DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)
AD HOC TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE (TRSS)
MEETING

Summary of Meeting
October 5, 2020

Webinar

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
***AD HOC* TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE**
Summary of Meeting
October 5, 2020

A meeting of the *ad hoc* Translational Research Strategy Subcommittee (TRSS) of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held by webinar on Monday, October 5, 2020, at 1:06 p.m. The TRSS chairs, Dr. Davidson and Dr. Dang, presided.[1] The meeting was adjourned at 2:34 p.m.

Co-Chairs
Chi V. Dang
Nancy E. Davidson

TRSS Members
Francis Ali-Osman
Walter J. Curran, Jr. (absent)
David A. Mankoff
Lynn M. Matrisian
Roman Perez-Soler
Kevin M. Shannon
David A. Tuveson
Kevin P. White
Max S. Wicha (absent)

Ex Officio Members
James H. Doroshow, NCI

Executive Secretary
Peter Ujhazy, NCI

Presenters

Chi V. Dang, MD, PhD, Scientific Director, Ludwig Institute for Cancer Research, New York; Professor, The Wistar Institute
Nancy E. Davidson, MD, Senior Vice President, Director and Full Member, Clinical Research Division, Fred Hutchinson Cancer Research Center
Adam P. Dicker, MD, PhD, Professor, Department of Pharmacology and Experimental Therapeutics and Department of Radiation Oncology, Thomas Jefferson University
James H. Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis, NCI
Silvia C. Formenti, MD, Sandra and Edward Meyer Professor of Cancer Research and Chair, Department of Radiation Oncology, Weill Cornell Medicine; Radiation Oncologist in Chief, NewYork-Presbyterian/Weill Cornell Medical Center
Peter Ujhazy, MD, PhD, Deputy Associate Director, Translational Research Program, Division of Cancer Treatment and Diagnosis, NCI

[1]A roster of TRSS members and their affiliations is included as an appendix.

TABLE OF CONTENTS
Monday, October 5, 2020

I. Call to Order and Opening Remarks

Chi V. Dang, MD, PhD
Nancy E. Davidson, MD

Dr. Davidson reviewed the confidentiality and conflict-of-interest practices required of TRSS members during their deliberations. She invited members of the public to send written comments on issues discussed during the meeting to Dr. Ujhazy within 10 days of the meeting.

II. TRSS Overview

James H. Doroshow, MD
Peter Ujhazy, MD, PhD

Dr. Doroshow welcomed TRSS members to this meeting. After reviewing the meeting agenda, Dr. Ujhazy explained that the TRSS mission is to survey scientific horizons and provide advice to NCI's advisory boards and leaders on enhancing and broadening NCI's translational research portfolio.

The CTAC *ad hoc* Glioblastoma Working Group, chaired by Dr. Curran and Dr. Dang, presented its draft report to TRSS at the subcommittee's meeting on July 8, 2019. TRSS accepted the report, which was then presented to CTAC on July 17, 2019. CTAC also approved the report, and the NCI Board of Scientific Advisors subsequently approved a request for applications (RFA) to establish the NCI Glioblastoma Therapeutics Network. Applications in response to this RFA are due on November 19, 2020.

Dr. Ujhazy communicated that the CTAC *ad hoc* Radiation Oncology Working Group, chaired by Dr. Dicker and Dr. Formenti, would present its report to TRSS for its approval at this meeting. If TRSS approves the report, the next step is to present the report to CTAC on November 4, 2020, for its approval.

III. Radiation Oncology Working Group Report

Adam P. Dicker, MD, PhD
Silvia C. Formenti, MD

Dr. Dicker explained that the mission of the CTAC *ad hoc* TRSS Radiation Oncology Working Group (see roster), which he and Dr. Formenti chair, is to survey the scientific horizons to identify:

- Radiation oncology translational research knowledge gaps
- The most provocative and impactful radiation oncology translational research questions to advance cancer treatment
- The most important opportunities for the application of new technologies to radiation oncology translational research

The working group was formed in May 2019, and it met in person on October 7, 2019, to review the research landscape, identify gaps and opportunities, and develop draft recommendations.

Radiation Oncology: Background and Challenges. Radiotherapy has been used for cancer treatment for more than 100 years, and more than half of patients with cancer receive this treatment at some time during their disease course. Radiotherapy can cure early-stage tumors and improve tumor control and survival in combination with surgery, chemotherapy, or both for many locally advanced tumors. The addition of chemotherapy to radiotherapy has increased the cure rate for many cancer types and is one of the most important advances in cancer care over the past 30 years.

Innovation in the past two decades has been driven primarily by the convergence of advances in medical physics and computer science and not in biology or industry research. Recent advances include the development of stereotactic radiation treatment, proton and particle therapy, and brachytherapy.

Tumor irradiation causes various biological consequences that can be leveraged to enhance the effects of radiation. Like drugs, radiation therapy can be used in different ways and at different doses. But radiotherapy is different from drug therapy in that radiation oncologists know with extreme precision which dose of radiation is reaching a specific area of the body.

Major knowledge gaps remain in understanding the effects of radiotherapy on healthy and malignant tissue in humans. Most radiobiology studies have been done with established cell lines, and the clinical focus has been on the precise physical delivery of radiation rather than on understanding its biological impact. For precision medicine, a better understanding of the biological consequences of radiation therapy is required to incorporate molecular tumor characteristics and the immune microenvironment into treatment planning.

The combination of conventional cytotoxic agents and ionizing radiation has had a significant impact on solid tumors in almost every area of the body. However, combinations of radiation therapy with molecularly targeted agents have been less successful. One challenge is that the pharmaceutical industry is often more interested in supporting medical oncology advances than those in radiation oncology, because of the difficulty of identifying a pathway to registration. Few biological agents have been combined with radiotherapy in phase III clinical trials, and few academic institutions have the resources, expertise, and quality assurance mechanisms to conduct such studies.

Large volumes of data are generated through radiotherapy, including imaging and dosimetry data, and these data are integrated into electronic medical records. However, radiation oncologists believe that they lack training opportunities in bioinformatics, genomics, and immunology to leverage these large amounts of data for research.

Working Group Recommendations. Dr. Formenti reported that the working group's overarching recommendation is to establish an agile and effective, coordinated, national effort for radiation oncology to advance the study of the biologic mechanisms of radiotherapy through preclinical and translational research studies to develop promising radiotherapeutic approaches to advance cancer care.

Other recommendations were to:

- Prioritize and support research to investigate the translational mechanistic interactions and biologic consequences of ionizing radiation to facilitate bench-to-bedside-and-back research.
- Support longitudinal collection of clinically annotated biospecimens before, during, and after radiation therapy for research purposes.
- Develop a coordinated infrastructure to support translational research, which could include a centralized validation laboratory designed to leverage the expertise of investigators, accelerate discovery, and validate key findings.
- Prioritize and support development of animal and preclinical model systems that are specific to radiation therapy (normal tissue toxicity and radiation response) and utilize shared resources.
- Develop a multidisciplinary workforce and engage stakeholders with the expertise to conduct studies in translational, preclinical, and clinical radiation oncology, including leveraging data science and informatics approaches.

Questions and Discussion

Collaborations. Dr. Dang asked how NCI could catalyze interactions with industry or, given the mention of space biology and the effects of radiation on normal biology, with the National Aeronautics and Space Administration. Dr. Formenti said that the drivers of support for preclinical studies differ for pharmaceutical and radiation device manufacturing companies, but NCI might be able to catalyze such partnerships.

Dr. Dang asked whether NCI could use the approach that it used for collaborative studies with pharmaceutical companies of combination therapies to advance collaborations with radiation oncology machine companies. Dr. Doroshow explained that NCI-ComboMATCH brings together several companies that provide compounds for combination treatment studies. Various kinds of drugs are biologically synergistic with radiation, and evidence showing that such combinations are effective would make it easier to promote these types of partnerships.

Dr. Formenti agreed that generating mechanistic data is a key first step and is a reason for the working group's third recommendation, to develop a coordinated infrastructure to support research. Radiation oncology research needs to move beyond cell lines and into modern tools, and the value of adding radiation oncology to drugs needs to be convincing to persuade pharmaceutical companies to participate in this research. Dr. Dicker pointed out that in every field, it takes a while to appreciate the initial reports on a new development, but a herd mentality often develops. Developing such perspectives is challenging in radiopharmaceutical research because of the limited evidence available and the small number of researchers who can study radiopharmaceutical agents in model systems.

Dr. Mankoff, a member of the Radiation Oncology Working Group, commented that large radiation oncology companies make money by selling large and very costly pieces of equipment. Their regulatory framework does not necessarily require clinical trials to support approval of a new instrument. These companies will therefore need special incentives to collaborate with drug companies. Examples might include facilitation of the use and/or regulatory approval of their equipment or opportunities to sell more of their machines. Radiopharmaceuticals might provide a good starting point for such collaborations.

Coordinated Infrastructure. Dr. White asked for more information on the proposed centralized validation laboratory. Dr. Formenti replied that that the "bread and butter" of the proposed radiation therapy preclinical core is an animal irradiator that has imaging and stereotactic radiosurgery capacity and that is integrated into a matrix of other tools ranging from single-cell technologies to organoids. The productive operational use of preclinical units in the country is not synchronized, so efforts are needed to standardize preclinical cores. These cores are often not part of an NCI-designated cancer center, and the instruments are purchased with proceeds from clinical practice or with NCI funding for small instruments. The proposed preclinical core would accelerate the validation of findings.

Dr. Ali-Osman said that a major challenge for translational research in general is the need to test new interventions on a much broader scale instead of in individual laboratories. The recommendation for a centralized facility is timely, but the working group might consider recommending more than one such facility to ensure that the entire research community has access to this resource.

Dr. Formenti explained that historically, radiation oncologists delivered a radiation dose to a phantom and sent the phantom to a centralized physics laboratory to verify the findings. This accountability is part of the field's culture, and radiation biology could have the same standards.

Dr. Tuveson said that combining radiation oncology and biology is an obvious goal, given the new molecular approaches available in medical oncology. Medical oncology interventions have side effects, especially bone marrow suppression and vital organ damage. For this reason, these agents must be dosed intermittently. Targeted agents are used to avoid this problem, but they fall far short.

Training. Dr. Dicker pointed out that the radiopharmaceutical world is sometimes siloed. Some people have expertise in nuclear medicine, and others have expertise in radiation oncology. These specialties are not often leveraged for preclinical development of radiopharmaceuticals. Efforts to coordinate the contributions of these different areas of expertise would offer clinical benefit.

Dr. Tuveson noted that radiation oncologists complete a 1-year internship and then a 4-year residency, so they miss the breadth of training in human biology and internal medicine. Effort is needed to determine whether enough individuals are completing this training and whether medical or pediatric oncologists should also be trained in radiation oncology.

Dr. Dicker agreed that some radiation oncologists have a very narrow and clinical focus. However, to obtain certification, radiation oncologists must pass a written and oral clinical examination as well as medical physics and radiobiology examinations. The specialty is governed by the American Board of Radiology, which determines the content of training for radiation oncologists. Although some programs in other countries have tried to combine radiation and medical oncology training, they have found that keeping these programs separate is better.

Dr. Formenti explained that instead of cancer biology and how to use a tool to treat cancer in the context of all the other tools, the training for radiation oncologists focuses on developing them as members of interdisciplinary teams who deliver radiation doses and fractionation in accordance with national standards. Their training does not reinforce the concept of radiation as a drug or a tool, and their frame of mind is completely different from that of medical oncologists. Dr. Formenti proposed fellowships or K08 awards to compensate for any missing training and create the workforce of the future.

Dr. Mankoff agreed that fellowship training would benefit both the clinical and science sides of the field. Trainees typically gain experience with radiopharmaceuticals through nuclear medicine fellowships, but some providers who administer these agents have radiation oncology training. Dr. Mankoff proposed a joint fellowship for individuals with training in radiation or in nuclear medicine. Postdoctoral fellowships and K awards could bridge such specialties as fundamental molecular biology, pharmacology, radiobiology related to radiopharmaceuticals, and artificial intelligence. Modest investments in such training could have a huge impact.

Specific Guidance. Dr. Dang asked how the working group proposes to offer more specific guidance on its recommendations, which are broad. For example, he wondered whether the recommendations might cover research on the physics of flash radiotherapy (ultrafast delivery of very high doses) or on immunology and radiation. Dr. Dicker replied that one possibility is to develop a Specialized Program of Research Excellence (SPORE)–like infrastructure to support research, education, and training. Applications for funding through this mechanism could focus, for example, on flash radiation therapy or single-cell transcriptomics or proteomics to improve radiation use. Dr. Formenti said that one part of the plan would be to create a validation laboratory or network, and a second part would consist of existing NCI mechanisms that could support the recommended strategies.

Dr. Dang pointed out that the SPORE program supports modality-specific groups. NCI could form a radiation oncology SPORE that brings radiation biologists together with radiation oncologists.

TRSS Suggestions for the Working Group Report. Dr. Shannon, a pediatric oncologist, pointed out that the report did not address the late effects of radiotherapy administered to children or young adults who become cancer suvivors, and these effects are a significant and growing problem. He also recommended a deeper dive into models, including genetically engineered mouse models and organoids. A third suggestion was to expand the number of physician-scientists in radiation oncology by aligning incentives in radiation oncology departments.

Dr. Formenti agreed that the issues that Dr. Shannon raised are important, and she welcomed his suggestions. Other topics to address are innate immunity and other determinants of responses to radiation, such as the diversity of clinical trial participants. The working group report could not cover everything, but it is a useful starting point.

Dr. Tuveson suggested that the working group consider whether the current system is training enough radiation oncologists to care for a larger patient population if molecular approaches are shown to be effective. Dr. Dang wondered whether the working group could offer recommendations that would achieve this goal. Dr. Doroshow said that the head of NCI's Center for Cancer Training is interested in addressing the need for more physician-scientists. If the working group and CTAC believe that this goal is important, NCI will try to accomplish it.

Dr. Formenti said that post-residency training might be an option. In addition, because of their scarcity, new radiation oncologists earn similar salaries to new surgeons. Many of these individuals might therefore be reluctant to apply for a K08 award for research because they expect higher compensation. Dr. Doroshow pointed out that if surgeons apply for K08 awards, which they do, radiation oncologists are likely to do so as well.

Motion. A motion carried to accept the report of the Radiation Oncology Working Group, with modifications,after the group addresses the late health effects of radiotherapy in people treated for cancer as children or young adults and explores mechanisms to expand training for physician-scientists in radiation oncology.

IV. Discussion: Future Role of TRSS

Chi V. Dang, MD, PhD
Nancy E. Davidson, MD

Dr. Davidson said that TRSS previewed the reports from the *ad hoc* Glioblastoma and Radiation Oncology Working Groups and provided feedback that was integrated into the versions submitted to CTAC. NCI should now determine how TRSS can best be utilized going forward. Dr. Doroshow explained that CTAC formed TRSS as a public group to vet the reports from the two working groups, and the discussions of both reports were very valuable. In addition to reviewing reports, TRSS could provide value to NCI by identifying gaps in translational research that need more attention from NCI.

Dr. Davidson said that TRSS has primarily been reactive to the two topics it was assigned to address, and the subcommittee has not met to discuss research gaps. Dr. Doroshow said that such discussions would be an important function for the subcommittee and for NCI because TRSS brings together very senior people from a broad spectrum of expertise. NCI cannot pursue every research gap, and Congress identifies some research topics that the institute must address. However, a prioritized list from a group of senior experts like TRSS would help NCI choose other topics on which to focus.

Dr. Doroshow clarified that TRSS is a CTAC subcommittee. Its members represent all NCI advisory committees as well as the extramural research community. TRSS can report on its activities to all of these advisory committees.

Dr. Formenti said that the feedback on the Radiation Oncology Working Group's report from TRSS, including its non-radiation oncologists, was very valuable.

V. Wrap-Up & Next Steps

Chi V. Dang, MD, PhD
Nancy E. Davidson, MD

Dr. Dang proposed that he and Dr. Davidson consider how TRSS can best respond to the need that Dr. Doroshow identified. Dr. Davidson welcomed input on how TRSS could identify high-priority research gaps in translational research from members of TRSS and the Radiation Oncology Working Group.

Dr. Davidson listed two main action items from this meeting:

- The Radiation Oncology Working Group will present its report to CTAC on November 4.
- Drs. Dang and Davidson will meet with NCI leaders to decide on next steps for TRSS. TRSS members are welcome to join this effort.

VI. Adjourn

There being no further business, the TRSS meeting was adjourned at 2:34 p.m.

11/9/2020 Chi Dang
Date Chi V. Dang, MD, PhD, Co-Chair

11/6/2020 Nancy E Davidson
Date Nancy E. Davidson, MD, Co-Chair

11/17/2020
Date Peter Ujhazy, MD, PhD, Executive Secretary

Appendix

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee
Ad Hoc Translational Research Strategy Subcommittee

CO-CHAIR
Chi V. Dang, M.D., Ph.D.
Scientific Director
Ludwig Institute for Cancer Research, New York
Professor, The Wistar Institute
Philadelphia, Pennsylvania

CO-CHAIR

Nancy E. Davidson, M.D.
Senior Vice President, Director and Full Member
Clinical Research Division
Fred Hutchinson Cancer Research Center
President & Executive Director
Seattle Cancer Care Alliance
Head, Division of Medical Oncology
Department of Medicine
University of Washington
Seattle, Washington

MEMBERS

Francis Ali-Osman, D.Sc.
Margaret Harris and David Silverman
Distinguished Professor of
Neuro-Oncology Research
Professor of Surgery
Professor of Pathology
Department of Surgery and Pathology
Duke University Medical Center
Durham, North Carolina

Walter J. Curran, Jr., M.D., F.A.C.R.
Executive Director
Winship Cancer Institute of Emory University
Atlanta, Georgia

David A. Mankoff, M.D., Ph.D.
Gerd Muehllehner Professor of Radiology
Vice-Chair for Research
Department of Radiology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Lynn M. Matrisian, Ph.D., M.B.A.
Chief Research Officer
Pancreatic Cancer Action Network
Washington, D.C.

Roman Perez-Soler, M.D.
Chairman
Department of Oncology
Montefiore Medical Center
Deputy Director
Albert Einstein Cancer Center
Director
Division of Medical Oncology
Albert Einstein College of Medicine
Bronx, New York

Kevin M. Shannon, M.D.
American Cancer Society Research Professor
Auerback Distinguished Professor
of Molecular Oncology
Professor, Department of Pediatrics
School of Medicine
University of California, San Francisco
San Francisco, California

David A. Tuveson, M.D., Ph.D.
Roy J. Zuckerberg Professor
Director of the Cancer Center
Cold Spring Harbor Laboratory
Cold Spring Harbor, New York

Kevin P. White, Ph.D.
President, Tempus Labs
James and Karen Frank Family Professor
Department of Human Genetics
Professor, Department of Ecology and Evolution
Director, Institute for Genomics and
Systems Biology
Knapp Center for Biomedical Discovery
The University of Chicago
Chicago, Illinois

Max S. Wicha, M.D.
Deputy Director of the Taubman Institute
Distinguished Professor of Oncology
Professor, Internal Medicine
Division of Hematology and Oncology
University of Michigan
Ann Arbor, Michigan

Ex Officio Member

James H. Doroshow, M.D.
Deputy Director
Clinical and Translational Research
Director, Division of Cancer
Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Executive Secretary

Peter Ujhazy, M.D., Ph.D.
Deputy Associate Director
Translational Research Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland