Board of Scientific Advisors

Meeting Minutes

March 5-6, 2007

Building 31C, Conference Room 10
Bethesda, Maryland

Quick Links

Members

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Meeting Minutes

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 36th meeting on Monday, 5 March 2007, at 8:00 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 from 8:00 a.m. until 5:00 p.m. on 5 March for the NCI Director's report, report on NCI Congressional relations, ongoing and new business, discussion regarding the impact of a flat budget, update on implementation of Clinical Trials Working Group (CTWG) recommendations, update on the clinical development of IL-15, consideration of Request for Applications (RFA) reissuance concepts presented by NCI program staff, and a mini-symposium of biobehavioral influences on cancer biology. The meeting was open to the public from 8:30 a.m. on 6 March until adjournment at 11:25 a.m. for updates on proteomics and the Interagency Oncology Task Force (IOTF).

Board Members Present:
Dr. Robert C. Young (Chair)
Dr. Paul M. Allen
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
Dr. William S. Dalton
Dr. Raymond N. Dubois
Dr. H. Shelton Earp III
Dr. Kathleen M. Foley
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. William N. Hait
Dr. Leland H. Hartwell

Board Members Present:
Dr. Lynn McCormick Matrisian
Dr. Kathleen H. Mooney
Dr. Edith A. Perez
Dr. Mack Roach III
Dr. Richard L. Schilsky
Dr. Ellen Sigal
Dr. Margaret Ruth Spitz
Dr. Jean Y. J. Wang
Dr. Jane Weeks
Dr. Robert A. Weinberg
Dr. James K. Willson

Dr. James R. Heath
Dr. Mary J. Hendrix
Dr. Hedvig Hricak
Dr. Eric Hunter
Ms. Paula Kim
Dr. Michael P. Link
Dr. Christopher J. Logothetis

Board Members Absent:
Dr. Susan J. Curry
Dr. Sanjiv S. Gambhir
Dr. Patricia A. Ganz
Dr. Leroy Hood
Dr. Robert D. Schreiber

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

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Minority-Based Community Clinical Oncology Program (RFA/Coop. Agr.)

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Centers of Excellence in Cancer Communication Research (CECCR) (RFA/Coop. Agr.)
Division of Cancer Treatment and Diagnosis
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Effects of Chronic Stress on Cancer Growth and Progression; Dr. Anil K. Sood
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I. CALL TO ORDER AND OPENING REMARKS - Dr. Robert C. Young

Dr. Young called to order the 36th regular meeting of the BSA and welcomed members of the Board, members of the Board of Scientific Counselors (BSC), NIH and NCI staff, guests, and members of the public. Dr. Young reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. He called attention to confirmed meeting dates through November 2009. 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 2-3 NOVEMBER 2006 MEETING MINUTES - Dr. Robert C. Young

Motion: The minutes of the 2-3 November 2006 meeting were unanimously approved.

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III. DIRECTOR'S REPORT - Dr. John Niederhuber

Dr. Niederhuber welcomed the Board and members of the BSC, who were in attendance to hear the Director's report. Members of the Boards were reminded that the Fiscal Year (FY) 2007 budget development process had been protracted because the NIH has been operating on the basis of two Continuing Resolutions (CRs) since the end of FY 2006.

Budget Update: FY 2007 and FY 2008 President's Budget (PB). On February 14, the Senate passed the FY 2007 joint resolution, which was signed by the President on the following day. The bill provides $28.9 B for the NIH, an increase of $620 M over FY 2006. Provisions of the Revised CR for FY 2007, are: 1) the Common Fund, which includes the NIH Roadmap, is set in the Office of the Director (OD), NIH, at the level of $483 M, an increase of about $150 M; 2) most Institutes and Centers (ICs) receive no specific increases but retain funds previously earmarked for the NIH Roadmap and funds that had been transferred to the Center for Medicare and Medicaid Services (CMS) in FY 2006; 3) the NIH will receive funds to pay partially for the 2007 Cost-of-Living Allowance (COLA) increases for Federal salaries; 4) the NIH is required to award about 500 more competing Research Project Grants (RPGs) than were awarded in FY 2005 or about 10,100, with an emphasis on new investigators; 5) the average cost of competing RPGs is to remain the same as in FY 2006 or about $324 K; and 6) Type 5 grants (noncompeting) are to be reduced by 3 percent.

Dr. Niederhuber highlighted and elaborated on a few items in the

NIH budget. The $40 M line item for Junior Pioneer Awards is now included in the Common Fund, and work is underway to execute those awards by September or October. Programs funded as part of the NIH OD include $91 M for the New Investigators initiative and $69 M for the National Children's Study. Of particular importance to the NCI is the $5 M appropriation to the National Library of Medicine (NLM) for the National Center for Biotechnology Information (NCBI), which is the repository for genomic data produced in various studies. Dr. Niederhuber noted that funding to support this rapidly growing resource could present a challenge for the future in terms of personnel needs to manage it. Members were told also that the Revised CR requires that ICs use one-half of the money they retain from the NIH Roadmap to fund additional RPGs, which will have an impact on future budgets because of the long-term, outyear commitments.

Under the Revised CR for FY 2007, the NCI budget allocation is more than $4.793 B, an increase of about $46.1 M over FY 2006, reflecting the restoration of the CMS and Roadmap taps. The promised funding to help pay for the mandated COLA increases for Federal salaries would add to that amount. With this level of funding and because of the requirement to fund additional RPGs with one-half of the Roadmap restoration, projections are that the NCI will fund 3,878 noncompeting grants for an estimated $1.548 B and award 1,314 competing grants for an estimated $427 M, an overall total of 5,192 grants from the NCI RPG pool. Members were reminded that, unlike most Institutes, the NCI uses many other mechanisms to support investigators and research, which are not reflected in the RPG count. Based on an average cost of $324 K per grant, an NIH-wide policy, the FY 2007 R01 payline is projected at the 12th percentile and the success rate is projected at about 19 percent.

Dr. Niederhuber reviewed the FY 2008 PB particulars. For the NIH, $28.849 B is requested, an increase of $232 M (0.8 percent) over the FY 2007 annualized CR. For the NCI, the PB request is $4.782 B, a $9 M decrease or 0.2 percent lower than the FY 2007 annualized CR. Members were reminded that the Department of Health and Human Services (DHHS) is funded from the discretionary portion of the Federal budget so the deliberative process begins with hearings in the House of Representatives, and that Dr. Niederhuber is one of the IC Directors scheduled to testify at the March 6 hearing before the House Appropriations

Subcommittee.

President Bush's Visit to the NIH. Dr. Niederhuber commented on the importance of the President's visit and the focus on the NCI that had been requested in the pre-planning. NCI events included a tour of the laboratory of Dr. W. Marston Linehan, Chief, Urologic Oncology Branch, Center for Cancer Research (CCR), visits with CCR patients, and a panel discussion of the issues, with input from patient advocates. As part of the visit, the President was able to announce the newly released American Cancer Society (ACS) figures showing a decrease in cancer mortality eight times greater in the period from 2003 to 2004 than it had been in the 2002-2003 period.

NIH Reform Act of 2006. Members were reminded that the third omnibus reauthorization in NIH history and the first in 14 years had been signed into law by the President on January 15. One change brought about by Congressional deliberations leading to the Reform Act was the establishment of the Office of Portfolio Analysis and Strategic Initiatives (OPASI) in the NIH OD. Dr. Niederhuber reported the recruitment of Dr. Alan M. Krensky as NIH Deputy Director, OPASI. Dr. Krensky also will have a laboratory in Building 37. An Ad Hoc Working Group of the NIH Steering Committee has been created to oversee implementation of the Reauthorization Act. The Working Group, which is chaired by Dr. Raynard Kington, Deputy Director, NIH, will conduct a detailed analysis of the Act and propose plans for its implementation. Implementation Groups, led by IC Directors and including a team of staff and lawyers, are working to address the various provisions. These relate to a Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), the Common Fund, a Council of Councils, a Scientific Management Review Board (SMRB), authorization of appropriations, reorganization, and reporting. Dr. Niederhuber is heading the Group involved with the issue of reporting within the NIH and to Congress.

Clinical Trials Advisory Committee (CTAC). The CTAC was established in response to the CTWG recommendation that an extramural oversight committee be formed to advise the NCI Director on clinical trials. Chaired by the NCI Director, the CTAC is the newest of NCI's Federal Advisory Committee-approved boards, which include the National Cancer Advisory Board

(NCAB), BSA, BSC, and Director's Consumer Liaison Group (DCLG). To emphasize the scope of NCI's clinical trials network, Dr. Niederhuber reminded members that a total of 1,878 treatment sites currently have patients enrolled on open trials. Moreover, the NCI's Clinical Trials Cooperative Group Program is distinctive among NIH-supported programs in that it provides an infrastructure that is continuously available to test new therapeutic strategies, one in which trials can be developed and conducted in multi-institutional settings. The Cooperative Group program also provides a flexible research agenda, which allows a change of strategy in response to changing scientific opportunities and new discoveries.

Progress Report on Specific Initiatives. Dr. Niederhuber reviewed the status of ***The Cancer Genome Atlas (TCGA) Project***. Glioblastoma, lung, and ovarian were announced on 1 September 2006 as the first tumor types to be studied. The Cancer Genome Characterization and Cancer Genome Sequencing Centers were announced on 16 October and 20 November, respectively, the latter by the National Human Genome Research Institute (NHGRI). All TCGA components met jointly for the first time in December, and the project is moving forward.

More than 200 scientists attended the first meeting of the ***NCI Alliance for Nanotechnology in Cancer***, held on 25-26 October 2006, in San Diego, CA. Currently, The Alliance comprises eight Centers for Nanotechnology Excellence, four NCI-National Science Foundation (NSF) Integrative Graduate Education and Research Traineeship Programs, and numerous principal investigators (PIs), co-PIs, postdoctoral students, and students who are being trained in this environment. Dr. Niederhuber called attention to the number of R01-type activities that are conducted in any one of the eight centers supported by this initiative.

The ***Clinical Proteomic Technologies Initiative for Cancer*** (CPTI) was launched in September 2006, with the announcement of eight awards to the lead institutions for clinical proteomic technology assessment for cancer, seven awards for advanced proteomic platforms, and eight awards for computational sciences. A Request for Proposals (RFP) for a clinical proteomic reagents resource is anticipated this year. Dr. Niederhuber commented that this initiative has been successful in leveraging a significant investment in the Centers from foundations and the private sector. In addition,

proteomics and protein chemistry are high on the list of next generation Roadmap opportunities under discussion.

The ***Integrative Cancer Biology Program*** currently supports six full and three planning centers. Accomplishments include the development of a validated siRNA library of cancer genes. He noted that this program is working in the forefront of the field and gives an indication of where the science is headed and how support for the science is going to develop over the next few years.

Office of Biorepositories and Biospecimen Research (OBBR). The OBBR has revised the first generation Guidelines for NCI-Supported Biospecimen Resources in response to the public comments that were received in response to the Federal Register posting. In collaboration with the Rand Corporation, a prototype of a searchable Web-based tool for published biospecimen research has been built. The Biospecimen Research Network involves collaboration with investigators at all three NCI campuses, Walter Reed Army Medical Center (WARMC), private industry, and academia partnerships. Dr. Niederhuber emphasized the importance of access to the highest quality of tissue for today's science and NCI's growing leadership role in this area across the NIH.

Therapeutically Applicable Research to Generate Effective Treatments (TARGET). Dr. Niederhuber thanked members of the BSA subcommittee convened to address issues surrounding this pediatric cancer program. TARGET is a collaborative project of the NCI and the Foundation of the National Institutes of Health (FNIH) to identify and validate childhood cancers. Progress has been accelerated over the past 6 months, with the goal of making major advances in target identification for two or more childhood cancers within 2 years of project initiation.

Experimental Therapeutics and Drug Discovery Program. Dr. Niederhuber characterized this Division of Cancer Treatment and Diagnosis (DCTD) program as a necessary resource for the NCI campus, other Institutes, and the extramural community. A group has been to upgrade these activities to link the biologic, chemical, and translational spaces in the continuum of science and bring them to bear on imaging work in the submolecular space. The foundation for this work is the Cancer Bioinformatics Grid (caBIGTM), which is moving from its successful product development and link generation phases to a new era known as Network-Centric

Biomedicine. The objective is to be able to support clinical trials and clinical trial research as well.

Trans-NCI Programs. Dr. Niederhuber cited the Clinical Imaging Programs in lung cancer, cancer stem cell biology, angiogenesis, translational genomics, and caBIGTM as examples. He noted that the NCI has been approached to help in developing informatics strategies across the NIH and to demonstrate what the NCI already has in place. Dr. Niederhuber underscored the importance of involving colleagues in imaging research in any consideration of a clinical research protocol here on the NCI campus and elsewhere. He reported that a three-dimensional (3D), high-resolution electron microscope will be located in the Clinical Center to enable linkage of the clinical research effort to imaging that provides real-time and submolecular assessment of what is being done.

In discussion, the following point was made:

- The OPASI was established at the behest of Congress to ensure that research is integrated across the NIH.
- Implementation of the Translational Research Working Group (TRWG) recommendations is nearing completion and will be reported at the June Board meetings.
- The payline for NCI's *R01 program for young investigators has been 6 to 8 points above the R01 payline since program initiation. In addition, proposals still on the list of unfunded R01s are reevaluated, and many are funded as exceptions at the end of the fiscal year.
- Large numbers of the brightest and best graduates and undergraduates no longer view basic biomedical research as viable career options. This has the potential to affect the course of biomedical research in the long term
- The Clinical Trials Working Group (CTWG) data regarding the number of senior investigators who participate in trial designs and working groups would be informative.

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IV. NCI/CONGRESSIONAL RELATIONS - Ms. Susan Erickson

FY 2008 Appropriations Outlook. Ms. Susan Erickson, Director, Office of Policy Analysis and Response (OPAR), reviewed the requests for the NIH and NCI ($28.86 B and $4.78 B, respectively) included in the FY 2008 PB. Ms. Erickson stated that the House Labor/HHS/Education Subcommittee hearing will employ the NIH overview format, with the Director, NIH, as principal witness. Dr. Niederhuber and several other IC Directors will attend to answer questions. She noted that DHHS Secretary Mike Leavitt had testified on the overall DHHS budget at hearings of several different committees. The Senate hearing on the FY 2008 PB is scheduled for 19 March.

Congressional Visits to the NIH. Ms. Erickson reported on the most recent Congressional visits. Senator Edward Kennedy (D-MA) met with Dr. Zerhouni in December and visited many of the Institutes. He received a presentation on molecular diagnosis of cancer at the NCI. Representative Michael Castle (R-DE), during his January visit, heard from the NCI, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute for Dental and Craniofacial Research (NIDCR).

Legislation. Ms. Erickson reported on the: 1) Family Smoking Prevention and Tobacco Control Act; 2) Breast Cancer Stamp Reauthorization Bill; 3) Stem Cell Research Enhancement Act; 4) Genetic Information Nondiscrimination; and 5) Cancer Testing, Education, Screening, and Treatment Act.

In discussion, the following point were made:

- The Genetic Information Nondiscrimination Bill in its present form could have an impact on the ability to develop information technology (IT) systems that permit a rapid exchange of information of benefit to the patient.

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V. ONGOING AND NEW BUSINESS - Drs. Robert C. Young and Norman Coleman

Dr. Norman Coleman, Associate Director, Radiation Research Program (RRP), DCTD, informed members that the “NCI Listens” session at the annual 2006 meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) began with an overview of the spectrum of activities at the NCI relating to radiation research, both intra- and extramural. Attendees were asked to provide feedback as to whether “NCI Listens” is a worthwhile program or how it could be improved. The question and answer sessions focused on: 1) reasons why clinical trials with low accrual rates are being terminated; 2) the need to encourage and support new investigators; 3) the need for an instructional grant Web site; 4) novel ways to obtain funding; 5) strategies for making the difficult transition from fellowship to grantee; and 6) the need for government agencies to work together following the example of the informal multi-agency group, Radiation Bioterrorism Research and Training (RABRAT), and the work of the Molecular Radiation Therapeutics Branch, DCTD. Dr. Coleman commented that, although only 50 were in attendance, due in part to the increasing complexity of the meeting, enthusiasm and interest were high. He expressed the view that the sessions are useful and that consideration should be given as to how to make them better, perhaps with more preliminary planning. He emphasized that the RRP continues to interact with the extramural radiation community in an attempt to keep the community as encouraged as possible in this difficult fiscal climate.

In discussion, the following points were made:

- A consolidated list of the 25 or 30 most frequently asked questions (FAQs) at NCI Listens sessions should be posted on the NCI Web site.

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VI. DISCUSSION: IMPACT OF THE FLAT BUDGET - Dr. John Niederhuber

Members were reminded that the process of increasing the budget began in FY 1998 and ended in FY 2004, and that the NCI has

been operating with a less than inflationary budget since then. Although approximately $4.8 B has been appropriated annually since 2004, the NCI has experienced a 12 percent loss in purchasing power when the budget is adjusted by the Biomedical Research and Development Price Index (BRDPI). Dr. Niederhuber noted that this loss of purchasing power applies not only within the NCI in terms of rent, leases, and salaries, but also by NCI grantees in terms of what they can do with their grant dollars. In reviewing the graph of NCI applications, awards, and success rates for competing RPGs from 1998 to 2007, he pointed out that the number of applications received by the NCI appears to have reached a plateau in FY 2007, possibly indicating a more stable situation after the period of significant growth in facilities, faculties, and programs at the major research universities. Members were reminded that about 15 percent of NCI's RPG monies is reserved to address exception issues.

Dr. Niederhuber then presented examples of what has been reduced, stopped, or put on hold, with the reminder that the FY 2007 appropriation has been in place only since the middle of January and work on the FY 2007 funding plan is still in progress. In the area of missed opportunities related to 2006 RPGs, a review of NCI divisional portfolios suggests that about 179 R01s went unfunded, which could have brought the payline to the 20th percentile (30 percent success rate). An estimated $58 M would have been needed to achieve that level. In the area of RPG competing Request for Application (RFA) awards, which are another significant source of support for the extramural community, the number of awards peaked in FY 2005 representing about $44.6 M in funding, and funding is estimated to decrease to $24.4 M in FY 2007. RFAs were cancelled or cut back across all NCI Divisions. In the area of the Special Programs of Research Excellence (SPOREs) and Cancer Centers, the overall SPORE program was reduced by $8 M in FY 2006 and further cuts may be necessary in FY 2007, and a 10 percent reduction in funding for the Cancer Centers may be necessary in FY 2007. He noted that noncompeting awards to the Centers have been flat for the past 3 years, and two new Centers will be part of the FY 2007 budget, both capped at $1.5 M levels.

Dr. Niederhuber reported that the funding plan in the area of clinical and translational trials is still a work in progress, but an across-the-board reduction may be necessary in both the Clinical

Cooperative Groups and the Community Clinical Oncology Program (CCOP). He noted that these programs, which are part of the NCI's clinical trials infrastructure, already have been subject to significant reductions and anything further would translate into fewer trials and fewer patients going into trials. In the area of cancer control, the budget has decreased from a high of $531.6 M in FY 2005 to $510.4 M in FY 2007, reflecting reductions to the Tobacco Control Research Branch, Division of Cancer Control and Population Sciences (DCCPS); Quality of Cancer Care Program; Cancer Survivorship Program; and Risk Factor Monitoring/Energy Balance Program. In the intramural research area, reductions were taken on the basis of a rigorous review by BSC site visit teams. Dr. Niederhuber gave examples of reductions taken in programs of the Division of Cancer Epidemiology and Genetics (DCEG), which allow these valuable programs to continue, albeit at a slower rate.

Next, Dr. Niederhuber called attention to the decrease in patient accrual in the CCR, from 4,210 in FY 2004 to 3,795 in FY 2006, brought about by the lack of resources to devote to this area of translational research. Members were reminded that the CCR not only conducts vital first-in-man and early Phase I studies, but also constitutes the infrastructure that supports translational research and drug development in the extramural community. Finally, Dr. Niederhuber reviewed budget decreases being implemented in the NCI OD, including a 10 percent across-the-board cut and an $8 M cut in the NCI-Frederick budget. The NCI-Frederick cuts were made in the areas of operational scientific support staff, advanced technologies capital equipment, and facilities repairs and maintenance. Members were reminded that NCI-Frederick houses many resources that support the extramural community, including its role as the world's largest supplier of live vaccines and its computing facilities that support genomic and proteomic research across the country. Additional savings were realized in the OD by the merging of the Office of Communication and the Office of Education and Scientific Initiatives, as well as by reducing Cancer Information Service regional contracts, the NCI Exhibit Program, the contract supporting the Enterprise Vocabulary System, and the number of issues per year of the NCI Cancer Bulletin. He stated that the reorganization and streamlining of the OD is an ongoing process that could continue into 2008.

In conclusion, Dr. Niederhuber informed members that it is relatively easy to count projects, trials, and patients affected by the

current budget climate, but it is more difficult to account for missed opportunities and ideas lost.

In discussion, the following points were made:

- Budget cuts already taken as a result of the intensive portfolio review by the EC during the previous fall are permanent, but funding plans for specific areas are still being formulated because of the delay in enacting the NIH appropriations. These include the SPORE and Cancer Centers programs and the Cooperative Group Clinical Trials. Another unknown at this time is the amount of money that the NCI will receive as a result of the appropriation to address mandated Full-Time-Employee (FTE) COLA increases.
- Although some of the budget cuts are not as draconian as originally expected, much damage already has occurred in the clinical trials arena. It is not likely that some of the reduction in activity in the Clinical Cooperative Groups will be restored because the Groups have had to take action in anticipation of budget cuts.
- The data as to how the below-inflation budget is being managed in a structured format should be distributed so that professional societies have the same figures to use for reference.

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VII. UPDATE: IMPLEMENTATION OF THE CLINICAL TRIALS WORKING GROUP (CTWG) RECOMMENDATIONS - Drs. James Doroshow and Sheila Prindiville

Dr. Doroshow reminded members of the common themes of the National Cancer Clinical Trials Enterprise restructuring plan: enterprise-wide/integrated management; prioritization/scientific quality; coordination; standardization; and operational efficiency.

Enterprise-Wide/Integrated Management. CTWG recommendations related to this theme were to establish an external clinical trials oversight committee to advise the NCI Director and

to develop a coordinated organizational structure within the NCI to manage the clinical trials enterprise. Implementation of the first recommendation led to the formation of the federally chartered CTAC, which met for the first time in January. The CTAC is charged with providing advice regarding the entire NCI clinical trials portfolio, advising on the use of correlative science and quality-of-life (QOL) funds, developing recommendations for additional refinements to the NCI-supported clinical trials system, and advising on the outcome of formal evaluations.

Three working groups formed at the January meeting were the: 1) Informatics Working Group, 2) Public/Private Partnership Working Group, and 3) Coordination Working Group. Members were reminded that the trans-NCI Clinical Trials Operations Committee (CTOC), chaired by Dr. Niederhuber, had been established in December 2005 to provide strategic oversight for NCI clinical trials programs and infrastructures. CTOC activities have included reviewing all RFAs and Program Announcements (PAs) involving clinical trials in the past year; providing input to the NCICB on the CTWG informatics implementation plan; evaluating the feasibility of modifying clinical trials data reporting requirements for grant-funded trials; approving minority accrual supplements; and initiating and executing economic- and disease-specific portfolio reviews. The objective of the latter activity is to consolidate data to show how much money is spent on clinical trials, how it is spent, what the trials are and how they interact, and how the clinical trials activities are supported by the NCI. The CTWG recommendation for integrated management of the infrastructure was implemented with the recruitment and establishment of the Coordinating Center for Clinical Trials (CCCT). This management system integrates the activities of the extramural clinical trials community, all NCI Divisions, Centers and Offices, the NCI Director, CTAC, and CTOC.

Prioritization and Scientific Quality. Dr. Shelia Prindiville, Director, CCCT, reviewed the progress made in implementing the CTWG recommendation in this area. Six initiatives mark the progress: 1) the Investigational Drug Steering Committee and five Task Forces have been established and integrated into the Cancer Therapy Evaluation Program (CTEP), DCTD, drug development planning scheme; 2) Disease-Specific Steering Committees (SCs) have been established (gastrointestinal [GI], gynecologic [GYN]), launched (head and neck [H&N]), or about to be launched

(symptom-management/health-related QOL); 3) SPORE members, community oncologists, and patient advocates have been elected to all SCs; 4) prioritization criteria for correlative science studies have been defined by the Task Force in collaboration with the Cancer Diagnosis Program, Division of Cancer Biology (DCB), and the Path Program criteria currently under review are to be completed by the summer. Goals for 2007 in the prioritization/scientific quality area are to: 1) expand the role of Investigational Drug Steering Committee (IDSC) for early-phase trial prioritization utilizing the evolving Task Forces; 2) complete implementation of the H&N and Symptom Management SCs and host GI and GYN state-of-the-science meetings to help identify critical questions and prioritizations for clinical trials; and 3) establish a process to ensure that correlative science and QOL studies conform to standard protocols and standardized laboratory practices.

Coordination. Members were reminded that progress made toward implementing the recommendation for coordination of clinical trials research through data sharing and providing incentives for collaboration included: 1) establishment of a comprehensive database containing regularly updated information on all NCI-funded clinical trials and 2) realignment of NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.

Standardization. Dr. Prindiville explained that standardization initiatives focus on 1) ensuring that the clinical trials informatics infrastructure is interoperable with caBIGTM, 2) developing case report forms (CRFs) incorporating common data elements (CDEs), and 3) establishing a credentialing system for investigators and sites that is recognized and accepted by the NCI, industry sponsors, clinical investigators, and clinical trial sites. In addition, commonly accepted clauses are being established for clinical trial contracts.

Operational Efficiency. Dr. Prindiville noted that operational efficiency initiatives relate to restructuring the funding model for Phase III efficacy trials to promoting more rapid rates of accrual, identifying institutional barriers to timely initiation of trials, expanding recruitment of minority populations to cancer clinical trials, and developing approaches for enhancing adoption of centralized Institutional Review Board (IRB) processes. Progress made in implementing the first initiative includes a financial analysis of Phase III trials costs to identify areas of inadequate

funding; areas of overlap, duplication, or redundancy; and best practices for budget allocations and financial management. An assessment is being made of the potential cost savings to be realized by closing sites with low accrual. In regard to identifying institutional barriers to trial initiation, Dr. Prindiville called attention to a recent analysis of Cancer and Leukemia Group B (CALGB) from concept to initiation of trials, which identified protocol development and regulatory affairs issues as areas that slow progress. The NCI plans to conduct similar analyses of other Cooperative Groups, the Cancer Centers, and internal CTEP processes to identify areas that can be modified to accelerate initiation of trials. To increase minority accrual, a trans-NCI partnership was formed in FY 2006 to propose mechanisms and solicit concepts to enhance funding to current programs. Programs receiving FY 2006 supplemental funding included the Cancer Disparities Research Partnerships, the Minority-Based Community Clinical Oncology Program (MB-CCOP), and Patient Navigator Research Programs. The timeline calls for expansion of this initiative in FY 2007, pending available funding. The attempt to enhance adoption of the NCI Central IRB has begun with an analysis of barriers and the potential cost savings that could result from the Central IRB. Dr. Prindiville concluded by describing the structured process that has been developed to evaluate the restructuring of the NCI clinical trials system.

In discussion, the following points were made:

- Community physicians are involved in decisions at the SC level to ensure that NCI supported trials are those that can accrue successfully and have major input from the community in their design.
- External investigators on the scientific steering committees are driving the implementation process, and non-senior individuals can participate on the Task Forces to play a major role in national trials.
- In the redesign of clinical trials, imaging biomarkers should be promoted as the new surrogate endpoints so that questions can be answered with fewer patients.
- The feasibility and desirability of involving the FDA on some of the SCs early in clinical trial development should be explored, possibly through such mechanisms as the IOTF and the FNIH.
- Currently, the incentives for the vast majority of

practitioners who see the majority of patients who participate in trials exist but are not sufficient. With the plethora of new drugs being approved, it is becoming more expensive and time consuming and less efficient for academic centers to participate in clinical trials, and drug companies are looking abroad. The result could be that the best new treatments no longer will be available in early development to the people of the United States.

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VIII. UPDATE: CLINICAL DEVELOPMENT OF IL-15 - Drs. Thomas A. Waldmann and Stephen P. Creekmore

Drs. Thomas A. Waldmann, Chief, Metabolism Branch, CCR, and a member of the National Academy of Sciences, and Stephen P. Creekmore, Chief, Biological Resources Branch, Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnostics (DCTD), provided an update on the clinical development of interleukin (IL)-15 for use in the treatment of metastatic renal cancer and malignant melanoma and also for use in HIV-AIDS patients receiving highly active anti-retroviral therapy (HAART).

Dr. Waldman told members that IL-15 was discovered as part of an observation that treatment of HTLV-1 associated adult T cell leukemia with antibody therapy to block IL-2 from its receptor resulted in leukemic cells ceasing to express IL-2 receptor and instead secreting a cytokine that used parts of the IL-2 receptor but was distinct from IL-2. IL-2 and IL-15 share delta and gamma receptor subunits and signaling pathways, but each has its own unique alpha subunit. Both IL-2 and IL-15 stimulate proliferation and differentiation of T and B cells; IL-15 also plays a role in the generation and maintenance of natural killer (NK) cells and NKT cells. The adaptive immune responses of these cytokines are unique. IL-2 is involved in activation, induced cell death, and the maintenance and fitness of regulatory T cells that suppress and prevent a T cell-mediated immune response. IL-15 inhibits IL-2 mediated activation-induced cell death (AICD) and stimulates development of NK cells and memory B cells to maintain a long-term memory response to invading pathogens. Knockout of IL-2 or its receptor results in massive enlargement of peripheral lymphoid

organs, high levels of select immunoglobulin classes, and potential development of several types of autoimmune diseases. Knockout of IL-15 or its receptor results in a marked reduction in the number of NK cells and CD8 cells, particularly memory CD8 cells.

IL-2 has been approved for use in metastatic renal cancer and malignant carcinoma. However, IL-2 causes capillary leak syndrome and the cytotoxic lymphocytes generated by the presence of IL-2 may undergo a process similar to AICD and may be inhibited by regulatory T cells that require IL-2 for their maintenance and fitness. IL-15 also activates T cells and NK cells, but because of its inhibitory action against AICD and its facilitation of the action and persistence of CD8 cells, it could be superior to IL-2 in the treatment of cancer.

Current progress in clinical development of IL-15 includes creation of molecular constructs expressing IL 15 and development of a purification scheme that yields a pure IL-15 molecule. A validated assay that measures patient and primate antibodies to IL-15 recently was developed by the Biopharmaceutical Development Program (BDP) for use in pharmacokinetic analyses in both rhesus macaques and tumors. Approval has been obtained for a preclinical study to evaluate the safety, toxicity, pharmacokinetics, immunogenecity, autoimmunity, and impact on immune system elements such as NK cells and CD8 cells. Technical materials have been prepared for a pre-pre-investigative new drug (IND) meeting with FDA's Center for Drug Evaluation and Research (CDER) to discuss clinical development of IL-15. A protocol also has been prepared for FDA approval of a Phase I intergroup dose escalation study of good manufacturing practice (GMP)-produced human IL-15. These studies will be performed by the clinical trials team in the Metabolism Branch in collaboration with other groups. The long-term goal is to define whether IL-15 is safe and of value in the treatment of malignant melanoma and renal cell cancer.

Dr. Creekmore presented progress on the development of recombinant human IL-15 into a cGMP product. He noted that the Biological Resources Branch and BDP have begun the process of developing a GMP IL-15. IL-15 has significant potential for immunogenecity, which is a concern in the clinical setting because it could lead to autoimmune reactions or amplified response to contaminants in the product. An intermediate production goal is to obtain 100 to 500 mg per production run, which is the scale needed

for proof-of-principle and for assay and process development for reformulation and stability studies, pharmacokinetic and toxicology studies, and the first clinical studies. The current production rate is approximately 200 mg per run, which likely could be scaled up by three- or four-fold.

At this time, technology transfer from the Waldmann/Perera laboratories, including transfer of protocols and the nucleotide sequence, has been completed. Reference standards and characterization assays have been identified. A bacterial expression system, E. coli BL-21AI, has been chosen, although in the future a mammalian system might be needed. Major parameters to include on a certificate of analysis for the product have been identified, including: purity by size-based, charge-based, and light scattering methods; protein content; some sequencing of both ends; and HPLC.

The present purification scheme includes nine steps from fermentation to formulation and vialing, with an overall recovery of approximately 10 percent of starting materials. A hydrophobic interaction chromatography step may be added before the final formulation step as additional purification. Comparison of bioactivities of recombinant IL-15 from various sources showed that the range and reproducibility is sufficient to move forward. The quality of protein refolding was tested using light polarization measurements. Slight unfolding resulted in a drop in potency. Elementary stability studies have been performed using two preparations of IL-15 made with BDP. Light scattering studies to detect misfolding and aggregation are required for clinical application of IL-15. These studies have suggested that long-term storage at 4ºC could result in formation of aggregates.

Current efforts in IL-15 production include continued product characterization (impurity profile and physiological analyses), identification of stability-indicating assays, and stability assessment. The timeline for production proposes tox lot production and non-human primate studies in Q3 of 2007, GMP production of 100-200 mg lots in Q4 of 2007, and larger scale GMP production and National Institute for Allergies and Infectious Diseases (NIAID) studies in 2008 with intramural and extramural NCI researchers to determine whether production of other cytokines, such as IL-12, IL 14, and IL-7, is of interest to the community.

In discussion, the following points were made:

- The Frederick facility may want to consider partnering with local companies that have large facilities for producing biologicals. The NCI is working to develop a plan for an experimental therapeutic drug development program that has both in-house capabilities and relationships with experts in the private and academic sectors.
- Approximately 70 percent of Frederick's production of GMP-grade biologics is in partnership with external academic collaborators, largely through the Rapid Access to Intervention Development (RAID) program, which encompasses institutes other than the NCI. Approximately 30 percent of production can be for therapeutics for conditions other than cancer. The RAID program provides an efficient path for developing biologicals.
- Although partnering with large companies is desirable, most companies are not interested in the early phases of development. The NCI and its partners can develop efficacy data and later license products to companies with the capabilities to efficiently and cost-effectively scale up production of biologicals for use in large trials. Once a product shows proof-of-principle and passes FDA safety concerns, companies may have more interest in the product.

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IX. RFA/COOPERATIVE AGREEMENT CONCEPTS - Presented By NCI Program Staff

Division of Cancer Prevention

Community Clinical Oncology Program (RFA/Coop. Agr.)

As requested by the Subcommittee charged with evaluating reissuance concepts on behalf of the BSA, Dr. Lori Minasian, Chief, Community Oncology and Prevention, DCP, reminded members that the program's three major components are the Research Bases (Cooperative Groups, Cancer Centers); CCOPs and MB-CCOPs, which accrue patients to the clinical trials designed by

the Research Bases; and members and affiliates, which accrue patients to prevention and control protocols. Currently, there are 50 funded CCOPS, 13 funded MB-CCOPS, and 400 affiliated hospitals distributed across the Nation, some of them located in states without Cancer Centers. Consistently over the past 16 years, the CCOPS and MB-CCOPS have accounted for one-third of the accrual to Cooperative Group treatment trials and an even greater percentage of accrual to prevention trials with the addition of Member and Affiliate accrual.

Funding. CCOP grants fund research personnel on an FTE basis, but the funding is equivalent to per-case reimbursement of about $2,000 per patient. CCOPs have varying numbers of structures, ranging from 1 to 25 with an average of 7. The hospital and private practices that comprise the CCOP community match federal funds, on average at about 76 percent, to support the research activity. The community also contributes experienced investigators who participate in other NCI and NIH projects. As a CCOP participant, the community gains access to state-of-the-art cancer care, patients can receive high-quality cancer care in their communities, and minorities and the underserved have access to trials. The communities also gain by their participation in a precedent-setting network in that the CCOP was one of the first programs that facilitated linkages between academia and the community and has served as a model to other Institutes and the NIH Roadmap. In addition, the community hospitals actively engage in large prevention trials because those trials provide a venue for the health systems and hospitals to educate and communicate about the full spectrum of cancer care.

Research Bases. Eight Cooperative Groups and 6 Cancer Centers comprise the 14 funded CCOP Research Bases. Through the CCOP Research Base Grant, the components receive support for treatment accrual by the CCOPs in the form of funding for QOL endpoints on treatment trials. In addition, these grants fund the development and implementation of cancer prevention and control trials.

Portfolio of Trials. During the past 16 years, the CCOPs have conducted a wide range of prevention and cancer control trials, including large and smaller Phase III trials and more than 100 symptom management trials. A sizable amount of translational research is conducted in conjunction with the prevention and control studies. All large prevention trials and most small ones

have associated biorepositories, so there are ongoing collaborations with SPOREs and Cancer Centers, particularly with repositories for prostate and breast cancer prevention trials. In addition, the CCOPs have ongoing collaborations with other NIH Institutes and have been promoting translational components to symptom management studies.

Program Management. Typically, the RFA is reissued annually and awards are made for 3 to 5 years. Each year, about one-third of the overall program recompetes, and budgets are readjusted annually based on performance (Type 5 adjustments). The CCOP RFA was presented for concurrence with its reissuance in 2003, and the Board approved five Reissuances. Dr. Minasian informed members that CCOP Program Management would be optimized if staff had multi-year authority to reissue the RFA. Another option would be to develop standing guidelines and a PA for annual release.

Budget. The overall program budget for FY 2006 was $89 M distributed among the three components and large prevention trials, with an additional $28 M in matching funds from the communities and untold amounts of in-kind support. The estimated CCOP budget for FY 2007 is $81 M.

Subcommittee Review. Dr. Kirby Bland, Deputy Director, Comprehensive Cancer Center, and Fay Fletcher Kerner Professor and Chairman, Department of Surgery, University of Alabama-Birmingham School of Medicine, informed members that the Subcommittee had asked for refinement of some aspects of the RFA and that all questions had been answered by the presentation. The questions related to: 1) the alignment of the CCOP with the new National Community Centers Program and whether the two programs were duplicative; 2) clarification of the accomplishments of the CCOP; and 3) clarification of the cost per patient that is reimbursed.

Motion: A motion to concur on the reissuance of the Division of Cancer Prevention's (DCP) Request for Application (RFA)/ Cooperative Agreement entitled "Community Clinical Oncology Program" was approved with 5 abstentions. The Board requested that the Executive Committee consider a 3-5 year cycle for reissuing the RFA.

Minority-Based Community Clinical Oncology Program (RFA/ Coop. Agr.)

Subcommittee Review. Dr. Edith A. Perez, Professor of Medicine, Director, Clinical Investigations, and Director, Breast Cancer Program, Division of Hematology and Oncology, Mayo Clinic, informed members that the Subcommittee recognized the significant contributions made by the MB-CCOPs to the overall CCOP program, particularly with the emphasis now on reducing health care disparities. MB-CCOP sites accrue about 21 percent of minority enrollment to NCI-approved clinical trials and are a successful addition to the overall program. The Subcommittee recommended that the BSA concur in reissuance of the RFA.

Motion: A motion to concur on the reissuance of the DCP RFA/ Cooperative Agreement entitled "Minority-Based Clinical Oncology Program" was approved with 6 abstentions.

Division of Cancer Control and Population Sciences

Centers of Excellence in Cancer Communication Research (CECCR) (RFA/Coop. Agr.)

Members were reminded that a presentation on science of what is emerging from the CECCRs had been heard during the November 2006 meeting and that the Subcommittee to review the reissuance had asked for an additional presentation, this time on the mechanics of the RFA itself.

Dr. Bradford Hesse, Health Communication and Informatics Research Branch, DCCPS, reminded members that the CECCRs were modeled after the successful Transdisciplinary Tobacco Use Research Centers. He noted that the objective was to bring together the necessary disciplines (e.g., communication and informatics specialists) to address problems being confronted in cancer communication. He briefly reviewed four trends that emphasize the continuing importance of this initiative: 1) rapid advances being made in the biomedical sciences and the need to communicate the science of prediction and to personalize information; 2) advances in consumer informatics that can be exploited to improve messages; 3) informatics support, for example, the need to address the long-term implications related to the use of evolving technologies like

electromagnetic radiation (EMR) in communicating health information; and 4) health disparities and the potential for creating great displacements as information technologies are focused on health. Four centers were funded from the original RFA: St. Louis University, University of Michigan (UM), University of Wisconsin, and University of Pennsylvania.

The PIs from the St. Louis and UM CECCRs presented examples of their experiments. Specifically, the St. Louis experiments illustrated that: 1) a transdisciplinary center could be created; 2) a new approach could be adopted to solve the problem of reaching out to those most at risk for breast and cervical cancer by targeting the wire service with localized resources; and 3) strategies could be effective in optimizing the reach and impact gained from kiosks. Whereas, the UM experiments employed a multidisciplinary approach to tailor a tobacco cessation tool that people could access for a fraction of the cost of group support or tailored interviews. The results from a large-scale Health Maintenance Organization (HMO) trial showed a 6-month cessation rate of 44 percent among those receiving the largest number of high-tailored sections.

As the BSA requested at the November 2006 meeting, an initiative-wide evaluation was undertaken by an external panel and an internal committee. Recommendations from CECCR evaluators were to recognize the importance of connecting communication with the larger cancer control enterprise by linking research within the CECCRs with NCI-funded Cancer Centers, other DHHS agencies, other NIH/NCI initiatives, HMOs, community-based organizations (CBOs), medical and public health schools, media and other institutions, and offices within the NCI.

Dr. Hesse reminded members that the P50 mechanism was chosen for the CECCRs funded in 2003 and that the objectives were innovation; synergy among disciplines; provision of a training ground for new communication scientists; and extended reach, effectiveness, and efficiency. In the proposed reissuance, the P50 “centers” mechanism and the objectives are the same as the original RFA with the addition of patient-centered communication as a new topic area, integration of CECCR measures with caBIG^{TM}, and improved integration with the Cancer Centers.

An estimated budget of $8 M per year is proposed, for a total of $40 M for the 5-year project period.

Subcommittee Review. Dr. Jane Weeks, Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School, and Chief, Division of Population Sciences, Dana-Farber Cancer Institute, stated that members of the Subcommittee agreed unanimously with the reissuance. She noted that the structure and perhaps size of the program was an issue that remained to be resolved. The Subcommittee was unanimous about the importance of continued NCI investment in this area, but a couple of members recommended that consideration be given to the reissuance as an RFA but for the solicitation of multiple R01 applications, with a somewhat lower level of funding.

In discussion, the following points were made:

- Input from and collaborations with experts in the ACS should be explored. The ACS makes a huge investment annually in this scientific area to market to and focus on the right audiences.
- The science demonstrated in this initiative is commendable, but the scope is limited. Emerging issues in cancer diagnosis and therapeutics, which raise huge communication issues, also should be addressed.
- The clinical component and issues related to underserved populations and health disparities should be strengthened in the RFA.

Motion: A motion to concur on the reissuance of the Division of Cancer Control and Population Sciences' (DCCPS) RFA entitled "Centers of Excellence in Cancer Communication Research" was approved with one vote in opposition. NCI staff should consider the issues raised by the Board in developing the full RFA, including those regarding the needs of underserved populations and adding a clinical component.

Division of Cancer Treatment and Diagnosis

A Data Resource for Analyzing Blood and Marrow Transplants (RFA/Coop. Agr.)

As the subcommittee chair, Dr. Michael P. Link, Lydia J. Lee Professor of Pediatrics, Chief, Division of Hematology and

Oncology, Stanford University School of Medicine, reminded members that the proposed reissued RFA concept is a limited recompetition for the Center for International Blood and Bone Marrow Transplant Research (CIBMTR), which is funded jointly by the NCI; National Heart Lung and Blood Institute (NHLBI); and NIAID. The CIBMTR is a database resource for investigators interested in hematopoietic stem cell transplants, most of which are performed for patients with cancer. The database captures 60 percent of the transplants performed in the United States as well as transplants done in a variety of centers throughout the world. Dr. Link noted that the Subcommittee unanimously concurred with reissuance.

Motion: A motion to concur on the reissuance of the Division of Cancer Treatment and Diagnosis' (DCTD) RFA/Cooperative Agreement entitled "A Data Resource for Analyzing Blood and Marrow Transplants" was approved unanimously.

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X. MINI-SYMPOSIUM: BIOBEHAVIORAL INFLUENCES ON CANCER BIOLOGY — Drs. Robert Croyle, Paige G. McDonald, Anil K. Sood, Suzanne Conzen and Steven W. Cole

Dr. Robert Croyle, Director, DCCPS, informed members that the NCI has supported innovative, high-risk research of cancer progress and prevention through studies in neuroscience, such as neuroendocrinology and psychoneuroendocrinology, the role of the brain in mediating emotional experiences and stress, and the physiological impact on cancer. Dr. Croyle introduced the four speakers: Drs. Paige G. McDonald, Chief, Basic and Biobehavioral Research Branch, DCCPS; Anil K. Snood, Professor, Departments of Gynecologic Oncology and Cancer Biology, and Director, Ovarian Cancer Research, University of Texas MD Anderson Cancer Center; Suzanne Conzen, Associate Professor, Department of Medicine and the Ben May Department of Cancer Research, University of Chicago; and Steven W. Cole, Associate Professor, Department of Medicine, Division of Hematology/Oncology, School of Medicine, University of California-Los Angeles (UCLA).

Biobehavioral Influences on Cancer Biology: An Emerging Opportunity. Dr. McDonald defined biobehavioral science as the study of interactions between social, psychological, and biological factors in health. Biobehavioral factors are distinguished from other behavioral risk factors by neuroendocrine mediation, and differ from systemic and environmental stress; examples of biobehavioral risk factors include social isolation, social support, depression, and chronic stress. To obtain clarity about the influence of biobehavioral factors on cancer biology, researchers have revitalized the use of experimental animal models of human cancer.

Members were informed that the association of biobehavioral influences with cancer incidence has been inconsistent, but its association with cancer progression and mortality is more suggestive. Stress, for example, has been studied as a biobehavioral influence. Experiences are interpreted as stressful when there is a perception that a threatening or challenging event or stressor exceeds an organism's ability to respond. These perceptions initiate a cascade of information processing pathways in the central nervous system and the periphery and activate the autonomic nervous system (ANS) or the hypothalamic pituitary adrenal (HPA) axis, and thus catecholamines, glucocorticoids (GCs), and other stress hormones are released from the brain, adrenal gland, and sympathetic nerve terminals. Individual differences in the perception and evaluation of external events create variability in the ANS and HPA responsivity to similar stressors. Every day experiences and one's environment can modulate physiological pathways leading to transient and permanent biological changes in nuclear cellular and organ system function and structure. This paradigm has implications for cancer control because cancer is viewed as an organ with its own microenvironment.

Dr. McDonald described recent studies addressing biobehavioral influences on cancer. He noted that Albeny and Sporn (2007) described the tumor microenvironment as a complex system of many cell types, all of which can participate in tumor progression, and noted the importance of the immediate microenvironment within a developing tumor.

Effects of Chronic Stress on Cancer Growth and Progression. Dr. Sood presented information about what the response to stress tends to be and some of the mechanisms that are related to how chronic stress influences the tumor microenvironment. She stated

that following exposure to chronic stressors, the HPA is activated, thus producing hormones that activate GCs from the adrenal cortex; catecholamines also are produced from the sympathetic nervous system (in response to chronic stress settings) and the adrenal medulla. There have been a number of studies conducted on how the immune system is impacted by chronic stress and associated factors; published papers describe decreased cell mediated immunity, and emerging data show how humeral responses are affected by stress and associated factors.

Members were told that there has been a focus during the past several years on palliative cancer biological processes, including steps in the metastatic cascade that might be influenced by chronic stress and associated factors. VEG-F levels, for instance, have been shown to be elevated in individuals with chronic distress but lower in ovarian cancer patients who have higher levels of social support. Dr. Sood shared details of an in vivo model that has been established to study the influences of chronic stress in an ovarian cancer. She noted that the effect of chronic stress on angiogenic pathways also was studied, and results were published in Nature Medicine (2006).

Dr. Sood stated that chronic stress accelerates ovarian cancer growth and causes a more invasive pattern of spread in this model. Moreover, these effects are mediated by beta receptors that establish a favorable microenvironment for tumor growth. Several areas for further study include the microenvironment in human tumors in the context of behavioral factors, mechanisms (immune and non-immune) by which biobehavioral factors affect tumor growth, and development of behavioral or pharmacological intervention strategies.

In discussion, the following point(s) was made:

- The expression of beta two adrenergic receptors in human ovarian cancers was associated with poor
- survival and was associated with a number of progressive tumor features. Future studies may determine whether these and other findings of the ovarian cancer model can be generalized to other tumors beyond the breast.

Social Environment and Tumor Biology: The Role of

Glucocorticoid-Mediated Tumor Cell Survival. Dr. Conzen described studies of another pathway involved in the stress response that might be contributing to the effect explained by Dr. Sood—specifically, the role of GCs in tumor cell biology. He informed members that to identify novel anti-apoptotic signals in breast epithelium and early breast cancer that would contribute to an increase in breast cancer, the apoptotic pathway was studied, and GCs were discovered to be inhibitors. This led to the question of whether GC signaling might increase tumor growth. By using MCF 10A-Myc cells, withdrawing growth factors, and adding back the essential growth factors that have been known to protect against apoptosis in cultured cells and cause their proliferation, GCs were found to be a potent anti-apoptotic pathway. Dr. Conzen shared to-be-published data that confirm that this receptor is expressed in human breast epithelium. Regarding breast cancer, it appears to be expressed in the triple negative breast cancer, which is estrogen receptor, progesterone receptor, and HER2neu negative breast cancer.

Dr. Conzen also described collaborative efforts between her laboratory and biopsychologist Dr. Martha McClintock, University of Chicago, involving GCs and social isolation. Dr. McClintock had shown that relative social isolation of Sprague-Dawley rats and Norwegian rats causes an increase in both the size of mammary gland tumors and an earlier onset of these tumors; she conducted her studies without adding any of the agents that usually are used to cause earlier mammary glands. Her studies have revealed spontaneous and much earlier development of mammary glands. Drs. Conzen and McClintock, with support from a P50 grant from the Center for Population Health and Health Disparities (CPHHD), collaborated on the research question of whether an increased corticosterone response favors tumor growth in rats and potentially in models of mammary cancer, that is, whether the social environment affects tumor growth. She noted that there are a number of translational implications from these findings about GC receptor expression in breast cancer and early DCIS. These include: GC receptor’s potential as a predictive or prognostic marker; the role of GC receptor inhibitors and GC receptor downstream effectors in preclinical models and Phase 0 and 1 clinical trials; GC premedication in clinical trials; and further collaboration between scientists to examine cortisol and GC receptor expression in studies on social isolation and cancer.

In discussion, the following point was raised:

- A concern was raised about allocating funds to a fascinating area of study that might not contribute significantly to an understanding of cancer biology, particularly during a tight funding environment.

Gene-Social Environment Interactions in Cancer: A Bioinformatic Approach. Dr. Cole explained the kinds of biobehavioral signaling dynamics that help structure gene expression profiles in primary human clinical tumors. Members were told that this research relies on recently developed strategies from bioinformatics that facilitate understanding of how upstream transcription controlled pathways are structuring broad patterns of differential gene expression at the level of primary tumors. Dr. Cole described the physical architecture that allows external social factors to regulate gene transcription within cells, particularly whether social signal transduction pathways are operative in human clinical tumors. The central nervous system has the capacity to interpret a social environment as threatening or uncertain, and it causes neuroendocrine-mediated stress responses in the periphery through the activation of either the hypothalamic pituitary adrenal axis (and thus the production of GCs) or sympathetic neurons that directly innervate tissue structures in peripheral biology. In either case, the activation of these kinds of signaling molecules has the capacity to regulate gene expression through classical receptor-mediated signal transduction pathways.

Two questions have guided Dr. Cole's research: Which particular transcription factors are sensitive to these dynamics? Which large ensembles of genes are regulated by these kinds of transcription factors? He summarized three ways in which social and environmental influences can get into the genome of a tumor: 1) the capacity of human transcription factors to regulate the activity of pathogens that contribute to cancer, as described by Dr. McDonald, and as seen in Dr. Cole's work on the Kaposi's sarcoma that is associated with the herpes virus; 2) the capacity of neuroendocrine factors to regulate gene expression by healthy cells in the tumor microenvironment; and 3) as explained by Drs. Sood and Conzen, the capacity for direct neuroendocrine regulation of the tumor cell biology itself of the gene expression by that cell.

Circumstantial evidence from associative studies shows that social

signal transduction pathways are active in human clinical cancer. An overview of a pilot study that used bioinformatics of sequenced human genome to reverse engineer patterns of gene expression based on the distribution of transcription factor binding motifs in the promoters of those genes was given. Focusing on five primary ovarian cancers, the analysis looked at the promoters to determine which transcription factor binding motifs are selectively over-represented in those promoters compared to promoters of genes that are not differentially expressed. It was observed that cancer is not driven by just one transcription factor; a preliminary study has begun to look at which other major transcription control pathways also might show differential activity as a function of this biobehavioral risk. Regarding the evolution of the tumor genome, Dr. Cole shared evidence of selection for beta-AR/PKA genes in ovarian cancer.

He concluded by stating that protective interventions include well-developed bioinformatics strategies for identifying pathways that mediate the effects of stress biology on tumor biology. This information will help in the selection of agents and the identification of at-risk individuals. There also are implications for the beta adrenergic signaling pathway itself, which is pharmacologically accessible; its impact on the biology of these tumors currently is unknown.

In discussion, the following points were made:

- Regarding the correlation between the stage at diagnosis and the stress level, tumors likely started at different points in time but grew to the same size by the time they were surgically removed, at agreater rate of growth in the case of the more stressed people.
- ?Bioinformatics can point researchers to appealing hypotheses that they can investigate more rigorously in an experimental setting. It can be used to suggest targeting evidence, rather than produce decisive experimental evidence. In bioinformatics, association is used to determine whether behavioral influences are activating a given pathway.
- For conditions of severe stress that are sustained, such as post traumatic stress syndrome, three studies have looked at solid tumors; two have found that beta blockers offer a protective effect.

Conclusion. Dr. McDonald summarized overarching themes in biobehavioral research. He noted that stress biology can influence tumor biology. Mechanisms are being elucidated, as shown by neuroendocrine regulation of angiogensis, invasion, cell mediated immunity, apoptosis, tumor gene expression, and viral replication. Chronic stress accelerates ovarian cancer growth and causes a more invasive pattern of spread in an orthotopic mouse model; these effects are mediated by beta receptors that establish a favorable microenvironment for tumor growth. Moreover, chronic social isolation was associated with increased corticosterone responses to a mild stressor and increased mammary tumor growth in transgenic mice; corticosterone responses to stress differed depending on social environment and support systems. Social factors are noted to regulate gene expression through neuroendocrine activation of cellular signal transduction pathways. Early evidence of risk-related activation of several pathways in ovarian cancer patients has been found, as well as evidence of selection for beta adrenergic PKA genes, suggesting opportunities to test the inhibition of beta adrenergic and GC receptors in clinical models and to develop targeted behavioral interventions.

This research program is based on the fundamental perspective that any causal influence of biobehavioral signaling pathways in cancer pathogenesis must ultimately be mediated by changes in the complex system of cells that comprise the tumor and its microenvironment. Future directions encompass the breadth of effects, biological mechanisms, and clinical impact, using basic, translational and transdisciplinary sciences. There is a critical need for in vivo studies using clinical samples. In addition, relevant animal models (e.g., immunodeficient transgenic and knockout mouse models) of human cancers can be used to more accurately recapitulate the dynamics of human cancer in vivo.

In discussion, the following points were raised:

- It would be helpful to identify logical partners to obtain additional funding and conduct further studies. Any plan should look at 3 to 4 years ahead and collect enough critical evidence to justify a major investment; the military might provide both a stressed environment and a magnitude of people for a large study.
- The effect of stress on response to therapy should be

considered, such as whether the stress of diagnosis impacts treatment, or how the stress of surgery affects recovery.

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XI. UPDATE: CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER INITIATIVE — Drs. Anna Barker, Henry Rodriguez, and Steve Carr

Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, presented an update on NCI's work on proteomics. Informed members that in late 2005, 1,261 putative cancer protein or peptide biomarkers were described in the literature, but only 9 of them were approved by the FDA as tumor-associated antigens. This rate of approximately one approved biomarker per year since 1998 is approximately the same rate experienced in other disease industries. The NCI identified technology barriers; these include the inability to reproduce experimental data and an enormous diversity, range, and dynamic nature of proteins to be measured. Moreover, there is limited inoperability across instruments and platforms; difficulty in measuring large number of features simultaneously; and insufficient tolls for data capture, analysis, and knowledge creation. Systems barriers in the early stages of the pipeline include: insufficient high-quality reagents; inadequate supply of biospecimens and clinical data; lack of standards and protocols; and no coordinated system for cancer proteomic technology, reagent, and bioinformatics development. The NCI worked diligently from 2002 through 2005 to identify and address these early pipeline issues. This culminated in December 2005 with a Proteomic Affinity/Capture Methods Workshop, which led to a proposal for a promising Roadmap initiative called the Clinical Proteomic Technologies for Cancer Initiative (CPTCI). She noted that presentations would be given by Drs. Henry Rodriguez, Director, Clinical Proteomic Technologies for Cancer, and Steve Carr, Director of Proteomics, Broad Institute of Harvard University and Massachusetts Institute of Technology (MIT).

The Clinical Proteomic Technologies for Cancer Initiative. Dr. Rodriguez explained that the CPTCI is a 5-year initiative that addresses barriers in proteomic technologies, reagents, and systems early in the pipeline by building a foundation of technologies, data,

reagents and standards, analysis systems, and infrastructure that will help systematically advance the understanding of protein biology in cancer. It is organized in an integrated manner to work with and benefit the Early Detection Research Network (EDRN), SPOREs, clinical trials, systems and structural biology, and technologies, as well as caBIGTM- and community resource-compatible informatics. It also aims to accelerate the translation of discovery research and clinical applications. The CPTCI is comprised of three components:

1) **The Clinical Proteomic Technology Assessment for Cancer (CPTAC) teams** organized under the U24 cooperative agreement vehicle, involve a multidisciplinary network to evaluate proteomic analysis platforms to reliably identify, quantify, and compare peptides and proteins in complex biological mixtures, particularly with a focus on mass spectrometry and affinity-based technologies. Specific objectives include the development and implementation of uniform algorithms for sharing bioinformatics and proteomic data and analytical and data mining tools, as well as the development of well-characterized material and bioinformatics resources for the entire cancer research community. The RFA was issued in February 2006. A collaborative network of five CPTAC teams was formed in September 2006, and they are working cohesively to address technical hurdles for various technology platforms. The teams include the Broad Institute of Harvard University and MIT; Memorial Sloan-Kettering Cancer Center; Purdue University; University of California-San Francisco (UCSF)/Lawrence Berkeley National Laboratory; and Vanderbilt University School of Medicine.

2) **Advanced Proteomic Platforms and Computational Sciences** support highly innovative R01, R21, and R21/R33 research in the quantitative analysis of peptides and proteins of interest in clinical cancer studies. Two specific areas of interest include: 1) the detection, recognition, measurement, and characterization of biological fluids; and 2) computational, statistical, and mathematical approaches for the analysis, processing, and facile exchange of large proteomic data sets. The RFA was issued in December 2005, and 15 awardees were announced in September 2006. Seven are focusing on the proteomics platform and represent a broad range of promising approaches and innovative affinity-based and mass spectrometry technologies and 8 are addressing computational sciences, such as statistical and mathematical

approaches for the analysis, processing, management, and exchange of clinical proteomics data among the research community. Dr. Rodriguez mentioned that results already have been realized for the CPTAC, through the work of Dr. David L. Tabb, Vanderbilt University, who described his development of a software system called MyriMatch in a recent article in the Journal of Proteome Research (February 2007). MyriMatch offers the ability to score peptide matches based more on the multivariate hypergeometric distribution of the peptides themselves and, through this computational infrastructure, ensure a more accurate high-throughput identification of proteins.

3) **The Proteomics Reagents Resource** provides a central, public source for well-characterized data on proteomics reagents and resources, including human and mouse tissue samples and plasma, antibodies and affinity capture reagents, labeling reagents, protein and peptide mixtures, and other reagents. Its key features involve the development of standard and characterized reagents as well as the development of appropriate quality assurance/quality control (QA/QC) procedures, and the provision of data on reagent performance. The Proteomics Technologies Reagents Resource Workshop was held in December 2005, and an RFP is expected to be released in the summer of 2007. The program is collaborating with NCI's Mouse Proteomics Technologies Initiative (MPTI) to make the best use of NCI's resources in working with mouse biospecimens. The MPTI, which is comprised of eastern and western consortia, develops resources and data in support of innovative research and engineering approaches that improve technologies for the measurement of proteins and peptides that are linked to cancer processes in a spectrum of different mouse models. A joint meeting between MPTI and CPTAC team leaders will occur in March 2007.

Project outcomes include a system to support reliable protein identification and measurement, as well as broadly available, optimized mass spectrometry and affinity technology platforms. Moreover, innovative technologies to support more rapid and specific proteomic analysis and the development of standard proteomic databases are expected. High-quality biospecimen, antibody, and reagent resources will support investigator-initiated proteomics research.

Challenges of Clinical Proteomics and Path Forward Defined

by the CPTAC. Dr. Carr described the science that is developing in the context of existing underpinning technologies, including three approaches to biomarker discovery, and CPTAC's role as a technology assessment program. A pattern-based approach currently is used to discover biomarkers. Dr. Carr stated that this approach is limited in its ability to discover markers, validate the utility of those markers, and progress into a clinical assay environment. For this reason, the proteomics community has embraced an identity-based approach. This commences with a biological sample that is directly broken up into peptides, rather than being analyzed at the protein level; the peptides then are to produce sequence information. A third approach takes advantage of pattern in addition to identity and uses high-performance devices, which brings resolution into the equation. Resolution offers the ability to separate species that have nearly identical molecular weights and to determine the masses with great accuracy.

It was noted that analytical challenges of proteomics differ in important ways from genomics and microarrays. Unlike genomics and microarrays, for proteomics all possible features are not known, the sample is dynamic during analysis, and not all features are measured. In addition, when a signal is not detected in genomics and microarrays, it means that a feature is not present; in proteomics, however, a signal not detected could mean either that a feature is not present or that a feature is present but not detected.

Discovery leads to candidates, not biomarkers. With extensive fractioning, which is required to detect lower-level proteins, and low analysis throughput, the data have high dimensionality (i.e., more than 100 differences). This is a recipe for high false discovery rates, and therefore leads to candidates, which must be confirmed and quantified in blood through a different platform that is capable of high-throughput reproducible quantitative analysis. For this, a much larger sample set must be obtained. The best strategy has been identified as using: 1) all good platforms for unbiased discovery that can find a difference with depth, percent coverage, and short-term stability as the goals; 2) tissues and proximal fluids, not blood; and 3) all "statistically responsible" platforms for verification, with high-throughput, precision, and sensitivity.

To address clinical challenges in proteomics, CPTAC teams and the NCI met in October 2006, to develop a detailed experimental plan for a Preclinical Pilot Phase focused on technology

assessment. The intent was to identify key problems and design studies that furthered unbiased discovery and preclinical validation or verification, as well as to develop common reagents for the CPTAC and the community. Additionally, the plan could provide a common pipeline for data analysis and produce highly qualified raw and processed data sets that are made publicly available. A further goal was to develop and employ common sample collection methods to ensure high-quality samples for the clinical phase. Key issues to address include the representation of proteins present in a sample that are detected at each decade in an unbiased discovery experiment, and the effect of matrix complexity; the extent to which the various discovery platforms are reproducible in detecting real differences, as their detection efficiency and the numbers of peptides observed are highly dependent on the level of a given protein. Other questions include whether discovery and verification platforms require different measurement endpoints, different specifications on the same endpoints, or both; how reproducible and accurate are the verification platforms; and what is the impact of sample complexity?

The October 2006 meeting also discussed the need for standard samples, and the meeting attendees agreed to use common protein spikes and common matrices. Three matrices were chosen to mimic increasingly complex biological backgrounds that are encountered in proteomics. Metrics include: 1) the reproducibility of seeing a protein as measured by detection, coverage, and quantitation; and 2) the reproducibility of observing a statistically significant difference in protein concentration between two samples. Working groups have been established to assist with the design of experiments; the selection and production of matrices; the selection and protection of protein standards; data analysis, storage, and dissemination; and biospecimens. In addition, integrated genomic approaches are being used to enrich a curated candidate database. All CPTAC teams are participating in the first experiments, which involve a data analysis of 20-protein and 48-protein standards mix (which were provided by the National Institute of Standards & Technology [NIST]) into a yeast lysate background. Dr. Carr closed by noting the work of the Program Coordinating Committee (PCC) members.

In discussion, the following points were made:

- The technology assessment will be valuable for mouse

models in that it will provide lessons for discovery and verification assays.

- The cell lines will not be from the same individual; they will be grown in culture. e in proteins.
- Clinical scientists have been involved early in the process, such as with study designs. Rapid identification of biomarkers is important.
- An assessment of the sources of variability in the biospecimen collection methodology should be included as part of the technology assessment. A clear knowledge of the optimal specimen collection strategies should precede the actual collection.

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XII. UPDATE: INTERAGENCY ONCOLOGY TASK FORCE — Dr. Kenneth H. Buetow

Dr. Kenneth H. Buetow, Associate Director, Biomedical Informatics and Information Technology, and Chief, Laboratory of Population Genetics, provided and update of the bioinformatics work underway through the IOTF. The IOTF was created through an agreement between the FDA and the NCI, in which the two agencies share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. Its five highest priority areas are: markers of clinical benefit, nanotechnology, joint training, process, and bioinformatics.

The informatics challenges are daunting: a multitude of information systems, but no common data model or format, and few common vocabularies; no infrastructure for data sharing; security and privacy concerns; and data sharing and intellectual property (IP) concerns. Dr. Buetow described the challenges with a photograph of a typical clinical trials office at a major academic institution, which includes six different operating systems with six different data capture systems, all of which are necessary for operations. He noted that there is also a large morass of information standards or data standards in the area of biomedicine. Other challenges are posed by the need to integrate three distinct worlds: patient care, clinical research, and regulatory.

In the context of caBIGTM and clinical research IT, he stated that three areas, clinical systems, clinical trials, and external reporting, and their components need to be built out with interfaces and data resources. The IOTF bioinformatics activity is a collaborative effort among government, industry, and academia. In addition to the IOTF and the caBIGTM community, special interest groups concerned with regulatory data exchange are involved, such as the major standards body, the Clinical Data Interchange Standards Consortium/Health Level 7 (CDISC/HL7), pharmaceutical manufacturers, and the biotechnology industry. Regulatory data exchange goals include: a mechanism for secure electronic information exchange; sustainable and secure infrastructure for electronic submissions; a Global Investigator Registry for commonly used or referenced data; facilitation and implementation of information exchange standards; and legally enforceable digital signatures compliant with Title 21 Regulations and other guidelines from the outset.

Dr. Buetow informed members of the steps required to submit data and documents for regulatory processing. It will involve building a large, secure, and reliable infrastructure with leading-edge functionality and interactivity to support pharmaceutical grade data. The strategy adopted to accomplish this includes starting with small strategic pilots, leveraging existing international standards and data models, and evaluating and extending existing NCI infrastructure. The commitment from caBIGTM is for open source, open standards, open architecture, open access, and open development. The submissions process was divided into smaller pieces, starting with electronic submissions. The development strategy involves production infrastructure and infrastructure development. One of the first areas considered is that of standards. An inter-standards infrastructure called the Biomedical Research Integrated Domain Group (BRIDG) was developed, which provides the first integrated biomedical research models and standards that cross both care delivery and biomedical research and regulatory submissions.

FIReBIRD. Another infrastructure that is underway is the Federal Investigator Registry for Biomedical Informatics Research Data (FIReBIRD), which automates the generation and standardized collection of Form 1572 information. This infrastructure allows investigators to register online with the NCI and other sponsors, including the commercial sector. It leverages the secure access for

everyone (SAFE) standard for legally enforceable digital signatures. The intent is to construct ways that new investigators can build and submit forms electronically into a hosted service that the FDA could use as its registry for principal and other investigators, their laboratories, and other components, and that the NCI could migrate to as well. FIReBIRD version 1.0 manages investigator profiles, registration, query interfaces, registry set up modules, and other electronic document uploads; it also has electronic signatures attached to it.

Dr. Buetow introduced Dr. John Speakman, Associate Director, NCI Clinical Trials Products and Programs, who provided a brief demonstration of the active production class FIReBIRD application for Board members. Dr. Speakman demonstrated the ease and rapidity in completing the electronic form and creating an online curriculum vitae (CV). FIReBIRD includes 6,847 organizations from CTEP, 205,815 CLIA laboratories from the CMS Oscar database; and 3,029 IRBs from the Office for Human Research Protections certified IRB database. In addition, it currently includes 467 investigators and soon will include 100,000 investigators from the FDA database.

Janus Project. Dr. Buetow told members that the Janus data model had been previously constructed for the caBIGTM and serves as the building block for the basic observational data that are part of a clinical trial. It contains the information that the FDA uses for a registration trial or anything to be approved by the FDA: data on what happens (defining the events, the domains, the attributes, and the interventions); structured information on the protocol; and the associated analysis plans and results. It is available on the FDA Web site, as well as the definitions of the data that go into the model. Phase I of the Janus Project involved the establishment of technical infrastructure for data submission. Phase II moves to an operational pilot phase. Dr. Buetow provided brief video demonstrations that highlighted the Janus model's capabilities. The database's basic tools include study tabulation, information, and basic manipulations that one can do with respect to the individual studies that are a part of the larger database. It has role-based access, which allows the NCI and FDA to perform additional manipulations as well. A separate set of tools can be used for the ad hoc manipulation of data and creation of specialized reports based on desired characteristics of the data.

In conclusion, Dr. Buetow stated that the IOTF adheres to four production principles: 1) assemble, maintain, and extend pilot components; 2) employ open, transparent, and inclusive governance; 3) manage through Hosting services; and 4) create an infrastructure that is self sustaining. Its production model uses standards/pilot implementation software to transition a public-private partnership into an operating entity. Continued engagement from government, academics, and industry will be needed. To help move this forward, the FDA has held a public hearing on 21 CFR Part 15 regarding the electronic submission of regulatory information and the creation of an electronic platform for enhanced information management. Additionally, the NIH, NCI, and FDA are preparing a Request for Information that describes potential public-private partnership arrangements.

In discussion, the following points were made:

- The success of the Janus Project is more dependent on the FDA's agreement to utilize the infrastructure than its investment of monies into the system.
- Institutions that have been working with this have not found a way to interface this with their own electronic medical records. It would be better for institutions to build their systems with such compatibility up front.
- FIReBIRD and Janus, which were created for the regulatory submissions of drug trials, are not related to the SEER program and data. A suggestion is that to know who is on clinical trials and survivorship in the SEER program would be valuable for cancer epidemiology research.
- The cost of developing FIReBIRD and Janus is difficult to determine because their development has been heavily embedded in the standards-based infrastructure, and a number of their tools also were developed for use in other NCI systems. The quantifiable cost ranges between several hundred thousand dollars to the low millions.
- Provide members with the cost figures for developing the FIReBIRD operational pilot and JANUS database.
- Patient-reported outcomes or symptoms (e.g., pain or fatigue), or other subjective measurements, likely would not be captured in data collection because the infrastructure is organized to include information that can be systematically described.

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XIII. ADJOURNMENT - Dr. Robert C. Young

There being no further business, the 36th regular meeting of the Board of Scientific Advisors was adjourned at 11:24 a.m. on Friday, March 6, 2007.

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