Board of Scientific Advisors

Meeting Minutes

November 15-16, 2007

Building 31C, Conference Room 10
Bethesda, Maryland

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Members

Agenda & Future Meetings

Meeting Minutes

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 38th meeting on Thursday, 15 November 2007, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, President, Fox Chase Cancer Center, presided as Chair.

The meeting was open to the public from 8:00 a.m. until 5:45 p.m. on 15 November for the NCI Director's report; report on NCI Congressional relations; presentation on the NIH Research, Condition, and Disease Categorization (RCDC) Project; a report on enhancing peer review; a mini-symposium on the human papillomavirus vaccine (HPV); a discussion about the Request for Applications (RFA) annual report; a status report on the Centers for Population Health and Health Disparities (CPHHD); and consideration of RFA new and reissuance concepts presented by NCI program staff. The meeting was open to the public from 8:00 a.m. on 16 November until adjournment at 11:35 a.m. for a mini-symposium on the future of imaging in NCI's programs, an update on The Cancer Genome Atlas (TCGA) project, and a report on Phase 0 trials.

Board Members Present:
Dr. Robert C. Young (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
Dr. Curt I. Civin
Dr. Susan J. Curry
Dr. William S. Dalton
Dr. Sanjiv S. Gambhir
Dr. Todd R. Golub
Dr. William N. Hait
Dr. Leland H. Hartwell
Dr. James R. Heath
Dr. Mary J. Hendrix
Dr. Timothy Kinsella
Dr. Christopher J. Logothetis
Dr. James L. Omel
Dr. Edith A. Perez

Board Members Present:
Dr. Robert D. Schreiber
Dr. Ellen Sigal
Dr. Victor J. Strecher
Dr. Jean Y. J. Wang
Dr. Jane Weeks
Dr. James K. Willson

Board Members Absent:
Dr. Michael A. Caligiuri (Ad Hoc)
Dr. Kathleen M. Foley
Dr. Joe W. Gray
Dr. Leroy Hood
Dr. Marc A. Kastner
Dr. Kathleen H. Mooney
Dr. Richard L. Schilsky
Dr. Stuart L. Schreiber
Dr. Bruce W. Stillman
Dr. Irving L. Weissman

Others present: Members of NCI's Executive Committee (EC), NCI staff, members of the extramural community, and press representatives.

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The NCI Mouse Models of Human Cancers Consortium (NCI-MMHCC) (RFA/Coop. Agr.)

Division of Cancer Prevention

Community Clinical Oncology Program (RFA/Coop. Agr.)

Minority-Based Community Clinical Oncology Program (RFA/Coop. Agr.)

XI. Mini-Symposium: Future of Imaging in the NCI Programs: From Molecule To Man

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XII. Update: The Cancer Genome Atlas; Drs. James Tatum and Peter Choyke

XIII. Phase 0 Trials; Dr. James H. Doroshow

XIV. Adjournment; Dr. Robert C. Young

I. CALL TO ORDER AND OPENING REMARKS - Dr. Robert C. Young

Dr. Young called to order the 38th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff,guests, and members of the public. Dr. Young reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. He called attention to confirmed meeting dates through November 2009. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting.

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II. CONSIDERATION OF THE 28-29 JUNE 2007 MEETING MINUTES - Dr. Robert C. Young

Motion: The minutes of the 28-29 June 2007 meeting were approved unanimously.

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III. DIRECTOR'S REPORT - Dr. John Niederhuber

Dr. John Niederhuber, Director, NCI, welcomed new members and provided the Board with an update on NCI's fiscal year (FY) 2007 and 2008 budgets and described NCI leadership efforts at the NIH,

as well as the NCI's commitment to translational research.

FY 2007 Year-End Budget Summary. Dr. Niederhuber explained that research project grants (RPGs) were funded at more than the 15th percentile with additional exceptions for a 20 percent success rate. New investigator STAR R01s were funded at the 21st percentile. A total of 1,312 competing RPGs were funded in FY 2007, the NIH-recommended target. In addition, the NCI funded two new cancer centers at Baylor College of Medicine and Stanford University. Dr. Niederhuber expressed his appreciation to the NCI budget team, who successfully implemented the new NIH Business System (NBS) during the FY 2007 close out.

FY 2008 Appropriations and Operating Budget Development. Dr. Niederhuber reminded the Board that the President's Budget (PB) is $4.78 B for FY 2008. Congressional appropriations are higher, at $4.92 B. Based on the PB, the NCI's challenge is to address a 12 percent loss in purchasing power since 2004 caused by inflation. Dr. Niederhuber described a FY 2008 operating budget based on the Congressional Appropriations number of $4.92 B, and its increase of $128.1 M. NIH taps and assessments are estimated to increase by $20 M, and NCI requirements based on increases in competing RPGs, rents and utilities, small business program, and mandated salary increases, as well as the NCI Director's Reserve of $25 M, provide a subtotal available of $15.6 M. To create a pool of $70 M for new initiatives, expansions, and restorations, NCI planning involves a 3 percent decrease in Division, Centers, and the Office of the Director (OD) budgets.

NCI’s Leadership at NIH. Dr. Niederhuber said that the NCI has played a leadership role in a number of NIH activities, including the Foundation for the NIH (FNIH) Biomarkers Consortium, NBS, Clinical Research Center (CCR), Small Business Innovation Research (SBIR) program, Trans-NIH Angiogenesis Research Program (TARP), and AIDS research. All NCI activities aim to change the course of disease for patients, including prevention, the discovery of disease markers, and interventions. Cancer often provides models for other diseases; the study of these models has contributed to the understanding of the biology and treatment of other diseases.

Dr. Niederhuber shared an example of the unique role that the NCI plays in the world of drug development. He presented the results of

a African-American female patient with cutaneous T-cell lymphoma who was successfully treated at the NIH Clinical Center (CC) with fenretinide (4-HPR), a synthetic drug related to vitamin A. Fenretinide was developed initially by Johnson & Johnson in the 1970s as a chemopreventive agent and was brought to NCI's Rapid Access to Interventions Development (RAID) program by Dr. C. Patrick Reynolds of Children's Hospital in Los Angeles. The RAID program is instrumental in bridging the gap between the lead discovery and drug delivery and provides the academic and small business communities with access to preclinical contract research resources.

Other examples of NCI's leadership include the Chemical Biology Consortium (CBC) and the Life Sciences Consortium. The CBC is an integrated research cooperative at the interface of chemical biology and molecular oncology to establish a cancer drug discovery group on the scale of a small biotechnology concern and to focus on unmet therapeutic needs in oncology not currently addressed by the private sector. The Life Sciences Consortium, a subcommittee of the Clinical Trials Advisory Committee, is addressing issues related to common language for establishing contractual relationships for drug development between industry and the public sector, intellectual property (IP), and antitrust.

Dr. Niederhuber described other NCI initiatives, such as the: 1) NIH Genome-wide Association Studies (GWAS); 2) The Cancer Genome Atlas (TCGA) is a pilot project jointly sponsored by the NCI and National Human Genome Research Institute (NHGRI); 3) and the childhood cancer Therapeutically Applicable Research to Generate Effective Treatment (TARGET) initiative. TARGET has an established BSA subcommittee to provide oversight.

Dr. Niederhuber said that the enormous potential for more specific cancer treatment, coupled with the complexity of evaluating new, highly specific agents, requires a national clinical trials enterprise that integrates the knowledge, insights, and skills of multiple fields into a new kind of cross disciplinary, scientifically driven, cooperative research endeavor. This potential is being tapped by the Coordinating Center for Clinical Trials (CCCT), with resources from the Clinical Trials Working Group (CTWG) and the Translational Research Working Group (TRWG).

Current barriers to battling cancer include inadequate resources,

recruitment, and retention of the next generation of scientists, time and expense required for translation, an old clinical trials system and regulatory process, and access to care. Dr. Niederhuber stated that this is an exciting time in scientific discovery that will completely change diagnosis of disease and therapy. He expressed that great opportunities will exist in the near future for disease prevention and life extension, as rapidly advancing technology makes way for highly developed and personalized treatment solutions.

In discussion, the following point was made:

- NCI's international achievements include common grants funded to developed countries and recent activity in undeveloped parts of the world, including the funding of several clinical trials. The NCI recently recruited an individual who has experience setting up clinical trials in underdeveloped countries to work with the Fogarty Institute to identify new opportunities. In addition, NCI is pursuing a partnership with the National Institute of Allergies and Infectious Diseases (NIAID) and the Fogarty Institute to co-fund an RFA to provide an international training program for Fellows.

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IV. NCI/CONGRESSIONAL RELATIONS - Ms. Susan Erickson

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on the FY 2008 appropriations status and reviewed legislation of interest to the NCI. Specifically, Ms. Erickson provided an overview of the U.S. Food and Drug Administration (FDA) Amendments Act, the Conquer Childhood Cancer Act, Access to Cancer Clinical Trials, and the Ovarian Cancer Biomarker Research Act.

In discussion, the following point were made:

- A list of key congressional contacts should be made available to BSA members who wish to contact their

Congressional representatives regarding the passage of the appropriations bill. This contact list should also be sent to the American Association for Cancer Research (AACR) and American Association for Cancer Institutes (AACI).

- An update on the Genomics and Personalized Medicine Act (S. 3822) should be given at the March 2008 BSA meeting.

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V. NIH RESEARCH, CONDITION, AND DISEASE CATEGORIZATION (RCDC) PROJECTCDR. TIMOTHY HAYS

BSA at National Meetings: ASTRO

Dr. Timothy Hays, Project Director, RCDC, and Chief, Portfolio Analysis and Scientific Opportunities Branch, Office of Portfolio Analysis and Strategic Initiatives, Office of the Director, NIH, presented an overview of the congressional mandate to establish a knowledge management, data mining, and visual analytic tool to report and examine the NIH research portfolio. Each year, the NIH reports to the Congress and the public how much it spends on research. This information allows Congress and the public to better understand NIH research spending and priorities. Up to now, the Institutes reported their data using differing definitions, methodologies, and parameters, to the NIH OD for compilation. OD reports often did not reflect accurately actual spending because of these differences, so the RCDC was established by Congress in 2004 to help streamline the process and clarify outcomes. The RCDC provides an electronic reporting system designed to categorize and track spending across 27 Institutes and Centers (ICs) of the NIH. The categories include approximately 360 research and disease areas to provide consistent, transparent, and efficient reporting, as well as opportunities for further portfolio analyses. Each research project within each NIH grant will receive a project Afingerprint@ based on its medical and research concepts. These concepts will be matched against a weighted list of concepts developed by experts drawn from NIH Institutes to ensure that they are scientifically defensible. The NIH Office of Portfolio Analysis

and Strategic Initiatives (OPASI) worked on a pilot tool for approximately 2 years and presented it to Congress, who mandated its use in 2006. The NIH will introduce the RCDC tool to the public in the summer of 2008, and it will be launched in February 2009. Benefits of the RCDC include consistency of definitions, transparency, efficiency, and opportunities for further portfolio analysis.

In discussion, the following points were made:

- Each NIH research project can be assigned multiple categories using the new tool, depending on how many matches come up in the system. The topics will be taken from the project description, abstract, or specific aims. If one project is studying four specific cancers, for instance, each of those four cancer topics will be represented by its own category and reported as such. The ICs will determine how best to categorize and spend money on rare diseases that do not fall within one of the identified categories of the RCDC tool.
- Basic research, that is not disease specific, especially as it relates to all diseases, composes a large percentage of the NIH portfolio. Concerns were expressed that it would not be captured as its own category within the new system. It was explained that half of the categories are scientific areas and because much of NIH research encompasses basic research, it will be represented in each of the existing categories. Similar to applied research, it will not be reported as a separate item.
- It is disconcerting that AIDS and biodefense are given distinct categories in this system but not cancer. Eleven Institutes, including the NCI, have appropriations that are tied to a category. It was explained that cancer spending is not limited, because the study of cancer is supported by other NIH ICs in addition to the NCI.
- The RCDC tool is heavily dependent on what the investigator writes in the project abstract. Concern was expressed about the possibility of skewed results if an investigator attempted to tailor the abstract to get more or less hits from the automated category selection process. NIH has no current plans to provide instruction to investigators.
- The group discussed the possibility that the RCDC tool could be used to micromanage the NIH or dictate funding

allocations. Releasing data that currently are not publicly available could cause problems if individuals choose to use it against the NIH, but it could equally foster advancement at a much quicker pace. Congress receives reports on NIH activities now, so there is no way of anticipating a change in response from them.

- In response to the intent for the RCDC tool to eventually replace the CRISP system for tracking projects and identifying potential collaborations, members noted that the CRISP system is used widely throughout the cancer community to identify, for example, potential collaborations. Benchmarks and evaluation metrics that go beyond simple numbers are needed for the RCDC.

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VI. ENHANCING PEER REVIEWCDR. - LAWRENCE TABAK

Dr. Lawrence Tabak, Director, National Institute of Dental and Craniofacial Research (NIDCR), presented a self-study by the NIH in partnership with the scientific community to strengthen peer review. Dr. Tabak informed members that the study was designed to help the NIH and its partners meet the increasing breadth, complexity, and interdisciplinary nature of the biomedical sciences, as well as ever-growing public health needs. These changes are creating new challenges for the system used by the NIH to support biomedical and behavioral research, so the NIH must continue to adapt and work to ensure that the processes used to support science are as efficient and effective as possible. Members were told that the NIH is seeking input from the external and internal scientific community, including investigators, scientific societies, grantee institutions, voluntary health organizations, and NIH Institutes to help with all phases of the study, the diagnostic phase, piloting, and implementation. The Steering Committee's ad hoc Working Group is coordinating its efforts with current Center for Scientific Review (CSR) initiatives, which include the shortening of the review cycle, immediate assignment of applications to initial review groups (IRGs), realignment of study sections, electronic reviews, and shortening the size of applications. Dr. Tabak presented a list of external and internal working group members and highlighted some activities of the diagnostic phase. He noted that NIH

leadership, informed by diagnostic phase input, will determine the next steps, including the development and implementation of pilots. Pilot studies are expected to begin in March 2008. Final implementation will involve the expansion of successful pilots and the development of new NIH peer review policy. Briefings will be held for NIH staff, NIH Councils, scientific societies, advocacy organizations, legislative constituents, and the trade press. Dr. Tabak ended the presentation with a review of some emerging ideas, such as review criteria, new review models, maximization of reviewer quality, reviewer mechanisms, peer review culture, scoring, review system mechanisms, and other research support issues.

In discussion, the following points were made:

- The NIH is encouraged to include patient advocates in the self-study process to ensure clinical research issues are addressed.
- After the study feedback is submitted to the Advisory Committee to the Director and the steering committees, an interim report will be widely disseminated.

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VII. MINI-SYMPOSIUM: HUMAN PAPILLOMAVIRUS (HPV) VACCINE: DISCOVERY, DEVELOPMENT, AND APPLICATION

HPV Vaccine Development. Dr. Douglas R. Lowy, Chief, Laboratory of Cellular Oncology, informed members that in the 1980s, Dr. Harald zur Hausen's group cloned human papillomavirus (HPV)16 and HPV18 DNA from cervical cancer, and used deoxyribonucleic acid (DNA) as probes to identify HPV DNA in the majority of cervical cancers. Epidemiologic research conducted later by Dr. Mark Schiffman's group at the NCI and others determined that HPV was a necessary cause of virtually all cases of cervical cancer, and more recent research has implicated HPV in a variable proportion of other anogenital and head-and-neck epithelial cancers. Dr. Lowy discussed several studies from the 1990s through 2004 that tested the basic mechanisms of neutralizing antibody development, which led to HPV research

using virus-like particles (VLPs) in animals and humans. The research using HPV VLP-based vaccines showing positive results in both safety and immunogeneity and efficacy results from 2006 and 2007 were presented. Dr. Lowy noted that the GlaxoSmithKline vaccine can protect against 70 percent of cervical cancers by targeting HPV 16 and 18 and the Merck vaccine also protects against 90 percent of genital warts (caused by HPV 6 and 11). Vaccine limitations include protection only against new infections, not against established infections, and type-restricted protection. In addition, vaccination is very expensive for developing countries, and vaccinated women must continue to receive regular cervical cancer screening.

Human Papillomavirus Vaccines: Promises and Unanswered Questions. Dr. Allen Hildesheim, Senior Investigator, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics (DCEG), told members that in June 2006, the U.S. Food and Drug Administration (FDA) approved Gardasil7 as a vaccine against HPV types 6, 11, 16, and 18 for females ages 9-26. The Centers for Disease Control and Prevention (CDC) recommends vaccination of girls age 11-12 (as early as 9 years, if indicated) and catch-up vaccination for women ages 13-26. Gardasil7 has met with worldwide approval. CervarixTM currently is licensed for use in the European Union and Australia as a vaccine against HPV types 16 and 18 and the FDA expects to make a recommendation on its approval by January 2008. The promise of these vaccines lies in cervical cancer incidence worldwide, which is 600,000 cases annually (10 percent of all cancers in women) and 200,000 deaths, and the potential for reducing these numbers. However, there is concern that the vaccines may not reach the women who need it most. He noted that more developed countries have lower rates of invasive squamous cell carcinomas today as a result of pap smear screening, but 80 percent of cervical cancers occur in developing countries. Additionally, implementation decisions are difficult given unanswered questions concerning the length of protection, booster requirements, vaccination of adult women, efficacy of vaccinating men, possible cross protection vaccine effects, mechanisms of protection and failure, and the integration of vaccination and screening to maximize impact and cost effectiveness.

U.S. Cancer Prevention in the Era of HPV Vaccine: Will We Tolerate Failure? Dr. Joan L. Walker, Chief of Gynecologic

Oncology, Department of Gynecologic Oncology, University of Oklahoma informed members that the barriers and successes for cervical cancer prevention encompass political, economic, educational, cultural, and emotional factors. Studies show that HPV is associated with cancers of the cervix, vulva, vagina, anus, penis, larynx, and head and neck. Cervical carcinogenesis begins with HPV infection of the normal cervix, so vaccination is a key primary prevention strategy. Because HPV is related to multiple cancers, lessons learned from studying cervical cancer may help prevent other diseases. The American Cancer Society suggests HPV DNA testing in addition to pap smears for screening women 30 years and older, but physicians have not adopted this recommendation. The health community needs to consider instituting HPV screening and vaccination as a regular part of health care. Researchers must use absolute risk guidelines to decide how to triage vaccinated patients to identify HPV type involved, alter vaccination components, and match treatment.

Dr. Walker indicated that potential challenges in HPV vaccination include targeting girls at 11-12 years old or younger, compliance with receiving all three doses, need for boosters, and virulence of other HPV types. Monitoring will provide an opportunity for science to study a cancer that actually can be controlled, which can have positive downstream effects based on outcome measures from the cervical trials. New vaccine and screening strategies could potentially lead to a 75 percent reduction in cervical cancer in 25 years, but education is needed to change the current mindset.

A Behavioral and Social Sciences Perspective on Uptake of the HPV Vaccine in the U.S. Dr. Helen I. Meissner, Senior Advisor at the Office of Behavioral and Social Sciences Research, NIH, told Board members that prior to FDA approval of the HPV vaccine, Dr. Meissner said only 40 percent of U.S. women had ever heard about HPV, and of those, fewer than 50 percent knew that HPV infection could cause cervical cancer. The NCI Omnibus Survey in 2006 included several questions with regards to the HPV-cervical cancer link to measure changes in knowledge after FDA approval and the increased direct-to-consumer marketing and media coverage. Although awareness and acceptability of HPV vaccines has improved, a strategy for communicating accurate information to diverse populations is needed to meet differing social perspectives, including parental acceptability of the vaccine, individual choice, governmental authority, fear of side effects, and

sexual behavior and attitudes. Dr. Meissner stated that many states are considering legislation mandating HPV vaccination; however, individuals and groups have expressed concerns regarding costs, long-term safety and efficacy, and moral objections. There also is an issue of health disparities to consider. About 4,000 women are expected to die from cervical cancer this year, and studies show that black women have about twice the mortality of whites. Questions that need to be addressed include the best strategies for communicating accurate information to diverse populations and strategies for effective delivery, including integration into early childhood immunization.

HPV and the Changing Epidemiology of Head and Neck Cancer in the United States. Dr. Maura L. Gillison, Associate Professor of Oncology, Department of Oncology, The Johns Hopkins Medical Institution, told members worldwide head and neck squamous cell carcinoma (HNSCC) cases and associated deaths, numbered 563,823 and 298,408, respectively, in 2002. Dr. Gillison noted that established risk factors include use of alcohol and tobacco, infection with HPV, oral hygiene, diet, family history, age, gender, and race. Of the two distinct head and neck cancers, HPV-positive and HPV-negative, HPV type 16 is the most prevalent in HPV DNA- positive oropharynx cases. HPV-positive HNSCC is a distinct clinical entity that occurs in the oropharynx with a unique, poorly differentiated basaloid histology and accounts for the majority of these cancers in nonsmokers and nondrinkers. They tend to occur in younger men of high socioeconomic status (SES) and are associated with high-risk sexual behaviors and marijuana use. HPV-negative HNSCC occurs more frequently among older men of low SES who use alcohol and tobacco and have poor diet. HPV appears to be a very strong predictor of survival for HNSCC, but, as opposed to cervical cancer, there is no effective and well-accepted screening program for HNSCC in this country. She noted that future research issues include the role of HPV in non-oropharyngeal HNSCC, risk factors for and the natural history of oral HPV infection, potential role of HPV detection in oral cancer screening, potential of L1 VLP vaccines to prevent oral HPV infection and thereby head and neck cancers, and the effect of a diagnosis of HPV-positive HNSCC on therapeutic decision making.

In discussion, the following points were made:

- The challenge is to lower costs of the vaccine and provide access to the developing world. NCI is working with a company in India that is a major supplier to the World Health Organization (WHO) to have them consider regional manufacture and distribution to developing countries.
- Several cost-effectiveness analyses of vaccination and screening are being conducted, but it is clear that it is currently unaffordable in developing countries.
- Research on therapeutic vaccination of established HPV infection is ongoing, and more research is needed to determine the mechanisms involved with HPV's positive response to the treatment of certain cancers.
- Include the story of the Hepatitis B vaccine and drug costs when describing NCI's work on the human papillomavirus (HPV).

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VIII. REQUEST FOR APPLICATION (RFA) ANNUAL REPORT - DRS. ROBERT C.YOUNG AND PAULETTE S. GRAY

Dr. Young presented the annual report on RFA concepts from 1996 through June 2007. The report has been generated annually since the initial BSA request in 1999, to provide background information relevant to the concept review role played by the BSA. Dr. Young briefly explained to new members how the information in the report has been organized and the rationale or impetus for including certain categories. The report can be used as a tool for members to see how the system works and how the BSA figures into that system. Dr. Niederhuber explained the internal process for concept development and review and noted that the NCI Division heads are responsible for assuring the quality of all RFA initiatives, and that concepts should be integrated across the extramural Divisions and include intramural program staff to help inform and refine the proposal development process. Dr. Gray stated that the BSA reviews RFA and RFP concepts. RFA concept information is reported by the date presented to the Board and by the Division in which the concept originated. A brief overview of the report was given. She noted that all grants that are funded through an RFA are tracked and categorized by original concept.

In discussion, the following points were made:

- The data from the BSA annual report should be linked to the caBIGTM platform to help manage and offer real-time analysis of the NCI research portfolio, including RFA concepts and results. Linkage with the RCDC also was discussed.

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IX. STATUS REPORT: CENTERS FOR POPULATION HEALTH AND HEALTH DISPARITIES - DRS. ROBERT CROYLE, TIMOTHY REBBECK, OLUFUNMILAYO OLOPADE, AND NICOLE LURIE

Introduction. Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), told members the trans-NIH initiative, Centers for Population Health and Health Disparities (CPHHD), is being led by the National Institute of Environmental Health Sciences (NIEHS), and includes collaboration with the National Institute on Aging (NIA) and the Office of Behavioral and Social Sciences Research (OBSSR). Dr. Croyle stated that the initiative is not focused specifically on cancer, but on identifying common pathways and integrating the various determinants of health disparities. He introduced the speakers: Drs. Timothy Rebbeck, Professor of Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania; Olufunmilayo I. Olopade, Professor of Medicine and Human Genetics, Department of Medicine and Human Genetics, University of Chicago; and Nicole Lurie, Professor of Policy Analysis, RAND Corporation.

Overview of the Centers for Population Health and Health Disparities. Dr. Rebbeck stated that cancer health disparities, a longstanding and public health problem, impact many cancers. He noted that there are disparities in treatment, screening, and access to care across race, gender, age, and rural and urban locations with trends toward increased disparities. The causes are multi-level and complex, and their inter-relationships are poorly understood, so new paradigms for resolving these disparities are needed. The CPHHD mission involves integration of the basic, population and

clinical sciences, development of transdisciplinary methods, and creating linkages with the community. It incorporates basic science, animal models, biomarker studies, individual risk factors, social and cultural contexts, and the physical environment in hopes to alter cultural, institutional, and political situations that might influence a reduction or elimination of health disparities in our society.

Nature, Nurture and Breast Cancer. Dr. Olopade explained that breast cancer is not one disease; it has different classifications, with BRCA1 tumors having a distinct phenotype. Young African Americans with breast cancer have risk factors similar to BRCA1 tumors, which has been referred to as *triple negative breast* cancer (estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, no HER2 amplification). ER-negative breast cancer strikes younger women peaking at age 51, so the current mammogram screening paradigm does not reach this population. Thus, different screening and treatment approaches are needed.

As part of her CPHHD research, Dr. Olopade reported that her laboratory had developed a model to study if social environment could alter gene expression, patterned on a model studying social isolation in rats. The unified hypothesis was that chronic social isolation would result in an acquired vigilant behavioral phenotype, leading to measurable changes in the corticosterone response to acute stressors. These changes could alter mammary gene expression, which could lead to increased mammary growth in the animals predisposed or prone to mammary tumors. She noted that she and her colleagues will be following breast cancer patients in a prospective study, mapping their neighborhoods and collecting questionnaire data to determine if the environment influences their outcomes and gene expression.

Cancer Disparities and the Social Environment: Implications for Practice and Policy. Dr. Lurie informed members that the neighborhood environment can affect health disparities through behavioral and psychological risk factors, cumulative physiological dysregulation (endocrine, metabolism, inflammation, cardiovascular), changes in cellular function, and changes in gene expression. Levels of physiological dysregulation components are linked to cancer incidence and mortality and related to socioeconomic status (SES). Using the National Health and Nutrition Examination (NHANES) III data set, indices of

cumulative physiological dysregulation and social isolation were constructed. The impact of neighborhood SES on dysregulation depends on the level of social isolation, and the neighborhood contribution is large enough to affect mortality. Social isolation is associated with more physiologic dysregulation and dampens the physiologic benefits of living in higher SES neighborhoods. Early life exposure to neighborhood environment may have effects into adulthood.

Dr. Lurie stated that patients in low-SES neighborhoods may require more intensive prevention and treatment interventions, and personalized medicine alone will be ineffective in addressing population-level health disparities. Research must simultaneously address population-level risks and development of new individual-level treatments. Additionally, strategies are needed to build social capital to reduce social isolation and improve outcomes.

Scientific Highlights from CPHHD: Cells to Society. Dr. Rebbeck noted that the CPHHD is implementing a new transdisciplinary research paradigm that integrates biology, behavior, neighborhood, environment, and health care and includes training, dissemination, and community engagement. Innovative CPHHD methods include research innovation, the development of tools for health disparities research, and the emergence of common research synergies and themes. The Centers have helped increase research interactions and community engagement in breast, cervical, and prostate cancers, as well as cumulative physiological dysregulation. Emerging cross-Center themes are genetics and biomarkers, etiology, screening, and treatment; other themes include the dissemination of research, quality of life (QOL), and access to care. Dr. Rebbeck told members that the CPHHD vision for eliminating health disparities includes redefining health disparities research; instituting a transdisciplinary, multilevel research paradigm; translating research results to inform health care, the community, and policymakers; and mentoring the next generation of health disparities researchers.

In discussion, the following points were made:

- Racial differences in outcomes among breast cancer patients largely disappear after adjustment for clinical treatment. It is in prevention, screening, incidence, and access to treatment where disparities exist. Failure to receive appropriate

treatment should be considered in next presentation.

- The CPHHD centers should develop a common paradigm and testable hypothesis to present for the next round of funding. Evidence of integrated and value added research across the CPHHD is needed. One potential area of study is the survivor population, where accessible clinical data are available.
- Several BSA members commented that the CPHHD centers represent a combination of traditional and new methodology and cannot be expected to present aggregate group-level statistics. This is one of the few NIH initiatives that has brought team science to the issue of health disparities.

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X. RFA/COOPERATIVE AGREEMENT CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Biology and Division of Cancer Control and Population Sciences

Collaborative Comparative Systems Genetics of Cancer (RFA)

Drs. Cheryl Marks, Division of Cancer Biology (DCB), and Deborah Winn, DCCPS, described the Comparative Systems Genetics of Cancer RFA concept, which is a joint effort of the DCB and DCCPS. Dr. Winn defined systems genetics as systems biology that incorporates information about underlying genetic variation. The proposed concept uses the R01 mechanism to foster crossdisciplinary approaches across human genetics research, statistical genetics, computational biology, computer science, systems biology, and model organism genetics. Dr. Winn stated the RFA will encourage the use of existing resources, require data-sharing via caBIGTM resources, and will be managed by a cross-divisional team with an annual meeting of investigators. Goals include the integration of epidemiology and GWAS data with the systems biology approach, particularly by comparing and integrating human population and non-human model systems. Human model systems provide genetic genomics data, as well as environmental factors from public studies and case-control studies. Non-human biological model systems offer strengths in RNA and

protein expressions and cancer phenotype. Dr. Marks noted that the clinical outcomes of both systems can be compared. Examples of opportunities using two or more model systems include: 1) the characterization of genetic networks that produce variable manifestations of a specific human cancer; 2) integration of genetic networks (e.g., GWAS and model organism data); 3) development or evaluation of data models involving gene-environment factors or interactions; and 4) influence of genetic variation on systems-level responses to environmental factors relevant to human cancers.

Subcommittee Review. Dr. Jean Y.J. Wang, Distinguished Professor of Medicine, University of California, San Diego, School of Medicine, and Associate Director of Basic Research, said that the Subcommittee found the concept to be a forward-looking, worthwhile experiment to analyze data in a more creative manner via mathematical modeling. The subcommittee supported the RFA. The level of communication between the various R01 groups will be key to the project's success. Members suggested that interactions between groups occur more frequently than once each year, which could be accomplished through the use of portals created for cross-team collaboration.

The first year estimated costs are $3.0 M for 5-6 awards and a total cost of $15 M over 5 years.

In discussion, the following points were made:

- It was suggested that the RFA should require the multiple PI approach and include involvement by human and model organism genetics researchers, system biologists, and mathematicians.
- A stronger focus on how environmental exposures, and biomarkers of such exposures to study the impact on various pathways was suggested.

  Benchmarks for evaluation are needed. The NCI will examine the metrics used in other collaborative communities of science to develop measurements.

Motion: A motion to concur with the DCB's and Division of Cancer Control and Population Sciences'(DCCPS) Request for Application (RFA) concept entitled "Collaborative Comparative

Systems of Genetics of Cancer" was approved with fifteen yeas and two abstentions. Members noted that metrics to evaluate are needed.

Tumor Stem Cells: Basic Research, Prevention, and Therapy (RFA)

Dr. R. Allan Mufson, DCB, stated that the RFA goal is to support interdisciplinary research efforts to achieve the rapid translation of the understanding of the biology of tumor stem cells to the development of effective therapy. New cellular and mechanistic insights are needed to understand why current therapies often fail, and why tumor regrowth and metastases occur. Evidence suggests that rare populations of tumor cells, termed Atumor initiating or Atumor stem cells, are driving tumor growth and metastasis through asymmetric cell division and may provide new insights into cancer biology and therapy.

The RFA proposes using the R01 mechanism and requires multiple PIs to bring together expertise in tumor stem cell biology and translational development. The initiative is jointly sponsored by DCB, Division of Cancer Prevention (DCP), and Division of Cancer Treatment and Diagnosis (DCTD) and promotes research in basic studies that characterize these cells from solid and hematological tumors, understanding their role and progression to facilitate prevention of malignant progression, and the use of these cells and their unique genetic and immunological properties as targets for therapeutic interventions. Specific areas of interest include: 1) the relevance of tumor initiating or tumor stem cells to specific tumor types; 2) the differences between the tumor stem cell and normal stem cell epigenome; 3) the development of *in vivo* or *in vitro* models to characterize tumor stem cells; 4) the development of immunological or small molecules that differentiate between normal and tumor stem cells; 5) the involvement of tumor stem cells in tumor metastasis; and 6) the identification of tumor stem cell secreted proteins for use as diagnostic or prognostic markers.

Subcommittee Review. Dr. William S. Dalton, Chief Executive Officer and Center Director, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, stated that the RFA is likely to generate a large number of applications because of the great interest in tumor stem cell research. Dr. Dalton stated that

question to be considered is the connection between tumor stem cells and minimal residual disease, since the idea that the stem cells are the genesis of recurrent disease within the population of minimal residual disease needs to be proven. The comparison between normal and malignant stem cells is an excellent approach, and the NCI should consider an inter-institutional RFA with the National Heart, Lung, and Blood Institute (NHLBI). He noted that the Subcommittee had asked for clarification on differences between R01s to be supported by the initiative versus R01s currently being submitted on cancer stem cells. Staff responded that the RFA emphasized the team science approach to bring translational expertise to underinvestigated areas. The subcommittee was supportive of the concept but expressed concerns that the budget cap per grant would not allow sufficient support for the team science approach. Program project (P01) applications may also be appropriate for the goals of the RFA.

First year estimated cost is $2.25 M for 6-7 awards and a total cost of $11.25 M over 5 years.

In discussion, the following points were made:

- The NCI should consider the use of supplements to existing grants as a means to foster interdisciplinary team development.
- The NCI should pursue co-sponsorship with National Heart, Lung, and Blood Institute (NHLBI) to support research on the comparison of normal and tumor stem cells for hematologic malignancies.
- The private sector is expanding their interest in stem cell research and could provide an additional resource for collaborative work.

Motion: A motion to concur with the DCB's, DCP's and DCTD's RFA concept entitled "Tumor Stem Cells: Basic Research, Prevention, and Therapy" was amended during discussion with the suggestions to increase the amount of funding per grant and to expand its competition and potential award to both R01 and P01 investigators. The amendment was approved with sixteen yeas and one nay.

The NCI Mouse Models of Human Cancers Consortium (NCI-

MMHCC) (RFA/Coop. Agr.)

Dr. Marks described the NCI-MMHCC reissuance concept as a natural progression of the mouse models consortia accomplishments. She informed members that the concept focuses on integrating mouse models into scientific programs in four areas: cancer biology, experimental therapeutics, cancer susceptibility and resistance, and early interventions. These areas will encompass the metabolism of agents, target choice, tumor stem cells, background genetics and risk, genetic instability, safety of chronic use of interventions, micro-RNAs and DNA repair, and metastasis, as well as epistasis, new approaches to systems genetics, and adaptation and trans-generational mechanisms.

The NCI-MMHCC will consist of four multiproject grants (U19) and up to 20 cooperative agreement grants (U01) clustered by science. The U19 grants will propose cutting-edge science in the four focus areas, support resources for collaborative research, coordinate frequent communications, coordinate informatics resources with NCI's Center for Bioinformatics and caBIGTM, and support meetings that broaden input to the research. The U01 grants are expected to affiliate with one primary U19 cluster after funding and work within clusters to define common resources and propose pilot projects. A trans-NCI divisional management team will be formed, including representation from the Special Program of Research Excellence (SPORE) program.

Subcommittee Review. Dr. James K. Willson, Director, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, informed the Board that the Subcommittee was enthusiastic about the NCI-MMHCC progress and substantial documentation of its progress, and felt that the move to thematic areas with the U19 mechanism seemed reasonable. This reissuance provides an opportunity to stimulate crosstalk among a variety of independent groups within NCI's portfolio, including imaging development and developmental therapeutics. The Subcommittee suggested that the NCI consider additional ways to showcase the new NCI-MMHCC organization among other NCI activities to create new collaborations. Another suggestion was to advertise its gratis mouse models through additional channels, such as including the MMHCC site in the methods section of published manuscripts.

The first year estimated cost is $19 M for 4 U19 and 20 U01

awards. A total cost of $104 M over 5 years.

In discussion, the following points were made:

- It is extremely expensive to maintain multiple strains of mice in a colony with a shrinking budget. Additionally, mouse model research does not appear to have significant translational impact.
- Tumor immunology is not currently mentioned in the concept. The NCI should encourage immunologists to participate in this work.
- Metrics will be important to measure the uniqueness of the contribution of this program. The NCI is working on developing a baseline to assist with this, as well as ways to obtain input from intramural and extramural investigators.

Motion: A motion to concur with the re-issuance of DCB's RFA/ Cooperative Agreementconcept entitled "The NCI Mouse Models of Human Cancers Consortium (NCI-MMHCC)" was unanimously approved.

Division of Cancer Prevention

Community Clinical Oncology Program (CCOP) (RFA/Coop. Agr.)

Subcommittee Review. Dr. Christopher J. Logothetis, Chairman and Professor, Department of Genitourinary Medical Oncology, University of Texas, M.D. Anderson Cancer Center, told members That the CCOP is an efficient and critical resource that has accrued well and provided valuable

data. The CCOP's clinical trials portfolio that will be implemented for the next 2 years is well defined with large trials already planned or underway. It was noted that the data presented about the CCOP was amalgamated with the data about the Minority-Based CCOP (MBCCOP) and it would have been helpful to see the data for the two programs presented separately. The Subcommittee supported its reissuance.

The first year cost is estimated at $8.2 M for 10 awards and a total cost of $42.5 M over 5 years.

Motion: A motion to concur with the re-issuance of the DCP's RFA/Cooperative Agreement concept entitled "Community Clinical Oncology Program (CCOP)" for two years as recommended by the Executive Committee was approved unanimously.

Minority-Based Community Clinical Oncology Program (MBCCOP) (RFA/Coop. Agr.)

Dr. Worta McCaskill-Stevens, Community Oncology and Prevention Trials Research Group, Informed members that the MBCCOP, currently is in its 17th year, provides state-of-the-art clinical research, treatment, and cancer prevention and control in communities that have greater than 40 percent of their endowment in the minorities catchment areas. The program works to engage primary care physicians and other relevant specialties, as well as to contribute to decreasing health disparities in cancer treatment, prevention, and control. MBCCOP funding from FY 2000 to FY 2007 has doubled and the number of sites supported increased from 8 to 14, respectively. Dr. McCaskill presented updated data (FY 2000-2006) regarding the number of minority patients enrolled in the MBCCOP by treatment, prevention and cancer control, overall accrual rates, and the percentage of minority patients who were enrolled. She noted that from FY 1995 through 2006, 10,000 minority patients were enrolled for treatment and 7,000 for cancer prevention and control trials, in the CCOP network.

MBCCOP has been influential in minority accrual to a number of prevention and treatment trials, including Symptom Outcomes and Practice Patterns, Selenium and Vitamin E Cancer Prevention Trial (SELECT), Adjuvant Colon, Sentinel Lymph Node, and Adjuvant Trastuzumab in HER2+ Breast Cancer trials. In addition to improving minority accrual rates, MBCCOP has impacted research on health disparities through the identification and publication of targeted research, program evaluations, and NCI partnerships. The potential impact of the MBCCOP in the NCI clinical trials network includes: 1) a training ground for oncologists and related disciplines in oncological practice in minority communities; 2) a laboratory for identifying preclinical, clinical, and behavioral issues related to health disparities; and 3) a model infrastructure for stimulating interest in expanding the MBCCOP to provide clinical trial access to minorities in other communities.

Subcommittee Review. Dr. Hoda Anton-Culver, Chair, Department of Epidemiology, Department of Medicine, University of California, Irvine, said the Subcommittee supported the reissuance for the MBCCOP and agreed with the NCI Executive Committee that there would be no need for additional reviews of the program for the next 2 years. The Subcommittee appreciated that the presentation described the MBCCOP's impact on NCI's treatment trials as well as prevention and cancer control.

The first year cost is estimated at $1.1 M for 3 awards and a total cost of $5.5 M over 5 years

In discussion, the following points were made:

- NCI should consider using the MBCCOP as a model for other programs that need greater accrual of minority patients.

Motion: A motion to concur with the re-issuance of the DCP's RFA/Cooperative Agreement concept entitled "Minority-Based Community Clinical Oncology (MBCCOP)" for two years as recommended by the Executive Committee was approved with two abstentions.

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XI. MINI-SYMPOSIUM: FUTURE OF IMAGING IN THE NCI PROGRAMS: FROM MOLECULE TO MAN - DRS. ROBERT WILTROUT, SRIRAM SUBRAMANIAM, THOMAS MISTELI, JAMES TATUM, AND PETER CHOYKE

Introduction. Dr. Robert Wiltrout, Director, Center for Cancer Research (CCR), told members that the CCR's vision is to integrate basic, translational, and clinical research to make cancer preventable, curable, or chronically manageable. Imaging is an emerging area and priority for the CCR, which currently is focusing on the: connection between imaging and pathology; development of novel imaging approaches, technology, and instrumentation; improvement of imaging techniques; and

translational applications for non-invasive patient care. To realize success in these areas, the NCI is developing an integrated clinical oncology imaging clinic that initially will be located in the NIH Clinical Center. Dr. Wiltrout introduced the speakers: Drs. Sriram Subramaniam, Senior Investigator, Laboratory of Cell Biology, CCR; Thomas Misteli, Senior Investigator, Laboratory of Receptor Biology and Gene Expression, CCR; James Tatum, Acting Associate Director, CCR; and Peter Choyke, Senior Investigator, Molecular Imaging Program, CCR.

Towards Mapping Cellular Architecture at Molecular Resolution With 3-D Electron Microscopy. Dr. Subramaniam described the CCR's work in looking at cancer cells and viruses at resolutions that were unprecedented as recently as several years ago. He noted that the intent is to understand dynamic processes in objects by using developed and applied tools of high resolution looking at atomic structures; the methods currently used in the laboratory are referred to as 3 dimensional (3-D) electron microscopy. The CCR's general philosophy about imaging is based on electron tomography, a technology that records a specimen relative to an electron beam and collects and computationally combines a large number of projection images to make tomograms of small molecules, viruses, and cells. Dr. Subramaniam presented examples of the CCR's imaging work using image averaging where thousands of images are averaged to reconstruct 3-D structures and look at secondary structures. Using this technique to study components of the pyruvate dehydogenase complex has provided new insight into the structure and function of the complex. Current work on HIV is beginning to provide insights into the structural variation of the enveloped glycoproteins on HIV and related viruses and has led to some surprising and new discoveries on the nature of viral entry into CD4 positive T cells. Additional tomography research includes studies of antibody neutralization nature of HIV viruses and the discovery of the HIV entry claw. New methods using ion abrasion scanning electron microscopy have been developed to image large mammalian cells and extract information that might be clinically useful. In the case of a whole melanoma cell, one can begin to visualize the 3-D architecture of mitochondria, the relationship to endoplasmic reticulum, and essentially the entire complement of organelles in the cell. He noted that this is exciting from a computational point of view because it allows, for the first time, the development of reasonable models for the spatial architecture of different components in the

cell. In conclusion, Dr. Subramaniam described future challenges and opportunities for subcellular imaging, including ongoing collaborations to develop 3D compositional and drug maps in the cell.

Frontiers in Cellular Cancer Imaging. Dr. Misteli informed members that the goals of cellular imaging are to impact basic discovery through the visualization of intracellular structures and processes, the placement of cellular mechanisms into a spatial and temporal context, and to probe the contribution of spatial and temporal organization to function, which leads to the discovery of novel cellular and molecular mechanisms. Research in cellular imaging aims to impact applications by probing disease mechanisms in vivo, developing diagnostic tools based on morphological properties, and strengthening drug discovery and testing. Some of the recent breakthroughs include the visualization of virtually any cellular component, live cell imaging and the studying of molecular interactions in vivo, and the ability to image beyond the resolution limit (50 to 75 nanometers).

Dr. Misteli next described the most important imaging technologies and their impact on cancer biology: live-cell imaging, genome imaging, and high-throughput imaging. He noted that the live-cell imaging is based on the use of green fluorescent protein that can be fused to any other protein of interest and expressed in cells. Examples of live-cell imaging include probing the gene expression machinery in vivo to observe recruitment of transcription factors onto genes, studying metastatic cell migration in tumors, and visualizing DNA and RNA in living cells to study chromosomal translocation. Another technology is focused on imaging the genome. Recent work includes in situ hybridization on the interface cell nucleus, which has revealed that the genome inside the cell nucleus is non-randomly organized. Spatial positioning has potential as a diagnostic tool since the position of a gene often changes before its activity changes. Finally, high-throughput imaging focuses on the systematic and unbiased exploration of biological patterns through imaging and computation. Potential uses include pattern discovery and image based screening. High-throughput imaging can be used to look at growth patterns, intensity, shape, and localization of either genes or proteins, as well as for screening purposes. The process involves selection of a known biological pattern, such as the localization of a protein that is different in cancer and normal cells, performance of either RNAi

or small molecule library screens, and identification of factors that affect these patterns.

Developing Novel Imaging Biomarkers for Monitoring Cancer Treatment. Drs. Tatum and Choyke presented information about defining novel imaging agents. Dr. Tatum began by sharing an example of a positron emission tomography/computerized tomography (PET/CT) imaging of lymph node metastasis from a positive melanoma tumor. This work could not be completed with MR technology or any other current clinically diffuse techniques. A challenge remains in that the only PET probe currently approved and distributed commercially is fluorodeoxyglucose (FDG), although other probes are under development.

Dr. Tatum briefly described the imaging drug development pipeline, and NCI's efforts to address critical barriers in the clinical development of agents. Members were told that the Imaging Drug Group was created to look at the available resources involved in the development of imaging drugs, from discovering agents to the conduct of clinical trials. Approximately 80 CIP grants are currently funded to support the discovery, development, and application of molecular agents; 125 unique agents are in various stages of development. Dr. Tatum described the development of a fluorinated synthetic L leucine analog (FACBC), used to evaluate the L amino acid transport system, as it progressed through the NCI's Development of Clinical Imaging Drugs and Enhancers (DCIDE) program, synthesis and scale up, and successfully became an investigative new drug (IND). Several studies of FACBC were described involving glioma, bilateral prostate, and a sextant biopsy that predicted bilateral prostate cancer.

Dr. Choyke introduced the Molecular Imaging Program (MIP), CCR, that was formed in 2004. The MIP involves a multidisciplinary team of chemists, molecular and cellular biologists, and imaging physicists and specialists. The MIP in conjunction with the Joint Development Committee develops imaging agents intramurally with testing in Phase 0 clinical trials. Dr. Choyke described specific projects that have been brought to the clinic, including radiolabeled antibodies (111Indium Trastuzumab [Herceptin]), macro- molecular contrast agents (Gadolinium-Albumin), and novel PET agents for therapy monitoring.

In discussion, the following points were made:

- The NCI would like input on the need for a high-energy cyclotron in the Frederick Cancer Research and Development Center (FCRDC), which would be useful for intra- and extramural investigators. Based on the National Academy of Sciences report, an expert panel will be established to examine the infrastructure, its possible uses and technology upgrades, as well as for targets, physics, and training.
- The pharmaceutical industry has made a tremendous investment in imaging to accelerate drug development and thus their innovations remain proprietary. The NCI's role as principal innovator in the community was lauded, but the sustainability of this role was questioned. NCI is promoting collaboration among companies to develop standards for the imaging community.

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XII. UPDATE: THE CANCER GENOME ATLAS - DRS. JOHN NIEDERHUBER AND FRANCIS S. COLLINS

Dr. Francis S. Collins, Director, Human Genome Research Institute (NHGRI), reminded members that The Cancer Genome Atlas (TCGA) was recommended as a critical strategic project in accelerating progress against cancer by the NCAB Ad Hoc Committee report (Hartwell-Lander Report) of February 2005. Dr. Collins said the NCI-NHGRI Program Work Group was formed to develop and issue RFAs and RFPs in 2005, and TCGA was launched in late 2006 as a 3-year, $100 M pilot project. Goals for TCGA are to: develop and connect a high-quality biospecimen resource with genome characterization, sequencing, and bioinformatics centers into a network; define all relevant genomic changes in three tumors; and create and deploy a public TCGA database of the information. Members were told that the TCGA pilot project encompasses genomic sequencing centers (GSCs); cancer genome characterization centers (CGCCs); data management, bioinformatics, and analysis; human cancer biospecimen core resource; and technology development. Tumors selected for study are glioblastoma, squamous cell lung, and serous ovarian cancer. The seven CGCCs are focused on genome

expression and copy analysis with an epigenetic analysis component at one center. A mega-database, built on the caBIGTM platform, will store all data generated by the project for analysis and data will be publicly available. An Expert Science Committee, Steering Committee, and working groups were established.

TCGA has finalized a number of its policies and practices, including those regarding human subjects and IP, as well as best practices and standard operating procedures (SOPs) for the specimen sample collection. There are 100 high-quality glioblastoma samples in analysis by genome characterization, sequencing is underway, and data available at http://cancergenome.nih.gov/dataportal. Lessons learned about biospecimens are that 1) approximately 30 percent of existing tumor samples in biorepositories meet all criteria, 2) the requirement to have 80 percent of tumor nuclei is a very high standard, and 3) controls are important for nearly all platforms.

Early results on brain tumors reveal that samples with gene amplification also show a high level of expression in that gene. Genes with copy number changes and expression differences in some tumors also have point mutations in other tumors. The activation of these oncogenes occurs via multiple mechanisms, such as point mutation, gene amplification, and high expression. TCGA is releasing data for the initial list of 605 Acancer genes@, and in collaborative analyses of early CGCC data on glioblastomas, identified genomic elements containing 725 genes or other regions of interest. Sequencing centers currently are developing assays for the 725 targets.

Overall lessons learned and perspectives from the first year include: 1) need for team science involving both the cancer biology and genome cultures; 2) high quality samples are critical; and 3) data analysis needs are unprecedented. Dr. Collins noted the growing international interest in the application of the cancer genome approach to cancers that are prevalent in other countries. To this end, a meeting to organize the International Cancer Genomics Consortium was held in October 2007 with the goal of developing a comprehensive approach to all types and subtypes of cancer.

TCGA would be brought forward for scale up if: 1) tumor

biospecimen issues are resolved; 2) new cancer genes are discovered; 3) the ability to differentiate tumor subtypes is demonstrated; 4) technology approaches are improved to differentiate meaningful biologic data from baseline data; and 5) cost effectiveness and clinical relevance demonstrated.

In discussion, the following points were made:

- A focus on genes and the environment might help answer specific questions about environmental effects on genes associated with certain cancers; prospective sample collections with detailed exposure data are needed to address this question.
- A fundamental question involves the ability to distinguish between driver and passenger mutations. Tumors needed to address such question are currently being modeled and will depend on background mutation rates, but the TCGA expects to be able to address the issue.
- Stroma and the microenvironment, where mutations, lesions, and translocations occur, present challenges. The NCI has established a comprehensive network and steering committee to focus on issues regarding stroma, inflammation, infiltrates, and other related subjects.
- In its consideration of its prospective tumor selection, the NCI should look at those tumors that might not be technically perfect but are more reflective of what is occurring in the population. A suggestion was to bank more representative heterogeneous samples.

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XIII. PHASE 0 TRIALS - CDR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Director, DCTD, presented an overview of Phase 0 trials to show how earlier testing can lead to better understanding of the molecular mechanisms of action and decrease late-stage failure rates in oncology drugs. Dr. Doroshow stated that under the FDA's new exploratory IND program, investigational drugs and biologics may be administered to small samples of humans prior to clinical trials (hence, the term APhase 0@ trials) to conduct bioavailability studies, microdosing, and proof-of-concept

validation. Dr. Doroshow noted that they also provide a means for developing reliable SOPs for tissue acquisition, handling, and processing, which can improve histological results. Phase 0 trials may evaluate drug biodistribution and binding characteristics using microdosing and sensitive analytical techniques, including novel imaging probes. Phase 0 trials can improve the efficacy and success of subsequent trials by eliminating an agent early in clinical development because of poor pharmacokinetic (PK) and pharmacodynamic (PD) properties and by informing subsequent trials, providing a closer approximation to a safe but potentially effective starting dose and support for limited sampling. Most Phase I trials do not emphasize the use of PD assays because they have not been developed in the preclinical setting. Although Phase 0 trials offer promise for developing drugs with wide therapeutic indexes, they present unique statistical and ethical challenges and as such, require an integrated research team. Ethical issues or potential barriers to enrollment include the administration of multiple doses of an exploratory drug with no therapeutic intent or chance of benefit and the requirement of pre and post treatment biopsies.

Dr. Doroshow presented the results of a recent Phase 0 PK/PD study of ABT-888, an inhibitor of poly-ADP ribose polymerase (PARP). Trial objectives were to determine a non-toxic dose range at which ADT-888 inhibits PARP in tumor samples and in peripheral blood mononuclear cells (PBMC), determine the PK, and determine the time course of PARP inhibition. Trial results established that ABT-888 was able to achieve 90 percent PARP inhibition in tumor biopsies and PBMCs by performing real-time PK/PD analyses within 72 hours of obtaining samples. Time was saved by determining the agent PK and developing PD assays in the preclinical stage. Dr. Doroshow commented that the Phase 0 data made it no longer necessary to conduct a single agent Phase I trial to determine maximum tolerated dose (MTD) since full inhibition of the target had already been achieved. The company can proceed directly to Phase I combination trials. He noted that this example demonstrates the potential benefits of conducting Phase 0 studies: an overall decreased timeline for drug development, real-time PD/PK analyses, the efficient use of resources, and more defined targets and SOPs for tissue acquisition that work in the clinical setting.

In discussion, the following points were made:

- The FDA is supportive of conducting Phase 0 trials more broadly, with a special interest in imaging studies. Drug companies have also expressed interest, including for non-oncology agents.
- Phase 0 trials that fail to reach their assay endpoints may cause an agent to be dropped from development, and this could be seen as cost effective to industry. The key attribute in such an instance is the false negative rate, not the false positive rate. Thus, specificity of a test, as opposed to sensitivity, would be crucial.
- Phase III trials can be smaller if a biomarker driven approach is folded into the trial with two stages.
- Standard operating procedures are needed for how samples are collected from patients.

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IVX. ADJOURNMENT - Dr. Robert C. Young

There being no further business, the 38th regular meeting of the Board of Scientific Advisors was adjourned at 11:35 a.m. on Friday, 16 November 2007.

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