DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
119th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 11, 2001

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND

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The National Cancer Advisory Board convened for its 119th regular meeting on Tuesday, September 11, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. Because of the extraordinary events of September 11, 2001, the open session of the meeting was adjourned at 10:20 a.m., following the report of the Director, NCI. The meeting was closed to the public from 10:30 a.m. until adjournment at 11:00 a.m. Dr. Phillip A. Sharp, Institute Professor, Center for Cancer Research, Massachusetts Institute of Technology, and Chair of the NCAB, presided during both the open and closed sessions.

NCAB Members

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

President's Cancer Panel

Dr. Harold Freeman (Chairperson)

Alternate Ex Officio NCAB Members

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

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute

Dr. Alan Rabson, Deputy Director, National Cancer Institute

Ms. MaryAnn Guerra, Deputy Director for Management

Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis

Dr. Dinah Singer, Director, Division of Cancer Biology

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics

Dr. Peter Greenwald, Director, Division of Cancer Prevention

Dr. Marvin Kalt, Director, Division of Extramural Activities

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences

Dr. Carl Barrett, Director, Center for Cancer Research

Dr. Joseph Harford, Associate Director for Special Projects

Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Ms. Barbara Duffy Stewart, Association of American Cancer Institutes

Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.

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

Ms. Mary Mitchell for Dr. Stanley Zinberg, The American College of Obstetricians and Gynecologists

Ms. Kristen Simonson for Ms. Nancy Riese-Daly, American Society of Therapeutic Radiology and Oncology

Ms. Ruth Hoffman, The Candlelighters Childhood Cancer Foundation

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

Dr. Lovell Jones, Intercultural Cancer Council

Ms. Paula Bowen, Kidney Cancer Association

Mr. George Dahlman, The Leukemia and Lymphoma Society

Dr. W. Marston Linehan, National Cancer Institute

Mr. Steven Friedman, National Coalition for Cancer Survivorship

Dr. Linda Hyman for Dr. Eve Barak, The National Science Foundation

Ms. PaulaAnn Rieger, Oncology Nursing Society

Ms. Pearl Moore, Oncology Nursing Society

TABLE OF CONTENTS

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

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

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

Dr. Sharp 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. PHILLIP SHARP

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

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

NCI Budget Update. Dr. Klausner provided an overview of how the current year's budget had been spent. Of 442 million new dollars, two-thirds went into Research Grant activities, and two-thirds of that went into paying the cost of non-competing grants, which increased by 10 percent over FY 2000. There was a 123 percent increase in competing awards; in the last year, the NCI awarded about 1,200 new and competing grants, an increase of 7.5 percent. The total size of the NCI grant pool last year was 1.7 billion, which is larger than the entire budgets of all but three NIH Institutes.

A total of about 750 R01 grants were funded, which represents a 5 percent increase in numbers and a 20 percent increase in dollars. The average per-year cost of a grant increased from

$299,000 to $340,000. The payline remained in the 22nd percentile. The NCI expects to reduce the use of downward negotiation this year because a cap has been placed on increases in the amount that can be requested for P01 and R01 competing renewals. The fact that Type 2 R01s, which are competing renewals, increased an average of 45 percent last year will continue to be a major concern. Cancer Centers grew by 18 percent, and the SPORES program grew by 30 percent. The K Awards, a career program, also continues to be a priority. About 400 awardees will be supported with 2001 funds, an increase of about 25 percent. Over the last 2 years, the NCI has nearly doubled the career program.

Last year, about 7 percent of the dollars available for grants were set aside for new Special Initiatives based on priorities in the Bypass Budget. One such initiative is CANCORS, the Cancer Care and Outcomes Research and Surveillance consortium, which studies the impact of cutting-edge interventions on patient-oriented outcomes, investigates the dissemination of state-of-the-art science into community practice, and analyzes disparities in the delivery of quality care. The new Interdisciplinary Research Teams for Molecular Target Assessment program is looking at how to create technologies needed to measure molecular targets and develop molecularly targeted drugs in the context of the design of future clinical trials. Other initiatives in molecular targets include the Molecular Target Drug Discovery Initiative. By the end of FY 2001, the NCI will announce an award to establish large-scale national Molecular Target Labs, a program to definitively develop molecular probes for pathways and cancer targets.

Other new initiatives include pilot trials to evaluate chemoprevention agents in former smokers; planning grants for additional *in vivo* cell and molecular imaging centers; the reissue of an RFA for small animal imaging research programs; geographically based research in cancer control and epidemiology, oriented toward building upon the cancer mortality maps and toward further development of the new Geographic Information Systems (GIS) technology; and the Comprehensive Minority Institution Cancer Center partnerships.

Dr. Klausner said that the budget for FY 2002 is uncertain, calling attention to speculation in the media that a continuing resolution may be required this year. He reported that the NCI will soon release its 2003 Bypass Budget. The Institute has received a great deal of helpful feedback on the draft Bypass Budget from the NCAB and other sources.

Extraordinary Opportunities and New Initiatives. The NCI is beginning to plan for the next major edition of the Bypass Budget. Every 3 years, the Institute reevaluates what it calls "Extraordinary Opportunities" for investment in cancer research. This involves communication with many individuals and organizations through Web sites, interactions with professional societies, and other methods to solicit ideas on what constitutes Extraordinary Opportunities and how to use those ideas in planning several years in advance. Such planning results in the announcement of funding initiatives. An equally important aspect of planning is following up on those initiatives to measure what is being accomplished, although it can be difficult to quantify scientific discovery.

Dr. Klausner presented slides demonstrating a pilot Web site designed to collect feedback from NCI staff, grantees, contractors, and others to evaluate progress in the pursuit of the goals of various NCI initiatives. He added that members of the Board will be asked to volunteer to work with NCI staff to evaluate this Web site as it is being developed. Scientific priorities are linked in the Web site to the Extraordinary Opportunities from the Bypass Budget. Descriptions of Extraordinary Opportunities include a categorization of the initiatives associated with them, and descriptions of individual initiatives explain how each initiative relates to broader goals, what each is intended to accomplish, and who has been funded through each initiative. Abstracts of research projects, links to related publications, descriptions of research tools being developed, and information on emerging clinical trials are also included. Information is provided by investigators, and the site provides a new way for these investigators to communicate their results to a variety of audiences.

Dr. Klausner also presented slides demonstrating a draft version of a new report format that will be inaugurated at the December 2001 NCAB meeting. This report, developed by the Cancer Control Working Group within the Division of Cancer Control and Population Sciences, goes beyond traditional reporting on the burden of cancer to create a "cancer report card" across the continuum of cancer; the "report card" is linked to the Department of Health and Human Services' Healthy People 2010 goals. Colorful graphics are used to display data and trends on prevention, early detection, diagnosis, treatment, end-of-life care, economic issues, the cost of cancer, and other areas of concern to the NCAB. The report is designed not just to list planned activities and recent accomplishments but to provide a variety of ways to monitor how well the Institute and the Nation are achieving their objectives with regard to cancer.

In anticipation of the planned report of the Progress Review Group on lung cancer, Dr. Klausner reported on an important initiative related to tobacco control and the question of addiction. About a year ago, Dr. Klausner discussed with Dr. Alan Leschner, Director of the National Institute on Drug Abuse (NIDA), the need for an improved approach to identification and development of therapeutics for treating nicotine addiction—recognizing that a tobacco control program that does not address addiction is not likely to succeed. A working group on this problem was developed by the two Institutes with a special emphasis on the rapid clinical development and testing of new agents. This development is linked to changes in understanding of the genetics and biochemistry of addiction. A particular challenge for this group has been finding and validating molecular targets. Barriers include an inadequate infrastructure for drug discovery and testing; a perceived bottleneck associated with Food and Drug Administration (FDA) regulation and approval; disincentives for industry involvement in drug development; lack of reimbursement for treatment; intellectual property issues; marketing and regulatory impediments to developing prescription and over-the-counter treatments; lack of consumer-friendly and acceptable forms of nicotine treatment; lack of patient advocacy groups; lack of champions in industry or academia; and a perceived lack of interest among researchers in areas of research that go beyond smoking cessation.

The plan is to create an NCI/NIDA/FDA/industry forum for exchanging information, improving communication, and clarifying mutual expectations for dealing with the complex

scientific, business, and regulatory issues. Discussions are already underway to identify key regulatory issues relevant to trials that focus on addiction and smoking cessation. Other efforts will include providing incentives for industry, developing a Clinical Trials Registry, and produce a White Paper on the economics of drug development.

A major theme of the past 6 months, Dr. Klausner observed, has been the idea of moving from individual investigators to consortia, networks, networks of networks, and interactions among all consortia—in short, the idea that people need to work together. He called the attention of the Board to a new scientific finding that has emerged from the Mouse Models of the Human Cancer Consortium (MMHCC); this finding has led to an interaction with the Cancer Genetics Network (CGN) and others involved in molecular epidemiology. Dr. Klausner expressed the belief that this type of interaction can provide new approaches to the difficult problem of identifying the genetic components of susceptibility to cancer.

It has been relatively easy to find the limited number of single-gene, high-penetrance Mendelian traits that are overwhelmingly responsible for the small fraction of cancers described as high-penetrance familial syndromes. However, the vast majority of cancers result from interactions between genes and the environment. The genetic component is involved in determining, in complex ways, the nature of the cancer, its progress, how it responds to therapy, and other factors. The task of finding the low-penetrance genes involved in cancer will be much more difficult.

Much hope has been placed in the possibility of using the mouse, with its more tractable genetics based on our ability to control mating, to approach this problem. Dr. Klausner presented unpublished findings from a study led by Alan Balmain and Bruce Ponder in Cambridge, England, using the MMHCC. Collaborators included the University of California–San Francisco Comprehensive Cancer Center. The investigators used the mouse to identify modifier genes, and then moved between the mouse and the human to identify what appears to be a candidate for a susceptibility gene for breast cancer and, potentially, for colorectal and other cancers.

Different mouse species, and different strains within mouse species, have different susceptibilities to cancer. The various strains of *Mus musculus* that are generally used in the laboratory are relatively susceptible to cancer, though each strain has different sensitivities; the *Mus spretus*, by comparison, is relatively resistant to cancer. For example, Dr. Klausner presented data from a skin cancer study showing 20 cases of skin cancer among a *Mus musculus* sample, compared with zero cases in a *Mus spretus* sample. An examination of offspring of a cross between these two species shows the dominant effect of some genes from *spretus* that suppress susceptibility to this cancer. Finding these genes and understanding how they work could provide a route to prevention.

The method for finding the gene or genes in question is to breed mice to produce congenic strains that bear 3 to 7 percent *spretus* genes. By mapping the mice that do and do not develop cancer, it is possible to determine the minimum amount of the *spretus* genome that has to be mixed with the *musculus* genome to suppress cancer, and it can be assumed that within that small amount of DNA is a gene or genes that protects the *musculus* from cancer. Many modifiers

that either enhance or decrease susceptibility to cancer can be mapped in the genome. At the most sophisticated level of analysis, researchers can look at susceptibility to precancerous conditions, progression from precancer to cancer, metastasis, etc.

The standard approach to perform this analysis is very time-consuming and very expensive. Dr. Balmain's laboratory has developed a new approach that makes it possible to move very rapidly from a large amount of DNA, containing about 20 million bases, to a segment containing 1 million, which increases the feasibility of identifying genes. Researchers have located the modifier that reduces susceptibility in their mice in a small region at the distal part of Chromosome 2, which is homologous to a very highly conserved region on human Chromosome 20, a region well known as the site of an extremely common amplification in many human cancers, particularly breast, colon, and ovarian cancers.

When candidate genes have been identified, the next step is to find common polymorphisms in the genes of the region and test them. Dr. Balmain and collaborators have focused on a gene on Chromosome 20 called STK15, or the Aurora 2 kinase, which is a centrosome-associated kinase. Looking at two human case control studies in England and Finland, the researchers found that one polymorphism within this gene is associated with a 40 percent increase in risk of breast cancer.

Dr. Klausner addressed some implications of this work. He indicated that these findings may represent a new mechanism to study candidates for human susceptibility genes by bouncing back and forth between mouse and human studies conducted by a consortium. Perhaps more interesting is the potential fusion of population genetics with molecular genetics, in essence studying the population genetics of human tumors—the population of cells that make a tumor. Dr. Balmain's laboratory has shown that within certain tumors, the allele associated with population susceptibility is selectively, specifically, and nonrandomly amplified or overexpressed. This may represent a dramatically different approach to molecular epidemiology. The CGN and the MMHCC have received approval to examine whether overexpressed and amplified genes in tumors are randomly distributed across alleles in which there is heterozygosity. This new approach could reduce the number of patients required to answer this question from 8,000 to 50 or 100.

NCI Staff Changes. Dr. Klausner announced the news of the terrorist attack on the World Trade Center and reported that a break would follow a brief discussion of NCI staff changes. He acknowledged the work of two individuals who are leaving the National Cancer Institute. He first mentioned Sue Waldrop, who began in the 1960s in the Laboratory of Immunology and has for the past 2 years headed the Office of Scientific Opportunity, playing a critical role in the Institute's planning processes. She has been responsible for leading many "think tanks" across the Institute to ensure a link between planning and implementation. Dr. Waldrop thanked Dr. Klausner and acknowledged the mentorship of Dr. Alan Rabson. Dr. Klausner then mentioned Sue Sieber, who has served NCI for 30 years in a number of positions, from Acting Chief of the Laboratory of Chemical Pharmacology to Special Assistant to the Director of the Division of Cancer Etiology. She has also served as Deputy Director of the

Division of Cancer Epidemiology and Genetics, NCI's Associate Director of Special Projects, and, most recently, as the first Director of NCI's Office of Communications. Dr. Klausner announced that Mary McCabe will serve as the Acting Director of the Office of Communications. Dr. Sieber thanked Dr. Klausner and the many people she has worked with during the past 30 years.

Dr. Klausner read a letter that he sent to President Bush informing the President of his decision to step down as Director of the National Cancer Institute after 6 years of service. He stated that this has been the most challenging and rewarding experience of his career. In his letter, he stressed that the research enterprise is robust but fragile, requiring sustained nurturing. He said that he looked forward to a continuing close relationship with the NCI, the NIH, and the scientific community. Because he will remain in Washington, he will be available to the President, the administration, and the Congress to provide any help that may be required.

Dr. Klausner noted that he has spent his entire 22-year career at the NIH. The work of the NCI, he observed, is not done, but he feels that he has had the privilege of setting in motion most of what he had hoped to accomplish and has received more than he has given. For some time, he said, he has been interested in the possibility of establishing a new science and technology support enterprise designed to go beyond the constraints of funding of individual projects to attack larger public health and biomedical problems in novel ways. This vision is shared by Steve Case, founder of AOL and chairman of AOL/Time Warner, and his wife Jean. Through the Case family's foundation, the Case Institute of Health Science and Technology will be launched on October 1, 2001, and Dr. Klausner has agreed to serve as its founding President. The Case Institute will work to identify major challenges and novel solutions to problems that emerge from the interface and interaction of the biological, physical, and information sciences. The Institute will integrate scientific discovery with new technology by designing and funding initiatives in areas such as molecular technology, bioinformatics, knowledge management, translational science, public health-oriented technology, science education, and efforts to reduce the impact of the "digital divide." Dr. Klausner expressed his pleasure in the fact that the location of the new Case Institute in Washington will enable him to continue working at the NCI as an intramural scientist.

Dr. Sharp expressed to Dr. Klausner the appreciation of the entire NCAB for the opportunity to work with him, acknowledging his contributions to the country by helping the NCI evolve into a forward-looking organization on the cutting edge of technology.

IV. ADJOURNMENT - OPEN SESSION – DR. SHARP

After a brief break, Dr. Klausner announced that, because of the attack on the World Trade Center, the open session of the NCAB meeting would be suspended, and that the Board would proceed to its closed session to conduct necessary business. The open session of the 119th meeting of the National Cancer Advisory Board was adjourned at 10:20 a.m.

CLOSED SESSION

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

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

During the closed session of the meeting, a total of 1295 applications were reviewed requesting support of $371,224,123. Funding for those 1295 applications was recommended at a level of $365,751,170.

V. ADJOURNMENT—DR. PHILLIP SHARP

There being no further business, the closed session of the 119th meeting of the National Cancer Advisory Board was adjourned at 11:00 a.m. on Tuesday, September 11, 2001.