

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE**

56th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

**March 11, 2015
Building 31C, Conference Room 10
Bethesda, Maryland**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE**

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**MINUTES OF MEETING
March 11, 2015**

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 56th meeting on Wednesday, 11 March 2015, at 8:30 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Todd R. Golub, Director, Cancer Program, The Broad Institute of the Massachusetts Institute of Technology and Harvard University, presided as Chair. The meeting was open to the public from 8:30 a.m. until 3:34 p.m. for the NCI Director's report; a report on collaborative activities between the NCI and the National Institute of Standards and Technology (NIST); and consideration of request for applications (RFA) new and reissue concepts presented by NCI Program staff.

BSA Board Members Present:

Dr. Todd R. Golub (Chair)
Dr. Francis Ali-Osman
Dr. Kenneth C. Anderson
Dr. Dafna Bar-Sagi
Dr. Andrea Califano
Dr. Curt I. Civin
Dr. Graham Colditz
Dr. Chi V. Dang
Dr. Joseph M. DeSimone
Dr. Daniel C. DiMaio
Dr. Brian J. Druker
Dr. Karen M. Emmons
Dr. Betty Ferrell
Dr. Stanton L. Gerson
Dr. Joe W. Gray
Dr. Chanita Hughes-Halbert
Dr. Joshua LaBaer
Dr. Maria E. Martinez
Ms. Diane Zipursky Quale

Dr. Martine F. Roussel (Sherr)
Dr. Kevin M. Shannon
Dr. Lincoln Stein
Dr. Bruce W. Stillman
Dr. Gregory L. Verdine
Dr. Irving L. Weissman
Dr. Eileen P. White
Dr. Kevin P. White

Board Members Absent:

Dr. Ethan M. Basch
Dr. Sangeeta N. Bhatia
Dr. Arul M. Chinnaiyan
Dr. Theodore S. Lawrence
Dr. Luis F. Parada
Dr. Mary L. Smith
Dr. Cheryl L. Walker

Others present: Members of NCI's Scientific Program Leaders (SPL), NCI staff, members of the extramural community, and press representatives.

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I. CALL TO ORDER AND OPENING REMARKS DR. TODD R. GOLUB

Dr. Todd R. Golub called to order the 56th regular meeting of the BSA and welcomed current members of the Board, NIH and NCI staff, guests, and members of the public to the first virtual meeting of the Board. Dr. Golub reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. 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.

On behalf of the Board, Dr. Golub recognized Dr. Harold Varmus, Director, for his leadership and service to the NCI during the past 5 years.

II. NCI DIRECTOR’S REPORT—DR. HAROLD VARMUS

Dr. Harold Varmus, Director, welcomed members and referred to his letter announcing his departure on 31 March and stated that Dr. Douglas Lowy, Deputy Director will serve as the Acting NCI Director. He provided an update on other NCI personnel changes, including the departure of Dr. Linda Weiss, head of the Office of Cancer Centers, and her interim replacement, Dr. Henry Ciolino.

Budget. Dr. Varmus discussed the fiscal year (FY) 2015 and 2016 budgets. He noted that the NCI received an increase of less than 1 percent in the FY 2015 appropriations from the FY 2014 level. Members were told that R01 applications had increased by approximately 18 percent, which will affect the success rate but not the number of grants that are issued. The President’s Budget (PB) for FY 2016 proposed a \$1 billion (B) or 3% increase for the NIH, which would return the NIH budget to pre-

sequestration levels, and includes requests for anti-microbial resistance, the BRAIN Initiative, and the Precision Medicine Initiative (PMI). Members were told that Dr. Francis Collins, Director, NIH, provided testimony to the House Appropriations Committee on 3 March 2015, and responded to queries on such topics as brain and lung tumors.

Precision Medicine Initiative. Members were informed that Dr. Collins had published an article in the *New England Journal of Medicine* concerning the Precision Medicine Initiative, which the PB includes \$200 million (M) for the NIH, of which \$70 M is to be devoted to oncological precision medicine conducted by the NCI, and \$130 M is for a trans-NIH cohort study. The NCI's efforts will focus on genomics and cancer biology; the conduct of clinical trials, such as the Molecular Analysis for Therapy Choice (NCI-MATCH) trial; and expansion of informatics in the cancer domain. The NIH cohort study will enroll 1 million people and follow them over the course of many years with tools for observing genetic variation, behaviors, and environmental exposures.

NCI-Designated Cancer Centers. Dr. Varmus reflected on the importance of the NCI-designated Cancer Centers and the deep commitment of the Centers' Directors. Discussions about the inequitable budgets of Cancer Centers have resulted in new formulas to adjust the budgets to make them more reasonable and consistent across the centers. He noted that it has proven difficult to move forward on the new formulas since some centers would receive a substantial decrease in their budgets. After comparing center budgets across NIH, NCI has now proposed to increase the Cancer Center budget over the next four to five years from the current budget of \$260 M to \$310M. The proposed plan and new formulas will be vetted by a new BSA working group and brought to a future joint session of this group with the NCAB. The working group also will work to facilitate the sharing of Centers' reagents and equipment, identify topics to be presented at the retreats, and propose topics for supplementary activity.

Frederick National Laboratory for Cancer Research (FNLCR). Dr. Varmus described efforts to make the activities of the FNLCR more transparent as well as more exciting scientifically, such as the RAS Project, and to identify new initiatives and pilot projects that could lead to projects on the scale of the RAS Project. Recent activities have included a workshop on cryo-electron microscopy, which will be discussed by NIH Institute and Center (IC) Directors. He noted that the Frederick National Laboratory Advisory Committee (FNLAC) has been discussing how to involve neighboring academic institutions, including the University of Maryland and The Johns Hopkins University, in the workings of the FNLCR similar to other national laboratories.

Global Health Activities. Members were told that the Center for Global Health (CGH) provides a hub for NCI's efforts to study cancer abroad. Dr. Varmus remarked on the leadership of Dr. Ted Trimble, Director, CGH, in promoting the establishment of new relationships with a variety of other U.S. agencies and with Cancer Centers through the availability of supplements to promote partnerships with other countries. He noted that relationships have been expanded with India, China, Turkey, Indonesia, and Mexico, which are actively developing new cancer plans and cancer centers, building registries, and training people. Additional discussions about the rise of non-communicable diseases (e.g., tobacco, obesity, drug abuse) as a threat to world health have occurred with other NIH ICs, including the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergies and Infectious Diseases (NIAID), and the Fogarty Center. The CGH also has worked to build investigator networks (e.g., Burkitt's Lymphoma Network) to provide additional support. Collaboration with cancer research agencies in other countries continues as well.

NCI Intramural Research Program (IRP). Dr. Varmus expressed pride in the NCI IRP, a large, mostly laboratory-based program focused on basic, clinical, and population-based research. The Hatfield Clinical Research Center (CRC) is the centerpiece of the NIH; it is the largest hospital devoted to research in the world, provides training to many and diagnoses for patients from around the world with undiagnosed diseases. The CRC is threatened with funding issues and low recruitment rates for junior and senior

investigators; the new Laskers Scholar Program to attract young talent has had few recruits. Dr. Varmus stated that the CRC is central to the NCI mission and supports outstanding programs in such areas as immunotherapy, lymphoma, and renal carcinoma. Members were informed about efforts by an NCI intramural team to define the CRC objectives in clinical research over the next 10 to 20 years. Collaboration with approximately five ICs that also use the CRC is critical to ensure that the Center remains vital to the NIH campus and as a national institution. Dr. Varmus discussed the cooperative agreement program that has been established that allows extramural clinical investigators to make use of CRC resources.

NCI Support for the Investigator Community. Dr. Varmus reflected on the atmosphere of hyper-competition and frustration that has been created by too many people pursuing expensive research with too little money. Members were told about discussions among senior leadership of universities and major groups, such as the Federation of American Societies for Experimental Biology (FASEB), Association of American Medical Colleges (AAMC), American Association of Universities (AAU), and the National Academy of Sciences (NAS). Basic research is conducted almost entirely at universities, and many have medical research as a central feature. Members were told that efforts to help remedy the problem include the NCI's Outstanding Investigators Award (OIA), mechanisms to accelerate training, and revisions to the NIH biosketch. Other areas that need to be addressed include changes in the graduate school curricula, higher postdoctoral salaries, a shift in the perception about biology-based careers, appropriate credit for team science, more shared facilities, and relief in the administrative burden in universities. Dr. Varmus encouraged greater attention to evaluations and peer review, and he noted the expectation that everyone who holds an NIH grant should serve on a study section, if asked.

In closing, Dr. Varmus referred to recent structural changes in the way the NCI conducts clinical trials and works with the Cancer Centers, the successful Provocative Questions Initiative (PQI), and the current review of the SPOR Program, all of which have been carried out despite a flat budget. He thanked Dr. Golub for his leadership of the BSA, and commended Drs. Douglas Lowy, Deputy Director, and James Doroshow, Deputy Director for Clinical and Translational Research, for their support.

Modular R01 Grants. Dr. Lowy provided an update on modular awards. Based on input from the NCAB and BSA, NCI leadership will enact a policy to cut in half the automatic reductions for the modular R01 grants, with the long-term goal to eliminate the cuts completely. He noted that this does not apply to the non-modular grants and it does not apply to the R21 awards, although they also are modular.

Drs. Lowy and Doroshow thanked Dr. Varmus for his leadership and the opportunity to work with him during the past several years as his Deputy Directors.

In the discussion, the following points were made:

- Incentives are needed to encourage medical students to pursue research careers, such as a combined fellowship postdoctoral position in the CRC.
- Modular grant funding alone is inadequate to support an investigator. The NCI's OIA is trying to overcome this issue by allowing outstanding scientists to be supported for a longer term.
- Consider ways to promote a permanent coalition of cancer research funding agencies to promote more oncology research and better care in the global cancer domain.
- Consider establishing a BSA Working Group to advise on ways to spur earlier careers in oncology research.

- Develop a central authority or approach for benchmark datasets to ensure consistent results regardless of changes in software packages used in genomics.

III. NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (NIST) COLLABORATIVE ACTIVITIES/INTERACTIONS WITH NCI AND NIH— DR. LAURIE E. LOCASCIO

Dr. Laurie E. Locascio, Director, Material Measurement Laboratory (MML), NIST, presented on NIST's support of NCI oncology endeavors. As the National Metrology Institute, NIST provides good measurement science through partnerships with industry, and the development of standards and validation methods to support international trade and commerce. Dr. Locascio stated that the MML is responsible for biosciences, chemical sciences, material science, and engineering, and performs basic research in measurement science as well as the development of standards.

NIST collaborates with Federal agencies to provide confidence on bio-measurements, including NCI's Early Detection Research Network (EDRN) and Clinical Proteomics Tumor Analysis Consortium (CPTAC), the U.S. Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH), and Defense Advanced Research Projects Agency's (DARPA) Living Foundries Program. The Institute also has engaged with the NIH to address irreproducibility, is organizing a White House Symposium on confidence in data for innovation and data sharing, is discussing collaborative work in metrology training with the National Institute of General Medical Sciences (NIGMS), and is communicating with the NIH Associate Director for Data Science regarding the quality of data and other data issues.

Dr. Locascio described examples of how NIST advances measurement assurance of key technologies in the biological sciences. NIST has supported genetic and genomic measurement confidence by developing standards for deoxyribonucleic acid (DNA) microarray measurements for the External RNA Controls Consortium (ERCC), as well as protocols and materials for whole genome sequencing for the Genome in a Bottle Consortium. NIST has assisted with cell line authentication through the measurement of genomic sequence markers for identification of non-human cell lines used for basic research, cell therapy product quality control review with internal fluorescence reference methods for quantitative comparison of expression of markers for pluripotency, as well as stem cell qualification imaging methods with the NIH and others. NIST also developed the first international reference cell standard for CD4+ cell counting for human immunodeficiency virus infection (HIV)/acquired immune deficiency syndrome (AID) monitoring for low cytometry.

NIST's partnership with the NIH through the EDRN began in the mid 2000s with the recognition that external validation was critical for biomarker discovery as technologies have become more quantitative. NIST's support to the EDRN focuses on increased measurement accuracy and reproducibility of measurements on new biomarkers for cancer through the development of reference materials, interlaboratory testing, and assay validation and identifying areas that impact reproducibility. For mixed-tissue reference samples, NIST used tissue mixture fractions as surrogates for concentration with *in silico* modeling to predict mixture fraction from RNA-Seq signals of neat components and mixtures across the population of biomolecules. To advance intralaboratory studies, NIST developed metrics and figures of merit for comparisons for a variety of technologies developed for high-content profiling of differentially expressed microRNA. In addition, NIST performed assay validation for mitochondrial DNA biomarkers for prostate cancer.

In the discussion, the following points were made:

- Members encouraged NIST to establish standards for data exchange that would allow the research community to compare data and develop conclusions; and provide validation and standardization of software packages.
- The NCI is committed to setting up centralized assay development, particularly for early clinical trials activities.

IV. RFA/COOPERATIVE AGREEMENT CONCEPTS—NCI PROGRAM STAFF

The NCI Predoc to Postdoc Transition Award (K21/K00) (RFA)

Dr. Jonathan S. Wiest, Director, Center for Cancer Training (CCT), described an award that demonstrates the NCI's commitment to support early career development, specifically for researchers transitioning from the predoctoral (Predoc) to postdoctoral (Postdoc) stages. Dr. Wiest noted an unsustainable biomedical workforce expansion, with a doubling in students receiving doctorates in basic biomedical sciences, and tripling in postdoctoral fellows in these fields. In addition, the average age of receipt of the first R01 is 42 years of age. The award objectives are to engage and retain the best and brightest researchers in the cancer community by establishing a new transition award for late-stage graduate students to transition to postdoctoral studies. The award would provide support levels that exceed current National Research Service Award (NRSA) stipends, and provide flexibility in selecting postdoctoral training opportunities. The K21 predoc stage would provide support for up to two years while the postdoc K00 stage would provide up to 4 years support and position the individuals for applying for a K99/R00 award.

Dr. Wiest described review criteria for the K21 application, including quality of the applicant, recommendation letters, and brief description of current research. The K21 to K00 transition application includes recommendation letters, proposed mentor's support, and a short research description for postdoctoral training. He noted that the mentor must hold an R01 equivalent grant and K00 approval will be at the discretion of the NCI Program Director. Program evaluation will involve a team of external educators and quantitative metrics will be used, such as time to degree, application success rates, and age at first R01 award, as well as productivity and bibliometrics. Qualitative data will encompass surveys and in-depth interviews of participants, graduate student advisors, and postdoctoral mentors. The RFA demonstrates NCI's commitment to early career development and NCI anticipates up to 30 awards per year.

Subcommittee Review. Dr. Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President, and Chief Scientific Officer, and Professor, Department of Biochemistry and Molecular Pharmacology, NYU Langone Medical Center, New York University School of Medicine, expressed the Subcommittee's enthusiasm for a tool to recruit the best and the brightest cancer research students. The Subcommittee advocated for a higher level of support from either the NCI or matching support from the institution at both the predoctoral and postdoctoral levels to distinguish it from other graduate awards. It was suggested that the application review could weight candidate characteristics heavier than the mentor or proposed project. Dr. Bar-Sagi noted that NCI staff had confirmed that the award mechanism would be open to foreign nationals. Concerns were expressed that the award's proposed phasing might extend the time to the Ph.D. degree and postdoctoral work. She noted that the Subcommittee encouraged an emphasis on candidates who excel in all fields, such as intellectual property, commercialization, and science intelligence, as well as laboratory science.

In the discussion, the following points were made:

- Members recommended that interviews be conducted to discern the best candidates for awards and strongly encouraged institutional nomination to facilitate prescreening.
- Predoctoral students would benefit from guidance from NCI about the value of moving to another institution for postdoctoral research.

The first year cost is estimated at \$1.4 M for 30 awards, with a total cost of \$10.2 M for 5 years. One receipt date per year for the next five years is proposed for a total cost of \$51M.

Motion. A motion to concur on the request for application (RFA) entitled “The NCI Predoc to Postdoc Transition Award (K21/K00)” was approved unanimously.

Division of Cancer Biology (DCB)

Research Specialist Award (RFA)

Dr. Dinah S. Singer, Director, DCB, presented a concept for a Research Specialist Award (RSA) to encourage careers in biomedical research and re-establish a thriving, attractive research environment. The RSA would encourage the development of stable career opportunities for exceptional researchers who want to pursue research but who don't want to run their own lab as independent investigators. The award would support individuals in various positions, such as laboratory research scientists, core facility managers, and data scientists. Eligibility requirements include a higher level degree (Masters, Ph.D., D.V.M., M.D., D.D.S.); applicant sponsorship by their Principal Investigator (PI) and institution; and an expectation that only individuals who have made significant contributions to the cancer research program of a laboratory or to a core program would be sponsored.

The 5-year grant would be renewable and support that portion of the salary dedicated to cancer research up to 100 percent. Grantees would be expected to spend at least 50% of their effort on NCI-funded research. Salaries would follow host institution policies but be capped at the NIH PI level. In addition, the grant would not cover research expenses but could include travel funds, and grantees would have independence to move to other laboratories or institutions, contingent on approval of a revised proposal by NCI. Applications would include an NIH biosketch, a research proposal written jointly by the PI and applicant, and letters of recommendation. Initial applications could be made while the applicant is supported on a research grant. Review would be based on the accomplishments and contributions of the applicant and the scope and suitability of the proposed research area. The RFA pilot program for K05 awards will be evaluated based on awardees' research productivity, overall productivity of the laboratory or core, the stability of the laboratory, and assessment of the RSA by participants.

Subcommittee Review. Dr. Bar-Sagi expressed the Subcommittee's support for the concept. The Subcommittee encouraged the NCI to develop a review mechanism to handle a large applicant pool, debated the merits of limiting the award to researchers with Ph.D. degrees versus supporting data scientists who have an integral role in the laboratory, and agreed that eligible core managers would be innovative technology developers. The Subcommittee also considered whether the award's allowance to move between laboratories would foster instability for PIs. The Subcommittee also suggested that the amount of money provided by the grant be a percentage of the applicant's salary to ensure the retention of highly qualified individuals in bioinformatics and computer science.

In the discussion, the following points were made:

- Institutional and PI commitment should be an important factor in the evaluation of the RSA.

- NCI staff confirmed that population scientists are eligible for the award.
- The applicant’s identification of his or her contribution to the overall team and individual accomplishments described on the biosketch will be important in the evaluation.
- The cost-sharing paradigm reduces the risk that laboratories might become vulnerable because of personnel shifts.
- Members encouraged the NCI to develop a distribution plan regarding the number of awards to core directors versus research scientists supported by fewer laboratories.
- The award eligibility criteria should make clear that the RSA requires the applicant to be established in their career track, and should not be considered an extension of their post doc experience.
- The NCI will consider ways to prequalify applicants (e.g., letters of intent) so that the study section can provide adequate review of the applications.

The first year cost is estimated at \$5 M for 50–60 awards, with a total cost of \$25 M for 5 years.

Motion. A motion to concur on the DCB’s RFA entitled “Research Specialist Award” was approved unanimously.

Division of Cancer Biology (DCB) and Office of the Director (OD)

Provocative Questions in Cancer with an Underlying HIV Infection (RFA)

Dr. Elizabeth Read-Connole, DCB, presented a concept for a provocative questions initiative addressing cancer with an underlying HIV infection. The concept was proposed in collaboration with the Office of HIV and AIDS Malignancy (OHAM) and endorsed by the BSA *ad hoc* Subcommittee on HIV and AIDS Malignancy, and would advance understanding of the risks, development, progression, diagnosis, and treatment of malignancies observed in individuals with an underlying HIV infection. Based on an analysis of NCI’s HIV and AIDS portfolio and a Provocative Questions workshop that included experts in HIV/AIDS malignancies and related fields, research areas and questions were identified for: HIV-associated inflammation, HIV-mediated mechanisms underlying cancer risk, mechanisms underlying cancer risk in individuals with well-treated HIV infection, effects of aging, analogous tumors in HIV- and non-HIV-infected patients, and the prevalence of particular cancers in individuals with HIV infection. Members were informed that an RFA with two receipt dates for R01 and R21 applications is needed to incentivize investigators to propose high-risk projects.

Subcommittee Review. Dr. Daniel C. DiMaio, Waldemar Von Zedtwitz Professor and Vice Chairman of Genetics, Department of Genetics, Professor of Therapeutic Radiology and Molecular Biophysics & Biochemistry, and Scientific Director, Yale Cancer Center, Yale University School of Medicine, expressed the Subcommittee’s strong support for the concept. The Subcommittee recommended broadening the provocative questions so as not to constrain investigators and to better address host genetics and genetic mechanisms that might drive the interaction between cancer and HIV infection.

The first year cost is estimated at \$8 M for 24–30 awards, with a total cost of \$40 M for 2–5 years.

Motion. A motion to concur on the DCB’s and OD’s RFA entitled “Provocative Questions in Cancer with an Underlying HIV Infection” was approved unanimously.

Division of Cancer Biology (DCB)

Impact of Aging on Animal Models of Disease (RFA/Coop. Agr.)

Dr. Kevin Howcroft, Chief, Cancer Immunology and Hematology Etiology Branch, presented a concept on the impact of aging on animal models of disease that emerged from a 2013 trans-NIH scientific summit on the role of aging biology in the etiologies of chronic diseases. Barriers to using older animals in research studies include the high costs to sustain an aged colony and the specialized expertise and length of time required for such projects. Nevertheless, studies involving older animals might be critical for advancing basic research and translational studies from animal models to human populations.

The concept aims to determine whether the age of the animal when the cancer is induced is a critical factor in assessing the pathobiology of the cancer or the response of the intervention as a better predictor for the human condition. Existing, well-characterized, inducible mouse models that closely mimic human cancers would be used. Under the UH2/UH3 Cooperative Agreement, awardees in the UH2 phase would need to demonstrate that they have generated a sufficient number of aged animals and have conducted pilot experiments showing the ability to induce and study cancer in the aged animals. Each awardee would have a budget of \$150,000 in total costs over the 2-year UH2 period. In the UH3 phase, awardees would be required to characterize the cancer phenotype or response to intervention in the older animals in comparison with the established phenotype in younger animals. These awardees would be granted \$450,000 in total costs over the 3-year period. The National Institute on Aging would be the lead institute for this trans-NIH initiative.

Subcommittee Review. Dr. Bruce Stillman, President and Chief Executive Officer, Cold Spring Harbor Laboratory, reported that the Subcommittee members supported the concept idea but encouraged refinement. The Subcommittee recommended reframing the proposal into an explicit comparison of cancers affecting younger versus older individuals and suggested the use of newer types of mouse models developed through the Mouse Models of Human Cancers Consortium (MMHCC). The Subcommittee also emphasized the need for the existing mouse models to reflect as closely as possible the clinical outcomes of that particular cancer in human patients, noted a need to link the mouse studies with data in humans, and expressed concerns about stem cell issues related to aging.

In the discussion, the following points were made:

- Important factors in the development of cancer include the established role of aging, diet, and social environment of the host. A consortium-like feature incorporated into the concept would allow a comparison of results across research groups.
- The proposed funding may be inadequate to support the goals of the program.
- Multiple approaches (e.g., short-telomere mice, adoptive transfer models) could be employed to study the impact of aging on animal models of cancer.
- Members supported the concept in general but encouraged the NCI to reframe the concept. Alternative approaches emphasized better specificity of the experiment to ensure informative results, or advocated for a more open concept that focused on the important role of aging.
- The concept should refrain from limiting the UH2 phase to the breeding of animals but include a statement and allowance for developing aged mice.

The first year cost is estimated at \$375,000 for 6 awards, with a total cost of \$3 M for 5 years.

Motion. A motion to concur on the DCB's RFA/Cooperative Agreement (Coop. Agr.) entitled "Impact of Aging on Animal Models of Disease" was deferred, with the understanding that the BSA Subcommittee would review a revised concept prior to being reviewed by the full BSA by mail ballot, with 23 yeas, 2 nays, and 1 abstention. [**Addendum:** The concept was approved by mail ballot on 13 April 2015 and the vote was 27 yeas, 2 nays, and 4 abstentions.]

Division of Cancer Treatment and Diagnosis (DCTD)

Childhood Cancer Survivor Study (Reissue RFA/Coop. Agr.)

Dr. Nita Seibel, Cancer Therapy Evaluation Program (CTEP), presented a reissue concept for the Childhood Cancer Survivor Study (CCSS), a retrospectively ascertained cohort of survivors of pediatric cancer diagnosed during the past 3 decades. Dr. Seibel stated that two cohorts were initiated in 1994 and 2007, and total more than 24,000 childhood cancer survivors, along with 3,700 sibling controls who were recruited for comparison purposes. The CCSS collected clinical data on malignancy and treatment, self-reported data on risk factors and health, and psychosocial outcomes data as well as more than 7,000 biospecimens, including tissues on second malignancies and paired specimens for germline DNA. A public use dataset from the first cohort is available for investigators. Key CCSS accomplishments include informing late effect guidelines in North America and Europe, and evidence of an increased health gap over time between survivors and siblings.

Dr. Siebel described genomics projects using CCSS biospecimens, including studies that found significant association of PRDM-1 with radiation-associated second cancers in Hodgkin's lymphoma survivors; and a statistically significant inverse relationship between telomere content and the occurrence of second malignant neoplasms among survivors of childhood cancer, particularly pronounced with secondary thyroid cancer. In addition, the Division of Cancer Epidemiology and Genetics (DCEG) has conducted a genome-wide association study (GWAS) to identify genetic variants that modify the effect of radiation and chemotherapy on the risk of subsequent neoplasms, and of risk independent of treatment exposure.

Members were informed about CCSS' approach to patient-reported outcomes verification, support for intervention studies, clinical accruals compared to the Children's Oncology Group (COG), and comparison with St. Jude Life. In comparison to Children's Oncology Group (COG), CCSS has a larger enrollment pool and focuses on survivor research involving research subjects who generally are 10 or more years from diagnosis, whereas COG focuses on therapeutic research in which patients are followed closely for 5 to 10 years. Differences between CCSS and St. Jude Life include cohort size, cancer diagnoses, geographic coverage, specimen collection for second tumors, open resource, and data collection method. CCSS is better suited to conduct large-scale studies and randomized intervention studies while St. Jude Life is well positioned to do studies that require direct assessment. Dr. Seibel stated that the concept is a trans-NCI endeavor with several new opportunities, particularly to identify the impact of risk stratification, such as pattern of late effects in Hodgkin's lymphoma and ALL patients, and impact of multimodality therapy in high-risk neuroblastoma patients.

Subcommittee Review. Dr. Curt I. Civin, Director, Center for Stem Cell Biology & Regenerative Medicine, Professor of Pediatrics & Physiology, and Associate Dean for Research, University of Maryland School of Medicine, expressed the Subcommittee's unanimous enthusiasm for the concept re-issue, noting its value as a resource during the past 20 years, collection of second cancers that arise in this cohort for genomic analysis, and complementarity with the St. Jude's study. The Subcommittee suggested it would be an ideal cohort to link to the PMI, which likely will have interest in genomic risk and environmental interactions, and encouraged support for a cohort that addresses young adults, a

population that the CCSS does not cover. The project was encouraged to strengthen its intervention work through a more proactive approach as well as continue its emphasis on minority participation.

In the discussion, the following points were made:

- Members noted the impact that childhood cancer survival has in the adult world of cancer and survivorship and encouraged development of early predictive markers, such as through single cell genomic techniques.
- An adolescent and young adults (AYA) cohort launched in Canada should elucidate issues and provide direction for research in pediatric cancer survivorship.

The first year cost is estimated at \$4.31 M for one U24 award, with a total cost of \$21.1 M for 5 years.

Motion. A motion to concur on the reissuance of the Division of Cancer Treatment and Diagnosis' (DCTD) RFA/Coop. Agr. entitled "Childhood Cancer Survivor Study" was approved unanimously.

Division of Cancer Biology (DCB)

Cancer Systems Biology Consortium (CSBC) Initiative (RFA/Coop. Agr.)

Dr. Daniel Gallahan, DCB, described a concept for the CSBC that represents the NCI's commitment in systems and computational biology. Dr. Gallahan told members that the goals are to continue the development of predictive computational models that integrate across multiple scales and to build a community of researchers who apply systems approaches to cancer biology problems. Recent advances in the cancer systems biology field encompass discovery of new regulatory networks, integration of multiple datasets, large-scale functional genomics, and predictive intervention through sequential application of anti-cancer drugs.

The CSBC would focus on developing predictive mathematical models that generate or test new biological hypotheses in cancer biology, develop a consortium of multi-disciplined, collaborating investigators and resources, and support a training and outreach program. The proposed organization includes research centers (U54), specialized research grants (U01), and a coordinating center (U24) to coordinate workshops and meetings with other programs. Dr. Gallahan noted the limited number of systems biology/modeling research grants in NCI's portfolio. He indicated that the CSBC would be evaluated based on the development and application of systems biology and computational modeling in cancer research, solutions provided for complex questions in the cancer research continuum, and expansion of the field through education and training. The RFA for research centers (U54) would have three receipt dates spread over 1 ½ years and the RFA for the coordinating center would have one receipt date in FY16. A program announcement (PAR) with no set aside of funds would be issued for the specialized research grants (U01) with two receipt dates each year for three years.

Subcommittee Review. Dr. Andrea Califano, Director, Columbia Initiative in Systems Biology, Director, Sulzberger Columbia Genome Center, Associate Director, Herbert Irving Comprehensive Cancer Research Center, Professor of Systems Biology, Department of Biochemistry and Molecular Biophysics, Biomedical Informatics, and Institute of Cancer Genetics, Columbia University Medical Center, noted the Subcommittee's strong support for the concept. The concept is considered to be timely as cancer research becomes more data driven and provides a means to build mechanistic models that support predictive needs and facilitate better understanding and manipulation of complex adaptive systems that drive cancer. Dr. Califano stated that the concept will assist in the field's transition from data analysis science to integration with underlying biology within the context of multidisciplinary efforts. The Subcommittee appreciated the emphasis on training, encouraged interaction with the Physical Science

Oncology Network (PSON), and commended the pivotal role of the coordinating center to promote new opportunities and connections among large and small centers. Members encouraged supporting both basic and translational efforts in this area, and expressed concerns about the ability of current study sections to evaluate cancer system biology grants.

In the discussion, the following points were made:

- The NCI Integrative Cancer Biology Program's (ICBP) annual DREAM Challenge brought the modeling community together to make objective decisions about which models were most predictive using a standardized data set. This approach should be continued.
- The CSBC aims to focus on both model organisms and human cancer, with an emphasis on studying cancer at the single cell level.
- Members encouraged the NCI to ensure that the concept retains an emphasis on modeling and is not a continuation of the previous integrative cancer activities.

The first year cost is estimated at \$12 M for 8-10 U54 awards and 0.75M for 1 U24 award, with a total cost of \$75.75 M for 6 years.

Motion. A motion to concur on the DCB's RFA/Coop. Agr. entitled "Cancer Systems Biology Consortium (CSBC) Initiative" was approved unanimously.

Division of Cancer Control and Population Sciences (DCCPS)

Smoking Cessation Within the Context of Lung Cancer Screening (RFA)

Dr. Robert T. Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), provided an overview to the concept, which was presented by Dr. Stephanie Land, Tobacco Control Research Branch, DCCPS. Dr. Croyle reminded members of the NIH-FDA partnership in tobacco regulatory science and support to NCI grantees using funds from the new FDA Center for Tobacco Products. Smoking cessation, however, lies outside of the purview of those regulatory funding mechanisms, and the proposed concept addresses a domain that has relevance for clinical practice in terms of tobacco control.

Dr. Land described the concept to provide models of smoking cessation services for a rapidly expanding lung cancer screening arena. Low-dose computed tomography (CT) lung cancer screening has been efficacious, as seen in a 20 percent reduction in lung cancer mortality for high-risk individuals in the National Lung Screening Trial (NLST) as well as recommendations by the U.S. Preventive Services Task Force (USPSTF), and coverage by Medicare and mandates by the Affordable Care Act. The NLST defined high risk as those aged 55-74 with a 30 pack-year smoking history, and having quit within 15 years, or being a current smoker. Approximately 8.6 million Americans are eligible for low-dose CT screening, with 50 percent of those screened being smokers. Rates of continued smoking are high even in screening trials, and concerns remain that screening could discourage cessation in some patients. The USPSTF, Centers for Medicare and Medicaid (CMS), and American College of Radiology encourage or require cessation at time of screening. Although effective cessation interventions, including behavioral counseling and pharmacotherapy, exist for the general population, research is needed because patients will enter low-dose CT through multiple pathways depending on the clinical setting and screening outcomes.

Members were told that the concept aims to identify the key components and characteristics of a successful cessation program at low-dose CT lung cancer screening, with the primary outcome of long-term cigarette smoking abstinence. Other relevant research topics include whether the success of specific

cessation methods differs by individual characteristics or exam results, and comparison of approaches in terms of intervention fidelity, provider reach, cost, cost-effectiveness, and ease of delivery. The research design should include innovative interventions in which the smoking cessation approach has a degree of novelty or implement an evidence based cessation approach in a novel way.

Subcommittee Review. Dr. Graham A. Colditz, Niess-Gain Professor of Surgery, Professor of Medicine and Associate Director of Prevention and Control, Alvin J. Siteman Cancer Center, Deputy Director, Institute for Public Health, and Chief, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, expressed the Subcommittee's support for the concept, which provides an opportunity to leverage the investments that the NCI already has made with respect to understanding cessation approaches and particularly by targeting it to smokers who are at extremely high risk for developing lung cancer. The Subcommittee appreciated NCI staff responses to their questions about engagement of primary care providers, the extent of focus on racially diverse smokers, concerns with the Medicare setting, and linkages to the radiology-mandated data systems that CMS requires.

In the discussion, the following points were made:

- To ensure that intervention services are available to low-dose CT screening facilities, proposals will need to include a dissemination plan that specifies the resources necessary to scale up the proposed intervention.
- Funding for six projects was deemed appropriate to test models in a variety of clinical settings, and to respond to the number of research questions envisioned.
- The possible use of e-cigarettes as a therapeutic strategy remains under debate with many issues unresolved.

The first year cost is estimated at \$4.5 M for six awards, with a total cost of \$22.5 M for 5 years.

Motion. A motion to concur on the reissuance of the Division of Cancer Control and Population Sciences' (DCCPS) RFA entitled "Smoking Cessation within the Context of Lung Cancer Screening" was approved unanimously.

Office of the Director (OD)

**Pilot Collaborations with LMICs in Cancer Control at NCI-Designated Cancer Centers
(informational only)**

Dr. Edward L. Trimble, Director, Center for Global Health (CGH), described a re-issuance proposal for administrative supplements to the NCI-designated Cancer Centers to promote cancer prevention and control research and training in low- and middle-income countries (LMICs) through collaborations and research partnerships between the NCI-designated Cancer Centers and LMIC institutions. Dr. Trimble stated that cancer is a leading cause of death worldwide with a disproportionate burden occurring in LMICs and noted that twinning between NCI-designated Cancer Centers and LMIC institutions will strengthen the cancer prevention and control activities in LMICs. The Cancer Centers participated in a 2011 survey of global health activities, the 2012 NCI CGH stakeholder meeting, and the 2013 Competitive Supplement Program that received 40 applications and provided 15 awards for up to \$200,000 per year for 2 years. Dr. Trimble reviewed the funded projects.

Topics for the 2015 pilot project include clinical and translational research, detection and diagnosis of cancer, health surveillance (cancer registries and death registries), knowledge sharing, implementation

science, informatics and mHealth, and malignancies associated with HIV and chronic infection. The administrative supplement program is proposed for 10 2-year awards totaling \$2 M in total costs each in FY 2015 and 2016. Dr. Trimble reviewed eligibility requirements, allowable costs, review criteria, and the review committee. He noted that the cancer center Director must serve as the PI of the supplement and an LMIC investigator must co-lead the project with at least 50 percent of funds directed to the LMIC institution. In addition, the CGH has initiated a global cancer mapping project in partnership with a nongovernmental organization to capture grants, contracts, institutional twinning, department and individual projects, and professional societies starting in March 2015.

In the discussion, the following points were made:

- Members remarked on the low dollar amount allocated for the supplements, specifically a \$200,000 award per year for 2 years, of which one-half is provided to the low-income country and one-half to the NCI-designated Cancer Center.
- Awardees will not be eligible to apply again for the same project.
- Two year summaries of the outcomes of the funded projects will be shared with the Board.

V. ADJOURNMENT—DR. TODD R. GOLUB

There being no further business, the 56th regular meeting of the BSA was adjourned at 3:34 p.m. on Wednesday, 11 March 2015.

Date

Todd R. Golub, M.D.
Chair, Board of Scientific Advisors

Date

Paulette S. Gray, Ph.D.
Executive Secretary, Board of Scientific
Advisors