) How do you standardize what is told

to contributors? (5) What are other appropriate incentives, both for the collector and the contributor?

There is an urgent need to standardize privacy terminology. Presently, many terms are used interchangeably but are interpreted differently in the United States and abroad. He gave a number of examples to demonstrate the confusion associated with the terms "anonymous," "anonymized," and "anonymously coded," "linked," "unlinked," and "delinked." Anonymization tends to be the term of choice in Europe. In the United States, anonymized is used to refer to something that is unlinked irreversibly and cannot be retrieved (i. e., the person who holds the repository cannot get back to the identified individual). That term may mean, however, that even though the researcher does not have direct access to the information, it may be held by a third party that has the ability to reach back to that information/individual. Dr. Caplan suggested that a national policy on anonymization using standardized terminology is needed. Priorities about access to materials also are needed, and policies to discourage propriety and territoriality are necessary. The public's trust is essential to ensure its willingness to participate in supplying materials. Standard guidelines need to be established for acceptable costs, profits, and access to materials. Those whose contributions further science and the development of new therapies need to reap some benefit.

In discussion, the following points were raised:

- When asked if there is an ethical and responsible way of doing science without the anonymization of collections because anonymization takes away a scientist's ability to inform a patient of an early detection of a problem and limits followup, Dr. Caplan responded that he is in favor of anonymization with linked information controlled by third parties so that in the future, response to the patient would be possible. He cautioned, however, that the knowledge base needs to be very secure before an individual is contacted and given information at the conclusion of a research investigation. Because biorepositories are still in the early stages of formation at this time, Dr. Caplan suggested that the researcher has no moral obligation to return to the individual until a "black box operation" that is standardized, approved, and trusted by the public is in place before making promises.

- The differences between tissue collected for its intrinsic biology and nothing else, compared with tissue collected for longitudinal epidemiological studies or clinical trials, were discussed. In the latter case, it is not a matter of going back to the patient to give them information, but rather a matter of going back to individuals because more information is needed to build a longitudinal view of the development of disease (e.g., in its therapeutic response or in its biology as it progresses). These are very clear and different purposes, and to group them together as biobanking is a serious problem. Very clear distinctions between these two kinds of activities are needed. Dr. Caplan noted that there might be different levels of protection triggered by different types of research.
- Now is the optimal time to weigh in on the issues of biobanking because policy formation is just beginning. Dr. Caplan agreed that there may be a short window of public trust and it is important at this time to influence policy.

top

XIV. ADJOURNMENT—DR. ROBERT YOUNG

There being no further business, the 30th meeting of the BSA was adjourned at 12:07 p.m. on Tuesday, 8 March 2005.

top