DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
May 22, 2001

Building 31C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

NATIONAL CANCER ADVISORY BOARD

BETHESDA, MARYLAND

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The National Cancer Advisory Board (NCAB) convened for its 118th regular meeting on Tuesday, May 22, 2001, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public from 8:45 a.m. to 4:00 p.m. The meeting was closed to the public from 4:15 p.m. until adjournment at 5:00 p.m. Dr. Phillip A. Sharp, Institute Professor, Center for Cancer Research, Massachusetts Institute of Technology, and Chair of the NCAB, presided during both the open and closed sessions.

NCAB Members

Dr. Phillip A. Sharp (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. James O. Armitage
Dr. Richard J. Boxer
Mr. Stephen C. Duffy
Dr. Ralph S. Freedman
Dr. James H. French
Dr. Elmer E. Huerta
Dr. Howard K. Koh
Dr. Frederick P. Li
Dr. Susan M. Love
The Honorable James E. McGreevey
Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Dr. Amelie G. Ramirez
Ms. Ellen L. Stovall

President's Cancer Panel

Dr. Harold Freeman (Chairperson)

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Ms. Raye Ann Dorn, VHA for Dr. T.G. Patel
Dr. Peter Kirchner, DOE
Dr. Hugh W. McKinnon, EPA
Dr. Richard Pazdur, FDA
Dr. John M. Powers, DOD, OASD, HA
Dr. Anita Schill, NIOSH

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. Dinah Singer, 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. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. Carl Barrett, Director, Center for Cancer Research
Dr. Joseph Harford, Associate Director for Special Projects
Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Mary Mitchell for Dr. Stanley Zinberg, The American College of Obstetricians and Gynecologists
Ms. Kristen Simonson for Ms. Nancy Riese-Daly, American Society of Therapeutic Radiology and Oncology
Ms. Paula Bowen, Kidney Cancer Association
Ms. PaulaAnn Rieger, Oncology Nursing Society

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I. CALL TO ORDER, OPENING REMARKS, CONSIDERATION OF MINUTES OF PREVIOUS MEETING AND REVIEW OF CONFLICT-OF-INTEREST/ CONFIDENTIALITY PRACTICES—DR. PHILLIP SHARP

Dr. Sharp welcomed guests representing liaison organizations and members of the public, and he invited members of the public to submit to Dr. Marvin Kalt, in writing and within 10 days, comments regarding items discussed. Dr. Sharp also reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

A motion was requested and made to approve the minutes of the February 2001 NCAB Meeting. They were unanimously approved by the Board.

II. FUTURE BOARD MEETING DATES—DR. PHILLIP SHARP

Dr. Sharp called Board members' attention to future meeting dates listed in the Agenda. Dates have been confirmed through 2002.

III. REPORT OF THE DIRECTOR, NCI—DR. RICHARD KLAUSNER

Dr. Richard Klausner, Director, National Cancer Institute (NCI), directed members' attention to a recent article in *Time* magazine on the newly approved anticancer drug Gleevec, or STI-571. He stated that researchers have long emphasized the importance of understanding the molecular basis of cancer for use in designing preventions or treatments. Gleevec represents the first example of the success that can be achieved through this approach. Gleevec has produced impressive results in treating patients with chronic myelogenous leukemia (CML). Moreover, it is newsworthy for its potential for treating some other types of cancers, the speed with which it was approved by the Food and Drug Administration (FDA), and its remarkably few side effects. Dr. Klausner applauded Gleevec most enthusiastically because of its breakthrough into the age of molecularly targeted therapies.

STI-571 inhibits three tyrosine kinases with high affinity. Gleevec was developed because of its ability to inhibit Abl—even the dysregulated form that characterizes CML. The two other known targets, kit and platelet-derived growth factor (PDGF) receptor, are also associated with various cancers. Patients with activating mutations in these tyrosine kinases have experienced dramatic results with Gleevec treatment. Early evidence indicates that gastrointestinal stromal tumors, which are associated with activation and expression of the kit tyrosine kinase, respond dramatically to treatment. This is the first treatment that holds promise for these patients, and the time from concept development to protocol implementation for the first clinical trials of Gleevec was only 4 weeks. Phase I/II trials have already been initiated in a third type of cancer—malignant glioma—that expresses the third type of tyrosine kinase susceptible to Gleevec: the PDGF receptor. Numerous other single-agent phase II studies are being planned. Importantly, accrual to trials with this exciting drug has not been a problem. How long the therapy will be effective in these patients, whether toxicities will emerge with prolonged treatment, and how long treatment must continue are issues that need to be evaluated.

A limitation of this new therapeutic drug is that the vast majority of patients treated in the blast phase of their disease relapse. Four underlying causal mechanisms have been identified: (1) genomic

amplification of the target protein; (2) increase in gene product; (3) accumulation of point mutations lowering tyrosine kinase affinity for Gleevec; and (4) a type of drug resistance mechanism. All four mechanisms reduce the effective dose of the drug but do not eliminate reliance on the tyrosine kinase, indicating that this enzyme is necessary for cancer maintenance.

The molecular approach to cancer treatment means that as the unique circuitries of different cancers are characterized, specific treatments can be designed. For example, in breast cancer, 14 classes of molecular targets, representing 68 different targets for which there are drugs, are identifiable. The new approach to fighting cancer goes beyond defining molecular signatures of cells to credentialing potential targets and developing drug candidates and probes and introducing them in clinical trials. Moreover, alternative pathways can be defined for molecular sensing and assessment of target-based therapeutics.

Therapeutics. Dr. Klausner noted that during the past 5 years, new funding mechanisms have been established to advance knowledge of molecular target-based therapeutics. One successful project has been the Cancer Genome Anatomy Project (CGAP), which has provided much of the gene annotation necessary for any molecular description of a cell. He then described the Cancer Molecular Analysis Project (CMAP), a newly created initiative. CMAP will provide a graphical, integrated platform for information to navigate the multidimensional and interacting pathways that define the circuitry of a cell. Currently, there is no comprehensive picture of the altered circuits in any particular cancer, primarily because so much of the cell circuitry is incompletely known. Highlighting the gaps in the picture will stimulate more directed investigation. In addition, a graphical representation of drugs in clinical trials can be achieved to ensure that logical testing is being performed with the available drugs, based on the biologic annotation.

Dr. Kenneth Beutow, Director, NCI Center for Bioinformatics, has been working with BioCarta to develop a Web site of cellular pathways. These pathways link to the rich CGAP database to illustrate the components of the pathways through which cancers are expressed. That information can, in turn, be linked to CGAP tools such as the Serial Analysis of Gene Expression (SAGE) and Recurrent Chromosomal Aberrations in Cancer project, and an annotation of the abnormalities that define the cancer can be generated. Overall, the idea is to use this information to drive drug development and the clinical trials portfolio. The model system for initial development of the CMAP database is brain tumors. Dr. Klausner indicated that CMAP will help integrate the information of basic research from many biological fields with the information from drug development and clinical trials. Such an effort will support not only the understanding that comes with viewing a broader picture, but also the recognition of areas of missing information.

Graphical representation provides a means of organizing information and of driving decisionmaking processes, and helps in creating a community through communication. Dr. Klausner spoke next about the communications efforts fostered by the NCI. The CancerNet site is a Web site that provides cancer information to the research, pharmaceutical, and biotechnology communities, as well as to patients. The new cancer.gov Web site will be launched in the summer of 2001. NCI's Cancer Information Service (CIS) has undergone restructuring to improve its operating characteristics regarding answering calls. Finally, a new informational tool is the Common Scientific Outline (CSO). CSO provides an interesting approach to the analysis, accessibility, and interpretability of the NCI research portfolio and can be used as both a monitoring and a planning tool. Many organizations, such as the

Department of Defense, the American Cancer Society, the California Breast Cancer Research Program, CaP Cure, California Cancer Research Program, the Oncology Nursing Society, the Susan G. Komen Breast Cancer Foundation, and the major cancer research programs of the United Kingdom, have agreed to be partners in this endeavor, with access to their research portfolios so that broad questions about cancer studies can be addressed—from issues such as survivorship and drug development research to the involvement of various institutions.

NCI Budget Update. Dr. Klausner then directed members' attention to NCI's budget. He reported that for Fiscal Year 2002, the President has proposed a budget that includes an 11.8 percent increase for the NCI, or 439 million new dollars. He explained that the NCI is already involved in developing its fiscal policy for the coming fiscal year because the first round of grant applications has already come in, and all of the applications for the year will probably come in before the final budget is decided. Depending on whether the final appropriation is less than or more than the President's request, he noted, there may be some discrepancies between grantee expectations and what the NCI is able to provide.

Dr. Klausner reported that the Research Project Grants (RPG) Working Group, which reports to the NCAB and is in its second year of operation, has begun its work of bringing together chairs and members of the NCI's advisory boards to share data needed for budgetary modeling and to bring the perspectives of external institutions and investigators into the decisionmaking process. Last year, he said, the result was a letter to grant recipients setting out the NCI's policies, and a similar communication will be prepared this year. Dr. Klausner added that, because a great deal of time was required last year to explain the policies after the letter was distributed, professional societies will be requested this year to provide assistance in explaining the decisions that affect success rates and funding levels. At its recent meeting, the RPG Working Group began to develop projections of success rates, numbers of grants, and average award costs.

Dr. Klausner observed that the greatest challenge in managing the grants portfolio is the dramatic increases in the number of applications and dollars requested per grant. He displayed a slide showing that for the past several years, increases in the average cost requested for investigator-initiated grants have been out of proportion to growth in the NCI budget. The slide also illustrated the difference between peer-review-recommended funding levels and what the budget allowed the Institute to pay. Dr. Klausner reminded the Board that the NIH Center for Scientific Review (CSR) has now stopped providing Institutes with peer-review-recommended funding levels for grant applications in most cases. The reasons for this change, he suggested, include the fact that reviewers prefer to focus only on scientific issues and the fact that the move to modular grants leaves reviewers with inadequate information to make specific recommendations about budgets. Dr. Klausner expressed his belief that it will be very difficult for the NCI to make budget decisions on reductions without the guidance of peer reviewers. He noted that in reviewing intramural programs, the NCI asks not only about the quality of the science but also about the availability of resources. Dr. Klausner said that his main difficulty in explaining NCI funding policies to investigators involves the arbitrary reduction in requested dollars in the absence of peer-reviewer recommendations. He said that he intended to continue arguing for a move back toward the provision of specific guidance from peer reviewers. He continued by noting that this aspect of modular grants makes it much more difficult to manage the budget.

Dr. Klausner reported that budget requests for Type 2 grants have increased from 20 to 50 percent, depending on the type of grant. He observed that the NCI cannot spend at that level and maintain a good success rate for grant applications. Therefore, he said, the NCI has decided to limit the increase in the cost of competing R01 grants to 20 percent. Other Institutes, Dr. Klausner added, have implemented similar caps. He described the situation as a stress on the system across the NIH. However, Dr. Klausner said, the NCI knows from its models based on the President's budget that it cannot allow the average cost to increase by 20 percent, given the increasing numbers of new and competing grant applications. Thus, if too many requested increases are as high as the 20 percent cap, the Institute will have to increase the "downward negotiation" of awards—a term, Dr. Klausner suggested, that should be changed, since the process does not actually involve negotiation.

Another trend that is causing stress, Dr. Klausner continued, is the increase in large R01 grants. He pointed out that the 2001 increase of $35 million for large R01 grants represents three full percentage points on the payline, or alternatively, 10 percentage points of downward negotiation. Dr. Klausner reported that an analysis of these large grants has shown that many are for epidemiological and behavioral research. He stated that the NCI is considering the release of a Program Announcement with a predetermined set-aside budget for large cohort studies. He explained that this would not be a Request for Applications (RFA), and that these projects would still be investigator-initiated R01 grants. A special review of the proposals submitted for these large grants would make it easier to evaluate the reasons for the large budget requests. Dr. Klausner expressed confidence that this approach would help make the budget process more predictable and would be good for science because it would make it possible to determine whether there were duplicate cohorts.

Dr. Klausner noted that the NCI budget is further strained by the necessary increase in the Institute's commitment base, or the amount that has to be spent on the "out years" of grants approved in recent funding cycles. In 2002, the commitment base requires a 16.5 percent increase in expenditures, while the Institute's entire budget has increased by only 11.8 percent. Comparing last year's and this year's budgets, Dr. Klausner reported that there has been a 33 percent decrease in funds available for new initiatives. Dr. Klausner stated that the goal for next year is to keep the number of new and competing grants the same. Assuming an increase of 5 percent in applications, this means the payline will fall. Dr. Klausner said that the NCI will try to reduce the downward negotiation and allow the average cost of grants to increase by 12 percent next year. The RPG Working Group, Dr. Klausner reported, has recommended that the NCI keep the accelerated review mechanism for exceptions. It had previously suggested suspending that mechanism in the search for dollars to move into the competing RPG payline.

Turning to the projected budget for 2003, Dr. Klausner said that the increase in the commitment base for that year is expected to be only 9 percent and that the budget will be moving toward more stability, and the Institute will have greater flexibility. However, he stated, a number of uncertainties still exist concerning the budget. The first, and the most obvious, is that the budget for 2002 has not yet been finally determined. Secondly, he continued, the White House has asked the NIH to propose approaches to funding projects in 2002 and 2003 that will prepare for the "post-doubling" period. Work is under way to develop these proposals, and one issue being considered is whether to fully fund projects now in order to lower the "out year" commitments. Dr. Klausner observed that any forward funding of projects in 2002 would reduce the amount of money available for new and competing grants, stipends, and other expenditures. The third unknown, he continued, is the behavior of the applicant pool. The Institute cannot

know in advance how many applicants there will be or what will be requested. Finally, he concluded, the budget of any Institute can be tapped by the NIH to fund information technology, business systems, and other infrastructure needs. Dr. Klausner also called attention to the issue of stipend growth. He said that there is concern in the research community over the NCI's policy to increase only new stipends by 10 percent. Another issue that will affect the budget relates to indirect costs for training grants, which currently are set at 8 percent. There is some effort to consider an upward revision of that amount.

In closing, Dr. Klausner stated that the RPG Working Group plays an extremely important fact-finding role and has been very helpful to him and to the Executive Committee in understanding the impact of funding policies on the extramural community. He said that the NCI will continue to seek the best way to communicate decisions to the research community and to explain policies in advance of the expectations of grantees.

Questions and Answers

Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, agreed that there is enormous concern with the review process but called attention to the dramatically increasing cost of doing research. He also suggested that some of the changes in requests for funding are related to changes in reimbursement for care provided in clinical trials. These are sociological and governmental changes, he stated, over which researchers have no control. Dr. Norton also mentioned the increasing ability of clinicians to focus on specific types of tumors, rather than on "breast cancer" or "lung cancer"; this, he suggested, also has implications for the research budget.

Dr. Norton referred to the "Gleevec revolution" and expressed the gratitude of the public and the research community for the fact that Dr. Klausner and the NCI have created an environment that was ready for such developments. The infrastructure that has been established for tying together advances in genome studies, clinical trials, and laboratory research, he said, makes it possible to move quickly to develop new therapeutics and new diagnostics based on increasing scientific knowledge. Dr. Norton noted that this preparation for implementing new discoveries is rare among Government agencies, which usually react to changes after the fact.

IV. REPORT OF THE PRESIDENT'S CANCER PANEL—DR. HAROLD FREEMAN

Dr. Harold Freeman, Chairman, President's Cancer Panel (PCP), summarized the results of the Regional Meetings held during 2000 and 2001. The PCP has held six of seven Regional Meetings (in Omaha, NE; Burlington, VT; Billings, MT; Nashville, TN; Los Angeles, CA; and Albuquerque, NM). The final meeting will be held in Washington, DC, May 24-25, 2001. The purpose of these meetings has been to hear about the concerns ordinary American citizens have about cancer and cancer treatment. He reported that four issues have emerged from those meetings that are critical to bridging the gap between research findings and health care delivery: financial issues, geographic issues, information and education, and cultural issues.

Financial Issues. Financial issues confront both those who have health insurance and those who do not. People who live in poverty have difficulties accessing health care that extend beyond the mere inability to pay, because they tend to live in substandard conditions, lead risk-promoting lifestyles, and

have little or no access to preventive and early care. For those covered by public or private insurance, a source of difficulty is the conflict among payment plans, which can result in payors' delaying or denying payment with the expectation that care will be covered by another entity. Dr. Freeman cited Government payment programs as particularly susceptible to confusion on the part of beneficiaries. Other groups adversely affected by the health care payment system in the United States are the working poor and many self-employed individuals, who are not poor enough to qualify for Government health care programs but not affluent enough to be able to afford private medical insurance.

Geographic Issues. Dr. Freeman noted he had learned a great deal in traveling to places like Billings, MT, which is surrounded by areas that are classified as "frontier," having population densities lower than those in rural areas. Cancer patients residing in such areas may need to travel 100 miles or more for treatment by specialists, and the travel difficulties are greatly exacerbated by severe winter weather in many areas.

Information and Education. Dr. Freeman observed that beliefs that cancer is contagious and a cause for shame persist in today's America. These beliefs can prevent people from seeking care in a timely manner. He also expressed concern about the extraordinary lack of information about cancer, the lack of cultural sensitivity in providing information, and the difficulty of navigating the health care system.

Cultural Issues. Dr. Freeman indicated that in addition to the three issues described above, there seems to be an element of bias in the health care system. Although it is unlikely that doctors consciously treat people differently according to racial or ethnic background, several studies in peer-reviewed journals have found such bias. Dr. Freeman concluded his report by illustrating such racial bias with two anecdotes from the PCP's Regional Meetings.

Questions and Answers

Dr. Sandra Millon-Underwood, Professor, University of Wisconsin–Milwaukee School of Nursing, asked Dr. Freeman if he had found new or different issues raised during the Regional Meetings as opposed to those identified during the hearings conducted by the American Cancer Society in 1989 and 1990. Dr. Freeman responded that for less affluent people and people of minority cultures, little has changed. Those with health insurance and more affluent people, however, have been able to take greater advantage of the progress in cancer treatment. Dr. Freeman added that the Panel's recommendations for addressing these challenges would be released in the PCP's Report to the President, planned for November 2001.

Ms. Ellen Stovall, President and CEO, National Coalition for Cancer Survivorship, observed that one major obstacle to bringing research results to the clinical setting is the health care system itself, and she asked Dr. Freeman if he thought opportunities for change in the system were better now than they were 10 or 20 years ago. Dr. Freeman replied that people seem to be more sensitive to problems in the current health care system, in particular the growing numbers of uninsured and underinsured Americans.

Dr. Amelie Ramirez, Deputy Director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, requested that the PCP report include the issue of the unequal burden of

cancer, as underscored in a recent report from the Institute of Medicine (IOM). Dr. Freeman said that this issue would be addressed by bringing together all the stakeholders from the scientific community and the advocacy community to deliver new discoveries to all Americans without regard for their ability to pay.

V. LEGISLATIVE UPDATE—MS. DOROTHY FOELLMER

Ms. Dorothy Foellmer, Director, Office of Legislative and Congressional Activities, NCI, described to the Board members the composition of the 107th Congress—the average and range of ages, the relative proportions of men and women, and the ethnic and racial makeup. She also listed the chairs of the Committees and Subcommittees in both the House and Senate that are key to NIH's and NCI's funding and mission. Members of Congress have expressed interest in specific diseases, such as Alzheimer's disease, mental retardation, and muscular dystrophy. Senator Arlen Specter recently held hearings on breast cancer, during which Dr. Klausner testified on progress made in discoveries of molecular targets for diagnosis and treatment of that disease. Recent and upcoming Congressional hearings deal with protection of human subjects in medical research, development of better drugs for children, and consumer access to health information.

Ms. Foellmer described the Breast Cancer and Environmental Research Act of 2001 (S. 830/H.R. 1723), sponsored by Senator Lincoln Chafee (R-RI) and Representative Nita Lowey (D-NY), which would authorize the Director of the National Institute of Environmental Health Sciences (NIEHS) to establish eight Centers of Excellence to conduct multidisciplinary and multi-institutional research on environmental factors related to the etiology of breast cancer. According to Ms. Foellmer, one of the more controversial provisions of the bill would authorize the establishment of a nine-member research advisory panel appointed by the Secretary of Health and Human Services (HHS). The panel would meet at least once a year to set parameters for the priorities of these Centers and to make recommendations for programmatic allocations of grant funds. The final decisions about funding would be made by the Director of the NIEHS, although the Director would be expected to give the panel's recommendations considerable weight in the decisionmaking process. Ms. Foellmer said that the panel envisioned under the bill is modeled after the integration panel used by the Department of Defense (DoD) in awarding breast cancer funds.

Questions and Answers

Ms. Stovall drew the Board's attention to another bill, the Access to Cancer Therapies Act of 2001 (H.R. 1624), which has 57 cosponsors in the House. A companion bill has been introduced in the Senate. She pointed out that the bill, which would provide Medicare coverage for oral anticancer drugs, was of particular relevance in light of the recent introduction of Gleevec, a new oral anticancer drug for the treatment of CML. Currently, the only oral anticancer drugs covered by Medicare are those that originally were administered intravenously; thus, Gleevec, which must be taken for many years, and other new cancer drugs like Tamoxifen, are not covered by Medicare. Dr. Norton noted that under current Medicare regulations, physicians cannot be reimbursed for supervising the administration of oral anticancer drugs. Ms. Stovall said the entire reimbursement system needs realignment to accommodate the new science.

VI. GENE SILENCING VIA RNA INTERFERENCE—DR. PHILLIP SHARP

Dr. Sharp remarked that the discovery of RNA interference (RNAi) in mammalian cells demonstrates that new phenomena are still to be discovered in biological systems. He also pointed out that RNAi will directly contribute to the CMAP database as scientists use RNAi technology to unravel cell circuits and regulation and, ultimately, define complex processes such as growth and development.

Earlier studies have shown that RNA virus replication in plants can silence genes—a phenomenon known as cosuppression or posttranslational gene silencing (PTGS). In 1998, Fire, Mello, and colleagues abandoned their gene-silencing work with antisense RNA in *C. elegans*. While they had obtained variable results with antisense, they found that double-stranded RNA (dsRNA) contaminating the antisense preparations consistently caused gene silencing in *C. elegans*. Shortly thereafter, a similar phenomenon was discovered in *Drosophila*. Furthermore, it was shown that dsRNA could silence a specifically targeted gene for up to seven generations of worms. The hypothesis to explain this activity is that an epigenetic sequence-specific agent must be acting to silence the targeted gene. Following these experiments, a mammalian effect was shown, but only when double-stranded RNA (dsRNA) was used in early mouse embryos that could not induce interferon production.

Dr. Sharp explained that Tuschl and colleagues reported in a recent article in *Nature* (*Nature* 411:494-498, 2001) that RNAi can be directed to specific mRNAs in mammalian cells by using complementary sequences called short interfering RNAs (siRNAs). dsRNA's 21 nucleotides are long enough to provide gene sequence specificity but short enough so that induction of interferon and subsequent widespread inhibition of proteins—a mammalian antiviral response—does not occur. An additional refinement for studying RNAi in mammalian cultures was the use of lipofectamine transfection of siRNA into the cells. The presence of siRNA resulted in RNA-specific inhibition of gene expression in cells in tissue culture. Initial experiments by Tuschl and colleagues targeted a luciferase transgene; subsequent experiments demonstrated inhibition of naturally occurring endogenous genes. Still other experiments used the specificity of siRNA to target individual splice variants. Although gene expression was not eliminated completely, RNAi with siRNA has proven to be more robust than antisense techniques.

Dr. Sharp noted that much work remains to be done to understand the mechanism of RNAi. Particularly interesting will be the role that RNAi plays in mammalian cell development and regulation. Most exciting, however, is the ability of RNAi to aid in studying control circuits in the cell by suppressing individual genes or a combination of genes. Currently, the only procedure available for gene targeting uses ES cells, which takes at least six months and costs thousands of dollars. Gene silencing through application of the siRNA technology can be done much more quickly and cheaply. Ultimately, siRNAs themselves may be used as therapeutic agents.

Questions and Answers

Dr. Klausner asked if genes had to be actively transcribed to be targets for RNAi. Dr. Sharp noted that in other biological systems the answer is no. The interference effect can be passed through plant tissue as well as *C. elegans* cells that do not express the endogenous gene. However, the experiments to date have been performed in systems of active transcription, so the answer to Dr. Klausner's question is

unknown. Likewise, the effect of interferon treatment at the time of siRNA treatment is not known, although Dr. Sharp, in responding to a second question by Dr. Klausner, refuted the idea that interferon would suppress RNAi.

Dr. Arthur W. Nienhuis, Director, St. Jude Children's Research Hospital, asked about the normal role of siRNA and natural occurrences of siRNA. Dr. Sharp speculated that RNAi is active in embryonic tissue and plays a role in gene regulation.

Dr. Robert Wittes, Deputy Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, inquired about the multigenerational effect of RNAi. Dr. Sharp replied that Dr. Tuschl noted that the mammalian genes were silenced for the 7 days he left the cells in culture.

VII. POLICY UPDATED: COMMON APPROACHES TO EARLY PHASE DATA SAFETY AND MONITORING PRACTICES—DR. ROBERT WITTES

Dr. Wittes provided an update to Board members on NIH requirements to extend data and safety monitoring beyond Phase III clinical studies to virtually all elements of its clinical trials program. He noted that the changes were motivated by increased public awareness about clinical trials and associated issues of adverse events and conflicts of interest, which, in turn, prompted the Federal Government to increase its level of surveillance of HHS-sponsored clinical trials. The NIH left to each Institute the decision on how best to implement a plan for extending data safety monitoring to phase I and II clinical trials. Dr. Wittes said that the new requirements posed a particular problem for NCI because its clinical trials extend across the spectrum of interventions from those that are inherently life saving to behavioral interventions.

Dr. Wittes noted that the requirements were part of the grant approval process, and that potential grantees needed to submit a general plan for peer review and a detailed plan for staff review and approval before funds could be disbursed. Since the majority of NCI's clinical trials are concentrated in a limited number of institutions, it was decided to encourage the submission of institutional plans from institutions that have large clinical trials portfolios. If an institutionally based plan was sufficiently clear and thorough, it could serve virtually all its investigators engaged in clinical trials. Dr. Wittes suggested that one approach could be to construct a modular plan, in which one module would describe the monitoring process for Phase I trials, another module would describe methods for behavioral studies, a third would describe nicotine addiction interventions, and so on.

In order to give institutions guidance on NCI's requirements, NCI staff identified four essential elements that would need to be part of the data safety monitoring activity. Dr. Wittes explained that the review process of the data and safety monitoring plans by NCI staff would focus on the adequacy with which the plan covers the four essential elements, evaluating whether the investigator has a serious process in place for ensuring the safety of research participants and the maintenance of data integrity.

Monitoring the Progress of Trials and the Safety of Participants. Dr. Wittes said that this element would answer such questions as: Who monitors the trials? How often are the data examined?

What do monitors look for? What procedures are in place to ensure adequate feedback of information to researchers? What is the oversight role of the Institutional Review Board (IRB)? Dr. Wittes added that this element would include explanations of how an institution might avoid conflict of interest if the Principal Investigator is the only monitor of the clinical trials.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events. Dr. Wittes said that NCI's requirements for adverse event reporting were already posted on NCI's Web site and were included in the investigator handbook. Fulfilling this requirement would include plans for the establishment of a central reporting entity for multicenter trials.

Plans for Assuring That Any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial Is Reported to the NCI Grant Program Director Responsible for the Grant. Such action might include actions by the Food and Drug Administration (FDA), the institution's own IRB, by a commercial sponsor of the trial, or by the investigator him- or herself.

Plans for Assuring Data Accuracy and Protocol Compliance. This element includes descriptions of quality control procedures that would ensure that data are accurate and complete.

The discussion on NCI's policy on data safety and monitoring practices continued during the working lunch held by the Committee on Clinical Investigation.

VIII. NEW BUSINESS—DR. PHILLIP SHARP

Dr. Sharp expressed concern about future funding levels for NCI because budget cuts might jeopardize current opportunities in cancer research. He told Dr. Klausner that he would oppose any effort to reduce funding, but he said it would not be helpful for the Board to express its concern to the Administration officially, since the NCI's proposed budget for FY 2002 was unknown. Dr. Klausner indicated that the Administration might ask for a report on NIH's funding requirements this summer. He said he would keep the Board informed as to the progress of the budget discussions. Dr. Norton asked whether there was any response to the NCAB's request to increase funding for NCI's infrastructure and management, and Dr. Klausner replied that those funds have increased as a proportion of the NCI's total budget, but they are not expected to grow.

IX. NEW HORIZONS IN HEALTH: AN INTEGRATIVE APPROACH—DRS. RAYNARD KINGTON AND BARBARA RIMER

Dr. Raynard Kington, Director, Office of Behavioral and Social Sciences Research (OBSSR), NIH, explained that his office was created in 1995 to pursue three goals: to enhance behavioral and social sciences research and training across Institutes at NIH; to expand a biobehavioral interdisciplinary perspective across NIH; and to improve communication among health scientists and with the public about important advances in the behavioral and social sciences. His office promotes these goals by working collaboratively with Institutes and Centers in developing research agendas; by supporting relevant RFAs and Project Announcements (PAs); and by consulting with Institutes and Centers as they develop programs in the behavioral and social sciences. OBSSR has no grant making authority.

In 1999, OBSSR asked the National Research Council (NRC) of the National Academy of Sciences (NAS) to form a committee whose charge would be to develop a research plan for the behavioral and social sciences to guide NIH in supporting high priority areas in those disciplines. The committee was to focus on: (1) areas of common interest across Institutes and Centers; (2) areas with the likelihood of greatest scientific payoff; and (3) areas of greatest importance to public health.

The committee identified 10 areas for future research priority:

Predisease Pathways. Dr. Kington said that the importance of understanding precursors of disease underlies all of the research areas in the report. The NRC committee recommended that NIH expand its support of research on key indicators of biologic influences and the related behavioral, psychological, and social influences that precede morbidity and mortality. Dr. Kington described the goal of such research as an "early warning system" that would ultimately lead to the development of interventions.

Interaction Between Environment and Gene Expression. Dr. Kington pointed out that the tremendous advances in understanding the human genome have raised new questions about the interaction between behavioral, psychological, and social factors and genetic factors. He acknowledged that most of the research on the relationship between gene expression and the environment in the near term will most likely continue to be in animal models, but he said that now is the time to lay the foundation for human genetics research that will decode the interactions between environment and gene expression. Dr. Kington stressed the need for developing conceptual models and methods for integrating evidence on related changes in the social and behavioral factors with data on gene expression.

Personal Ties. Dr. Kington indicated that although a large body of literature has demonstrated the importance of personal ties as risk factors for many health outcomes, the relationships between personal ties and gene expression, brain structure, neuroimmunologic activity-and ultimately physical health outcomes-are not well understood. The NRC committee called for a better understanding of the dynamic and cumulative impact of social ties on biological processes.

Healthy Communities. Evidence suggests that characteristics of communities seem to have a relationship independent of characteristics of individuals on health outcomes. In other words, two individuals may have the same demographic and socioeconomic characteristics, but they may have very different health outcomes based on the types of communities they live in. Dr. Kington emphasized that advancing this research requires overcoming complex methodological problems.

Population Health. Dr. Kington called for more understanding of large trends in population health and health care over time—for example, the recent significant decreases in disability among the elderly. Another aspect of population health is achieving a better understanding of the characteristics of population-level interventions such as tobacco education that affect their efficacy and their costs.

Health Promotion. Also known as "positive health," this term refers not only to the absence of disease, but to the presence of a healthy lifestyle. Dr. Kington observed that determining why some people have good health in spite of living in unhealthy environments and having multiple risk factors for disease is an important question facing health scientists today. Personal and social resources may have an

impact on whether individuals with certain combinations of risk factors actually contract the diseases for which they are at risk. Dr. Kington told the Board that while poor communities tend to have the worst health outcomes, these communities also have the greatest variance in health outcomes. He suggested that this variance might present a significant opportunity for studying resilience and resistance to disease.

Inequalities. Dr. Kington encouraged further study on why a person's position in various social hierarchies may affect his or her health outcomes.

Interventions. Research in behavioral and social factors is of no use unless it leads to improvement in the health of the public. Dr. Kington called for the development of new interventions to achieve real-world outcomes based on knowledge behavioral and social scientists have gained in controlled scientific studies. He cited as an example the translation of research on the role of social support as a health determinant into corresponding interventions. Such interventions, he said, should be appropriate to the heterogeneous population of the United States today.

Methodology. Dr. Kington pointed out the need for new measurement techniques to assess risk, especially those that integrate multiple levels of analysis-at the individual level, the family level, and the community level. He also noted that better measures of characteristics of social organizations-from families up to communities-that appear to influence health outcomes are needed.

Research Infrastructure. Longitudinal study populations that include biologic and genetic data as well as behavioral, social, and contextual data over a long period of time are a high priority for research. Dr. Kington observed that developing these studies will probably require new birth cohorts, but that some research questions can be addressed by adding biologic data to existing longitudinal studies that focus on behavioral and social factors, or, conversely, adding social and behavioral data to studies focusing on biologic processes.

Training. A new type of researcher whose training cuts across different disciplines is needed to integrate health knowledge. Dr. Kington called for recruiting a diverse scientific workforce that takes the greatest possible advantage of the best minds across racial, ethnic, and class divisions. Dr. Kington said that multidisciplinary training must begin at universities.

Dr. Kington acknowledged that no single Institute or Center could address every one of these areas, and he said that his office was seeking partnerships with NCI and other Institutes to leverage its resources. He directed NCAB members' attention to several other recent NAS and IOM reports. Next steps for OBSSR include collaboration with Institutes and Centers on health disparities research, which is important to OBSSR because behavioral and social factors explain much of the differences in health outcomes across racial and ethnic groups. His office also plans to support training on methodological work focused on strengthening behavioral and social science methods. An initiative on the relationship between education and health status is also planned.

Questions and Answers

Dr. Norton expressed support for multidisciplinary training for scientists and said that he was impressed with the sophistication of the research tools used by social scientists. Dr. Kington noted that his

office is exploring short-term training efforts to introduce researchers in one discipline to the basic language of other disciplines.

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences (DCCPS), NCI, described her division's Transdisciplinary Tobacco Use Research Centers (TTURCs) as examples of cross-disciplinary initiatives-for example, molecular biologists are working with specialists in communication, genetic epidemiology, and behavioral sciences in these Centers. She observed that perhaps the research setting is among the best venues for cross-disciplinary training because of the hands-on exposure and opportunities to work directly with other scientists.

Dr. Frederick Li, Division of Cancer Epidemiology and Control, Dana-Farber Cancer Institute, lauded the emphasis on positive health, but he indicated that health promotion and disease prevention are still in their infancies. He illustrated this point by noting that a recent annual meeting of a professional society for cancer prevention attracted around 200 participants, while the American Association for Cancer Research had more than 100 times that number. Dr. Kington responded that prevention research has a structural problem in that its outcome is the absence of disease, and it is more difficult to attract support for a lack of outcome than for a cure for a specific disease. He noted that the only strategy likely to be successful in supporting health promotion would be an integrated cross-Institute approach at NIH.

Dr. Howard Koh, Commissioner, Massachusetts Department of Health, said that as a State public health official, he recognized that current funding streams were constrained in a way that made integration of health care services difficult. He suggested that public health officials at all levels of government are well positioned to deliver preventive services through a commitment to integration. He listed the prevention and screening programs offered to Massachusetts citizens: breast and cervical cancer screening, assessment of cardiovascular risk factors, smoking cessation programs, nutritional services for pregnant women and women with infant children, and substance abuse prevention programs. Dr. Kington replied that he was aware of Massachusetts' programs, and he cited a program in Boston as an excellent example of a social solution to a health problem: City employees were given time off for certain screening procedures, which amounted to buying employees' time for disease prevention.

Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, Washington Hospital Center, described his concept of a "preventorium," which would provide preventive services to healthy people, as opposed to a sanatorium that serves sick people. He acknowledged that initially, preventoria would be empty, but over time, preventive services would be more widely accepted than they are now. Dr. Kington agreed that new nomenclature, as well as new ways of thinking, is needed for health promotion programs. He noted that the public seems to be receptive to new approaches to maintaining health, such as complementary and alternative medicine.

X. DISCUSSION OF NEW HORIZONS IN HEALTH: AND INTEGRATIVE APPROACH, AND ITS IMPLICATIONS FOR CANCER CONTROL

Dr. Rimer described initiatives that her division is sponsoring that correspond to the research priorities outlined by Dr. Kington. These include a number of studies on psycho-neuroendocrine function and cancer to identify predisease pathways; biobehavioral grants; grants for TTURCs, which provide funds to institutions to study new ways to combat tobacco use and its consequences; studies on the

concept of resilience; and research on environmentally induced gene expression, a field of study that cuts across her entire division. Dr. Rimer's division is also working on a proposal to bring together researchers in population health with other disciplines to investigate issues associated with health disparities, including the role of social ties. The Cancer Care Outcomes Research and Surveillance Consortium (CANCORs) program, recently initiated by DCCPS, will follow a cohort of cancer patients and provide insight on how health outcomes are affected by the health care system. Questions and Answers Dr. Koh asked if DCCPS's studies on population health and healthy communities tie into the national goals expressed in Healthy People 2010. Dr. Rimer responded in the affirmative, pointing to her division's work in health communications as well as in studying healthy communities. Dr. Robert Croyle, Assistant Director for Behavioral Research, DCCPS, observed that NCI is in a unique position to respond to many of the recommendations for research articulated in Dr. Kington's presentation because of its Cancer Centers infrastructure, which he described as a natural venue for interdisciplinary research. A particular strength is that Cancer Centers are in a position to forge links with academic departments in social and behavioral sciences.

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XI. EARLY DETECTION RESEARCH NETWORK UPDATE—DRS. PETER GREENWALD, SUDHIR SRIVASTAVA, DAVID SIDRANSKY, AND LANCE LIOTTA.

Introduction. Dr. Peter Greenwald, Director, Division of Cancer Prevention, NCI, provided the Board with several reasons biomarker research can have central importance in cancer prevention, early detection, and therapy. He explained that biomarkers have the potential to make clinical prevention trials more efficient by allowing trials to be of shorter duration; providing opportunities for true early detection, when therapy may be more successful than in later interventions; and by helping in the development of more informed and individualized interventions.

Instead of funding individual investigators, NCI decided to support a network of competitively funded investigators who agree, as a condition of funding, to collaborate with each other to move new discoveries into clinical validation. The Early Detection Research Network (EDRN) was established in October 1999 with the premise that integration of discovery, evaluation, and clinical validation is more likely to succeed when these phases are carried out in a coordinated, systematic fashion.

Scientific Management. Dr. Sudhir Srivastava, Chief, Cancer Biomarkers Research Group, NCI, described the EDRN as an infrastructure for supporting collaborative research on molecular, genetic, and other biomarkers in human cancer detection and risk assessment. Its goals include: (1) fostering interaction among academic, clinical, and industrial leaders to encourage development of biomarker assays for cancer detection and risk assessment; (2) establishing scientific criteria to evaluate biomarkers as indicators of early cancer, prognostic factors of preinvasive cancer, markers of risk, or as surrogate endpoints; and (3) developing and instituting a quality assurance program for biomarker testing and evaluation. In its initial year of existence, the EDRN accomplished the creation of an investigator-driven management structure; it established guidelines for collaborations, both inside and outside of the network, and for the translation of laboratory research into clinical settings; and it published these guidelines in a *Manual of Operations*. The network brings together diverse expertise in basic science, clinical science, epidemiology, and statistics and represents industry, academia, clinical institutions, and Government agencies.

The EDRN consists of 31 funded laboratories and Centers and approximately 120 participating institutions and 300 participating investigators. Dr. Srivastava noted that while this consortium strengthens the network by bringing in a diversity of expertise, it also presents management challenges in defining clear patterns of communications, developing strategy and management culture, and setting the basis for priorities, strategies, and plans to bring stakeholders together.

Dr. Srivastava reported that the EDRN's management structure is centered on a Steering Committee made up of all the Principal Investigators, which meets three times a year. The Steering Committee has seven subcommittees, the chairs of which constitute an Executive Committee, which meets monthly. An Advisory Committee provides scientific oversight, and a Data Management and Coordination Center, housed at the Fred Hutchinson Cancer Research Center in Seattle, assists with the design of studies and protocols. Four collaborative groups have been established to provide associate membership opportunities that focus on specific cancer sites that are not well represented within the consortium (breast and gynecologic; prostate and urologic; gastrointestinal and associated cancers; and lung and upper aerodigestive). The collaborative groups serve as gateways to investigators seeking EDRN sponsorship for research by reviewing proposals to determine whether the research meets Network guidelines for collaboration and whether it will enhance technology, resources, and information sharing.

The EDRN communicates with the scientific community through: its Web site; participation at conferences and Steering Committee meetings open to the public; and listservs. Network members also serve as liaisons for relevant professional societies, and opportunities for collaboration are published in major journals.

Dr. Srivastava outlined the process by which a marker is validated: After a researcher identifies a putative marker, it is reviewed by collaborative groups and then by the Steering Committee according to

preestablished criteria. An assay is then cross-checked by an EDRN biomarkers validation laboratory. If the assay is sufficiently robust, then a project team composed of members from the Data Management Coordinating Center, the Steering Committee, and the Advisory Committee establish the study design and protocols. According to Dr. Srivastava, the ultimate goal is to validate biomarkers to make them useful in clinical settings.

Dr. Srivastava went on to report on progress made in identifying biomarkers for cancers of the prostate, breast, ovaries, bladder, and colon. He also described the EDRN's bioinformatics infrastructure, which provides a standardized vocabulary and common data elements, along with other decision support tools such as the development of standard methods of biomarker analysis. The goal, according to Dr. Srivastava, is to provide performance characteristics, reference reagents and assay systems, and clinical data for any given biomarker.

Questions and Answers

Dr. Norton asked whether the EDRN planned to collaborate with investigators conducting research sponsored by the Director's Challenge, CGAP, and CMAP. Dr. Srivastava said that his division was considering holding a "research festival," to bring together for discussions grantees from the Director's Challenge, the Special Programs of Research Excellence (SPOREs), and the EDRN.

Scientific Highlights. Dr. David Sidransky, Director, Head and Neck Cancer Research, and Professor, Otolaryngology–Head and Neck Surgery, Oncology, Pathology, Cellular and Molecular Medicine, Johns Hopkins University, underscored the importance of the EDRN by pointing out that considerable research has been published on promising individual biomarkers, but that investigators have lacked the resources to move the markers forward to the point of reducing the burden of cancer. The necessary resources include the technology to make sure that the results are reproducible; the availability of a large cohort or large number of clinical samples; and the epidemiologic and statistical tools for testing each marker. The EDRN, he said, helps to provide these resources by combining the search for biomarkers with the development of technology, clinical epicenters, and information integration.

Dr. Sidransky explained that loss of heterozygosity and/or chromosome deletions as part of the inactivation of tumor suppressor genes are important components of molecular biomarkers. These genetic changes are associated with the early stages of cancer, and if they can be identified, physicians might be able to treat cancer early, when treatment is most effective, instead of at the end of a long process of disease progression. However, developing biomarkers is difficult, time-consuming, and expensive. Dr. Sidransky outlined five phases that the development of a biomarker must undergo:
(1) preclinical/exploratory—involves identification of promising directions; (2) clinical assay and validation—includes detection of established disease through clinical assays; (3) retrospective longitudinal—involves the detection of preclinical disease with the biomarker and the definition of a "screen positive;" (4) prospective screening—includes the detection of the extent and characteristics of disease by the testing and identification of the false referral rate; and (5) cancer control—the quantification of the impact of screening on reducing burden of disease on the population. He described these phases as a pyramid: Many potential biomarkers are identified in phase 1, but very few reach phase 5. The EDRN helps this process, he noted, by bringing experts together to select the most promising biomarkers and, thus, conserve resources.

Dr. Sidransky highlighted two specific biomarkers his team is currently investigating: mitochondrial DNA and promoter hypermethylation.

Mitochondrial DNA. It was originally suggested in the 1950s that abnormal mitochondria might promote tumor growth, but until recently little was known about this relationship. Dr. Sidransky's team looked at a variety of different tumor types, including head-and-neck cancer, lung cancer, and bladder cancer. In sequencing the mitochondria, they found a specific somatic mutation that was absent in the normal tissues but was present in cancer cells in about 60 percent of the tumors. In addition, they found detectable differences in fluids—for example, mutations in the mitochondrial DNA in urine.

Dr. Sidransky reported that his team was especially interested in studying the mitochondrial mutations in primary lung cancer. Lung cancer presents particular difficulty because there are relatively few cancer cells among the normal cells. As a result, studying cancer cells presents a "needle in a haystack" problem: Typically, bronchoalveolar lavage (BAL) of lung cancer patients contains about one cancer cell per 1,000 normal cells. To determine the proportion of mutant mitochondria, the team used a specific mismatch ligation assay, a more sensitive test than sequencing alone. They found about one mutant mitochondrion for every 10 normal copies.

To quantify this relationship further, Dr. Sidransky and his team selected two patients whose tumors had mutations in both the nuclear genome and in the mitochondrial genome to compare the relative proportions of normal p53 to mutant p53 and normal mitochondrial DNA to mutant DNA. In both patients, the proportion of mutant p53 to normal p53 was very small. However, they found molecules in mitochondrial DNA for one patient to be about one-third mutant, a finding that represented a 100-fold increase over the results of testing for nuclear p53. For the second patient, about one-half of the mitochondrial DNA was mutant, a 200-fold increase.

Dr. Sidransky emphasized that while these results are very promising, the use of mitochondrial DNA as a biomarker is only in the first phase of development. He announced that his team is collaborating with the National Institute of Standards and Technology (NIST) to develop a high-throughput assay that could take mitochondrial DNA as a biomarker through further phases of development.

Promoter Hypermethylation. Dr. Sidransky explained that methylation—the attachment of a methyl group to a molecule—is a common characteristic of neoplasia. Methylation, he said, completely knocks out transcription as thoroughly as it would a deletion or truncating point mutation. Molecular pathways affected by DNA methylation in cancer include altered cell-cycle control, DNA damage repair, controls or limits on apoptosis, invasion in tumor architecture, and growth factor response. Dr. Sidransky informed the Board that his team has developed a sophisticated rapid assay called methylation-specific polymerase chain reaction (PCR). This assay allows them to develop specific primers that can detect both unmethylated and methylated sequences.

To test the assay, Dr. Sidransky's team studied 30 patients with a primary disease of oral cavity cancers and cancers of the aerodigestive tract: 15 smokers and 15 nonsmokers. They tested three genes for methylation: DAP kinase, MGMT, and p16. They looked for the presence of methylation in both tumor tissue and saliva, and they found a high degree of specificity: Wherever methylation occurred in

the saliva, it also occurred in tumor cells. Their test also revealed a high level of sensitivity, in that generally, when methylation was found in the tumor tissue, it also was found in the saliva.

Dr. Sidransky went on to describe studies of methylation markers in blood serum. His team had particular success using APC as a marker in blood serum and/or plasma, since it was both highly sensitive and highly specific: methylated APC was found in 96 percent of tumor samples and 47 percent of serum or plasma samples. In control samples, the incidence of methylated APC was zero. Moreover, the levels of methylated APC in serum were found to increase in patients whose disease progressed, to decrease to near zero in patients who responded well to treatment, and to remain the same in patients whose disease did not change. Dr. Sidransky noted that such findings illustrate the value of a quantitative assay versus one showing only the presence or absence of the disease marker.

Dr. Sidransky pointed out that a major advantage of working with blood samples is that large serum banks exist, and he and his team are using these banks to perform longitudinal studies. He described the methylation marker as being in phase II of development, during which his team is working with epidemiologic and statistical centers to plan trials to give them more information about the marker. The team is pursuing prospective trials that would piggyback on ongoing studies of high-risk smokers, and it is working to get a robust assay into the validation laboratory. He concluded his remarks with a caution about avoidable cancer risk factors.

Questions and Answers

Dr. Klausner asked whether Dr. Sidransky's research on mitochondrial mutations focused specifically on those mutations that have a replication advantage compared to unmutated mitochondrial DNA. Dr. Sidransky responded that many of the mitochondrial DNA mutations appeared in the D loop, the area having to do with replication, but many functional mutations that tend to truncate amino acids or genes tend to reside in complex 1. There is a bypass for complex 1 that generates more reactive oxygen species, and therefore the mutation might be advantageous because it generates more oxygen radicals, which in turn cause mutations in the nuclear genome, thus allowing the cancer to progress. According to Dr. Sidransky, the signals from the mitochondria to the nucleus and back that allow the mitochondria to replicate are not well understood and warrant further study.

Dr. Norton suggested that the study of biomarkers be pursued with the Mouse Model Cancer Consortium. He asked how Dr. Sidransky's team would deal with multiple genes, commenting that the assays described by Dr. Sidransky might not apply to an array. Dr. Sidransky noted that members of the EDRN are developing microplate assays and chip assays that can detect various aspects of methylation—e.g., point mutations. Another approach is a robust capillary method that can detect and separate out PCR products quickly, enabling high throughput amplification.

Serum Proteomic Patterns and Disease-Associated Signatures of Early Ovarian Cancer. Dr. Lance Liotta, Chief, Laboratory of Pathology, Center for Cancer Research, NCI, reported on a new bioinformatics tool developed through the Clinical Proteomics Initiative (CPI). The focus of the initiative is to enable proteomic analysis of patients' tissues, and thereby to facilitate disease characterization, drug action, and early detection and therapy of cancer. The advantage of the new bioinformatics tool is that an

artificial intelligence (AI) recognition algorithm discovers patterns of low-molecular-weight serum proteins to distinguish between cancerous and noncancerous tissue in the ovary and prostate.

Dr. Liotta stated that the individual proteins need not be identified to provide important clues for early diagnosis. The algorithm correlates disease and normal tissues with their respective proteomic patterns of low-molecular-weight proteins in serum. The technology applied is surface-enhanced laser desorption/ionization (SELDI), using a low-resolution mass spectrophotometer to analyze the molecular mass of proteins in a high-throughput way. After a training period, the AI algorithm categorizes unknown samples into clusters defined as *diseased*, *healthy*, or *new*. This "new" cluster represents a fundamental difference between this program and other types of puristic learning algorithms.

Dr. Liotta summarized the mechanism of the AI algorithm as an iterative process in which a large number of prospective protein patterns are analyzed with a matching recombination test and a fitness test to develop a "survival of the fittest" pattern. The end result discriminates the healthy from the diseased sera with 100 percent accuracy.

Dr. Liotta acknowledged Dr. Petricoin at the FDA, and Correlogic Systems, Bethesda, MD, for help in developing the algorithm. Dr. Fishman, EDRN, provided serum samples from 200 patients from the national Ovarian Cancer Early Detection Program for the training set. In parallel, 300 serum samples from patients with prostate cancer were collected to constitute the training set for this second type of cancer. This latter group included patients who have had elective prostate resection for organ-confined cancer.

The differences in proteomic patterns between sera from healthy patients and sera from patients with biopsy-proven prostate cancer resulted in 100 percent discrimination of healthy patients from cancer patients. Dr. Liotta pointed out that a different set of molecular weight proteins distinguished healthy patients from cancer patients.

The patterns for either prostate or ovarian cancer were then applied to unknown, blinded cases. The resulting accuracy in detecting cancer ranged from 97 percent in cases of biopsy-proven prostate cancer to 100 percent in biopsy-proven ovarian cancer. Moreover, patients with healthy prostates were determined with 100 percent accuracy, and patients with no evidence of ovarian disease were detected 94 percent of the time.

Dr. Liotta reported that this study has been repeated with approximately 800 serum samples using a new SELDI machine and a retrained algorithm. An even larger study is envisioned using EDRN resources. He also indicated that results of a current clinical trial will help correlate changes in proteomic patterns with successful treatments and relapses in patients with ovarian cancer.

Dr. Liotta concluded by stating that proteomic patterns offer both a new window into the physiologic state of organs and a new paradigm for diagnosis of disease. In addition, this tool can be used to look at patterns of known proteins in signaling cascades in order to analyze the state of disease or even the response to treatment. Most importantly, however, is the ability of this tool to provide early detection of disease and thereby achieve a beneficial clinical outcome.

Questions and Answers

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, M.D. Anderson Cancer Center, asked whether peritoneal fluids were being used in the proteomic evaluation of ovarian cancer. Dr. Liotta replied that proteomic changes in the peritoneal fluid, as well as in serum, from patients with ovarian cancer are being followed in a clinical trial being conducted in collaboration with the Medicine Branch. Dr. Klausner announced that a special working group will be organized to discern sensitivity and specificity of this bioinformatics tool in assessing ovarian cancer. Dr. Liotta explained that most patients with ovarian cancer are currently diagnosed at stage III of disease—that is, after dissemination of cancer throughout the peritoneal cavity. Early detection of ovarian cancer is associated with a very good outcome using conventional chemotherapy.

Dr. Susan Love, Adjunct Professor, University of California School of Medicine, asked whether breast fluids were also being evaluated. Dr. Liotta responded that breast fluid samples currently are being evaluated, and preliminary data look promising. Dr. Klausner stated that resources across NCI will be solicited to aid this endeavor by the CPI, such that serum protein patterns can rapidly be validated as a tool for early detection of ovarian cancer.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5 U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Members were instructed to exit the room if they deemed their participation in the deliberation of any matter before the board to be a real conflict or would represent the appearance of a conflict. Members were asked to sign a conflict of interest/confidentiality certification to this effect.

During the closed session of the meeting, a total of 1,289 applications were reviewed requesting support of $364,080,348. Funding for those 1,289 applications was recommended at a level of $359,852,551.

XII. ADJOURNMENT—DR. PHILLIP SHARP

There being no further business, the open session of the 118th meeting of the National Cancer Advisory Board was adjourned at 5:00 p.m. on Tuesday, May 22, 2001.