

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
28th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH
ADVISORY COMMITTEE (CTAC) MEETING**

**Summary of Meeting
November 4, 2015**

**Building 31 C, Conference Room 10
National Institutes of Health
Bethesda, MD**

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MD
Summary of Meeting
November 4, 2015

The 28th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, November 4, 2015, at 9:00 a.m. in Conference Room 10, C Wing, Sixth Floor, Building 31, on the National Institutes of Health main campus in Bethesda, MD. The CTAC chair, Dr. James Abbruzzese, presided.¹ The meeting was adjourned at 12:33 p.m.

Chair

James L. Abbruzzese

CTAC Members

David F. Arons
Susan M. Blaney
Kevin J. Cullen
Walter J. Curran
Nancy E. Davidson
J. Philip Kuebler
Michael L. LeBlanc
Scott M. Lippman
David A. Mankoff
Mary S. McCabe (absent)
Edith P. Mitchell
Nikhil C. Munshi
Nancy Roach
George W. Sledge, Jr.
Chris H. Takimoto
Miguel A. Villalona-Calero
George J. Weiner (absent)
Louis M. Weiner

Presenters

James L. Abbruzzese, MD, Chief, Division of Medical Oncology; Associate Director for Clinical Research, Department of Medicine, Duke Cancer Institute, Duke University Medical Center, Duke University
James H. Doroshow, MD, Deputy Director for Clinical and Translational Research, NCI
M. K. Holohan, JD, Acting Director, Office of Government and Congressional Relations, NCI
Douglas R. Lowy, MD, Acting Director, NCI
Frank McCormick, PhD, RAS National Program Advisor, NCI

Ad Hoc Members

Gwendolyn A. Fyfe
David M. Gershenson
Patrick J. Loehrer, Sr.
Augusto C. Ochoa
Gloria M. Petersen (absent)

Ex Officio Members

James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, Centers for Medicare & Medicaid Services (absent)
Lee J. Helman, NCI (absent)
Michael J. Kelley, U.S. Department of Veterans Affairs
Richard Pazdur, U.S. Food and Drug Administration (absent)

Executive Secretary

Sheila A. Prindiville, NCI

¹A roster of CTAC members and their affiliations is included as an appendix.

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I. Call to Order and Opening Remarks

James L. Abbruzzese, MD

Dr. Abbruzzese called the 28th meeting of CTAC to order and welcomed participants to the meeting. He introduced the new CTAC members: Walter J. Curran, MD, PhD, Emory University School of Medicine; Gwendolyn A. Fyfe, MD, an independent consultant; David M. Gershenson, MD, University of Texas MD Anderson Cancer Center; Patrick J. Loehrer, Sr., MD, Indiana University School of Medicine; and Augusto Ochoa, MD, Louisiana State University Health Sciences Center.

Dr. Abbruzzese reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Prindiville within 10 days of the meeting. An announcement was made that National Institutes of Health Events Management was videocasting the meeting and that the videocast would be available for viewing following the meeting at <http://videocast.nih.gov>.

Motion. A motion to accept the minutes of the 27th CTAC meeting held on July 8, 2015, was approved unanimously.

II. NCI Acting Director's Update

Douglas R. Lowy, MD

NCI's Fiscal Year (FY) 2017 Professional Judgment Budget. Dr. Lowy began by noting that we are making progress against cancer, but that the progress is not sufficient. For example, cancer mortality rates in the United States have dropped over the past 20 years; however, worldwide mortality and incidence rates are expected to increase substantially by 2030, mostly in the developing world. NCI's current purchasing power is similar to what it was more than 15 years ago, restricting its ability to make progress at an optimal rate. NCI recently published the FY 2017 professional judgment budget, which is available on NCI's website. Priorities include basic research, clinical trials, precision oncology, prevention and early detection, immunotherapy, and cancer health disparities. In the FY 2017 budget, NCI recommended a 7 percent funding increase over the FY 2016 budget. Ten years of annual 7 percent increases would double the NCI budget by 2026 and optimize the institute's ability to make progress in cancer research.

The President's FY 2016 budget recommended a \$1 billion increase in the National Institutes of Health (NIH) budget, including a \$145 million increase for NCI. The House of Representatives passed a budget bill with the same amounts for NIH and NCI as the President's budget, and the Senate bill would increase the NIH budget by \$2 billion. Congress has now passed, and President Obama has signed, a bill establishing the overall budget parameters for FY 2016.

Precision Medicine Initiative (PMI) for Oncology. PMI for Oncology has four major components: developing and expanding clinical therapy trials in precision oncology; improving predictive oncology; creating a new array of laboratory models; and building a national cancer knowledge system that integrates cancer genomics, clinical, and laboratory model information.

NCI has already launched some precision oncology trials, including NCI Molecular Analysis for Therapy Choice (MATCH). NCI-MATCH is examining the molecular features of a variety of solid tumors and lymphoma in approximately 3,000 patients who have progressed on standard therapy. The

trial's protocol called for a pause when 500 patients were accrued, which occurred shortly before this meeting. The study's steering committee decided to use this pause to address some high-priority issues, including ensuring that underrepresented minorities are appropriately represented, that tumor specimens are analyzed within 2 weeks, and that at least 25 percent of participants have a rare cancer. NCI plans to develop a pediatric companion to NCI-MATCH to start in 2016.

The anticipated deliverables of the PMI for Oncology are to:

- Increase the number of drugs and indications for targeted treatment of cancer
- Expand understanding of drug resistance, how to overcome it, and the rules of targeted combination treatment, including immunotherapy
- Sharpen the ability to diagnose cancer at its earliest stages
- Improve predictive oncology (accurate prediction of the right treatment for the right patient)
- Establish a sustainable infrastructure for a progressively increasing cancer genomic database.

Current NCI Priorities. Dr. Lowy described several current NCI priorities, including the following:

- Investigator-initiated research, including the new Outstanding Investigator Award, which NCI recently awarded to 40 investigators
- Understanding and overcoming cancer health disparities in biology, lifestyle, and access
- Support for research infrastructure, which is critical for maximizing NCI's progress (e.g., by increasing the core grants for NCI-designated cancer centers)
- Precision oncology in cancer prevention and screening.

One example of the promise of precision oncology in cancer screening is ancillary testing for cervical cancer. Although human papillomavirus (HPV) testing can prevent more cervical cancers than cytology screening, HPV-based screening yields positive results for some women who do not have a short-term risk of invasive cancer. Researchers are studying the use of HPV methylation for risk stratification of women with positive HPV test results. Precision oncology can also be applied to cancer prevention by using molecular information for risk-benefit stratification of patients. The identification of who will benefit the most from chemoprevention with aspirin, which increases bleeding risk, for risk reduction of colorectal and other cancers is an example of this strategy.

Advice from CTAC. Dr. Lowy congratulated CTAC on their accomplishments, which include optimizing scientific opportunities by restructuring NCI's clinical trials infrastructure; integrating biomarkers, imaging, and quality-of-life studies into clinical trials in a timely manner; reducing the timeline for clinical trial activation to bring new therapies to patients more quickly; and enhancing the quality of National Clinical Trials Network studies through portfolio assessment and strategic recommendations. CTAC also recommended incentives for clinical trial collaboration between Specialized Program of Research Excellence, Cancer Center, and National Clinical Trials Network investigators by harmonizing program guidelines. Important ongoing activities include overseeing NCI's response to the Recalcitrant Cancer Research Act of 2012 for pancreatic ductal adenocarcinoma and small-cell lung cancer, periodically assessing NCI's clinical trials portfolio and making recommendations for improving it, and providing a vision and recommending actions to guide the NCI clinical trials enterprise over the next decade.

Questions and Discussion

Dr. Villalona-Calero asked whether NCI plans activities to prevent and treat cancer in other countries, such as efforts to reduce the impact of cervical cancer in Latin America. Dr. Lowy replied that NCI does collaborate with international partners. For example, NCI has interacted with the Pan American Health Organization to implement high-quality cervical cancer screening and HPV vaccination in Latin American countries. NCI also provides technical assistance in several countries that often focuses on cervical cancer screening, which is difficult to implement in low-resource settings. A presentation at the joint National Cancer Advisory Board/Board of Scientific Advisors meeting will describe a planned trial to determine whether a single HPV vaccine dose can provide long-term protection. If the results are positive, a higher proportion of the world's population will be able to be vaccinated.

Ms. Roach asked who is analyzing the NCI-MATCH data and what will happen during the current 2-month pause. Dr. Doroshov replied that the NCI-MATCH steering committee, which oversees the trial, will analyze the data. During the pause, NCI will conduct the analysis and request approval for the use of additional drugs in the study. The NCI-supported central institutional review board has agreed to meet more frequently to review the additional drugs and a request to allow patients who have already been screened to be treated with the additional drugs. After the board completes its review, NCI will need to respond to the board's comments and receive final approval for the initial analysis and the desired changes. NCI hopes to be able to end the pause in December 2015. Ms. Roach suggested that NCI shorten the pause if possible.

Dr. Louis M. Weiner remarked on the high degree of bipartisan support for increasing the NIH and NCI budgets and asked about the rationale for requesting annual 7 percent funding increases. Dr. Lowy explained that this number reflects the amount that NIH believes it might realistically obtain from Congress. A sustained, multiyear increase in funding would allow NIH to make plans in a way that is not possible now. In addition, a commitment from Congress in the form of a multiyear increase would show the importance of this area of research and encourage smart new investigators to consider careers in the field.

Dr. Lippman asked Dr. Lowy to comment on genomic analyses of premalignant lesions. Dr. Lowy reported that NCI supports some research in this area and plans to support more in the future. Technology advances have made genomic analyses on small, paraffin-embedded tissue samples feasible.

Dr. Davidson inquired about priorities with respect to the National Clinical Trials Network groups and the Early Detection Research Network collaborative groups. Dr. Lowy said that all of these groups make valuable contributions, and NCI is continually evaluating its investments to determine ways to maximize benefits.

Dr. Ochoa commented on the difficulty of enrolling minority populations in clinical trials in general and in genomic trials in particular. Dr. Lowy said that over the last 4 or 5 years, about 20 percent of participants in NCI-sponsored trials have come from underrepresented minority groups.

Dr. Mankoff recommended that, in addition to developing predictive markers, PMI for Oncology should develop pharmacodynamic markers. Dr. Lowy agreed.

III. Recognition Ceremony

James H. Doroshow, MD

2015 Cancer Clinical Investigator Team Leadership Awardees. The Cancer Clinical Investigator Team Leadership Awards recognize outstanding midlevel clinical investigators at NCI-designated cancer centers whose participation in NCI-funded collaborative clinical trials promotes a culture of clinical research. The awards also encourage the retention of clinical investigators in academic research careers. The clinical oncologists who receive these awards, which provide \$60,000 per year for 2 years, must devote at least 15 percent of their effort to the activities associated with the award. In addition to physicians, the award is open to oncology nurses, psychologists, and other individuals with doctoral degrees. The 2015 awardees are:

- Leora Horn, MD, MSc, Vanderbilt-Ingram Cancer Center
- David Hyman, MD, Memorial Sloan Kettering Cancer Center
- Matthew Katz, MD, MD Anderson Cancer Center, University of Texas
- Edward Kim, MD, PhD, UC Davis Comprehensive Cancer Center
- Frederick Lansigan, MD, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center
- Charles Leath, III, MD, MSPH, University of Alabama at Birmingham
- Elizabeth Plimack, MD, MS, Fox Chase Cancer Center
- Andrew Poklepovic, MD, Massey Cancer Center, Virginia Commonwealth University
- Yvonne Saenger, MD, Herbert Irvin Comprehensive Cancer Center, Columbia University
- Emma Scott, MD, OHSU Knight Cancer Institute, Oregon Health & Science University
- Liza Villaruz, MD, University of Pittsburgh Cancer Institute

Recognition of Retiring CTAC Members. Dr. Doroshow and Dr. Lowy thanked the retiring CTAC members—Dr. Kuebler, Dr. Lippman, Ms. Roach, and Dr. Abbruzzese—for their service.

Questions and Discussion

Dr. Abbruzzese asked about NCI's plans to review the impact of the Cancer Clinical Investigator Team Leadership Awards on career sustainability. Dr. Doroshow replied that NCI will assess awardees' careers and accomplishments in the near future. Dr. Curran suggested that NCI assess the distribution of specialists (e.g., pathologists, gynecologic oncologists, surgeons, radiation oncologists) among awardees. Dr. Doroshow agreed and offered to give a presentation on the results of this review at a future CTAC meeting.

Dr. Davidson wondered whether awardees have opportunities to interact with one another. Dr. Doroshow said that in the past, NCI supported a workshop for attendees in conjunction with a CTAC meeting, but federal restrictions on travel make doing this now more challenging. Dr. Villalona-Calero proposed bringing the awardees together at an American Society of Clinical Oncology meeting.

In response to a question from Dr. Munshi, Dr. Doroshow explained that the awardees primarily conduct clinical and translational research as opposed to preclinical, laboratory-based research.

IV. Legislative Update

M. K. Holohan, JD

On June 24, 2015, the House Labor, Health and Human Services, Education, and Related Agencies Subcommittee approved a fiscal year (FY) 2016 bill that provides \$31.2 billion (including \$5.081 billion for NCI) to the National Institutes of Health (NIH), a \$1.1 billion increase from FY 2015. The following day, the corresponding Senate subcommittee approved a bill that give NIH \$32 billion (including \$5.204 billion to NCI), a \$2 billion increase from FY 2015. Both the House and Senate bills provide full funding for the Precision Medicine Initiative, but neither bill has made progress.

The House of Representatives passed the Bipartisan Budget Act of 2015 on October 28, 2015; the Senate passed the bill on October 30; and President Obama signed the bill on November 2. This bill suspends the U.S. debt limit until March 15, 2017; partially rolls back the sequester; and increases discretionary spending caps to \$50 billion in FY 2016 and to \$30 billion in FY 2017, to be split equally between defense and nondefense spending. This budget deal does not make an appropriation for FY 2016; therefore, the federal government is operating under a short-term continuing resolution that expires on December 11, 2015.

Questions and Discussion

Dr. Curran asked about the timeline for determining the FY 2016 NIH budget. Ms. Holohan explained that Congress could pass an omnibus spending bill that includes a budget for NIH and other federal agencies before the current continuing resolution expires. If not, Congress might pass another short-term continuing resolution or the government might shut down. Another possibility is that Congress will pass an omnibus bill funding some government agencies and a continuing resolution for the remaining agencies (known as a “cromnibus” bill). Agencies that continue to operate under a continuing resolution in this scenario would not be permitted to start new programs, and their funding levels would be the same as or similar to their FY 2015 levels.

Dr. Mitchell reported that the Congressional Black Caucus had recently discussed cancer health disparities and asked about NCI efforts to address this issue with that caucus and others that might be interested, such as the Congressional Hispanic Caucus. Ms. Holohan reported that NCI reaches out to various groups in Congress and to individual members based on their interests. NCI plans to do more outreach to Congress focused on health disparities after the upcoming Towards Cancer Health Equity: Biology, Lifestyle, and Access National Cancer Institute Workshop on November 11–13, 2015, in Atlanta, Georgia.

V. Working Group Report: Progress in Pancreatic Adenocarcinoma (PDAC) Research

James L. Abbruzzese, MD

The [Recalcitrant Cancer Research Act \(RCRA\) of 2012](#) (Public Law 112-239, §1083) called on NCI to identify two or more recalcitrant cancers that have a 5-year relative survival rate of less than 20 percent and cause more than 30,000 deaths per year in the United States and to develop scientific frameworks that will assist in making progress against these cancers. PDAC is a recalcitrant cancer according to the definition of recalcitrant cancers, and its 5-year relative survival rate is less than 5 percent, translating into the loss of almost 40,000 lives per year. A [report](#) focusing on NCI’s scientific framework for PDAC was submitted to Congress in 2014 and posted on NCI’s website at

<http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf>. Approximately a year later, NCI convened the Progress in PDAC Research Working Group to advise NCI on the research progress of the four initiatives outlined in the scientific framework. Working group members represent the broad clinical and translational research and advocacy communities.

The RCRA requires the National Institutes of Health (NIH) to submit reports every 2 years to Congress on research grants, progress made in improving outcomes for patients, and activities related to each cancer. The RCRA also mandates that NIH review and update the scientific frameworks for each cancer within 5 years after development (in 2019) and then submit a report to Congress on the frameworks' effectiveness no later than 6 years after their initial development (in 2020). Both the Progress in PDAC Research Working Group and an internal NCI Action Planning Group are tracking NCI's progress related to PDAC research.

Dr. Abbruzzese provided updates on progress in each of the four initiatives from the scientific framework over the past year.

Initiative 1—Biological and Clinical Relationship Between PDAC and Recent-Onset Diabetes Mellitus (DM). Longstanding type 2 DM is a risk factor for pancreatic cancer. Pancreatogenic (also known as type 3c) DM increases the risk of pancreatic cancer four to five times, and being able to identify these patients prospectively might be useful for early identification of PDAC. NCI and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have funded 10 clinical centers and a coordination and data management center as part of the new Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer Clinical Centers (CSCPDPCC). In July 2015, NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) sponsored a workshop, Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease.

The implementation of this initiative is on target, but it is too early to assess scientific progress in this area. Recommendations include following the progress of the CSCPDPCC awardees, publishing the proceedings of the NIDDK/NIBIB workshop, organizing a joint NIDDK/NCI workshop on using animal models to study the relationship between PDAC and DM and to inform a funding opportunity announcement on identified scientific gaps, and engaging the DM scientific community in collaborations (including a symposium on pancreatogenic DM at the 2016 American Diabetes Association scientific session).

Initiative 2—New Molecular and Imaging Biomarkers for Early Detection. NCI issued a funding opportunity announcement ([PAR-15-289](#)) on June 30, 2015, for the Pancreatic Cancer Detection Consortium (U01). The July 2015 NIDDK/NIBIB workshop was also relevant to this initiative.

The implementation of this initiative is on target, but it is too early to assess scientific progress in this area. Recommendations include releasing and funding NCI program announcements, facilitating connections between NIH programs to support studies in high-risk populations, sharing biomarker validation information from NCI's Early Detection Research Network, improving coordination of biomarker validation, incorporating imaging research information that is relevant to pancreatic cancer from other NIH institutes and centers, and publishing the proceedings of the NIDDK/NIBIB workshop.

Initiative 3—New Immunotherapy Approaches Based on a Deeper Understanding of How PDAC Interacts with Its Potentially Immunosuppressive Microenvironment. The Cancer Immunotherapy Trials Network has prioritized PDAC immunotherapy studies to address gaps not filled by industry. In addition, NCI has increased its funding of pancreatic cancer immunotherapy research through multiple mechanisms over the past few years. Finally, NCI is planning an immunotherapy meeting in early 2016 that will include a breakout session on PDAC research.

Progress in this area has occurred through isolated efforts, and the initiative would benefit from more coordination within NCI and greater access to new immunotherapy agents. Recommendations included establishing an NCI “champion” of immunotherapy to coordinate efforts within NCI, collecting additional information about immunotherapy reagents from other NCI programs, expanding the initiative to integrate research on the relationship of tumor/stroma to immunotherapy, increasing the availability of immunotherapy reagents for PDAC research, supporting development of immunocompetent preclinical animal models to test combination therapies, developing scientific rationales for combinations of immune modifiers and other drugs in preclinical and clinical studies, monitoring the Cancer Immunotherapy Trials Network’s progress in designing and conducting therapy trials with promising immunotherapy agents, and monitoring PDAC therapy trials with promising immunotherapy agents at the Center for Cancer Research.

Initiative 4—Development of New Treatment Strategies That Interfere with RAS Oncogene-Dependent Signaling Pathways. The Progress in PDAC Research Working Group met with the RAS Initiative team to discuss progress of the RAS Initiative and potential PDAC-related opportunities.

The implementation plan for initiative 4 has been launched, and a great deal of progress has been made. However, the working group needs additional information to assess this initiative’s scientific progress. A recommendation is to identify other ongoing NCI and non-NCI RAS therapeutics PDAC research efforts and map all efforts to a drug-development pathway or continuum.

Questions and Discussion

Dr. Gershenson asked whether any diabetes researchers are involved in the CSCPDPC. Dr. Abbruzzese replied that the awardees have a variety of specialties, and some are gastroenterologists who study chronic pancreatitis.

Dr. Munshi asked about the expansion of the RAS Initiative and the scientific frameworks for PDAC and small-cell lung cancer to other cancers. Dr. Abbruzzese said that the work on RAS and immunotherapy has implications for many cancers. If the scientific framework strategy is successful in pancreatic cancer and small-cell lung cancer, it would be reasonable to expand it to other recalcitrant cancers.

Dr. Sledge inquired about plans to review the four initiatives and decide whether to continue or end them. Dr. Abbruzzese said that the Progress in PDAC Research Working Group reviews each of the initiatives with their respective subgroups on a regular basis and considers whether to remove, modify, or add any initiatives. Dr. Prindiville added that the RCRA calls for a report from NIH to Congress after 5 years on the effectiveness of this type of approach.

Dr. Lippman wondered whether any of the initiatives includes research on the biology of precursors, including the genomics of premalignant lesions. He also suggested that, given the role of

mTOR signaling in pancreatic cancer, for example, one approach is to conduct epidemiologic studies of metformin followed by an early-phase or N-of-1 trial to explore metformin's effects on the PI3K/mTOR pathway. Dr. Abbruzzese reported that epidemiologic data show that patients with DM treated with metformin have a substantially lower risk of pancreatic cancer, whereas insulin increases the risk. However, trials of metformin in combination with chemotherapy in advanced pancreatic cancer have had negative results. Studies responsive to initiative 2 could study this relationship and also explore ways to image precursor lesions of the pancreas and associated inflammation.

Dr. Louis M. Weiner suggested that NCI create an infrastructure for accumulating data on interactions between pancreatic cancer cells and the microenvironment and make these data accessible to the research community to make progress in initiative 3. A potential research question is, how do pancreatic cancers evade, disrupt, or deflect immune recognition and destruction as they develop? Answering this question could lead to immunotherapy and other treatment strategies. Dr. Abbruzzese said that discussions of initiative 3 have focused more on immunotherapy than on stromal-epithelial signaling pathways, but he hopes that initiative 3 or a new initiative will address this issue.

Dr. Villalona-Calero asked about the effects of gastric bypass surgery on pancreatic cancer in patients with pancreatogenic diabetes. Dr. Abbruzzese was not aware of data on this topic. However, altering glycemic control by bypass surgery in this setting might not change the incidence of pancreatic cancer because cancer cells are already present and are producing a substance that creates the diabetic state.

Dr. Curran suggested that NCI integrate its new PDAC-related initiatives into existing cross-cutting programs, such as the Early Detection Research Network. Dr. Abbruzzese said that the working group does not want to create a program that is specific to pancreatic cancer and that it must leverage existing programs at NCI and other NIH institutes and centers.

Motion. A motion carried to accept the report of the Progress in PDAC Research Working Group.

VI. The RAS Initiative

Frank McCormick, PhD

RAS mutations are common in many cancers. For example, *KRAS* mutations are the primary driving mutations in almost all pancreatic cancers and in one third of lung cancer cases. About 45 percent of patients with colorectal cancer also have *KRAS* mutations, although *KRAS* is not the primary driver mutation in these cancers. But in spite of the importance of *RAS* in cancer development, the research community has made little progress in targeting *RAS*-driven cancers. Specifically, no drugs are available that attack the *RAS* protein directly, and *RAS*-driven cancers are refractory to most therapies, especially targeted therapies. The practical challenge in targeting the *RAS* protein is that it lacks most of the properties of a suitable drug target, such as having “pockets” to which a small molecule could bind.

Dr. McCormick described *RAS* as a binary switch that turns on downstream cell signaling pathways. In cancer cells with a mutant *RAS* gene, the switch gets locked in the “on” position. NCI formed the *RAS* Initiative in 2013 to explore innovative approaches to attacking the proteins encoded by mutant forms of *RAS* genes and create effective new therapies for *RAS*-related cancers.

This initiative uses a hub and spoke model. The Frederick National Laboratory for Cancer Research is the hub, and the spokes are intramural laboratories, extramural NCI-supported laboratories, biotechnology companies, pharmaceutical companies, and advocacy organizations (such as the Pancreatic Cancer Action Network). The initiative's activities include:

- Determining the structures of mutant RAS proteins that are major drivers of human cancers
- Using new technology to develop new assays for small molecules that can inhibit RAS signaling; small-molecule screening by biotechnology and pharmaceutical companies
- Validating KRAS in different cell lines to identify the kinds of cancer that are most likely to respond to a RAS inhibitor once such a drug is developed
- Understanding how molecules in RAS signaling pathways interact with each other
- Learning about the biological, biochemical, and biophysical properties of RAS proteins in the cell membrane
- Providing high-quality, verified reagents to researchers

Dr. McCormick's slides can be found here: <http://deainfo.nci.nih.gov/advisory/ctac/1115/9-McCormick.pdf>.

Questions and Discussion

Dr. Abbruzzese asked whether any evidence shows that RAS protein levels vary between cell lines and, if so, whether this variation might affect cancer biology. Dr. McCormick replied that studies have shown that during cancer progression, expression of the mutant protein often increases, especially in pancreatic cancer. In addition, the wild-type allele is often lost, the mutant becomes amplified, and its expression increases. These studies also show that tumor cells have high levels of RAS, but the effect of these high levels on clinical outcomes are not known.

Dr. Mitchell inquired about animal models to identify wild-type or mutant RAS in cell membranes. Dr. McCormick said that technology is not sufficiently advanced to visualize RAS in live tumors, but some fluorescent tag proteins might be used for this purpose.

Dr. Louis M. Weiner asked about research to understand how RAS mutations alter the immune landscape and efforts to exploit this knowledge. Dr. McCormick explained that KRAS produces cytokines that are locally immunosuppressive, but the Initiative has not yet exploited this understanding. One potential approach is to describe all of the cytokines that KRAS makes in pancreatic cell lines and then determine how to use this knowledge to study immunotherapies.

Dr. Mankoff asked whether the RAS Initiative's partnerships to develop and use RAS assays have informed efforts to develop drugs that can inhibit RAS downstream signaling. Dr. McCormick replied that every cell line has its own secondary mutations, so the studies have not yet identified a pattern that can be used to identify a suitable drug target. Instead, Dr. McCormick and his colleagues will focus on cytokine readouts at the end of the pathway.

Dr. Abbruzzese wondered whether KRAS signaling is still necessary during late stages of pancreatic cancer. Dr. McCormick replied that all of the cell lines studied appear to remain dependent on KRAS. He added that in August 2014, NCI issued a program announcement, [New Approaches to Synthetic Lethality for Mutant KRas-Dependent Cancers \(U01\)](#), for the identification of targets whose inhibition would induce synthetic lethality in cancers that depend on the expression of mutant KRAS

alleles. NCI has funded five grants and is organizing these sites into a consortium that will meet in December 2015.

VII. Scientific Steering Committees' Strategic Priorities

James H. Doroshov, MD

In July 2014, the National Clinical Trials Network (NCTN) Working Group recommended the establishment of strategic priorities for trials under the purview of each scientific steering committee (SSC) to ensure that NCI's investment is sufficiently focused to provide optimal benefit. Most concepts would be expected to align with these priorities. SSCs could still approve concepts outside these priority areas, although this might require additional justification. Over the past year, each of the SSCs developed priorities for their respective area of responsibility. Participants in this process included SSC members, NCI Community Oncology Research Program research base leaders, NCTN disease committee leaders, and NCI clinical trials leaders. When NCI reviewed the lists of priorities for each SSC, some of them were true strategic clinical trial priorities, which identify areas of unmet clinical need, important unanswered clinical questions, new approaches to disease treatment or symptom management, and they encompass a wide range of potential trial concepts. However, some priorities were broad goals, trial design priorities, or translational research priorities rather than strategic clinical trial priorities.

Dr. Doroshov asked CTAC to provide an objective assessment of the SSC priority-setting process and to make recommendations for refining the process for future priority-setting rounds.

Questions and Discussion

Role of CTAC. Dr. Abbruzzese said that providing recommendations on the priority-development process is a critical role for CTAC. He added that setting priorities is difficult because it requires a different way of thinking than daily practice and clinical research.

Recommendations for Strengthening the Priority-Development Process. Dr. Gershenson said that the groups that developed the priorities have made an excellent start and that the process has been very open. He suggested that NCI provide the SSCs with examples from the first round of priorities that meet the definition and priorities that need additional refinement. Dr. Sledge agreed with strengthening the priority-development process through external oversight. Dr. Gershenson also suggested that the SSCs enhance their communications with each other to promote learning from each SSC's best practices. Dr. Loehrer suggested asking the NCI-supported cancer centers to be part of the priority-development process. Dr. Weiner recommended that NCI establish a more uniform priority-setting process to make sure that all participants understand the purpose of this process and the level of rigor required, possibly by providing facilitators to support this process. Dr. Blaney pointed out, however, that the SSCs are heterogeneous, and a single "cookie-cutter" approach might not be appropriate for all of them. Dr. Fyfe warned against establishing priorities that would lead the SSCs to compete directly with industry.

Dr. Kuebler commented that the large numbers of priorities identified for some SSCs might be difficult to manage, and Dr. Fyfe suggested limiting the number of priorities developed by each SSC. Dr. Gershenson pointed out, however, that each SSC operates very differently and must deal with different numbers of diseases, so the different SSCs might need different numbers of priorities.

Purpose of the Priorities. Dr. Louis M. Weiner commented on the importance of ensuring that the priorities are used and do not simply sit in binders on shelves. He asked how NCI will use the

priorities to guide resource allocations, approvals of concepts, and assessments of SSC efforts to achieve their goals.

Jeffrey S. Abrams, MD, Associate Director of the Cancer Therapy Evaluation Program, explained that the process that NCI established calls for the SSCs to conduct self-assessments of their clinical trials portfolios based on their priorities in a consistent way, and the Coordinating Center for Clinical Trials staff are developing a template for these self-assessments. CTAC's Clinical Trials Strategic Assessment Working Group will then review the self-assessment results and report on these findings to the full CTAC, and the SSCs will use this feedback to refine their priorities. Dr. Abrams added that the SSCs did a good job during this first round of priority setting, especially given that the groups that established the priorities are made up of volunteers, cover a variety of modalities, and must review many studies in addition to developing priorities. Dr. Abrams predicted that the process will be iterative and will improve over time.

Dr. Takimoto proposed making clear the purpose of the strategic priorities and the reasons why these priorities need to meet NCI's pre-established criteria. Dr. Mitchell agreed, emphasizing the importance of explaining how the priorities contribute to NCI's overall strategic plan.

Shared Priorities for All SSCs. Dr. Curran suggested expanding the priority-development process to an NCTN strategic-planning process. Dr. Munshi emphasized the need to identify overall goals for the NCTN, which the new Clinical Trials Strategic Assessment Working Group could help establish. Dr. Mankoff proposed identifying some trans-NCTN strategic priorities for correlative sciences to ensure a uniform approach to this type of research. Dr. Loehrer commented that the tumor microenvironment is important to many of the SSCs.

Expanded Role for the Clinical Trials Strategic Assessment Working Group. Dr. Abbruzzese commented that CTAC members seemed to agree to broadening the charge for the new Clinical Trials Strategic Assessment Working Group to include providing feedback on the strategic priority-development process for the SSCs. However, he wondered how the working group could best provide feedback to the SSCs. Dr. Doroshov replied that the NCTN Working Group was able to communicate CTAC's recommendations to the groups and disease committees in a timely way, and he recommended a similar process.

Motion. A motion carried unanimously to endorse the addition of "assessment of the strategic priority-development process" to the charge of the Clinical Trials Strategic Assessment Working Group.

VIII. Adjournment

James L. Abbruzzese, MD

There being no further business, the 28th meeting of CTAC was adjourned at 12:33 p.m. on Wednesday, November 4, 2015.

Appendix

National Institutes of Health National Cancer Institute Clinical Trials and Translational Research Advisory Committee

CHAIR

James L. Abbruzzese, MD, FACP **2015**
Chief, Division of Medical Oncology
Associate Director for Clinical Research
Department of Medicine
Duke Cancer Institute
Duke University Medical Center
Durham, NC

MEMBERS

David F. Arons, JD **2016**
(National Council of Research Advocates)
Director of Public Policy
National Brain Tumor Society
Watertown, MA

Nancy E. Davidson, MD **2018**
Director
University of Pittsburgh Cancer Institute
University of Pittsburgh
Pittsburgh, PA

Susan M. Blaney, MD **2019**
Vice President for Clinical and Translational
Research
Vice Chair for Research
Department of Pediatrics
Baylor College of Medicine
Texas Children's Hospital
Houston, TX

Gwendolyn A. Fyfe, MD* **2020**
Independent Contractor
San Francisco, CA

David M. Gershenson, MD* **2020**
Professor of Gynecology
Department of Gynecologic Oncology and
Reproductive Medicine
Division of Surgery
The University of Texas MD Anderson Cancer
Center
Houston, TX

Kevin J. Cullen, MD **2016**
(National Cancer Advisory Board)
Director
Marlene and Stewart Greenebaum Cancer Center
University of Maryland
Baltimore, MD

J. Philip Kuebler, MD, PhD **2015**
Principal Investigator
Columbus Community Clinical Oncology
Program
Columbus Oncology and Hematology Associates,
Inc.
Columbus, OH

Walter J. Curran, MD, PhD **2019**
Professor and Chairman
Department of Radiation Oncology
Emory University School of Medicine
Atlanta, GA

Michael L. LeBlanc, PhD Member Fred Hutchinson Cancer Research Center Research Professor Department of Biostatistics University of Washington Seattle, WA	2019	Nikhil C. Munshi, MD Associate Director Jerome Lipper Multiple Myeloma Center Dana-Farber Cancer Institute Associate Professor of Medicine Harvard Medical School Boston, MA	2016
Scott M. Lippman, MD Director, Moores Cancer Center Senior Associate Dean, Associate Vice Chancellor for Cancer Research and Care, and Chugai Pharmaceutical Chair in Cancer Research University of California, San Diego La Jolla, CA	2015	Augusto C. Ochoa, MD* Director Stanley S. Scott Cancer Center Professor Department of Pediatrics Louisiana State University Health Sciences Center New Orleans, LA	2018
Patrick J. Loehrer, Sr., MD* Director Melvin and Bren Simon Cancer Center Associate Dean for Cancer Research Indiana University School of Medicine Indianapolis, IN	2020	Gloria M. Petersen, PhD* Professor of Epidemiology Department of Education Administration Mayo Clinic College of Medicine Rochester, MN	2019
David A. Mankoff, MD, PhD Gerd Muehlelehner Professor of Radiology Division Chief, Nuclear Medicine and Clinical Molecular Imaging Perelman School of Medicine University of Pennsylvania Philadelphia, PA	2016	Nancy Roach Consumer Advocate Fight Colorectal Cancer Coalition Alexandria, VA	2015
Mary S. McCabe, RN Director Cancer Survivorship Initiative Memorial Sloan Kettering Cancer Center New York, NY	2016	George W. Sledge, Jr., MD Chief Division of Medicine–Oncology Stanford University School of Medicine Palo Alto, CA	2016
Edith P. Mitchell, MD Clinical Professor of Medicine and Medical Oncology Program Leader, Gastrointestinal Oncology Sidney Kimmel Cancer Center Thomas Jefferson University Philadelphia, PA	2016	Chris H. Takimoto, MD, PhD Vice President Translational Medicine and Early Development Janssen Research & Development, LLC Radnor, PA	2016
		Miguel A. Villalona-Calero, MD Deputy Director and Chief Scientific Officer Miami Cancer Institute Baptist Health South Florida Coral Gables, FL	2016

