DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
9th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting

November 4, 2009

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) convened for its 9th meeting on Wednesday, November 4, 2009, in Conference Room 10, C-Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD from 8:00 a.m. – 4:15 p.m. Dr. John Niederhuber, Director, NCI, presided during the meeting.

CTAC Members
John Niederhuber, Chair
James L. Abbruzzese
Peter C. Adamson
Deborah W. Bruner
Curt I. Civin
Kenneth H. Cowan
Everett Dodson
Olivera Finn (absent)
Stephen S. Grubbs
Sandra J. Horning (absent)
K. Gabriel Leung
Scott M. Lippman (absent)
Nancy P. Mendenhall (absent)
David R. Parkinson
Edith A. Perez
Nancy Roach
Carolyn D. Runowicz
Daniel J. Sargent
Richard L. Schilsky
Mitchell Schnall
Joel E. Tepper
James L. Wade, III

***Ex Officio* Members**
Anna Barker, NCI (absent)
James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, CMS
Lee Helman, NCI (absent)
Michael J. Kelley, VA (absent)
Richard Pazdur, FDA
John F. Potter, DOD
Alan Rabson, NCI (via conference call)

Executive Secretary
Sheila A. Prindiville, NCI

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WEDNESDAY, NOVEMBER 4, 2009

I. CALL TO ORDER AND OPENING REMARKS—DR. JOHN NIEDERHUBER

Dr. John E. Niederhuber, Director, National Cancer Institute (NCI), called to order the 9th Clinical Trials and Translational Research Advisory Committee (CTAC) meeting. He welcomed the Committee and *ex officio* members and formally introduced the four new CTAC members: Drs. Olivera Finn, Scott Lippman, Rosemarie Hakim, and Mitchell Schnall. Dr. Niederhuber then reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. Members of the public were welcomed and invited to submit comments related to items discussed during the meeting in writing to Dr. Sheila A. Prindiville, Director, NCI Coordinating Center for Clinical Trials (CCCT), within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Future meeting dates were confirmed through November 2011.

Motion. A motion was made to approve the minutes of the July 15, 2009 CTAC meeting. The motion was seconded, and the minutes were approved unanimously.

II. DIRECTOR'S UPDATE—DR. JOHN NIEDERHUBER

For fiscal year (FY) 2009, the NCI budget increased for the first time since 2004. The increase over FY2008 was almost $140 million, or 2.9 percent. NCI staff did an excellent job on closing out the almost $5 billion FY2009 appropriation with a balance of $4,432. Their workload was increased by the necessity of keeping track of American Recovery and Reinvestment Act (ARRA) funds separately from the FY2009 appropriation. To mitigate the temporary nature of ARRA funding, NCI is also engaged in careful planning to illustrate the need for long-term investment in cancer research.

A total of $10.4 billion in ARRA funds was allotted to the National Institutes of Health (NIH) to increase employment and protect jobs in the research community and to stimulate new science. Of the $7.4 billion allotted to Institutes and Centers, NCI received $1.26 billion. The National Center for Research Resources (NCRR) is managing the expenditure of $1.3 billion for extramural construction and shared instrumentation, and NIH received an additional $500 million for construction projects (including acceleration of the renovation of Building 10). NCI is working closely with the Agency for Healthcare Research and Quality (AHRQ) in applying ARRA funds set aside to support comparative effectiveness research.

Concerned about the out-years of grants that would receive ARRA support for only 2 years, NCI staff used budget modeling to create a plan in which appropriated FY2009 funds were used to support grant applications through the 16th percentile of scoring. Applications in the 16th through 18th percentiles were supported with 2 years of ARRA funds to be followed by appropriated funds (based on anticipated budget increases), and a mix of 2-year and 4-year grants were available for applicants in the 18th through 25th percentiles, again using 2 years of ARRA funding. NCI was able to fund 369 additional grants by using ARRA funds to extend paylines.

Almost 60 percent of NCI's ARRA funds were used to support grants, and most of the remaining dollars went to research and development contracts for the academic community, including activities related to The Cancer Genome Atlas (TCGA) and caBIG. More than 106 million ARRA dollars were spent by the Office of the NIH Director to fund 140 cancer-related grants, including comparative effectiveness grants, Challenge grants, Grand Opportunities (GO) grants, and grants for summer students working in Cancer Center laboratories. NCI's success rates in obtaining Challenge grants and GO grants

were approximately 20 percent and 17 percent, respectively. Institutions that are home to NCI-designated Cancer Centers received 29 GO grants. NCI used appropriated dollars to support 41 additional high-priority Challenge grants and 33 additional GO grants. NCI is also using ARRA funds for training and faculty support and as supplements for clinical and translational research.

NCI used ARRA funds to create the Accelerated Clinical Trials of Novel Oncologic Pathways (ACTNOW) program designed to advance targeted, personalized cancer treatment in an accelerated timeframe, so that the results benefit patients and the research community as quickly as possible. This effort has resulted in 37 early-phase trials of new treatment regimens, including awards to 11 NCI-designated Cancer Centers and 6 Cooperative Groups.

Because most of NCI's ARRA funds are obligated for the second years of the grants that have been awarded, no major NCI ARRA initiatives are planned for FY2010. There will be several opportunities for grantees to compete for FY2010 NIH-funded ARRA opportunities. Investigators should monitor the NIH Web site for information on those opportunities.

NIH has selected TCGA as one of seven Signature Projects. ARRA funds will enable this project to expand its studies to 25 tumors. ARRA funds will also be used to facilitate the ongoing implementation of caHUB, a centralized public resource designed to ensure the adequate and continuous supply of high-quality human biospecimens and associated data for cancer research. Biospecimens are a critical part of the NCI therapeutics platform that encourages investigators to identify molecular targets and functions, develop new agents, perform toxicology and preclinical testing, conduct market-driven clinical trials, and deliver targeted therapies to patients. Challenges include working with the Food and Drug Administration (FDA) to find ways to approve testing of multiple agents at the same time and creating pilot patient and tumor characterization centers to collect and store data and translate them for the use of practicing oncologists.

Questions and Discussion

Dr. Joel Tepper, Hector MacLean Distinguished Professor of Cancer Research at the University of North Carolina's Lineberger Comprehensive Cancer Center, asked for a more detailed discussion of the effect of 2-year ARRA funding on the R01 pool in subsequent years. Dr. Niederhuber explained that NCI's modeling was an attempt to predict how much funding for out-years of grants could be provided if the budget remains flat. If additional funds are not available, the success rate could drop from 25 percent to 20 percent or lower. Dr. Niederhuber noted that many investigators who unsuccessfully competed for special ARRA-support grants are likely to resubmit their applications as R01 proposals in the near future.

Dr. Curt Civin, Director of the Center for Stem Cell Biology and Regenerative Medicine at the University of Maryland School of Medicine, asked how many grants NCI expects to award in FY2011 and FY2012. Dr. Niederhuber replied that the Institute receives approximately 7,000 applications per year and funds approximately 20 percent. It is unclear, he added, how many additional applications will be submitted within the next 2 years.

Ms. Nancy Roach of the Colorectal Cancer Coalition observed that she and her fellow advocates have found that when speaking to the Congress, emphasizing the potential impact of scientific advances on patients is more persuasive than simply asking for increases in the numbers of grants awarded to scientists. Dr. Niederhuber agreed that both the Congress and the Executive Branch are not interested in

hearing about priority scores and success rates among grantees. They want to know about how science makes a difference in the health of patients.

Dr. David Parkinson, President and CEO of Nodality, Inc., suggested that NCI has had great success in the discovery end of the therapeutic platform, especially in supporting novel agent development and characterization of biomarkers, but faces enormous challenges in providing leadership to change health care delivery at the other end of the continuum. Dr. Niederhuber stressed that NCI shares the vision of changing medical practice. He noted that the NCI Community Cancer Center Program (NCCCP) is making encouraging progress in changing the way cancer care is delivered in communities.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and highlighted recent congressional activities.

FY 2010 Appropriations Activities. In July 2009, the House and Senate each passed their appropriations bill for health, education, and labor programs. The House allocated $31.3 billion to NIH and the Senate allocated $30.8 billion. Two continuing resolutions were passed to extend the FY2009 budget through December 18, 2009 and allow time for a Conference Committee to reconcile the differences between the House and Senate FY2010 appropriations bills. It is likely that Congress will either pass the appropriations legislation in two small packages (minibuses) or one large package, an omnibus. It is hoped that the Conference Committee will reconcile differences and the appropriations will be passed by December 18.

Congressional Briefing. Dr. Christine Berg, NCI, presented Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) findings related to prostate cancer in African-American men in a briefing requested by the Congressional Black Caucus.

Legislation. Healthcare Reform Bill provisions related to comparative effectiveness research are the most relevant to NCI. Currently in health care discussions, the terms “comparative effectiveness research” and “patient-centered outcomes research” are being used interchangeably. Once provisions of the reform bill are agreed upon, legislation should focus on only one of these terms. There are two strategies to carry out comparative effectiveness research. The first approach would establish the Center for Comparative Effectiveness Research within AHRQ. The second approach, outlined by the Senate Finance Committee, would establish a nonprofit/nongovernmental organization to carry out comparative effectiveness research.

The Small Business Innovation Research (SBIR) Program, which exists across 11 Federal departments, expired about a year ago and needs to be extended and reauthorized. The Congress is providing temporary extensions until terms of the reauthorization are agreed upon. Issues delaying an agreement include an increase to the SBIR set-aside (i.e., percent of the NIH appropriation allocated to SBIR) and the allowed percentage of venture capital funds that can be used by a company receiving an SBIR grant. In addition, Senator Mary Landrieu introduced legislation that removes a provision from the American Recovery and Reinvestment Act exempting NIH from a set-aside for SBIR—this would require NIH to obligate $150 million of ARRA funds to the SBIR program.

Questions and Discussion

Dr. Parkinson commented that the congressional delay related to the SBIR program means that all venture capital majority-owned small businesses—which are likely the small businesses with the greatest technology in the U.S.—are ineligible to receive Federal funding.

Dr. Niederhuber expressed his satisfaction with NCI's SBIR program, which has been completely restructured over the past 2 years. The program serves as a model at NIH for its success in structuring competitive reviews that involve both peer review and review by experts in business and venture capital investing. As a result, funded SBIR projects represent very high-quality investments for NCI.

IV. OPERATIONAL EFFICIENCY WORKING GROUP (OEWG) UPDATE—DR. JAMES DOROSHOW

Dr. James Doroshow, Director of the NCI Division of Cancer Treatment and Diagnosis (DCTD), provided an update on the nearly completed final report of the OEWG.

Background. OEWG was established approximately 1 year ago and charged with developing strategies to reduce the time to activation of Cooperative Group and Cancer Center clinical trials. It was noted that OEWG did not focus on the quality of trials; this issue is being addressed by other CTAC-related initiatives. OEWG comprises 63 clinical trial stakeholders, including Cooperative Group chairs, Cancer Center directors, clinical investigators, statisticians, protocol/trial specialists, a community oncologist, NCI clinical trials leadership and staff, and patient advocates, as well as representatives from industry, FDA, the Centers for Medicare and Medicaid (CMS), and the Cancer Trials Support Unit (CTSU). It is hoped that involving stakeholders from across the clinical trials community will foster support for the recommendations of the group.

OEWG is addressing Cooperative Group Phase III trials, Cancer Center investigator-initiated trials, Cancer Center activation of Cooperative Group trials, and Phase II trials involving drugs for which the NCI Investigational Drug Branch (IDB) holds the Investigational New Drug (IND). Other topics, such as industry-sponsored trials, human subjects protection, CMS coverage determinations, state laws and requirements, and congressional funding mandates are outside of the purview of OEWG and were not discussed by the group.

Through frequent deliberations, OEWG members came to agreement on key barriers to timely trial activation and developed a shared sense of commitment to achieve new target timelines for trial activation. The group then developed a series of new process maps for trial activation and identified external factors (i.e., outside of NCI or investigator control) that delay activation. Finally, recommendations and implementation plans were developed to achieve target timelines, and firm dates were established by which all protocol issues must be resolved. Protocols not activated by the applicable firm date will be terminated, even if the delay is caused by factors outside the control of the investigator or Cooperative Group.

Cooperative Group Phase III Trials. An analysis of Cooperative Group Phase III trials activated in 2006 to 2008 revealed that the median time to activation was 830 days, with nearly 60 percent of studies taking more than 2 years to be activated. One step in this process that is of particular concern is the time from protocol receipt to approval (348.5 days). One of the reasons for this protracted timeframe is that the vast majority of protocols require three or more revisions before they are approved.

The OEWG is proposing a 300-day timeline beginning with concept submission and ending with trial activation. The 300 days excludes issues related to Institutional Review Board (IRB), contracting, and drug supply, which are out of the control of the Cooperative Group; however, protocols will be terminated if they are not activated within 2 years of concept submission, regardless of the reason for the delay. This decision was based on data from Dr. David Dilts indicating that trials taking more than 2 years to activate are rarely completed. In order to achieve this 300-day goal, the OEWG target for time from protocol submission to approval is 120 days; this represents a significant reduction from the 348.5 days this process has taken over the past few years.

OEWG developed a series of recommendations and implementation plans to drive Cooperative Group process improvement. The first recommendation calls for changes within the Cooperative Groups. These changes will likely involve addition of staff—such as physician senior protocol officers, nonphysician trial development managers, and medical writers—tasked with keeping track of protocol development and making leadership aware of any issues that arise. Processes will need to be created to allow protocol development steps to be performed in parallel and issues to be resolved in a direct, coordinated fashion. Also, appropriate project management and tracking tools will need to be put into place so that leadership can determine the status of a protocol at any given time. The second recommendation relates to changes within the Cancer Therapy Evaluation Program (CTEP). CTEP should have project managers to oversee the protocol review, revision, and approval process and facilitate interactions with the Cooperative Groups. Communication must be streamlined. It is also important that all scientific issues be identified and resolved at the time of initial concept review; revisiting these issues during protocol review is time consuming and inefficient. The third OEWG recommendation addresses the need for a collaborative Cooperative Group-CTEP process for concept and protocol revision. There must be direct, coordinated interactions to resolve issues, and fundamental aspects of study design must be addressed at the concept stage. Discussions regarding protocols should involve prompt resolution of major differences and minimal time spent on noncritical differences of opinion and routine revisions. The fourth recommendation calls for development of approaches to reward performance relative to the established timelines. To do this, a reliable system must be established for reporting timeline performance; this must be accompanied by clear definitions of what needs to be done when. After the first year, performance data should be assessed to determine the value and accuracy of the reports. Individual Cooperative Group performance and performance across the Groups should be analyzed and incentives linked to performance. CTEP should also include timeline performance in its annual staff performance evaluations.

Cancer Center Investigator-Initiated Trials. Currently, it takes an average of 180 to 200 days to activate an investigator-initiated clinical trial at a Cancer Center. OEWG determined that the target timeline for this process should be 90 days, excluding protocol writing, contracting, institutional finance review, and drug supply issues. To achieve this, OEWG recommends Center-specific action plans be developed. Implementation will likely include specialized staff and direct, coordinated interactions to resolve differences, as well as project management and tracking tools. OEWG recognizes that different timelines may be appropriate for different Cancer Centers depending on the size of the Center and other factors; each Center should establish a reasonable target timeline for itself and measure performance against this benchmark. Guidelines should be modified as necessary to make it possible for Centers to utilize Cancer Center Support Grant (CCSG) funds for protocol development, and additional funds should also be made available if necessary.

OEWG also recommends that university contracting and financial review processes be streamlined. NCI has developed Standardized Clauses for Clinical Trial Agreements, which are being utilized by some companies and universities. Efforts have been initiated to develop standardized clauses for Material Transfer Agreements. NCI is also working with the NIH Clinical and Translational Science

Awards program on issues related to standard clause development. Institutions need to make whatever changes are necessary to facilitate contracting and financial review.

IDB Early Drug Development Phase II Trials. Phase II trials of agents for which NCI holds the IND are conducted by Phase I/II grantees and contractors and Cooperative Groups. Nearly one-quarter of these trials take more than 2 years to activate, and the median time to activation is on the order of 520 and 550 days. One of the primary reasons for this protracted time to activation is the number of protocol revisions being done; most protocols are revised two or more times, with some protocols being revised and resubmitted five or more times. Another time-consuming step is obtaining industry approval of letters of intent (LOIs). OEWG has established a target timeline of 210 days for these trials. The 210 days excludes issues related to IRB, contracting, drug supply, and FDA review; however, protocols will be terminated if they are not activated within 18 months of concept submission, regardless of the reason for the delay.

OEWG recommends that CTEP develop an action plan to achieve this timeline for IDB early drug development Phase II Trials. Implementation will involve engagement of project managers, who will manage the overall process and facilitate interactions among CTEP, investigators, and industry. Also important for these types of trials will be the development of efficient communication processes. Investigators should be promptly informed of disapprovals in advance of the review letter. Teleconferences should be held to rapidly resolve issues related to LOIs so that investigators can begin protocol development as quickly as possible. The second OEWG recommendation in this area relates to the need for a collaborative Cooperative Group-N01-CTEP process for LOI and protocol revision. This process should include direct, coordinated interactions to resolve issues within 14 days of LOI review and focus on scientific issues rather than the mechanics of completing a protocol.

Process Improvements Applicable Across Trial Categories. OEWG has also discussed several overarching issues that affect timelines to trial activation. One recommendation resulting from this is that a working group involving NCI, Cooperative Group, and Cancer Center staff be formed to coordinate efforts to standardize tools and templates in order to facilitate rapid assembly of protocols. This would involve analysis of existing resources and ongoing standardization efforts as well as development of a coordinated process for implementing standards. This would be a relatively low-cost way to improve the NCI-funded clinical trials system.

Another OEWG recommendation is that Cancer Centers perform rigorous review of clinical trial concepts in advance of protocol development, which would help optimize use of resources by reducing the number of protocols in development. Concept review processes could be described in CCSG guidelines, although NCI should not mandate a specific process or criteria.

OEWG recognizes that biomarkers are becoming an important part of cancer clinical trials and that securing funding for biomarker components of trials can be time consuming and result in significant delay. Thus, the Group recommends that funding and capabilities for use of biomarkers in NCI-funded trials be enhanced. One possibility would be to develop a process by which a request for funds to support biomarker development could be reviewed during concept development. Standards should also be developed to allow qualifying sites to conduct imaging studies associated with clinical trials.

Process Improvements to Enhance the Overall Clinical Trials Program. OEWG also discussed a number of issues not directly related to trial activation but relevant to improvement of the overall NCI-funded clinical trials enterprise. Efforts should be made to enhance Cancer Center participation in Cooperative Group trials. Strategies to accomplish this include integrating accrual to Cooperative Group trials into CCSG review criteria, recognizing investigators for their role in the design and conduct of Cooperative Group trials, and enhancing the stability and amount of funding available to

support accrual to these trials. OEWG also discussed requiring Cancer Centers to develop strategic plans to help determine the best ways to allocate clinical trial resources based on research strengths and available patient populations. Changes also need to be made to enhance clinical research mentorship and training.

Summary and Next Steps. A joint commitment among stakeholders is needed to achieve the changes discussed. If the time taken to activate clinical trials is not shortened, the entire clinical trials enterprise will be in jeopardy. If the OEWG recommendations are viewed favorably by CTAC, a request for proposals (RFP) will be issued in the near future to solicit applications from Cancer Centers and Cooperative Groups regarding support needed to begin to implement the changes necessary to speed trial activation. It is hoped that ARRA funds could be distributed as early as January 2010 to begin this process. The current plan is to implement the firm termination deadlines (24 months for Phase III trials and 18 months for Phase II trials) beginning January 2011. It will be necessary to create long-term economic incentives for meeting target timelines.

OEWG is in the process of finalizing its formal report, which will be available at the next CTAC meeting. The next phase of OEWG's work will focus on accrual issues and time for trial completion. The ultimate vision of OEWG is the achievement of coordinated, collaborative, interactive processes for timely development, review, revision, and approval of all NCI-supported clinical trials.

Questions and Discussion

Dr. Richard Schilsky, Associate Dean for Clinical Research at the University of Chicago, stated that using ARRA funds to jumpstart the changes recommended by OEWG is a good idea. However, it will take at least 6 months for Cooperative Groups and Cancer Centers to hire and train the staff needed to implement these changes, and the ARRA money will be gone shortly thereafter. Dr. Schilsky asked what the longer-term funding plan is for supporting these activities. Dr. Doroshow responded that this is a high priority and that funds will be found to ensure that Cooperative Groups and Cancer Centers can meet their staffing needs. Mr. Gabriel Leung, Executive Vice President and President of Oncology at OSI Pharmaceuticals, added that in addition to providing funding NCI should be very rigid about enforcing its timelines. People will adjust their behavior and make improvements if there are consequences.

Dr. Richard Pazdur, Director of the FDA Division of Oncology Drug Products, asked how the OEWG timelines compare to industry standards related to activation of Phase II and III trials. Mr. Leung commented that it generally takes companies 180 to 200 days to start a Phase II or III trial, with an additional 90 days before the first patient is enrolled. In light of the fact that NCI-funded trials are set up in a more complex environment, the OEWG goals are appropriate.

Dr. Parkinson commented that the NCI clinical trials portfolio should be assessed and unpromising protocols removed from the system as soon as possible rather than waiting until 2 years after the proposed process is implemented. Dr. Doroshow agreed and explained that it was not his intention to wait until 2013 to begin to enforce the "drop-dead" dates.

Dr. James Abbruzzese, Chairman of the Department of Gastrointestinal Medical Oncology at the M.D. Anderson Cancer Center, expressed concern about the strategy of expanding personnel to accomplish the goals of OEWG. The number of personnel necessary to carry out the tasks described will vary by institution, and it may take a large number of people to have an impact at large Cancer Centers. It might be preferable to have Centers identify existing employees who can be transitioned into providing these services and helping facilitate meeting timelines. Dr. Doroshow responded that Centers that have

begun to implement the sorts of ideas presented by OEWG have found that it does not require a large number of people. It will require at least one person charged with making sure that the necessary tools are in place, overseeing data collection, and monitoring adherence to timelines. He added that it is vital that processes are reengineered to ensure that the number of concepts approved is in alignment with the capacity of the clinical trials system. It is also necessary that everyone involved understands that time to trial activation is a critical output and that it is important to establish and meet target dates.

Dr. Daniel Sargent, Director of Cancer Center Statistics at the Mayo Clinic Foundation, reported that the Mayo Clinic has reduced its time to trial activation by 50 percent without hiring additional staff. This was done by eliminating non-value-added steps. Another thing that would facilitate efficiency in trial activation is the standardization of protocols; in particular, the development and adoption of electronic protocol tools. Use of these types of tools can help ensure consistency throughout a protocol and reduce the number of protocol revisions. Through caBIG, NCI will be supporting a review of electronic protocol tools, but the results of this evaluation will likely not be available for a year. It would be helpful if this process could be accelerated so that Cooperative Groups and Cancer Centers could access this type of technology as they work to achieve the OEWG timelines. Dr. Niederhuber replied that he would discuss this with Dr. Ken Buetow.

Dr. Tepper asked Dr. Doroshow to provide more details regarding the short-term timeline for implementing the OEWG proposals. Dr. Doroshow reiterated that if CTAC agrees with the recommendations presented, an announcement will be released within the next few weeks and funding decisions will be made so that administrative supplements can be awarded in January 2010.

Dr. Schilsky emphasized that in order to reduce the number of protocol revisions, it is necessary to focus the review process on critical scientific and operational issues. He pointed out that many of the current revisions are made necessary by NCI requirements and that NCI plays an important role in the process of trial activation. If Cooperative Groups are going to be evaluated based on their performance in this area, it is important that NCI not hinder this performance. He asked Dr. Doroshow how NCI's role in the process will be reviewed. Dr. Doroshow agreed that Cooperative Groups should not be penalized for NCI's failures and stated that this is one reason why it is important to develop agreement among all stakeholders regarding timeline measures.

Ms. Roach asked whether the data on timelines would be publicly available. Dr. Niederhuber responded that NCI is increasingly interested in transparency and recognizes the importance of making data available. Dr. Doroshow stated that data from the first year will be presented at the CTAC meeting in 1 year, which will provide some indication of whether major improvements are possible. Ms. Roach replied that having proof that NCI is eliminating unnecessary bureaucracy would be helpful to advocates who are trying to convince the Congress to support cancer research.

V. UPDATE ON COOPERATIVE GROUP CLINICAL TRIAL COMPLEXITY FUNDING—DR. MARGARET MOONEY

Dr. Margaret Mooney, Branch Chief of the CTEP Clinical Investigations Branch, provided an update on the Cooperative Group Clinical Trial Complexity Funding Initiative.

Background. In accordance with one of the Clinical Trials Working Group (CTWG) Operational Efficiency Initiatives, the objective of the complexity model was to align reimbursement with clinical trial complexity. It was important to maintain the current $2,000 base capitation rate for all Phase III trials. The goal was to develop a system capable of ascertaining trial complexity that could be used to determine

which trials should receive additional funding, if available. The Complexity Trials Working Group was headed by Ms. Andrea Denicoff of the NCI Clinical Investigations Branch in CTEP/DCTD and included members from the Division of Cancer Prevention (DCP) as well as representatives from Cooperative Groups and other centers.

Complexity Model Criteria. The initial draft model, presented to CTAC last year, calculated trial complexity based on five main elements: number of study arms, informed consent process, number of registration or randomization steps, complexity of investigational treatment, and length of investigational treatment. Since that time, an additional five criteria have been added to the model; these include: personnel impact to run and monitor the study, data collection complexity, follow-up requirements, ancillary studies, and patient feasibility and enrollment. A complexity score is obtained by assigning points for each element (0=standard, 1=moderate, 2=high) and calculating the sum over all 10 elements.

Complexity Model: Fiscal Year 2008. In fiscal year 2008, the draft model comprising the original five elements was tested by the Cooperative Groups. Each participating Group used the model to recommend ongoing or pending Phase III treatment trials for complexity funds. In addition to providing information about the original five elements, the Groups were asked to add additional elements or other information they thought relevant. CTEP reviewed the Group recommendations and complexity scores and selected 14 trials to receive supplemental funding. An effort was made to balance the funding across disease types; the Groups sponsoring the trial and the existence of support from industry were also taken into account. The selected trials received an additional $1,000 per patient beginning with patients accrued on June 1, 2008. Funds were distributed through the CTSU and the Community Clinical Oncology Program (CCOP).

The 14 trials funded accrued 2,508 patients between June 1, 2008, and August 24, 2009. An additional 6,472 patients will be enrolled if accrual targets are met for these trials. Of the 14 trials, one was stopped early based on an interim analysis that showed a positive result; this will save money for the complexity funding program because the trial was 73 patients below its target accrual rate when it was closed. Most of the trials are currently at or above their planned accrual rate, but it is somewhat difficult to interpret these data because several of the trials are early in the accrual process. One trial completed accrual ahead of schedule. A few of the trials are below or at risk of falling below their planned accrual rates. NCI is considering interventions for these trials and is carefully monitoring whether the additional complexity funding is making a difference.

Complexity Model: Fiscal Year 2009. In fiscal year 2009, the complexity funding process was implemented in a manner similar to that in fiscal year 2008. Cooperative Groups were asked to nominate trials that should receive complexity funds. Complexity scores were calculated using all 10 model elements, and 6 Phase III trials were selected based on score and the need to balance awards across diseases and Groups. Currently, funding is spread across nine Cooperative Groups and eight disease sites.

There were some adjustments made to the funds available because of early closure of trials. Initially, funds had been allocated for CCOPs for only 1 year and an adjustment was made in the second year of funding of this initiative to ensure that CCOPs will continue to be supported until target accrual is attained. Hence, funding adjustments were also made to extend CCOP participation; NCI is also considering making complexity funding available for Phase II trials.

Further Evaluation and Follow-up. It is important to assess the impact of complexity funding on accrual and data collection. It was difficult to measure this for the first year because trials were not selected until late in the fiscal year. It is hoped that a process will be developed over the next 6 months to determine whether funding has improved accrual and, if not, why it has not helped. It has also become

clear that it will be necessary to further refine the current model and element definitions to ensure consistency.

Questions and Discussion

Dr. Peter Adamson, Chief of Clinical Pharmacology and Therapeutics at the Children's Hospital of Philadelphia, University of Pennsylvania, asked how many Cooperative Group Phase III trials are activated each year. Dr. Mooney replied that 15 to 20 new Phase III trials have been activated each year over the past few years. In total, there are currently 60 to 65 active adult Cooperative Group Phase III trials and approximately 30 active pediatric Phase III trials.

Dr. James Wade, Director of Medical Oncology at the Decatur Memorial Hospital Cancer Care Institute, asked how many trials each Group was allowed to nominate and inquired about how existing supplemental industry funding was taken into account in the complexity funding review process. Dr. Mooney stated that each Group was asked to nominate up to five trials; however, all but one Group nominated fewer than five trials, in part because trials close to their target accruals were not eligible. Groups were permitted to nominate trials with supplemental industry funding if they could provide a rationale for why additional funding was needed. Only one or two trials with industry funding were nominated, and none of these was selected for funding in fiscal years 2008 or 2009.

Dr. Adamson observed that the complexity funding reduces the money lost on each patient accrued to a complex trial, but money is still lost even with this supplemental funding. Cooperative Group trials should aim to improve outcomes, but the most dramatic improvements will not necessarily come from more complex studies. Rather than funneling more money into complex trials, it might make more sense to provide Cooperative Groups the flexibility to provide supplemental funds to those trials with the potential to have the greatest impact. Dr. Prindiville reminded the group that the complexity funding model was developed as an interim step pending collection of additional financial analyses of the Cooperative Groups. NCI has been looking carefully at the Cooperative Groups to determine the best way to support science and promote accrual; a report on this effort should be completed within the next 6 months.

Dr. Stephen Grubbs, Chief of Oncology at Medical Oncology Hematology Consultants, asked how the first 2 years of complexity funding was distributed across institutions (e.g., Cancer Centers, CCOPs). Dr. Mooney responded that the data had not yet been analyzed in this way. Dr. Grubbs offered the anecdotal observation that at his CCOP, the supplemental complexity funding helps get a trial "in the door" and may be important in gaining support of research nurses and other support staff but does not seem to influence whether an individual investigator will offer the trial to patients. NCI may want to consider ways to encourage investigators to make efforts to accrue patients to trials receiving complexity funding. In the end, the most important things affecting accrual are whether the study is interesting and whether patients are willing to participate.

VI. BIOMARKER, IMAGING AND QUALITY OF LIFE STUDIES FUNDING PROGRAM (BIQSFP): 2010 PROGRAM CHANGES—DR. RAYMOND PETRYSHYN

Dr. Ray Petryshyn, Program Director, NCI Coordinating Center for Clinical Trials, discussed changes to the Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP).

The purpose of BIQSFP is to ensure that the most important biomarker, imaging, and quality-of-life (QOL) studies are initiated in a timely manner in association with clinical trials. The Program funds studies conducted in association with Phase III trials when the cost is too high to be covered by the Cooperative Group mechanism. OEWG's goal for BIQSFP is to facilitate rapid activation of trials involving critical biomarker studies. To achieve this, it was proposed that the role of CTAC should change. Rather than reviewing each BIQSFP award as it currently does, CTAC should provide strategic oversight and advice to the Program.

BIQSFP proposals undergo three levels of review before they arrive for approval by CTAC. The proposals are evaluated by Scientific Steering Committees (SSCs) or CTEP/DCP with external expert input. There is also discussion and recommendation by the appropriate NCI Divisions, as well as the Clinical and Translational Research Operations Committee (CTROC). This current process poses serious logistical concerns. BIQSFP applications are received, reviewed, and recommended for funding on a rolling cycle. However, CTAC only meets three times per year, which may result in up to a 4-month delay for final recommendation of an application. If approved, CTAC's new role of strategic oversight would entail identifying the types of studies eligible for funding; advising on priorities for particular types of studies (i.e., prevention, chemotherapy, imaging); advising on prioritization criteria (i.e., Phase II versus Phase III concepts); and annually reviewing program implementation.

Questions and Discussion

Dr. Adamson asked how many BIQSFP proposals enter the review process each year. Dr. Petryshyn said that 23 proposals were submitted in the first year of the program, three of which underwent final funding approval. This year, about 12 proposals were submitted and, so far, 1 has been selected for funding. Dr. Adamson added that if CTAC assumes the new role of strategic oversight, it would be helpful to receive periodic summaries of the status of all submitted proposals.

Dr. Schilsky commented that a high-level oversight board such as CTAC should not have to review individual funding projects. It was noted that BIQSFP proposals are extensively reviewed through normal clinical trial review mechanisms before they reach CTAC for approval.

Motion. A motion to change CTAC's role from one that reviews individual awards to one of strategic oversight and advice in relation to BIQSFP was approved unanimously.

A RANDOMIZED PHASE III DOUBLE-BLIND TRIAL EVALUATING SELECTIVE COX-2 INHIBITION IN COX-2 EXPRESSING ADVANCED NON-SMALL CELL LUNG CANCER—DR. CLAUDIO DANSKY ULLMAN

Dr. Claudio Danksy Ullman, Senior Investigator, Clinical Investigations Branch, CTEP, discussed the therapeutic objective of CALGB 30801: Randomized Phase III Double-Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced Non-Small Cell Lung Cancer (NSCLC). The primary objective of this trial is to determine if preselected patients with NSCLC with moderate to high overexpression of COX-2 will benefit from standard chemotherapy plus celecoxib treatment.

COX-2 is induced by tobacco carcinogens and overexpressed in the tumors of about 80 percent of NSCLC patients; its expression has been shown to be a marker of poor prognosis in Stage I NSCLC

patients. Preclinical studies suggest that COX-2 inhibition has antitumor and chemopreventive effects; it induces apoptosis and antiangiogenic effects, restores antitumor immunity, and decreases tumor invasiveness, among other effects.

Most clinical trials in NSCLC and other tumor types have been performed in unselected patient populations. The preclinical rationale for combining COX-2 inhibitors and chemotherapy has not translated to a clear clinical benefit in the therapeutic setting. Therefore, a precursor study was conducted by the Cancer and Leukemia Group B (CALGB) to address the effect of eicosanoid modulation on NSCLC patients' outcomes (CALGB 30203). Study results showed that COX-2 overexpression is a negative prognostic marker for patients who do not receive celecoxib and a positive predictive marker for patients who do receive celecoxib. Higher COX-2 expression correlates with increased benefit from celecoxib inhibition. CALGB 30801 will also look at levels of PGE-M—a stable urinary metabolite of PGE-2. Other studies have shown that PGE-M levels decrease with COX-2 inhibition. Patients whose PGE-M levels decreased upon COX-2 inhibition had superior outcomes, which indicates PGE-M as a possible biomarker for COX-2-dependent disease. An additional aspect to be explored in the proposed COX-2 inhibition study is the association of the PTGS2 polymorphism with high COX-2 expression.

Overall, significant preclinical and clinical data support the importance of COX-2 in development and progression of NSCLC; however, clinical trials of COX-2 inhibition in NSCLC have been disappointing. Based on the precursor study described above, the reason for this is that COX-2 inhibition may be effective only in COX-2-overexpressing tumors. Future COX-2 inhibition trials must select patients based on tumor COX-2 expression. The proposed CALGB 30801 study will be the first therapeutic Phase III trial to test the role of selective COX-2 inhibition in a preselected population based on COX-2 expression level. COX-2—the integral patient selection marker—will be measured by immunohistochemistry (IHC) in a Clinical Laboratory Improvement Amendments (CLIA)-approved and College of American Pathologists (CAP)-accredited laboratory at The Ohio State University. Patients will be classified as overexpressed (COX-2 index ≥4), moderately expressed (COX-2 index ≥2 and <4), or negative (COX-2 index <2); only patients with a COX-2 index of ≥2 will be eligible to proceed in the clinical trial. Urinary PGE-M will also be evaluated as an integrated biomarker.

Questions and Discussion

Dr. Wade questioned whether the CALGB 30801 trial will also address COX-2–folic acid interaction, since patients receiving celecoxib will also be taking folic acid. Dr. Dansky Ullman stated that the study aims proposed for BIQSFP funding will not specifically look at the effects of folic acid, but there are additional exploratory components to the study.

Mr. Leung wanted to know the relative distribution of patients with a COX-2 index greater than 4. Based on the precursor study, the assumption is that 35-40 percent of patients will qualify as a COX-2 index ≥4. The CALGB 30801 study will initially screen almost 800 patients; it is assumed that 600 of those patients will be eligible for treatment with the COX-2 inhibitor.

VII. CENTRAL INSTITUTIONAL REVIEW BOARD (CIRB): REVISED PROCEDURES, ACCREDITATION UPDATE AND COST-BENEFIT ANALYSIS—DRS. MARGARET MOONEY AND TODD WAGNER, AND MS. JACQUELYN GOLDBERG

Dr. Mooney provided an overview of the revised procedures for initial review of Phase III trials by the Adult Central Institutional Review Board (CIRB). Ms. Jacquelyn Goldberg, Review Board Administrator in the NCI Clinical Investigations Branch (CIB), gave an update on the accreditation processes for the Pediatric and Adult CIRBs. Ms. Goldberg and Dr. Todd Wagner, Consulting Associate Professor in the Department of Health Research and Policy, Stanford University School of Medicine, presented a summary of the cost-benefit analysis conducted for the CIRB.

CIRB: Revised Initial Review Procedures. Several issues prompted revision of the initial CIRB review procedures. One was the need to improve timelines for initial review, particularly for the Adult CIRB. Also, it became clear that sites not participating in the CIRB were experiencing delays in trial activation because CIRB review was integrated with final CTEP approval. There was also a desire to promote dialogue about the importance of human subjects protection issues related to trials.

In the past, CTEP protocol approval was not finalized until completion of CIRB review and approval. This process could take a substantial amount of time because CIRB comments and concerns needed to be addressed by Cooperative Groups prior to approval. Trial activation took place only after CIRB and final CTEP approval. A revised procedure called CIRB Process for Initial Review (C-PIRAT) has been established. Under this process, CTEP approves protocols before CIRB review. This allows a trial to be activated immediately upon CTEP approval and sent out to sites not participating in CIRB while CIRB review is underway. It was agreed that if important human subjects protection issues were identified by the CIRB, a quick amendment would be made if the trial had already been activated.

Other changes to the process include adoption of timelines mutually agreed upon by the Groups, CIRB, and CTEP, and revamped internal CTEP and CIRB processes. The Adult CIRB has also developed its own model informed consent document, which is amenable to modification by NCI and the Groups, as necessary. Steps have also been taken to improve communication among the Groups, Principal Investigators (PIs), CTEP, and the CIRB. If the Adult CIRB has any questions about a protocol, the protocol PI and statistician, as well as the CTEP CIRB physician, join the CIRB call to resolve issues in real time; the goal is to minimize the number of CIRB stipulations. Outcome letters will now be sent to Groups within 5 to 7 calendar days of the initial review. Efforts are made to resolve outstanding issues within 14 days of Group receipt of the outcome letter. Of note, the last seven CIRB Study Outcome Letters have been limited to informed consent issues not requiring an amendment; CIRB has had no protocol stipulations.

Data were presented on the timelines of CIRB approval in 2007 and 2008 and since implementation of C-PIRAT in May 2009. Using C-PIRAT, median time from protocol receipt to review has been decreased to 21 calendar days from 28.5 days in 2007. Time from review to approval has been dramatically reduced—this process has taken a median of 21 days using C-PIRAT, compared with 114 days in 2007. Together, these improvements have resulted in a median time from protocol receipt to approval of 45 calendar days using C-PIRAT (range is 31 to 55 days), which is significantly lower than the 157 days necessary for this process in 2007. Of the first nine trials that have been reviewed through C-PIRAT, six have received CIRB approval prior to Group activation. For the remaining trials, CIRB approval has been obtained 17 to 37 days following Group activation.

CIRB Accreditation. The CIRB Evaluation Advisory Panel recommended several years ago that the CIRB become accredited by the Association for the Accreditation of Human Research Protection

Programs (AAHRPP). AAHRPP accreditation is considered the gold standard for IRBs and is an asset for recruitment. The process to obtain accreditation has begun: the AAHRPP fee has been paid, and CTEP representatives have met several times with AAHRPP leadership. Ms. Goldberg; Ms. Jeanne Adler, Nurse Consultant in the NCI CIB; and a half-time equivalent contractor are involved in this effort. The estimated timeline to completion is 1 year.

The first step of accreditation is self-assessment of the Human Research Protection Program (HRPP) and implementation of improvements based on this evaluation. This process can take up to 12 months. AAHRPP has expressed an interest in working with the CIRB during this process rather than waiting until the formal application is submitted. The application consists of a program overview, copies of documents used by the CIRB, and an index to CIRB documents. Following application submission, AAHRPP conducts a site visit to evaluate CIRB performance relative to accreditation standards. The AAHRPP Council on Accreditation Review and Notification then reviews the application and site visit report, as well as NCI's response, and then determines accreditation status. To date, AAHRPP has accredited 194 organizations. Organizations must be reaccredited every 3 years.

CIRB Cost-Benefit Analysis. In 2006, NCI funded a study to assess the time, effort, and cost associated with the CIRB. The study was conducted by Dr. Wagner, a health economist, and focused on the Adult CIRB, as the Pediatric CIRB was relatively new and involved comparatively few sites. The objectives of the cost-benefit analysis were to: (1) determine whether participation in the CIRB was associated with lower effort, time, and cost compared with not participating in the CIRB; and (2) assess whether the CIRB was saving society (taxpayer) money.

To assess the first objective, researchers and IRB staff at CIRB-affiliated and -nonaffiliated sites were surveyed to gain an understanding of the time and effort necessary to achieve IRB approval. Respondents were asked about the most recently approved adult oncology trial at their institutions. The response rate was 60 percent for research staff and 42 percent for IRB staff. Hours of effort were translated into costs using national average wages, education, and position. One caveat to these data is that they are self-reported. For the initial review process, CIRB affiliation was associated with 6.1 hours of effort saved for research staff, 34 fewer days between the time research staff started paperwork and IRB approval, and more predictable review times. CIRB affiliation was also associated with 2.3 hours less effort for IRB staff and use of less-expensive staff to review CIRB protocols. These differences translated to a cost savings of $717 per initial review ($321 related to research staff savings and $396 associated with IRB staff savings). There were no significant differences between CIRB-affiliated and - nonaffiliated sites regarding continuing reviews or amendments.

To assess the second objective, an analysis was conducted to compare the average monthly costs of running the CIRB to the average savings for participating sites. Estimated monthly CIRB costs were calculated based on personnel costs—obtained from the CIRB contractor (January 2007 through June 2008)—and the number of protocols reviewed per month, which was determined using CTSU data (March 2006 through May 2008). The analysis revealed that the CIRB cost approximately $160,000 per month to operate in 2008. Based on the fact that the CIRB conducted approximately 148 initial reviews per month over this timeframe, the monthly savings for the sites was $106,175 (based on the $717 savings per protocol calculated in the assessment of the first objective). This means that CIRB yielded a societal cost of approximately $55,000 per month in 2008. It was noted that societal savings is not a conventional goal for health interventions and that savings would be higher if more sites joined the CIRB and enrolled institutions used the CIRB as intended. It was also pointed out that the calculations did not take into account the benefit of faster, more predictable reviews and the savings of $10 per adverse event.

In conclusion, the CIRB appears to save local researchers and IRB staff time and effort. Increasing CIRB enrollment would likely lead to increased savings for society. Also, it was noted that the efficiencies of C-PIRAT may alter the cost-benefit assessment of the CIRB.

Questions and Discussion

Ms. Roach asked whether implementation of C-PIRAT was associated with changes in the level of CIRB protocol examination and inquired about other reasons for the reduction in time needed for review and approval. Dr. Mooney replied that the new process has not changed CTEP or CIRB review processes. The change that has resulted in the most dramatic time savings has been the ability to address questions and issues at the time of CIRB initial review. Separating review of the informed consent document from protocol review has also been very helpful.

Dr. Sargent commended the improvements in the CIRB initial review process and stated that it will be important to continue to monitor this process to ensure that delays do not begin to occur in the future. He suggested that if the median time from receipt to approval rises above 50 or 60 days, the process should be reevaluated. Dr. Mooney replied that the Clinical Investigations Branch and the CIRB are monitoring these timelines on a monthly basis.

Dr. Wade also commended the improvements in the CIRB review process. He then asked whether there are audit data from 2008 or 2009 regarding compliance, timeliness of amendment approval, and timeliness of annual reviews, stating that several sites have discontinued use of CIRB because CIRB was sometimes not compliant with Office for Human Research Protections (OHRP) regulations. Dr. Mooney stated that timelines have been approved for these steps but audit data have not been reported.

Dr. Adamson asked whether comparison data regarding initial review timelines were available for the Pediatric CIRB. Dr. Mooney responded that the Pediatric CIRB, which reviews all Children's Oncology Group (COG) trials, is still integrated with the CTEP approval process. Ms. Adler reported that the Pediatric CIRB median time from protocol receipt to approval is between 60 and 70 days. Dr. Mooney stated that efforts will be made to improve communication within the Pediatric CIRB, but differences in timelines will always exist because of several differences between the two CIRBs: the Pediatric CIRB meets only once per month while the Adult CIRB meets twice per month, the Pediatric CIRB reviews trials of all phases while the Adult CIRB reviews only Phase III trials, and 60 to 70 percent of COG institutions participate in the CIRB.

Dr. Sargent asked what NCI will do to increase the number of institutions using the CIRB. Dr. Goldberg explained that the CIRB will be increasing its presence at the annual meeting of the national IRB organization, Public Responsibility in Medicine and Research (PRIM&R), to do more outreach. Also, NCI is hoping to increase the participation of COG researchers by word of mouth. Obtaining accreditation should also help with recruitment. Dr. Niederhuber asked for insight on what needs to be done on a local level to convince institutions to participate in the CIRB. Dr. Goldberg responded that many institutions perceive the CIRB as having bottlenecks that result in delays; however, it may be possible to share data showing that these bottlenecks have dissipated. The CIRB contractor is conducting audits more frequently, and the audits are showing better outcomes than before.

Dr. Schilsky stated that it would be useful to inform institutions of the results of the cost-benefit analysis, though the analysis addresses only one aspect of the potential value of the CIRB to these institutions. He asked whether the analysis provided any insight into the larger potential value of the NCI CIRB—the fact that it removes the burden of reviewing Cooperative Group protocols from the local

IRBs, allowing them to focus more staff, time, and effort on other protocols. Dr. Wagner responded that the current analysis did not collect information on what the local institutions did with the resources saved by using the CIRB.

Ms. Roach described a concept that has emerged in England regarding local and central IRBs. The concept asserts that local review is more focused on protecting institutional interests than patient interests and is, thus, ethically inappropriate. Based on this, England is moving to a completely centralized form of ethical review for all clinical trials. Although it is acknowledged that the health care systems are quite different in the U.S. and England, the U.S. should consider this type of approach. Dr. Niederhuber added that the U.S. may be better positioned to do this following health care reform.

Dr. Kenneth Cowan, Director of the Eppley Cancer Center, University of Nebraska Medical Center, commented that many institutional IRBs are reluctant to give up the authority they have established within the institution. Thus, it may be necessary to provide information about savings and benefit to the institutional leadership. Dr. Carolyn Runowicz, Director of The Carole and Ray Neag Comprehensive Cancer Center and Northeast Utilities Chair in Experimental Oncology at the University of Connecticut Health Center, stated that institutional deans must be convinced that using a central IRB is a good idea. Dr. Niederhuber added that legal operations within the university generally dictate the final decision about issues such as central IRB use. Most universities are self-insured and view using the CIRB as a large risk. Dr. Mitchell Schnall, Matthew J. Wilson Professor at the University of Pennsylvania Medical Center, stated that indemnification against risk would encourage institutions to use the CIRB. Dr. Niederhuber replied that this would require major government action.

Dr. Grubbs stated that because informed consent documents must address state laws about use of genetic information and other issues, some local review is still necessary.

Dr. Goldberg reported that OHRP has released a request for comments regarding whether the accountability of central IRBs should be more clearly delineated. This illustrates that this issue is being considered by OHRP, although it may take considerable time for it to be resolved.

VIII. ISSUES RELATED TO THE REVISION OF THE INTELLECTUAL PROPERTY (IP) OPTION IN DCTD-SPONSORED CLINICAL TRIALS—DRS. JEFFREY ABRAMS AND JASON CRISTOFARO

Dr. Jeffrey Abrams, Associate Director of the NCI CTEP/DCTD, noted that many FDA-approved oncology agents have resulted from trials conducted by participants in the CTEP Cooperative Groups program using INDs held by CTEP, and many more are in preclinical or early development stages. The CTEP program sponsors more than 100 Investigational New Drugs and supports a network of more than 11,000 investigators at more than 3,300 institutions. CTEP coordinates more than 750 active protocols ranging from Phase 0 to Phase III and opens between 150 and 250 new protocols per year. CTEP trials accrue approximately 30,000 patients each year. CTEP maintains an average of 80 collaborative agreements with pharmaceutical companies, including Cooperative Research and Development Agreements (CRADAs), Clinical Trials Agreements (CTAs), and Clinical Supply Agreements (CSAs). These companies are referred to as Collaborators.

In 1997, NCI initiated discussions with NIH on methods to assist Collaborators in gaining access to extramural inventions that use their proprietary agents. In January 1999, CTEP began adding a new term—the "IP Option"— to grants and contracts for clinical trials. The IP Option states that extramural Institutions agree to grant to Collaborators nonexclusive, nontransferable, royalty-free, worldwide

licenses to all Institution inventions for research purposes only. It also requires Institutions to grant to Collaborators time-limited first options to negotiate exclusive, or co-exclusive if applicable, worldwide royalty-bearing licenses for all commercial purposes, including the right to grant sublicenses, for all Institution inventions on terms to be negotiated in good faith by Collaborators and Institutions. In 2001, the IP Option was added to Material Transfer Agreements (MTAs), through which agents are provided for nonclinical or preclinical studies.

In 2003, the IP Option was modified to provide nonexclusive royalty-free (NERF) commercialization licenses for inventions arising from combination studies to all Collaborators providing an agent used in that study. In January 2009, CTEP began the process of developing a new revision of the IP Option to address issues related to correlative science projects in which both Collaborators and the participating Institutions are involved.

Changing times are creating new issues related to IP. The introduction of molecularly targeted agents into clinical trials has changed relationships among parties involved in CTEP agreements. Trials now often focus on defining targets and developing biomarkers. The current IP Option and most CTEP collaborative agreements and funding agreements are silent as to the disposition of agent-treated human tumor samples and rights related to them. The IP framework surrounding agent-treated samples and associated clinical data has become increasingly important.

Pharmacodynamics and biomarker development are now an important part of early drug development. The potential to generate new IP during nonclinical studies is usually much greater than for clinical trials. DCTD receives requests from extramural investigators, especially those engaged in early-phase clinical development, for greater and earlier access to samples from trials using cutting-edge therapeutics for both nonclinical and clinical evaluation. Collaborators are concerned that studies in this area have the potential to generate "blocking" IP that would prevent them from using new applications of their agents.

Collaborators have requested the freedom to operate provisions for "blocking" IP generated using their proprietary agent-treated samples and resulting clinical data as a condition of making agents available. Cooperative Groups have asked for the freedom to interact with small diagnostic companies to develop assays based on data from their clinical trials.

Dr. Jason Cristofaro of the Office of the Director, DCTD, provided an overview of NCI's proposed modifications to the IP Option. Academic Institutions, Collaborators, and Cooperative Groups have been asked to provide feedback on several proposed changes, and NCI has made changes to its proposal in response to the feedback received. A final draft of the new IP Option language will be released for public comment prior to implementation.

The academic community has argued that investigators should be free to use the data they generate in trials for their own use and the public's benefit. Investigators do not want their early-stage IP to be subject to a nonexclusive licensing requirement, believing that this will remove the incentive for investigators to conduct research with small businesses and partner with them in assay development. Academic Institutions lobbied for removal of language stating that any intellectual property generated from unauthorized research using an agent would be assigned to the Collaborators. Many Cooperative Groups and other sites argued that this stipulation would endanger their tax-exempt status.

Industry feedback has focused on issues related to blocking patents. Concern has arisen over the past few years regarding the development of assays that FDA may require for treatment. This could lead to a requirement of licensing this ancillary technology to practice the main invention. Most companies want to be certain that they have at least the option to negotiate that license to ensure that they will be

able to practice main inventions (i.e., drugs). Collaborators are also concerned that their development plans could be impacted by inventions that they did not foresee. They asked for a more efficient reporting process so that they can learn about inventions in a timely manner. Another concern expressed by companies is related to the development of new indications by others based on their technology. All of these issues factor into Collaborators' decisions on whether they should work with NCI.

NCI's concerns relate to academic freedom and the public good. Researchers must be free to conduct experiments that may enhance development and/or optimal use of new treatments with minimal outside interference. NCI will support policies that it believes provide the highest likelihood of developing treatments and tools beneficial to the broader cancer community and the patients it serves. NCI seeks to reach a compromise between the competing but legitimate interests of academia and industry.

The revised IP Option is intended to identify the types of activities that should involve nonexclusive royalty-free licensing. Section A of the proposed language stipulates a royalty-free, worldwide, nonexclusive license for commercial purposes and a time-limited first option to negotiate an exclusive, or co-exclusive if applicable, worldwide, royalty-bearing license for commercial purposes for "inventions arising from clinical studies involving the Collaborator's agent that use or incorporate the Collaborator's agent or inventions arising from nonclinical studies under an MTA that directly utilize a Collaborator-supplied agent." The types of inventions that NCI wants to capture under this licensing agreement are new indications. This language applies only to inventions from studies for which the Collaborator directly supplies the agent. It does not apply, however, to studies using tumor-treated samples or related data.

Section B of the IP Option language relates to biomarker-related inventions (e.g., pharmacogenomic assays). These are inventions "arising from studies utilizing clinical data or specimens collected from patients enrolled in a clinical trial that utilized the Collaborator's agent (including specimens obtained from NCI-funded tissue banks)." For these inventions, the IP Option requires a nonexclusive, nontransferable, royalty-free, worldwide license to all Institution inventions for research purposes only, and a time-limited first option to negotiate an exclusive, or co-exclusive if applicable, worldwide royalty-bearing license for all commercial purposes, including the right to grant sublicenses, for all Institution inventions on terms to be negotiated in good faith by the Collaborator and the Institution. This will cover inventions that are generated from Collaborator-provided agents in clinical and nonclinical studies in which the agent is not incorporated into the invention itself, as well as inventions generated from data from clinical trials and Collaborators' agent-treated tumor specimens. For these inventions, NCI will not offer a nonexclusive royalty-free commercial license.

The revised IP Option also incorporates specific information for various licensing options on the length of time each party is allowed to negotiate. More time is allowed for Section B inventions because the required technology evaluation is complex. In all cases, the Academic Institutions will retain the right to make and use any inventions for internal noncommercial research use and educational purposes and extend that license to other educational and noncommercial entities. In response to a request from the Cooperative Groups, a 10-year limit has been placed on the period in which licensing options must be given to Collaborators.

To address concerns about assignment of inventions, NCI has modified the agreement so that it no longer requires an assignment; instead, it grants an exclusive royalty-free license to the Collaborator. This means that the invention is not owned by the company and the partner organization does not lose its tax-exempt status. The revised IP Option also stipulates that no unauthorized modifications to agents will be created and no unauthorized research using agents will be conducted.

A second draft of the revised IP Options is under development. Following NCI and NIH review, the draft will be posted on the *Federal Register* for a review and recommendation period. The final version will be posted on the CTEP Web site.

Questions and Discussion

Dr. Schilsky asked for clarification of the types of inventions that no longer are subject to nonexclusive royalty-free license for commercial purposes. Dr. Cristofaro explained that Section A is designed to make it clear that only inventions that directly use or incorporate a Collaborator-provided agent receive nonexclusive royalty-free licenses for commercial purposes. This was done in response to major concerns expressed by companies about those types of inventions. Inventions that use clinical data are covered in Section B, which does not grant nonexclusive royalty-free licenses for commercial purposes.

Dr. Tepper asked for clarification of the scope of the term "invention." Dr. Cristofaro cited an example of method of use as an invention. Minoxidil is a drug for which a new method is considered to be an invention. Patentable inventions can include composition of matter, methods of use, or treatment regimens.

Dr. Abrams noted that the new language is designed to address legal concerns of companies. The development of inventions by Institutions in research covered by Section A is quite rare.

Mr. Leung asked for clarification on the deadlines for negotiation of exclusive licenses. Dr. Cristofaro explained that deadlines for negotiating licenses have been modified to allow additional time for Section B inventions. In addition, the revised IP Option specifies that Institutions that develop inventions based on trials more than 10 years old are no longer required to offer Collaborators licensing options.

Dr. Civin suggested that 10 years is too long to provide Collaborators with licensing options. Dr. Abrams responded that NCI may consider varying this stipulation based on the size of the trials involved and the time required to obtain survival data.

Dr. Parkinson asked how much control Collaborators will have over the use of their drugs. Dr. Abrams said that companies would be notified when correlative studies are planned and given the opportunity to review planned studies and resulting publications and receive responses to their concerns. However, they will not have the right to prevent those studies.

Ms. Roach asked whether nanotechnology inventions would fall under Section A. Dr. Cristofaro replied that most nanotechnology studies involve incorporation of an agent into an invention, which would be covered by Section A of the IP Option.

Dr. Parkinson argued that the public good will be best served by limiting the amount of control Collaborators have over NCI's ability to develop knowledge about the use of the agents they supply.

Dr. Niederhuber agreed that the language used in the IP Option should be made more explicitly patient-centric and should emphasize the goal of the public good in allocating IP rights.

Dr. Schilsky noted that until the new IP Option language has been finalized, the fact that it is available for public comment may act as a hindrance to the negotiation of agreements between Cooperative Groups and Collaborators.

IX. NCI'S EXPERIMENTAL THERAPEUTICS PROGRAM (NExT)—DR. JAMES DOROSHOW

Dr. Doroshow discussed the changes NCI has made to its experimental therapeutics platform and how they better serve the research and academic communities. Prior to these recent changes, NCI had a very complicated process for drug development that was accomplished through a variety of different pipelines. The decentralized process created inefficiencies (i.e., duplication of experimental work), fostered resource silos (staff with expertise in an area could be unintentionally excluded from a project), and confused both collaborators and staff.

Starting with an extramural review of the Rapid Access to Intervention Development (RAID) program, NCI has worked very hard to develop the unified NCI Experimental Therapeutics (NExT) pipeline for development of experimental therapeutics. In addition, NCI also created a Chemical Biology Consortium (CBC) to dramatically increase the flow of early-stage drug candidates into the NExT pipeline. CBC is an integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support. It will enable a clear, robust pipeline to focus on unmet needs in therapeutics: "undruggable" targets and underrepresented malignancies. CBC and NExT are not intended to replicate the pharmaceutical industry; the purpose is to develop and make available to patients drugs that affect targets and molecules characterized in academic institutions. The success of CBC depends on appropriate sharing of intellectual property. All participants in CBC sign Consortium Agreements that address data transfer, sharing, and ownership.

There are quarterly receipt dates for extramural scientists to propose targets, screens, or molecules for entry into the NExT pipeline; the next receipt date is November 15 (https://dctd.cancer.gov/nextapp or https://dctd.cancer.gov/nextregistration). A total of 52 proposals were received in the first cycle of the application process, which is a considerable increase from the average of 13 proposals that the RAID program received during its biannual application cycle. Two Special Emphasis Panels (SEPs) were created to assist the Senior Management Committee, the NExT Senior Advisory Committee and the NExT Discovery and Development Committee in the application selection process. The SEPs consist of expertise from industry and academia; one panel focuses on discovery and the other on development. The Discovery SEP includes several members with expertise in chemistry and also includes toxicologists and pharmacologists. The Development SEP consists of clinicians and those with expertise in transitioning compounds into the clinic. In addition to assisting with the selection process, the SEPs also prioritize the NExT pipeline on a quarterly basis. The NExT Development and Discovery Committees manage budgets and allocate funding to prioritized projects.

Dr. Doroshow reiterated the goals of the NExT program. NCI's new therapeutics platform seeks to: develop treatments for unmet medical needs (e.g., rare cancers and pediatric tumors); provide resources for natural product development and the development of high-risk targets; and move discoveries from The Cancer Genome Atlas into drug discovery. Success of the NExT program will be measured by IND filings, licensing of novel therapeutics, improved cancer therapeutics success rates, and approved New Drug Applications developed from academic and small biotechnology research.

Questions and Discussion

Dr. Niederhuber commented that a major challenge accompanying NExT is ensuring that this new therapeutics platform is tightly interfaced with data generated from TCGA.

Dr. Abbruzzese expressed concern over the metrics being used to evaluate the success of NExT. The purpose of the program is to develop treatments for unmet medical needs (i.e., nontraditional targets), yet traditional endpoints (e.g., INDs) will be used to assess success. The success measures should be broadened to reflect the true value and difficulties of the program.

Dr. Schilsky questioned how the research community will access NExT resources in the context of the peer review process when applying for P01, Specialized Program of Research Excellence, or Special Translational Research Acceleration Project (STRAP) funding—peer reviewers might not be aware of NExT. Dr. Doroshow stated that the NExT program has worked very hard to avoid double review that may delay development of therapeutics. In terms of STRAP awards, the NExT review process will be the primary method by which review occurs for the Translational Research Working Group (TRWG) small-molecule pathway.

Dr. Parkinson suggested that NExT consider ways to interface with pharmaceutical companies downstream. Creating drugs is hugely risky and expensive and it would be advantageous to utilize industry expertise to leverage resources and accelerate the drug development process. Dr. Niederhuber commented that ground was broken about a month ago for an advanced technology research facility aimed at enabling scientists to more rapidly develop a new generation of highly targeted treatments for cancer patients. The initial phase of the project, in which NCI will be the anchor tenant, will provide up to 330,000 square feet of space for offices and state-of-the-art laboratories. This research park will facilitate interactions between the government, the academic community, and the private sector.

X. UPDATE ON THE TRANSLATIONAL RESEARCH ACCELERATION INITIATIVE—DR. LYNN MATRISIAN

Dr. Lynn Matrisian, Special Assistant, Office of the Director, NCI, provided an update on the Translational Research Acceleration Initiative.

Translational Research Acceleration Initiative Background. The Translational Research Acceleration Initiative stems from the work of the TRWG. The TRWG developed a series of Pathways to Clinical Goals and defined the challenge of early translational research as ensuring that the most promising concepts enter the Pathways and that concepts advance to clinical testing or productive failure as rapidly, efficiently, and effectively as possible. The Translational Research Acceleration Initiative aims to look across the spectrum of ongoing translational research, select several projects each year that are "ripe" for translation, and provide these projects with the resources and project management necessary to move them into early clinical testing. The Initiative will not impact discovery research or replace existing NCI infrastructure or mechanisms for supporting clinical or translational research. In December 2008, CTAC recommended that NCI proceed with establishing a process to accelerate translational cancer research that involved gathering information, prioritizing concepts, and determining how to fund and manage projects.

Immune Response Modifier Pilot Prioritization Process. It was decided that the Process to Accelerate Translational Research (PATS) would be piloted using the Immune Response Modifiers

(IRM) Pathway. The IRM Pathway was chosen because it is the most complex of the Pathways and there have already been efforts to prioritize agents within the IRM Pathway. The IRM Pilot Prioritization Process was conducted in two phases. Phase I of the process focused on antigen identification (one small part of the Pathway), with the goal of developing a well-vetted, ranked priority list of cancer vaccine target antigens based on predefined and preweighted objective criteria. To do this, a group of experts developed a list of "ideal" cancer antigen criteria/characteristics, which were subsequently prioritized and weighted using pairwise comparisons. Next, 100 representative antigens were identified. With input from experts, information related to the predefined criteria was assembled for each antigen, and the antigens were ranked. The results of this effort were published in *Clinical Cancer Research* in September 2009.

For Phase II of the IRM Pilot Prioritization Process, the IRM Subgroup of the CTAC PATS Working Group used a similar process to prioritize elements along the entire Pathway according to predefined and preweighted objective criteria. Seven Pathway components were identified as requiring prioritization: target identification (antigen/T cell), formulation, immune modifier agent (IMA), combination regimen, assay for immune response, assay to select patient population, and availability of patients for clinical trials. For each of these components, scientific validity, feasibility, and levels of evidence were considered. The Analytical Hierarchy Process (AHP), a structured technique for complex decision making, was used to assist in this process. AHP is based on mathematics and human psychology and provides a comprehensive framework to structure a problem, represent and quantify key elements, relate key elements to overall goals, and evaluate alternative solutions.

The next step was to gather information about IRM translational research opportunities. A request for information (RFI) was released to obtain input from the research community. In addition, information was drawn from work of the NCI Division of Cancer Biology (DCB), led by Dr. Martin (Mac) Cheever, Director of the Solid Tumor Research Program at Fred Hutchinson Cancer Research Center that identified the top immune-modifying agents. Finally, abstracts submitted by researchers for presentation at the NCI Translational Science Meeting were scanned for information relating to IRM research.

Once the relevant information was assembled, the CTAC IRM Prioritization Working Group was convened to determine which IRM opportunities were most "ripe" for acceleration. The AHP-based Decision Lens tool was used to facilitate this process. Decision Lens is a Web-based platform that supports collaborative decision making. Importantly, it does not make decisions; rather, it facilitates evaluation of information. Through this process, 113 IRM translational research opportunities were identified. The components of these opportunities were extracted and linked to the Pathway; additional key components were added as necessary. This resulted in identification of 174 key component candidates. These components were organized into "buckets" (e.g., antigens, adjuvants) and prioritized within these buckets by Working Group members based on scientific validity and feasibility. These prioritized components were then reconstructed into "scaffolds," which included all of the elements needed to research a particular immunotherapy approach (e.g., vaccine, adoptive therapy).

Dr. Cheever discussed components of the IRM Pathway and recent activities of the IRM Prioritization Working Group at this time (see section XI below).

XI. IMMUNE RESPONSE MODIFIERS PRIORITIZATION WORKING GROUP REPORT—DR. MARTIN CHEEVER

Dr. Cheever discussed components of the IRM Pathway and recent activities of the IRM Prioritization Working Group.

The IRM Pathway differs from the Agents Pathway in that the agents used do not directly affect cancer cells; the agents induce an immune response, which then impacts cancer cells. An advantage with the IRM Pathway is that there have been phenomenal advances in the discovery and invention of immunotherapy agents—many of which can be readily manufactured. These agents would have great potential for benefitting cancer patients if they were available for efficacy testing and if focused funding were available to conduct clinical trials to determine proper usage. For example, a number of agents have been discovered that could substantially improve cancer vaccines but are not available for use; these agents include dendritic cell activators and growth factors, vaccine adjuvants, and T-cell stimulators and attracting agents. Similarly, agents to increase antibody-dependent cellular cytotoxicity (ADCC; i.e., the host component of antibody therapy) have been discovered but are not in standard use.

Translation through the IRM Pathway begins with credentialing of the antigen target and immune modifier agent of interest, followed by creation of the modality or regimen and development of supporting tools (e.g., assays), concurrent scale-up and manufacturing of agents, and, finally, iterative clinical trials. Many of the immunotherapy agents previously discussed have already moved down the IRM pathway, but a persistent gap exists at the clinical trial stage. One reason for this gap (or barrier) is that concurrent development of several unapproved agents is exceedingly difficult and many immune modifier agents are unlikely to work as monotherapy. Also, current funding mechanisms support the best grants or research groups and not necessarily the best trials.

The newly developed funding strategy, STRAPs, may provide a mechanism for designing and funding the best trials possible by bringing together the most promising components of an immunotherapy regimen. STRAPs provide the organizational structure and funding mechanisms for top-prioritized trials and teams of experienced investigators. STRAPs also support the capacity to elucidate reasons for success or failure and provide adequate and timely funding, as well as project management.

The IRM Prioritization Working Group decided to focus on four IRM categories for pathway prioritization and development for STRAPs: vaccines, autologous T-cell therapy, antibody therapy, and combinations of immune modifier agents. IRM cancer vaccines activate and expand the number of patient T cells capable of specifically killing cancer cells. T cells combat microbes, including viruses and bacteria, and have an infinite repertoire to recognize any pathogen in the body. NCI supported various workshops to determine prioritization schemes of the three components of cancer vaccines: antigens, immune modifying agents, and regimens. The first phase of this pilot prioritization project focused on developing a well-vetted, ranked priority list of cancer vaccine target antigens based on predefined and preweighted objective criteria. The goal was to identify the vaccine regimen with the highest potential for success.

The Cancer Antigen Prioritization Project was held in October 2008—none of the 75 analyzed antigens had all of the criteria/characteristics of an "ideal" cancer antigen; 20 antigens had suggestive clinical efficacy and 46 were immunogenic in clinical trials. Dr. Cheever discussed a few examples of immunotherapies that have exhibited some clinical efficacy. The WT1 peptide-based vaccine induces cytotoxic T-lymphocyte response and tumor regression in some patients. HER2-positive breast cancer patients in remission who received a HER2 peptide-based vaccine remained disease-free longer than control patients. Treatment with a MUC1 peptide-based vaccine resulted in higher survival of advanced-stage NSCLC patients compared with best supportive care, although the increase in survival was not statistically significant. Similarly, the MAGE-A3 protein-based vaccine resulted in an improvement in disease-free survival among NSCLC patients that did not reach statistical significance.

Prior to the antigen workshop, NCI held an informal Immunotherapy Agents Workshop to prioritize agents with high potential for cancer therapy. A group of immunotherapy experts developed a ranked list of agents from submissions to the Workshop Web site. The list comprised agents with

potential that were not broadly available for testing in patients with cancer. These agents include T-cell growth factors, dendritic cell activators, compounds that attract T cells to sites, and inhibitors of T-cell checkpoint blockade. T-cell expansion is strictly limited, but agents (some just listed) have been created to circumvent the limitations of T-cell proliferation.

The most recent NCI-supported prioritization effort—the Immune Response Modifier Pathway Pilot Project—focused on combining the antigens and agents into regimens with the highest potential of success to develop concepts for an IRM STRAP. The ideas collected through the RFI and the Translational Science Meeting abstracts were good; however, investigators had a tendency to propose doing work similar to what they were already doing and using readily available reagents rather than the best possible reagents. This is why it was necessary to deconstruct the proposed regimens into "buckets" (i.e., types of components, such as vaccine antigens, T-cell targets, adjuvants, suppressors) and prioritize the regimen components within the buckets. To prioritize antigens with a high potential for success, antigens identified through the previously described processes were evaluated for therapeutic efficacy and immunogenicity as well as their appropriateness for STRAP support (i.e., antigens must be defined and common enough that patients can be accrued to clinical trials in a reasonable amount of time; the approach should be not be currently ready for Phase III trials). Similar criteria were used to prioritize immune modifying agents.

Prioritized components were reconstructed into various "scaffolds." For example, the cancer vaccine scaffold requires a component from the following buckets: an antigen, a formulation, an assay to measure response, and an assay to support patient selection. To maintain an effective immune response, it is also necessary to utilize an adjuvant and at least one T-cell modulatory factor (e.g., T-cell factors, inhibitors of T-cell checkpoint blockade, inhibitors of suppressive factors). Scaffolds were also created for adoptive therapy, antibodies, and immune modifier agents. The challenges and opportunities associated with the scaffolds vary. For example, there are already a number of therapeutic antibodies approved by FDA; however, it may be possible to increase the efficacy of these agents by combining them with a drug that augments antibody-dependent cell-mediated cytotoxicity.

The IRM Prioritization Working Group recommends four potential STRAPs representing three scaffolds: viral antigen vaccine, self-cancer antigen vaccine, adoptive therapy, and antibody therapy. The Working Group determined that NCI should anchor two of the necessary buckets by providing T-cell stimulators or T-cell growth factors, as well as inhibitors of T-cell checkpoint blockade. NCI should also provide adjuvant. Investigators would identify a target and be responsible for formulation, as well as assays for selecting and monitoring patients.

Several examples of IRM translational research opportunities that might become STRAPs were described. The first is a human papilloma virus (HPV) vaccine for cervical cancer *in situ*. This prime-boost (primed DNA followed by vaccinia boost) regimen is very effective for generating an immune response. NCI would provide the appropriate adjuvants and IL-7 or T-cell-stimulating antibodies to maintain the immune response generated by this vaccine. The second example uses three to four separate peptides with dendritic cells as adjuvants. NCI would provide appropriate adjuvants and an IMA such as a T-cell growth factor or inhibitor of T-cell checkpoint blockade, to sustain the immune response. The third opportunity involves a combination of tumor-infiltrating T-cells with highly toxic, myelosuppressive therapy followed by IL-2. The STRAP would be similar, but a more appropriate T-cell growth factor, such as IL7, IL15, or IL21 would be use instead of IL2. The final opportunity would involve modification of commercial antibodies known to function in part via ADCC and supply IRM agents known to increase ADCC for iterative early-phase trials.

SUMMARY OF IRM PRIORITIZATION WORKING GROUP RECOMMENDATIONS AND PATS FOR OTHER PATHWAYS—DR. LYNN MATRISIAN

Dr. Matrisian summarized the IRM Prioritization Working Group's recommendations as well as next steps of IRM pathway development. Dr. Matrisian also discussed planned PATS for other TRWG pathways.

IRM Next Steps. If CTAC approves the Working Group's recommendations, they will undergo an internal NCI prioritization process that will involve consideration of logistical feasibility, clinical need, and appropriateness for NCI investment. Based on the results of this process, one to four STRAP concepts would be developed. The goal of a STRAP is to move a project forward to the end of one of the Pathways (i.e., early-stage human testing). It is envisioned that STRAPs will leverage ongoing work, and project management will help link the various components of the effort. The STRAP concepts would need to be approved by NCI leadership and advisory boards, as appropriate, and then be presented to the extramural research community as a request for supplements, request for proposals, or request for applications. Submissions would undergo peer review using the criteria established by the IRM Prioritization Working Group. Final funding decisions would depend on NCI leadership and advisory board approval.

PATS for Other Pathways. Plans are under way to conduct pilot projects for each of the other TRWG Pathways. Work will begin on the Agents, Biospecimen, and Lifestyle Alterations Pathways in late 2009 through early 2010. Efforts related to the Agents Pathway will be integrated with the NExT program. Work is slated to begin on pilot projects for the Imaging and Interventive Devices Pathways in Spring 2010.

Summary. The prioritization and acceleration process described is consistent with what was envisioned by the TRWG: it evaluates the status of NCI's investment in translational research and envisions its future in an inclusive, representative, and transparent manner. This process should help overcome barriers resulting from the dispersal of translational research across NCI's Divisions, Offices, and Centers, and represents a departure from "business as usual." The ultimate goal is to accelerate translational research. Metrics are being constructed so that the success of the STRAP effort can be evaluated once it has been implemented.

IRM Prioritization Working Group Recommendations. The Working Group recommends that four STRAPs representing three scaffolds be developed; these would include a vaccine for a viral antigen, a vaccine for a self-cancer antigen, an adoptive cellular therapy, and an antibody therapy. NCI would anchor some "buckets" by providing the necessary immune modifying agent and/or adjuvant to awardees. This would allow investigators to focus their applications on target development.

Questions and Discussion

Dr. Edith Perez, Professor of Medicine in the Mayo Medical School Division of Hematology/Oncology and Director of the Mayo Clinic Foundation Breast Cancer Program, expressed concern about testing new combinations (e.g., vaccine-adjuvant combinations) even when existing data suggest that a previously tested combination may have some clinical effect. Dr. Cheever responded that if a previously tested vaccine-adjuvant combination has been shown effective enough to warrant a randomized Phase III clinical trial, this regimen should be pursued. However, most cancer vaccines tested to date have not exhibited sufficient clinical efficacy, in part because there has been a general lack of

good adjuvants and immune modifying agents to administer with them. For these vaccines, it is important that researchers try new combinations to achieve a high-level immune response that warrants randomized Phase III testing.

Dr. Abbruzzese expressed concern about focusing on the IRM Pathway for the first PATS pilot test. There is a tremendous amount of complexity in the immune system, as well as uncertainty about many immunotherapy agents. Given the fact that there has been relatively little clinical success using immunotherapies, it may be difficult to evaluate whether the STRAP process is effective in promoting progress. Dr. Matrisian responded that one of the reasons for selecting the IRM Pathway was that researchers in this area reported being unable to conduct clinical trials to test combinations; developing an effective way to prioritize and test combinations would be an important advancement. Although it is impossible to predict whether these immunotherapy regimens will be clinically effective, there is reason to be optimistic that enhancing the antitumor immune response would be beneficial. Dr. Cheever reiterated that it is very likely that achieving a sustained antitumor immune response will benefit cancer patients; the immunotherapy research community needs access to immunotherapeutic agents in order to learn how to use them effectively. Dr. Abbruzzese stated that intermediate immune response does not necessarily translate to clinical benefit.

Dr. Schilsky asked how clinical need would be incorporated into the prioritization process. Dr. Matrisian responded that the initial efforts of the Working Group focused on scientific validity and feasibility and that decisions based on clinical need would be made later. Some thought has been given to the criteria that should be used to evaluate clinical need, and efforts have been made to work with patient advocates and oncologists on this issue.

Dr. Adamson asked which of the four STRAPs proposed would be most likely to represent an "early win" (i.e., exhibit clinical benefit in the short term). Dr. Cheever provided his personal opinion that T-cell therapy is likely the most promising from this standpoint because it is already in use as a treatment for melanoma. Although it may be possible to achieve a strong immune response using a vaccine, showing an effect on disease progression would likely require randomized clinical trials, which take time. It may also be possible to have an "early win" with antibody therapy by finding a way to increase antibody-dependent cell-mediated cytotoxicity in patients who currently do not respond to these therapies. Dr. Matrisian added that the IRM Prioritization Working Group was asked not to prioritize among the four proposed STRAPs in order to provide NCI with some leeway moving forward.

Ms. Roach asked whether metrics had been identified to determine short-term success of the STRAP effort (e.g., more trials opening, more patients on trials). Dr. Matrisian responded that there will be a multipronged approach to look at short-term, as well as some longer-term, measures; however, the details are still being developed. Dr. Cheever added that many immunotherapy trials are ongoing, but it is hoped that this process will help focus resources on those most likely to be effective.

Dr. Schilsky made a motion to approve the recommendations of the Working Group. The motion was seconded and discussion continued.

Dr. Niederhuber informed the members that two committee members—Drs. Abbruzzese and Cowan—had read the Working Group report prior to the meeting. Drs. Abbruzzese and Cowan were asked to provide their review.

Dr. Abbruzzese commended the work done to organize and clarify the state of the immunologic therapies field and stated that the process used for prioritization was great. However, he expressed uncertainty about the initial STRAP investment being in the area of immunotherapy because it is unclear that immunotherapy will translate into significant clinical benefit for patients. This concern may be

mitigated in part by the fact that the pilot tests for the other Pathways will begin soon. He stated that the Committee should have been asked about prioritizing different areas before extensive work was put into developing the IRM concepts. The work that has been done by Drs. Matrisian and Cheever and the Working Group should be rewarded, but the Committee might not have selected IRM as an optimal area for investment if it had been offered a choice.

Dr. Cowan commended the immunotherapy research community for working together to establish a paradigm for prioritization of different types of agents. He reminded the group that the effort to prioritize immunotherapeutic targets and agents goes back to 2006, predating much of the work of the TRWG and setting the stage for development of the STRAP concepts. He expressed some concern that the IRM efforts could consume all of the STRAP resources for the next 2 years. Much could be learned from moving forward with the IRM STRAPs. NCI will need to find a way to prioritize among the four ideas proposed by the Working Group. Also, the research community will find out whether testing the desired combinations will lead to more robust clinical responses and improved clinical outcomes.

Dr. Runowicz gave her view that with a new program it is important to invest in projects with a high likelihood of success. A negative outcome after a large investment will have ripple effects on future efforts. Dr. Runowicz also expressed concern that HPV is listed as a high-priority target because, relative to other cancers, cervical cancer is not a major problem in the U.S. Ms. Roach reminded the group that HPV is associated with other cancers aside from cervical cancer.

Ms. Roach suggested that it is impossible to know whether something will work unless it is tested. She reported observing paralysis in the medical research community because researchers are afraid to test a concept they think might fail. There are important lessons to be learned from failure, and most medical research ends in failure. There is a cost associated with investing in an IRM STRAP, but there is also a cost associated with allowing the immunotherapy field to continue pursuing research in a fragmented, suboptimal way.

Dr. Doroshow marveled at the complexity of the process undertaken by Drs. Matrisian and Cheever and the Working Group and expressed uncertainty about whether the process could be replicated in the future. He also pointed out that NCI already devotes considerable funding to immunotherapy, in part through program projects; however, none of the funded institutions has the wherewithal to put all of the necessary pieces together. It might be worthwhile to fund a STRAP to link together the various aspects of immunotherapy research rather than having them continue to be fragmented.

Dr. Schilsky acknowledged the skepticism of several of the Committee members about the potential of immunotherapy but pointed out that some immunotherapies do work. These include allogeneic bone marrow transplants and monoclonal antibodies, as well as some therapeutic vaccines that have shown promise in randomized clinical trials. He proposed that it would be worth the investment to conduct a few well-designed immunotherapy studies with strong scientific rationales to gain insight into the potential of these types of treatments. Dr. Niederhuber pointed out that the most progress has been made in the area of prevention vaccines.

Dr. Deborah Bruner, Independence Professor in Nursing Education at the University of Pennsylvania School of Nursing, questioned whether approval of the Working Group recommendations would mean that the IRM Pathway would be prioritized above the other Pathways given the limited resources available. Drs. Doroshow and Niederhuber stated that this process was not meant to prioritize the IRM Pathway above the other Pathways. Also, funding for the IRM STRAP or other STRAPs will depend on the decision of an internal NCI committee and be dictated in part by the NCI 2010 budget. Dr. Niederhuber explained that this pilot project is meant to provide insight into whether the STRAP process would be a feasible and appropriate way to prioritize and accelerate translational research.

Dr. Adamson reiterated the importance of an "early win." He stated that neither the Working Group nor NCI should prioritize among the four proposed STRAP concepts. Rather, applicants should be asked to develop ideas in any of the four areas and clearly describe their plans to move forward.

Dr. Niederhuber expressed concern that the very complex process described would take months to years to implement (i.e., solicit and review applications, distribute funding). The Congress and the public do not want another drawn-out process and are looking to NCI to create new ways to answer questions more rapidly. This is why the Chemical Biology Consortium and the Functional Biology Consortium were designed to facilitate quick decisions and support tasks with clearly defined deliverables and timelines. Dr. Abbruzzese agreed that although some good might come of the investment in immunotherapy, the process described is not the facile process envisioned by the TRWG. He speculated that it might be a good idea to rethink the STRAP awards and try to develop a more efficient process with less bureaucracy.

Dr. Tepper stated that CTAC should support the Working Group recommendations; however, he thought the support should be somewhat limited (i.e., not all four STRAPs). He pointed out that although the research being proposed is complex, the direction of the concepts is well defined. He also expressed serious concerns regarding whether the approach used for the IRM Pathway would work for the other Pathways.

Dr. Cowan observed that most of what could be done through the STRAP mechanism could also be supported through NExT, which has processes in place for prioritization. Dr. Doroshow responded that the need for the various adjuvants may not have come through as clearly through the normal NExT application process.

Dr. Niederhuber stated that the STRAP process as described might be a better idea if there were unlimited resources. The projects described would result in new knowledge; however, it is likely that the NCI budget will be austere over the next few years, and it may not be prudent to invest in this type of endeavor.

Dr. Perez reported that she and her group had recently proposed a Phase III vaccine trial, but reviewers felt the trial was not ready because there may be a more effective adjuvant than the one proposed. Her group must now conduct additional earlier-phase studies. This is a problem that plagues the immunotherapy field—hesitancy moving forward because of the possibility that there might be something better.

Motion. Dr. Tepper moved that CTAC accept the Working Group report, per Dr. Schilsky's motion, and move forward with the IRM STRAP pilot project. The motion was seconded. Dr. Adamson suggested amending the motion to move forward with limited resources to allow a proof of concept. Dr. Schnall asked whether it would be possible to determine STRAP opportunities for the other Pathways before investing in the pilot. Dr. Niederhuber pointed out that this process could take years and consume too much time and too many resources.

The motion was passed with seven yeas, five nays, and no abstentions.

Dr. Niederhuber thanked the Committee for its discussion and consideration.

Dr. Tepper asked whether efforts similar to those for the IRM Pathway should be conducted for the other Pathways. Dr. Niederhuber reiterated that this would take tremendous time and resources, and

stated that he and Dr. Doroshow and others will discuss the idea internally and report back to the Committee.

XII. NEW BUSINESS—DR. SHEILA PRINDIVILLE

Dr. Prindiville informed CTAC members that she could e-mail the new business items to those interested. She also thanked the members who participated in the agenda planning. Future teleconferences will be arranged with CTAC members to plan the agenda for the March 10, 2010 meeting.

ADJOURNMENT—DR. JOHN NIEDERHUBER

Dr. Niederhuber expressed his gratitude to all of the CTAC members for their participation and input.

There being no further business, the 9th meeting of the CTAC was adjourned at 4:15 p.m. on Wednesday, November 4, 2009.