Board of Scientific Advisors

Meeting Minutes

June 29-30, 2006

Building 31C, Conference Room 10
Bethesda, Maryland

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Meeting Minutes

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 34th meeting on Thursday, 29 June 2006, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert 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 29 June for the Acting Director's report, a report on NCI/ Congressional relations, ongoing and new business, special recognition of retiring members, an update on the Nanotechnology Program, the NIH Director's report, an update on the National Biospecimen Network, and consideration of Request for Applications (RFA)/Cooperative Agreement concepts presented by NCI program staff for reissuance. The meeting was open to the public from 8:30 a.m. on 30 June until adjournment at 12:00 noon for updates on Division of Cancer Prevention (DCP) initiatives, the NCI/Food and Drug Administration (FDA)/Center for Medicare and Medicaid Services (CMS) memo of understanding (MOU) and imaging component, and a status report on the Translational Research Working Group (TRWG).

Board Members Present:
Dr. Robert Young (Chair)
Dr. Hoda Anton Culver
Dr. Kirby I. Bland
Dr. Esther H. Chang
Dr. Susan J. Curry
Dr. William S. Dalton
Dr. H. Shelton Earp III
Dr. Kathleen M. Foley
Dr. Sanjiv Sam Gambhir
Dr. Patricia A. Ganz
Dr. William N. Hait
Dr. James R. Heath
Dr. Mary J.C. Hendrix
Dr. Susan B. Horwitz
Ms. Paula Kim
Dr. Kenneth W. Kinzler
Dr. Christopher J. Logothetis
Dr. Kathleen Mooney
Dr. John D. Potter

Board Members Present:
Dr. Mack Roach III
Dr. Richard L. Schilsky
Dr. Robert D. Schreiber
Dr. Ellen V. Sigal
Dr. Robert Tjian
Dr. Jane Weeks

Board Members Absent:
Dr. David S. Alberts
Dr. Raymond N. DuBois
Dr. Joe W. Gray
Dr. Leroy Hood
Dr. Hedvig Hricak
Dr. Eric Hunter
Dr. Michael P. Link
Dr. Lynn M. Matrisian
Dr. Edith A. Perez
Dr. Margaret Ruth Spitz

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

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XIV. Adjournment; Dr. Robert C. Young

I. CALL TO ORDER AND OPENING REMARKS - Dr. Robert C. Young

Dr. Young called to order the 34th regular meeting of the BSA and

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

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II. CONSIDERATION OF THE 13 MARCH 2006, MEETING MINUTES - Dr. Robert C. Young

Motion: The minutes of the March 13, 2006, meeting were approved unanimously

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III. ACTING DIRECTOR'S REPORT - Dr. John Niederhuber

Dr. John Niederhuber, Acting Director, NCI, acknowledged the imminent retirement of Dr. John Sogn, Deputy Director, Division of Cancer Biology (DCB), and thanked him for his contributions and many years of service. Dr. Niederhuber recognized those staff members and programs who had received awards and/or special recogition: Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG) - the Medal of Honor by the International Agency for Research on Cancer (IARC); Dr. Carl Wu, Chief, Laboratory of Molecular Cell Biology (LMCB), Center for Cancer Research (CCR) - elected to the National Academy of Sciences (NAS); NCI's Cancer Bioinformatics Grid (caBIGTM), under the leadership of Dr. Kenneth Buetow, Director, Center for Bioinformatics, Office of the Director (OD) - received the 21st Century Award—Science from Computerworld magazine.

Update: Implementation of Clinical Trials Working Group (CTWG) Recommendations. Dr.Niederhuber reported that the Coordinating Center for Clinical Trials had been established with Dr. Sheila Prindiville as Director and Drs. Deborah Jaffe, LeeAnn Jensen, and Ray Petryshyn as Program Directors. The office will

provide support and infrastructure for the Clinical Trials Operating Committee. Members of the Clinical Trials Advisory Committee (CTAC) are being selected and will include representatives from the current adivisory boards, as well as representatives from the larger cancer research community.

Trans NIH and NCI Programs. Members were told that the NCI has an important role to play in trans NIH activities. The Trans NIH Angiogenesis Research Program (TARP) and the Pharmacogenomics: Pathway to Personalized Medicine programs are examples of such activities. Both of these were on the list submitted by NCI Divisions at the request of the NIH Director for research areas of great interest that also have the potential to be trans NIH in nature and could be used in advocating for NIH science before the Department of Health and Human Services (DHHS) and Office of Management and Budget (OMB). The Pharmacogenomics program subsequently was chosen by NIH Institutes and Centers (ICs) as the top trans NIH priority, and TARP was second.

Trans NCI scientific programs that have been initiated recently are the Lung Cancer Program and the Breast Cancer Stamp Premalignancy Research Program. Trans NCI programs currently in planning and developmental stages are in the areas of: 1) epidemiology and prevention, and 2) computational biology and biostatistics.

Director's Consumer Liaison Group (DCLG) Summit. A brief update on the 19 20 June summit entitled Listening and Learning Together: Building a Bridge of Trust, which was held on the NIH campus was presented. The purpose of the Summit was to introduce members of the advocacy community to campus facilities and operations and to provide instruction in terms of performing the work they do as advocates. Approximately 300 people attended the event.

Budget Update. Members were given a summary of the NCI budget as the final quarter of FY 2006 begins: 1) the NCI has been faced with a mid year increase in taps for direct utility costs to the NIH and an unexpected tap for support of the CMS 1 800 numbers that address drug availability issues for seniors; 2) the Research Project Grant (RPG) payline is at the 11th percentile, with 15 percent of the competing pool in reserve for exceptions; 3) Type 5 grants are

2.35 percent below the commitment of record; 4) Special Programs of Research Excellence (SPORES) are 2 percent below FY 2005, and the Centers budget is essentially flat; and 5) training is 1 percent above the FY 2005 level. Members were told that with the concurrence of the Executive Committee (EC) the R01 payline had been raised to 12 percent and the *R01 payline (new investigators) to 18 percent.

FY 20007 Budget Planning. Dr. Niederhuber informed members that planning for the FY 2007 budget is based on the President's Budget of approximately $4.8 B which is $39.7 M less than NCI's FY 2006 appropriation. He described processes that were being used within the Institute to develop a sound approach to budgeting, with an eye toward the probability that budgets for the foreseeable future will be reduced or flat. Data from these deliberations will be compiled and considered by the EC through several vettings to decide what the science emphasis and priorities should be in the overall NCI portfolio, both intra and extramural. The EC also will review "infrastructure like" programs towards developing a budget that will meet the scientific needs of the Institute.

Dr. Niederhuber noted the frequent comments from the research community that the NCI made more investments in solicited request for applications (RFAs) rather than unsolicited (R01 and RPG) research during the NIH doubling. Data to clarify that the NCI's unsolicited RPGs continued to far outnumber the solicited RPGs during the doubling and continues on that trajectory were presented. Members were reminded that medical schools across the country viewed the doubling as an opportunity to grow their research programs in the medical sciences, and new research space was built and new faculty was recruited. The result of this increase in capacity and number of researchers can be seen in the increase in the number of new applicants for NCI funding during the past 2 years compared with the increase in the 5 years of the doubling. Similarly, NCI's new applications numbered 1,076 during the past 2 years compared with 1,371 during the previous 5 years. Dr. Niederhuber noted that the NCI experience parallels that of the NIH as a whole.

Lung Cancer Program. Dr. Niederhuber reminded members of incidence and mortality data since 1975 to underscore the need for continued emphasis on lung cancer in NCI research programs. To that end, he noted that an Integration and Implementation (I2)

Team was established to advise the NCI in relation to the development of a lung cancer program. The I2 Team's recommendations and estimated investments addressed organizational structure and program leadership, the Cancer Intervention & Surveillance Modeling Network (CISNET), tobacco control, early detection, and new drug development and response to therapy. NCI implementation of I2 Team recommendations is that 1) recruitment is underway for a senior clinician to oversee the Lung Cancer Program; 2) additional support for CISNET has been provided in the amount of $400 K; 3) additional funding and support has been provided to the National Lung Screening Trial (NLST) biorepository to ensure the safety of the early disease biospecimens that are being obtained; 4) a biomarkers trial in non small cell lung cancer (NSCLC) is under development in collaboration with the FDA and CMS and an early phase epigenetic trial is in planning stages, 5)an investment has been made in novel imaging probes to monitor tumor uptake in the early phase epigenetic trial; and 6) in the area of tobacco control, it has not been possible yet to identify additional resources to respond to the I2 team recommendation, but the effort will be continued. Currently, the NCI has 187 funded projects representing an investment of $137 M in tobacco control and mechanisms of nicotine addiction.

Human Papilloma Virus (HPV) Vaccine. Dr. Niederhuber commented on the potential of the HPV vaccine to have an impact on the burden of cervical cancer world wide, more so in less developed countries, which account for 80 percent of cervical cancer incidence. He noted that his recent discussions with India's Prime Minister for Health provided a valuable perspective on the extent of the problem in that country. BSA members were reminded that NCI research on AIDS, which began approximately 25 years ago, has changed how acquired immune deficiency syndrome (AIDS) is understood as a disease and was instrumental in developing therapies to combat the disease. In a similar leadership role, NCI investigators have contributed greatly to the development of the HPV virus like particles (VLP) vaccine. NCI investigators continue to work toward developing an oral formulation of the vaccine, one that does not require refrigeration, to increase the likelihood that the vaccine will reach the women who need it most.

In Memoriam: Dr. Anita Roberts. Dr. Niederhuber ended his report

with a tribute to the memory of Dr. Anita Roberts, Chief, Laboratory of Cell Regulation and Carcinogenesis, CCR, who died on 26 May 2006 after years of battle against gastric cancer.

In discussion, the following points were made:

The current emphasis on inter and cross disciplinary research in planning for future scientific endeavors is to be commended; however, the NCI in planning for future budgets does not yet appear to be addressing the need for more investment in translation of the discoveries to the population.

- Think tanks, where the intra and extramural programs meet to discuss new ideas and concepts, would be a suitable mechanism through which the extramural community could provide input on what it believes are priorities as the NCI leadership continues in the process of planning for FY 2007 and prioritizing the broad spectrum of budgetary decisions.

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IV. NCI/CONGRESSIONAL RELATIONS - Ms. Susan Erickson

Ms. Susan Erickson, Director, Office of Policy Analysis and Response, presented a status report on FY2007 appropriations, reminding members that the President's Budget included appropriations of $28.6 B for the NIH and $4.8 B for the NCI. The House of Representatives proposed appropriations in the same amounts. Ms. Erickson informed members of House action to date on the Labor, DHHS, Education Bill (HR 5647) and recent Congressional briefings and other activities. Members were told that the Senate passed a resolution recognizing 5 8 June as Health Information Technology (IT) Week; at least eight stand alone health information bills have been introduced. Provisions in the bills would establish an Office of the National Coordinator for Health IT and recommend uniform national policies to support the widespread adoption of health IT. A variety of other provisions are included in the bills, such as incentives for health care providers to implement information infrastructure, protection of individually identifiable health information, and a requirement to develop

measures of quality of care. Ms. Erickson indicated that the Health Information Technology Promotion Act and the companion bill, Wired for Health Care Quality Act, appear to have momentum for further activity in Congress.

In discussion, the following point were made:

- Congressional action on the NIH reauthorization bill and the Enzi Kennedy safety bill appears to be imminent, and both will have a dramatic effect on cancer research, the latter on clinical trials and translational research.

- Provide Board Members with information on ramifications for the NCI budget if the tap were increased to 5 percent.

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V. ONGOING AND NEW BUSINESS - Dr. Robert C. Young

BSA at National Meetings: Reports; Drs. Susan Curry and Paulette S. Gray

Society for Behavioral Medicine (SBM). Dr. Susan Curry, Director, Institute for Health Research and Policy, University of Chicago, presented the report on the NCI Listens session held at the SBM meeting in San Francisco, CA on 24 March. Dr. Curry reported that questions and discussion focused on large initiatives, maintaining a pipeline of investigators, and the NCI budget, as well as several miscellaneous questions. She commented that the offsite location of the meeting appeared to have an effect on the number of participants and recommended that future meetings be more accessible. Discussion on the issues, however, was lively and worthwhile, and evaluations were uniformly positive.

Oncology Nursing Society (ONS). Dr. Gray reported on the NCI Listens session at the ONS Annual Conference on Cancer Nursing Research, held on 5 May in Boston, Massachusetts, with 80, primarily senior nurse scientists, in attendance. Dr. Gray reported good discussion on K awards, program announcements (PAs), Community Clinical Oncology Program (CCOP) funding, Clinical Trials Advisory Committee membership, how to increase nurse

representation on advisory boards, and the electronic submission timeline for grant applications, the Translational Research Working Group (TRWG), and the impact of a flat or decreased funding.

NCI Listens Sessions: 2006; Dr. Robert C. Young

Dr. Young reported that the American Society for Therapeutic Radiology and Oncology (ASTRO) had requested that an NCI Listens session be held at its fall meeting. The BSA participant is Dr. Mack Roach III (Chair), Professor, Department of Radiation Oncology, University of California, San Francisco.

Office of Liaison Activities: Process for Meeting with Professional Societies; Ms. Brooke Hamilton

Ms. Brooke Hamilton, Acting Director, Office of Liaison Activities (OLA), informed members that the primary office's focus is working with patient advocates and the patient advocacy community to include them in the work of the NCI and to communicate important NCI initiatives and programs. The advocates in this context are involved mostly in research advocacy. Ms. Hamilton described several formal and informal OLA programs focusing on the advocacy community, including the DCLG, which is a chartered federal advisory board, and the Consumer Advocates in Research and Related Activities (CARRA) program through which members participate in NCI peer review of clinical and translational research. Other activities for advocates include monthly educational teleconferences and ad hoc hot topic teleconferences, the NCI Nealon Digest of federal cancer news, the pilot Web Site NCI Listens and Learns, and the recent summit meeting for advocates.

In the area of professional society interactions, Ms. Hamilton stated that the meeting coordination performed in the OLA is one of the many ways in which the NCI interacts with professional societies. She emphasized that the meetings coordinated in the OLA in no way limit ongoing partnerships and interactions that exist between the NCI Director and the society Boards of Directors and between NCI Divisions, Offices and Centers, and the societies. Professional society leadership meetings were established in 1997 by then Director Dr. Richard Klausner. Meetings are 1) requested by the society through a formal letter to the Director, and the agenda is

created collaboratively by the NCI and the society; and 2) attended by the Director, relevant NCI staff, and society leadership. The OLA 1) provides coordination prior to and during the meeting, then follows up on any issues raised in the meeting or responds to requests for further information; 2) works closely on meeting development with Dr. Alan Rabson, Deputy Director, NCI to identify relevant issues and NCI experts; and 3) coordinates with the Offfice of Communications (OC) and Office of Science Planning and Assessment (OSPA), as well as Divisions, Centers, and other Offices as appropriate to the society in question. Typical agenda items include peer review and funding issues, ideas for collaborations, updates on new NCI programs or initiatives, and communication ideas. Since 1997, 62 meetings have been held with professional societies.

In discussion, the following point were made:

- The BSA NCI Listens session does not appear to overlap with OLA activity in relation to the advocacy community. The meetings coordinated by the OLA in which the Director meets with leadership of national organizations seem to approximate what the NCI Listens tries to accomplish in reaching out to organizational members as opposed to the leadership.

Future NCI Listens Sessions: Format; Ms. Paula Kim

Ms. Paula Kim, Chair, NCI Listens Subcommittee, reported that the Subcommittee members (Drs. Kirby Bland, Mary Hendrix, Hedvig Hricak, and Young) concluded that there might be an opportunity for the BSA program to build on the OLA activities and develop an overarching strategy that aligns with what the NCI is attempting to do with respect to outreach and communication among both the general membership of the societies and the advocacy groups. The Subcommittee indicated that the BSA does have a role and should continue scheduling NCI Listens sessions and proposed to continue its efforts to develop a more comprehensive strategy for the BSA NCI Listens sessions.

In discussion, the following points were made:

- The NCI Listens program was initiated partly to introduce a

relatively unknown NCI Director to the community. Directors since that time have been well recognized.

- Success of the program depends on the presence of senior NCI leadership at the meetings and not representatives from the various offices. There potentially is a great value in having NCI leadership hear directly from the scientific community about its concerns so that efforts can be made to address them. However, the presence senior NCI leadership at NCI Listens sessions should be integrated with their other activities to ensure that time and travel demands are reasonable.

- The NCI Listens sessions should continue. Emphasis should be placed on developing a format and strategy that reflects a more individualized approach for each society with an emphasis on reaching younger researchers (young investigators, post-doctoral candidates and graduate students) who are unfamiliar with the NCI.

Other Issues; Dr. Robert C. Young

Dr. Young informed members that the annual report on grant awards and projections prepared by Mr. Stephen M. Hazen, Chief, Extramural Financial Data Branch (EFDB), at the request of the BSA, was in their books. Members were reminded that the report had been given orally in the past and asked whether the written report would be sufficient from this meeting forward. The consensus of the Board was that the written report would be sufficient and questions resulting from individual members' review of the report could be addressed to the EFDB.

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VI. SPECIAL RECOGNITION OF RETIRING MEMBERS - Drs. John Niederhuber and Robert C. Young

On behalf of the NCI, Drs. Niederhuber and Young recognized the contributions made by four retiring BSA members: Drs. David Alberts, Regents Professor of Medicine and Pharmacology, Public Health and Nutritional Science, University of Arizona College of Medicine; Esther Chang, Professor, Department of Otolaryngology/

Head and Neck Surgery, Georgetown University Medical Center; Susan Horwitz, Falkenstein Professor of Cancer Research, Albert Einstein College of Medicine; and Kenneth Kinzler, Professor of Oncology, Johns Hopkins Oncology Center. They were recognized for the importance of their contributions to the success of the Institute and the valuable volunteer hours that each donates to the NIH and the NCI.

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VII. UPDATE: NANOTECHNOLOGY PROGRAM - Drs. Anna Barker and Piotr Grodzinski

Dr. Anna Barker, Deputy Director for Advanced Tehnologies and Strategic Partnerships, OD, stated that NCI's investments in novel technologies began 6 7 years ago with the Unconventional Innovations Program and a biomarkers program in collaboration with the National Aeronautics and Space Administration (NASA). In the recent past, these two programs were evaluated and found to be allied less closely in oncology as they should have been and were ended. The decision to design a new program was based on the belief that nanotechnology presaged the future in terms of team science and the science itself and on the need to ensure that adequate metrics were in place for evaluation of the changes that should be taking place. Extensive counsel was sought from the scientific, research, and advocacy communities, and a relationship was developed with the National Science Foundation (NSF) to bring additional resources focused on training in this particular area of science. On the basis of this input and with help from the BSA, a comprehensive Cancer Nanotechnology Plan was designed to drive systems level changes and catalyze product development. The NCI Alliance for Nanotechnology in Cancer was launched in 2004 with a series of goals in areas thought to be critical to the future of medicine and molecular oncology. It is built on multidisciplinary team science and the . components of the Alliance are the 1) Centers of Cancer Nanotechnology Excellence (CCNE); 2) Nanotechnology Platforms for Cancer Research allied with the various centers; 3) Multi-disciplinary Research Teams, which involve training and interagency collaborations; and 4) a Nanotechnology Characterization Laboratory (NCL).

Dr. Piotr Grodzinski, Program Manager, NCI Alliance for

Nanotechnology in Cancer, informed members that a major differentiator of the NCI Nanotechnology Alliance is the attempt to develop applied technologies that will translate to the clinic and have an impact on patient health in the fairly near future. Key attributes of the Alliance are: 1) multidisciplinary team science; 2) partnering with the private sector to facilitate the commercialization aspect; 3) rapid development of novel clinical applications; 4) progress evaluation by performance milestones on a yearly basis; 5) a governance committee with researcher, advocate, and NCI representation; 6) collaboration among all Alliance programs and NCI's existing intra and extramural portfolio; 7) resource and data sharing through leveraging the caBIGTM platform; and 8) communication, education, and community outreach. Interagency collaborations include the: 1) National Institute for Standards and Technology (NIST) for standards and precision measurement capabilities; 2) FDA for training and dissemination of results; 3) NIH for shared data and platforms; and 4) National Nanotechnology Initiative for the public interface it provides and data interpretation on the environment, health, and safety.

Dr. Grodzinski stated that the NCL has the capability of unifying the health community around characterization of nanoscale materials. He noted that the NCL already has developed a fairly comprehensive assay cascade for the characterization of nanotechnology materials in a number of different realms, from physical characterization to cell culture based in vitro characterizations. It also provides this service not only to funded centers but also to the community at large.

Dr. Grodzinski reported that over the 6 months since the Alliance was launched, it had: 1) established its infrastructure; 2) defined and implemented a governance structure; (3) established a progress reporting mechanism; 4) completed site visits; 5) initiated development of an intellectual property (IP) management plan; 6) initiated training programs; 7) initiated materials testing at the NCL; and 8) established the process to apply caBIGTM tools for data management and dissemination across Alliance projects. In addition to the organizational and administrative progress, technology developments have been published in a significant number of peer reviewed journals, such as Science, Nature, Nature Materials, and Cancer Research. Examples of progress that had been made in 1) in vivo and in vitro detection techniques, 2)

targeting of angiogenesis, and 3) targeted, nanoparticle based delivery of docetaxel were presented.

In discussion, the following points were made:

- In evaluating the success of the NCI Nanotechnology Program, the BSA will need to determine, not whether good science is being done, but whether good science was created that would not have been possible without the NCI Alliance construct.

- The NCI Alliance through the NCL component provides a resource for the community similar to that provided by the Trans NIH Angiogenesis Research Program with its standards laboratory. The Alliance also is an example of an NIH peer reviewed program that has been successful in leveraging a significant amount of matching funds and resources from the private sector.

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VIII. NIH DIRECTOR'S REPORT — Dr. Elias Zerhouni

Dr. Elias Zerhouni, Director, NIH, recognized and acknowledged the benefit to the NIH of the more than 31,000 scientists who serve as peer reviewers and board members and in many other capacities. Dr. Zerhouni noted the importance of the synergy created, in terms of understanding the issues.

Dr. Zerhouni briefly reviewed the circumstances that have contributed to the "perfect storm" that the NIH budget is facing in 2006. Members were told that three phenomena that contribute to understanding the current situation are that 1) success rates per application somewhat understate the chances of being funded because applicants now apply for about 1.4 grants per applicant as opposed to the historical 1.2; 2) increased demand, not a reduced supply of dollars, is the principle driver of the stress on the FY 2006 budget; and 3) the budget cycling effect will improve the supply of funding slightly for grants versus the demand. Even if the FY 2007 appropriation stays at $28.6 B as proposed in the President's Budget, the NIH will only be able to issue 3 percent more grants.

Data was presented to refute three common misperceptions heard in the community, i.e the NIH: 1) is over emphasizing applied research; 2) is shifting toward solicited research; and 3) Roadmap is shifting funds away from the grant pool. Members were told that, in regard to the first point, data show that 53.9 percent of the NIH budget funded basic research in 1998 and the percentage is projected to increase to 56.1 percent in FY 2007. Dr. Zerhouni noted that the only dip in the line occurred when the bio-defense budget increased from approximately $50 M to $2 B in 2 years, but the funds were restored to the RPG pool in 2004 2005. In regard to the second misperception, data show that unsolicited research increased from 91 percent of the NIH budget in 1995 to 93 percent in 2004. In regard to the third misperception, Dr. Zerhouni reminded members that the Roadmap was developed to increase synergy across the NIH and respond to concerns about the functional integration of programs. The Roadmap is not a single initiative but more than 345 individual awards in FY 2005 made to 133 institutions in 33 states. Moreover, the balance throughout the life of the Roadmap has been about 40 percent each for basic and translational research and 20 percent for high risk research, including the Pioneer Awards. Dr. Zerhouni acknowledged the particular concern that the NCI, as the largest Institute, contributes the greatest amount to the Roadmap on a proportional basis. He pointed out, however, that the NCI grantees in FY 2005 received 53 Roadmap awards (15 percent of the total) for a total funding of $42.1 M (18 percent). NCI's 2005 investment in Roadmap was $30.5 M, or 13 percent of the total.

Dr. Zerhouni addressed future directions for the NIH and emphasized the need for developing adaptive strategies based on the key principles that have been formulated by the NIH leadership and Institute Directors: 1) Protect Core Values and Mission; 2) Protect the Future; 3) Focus on Balancing Supply and Demand; 4) Proactive Communication about Investment in the NIH; and 5) Promote NIH's Vision for the Future. He noted that the NIH's future vision is the transformation of medicine and health through discovery.

In discussion, the following points were made:

- It is critical to preserve the competitiveness of the U.S.

health care system by co investing in partnerships with the private sector. In addition, more international partnerships are needed.

- The barriers associated with application review are being addressed by initiating pilot experiments such as accelerating the review cycle for new investigators.

- The NIH works better when there are predetermined funds allocated for a common purpose or goal. The best science gets funded and incubator space is provided for 5 and 10 year programs. The Common Fund as proposed in the NIH reauthorization legislation would provide such a fund; however, the challenge will be to implement a 5 percent tap from all Institutes and Centers in such a way that existing programs are not damaged, particularly in the present fiscal climate.

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IX. UPDATE: NATIONAL BIOSPECIMEN NETWORK PROGRAM - Drs. Anna Barker and Carolyn Compton

Dr. Barker provided a brief update on NCI's National Biospecimen Network. She noted that In 2002, the NCI had a sense that biospecimens and biorepositories would increase in research importance, although they did not fully understand the policy implications of biospecimens or the meaning of personalized medicine.

Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research (OBBR), stated that this project was initiated with the intent to help the community prepare for post genomic changes in requirements and needs for biospecimens and biorepositories, optimize and standardize the quality of human specimens for the research that will drive personalized cancer medicine, and ultimately remove current and future barriers to cancer research represented by the limited availability of high quality human specimens. The Network's accomplishments thus far include the development of an overall understanding of the status of biorepositories in the United States in general, and NCI's biorepositories in particular. With broad input from the intramural,

extramural, scientific, clinical, bioethical, and bio banking communities, the Network defined and refined the requirements for achieving the required quality and uniformity of biospecimens for post genomic research.

Dr. Compton noted that the approaches adopted as part of the integrative planning and implementation process included the 1) development of guidelines based on best practices recommendations from the current evidence; 2) employment of a systematic approach to evidence based bio banking processes to incorporate new and existing data; 3) integration with, and support from, other strategic NCI initiatives, such as The Cancer Genome Atlas (TCGA) Project and the Clinical Proteomics Project, etc; 4) establishment of external partnerships to bring in additional expertise, education, and implementation; advocacy outreach also is being planned; 5) harmonization of bio banking processes across the NCI, including with the clinical trials groups and the SPORES; and 6) facilitation of both NIH wide and international dialogue on the harmonization of bio banking practices because of the globalization of translational research and clinical trials. The future action plan includes the development of second generation guidelines that are evidence based standard operating procedures, a biorepository accreditation program to monitor compliance with guidelines, and educational programs and training initiatives to help achieve those goals.

Following a brief overview of the Network's establishment, Dr. Compton stated that the first generation guidelines had been developed and published in the Federal Register. Public comments were accepted through 3 July 2006. The guidelines offered six recommendations: 1) Development of common best practices for research biorepositories on a physical specimen level; 2) Establishment of quality assurance and quality control programs; 3) Implementation of enabling informatics systems; 4) Addressing ethical, legal, and policy issues; 5) Establishment of reporting mechanisms; and 6) Provide an administrative and management infrastructure. The guidelines will be finalized and distributed to the managers of all NCI supported biorepositories. Periodic revisions will occur as new policies and practices emerge.

Pilot projects that the Biorepository Network have designed include: 1) a comparison of colon cancer and the normal colon to determine how anesthesia time and arterial clamp time intra

operative affect DNA expression microarrays; 2) urine as a type of biospecimen that can be used to analyze VEGF as a biomarker for recurrent prostate cancer; 3) how different types of collection containers for serum and normal plasma affect proteomic results by MALTI TOF, to determine how best to collect these specimens; and 4) blood and tumor (renal cell carcinoma) as to the preservation type, storage conditions, and DNA extraction methods.

In closing, Dr. Compton stated that the Network is partnering with the College of American Pathologists to develop second generation guidelines. She noted that this is the College's first initiative directed toward research rather than clinical medicine. A MOU is being developed.

In discussion, the following points were raised:

- The first generation guidelines do not expect biorepositories to assert intellectual property claims on research developed from the use of biospecimens; rather, they serve as custodians of those biospecimens. Litigation is ongoing regarding the intellectual property ownership of biospecimens

- Manufacturers of surgical instruments, such as robots, should be engaged in biospecimen issues to ensure the perseveration of specimens that are removed through surgery.

- Researchers in population sciences and health services should be engaged in the discussion. CMS and third party payers should be involved because of the enormous effect on costs.

Many patients now understand that the research community historically has different ideas of how data are shared or not shared and are expressing their concerns about ownership issues.

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X. RFA/COOPERATIVE AGREEMENT REISSUANCE CONCEPTS - Presented By NCI program Staff

Division of Cancer Treatment and Diagnosis (DCTD)

Cooperative Trials in Diagnostic Imaging

Dr. Carl Jaffe, Program Director, Cancer Imaging Program (CIP), DCTD, briefly reviewed the establishment and programmatic goals of the American College of Radiology Imaging Network (ACRIN) Cooperative Trials in Diagnostic Imaging concept. Members were told that through the reissuance of the RFA, ACRIN will continue to focus on investigator initiated research involving key aspects of imaging technology assessment in oncology, including: 1) providing a flexible organizational structure that allows for the catchment of the geographic differences of technology and the advance of technology in an asymmetric way across the oncology communities; 2) conducting clinical imaging science research; 3) conducting biostatistical methodological research that is specific to imaging trials; and (4) sharing research resources.

Dr. Jaffe focused on the subcommittee questions: 1) Were the weaknesses noted by the July 2003 review committee addressed? ACRIN has 1) developed a formalized concept and protocol development process, 2) established a strong proactive patient advocate committee, 3) reorganized the committee organization structure, and 4) established an Institutional Participation Committee. Quality assurance processes and a committee were established to perform routine site functional area reviews and provide feedback to the sites; strengthen their qualification and management; and provide expanded and qualified regulatory oversight and education of the sites, specifically on issues of trial approval and activation, site auditing, adverse event reporting, and the internal review board issues. ACRIN also set up a best practices procedure for conducting analyses and enhanced collaborations with other cooperative groups, industry, academia, the FDA, the CMS, and other NCI/federal projects.

2) How, in general, are such weaknesses addressed for the networks like this one? The general approach to address concerns is to conduct programmatic reviews at routine intervals aligned with the specific grant mechanism. Internally, ACRIN relies on biannual

meetings, weekly individual teleconferences on particular protocols, monthly steering committee teleconferences, and an external scientific advisory committee. There are monthly leadership teleconferences and active program staff involvement between ACRIN and the CIP.

3) What new ideas has ACRIN been working on since the last update? Since the last update and with funding from complementary resources, a first rate positron emission tomography (PET) imaging analysis laboratory with national stature at the Philadelphia office and headquarters has been established, along with a national PET registry that is being integrated with CIP work. ACRIN activities are being integrated with the CIP as well, such as the Lung Image Database Consortium. Additional ideas being pursued involve image guided treatment using radio frequency ablation and high frequency ultrasound; response to treatment, particularly on the issues of traditional anatomic measurement in multi institutional settings and functional imaging to evaluate therapeutic response; Phase I and II trials of novel imaging agents to assist in approval/rejection decisions about drug development; and the development of enabling methodologies to expand ACRIN's trial capabilities and evaluate the value added of information in that analysis. The new projects include the OBQI, the FDA's Critical Path Initiative, the CMS' national coverage decision, image/meta data archive and data sharing (caBIGTM), and dissemination of imaging standards of quality for imaging trials.

Dr. Jaffe concluded that ACRIN: 1) is at an appropriate level of organizational development; 2) is responsive to the NCI, the FDA, the CMS, and to the imaging and oncology communities' goals and objectives; 3) serves as an exemplary, well leveraged resource for the NCI; and (4) provides multidisciplinary, multi institutional, interorganizational clinical research that is pertinent, valid, and reliable, and it provides more general findings that would not be attainable through single institutional observational studies.

Flat funding at the FY 2006 level for 5 years at approximately $39 M and a first year set-aide of $7.3 M for 2 U01s, with incremental increases to cover the cost of living is estimated. It is a combined U01 mechanism in which there is a headquarters for the clinical imaging repository and the clinical science drive in Philadelphia, Pennsylvania, and a biostatistical headquarters at Brown University

Data Center.

In discussion, the following points were raised:

- ACRIN employs a flexible structure; some institutions participate regularly, whereas others are involved intermittently. Because there are many ACRIN institutions that overlap with institutions that are part of the other cooperative groups, it would make sense to structure some intra institution partnerships.

Motion: A motion to concur with the re-issuance of the DCTD RFA/Cooperative Agreement entitled “Cooperative Trials in Diagnostics” with a recommendation to address closer integration with the Clinical Cooperative Groups was unanimously approved.

Pediatric Phase I/Pilot Consortium

Dr. Malcolm Smith, Cancer Therapy Evaluation Program, DCTD, described the concept proposal for reissuance of the Children’s Oncology Group (COG) Phase I Consortium RFA re-issuance concept and addressed the subcommittee’s issues in three areas: 1) a conceptual framework for pediatric drug development and how the consortium meets that framework, 2) the consortium during the past funding period; and 3) the future direction for the consortium in the next funding period.

Members were told that the NCI has been essential to pediatric drug development during that last 3 or 4 decades, providing primary support for childhood cancer Phase I trials in North America. Dr. Smith briefly reviewed the establishment in 1992 of the Children’s Cancer Group (CCG) and the Pediatric Oncology Group (POG) Phase I Consortia and the merge of the CCG and POG in 2002 to form the COG, and the subsequent establishment of the COG Phase I Consortium. He noted that there remains a high need for new treatment approaches for children with cancer and hence new treatments. While there was a steady decline in childhood cancer mortality rates from1975 until 1998, since 1998, new, more effective treatments have not been identified.

Dr. Smith informed members that the current COG Phase I Consortium possesses a number of strengths, including strong

scientific leadership, a fully implemented remote data entry system that allows rapid submission of data and timely monitoring of studies, efficient protocol development teams, and high data quality standards with yearly monitoring of sites and good clinical practice training for clinical research associates (CRA) and private investigators (PI). Additionally, the consortium established an imaging center in Year 3, is now incorporating imaging more into its studies, incorporated PK/PD endpoints into multiple trials, and holds a strong publication record.

Dr. Smith informed members that the consortium has been conducting studies on agents (e.g., dasatinib, sunitinib, vorinostat, ispinesib, and sorafenib) that are at the forefront of adult cancer drug development and are on an appropriate timeline for pediatric evaluation. Regarding pilot studies, the consortium performs single agent Phase I studies, which are critical for the “first in children” experience, combining experimental agents with standard treatments, and hopes to move into Phase III testing. During the next 5 years (2007 2012), the consortium hopes to introduce six or seven new agents per year into the childhood cancer setting, as well as to pilot two to three new regimens per year for specific diseases and include PK/PD endpoints, as appropriate. In addition, it is hoped that imaging endpoints will be used to identify pharmacodynamic effects of the agent upon administration to children. The agents will be prioritized in the coming funding period based on their distinctive mechanism of action, the level of activity against adult cancers, and the potential applicability in the pediatric setting based on the biology of specific childhood cancers. Additional information about the PPTP is available at http://ctep.cancer.gov/resources/child.html. Also, in the next funding period, the consortium will be emphasized as a public private partnership. Public support is important to allow pediatric researchers to establish the research agenda for the consortium.

A flat budget is requested at a total cost of $ 16.5 M and a first year set-aside of approximately $3.3 M over 5 years. Funds will support scientific leadership, protocol development and regulatory oversight, data management and analysis, basic site support, and pharmacokinetic and pharmacodynamic studies, including research imaging studies.

In discussion, the following points were raised:

- The appropriateness of calling this RFA reissuance a “pilot” program was raised. It was suggested that removing the term “pilot” will help to ensure a solid structure and prioritization.

Interaction with adult oncologists should be given more thought, perhaps even to the level of establishing or formalizing alliances with adult oncologists who have experience in malignancies or diseases in the same category in which these drugs are used. This would help in developing markers and gleaning insight into the proper definition of trials.

- In response to a suggestion to fold the consortium into the COG, staff explained that the two mechanisms operate under separate funding; moreover, the NCI’s rules for review differs between them, and they are reviewed in separate cycles. However, the COG does receive some resources from this mechanism to provide the necessary infrastructure to support these trials.
- The Pediatric Phase I Consortium could leverage the work of the NIH Foundation’s Best Pharmaceuticals for Children Project regarding off patent drugs that the research and pediatric communities agree have not been studied adequately in children.
- The consortium includes a patient advocate representative on its steering committee. The COG also has an advocate committee for input. The RFA will specify that there is a role for advocates in the steering committee process.

Motion: A motion to concur with the RFA re-issuance of the concept entitled “Pediatric Phase I/Pilot Consortium” was unanimously approved.

Early Clinical Trials of New Anti Cancer Agents With Phase I Emphasis

Dr. S. Percy Ivy, Investigational Drug Branch, DCTD, informed members that early clinical trials of new anti cancer agents, with an emphasis on Phase I studies is a program within the Clinical Therapy Evaluation Program (CTEP). Dr. Ivy stated that CTEP is an integrated program that involves multiple phases of development. The resources include Phase I programs (such as the

Pediatric Phase I Program), a Phase II program that investigates activities of new agents, and a Phase III program that works very closely with cooperative groups who perform at least 50 percent of CTEP's Phase II development and, on occasion, some Phase I development. Phase I is used to bring new agents into the program. Specialty resources include the adult and pediatric central nervous system (CNS) Consortia. The CTEP collaborates with other groups, such as the cancer centers, SPORES, many of the investigator initiated or hypothesis driven grants, and the CCOPs. Phase I program accomplishments since 2003 include: 62 NCI IND agents studied; 25 investigational agent combination studies; 295 letters of intent submitted, with 31 percent approved for studies; and 185 ongoing clinical trials, 135 of which are uniquely Phase I and 50 that are either Phase I/II trials, pilots, or other types of studies. Dr. Ivy presented data on single agent Phase I studies that the CTEP has conducted since 1999. She reported that combination therapies in Phase I have become critically important, and the CTEP has identified three possible approaches: 1) maximize target inhibition by combining an antibody and a small molecule receptor tyrosine kinase inhibitor against the same target; 2) maximize a specific pathway inhibition by combining an epidermal growth factor receptor (EGFR) inhibitor with a Mek inhibitor; or 3) target multiple cellular mechanisms or pathways. Combination treatment strategies pose many challenges. Data was presented to show that there are more than 20 ongoing clinical trials that combine novel or targeted agents. She observed that the NCI is uniquely positioned to perform novel agent combinations because of its extensive collaborations with industry and academia. The CTEP has worked to define patent rights. In its agreements with industry and academia, terms include intellectual property actions to the collaborator. Single agent studies include rights of first negotiation to study, such as the first negotiation to the invention. In addition, there is the granting of a nonexclusive royalty free license to all collaborators providing an agent for a clinical trial. The CTEP has brokered 104 agreements. The estimated total cost is $41.3 M and a first year set-aside at approximately $8.3 M for 14 U01s. In discussion, the following points were raised:

Patient advocates are involved as part of the Information and Decision Support Center (IDSC) and are brought in to answer serious ethical problems. Advocate input is not solicited, however, for every letter of intent that is reviewed.

- When questioned as to NCI's role in Phase I trials of new chemotherapeutic agents when up to 9 large pharmaceutical companies and 1,400 biotechnology firms are involved in this arena, staff stated that integrating the combination studies, which are a new form of Phase I studies, with the collection of information where clinical investigation informs as well as mouse studies do, provides a unique opportunity and role for the NCI. The CTEP's goal is to complement the work of pharmaceutical collaborators, rather than duplicate.
- A major strength of the CTEP is that it can move beyond the issue of intellectual property rights with private companies. There currently is no other NCI mechanism for bringing together multiple agents that were developed under different intellectual property rights.

Motion: A motion to concur with the re-issuance of the DCTD RFA/Cooperative Agreement entitled "Early Clinical Trials of New Anti-Cancer Agents with Phase I Emphasis" with the recommendation that there be an emphasis in the reissued program on combination therapies and systems biology was approved with one abstention.

Advanced Technology Radiation Therapy Clinical Trials Support

The subcommittee informed members that the purpose of this re-issued RFA concept is to fund a site that has been building the infrastructure as the a central source for prospective clinical trials to obtain and analyze data for conformal and other types of novel radiation therapies, and eventually to mine the data and create other applications by looking at the imaging data. There are about 19 clinical trials open and 5 or 6 soon to open using this particular mechanism. The program's overall goals are important, and there has been relatively good success in the past several years. The subcommittee noted that it was unusual for only one institution to recompete for this funding but recognized that it is not practical to have other groups rebuild the infrastructure. The incumbent covers many different elements of credentialing, such as quality assurance, work with data exchange methodologies, and commercialization of software.

The subcommittee posed several questions, which included the

issue of project close out, and was satisfied with the answers it received. It was noted that certain components of this project will be closed down as goals are achieved, and others will be transferred to commercial products. The relationship between this mechanism and other mechanisms that also perform quality assurance in trials for radiation therapy was clarified; this vehicle is focused more on complex treatment protocols for conformal therapy, which none of the other mechanisms currently support. Another query concerned the determination of which clinical trials to support. To increase the educational missions of this particular RFA, Web sites will include more educational components in addition to the existing data analysis components.

The estimated total cost is $8.75 M and a first year set-aside of approximately $1.75 M for 1 U24.

In discussion, the following points were raised:

Several suggestions were offered regarding the program's evaluation criteria, including that the level of improvement to patient outcomes should be a criterion. The NCI also should provide more guidance for specific metrics for success rather than leave the measurements entirely up to the applicant.

Motion: A motion to concur with the re-issuance of the DCTD RFA/Cooperative Agreement entitled "Advanced Technology Radiation Therapy Clinical Trials Support" was unanimously approved.

Office of the Director (OD)

Minority Institution/Cancer Center Partnership

The subcommittee shared its questions about the RFA concept reissuance and the answers, and expressed its approval. One question was to clarify the mechanisms, particularly the differences in the numbers of the P20s, U56s, and U54s, and their relationship to each other. Another query concerned the low productivity in relation to funded grants, especially R03s and R21s, as achievements. An issue was raised about expectations for the next

funding period and possible delays. A fourth question focused on how minority investigators are encouraged to submit grants and the steps that have been taken to ensure the funding. In addition, the process that was developed to encourage cancer centers to emphasize the importance of including minority junior investigators was described. The subcommittee asked whether this reissuance was limited to current centers and received the response that it will not be limited to the current centers and will be promoted to other cancer centers and for other communities. Finally, the issue of encouraging expansion into other communities, particularly underserved communities, was raised.

An estimated total cost of $37.5 M and approximately $7.5 M, first year, for 3 U54s over 5 years.

In discussion, the following points were raised:

- Through this project, tangible results were achieved that would not have been accomplished without this RFA. For example, there are more than 77 published papers, 26 additional submitted papers with requirement of joint authorship, and 14 funded grants. Furthermore, in the non tangible arena, a whole new set of investigators, both students and faculties at the minority serving institutes, is being exposed to research and recruiting a great resource, as well the patient populations that would not be enrolled in trials otherwise.

Motion: A motion to concur with the re-issuance of the OD RFA/ Cooperative Agreement entitled “Minority Institution/Cancer Center Partnership (MICCP)” was approved with 5 abstentions.

Division of Cancer Control and Population Sciences (DCCPS)

Cancer Care Outcomes Research and Surveillance Consortium

Drs. Robert Croyle, Director, DDCPS, and Arnold Potosky, Health Services and Economics Branch, DCCPS, briefly reviewed the background of this concept. The subcommittee explained that its questions concerned 1) how the NCI would move from the detailed

assessment protocols that have been developed as part of the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) toward having them integrated as a routine part of the cancer care quality assurance process; 2) how or if CanCORS interfaces with other initiatives and organizations focused on developing protocols for assessing the quality of care; 3) if there was a planned exit strategy for the initiative; and 4) whether there are explicit prior performance criteria for sites to be eligible for renewal. A request was made for more information on the estimated number of cases that will be available for further followup, as this was one of the scientific aims of the RFA.

Dr. Croyle informed members that the initiative helps to move the quality care world from describing to understanding, i.e., it is more focused on "how" rather than just "what." Unlike other initiatives, this initiative addresses outcomes research. He noted that the Veterans Administration (VA) is a major collaborator and brings unique capacity and skills to the effort. The RFA triangulates different types and sources of data, such as from medical records, physician surveys, patients, and care givers. Such multi prong triangulation has been discussed for a long time but has not been implemented until now. The investigators remain involved in the primary data collection for this cohort study, which encompasses 5,000 lung and 5,000 colon cancer patients. The original data still are being collected, including the medical record abstraction. Finally, the initiative uses the CARRA program, through which patient advocates are identified.

Dr. Potosky explained that in approximately 3 years, more than 4,500 patients likely will be available to provide followup information. The initiative will include more than just patient contact and patient survey information; medical records will be re abstracted to understand what occurs beyond 1 year after diagnosis and the crucial phase of care when metastatic and recurrent disease are being treated with new drugs and new treatments.

Regarding the inclusion of specific eligibility criteria for renewal, the RFA will include specific performance measures. Dr. Potosky explained that CanCORS is a complex undertaking by eight sites with different capabilities, settings, and populations; the focus of the RFA is to identify those areas of strengths and weaknesses across the participating sites to take corrective steps and cost effectively allocate resources during the second phase of work.

This will be feasible in Phase II because the CanCORS structure is different than Phase I. Additionally, moving quality assessment from research into clinical practice remains an important goal for CanCORS.

Dr. Potosky informed members that CanCORS is a unique mechanism in that it fosters collaboration among multidisciplinary teams of scientists who work in cancer centers, health maintenance organizations (HMOs), the VA, and cancer registries. Of particular importance is the range of populations covered, which includes urban and rural populations, minority populations, and populations that are treated in a variety of health care delivery systems. Dr. Potosky closed with four points about the future of CanCORS: 1) a follow on project to Phase II is not anticipated; 2) the potential exists to study other cancers; 3) building a data collection infrastructure is necessary to monitor the quality of care in a more systematic and cost effective way; and (4) it is hoped that CanCORS will serve as an evidence base from which to identify opportunities for interventions that change care.

An estimated total cost of $30 M and approximately $6 M, first year, for 8 U01s and U24s over 5 years.

In discussion, the following points were raised:

- The limited number of existing publications and lack of available data, specifically on lung cancer patients, in proportion to the amount of Phase I funding is a concern. In addition, the RFA concept appears to describe the creation of a new cohort rather than build on the cohort from Phase I; the establishment of a scientific chair suggests a characteristic of permanence. It appears that the RFA concept has shifted from the original idea of what happens to people when they are treated.
- This initiative offers a valuable program of research as it works with the front line clinical practice and triangulates biologic patient data, caregiver data, and physician data to understand what is being delivered, why it is delivered, and the outcomes.
- Even though data was collected from colorectal cancer patients in Phase I, there are no plans to continue this CanCORS wide during Phase II.

Motion: A motion to concur with the re-issuance of the DCCPS Letter RFA/Cooperative Agreement entitled “Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)” was defeated with 4 yeas, 11 nays, and 5 abstentions. A BSA subcommittee (Drs. Bland, Curry, Dalton, and Young) was established to work with staff to address issues raised by the Board.

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XI. UPDATE: DIVISION OF CANCER PREVENTION (DCP) — Dr. Peter Greenwald

Dr. Peter Greenwald explained that this update would provide snapshots of different aspects of the Division of Cancer Prevention (DCP) sponsored programs; namely, the Study of Tamoxifen and Raloxifene (STAR) Breast Cancer Prevention Trial, the Prostate Cancer Prevention Trial (PCPT), and pancreatic cancer biomarker research.

Study of Tamoxifen and Raloxifene (STAR) Trial—Dr. Larry Wickerham

Dr. Larry Wickerham, National Surgical Adjuvant Breast and Bowel Project (NSABP), stated that the NSABP, one of the NCI’s Cooperative Trials Groups, has approximately 200 centers and an additional 300 satellite centers located throughout the United States, Canada, and Puerto Rico. A number of these sites are located at comprehensive cancer centers and major universities, but most are at non university community based sites, including most of the CCOPs. This widespread distribution of centers allows women to enter breast cancer prevention trials without assuming the burdens and costs associated with travel. The NSABP’s prevention program began in 1992 as a direct extension of its treatment trial activities. Tamoxifen had been shown in treatment trials to be a potential preventive agent. At that time, there was concern that oncologists would not be capable of performing prevention research, but the NSABP has established a successful program. More than 33,000 women have participated in the project’s acute prevention randomized trial, and more than 250,000 women have been screened without risk assessment tools. In addition, the NSABP has developed a cadre of experienced

investigators, comprised of physicians, nurses, coordinators, and other medical professionals.

The NSABP's first breast cancer prevention trial studied Tamoxifen versus placebo in high risk women and entered more than 13,000 women. In 1998, it reported that Tamoxifen could reduce the risk of breast cancer by about 50 percent but it came with side effects: specifically, there was a three to four fold increase in endometrial cancer, and an increase in deep vein thrombosis, pulmonary emboli, and cataracts. These results were presented that year at the ASCO convention's plenary session. The results of the Multiple Outcomes of Raloxifene Evaluation Study (MORE) also were reported during that session. MORE was a fracture prevention study of osteoporosis, but the women taking Raloxifene had more than a 70 percent reduction in primary invasive breast cancer. There also was no excessive risk of endometrial cancer, making it potentially an attractive alternative to Tamoxifen. The MORE trial, however, did not involve women who were at increased risk for breast cancer. This led to the design of the STAR trial, which enrolled postmenopausal women who were at increased risk for the future development of breast cancer based on the Gail Model. STAR assigned them to either Tamoxifen or Raloxifene for a 5 year period to determine whether Raloxifene was as effective as Tamoxifen in the prevention of primary invasive breast cancer. The secondary aims included the evaluation of noninvasive disease, endometrial cancer, fractures, ischemic heart disease, and quality of life.

The trial screened more than 184,000 women, including close to 40,000 minority individuals, and randomized more than 19,000 women in less than 5 years. Established as a postmenopausal trial, the age distribution involved 9 percent of the participants under the age of 50; 50 percent in their 50s; 32 percent in their 60s; and 9 percent 70 years or older. The participants' racial/ethnic distribution included 93.5 percent White and 6.5 percent minorities, which reflects twice the number of minority women who entered the first prevention trial, albeit there is substantial room for improvement in minority enrollment.

Dr. Wickerham presented the Gail Model scores of the participants. He noted that in addition to their Gail scores, potential trial participants were given a risk/benefit estimate comparing the risks and benefits of receiving Tamoxifen or Raloxifene. No untreated

control group was included in this study, but the Gail Model allowed researchers to project that, in such an untreated group at this point in time, there would have been approximately 8 invasive breast cancers cases per 1,000 per year, and that Tamoxifen and Raloxifene were equally effective in reducing that risk by about 50 percent to approximately 4 cases per 1,000 per year. The benefits were apparent in all subgroups in the trial and equally effective in patients with prior lobular carcinoma in situ or atypical hyperplasia. The cancers that did occur were similar in both groups.

In a comparison of the effects of Tamoxifen and Raloxifene, Dr. Wickerham reported that Raloxifene was not as effective as Tamoxifen in preventing noninvasive breast cancer, lobular carcinoma in situ (LCIS), and ductal carcinoma in situ (DCIS) combined. The clinical impact of that, if any, remains to be seen. The number of uterine cancers was reduced by about 38 percent in the Raloxifene group, which was not a statistical significance. During the course of the trial, more than twice as many women in the Tamoxifen group had a hysterectomy for benign disease, further reducing the ability to show significance. However, hyperplasia was increased dramatically in the Tamoxifen group. Several large Raloxifene placebo trials clearly showed that Raloxifene does not increase the risk of endometrial cancer. Raloxifene also had a 30 percent reduced risk of thromboembolic events. Moreover, Tamoxifen in the placebo tamoxifen trial increased the risk of cataracts about 14 percent, whereas Raloxifene does not appear to have that increased risk.

Formal quality of life evaluations conducted in this study showed that there were no significant differences in the primary quality of life endpoints, and there was minimal symptom severity in both of these agents. Minor differences were found in the symptom profiles, most of which favor Raloxifene, although sexual function slightly favored Tamoxifen therapy.

The STAR trial demonstrates that Raloxifene clearly is an effective alternative to Tamoxifen in the chemoprevention of breast cancer in this postmenopausal group although it is less effective in the prevention of noninvasive disease. Compared with Tamoxifen, the use of Raloxifene resulted in fewer thromboembolic events, fewer endometrial cancers, and fewer cataracts. The value of such trials clearly extends beyond the primary endpoint. The potential exists

to provide valuable resources to further basic and applied research. A serum and lymphocyte bank for both of these trials includes specimens from more than 30,000 women at increased risk for breast cancer. A tumor bank includes tumor blocks, paraffin imbedded, formalin fixed blocks of breast cancer and other cancers. Qualified investigators can access these specimens.

In discussion, the following points were raised:

- The few women who remained on Tamoxifen when the trial was unblended are being offered the option of switching to Raloxifene but a significant impact attributable to the change is unlikely. The DCIS is real, but it is not life threatening; the distinction is not a defining reason to avoid Raloxifene treatment.
- To increase the accrual of minority populations, future trials will enforce a minority recruitment plan from the start and focus on the importance of minority outreach, both for prevention and treatment.
- The osteoporosis trials were the foundation for the STAR study; however, because the Phase IV reporting would not be for secondary endpoints, such as breast cancer, additional information was not attained about breast cancer in the women who were enrolled in the osteoporosis trials.
- The information resulting from this study should be linked to important biomarkers.
- Regarding the diffusion of these results into medical practice, with the issue of Fosamax®, the use of Raloxifene may increase. An education program to educate women about breast cancer prevention, including the pros and cons of the different options (similar to the Heart Institute's cholesterol education program) would be helpful.

Recent Findings From the Prostate Cancer Prevention Trial (PCPT) — Dr. Howard L. Parnes

Dr. Howard L. Parnes, Prostate and Neurological Cancer Research Group, DCP, stated that the PCPT was a randomized trial of finasteride versus placebo for 7 years in nearly 19,000 men who were aged 55 and older and had a prostate specific antigen (PSA) less than three and a normal digital rectal exam at baseline. The primary findings were published in "The Influence of Finasteride on the Development of Prostate Cancer" (Thompson IM, et al.

NEJM 2003;349:215 224).

During the last several years, a study team led by Dr. Scott Lucia, who is the lead study pathologist for PCPT, has been investigating the explanations for the finding that a small but statistically significant increase in the rate of high grade disease among the men who were randomized to finasteride; 6.4 percent of the men on finasteride versus 5.1 percent of men on placebo were diagnosed with a Gleason 7 to 10 prostate cancer. The three leading explanations are that: 1) finasteride introduced morphologic artifact; 2) there may have been a true increase in high grade disease induced by finasteride; or 3) finasteride may have led to a detection bias. The possibility that finasteride, which is a hormonal agent, could introduce a morphologic artifact is highly plausible biologically; Dr. Donald Gleason has warned that one cannot use the Gleason system to grade tumors that have been treated with finasteride. An expert panel of pathologists who undertook a comprehensive analysis concluded that grading bias caused by an effect of finasteride on tumor morphology is unlikely to explain the observed increase in high grade tumors. Moreover, the time course of the emergence of high grade disease is not consistent with the true induction effect.

This large placebo controlled trial with prospectively collected biospecimens that are linked to a clinical outcome database, provides a unique opportunity to study prostate carcinogenesis to validate hypotheses regarding prostate cancer risk. It also could help discover new targets for prevention and be useful for diagnosis and treatment.

Investigators at 10 cancer centers and SPORES sites throughout North American are seeking to identify the genetic, metabolic, and environmental factors associated with prostate cancer risk and the efficacy, or lack thereof, of finasteride to develop comprehensive models of prostate cancer risk and finasteride risk reduction. An effort is underway, for instance, to investigate the risks associated with polymorphisms in genes that regulate hormone metabolism, DNA repair, and the response to oxidative damage. Dr. Parnes provided several examples of accomplishments to date. He noted that the purpose of this study is to develop risk models on the basis of genetic, environmental, and metabolic factors to identify men at high risk of prostate cancer and with high risk reduction potential. This would help limit the number of people exposed to a particular

prevention strategy or needed to participate in a prevention study. It also facilitates the stratification into low risk and high risk cohorts to ascertain those who would most likely benefit from finasteride or would be better suited to other intervention strategies.

In discussion, the following points were raised:

- Regarding the differences between the responses to different treatments by an African American versus non African American, it was noted that the primary results, and therefore the risk reduction of finasteride, were similar in all risk groups based on age, entry PSA, and race/ethnicity.

Pancreatic Cancer Biomarker Research—Dr. Michael A. Hollingsworth

Dr. Michael A. Hollingsworth, Epley Institute, University of Nebraska, presented an overview of the Early Detection Research Network (EDRN) and its work in pancreatic cancer biomarker research. Dr. Hollingsworth stated that the goal of the EDRN is to provide an infrastructure that discovers, develops, and validates biomarkers for cancer detection, diagnosis, and risk assessment. It also aims to conduct correlative studies to validate biomarkers as indicators of early cancer, pre invasive cancer, risk, or as surrogate endpoints. Other objectives are to develop quality assurance programs for biomarker testing and validation, and to forge public private partnerships. There are five defined phases for biomarker validation: preclinical exploratory studies, clinical assay and validation, retrospective longitudinal studies, prospective screening, and cancer control.

The infrastructure established for the EDRN involves three groups of investigators and 25 biomarker developmental laboratories; 6 biomarker reference laboratories and 10 clinical epidemiology and validation centers. There are established collaborations with various federal agencies, including the NIST as a reference laboratory, NASA’s Jet Propulsion Laboratory (JPL) as an informatics center, the CDC as a clinical epidemiology and validation center, the Department of Energy’s (DOE) Pacific Northwest National Laboratory as a reference laboratory for antibody and MS, and the National Institute of Environmental Health Sciences’ (NIEHS) Genes Environment Initiative. Dr.

Hollingsworth showed a listing of all 25 biomarker developmental laboratories, noting that 3 are dedicated to research in pancreatic cancer (the Epley Institute at the University of Nebraska, MD Anderson, and the University of Pittsburgh Cancer Center). There are six reference laboratories, including the University of Alabama, Birmingham, that conduct pancreatic cancer research in some coordination with the SPORES program. Among the clinical and epidemiological research centers, Creighton University focuses on patients with pancreatic cancer and inherited diseases. Furthermore, the Fred Hutchinson Cancer Research Center houses a coordinating center for the computational research for analysis. Approximately 10 percent of all investigators in the EDRN are working on pancreatic cancer.

Dr. Hollingsworth next presented examples of the types of research being pursued. The three biomarker developmental laboratories have two aims to: 1) improve the utility of the CA19 9 test, which is the only test approved currently for many gastrointestinal cancers, including pancreatic cancer; and 2) identify novel proteins that are expressed in the serum and body fluids of patients who have premalignant lesions of the pancreas. The three biomarker developmental laboratories are collaborating with different investigators and associate EDRN members around the United States to compile a reference set of samples that can be used for validation. In addition, two platforms are being considered: the luminex assay and an antibody array methodology that is capable of detecting multiple markers.

In discussion, the following points were raised:

- The EDRN is a “big science” initiative that has assembled an enormous array of people around a concept to generate biomarkers and apply them clinically, but it has not moved far along those steps to clinical application.
- The advantages of the EDRN mechanism versus the R01 environment is that the R01 does not fund translational studies. An infrastructure, such as the EDRN or a translational working group, is needed as a way of moving those basic discoveries into the clinic.
- Reproducible early stage serum is best available through the mouse model. The oligosaccharides in the mouse, however, are different than in the human, and reagents do not exist to discriminate the posttranslational modifications in mice.

Using proteomics techniques to examine these different model systems in view of other proteins might be an effective approach.

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XII. UPDATE: NCI/FDA/CMS MEMO OF UNDERSTANDING AND IMAGING COMPONENT — Dr. Anna Barker

Dr. Barker provided an update about the Oncology Biomarker Qualification Initiative (OBQI): NCI/FDA/CMS Collaboration to Speed Development of Cancer Therapies. She noted that past collaborations between the NCI and the FDA posed significant challenges, but when the Interagency Oncology Task Force (IOTF) recently met, up to 80 people attended. In addition, the FDA has undertaken its own initiative, called the Critical Path Initiative, which offers a scientific opportunity to bring significant amounts of science into the way regulatory review is performed. One of the major elements of the Critical Path Initiative is developing biomarkers and disease models. Dr. Barker cited Drs. William A. Dalton and Stephen H. Friend regarding the challenges in biomarkers and the promise that they hold for personalized medicine: “The emerging use of cancer biomarkers may herald an era in which physicians no longer make treatment choices that are based on population based statistics but rather on the specific characteristics of individual patients and their tumor.” (Science, May 26, 2006).

She told members that the IOTF was established in 2003 to enhance the efficiency of clinical research and the scientific evaluation of new cancer treatments. It emphasizes the establishment of joint training and fellowships. The discovery and development of biomarkers for clinical benefit remains another focus area. Through the use of caBIGTM, the IOTF aims to support standardization and organization of data reporting from clinical trials, as well as to support electronic filings to accelerate regulatory reviews. Another key focus is to address specific regulatory barriers impeding cancer drug development.

In addition to the OBQI, the IOTF has begun initiatives in several

areas, including overcoming regulatory barriers for exploratory INDs for small molecules, as well as good manufacturing practice (GMP) regulations for experimental agents. The task force also is working on advanced technologies, such as nanotechnology pathways and molecular diagnostics, and standards for clinical trials submissions. Training and joint appointments remain areas of interest for the IOTF. In terms of the Critical Path Initiative, in addition to developing biomarkers and new disease models, the FDA is streamlining clinical trials, applying bioinformatics, and enabling 21st century manufacturing. It also is addressing urgent public health needs.

After approximately 2.5 years of initial work, the OBQI was announced as a unique DHHS partnership, the first collaboration among the NCI, the FDA, and the CMS. The initiative coordinates cross DHHS goals for biomarker validation and clinical use. The NCI works to develop biomarker technologies and validation protocols to improve the detection, diagnosis, treatment, and prevention of cancer. The FDA's role is to develop guidance for the use of biomarkers to facilitate cancer drug development. The CMS needs to make informed decisions about the reimbursement of new or existing treatment regimens based on biomarker guided knowledge. Dr. Barker noted it has been an interesting experience for the NCI to understand what the FDA understands about biomarkers. The OBQI will validate particular biomarkers to evaluate new, promising technologies in a manner that will facilitate and accelerate clinical trials, reduce the time and resources spent during the drug development process, improve the linkage between drug regulatory review and drug coverage, and increase the safety and improve the efficacy of drug choices for cancer patients.

Focus areas for OBQI include cancer imaging, molecular assays and targeted therapies, clinical trials, and data mining. The FDA is inclined to look at trials using imaging as a surrogate endpoint, particularly in hypothesis driven approaches; the fluorodeoxyglucose (FDG) PET is the first area selected by the OBQI. Validated biomarker imaging data could lead to smaller clinical trials, earlier approval or rejection decisions on compounds, accelerated regulatory review, shorter time to public availability, and surrogate markers of efficacy. The OBQI believes that the FDG PET holds the promise to accomplish this and can make a difference in cancers. With additional studies, FDG PET

could facilitate drug development and patient care by resulting in shorter Phase II trials, accelerated approval in Phase III (with full approval based on the evidence of clinical benefit), and better patient care by halting ineffective therapies.

The initial two trials are focused on imaging based biomarkers found in non Hodgkin's lymphoma (Project 1) and non small cell lung cancer (NSCLC - Project 2, conducted through the ACRIN mechanism) to predict tumor response to treatment. These trials will help set the stage for how other NIH entities will use this partnership. Once the protocol has been developed by the three agencies, the Foundation for the NIH (FNIH) will open the protocol to the industry for people to sign up and pay for the trial that they are most interested in supporting. The FNIH will participate in other parts of the trial, such as finalizing the clinical question, collaboratively developing the protocol with community experts, and finalizing the protocol. Non Hodgkin's lymphoma is being targeted because successful clinical management is in place, effective drugs exist, clinical data for diagnosis and staging is available, and there is agreement on the established treatment response criteria that can be refined by FDG PET. Both projects embrace a new approach, involving multiple clinical trial sites, all following the same protocol and sharing data in real time via caBIGTM, and both will adhere to the agreement made about how these particular images will be read.

The next steps for the OBQI include the NIH's finalization of the organizational structure for the public private partnership to fund biomarker trials and to select the team sites for these initial trials. This will be followed by a determination of the next OBQI trials.

Dr. Barker closed with information about an activity to qualify biomarkers that is occurring within the OBQI initiative. She noted that this activity involves EGFR, for which there are about 10 different tests; to validate each separately would take many years. Dr. Janet Woodcock, FDA, has begun using the C Path organization, a nonprofit foundation closely associated with the FDA, to engage all the EGFR companies that are working on a particular test to qualify and select the best of the EGFR technologies for use in a NSCLC trial.

In discussion, the following points were raised:

- The affected community should be involved during the discovery and transition phases, and not limited to the delivery side of the trial.
- Institutions are declining to enroll patients in imaging trials because they are concerned about being charged with Medicare fraud based on its secondary payer rules that mandate that Medicare must be the payer of last resort.

Because the FDA's approval criteria are not based on clinical use but rather on evidence based regulatory policy, NCI's focus should center on the linkage between the diagnostic and the therapeutic. In the OBQI, biomarkers serve as a tool to improve patient care and accelerate oncologic drug development.

Serum samples, such as blood, should be archived as a routine practice for later biomarker studies or other tests.

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XIII. STATUS REPORT: TRANSLATIONAL RESEARCH WORKING GROUP — Dr. Ernest T. Hawk

Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources, OD, in an update on the progress TRWG stated that the co chairs are Drs. Lynn Matrisian, Vanderbilt University, and William O. Nelson, Sidney Kimmel Cancer Center, Johns Hopkins University. Dr. Hawk informed members that the TRWG was charged during the summer of 2005 to evaluate the current status of NCI's investment in translational research and envision its future in an inclusive, representative, and transparent manner. To build on the Clinical Trials Working Group (CTWG) efforts, without duplication, several CTWG members are on the committee. Moreover, a Web based communication platform (www.cancer.gov/trwg) allows the working group to disseminate information in a real time basis. The TRWG used the Web portal to solicit information from the broad community, incorporating 19 specific questions and an open ended question concerning translational science. NCI's current investments in translational research was also analyzed.

Dr. Hawk reported that five products have been developed to date:

a definition of translational research, the five developmental pathways to clinical goals, a portfolio analysis, a process analysis, and draft Phase I recommendations. The TRWG defines translational research as research that transforms scientific discoveries arising in the laboratory, clinic, or population into new clinical tools and applications that reduce cancer incidence, morbidity, and mortality. The five pathways to clinical goals are: agent, immune response modifier, interventive device, risk assessment device, and lifestyle alteration. Key findings from the portfolio analysis are that: 1) awards are not categorized adequately for translational content to provide meaningful quantitative assessment; 2) translational research is funded by most NCI Divisions, Offices, and Centers; 3) translational research is funded by a range of mechanisms, individual approaches as well as collaborative; 4) the majority of these awards are to NCI designated cancer centers; 5) translation occurs through diverse mechanisms, such as single facilitated programs (e.g., SPORES or EDRN), a series of individual investigator awards, NCI's intramural research program, combinations of NCI programs, or between the NCI and other institutes.

Early translation poses the challenge of how to ensure that: 1) the most promising concepts enter the developmental pathway; 2) concepts that enter advance to the clinic or to "productive failure;" and 3) progress is as rapid, efficient, and effective as possible. The four subcommittees identified seven obstacles to meeting this challenge: 1) Insufficient coordination and integration across the NCI results in a fragmented translational research effort that risks duplication and may miss important opportunities. 2) The absence of clearly designated funding and adequate incentives for researchers threatens the perceived importance of translational research within the NCI enterprise. 3) The absence of a structured, consistent review and prioritization process that is tailored to the characteristics and goals of translational research makes it difficult to direct resources to critical needs and opportunities. 4) Translational research core services often are duplicative and inconsistently standardized, with capacity poorly matched to the need. 5) The multidisciplinary nature of translational research and the need to integrate sequential steps in complex development pathways warrants dedicated project management resources. 6) Insufficient collaboration and communication between basic and clinical scientists, as well as the paucity of effective training opportunities, limit the supply of experienced translational

researchers. 7) Inadequate collaboration with industry delays appropriate developmental hand offs.

The TRWG's draft recommendations are to: 1) establish a flexible, integrated organizational approach that coordinates early translational research opportunities across the Institute; 2) designate a specific portion of the NCI budget for early translational research, thereby manifesting NCI's commitment to translational research and helping to manage translational research as an enterprise; 3) establish a prioritization process for translational research to prioritize the goals and select specific projects to achieve the goals; 4) establish a tailored funding and review mechanism to facilitate and create incentives for researcher participation; 5) establish a system to coordinate core services and other infrastructure components essential for early translational research; 6) establish a formal management structure for early translational research to help accelerate the translational research process, facilitate the recognition of and access to internal and external resources, and promote coordination and communication between the project scientific leads and the multidisciplinary project team; 7) develop a coding and tracking system that allows a real time analysis; and 8) establish a formal evaluation system to assess impact.

Dr. Hawk concluded the presentation by informing members of future TRWG activities. He stated that as Phase I subcommittee work continues, the TRWG will constitute Phase II subcommittees to develop draft recommendations on external integration and workforce training. An interim progress report will be presented to the NCAB in September. In the fall of 2006, public comments will be solicited via the Web about the draft recommendations, a second public roundtable will be convened, an implementation plan will be designed, and the final presentation will be given to the NCAB in the winter of 2007.

In discussion, the following points were raised:

- TRWG's focus on those areas that are "upstream" of the CTWG causes the definition of translational research to shrink significantly and eliminates other translational arenas. Even while working within a narrow definition of translational research, the TRWG should keep in mind that the science base should move along the full continuum of

translational research. Disciplines should not be cast out because they do not fit within the boundaries of early translation.

- The workforce and training subcommittee will consider innovative models for training, such as grant mechanisms to encourage interest in translational research
- The upcoming external integration committee will assess if and how a mechanism, such as the Rapid Access to Intervention Development (RAID) Program, could be employed to tie translational research to regulatory issues.

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XIV. ADJOURNMENT—DR. ROBERT C. YOUNG

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

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