Board of Scientific Advisors

Meeting Minutes

June 27-28, 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 31st meeting on Monday, June 27, 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 8:00 a.m. until 5:39 p.m. on June 27 for presentation of the NCI Director's Report, a report on the NCI and Congress, ongoing and new business, special recognition for retiring BSA members, final reports from the National Cancer Advisory Board (NCAB) Advanced Biomedical Technology Working Group and the NCAB Clinical Trials Working Group (CTWG), an update on the U.S. Food and Drug Administration (FDA)/NCI Interagency Oncology Task Force (IOTF), an overview of the National Advanced Technologies Initiative (NATIc), Requests for Applications (RFAs), a Request for Proposals, and the reissuance of an RFA. On Tuesday, June 28, the meeting was open to the public from 8:30 a.m. until adjournment at 12:00 noon. Presentations included an update on the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Initiative, a status report on the National Biospecimen Network, and a tumor microenvironment mini-symposium.

Board Members Present:
Dr. Robert Young (Chair)
Dr. David S. Alberts
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
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. Leroy Hood
Dr. Hedvig Hricak
Dr. William G. Kaelin, Jr.
Ms. Paula Kim
Dr. Kenneth W. Kinzler

Board Members Present:
Dr. Michael P. Link
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. David B. Abrams
Dr. Esther Chang
Dr. Neil J. Clendeninn
Dr. Susan B. Horwitz
Dr. Eric Hunter
Dr. Christopher J. Logothetis
Dr. Christine A. Miaskowski

NCAB Liaison:
TBN

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

TABLE OF CONTENTS

VIII. Working Lunch: FDA/NCI Task Force Update; Dr. Anna Barker

IX. Final Report: NCAB Clinical Trials Working Group; Dr. James Doroshow

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

Office of the Director

Clinical Proteomic Technologies Consortia (RFAs & RFP)

Division of Cancer Control and Population Sciences (DCCPS)

The Molecular Epidemiology of Pancreatic Cancer (RFA)

Division of Cancer Treatment and Diagnosis (DCTD)

Small Animal Imaging Resource Projects (SAIRPs) (RFA Re-issuance)

XI. Overview of the National Advanced Technologies Initiative (NATIc); Dr. Anna Barker

XII. Update: CanCORS Initiative; Drs. Robert Croyle, Arnold Potosky, David Harrington, Robert Sandler, and Elizabeth Chrischilles

XIII. Status Report: National Biospecimen Network; Drs. Anna Barker, Julie Schneider, and Carolyn Compton

XIV. Tumor Microenvironment Mini-Symposium; Drs. Dinah Singer, Suresh Mohla, Joan Brugge, and Kenneth Anderson

XV. Adjournment; Dr. Robert Young

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

Dr. Young called to order the 31st 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 future meeting dates. The November BSA will be a one day meeting (14 November). He noted that comments from the public regarding items discussed during the meeting may be submitted to Dr. Paulette Gray, BSA Executive Secretary and Director, Division of Extramural Activities (DEA), in writing and within 10 days of the meeting.

top

II. CONSIDERATION OF THE MARCH 7-8, 2005 MEETING MINUTES — DR. ROBERT YOUNG

Motion: The minutes of the 7-8 March 2005 meeting were approved unanimously.

top

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

Dr. Andrew von Eschenbach, Director, NCI, thanked the Board members for the time and effort that they put into supporting the BSA. Dr. Von Eschenbach noted that 3.5 years ago, the NCI and the broader cancer community had begun to see evidence that progress in the field had moved from the traditional macroscopic and microscopic view of cancer to a molecular view. This progress, made through the ability to discover, develop, and deliver effective interventions based on the molecular view of cancer, has generated enthusiasm, excitement, and anticipation that have been apparent during recent cancer-related meetings. Members were reminded that although many initiatives operate across the discovery, development, and delivery continuum, the importance of maintaining focus on the goal of eliminating the adverse outcomes of cancer is key. All of the NCI initiatives and activities are critically important and need to be nurtured, coordinated, and integrated, especially in this time of limited resources. In addition, the focus on a particular set of initiatives that are of immediate importance does not mean that others have been forgotten or are less important.

Clinical Research Infrastructure: NCI's efforts to re-engineer the clinical research infrastructure, which began in January 2004 were described. Dr. von Eschenbach reminded the Board that his charge to the CTWG to refine the systems of the past to go forward into the era of molecular oncology. Some of the infrastructure from the past needed to be replaced, and some needed modification or adaptation to serve future needs and fit into the new reality of

clinical operations more effectively. The 18-month review yielded 22 specific recommendations with specific milestones, metrics of progress, and outcomes designated to take place over a 5-year period. The recommendations constitute a fluid plan that focuses on the delivery end of that discovery, development, and delivery continuum and emphasizes delivery. Members were told that the NCI has begun to implement the CTWG recommendations and the associated plans will be revised as required during the 5-year implementation process. Dr. von Eschenbach asked the Board to consider the report as part of an ongoing redesign effort that will continue to need its advice, direction, and guidance.

Translational Research Working Group (TRWG). Members were told that, as part of the NCAB, the TRWG had recently been established and would function in a manner similar to that of the CTWG over the next year. He stated that the TRWG will develop a definition for translational research and arrive at a consensus or agreement on what programs and projects in the NCI portfolio would be included. The Group also will examine the entire landscape of translational research and determine whether programs are appropriately aligned, integrated, coordinated, and balanced across the portfolio in a way that achieves optimal outcome at minimal amount of cost. The TRWG will begin to define what would optimize the opportunities in translational research and create a context and blueprint for much more effective management of resources to meet the opportunity presented. The work of the TRWG will build on the outcomes of other working groups, such as NCAB's P30 and P50 Working Group and the NIH Roadmap Initiatives, paying particular attention to the Specialized Programs of Research Excellence (SPOREs) Program because it has been extraordinarily successful. The TRWG also will try to position part of NCI's portfolio to accelerate the discovery, development, and delivery continuum. Dr. Ernest Hawk, Director, Office of Centers, Training, and Resources (OCTR), Office of the Director (OD), will lead the TRWG.

Other Activities. Dr. von Eschenbach informed members that the NCI is moving ahead on many fronts, i.e., the 1) NATIc Initiative, the Human Cancer Genome Project, 2) Biomarkers Project, 3) recently launched Nanotechnology Initiative, and 4) ongoing efforts to move information technologies forward through the Cancer Biomedical Informatics Grid (CaBIG) and the Department of Health and Human Services' (DHHS) Electronic Health

Initiative activities involving Dr. David Brailer, National Health Information Technology Coordinator, DHHS. He also noted that the NCI is attempting to increase opportunities for synergy and leverage of resources by creating more formal relationships with other federal agencies highlighting activities that have occurred within the DHHS, current relationships with the Centers for Disease Control and Prevention (CDC), the FDA, the Centers for Medicare and Medicaid Services (CMS), and other NIH Institutes and Centers. The NCI is also reaching out to the Department of Energy and several Cancer Centers have established relationships with federal laboratories.

NCI Staff Appointments. Members were informed of recent personnel changes: Dr. Paulette Gray, Director of the Division of Extramural Activities; Dr. Carolyn Compton, Director of National Biospecimen Research; and 3) Dr. Piotr Grodzinski, Program Director for Cancer Nano-technology.

In discussion, the following points were made:

- In response to members concern regarding the the need to engage in conversations with academic institutions, membership organizations, or other appropriate entities to discuss the need to realign promotion and tenure processes with the emerging realities of shared credit for shared work conducted by NCI's research grant staff, Dr. von Eschenbach stated that he had been discussing the issue with Dr. Elias Zerhouni, NIH Director, i.e., in terms of making it an NIH initiative and part of the overall agenda. Cancer Center Directors, the Deans of medical schools, and several membership organizations were mentioned as potentially having influence in such matters. A suggestion was that the BSA develop some measures for rewarding team science and put them into guidelines to assist any entity that might not be certain of the best way to determine or divide such rewards.

- Board members expressed an interest in the central role of program projects that are translational in nature and the need to review and evaluate translational research projects more carefully. It was suggested that the Board have a major discussion to consider the metrics of evaluation, look closely at the details of the review process and the

budgetary decisions at the review level, and think about how the NCI portfolio should be balanced for the future. Dr. von Eschenbach remarked that the TRWG will be asked to examine the entire portfolio and identify the synergies and where efficiencies can be applied, emphasizing metrics, milestones, outcomes, and deliverables. The Group also will be asked to examine projects' business plans against funding strategies with regard to what is expected in return for the investment.

- Members asked staff to send them the FY05 budget justification that was sent to Congress. They also asked that future budget justifications be shared with them prior to sending to Congress, i.e., as soon as the document is prepared.

top

IV. NCI AND CONGRESS—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response, OD, NCI, reported that the President's Budget gives the NIH $28.5 B and that the NCI would receive $4.8 B of that amount. The House has requested an annual report on prostate cancer from the NCI, which is to be delivered each year in January; the House report encourages the NCI to maintain the ovarian SPOREs; and the committee recommended that the NCI "take bold action to address lymphoma and strengthen our investment in translational and clinical research."

NIH items contained in the House report gives the NIH Director a new transfer authority for NIH Roadmap activities; and $2 M to implement a new office within the Office of the Director called the Office of Portfolio Analysis and Strategic Initiatives (OPASI) to review the NIH research portfolio and address disease coding. Ms. Erickson also presented information on five congressional hearings and highlights of the following bills: the Patient Navigator Outreach and Chronic Disease Prevention Act, the Stem Cell Research Enhancement Act, and the Stem Cell Therapeutic Research Act.

In discussion, the following points were made:

- In response to questions about the probability of the Congress reauthorizing the NIH, members were told that in public statements, Senator Barton has reiterated the intention to reauthorize the NIH.

- Congress's denying funding to existing grants that have been reviewed and approved through the peer review process was of major concern to mmembers. The potential role that they as members of an advisory committee could play in expressing deep concern about this kind of Congressional approach was queried. Members noted that such actions hold enormous ramifications in terms of peer review, especially how different areas of science are interpreted and the process by which research is funded.

- Information on the proposed OPASI regarding public availability of information on its deliberations should be sent to Board members.

- The progress of S. 470, which deals with creating clinical trials registries, should be tracked.

top

V. ONGOING AND NEW BUSINESS—DR. ROBERT YOUNG

NCI Listens Reports - BSA Members

Society of Behavioral Medicine (SBM). Drs. Jane Weeks (Chair), Robert Croyle, and Paulette Gray represented the BSA and the NCI at the SBM meeting on 14 April 2005. Dr. Croyle presented information on the status of the NCI budget, paylines, and other program initiatives of interest to the audience. Grant related concerns and questions were discussed.

American Association for Cancer Research (AACR). Drs. William Hait (Chair), Suresh Mohla (Presenter), Esther Chang, James Doroshow, Paulette Gray, Susan Horwitz, and Carolyn

Strete represented the NCI and the BSA at the AACR meeting on Tuesday, 19 April 2005. Approximately 140 people attended that meeting, which Dr. Gray facilitated. Dr. Mohla presented information on the status of the NCI budget and other programmatic issues.

BSA at National Meetings - BSA Members

Dr. Young reminded Board members that approximately 10 years ago, the BSA suggested “NCI Listens” as a mechanism for dialogue between the NCI and major cancer-related scientific organizations, with the BSA as a conduit for such conversations. Since that time, a considerable amount of effort has been devoted to reaching out to specific organizations within the cancer community and addressing their concerns at their national meetings. The “NCI Listens” sessions have been ongoing since inception, with varying degrees of success. Some organizations have found that they now have appropriate access to the NCI and have stopped holding these sessions, while others continue to hold successful “NCI Listens” sessions. Given the changes that have taken place over the last decade and declining attendance at “NCI Listens” sessions, Dr. Young asked the Board to reassess the value of the program and decide whether or not it should continue.

In discussion, the following points were made:

- Although NCI Listens represents a good public relations effort, it is not a necessary endeavor. However, there is serious concern that ending the program would send the wrong message.
- The incorporation of new focus areas and different kinds of organizations was discussed at length.

- A subcommittee (Ms. Kim (Chair) and Drs. Bland, Hendrix, and Hricak) was established to develop a plan for restructuring the BSA NCI Listens sessions. A progress report should be given at the November BSA meeting.

top

VI. SPECIAL RECOGNITION OF RETIRING BSA

MEMBERS—
DRS. ANDREW VON ESCHENBACH AND ROBERT YOUNG

Dr. von Eschenbach recognized retiring BSA members Drs. Christine Miaskowski, Neil Clendeninn, Thomas Curran, and William Kaelin. On behalf of the BSA, Dr. Young presented those members in attendance, i.e., Drs. Curran and Kaelin, with the Director's Service Award for their service n the BSA from 1999-2005.

top

VII. FINAL REPORT: NCAB ADVANCED BIOMEDICAL TECHNOLOGY WORKING GROUP—DR. ERIC LANDER

Dr. Eric Lander, Director, Broad Institute of the Massachusetts Institute of Technology and Harvard Medical School, Professor of Biology, Massachusetts Institute of Technology, Professor of Systems Biology, Harvard Medical School, and Member, Whitehead Institute for Biomedical Research, reminded the Board that the final report of the NCAB Advanced Biomedical Technology Working Group (ABTWG) was issued in February. Dr. Lander noted that the BSA plays a crucial role in thinking through this project. In a brief description of the report's key recommendation, members were told that one was for a Human Cancer Genome Project to be pursued over the next 9 to 10 years. Significant input on the content and structure of work in this area is expected from the scientific community, advisory groups, and the BSA. One of the important conclusions of the ABTWG was that it is possible to obtain a comprehensive understanding of the genomic basis of cancer and that researchers need to seize the opportunity to do so in an organized manner. Dr. Lander informed the Board that the focus of his remaining remarks would address that conclusion.

The premise of a cancer genome project is that cancer is a genetic, highly heterogeneous, but understandable disease and that understanding the heterogeneity of cancer is crucial to cancer prevention and treatment. The systematic understanding of the cancer genome is technologically feasible within the next decade, and the cost of undertaking such a project is reasonable when

considered in context of the need. Steady progress in this area of research has been made since the 1960s. Genome-wide studies must be done. Across the field, studies of 50-100 “favorite” genes have begun to yield important new connections not seen previously. Some of these connections shed very important light on cancer treatment. Dr. Lander cited Gleevec® with Bcr-Abl as the most prominent example across the field, but also recognized recent work with mutations in epidermal growth factor receptor (EGFR) that highlights the subset of lung cancer patients who are most responsive to the EGFR emitters Iressa® and Tarceva®. One of the important implications of these discoveries is that this is a very good way to identify cellular pathways that underlie cancer. From a therapeutic point of view, the discoveries are important for identifying targets for therapeutic development.

Continued work on biomedical technology should yield improved applications of drugs and spawn the design of epidemiological studies. In light of rapidly moving technologies, cancer scientists and researchers are obligated to patients worldwide to take on projects immediately with the knowledge that research can drive technology, including generating private sector interest in trying to produce newer and improved technologies to make better research possible.

Dr. Lander commented that the goal of the Human Cancer Genome Project would be to identify all of the genomic alterations significantly associated with all major types of cancer by creating a large collection of appropriate clinically annotated samples from all major cancer types. From these, work would proceed toward completely characterizing each sample in terms of the regions of copy number change, chromosomal rearrangement, mutations in coding regions, aberrant methylation, and expression profile. The best technology to use for each process may change, but the goal of characterization is clear.

Operationally, the field can learn the most from matched normal DNA for the 50 major cancer types times 250 tumors each. The challenge is obtaining the right samples. Cell lines also are very important, so the ABTWG suggested that working with 1,000 cell lines appeared to be appropriate based on what is known currently. Some very important mouse models and a few dog models might be of interest, but these would represent a minor subset of the work. The right balance between primary cancers and metastases

should be established, but the Working Group did not proscribe a ratio for this. Sequencing targets were suggested, as were coding regions representing about 1 percent of the genome.

In terms of organizational issues, the ABTWG suggested sample acquisition centers and genome analysis centers, but did not indicate the number of either type that might be needed. A crucial part of the Human Cancer Genome Project is a technology development grant mechanism, which is designed to support the new and improved technologies that are expected to develop not only from cancer genome research, but also across all NCI research projects. The Working Group determined that any data generated under the project should be released to other researchers immediately and be available with unrestricted access. Cost, as expected, was a large part of the ABTWG's discussions. With the clear understanding that costs associated with a projected 10-year project were difficult to identify, the ABTWG combined current costs and a time-averaged set of costs to develop the budget.

Members were told that there are concerns regarding the potential decrease in the number of R01s, the balance of project activities, and whether the project should go forward at all. While, the majority of the project should be funded by new money, the ABTWG recognizes there will probably be a need to reprogram some monies to launch a pilot project.

In discussion, the following points were made:

- The Human Cancer Genome Project was a recommendation of the ABTWG and the costs discussed were consensus estimates. Intentions to achieve cost savings through the involvement of private industry and coordination with the international community were discussed as cost-reducing mechanisms. Cost leveraging across projects and managing existing infrastructures in a more cost-effective way were discussed as well.

- A pilot phase would not focus on all genes, but on a subset of genes, the number of which scientific results would dictate.

- Several organizations in the scientific community are

working on specific tumors, conducting array studies, performing some level of resequencing, or otherwise have developed or are developing special expertise in genome research. A major challenge to the NCI lies in capturing some of the existing expertise to support the human cancer genome project.

- RFAs are expected to solicit collaborative responses as well as incorporate the high levels of expertise needed to attract researchers with the experience and credentials to conduct high-level projects. It is expected that the community will assemble itself to tackle the challenges put forth in RFAs. Competition is important to the quality of this endeavor.

top

VIII. WORKING LUNCH: FDA/NCI TASK FORCE UPDATE—DR. ANNA BARKER

Dr. Anna Barker, Deputy Director, Advanced Technologies and Strategic Partnerships, NCI, informed members that the IOTF represents the first time that the NCI and the FDA have proactively teamed to accelerate progress. Dr. Barker highlighted the following issues as most important to the IOTF are biomarkers, imaging and imaging endpoints, nanotechnology, bioinformatics, prevention, and training.

One of the areas that the IOTF focused on initially was the exploratory Investigational New Drug (IND). An exploratory IND is defined as a new drug designated to be given to a small number of patients to see how the agent is going to behave. The need is to have new drugs be highly effective, very safe, and approved rapidly. Driven by the biologics community and the desire for endpoints, the advent of the exploratory IND will have a major impact on the way drugs are developed in the future. The Task Force also is working on a guidance document for Good Manufacturing Practice (GMP) regulations for these and other cancer agents. Dr. Joseph Tomaszewski, Chief, Toxicology and Pharmacology Branch, Developmental Therapeutics Program, NCI, has drafted the GMP guidance and currently is compiling white papers on toxicology and combination therapy.

Although many clinical trials' reporting systems feed into the FDA, the Agency looks at different incoming systems in one basic way. To address this issue, the IOTF is working on the development of an electronic IND (eIND), which is under construction. One of the components associated with this effort is the Cancer Investigator Exchange (CRIX), which will list investigators and all of the information about completed clinical trials. The NCI is working on eIND standards with the FDA, Health Level 7 (HL7), and other standards bodies. This activity is moving very quickly, and many private partners are anticipated.

Dr. Barker stated that the IOTF Process Subcommittee has been diligent in identifying the barriers to the IND process and what can be done to mitigate them, offering several approaches to understanding the process and its procedures. To that end, the Task Force has implemented three scientifically based training programs for Ph.D.s and M.D.s to assist them in traversing the FDA regulatory path and understanding the regulatory process. Two points of contact had been developed. One is a regulatory affairs liaison that helps investigators use existing channels effectively in resolving questions or disputes. The second is a senior leadership team, composed of senior NCI and FDA personnel that will resolve questions or disputes when a satisfactory resolution using standard mechanisms has not been achieved. The exploratory INDs are geared toward allowing early evaluation of new drugs in limited numbers of patients. Making these processes simpler and clearer should accelerate the development of new agents and reduce some of the risks involved. This service will be announced in the Cancer Bulletin very soon, and it is expected to expand beyond the NCI to other NIH investigators. Many NCI investigators already have taken advantage of this service. Interested parties should expect to see more movement in this area, especially as FDA's biomarker-enabled critical path continues to evolve.

Dr. Barker recognized the work done by Dr. Michaele Christian, Associate Director, Division of Cancer Treatment and Diagnosis (DCTD), Cancer Therapy Evaluation Program (CTEP), NCI, and Dr. Janet Woodcock, Acting Deputy Commissioner for Operations, and Director, Center for Drug Evaluation and Research (CDER), FDA, on FDA's GMP guidance for exploratory IND studies. This report documents how one would navigate the issues that arise when attempting to obtain FDA approval for a new drug. It is important for NCI's clinical trials staff to understand this process.

The FDA Web Site has posted the draft guidance document for comment. Board members were advised to take advantage of the opportunity to review the guidance and comment on it through the Web site or through Dr. Christian.

Advanced Technology. In the area of advanced technologies, nanotechnology is of greatest concern. Along with the FDA, the NCI is developing a strategic plan for nanotechnology. The current NCI/FDA nanotechnology initiatives are the first examples of jointly creating a path from which the new diagnostics could be reviewed and used. The FDA also realized that work with the NCI on new drug approvals and the processes surrounding them were evolving into a major undertaking, so it created a new division to address those issues. Dr. Richard Pazdur, Division Director, Division of Oncology Drugs, FDA, was appointed to direct the new Office of Oncology Products at the FDA. The Office addresses a combination of extramural and intramural activities. Over the last few months, Dr. Pazdur has been leading several workshops on first-generation endpoints; more are planned. A guidance document has been developed through this venue and the NCI expects some of the first-generation markers, such as prostate specific antigen, to proceed into trials. Dr. Barker then asked Dr. Gary Kelloff, Chief, Chemoprevention Branch, Division of Cancer Prevention (DCP), NCI, to discuss progress in the area of imaging.

IOTF Imaging. Dr. Kelloff noted that the IOTF imaging effort to date has led to completion of one of the three comprehensive state-of-the-science papers planned. The paper examining fluorodeoxyglucose positron emission tomography (FDG-PET) imaging will be published in Clinical Cancer Research in mid-April. FDG-PET was chosen because it is a well-known clinical procedure used to manage cancer patients as well as a tool for oncologic drug development. It also offered an opportunity to look at the multiple disciplines involved in oncologic drug development and show how FDG-PET could facilitate that development. A second completed collaboration document, which has been submitted for peer review, focuses on molecular probes that can evaluate basic properties of neoplasia like proliferation and apoptosis, angiogenesis, and hypoxia. The third paper’s topic is volumetric imaging, and it addresses the need to update the area of anatomical imaging. In the last decade, anatomical imaging has played a key role in approximately one-half of the 22 accelerated approvals for oncologic drugs. The state-of-the-science paper on

volumetric imaging likely will be completed by the end of the year. These three papers constitute the first wave of state-of-the-science manuscripts. Ongoing collaborations led by Drs. Barker and Woodcock will create more specific deliverables, such as prototype clinical trial protocols on which the NCI and FDA can agree. Subsequently, the FDA may issue a guidance document and the NCI then may issue either a series of clinical trials or an analysis of the data.

Under the recently formed IOTF Training Subcommittee, two of the three training programs are soliciting participants. Brochures are available for the third program, which is for M.D.s exclusively. The IOTF Communications Subcommittee is working on community awareness.

In discussion, the following points were raised:

- Clarification was requested concerning which NCI review committee will have responsibility for evaluating multifunctional nanoparticles, which can be used for imaging and drug delivery purposes.

- Clarification was requested about whether the NCI provided input to either the FDA or Congress about pending legislation that will impact cancer research projects dramatically.

top

IX. FINAL REPORT: NCAB CLINICAL TRIALS WORKING GROUP—DR. JAMES DOROSHOW

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, reminded the Board that the CTWG began with a vision of the future direction of cancer clinical trials that encompassed enhancing the best components of the NCI-supported clinical trials system to develop a cooperative enterprise built on a strong scientific infrastructure and a broadly engaged coalition of critical stakeholders. The scientific rationale for changing the current clinical trials system addressed advances in cancer biology that provide the opportunity to move beyond

cytotoxic treatments to more effective therapies and recognized the potential to improve the practice of clinical oncology. Dr. Doroshow explained that successfully restructuring NCI's clinical trials enterprise to optimize patient outcomes requires: 1) the routine incorporation of the tools of cancer biology into cancer clinical trials; 2) a cooperative, interdisciplinary, efficient, and functionally integrated approach to diverse elements of the current system that improves effectiveness and retains innovation while conducting clinical trials; and 3) an implementation strategy that recognizes the essential value of components of the current clinical trials system, and simultaneously challenges those components to work together in new ways. Key elements of the implementation strategy incorporate the values of Cancer Centers, SPOREs, Cooperative Groups, grant-supported clinical trials staff, the Community Clinical Oncology Programs (CCOPs), community oncologists, and patient advocates. In addition, successful implementation requires acknowledgment of the enhanced commitment of the extramural community to the increases in effort and responsibility required to assist the NCI more broadly with governing the cancer clinical trials enterprise.

The CTWG proposed plan is organized around five common themes: (1) coordination - enhancing information sharing, developing incentives for collaborative team science, and coordinating the regulatory process in the scientific enterprise; 2) prioritization and scientific quality - establish new transparent processes for the design and prioritization of clinical trials and for facilitating the conduct of correlative science and other ancillary studies conducted during NCI-funded investigations; 3) standardization - promote the development of defined clinical research tools and procedures that would minimize duplication and reduce the effort required to initiate and conduct clinical trials; 4) operational efficiency - improving patient accrual rates and cost effectiveness as well as expediting the initiation and conduct of clinical trials; and 5) integrated management - creation of a permanent Clinical Trials Oversight Subcommittee of the NCAB to continually advise the NCI Director regarding the conduct of clinical trials across the Institute; and development of recommendations by NCI senior leadership for a more coordinated management and oversight structure for the full spectrum of clinical trials supported throughout the Institute. Within those themes, 22 specific initiatives were developed. Full implementation of the restructuring plan is projected for completion in 4-5 years,

with a majority of the initiatives scheduled for implementation by the end of Year 3. It is expected that all initiatives will be established as routine practice by the end of Year 7.

Dr. Doroshow noted that the 22 initiatives proposed by the CTWG are interactive and interdependent. The coordination initiatives to develop a comprehensive clinical trials database and realign funding guidelines are essential to a more transparent prioritization system. Better coordination of NCI's clinical trials system with the FDA and CMS will enhance the efficiency of developing new therapies and support more rapid rates of patient accrual. The increased involvement of community trials staff and patient advocates in the protocol prioritization process will increase patient accrual rates by developing clinical trials that are more attractive at the local level. Increased operational efficiencies that lead to enhanced clinical trials accrual rates will allow studies to be completed more rapidly, facilitating overall prioritization. A standardized interoperable clinical information technology structure will support all other areas by providing common electronic case report forms and by improving coordination, prioritization, and the efficiency of NCI-funded clinical trials. The entire system needs to be overseen by an integrated clinical trials management system that is advised by an expert panel of extramural clinical investigators. The estimated cost for Year 1 of the restructuring plan is $7.1 M, increasing to $20.6 M in Year 2. It reaches a steady state at approximately $29 M annually by Year 3. The largest portion of projected expenses (75%) supports extramural clinical trials directly.

The CTWG also suggested mechanisms to evaluate the success of the implementation process. One of the expected difficulties in this area will be the absence of a common evaluation system outside of the grant review process. Thus, evaluation poses a challenge in terms of the establishment of a structured evaluation system. The group's suggestion was to engage experienced evaluation specialists to assist in the development of the appropriate tools with the critical baseline evaluation, which underlies NCI's ability to determine the impact of these initiatives.

The CTWG also indicated that any evaluation process should involve external clinical trial experts and the acquisition of new forms of empirical data, both subjective and objective. The focus of the evaluation should be on the management of the implementation

program, defined management measures, documented changes in the performance of the clinical trials system produced by the measurable initiatives, and any improvements observed in overall clinical trials outcomes that could be related to the restructuring process directly. Dr. Doroshow noted that ultimately, the value of the restructuring plan would depend on whether the initiatives measurably increased the number of clinical trials that improve medical practice either through the development of new therapies or diagnostic procedures, or through the development of better biomarkers that meaningfully enhance the specificity with which cancer treatments are delivered. Fifty years ago, the NCI had the foresight to initiate support for networks of investigators and institutions engaged in clinical trials that could speed the development of new cancer therapies. Over the next half century, with enhanced commitment from extramural investigators, physicians, patient advocates, and the new investment called for by restructuring, the NCI, in collaboration with the clinical trials community, will lead the process of translating extraordinary advances in cancer biology into clinical trials that materially improve the outcome of cancer patients everywhere.

In discussion, the following points were made:

- There is the potential for disconnects between committee-based clinical trials development and individual physician's acceptance of and participation in trials that they did not design.

- The specific roles and operational responsibilities of the proposed scientific steering committees and other proposed oversight entities should be clearly defined.

- The interface between adult and pediatric local and central Institutional Review Boards (IRBs) should be addressed. Methods of eliminating some of the inherent problems associated with IRBs and obtaining the cooperation of IRBs with new clinical trials procedures must be established.

- CTWGroup recommendations, progress reports should periodically be disseminated to members.

top

X. RFA/RFP CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Office of the Director (OD)

Clinical Proteomic Technologies Consortia (RFAs and RFP).
Dr. Joseph Gray, Professor, Laboratory Medicine and Radiation Oncology, University of California - San Francisco, and Chair, BSA Ad Hoc Subcommittee on the Clinical Proteomic Technologies Initiative, introduced the initiative by stating that since the last BSA meeting, the initiative had been revised the proposal substantially and now was consisted of three different subtopics. Dr. Barker noted that the Subcommittee had addressed every question raised during the previous BSA meeting, and has considered issues that have evolved and some that will evolve as the field begins to move forward.

Dr. Gregory Downing, Director, Office of Technology and Industrial Relations, OD, NCI, presented updated information that addressed all major issues and challenges raised at the March BSA meeting. Collectively, the two RFAs and the RFP are represented as the Clinical Proteomics Technology Initiative, for which the objectives are to integrate approaches to develop and enhance technology capabilities, enhance public resources for investigator-initiated research on protein discovery, accelerate these discovery efforts, and enhance the knowledge base. The expected results are designed to be broad, and CaBIG will play a major role. Some of the critical components are multidisciplinary teams of clinical investigators, technologists, and statisticians that will attempt to enhance the capabilities of existing technologies and develop new ones, integrate different platforms, and establish biological resources. Public databases are a major issue. Enabling the ability to reproduce separation capture and identification as well as quantification and validation of protein measures is a major component of the initiative, as is developing and evaluating new technical approaches to separate and recognize proteins of clinical significance.

The Clinical Proteomic Technology Assessment Consortia RFA would encompass five awards to establish a multidisciplinary network that will conduct rigorous technology assessment, develop

standard protocols and clinical reference sets, and evaluate methods to ensure data reproducibility. The first RFA is entitled “Clinical Proteomic Technology Assessment Consortia.” It requires development of a multidisciplinary network that conducts rigorous technology assessment and develops protocols, clinical biological reference sets, and evaluation methods to ensure data reproducibility. Key elements include assembling the expertise necessary to work as a team to evaluate these technologies, focusing on experimental design and methods and standards development, and establishing highly annotated clinical reference sets. The latter is an addition to the concept. Awards through the U24 Cooperative Agreement will allow for inter-institutional and multi-sector platform evaluation in terms of the design aspects.

The Advanced Proteomic Platforms, Analytic Methods, and Computational Sciences RFA will support the development of innovative tools and enabling technologies for protein/peptide measurement and support algorithm development and computational methods to interrogate emerging preprocessed data sets. It is an R01-based program that is designed for assembly of new ideas in terms of technology development as well as algorithm and computational capabilities for the interrogation of emerging preprocess data sets.

The Clinical Proteomic Reagents Resource RFP will support the development of a system to design antibodies, proteins, and peptides necessary for developing standards, coordinating technology measurements, and establishing new imaging and measurement capabilities on protein array platforms. The system would perform many of the functions that currently are not coordinated in terms of characterization, provide quality assurance, and facilitate interactive dialogue with the investigators. The system also would have a mechanism for expediting the acquisition and distribution of reagents and the data about them through CaBIG and independent vendors that have nonexclusive licensing.

Dr. Mitchell Gail, Chief, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, NCI, briefly reviewed several of the goals, such as developing or improving technologies; developing procedures for sample handling, including fractionation, protein separation, and identification; assessing inter- and intralaboratory variability and reproducibility for a given technology; comparing the validity and reliability of various technologies; developing

standards and algorithms for data management and analysis; developing reagents that can be used throughout the program; and providing statistical support. Dr. Gail stated that responses to the RFA should have statistical components and ideally, statistical resources to support them. He also defined and described some of the terms used in the RFA.

Estimated costs for the 5-year project period is $104M and a first year set-aside of approximately $19 M for 5 (U24s), 10 (R01s, R21s, R33s) and 2 contracts.

In discussion, the following point was made:

- The first and third components of the resulting RFA will be extraordinarily useful because the field of epigenomics will lead into proteomics.

Motion: A motion to approve the OD RFA/RFP concept entitled "Clinical Proteomic Technologies Initiative" was approved unanimously.

Division of Cancer Control and Population Sciences (DCCPS)

The Molecular Epidemiology of Pancreatic Cancer (RFA). Dr. Robert Croyle, Director, DCCPS, NCI, introduced the RFA concept by outlining the collaborative, proof-of-principle study structure of the Breast and Prostate Cancer Cohort Consortium (BPCCC). Dr. Croyle informed members that the Executive Committee (EC) indicated that the pancreatic cancer RFA should be designed as a collaborative study, similar in structure to the Cohort Consortium. The design will take full advantage of up to 20 years of existing exposure data from the BPCCC cohorts in addition to those collected in the clinic at the time of diagnosis. The plan is to use historical data on critical exposures to pool sufficient samples to obtain at least 1,500 case/control pairs of biological specimens, which are different from those belonging to newly accrued patients. Four to seven grants are projected along with a logistical coordinating center to be procured through a small support contract. One laboratory will serve all of the grantees, and will be selected post-award to take advantage of the best

technology available among the grantees. Involvement from some of the intramural cohorts in the Division of Cancer Epidemiology and Genetics (DCEG), which has played a key collaborative role in the BPCCC study, is expected and will be encouraged.

Estimated costs for the 3 year project period is $15 M and a first year set-aside of approximately $5M for the U01. Each year $500,000 will come from the DCCPS operating budget to fund the logistical coordination contract.

In discussion, the following points were made:

- Several Board members expressed enthusiasm about the creation of a pancreatic cancer RFA, citing the potential work as being long overdue.

- The proposed use of the R01 or other funding mechanisms should be further addressed.

- The Board concurs that there is an urgency of moving the pancreatic cancer research concept forward.

Motion: A motion to approve the DCCPS RFA concept entitled "The Molecular Epidemiology of Pancreatic Cancer" with the provision that NCI staff work to refine the concept according to Board discussion with the help of a BSA Subcommitte (Drs. Earp (Chair), Anton-Culver, Potter, Spitz, and Ms. Kim) was unanimously approved. The concept will be disseminated to the Board for concurrence.

Division of Cancer Treatment and Diagnosis (DCTD)

Small Animal Imaging Resource Projects (SAIRPs) (RFA Re-issuance). Dr. Hedvig Hricak, Chair, Department of Radiology, Memorial Sloan-Kettering Cancer Center, Professor of Radiology, Cornell University Medical College, presented a request for a one-time re-issuance for the SAIPRs RFA. She reminded the Board that small animal imaging is a key resource. It helps to develop animal tumor models that facilitate tumor model development, assists understanding of tumor biology, and helps to monitor tumor

growth and development of metastases with a temporal resolution. Small animal imaging also is important to drug development, especially in the design of the new probes that are combinations of imaging and targeted therapy. There are three changes to the RFA. First, in terms of classification, the funding mechanism is changing from an R25 to a U24, which mandates that awardees use at least one-half of their time for other research projects. Second, it allows the purchase of new equipment only for the first-time applicant. Third, project plans must show the ability to achieve partial cost recovery. The last change ensures cooperation between awardees, the Mouse Models of Human Cancers Consortium, and Integrated Cancer Biology Programs. Renewal applications will be funded for operational costs only. Dr. Hricak expressed strong support for this RFA.

The estimated first year cost is $3.6M for an estimated 8 awards and total costs of approximately $18M over 5 years.

Motion: A motion to reissue the DCTD concept entitled “Small Animal Imaging Resource Projects (SAIRPs)” was unanimously approved.

top

XI. OVERVIEW OF NATIONAL ADVANCED TECHNOLOGIES INITIATIVE (NATIc)— DR. ANNA BARKER

Dr. Barker informed members that the idea of a national advanced technologies initiative emanated from the NCI about 3.5 years ago. Based on NCI’s 2015 goals, the NATIc is attempting to leverage the Institute’s vast portfolio of resources to develop the networks needed to create a model that can take advantage of the science and the advanced technologies simultaneously. Because research barriers are more technology-based than science-based, networks are going to be the working models for the future and create a “network of networks” to advance biomedicine and must be developed.

Dr. Barker emphasized the fact that cancer research must be conducted across and with other sectors, such as academics,

government, the public, survivor groups, and internationally. Partnerships of all types will drive future research. So much of the work in bioinformatics, advanced computing, advanced imaging, drug discovery and high throughput screening, proteomics, biomarkers and diagnostics platforms, computational and systems biology, and nanotechnology, among others, is taking place in multiple locations and there is an overwhelming need to connect those studies.

The NCI has built a business plan for the NATIc that has enormous ramifications for public health. The idea is to begin creating the required network of networks. One idea that emerged was the creation of a national network to leverage existing and emerging advanced technology development resources. CaBIG responds to this need and is the largest enterprise initiative undertaken to date. Already, it has brought enormous change to researchers' thinking. Simply having common language, software, and systems is a huge step forward, although many challenges still exist. The biology is the biggest challenge. The technology is in process, but the epigenomists have raised several issues; for example, there is no experience base in this country for putting whole genome sequences into databases.

Since the NCI is a leader in nanotechnology, it has programs that are moving the field forward in areas such as drug delivery capabilities, cancer cell targeting capabilities, and therapeutics. Response to the recent NCI nanotechnology RFA garnered an enormous number of responses from extremely good investigators. The NCI underestimated the extent to which cancer investigators have reached out and are building the kind of teams envisioned for the future. In addition, the attendance at the AACR meeting on information transfer and nanotechnology attracted about 20 times the number of people expected. The events make it clear that the young research community understands the importance of this technology and the level at which they will have to operate. The NCI is probably the major source of biomedical research input for the National Nanotechnology Initiative, and the private sector is investing in biomedical research in terms of nanotechnology, much of which is in the area of oncology.

Biomarkers will inform every aspect of the design, development, and delivery continuum beginning with target identification, lead development, animal studies, and clinical trials. This work will

affect early detection in particular. Much of what will be accomplished in early detection will be driven by proteomics.

The NATIc business plan calls for some additional funds in terms of federal money, but most of the money for technology efforts is expected to come from states, the private sector, and potentially, venture capitalists and others who are very interested in seeing products.

In summary, Dr. Barker suggested that over the past 1.5 years, the NATIc has put in place some of the infrastructure and underpinnings of the advanced technologies that will allow the NCI to move forward on new ideas.

In discussion, the following points were raised:

- In addition to national networks, creation of global networks is encouraged. Several examples of working international partnerships were given. A few members discussed their involvement in facilitating or working with global networks and similar international entities. Clinical trials at the international level were discussed at length.

top

XII. UPDATE: CanCORS INITIATIVE—DRS. ROBERT CROYLE, ARNOLD POTOSKY, DAVID HARRINGTON, ROBERT SANDLER, AND ELIZABETH CHRISCHILLES

Dr. Croyle reminded members that this update was being provided in response to the Board's request for mid-term progress reports on approved RFA concept initiatives. The theme of the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) initiative is to measure the dissemination and impact of cancer care delivery in clinical practice, a key part of the NCI agenda and mission. CanCORS, which focuses on patients with lung and colorectal cancer and their outcomes, is intended to serve as a prototype for this type of research. By contrast the NCI-sponsored Cancer Research Network (CRN), which is a collaborative effort with several managed care organizations, includes a large component that focuses on primary care and its role in early

detection, smoking cessation, and cancer control. Dr. Croyle noted that the update would include background information and key elements and objectives of CanCORS. He welcomed BSA feedback that would help inform and shape future directions in the area of health services research that would, in turn, inform what is done in other areas of scientific interest.

Rationale and Background. Dr. Arnold Potosky, CanCORS Program Director, Applied Research Program, DCCPS, NCI, reviewed what is known about cancer care delivery in 2005 to illustrate the need for this initiative: 1) dissemination and implementation of evidence-based care is suboptimal; 2) disparities persist by age, race/ethnicity, and provider; 3) randomized clinical trials (RCTs) include small and biased samples; and 4) RCTs cover only a small fraction of cancer care, which limits the evidence base and suggests that quality of care guidelines may not be developed using the best available evidence. Dr. Potosky illustrated the types of questions that the CanCORS initiative is designed to address, using examples based on Surveillance Epidemiology and End Results (SEER) Medicare data.

Members were told that the specific aims are to 1) determine how patients, physicians, and characteristics of health care organizations influence treatments and outcomes (spanning the continuum of cancer care), and 2) evaluate the effects of care delivery on patients' survival, quality of life, and satisfaction with care. These aims are designed to develop a better understanding of why patients do not receive proven therapies and to complement the NCI clinical research enterprise by collecting data on patients who typically are not represented in RCTs and for whom doctors have less guidance on how to treat. CanCORS structure includes seven research teams—six data collection teams and the Statistical Coordinating Center. It is a core study, essentially, with two cohorts of 5,000 patients each for lung and colorectal cancer. Data will be collected from multiple sources, including patient interviews, medical records, physician surveys, caregivers, linkages to insurance claims, and other sources. CanCORS is a trans-NCI collaboration and includes partnerships with the Veterans Health Administration (VHA), CDC, Agency for Healthcare Research and Quality (AHRQ), American Cancer Society (ACS), and professional societies. Annual review is conducted by an external expert panel of 12 scientists and patient advocates unaffiliated with CanCORS.

Research Highlights. Dr. Elizabeth Chrischilles, Professor and Associate Head for Admissions and Curriculum, Department of Epidemiology, The University of Iowa College of Public Health, began by illustrating that the national distribution of CanCORS sites reflects a wide diversity of types of research settings to represent more fully the vast array of community practice settings in the United States. Included are population-based cohorts in geographic areas, patients from integrated health care delivery systems, and patients at VHA hospitals. Baseline interview enrollment goals are large and include oversampling by race and ethnicity to ensure that adequate power is achieved for solid estimates within sociodemographic subgroups where there is evidence of health disparities. The sample also addresses the need for clinically relevant subcategories, such as by diagnosis, performance status, and morbidity. Dr. Chrischilles described the basic data collection process, and noted that array of data sources is important to populate a fully specified model of treatment decisions and outcomes. The CanCORS conceptual model of factors associated with cancer care shows four principal domains—patient factors; physician, hospital, and health system factors; care received; and outcomes, with multiple subdomains under each. The broad array of data is collected in all of the domains and subdomains for this research initiative and contrasts with most other research studies that explore perhaps only two domains.

Preliminary distributions resulting from the first-stage analysis of CanCORS data, with the caveat that the data are unadjusted and preparatory to more complex modeling were presented. She noted that, even in preliminary stages of analysis, the various CanCORS instruments and surveys can shed light on the question of why patients in a community did not receive the recommended care.

Dr. Chrischilles ststed that CanCORS also is more representative of the community practice setting than are clinical trials, and thus is better positioned to address the question of what outcomes are in the usual care setting: CanCORS collects the full spectrum of outcomes from patient interviews and medical record abstracts and captures aspects of community care and patient characteristics (such as comorbidities) that may differ from the clinical trial setting. She pointed out the variability that is displayed in some samples of patient-reported outcomes. She noted that the data serve as a reminder that patients need quantitative estimates of the impact

of their disease and the treatments they receive on the various domains of health outcomes, both biologically oriented and patient-centered health outcomes. In conclusion, Dr. Chrischilles showed a listing of other research questions being investigated by about 50 CanCORS working groups, including how well physicians help patients plan for end of life.

Current Status, Lessons Learned. Dr. David Harrington, Professor and Chair, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, and CanCORS Biostatistician, presented an update on the study status in the areas of administration and patient participation. Along with the report on status and enrollment, his remarks included a discussion on lessons learned about enrolling a newly diagnosed cohort, enrolling minorities and the elderly, and identifying potential participants. Dr. Harrington stated that there was a delay in getting to the field with the baseline interview because no national infrastructure existed for capturing incident cases and talking with the patients in large numbers. Moreover, no available instrument was as comprehensive as needed. He presented the enrollment numbers for participants in both disease categories, and pointed out that they are on track with projections and goals for the most part. Response rates for the followup interviews are expected to be very good because of the diversity of instruments planned. Medical record abstraction did not start when planned and projections are that numbers will be lower than the goal because of the effects of the Health Insurance Portability and Accountability Act (HIPAA) as they relate to patient consent. Steps to address this include working with IRBs on the possibility of reviewing records of deceased patients who had not refused to participate in the study. Physician survey numbers are higher than expected because more physicians are involved than initially estimated.

Dr. Harrington reviewed enrollment numbers for patients with lung cancer as of June 2005. Of the 12,836 cases that were ascertained, the enrollment rate after the baseline interview was 53 percent, or 8,294 patients. Of the 7,735 who were found to be eligible after contact, 4,406 were successfully enrolled for participation, for an interview rate of 57 percent. Similarly, the enrollment rate for 12,691 ascertained cases CRC was 55 percent and the interview rate was 58 percent. Dr. Harrington attributed the similarity of these numbers to the wide array of instruments that were fielded for the baseline interview, which made it possible to interview people

in any setting. Without the extensive design period to ensure good mapping between all of these instruments, a significant portion of patients with lung cancer might have been lost because of their burden of disease at the time of enrollment (4 months after diagnosis).

In a comparison of CanCORS, national (SEER), and clinical trials in the Eastern Cooperative Oncology Group (ECOG) enrollment figures for the elderly, Dr. Harrington pointed out that the CanCORS lung cancer cohort at diagnosis is slightly younger than the national group, but much closer to the national age than the ECOG clinical trials group. The differences are more dramatic in those over 86 years of age: the CanCORS cohort is 3 percent of the total, the national group is about 7 percent of the total, and the ECOG clinical trials group is 0.1 percent of the total. The findings are similar in the comparison of median ages for the CRC cohorts in the same three groups.

Dr. Harrington concluded with a review of other lessons learned since initiation of CanCORS. He stated that it has been found that interviewers need special support in this difficult study.

New Directions and Potential Next Steps. Dr. Robert Sandler, Chief, Gastrointestinal (GI) Service, University of North Carolina (UNC), Chapel Hill, and Principal Investigator at the UNC CanCORS site, discussed how the CanCORS instruments and infrastructure are being leveraged to attract independent funding for additional research. In an ancillary project to the UNC core study, tumor blocks and blood specimens were collected. That project was leveraged to obtain additional funding through the GI SPORE mechanism to investigate prognostic and predictive factors that make it possible to tailor therapy for greater benefits and reduced cost. The rationale for the study was that molecular characteristics of tumors might explain racial disparities in CRC mortality as much as the processes of care might.

Dr. Sandler then reported on the new Caregivers Survey, which was added to the list of CanCORS data sources. Funded through an NCI supplement, the Caregivers Survey has the specific aim of evaluating the impact of cancer care on caregivers, as well as the impact of caregivers on outcomes and quality of life. The methodology involves surveying caregivers recruited during the baseline survey. By acting on this new opportunity, the study will

provide data that would not otherwise be collected in the core study, with minimal burden to respondents. Dr. Sandler described the linkage with Medicare as another opportunity that has been exploited in CanCORS. Initially supported through an NCI grant to a Harvard University investigator looking at end-of-life issues, the linkage was subsequently extended and expanded with additional funds received from the CDC to develop user-friendly analytical files and to conduct a pilot study using the linked data. Medicare claims data for the period 2002 to 2006 for CanCORS cohort members, CanCORS nonresponders, and cancer patients from CanCORS areas will be mined to determine how representative the cohort is of the base population. From the linked data, it will be possible to study health care use, treatments and their consequences, and the costs of cancer care.

Dr. Sandler discussed the opportunity that CanCORS investigators have to study cancer care dynamics. New drugs like Tarceva® and Avastin® could have profound implications for cancer outcomes and cost of care. CanCORS presents a unique opportunity to understand the diffusion of these new treatments into the community; identify age, race, or geographic disparities in their application; and examine their costs. A second wave of CanCORS data collection could capitalize on the original experiment and permit before-and-after comparisons. Dr. Sandler called attention to the fact that the 14-month followup interval from the time of diagnosis specified in the CanCORS initiative does not address the importance of knowing longer term outcomes. Longer term followup would permit better understanding of the issues related to disease-free survival, cancer-related deaths, and longer term quality of life.

Dr. Sandler concluded by summarizing new directions and potential next steps that would be possible if a new cohort were enrolled. With existing cohorts, the first phase of CanCORS will deliver on the promise to answer important questions related to treatment choice, treatment decisions, disparities, and trial participation. With existing cohorts, it will be possible to understand the impact of treatment on longer term outcomes across populations, as well as quality of care (QOC) and survivorship. With a second cohort, it would be possible to expand understanding of disparities, dissemination, the cost of new therapies, and the importance of biological factors on treatment and prognosis.

In discussion, the following points were made:

- Even though it is apparent that the CanCORS cohort is population-based as originally envisioned, it is not clear that it presents a balanced and representative picture of the total population.

- The study will have objective measures for the QOC received, not just the patients' opinion about whether they receive quality care.

- The study objectives will not be compromised by the absence of the proportion of potential participants who are non-responders.

- Efforts are taken to ensure the reliability and validity of the questions of quantity of life versus quality of life versus cost in the patient interview.

top

XIII. STATUS REPORT: NATIONAL BIOSPECIMEN NETWORK—DRS. ANNA BARKER, JULIE SCHNEIDER, AND CAROLYN COMPTON

Dr. Barker reminded members that the NCI has been addressing the range of issues surrounding biospecimen repositories. These include ethical issues discussed at a previous BSA meeting, issues surrounding intellectual property that are evolving out of biospecimen banking, issues surrounding access, and a whole range of informed consent issues relative to HIPAA. Added to these are the new sets of problems related to research in the post-genomics era, how to pay for the repositories, and patients' rights relative to ownership of and access to the biospecimens. Another set of issues to be addressed relates to how biospecimens are to be collected, maintained, and stored, and what is expected of the banks that are being built. Dr. Barker noted that the NCI in concert with the cancer research community contributed to developing the National Biospecimen Network, a plan for beginning to analyze how to ensure that biospecimen repositories are positioned to support "big science" as well as R01 science. In addition, the NCI, responding

to a BSA request, conducted a meta-analysis of its resources, the results of which were reported at a previous Board meeting. Dr. Barker stated that the NCI, at the request of the BSA, has established a trans-Institute Biospecimen Coordinating Committee (BCC) to address issues related to NCI-funded biospecimen repositories. Two biorepository-related workshops will be held later during the summer. Workshop recommendations will be reported to the NCAB in September and the BSA in November.

As background and rationale for the workshops, Dr. Julie Schneider, Technology Program Manager,Office of Technology and Industrial Relations, NCI, reminded members of the importance of biorepositories and the need for high-quality specimens and data in the era of molecular medicine. Scientists need biorepositories for the following reasons to: 1) manage and apply large amounts of molecular and clinical data, 2) develop a molecular-based taxonomy for cancer to support the development of targeted drugs, 3) help identify new uses for existing targeted drugs, and 4) accelerate the era of personalized medicine. In addition, a recent report by the RAND Corporation has suggested that, for the many millions and steadily increasing numbers of biospecimens currently stored in the United States, a relevant issue is harmonization in terms of how these specimens are collected, stored, and consented. Several lines of evidence have suggested that this is becoming a major barrier to advancing the science of genomics and proteomics. The focus of these workshops, therefore, will be developing common policies and principles for NCI-supported biorepository resources.

Dr. Schneider briefly reviewed the findings of the earlier NCI Biorepository Report, which provided an overview of the larger repositories over which the NCI exercises some degree of program management. Those findings were that: 1) NCI's annual investment in these larger repositories was more than $50 M; 2) the programs collected and stored more than 4 million specimens in fiscal year (FY) 2003; 3) the specimens support both genomic and proteomic research, but the repositories lack common operating standards and quality-control measures; 4) there is no common database for the programs nor any way to define access or track specimens; and 5) there is a tremendous heterogeneity in the types of research these repositories support. Dr. Schneider explained that the BCC has the task of improving the harmonization of these repositories and has planned two workshops toward that end. The first workshop

focused on ethical, legal, and policy (ELP) issues surrounding biorepositories; the second will address technical issues relating to the collection, processing, storage, and dissemination of specimens. The BCC will develop a set of recommendations to be presented to the NCAB in September. Dr. Schneider emphasized that the biorepository meta-analysis and workshops are only the beginning of a longer term process that will involve, at the outset, making the recommendations available for public comment.

Dr. Carolyn Compton, Director of National Biospecimen Research, OD, NCI, continued the update by providing greater detail about the workshops. The ELP workshop, which was held on June 23-24, addressed issues related to informed consent, privacy/ confidentiality and data security, IRBs, ownership, and access to biospecimens and data. With Dr. Arthur Caplan, University of Pennsylvania Bioethicist, and Dr. Rihab Yassin, BCC member, as Co-Chairs, the ELP workshop included participants from academia and industry, lawyers, IRB experts, patient advocates, and researchers. Also included were representatives from all NIH Institutes and Centers that fund biorepositories and biorepository-based research. Dr. Compton noted that the NCI has formulated the following assumptions as to the essence of the best biorepository: 1) the biospecimen's value is related to the physical quality of the specimen and its associated clinical data, as well as to the ethical, legal, and regulatory limitations on its access and use; 2) biobanking practices are, to some degree, specific to the type of specimen and the type of scientific analysis the specimen will undergo; and 3) the best biobanking practices are data driven.

Experts from the academic, government, and private sector communities will address the biospecimen collection process (BCP) at the second workshop to be held on July 18-20. The goal is to derive guidelines that will inform best practices to harmonize biorepositories across the country and serve as a framework into which new knowledge can be inserted for emerging initiatives such as the human cancer genome sequencing and proteomics projects. Dr. Compton noted that this effort to establish best practices will contribute to the work of the National Biospecimen Network.

In discussion, the following points were made:

- The role of the BSA, which represents a cross-section of those who work with biorepositories, will be to help shape

the final set of harmonization recommendations and provide advice on their implementation in the cancer research community. The BSA also should be at the table during the planned fall summit with other countries that now have central biospecimen harmonization approaches and that are requesting an interface with the NCI.

- Another important issue associated with biorepositories is the lack of information about the patients who contribute tissue, not only in the sense of annotation, but also in terms of how they were sampled. Therefore, standardization should extend to obtaining information on the identity of contributors, whether they were a convenience sample, and parameters of the sampling frame.

- Compliance with the final set of standard operating procedures that are developed relative to biospecimen collection, storage, and access should be mandatory for all NCI-funded initiatives.

- An issue is emerging regarding the requests by the private sector to purchase biospecimens that have been obtained through NCI-funded tissue retrieval services. Criteria should be developed by which data and samples are shared with academic and NCI-funded institutions, inasmuch as using the biorepositories for good research purposes as early as possible provides the greatest return on the invested dollar.

- Topics that should be included in the discussion at the biospecimen collection workshop are: 1) the need for a rigorous review process to ensure the quality of banked specimens; 2) what tissue samples are needed and what informational units should be preserved; 3) the emerging need for international criteria for collecting and preserving samples, biobanking, and the associated bioinformatics to facilitate exchange across nations; and 4) ensuring that the quality of the specimen and its data are matched to the question being asked when access to publicly funded specimen biobanks is claimed.

- An Ad Hoc Subcommittee of the BSA, co-chaired by Dr. Richard Schilsky, Professor of Medicine, University of

Chicago, and Ms. Paula Kim, President, Paula Kim Consulting, will be convened at the conclusion of the two workshops with the role of participating in the recommendation review process.

top

XIV. TUMOR MICROENVIRONMENT MINI-SYMPOSIUM—DRS. DINAH SINGER, SURESH MOHLA, JOAN BRUGGE, AND KENNETH ANDERSON

As background for the mini-symposium, Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), NCI, reminded members that the DCB conducted an assessment of the status of cancer biology research across the entire spectrum of initiation, progression, and metastases. The goal was to identify emerging concepts and promising new ideas in each of those areas. To that end, a series of think tanks were sponsored to determine the status within specific segments of cancer biology research and to solicit expert opinion on directions the NCI could take to facilitate progress in those areas and in the basic understanding of cancer biology. Scientific areas covered in the think tank workshops included susceptibility, etiology, inflammation, epigenetics, tumor immunology, cell death and proliferation, tumor stem cells, and tumor microenvironment. Workshop participants were charged to identify major challenges and opportunities within their areas of expertise and make specific recommendations to address them. The think tank report has been published and posted on the DCB Web Site.

Dr. Singer stated that an overarching theme that emerged from the insights and recommendations specific to each area was the need to understand the tumor microenvironment, its composition, and its function both normally and within the context of the tumor, and how the tumor and its microenvironment interact. In an initial response to think tank recommendations, the NCI established a hands-on program that is expected to train up to 100 investigators in techniques associated with various aspects of studying the tumor microenvironment. Responses to other recommendations are being developed, with particular attention to integrating the recommendations from all of the think tanks into a common approach. Dr. Singer noted that the speakers invited to bring the

topic of tumor microenvironment before the BSA are major contributors in the field and were participants in that think tank.

Dr. Suresh Mohla, Chief, Tumor Biology and Metastasis Branch, DCB, NCI, introduced Drs. Joan Brugge, Department of Cell Biology, Harvard Medical School, and Dr. Kenneth Anderson, Director, Jerome Lipper Multiple Myeloma Center, Medical Director, Kraft Family Donor Center, Kraft Family Professor of Medicine, Harvard Medical School.

The Tumor Microenvironment: A Critical Component of Tumor Progression and Metastasis and a Target for Therapeutic Intervention. Dr. Brugge began by contrasting the former and current views about cancer initiation and progression. Tumors were formerly viewed as autonomous cell masses whose progression is driven by epigenetic alterations in the genome of the tumor cells themselves. The current view is that tumors are "organs" composed of many interdependent cell types that contribute to tumor development and metastasis. This has led to a greater appreciation for the role of the tumor microenvironment and the understanding that the cross talk between the neoplastic cells and the cells within the microenvironment is responsible for the evolution of the tumor and progression toward metastasis. Dr. Brugge highlighted important contributions by researchers in this area; cited studies that illustrated that the microenvironment can exert both positive and negative influences on tumors; and highlighted a few important workshop themes related to the tumor-promoting influence of the microenvironment.

Dr. Brugge told members that studies of inflammatory cells and their influence on tumor progression have produced a significant increase in data in this research area. She cited the work of Dr. J.W. Pollard's laboratory at Albert Einstein Medical Center as paradigm-setting, which showed that inflammatory cells are important for the evolution and development of the normal mammary gland together with interactions with the basement membrane, fibroblasts, and fat cells in the microenvironment. She noted that these studies strongly implicate macrophages in the development of invasive and metastatic lesions and are possibly the clearest model for demonstrating the role of inflammatory cells in the development of tumors. She summarized their functions as promoters in early stages of tumor development and promoters of metastasis in late stages. As a final example of tumor-promoting factors in the

microenvironment, Dr. Brugge noted that there is evidence supporting the influence of stromal cells (fibroblasts and other mesenchymal cells) on tumor progression.

Dr. Brugge concluded the microenvironment presentation with a discussion on tumor metastasis. She credited Dr. Steven Paget as the first to recognize the role of the microenvironment of tumor cells. In 1889, he proposed a seed and soil hypothesis stating that the growth of tumors outside the primary tumor site is dependent not only on the tumor cells having metastatic activity, but also on being placed in the right soil in which to develop. She presented research examples illustrating that at every stage in the metastatic sequences, there are critical interactions with the tumor microenvironment that are essential to allow and facilitate the metastases to distant sites. Findings from these studies suggested that there are important influences in the microenvironment, but as Dr. Brugge pointed out, investigators are now in a position to start identifying specific factors that are responsible. As an example of this type of research, Dr. Joan Massague's research on defining the molecular basis of site-specific metastasis was cited.

To suggest the opportunity inherent in targeting the microenvironment, Dr. Brugge stated that think tank participants believe that understanding the tumor microenvironment will: 1) lead to the development of therapeutics that significantly increase tumor cell killing ability or suppress growth and invasion, 2) reduce the likelihood of drug resistance development because the microenvironment cells are not as genetically unstable and plastic as the tumor cells, and 3) lead to diagnostic tests that assess the state of the microenvironment for evidence of predisposition to tumor or for outcome of tumor.

Dr. Brugge concluded this portion of the mini-symposium with a review of the three workshops in the area of the microenvironment and of the recommendations that resulted from them. The panel of experts included not only the stakeholders but also many who work in other areas of tumor biology, broad perspectives were represented and recommendations were well conceived and logical. The panel was given the charge to identify strategies that: 1) would define the role of the tumor microenvironment in tumor initiation, progression, and metastasis; 2) could use the information to develop applications that will impact the diagnosis, prevention, and treatment of cancer; and 3) whereby the NCI can facilitate the

acquisition of this information and its application. Key questions to be addressed were what information would facilitate diagnosis, prevention, and treatment, and how this information could be used.

The panel recommended that the initial goal of preclinical studies be to further the understanding of how the tumor microenvironment contributes to tumor cell progression and metastasis by identifying in Stage I the key components and defining how they are altered during tumor development. In Stage II, research should determine which alterations in the tumor microenvironment are critically involved in tumor development, progression, and metastasis and elucidate the mechanisms responsible for induction of these changes. Research in Stage III focusing on translation should develop therapeutic strategies to target the microenvironment, develop diagnostic tests to predict outcome and/or design treatment, and develop strategies to prevent the development of tumors based on understanding the microenvironment changes required for tumor development. Recommendations for funding these initiatives were presented.

Targeting Myeloma in the Bone Marrow Microenvironment. Dr. Anderson informed members that myeloma is thought of as a model for the microenvironment. In 1998, thalidomide came into new use in myeloma because of its anti-angiogenic activity. Subsequent laboratory studies showed that the drug also acted directly against myeloma cells by inhibiting cytokine production in the bone marrow microenvironment. The paradigm that myeloma represents is for starting with a novel drug such as thalidomide in the advanced disease setting (relapsed refractory patients), quickly combining it with other therapies such as Decadron®, and using it in a frontline setting. Dr. Anderson reminded members that the steps for rapidly moving a novel drug from bench to bedside are target identification using models of the tumor in the microenvironment; validation of targets in vitro and in animal models; and translation of the therapy through Phase I, II, and III clinical trials. He pointed out that three novel myeloma therapies—thalidomide, Revlimid®, and bortezomib—were developed within the past 5-7 years following that strategy. He emphasized the importance of teamwork in the research efforts that involved investigators from academia, NCI, FDA, and the pharmaceutical industry as well as the patients and their advocates. These drugs target both the tumor and the microenvironment and highlight the importance of studying the tumor in the microenvironment.

Dr. Anderson described the target as cell adhesion-mediated drug resistance that is conferred both by cell-cell contact and by the secondary induction of cytokines, which further growth survival and drug resistance in the bone marrow. The mechanism of how thalidomide and Revlimid® act to induce apoptosis of the drug-resistant myeloma cells and thereby overcome intrinsic resistance was described.

Dr. Anderson also described the ECOG Study, in which thalidomide advanced rapidly from bench to bedside in a two-arm study of thalidomide plus Decadron® (dexameth) versus Decadron® alone. A statistically significant increase in response was seen when thalidomide was added to the traditional Decadron® therapy. The combination has become the most common regimen for treating myeloma patients who are eligible for bone marrow transplant. He noted that Revlimid®, an oral form of a more potent thalidomide-like drug, produced results that are even more exciting.

As a final example of rapid bench-to-bedside translation, Dr. Anderson reviewed the discovery and development history of bortezomib, a proteosome inhibitor. Much like thalidomide and Revlimid® bortezomib can kill myeloma cells directly in laboratory models and can overcome intrinsic drug resistance. Of greater interest as a microenvironment paradigm is bortezomib's ability to downregulate adhesion molecules on both the tumor and the stroma. It blocks constitutive and myeloma cell binding-induced transcription and cytokine secretion and it inhibits angiogenesis. Bortezomib's myeloma history began in 2000, when a Phase I trial showed that it was safe and suggested that it mediated anti-myeloma activity. A multi-center Phase II trial was launched in 2001, in which one-third of the patients responded, including complete and durable responses. FDA accelerated approval was granted in May 2003, based on the Phase II trial, and a Phase III trial of Decadron® versus bortezomib (Velcade®) was initiated in 660 patients with relapse myeloma, slightly earlier in the disease course. The trial was unblinded early because of the statistically significant increase in time to progression seen in patients on bortezomib. Dr. Anderson commented that this incident illustrates the importance of collaborations, in this case with the FDA. This was the first FDA acceptance of time to progression as a surrogate endpoint, an action that has the potential to accelerate

clinical trials. Subsequent survival curves in the patients who received bortezomib versus Decadron® provided validation that a statistically significant improvement in time to progression at 1 year did predict for survival.

Dr. Anderson reported that the next step was to combine bortezomib and Decadron® as a frontline therapy. The results were that 25 percent of the patients have had a complete or near-complete response and another two-thirds have had a partial response. The goal now is to combine drugs based on three principles: 1) enhance cytotoxicity, 2) avoid drug resistance, and 3) combine drugs that produce a more favorable side effect. Dr. Anderson briefly reviewed the science on which drugs are being combined for greater efficacy. Dr. Anderson expressed the view that combination therapies using proteosome inhibitors and aggresome inhibitors are the future of myeloma research because they have been shown to work in myeloma, in part, by blocking the degradation of ubiquinated, mutated, and misfolded protein. Dr. Anderson noted that normal cells use the aggresome garbage disposal system very little if at all, so there is a huge therapeutic index.

In summary, Dr. Anderson stated that the new paradigm for multiple myeloma therapies is to target the tumor cell in the bone marrow microenvironment. The other aspect of the paradigm is that science, through microarray profiling, signaling, and proteomics, can inform how drugs work and how clinical trials can be designed. He emphasized the importance of the team approach between laboratory and clinical components for accelerating the translation of new drugs to the bedside. He expressed the view that successes like Revlimid® and bortezomib should and could happen every day with teamwork involving academia, industry, the NCI, FDA, and patients.

In discussion, the following points were made:

- Close cooperation should be maintained between the cancer and developmental biology communities inasmuch as many of the microenvironment concepts evolved from developmental biology.

- The study section dealing with the microenvironment

contributed much to the successes achieved over the past few years in this area; therefore, future teams should include investigators funded through individual R01s.

top

XV. ADJOURNMENT—DR. ROBERT YOUNG

There being no further business, the 31st regular meeting of the Board of Scientific Advisors was adjourned at 12:35 p.m. on Tuesday, June 28, 2005.

top