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

2nd Virtual Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

October 31, 2016
Conference Room TE 406, East Wing, Shady Grove Campus,
Bethesda, Maryland

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

BOARD OF SCIENTIFIC ADVISORS

MINUTES OF MEETING
October 31, 2016

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 2nd virtual regular meeting on Monday, 31 October 2016, at 1:00 p.m. BSA members attended virtually, and NCI staff attended in Conference Room TE406, East Wing, Shady Grove Campus, National Institutes of Health (NIH), Bethesda, MD. Dr. Chi V. Dang, Professor of Medicine, Division of Hematology-Oncology, Department of Medicine, Director, Abraham Cancer Center, Director, Abramson Cancer Research Institute, Perelman School of Medicine, University of Pennsylvania, presided as Chair. The meeting was open to the public from 1:00 p.m. until 4:00 p.m. on 31 October for the consideration of new request for applications /cooperative agreement (RFA/Coop. Agr.) concepts presented by NCI program staff.

BSA Board Members Present:

Dr. Chi V. Dang (Chair)
Dr. Kenneth C. Anderson
Dr. Ethan M. Basch
Dr. Michael John Becich
Dr. Sangeeta N. Bhatia
Dr. Melissa Bondy
Dr. Arul M. Chinnaiyan
Dr. Daniel C. DiMaio
Dr. Karen M. Emmons
Dr. James V. Lacey
Dr. Luis F. Parada
Dr. Sylvia Katina Plevritis
Ms. Diane Zipursky Quale
Dr. Kevin M. Shannon
Dr. Mary L. Smith
Dr. Ian M. Thompson

Dr. David A. Tuveson
Dr. Eileen P. White
Dr. Cheryl L. Willman

Board Members Absent:

Dr. Dafna Bar-Sagi
Dr. Graham A. Corditz
Dr. Christopher M. Counter
Dr. Joseph M. DeSimone
Dr. Carol E. Ferrans
Dr. Chanita Hughes-Halbert
Dr. Maria Elena Martinez
Dr. Martine F. Roussel
Dr. Victoria L. Seewaldt
Dr. Cheryl L. Walker
Dr. Kevin P. White

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

TABLE OF CONTENTS

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I. CALL TO ORDER AND OPENING REMARKS—DRS. CHI V. DANG and DOUGLAS R. LOWY

Dr. Dang called to order the 2nd virtual regular meeting of the BSA and welcomed current members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Dang 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.

Dr. Dang welcomed new BSA members: Drs. Michael John Becich, Professor, Pathology Information Sciences/Telecommunications, Clinical/Translational, Department of Biomedical Informatics, University of Pittsburgh School of Medicine; Melissa L. Bondy, Professor and Associate Director, Department of Pediatrics, Dan L. Duncan Cancer Center, Baylor College of Medicine; Christopher M. Counter, Professor, Department of Pharmacology and Cancer Biology, Associate Professor, Radiation Oncology, Duke University School of Medicine; Sylvia Katina Plevritis, Professor, Department of Radiology, Department of Biomedical Data Science, Stanford University School of Medicine; Ian M. Thompson, Jr., Mays Family Foundation Distinguished University Professor Presidential Chair, Glenda and Gary Woods Distinguished Chair in Genitourinary Oncology, Director, Cancer Therapy and Research Center, The University of Texas Health Science Center; David A. Tuveson, Professor and Deputy Director, Cancer Center, Cold Spring Harbor Laboratory; and Cheryl L. Willman, The Maurice and Marguerite Liberman Distinguished Chair in Cancer Research, Director and CEO, The University of New Mexico Comprehensive Cancer Center, University of New Mexico.

Dr. Douglas R. Lowy, Acting Director, NCI, joined Dr. Dang in welcoming new and continuing BSA members. He noted that the NCI Director's report was not included on the agenda to accommodate discussions of the five new RFAs that represent key components of the Precision Medicine Initiative in Oncology (PMI-O). Dr. Lowy expressed appreciation to the members of the Board and *ad hoc* members for their efforts in reviewing the proposals.

II. PRECISION MEDICINE INITIATIVE RFA/COOP. AGR. CONCEPTS—NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis (DCTD)

Canine Immunotherapy Trials and Correlative Studies in Collaboration with the Comparative Oncology Trials Consortium (New RFA/Coop. Agr.)

Dr. Toby T. Hecht, Deputy Director, DCTD, presented a new concept on canine immunotherapy trials and correlative studies to be conducted in collaboration with the Comparative Oncology Trials Consortium (COTC). The short-term goals of this RFA are establishing a network of laboratory scientists and canine clinical trials to study primarily the anti-tumor effect of immunotherapy agents, as well as organizing a coordinating center to assist in developing and implementing clinical protocols. The long-term goals for the NCI are to establish the suitability of canine models to study single and combinations of immunomodulating agents with targeted drugs, chemotherapy, or radiation and to determine whether canine cancer research will inform the design of human cancer studies, particularly immunotherapy. To better understand the relationship between canine and human immune system mechanisms and the mechanism of response, the NCI anticipates that the proposed structure will increase the ability of the cancer community to answer those questions.

Canine patients with spontaneously occurring tumors present advantages over mice as therapeutic models because the canine genome is similar to that of humans, dogs are immunocompetent, and spontaneously-occurring cancers in dog increase with age. Although research has provided some insights into the canine immune checkpoints and inhibitors and other immunmodulators, whether the immunogenic mutational load or treatments are associated with increased survival in canines remains unknown. As part of the PMI-O, NCI awarded eight 1-year Administrative Supplements in fiscal year (FY) 2016 to support research in canine immunotherapy via collaboration with NCI-Designated Cancer Centers and Veterinary Medical Colleges. These studies are investigating six canine tumors and using predictive algorithms to discover neoantigens. Preliminary results are promising.

This RFA will support conducting canine clinical trials using immunotherapeutic agents and novel combinations (e.g., immune modulators, molecular targeted agents, chemotherapy, radiation), as well as laboratory correlative studies. These correlative studies will seek to describe, characterize, and understand the cellular and molecular mechanisms that determine the antitumor response in dogs with spontaneous tumors. This will require a network of as many as five laboratories and canine clinical trial sites (UM1), as well as a coordinating center (U24) assisted by NCI's Comparative Oncology Program (COP), which will help develop and conduct the clinical studies across funded sites.

Subcommittee Review. Dr. Kenneth C. Anderson, Kraft Family Professor of Medicine, Harvard Medical School, Director, Lebow Institute for Myeloma Therapeutics, Dana Farber Cancer Institute, expressed the Subcommittee's enthusiasm and strong support for the concept, noting the unmet need for new immunotherapy cancer research model systems. The Subcommittee commends the current canine studies that the NCI has funded; however, canine clinical trial results (e.g., *in vivo* studies) demonstrating the effectiveness of immunotherapy (e.g., checkpoint inhibitors) are needed. Addressing this need, the concept presents a unique opportunity to conduct canine immunotherapy trials in a collaborative effort and aligns with the emphasis of the PMI-O and Cancer Moonshot—doubling the rate of progress in cancer immunotherapy.

In the discussion, the following points were made:

- Members expressed concerns that major epithelial adult cancers are not very common in dogs and could be a limitation of the proposal. Also, considerations should be given to the safety issues involved in doing studies in the large-animal models with spontaneously developing cancers.

- This RFA addresses a more focused and limited approach that will investigate an underutilized animal model, the canine, where tumors occur spontaneously and develop slowly. Conducting companion studies using the newer mouse models that replicate the genetic complexity of human cancers is outside of the scope of these studies. However, to augment the substantial amount of research already performed in mouse models, the NCI is considering ways of improving the current mouse models of cancer as emphasized in the Cancer Moonshot recommendations.

- The proposal will involve studies of animals in many regions of the United States, and obtaining adequate statistical power could be challenging. One strategy would be to develop ways to engage groups conducting research in large-animal models (e.g., genetically engineered pigs, aging nonhuman primates) that may not be included in this veterinary medicine approach, but also are prone to developing cancer.

The first year's cost is estimated at $2.5 million (M) for five UM1 awards and $0.5 M for one U24 award, with a total cost of $15 M for 5 years.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' RFA/Coop. Agr., entitled "Canine Immunotherapy Trials and Correlative Studies in Collaboration with the Comparative Oncology Trials Consortium," was approved unanimously.

Consortium for Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment (New RFA/Coop. Agr.)

Dr. Peter Ujhazy, Associate Deputy Director, Translational Research Program, DCTD, described a new concept to support establishing a PDAC consortium to conduct translational studies on the tumor microenvironment. This proposal is continuing NCI's response to the Recalcitrant Cancer Research Act of 2012 to conduct and support research on recalcitrant cancers—cancers with a 5-year survival rate of less than 50 percent. Pancreatic cancer is a recalcitrant cancer. The purpose of this RFA is to stimulate research in the PDAC microenvironment with the goal of understanding this interaction between tumors and the microenvironment to design new immunotherapy and other treatment interventions. The NCI plans to establish a PDAC Microenvironment Consortium to achieve these goals.

PDAC has a low mutational load with few neoantigens (e.g., immunologically cold tumor) due to the absence of effector T cells in the tumor microenvironment, complex immunosuppressive tumor infiltrates, and desmoplastic tumor stroma that can support tumor growth. However, new evidence has revealed methods that will reprogram the PDAC microenvironment by normalizing structural proteins (e.g., hyaluronan, collagen, osteonectin), normalizing an immunologically protumor environment to a less growth-supportive environment, and reversing the epithelial-to-mesenchymal transition.

In its PMI-O efforts in 2016, the NCI awarded nine Administrative Supplements to support studies for determining the mechanistic effects of immunotherapy on the PDAC microenvironment. The response rate far exceeded expectations, with 36 applications demonstrating the readiness of the scientific community to pursue these types of studies. The proposed consortium will allow the most advanced scientific and clinical teams to perform their work in a more coordinated way, with access to common resources and with the option of conducting early-phase clinical trials. This research will enable a deeper

understanding of the complex PDAC microenvironment, its individual components, their interactions with the tumor, and their potential role in facilitating immunotherapeutic and other interventions.

Subcommittee Review. Dr. Tuveson expressed the Subcommittee's support for the concept. Studies on immunotherapy and pancreatic cancer are clinically relevant, and the Subcommittee lauded the concept's planned consortium to bring together investigators to address this recalcitrant cancer. The Subcommittee recommends incorporating a co-clinical approach by performing PDAC research studies in tandem with clinicians who are conducting translational clinical trials; engaging the bioengineering and physical sciences communities in the research efforts; and promoting data sharing internal and external to the consortium.

In the discussion, the following point was made:

- More clarity on how the consortium for PDAC aligns with existing pancreatic Specialized Program of Research Excellence (SPORE) grants should be provided.

The first year's cost is estimated at $2.5 M for five U01 awards and $0.5 M for one U24 award, with a total cost of $15 M for 5 years.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' RFA/Coop. Agr., entitled "Consortium for Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment," was approved unanimously.

Patient-Derived Xenograft (PDX) Development and Trial Centers (PDTCs) Network (U54) and PDX Data Commons (PDCC) (U24) for the PDTCRNet (New RFA/Coop. Agr.)

Dr. Jeffrey A. Moscow, Medical Officer, Investigational Drug Branch, Cancer Therapy Evaluation Program, DCTD, presented a new concept to form a collaborative network, termed PDTCRNet, of PDTCs, as well as an associated PDX data commons (PDCC). Dr. Moscow remarked on the advancements in technology that have provided the opportunity to use PDX models on a large scale to advance precision medicine through comprehensive preclinical evaluation of novel agent combinations in a small and molecularly defined tumor subgroup. However, the application of PDXs in precision medicine thus far has been limited by the silo character of academic PDX programs, lack of standards for determining the quality of PDX models and of PDX response to therapeutic intervention, lack of defined mechanisms to assess reproducibility of results between centers, and limited data sharing between PDX centers. NCI's initial PDX PMI-O efforts to address this issue was pursued through 1-year Administrative Supplements for development of PDXs and drug response testing of PDX models. This effort provided a portrait of PDX activities in the United States and revealed the existence of a total of 4,800 PDX models from 65 applicants—42 PDX models per applicant. Also recognized was evidence that PDX collections are not large enough to reflect the necessary human tumor diversity and the existence of multiple noncollaborative PDX collections.

The goals of the PDTCRNet are to apply PDX models for the specific purpose of providing more efficient and precise development of NCI investigational new drug (NCI-IND) agents in the Experimental Clinical Trials Network (ETCTN), and use of the PDTCRNet resources to test original concepts of extramural investigators. Development of the PDTCRNet will be achieved by leveraging the resources of the NCI Patient-Derived Models Repository (PDMR) at Frederick National Laboratory for Cancer Research (FNLCR). The PDMR is a national repository of PDMs that serves as a resource for academic discovery efforts and public-private partnerships for drug discovery. It houses clinically annotated PDXs, as well as patient-derived tumor cell and fibroblast cultures, in a publicly available database.

Subcommittee Review. Dr. Willman reported that that Subcommittee members supported the concept idea but encouraged refinement. The Subcommittee strongly supports leveraging the resources of the PDMR at FNLCR; however, concerns were expressed that use of the U54 funding mechanism for establishing the PDTCRNet could be challenging to implement and might not be the best option. The Subcommittee thinks that limiting investigators to using only NCI-IND agents might be too restrictive and would not take advantage of the enabling capabilities within the network.

In the discussion, the following points were made:

- The idea of a PDTCRNet is scientifically relevant; however, establishing protocols, good quality control methods to guard against confounders (e.g., xenograft proliferative disease), and a centralization of assays would be necessary. In addition, including details in the proposal on collecting and validating biospecimens, as well as identifying the party or parties that will be responsible for doing the molecular characterizations, is necessary for producing biologically useful data.

- NCI's DCTD envisions the PDTCRNet as providing PDX models that optimize investigators' approaches to research, catalyzing the performance of prospective clinical trials using PDX models, and engaging the extramural community in the PDX PMI-O efforts.

The first year's cost is estimated at $5 M for four U54 awards, $1 M for one U 24 award, $1 M for P30/P50 Administrative Supplements, with a total cost of $35 M for 5 years.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' RFA/Coop. Agr., entitled "Patient-Derived Xenograft (PDX) Development and Trials Centers (PDTCs) Network (U54) and PDX Data Commons (PDC) (U24) for the PDTCRNet," was approved with 14 ayes, 2 nays, and 2 abstentions.

Development of Clinical Application of Approaches to Identify and Treat Cancer Sensitivity or Resistance to Anticancer Therapy (New RFA/Coop. Agr.)

Dr. L. Austin Doyle, Senior Investigator, Investigational Drug Branch of Cancer Therapy Evaluation Program, DTCD, presented a new concept for developing a Drug Resistance/Sensitivity Network (DRSN) to study the mechanisms of cancer resistance and/or sensitivity to therapy. The DRSN will consist of as many as five sites (U54) or Drug Sensitivity Centers (DSC). Each of these U54 project teams will focus on unique areas of drug resistance/sensitivity research using human tumor samples and will provide the NCI with expertise in novel drug development. These 5-year U54 projects will be part of NCI's PMI-O to improve cancer treatment through the network program. In addition, the DRSN will include linked projects in the proposed research area and interact with a centralized coordinating committee. DRSN's focus includes—but is not limited to—new models, diagnostic techniques, and studies involving "druggable" targets. Projects using NCI-IND agents (e.g., small molecule and antibody inhibitors) are preferable; however, understanding resistance/sensitivity to other agents will be acceptable for this RFA.

The NCI awarded 11 1-year Administrative Supplements to NCI-Designated Cancer Centers and other grantees for the purpose of accelerating preclinical development of novel agents and therapies. It is anticipated that these efforts will foster collaborations with the DRSN. In light of the fact that these 1-year awards are supplementary, thus limited in scope, this RFA will permit broader and more thorough investigations. A Drug Resistance and Sensitivity Coordinating Committee (DRSCC) will facilitate the DRSN's activities to encourage scientific interaction and utilization of resources.

Subcommittee Review. Dr. Dang expressed the Subcommittee's support of the concept. Resistance to anticancer therapy is a common clinical problem, and the Subcommittee lauded the integrated efforts put

forth to address this problem. The concept aligns with the Cancer Moonshot recommendations to develop therapeutic targets to overcome resistance.

In the discussion, the following points were made:

- The proposal encompasses broad areas of drug resistance/sensitivity research to attract disparate participation. The projects selected will focus on separate and unique areas of drug resistance/sensitivity.

The first year's cost is estimated at $6.25 M for five U54 awards and $0.78 M for P30/P50 Administrative Supplements, with a total cost of $35.15 M for 5 years.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' RFA/Coop. Agr., entitled "Development and Clinical Application of Approaches to Identify and Treat Cancer Sensitivity or Resistance to Anticancer Therapy," was approved unanimously.

Cancer Immune Monitoring Analysis Centers (CIMACs) Network (U24) and Cancer Immunologic Data Commons (CIDC) (U24) for the CIMACs Network (New RFA/Coop. Agr.)

Dr. Magdalena Thurin, Program Director, Diagnostics Evaluation Branch, DCTD, described a new concept for establishing a network of cancer immune monitoring analysis centers (CIMACs) and a single, centralized bioinformatics resource, or cancer immunologic data commons (CIDC). The overall objectives of the network will be to support correlative studies in NCI-sponsored, early-phase (Phase I and Phase II) clinical trials to improve treatment outcomes and to use early-phase studies as a proving ground for clinically informative biomarkers that can be validated in late-phase clinical trials. The CIMACs will comprise as many as three multidisciplinary laboratory centers aligned with one or more NCI-supported networks (e.g., Cancer Immunotherapy Trials Network, NCI Clinical Trials Network, Experimental Therapeutics Clinical Trials Network), which will serve as the primary partner(s). The functions of the CIMACs will include carrying out retrospective and prospective analysis using standardized biomarker assays, providing access to trial specimens, and updating or developing technologies. The CIDC will be responsible for data collection and harmonization across CIMACs, collaboration with other data centers, and establishment of a database. To coordinate such efforts, a Laboratory Coordinating Committee will be established to serve the entire network.

Subcommittee Review. Dr. Luis Parada, Albert C. Foster Chair, Director, Brain Tumor Center, Member, Cancer Biology and Genetics Program, Attending Neuroscientist, Department of Neurology and Department of Neurosurgery, Sloan Kettering Cancer Center, expressed the Subcommittee's support for the concept. This is the second time that this concept was reviewed, and the Subcommittee lauded the efforts of the NCI staff in modifying the design to one that better meets the needs of the community.

In the discussion, the following point was made:

- Consider adopting more futuristic views on funding within the DCTD when programmatically matching the scientific needs to support encouraging research beneficial to the cancer community. Establishing coordinating centers may not be strategic in all cases.

The first year's cost is estimated at $6.5 M for three U24 awards (CIMACs) and $1 M for one U24 award (CIDC), with a total cost of $37.5 M for 5 years.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' RFA/Coop. Agr., entitled "Cancer Immune Monitoring and Analysis Centers (CIMACs) Network (U24) and Cancer Immunologic Data Commons (CIDC) (U24) for the CIMACs Network," was approved unanimously.

III. ADJOURNMENT—DR. CHI V. DANG

There being no further business, the 2nd virtual regular meeting of the BSA was adjourned at 3:38 p.m. on Monday, 31 October 2016.

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Date   Chi V. Dang, M.D.
                                                                             Chair, Board of Scientific Advisors

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