# DEPARTMENT OF HEALTH AND HUMAN SERVICES
# PUBLIC HEALTH SERVICE
# NATIONAL CANCER INSTITUTE

# 120th NATIONAL CANCER ADVISORY BOARD

## Summary of Meeting
## December 4-5, 2001

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

# NATIONAL CANCER ADVISORY BOARD
# BETHESDA, MARYLAND

## Summary of Meeting
## December 4-5, 2001

The National Cancer Advisory Board (NCAB) convened for its 120th regular meeting on Tuesday, December 4, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, December 4, 2001, 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. The meeting was reopened to the public on Wednesday, December 5, 2001, at 8:30 a.m. until adjournment at 12:00 noon. Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, served as Acting Chair of the NCAB and presided during both the open and closed sessions.

**NCAB Members**

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. Frederick P. Li
Dr. Susan M. Love
Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis
Dr. Larry Norton (Acting Chairperson)
Dr. Amelie G. Ramirez
Dr. Ivor Royston
Ms. Ellen L. Stovall

**President's Cancer Panel**

Dr. Harold Freeman (Chairperson)
Ms. Frances Visco

**Alternate Ex Officio NCAB Members**

Dr. Steven K. Akiyama, NIEHS
Dr. Michael A. Babich, USPSC
Dr. T. G. Patel, VHA
Dr. Peter Kirchner, DOE
Dr. Hugh W. McKinnon, EPA
Dr. John M. Powers, DOD, OASD, HA
Dr. Richard Pazdur, FDA

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

Dr. Alan Rabson, Acting Director, National Cancer Institute

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.

Ms. Julie Taylor, American Society of Clinical Oncology, Inc.

Dr. Robert W. Frelick, Association of Community Cancer Centers

Ms. Shalini C. Vallabhan, American Cancer Society

Ms. Alicia Luchowski, The American College of Obstetricians and Gynecologists

Ms. Nancy Riese Daly, American Society of Therapeutic Radiology and Oncology

Ms. Barbara LeStage, NCI, Director's Consumer Liaison Group

Ms. Alexine Clement Jackson, Intercultural Cancer Council

Dr. Carl Mansfield, American Society of Therapeutic Radiology and Oncology

Ms. Patricia Jassak, Oncology Nursing Society

## TABLE OF CONTENTS

## DAY ONE—TUESDAY, DECEMBER 4, 2001

## DAY TWO—WEDNESDAY, DECEMBER 5, 2001

**Center for Cancer Research Reports (continued)**

***Representative Vaccine Initiatives***



***New Technology Initiatives***

## DAY ONE—TUESDAY, DECEMBER 4, 2001

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

Dr. Norton welcomed Board members, representatives of liaison organizations, and members of the public, and he invited the public to submit to Dr. Marvin Kalt, Director, Division of Extramural Activities, and Executive Secretary, NCAB, in writing and within 10 days, comments regarding items discussed during the meeting. Dr. Norton 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 September 2001 NCAB Meeting. They were unanimously approved by the Board.

Dr. Norton reminded Board members that the material furnished for review and discussion during the closed portion of the meeting is considered privileged information.

He stated that advisors and consultants serving as members of chartered advisory committees may not participate in situations wherein any violation of conflict-of-interest laws and regulations might occur. He indicated that responsible NCI staff would ensure that Board members would not perform duties or render advice that might have a direct and predictable effect on the interest of any organization or institution in which they had a financial interest. In particular, Board members were informed that they could not participate in the evaluation of grant applications or projects for Federal funding in which, to the member's knowledge, any of the following had a financial interest: the committee member; his or her spouse; any individual with whom the member has a close personal relationship; a dependent child, parent, or partner (including close professional associates); or an organization with whom the member or other parties named is seeking employment or serving as an officer, director, trustee, general partner, agent, attorney, consultant, or contractor.

### II. FUTURE BOARD MEETING DATES—DR. LARRY NORTON

Dr. Norton called Board members' attention to future meeting dates listed in the Agenda. Dates have been confirmed through 2003.

### III. RECOGNITION OF THE FORMER NCI DIRECTOR—DR. LARRY NORTON

Dr. Norton welcomed Dr. Richard Klausner, former Director, NCI, to the Board meeting. He read a resolution that praised Dr. Klausner for his many contributions to the NCI since his appointment as Director in 1995, and thanked him for his dedicated service. Dr. Klausner expressed gratitude for the opportunity to serve and for his association with the Board.

### IV. REPORT OF THE ACTING DIRECTOR, NCI—DR. ALAN RABSON

Dr. Alan Rabson, Acting Director, NCI, called the Board's attention to the new security arrangements on the NIH campus that have been instituted in the wake of the September 11 events. Increased security measures, including car searches at the new Clinical Center underground parking garage and a planned perimeter fence around the campus, will be very expensive; supplemental funds for

security are being sought by the Secretary of the Department of Health and Human Services, but the amount of that additional support is still unknown.

In reviewing his many years of service at NIH, Dr. Rabson observed that he has worked for eight different NCI Directors during his career at the Institute. He added that the Director he felt closest to, and the one he considered the most brilliant and creative, was Dr. Richard Klausner. To create a context for the current search for a new Director, Dr. Rabson provided a survey history of the National Cancer Institute. In 1971, when the National Cancer Act was passed, the original intent of the legislation was to remove the NCI from NIH and create a separate program that reported directly to the President. The scientific community expressed many concerns about the impact this change would have on biomedical research in general and cancer research in particular. A compromise was reached, which left the NCI within NIH but also gave the Institute special privileges. These included Presidential appointment of the Director, the establishment of special advisory panels—the NCAB and the President's Cancer Panel—and the power to develop a Bypass Budget to be delivered directly to the President, bypassing the Department Secretary. To ensure that the NIH Director had a higher status than the NCI Director, it was also decided that the NIH Director would be a Presidential appointee with Senate confirmation.

Dr. Rabson asked Dr. Robert Wittes, Deputy Director for Extramural Science and Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, to present a report on the NCI budget and an update on extramural research programs.

## V. STATUS OF FY 2002 EXTRAMURAL FUNDING—DRS. ROBERT WITTES AND MARVIN KALT

Dr. Kalt reminded the Board that projections for FY 2002 were based on the advice of the Research Project Grant (RPG) Working Group chaired by Dr. Phillip Sharp and comprising NCAB members, Institute staff, and members of the NCI Board of Scientific Advisors (BSA) and Board of Scientific Counselors (BSC). The efforts of the RPG Working Group concentrated on maintaining stability in numbers of grants awarded and ensuring reasonable growth in average costs.

Dr. Wittes explained that the NCI is operating under a continuing resolution pending approval of the FY 2002 budget, and spending is limited to FY 2001 levels. The President's FY 2002 budget request includes $4.177B for the NCI, increasing the budget by 11 percent, and the funding approved by the House of Representatives is close to that amount. The Senate's proposed spending is about $81M higher, representing an increase of about 14 percent. The next step is a conference between the House and the Senate to reconcile their appropriations bills.

The NCI's objectives for the RPG pool, Dr. Wittes stated, are to fund approximately the same number of new and recompeting awards as last year, continue using the exceptions pool, use the shrinking exceptions pool to continue the Accelerated Executive Review (AER) program, and fund other applications of particularly high priority, including the R41 Small Business Technology Transfer Research (STTR) grants to first-time investigators.

The Institute is approaching cost control in several ways, including capping allowable increases in major RPG mechanisms, trying to control growth in the average costs of awards, continuing a policy of reductions from recommended funding through the process known as downward negotiation, and restraining the growth of the RFA line.

Dr. Wittes explained that Type 5 RPG commitments—noncompeting continuations that total over $1.3B—will require an increase of $170M, representing over 40 percent of the Institute's expected budget increase. To avoid a backlog of grant award actions while waiting for the 2002 budget to be approved, the NCI has established an interim policy for noncompeting RPGs and has begun making awards to grantees who have December 2001 and January 2002 start dates at the same levels committed in their most recent notices of grant award. The NCI is also developing policies for competing awards.

While the receipt of applications for the third review round is not complete, Dr. Wittes said, the NCI anticipates an increase of 4 to 8 percent in the number of R01 applications received. To maintain the same success rate as in FY 2001, the payline may have to drop slightly, from the 22nd percentile to around the 20th. To avoid a backlog, as with noncompeting grants, the NCI has started making awards to competing R01s with scores better than the 17th percentile.

A two-tiered policy has been established for downward negotiation, with an average 5 percent reduction for grants under $175,000 and an average 11 percent reduction for larger R01s. These are not across-the-board reductions, but averages for the portfolio, and Program Directors have flexibility in negotiating specific reductions within those averages. Restrictions implemented last May on accepting R01s over $1M in total costs have had some effect on average requested costs through the second round; if this trend continues, the NCI may be able to fund competing R01s at levels closer to those recommended by study sections. The cap on increases for Type 2 R01 and P01 applications will continue, Dr. Wittes added, and exceptions will be infrequent. Applications that request increases greater than 20 percent without prior approval may be selected for funding at a level of increase that conforms to the cap. The NCI is endeavoring to make sure the grantee community is aware of these policies so that the contents of grants, in addition to their budgets, do not have to be renegotiated. The increase in P01 applications and the cost of Type 2 renewals of large grants this year may require a reduction in the success rate for P01s, even if the amount available for competing grants is increased.

Dr. Wittes reported that the NCI intends to keep funds allocated to RFAs at around 7 percent of the total competing budget, which is close to last year's level. This may require delaying support for some worthy initiatives that require the identification of available funds beforehand, including the publication of concepts already approved by the BSA. This policy is motivated by the need to ensure adequate continued support for important existing initiatives. The planned release of Program Announcements (PAs) will go forward because the funding of grants submitted in response to PAs is determined primarily by the payline.

Dr. Wittes described the review, during a recent BSA meeting, of a large randomized clinical trial proposed by NCI staff to study the use of spiral computed tomography (CT) in lung cancer early detection—a project that would consume tens of millions of dollars per year for a number of years. The proposal considered by the BSA was a revision of a concept reviewed at a previous meeting and revised by NCI staff in collaboration with a BSA subcommittee. The BSA had no significant criticisms of the revised concept, but engaged in a spirited discussion of the possible loss of scientific opportunity that could occur in other areas due to the cost of the proposed study. Those in favor of approval argued that the study promised to make significant reductions in mortality from a very important disease for which no alternative means for such reductions are available. The BSA approved the concept by a vote of about 2 to 1. The NCI now has the task of deciding whether to proceed with the study. The decision will depend on budget levels for the coming years, but Dr. Wittes stressed the fact that this trial cannot be conducted without cost to other research opportunities. He added that discussions have been initiated with European investigators concerning collaborative efforts in spiral CT research. Contacts have also been made with

managed care providers and the insurance industry to explore the possibility of additional financial support, based on the premise that the entire health care community would benefit from learning whether spiral CT is effective in lung cancer screening.

To reduce a downward trend in the number of new investigators, Dr. Wittes continued, the NCI expects to allocate additional funds in FY 2002 for R41 STTR awards. The President's budget reflects an estimated 12 to 13 percent increase for Centers and for Specialized Programs of Research Excellence (SPOREs). Although the NCI feels that the SPOREs program should continue its recent growth, Dr. Wittes acknowledged that if additional funds are not forthcoming, growth may have to be constrained. The President's budget also contains an estimated 11 percent increase in the Careers Program and a 12 percent increase for Prevention and Control.

Dr. Wittes reminded the Board that the NCI budget, like those of other NIH components, is subject to "taps" at the NIH level to support agencywide needs, such as information technology and business systems. Security has been a significantly greater concern for the NIH since September 11, and is likely to result in additional taps that will affect the NCI budget.

The NCI Executive Committee (EC), Dr. Wittes reported, discussed the FY 2004 Bypass Budget during its most recent meeting. There was a consensus that the current format of the Bypass Budget, envisioned and implemented by Dr. Klausner, remains a clear articulation of NCI priorities and that the document should continue to provide a visionary statement of the NCI's best professional judgment of need. It was also agreed that while Extraordinary Opportunities (EOs) within the Bypass Budget should be subject to revision, there should not be a great deal of turnover among these concepts. Ideas that are suggested to the NCI as potential EOs may be viewed by the EC as being extraordinarily important without meeting the criteria used to define EOs for the purposes of the Bypass Budget. The EC is contemplating some modifications in the Bypass Budget that will make this distinction clearer.

One source of such ideas, Dr. Wittes noted, is the series of Progress Review Groups (PRGs) that have convened experts to assess progress in the fight against particular diseases and offer recommendations for action. The NCI faces a challenge in converting these recommendations into implementation strategies and in assessing the success of these strategies. The Institute also faces a challenge in dealing with the expectations that arise as a result of interactions between the NCI and disease-oriented communities. Dr. Wittes noted that the NCI has been more successful in formulating recommendations and translating them into strategies than in follow-up and analysis. Therefore, he reported, the NCI has decided to temporarily suspend the creation of new PRGs to ensure that the Institute can adequately handle what has already been set in motion. The NCI also wants to rethink aspects of the PRG process to make the initial stages less labor-intensive (both for NCI staff and for external experts) and to improve the process for continuing dialog with the communities that are created by the establishment of the PRG process.

Finally, Dr. Wittes announced that on March 1, 2002, he will join the Memorial Sloan-Kettering Cancer Center as Physician in Chief. He said that this gives him an opportunity to return to working with patients and to help that institution build on its strength as a leader in the molecular revolution in cancer research and the development of humane and effective interventions. Dr. Wittes thanked the NCI staff and the NCAB for the pleasure of working with them during his years at the National Cancer Institute.

Dr. Rabson reported that he had appointed Dr. Ellen Feigal, Deputy Director, DCTD, to serve as Acting Director of the same Division.

**Questions and Answers**

Dr. Norton asked whether adequate accrual to the spiral CT study is considered to be possible in the United States, considering the fact that, in some areas, spiral CT scans are becoming a standard form of screening for smokers. Dr. Wittes said that early concern on the part of the EC led to a pilot study that provided evidence that randomization to a control arm in this trial can be accomplished. He added that a delay of 1 or 2 years to deliberate on whether to conduct the study could close the window of opportunity to accomplish the needed accrual.

Dr. Frederick Li, Chief, Division of Cancer Epidemiology and Control, Dana-Farber Cancer Institute, suggested that the NCI emphasize the fact that twice as many Americans die each week from cancer as the total number of lives lost so far in the war on terrorism. Dr. Rabson said that the NCI and the NIH are doing everything possible to make it clear that both the war against terrorism and health research are important. He added that the Bypass Budget is an excellent mechanism to outline the importance of high-priority research objectives, estimate their cost, and explain the cost of not conducting the recommended research. Noting the statement made during the recent BSA meeting that the proposed spiral CT concept is "a study that you can't *not* do," Dr. Rabson asked Dr. Wittes to comment on its likely impact on the NCI payline. Dr. Wittes said that the annual cost of the spiral CT study for the first 2 or 3 years of the trial would represent 2 or 3 percent of the RPG payline; he stressed, however, that such a reduction in the payline may not be the way NCI pays for the study, since there are other ways of controlling costs.

Dr. Ralph S. Freedman, Professor, Department of Gynecologic Oncology, M. D. Anderson Cancer Center, University of Texas, asked how much support can be expected from industry to help pay for the spiral CT trial. Dr. Wittes said that initial contact has shown that some companies are interested in working with the NCI on the study. Some may provide financial support, while others may provide technical support through maintenance of or upgrades to performance sites.

## VI. NCI CANCER PROGRESS REPORT—DRS. BARBARA RIMER AND ROBERT HIATT

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences (DCCPS), explained that the *NCI Cancer Progress Report* was prepared to respond to concerns about accountability and evaluation in government. Ultimately, she noted, the public has a right to know how the investment in cancer research is faring. The intended audience for the report consists of policymakers, the scientific community, and the general public, and its development was a collaborative effort among NCI and its contractors, other Federal agencies, state health agencies, professional associations, and the advocacy community.

Dr. Robert Hiatt, Deputy Director, DCCPS, told the Board that the report was designed to provide a single accessible source of national cancer information and trends. The report compares current cancer statistics with the cancer-related targets set forth in *Healthy People 2010.* Measures were selected based on scientific evidence and the availability of long-term national, rather than state or local, data collection and analysis efforts. Progress was tracked over time, generally starting in 1990. Criteria for selecting data included their relevance in terms of impact on cancer and policy implications; their scientific rigor, including validity and reliability; their feasiblity in terms of durability, scope, and availability; and their usability at a national level. The report is organized by domains of cancer research: prevention, early detection, diagnosis, treatment, survivorship, and the end of life.

Dr. Hiatt stated that, according to the report, the nation is making good progress against cancer as reflected by decreases in mortality and incidence and by changes in behavior that reduce risk factors. Certain trends are in the wrong direction, however—for example, some cancers, including melanoma and esophageal cancer, are on the increase. The report also reveals the need for better measures for treatment, environmental exposure, quality of care, and quality of life. A "highlights" section in the report displays measures on a grid that can be used for comparison purposes. Dr. Hiatt explained that the grid defines the measure, the time period covered, the trend over time, the desired direction of the trend (increase or decrease), the most recent estimate, the *Healthy People 2010* target and the progress relative to that target, and the page of the report where more detailed information can be found.

Dr. Hiatt announced that an online version of the report is available in addition to the print version distributed to Board members, and a CD-ROM would be available shortly. The online version will be updated annually or semiannually, and the print version may be updated every 2 years. Dr. Hiatt concluded his remarks by reminding the Board that behind the statistics are people who have had cancer or who are concerned with cancer on behalf of family members or for other reasons, and he expressed the hope that the report would be helpful to these individuals.

**Questions and Answers**

Dr. Sandra Millon-Underwood, Professor, University of Wisconsin-Milwaukee School of Nursing, suggested that information on interventions known to be effective in addressing issues such as screening and behavior would be a helpful addition to the report. Dr. Hiatt responded that the *Guide to Community Preventive Services,* now being produced through a joint effort of the Centers for Disease Control and Prevention (CDC), the NCI, and other agencies, focuses on such interventions.

Dr. Hugh McKinnon, Associate Director for Health, National Risk Management Research Laboratory, U.S. Environmental Protection Agency (EPA), praised the report and pointed out that it can be very difficult to find the linkages between environmental data and human consequences. He stated that EPA Administrator Christine Todd Whitman has initiated a "state of the environment" report, due to be issued in September 2002, that will represent a first step in progressing from process and output measures to outcome measures. Dr. Hiatt noted that his team had made use of EPA information in developing the *NCI Cancer Progress Report*.

Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, Washington Hospital Center, asked whether there were plans to broaden the reach of the report through the use of television. Dr. Hiatt explained that the usability testing of the report indicated that the public liked the report, and he told Dr. Huerta that DCCPS would consult with him regarding accessibility to specific communities, particularly special populations. Dr. Norton agreed that making the report available in other languages would be extremely useful.

Ms. Frances Visco, President, National Breast Cancer Coalition, and member, President's Cancer Panel, wondered whether the data in the report could be made available in more detail—for example, analyzed by age. Dr. Hiatt replied that readers are referred to *Healthy People 2010* to find such an analysis, and that in the report, sources of the data are noted, and scientific papers are cited for those seeking more detailed information.

## VII. IMPROVING PALLIATIVE CARE FOR CANCER: NATIONAL CANCER POLICY BOARD REPORT—DRS. KATHLEEN FOLEY AND ROBERT WITTES

Dr. Kathleen Foley, Attending Neurologist, Memorial Sloan-Kettering Cancer Center, and Professor of Neurology, Neuroscience, and Clinical Pharmacology, Weill Medical College of Cornell University, explained that *Improving Palliative Care for Cancer,* the National Cancer Policy Board (NCPB) Report for 2001, builds on other reports of the Institute of Medicine (IOM), National Academy of Sciences (NAS), such as *Approaching Death: Improving Care at the End of Life* and *Ensuring Quality Care for Cancer.* The NCPB report contains two parts: Part I, which includes a summary and ten recommendations; and Part II, which is composed of eight commissioned chapters. The report identifies barriers to excellent palliative and hospice care and makes recommendations for overcoming them. Dr. Foley described the identified barriers:

**1) Separation of palliative and hospice care from potentially life-prolonging treatment.** Medicare offers a restricted benefit for hospice care that allows patients to receive active curative therapy or hospice care, but not both. The report calls for the funding of demonstration projects for service delivery and reimbursement that integrate palliative care and potentially life-prolonging treatments throughout the course of disease.

**2) Inadequate training for health care professionals.** Dr. Foley reported that there are 33 fellowship training programs in palliative care in the United States, and the overwhelming majority are funded by philanthropies or the institutions themselves. Most of these programs are based in cancer centers, demonstrating that oncologists are taking the lead in this area. A recommendation to provide clinical and research training fellowships, create faculty development programs, and provide in-service training for local hospice staff is included in the report.

**3) Disparities in care among racial groups.** For example, less than 14 percent of African Americans receive hospice care at the end of life. The report recommends uncovering the determinants of disparities in access to care and developing initiatives to increase access

**4) Lack of information resources for the public.** Dr. Foley stated that she had reviewed patient information materials from major cancer organizations and found only one that mentioned death as a possible outcome for patients with cancer—a publication entitled *Living with Cancer*. She encouraged the American Cancer Society (ACS), the NCI, and other organizations that provide cancer information to the public to include comprehensive and accurate information on palliative and hospice care to help patients with cancer make appropriate choices.

**5) Lack of reliable data on quality of life and quality of care for patients at the end of life.** Support for cancer registries, new mechanisms for quality-of-care data, a core set of cancer-care quality measures, technologies to improve clinical data to assess quality of cancer care, and demonstration projects on the impact of quality monitoring programs are among the report's recommendations to enhance data systems to improve the quality of cancer care.

**6) Lack of accountability for providing quality care and absence of measures to evaluate quality of care.** A major recommendation of the NCPB was that NCI-designated cancer centers should play a central role in advancing palliative care research and clinical practice. Cancer centers could test and evaluate practice guidelines, pilot-test quality indicators, and incorporate best practices in palliative

care into NCI-sponsored clinical trials. This initiative would also begin to meet the need for data collection to validate practice guidelines.

**7) Low level of public sector investment in palliative care research and training and inadequate reimbursement rates under government health programs for palliative care.** Less than 1 percent of the NCI budget is currently focused on palliative care. A recent survey of oncologists revealed their frustration with the fact that they are reimbursed only for treatment and not for advising patients on options for the end of life. An unintended consequence of this policy is that some oncologists may administer aggressive chemotherapy beyond the time when it is likely to benefit the patient. Dr. Foley added that one study has found palliative care to be cost-effective. NCPB recommends that NCI convene a "State of the Science" meeting on palliative care and symptom control. Other Institutes and government research agencies with shared interests should be invited to collaborate and develop a high-profile strategic agenda.

Dr. Wittes pointed out that a number of recommendations in the report are directed at societal factors and health care reimbursement issues, which are outside NCI's purview. He stated that NCI would be receptive to the issuance of a program announcement for investigator-initiated research on palliative care and end-of-life issues. Moreover, the R25 funding mechanism is suitable for grants in this and other areas that require transdisciplinary training programs. Dr. Wittes observed that palliative care and end-of-life issues cut across the expertise and resources of several NCI Divisions, and, therefore, the NCI coordinating function on palliative care might best be carried out in the Office of the Director. NCI is planning a meeting in February 2002 to bring in other interested groups to share ideas and define areas of common interest. The recommended State of the Science meeting, which has already been scheduled for July 15-17, 2002, will concentrate on symptom management. The NCI Office of Communications has an interest in assessing and expanding educational information, both on the NCI Web site and in print format, relating to palliative care and end-of-life issues. The American Society of Clinical Oncology (ASCO) has also been active in developing educational materials for its membership. Dr. Wittes suggested that the NCAB Subcommittee on Cancer Centers take up the issue of the centers' roles in research and practice guidelines for palliative care.

**Questions and Answers**

Dr Freedman asked for information on the number of grants issued on palliative care and the proportion in relation to other grants. Dr. Wittes replied that these grants receive the same level of attention as other grants, and aggressive publicity for NCI's interest in this field might be sufficient to attract more investigator-initiated applications.

Dr. Millon-Underwood inquired as to whether the NCI Executive Committee would discuss the NCPB report in the near future. Dr. Wittes responded that decisions on a budget and on the involvement of other Institutes and nongovernmental partners need to be discussed prior to Executive Committee decision making.

Dr. Norton concluded the session by pointing out that NCPB and other IOM reports have been very influential in initiating discussions on a variety of cancer care issues.

## VIII. PRESIDENT'S CANCER PANEL REPORT—DR. HAROLD FREEMAN

Dr. Harold Freeman, Director of Surgery, North General Hospital; Director, North General Cancer Center; and Chairperson, President's Cancer Panel (PCP), reminded Board members that December 2001 is the 30th anniversary of the declaration of the War Against Cancer by President Richard Nixon. Dr. Freeman acknowledged the major advances made in cancer research, but he pointed out that problems with the cancer care delivery system persist. He reported that the hearings held during 2000 and 2001 in seven cities (Omaha, NE; Burlington, VT; Billings, MT; Nashville, TN; Los Angeles, CA; Albuquerque, NM; and Washington, DC) provided forums for nearly 400 people to testify about barriers to cancer care. Dr. Freeman expressed his appreciation of the work of the other members of the Panel: Ms. Frances Visco, President, National Breast Cancer Coalition, and Dr. Dennis J. Slamon, Chief, Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles.

Dr. Freeman listed the barriers to cancer care: barriers to access, including system-related, financial, and physical; barriers to information or education; and barriers based on culture or bias, including those related to the patient or public and the provider. Dr. Freeman then outlined several recommendations the Panel has made to lower such barriers: 1) provision of immediate medical insurance coverage for those without insurance upon a diagnosis of cancer; 2) reimbursement for cancer drugs regardless of their route of administration; 3) provision of a standard health benefits package for cancer care that would be applied to all Americans; 4) creation of community programs to help people with cancer navigate through the insurance and health care delivery systems; 5) establishment of insurance reimbursement policies for nonphysician personnel such as nurse practitioners and physician assistants; 6) clarification of the order of responsibility for payment when an individual is eligible for benefits under more than one public health care program; 7) establishment of training programs both to eliminate cultural and racial bias, not only among providers but also among patients, and to develop systems for continued monitoring to ensure that treatment equity is an integral part of quality cancer care; 8) minimization of disparities in the provision of cancer care by educating primary care providers about the nature and application of evidence-based medicine and developing better tools to assist health care providers in conveying information about cancer care options; 9) expansion of telemedicine usage as a way to deliver care more effectively to sparsely populated areas; and 10) allowance for a more flexible use of categorical funding so states will have the opportunity to fashion more rational and comprehensive cancer care programs.

The Panel's report reached several conclusions: no person with cancer in America should go untreated; no person in America should experience insurance-related diagnosis and treatment delays; and no person in America should be bankrupted by a diagnosis of cancer.

Dr. Freeman concluded his presentation by showing a 9-minute video to the Board, *Voices of a Broken System: Real People, Real Problems*, depicting the highlights of the hearings.

### Questions and Answers

Dr. Richard Boxer, Clinical Professor of Health Policy, Medical College of Wisconsin, University of Wisconsin-Madison, encouraged the Panel to emphasize the need for insurance coverage of diagnostic evaluations; otherwise, diagnosis may be too late to allow for effective cancer treatment.

Dr. Norton asked what role NCI could play in terms of evaluation or implementation of the Panel's recommendations. Dr. Freeman responded that NCI could take a more aggressive role in public education and in influencing the training of medical doctors. Dr. Hiatt added that NCI could develop measures for some of the panel's recommendations and track them over time. He pointed out that IOM's reports have repeatedly stressed the lack of good data systems for tracking quality of care over time. Dr. Freeman pointed out that these changes require influencing people, and research results seldom are persuasive in changing opinions.

## IX. LEUKEMIA, LYMPHOMA, AND MYELOMA PRG REPORT—DRS. WYNDHAM WILSON, KENNETH ANDERSON, AND CLARA BLOOMFIELD

Dr. Clara Bloomfield, Director of the Comprehensive Cancer Center; Deputy Director, Arthur G. James Cancer Hospital, Richard J. Solove Research Institute; and Co-Chair, Leukemia, Lymphoma, and Myeloma (LLM) Progress Review Group (PRG), noted that the charge to the PRG was to help the NCI develop an agenda for research on LLM. The goals were to identify and prioritize research opportunities and needs, examine the required scientific priorities in the context of the current NCI research portfolio, and prepare a written report, which was issued in May 2001.

Taken together, leukemia, lymphoma, and myeloma constitute the fourth most common type of cancer, and more than 700,000 people are currently living with these diseases. An estimated 60,000 people are expected to have died of these diseases in 2001. The 5-year survival rate for LLM is low, and in the United States, leukemia and lymphoma cause more deaths in children than any other disease. The incidence rate for lymphoma has increased dramatically since the 1970s; in contrast, the death rate for many other cancers is dropping. However, scientists' understanding of the pathogenesis and pathophysiology of LLM is well advanced, and this knowledge affords the opportunity to develop therapeutic approaches that not only will cure or eliminate these diseases but will translate to all other malignancies. The success of molecularly targeted therapy in acute promyelocytic leukemia is an excellent example of molecularly targeted therapy for curing cancer.

The LLM PRG convened a roundtable meeting with 180 participants in December 2000. Small groups divided according to research area met to identify their top research priorities for the next 5 to 10 years. The small groups agreed on many important research priorities, and the LLM PRG used these priorities to create an "Agenda for Action." Dr. Kenneth C. Anderson, Associate Professor, Department of Medicine, Dana-Farber Cancer Institute, outlined the first two elements of the Agenda, while Dr. Wyndham Wilson, Staff Clinician, Experimental Transplantation and Immunology Branch (ETIB), Center for Cancer Research (CCR), NCI, discussed the last three elements:

**1) Etiology.** Understanding the interactions among genotype, immune function, infectious agents, environmental toxins, and lifestyle factors that can lead to hematopoietic malignancy. The PRG strongly recommended a large national longitudinal case-control and cohort study to help identify causes of LLM.

**2) Pathobiology.** Identifying the basic mechanisms responsible for genome instability, chromosome translocations and other mutations in hematologic malignancies; defining the relationship between the development of hematologic malignancies and the host biological environment; targeting not only the tumor cell, but also the stromal microenvironment; providing molecular characterization of hematological malignancies; and further developing research on stem cells, both multilineage and single lineage. NCI initiatives currently underway—e.g., the Cancer Genome Anatomy Project—are already

addressing some of these issues with new methodologies such as gene array, proteomics, spectral karyotyping, and comparative genomic hybridization.

**3) Drug Development and Therapeutics.** Developing the resources to translate lead structures and molecules into effective therapeutic agents and fostering partnerships among the NCI and academia, advocates, cooperative groups, the Food and Drug Administration (FDA), and industry to expedite drug development and availability of therapies.

**4) Education, Communication, and Survivorship Research.** Determining how to provide accurate, timely, and tailored information to patients to improve medical decision making; developing education and training programs for certification of physicians and centers for diagnosis, treatment, and clinical trials in hematological malignancies; and identifying individuals and populations at high risk for adverse outcomes.

**5) A New Initiative, the Cancer Translational Research Allied Consortium (C-TRAC).** Comprising experts across multiple disciplines and institutions to participate within a formalized infrastructure, identifying, validating, and credentialing targets; and developing a "virtual enterprise" to coordinate the rapid development of validated targets into treatments, with services ranging from discovery and preclinical testing to early clinical trials. The goal of C-TRAC would be to shorten drug development from 5 to10 years to 2 years through a novel alliance among academia, industry, government, and patients.

The LLM PRG met with Dr. Rabson in November 2001 to identify those recommendations that are being addressed within the current NCI portfolio, determine which recommendations are not addressed by current NCI initiatives and projects, and discuss strategies for implementing these recommendations. NCI is now preparing a plan to implement high priorities not currently addressed, and the PRG will track NCI's progress. NCI will report back on its progress in 3 years.

**Questions and Answers**

Dr. Wittes reported that the Executive Committee will discuss the LLM PRG report at its next meeting and report back to the Board at the next NCAB meeting. The C-TRAC is a novel feature of the PRG report, but given the large number of tasks assigned to this initiative and the coordination required for accomplishing those tasks, it would need to be a formal structure rather than a virtual enterprise. Dr. Wilson clarified that the focus of the C-TRAC would be to coordinate existing endeavors, and therefore, it should be viewed as a formal structure. He further explained that because this initiative is not framed in an organization similar to that of a drug company, the term *virtual enterprise* was used to characterize it.

Dr. James O. Armitage, Professor and Dean, College of Medicine, University of Nebraska Medical Center, asked how NCI and the FDA might handle a situation in which two drug companies had drugs in development that acted similarly. Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, stated that such a situation represented no regulatory hurdle as long as strong preclinical and clinical rationales for each agent are available. He noted that proprietary issues might, however, pose a problem, preventing the two companies from cooperating with one another. Dr. Pazdur expressed FDA's willingness to work with NCI on this project.

## CENTER FOR CANCER RESEARCH REPORTS

## X. OVERVIEW—DR. CARL BARRETT

Dr. Carl Barrett, Director, CCR, NCI, presented NCAB members with an overview of the administrative and organizational changes the CCR has undergone to facilitate translational research within the Intramural Research Program (IRP) and to promote new clinical initiatives. The CCR was formed in March 2001 by merging the Divisions of Basic and Clinical Sciences. It is composed of 54 Laboratories or Branches, 330 Principal Investigators (PIs), and more than 3,000 employees. Dr. Barrett enumerated four goals of the CCR: fostering interdisciplinary research, facilitating translational research, expediting technology development, and enhancing training.

**Fostering Interdisciplinary Research.** Dr. Barrett described the CCR's organization and new initiatives, which are designed to meet this goal. The primary scientific organizational entity remains the individual PI, who sets his or her own research path. High-quality science is maintained through the Board of Scientific Counselors' (BSC) review process. Laboratories and Branches continue to be the primary administrative structures, but new organizational components and appointment mechanisms have been initiated that bridge these structures and provide new venues for interdisciplinary and translational research: Faculties and Adjunct Appointments.

The NCI Faculties are composed of scientists from diverse laboratories working cooperatively with a common interest in a particular discipline, disease, or approach to scientific discovery. They provide a forum to enhance and enable collaboration, interdisciplinary research, and translational science. Currently, there are 11 Faculties: 7 discipline-based, 3 disease-based, and 1 focused on molecular targets. Membership varies—over 80 percent of the PIs belong to at least one Faculty, with most PIs participating in more than one group. In addition to the Faculties, the CCR also sponsors eight Working Groups. Faculty and Working Group activities include holding seminars and retreats, sponsoring visiting scientists, conducting special research projects, fostering training opportunities, promoting technology development, and being involved in strategic planning. Dr. Barrett gave examples of each of these activities.

Adjunct Appointments represent a formal mechanism to allow a scientist in one Laboratory or Branch to become a functional member of another Laboratory or Branch. Dr. Barrett explained that laboratories can be somewhat isolated environments, and that adjunct appointments are now being used to encourage scientific collaborations, provide access to translational research opportunities, promote integration of different disciplines, and permit access to needed expertise.

**Facilitating Translational Research.** Dr. Barrett pointed out that the creation of the CCR itself was designed to break down the barriers between basic and clinical sciences. The CCR's Medical Oncology Clinical Research Unit was recently reorganized into clinical research sections, clinical cores, and offices to provide an institutional infrastructure to support translational initiatives. A more detailed report on the reorganization of the Medical Oncology Research Unit was provided by Dr. Ronald Gress.

**Expediting Technology Development.** The CCR has been heavily involved in technology development. Examples of some of the technology initiatives are in the areas of microarrays, proteomics, animal models, molecular targets, imaging technologies, molecular and comparative pathology, genome analysis, and bioinformatics. The CCR's molecular targets initiative is expected to attract investigators who will bring forward new molecular targets that promote the understanding of the basic biology of a

particular gene or gene product and lead to new drugs, as well as the generation of new research reagents. The CCR is also working on transgenic and knockout mouse strains and a Web-based database to make these animal model more widely available. Moreover, scientists from the Mouse Models of Human Cancer Consortium (MMHCC) are working with scientists from other Institutes to develop phenotyping programs for mouse models, taking advantage of opportunities that cut across NIH boundaries.

Proteomics is a major emphasis, and the CCR has established the Mass Spectrometry Center and the Protein Expression Laboratory to work with Dr. Lance Liotta and Dr. Emanuel Petricoin in an NCI/FDA Clinical Proteomics Program to identify proteomic markers from tumor versus normal tissue.

**Enhancing Training.** One emphasis of the CCR's training program is on interdisciplinary and translational research. The Center is seeking to identify training areas that take advantage of the basic and clinical strengths of the IRP. Dr. Barrett listed 16 training programs offered by the CCR, and he described a new program, the Graduate Program Partnerships, where the NCI partners with academic centers to offer interdisciplinary training programs in chemistry, bioinformatics, comparative molecular pathology, and cancer epidemiology.

Dr. Barrett summarized his overview of the CCR by pointing to the IRP's excellence in the areas of cancer vaccines, clinical proteomics and genomics, and molecular targets and pathways, as examples of where intramural scientists can pursue long-term, high-risk projects with public health importance. The CCR plans to continue to build partnerships with academic centers, extramural investigators, NCI SPOREs, and biotechnical and pharmaceutical companies, to further the goals of the IRP.

**Questions and Answers**

Dr. Norton and Dr. Arthur Nienhuis, Director, St. Jude Children's Research Hospital, asked Dr. Barrett about the functionality of the organizational and administrative structures in an environment that encourages transdisciplinary research and where investigators serve on multiple Faculties or multiple programs. Dr. Barrett explained that the major organizational and administrative structures are the Laboratories and Branches, and each investigator has his or her own budget that is reviewed by peer reviewers and the BSC. The NCI Faculties serve as intellectual engines to drive the creative process, and provide a forum for scientific collaboration. They also serve as oversight groups for decisions on investments in new technologies. He acknowledged that PIs have expressed reservations about the system in that they felt they could be penalized for doing translational or institutional research, because in past reviews they were reviewed solely on the basis of their independent work. Dr. Barrett noted that he is seeking to change the way to evaluate investigators not only on their independent research, but also on their transdisciplinary efforts.

Dr. Nienhuis also asked about how the CCR shared its resources. Dr. Barrett replied that some resources are centrally located core resources and some are in Laboratories and Branches, and although for some services usage is charged back to the scientists, access to technical expertise is readily available to all PIs.

## XI. NEW CLINICAL RESEARCH CENTER—DR. JOHN GALLIN

Dr. John Gallin, Director, NIH Clinical Center, described some recent Clinical Center activities to put in perspective NCI's substantial investment in the intramural clinical program. The Clinical Center's

budget in FY 2001 was $274M, which funded about 1,900 full-time-equivalent (FTE) employees. The Clinical Center supports more than 1,000 clinical research protocols run by 1,200 credentialed physicians. In FY 2001, the Center admitted approximately 7,000 inpatients and scheduled about 72,000 outpatient visits. The funding is derived from the so-called "school tax levy": once the Center's annual budget is determined, the Institutes are assessed in proportion to the size of their intramural programs. NCI's annual levy is about 30 percent of the Center's total, although NCI activity can amount to as much as 36 percent of the Center's total activity. Patients are not charged for their care, and their travel expenses are paid as needed.

The Clinical Center strongly emphasizes clinical research training. Courses include an introduction to the principles and practices of clinical research, clinical pharmacology, and bioethics. The Center has successfully developed long-distance learning programs in conjunction with Duke University and the University of Pittsburgh. The Center's bioethics course is available for all investigators. In addition, required training in clinical research for all Principal Investigators authoring protocols is available on the Center's Web site. Dr. Gallin reported that many non-NIH personnel have taken the course as well.

Dr. Gallin noted that the Clinical Center has a unique physical design, in terms of the proximity of the laboratories to patient care areas. He then outlined some of the Clinical Center's major accomplishments: lithium for bipolar disorder; blood tests for AIDS and hepatitis; the first gene therapy for ADA (adenosine-deaminase) deficiency; vaccines for *H. influenzae* Type b and hepatitis B; treatment of sickle cell disease with hydroxyurea; pathogenesis and treatment of AIDS; chemotherapy and immunotherapy for cancer; the first successful artificial heart valve; and first use of immunosuppressive drugs for nonmalignant diseases, such as lupus and Wegener's granulomatosis.

The Clinical Center's governance consists of a Board of Governors, made up of eight members from outside of NIH, including university presidents, hospital CEOs, and clinical investigators, and seven members from inside NIH who represent the leadership of the NIH intramural program. A Clinical Center Research Steering Committee helps the Clinical Center Director set funding priorities for research projects, and a Medical Executive Committee advises the Director on clinical issues. The Clinical Center's BSC reviews the independent research conducted by Clinical Center-based investigators. The Director also meets with a Patient Advisory Group, made up of patients from each Institute, that provides advice on patient needs as they relate to management of the Center.

Clinical trials make up about half of the Center's portfolio of protocols, and the other half is nearly all studies of natural history and disease pathogenesis. Small numbers of screening and training protocols make up the remainder. About 90 percent of the Center's clinical trials are Phase I and Phase II trials, and 8 percent are Phase III studies. However, 39 percent of NCI's portfolio at the Clinical Center consists of Phase III trials.

**New Initiatives.** The Clinical Center is developing a major clinical research information system, which will support hospital management and protocol writing and mapping. It will also capture data on clinical alerts, adverse event detection and reporting, data presentation for regulatory requirements, and training. The goal is the development of a uniform framework for writing protocols with recommended language for specifics. The protocol map is designed to define in detail what happens to the patient on each outpatient visit or each inpatient day. It will enable automated resource projections, define activities for each patient visit, facilitate scheduling, track those activities, generate milestone letters, and produce

reports for Data Safety Monitoring Boards, IRBs, regulatory agencies, and other audits. Dr. Gallin anticipated that the system would be fully operational in a year or two.

Dr. Gallin outlined areas of growth projected by NCI branches: Pediatric Oncology Branch—orthopedics activity, neuroblastoma, nonmyeloablative surgery, and pediatric renal cell cancer; Medicine Branch—clinical application of proteomics and imaging, increased outpatient neuro-oncology, and new approaches to use radiopharmaceuticals in cancer treatment; Surgery Branch—increased use of cellular therapies, increase in thoracic surgery, and increased patient acuity in cell-transfer protocols; and Radiation Oncology Branch—development of molecular targets for treating prostate, cervical, and ovarian cancer.

Dr. Gallin also described the new Mark O. Hatfield Clinical Research Center, which is under construction on the NIH campus. Displaying floor plans, he pointed out space available to NCI: Radiation Oncology, a vivarium for animal research, Pediatric and Urologic Laboratories, Critical Care Unit, Oncology Patient Care Unit, Bone-Marrow Transplant Unit, Surgery Branch Laboratory and Medicine Branch Laboratory. The NCI laboratory space totals about 76,500 square feet. The facility is designed in modules to facilitate movement of investigators back and forth from the laboratories. The building is scheduled to open in the summer of 2004.

**Questions and Answers**

Dr. T. G. Patel, Captain, MC USN (Retired), Program Chief, Veterans Health Administration, Department of Veterans Affairs, advised Dr. Gallin that the Veterans Health Administration was also working on electronic health information systems and suggested that the Clinical Center form a partnership with his Administration to perfect such a system.

Dr. Freedman inquired about the proportion of Clinical Center cancer patients who are not covered by health insurance. Dr. Gallin stated that a high percentage are uninsured or have nearly exhausted their insurance coverage. The Clinical Center's Board of Governors rejected the idea of collecting third-party payments because, since patients come from all over the country, the Center would have to deal with a multiplicity of third-party payers. Moreover, the Center does not have a billing system. To install such a system, Dr. Gallin pointed out, might cost more money than could be recovered. Dr. Freedman also asked whether information about the Clinical Center is available to people around the country. Dr. Gallin noted that with the establishment of the clinical trials Web site, www.clinicaltrials.gov, there have been shifts over the past 10 years in how patients are referred to the Center. Formerly, all patients were referred by private physicians. Today, 60 percent are self-referred, and about one-third of those patients obtained information from the Web. He observed that NCI does its own recruitment and does not use the Clinical Center's recruitment center.

Dr. Li expressed interest in the protocol writing and mapping systems and hoped that Dr. Gallin would be willing to share these tools with extramural investigators. Dr. Gallin responded that when the systems are completed, they will be freely accessible to the public. Dr. Amelie Ramirez, Associate Professor, Department of Medicine, and Deputy Director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, stressed that such tools will become more necessary as IRBs' requirements become more challenging.

Drs. Norton, Gallin, and Barrett agreed that the Clinical Center might offer an opportunity for extramural investigators to work with intramural investigators. Dr. Gallin pointed to telemedicine as a way to facilitate such collaborations.

## XII. MEDICAL ONCOLOGY PROGRAM—DR. RONALD GRESS

Dr. Ronald Gress, Chief, ETIB, and Associate Director of the Medical Oncology Program (MOP), CCR, NCI, described to the Board the reorganization of medical oncology activities within the NCI. He explained that the Medical Oncology Clinical Research Unit (MOCRU) was established in response to two primary events: a series of site visits that took place in the Medicine Branch of the former Division of Clinical Sciences, which challenged the NCI leadership to reconsider the structure of the medical oncology research within the IRP; and the reorganization of the IRP into the CCR. Dr. Gress noted that 9 different branches and laboratories of the 54 that make up the CCR are already engaged in medical oncology research at the level of clinical trials and currently admit patients to the NIH Clinical Center. Dr. Gress reported that the number of accruals from these branches and laboratories amounts to approximately 80 to 120 patients accrued over a 12-month period. He further pointed out that of these patients, 60 were accrued from branches of the former Division of Basic Sciences.

**Mission.** The new infrastructure of the Medical Oncology Program should permit open access to ideas emanating from the basic science branches, but it must also have a high degree of standardization in the conduct of clinical research. Moreover, Dr. Gress stated, the branches engaged in clinical research must be respected as independent scientific communities, and the new infrastructure must not limit programs that are already instituted. Clinical training, such as the Clinical Fellowship Program and other mechanisms for career growth, must be part of the reorganization's mission.

Dr. Gress emphasized two principles that he viewed as essential to the reorganization: excellence in achieving the goals of the MOP, and optimization of clinical investigation through team efforts. He acknowledged that the team approach has not always been NCI's paradigm for clinical research, but now it is believed that teams encompassing expertise across a spectrum of translational research, clinical research, and basic science research represent the best approach to clinical investigation.

**Organization.** Dr. Gress described the organizational components of the MOCRU. The Unit is composed of six Clinical Research Sections (CRSs), which represent diseases or therapeutic approaches. The second level of stratification is provided by Scientific Cores, which provide laboratory support and are dedicated to developing new assays in conjunction with clinical researchers. The third component, eight Offices, provides a clear delineation of responsibilities to carry out the many missions of the MOCRU.

The six CRSs are: Genito-urinary/Gynecological Oncology, Vaccine Therapies, Lymphoma, Transplantation, Immunotherapy, and AIDS Malignancy. Four additional CRSs are in the planning stage: Lung/Gastrointestinal, Phase I Clinical Trials, Clinical Genetics, and Neuro-oncology. The CRSs can be headed either by an investigator who has a primary appointment within the MOCRU or an investigator who has his or her primary appointment in another Clinical Research Unit. This structure serves to wrap the MOCRU infrastructure around all clinical efforts of the IRP.

The three Scientific Cores are: Molecular Targets, which will develop novel endpoints for clinical trials and will serve as an avenue of access to other CCR facilities, such as the array facility or the

proteomics facility; Clinical Pharmacology; and Preclinical Development, which is dedicated to helping scientists get products out of their laboratories and into the clinic.

The eight Offices of the MOCRU are: the Office of Clinical Operations; the Office of Fellowship Training; the Office of Scientific Review; the Office of Protocol Support; the Office for Research Nursing; the Office of Nurse Practitioners and Physician Assistants; the Office of Translational Research; and the Office of Navy-Oncology. The Office of Scientific Review is the mechanism for open access to ideas. Suggestions from any investigator in the CCR are sent to the MOCRU Director, who then refers them to the appropriate CRS. The CRS develops the idea and then submits it to the Office of Scientific Review for prioritization. Dr. Carl Barrett, CCR Director, makes the final decision on whether to develop the idea in the clinical setting. This Office also serves as the protocol review office, and it performs audits to monitor quality.

The Office of Protocol Support is a new Office, and it is a formal group for quality assurance and quality control. One activity it will carry out is monitoring protocols for patient accruals every 6 to 12 months. The Office of Research Nursing has been reorganized, with a new layer of leadership at the Ph.D. level designed to increase career opportunities and improve job satisfaction.

Dr. Gress concluded his presentation by explaining how the CRS organization eliminates boundaries between scientists from different branches. Dr. Gress used lymphoma as an example. Seven different branches in CCR are currently conducting clinical protocol activities for patients with lymphoma. Under the reorganization, members of these branches will work together as colleagues, within a CRS, in terms of protocol development, new directions in lymphoma care, and other clinical issues. Basic science investigators will work with clinical investigators and with extramural scientists as well. According to Dr. Gress, this elimination of boundaries is designed to reinvigorate medical oncology in the IRP.

**Questions and Answers**

Dr. Nienhuis asked whether CRS heads were responsible for development of the scientific program in a specific disease area or approach or whether they served as facilitators for others' research. Dr. Gress responded that CRS heads are mainly facilitators. The Lymphoma Working Group is an example of the success of this approach.

Dr. Freedman asked how medical oncology was integrated with other disciplines, such as surgery and radiotherapy. Dr. Gress indicated that such integration is under discussion, and it will be carried out at the level of the MOCRU directorship, not the CRS.

Dr. Norton praised the reorganization effort and suggested that research organizations could learn much from business organizations. Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, agreed, pointing out that organizational change, a field that helps people adapt to change, would be helpful in a major reorganization such as MOCRU's. Dr. Nienhuis observed that laboratory-based investigators tend to seek recognition from peers outside of their own environment, whereas clinically based researchers tend to look for recognition and support from within their local environment. This difference has had an effect on academic institutions.

Dr. Norton stated that the real question is why the Intramural Research Program is necessary and what does it do that cannot be done (as rapidly or as well) by academic institutions, cooperative groups,

and other extramural groups. He suggested that the uniqueness of the mission of the IRP be more clearly articulated.

## XIII. NEW BUSINESS AND SEPTEMBER SUBCOMMITTEE REPORTS—DRS. LARRY NORTON, ARTHUR NIENHUIS, AND SUSAN LOVE

The following issues were suggested as future agenda items:

- NCAB discussion on the findings and recommendations contained in Dr. Harold Freeman's December 2001 report to the NCAB on the President's Cancer Panel meetings during 2000-2001, with a particular focus on issues related to providing cancer care for underserved populations; it was suggested that the Board consider making a statement on these issues following discussion (Dr. Boxer).

- Update on activities of the Center for the Reduction of Cancer-Related Health Disparities and the efforts undertaken by the NCI to address health-care disparity issues (Dr. Millon-Underwood).

- Progress report on evidence-based research on access to cancer care and on cancer information dissemination so that the NCAB can identify existing gaps and develop research questions that can potentially be elucidated with the assistance of the NCI (Dr. Ramirez).

- Followup on palliative care issues (e.g., quality control, research, education) (Dr. Norton).

**Subcommittee on Cancer Centers.** Dr. Arthur W. Nienhuis, Chair, Subcommittee on Cancer Centers, reported on the meeting held on September 10, 2001. Four changes in the Cancer Center Support Guidelines, Part I, Section 7.3, were proposed, dealing with the definition of Prevention, Control, and Population Research: 1) Include human biomarkers studies among the range of possible investigations on cancer prevention, control, and population research; 2) Call for centers to demonstrate their understanding of the applications of both basic laboratory and clinical research to human populations; 3) Emphasize that cancer prevention, control, and population research are inherently interdisciplinary; and 4) Encourage centers to use population research as the platform from which to reach out to diverse communities, with the ultimate goal of reducing the cancer burden.

The Subcommittee proposed a new section to the Guidelines, Part II, Section 6.2, Retaining the Comprehensive Designation. The proposal would limit the use of the term “comprehensive” to centers only during the peer-approved period of funding or the period of peer-approved renewal. Additionally, since “comprehensive” is used by many institutions for various purposes, NCI should use the phrase “NCI-designated Comprehensive Cancer Center.”

A final change to the guidelines related to wording changes to make them more user-friendly for small cancer centers and to make it more feasible for them to compete for funds.

**Discussion.** Dr. Li drew attention to the section of the minutes that discussed the support of basic research for population studies, asking whether population studies could support basic research as well. Dr. Nienhuis noted that the emphasis was on the inherently interdisciplinary nature of prevention/control/population studies. Dr. Brian Kimes, Executive Secretary, Subcommittee on Cancer Centers, reported that the guidelines were not designed to cover every nuance; instead, peer reviewers were expected to be able to recognize studies of prevention and control.

- A motion was made to approve a recommendation from the NCAB Subcommittee on Cancer Centers for changes to the Cancer Center Support Grant Guidelines as described in the Subcommittee's September 2001 summary minutes. The motion was seconded and unanimously approved.

A second issue for full NCAB approval concerned calculations of new submission budget caps for cancer centers. NCI's budget for FY 2002 is expected to experience slower growth than in past years, so for competing renewal cancer center grants, applicants are asked to limit their requests for budget increases to an amount that results in a ratio of 0.2 or less. This ratio is calculated by dividing the budget request by the amount of the NCI-funded base for cancer center for the last full fiscal year. If an applicant requests an amount that results in a ratio equal to or larger than 0.2, then the applicant is limited to a 3 percent cost of living increase. The Subcommittee proposed a recommendation that included a 20 percent submission cap for centers whose funding requests are over the 0.2 ratio.

- A motion was made to maintain the current system for negotiating budgets for Cancer Center grants, rather than adopting the recommendations for changes to this system contained in the minutes from the September 2001 meeting of the NCAB Subcommittee on Cancer Centers. The motion was seconded and unanimously approved.

**Ad Hoc Subcommittee on Communications.** Dr. Susan Love, Chair, Ad Hoc Subcommittee on Communications, reported on the meeting held September 10, 2001. There were two agenda items: a continuation of the discussion on "What Should a Communications Programs Look Like?" from the Subcommittee's last meeting, and a discussion of the NCPB report, *Improving Palliative Care.*

- A motion was made to approve the minutes of the September 2001 meetings of the NCAB Subcommittee on Cancer Centers and the NCAB Subcommittee on Communications. The motion was seconded and unanimously approved.

## CLOSED SESSION

**REVIEW OF APPEALS, INTRAMURAL SITE VISITS, TENURE APPOINTMENTS, PERSONNEL, AND PROPRIETARY ISSUES**

*This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(6) and 552b(c)(9), Title 5 U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).*

There was a review of intramural site visits and tenured appointments, committee discussions, and recommendations. There was also a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussion for which there was potential conflict of interest, real or apparent. Members were asked to sign a statement to that effect.

## DAY TWO—WEDNESDAY, DECEMBER 5, 2001

## CENTER FOR CANCER RESEARCH REPORTS (CONTINUED)

## REPRESENTATIVE VACCINE INITIATIVES

### XIV. INTRODUCTION—DR. CARL BARRETT

Dr. Barrett introduced the developments in cancer vaccine research at the CCR. He emphasized how significant it is for investigators to have access to the NIH Clinical Center, since it provides researchers with a unique opportunity for using the discoveries resulting from the IRP for designing and conducting clinical studies. There are several new discoveries in the development of vaccines, and though the development of cancer vaccines is not a new concept, it remains an area of excellence in the CCR. Dr. Barrett noted that there are 32 vaccine or immunotoxin trials in progress. Four trials are scheduled for 2002, and there are more than 20 agents in preclinical studies. These agents target a variety of neoplasms, including melanoma, carcinoma, T- and B-cell malignancies, glioblastomas, mesothelioma, Ewing's sarcoma, and vaccines for AIDS. In 2002, the CCR is planning to clinically evaluate new breast and prostate cancer vaccines, an AIDS vaccine, and a preventive vaccine for cervical cancer. Dr. Barrett then introduced the two speakers for the morning: Dr. Rosenberg and Dr. Schlom.

### XV. MELANOMA VACCINE TRIALS—DR. STEVEN ROSENBERG

Dr. Steven Rosenberg, Chief of the Surgery Branch, NCI, presented a research update of immune-based treatments for melanoma. The goal of this research is to develop immunotherapy approaches based on the molecular identification of tumor antigens. Dr. Rosenberg noted that he is specifically interested in identifying new cancer-associated antigens and then using these antigens to develop and evaluate active immunization in cell-transfer therapies for patients with metastatic cancer.

Early trials involved the administration of interleukin-2 (IL-2), an immunostimulant, to 409 patients with either metastatic melanoma or kidney cancer. Thirty-three of those patients, (8 percent), exhibited complete regression of the tumor, and another 10 percent had a partial regression. In patients whose tumors had disappeared, there was no evidence of recurrence. Dr. Rosenberg commented on how these experiments were important because they demonstrated that the immune system could be manipulated to treat invasive cancers.

Dr. Rosenberg explained that he wanted to understand the fundamental principles behind the tumor response to IL-2, and began by looking at the lymphocytes. He identified specialized lymphocytes responsible for the tumor regression, called tumor-infiltrating lymphocytes (TILs). These cells were isolated from tumors, reinfused with IL-2, and administered to patients in a pilot study at the NIH Clinical Center. This procedure yielded a 33 percent response rate and included many patients who had not responded to the IL-2 treatment in the previous trial.

Dr. Rosenberg stated that these preliminary data led him to design a four-part strategy to identify tumor regression antigens and develop immunotherapies based on those findings. The strategy consists of growing large amounts of TILs that recognize unique cancer antigens; administering these TILs to cancer patients, and identifying the antigens that are associated with tumor regression; cloning the genes that encode these unique antigens (by using the lymphocytes to screen cDNA libraries made from tumor cells); and developing cell-transfer therapies or active immunization vaccines based on this information.

Epithelial cancer cells express a wide variety of antigens, and many are overexpressed in tumor cells. Discovering which antigens are important is no small task; it is estimated that there are 11,000 genetic alterations in an average colon cancer cell, and any of these has the potential to give rise to a tumor antigen. Dr. Rosenberg noted that he and his colleagues have identified and cloned about 12 antigens that include 85 percent of all the human lymphocyte antigen (HLA) immunodominant epitopes. These are all Class I-restricted antigens, which are recognized by CD8-positive (killer) T cells. Dr. Rosenberg added that he has recently published a method in *Science* for identifying Class II-restricted cancer antigens, which are recognized by CD4-positive (helper) T cells. This is a key step in the vaccine process, as discovered in recent clinical trials: the interaction between the killer T cells and helper T cells is critical for tumor regression.

To determine the best approach to immunizing patients with the identified antigens, more than 680 patients have been treated in the NIH Clinical Center over the past 5 years using either recombinant viruses engineered to express antigens or peptides. Dr. Rosenberg focused his presentation on the use of peptides, since he found that immunizing patients with peptides was an effective method of raising reactive immune cells.

Dr. Rosenberg then described how the peptides were designed. T cells recognize a series of 9 to 11 amino acids (and not the entire protein) in the surface of the major histocompatibility complex (MHC) molecule. Dr. Rosenberg noted that he and his colleagues identified several of these peptides from tumor antigens, but discovered that they were not immunogenic. However, modification of the gp100 peptide at a single amino acid site induced a strong immune response in patients. These results were obtained after a single course of immunization and were improved through multiple courses of immunization.

Dr. Rosenberg then explained that a rational approach to immunotherapy requires an understanding of the mechanism that tumors use to escape recognition by the immune system, so that the vaccine can be designed to overcome these tumor defense mechanisms. For example, TILs isolated from tumor cells do not mediate tumor regression on their own. In animals, both CD4 helper cells and CD8 killer cells are required for tumor regression. Dr. Rosenberg reported that he then designed a clinical trial to add an immune system "helper factor," such as IL-2, to the peptide vaccine. The response rate for peptide plus IL-2 was three times that of the response rate for peptide alone. There was no improvement when other cytokines, such as IL-12 or granulocyte/macrophage colony stimulating factor (GM-CSF) were used. A pilot study was then conducted in which patients were given four peptides, three of which were modified from three different antigens, for the purpose of overcoming any immune selection process that might be occurring. Two of sixteen patients experienced complete tumor regression with the peptide injections.

Dr. Rosenberg mentioned that other tumor defense mechanisms may have contributed to the lack of response in this trial, including: insufficient number of cells being generated, the correct activation signal not being sent by the tumor, and the immune reaction potentially being suppressed by other regulatory cells. To address these concerns, a new clinical protocol was designed for patients with metastatic melanoma who had failed other treatments. This new approach was founded on the premise that an individual's peripheral blood cells or TILs could be cloned. These clones can then be screened to find lymphocytes with the highest anticancer activity, grown to large numbers, and then transferred back to the patient. In addition, this method allowed the clinician to measure the lymphocytes for lytic activity or the amount of a particular cytokine produced by the cell. The individual properties of these cells can then be identified and the aspect of the immune response that is responsible for tumor regression can be determined.

Twelve patients had their immune systems ablated and were infused with the cloned lymphocytes. IL-2 was added to keep the cells alive. None of the patients displayed tumor regression. In the next study, the same protocol was used, except that the patients received both CD8 killer cells and CD4 helper cells. Dramatic tumor regressions (between 96 to 99 percent) have been observed in three patients so far.

Dr. Rosenberg concluded his presentation by listing the clinical trials being designed based on the basic immunologic principles that have been established. In a variation of the last trial, patients would be immunized with both Class I and Class II peptides (to stimulate both CD8 and CD4 lymphocytes, respectively). Another protocol involves the genetic engineering of helper factors, such as IL-2, into CD8-positive clones, so that researchers need to generate only one type of cell. Efforts to include patients who are in earlier stages of disease are also underway, and this would allow physicians to treat patients with multiple courses of treatment, which would increase the number of circulating antitumor lymphocytes in the patient.

**Questions and Answers**

Dr. Norton wondered whether CD8 cells are essential for tumor regression. Dr. Rosenberg responded that his group has not performed studies using only CD4 cells. Generally, the CD4 cells support CD8 cell survival, probably by stimulating necessary cytokines.

Dr. Armitage asked why the allogeneic transplantation work described by Dr. Rosenberg worked in renal cancer but not in melanoma, and if the rate of tumor growth determined the rate of tumor regression. In response to the first question, Dr. Rosenberg speculated how kidney cancer could be different from leukemias and melanomas. Renal cancers might be more susceptible to cytokines, especially in a cytokine-rich environment due to a chronic graft-vs-host condition. He added that the types of cancers that are likely to respond to allotransplant regimens are those that generate specific antitumor immune responses. An example of this concept is found in epithelial cancers, where some of the peptides expressed on epithelial tumors have been identified, modified, and then used for immunizations. Clinical trials illustrating this point are in progress. Dr. Rosenberg concluded by acknowledging that more work was needed to prove these ideas, but that antigens could be identified and targeted for any cancer. Dr. Rosenberg replied to the second question by indicating that all of the patients treated had aggressive melanomas, and that his research group had not observed any correlation between fast-growing tumors and response to treatment.

Dr. Ivor Royston, Managing Member, Forward Ventures, wanted to know when large-scale clinical trials of these vaccines could begin. Dr. Rosenberg admitted that it was difficult to know when to continue to improve upon a protocol and when to bring it to the patients. He noted that IL-2 has been approved by the FDA but is not widely used. There are trials in 13 institutions around the country using these vaccine immunizations with the CD8-positive Class I-restricted peptides. The research regarding the addition of CD4-positive peptides to the immunization protocol is so new that is has not been incorporated into clinical protocols at this time. Dr. Rosenberg noted that the adoptive transfer studies would be ready to go to the clinic shortly; however, raising all of the cells requires a large laboratory capable of performing that procedure. He also stated that it might be feasible to use retroviral vectors containing IL-2 sometime in the future, but this method is still under development.

Dr. Freedman wondered if these vaccines might be used for high-risk patients, such as women with BRCA1 mutations. Dr. Rosenberg answered that many of the antigens his laboratory is studying are shared antigens restricted by HLA types, and if high-risk patients could be identified, then a trial using

shared antigens was possible. Dr. Boxer inquired about the toxicity of the adoptive transfer therapy. Dr. Rosenberg stated that the adoptive transfer studies have shown no toxicity. High doses of IL-2 have some associated toxicity, but there has been no treatment-related mortality in more than 800 patients who were given IL-2, making it safer than combination chemotherapy. Since the peptide vaccines are administered as an incomplete adjuvant, they cause some irritation and induration at the injection site, but otherwise are nontoxic.

## XVI. COLORECTAL, PROSTATE, AND BREAST CANCER VACCINE TRIALS—DR. JEFFREY SCHLOM

Dr. Jeffrey Schlom, Chief, Laboratory of Tumor Immunology and Biology, CCR, NCI, stated that because tumor-associated antigens (TAAs) are—by definition—either weakly immunogenic or functionally nonimmunogenic, vaccine strategies must be developed in which the presentation of the TAAs to the immune system results in far greater activation of T cells than naturally occurs in the tumor-laden host. In particular, three antigens that are overexpressed in tumors have been the focus of research in Dr. Schlom's laboratory: carcinoembryonic antigen (CEA), MUC-1, and prostate-specific antigen (PSA). Dr. Schlom highlighted CEA as a prototypic antigen for vaccine development.

CEA is expressed in high levels in fetal gut and in low levels in normal colonic mucosa, and is presumably tolerated by the body as a self-antigen. Many cancers overexpress this antigen, including 95 percent of colorectal, gastric, and pancreatic cancers. To make this TAA immunogenic, several strategies are used. Dr. Schlom discussed the use of vaccinia and avipox viruses as vectors for not only the CEA TAA, but also for costimulatory molecules that help generate vigorous T-cell activation. Dr. Schlom noted that although vaccinia elicits a strong immune response, immunity developed by the host limits its continuous use. In contrast, avipox can be used repeatedly because the proteins are under the control of early promoters and, thus, none are produced that can be used in neutralizing the avipox virus. Of note is the fact that the avipox vector cannot replicate in mammalian cells, and the vaccinia vector that is used is a replication-defective mutant.

An additional approach to increasing the antigenicity of CEA is to use a diversified vaccine prime-and-boost strategy. Dr. Schlom discussed the preclinical studies demonstrating vaccination with the CEA-vaccinia construct followed by multiple vaccinations with the CEA-avipox construct as a much more efficacious strategy than the continued use of a one-vaccine construct. Furthermore, the pox virus-based vaccines elicit both cytotoxic (CD8) and helper (CD4) T-cell subsets and generate antitumor activity in the absence of toxicity. The conclusion from these studies was bolstered by use of transgenic mice expressing human CEA. Although functionally tolerant of this self-antigen, these mice responded to CEA antigen encoded in the pox vectors by producing very potent antigen-specific CD8 and CD4 T cells. Clinical data support these findings; most importantly, generation of CEA-specific T-cell responses in patients with colorectal and pancreatic cancer was associated with increased survival—after accounting for disease status. Moreover, survival duration was unrelated to levels of CEA-specific T cells prior to vaccination.

A further enhancement of antigenicity of CEA vaccines relies on the immunostimulatory properties of the cytokines GM-CSF and IL-2. Dr. Schlom noted that the combination of the diversified vaccine prime-and-boost strategy plus vaccination with GM-CSF increased the CEA precursor frequency in one patient by more than 10-fold.

A final strategy mentioned by Dr. Schlom to increase vaccine efficacy is called "epitope enhancement." Agonist peptides have been generated where a sequence change in a single amino acid enhances T-cell activation, presumably by increasing either the interaction of peptide with MHC molecule(s) or the interaction of the peptide-MHC complex with the T-cell receptor. Such an enhancement was determined for one of the immunostimulatory peptides from CEA in which T cells responding to the agonist produced more of the cytokine interferon-gamma than they did in response to the original peptide. Phase I clinical trials using dendritic cells pulsed with these agonists resulted in complete tumor regression in some patients.

Future clinical trials will make use of agonist vaccines, injection with cytokines such as GM-CSF, the diverse prime-and-boost strategy, and the introduction of costimulatory molecules to help activate a protective T-cell response. A major issue at the current stage of clinical vaccine development is whether the potency of T-cell responses can produce a therapeutic response. Currently, three costimulatory molecules—B7, ICAM-1, and LFA3 (together referred to as "TRICOM," or **TRI**ad of **CO**stimulatory **M**olecules)—have been used in mouse models and are just beginning to be evaluated in clinical trials. Preclinical results are promising. Dr. Schlom also briefly mentioned the use of a mouse model of colon cancer that demonstrates the efficacy of CEA-TRICOM vaccines in the prevention of spontaneous tumors.

Dr. Schlom concluded his talk with the recognition that science-based clinical trials develop from hypothesis-driven preclinical studies and that an interrelationship between "bench-to-bedside" and "beside-to-bench" is essential for science-driven clinical development. The principles under investigation in Dr. Schlom's laboratory and in other laboratories have broad implications for recombinant vaccines for a range of infectious diseases, including HIV and malaria, among others.

**Questions and Answers**

Dr. Schlom responded to a question from Dr. Armitage about the type of cancer affecting patients who have survived 3 to 4 years with ongoing CEA vaccinations. It is highly unusual for patients with pancreatic cancer to survive beyond 12 months. The patients with colorectal and pancreatic cancer who were selected for this trial had already failed two to six conventional therapeutic regimens.

## NEW TECHNOLOGY INITIATIVES

## XVII. CLINICAL PROTEOMICS—DR. ELISE KOHN

Dr. Elise Kohn, Laboratory of Pathology, NCI/FDA Clinical Proteomics Program, CCR, discussed the goals and research efforts regarding the clinical applications of proteomics. She began by defining cancer as disease of deranged, dominating, or defective protein pathways and networks. The goal of the Clinical Proteomics Program is to discover protein targets and profile these targets within networks, for the purpose of tailoring therapy to the individual. Dr. Kohn outlined four target applications for clinical proteomics: dissect the tissue microenvironment in an effort to understand the proteomic cross-talk between the tumor and the underlying stroma; profile the signal transduction events in both the development of cancer and the transition from *in situ* to invasive carcinoma; monitor signal transduction pathways and cellular targets during clinical trials; and identify and validate markers in a high-throughput format. New technologies are being developed by the Clinical Proteomics Program Group to achieve these goals.

Laser-capture microdissection followed by differential expression analysis has been used to discover new targets for ovarian cancer. Tumors with a low malignancy potential were compared to invasive tumors using two-dimensional electrophoresis. Any protein "spots" that were unique between the two tumor types were sequenced with mass spectroscopy. More than 150 new targets have been identified with this method and are being studied further.

Drs. Petracoin and Liotta developed a protein microarray so that the functions of cancer-related proteins could be established. In one experiment, Dr. Kohn noted, phosphorylation patterns of 267 cell-signaling molecules were compared in both normal and malignant breast epithelium. The data indicated that several key cell-signaling molecules were activated differently in tumor cells when compared with their activity in normal cells.

Dr. Kohn then described how the Clinical Proteomics Program Group is collaborating with the Vaccine Working Group to identify candidates for vaccine development. Microdissected tumor cells from patients are analyzed in a dilution series next to a series of normal cells, allowing the recognition of antigens for candidate vaccines. This technology has a level of sensitivity 1000-fold greater than immunohistochemistry.

Profiling signal transduction pathways within a tumor allows investigators to identify new targets and biomarkers and to monitor these targets in response to a drug. Clinical trials involving the analysis of biopsies from patients who were treated with Herceptin and Taxol were designed to evaluate biochemical changes during Herceptin treatment using this approach. In the patients who responded to Herceptin therapy, investigators discovered a reduction in a phosphorylated enzyme relative to its nonphosphorylated form, and this enzyme is known to control a tumor-survival pathway.

The Clinical Proteomics Program Group has developed an artificial intelligence (AI) bioinformatics system for proteomic pattern discovery. The goal of this system is to find buried proteomic patterns that correlate to a particular disease state, biochemical or immune function, toxicity, or treatment outcome. Dr. Kohn then explained how the pattern matching works. Low molecular weight proteins (<20kD) are being targeted for these studies since there is not a suitable method available for analyzing proteins that are this size. Proteins are analyzed with a sophisticated mass spectroscopy method and then the software takes the resulting pattern and creates a diagnostic "fingerprint." Using previously identified samples, the system can be trained to recognize "normal," "cancerous," or "new event" fingerprints. Dr. Kohn indicated that her group tested this system with ovarian cancer and found that all 50 cancerous samples of the 116 blinded samples tested were correctly identified. Eighteen of the cancerous samples were in stage 1, typically a disease stage where ovarian cancer cannot be diagnosed. The program identified as "new events" nine of ten cases of patients with benign gynecologic disease nonovarian cyst, meaning they were neither cancerous nor noncancerous. The positive predictive value for this technique was 94 percent in this validation cohort. A similar study was conducted with prostate cancer and yielded analogous results. In this test, the validation set was queried with samples from patients with benign prostatic hypertrophy (BPH). Seventy percent of these cases were identified as a new phenotype, and 30 percent were classified as cancerous. Since samples were obtained 3 to 5 years prior to this test, there was an opportunity to follow up with the patient records. As expected, many of the positive samples corresponded to a subsequent clinical diagnosis of prostate cancer, indicating that this pattern recognition program could identify a risk for future development of cancer from BPH.

Dr. Kohn described future proposals for clinical trials based on these results. One proposed trial is a collaborative effort between the NCI/FDA Clinical Proteomics Program and the Medical Oncology

Clinical Research Unit of the CCR. The study is designed to profile STI571 (Gleevec) in patients with relapsed epithelial ovarian cancer. The objectives of the study are to: describe the biochemical modulation by STI571 in the tumor cell and to correlate pathway regulation with clinical outcome; investigate the antiangiogenic activity of STI571; investigate receptor tyrosine kinase regulation by STI571; characterize the expression of platelet-derived growth factor receptor (PDGFR) and c-kit (stem cell growth factor) in response to STI571; apply the cluster bioinformatics analysis to serum samples to predict the response to or toxicity of STI571; and develop a database of signal regulation by small molecules in ovarian cancer tissue. Several current clinical proteomics trials involve the proteomic profiling of biomarkers in patients who are being treated with anticancer compounds. Future trials will focus on fingerprint analysis of STI571 in ovarian cancer, and ZD1839 (Iressa) in ovarian and cervical cancer. An early detection biomarker validation study for ovarian cancer will also be conducted in collaboration with the Pacific Ovarian Cancer Research Consortium.

**Questions and Answers**

Dr. Boxer asked whether the ovarian cancer samples that were identified as "new events" eventually developed into disease similar to the prostate cancer samples. Dr. Kohn replied that there was a 5-year follow-up of all unaffected (no disease) patients, and none of the patients for whom follow-up was obtained had developed cancer at that time. Further observations are needed to validate this finding, and several prospective studies will be designed in collaboration with the SPOREs program and the Cancer Genetics Network.

Dr. Freedman commented on the great need for early detection and diagnosis in ovarian cancer. Testing efforts for preliminary markers are incomplete. Discovering more molecular targets and understanding their mechanisms of action will assist in the characterization of markers that can be used for early diagnosis.

Dr. Li wondered if the choice of serum, as opposed to other body fluids, affects the sensitivity of the surface-enhanced laser desorption/ionization (SELDI)/AI tests. Dr. Kohn responded that other body fluids, such as nipple aspirate, are being tested for breast cancer. The main issue is to find a fluid or tissue that is readily available in the clinical setting. Dr. Li mentioned that his group is trying to implement a system for collecting the small droplet of fluid from a mammography.

Dr. Samir Abu-Ghazaleh, Gynecologic Oncologist, Avera Cancer Institute, commented on some false-positive results from the ovarian cancer study. Dr. Kohn acknowledged that 3 of the 66 samples were misidentified by this experimental approach, but with 5-year follow-up there has been no development of cancer in those patients. Ethical considerations prevent additional questioning of patients at this time, which is the reason for designing the prospective studies mentioned earlier.

Dr. Love returned to the subject of using nipple aspirates in the SELDI/AI tests and the possibility of discovering atypical cells in the fluid that had not yet reached the stroma. She suggested that finding such a cell would enable the researcher to isolate events that occur in the epithelial cell before it is complicated by stromal interactions. Dr. Kohn concluded that there were great opportunities for proteomics research using this approach.

## XVIII. CLINICAL AND MOLECULAR TARGETS—DR. ALLAN WEISSMAN

Dr. Allan Weissman, Chief, Regulation of Protein Function Laboratory, CCR, NCI, discussed the use of molecules such as E3 ubiquitin ligase as potential therapeutic targets. He reviewed the ubiquitin conjugating system, described relevant research in his laboratory relating to ubiquitin protein ligases and the role that they play in the cell, and discussed how ubiquitin ligases could be a clinically relevant targets.

Ubiquitination is a multienzyme process resulting in the degradation of proteins. Dr. Weissman explained how ubiquitination has other roles in the cell, which have only recently been identified. These include the targeting of proteins for endocytosis, lysosomal degradation, and DNA repair. Three enzymes, E1, E2, and E3, are key to ubiquitination. E3 is a member of a class of proteins known as the ubiquitin protein ligases. Dr. Weissman described how members in his laboratory discovered a novel E3 enzyme and determined that the RING-finger domain on this protein was necessary for the binding of E2 to E3 during the ubiquitination reaction. This RING domain was used to identify five other related ubiquitin protein ligases.

Dr. Weissman then explained how the Cbl protein, initially identified as a component of the receptor tyrosine kinase cell-signaling pathway, also has a RING domain that mediates its own ubiquitination. In the epidermal growth factor (EGF)-signaling cascade, Cbl targets the EGF receptors and itself for degradation, thus making Cbl a downregulator of EGF signal transduction. Dr. Weissman explained that his laboratory has discovered that another ubiquitin ligase associates with Cbl, causing the degradation of Cbl, and that this association is constitutive and not dependent on receptor activation. He speculated that, given the importance of Cbl in the cell, it is likely that this other ubiquitin ligase is overexpressed or overactivated in tumor cells.

Dr. Weissman presented information on current research in his laboratory relating to how E2s and E3s may be involved in the degradation of T-cell receptors from the endoplasmic reticulum (ER). A protein first identified as the autocrine motility factor receptor, gp78, was found to have a RING-finger domain and the ability to target itself for degradation. He noted that gp78 has a role in recruiting a specific E2 implicated in degradation from the ER through a domain distinct from its RING finger, yet it also functions as a RING finger-dependent E3 for heterologous proteins. There is eveidence that overexpression of gp78 is correlated with the metastatic potential of tumors. He hypothesized that this may relate to the ubiquitin ligase function of this protein.

The possibility of targeting E3 enzymes for cancer therapy was discussed. Dr. Weissman noted that the first challenge is finding ubiquitin ligase inhibitors that are specific. He explained that such agents must recognize the E3s as a class of proteins, but they must also be specific for a particular E3 in the targeted system. Determining which targets are worth exploring further is another issue for designing therapeutics. Dr. Weissman then focused his presentation on MDM2, a regulator of a common tumor suppressor, p53. MDM2 is a good candidate because it targets both itself and p53 for degradation. MDM2 is overexpressed in many tumors expressing wildtype p53. So, even when the p53 is functioning as a tumor suppressor, the extra ligase activity of MDM2 is degrading the p53. Dr. Weissman suggested that by inhibiting the ubiquitin ligase activity of MDM2, the tumor suppressor activity of p53 can be restored. Dr. Weissman then described assays being developed in his laboratory to test potential MDM2 ubiquitin ligase inhibitors. Once the inhibitors are characterized and the specificity of those agents tested, the next steps are to perform large-scale cell screening assays and test the effectiveness of the inhibitors in animal models.

**Questions and Answers**

Dr. Norton commented on the number of interesting molecules defined in this research. He inquired about the possibility of interacting with the proteomics researchers to better define the mechanism for these molecules. Dr. Weissman assured Dr. Norton that finding a mechanism of action for these new targets was one of his goals. He mentioned that he was a member of the Molecular Target Faculty, which is designed to create a forum for interaction and collaboration. Dr. Weissman noted that while these interactions may not be formal, he would certainly facilitate any discussions. Dr. Norton suggested the possibility of having Dr. Weissman present an update on his work in the next year or so.

Dr. Love requested clarification on the ubquitination process. Dr. Weissman defined ubquitination as the process for removing from the cell not only proteins, but also lysosomes. This process is reversible. He noted how the concept of proteins regulating other proteins is becoming a common theme in biology.

Dr. Norton suggested the use of mathematical models to understand how mechanisms of autoregulation, such as the ubiquitin system, achieve stability.

## XIX. TRANS-NIH NEURO-ONCOLOGY INITIATIVE—DR. HOWARD FINE

Dr. Howard Fine, Chief, Neuro-Oncology Branch, Center for Cancer Research, reported that primary brain tumors may soon be the leading cause of cancer mortality in children; they are the fourth leading cause of cancer mortality in patients under age 45. Most physicians in the community do not know how to care for patients with primary brain tumors, in part because such tumors are relatively uncommon. The Neuro-Oncology Branch is intended to fill gaps in research and clinical science by becoming a center of clinical excellence and expertise in the management and treatment of central nervous system (CNS) malignancies. As a joint effort of NCI and the National Institute for Neurological Disorders and Stroke (NINDS), the Neuro-Oncology Branch has many resources available with which to stimulate clinical and translational efforts.

**Goals**

**National Resource for Patients With CNS Malignancies.** The Neuro-Oncology Branch offers free consultation services nationally and encourages patients to send in scans and medical records. A multidisciplinary NIH-wide brain tumor clinic, with active participation by three NCI Branches, three different Institutes, and three different clinical programs, offers a wide diversity of services to patients with CNS malignancies.

**Collaboration With Extramural Investigators.** The Branch collaborates with the extramural community through three NCI-sponsored consortia, and staff serve as members of the Brain Tumor Steering Committees of both the Radiation Therapy Oncology Group and the Southwestern Oncology Group (SWOG). These partnerships enable the Branch to move the most promising agents tested in the Phase I program into consortia trials for Phase II evaluation, and PIs have more opportunities to run large national trials. Working with consortia also permits Branch investigators to devise specialized corollary studies associated with ongoing trials. Through connections with the Cooperative Groups, the Branch can move the most promising Phase II agents into Phase III trials.

**Developing Experimental Therapeutics.** Dr. Fine explained that only a few drugs have been specifically targeted for CNS neoplasms because of anatomical and physical constraints, the microenvironment of the CNS, and the fact that the CNS is immunologically sequestered. The field is moving to alternate delivery strategies for treating brain tumors, but few pharmaceutical companies and few academic centers have the expertise, resources, or interest to initiate CNS preclinical modeling programs.

**Working With the Private Sector.** Dr. Fine observed that some of the most exciting agents come from the private sector. The Branch is encouraging the private sector to develop agents specifically for CNS neoplasms through two development programs: 1) the Preclinical Development Program, which includes the CNS Animal Core, small animate imaging facilities, the Nonhuman Primate CNS Pharmacology And Microdialysis Unit, and developing surrogate endpoints of drug activity; and 2) the Clinical Drug Development Program, which runs Phase I feasibility trials and then quickly moves agents into further trials with consortia and Cooperative Groups.

**Stimulating Interactions Among NIH Scientists.** The Branch plans to engage the scientific resources of the NINDS, the National Institute of Mental Health (NIMH), the National Eye Institute (NEI), and others, by establishing working groups focusing on nontraditional cancer biology areas such as glial biology, neural stem cell biology, neural damage and repair, and the blood-brain barrier.

**Accomplishments**

**Collaborations.** According to Dr. Fine, the Branch is now a major brain tumor referral center. In the first year of the Branch's activities, the number of patients with primary brain tumors increased from 10 to 300. Importantly, referred patients are potentially available for clinical trials. The Branch holds biweekly NIH-wide conferences that include staff from the NCI Cancer Therapy Evaluation Program (CTEP) and the FDA. The Branch has established a combined pediatric neuro-oncology clinic program with Children's National Medical Center in Washington, DC, and works with clinical programs at Johns Hopkins University, George Washington University, Walter Reed Army Medical Center, and the National Naval Medical Center.

**CNS Tumor Drug Development Program.** The Neuro-Oncology Branch has established a CNS tumor animal therapeutic core for both intra- and extramural investigators for the systematic analysis and modeling of new agents and delivery technologies. The core is equipped for animal breeding, surgery, pharmacologic studies, toxicology studies, histopathology, and imaging. This resource is available to research teams involving extramural researchers and the private sector through Cooperative Research and Development Agreements (CRADAs). The Animal Therapeutics Core has been successful in bringing 13 new drugs to the clinic in Phase I trials, including 6 new antiangiogenic agents specifically for brain tumors.

**Glioma Molecular Diagnostic Initiative.** Dr. Fine asserted that current classification of glioma is not biologically based, fails to predict prognosis consistently, gives little insight into pathogenesis, and is rarely predictive of responsiveness to specific therapies. The Neuro-Oncology Branch, in an effort to correct these deficiencies, plans to develop an international public database through the Cancer Molecular Analysis Project (CMAP), containing in-depth pathologic, molecular, and genetic data with detailed clinical corollary data for hundreds of individual tumors. The goal is to allow researchers and clinicians to identify and evaluate molecular targets using information integrated from basic and clinical cancer research programs. The unique value of the database is its display of molecular profiles of individual

tumors. Researchers can identify over- or underexpression of specific genes, find specific agents that target the particular anomaly, and determine whether clinical trials are underway and if an individual patient would be eligible.

Such a system requires hard data, and the Branch is collecting data in a retrospective phase, which now consists of more than 500 banked glioma specimens with extensive clinical data. This phase represents the beginning of a new classification system. A prospective phase will test these models in a clinical trial to be carried out in conjunction with Cooperative Groups. The plan involves obtaining extensive prospective clinical and molecular data for 800 new gliomas. Molecular data will include gene expression profiles, chromosomal abnormalities, gene sequencing, and SNP analysis.

Another product of this initiative is an NCI-designated glioma microarray chip, the result of data-mining Cancer Genome Anatomy Project (CGAP) libraries and glioma serial analysis of gene expression (SAGE) libraries. The chip includes 1,600 previously unknown genes that are seen only in gliomas, and not in any other cancer or any other part of the body. Each element has been sequenced, verified, and rearrayed. Dr. Fine stated that the database and microarray chip will be invaluable resources, both for basic scientists for gene discovery and for clinicians for the generation of a meaningful classification system.

**Neural Stem Cell Initiative.** Dr. Fine discussed the potential benefits of using adult neural stem cells in CNS malignancy treatment, as well as the difficulty in obtaining them. Dr. Fine's team had asked whether it would be possible to generate neural stem cells from other tissues that are more readily accessible. They found that a multipotential stem cell within the adult human bone marrow has the capability of differentiating toward multiple lineages. The Neuro-Oncology Branch has developed the technology to take bone marrow from adults, expand the population of these cells, and, through culture manipulations, promote their development towards a neural stem cell lineage. These cells were implanted into fetal mouse brains, and after 2 months, the brains were harvested, and the genetically marked marrow-derived human cells were shown to differentiate into multiple neuronal subtypes. The neural stem cells developed from marrow-derived stem cells were compared to fetal-derived neural stem cells through microarray analysis. The proteins expressed by both stem cell types were nearly identical. Other analyses showed similar results.

One of the most important functional capabilities that neural stem cells have is the ability to migrate toward injured brain sites. Dr. Fine and his team set up an *in vitro* migration assay to determine if the marrow-derived stem cells also had this capability to migrate towards brain lysates and found that they did. They then repeated this assay *in vivo,* by first causing injury to the mouse brain and then injecting the cells at the opposite side of the brain. After 7 days, all the marrow-derived cells had migrated to the site of the injury; after 30 days, they were contributing to the injury response to the damaged area.

To determine whether the marrow-derived cells responded to tumors as well as to injuries, the investigators implanted human glioblastoma xenografts in immunodeficient animal brains. Seven days later, marrow-derived cells were transduced with vectors expressing either a marker protein or a therapeutic gene, and these cells were injected at the opposite side of the brain from the tumor. Not only did the cells migrate, but further investigation revealed that the migration was stimulated by the tumor's encroachment on normal brain tissue. Moreover, marrow-derived cells transduced with antiangiogenic genes elicited a marked antiangiogenic response in the tumor, significantly prolonging the survival of these animals. Dr. Fine and his team are now devising a clinical study to use autologous marrow-derived stem

cells, transduced with marker proteins, on patients with brain tumors who are already scheduled for surgery.

Dr. Fine concluded his presentation by stating that marrow-derived stem cells exist that are highly similar to fetal stem cells. They can be generated from every individual in nearly unlimited quantity, obviating issues relating to immune rejection, tumor genicity, or difficulties in obtaining stem cells from other sources.

**Questions and Answers**

Dr. Love asked whether the marrow-derived stem cells simply migrated, or whether they displayed any activity on their own. Dr. Fine replied that they had no activity of their own but could be used to deliver therapeutics. Dr. Love also wanted to know if marrow-derived stem cells could be used for other organs, and Dr. Fine pointed to research showing that these stem cells can contribute to the repair of cardiac infarcts; he stated that it is his hypothesis that bone marrow can act as the reservoir for cells involved in tissue repair.

Dr. Norton observed that the stem cells look like functional dendritic neurons, and he asked if the cells could be used to regenerate damaged neural tissue. Dr. Fine responded that the cells could not serve that purpose for neuro-oncology, but scientists in other Institutes, notably those who work with Parkinson's disease and with injuries, were working with his Branch to explore the possibility of tissue regeneration.

## XX. SUMMARY REMARKS AND FUTURE AGENDA ITEMS

Dr. Norton pointed out that the Board has the opportunity to set its own agenda, and he asked members to make suggestions for future agenda items, either at this point in the meeting or later via e-mail. Two suggestions for future agenda items were:

- NCAB discussion on mechanisms by which the unique resources of the NIH Clinical Research Center can become accessible to the extramural research community (Dr. Norton).

- NCAB discussion on the possibility of recommending the establishment of a Cancer Prevention and Detection Unit within the new NIH Clinical Research Center (Dr. Huerta).

## XXI. ADJOURNMENT—DR. LARRY NORTON

There being no further business, the 120th meeting of the National Cancer Advisory Board was adjourned at 12:00 noon on Wednesday, December 5, 2001.