**NATIONAL CANCER ADVISORY BOARD**

convened on December 8-9, 1998, at the:
National Institutes of Health
Building 31-C, Conference Room 10
Bethesda, Maryland 20892

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## ATTENDEES

**The National Cancer Advisory Board (NCAB) convened for its 108th regular meeting at 9:00 a.m., December 8-9, 1998, in Conference Room 10, C Wing, Building 31, National Institutes of Health.**

**NCAB Members**
Dr. J. Michael Bishop (Chairperson)
Dr. Richard J. Boxer
Dr. Kay Dickersin
Dr. Alfred L. Goldson
Dr. Elmer E. Huerta
Dr. Frederick P. Li

**President's Cancer Panel**
Dr. Harold P. Freeman (Chairperson)
Dr. Paul Calabresi
Ms. Frances Visco (absent)

**Alternate Ex Officio NCAB Members**
Dr. Steven K. Akiyama, NIEHS
Col. Louis E. Diehl, DoD (absent)

Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis
Dr. Amelie G. Ramirez
Dr. Ivor Royston
Dr. Philip S. Schein
Dr. Phillip A. Sharp
Ms. Ellen L. Stovall
Dr. Vainutis K. Vaitkevicius

Col. Louis F. Diehl, DoD (absent)
Dr. Michael Hodgson, NIOSH
Dr. Peter Kirchner, DOE
Ms. Rachel Levinson, OSTP (absent)
Dr. Alison Martin, FDA
Dr. Angela Auletta, EPA
Dr. Lakshmi C. Mishra, CPSC (absent)
Dr. T. G. Patel, DVA
Dr. Eugene Schwartz, DOL (absent)
Dr. Michael Viola, DOE

**Members, Executive Committee, National Cancer Institute, NIH**

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Ms. MaryAnn Guerra, Deputy Director for Management
Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis
Dr. Norka Ruiz Bravo, Acting Director, Division of Cancer Biology
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. George Vande Woude, Director, Division of Basic Sciences
Dr. Margaret Tucker, Chairperson, Intramural Advisory Board, Board of Scientific Counselors
Dr. Edward Harlow, External Advisor, Office of Science Policy; Member, Massachusetts General Hospital
Dr. Martin Abeloff, External Advisor and Co-Chair, Clinical Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor and Director, Johns Hopkins Oncology Center
Dr. David Livingston, External Advisor, Chairperson of the NCI Extramural Board of Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
Dr. Matthew Scharff, External Advisor and Co-Chair, Basic Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor, Albert Einstein College of Medicine
Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer Epidemiology and Genetics; Acting Director, Intramural Genetics Program; Senior Member, The Institute for Cancer Research, Fox Chase Cancer Center
Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel

**Liaison Representatives**

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Margaret Foti, American Association for Cancer Research
Dr. Marc E. Lippman, American Association for Cancer Research

Dr. Robert Martuzza, American Association of Neurological Surgeons
Ms. Kerrie B. Wilson, American Cancer Society
Dr. John Stevens, American Cancer Society
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Eli Glatstein, American Society of Therapeutic Radiologists
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Laura Liebermann, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Dr. Armin D. Weinberg, Intercultural Cancer Council
Ms. Katharine R. Boyce, Intercultural Cancer Council
Ms. Martha M. Kendrick, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Ms. Dorothy J. Lamont, National Cancer Institute of Canada
Dr. Robert A. Phillips, National Cancer Institute of Canada
Dr. Tracy M. Walton, Jr., National Medical Association
Dr. Eve I. Barak, National Science Foundation
Ms. Pamela Haylock, Oncology Nursing Society
Dr. Linda U. Krebs, Oncology Nursing Society
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.
Dr. Marston Linehan, Society of Urologic Oncology

## CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETINGS

Dr. J. Michael Bishop

Dr. Michael Bishop called to order the 108th meeting of the National Cancer Advisory Board (NCAB) and introduced guests representing cancer education, research, and advocacy associations. He welcomed members of the public and the press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the September 1998 meeting. They were approved by the Board unanimously. Dr. Richard Klausner, Director, National Cancer Institute (NCI), announced the names of the six new appointees to the NCAB and gave a brief biographical sketch of each new nominee: Dr. Elmer Huerta, Dr. Susan M. Love, Mr. James McGreevey, Dr. Arthur Nienhuis, Dr. Larry Norton, and Dr. Amelie Ramirez.

## FUTURE BOARD MEETING DATES

Dr. J. Michael Bishop

Dr. Bishop called Board members' attention to the meeting dates listed in the agenda. Dates have been confirmed through the year 2000.

# REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE
Dr. Richard Klausner

**FY99 Budget.** Dr. Klausner began by noting that, since the previous NCAB meeting, the FY99 budget was passed by Congress and signed by the President. The NIH received a $2.03B increase and the NCI received a $384M increase (15.1% increase). There will be an increase of approximately 22 percent in the Research Project Grant (RPG) pool for new and competing grants (representing an additional 230 new and competing grants), with an overall success rate of about 33 percent.
There will be an estimated 28 percent increase in R01s (funding an additional 170-175 grants) resulting in a total of about 880 new grants (versus 700 in FY98). These increases will be achieved at the same pay line (the 24th percentile for R01s). The cutoff lines for Accelerated Executive Review (AER) will be raised to the 35th percentile for patient-oriented research and to the 30th percentile for all other R01s. The size and number of P01 requests have increased; the pay line will remain at a priority score of 135; funding will increase by 16 percent; and the estimated success rate will be about 41 percent. An additional $8M has been set aside in the R01 pool to replace the discontinued R29; and the R21—particularly the R21/R33 phased innovation award—represents a growing area with approximately 77 awards totaling $11M.

**Training and Career Development.** Dr. Klausner reported a 28 percent increase in funding from $87M to almost $112M—the largest ever increase—as a result of a 2-year reconfiguration. The number of research career trainees will increase from 276 to 351 with a 27 percent increase in numbers and a 57 percent increase in dollars. Dr. Klausner discussed the new K22 transition award—that is waiting for NIH approval—to be funded in FY02. The revised training program includes new tracks for basic science, population science, and behavioral science and the number of the National Research Service Award (NRSA) trainees remains at 1,672, but the stipends will increase by 25 percent. Dr. Klausner asked that the Board develop a new name for the currently titled "K24" award.

**Clinical Trials.** Dr. Klausner announced a 23 percent increase for clinical trials, both for treatment and for prevention, an additional $8-10M for new pilot projects, and noted that efforts are underway to restructure and streamline clinical trials activities—central to this effort is the provision of an informatics infrastructure. The NCI plans to spend approximately $10M in FY99 for clinical research and clinical trials to develop the National Cancer Informatics Infrastructure—a national network that will include a component that will provide access to clinical trials support for physicians and patients.

**Tissue Access.** Dr. Klausner cited a need to ensure that researchers with the best ideas are able to collaborate with the NCI-funded entities and to have access to tissues. Efforts are underway to: develop new funding approaches; create greater awareness of available resources; develop collaborations; streamline funding for collaborative research; develop a tissue access system that is available through the Web; create and advertise the position of Tissue Expediter; and modify the Informed Consent procedure.

**Prevention.** Dr. Klausner reported a 23 percent increase in the funding of prevention trials—independent of the $15M increase for followup to large clinical trials already in place. He reviewed efforts to improve the clinical trials system, the ongoing successful initiative to revise the informed consent process, changes in the Institutional Review Boards (IRBs), the new CSR clinical study section, and training programs. In addition, he discussed the NCI's efforts to establish a central IRB to review all Phase II and Phase III protocols submitted to the Cancer Therapy Evaluation Program (CTEP) with a trial project with the Cancer Acute Leukemia Group-B (CALGB)

**Results of Clinical Trials.** Dr. Klausner reviewed the results of several clinical trials from the past year: the National Surgical Adjuvant Breast and Bowel Program (NSABP)/B13 and B14 studies of early breast; a trial of nasopharyngeal cancer; the Children's Cancer Group Study; a study of 13-cis- retinoic acid in the treatment of childhood neuroblastoma; a trial of the inclusion of adriamycin in women with breast cancer; and another study from the NSABP in which women were given preoperative chemotherapy followed by post-operative adjuvant therapy.

**The Cancer Genome Anatomy Project (CGAP).** Dr. Klausner reported that CGAP was going well—between 350,000-400,000 sequences have been identified to date. The rate of gene discovery remains linear—about 11,000-12,000 genes have been discovered in the past year.

**The Director's Challenge.** Dr. Klausner announced the creation of the new funding initiative "The Director's Challenge" and its goal is to move from pathologic diagnosis to molecular classification schemes. The initiative will be funded at a total long-term cost of approximately $50M and will allow access to the genetic resources of CGAP.

**The Early Detection Research Network.** The Board of Scientific Advisors (BSA) has approved the development of an Early Detection Research Network, whose goal is to link biomarker development laboratories with validation laboratories. The Early Detection Research Network will develop experiments and fund research into analytic tools, decisionmaking processes, as well as establish accepted criteria for tests.

**The Rapid Access to Intervention Development (RAID) Program.** The RAID program is designed to speed the movement of ideas from the laboratory to therapeutic intervention. Dr. Klausner reported that the first round of evaluation of RAID applications has been completed, about 30 applications were received, and that a funding plan will be presented at the next NCAB meeting. Rapid Access to Prevention Intervention Development (RAPID), a program analogous to RAID, has been developed for the peer-review open competition of developmental funds for preventive compounds.

**Cancer Control.** Dr. Klausner stated that approximately $30M new dollars will be provided to the Division of Cancer Control and Population Sciences (DCCPS) to support new initiatives with special increases in surveillance studies, behavioral research, and tobacco. Also, the Tobacco Research Implementation Group (TRIG) had identified nine high-priority areas for further work, the most important being centers for

transdisciplinary tobacco research. The NCI will provide $50M in funding for these centers over the next 5 years. The centers will provide training, serve as a venue for collaboration for international studies, and create a new science-based/research-based program in multidisciplinary approaches to tobacco research. A second tobacco-related initiative, funded at $72M over four years, will involve state and community tobacco control intervention research—one of the goals of this program is to link independent and Center for Disease Control and Prevention (CDC) researchers with state tobacco control officers.

**Surveillance.** Scheduled for release within the next few months is the annual report on cancer statistics that the NCI, the American Cancer Society, CDC, and the National Center for Health Statistics have been developing. Also, the Division of Cancer Epidemiology and Genetics is preparing the 25-year update of the county-by-county cancer mortality maps.

**Research in Special Populations.** The Office of Special Populations is preparing booklets and Web-based information related to minorities, underserved populations, opportunities for research and training, and questions about the burden of cancer across society. A report from this Office will be presented at the next NCAB meeting. In addition, Dr. Klausner noted that the NCAB is awaiting the Institute of Medicine (IOM) report on research and minorities.

**Board of Scientific Advisors.** Dr. Klausner noted that the BSA has approved a program examining leadership initiatives aimed at fostering cancer awareness and community-based educational activities, and promoting research and participation in minority communities. This expanded endeavor will be funded with $30M new dollars over 5 years and differs from its predecessors in several ways (e.g., the number of minority groups will be expanded and it will provide opportunities for multisite projects as well as small-scale projects targeting one or more regions).

**Intramural Research Program.** Dr. Klausner stated that the Intramural Research Program (IRP) will receive approximately $20M new dollars in FY99 (a 3-4 % increase). The IRP overall budget has declined to 15.7 percent of the NCI budget, which is close to the Bishop-Calabresi Report recommendation. He noted that there have been significant cost reductions within the IRP while spirit and function have improved. Recruiting in the Intramural Program, particularly in the clinical sciences, has been successful and he noted that Dr. Norman Coleman, Harvard University, will be coming to the NCI to head the Intramural Radiation Oncology Program. Dr. Klausner stated that plans are underway to create a national center for technology assessment within the IRP.

**Communication.** Dr. Klausner noted that previously, Dr. Philip Schein had raised a number of helpful questions regarding communication of the NCI's initiatives and that there is an ongoing effort in this area (e.g., the development of a "proto-pamphlet" describing these initiatives, a Web-based communication mechanism). These efforts are underway with the cooperation from professional societies and are relevant to the

extraordinary opportunities expressed in the Bypass Budget and will further communicate the NCI's efforts and activities to the scientific community.

**Bypass Budget.** Dr. Klausner reported that about 30 new opportunities have arisen as a result of the Bypass Budget and solicited suggestions for the FY01 Bypass Budget. Dr. Klausner concluded his presentation by stating that decisions will be made later in the month concerning new opportunities for the next 3-year Budget cycle.

## QUESTIONS AND ANSWERS

Dr. Bishop asked Dr. Klausner to comment on the potential overlap between private sector efforts at gene mapping and those of CGAP. Dr. Klausner stated that the potential for overlap did exist, but the true content of private databases is usually unknown and the lack of availability of private databases to the broader research community to some extent renders them functionally nonexistent. Dr. Klausner added that discussion is continuing with a variety of private companies regarding access to their databases. Dr. Phillip Sharp asked about budget increases for clinical versus basic science. Dr. Klausner stated that over half of the increase was for (primarily clinical) training or clinical and patient-oriented research and noted that efforts to categorize activities as clinical or basic research can often be difficult.

Dr. Kay Dickersin raised the issue of training awards for non-basic science Ph.D.s—particularly people in public health. Dr. Klausner commented that the non-K and R-type awards are used for this purpose—and those mechanisms are expanding. Dr. Dickersin then asked if the K-type awards are available for public health prevention researchers. Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), stated that K-awards are available for prevention researchers—but there is not a big pool of applicants for these awards—and the major research institutes are not necessarily encouraging applications in those areas. Dr. Greenwald added that the R25 has been a successful initiative to support cancer control and prevention. Dr. Dickersin noted that the applicant pool may be low because individuals believe they do not have access to such awards and suggested that the Board be provided more information concerning training opportunities for persons in public health.

Ms. Ellen Stovall commented that she was pleased with the recruitment to the NCI of Dr. Norman Coleman and asked whether there had been any consideration of collaboration with such entities as the Robert Wood Johnson Foundation. Dr. Klausner replied that such collaboration is ongoing. Dr. T. G. Patel asked whether it would be possible to increase or streamline the collaborative efforts between the NCI and the Veterans Administration (VA). Dr. Klausner commented that a meeting should be arranged with the VA to examine how this might be accomplished.

## LEGISTLATIVE UPDATE
Ms. Dorothy Foellmer

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities (OLCA), updated the Board on final events of the 105th Congress. Ms. Foellmer reviewed the results of the November election for both the House and the Senate, remarked upon the increase in NCI and NIH funding, and noted Congressional areas of interest with respect to NIH and NCI activities (e.g., the report on cancer among minorities and studies of thyroid cancer and leukemia resulting from the Chernobyl accident). Ms. Foellmer pointed out that the maximum reimbursement rate for grantees has been changed to Executive Level III ($125,900). She noted that there is a requirement that the Office of Management and Budget (OMB) modify regulations (OMB A-110) to require that federal agencies making funding awards mandate that all data produced under the awards be made available to the public through the Freedom of Information Act (FOIA). This provision has profound implications for the grantee and research community. Ms. Foellmer concluded her report by noting issues that may arise in the 106th Congress: the patient bill of rights, confidentiality and patient access to medical records, and the tobacco settlement. Dr. Klausner stated that Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), would next provide more detail concerning the OMB A-110 proposal.

## OMB A-110 IMPLICATIONS
### Dr. Marvin Kalt

Dr. Kalt reviewed the existing FOIA mechanism for obtaining the release of information under governmental control and noted how the change to OMB A-110 would extend the ability of an individual to request that the NIH ask for and receive data from the individual awardee. One troublesome issue is that the term "data" is not defined in the OMB A-110 modification. A "Notice of Proposed Rule- Making" regarding this initiative will be published in the *Federal Register* and a copy of the notice will be sent to NCAB members when it appears. Dr. Kalt suggested that the Board, as well as any professional organizations or institutions with which members may be affiliated, transmit their comments to the OMB. Dr. Kalt provided several illustrations of potential issues associated with the A-110 change and remarked that both awardees and the NIH would incur a cost in providing the information to the requestor.

## QUESTIONS AND ANSWERS

It was agreed that the OMB A-110 issue was appropriate for consideration as new business. Discussion among NCAB members centered on conflict between the A-110 initiative and existing laws on data ownership, the ambiguity inherent in the proposal—particularly the absence of a definition of the term "data,"—and the need to provide input to OMB in clarifying its terms. Dr. Kalt suggested that a response to the OMB proposal be issued as soon as the notice appears in the *Federal Register*. Dr. Robert Wittes, Deputy Director for Extramural Science (DDES), remarked that existing FOIA exemptions should be considered when preparing the Board's response. Dr. Sharp asked for comment on a report that congressional oversight would be sought relative to the large NIH and NCI budget increases and what efforts were being made to speak to a larger audience than Congress. Dr. Klausner responded that he had begun setting up

meetings with members of Congress and the appropriate committees in order to explain the NCI's priorities and that a variety of initiatives are under review and discussion. Dr. Klausner, responding to the earlier comments of Ms. Foellmer regarding issues of interest to Congress, added that the NCI prepares a response to all issues raised by Congress and that there were three areas of interest that were receiving special attention: prostate cancer research, the Cancer Information Service (CIS) report, and complementary and alternative cancer therapies.

## REPORT OF THE PRESIDENT'S CANCER PANEL
### Dr. Harold Freeman

Dr. Harold Freeman, Chair, President's Cancer Panel, presented a summary of the Panel's recent meeting addressing cancer prevention and control research in the 21st century. At the meeting, held in Tucson, AZ, the Panel heard from researchers who stressed the need to increase the resources devoted to cancer prevention and control. One theme developed at the meeting was that basic research creates opportunities for better prevention (e.g., chemoprevention). Also addressed at the meeting were lifestyle factors such as diet and physical activity, as studied from the molecular perspective, and how these factors may promote or protect against such cancers as breast or colon. The ability to identify at- risk individuals through the use of biomarkers was also addressed. The Panel also heard about future interventions designed for high-, moderate-, and low-risk groups—thus tailoring specific types of prevention to particular risk-determined target groups. The issue of ethnic and racial disparities in cancer was addressed (e.g., cervical cancer mortality among Hispanic women) as was the role of promising technologies (such as telemedicine). A challenge cited was the need to effectively communicate to the public the importance of adopting a healthy lifestyle. The Panel strongly believes that a balanced national cancer program should emphasize discovery, translation, and application of its findings to the population to this point, the medical oncology model has been the dominant paradigm. It was suggested that a new paradigm incorporate the concepts of preventive oncology. Such an approach would move from a reactive orientation to a proactive view, resulting in a change from an emphasis on "sick care" to "health care." The Panel is also developing its annual report to the President on quality of cancer care and cancer survivorship. Dr. Freeman concluded by mentioning that the Panel will examine, in its next three meetings, the National Cancer Program—using the Subcommittee to Evaluate the National Cancer Program (SENCAP) report as a reference point.

## QUESTIONS AND ANSWERS

Dr. Sharp asked Dr. Freeman to comment on the implementation of school-based programs dealing with lifestyle risks (e.g., tobacco, weight, etc.) that might be funded through tobacco settlement monies. Dr. Freeman replied that a wonderful opportunity existed for such activities but that additional research was necessary regarding what constituted the most effective programs. Dr. Klausner commented that it was not clear yet how the tobacco settlement monies would be used but that an opportunity did exist to link national with state efforts in modifying risk behaviors. Dr. Freeman concluded by

reiterating the importance of a transdisciplinary approach to cancer prevention and control—one that combined elements of basic science with epidemiology, nutrition, and the behavioral sciences.

## NEW BUSINESS I
Dr. J. Michael Bishop

Regarding the A-110 matter, Dr. Bishop proposed that a working group prepare a statement as soon as possible for transmission to OMB. He asked that Dr. Schein chair the group and that Dr. Kalt coordinate the effort. Other members of the group appointed by Dr. Bishop were Dr. Sharp, Dr. Nienhuis, Ms. Stovall, and Dr. Michael Hodgson. NCAB members were encouraged to submit their input to Dr. Kalt. Dr. Bishop further stated that the working group's response would be circulated to the entire Board, but that a rapid response was needed.

## CLINICAL TRIALS IMPLEMENTATION REPORT
Dr. Robert Wittes, Dr. Micheale Christian

Dr. Wittes began by noting that the treatment arm of the Clinical Trials Program has been under review for the last 2 years; the review was instigated by the NCI to meet challenges brought about by health care reform; and that numerous experts have, over the last 2 years, provided their input to the Clinical Trials Implementation Group Report.

**Process.** Dr. Christian began by describing the composition of the Committee, its representative nature, its meeting schedule, and its charge—defining a clinical trials program that would be scientifically- based, flexible, efficient, and rapidly responsive to scientific opportunity.

**Recommendations.** Dr. Christian's remarks focused on the Cooperative Group Program, currently composed of 12 groups—8 adult and 4 pediatric—representing a range of multimodal, unimodal, and specialty groups. Dr. Christian reviewed the numbers of: persons currently enrolled in clinical trials; ongoing ancillary laboratory clinical studies; ongoing Phase II and Phase III trials; and investigators and institutions currently participating in clinical trials. Major objectives of the Group included: (1) ensuring that the best science was incorporated into large clinical trials; (2) developing state-of-the-science meetings to identify new research opportunities in specific cancers or gaps in the research portfolios and implementing an enhanced peer review of the entire cooperative group system; (3) substantially increasing the accrual and access of patients and physicians; (4) increasing the efficiency and decreasing the complexity of Clinical Trials Support Units (CTSUs); (5) developing a fair and functional system; and (6) ensuring that clinical trials represent state-of-the-art cancer care. Dr. Christian then reviewed the Group's plans for pilot testing the initiatives, as well as its conclusions on needs in uniform informatics, common case report forms, and credentialing and auditing. Dr. Christian noted that: proposed changes are also being developed for the Early Clinical Trials Program; protocol authoring and management tools are in development, as are mechanisms to streamline protocol development; collaborations are being forged with

industry and the Food and Drug Administration (FDA); and the role of IRB review and multicenter studies has been examined. Dr. Christian concluded by noting that information on all the Implementation Group's activities soon will be available on the NCI Web site.

## QUESTIONS AND ANSWERS

Dr. Freeman commented that some important findings had resulted from the report but that the issue of disparities in the inclusion of certain groups in clinical trials remained a concern. Dr. Christian responded that the issue of disparity was recognized and that certain mechanisms mentioned in the report (e.g., the Disease-Specific Concept Committees, the State-of-the-Science Meetings) provided a means for addressing these questions. Dr. Klausner commented that time was needed to evaluate the changes recommended in the report. In response to a question from Dr. Dickersin, Dr. Christian clarified the role of the statistical centers—as distinguished from that of the administrative functions of the CTSUs. Dr. Klausner added that the statistical centers need not be the only places to do statistical or analytic work. Dr. Dickersin asked whether an advisory or oversight group existed and Dr. Christian replied that the BSA would receive regular updates and a formal evaluation plan is under development. Dr. Frederick Li commented on the cost-benefit of the patient accrual mechanism and the mechanics of the decisionmaking process and added that, while the clinical trials portion of the Clinical Trials Group effort works well, there were unexploited opportunities in the cooperative groups regarding correlative sciences and ancillary studies that the report did not address. Dr. Christian replied that the report addressed funding for correlative science and that a developmental fund for each group was proposed to facilitate early translational research and it also considered methods to improve the speed with which the system operates. Dr. Klausner added that the process is meant to operate such that an investigator may receive a rapid decision on funding from the peer-review system. Dr. Li suggested that the Board receive an annual update of the progress of the plan. Dr. Klausner agreed and stated that Dr. Christian and CTEP would prepare such an evaluation with an external evaluation of the plan also a possibility.

Dr. Royston asked for clarification on two points: the funding for Phase III trials outside the cooperative group and the means by which an investigator (who is not a member of the cooperative) would implement the trial. Dr. Christian replied that each Phase III trial approved through this mechanism would have leadership funds associated with that trial and that the protocol will be developed in conjunction with the CTSU. Dr. Royston asked whether a protocol need not be accepted by an individual cooperative group. Dr. Christian replied that it could be conducted outside the group but there were certain incentives (e.g., standing statistical/data management centers) that might limit this activity. Dr. Royston asked what funding mechanism existed for protocols outside the cooperative group. Dr. Klausner responded that, in the first year, about $8M has been set aside specifically for such circumstances. Dr. Christian added that these monies would be distributed through the CTSU. Ms. Stovall asked whether a benchmark existed regarding what constituted accrual "success." Dr. Christian acknowledged that this was an important point and further stated that it will be examined during the formal evaluation.

Dr. Vainutis Vaitkevicius inquired as to what mechanisms existed for early testing of unconventional ideas. Dr. Christian replied that efforts are being made to provide developmental funds and that a mechanism also exists to bring concepts directly to the Concept Review Committee. Dr. Ramirez asked whether any consideration was given to the enhancement of minority recruitment into clinical trials. Dr. Christian answered that a number of initiatives are underway, including examination of the compensation issue. Dr. Schein expressed the hope that one test of the new system would be the efficiency with which a protocol is initially developed and ultimately brought to fruition relative to the old system. Additional considerations, noted Dr. Schein, were the need for adequate access and inclusiveness as well as the fate of the existing cooperative group system and whether a cooperative group would have the opportunity to implement its own protocols. Dr. Christian responded that the existing programs and new cooperative groups would be integrated over time. Dr. Nienhuis inquired into the process used by the review groups to fund studies and Dr. Christian replied that studies would be given a priority score. Dr. Klausner commented that Dr. Wittes is preparing a pamphlet describing the new system and that the pamphlet will be available to the entire research community. The information also will be placed on the Web and the Board was encouraged to supply feedback.

## DEVELOPMENTAL THERAPEUTICS REVIEW PROGRAM
### Dr. Susan Horwitz

Dr. Bishop introduced Dr. Susan Horwitz, Professor of Molecular Pharmacology at the Albert Einstein School of Medicine. Dr. Horwitz reported on the study conducted by the Developmental Therapeutics Program (DTP) Review Group. Dr. Horwitz reviewed the Group's activities, its charge, goals, the basis for its conclusions, and made the following recommendations: the entire intramural DTP budget should be limited to 15 percent of the total DTP budget; DTP should assume a leadership position in informatics; the resources of DTP should be made more available to qualified investigators; and extramural funding should support cooperative groups and centers of excellence. Dr. Horwitz next addressed the need for changes in the Decision Network Committee that should be broad based and expand to include representatives of academia as well as NCI staff. The entire group believed that the DTP needed more flexibility and a faster response rate. They proposed a committee of five to eight leading scientists that would be empowered to create a discovery and development process for any drug target or drug candidate. Such a committee would have the ability to: (1) form coalitions of mutually interested scientists; (2) provide seed money; (3) issue Request for Applications (RFAs) and task orders; and (4) conclude contracts. The budget for this committee should be no less than $50M that should come from the existing DTP budget.

**Major Recommendations.** Major recommendations of the Group included: support of research on small molecules that can be used to modulate the function of all proteins relative to cancer; an interdisciplinary initiative to acquire structural information on cellular targets potentially relevant to cancer; reduction of the current 60-cell line screen to three cell lines; movement away from total concentration on compounds that are just antiproliferative to additional areas such as anti-angiogenic and metastatic; expansion of the Biological Resources Branch; expansion of chemical libraries and of the Natural

Products Collection Program into new geographical areas and ecological niches; development of a cell- based assay program (possibly costing $10M per year for 10 years); an emphasis on hybridization array technology; the need for more synchrotron radiation sources as well as training in this area; development of new and innovative protein expression technology; greater understanding of ligand receptor interactions; improved animal models; development of national pharmacology/toxicology core facilities serving as centers of excellence; development of post-doctoral training; improved interaction with FDA; greater use of mouse models in transgenic systems; development of the biologics area and creation of a rapid, formal, and merit-based review structure for their evaluation; and expansion of the National Cooperative Drug Discovery Groups. Dr. Horwitz summarized the report by stating the NCI's drug development program needs to assure that the most talented and best-trained scientists throughout the Nation are working on the development of chemical and biological therapies for the treatment of cancer and that the information they acquire be available to all scientists.

## QUESTIONS AND ANSWERS

Dr. Schein asked Dr. Horwitz to rank developmental therapeutics as an NCI priority. Dr. Horwitz replied that DTP was crucial. Dr. Schein requested clarification on the funding devoted to extramural and intramural funding. Dr. Edward Sausville, Associate Director, DTP, responded that, in the contract line, about $20M would go to extramural sites but that the total budget—including contract work as opposed to grants—would be on the order of $40M. Dr. Sharp asked how DTP would interact with private sector activities. Dr. Horwitz replied that there was great awareness of the importance of such interaction and the issue was discussed in greater detail in the report. Dr. Calabresi asked whether she envisioned regional centers (of excellence) that might work on drug development. Dr. Horwitz was supportive of this idea and added that such a venture might be funded through a program project or center structure. Dr. Calabresi next asked how the hurdle of doing large animal toxicology studies in academia might be overcome. Dr. Horwitz answered that collaborative efforts with industry or the use of centers doing such work was important and that more training of individuals in doing pharmacokinetics and toxicology was needed. Dr. Schein stated that there was a need to move quickly from drug discovery laboratories into human testing; that models have not really proven effective; that current toxicology does not really work and that there was a need for more sophisticated toxicological work. Dr. Horwitz concurred with Dr. Schein's comments.
In response to a comment by Dr. Nienhuis, Dr. Horwitz stated that there was a need to expand the role of the Biological Resources Branch and Dr. Wittes added that the implementation of RAID would speed the development of this process. Ms. Stovall commented that it appeared that the therapeutics area was underfunded and that additional work in this area represented a great opportunity. Dr. Klausner commented that work is already underway toward implementation of the Report's recommendations. Dr. Klausner added that a number of themes present in the report are echoed in other NCI initiatives (e.g., the need for the NCI to create connections and enable infrastructures). Dr. Klausner noted that industry was very much interested in such collaborative efforts (e.g., RAID) and that efforts were underway to rethink the NCI's relationship with the extramural community so as to enhance collaborative activities. Dr. Bishop asked Dr.

Horwitz to distinguish between the NCI's role and that of the pharmaceutical industry. Dr. Horwitz replied that the Committee had a divergence of opinion on this subject—some committee members believed that the NCI should act as a drug company, while others were strongly opposed to such an idea—but the one critical difference between the drug companies and DTP and the NCI was that DTP and the NCI were open organizations, their goal is not to make a profit. Dr. Horwitz concluded by emphasizing the importance of making information available widely. Dr. Wittes agreed with this and added that another critical issue was the difference in the level of risk that the NCI—as contrasted with industry—would tolerate. Dr. Bishop concluded the discussion by adding that the two issues of availability of information and differences in level of risk acceptable by the NCI and industry were critical points.

## PAPILLOMAVIRUS VACCINE AGAINST CERVICAL CANCER
### Dr. John Schiller

Dr. John Schiller began by discussing the basic principles and rationale behind development of a cervical cancer vaccine; the high worldwide prevalence and mortality associated with cervical cancer; the active interest in the development of both therapeutic and prophylactic human papillomavirus (HPV) vaccines; and the factors affecting the development of a prophylactic relative to a therapeutic vaccine. Dr. Schiller reviewed the nature of the major capsid protein of HPV, L-1, and noted that HPVs do not induce pathological changes in animal models.

Dr. Schiller identified two companies currently involved in Phase I clinical trials of a virus-like particle-based (VLP)-based vaccine and commented on the Phase I trial of HPV-16 VLPs being conducted by the NCI in collaboration with the National Institute of Allergies and Infectious Diseases (NIAID) and Johns Hopkins University. Given the continued positive results, Dr. Schiller stated that his group plans to conduct an efficacy trial in Guantacaste, Costa Rica, by using the existing infrastructure of an ongoing study there of HPV and cervical neoplasia. The study question to be examined is whether simple parenteral injection of VLPs induces effective immunity against genital mucosal infection in women. It is estimated that the trial will consist of about 3,000 vaccinated women and 3,000 controls, followed for 3-4 years. Both virologic and disease endpoints will be used as measures of efficacy.

Dr. Schiller cited the following as being important questions related to the development of a prophylactic vaccine: (1) Are specific genital mucosal immune responses required for protection? (2) Is there a need for cell-mediated response to nonviral proteins? and (3) Can a vaccine be developed for underdeveloped countries? Dr. Schiller outlined three strategies that might result in the development of a vaccine with worldwide applicability: live bacteria, transgenic plans, and naked DNA. Dr. Schiller commented that he did not believe the DNA approach had been shown to be clearly effective and expressed concern over the potential oncogenic risk of injecting strong promoters of transcription into healthy young people. Dr. Schiller added that, ultimately, the transgenic plant approach might prove the most feasible but, in the shorter term, the live recombinant bacteria

approach may be best; and speculated that a live bacterial vector with HPV may be tested in humans in the next few years.

Dr. Schiller did not believe that VLPs themselves would be effective in eliminating preexisting lesions and cited two methods of increasing the therapeutic potential of a VLP-based vaccine: production of pseudovirions and development of chimeric VLPs—noting that it may be worthwhile to begin thinking about human clinical trials examining chimeric VLPs. He explained that papilloma virus may not have evolved mechanisms to evade recognition by a systemic immune system response and addressed the premise that papilloma virus might serve as a good platform for generating immune responses to other disease targets.

Dr. Schiller concluded his presentation with three points: (1) the safety and strong antibody responses to HPV-16 VLPs in Phase I clinical trials are encouraging of further clinical testing of a VLP- based prophylactic vaccine; (2) the L-1/L-2 chimeric VLPs are able to induce strong CTL responses to inserted proteins in animal models and this finding warrants clinical trials of chimerics containing HPV early proteins in both the therapeutic and prophylactic settings; and (3) the therapeutic potential and safety of autoantibody inducing vaccination via chimeric VLPs should be investigated in animal models.

## QUESTIONS AND ANSWERS

Dr. Nienhuis asked whether there was currently sufficient evidence to justify a prophylactic trial with the VLPs or would it be more beneficial to wait until more experience had been obtained with the chimeric proteins. Dr. Schiller answered that he would be satisfied with obtaining good protection from the nonchimeric and that if good protection could be obtained from the parenteral, then a chimeric VLP vaccine could deliver antigens of other infectious agents at no additional cost. Dr. Royston inquired whether any data existed on L-1- or L-2-derived peptide vaccines and Dr. Schiller replied that, in animal models, denatured VLPs do not produce any neutralizing antibodies. Dr. Sharp asked whether there was another antigen carried by the particle that could be examined for seroconversion. Dr. Schiller replied that in premalignant disease there did not appear to be a good antibody response to any early protein. Dr. Huerta concurred with the importance of the cervical cancer research—particularly in the less developed world—and asked to what degree recruitment of ethnically diverse populations was a consideration in this work. Dr. Schiller acknowledged the importance of research in ethnically diverse groups and answered that the work being done at Johns Hopkins included strong representation by African Americans and that the work in Costa Rica will be conducted among a primarily Hispanic population.

## OVERVIEW OF NCI BOARD OF SCIENTIFIC ADVISORS
### Dr. David Livingston

Dr. Bishop introduced Dr. David Livingston, Dana Farber Cancer Center, and Chairman BSA, who provided an overview of the BSA activities of the past year. Dr. Livingston

reviewed the BSA's meeting schedule and noted that this year was exceptional in that the BSA held an additional meeting to review the Clinical Trials and DPT reports. Important issues dealt with at every meeting included review of grant pay lines and discussion of extramural activities (e.g., CGAP and tobacco control) and training. Other topics of interest to the BSA included the evolution of the Cancer Genetics Network, the redesign of the Physician's Data Query (PDQ) System, and the Director's Challenge of the Unconventional Innovation Program. In addition, Dr. Livingston cited the BSA's approval of the Phased Innovation Award, its support of the RAID program, and discussion of molecular imaging technologies. The BSA strongly approved the analysis and review reports of the Cancer Centers Review Committee, the Clinical Trials Review Committee, the Cancer Control and Behavioral Science Review Committee, the Prevention Review Committee, the DTP Review Committee, and the breast and prostate cancer Program Review Group reports, as well as the NCI's plans for implementing these reports. Additionally, the BSA has: begun to discuss future NCI plans regarding chemoprevention and nutrition; approved an RFA dealing with early detection of the commonest neoplasms; worked closely with the NCI leadership and staff in evaluating the Specialized Program of Research Excellence (SPORE) program; helped develop a new 6- year review cycle for major extramural programs; identified or dealt with emerging problems involving extramural operations (e.g., data access); discussed RFA concepts (e.g., in the areas of tobacco research, functional imaging, and molecular tumor classification); recommended the initiation of a program to maximize communication of new NCI research directions to the scientific community and to the public (e.g., through its program called "NCI Listens"); and has initiated a 2-hour luncheon meeting with Dr. Klausner to discuss new issues, opportunities, and problems. Dr. Livingston concluded his report by stating that the BSA would continue its active range of activities in the future.

## QUESTIONS AND ANSWERS

Dr. Klausner asked Dr. Livingston to comment on the process of critique of proposals presented to the BSA. Dr. Livingston replied that the BSA is a congenial but critical group of overseers. Dr. Sharp asked what problems Dr. Livingston foresaw in the extramural community. Dr. Livingston replied that he thought closer relationships were necessary among members of the BSA and the extramural research community in order to come to agreement on what constitutes a national cancer plan. Implementation of the clinical trials system was cited as an additional potential concern. Dr. Sandra Millon-Underwood asked whether there would be any new initiatives addressing minority and underserved populations. Dr. Livingston replied that Dr. Otis Brawley had spoken on this subject at the previous BSA meeting. Dr. Klausner added that specific studies are constantly being added and the entire portfolio will be presented to NCAB members at their next meeting and that certain issues do not fall under the purview of the BSA. Dr. Bishop asked how Dr. Livingston saw the role of RFAs. Dr. Livingston answered that this matter would be discussed at a future BSA meeting but that the RFAs dealt with by the BSA had been exciting. Dr. Klausner further stated that the BSA had requested the development of performance metrics for certain new initiatives (e.g., the Early Detection

Research Network) and that the development of such metrics would be a collaborative effort.

## DCCPS TOBACCO INITIATIVES
### Dr. Barbara Rimer and Dr. Marc Manley

Dr. Barbara Rimer, Director, DCCPS, addressed the Board members on the importance of tobacco in terms of being the greatest cause of cancer-related mortality and morbidity—more than 30 percent of all cancer deaths can be attributed to tobacco use. Dr. Rimer introduced Dr. Marc Manley, Chief, Tobacco Control Research Branch, who provided a brief synopsis of past and current trends in smoking and tobacco use. Dr. Manley reported that although smoking rates in the United States had declined at a steady rate during the 1970s and 1980s, there has been a markedly leveling off of this decline in the 1990s for all smoking groups—based on age, gender, race, and socioeconomic status. Recently published data indicates that smoking rates among youths had increased during the period from 1993 to 1997, which Dr. Manley described as "the most ominous sign for the future." He noted that adolescents underestimate the addictive nature of nicotine and most youth smokers who smoke on a daily basis state that they will not be smoking in 5 years; in fact, 75 percent of these youths will be smoking 5 years later. Youth smoking has become a high priority for research and the NCI has joined with several other Institutes to fund 28 new research projects looking at the prevention, cessation and, in particular, treatment issues of tobacco use among youth.

The NCI has developed a close working relationship with the Agency for Health Care Policy and Research (AHCPR), which published a Clinical Practice Guideline on smoking cessation; the guidelines—comprised of recommendations for clinicians to use when treating smoking patients—currently are in the process of being updated with the help of both NCI staff and investigators.

Dr. Manley mentioned that in recent years, there have been new advances in the field of treatment research, including the development of more pharmacologic products to aid in smoking cessation. Additionally, more basic research is being performed that looks at molecular mechanisms of addiction for the purpose of identifying specific behaviors and effects of nicotine, which will assist researchers in developing new and more precise treatments for smoking cessation.

Dr. Manley then gave a brief overview of the impact that policies have had in the area of tobacco control. Rising tobacco prices as a result of increased excise taxes has caused a more rapid and widespread impact on tobacco consumption than any other single intervention. Although traditional advertising by tobacco manufacturers has not increased dramatically in recent years, advertising expenditures have increased exponentially, since the mid-1980s, for cigarette promotions (i.e., sponsorship of sporting and musical events, giveaways, etc.). The increase in the advertising expenditures for promotional activities, in addition to the introduction of the Joe Camel campaign—which was the first major cigarette campaign that was clearly targeted to youths—coincides with the large increase in youth smoking initiation rates.

Dr. Manley concluded his presentation by commenting on the American Stop Smoking Intervention Study (ASSIST), the NCI's large demonstration project that funded tobacco control programs in 17 states and which will end in September 1999. The Department of Health and Human Services (DHHS) has recognized the importance of what ASSIST has accomplished and is planning to implement tobacco control programs in all 50 states, with funding through the CDC. The NCI will be collaborating with the CDC to ensure that information obtained from ASSIST will be transferred to these new state programs. Next, Dr. Rimer gave an overview of the TRIG's Tobacco Research Implementation Plan, which details the NCI's tobacco-related cancer research priorities for the next 5-7 years. The plan was based on recommendations made by the TRIG, which was comprised of scientists from across the NCI (both the intramural and the extramural program), and from various outside organizations. The TRIG was charged with: (1) examining the Institute's portfolio in tobacco; (2) determining priorities for the next 5-10 years; and (3) making recommendations that were research-focused and would have a major public health impact, as well as understanding the process of addiction, which is very important to developing treatments. The group concluded that an "unequivocal commitment at the NCI to a comprehensive focused program of research on tobacco use could help to reverse the existing epidemic of tobacco- related cancers," and identified and recommended nine high-priority areas for implementation:

- Transdisciplinary Tobacco Research Centers that would study all facets of tobacco use, from the basic biology of tobacco to understanding the nature of addiction, new treatments, and policies;
- Basic biobehavioral research to understand sociocultural, genetic, psychological, and physiological factors in tobacco use, progression, and cessation;
- Research on the treatment of nicotine addiction to find the best ways to tailor interventions;
- Research to improve state and tobacco control programs;
- Research to identify mechanisms for optimal dissemination of proven interventions;
- Research to understand the impact of tobacco policies;
- Basic biological research to identify and validate biomarkers of tobacco exposure and tobacco-induced cellular events;
- Research to understand genetic and environmental interactions in cancer susceptibility and identify groups at risk; and
- Research on expanded surveillance system.

As a result of the TRIG's recommendations, two major research initiatives are being implemented that will be funded at $142M over a period of 5 years. The first, the Transdisciplinary Tobacco Use Research Centers (TTURC) program, would create centers that could develop a critical mass of investigators. Collaboration would be possible, both within and across centers, to develop a comprehensive understanding of tobacco use. There would be a unique context for training, the ability to have pilot projects, and shared resources—which would provide greater efficiency. The P50 SPORE mechanism will be used, which will require at least three projects related to a theme. Applications for these 5-year awards are due in April and will be funded in FY99. The second initiative provides NCI funding, over a period of 4 years, for state and community tobacco control intervention research. Increasing the effectiveness of tobacco control programs in all 50 states will foster reductions in tobacco use and will lead to a greater national impact on tobacco use. Randomized, controlled trials will be preferred and will be funded through R01s in FY00.

## QUESTIONS AND ANSWERS

Dr. Bishop asked if other NIH Institutes are involved with this mission to reduce tobacco use and, if so, if they will be contributing to the funding pool. Dr. Rimer referred to Dr. Robert Croyle, Associate Director, Behavioral Research Program, DCCPS, who responded that a partnership was established with the National Institute of Drug Abuse (NIDA) because of its established portfolio of programs in tobacco and because of the time frame involved to make funding available in FY99. Dr. Croyle added that if more time had been involved, participation from the National Heart, Lung, and Blood Institute (NHLBI) would have been desirable and he added that attempts are being made to entice NHLBI to participate in a significant way. Dr. Bishop responded that the NCAB is available to provide any assistance in this effort. He then asked what type of institutes and organizations in the professional community would be submitting R01s. Dr. Manley answered that the program is clearly for community investigators—though it is strongly encouraged that a connection should exist with the organizations and people who are managing these new programs in the states. Dr. Rimer added that Dr. Manley's relationship with the public health community is excellent and she anticipates that more excellent applications will be received than can be funded. Dr. Klausner commented that the Tobacco Research Implementation Plan is quite remarkable and it is critical to let the community know that a very eminent group has reached a consensus on a real blueprint for a comprehensive tobacco research program. He suggested that an aggressive approach is necessary to disseminate this information to the professional community. Dr. Li asked about a worldwide moral responsibility for the tobacco epidemic and Dr. Rimer responded that this issue is important and a section in the report highlights the need for international collaborations. She also noted that the report would not have been possible without a collaborative effort by the entire Institute. Dr. Klausner added that it is important that the NCI report regularly to the NCAB members—who should be engaged in the oversight of this new set of initiatives. He stated that this is the type of program that clearly challenges the issue of what the NCI's boundaries are and how it should interact with other agencies.

## OPTIONS TO RESTRUCTURE THE CANCER INFORMATION SERVICE
### Ms. Susan Hubbard

Dr. Klausner announced to the Board members that he will be reporting to the Congressional appropriation legislation on the NCI's response to the Office of the Inspector General's (OIG) report on the CIS. He introduced Ms. Susan Hubbard, Director, International Cancer Information Center (ICIC), to present how the NCI will respond to the report, and to ask the Board members for any feedback and guidance they can provide about the NCI's decisions about reconfiguring the CIS.

Ms. Hubbard prefaced the presentation on restructuring the CIS with a brief overview of the toll- free information service—currently with a $20M budget—that was initiated in 1975 and provides information to approximately 600,000 callers annually who have questions about cancer. The OIG, prompted by concerns about the frequency of busy signals on the toll-free number, conducted a study of the CIS and issued a report with recommendations on how to improve the system. In response to these recommendations, the NCI: (1) established new performance standards; (2) invested $1.6M to upgrade the computers; (3) modernized the telecommunication system; and (4) discontinued the collection of community service data. In addition, the NCI currently is revamping the PDQ system and is reconfiguring the existing regional structure.

Ms. Hubbard explained that the purpose of this discussion was to respond to the OIG's recommendations about reevaluating the current regional structure and considering a centralized service. She stated that the NCI's primary goals for the CIS in the evaluation of the regional structure are: (1) to meet the public's needs through an integrated regional program; (2) expand access to the telephone service and maintain a busy rate of less than 5 percent; (3) strengthen the outreach program; (4) enhance the CIS' capacity to participate in cancer control and health communications priorities; and (5) maintain and enhance quality while containing costs. Options to reconfiguring the regional structure included maintaining the current configuration of 19 regions, reducing the number of centralized offices to one, or creating a smaller, more efficient network of regional offices. In addition, criteria used in evaluating the various options for regional reconfiguration included time zone coverage, total call volume in 1997 (analyzed by state) and estimated call volume for 1998, estimated new cancer cases for 1998, total population for the area, population characteristics (i.e., ethnic and cultural distribution) within the region, regional composition, clusters of states, and access to resources—such as cancer centers—for partnering.

Ms. Hubbard stated that after considering all goals and set criteria, the NCI determined that the current 19 regional offices should be reconfigured and reduced to 14. This reconfiguration plan was reviewed by senior leadership at the NCI and other federal agencies and it was unanimously endorsed by the Executive Committee, as well as staff from the FDA and the CDC. In addition, the proposed reconfiguration was posted on the Acquisitions Management Branch Web site to solicit comments that will be reviewed and considered. Also, it was proposed that a draft Request for Proposal (RFP) be issued that would allow the community to comment on the draft before the final RFP is published.

Ms. Hubbard noted that the major reconfiguration included integrating Hawaii into a Pacific region as opposed to maintaining its own region, consolidating offices in northern and southern California to one office, integrating offices in New York into one office, and transferring West Virginia from a mid- Atlantic region into a mid-south region. She stated that future plans include issuing the final solicitation in February 1999 and awarding a contract in October 1999.

Ms. Hubbard concluded her presentation by inviting the Board members to advise and comment on the reconfiguration plans to reduce the CIS network from 19 to 14 regions.

## QUESTIONS AND ANSWERS

Dr. Klausner began the discussion by commenting that the reconfiguration would not preclude consortia of what would be previously separate CIS contractors into, for example, a New York State consortium or a Pacific consortium. Ms. Hubbard concurred, and added that it is up to the organizations submitting to determine where their outreach staff will be and how they will deal with the outreach. Dr. Klausner asked Ms. Hubbard to respond to CIS's current levels of performance since the new standards have been put into place. Ms. Hubbard responded that the busy rate has decreased to well under 10 percent (down from the previous 20-30% rate), and the new telecommunication and telephone services have been installed. Dr. Patel questioned the OIG's recommendation about using a centralized telephone service system and wondered if there is any cost savings between a centralized system versus 14 regional offices. Ms. Hubbard replied that there is a cost savings but, more importantly, implementing a centralized service would compromise both the ability to perform capacity-building outreach and to participate in community-based cancer control research; the NCI wants to ensure that these two components are maintained. Dr. Ramirez expressed concern about the cultural sensitivity in isolating a region such as Hawaii and suggested that the Hawaii site be maintained. Dr. Patel added that other Pacific islands could be placed into the Hawaiian region. Ms. Hubbard replied that the NCI is proposing requiring that the Pacific region—no matter who the offeror or where they are located— be staffed with telephone information specialists who understand the Hawaiian language and its culture. She added that it would cost an additional $2-3M to maintain a separate regional office in Hawaii if it were separate from a Pacific regional center.

Dr. Klausner announced that the NCI has a responsibility to keep the NCAB members informed of how the system is performing. He encouraged Board members to periodically call the CIS and provide feedback about the service at the next NCAB meeting. Dr. Calabresi made a motion to support the reconfiguration to 14 regions, with a reevaluation in 6 to 12 months. The motion was seconded and unanimously approved.

## INTRAMURAL BREAST CANCER INITIATIVES
### Dr. Edison Liu

Dr. Edison Liu, Director, DCS, reported on the efforts within the NCI's Intramural Program for a comprehensive breast cancer program. He stated that even though there

were excellent investigators working on breast cancer, the key was to bring together the individuals and the groups working on common themes. The challenge was then to integrate the program with the breast cancer programs throughout the country. Dr. Liu remarked that one of the program's initiatives, the Breast Cancer Think Tank (BCTT), is a community-building process that is mission-oriented, engages all scientific disciplines outside the branch structure, and is a self-governing process that is not "top-down." Infrastructure had to be developed for scientific collaboration and collective approaches. In addition, its focus had to be on curing the disease. The first Think Tank meeting took place in October 1997; 80 attendees met for an all- day discussion of how to develop the community and to create action items. Two task forces were formed —pre-clinical and clinical—and met to identify important scientific questions and platforms. The clinical task force decided that there were two complements that were of great importance: (1) build an infrastructure that includes recruitment of patients and dissemination of clinical trials; and (2) develop trials for prevention, disease quantitation, and novel therapeutics. Dr. Liu listed the prevention trials that have begun as a result of the BCTT: effects of Raloxifene in premenopausal women; biochemical effects of weight gain during chemotherapy; biochemical effects of alcohol in women; and repository for the P2 chemoprevention trial of Raloxifene vs. Tamoxifen.

Dr. Liu commented that the Navy Breast Center was a research component of the National Navy Medical Center (NNMC) in Bethesda; the NCI will manage the research component and the clinical component will be managed by NNMC, which will provide a standard of care outlet for the DCS's research. Dr. Liu concluded his discussion by stating that a $300,000 per-year line item budget has been assigned to the BCTT, a steering committee has been developed that has representation from all divisions to manage the funds, and the representation in all aspects of the breast program includes advocate representation.

## PERSONAL REFLECTIONS
## Dr. Frederick Li

Dr. Frederick Li commented that Dr. Bishop had set aside time during the meeting for NCAB members to introduce themselves to each other. Dr. Li took the opportunity presented by Dr. Bishop to share with the members his personal observations of the opportunities, work scope, and the output of the two major phases of his career; namely, the more than 20 years he spent in the NCI Intramural Program as a Public Health Service (PHS) officer, and then as an extramural investigator at Harvard. He mentioned that one of the greatest highlights of his career was the opportunity to build a program to recruit young investigators and to watch them evolve into accomplished scientists with successful careers. Dr. Li came to the United States when he was a child and has risen from a humble beginning to achieve many things that he had never imagined would be possible. He remarked that he knew of no other place in the world where this would have been possible.

## NEW BUSINESS II
## Dr. J. Michael Bishop

Dr. Bishop asked Board members to provide any items of new business for consideration. No items were received, and Dr. Bishop proceeded to the next item on the agenda.

## INTRAMURAL ADVANCED TECHNOLOGY INITIATIVES
Dr. Edison Liu, Dr. Ken Buetow, Dr. Louis Staudt

Dr. Liu reported on the Advanced Technology Center (ATC), which was initiated almost 2 years ago and is in the final stages of completion. The concept of the Center was to have a facility whereby individuals (geneticists, cell biologists, and laboratory-based clinicians) could assemble in an arena to review technologies that are mature enough to span both science and clinics. One section of the ATC is the genome's National Institutes Sequencing Center (NISC)—where the NCI sequencing and genotyping group will be located, and another part is the array facility. Dr. Liu then presented a series of slides showing the physical structure of the Center. Next, he introduced Dr. Ken Buetow, Chief of the Laboratory of Population Genetics, to describe the genotyping and sequencing facility for the NCI.

**Genotyping and Sequencing Program.** Dr. Buetow stated that there is a growing demand for the capacity to perform comprehensive genetic analysis of cells, people, and populations and the NCI's mission is to enable such genomic analysis through the ATC. Strategically, there are three inter-related approaches to this program: (1) build an infrastructure to perform the large-scale characterizations necessary; (2) concurrently evaluate the next generation technologies for performing the genetic analysis—sequencing and genotyping—that are critical to the success of this approach; and (3) build a conduit for technology transfer to the intramural community and the larger cancer research community. Dr. Buetow next listed the key technologies that must be implemented if large-scale genomic analysis is to be conducted: large-scale PCR, automation, electronic data capture, data tracking, quality control, and data distribution. He noted that a primary focus will be to support large-scale genetic analysis of intramural projects that will be submitted to the program, in addition to CGAP and the NCI's Genetic Annotation Initiative. Dr. Buetow added that this information also would be available to the entire NCI and the world community via the Web. He described key areas of opportunity, including the different types of sequencing supported, different approaches taken, different types of genetic analysis that would be supported, and support for DNA fingerprinting.

Dr. Buetow stated that when fully deployed, the facility would expect to support the generation of about 2,000 sequencing reads per week. He presented an overview of the facility, the equipment, and staffing that was needed to accomplish their goals. Dr. Buetow stated that the program would have an external advisory committee that would provide guidance and support and assist with prioritization. He added that there should be a realistic assessment of the costs of conducting this large-scale analysis. In an effort to reduce some of the costs involved, it is anticipated that some expenses can be charged back for consumables associated with each of these projects—at competitive market prices.

Dr. Buetow ended his presentation by indicating some of the strategic directions that are being taken and stating that partnerships with outside organizations are being explored. He added that technology is changing more rapidly than it can be deployed in the individual field, which adds to the complexity of establishing an infrastructure of this caliber. As new equipment is being purchased, the next-generation equipment already is being evaluated.

**Microarray Development.** Dr. Liu discussed the development of the array program, in particular, its history, organizational components, and the mechanics of its printing. Recently, a steering committee determined that the array packages from commercial entities were either unavailable, not cost- effective, or did not have the specifications required by the research community. The committee concluded that the NCI and the DCS should have array technology available onsite instead of relying on outside facilities to provide this technology. Components of the array program were identified, which included the printing and reading of arrays, understanding the results, managing the clones that feed into the printing, and providing adequate training to disseminate the technology. The NIH provided funding in August 1998 to develop an informatics platform for the entire array process. At present, two facilities are operational; printing and reading will be available in one facility and the reading and informatics group will be located in the other facility.

**Microarray Development and Informatics Challenges.** Dr. Louis Staudt continued the discussion by providing detailed examples of how the microarray technology works. He also discussed the uses of cDNA microarrays in cancer research, which include: (1) discovery of novel cancer subtypes; (2) identification of signaling pathways active or defective in cancer cells; (3) definition of molecular differences between chemotherapy responders and non-responders; (4) identification of novel lineage-restricted and developmentally-timed genes; and (5) identification of target genes of oncogenic transcription factors and signaling molecules.

Dr. Staudt stated that these efforts will be important in terms of treatment outcome and he noted that there is a need to move into clinical trials settings where it will be possible to evaluate the profiling of gene expression and possibly determine who responds or does not respond to chemotherapy or other therapies. He continued by stating that patterns will be compared to determine if all the patients with a given disease have the same pattern of gene expression.

## QUESTIONS AND ANSWERS

Dr. Bishop asked Dr. Liu to expand on the issue about making this plan accessible to the extramural community. Dr. Liu responded that the plan calls for the informatics module to be Web-based and exportable. Also, assistance is being provided to institutions that are establishing their own array facilities. Dr. Klausner anticipates that a prototype of a funding package with designs and design plans will be developed soon to assist with the

setup in protocols. Funding for part of the setup will be provided in a variety of locations around the country.

## COMPETITIVE INTRAMURAL PROGRAMS AWARDS
### Dr. George Vande Woude

Dr. George Vande Woude, Director, Division of Basic Sciences (DBS), reported that in the reorganization of the competitive intramural program awards process, it was established that a principal investigator's (PI) budget would be determined as a result of the site visit review process; this would serve as the baseline until the next site visit review—for a period of 4 years. In the past, a PI could contact the Division and ask for additional resources. Because of the large numbers of requests, it became very difficult to determine what, if any, additional resources could be allocated. It became necessary to reorganize this process and to establish priorities in funding.

The Intramural Research Awards for the Division of Basic Sciences (DBS) provide opportunities for a postdoctoral researcher to obtain funding in the amount of $60,000 for 3 years. Applications are evaluated very rigorously; and in the first year, 10 of 44 applications were funded. The applications were first prioritized by both intramural and extramural scientists, and final priorities were determined by the Board of Scientific Counselors (BSC).

Next, Dr. Vande Woude described the Collaborative Project Award, a new process that was established this year to foster collaboration among scientists within the NCI Divisions. There are three types of collaborative project awards; Dr. Vande Woude described Types I and II, which have been initiated. Any investigator who wants to collaborate with another PI within the DBS can submit for a Type I award. The Type II award involves a collaboration with PIs within the government; for this type of award, the other organization has to agree to provide funding for its PI if the application is awarded and funded. Ten Type II applications have been received for 12 DBS PIs and PIs from outside DBS. Dr. Vande Woude explained that the evaluation criteria for this year will be based solely on scientific merit and approximately 25 percent would be funded. The process will consist of a mail-out review to both intramural and extramural reviewers. They will prioritize the applications, and final priorities again will be made by the BSC. Dr. Vande Woude expressed concern that the review process activities will continue to increase and a study section will be established in FY99 to review the Intramural Research Awards and the Collaborative Project Awards.

Dr. Vande Woude discussed issues that needed to be resolved for the Type III Collaborative Project Award. In this process, an intramural investigator can collaborate with a scientist in the extramural community. Dr. Vande Woude explained that there are substantive reasons that this has not been possible in the past. A significant number of intramural investigators already are collaborating with and providing major resources to extramural collaborators, but these major contributions by intramural PIs are not always recognized during site visits. Dr. Vande Woude stated the Type II Award would correct this and would provide recognition of those efforts during the site visit process. Dr.

Vande Woude anticipates that these issues will be resolved in the next 6 months. Additionally, he believes that this could be an exciting opportunity for the intramural scientists.

## ADJOURNMENT
Dr. J. Michael Bishop

There being no further business, the 108th meeting of the National Cancer Advisory Board was adjourned at 12:27 p.m. on Wednesday, December 9, 1998.