Board of Scientific Advisors

Meeting Minutes

March 13, 2006

Building 31C, Conference Room 10
Bethesda, Maryland

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 33rd meeting on Monday, 13 March 2006 at 11:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, President, Fox Chase Cancer Center, presided as Chair.

The meeting was open to the public on 13 March for ongoing and new business, an update on the American College of Radiology Imaging Network (ACRIN), a report on cluster reviews of Program Project (P01) grants, an update on implementation of recommendations of the Clinical Trials Working Group (CTWG), presentation of a concept for re-issuance of a Request for Applications (RFA) and Cooperative Agreement, and reports on reinventing early drug development at the NCI and on the Colorectal Cancer Family Registries (CFR).

Board Members Present:
Dr. Robert Young (Chair)
Dr. David S. Alberts
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
Dr. Susan J. Curry
Dr. William S. Dalton
Dr. Raymond N. DuBois
Dr. H. Shelton Earp III
Dr. Kathleen M. Foley
Dr. Sanjiv Sam Gambhir
Dr. Joe W. Gray
Dr. William N. Hait
Dr. James R. Heath

Board Members Present:
Dr. Michael P. Link
Dr. Christopher J. Logothetis
Dr. Kathleen Mooney
Dr. Mack Roach III
Dr. Richard L. Schilsky
Dr. Ellen V. Sigal
Dr. Margaret Ruth Spitz
Dr. Jane Weeks

Board Members Absent:
Dr. Esther H. Chang
Dr. Patricia A. Ganz
Dr. Mary J.C. Hendrix

Dr. Leroy Hood
Dr. Susan B. Horwitz
Dr. Hedvig Hricak
Dr. Eric Hunter
Ms. Paula Kim
Dr. Kenneth W. Kinzler
Dr. Lynn M. Matrisian
Dr. Edith A. Perez
Dr. John D. Potter

NCAB Liaison:
TBN

Others present: Members of NCI's Executive Committee (EC), NCI staff, members of the extramural community, and press representatives.

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I. CALL TO ORDER AND OPENING REMARKS—DR.

ROBERT YOUNG

Dr. Young called to order the 33rd regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. He reminded Board members of the conflict-of-interest guidelines and confirmed meeting dates through November 2008. The dates to be confirmed extend to November 2008. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting.

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II. CONSIDERATION OF THE NOVEMBER 14, 2005 MEETING MINUTES — DR. ROBERT YOUNG

Motion: The minutes of the November 14, 2005 meeting were approved unanimously.

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III. ONGOING AND NEW BUSINESS—DR. ROBERT C. YOUNG

NCI Listens Subcommittee Report—Ms. Paula Kim

Ms. Paula Kim, President and Founder, Translating Research Across Communities Network, presented the report of the NCI Listens Subcommittee (Drs. Kirby Bland, Mary Hendrix, Hedvig Hricak, and NCI staff Drs. Alan Rabson Paulette Gray). The Subcommittee's charge was to ascertain whether NCI Listens sessions at relevant cancer related meetings should continue and if yes, to recommend an appropriate format. Ms. Kim briefly reviewed the Subcommittee's analysis of events held throughout the past 6 years and the issues that were raised. She stated that, on the basis of its deliberations, the Subcommittee recommends that the program be continued but with the development of a more

systematic process for identifying host organizations and areas of discussion that are important to the NCI and relevant to its strategic initiatives. Another suggestion was that a mechanism be developed internally for cross-communication with the NCI Office of Communications, Office of Liaison Activities, and Office of Science Planning and Assessment.

In discussion, the following point was made:

- Larger organizations increasingly have independent means of communicating with the NCI. Other organizations that have not had an opportunity to interact with the NCI and raise issues of importance to their constituencies, in particular, those in the biomedical imaging community.
- A future topic for the sessions might be to describe the decision-making process relative to the budget and funding priorities currently employed in the NIH and NCI and the changes in structure, management, and process that are being considered so the constituencies have an opportunity to weigh in on the issues.
- The NCI Listens sessions provide an opportunity for large numbers of people, from students to retired professions, to interact with the NCI and, as such, are especially important at this time. However, the sessions should be restructured to focus on a few topics, and care should be exercised to retain the emphasis on listening.
- The consensus of the BSA appeared to be that the NCI Listens sessions should be continued. Drs. Gray, Rabson, Young, Niederhuber and Ms. Kim will propose a strategy to incorporate the Subcommittee's recommendations for presentation at the next BSA meeting. Dr. Niederhuber suggested that visits to the NCI by the leadership of the organizations would promote valuable dialogue and information dissemination. Young faculty and trainees should be a particular focus of the sessions.

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IV. AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK (ACRIN) UPDATE—DRS. DANIEL SULLIVAN AND BRUCE HILLMAN

Dr. Daniel Sullivan, Associate Director, Cancer Imaging Program (CIP), Division of Cancer Treatment and Diagnosis (DCTD), reminded members that ACRIN was funded as a cooperative group in 1999. NCI leadership will consider re-issuance of the Request for Applications (RFA)/Cooperative Agreement soon which would then come to the Board for concurrence. Dr. Sullivan introduced Dr. Bruce Hillman, Professor of Radiology and Professor of Health Evaluation Sciences, University of Virginia, and ACRIN Chair

Dr. Hillman reminded members that ACRIN is an all-electronic clinical trials network that focuses on diagnostic imaging and image-guided treatment as it relates to cancer. The network is funded through two linked U01 grants, which are organized and supervised by the Cancer Imaging Program. ACRIN headquarters is located in the ACR research offices in Philadelphia, and the Biostatistics and Data Management Center is located at Brown University. Unlike other cooperative groups, ACRIN is a completely open, non-member network that includes physicians, scientists, methodologists, industry, and patient advocates. More than 130 sites are now qualified to participate in ACRIN trials, and currently, more than 60 are involved in at least one. ACRIN strategy subsumes five key hypotheses: 1) image screening reduces mortality; 2) image-guided treatment provides local control and may extend life; 3) molecular imaging allows for earlier and improved detection, diagnosis, staging, and treatment; 4) metabolic/ functional imaging can serve as an early indicator of therapeutic effectiveness; and 5) imaging informatics can improve diagnosis and treatment. Dr. Hillman summarized the major achievements of the past 7 years.

Dr. Hillman informed members that every image (about 7 million) from every ACRIN trial has been archived electronically and is available for secondary research and education, particularly for the development of smart systems. Consciousness about the importance of imaging to cancer trials has been raised. Standards of quality for imaging in therapeutic trials have been disseminated, and the Network has become integrated and involved in the cancer research community. Dr. Hillman called attention to ACRIN's extensive collaborations with treatment cooperative groups, industry and foundations, patient advocacy groups, academia, cancer centers, the Special Programs of Research Excellence (SPOREs), community hospitals and clinics, and other government agencies, such as the Food and Drug Administration (FDA). Of

particular note was the strong Patient Advocate Committee, members of which have been integrated into everything ACRIN does, from decision-making committees to clinical trials.

Dr. Hillman pointed out that imaging can be applied to the four areas of cancer care: screening, diagnosis and staging, treatment, and marker of response. As examples of imaging applications, he briefly described four trials that focus on two of the areas—screening and imaging as a biomarker for therapeutic effectiveness. The first was the Digital Mammographic Imaging Screening Trial (DMIST), which compared the diagnostic performance of digital and screened-film (SF) mammography. He stated that the accrual record on this trial was excellent, due partly to the role played by patient advocates. The primary objective was published online in September 2005 and in the *New England Journal of Medicine* the following month. Digital and SF mammography performance was shown to be equivalent for the general population, but digital was shown to be superior for women who represented almost 40 percent of the cohort. These included women under age 50, perimenopausal women, and women who have dense breasts. Dr. Hillman noted that this finding has had an immediate impact on clinical care in that women are asking whether they fit these categories and are asking for the digital procedure if they do. As a result, the demand for digital mammography is exceeding the supply.

As a second example of imaging application, Dr. Hillman described the ACRIN-generated National Lung Screening Trial (NLST), which tests screening by chest radiography versus computed tomography (CT). The imaging-related primary objective of the NLST—to determine whether mortality is reduced by screening—has important health and health care cost implications. NLST is a randomized trial of more than 50,000 older subjects (18,893 accrued by ACRIN) who are at high risk because of a long-term smoking history. He noted that the NLST is being conducted in partnership with the Lung Screening Study (LSS). In addition to the ACRIN/LSS primary goal of studying the effect of screening on lung cancer-specific mortality, ancillary goals are to study the impact of screening on smoking behaviors and the effect of screening on medical resource utilization, cost, and quality of life. A significant, additional focus for the ACRIN side of the study is the development of a biospecimen archive for future research into molecular markers. Accrual expectations were also met in this

study. He explained the planned accrual timeline that is laid out for every trial, with benchmarks every 3-6 months and plans for remediation if accrual does not meet those goals. For this trial, remediation was necessary, and ACRIN joined forces with the American Cancer Society and initiated community-based efforts at all accrual sites to address the problem.

In the third ACRIN study discussed by Dr. Hillman, imaging is studied as a marker for therapeutic success. The study, a collaboration with the Cancer and Leukemia Group B (CALGB) and the Breast Special Program of Research Excellence (SPORE), is an assessment of response to neoadjuvant chemotherapy using dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI). He reviewed the complicated schema for the trial and noted that, although participation is rigorous for the patient, accrual was successful at 10 sites and nearly everyone was retained in the sample. Goals of the study are to: 1) demonstrate the feasibility of a multi-institutional trial of DCE-MRI; 2) evaluate DCE-MRI as a predictor of initial treatment response; 3) determine the relationship between DCE-MRI and survival; and 4) correlate DCE-MRI characteristics with those of histopathologic markers.

The final trial presented was a correlative trial to be conducted in collaboration with the South West Oncology Group (SWOG), testing another functional technology. Members were told that positron emission tomography (PET) will be tested as an early indicator of treatment response to combined treatment for metastatic melanoma. PET scans will be obtained prior to treatment and at 3 and 9 weeks following treatment, with a 3-year followup. PET findings will be correlated with conventional CT or MRI response, characteristics of pathologic specimens, and clinical outcome. Accrual of 110 subjects is planned to begin in 2006. Study goals are to demonstrate the feasibility of standardizing PET acquisition and analysis over multiple sites and to validate PET as a predictor of initial therapeutic response, survival, and therapeutic response based on tumor molecular characteristics.

On behalf of ACRIN leadership and participants, Dr. Hillman expressed the belief that ACRIN’s multicenter, rigorous, and generalizable clinical trials are essential to the improved use of imaging in cancer care. They have the potential to improve the appropriateness of cancer care, hasten the implementation of promising new diagnostic methods and cancer treatments, facilitate

the valid incorporation of imaging into therapeutic trials, and advance imaging science as it applies to cancer. He concluded by stating his own belief that ACRIN is a unique clinical trials resource whose capabilities are not duplicative of any other NCI endeavor. Moreover, ACRIN's successful formative years presage the potential for considerable future contributions, and, given sufficient resources, ACRIN bears the potential to help reduce death and illness from cancer.

In discussion, the following point was made:

- Patients identified in DMIST as having positive outcomes will continue to be studied; many publications are expected to result from this trial.
- The Center for Medicare and Medicaid Services (CMS) has begun coverage of PET in trials, which has been helpful as a source of additional funding for ACRIN in the over-65 population.
- At this time, nearly all monies for funding ACRIN core trials are NCI funds, with some additional funding from the AVON Foundation. The hope is that the core funding can be sustained and sources for new revenue can be identified to build from there.
- The Memorandum of Understanding signed recently by the CMS, FDA, and NCI presents an opportunity to move the whole area of imaging forward.
- ACRIN 6677, which is in final protocol development stages, will study PET as an intermediate endpoint for treatment for lung cancer.
- The real test of intermediate markers is whether they translate into an impact on survival or late downstream effects. They are a real advance only if they are shown to be an early marker for survival benefit or if they alter therapy in a major way.

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V. WORKING LUNCH: UPDATE ON REVIEW OF PROGRAM PROJECT APPLICATIONS—MS. DIANE BRONZERT AND dR. OLIVIA BARTLETT

Ms. Diane Bronzert, Associate Director, Office of Referral, Review and Program Coordination, DEA, provided an update on the review of program projects applications. In Fiscal Year (FY) 2005, there were 176 P01s, including competing and noncompeting continuation applications worth approximately $338 M in total costs. The number of P01s has been consistent during the last several years, ranging between 174 and 178, and the dollar amount has been generally steady, with only a small decrease in the percent of the research project grant (RPG) budget. In FY 2005, 129 P01 applications were reviewed and 39 were funded at $66.9 M total cost. Approximately 80 percent of those 39 awards were amended applications, either A1s or A2s, and the ones that made it through the first time were usually renewal applications.

The P01s are multiproject grants and NCI's standard mechanism for conducting collaborative interdisciplinary research. Following a review of the changes in the P01 review process, Ms. Bronzert informed members that in 2003, a NCI Program Project Working Group, composed of review staff and representatives from the extramural program divisions, recommended the implementation of small cluster reviews and the elimination of the site visits and individual teleconferences. The cluster review panels would score the projects and cores, and a second-tier review of the P01 chartered committees would provide the final priority scores. It was implemented in February 2004 in time for the 2005 awards, and an evaluation of this process is underway. In 2005, the Working Group reconvened to evaluate the cluster review pilot. Ms. Bronzert next described the process used and outcome of that evaluation. Specifically, the Working Group recommended 1) continuation of the P01 cluster reviews; 2) no site visits; 3) triage of poor applications; 4) eliminate the applicant teleconference during the review meeting; and 5) a 1-year pilot of single-tier peer review of large clusters by special emphasis panels (SEPs), which was implemented for applications with a February 1, 2006, receipt date.

The implementation plan is to distribute the current chartered members among the SEPs and continue the recruitment for new chartered members in 2006. Three current committees will be replaced by five SEP committees during this pilot, and the SEPs will form the basis for new chartered committees after the evaluation of the pilot. The P01 guidelines are posted on the Web site.

Dr. Olivia Bartlett, Branch Chief, Grants Review Branch, DEA, presented the SEP research topic areas. Dr. Bartlett explained that in conjunction with NCI program and review staff SEPS have been estalished based on the following parameters: 1) a maximum of four to six SEPs; 2) an even distribution of applications across clusters each round; 3) areas of overlap to allow assignment to more than one cluster, thereby addressing workload management and member conflict issues; and (4) clusters crossing NCI's extramural research programs.

Dr. Bartlett reviewed the current P01 chartered committees and their research areas. Subcommittee C (basic sciences), Subcommittee D (clinical sciences), and Subcommittee E (cancer epidemiology, prevention, and control). The five P01 SEP topic areas are 1) molecular biology; 2) cell and tissue biology; 3) discovery and development; 4) clinical studies; and 5) prevention, control, and population sciences. Members were told that the pilot will be evaluated 1 year from inception.

In discussion, the following points were made:

- Reviewers and parent committee members indicated through formal surveys, informal discussions, and feedback during the 2-year evaluation of the cluster pilot, that the teleconference did not have an impact in the final scoring. Rather, the reviewers already knew how the applicants were going to answer their questions. In addition, the questions in the teleconference were often perceived as very subjective and varied greatly for different reviews, sometimes very detailed oriented and sometimes very broad conceptually.
- The SEP groupings can be adjusted as necessary such that reviewers will overlap to cover the science and scoring calibration, just as has been done with the parent committees.
- Approximately 80 percent of the investigators are not funded the first time; this percentage probably would not change even with site visits. With the elimination of site visits investigators should be allowed to submit their applications in the best possible form, including the use of color.
- P01s are not funded according to a payline but rather on a case-by-case basis based on programmatic relevance.

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VI. UPDATE: CLINICAL TRIAL WORKING GROUP (ctwg) IMPLEMENTATION— DR. jAMES DOROSHOW

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis, reminded members of the five overarching themes around which the 22 recommendations from the CTWG were structured: 1) prioritization/scientific quality, involve all stakeholders in design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology; 2) standardization of IT infrastructure and clinical research tools; 3) coordination of clinical trials research through data sharing and providing incentives for collaboration; 4) operational efficiency, i.e., using resources most efficiently through improved cost-effectiveness and accrual rates, and more rapid trial initiation; and 5) integrated management by restructuring extramural and intramural oversight of NCI's clinical trials.

Dr. Doroshow informed members the implementation goals for 2006, as given on the original timeline, include the: 1) the establishment of an investigational drug steering committee for early phase clinical trials; 2) establishment of an initial, disease-oriented scientific steering committee for Phase III studies; and 3) development of criteria for correlative science and quality-of-life studies. Four IT-related activities in the area of standardization involve caBIG to develop electronic case report forms and a credentialing system, as well as a comprehensive database of information about all of the trials that the NCI supports. A further aim involves expanding the cancer trials support unit to enhance the coordination of clinical trials in SPOREs and cancer centers in NCI's cooperative groups. Likewise, there are efforts to enhance interactions between the NCI, FDA, and the pharmaceutical industry. The operational efficiency goals for 2006 involve the completion of a management analysis of barriers to a timely trial initiation, the implementation of funding to expand minority research and minority clinical trials outreach, and further interactions with the patient advocacy community. Integrated management goals advocate for an extramural clinical trials committee, operational integration of clinical trials within the NCI, and an evaluation system and baseline assessment.

Dr. Doroshow reviewed the Working Group's implementation activities for 2006: 1) Standardization involves four critical IT activities, including a detailed implementation plan, which has been completed with the help of Dr. Kenneth Buetow and caBIG; 2) nominations will be sought soon from BSA members, cooperative groups, cancer centers, and the SPORE community to serve on a significantly expanded clinical trials work space; 3) Cancer Trials Support Unit (CTSU) coverage will be expanded to cover cancer center and SPORE trials; 4) Use funds to encourage more active collaboration between individuals in gynecological (GYN) SPORE trials and GOG members; 5) Expand meetings and interactions with FDA, Cancer Therapy Evaluation Program (CTEP) staff; this has resulted in the designed of a standard operating procedure covering special protocol assessments for interactions between FDA and industry; 6) The first barriers analysis, which was completed in the summer of 2005 with the help of the CALGB operations office and Dr. David Gilts at Vanderbilt University, was presented to the CALGB leadership and will be presented to CTEP in the very near future; 7) A budget now exists to help develop ways to enhance minority outreach, either through the cancer centers' minority program, the minority Community Clinical Oncology Program (CCOP) program, or other programs that can enhance minority accrual; 8) Development of a formal mechanism, created with Dr. Gray's assistance, to develop the investigational drug steering committee, a group that will evaluate NCI's drug development plans. It will provide more extramural input into how the NCI deals with early phase clinical trials; 9) Held an inception meeting in September and in early March; 10) Policies and procedures are under construction, and co-Chairs have been elected; 11) Established a mechanism to develop disease-based steering committees to expand the intergroup process and thereby to encourage the inclusion of cooperative groups, SPOREs, cancer centers, community physicians and advocates, and the NCI; 12) The GI Cancer Steering Group is underway, and a number of conference calls have been made among the various task forces and disease groups in GI. In addition, the GOG's Executive Committee expressed interest in pursuing how to integrate the SPOREs and P01s into the activities of the national cooperative group and thereby facilitate the science-based research in that activity; and 13) In December, Dr. Doroshow met with the Head and Neck Intergroup Chairs and the Head and Neck SPOREs Chairs who expressed an interest in connecting the investigators

who perform the developmental work . NCI will provide the underlying support and facilitative infrastructure for these activities.

Integrated management components address two overarching initiatives: 1) Creation of an external Clinical Trials Advisory Committee to advise the NCI Director on NCI's spectrum of clinical trials. Dr. Doroshow acknowledged the efforts of Dr. Paulette Gray in helping to establish this committee. With her assistance, the HHS and the NIH approved the first new advisory committee for the NCI in more than a decade. This committee will provide the needed external oversight essential for all of the CTWG initiatives, particularly when mid-course corrections are needed. Its existence also raises to an appropriate level of awareness the work conducted by clinical trialists and clinical trials per se, as well as the correlative work that occurs with those activities. This committee will be comprised of 25 members: 10 from among the current NCAB, BSA, BSC, or DCLG committees, and the majority from the extramural clinical trials community. It is hoped that the committee's charter will be published soon in *The Federal Register*. The committee's first meeting is scheduled for June 2006.

The Clinical Trials Operations Committee will provide strategic oversight for NCI clinical trials' programs and infrastructure. The committee is comprised of members from all NCI Divisions, Offices, and Centers involved in NCI-supported clinical trials. Its duties are to: 1) review and prioritize clinical trial programs proposed by Divisions, Centers, and Offices to coordinate clinical trial efforts NCI-wide including the intramural program; 2) evaluate organizational infrastructures to reduce duplication and advise NCI's Center for Bioinformatics on development of IT infrastructure and tools for support of clinical trials; 3) provide guidance, review, and comment on policies, procedures, processes, and tools for prioritization, coordination, administration, and support of NCI-funded clinical trials with the operating Divisions, Centers, and Offices; and 4) evaluate all RFAs and Program Announcements (PAs) involving clinical trials prior to review by the Executive Committee. The committee's first meeting was held in December 2005. Both the Clinical Trials Operations Committee and the Advisory Committee report directly to the NCI Director and the Deputy Director for Translational and Clinical Sciences.

Dr. Doroshow introduced Dr. Sheila Prindiville, the Director of the Coordinating Center for Clinical Trials. Dr. Prindiville works in the intramural NCI program but spent many years at the University of Colorado. In addition, she worked in NCI's Division of Cancer Prevention (DCP), and so is one of those few individuals who has worked in the outside extramural world and NCI's extramural and intramural worlds. Other members of the Center include Drs. Deborah Jaffe, Ray Petryshyn, and Lee Ann Jensen. Dr. Jaffe comes from the DEA, where she oversaw all of the clinical cooperative group reviews. Dr. Petryshyn was involved in reviews of cancer centers, and Dr. Jensen worked with CTEP. These staff report to the NCI Director through the Deputy Director for Translational and Clinical Sciences and will provide the essential glue to make and facilitate the activities that are underway. With respect to Phase III trials, this project management team will facilitate scientific steering committees; coordinate state-of-the-science meetings; prepare summaries and action items; and develop policies and procedures. Most importantly, they will ensure that timelines are met.

Dr. Doroshow concluded the presentation by noting the work that has been done to develop a structured evaluation system. This includes a series of detailed implementation questionnaires around many of the initiatives to perform baseline evaluations. The launch for the questions should occur in March 2006. He noted that BSA members might be contacted for their input soon, which will help to provide a baseline for comparison when the next interim review is conducted in about 2.5 years.

In discussion, the following points were made:

- The concept behind the scientific steering committees for the design and prioritization of Phase III trials should be more fully developed.
- A suggestion was that the process of conducing clinical trials should be transformed such that the raw data are made available for the whole community's perusal. In discussion, issues were raised about sharing data that were gathered during cooperative group trials, as well as the time that investigators have invested, and even volunteered, in the trials.
- The vast majority of eligible patients (90 percent or more) do not go on protocol in a given year. Constraints on

resources and the need for a universal, front-end IT structure hinder improvements in this area.

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VII. RFA CONCEPT REISSUANCES—PRESENTED BY BSA SUBCOMMITTEE MEMBERS

Division of Cancer Control and Population Sciences
Cancer Research Network RFA/Cooperative Agreement

Dr. Bland, chair subcommittee, reminded the BSA that this was a reissuance of a RFA/Cooperative Agreement concept and, at the BSA's last meeting, there was a presentation by the investigators who were involved with the CRN-1 grant, which was funded in 1999. CRN-2 was renewed in 2003 and will terminate in March 2007. The purpose of the CRN was to enhance the research on cancer epidemiology, prevention, early detection, and control in the context of a community-based health care delivery system. The objectives were to 1) formulate and implement a joint agenda that resulted in three or more specified projects related to cancer control and population studies, and 2) develop a standardized collection of data for instruments, surveys, and analytical methods. The cancer research is oriented to community care; this mechanism provides access to a large, stable diverse population such as in an HMO like Kaiser Permanente, utilizes existing integrated databases to improve the information for collection in the cancer control agenda, and encourages research that is rooted in community-based delivery systems.

The CRN is unique in that it has addressed key questions in cancer care delivery. It has established itself as a cooperative among 12 health care delivery organizations. These organizations cover 10 million patients (4 percent of the U.S. population), and 14 percent of all HMO plans in the United States. The patients are racially and ethnically diverse. The NCI administration core has provided scientific administration review, coordination, and communication across these 12 CRN sites, which have multiple collaborations at various academic health centers. They interact with the intramural

and the extramural branches of the NIH that include the NCI, the National Human Genome Research Institute (NHGRI), National Heart, Lung, and Blood Institute (NHLBI), and Agency for Healthcare Research and Quality (AHRQ), as well as the Centers for Disease Control and Prevention (CDC).

The CRN-1 supported three projects: promoting tobacco cessation control, evaluating measures for breast and cervical cancer screening, and evaluating prophylactic mastectomies. Whereas, CRN-2 looked at informatics-based measures to enhance tobacco cessation. It also integrated dietary patterns into the Web-based technology interventions and began a study of prognostic factors related to ductal carcinoma *in situ* in high-risk women.

A recommendation that was proposed by the NCI staff is to make new resources available to promote an effective assessment of the CRN and for use by the general research community. For this RFA, the question is whether collaborative cancer research among the health care provider organizations that are linked to community care can continue to be supported. The research focuses on innovative prevention, control, and therapeutic measures to be implemented in the health care system. In addition, studies will address relationships between the delivery system for health care organizational structure and the distribution of the cancer risks, prognostic factors, and burden of disease among the CRN's control population.

In his review of the CRN's current portfolio, Dr. Bland informed members that there are: 35 funded projects: 13 supplements; 6 pilot projects; 7 competitively funded grants (R01s, U01s, P50s); and 3 contact projects. A timeline that includes the CRN's funding history of $57 M was provided. Of this amount, $33.2 M is contained within the main grant. In November 2005, Dr. Elias A. Zerhouni, Director, National Institutes of Health, selected the CRN to be in the NIH Roadmap as an IECRN project for which an in-depth assessment analysis would be conducted. The funding requested for CRN-3 is $30 million over 5 years.

Dr. Bland noted that several subcommittee members had wondered whether the budget level was appropriate for this very vigorous agenda. A second concern involved the desire for more diversified research publications and higher quality research outcomes. The subcommittee agreed that the RFA concept should be reissued as

requested. It was further noted that the network involves about 14 percent of HMO patients, reaches out to the community through dissemination, builds standardization of platforms for a database, and works closely with caBIG.

In discussion, the following points were made:

- The HMO community provides a data system, the electronic medical record, the followup, and the treatment information on these patients, that represents a unique resource with relatively small incremental costs that could be of great use for future pharmacogenetic research. In addition, most HMOs are contributing about $1 M or more per year to help provide core funding for the existence of the public domain research centers that are participating in the HMO research network.
- The BSA will want to hear discussion about the leverage mechanism produced by each of the individual grants that it reviews in the future, as well as to see other institutions that are participating in these enterprises that are contributing actual funds to facilitate these grants.

Motion: A motion to approve the CRN RFA reissuance was unanimous.

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VIII. REINVENTING EARLY DRUG DEVELOPMENT AT THE NCI—DRS. JAMES DOROSHOW, JERRY COLLINS, AND LEE HELMAN

Dr. Doroshow introduced Drs. Jerry Collins, Associate Director, Developmental Therapeutics Program (DTP), NCI's DCTD; and Lee Helman, Scientific Director, CCR. He posed the question of why there is a need to rethink oncologic drug development. He pointed out that, despite increasing investment, there is a decline in the NME filings and an increase in failure rates. Moreover, the predictive screening tools for activity and toxicity are inadequate, and the development timelines remain excessive. Finally, there has been a recent introduction of the exploratory IND that aims to improve the timelines for early drug discovery. The NCI entered

the cancer drug development business in the early 1950s to work with academicians and representatives from the pharmaceutical industry to develop a proposal to handle proprietary materials. That led in the fall of 1955 to a $5.2 M appropriation that started the NCI's development therapeutics and drug developmental program and also began the clinical cooperative groups.

Current challenges to cancer drug development for the NCI and other entities include:1) lack of *in vitro* or animal model systems that predict efficacy or safety in human clinical trials; 2) modest resources in academic laboratories to support the transition from molecular target discovery to the development of a drug; 3) suboptimal use of target assessment and imaging techniques in early therapeutics development that could reduce late drug failures; and 4) limited channels for cooperation between intramural and extramural drug development investigators, as well as enhanced investment by the pharmaceutical and biotechnology industries in cancer drug development since 1990, competition for molecules, investigators, and clinical sites.

Challenge 1: Lack of Appropriate Model Systems—Dr. James Doroshow

The inability to develop and use *in vitro* and animal model systems that are highly predictive of either efficacy or safety continues to pose a challenge. Thus, the NCI is working to develop and validate pharmacodynamic assays well in advance of early phase clinical trials, first in animals and then in human tissues. Dr. Doroshow informed members that Dr. Dinah Singer and her staff in the Divison of Cancer Biology (DCB) are working vigorously to develop new animal models that mimic human cancers produced by the NCI's Mouse Models Consortium to test sensitivity to targeted and cytotoxic agents. Another area revolves around the need to develop better molecular toxicological profiling capabilities.

Challenge 2: Limited Resources in Academia To Support Transitionfrom Molecular Targets to Drugs—Dr. Jerry Collins

Dr. Collins focused on two issues: 1) identifying the resources available to the extramural community, and 2) understanding how and for what purpose these resources are used. The principal

customers and output for the DTP reside in the extramural community. The Program provides expertise and materials in areas, such as chemistry, toxicology, and pharmacology, that are sometimes difficult for extramural investigators to obtain. The clinical domain is handled through the CTEP.

The extramural resources for drug discovery and development involve: 1) grants, which are the largest sources of funding, especially for early-stage research; 2) the National Cooperative Drug Discovery Groups (NCDDG); 3) the Rapid Access to NCI Discovery Resources (RAND); 4) repositories for drugs, natural products, biologics, cell lines, and animal models; and 5) the Rapid Access to Intervention Development (RAID) prgram. Regarding repositories, there are multiple warehouses. The NCI has 140,000 synthetic compounds that are made available to investigators who need a greater diversity of samples to test an idea and, hopefully, develop a lead compound. Biological resources, such as cytokines, antibodies, and growth factors, are also available from the DTP to extramural investigators to facilitate their research programs. Natural products are an increasingly hard-to-find resource these days; the Program possesses extracts of more than 50,000 plant materials and 10,000 marine materials. Moreover, the Program provides human and murine cell lines for research as well as tumor specimens from specialized animals that can no longer be obtained commercially.

Dr. Collins stated that RAID began 8 years ago to provide access to the resources that have been assembled within the DTP and make them available to the academic and small business community through a competitive, external, peer-reviewed process. This program supports studies under investigator or academic center sponsorship instead of the NCI. RAID tasks have included the acquisition or formulation of bulk drugs, the production of biologicals, the testing of the efficacy of an agent in animal models, and the conduct of pharmacology and toxicology studies. The Program aims to match the needs in the external community with NCI’s internal resources. The output from this program are data suitable for an IND submission, data that might enable an academic or nonprofit investigator to license their invention to a third party, data to enable licensing to third parties, and products for clinical trials. Academic and nonprofit investigators are eligible to apply. In addition, research collaborations between academic and any size corporate partner are acceptable provided the technology is not yet

licensed. If investigators have partnered with a small business community, they remain eligible for the RAID program. Since the program's inception in August 1998, 300 applications have been received, and more than 100 have become approved projects. A total of 28 of those projects have already led to the IND filing stage; 61 are completed, 16 have been licensed, and a total of 24 INDs have been filed with several others and are ready to be filed. The Program has spawned several clones, including the DCP's Rapid Access to Preventive Intervention Development (RAPID) program, DCTD's Discovery Resources (RAND), DCTD's Development of Clinical Imaging Drugs and Enhancers (DCIDE), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Type 1 Diabetes RAID, and NIH RAID Pilot (a component of the NIH Roadmap).

The Drug Development Group, which originally was called the Decision Network Committee, processes new molecules to enter NCI's drug development pipeline from any source, including clinical development. This occurs through support to academic investigators (especially grantees), intramural NCI investigators, or industry and by the offering of a range of services: preclinical efficacy; PK/PD; range-finding toxicology; GMP synthesis; formulation; IND toxicology; clinical lot manufacture; and Phase I, II, or III clinical trials. Each project is peer-reviewed by two extramural experts and NCI staff from DTP and CTEP. There is a focus on novel compounds or targets coming from small academic or industry laboratories. Approved projects total 142 (52 biologics, including 30 vaccines and 13 antibodies).

Dr. Collins referred the BSA to the DTP Web Site for further information. He noted that the highest priority for the Program is enabling early clinical studies. The Program's strategy is to use new regulatory flexibility in terms of the exploratory IND and emerging scientific tools such as noninvasive imaging (pharmacogenomics). Dr. Collins concluded with a list of six molecules that are graduates of the Program and are in early stages of clinical development.

Challenge 3: Sub-Optimal Use of Target Assessment and Molecular Imagingin Early Therapeutic Studies—Dr. Lee Helman

Dr. Helman described the NCI Intramural Clinical Research

Program and noted that it is a research-focused, patient-intensive clinical program that emphasizes early drug clinical trials. Its goals are to facilitate targeted therapies that are entering early phase studies, where the target can be monitored in the clinical setting to make informed decisions. Additional aims are to break down the barriers between intramural and extramural drug development within NCI's portfolio and to improve the ability to bring novel promising therapeutics into patient care, including agents from extramural laboratories.

The Center for Cancer Research (CCR) therapeutics development involves state-of-the-art preclinical and clinical imaging; pharmacodynamic cores; caBIG compliant clinical data management; and clinical resources available for any approved RAID project. Moreover, a clinical molecular profiling core will help to ensure that any patient who enters a clinical study within NCI's intramural program has at least the high likelihood to have their tumors biopsied. The samples will be sent directly to a tissue acquisition core laboratory. It is expected that most of these will undergo laser capture microdissection of the tumor, the stroma annotation, and perhaps various profiles.

Dr. Helman informed members that 33 projects ranging from small molecules and biologics to imaging had been submitted. Twenty-three of those projects were presented to the Molecular Targets Steering Committee and prioritized for the Joint Development Committee. Of those, nine projects were selected by the Joint Development Committee; five were approved for allocation of resources, two received tentative approval but require additional chemistry work, and two of the compounds were recommended to continue with a co-development plan proposed to the principal investigator. Dr. Helman reviewed the drugs that are in the pipeline at 2-year and 1-year intervals and those ready for IND. He presented data about a chelating agent, CHX-A, that has been successfully chelated to a number of radiolabeled elements, including indium, yttrium, and bismuth and forms stable complexes with these and herceptin.

Challenge 4: Limited Cooperation of Intramural and ExtramuralDrug Development Investigators—Dr. James Doroshow

Dr. Doroshow discussed the overall opportunities that favor the

strengths of an NCI academic partnership. First, the NCI is able to tolerate the level of risk to support academic investigators in the development of innovative ideas because it is not limited by precedent or intraperitoneal therapy issues and, most importantly, it can focus on niche markets. Second, the focus on novel technological approaches, such as molecular imaging, complex drug screening processes, and developing core resources to help extramural investigators, is an advantage. Third, a scientifically driven development agenda may require a substantive timeframe; the DTP and other NCI activities allow this time for germination and development of ideas. Dr. Doroshow mentioned that the NCI is interested in making sure that translation actually leads to the development of an IND that is used in a human clinical trial.

Dr. Doroshow stated that the NCI remains involved in the cancer therapeutics development business in 2006, which is to: 1) continue support for the direct involvement of academic investigators in preclinical drug development by providing access to drug development resources; 2) facilitate the preclinical and clinical testing of all new agents, and particularly combinations of new agents from multiple partners, which the increasing number of potential targets makes difficult to complete outside the government-sponsored arena; and 3) take advantage of current opportunities with academic partnerships to change the model of clinical cancer drug development.

In discussion, the following points were made:

- Ninety-five percent of NCI's drug development programs currently is extramural. A dialogue is needed to determine the opportunities for extramural investigators who have a particular need to use resources within the intramural program.
- The Small Molecular Screening Centers use the DTP's resources; close to 95 percent of the data were generated by DTP, and several of the screening centers' staff members are on DTP's coordinating committees.
- The majority of new targets and new molecules result from academic research, while the funding for Phase I, II, and III trials mostly comes through private companies.
- The NCI partners extensively with small and large biotechnology companies and the pharmaceutical industry to help develop compounds through all phases. A number of

drugs would not have been developed without the involvement of the DTP.

- The DTP serves as a prime example of leveraging intramural resources and presenting an unparalleled opportunity for discovery. Unique resources will be needed for exploratory INDs.
- It was recommended that the $50 M be differentiated so that it fills a niche, and experts weigh in regarding alternate ways to accomplish the purpose. The response was that an external review of the RAID program has been conducted and recommendations from academic and pharmaceutical colleagues will be shared with the BSA once it has been documented, possibly as early as the BSA's next meeting. The RAID program spends two-thirds of its funds on biologicals. One of the recommendations in the forthcoming report is to direct funds to study molecules that the immunotherapy community thinks are important to go into a clinical trial.
- To improve the low number of drugs that get into the clinic, the NCI is reevaluating and restructuring the SBIR program; in addition, the CRADAs are another mechanism to help small companies market their technology.

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IX. STATUS REPORT: COLORECTAL CANCER FAMILY REGISTRY (CFR)— DRS. ROBERT CROYLE, ROBERT HAILE, NORALENE M. LINDOR, STEVE GALLINGER, STEPHEN N. THIBODEAU, AND JEREMY R. JASS

Dr. Robert Croyle, Director, NCI's Division of Cancer Control and Population Sciences, reminded members that the scheduled presentations represent a periodic scientific progress update that occurs when the NCI is preparing for an internal evaluation of an initiative's impact and progress. The Colon CFR is an infrastructure to facilitate and synergize research on familial colon cancer in families and populations. It provides resources for a wide range of studies designed to understand the etiology and effects of colon cancer. Dr. Croyle informed members that the presentations would focus on scientific results and products. The CFRs were designed using clinic-based and population-based ascertainment. These strategies help to eliminate biases in terms of ascertainment,

perform good gene discovery, and examine allele frequency in the population, which is of great clinical and scientific importance. The Colon CFR was involved in the analysis of issues concerning biospecimen policies, acquisition, and sharing, and has served as a good model for how to do this.

Overview of the Research Activities of the Colon CFR—Dr. Robert Haile

In an overview of the Colon CFR, Dr. Haile informed members that the data collection is extensive, with more than 10,000 population-based families, more than 1,000 clinic-based families, 40,000 questionnaires, and more than 20,000 blood samples. Major areas include etiological research, clinical research (molecular profiles), behavioral research, and prevention trials. Etiological heterogeneity remains one of the major challenges in cancer research. In colon cancer, there are molecular markers, particularly microsatellite instability (MSI), to account for that heterogeneity. The registry classified more than 5,000 cases by MSI-high, -low, and stable status. Because each of the causes appears to be different, the genetic and environmental risk factors and pathology are under study.

The MSI-high group is caused either by germline mutations and a set of genes called the mismatched repair (MMR) genes or hypermethylation (MLH1) of one of those genes. Dr. Thibodeau confirmed the completion of testing on about 1,700 probands, which has revealed the underlying cause. This allows the registry to identify and categorize again cases as mutation carriers, MLH1 methylated, or normal sequence. MSI status, and immunohistochemistry can be used to help predict MMR gene mutations. By itself, preliminarily family history, although currently a common practice, is not a good predictor as it misses most of the mutation carriers. The field will begin to increase its use of molecular markers to identify carriers for testing.

Dr. Haile noted that hereditary nonpolyposis colorectal cancer (HNPCC) is a genetic syndrome that is defined by family history. The registry centers are able to push that phenotypic definition to a molecular definition. He described specific candidate genes that are being targeted. The focus has shifted from simple polymorphisms in a single gene to pathways. Epigenetic research is being conducted as well. Loss of imprint of IGF2 is very prevalent in

colon cancer, especially in MSI-high cases, and quite detectable in the blood. The goals are to confirm the prevalence, estimate the risk ratio, and assess familial aggregation of the loss of imprint. The University of Southern California consortium has launched, with the CFR, a large study of methylation. There also is a pending grant to perform a CIMP panel on approximately 5,000 cases.

Regarding minority populations, Japanese Americans and African Americans are being targeted because they have very high rates of colon cancer, and African Americans have a shorter, stage-adjusted survival than Caucasians. The goal is to involve 1,500 African American and 750 Japanese families. As the science grows, other centers are added judiciously.

Dr. Haile concluded with other pertinent points: every R01-type grant has been funded; 50 percent of principal investigators are junior- or mid-level; there are approximately 20 postdoctoral researchers involved with the research; and 10 major outside collaborators are involved.

Amsterdam I Families Without DNA Mismatch Repair Deficiency:
Familial Colorectal Cancer Type X—Dr. Noralene M. Lindor

Dr. Lindor described a study that yielded valuable results based on a single family that she saw in the clinic. The subject was a 46-year-old woman who developed colon cancer. She had a family history of cancer in two relatives at later ages; they discovered through an Internet search that they fit the Amsterdam criteria for HNPCC. The Amsterdam criteria was developed in 1991 to facilitate linkage analysis for what Dr. Henry Lynch identified as a highly penetrant autosomal dominate condition. The assumption currently is that anyone with a family that meets the Amsterdam criteria likely has germline mutations in the DNA MMR defect gene. This assumption is true, however, only about 60 percent of the time. The corollary is that a subject with HNPCC should follow rigorous screening guidelines for colon and endometrial cancer. When the tumor on this individual was tested, however, her tumor did not show evidence of a DNA MMR deficiency; the test revealed normal immunohistochemistry and no MSI. The relationship between these Amsterdam criteria and the HNPCC are as follows: there are people who have MMR deficiency who meet the pedigreed criteria, and people who have MMR deficiency and do

not meet the pedigreed criteria; for these two groups, the risks are known. There are also families, however, that meet this criteria that do not have MMR deficiency. This group previously had never been recognized, and their clinical risks were unknown.

The CFR database was used to study the age-related, site-specific risks for families that fulfill these classical criteria but do not have DNA MMR defects (i.e., they do not have Lynch syndrome). There were 161 families identified that could be studied (published in *JAMA* in 2005); of these, 90 families had the Lynch syndrome and 71 families did not. The standardized incidence ratio of these cancers was analyzed in several ways. A conservative analytical approach was used to remove three people who defined that Amsterdam trial of affected individuals; yet more than 1,800 relatives remained in the Lynch syndrome group and 1,500 in the other group. For the family with the Lynch syndrome, elevated risks were identified by family history and all of the expected tumors for this syndrome. The families without the DNA MMR defects had elevated risks for colorectal cancer, but nothing else was evident. Furthermore, the age at diagnosis of the colorectal cancers was intermediary in this new group of families compared to the Lynch syndrome or to the general population. Subsequently, a group from Germany published a similar observation in December 2005 entitled “Hereditary Non-Polyposis Colon Cancer Syndrome: Clinical and Molecular Evidence for a New Entity.” Combining the observations from the Colon CFR and German researchers, this group has been termed the “Familial Colorectal Cancer Type X.” This means it is familial but unclear if it is hereditary; the “X” indicates the unknown. It is a distinct group of families that have a risk for colorectal cancer, although probably not other sites, with a predilection for the left side of the colon. The median age at diagnosis is young but not as young as in Lynch syndrome. In addition, there is less synchronous in the colorectal cancers. Finally, the German group observed more adenomas, suggesting slower adenoma-to-carcinoma progression. This group merits further examination from clinical, epidemiological, and molecular pathology perspectives.

MSI and Prognosis and Future Clinical Research—Dr. Steve Gallinger

Dr. Gallinger explained that during the past 25 or 30 years, it was assumed that all cancer patients should receive the same treatment.

It is becoming clear, however, that tumors respond differently. The Colon CFR can provide new evidence for these differences in clinical behavior of patients with colon cancer. A set of 100 new cases can be separated quite discreetly into at least two groups: MSI stable and MSI high. HNPCC, which is one type of MSI-high tumor, is relatively rare, affecting approximately two patients out of 100. Other MSI-high tumors are called sporadic and account for a large fraction of colon cancer. The question being addressed from a clinical perspective is whether the patients behave differently.

The process of an adenoma turning into a cancer takes about 10 years. The tumors seem to make a decision as to which of two pathways, the chromosomal instability pathway (MSS) or the MSI pathway (MSI-H), to follow, which is important because the molecular changes in those two pathways are very different. There are genes that are commonly mutated as somatic events, but the nature of the mutation is different. More important is that there are entire genes that are actually mutated in only one pathway and not the other, and this knowledge advances a new era of molecular classification. In a comparison of MSI and MSS colon cancer cell lines that illustrated discreet patterns, Dr. Gallinger informed members that these lines are not just one gene, such as the HER2; they encompass entire pathways. This is an important breakthrough because patients have been naively classified with one set of diseases for many years.

The Colon CFR centers have generated the largest data set as yet published, involving 2,000-3,000 cases, including about 400 MSI-high cases. The stage of cancer is a strong predictor of survival and survival based on age. It is quite dramatic to think that there are some patients with Stage 4 disease who are doing well 4 and 5 years out; this is the power of molecular classification, specifically MSI in colon cancer. Dr. Gallinger stated that what is known about MSI is that there are distinct clinical pathologic features, such as an intense lymphocytic infiltrate. He noted that the Colon CFR also has been confirming the observations that clinicians have made for years: a patient with small tumors with many nodes dies, but a patient with large tumors with no nodes lives. The molecular observations will be translatable soon into clinical observation. Even the pattern of disease and the nature of metastatic disease appear to be different. Some of the simple observations that clinicians are making, such as the manner of spread of colon cancer to the liver or lung versus peritoneal carcinomatosis, seem to be

based on the molecular features of the tumor.

Prognosis and treatment are important for patients. The drug 5FU has been used as a chemotherapeutic agent since 1957, and for 40 years, until the mid 1990s, was the only drug that worked. It was thought to benefit all patients but in fact helped only the patients with MSS tumors. The patients with the MSI-high tumors did worse with adjuvant therapy. The CFR is well positioned to conduct a long followup study, drawing on a large database and conducting many molecular tests to answer some of these questions in more detail. During the past 10 years, four or more drugs have been developed. Although data exist regarding their benefit, little information exists about the drugs' interaction with molecular changes in the case of colon cancer, which the CFR could help to determine. Dr. Gallinger concluded by reviewing the CFR Clinical Working Group's research agenda.

DNA MMR Gene Characterization of C-CFR—Dr. Stephen N. Thibodeau

Dr. Thibodeau informed members that the status of the defective MMR in the collection has been derived by looking at both tumor MSI and immunohistochemistry for loss of protein expression. Ten micro satellites were used across this collection, and the set includes an increased number of mononucleotide repeats which, in retrospect, has been quite important for the study. Approximately 4,500 to 4,700 individuals have been typed using MSI. In addition to looking at the tumor, the frequency of germline mutations within that group, specifically, MLH1, MSH2, and MSH6, has been explored, again considering both germline and somatic alterations.

He indicated that the total population of MLH1 and MSH2, samples that have been tested is approximately 1,700 samples and about 150 deleterious mutations identified. In addition, another 45 mutations were identified that would not have been detected by sequence analysis for that group. There also are a significant number of variants that could not be classified as well as polymorphism. For MSH6, the frequency is roughly the same. In sum, more than 200 probands have been identified with clear cut deleterious mutations. The MMR gene analyses, and penetrance in particular, have become the cornerstone of much of the work being done. The analyses have identified hundreds of families with definite MLH1, MSH2, or MSH6 mutations that represent both

clinic- and population-based sample sets. It allows the potential to estimate penetrance by a number of variables that can be better examined within the CFR. Dr. Thibodeau also described a study that looked at the overall penetrance of colon cancer and revealed in the 10-year penetrance for each category (male and female, as carriers and population) is considerably lower than what was previously seen.

In conclusion, Dr. Thibodeau outlined a number of future research topics: 1) understand reasons for discrepant MSI/IHC/MMR results; 2) mechanism of "second hit;" 3) molecular and statistical analyses of unclassified variants; 4) relationship between selected pathology variables and tumors caused by MMR mutations; 5) case-control analyses of selected risk factors stratified by MSI status; 6) prognostic significance of MSI status; 7) sensitivity, specificity, and predictive values of MSI, IHC, and family history criteria for predicting MMR germline mutations; 8) development and validation of a predictive model for MMR mutations; and 9) age-specific penetrance, including heterogeneity by gender, race, family history, and clinic versus population-based ascertainment, as well as genetic and environmental modifiers of risk.

Morphological and Molecular Correlations: Past, Present, and Future—Dr. Jeremy R. Jass

Dr. Jass presented information about pathology, beginning with the collection of pathology data during the past 8 years. He informed members that the guidelines were developed by key entities: International Union Against Cancer (UICC)/Tumor, Nodes, Metastasis (TNM) Staging Classification, UICC/World Health Organization (WHO) Tumor Classification, American Joint Committee on Cancer (AJCC), College of American Pathologists, Association of Directors of Anatomical and Surgical Pathology, and Bethesda Guidelines (revised).

The Pathology in Research Plan 2006 aims to accomplish three goals: 1) correlate germline alterations in MMR genes (pathogenic mutations, missense mutations, unclassified variants, and hemi-allelic methylation MLH1)/ 2) examine morphologic features of CRCs and polyps stratified by somatic alterations status (e.g., CIMP/BRAF/MSI) and cancer family syndromes (e.g., Lynch, FCC-X); and 3) l focus on the prediction of MMR status (Bethesda Guidelines for Lynch syndrome). The study's objectives include

the identification of the pathology features that can predict MSI-high status in cancers presenting in the under-60 population, which is criterion three of the Bethesda Guidelines. “Under 60” means that the subjects likely will have HNPCC or Lynch syndrome if the cancers show much cellular instability. Other aims are to develop a predictive model based on the features that were independent and discover how many cancers can be identified just by pathology that would otherwise have been missed.

Currently, study results are MSI high 72, MSI low 66, and MSS 418, for a total of 556 cases examined. When this study is published, approximately 2,000 to 3,000 cases of these cancers will have been studied. The features that predicted MSI-high status include: tumor infiltrating lymphocytes, a Crohn-like reaction where B lymphocytes are present, proximal location, and mucinous histology. Scores were derived from these observations and revealed that, with the increasing scores, the cancers were more likely to show MSI. Dr. Jass stated that this test has a sensitivity of 99 percent. The positive predictive value is 21 percent, meaning that for every five that are identified with the test, about one will turn out to be MSI high and likely will have HNPCC because of the under-60 age. He concluded that 1) the pathology is highly sensitive to MSI-high status; 2) there is no need to test colorectal cancers that lack the pathology features; and 3) pathology can identify MSI-high cancers between the ages of 50 and 59 that may be attributable to HNPCC in which there may be no other features to suggest that these patients have the Lynch syndrome.

Colon CFR Core Activities: What Has Changed and What Is the Same?—Dr. Noralene M. Lindor

Dr. Lindor described the future plans for the Colon CFR and its cores. He noted that the 1) recruitment (new) will be used for population clinic-based probands, primarily to increase the number of MMR gene carriers as well as any other family that appears to be segregating yet-undiscovered genes. The current plan is to select young onset cases and to fully ascertain the proband. There would be a full recruitment of the family if this individual’s tumor showed MMR deficiency or the family history met predetermined, high-risk criteria; 2) retention and followup (unchanged) monitors to see who is living and who is deceased after 1 year. An active followup occurs by having participants complete a risk factor questionnaire and updating the family history every 5 years; 3) biospecimen core

(major changes) - plans are to develop a centralized biospecimen repository for almost all of the blood activities in the CFR. Another is to extract DNA from blood and tumor, establish EBV cell lines on as many enrollees as possible, and to perform whole genome amplification for those for whom this is not possible. Tissue microarrays will be developed for a subset of tumors to allow a more judicious use of tumor tissue and to introduce the digitized images of pathology sections for the type of research that Dr. Jass proposed could be conducted long distance; 4) molecular characterization core (changed) will continue the MMR characterization that has been underway. Also proposed is adding tumor BRAF mutation, which correlates with this epigenetic silencing of MLH1 and needs to be completed as an infrastructure piece across the CFR. Germline MYH mutations are beginning to be recognized as important, and those families need to be identified; 5) clinical characterization (new core) involves more systematic collection, abstraction, and coding of the clinical data. Data are needed regarding CRC stage at diagnosis and recurrence, as well as detailed treatment information provided in a consistent manner; 6) behavioral core (new) will facilitate the biobehavioral and psychosocial research by developing some standard instruments and introducing core items into current surveys, and advising on some of the ethics and communications with participants; and 7) data management core (minimal change) - tasks are performed locally and transmitted as high-quality data in a standardized format to the Central Informatics Center.

In conclusion, Dr. Lindor noted that the changes will: 1) for consistency, build on prior structures but seek areas to improve; 2) target specific areas for enhancement, including more gene carriers and other high risk families, as well as greater depth of clinical data to enhance translational research possibilities; and 3) embrace greater centralization of handling biospecimens, conducting molecular analyses, and distribution of new types of data (digital images).

In discussion, the following points were made:

- The next 5 years will address a cohort of high-risk subjects, and those studies will report their results back to the CFR within 3 years. There will be exquisite haplotype data on more than 100 genes plus the MSI methylation data, made available to other research groups. Linkages also will start

with other NCI initiatives, such as Early Detection Research Network (EDRN) and The Cancer Genome Atlas (TCGA).

- Data will be available to everyone, including nonregistry participants, who meets the scientific merit review criteria.
- Using and building the existing resource is of primary interest, but two areas that need additional data are: 1) MMR repair gene mutation carriers, particularly regarding racial and gender differences in penetrance; and 2) mapping the genes for the Type X families.
- In order to ascertain the success of the Colon CFR program, the BSA requested that notations be made in the bibliography of those papers that could not have been generated in the absence of this registry.

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X. ADJOURNMENT—DR. ROBERT C. YOUNG

There being no further business, the 33rd regular meeting of the Board of Scientific Advisors was adjourned at 5:30 p.m. on Monday, March 13, 2006.

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