Board of Scientific Advisors

Meeting Minutes

November 14-15, 2002

Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

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Meeting Minutes

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The Board of Scientific Advisors (BSA or Board), National Cancer Institute (NCI), convened for its 22nd regular meeting on Thursday, November 14, 2002, in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Frederick Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, presided as Chair.

The meeting was open to the public from 8:30 a.m. until adjournment for opening remarks from the Chair; the NCI Deputy Director's and NCI/Congressional Relations reports; ongoing and new business; and presentations and discussions on Translating Research Into Improved Outcomes (TRIO) program progress report; Cancer Regression in Patients Following Clonal Repopulation with Antitumor Lymphocytes report; Transdisciplinary Tobacco Use Research Centers (TTURCs) update:Development of New Methods for Measuring the Impact of Scientific Initiatives; the annual BSA concept report;; a status report on the Cancer Therapy Evaluation Program (CTEP) Concept Evaluation Panels; Early Detection Research Network (EDRN) progress repor; Mouse Models of Human Cancers Consortium (MMHCC) update; new and reissued Requests for Applications (RFAs) concepts; and a Request for Proposal (RFP).

Board Members present:
Dr. Frederick R. Appelbaum (Chair)
Dr. David B. Abrams
Dr. David S. Alberts
Dr. Hoda Anton-Culver
Dr. Thomas Curran
Dr. Raymond Dubois
Dr. Mary Beryl Daly
Dr. Patricia Ganz
Dr. H. Shelton Earp
Dr. Susan B. Horwitz
Dr. Hedvig Hricak
Dr. William G. Kaelin, Jr.
Ms. Paula Kim
Dr. Michael Link
Dr. Lynn Matrisian
Dr. Christine A. Miaskowski
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal
Dr. Margaret Spitz
Dr. William C. Wood
Dr. Robert C. Young

Board Members absent:
Dr. Esther H. Chang
Dr. Neil J. Clendeninn
Dr. Eric Hunter
Dr. Kenneth W. Kinzler
Dr. Herbert Y. Kressel
Dr. W. Gillies McKenna
Dr. Mack Roach, II

NCAB Liaison:
TBN

Others present: Members of NCI's Executive Committee (EC), NCI Staff, Members of the Extramural Community, and Press Representatives.

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XI. Reissued RFAs; Presented by NCI Program Staff
- National Cooperative Drug Discovery Groups (NCDDGs) for Cancer; Dr. Mary Wolpert
- Long-Term Cancer Survivors: Research Initiative; Drs. Julia Rowlandand Noreen Aziz

XII. RRFP Concept; Presented by NCI Program Staff
- Division of Cancer Treatment and Diagnosis Pediatric Preclinical Testing Program ; Dr. Malcolm Smith

XIII. Public/Private Partnerships: Overcoming the Barriers to Early Clinical Trials; Drs. Peter Greenwald, Sudhir Srivastava, David Sidransky, Mark Thornquist, Mr. Dan Crichton,and Dr. Larry Norton

XIV. Mouse Models of Human Cancers Consortium (MMHCC) Update; Drs. Dinah Singer, Tyler Jacks, Betty Tarnowski, and Cheryl Marks

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I. CALL TO ORDER AND OPENING REMARKS - DR. FREDERICK APPELBAUM

Dr. Frederick Appelbaum called to order the 22nd regular BSA meeting and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Appelbaum welcomed new members to the Board: Drs.Thomas Curran, Chairman and Member, Department of Developmental Neurobiology, St. Jude Children's Research Hospital; Raymond N. DuBois, Jr., Director, Department of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center; H. Shelton Earp, Director, Lineberger Comprehensive Cancer Center; Patricia A. Ganz, Director, Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center; Hedvig Hricak, Professor of Radiology, Cornell University Medical College; Michael P.

Link, Professor of Pediatrics, Stanford University School of Medicine; Lynn M. Matrisian, Professor and Chair, Department of Cancer Biology, Vanderbilt University Medical Center; Margaret R. Spitz, Professor and Chair, Department of Epidemiology, MD Anderson Cancer Center, and Ms. Paula Kim, Founding CEO, Pancreatic Cancer Action Network, Inc. Board members were reminded of the conflict-of-interest regulations and future meeting dates.

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II. CONSIDERATION OF THE 14-15 NOVEMBER 2002 MEETING MINUTES - DR. FREDERICK APPELBAUM

Motion: The minutes of the 24-25 June 2002 meeting were unanimously approved.

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III. REPORT OF THE DIRECTOR, NCI-DR. ALAN RABSON

Dr. Alan Rabson, Deputy Director, NCI, informed members that Dr. von Eschenbach had been called upon to accompany Mr. Tommy Thompson, Secretary of the Department of Health and Human Services, and Dr. Elias Zerhouni, NIH Director, to Ireland. Dr. Rabson welcomed new BSA members and emphasized the Board's importance to the NCI Director in providing oversight of the Institute's extramural programs. In the Director's absence, Dr. Rabson reviewed a number of issues.

NCI Retreats: NCI's Executive Committee is discussing the Institute's strategic plan for the next few years. Similar discussions are occurring at the NIH level.

NCI Staffing Changes: Dr. Rabson reported that Dr. Barbara Rimer, former Director, Division of Cancer Control and Population Sciences (DCCPS), had accepted a position at the University of North Carolina (UNC) as Professor of Health Behavior and Health

Education, School of Public Health, and Deputy Director for Population Sciences at the Lineberger Cancer Institute. Dr. Robert Hiatt, Deputy Director of DCCPS, will assume the position of Director, Population Sciences, University of California at San Francisco. Dr. Robert Croyle, Associate Director, Behavioral Research Program, has been appointed Acting Director, DCCPS.

Ongoing Initiatives: The draft report from the National Cancer Advisory Board's (NCAB) ad hoc committee review of the P30/ P50 program of Cancer Centers and Specialized Programs of Research Excellence (SPOREs) will be given at the NCAB's February 2003 and the BSA's March 2003 meetings. The National Lung Cancer Screening Trial, designed to compare spiral computerized tomography with chest X-ray, is going well in that recruitment efforts have been initiated. Dr. Lance Liotta's group continues to make good progress on its proteomics screening project. The National Academy of Science's (NAS) study on NIH restructuring, mandated by Congress in its fiscal year 2001 Appropriations Act, was ongoing. He noted that the mandate was to consider whether the current NIH structure is optimal for the scientific needs of the 21st century. The current and several former NIH Directors are on the committee.

NCI Budget: Dr. Rabson informed members that NIH is operating under a continuing resolution pending enactment of the Department of Health and Human Services (DHHS) FY 2003 appropriations. In the interim, the NCI and other Institutes will operate on a flat budget based on FY2002 allocations. Until the FY2003 budget has been approved, the launching of new programs will be postponed. The Senate has recommended an NCI appropriation of $4.642B for FY2003, an increase of about 12 percent, which matches the President's request and would complete the doubling cycle of the NIH budget. The recommended appropriation includes $60M in transfers of ongoing grants to the new National Institute of Biomedical Imaging and Bioengineering (NIBIB). Regardless of the final budget, approximately $122M of any increase will need to be used for noncompeting Research Project Grants (RPGs) to maintain the current commitment to grantees in the middle of the renewal cycle. An 8 to 10 percent increase in R01 applications in FY2003 is projected. FY2002 obligations totaled $4.177B, an increase of 11 percent over FY2001. Of an estimated $197M increase in the RPG pool, about $123M, 62 percent, went into noncompeting Type 5 awards. The total RPG pool was

approximately $1.9B. The FY2002 payline was at the 22nd percentile. Program Project grants (P01s) were approximately 3 percent of the number of awards but accounted for 17 percent of the funds. Cancer Centers and SPOREs increased by 14 percent; the Careers program increased by $3.7M; National Research Service Awards (NRSAs) remained at about 1,600 trainees, and the stipend increased about 10 percent; the intramural research program remained stable at about 15 percent following a percentage reduction that followed recommendations of the Bishop-Calabresi Committee in the mid-1990s; and Cancer Control programs expanded to approximately $40M, an increase of approximately 9 percent.

In discussion, the following points were made:

- An update on the new training program presented to the Board to support researchers at NCI for 3 years and then assist them in finding and maintaining employment in the larger cancer research community should be given at a future Board meeting.

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IV. NCI/CONGRESSIONAL RELATIONS-MS. SUSAN ERICKSON

Ms. Susan Erickson, Acting Director, Office of Policy Analysis and Response, stated that Congress is operating in a "lame duck" session. Ms. Erickson informed members that at the end of the 107th Congress, the Benign Brain Tumor Registries Amendment Act, requiring state registries to collect data on benign tumors, was passed. She explained that other bills pending in the 107th Congress have expired but may be reintroduced in the new Congress. Quality of cancer care, health disparities, prevention of obesity, and survivorship were themes from the 107th Congress that may be revisited in new legislation in the 108th Congress. Both the Cancer Survivorship Research and Quality of Life Act of 2002 and the National Cancer Act of 2002 mandated the establishment of an Office of Cancer Survivorship with an earmark for funding.

In discussion, the following points were made:

- The Board expressed interest in hearing from Dr. von Eschenbach at a future meeting on the effects of the anti-bioterrorism effort on the NCI budget and the potential level of NCI involvement in that effort.

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V. ONGOING AND NEW BUSINESS-DR. FREDERICK APPELBAUM

BSA at National Meetings:

Dr. Appelbaum explained that "NCI Listens" sessions at national meetings provide an 0pportunity for the BSA to act as the eyes and ears of the NCI Director and bring back concerns and recommendations from the NCI constituents in the scientific world, as well as provide information of interest to those organizations.

Cold Spring Harbor Laboratory (CSHL) Symposium: Dr. William Kaelin, reported that most of the approximately150 attendees at the "NCI Listens" session at the Cold Spring Harbor Laboratories meeting in August 2002 were trainees or young investigators. NCI staff participants were Drs. Dinah Singer and Paulette Gray. Dr. Kaelin reported that most questions related to funding and that many of the participants felt that tight budgets affected young investigators disproportionately. Discussion also focused on tension between small and large science projects, i.e., investigators felt that the funding of some "big ticket" projects during recent periods of increased budgets may create problems in the future.

American Society for Therapeutic Radiology and Oncology (ASTRO): The "NCI Listens" report from the October 2002 ASTRO meeting will be given at the March BSA meeting.

Members representing the BSA during "NCI Listens" sessions at upcoming annual national and other meetings are:

- **Oncology Nursing Society (ONS)**: Seventh National Conference on Cancer Nursing Research, February 6-8, 2003, San Diego, CA; Dr. Christine Miaskowski (Chair).

- **American Society of Preventive Oncology (ASPO)**: March 9-11, 2003, Philadelphia, PA;Drs. Nancy Mueller (Chair), Mary Daly, Patricia Ganz, and Margaret Spitz.

- **Society of Behavioral Medicine (SBM)**: March 19-22, 2003, Salt Lake City, UT; Dr. Abrams (Chair).

- **American Association for Cancer Research (AACR)**: April 4-11, 2003, Toronto, Ontario, CAN; Dr. Hoda Anton-Culver (Chair), Tom Curran,, Shelton Earp, and Enrico Mihich.

- **Oncology Nursing Society (ONS)**: May 1-4, 2003, Denver, CO; Dr. Christine Miaskowski (Chair) and Ms. Paula Kim.

In discussion, the following points were made:

- NCI should continue to preserve the K series awards and R01 paylines and should study the impact of future budget priorities on the ability of new scientists to establish their careers.

- The upcoming report by the National Cancer Policy Board on the issue of the impact of big science on science in general and on young investigators in particular should be reported to the BSA at a future meeting.

- A subcommittee, Drs. Horwitz (Chair), Kaelin and Mihich, was established to identify the types of NCI career grants training program presentations that would be most informative for the Board. A report will be given to the full Board at a future Board meeting.

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VI. TRANSLATING RESEARCH INTO IMPROVED OUTCOMES (TRIO) PROGRAM PROGRESS REPORT-DR. JON KERNER

Dr. Jon Kerner, Assistant Deputy Director, DCCPS, provided an overview of strategies for disseminating scientific research to clinical practice. Dr. Kerner reminded the Board that the central goals of *Healthy People 2010* are to increase quality and years of healthy life, and to eliminate health disparities. The NCI has supported a considerable amount of research in the area of health disparities and has articulated this area as a challenge to close the gap between research discovery and program delivery. While the NCI research portfolio is diverse and hundreds of billions of dollars are spent on research and health care services, remarkably little is spent on linking the two through what is referred to as the "discovery/development/delivery continuum."

Dr. Kerner illustrated the challenges to diffuse and disseminate information on cancer research. He stated that dissemination has been limited to a process of passive diffusion: the interaction between scientists sharing information at conferences and through scientific publications. This information is rarely recognized and applied in the medical practice setting, because there is just too much of it to digest and synthesize. The Agency for Healthcare Research and Quality (AHRQ) estimated that it takes 17 years to turn 14 percent of original research to the benefit of patient care. Dissemination should be a more active process through which target groups are made aware of, receive, accept, and use information and other interventions.

Dr. Kerner described NCI's TRIO program which was developed to address the lack of an effective dissemination strategy. He also briefly described the new PLANET (Plan, Link, Act, Network with Evidence-Based Tools) Web portal, developed in partnership with the Center for Disease Control and Prevention (CDC), American Cancer Society (ACS), and the Substance Abuse and Mental Health Services Administration (SAMHSA). PLANET is a searchable database designed to link researchers with practitioners.

In discussion, the following points were made:

- Practitioners who wish to list their programs in the

PLANET database, but lack the resources to evaluate the programs, may be partnered with an appropriate researcher to conduct testing through an R01 grant.

- Limitation of resources at the primary care physician level should be considered when implementing new programs.

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VII. CANCER REGRESSION IN PATIENTS FOLLOWING CLONAL REPOPULATION WITH ANTITUMOR LYMPHOCYTES- DR.STEVEN ROSENBERG

Dr. Steven Rosenberg, Chair, Surgery Branch, Center for Cancer Research (CCR), described the history of immunotherapy, the obstacles future therapies need to overcome, and clinical studies that demonstrate how immune cells can be manipulated to induce the regression of invasive cancers. He explained that Interleukin 2 (IL 2) is a growth factor that stimulates activation of immune cells with no direct effect on cancer cell growth. Patients with metastatic melanoma or kidney cancer treated with IL 2 showed complete tumor regression; 10 percent of the original 407 patients were in remission 15 years after treatment. Despite the significant response to IL 2, safe administration issues have prevented its widespread use in the United States. In addition, IL 2 treatment is only effective for patients with melanoma, kidney, cancer, or disseminated lymphoma.

Dr. Rosenberg explained that cancer-specific lymphocytes have been generated in patients immunized with cancer antigens. These studies demonstrated that amino acid modifications in the immunodominant peptides increased the avidity of the peptides to bind to the human leukocyte antigen (HLA) molecules that present the antigens to T cells. Patients immunized with these modified peptides showed a dramatic increase in the number of tumor-specific T cells. Despite the ability to generate antitumor lymphocytes in vivo, numerous mechanisms limit tumor cell regression. Dr. Rosenberg remarked that these mechanisms must be overcome to fully use the patients' immune systems in cancer treatment.

Recent research CD8+ T cells that were isolated from patients, then activated ex vivo and expanded before being returned to the patients was described. A protocol used to increase the survival of the transferred T cells was also presented. Dr. Rosenberg stated that patients with metastatic melanoma were treated with non-myeloablative chemotherapy to deplete their lymphocyte population for approximately one week. When a patient's white blood cell count was zero, and before the immune system begun to recover, high-avidity T cells were administered along with IL 2. Tumor regression was not observed in any of the six patients. The protocol was amended so that the patients were treated with chemotherapy (a non-myeloablative but lymphocyte-depleting regimen) before transfer of both CD8+ high-avidity clones and CD4 + cells. Patients were also treated with IL 2. The Food and Drug Administration (FDA) approved this protocol under a compassionate exemption.

The outcome of several patients treated with the amended protocol was described. A 16-year-old male with metastatic melanoma showed no signs of disease 7 months after treatment. The patient is still disease-free 2 years after treatment. Eleven additional patients were treated with the same adoptive immunotherapy. Six patients show complete tumor regression. He noted that these data suggested that treatment with high-avidity CD8+ plus CD4+ T cells could overcome tolerance to normal, nonmutated antigens. Future studies will focus on identifying how the CD4+/CD8+ mixture of T cells mediate tumor regression.

Dr. Rosenberg concluded his presentation by describing another approach that involves transduction of patients' peripheral blood mononuclear cells with a gene that encodes highly avid T-cell receptors that recognize tumor antigens.

In discussion, the following points were made:

- Concern was expressed about the development of more serious types of autoimmunity induced by the adoptively transferred T cells.

- If one could learn how to differentiate stem cell lines into lymphocytes, stem cells could be useful in the field of adoptive transfer therapy. At this time, the laws and

regulations for stem cell transfer therapy are extremely limiting, even in the treatment of patients with metastatic disease.

- Follow-up data on adoptive transfer therapy have been collected for only 2 years. Long terminformation needs to be obtained to ensure that the transferred T cells do not mutate and result in a lymphoma or leukemia. A fail-safe mechanism may need to be added to this type of immunotherapy.

- Frozen stocks of the adoptively transferred T cells are maintained, both to ensure the safety of the cells before treatment and as a backup should the patients require future treatments.

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VIII. TRANSDISCIPLINARY TOBACCO USE RESEARCH CENTERS UPDATE: DEVELOPMENT OF NEW METHODS FOR MEASURING THE IMPACT OF SCIENTIFIC INITIATIVES-DRS. ROBERT CROYLE AND WILLIAM TROCHIM

Dr. Robert Croyle, Acting Director, DCCPS, described a pilot project to develop methods and measures for evaluating the impact and success of large scientific initiatives. The pilot is a proactive step toward determining accountability with respect to such initiatives. The Transdisciplinary Tobacco Use Research Centers (TTURC) initiative will apply scientific findings from the field of program evaluation to determine its impact. Dr. Croyle explained that TTURCs are public-private collaborations among NCI, the National Institute on Drug Abuse (NIDA), and the Robert Wood Johnson Foundation. Investigators from a variety of research institutions across the country are brought together from fields and institutions that ordinarily would not interact on such a level. The TTURC initiative was created to integrate levels of analysis and disciplines to develop a new conceptual model of tobacco use, its etiology, and interventions that work.

Dr. William Trochim, Visiting Scientist, DCCPS, provided details

on the evaluation effort and reiterated that the evaluation of the TTURC initiative will allow NCI to obtain better empirical data by applying scientific standards to the process. Dr. Trochim stated that the project will improve the understanding of how these initiatives work, what kind of results are achieved, and how resources are managed, providing the means for greater accountability. The pilot project began by creating a conceptual framework with extensive involvement of research scientists, funders, and consultants. The framework was created with the objective of using as few new resources as possible and limiting the burden on respondents. Ensuring the objectivity and credibility of the evaluation were also high priorities, as was designing a model that could be reused to evaluate other initiatives and address multiple purposes and audiences. The process used and the development of the model to collect data and measure progress toward the outcomes were described. The Evaluation of Large Initiatives (ELI) project was briefly described. He noted that his team is trying to develop general models, tools, procedures, and templates that can be widely used and that would affect the whole system of science.

In discussion, the following points were made:

- The evaluation as proposed creates too much of a burden on the researcher and institution, and much of the data generated would not be helpful to the NCI Director in justifying the creation or guaranteeing the success of such a program to Congress.

- The Board's general consensus was that the level of detail in the pilot project, as presented, was too broad and more emphasis should be placed on the ultimate deliverables and external review.

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IX. WORKING LUNCH

Dr. Appelbaum announced that discussion of how the BSA can be most helpful in evaluating NCI Divisions would be postponed pending further feedback from the NCI Director on the preferred evaluation process.

Annual RFA Report

Dr. Paulette Gray, Executive Secretary, BSA, described the contents of the *BSA Concepts Review Report, November 1995-June 2002*. A brief overview of the new charts created in response to the Board's request at the November 2001 meeting for a visual representation of data on the concepts reviewed was presented. Dr. Gray noted that pie charts represented 1) BSA-approved RFAs; 2) the proportion of RFAs set aside for various Divisions from FY1997 through FY2002; and 3) allocation of RFAs by concept area for FY1996 through FY2001.

In discussion, the following points were made:

- The *BSA Concepts Review Report* should be modified to include: 1) a pie-chart (with percents) that displays total NCI funding and those RFA budget categories that are brought before the BSA; 2) abstracts for only those projects whose funding differed from that approved by the Board. A complete set of abstracts for all RFA awards should be provided on CD-ROM.); 3) information on approved concepts for which no RFA was issued; was issued and no grants were received or no grant applications were funded; and 4) difference between targeted funding and actual requested funding.

- The possibility of tracking each concept from RFA issuance to an adequate number of awarded grants should be evaluated. This data would help the Board ascertain whether enough grant support had been awarded in response to a specific RFA. The data would also assist the Board in deciding whether to concur with an RFA re-issuance.

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X. STATUS REPORT: CTEP CONCEPT EVALUATION PANELS- DR. JEFFREY ABRAMS

Dr. Jeffrey Abrams, Pilot Projects Coordinator, Cancer Therapy Evaluation Program (CTEP), DCTD, presented the final evaluation of the Concept Evaluation Panels (CEPs) pilot program. The Cancer Clinical Trials Review Group recommended in 1996 that outside experts be included in the Phase III clinical trials review process. CEPs were created to evaluate Phase III clinical trials for two diseases, lung cancer and genitourinary cancer (GU), and met from 1999 until the fall of 2002. Dr. Abrams indicated that the CEPs were part of the overall restructuring of large Phase III trials sponsored by CTEP. He described the overall CEP process.

In March 2001, CEP members evaluated the review process to ensure that the pilot program's goals were being met. Investigators submitting their concepts for CEP review were asked to compare and evaluate the quality of the CEP and CTEP reviews. Responses were received from 192 of 288 individuals invited to participate. The investigators recommended that interactions between the CEPs and the investigators be more interactive, turnaround time for the review process be reduced, and comments made by the reviewers be more focused. The majority of respondents also felt that the CTEP and CEP review processes were similar, and there was no overall preference for one process over the other.

The total cost for both CEP panels, including honoraria for members, management of the CEP Web tool, and additional management provided by the protocol office, is about $180,000 per year. An additional five to six panels would be required to cover the evaluation of clinical trials for all cancer types. Based on the financial costs, the time involved, and the fact that the surveys did not determine that the CEP review process was superior to the CTEP reviews, the cooperative group chairs had recommended that the CEPs not be continued. Dr. Abrams agreed that the benefits to the Phase III clinical trials program were not sufficient to offset CEP costs and recommended that the Board approve not continuing or expanding this pilot program.

In discussion, the following points were made:

- One of the goals of the CEPs was to minimize the number

of competing studies being performed on the same disease, or to identify those studies that are most needed for that disease. Neither CEP nor CTEP reviews have been very successful in this respect.

- The ePanel Web tool should be adapted for use by study sections and cooperative group meetings and for analysis of other grant review processes at NIH. If combined with videoconferencing, the Web toolwould reduce the cost and inconvenience of traveling.

Motion: A motion to accept the CTEP recommendation that the CTEP Concept Evaluation Panels pilot project be discontinued was unanimously approved.

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XI. REISSUED RFAs - PRESENTED BY NCI PROGRAM STAFF

Developmental Therapeutics Program

National Cooperative Drug Discovery Groups (NCDDGs) for Cancer (RFA Reissue). Dr. Mary Wolpert, Chief, Grants and Contracts Operations Branch (GCOB), Developmental Therapeutics Program (DTP), DCTD, stated that the NCDDG initiative was created in 1982 to foster the discovery and development of new and improved anticancer therapies through a multidisciplinary approach and interactions among the Federal Government, academia, and the private sector. Success of the program is due in part to its multidisciplinary and multi-institutional collaborative approach, in which intellectual property is protected and all parties are engaged in a "win-win" relationship. Twelve investigational new agents developed through the initiative have been tested in clinical trials, and three agents have been marketed. The total grant dollars spent from 1982 to 2002 is $179M. The asset allocation for FY2002 was $12M, corresponding to 8 percent of the biochemistry and pharmacology grant portfolio. Thirteen Groups are currently funded: seven are involved with

mechanism-of-action studies; five focus on natural products; and one is developing biological agents. All the projects emphasize molecular targets and signaling pathways rather than cancer types. With the current understanding of cancer processes, new technologies, and new programs to reduce barriers to drug development, as well as with the excellent track record of the initiative and the new pool of talent within the Molecular Targets for Drug Discovery Program, representing potential future candidates for NCDDGs, reissuance of the RFA is highly justified.

The estimated set-aside for the first year is $12M for 12 cooperative agreement (U19) awards, and the estimated total for the 5 year project and one-time reissuance solicitation is $60M.

In discussion, the following points were made:

- The exchange of information between NCDDG researchers and Phase I clinical investigators should be strongly encouraged.

- Although informal coordination of activities between members of the NCDDG and the MMHCC currently occurs, a more systematic approach to bringing the two groups together for exchange of information and collaboration should be explored. Similarly, coordination of efforts between NCDDGs and other NCI funded research programs should be examined.

- Large initiative reissued reports/presentations should include evaluations from the advisory groups established for those initiatives. An integrated report on collaborations among large ongoing initiatives should also be provided.

Motion: A motion to concur with NCI's decision to reissue the DCTD RFA concept entitled "National Cooperative Drug Discovery Groups (NCDDGs)" was unanimously approved.

Office of Cancer Survivorship

Dr. Julia Rowland, Director, Office of Cancer Survivorship (OCS),

DCCPS, described the mandate of the OCS as directing, championing, and driving the science related to understanding and improving the length and quality of life of all cancer survivors and family members affected by long-term cancer survivorship. Dr. Rowland indicated that the Long-Term Cancer Survivors RFA was the first large research initiative launched by the OCS.

Dr. Noreen Aziz, Program Director, OCS, DCCPS, stated that the main goal of the concept wasto support research aimed at examining diverse and interrelated sequelae of cancer and its treatment among long-term survivors (5 or more years post treatment). In a review of the response to the original 1997 RFA, sixteen of 79 submitted applications were funded through either R01 or R03 grants. The approved projects generated numerous peer-reviewed publications and seven long-term survivorship measurement tools. Five of seven completed studies have submitted competing renewals. The focus of the funded applications included physiologic and psychosocial sequelae and the interrelationship between the two. Only two studies focused on intervention or epidemiological modeling. A major finding of the studies is that long-term adverse outcomes are more prevalent, serious, and persistent than expected, particularly in adult cancer survivors.

Reissuance of this concept will provide opportunity for future studies to build upon the research base established by the previous RFA, with a primary focus on patients who have survived 5 or more years after diagnosis, as well as on research areas and populations that are understudied. The current dependence on investigator-initiated grants is insufficient to maintain present research needs, and there are no other sources of funding in this research area. The reissuance of the RFA would complement other large NCI initiatives.

The estimated set-aside for the first year is $4M for 15 (R01, R03, or R21) awards, and the estimated total for the 2 to 5 year project and one-time reissuance solicitation is $20M.

In discussion, the following points were made:

- Partnerships with the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the

National Heart, Lung, and Blood Institute (NHLBI) should be explored.

- The R03 and R21 grant mechanisms would promote funding of junior investigators, while investigators funded through the original RFA could be funded through the R01 mechanism.

- A registry of long-term survivors would be a key resource and could provide a standard protocol for contacting patients to participate in new studies. A registry should include archival materials that would allow genetic characterization of tumors and cancer survivors.

- An incentive to recruit new investigators in the Long-Term Cancer Survivors research initiative with the reissuance of the RFA and ensure that investigators funded through the current RFA are not overrepresented among the new awardees.

- Emphasis in the reissued RFA should be on rehabilitation, chemoprevention, and risk factors for recurrence; studies on elderly long-term survivors (10 years or more); and studies on the methodology of survivorship research. A link to other resources, such as pediatric and adult clinical trials, and the inclusion of psychosocial and behavioral interventions should also be emphasized.

Motion: A motion to concur with the NCI decision to reissue a DCCPS RFA concept entitled "Long-Term Cancer Survivors" was unanimously approved. Board members suggested that staff look into the possibility of collaborating with other Institutes, such as the National Institute of Aging (NIA) and National Institute of Nursing Research (NINR); investigate ways to attract new investigators; emphasize rehabilitation, chemoprevention, and risk factors for recurrence; emphasize elderly long-term survivors (10 years or more); include studies on the methodology of survivorship research; link to other resources, such as pediatric and adult clinical trials; and include psychosocial and behavioral interventions.

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XII. RFP CONCEPT-PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis

Pediatric Preclinical Testing Program (RFP). Dr. Malcolm Smith, Head, Pediatric Section, CTEP, DCTD, stated that only a small subset of new agents tested in adults with cancer can be systematically evaluated in children. Predictive preclinical models of childhood cancers may, however, help clinical investigators prioritize new anticancer agents for testing in children. The intent of the proposed initiative is to systematically test agents in childhood cancer preclinical models. This initiative would complement existing NCI preclinical activities.

The Best Pharmaceuticals for Children Act of 2002 directed the NCI to expand and intensify activities related to preclinical drug testing. This RFP will require the testing of each agent against a panel of six to ten tumor models of a specific cancer type, most likely using xenografts. The panel of tumors will also be used to assess the level of expression of the drugs' molecular targets. This initiative will provide the initial screening steps to determine whether a drug has any interesting activity to justify further studies.

The contract mechanism is the most rapid, efficient, and cost effective way to fund this initiative, because timelines and quality control would be closely monitored, and deliverables would be the anticipated outcome. This mechanism provides the flexibility to include new models or test additional models on a case-by-case basis. Using the contract mechanism, the estimated set-aside for the first year is $1.97M, and the estimated total cost for the 5-year project and one-time solicitation is $10.55M.

In discussion, the following point was made:

- Xenografts should be molecularly characterized whenever possible and investigators conducting Phase I studies in adult populations should be included in the pediatric preclinical decision group.

Motion: A motion to approve a DCTD RFP concept entitled "Pediatric Preclinical Testing Program" was approved with one abstention. Board members suggested that xenographs should be molecularly characterized whenever possible and that investigators conducting Phase I studies in adult populations be included in the decision group.

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XIII. EARLY DETECTION RESEARCH NETWORK (EDRN) PROGRESS REPORT-DRS. PETER GREENWALD, SUDHIR SRIVASTAVA, DAVID SIDRANSKY, MARK THORNQUIST, MR. DAN CRICHTON, AND DR. LARRY NORTON

Introduction. Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), informed members that the EDRN was launched in April 2000 as an investigator-led system to discover validate, and perform early clinical testing of biomarkers important for cancer prevention, detection, and therapy. Dr. Greenwald stated that validated biomarkers hold the promise of decreasing the time needed to conduct clinical prevention trials, providing truly early cancer detection, and helping target and individualize cancer therapy.

Programmatic Progress. Dr. Sudhir Srivastava, Chief, Cancer Biomarkers Research Group, Early Detection Branch, DCP, described the EDRN's infrastructure, scientific excellence, collaborations, public-private partnerships, and validation studies in progress. He noted that the EDRN: 1) had published 100 peer-reviewed articles since its inception, many attracting inquiries from the media and the public; 2) investigators have received additional financial support from SPOREs and Program Projects; 3) has four major collaborative groups, as well as many collaborations with industry and the clinical trials community; and 4) investigators can join the EDRN consortium through an Associate Membership program that provides nominal initial funding for feasibility studies.

Dr. Srivastava concluded his presentation by emphasizing that the EDRN has established a national consortium for collaborative

biomarker research in a very short period of time while also succeeding in attracting participation from grassroots organizations in local communities.

Scientific Directions. Dr. David Sidransky, Director, Head and Neck Cancer Research Division, Johns Hopkins University, and Chairman of the EDRN Executive Committee, presented selected highlights of the scientific biomarkers discovery and validation program. Dr. Sidransky described the molecular progression of head and neck cancer, in terms of the various genetic changes that occur during disease progression. He noted that each specific mutation, epigenetic change, or viral integration may be a potential marker for cancer. Members were told that the EDRN has provided a unique opportunity to define mtDNA mutations through collaboration with the National Institute of Standards and Technology (NIST). NIST has developed a high-throughput assay that detects 98 percent of the mitochondria's sequence and identifies the mutations. Future studies will assess the distribution of these mutations in cancer, which, in turn, will provide some insight into the type of assays that need to be developed to detect such mtDNA mutations in fluids such as sputum and urine. Dr. Sidransky indicated that he is interested in identifying markers from paired DNA samples of serum or sputum and primary tumor tissue. Data showing that APC is methylated in virtually all primary lung tumors, suggesting that APC methylation is a promising marker for lung cancer was presented. He noted that several of the investigators developing methylation assays have formed a working group. The working group and the DMCC have performed blinded methylation analysis on several primary lung cancer samples and cell line DNAs with known status.

Dr. Sidransky then discussed proteomic analysis. He indicated that Eastern Virginia MedicalCenter has taken the lead in this area, comparing serum samples from patients with prostate cancer with those from control subjects. He also presented work performed by Dr. Sam Nash, of the University of Michigan, that discriminates between proteins in normal and tumor tissues using giant 2-D polyacrylamide gel electrophoresis (PAGE). A large prospective clinical trial, that was to begin December 12, 2002, will evaluate microsatellite alterations in urine as markers for bladder cancer was also described.

Dr. Sidransky concluded by acknowledging the significant input

from the EDRN that has been instrumental in allowing investigators across the United States to participate in the trial. He emphasized that the EDRN's success is driven by strong science, and in addition to other attributes, collaborations, funding, and access to technology.

Bioinformatics and Statistical Tools. Dr. Mark Thornquist, Co-Investigator, Cancer Prevention Research Program/Public Health Sciences, Fred Hutchinson Cancer Research Center (FHCRC), reported on the collaborative research performed by DMCC statisticians under the leadership of Drs. Margaret Pepe and Zideng Feng, FHCRC. Two research areas presented were the design of microarray experiments for gene selection and the analysis of high-dimensional data sets for marker discovery.

Dr. Thornquist explained that sample size for gene discovery studies should be calculated based on the probability that a truly differentially expressed gene will rank high among all the genes examined. Computer simulations are required for sample size calculations. He provided an example of such computer simulations for ovarian cancer data. The statistical methods for biomarker discovery from high-dimensional data sets were reviewed.

Dr. Thornquist concluded by stating that while most of the method development performed so far by the DMCC has focused on Phase I and II studies, research is now moving into larger Phase III and IV validation studies.

Informatic Infrastructure. Mr. Dan Crichton, Principal Investigator/Senior Computer Scientist, Jet Propulsion Laboratory (JPL), National Aeronautics and Space Administration, stated that the key challenges to EDRN informatics goals are that the data are geographically distributed across heterogeneous systems, and the data collected at each site are in different formats; access at each site is limited to local tools and users; and the level of information technology support differs at each institution. Privacy and confidentiality must be considered when sharing data. The EDRN approach to informatics was to establish a cross-disciplinary team of biomedical and computer scientists working on common data elements (CDEs). He noted that this allows seamless access to the disparate databases spread throughout the EDRN. Epidemiological and biospecimen data sets were described. Members were told that the EDRN Resource Network Exchange (ERNE) allows

researchers to share data across all EDRN databases. As of September 2002, the ERNE included seven integrated sites across the United States. Three additional databases will be added in the next few months.

Mr. Crichton concluded by outlining the key accomplishments and membership of the EDRN Informatics Working Group. He also described the JPL and how its similar data management system has resulted in interagency agreements with NIH and NCI.

Network Consulting Committee Report. Dr. Larry Norton, Head, Division of Solid Tumor Oncology, Memorial Sloan-Kettering Cancer Center, outlined the role of the EDRN Network Consulting Committee (NCC) in evaluating the current progress of the EDRN and submitting recommendations to the EDRN leadership and NCI. Dr. Norton described NCC members as a broad-based group of individuals representing different points of view and different areas of expertise. The NCC meets annually; members actively participate in EDRN-sponsored meetings and workshops and assist in conducting site visits.

The NCC discusses the relevance of the studies sponsored by the EDRN: Is the science relevant to real people with real diseases? Is EDRN adequately addressing the biological questions relevant to early detection and risk identification, and is it doing this within a realistic timeframe? and Is the EDRN facilitating biomarker development and evaluation? Other items discussed by the NCC relate to the identification of both gaps in the allocation of resources and areas for expansion. The committee has also assessed whether the EDRN is adequately addressing the private-public partnership and whether the 5-year cycle of EDRN renewal is an appropriate funding model considering that emerging validation studies may take longer than 5 years to complete. After the last NCC meeting, held in February 2002, committee members noted significant progress in addressing the goals of the EDRN in scientific excellence, collaboration, and communication. They recommended that the 1) accomplishments of the EDRN be more widely disseminated; 2) partnership with industry continue and be expanded; 3) level of collaborative work in coming years be increased; and sustained funding continue.

Dr. Norton noted that significant progress has already been made, but continuity is very important. Researchers are more inclined to

network if they feel their funding is secure.

In discussion, the following points were made:

- Interproject and interdivisional cooperation will be fundamental to EDRN reissuance. BSA will be evaluating collaboration between division chiefs and/or program directors, and a high degree of interaction is expected between large programs.

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XIV. MOUSE MODELS OF HUMAN CANCERS CONSORTIUM (MMHCC) UPDATE-DRS. DINAH SINGER, TYLER JACKS, BETTY TARNOWSKI, AND CHERYL MARK

Introduction. Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), informed members that the original idea for the Consortium came from the understanding that cancer is fundamentally a genetic disease and the realization that human models of cancer could be generated by the appropriate genetic manipulation of mice. The original goal of the MMHCC was to create an infrastructure that would support the development of genetically engineered models and the validation of those models, with particular emphasis on determining the similarities to and differences from human disease. Development of new validation technologies was also envisioned. The long-term goal of the MMHCC was to use the developed models in preclinical trials. In recognizing the existence of key differences between mice and humans, understanding the metabolism, pharmacokinetics, and the pharmacodynamics of therapeutic agents in mice is critical.

Dr. Singer stressed that no one expected that a single germ line mutation in an oncogene or tumor suppressor gene would completely replicate the course of human disease. Recognition that other innovative technologies would need to be developed to introduce somatic mutations in genes was also important in of defining the Consortium infrastructure. She indicated that disseminating the information about the mouse models to the research community would require establishing databases, Web

sites, and outreach programs, as well as making the mouse models available to the community.

The U01 Cooperative Agreement funding mechanism was used to establish the Consortium. The first grant was awarded in September 1999. A total of eighteen U01 grants were funded. The funding for the FY2002 RFA was approximately $15M.

Impact of the MMHCC on the Research Community. Dr. Tyler Jacks, Investigator and David H. Koch Professor of Biology and Director of the Center for Cancer Research, Massachusetts Institute of Technology (MIT), stated that the MMHCC Preclinical Models Working Group recognized that 1) the therapeutic evaluation of cancer is best studied in animal models and that the preclinical models available were inadequate for determining which drugs should be tested clinically; 2) the existing R01 mechanism would support only the analysis of models, but not the development of both models and technology; 3) it would be necessary to disseminate to the scientific community information on newly developed animal models through workshops, meetings, and databases; 4) creation of repositories for the mouse models of cancer, reagents, and plasmids would be necessary; and 5) use of the mouse models should be facilitated by addressing inhibitory intellectual property positions, especially those of industry.

Dr. Jacks stated that numerous workshops for technology dissemination and model characterization have been held; databases containing mouse model, plasmid, and reagent information have been developed; and a mouse models repository at NCI-Frederick has been established. Efforts have been made to engage industry in discussions of preclinical testing and intellectual property.

He noted that the MMHCC was also charged with demonstrating that the models created are actually relevant to human disease. This first required the validation of the models by histopathological analysis, gene expression profiling, and mutational analysis. Then, chemotherapeutic evaluation was needed to determine the degree of resemblance of these models to human cancers. The validation process was expected to create know-how standards and best practices for model development and characterization, as well as generate interactions with individuals working with human cancer. Researchers have met for the last 2 years to determine the degree to

which mouse model tumors resemble human tumors. Data showing that some mouse models appear relatively similar to human disease, at least histopathologically was presented. Researchers have concluded, however, that the available models do not adequately cover the full spectrum of human lung cancers; in particularly, squamous-cell lung cancer models are lacking. Similar validation efforts have been taking place with models resembling other tumor types.

Additional validation methods currently being explored by MMHCC researchers, i.e., array-based analysis of gene expression, competitive genomic hybridization for detecting chromosomal alterations, novel imaging technologies, and chemotherapeutic and chemopreventive testing, were presented. Results from gene expression array analysis of lung tumors from mouse models showing the hierarchical clustering that distinguishes tumor samples from normal samples were also presented. Work is ongoing to determine the mouse tumor profiles that are most similar to human lung cancer subtypes. Dr. Jacks also presented bioluminescence imaging data.

In conclusion, Dr. Jacks explained that members of his group have applied their technical expertise to help other Consortium members develop models for ovarian and pancreatic cancers for which there are currently no acceptable mouse models.

Resources Developed by the MMHCC. Dr. Betty Tarnowski, Executive Director, MMHCC, DCB, presented a synopsis of four resources created by the MMHCC: the Mouse Models Repository, Web-based public resources, the Cancer Models database, and the Cancer Images database. Formation of a mouse models repository was deemed absolutely crucial by the Consortium because genetically engineered models were not available anywhere else. Information on available strains is available on line, and 50 strains are currently offered at no cost. Researchers may search the Web site (http://mouse.ncifcrf.gov) by common strain name, gene or transgene, organ site, mutation type, and genetic background. Since the launch of the Web site in January 2001, 172 breeding pairs of mice have been distributed. Eighty five percent of these pairs went to non-MMHCC members, an indication of the value of this repository to the general scientific community.

Dr. Tarnowski described the various databases: 1) eMICE Web site

(http://emice.nci.nih.gov) - a comprehensive, available-to-the-public source of information about mouse models and mouse research; 2) Cancer Models database (http://cancermodels.nci.nih.gov) - generated for the scientific community by the scientists who either generated or worked with each model; and 3) Cancer Image database (caImage: http://cancerimages.nci.nih.gov) - an archive of scans from magnetic resonance (MR), computer tomography (CT), micro positron emission tomography (PET), and in vivo imaging. Dr. Tarnowski emphasized that each of these Web-based resources was fully integrated with the NCI and National Center for Biotechnology Information (NCBI) databases, such as PubMed, Entrez, BLAST, and Genebank.

Scientific Advances in Developing and Characterizing Mouse Models. Dr. Cheryl Marks, Associate Director, DCB, presented selected examples of the scientific research conducted by the Consortium to address the following questions: 1) Does temporal alteration of gene expression provide information about the genes that are needed for tumor progression? 2) What strategies in addition to germline modification to derive cancer models should be pursued? 3) What can be learned from cancer models about other disease processes and etiologic factors in cancer risk? 4) Can mouse models be used to isolate genes that confer susceptibility to cancer? Brief synopsis of research by select investigators working on the various questions was presented.

She announced that the Consortium would be holding a meeting in conjunction with the Cancer Genetics Network and the Cancer Family Registries to discuss applying mouse models to human population sciences. The Consortium also has connections with the Comparative Mouse Genomics Centers Consortium of the National Institute of Environmental Health Sciences (NIEHS) and the International Ethylnitrosourea (ENU) Mutagenesis Project in both membership and interest.

Dr. Marks briefly mentioned the preclinical trials roundtable held in conjunction with the Toxicogenomics Consortium at NIEHS to discuss the use of mice in preclinical research. The panel discussed the advantages and disadvantages of engineered models, cell-based assays from engineered models, and how to gain therapy-related experience with engineered models. As a result of the roundtable discussion, the NCI is encouraging the innovative use of transgenic mice for therapy; a Program Announcement (PA) was issued for

cancer therapy-related use of genetically engineered mice. Eight grants will be funded in response to that announcement.

Dr. Marks concluded by outlining new directions for the Consortium in biology and gene discovery, as well as cancer susceptibility. She stressed the need for innovation in the areas of computation, statistical sciences, and mouse phenotyping, reiterating the need to embed imaging strategies into preclinical science.

Adjournment: The meeting was adjourned at 12:12 p.m. on Friday, 15 November 2002.

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