Board of Scientific Advisors

Meeting Minutes

June 23-24, 2008

Building 31C, Conference Room 10
Bethesda, Maryland

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 40th meeting on Monday, 23 June 2008, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, Chancellor, Fox Chase Cancer Center, presided as Chair. The meeting was open to the public from 8:00 a.m. until 5:55 p.m. on 23 June for the NCI Director's report; report on NCI Congressional relations; ongoing and new business; recognition of departing members; a status report on nanotechnology; a report on linked investigator research in cancer biology; and consideration of request for applications (RFA) new and reissuance concepts and request for proposal (RFP) reissuance concepts presented by NCI Program staff. The meeting was open to the public from 8:30 a.m. on 24 June until adjournment at 11:40 a.m. for reports on The Cancer Genome Atlas (TCGA) and the Integrative Cancer Biology Program (ICBP).

Board Members Present:
Dr. Robert C. Young (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
Dr. Michael A. Caligiuri
Dr. Susan J. Curry
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. William N. Hait

Board Members Present:
Dr. Edith A. Perez
Dr. Richard L. Schilsk1y
Dr. Robert D. Schreiber
Dr. Stuart L. Schreiber
Dr. Bruce W. Stillman
Dr. Victor J. Strecher
Dr. Jane Weeks
Dr. James K. Willson

Board Members Absent:
Dr. Curt I. Civin
Dr. William S. Dalton

Dr. Leland H. Hartwell
Dr. Marc A. Kastner
Dr. Timothy Kinsella
Dr. Christopher J. Logothetis
Dr. Kathleen H. Mooney
Dr. James L. Omel
Dr. James R. Heath
Dr. Mary J.C. Hendrix
Dr. Leroy Hood
Dr. Ellen Sigal
Dr. Jean Y. J. Wang
Dr. Irving L. Weissman

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

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I. CALL TO ORDER AND OPENING REMARKS - DR. ROBERT C. YOUNG

Dr. Robert C. Young called to order the 40th regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Young reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. He called attention to future Board meeting dates through 2010. 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 3-4 MARCH 2009, MEETING MINUTES—DR. ROBERT C. YOUNG

Motion: The minutes of the 3B4 March 2008 meeting were approved unanimously.

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III. REPORT OF THE NCI DIRECTOR—DR. JOHN NIEDERHUBER

Fiscal Year (FY) 2008 Appropriations and FY 2009 and FY 2010 Budgets. Dr. John Niederhuber, Director, NCI, explained that

the FY 2008 budget increased only minimally from the FY 2007 operating budget ($4.805 M vs. $4.797 M, respectively). In 2008, more than 5,000 NCI grants will be in place. The payline for the end of the year is estimated at the 14th percentile for existing investigators and the 19th percentile for new investigators. Approximately 11 percent of the competing pool is reserved for exceptions. Type-5 grants are targeted to receive a 1 percent cost of living adjustment (COLA), while the Special Programs of Research Excellence (SPOREs) and Centers funding are flat at FY 2007 levels.

In anticipation that the FY 2009 budget will be flat, the budgets for all divisions and offices are expected to decrease by 3 percent across the board. The Cancer Centers, SPOREs, Clinical Cooperative Groups, and Community Clinical Oncology Programs (CCOP), however, will begin the year with flat budgets. The Office of the Director also is drafting the NCI progress report and NCI Bypass Budget in preparation for 2010 congressional justifications and the budget submission to the Office of Management and Budget (OMB). A transition team is being established to ensure that the NCI is prepared to respond to and promote the cancer agenda to the new administration. A list of outstanding clinician-scientists qualified to fill government positions is being compiled and members were encouraged to send suggestions to the Office of the Director.

Challenges and Opportunities. Dr. Niederhuber stated that the NCI continues its efforts in drug development, including implementing strategies of both the Clinical Trials and Translational Research Working Groups (CTWG & TRWG), expanding therapeutic programs such as the Rapid Access to Invention Development (RAID) Program, the Chemical Biology Consortium, and the new Small Business Innovation Research (SBIR) Phase IIb awards. NCI is working to develop a new research park facility in Frederick as part of the new Advanced Technology Research Initiative (ATRI) that would encourage partnership with pharma and biotechnology companies. Partnerships with two neighboring facilities, Suburban Hospital and the Naval Medical Center, have facilitated NCI's ability to conduct translational research on a larger, more diverse patient population. Further collaborative opportunities will arise when the Walter Reed National Military Medical Center relocates to the Naval Medical Center campus.

Dr. Niederhuber updated the Board on the progress of The Cancer Genome Atlas (TCGA), a pilot program that has concentrated on glioblastoma but also will study ovarian and lung cancers. He stated that NCI is also interested in other research areas, such as transcriptional regulation, epigenetics, microRNA-translational regulation, germline differences in predicting risk, biomarker discovery, and tumor microenvironment and new targets. He reported that the February meeting of leaders in applied mathematics, theoretical physics, and cancer cell biology has led to subsequent workshops to better understand the impact of basic physical principles on cancer and to develop mathematical models to explain the association between tumor cells and their microenvironment. Future opportunities include creating centers of excellence on theoretical cancer biology.

Dr. Niederhuber provided updates on 1) the contract renewal with Science Applications International Corporation (SAIC) to manage the NCI-Frederick campus; 2) plans for a molecular prevention meeting cosponsored by the American Association of Cancer Research (AACR); 3) a series of meetings with immunology leaders on developing an immunotherapy network, and meetings with Dr. Robert Gallo at the Institute of Human Virology, University of Maryland, to advance the AIDS/cancer vaccine initiative; 4) the NCI Community Cancer Centers Program (NCCCP) pilot program, commenting that it needs to be transitioned into a permanent program; 5) the Research, Condition, and Disease Categorization (RCDC) electronic coding system that all NIH Institutes, and Centers must use beginning in 2009. Members were reminded of the concern that this electronic word-recognition system will not accurately replace the coding processes that the NCI currently uses; 6) changes within the NIH's Roadmap & Common Fund priorities including a new initiative for transformative R01s; and other NCI challenges, such as diminishing clinical trials patient reimbursement and the aging infrastructure on NCI campuses.

In discussion, the following point was made:

- The initial target of 3 percent across-the-board cuts enable the NCI divisions to create a funding pool for new initiatives while identifying programs that should be eliminated.

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IV. NCI/CONGRESSIONAL RELATIONS - MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on FY 2008 spending and the status of FY 2009 appropriations and reviewed recent hearings and briefings, including the Senate Health, Education, Labor, and Pensions (HELP) Committee hearing on "Cancer: Challenges and Opportunities in the 21st Century" and the House Energy and Commerce Subcommittee on Health hearing on the Breast Cancer and Environmental Research Act. Ms. Erickson also reported on other legislation of interest to NCI, such as the 1) Genetic Information Nondiscrimination Act (GINA), 2) Conquer Childhood Cancer Act; 3) SBIR/STTR Reauthorization Act; etc.

In discussion, the following point were made:

- The GINA's genetic services provision bans discriminating against patients enrolling in clinical trials, who may undergo genetic testing.

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V. ONGOING AND NEW BUSINESS

ASPO-NCI Listens Report - Dr. Victor J. Strecher

Listens Session was held at the American Society for Preventive Oncology (ASPO) annual meeting on 17 March 2008. Dr. Strecher informed members that comments included increased funding for cancer training to strengthen the preparation of young investigators. He noted that suggestions to strengthen the environment that allows early career investigators to succeed were to: examine methods that shorten the time to the receipt of first grant, reduce the amount of unscored grants (triaging), and provide new investigators with a

separate study section. Additional ideas were to: better integrate cancer prevention and control research into NIH Roadmap initiatives and provide greater cancer prevention and control representation on K99 grant reviews; and eliminate large grant administrative funding, even if this reduces the number of grants funded.

TARGET Subcommittee Report - Dr. Malcolm Smith

Dr. Malcolm Smith, Head, Pediatric Section, Cancer Therapy Evaluation Program (CTEP), presented an update on the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, which supports research to identify new therapeutic targets for childhood cancers by using transcriptomic and genomic profiling combined with selective gene resequencing. Dr. Smith stated that the initial focus is on high risk B-precursor acute lymphoblastic leukemia (ALL) and neuroblastomas.

Members were told that for the ALL TARGET project, high resolution genomic and transcriptomic profiles are being obtained for approximately 200 B-precursor ALL cases, with sequencing of approximately 120 genes to be completed in 2008. Copy number alteration (CNA) analyses showed that the most frequently deleted gene was CDKN2A; that most CNAs were deletions, not gains; and that many of the deleted genes play key roles in B cell development. Gene sequencing work has detected more than 2,000 variations in 52 genes and has provided strong confirmation of the role of PAX5 deletions and mutations in B-precursor pediatric ALL. The neuroblastoma TARGET project includes genomic characterization, transcriptomic profiling, bioinformatics support, and gene sequencing with the transcriptomic and genomic profiling in progress. Gene selection criteria for sequencing were developed with most of the 117 gene candidates meeting at least two criteria. Findings include the discovery of constitutional ALK tyrosine kinase domain (TKD) mutations in familial neuroblastoma and the amplification of the ALK locus in a subset of neuroblastomas.

Future activities include: the development of a data portal (http://target.cancer.gov); integration of mutation, CNA, and gene

expression data; replication of discoveries in independent patient cohorts and identification and validation of therapeutic targets in the poor outcome cluster in the ALL project; and epigenomic profiling and validation of candidate therapeutic targets in the neuroblastoma project.

In discussion, the following points were made:

- The ALL group is enriched for adolescents since they are at higher risk for treatment failure than young children; findings should translate into the young adult population.
- The pediatric research community is an interactive group with many investigators involved in both TARGET and the Pediatric Preclinical Testing Program (PPTP). The research is complementary and therapeutic leads from TARGET would be taken to the PPTP for validation.
- Consider ways to encourage collaboration among pediatric research groups, such as the Acute Lymphoblastic Leukemia (ALL) Project and the Pediatric Preclinical Testing Program.

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VI. RECOGNITION OF DEPARTING MEMBERS - DRS. JOHN NIEDERHUBER AND ROBERT C. YOUNG

On behalf of the NCI, Drs. Niederhuber and Young recognized the contributions made by two retiring BSA members: Dr. Hoda Anton-Culver, Chair, Department of Epidemiology, Department of Medicine, University of California at Irvine; and Dr. William Hait, Senior Vice President and Worldwide Head, Hematology/ Oncology, Ortho Biotech Oncology/Hematology Research & Development, A Unit of Centocor Research & Development, Inc. Dr. Niederhuber acknowledged the importance of their contributions to the Institute's success and the valuable hours that each donated to the NIH and the NCI.

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VII. STATUS REPORT: NANOTECHNOLOGY - DRS.

ANNA D. BARKER, PIOTR GRODZINSKI, JOSEPH M. DeSIMONE, SAM GAMBHIR, JAMES R. BAKER, JR., AND ROBERT S. LANGER

Introduction and Status of the NCI Nanotechnology Alliance
Drs. Anna Barker and Piotr Grodzinski

Dr. Anna Barker, Deputy Director, NCI, provided a brief background of the beginning of the Alliance for Nanotechnology in Cancer and the rationale for presenting a state-of-the science update to the BSA. Dr. Piotr Grodzinski, Program Director, Nanotechnology for Cancer Program, introduced the speakers: Drs. Joseph M. DeSimone, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; Sam Gambhir, Director, Molecular Imaging Program, Professor of Radiology and Bioengineering, Stanford University; James R. Baker, Jr., Ruth Dow Doan Professor of Medicine, University of Michigan, Director of the Michigan Nanotechnology Institute for Medicine and Biological Sciences; and Robert S. Langer, Professor of Chemical Engineering at Massachusetts Institute of Technology (M. I.T.).

Dr. Grodzinski updated the members on the major accomplishments of the NCI Alliance for Nanotechnology in Cancer over the last 2.5 years. He noted that researchers had published 475 journal articles, filed 150 patents, and formed more than 30 companies associated with nanotechnology diagnostics and therapy. Further, leveraged funding has included more than $80 M of new, peer-reviewed government research funds and $150 M from philanthropic sources to establish infrastructure and perform research. The eight Centers for Cancer Nanotechnology Excellence (CCNEs) and 12 Cancer Nanotechnology Platform Partnerships (CNPPs) are staffed by multidisciplinary teams working toward the common goal of finding clinical applications for nanotechnology in cancer.

Novel Platform Nanotechnologies for New Cancer Interventions
Dr. Joseph M. DeSimone

Dr. DeSimone explained that the goal of the Institute for Advanced Materials, Nanoscience, and Technology is to develop a systems engineering approach to particle design that affords total control over size, shape, matrix chemistry, deformability, and surface chemistry, resulting in a platform technology that provides a variety of products and dosage forms. Researchers have developed a fabrication process called Particle Replication in Non-wetting Templates (PRINT) that involves harvesting nanoparticles of a variety of sizes and shapes on two-dimensional arrays. The process allows the creation of nano particles of diverse, precise shapes, including flexible worm-like particles that will be difficult for macrophages to clear. Particles made from 100% biologicals are of particular interest for developing immunotherapies that can be administered subcutaneously. Detailing how particles enter different cancer cells is guiding efforts to extract design principles and identify the roles of size and shape in internalization and intracellular localization. Using high-resolution video microscopy, the entry of PRINT particles into macrophages has been observed; those internalized the fastest are the rod-like particles.

Dr. DeSimone told members that the technology allows tailoring of the degradation rates and permeability of particles and therefore of the cargoes that they release. The matrix solubility characteristics can be tailored to the solubility of the drug, which may permit the use of agents that were previously difficult to deliver. Placing imaging beacon cargoes into particles for use in T-cell targeting during PET and MR scans is being investigated. Ongoing preclinical research includes targeted therapies for B-cell malignancies, a prostate-specific membrane antigen (PSMA) targeted orthotopic prostate mouse model, a folate receptor and HER2/neu orthotopic breast cancer model, targeted siRNA delivery, and cytochrome C delivery.

Integrated Nanotechnologies for Imaging and Diagnostics
Dr. Sam Gambhir

Dr. Gambhir described the emerging area of nanotechnologies in diagnostics. An integration of in vitro diagnostics and in vivo imaging strategies will be necessary to improve the ability to predict who will benefit from a given therapy and to know who is

responding early in a treatment cycle. Using magnetonanosensors for blood analyses, tumor proteins can be detected using antibodies and hundreds of biomarkers can be multiplexed simultaneously. Small changes in local magnetic fields are recognized and then processed electronically, allowing the detection of very low levels of a given biomarker.

Researchers are working to develop imaging probes with greater specificity for tumor targets and to amplify signals from deep within the body. With photoacoustics imaging, nanoparticles that have been injected into the body absorb light from pulsed lasers, which causes thermal expansion creating a sound wave that is acoustically detected. This emerging technology has the advantages of deep penetration, high resolution, and specificity. The nanoparticles can be modified to aim at different targets, and multiplexing is possible. The technology currently does not work well with bone or air.

Members were told that molecular imaging, using Surface Enhanced Raman Spectroscopy (SERS), uses gold nanoparticles with cores of small molecules that scatter light inelastically. The inelastic light scattering associated with each particular nanoparticle signature allows investigators to image its location and assay multiple events in a single animal. Pilot studies in mice have not shown significant toxicity and an application for Food and Drug Administration (FDA) approval to administer Raman nanoparticles into the bowel for endoscopic applications is pending.

Multi-Functional Nanotechnology Systems for Cancer Therapy
Dr. James R. Baker, Jr.

Dr. Baker stated that the initial goals at the Michigan Nanotechnology Institute were to: develop targeted therapeutics to locate and penetrate cancer cells, construct imaging capabilities to document the target's presence, and detect pathophysiologic changes occurring in cancer cells. Particles need to be nano-sized to get out of the bloodstream and diffuse into the cancer cell. Dr. Baker described their research on dendrimers (artificial proteins made of subunits of amino acids); specifically, the G5 dendrimer

that was chosen because its size is equivalent to hemoglobin and is below the renal filtration threshold. He noted that one problem with targeting is that many ligands in cancer cells are not avid enough for particles to bind to. By taking one ligand and multipolymerizing it with multiple antibody molecules, much greater avidity for the target cell was achieved. In a mouse experiment, researchers compared the results of giving free methotrexate versus administering methotrexate via a targeted delivery system using nano-dendrimers. Better efficacy and less toxicity with 100 fold improvement in therapeutic index were achieved with the dendrimer. A clinical trial may be initiated next year in patients identified with folate receptors on their tumors.

Dendrimer nanodevices may have potential for detecting cancer recurrence. Quantifying the flow of cancer cells through mice tympanic membrane capillaries might detect recurrence. Significant challenges to developing individualized therapy exist, but by linking targeting dendrimers to drug dendrimers using complementary DNA-strands, a bimodal therapeutic dendrimer nanocluster might be possible.

Leveraging Nanotechnology for Targeted Drug Delivery and Biosensing
Dr. Robert S. Langer

Dr. Langer described three Harvard/M.I.T CCNE projects: 1) targeting nanoparticles for cancer therapy, 2) devising ways for nanoparticles to deliver siRNAs to tumor cells, and 3) developing discrete sensor devices for determining cancer targets. He stated that significantly less macrophage ingestion occurred in vitro when polyethylene glycol (PEG) chains were placed on biodegradable cores carrying the therapeutic agent. In animal studies, the amount of liver uptake depended on the chain length for PEG coated nanoparticles. The researchers were able to prevent reticuloendothelial system reuptake by modifying the chain's molecular weight and structure. When aptamers (nucleic acid ligands that act as targeting molecules) were attached to docetaxel, targeted uptake of these nanoparticles led to reproducible tumor shrinkage in mice.

Members were told that to create a more efficient delivery system for releasing siRNA to target cancer cells, researchers created a library of lipids with chemical diversity through variation in R groups and tail length that could be used to form liposomes for drug delivery. Liposomes protected the formulation from immune recognition during circulation, resulting in intracellular delivery of siRNA in tumor cells in mice. Using engineering and microfabrication approaches, a series of microchips with different magnetic resonance switches to detect different analytes bound to a semi-permeable membrane could to be used as an implant or transdermal patch. In one experiment using these sensors in vivo, tumors transmitted a different type of T2 signal than controls, suggesting future potential for noninvasive, continual monitoring of the cancer patient.

Summary
Dr. Anna R. Barker

Dr. Barker applauded the progress made by the NCI Alliance for Nanotechnology in Cancer. She informed members that the state-of-the-science has far exceeded the Board's initial expectations. The current major barrier is translation. Although the science is moving rapidly, translating innovations into the clinic is difficult because of dwindling investment. The NCI is working with the Foundation for the NIH and other groups to raise funds to allow the translation of new nanotechnologies.

In the discussion, the following point was made:

- Careful consideration must be given to the toxicity of nanoparticles. The Nanotechnology Characterization Laboratory has provided toxicological guidance for the CCNEs and plans have been developed with the FDA.
- The traditional clinical trials approach is inadequate for translating new nanotechnology drug delivery or diagnostic systems. Staff mentioned that the Health Policy Forum, Institute of Medicine, is planning a forum on the structure needed to do clinical and translational research.
- New mouse models that better reflect the clinical condition, instead of xenograft models, should be used in these studies.

- The extent to which nanotechnologies, such as biosensing, can be applied to prevention and exposure assessment is undetermined. A meeting with these researchers and investigators involved in prevention at the population level should be considered.
- Consideration should be given to new approaches to clinical trial design to facilitate the investigation of advances in nanotechnology. The application of nanotechnology to cancer prevention and exposure assessment should be explored.

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VIII. LINKED INVESTIGATOR RESEARCH IN CANCER BIOLOGY (PAR)- DR. SURESH MOHLA

Dr. Suresh Mohla, Chief, Tumor Biology and Metastases Branch (TBMB), Associate Director, Division of Cancer Biology (DCB), provided information about a new program announcement (PAR) to promote linked investigator research in cancer biology through the Integrated Cancer Biology Program (ICBP) and Tumor Microenvironment Network (TMEN) Program. Dr. Mohla informed members that there is an emerging focus to understand and model the tumor as an organ with many interacting systems such as: gene networks in cancer cells, signaling pathways, and the tumor microenvironment. The goals of the PAR are to: enhance collaborations between the research community and the ICBP and TMEN; extend the scientific scope of the ICBP and TMEN to new organ sites and approaches, new technologies and models, new PIs; and increase the broad impact of ICBP and TMEN Programs. The proposed mechanism is a multiple Principal Investigator (PI) R01 in which one PI is associated with one of the programs, and one PI is outside of the program. Applications will be reviewed by the NCI DEA, with one or two receipt dates each year. Between six to eight awards are estimated for each year; there will be no budget set aside, but the R01 payline established by the NCI will be used.

Potential ICBP topics are: 1) the integration of models across temporal and spatial scales, 2) application of new technologies for quantitative measurements of cancer processes, 3) application of integrative approaches to the identification and testing of new therapeutic agents, and 4) integration of current ICBP modeling

approaches to additional organ systems. Possible TMEN-related research could include: 1) alterations in normal organ- and tumor-associated stroma and the microenvironment responsible for tumor development, progression, and metastasis; 2) roles of the inflammatory/immune and bone marrow derived cells in tumor initiation, progression, and metastasis; 3) identification of tumor stem or progenitor cells and characterization of their interactions with stromal cells: and 4) development of novel technologies and model systems or characterization of the tumor microenvironment in additional organ sites.

In the discussion, the following point was made:

- The multiple PI grant is a new mechanism that allows two or more PIs to work as a team, and is appropriate for multi-disciplinary applications and for bringing new investigators into a field.
- Concerns were raised regarding the requirement for inclusion of an ICBP or TMEN investigator as PI. It also presents a seeming conflict in that investigators who already are funded will receive more funding. Staff clarified that researchers have the option to write an independent R01 grant.
- A concern was expressed that applications will be reviewed in a vacuum with reviewers having no knowledge of the ICBP or the TMEN. NCI staff responded that reviewers can be provided with background information about the programs. Additionally, the requirement for inclusion of ICBP or TMEN PIs could be eliminated by including a description of collaborative activities. Collaborations would then be established at the time of funding.
- The BSA encouraged the NCI to provide a follow-up presentation on this program to address whether it was successful in bringing new investigators into the field.

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IX. RFA/COOPERATIVE AGREEMENT CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Biology

Erythropoietic Stimulating Agents (ESAs) and Tumor Growth (RFA)

Dr. R. Allan Mufson, Chief, Cancer Immunology and Hematology Branch, Division of Cancer Biology (DCB), stated that the RFA was developed to address the knowledge gaps delineated at the NCI Workshop on ESAs and Tumor Growth, held in December 2007. In 1993 and 2002, ESAs were approved by the FDA to reduce the need for transfusions for anemia associated with chemotherapy in patients with non-myeloid malignancies. Concerns over this application of ESAs developed in 2003, when it was observed that patients undergoing chemotherapy for breast cancer or radiotherapy for head and neck cancer and were treated with ESAs, showed poorer survival than control groups. These and subsequent clinical trials have raised questions about the role of ESAs in tumor progression. Knowledge about ESAs and tumor progression is fragmentary and conflicting, in both in vitro and preclinical in vivo studies. The RFA aims are to investigate the: 1) regulation of EPO receptor expression; 2) effects of EPO on apoptosis and/or cell proliferation in non-hematopoietic cells; 3) use of animal models to study the pharmacological effects of ESAs on tumor growth and progression; and 4) effects of ESAs on tumor angiogenesis, as well as on tumor invasiveness and migration.

The proposed budget of $5 M would be derived from unrestricted drug company donations and administered through the Foundation of the NIH (FNIH). The companies would have no input into the grant proposal reviews or have advanced access to research data. The RFA's success would be evaluated by NCI staff in conjunction with experts who participated in the December 2007 workshop.

Subcommittee Review. Dr. Paul M. Allen, Robert L. Kroc Professor of Pathology and Immunology, Washington University School of Medicine, voiced concern about the RFA's focus and questioned the lack of emphasis on the important clinical questions and diseases. The source of the funding coming from pharmaceutical companies that manufacture ESA products also was a concern.

The first year cost is estimated at $1 M for 2-3 R01 awards and a

total cost of $5 M for 5 years.

In the discussion, the following points were made:

- A member suggested that the Center for Scientific Review (CSR) might be the best place to evaluate incoming grant proposals. Staff responded that NCI would take the necessary steps to ensure that the review is done in the most appropriate locus.
- The FNIH has received resources in the past from private companies that have vested interests in the results of discovery research. Managing public perception and establishing a system of checks and balances will allow beneficial relationships between the public and private sectors.
- The best way to study whether ESAs are safe may not be through basic cell biology research, but through conducting relevant clinical trials and mining existing databases.
- A contract mechanism was suggested as a better way to fund the appropriate studies and allow the NCI to frame research questions that are relevant to patient safety.
- A member suggested that NCI should provide funds so that the RFA is not solely supported by drug companies. The NCI hopes FNIH is successful in raising funds from other sources.

Motion. A motion to defer the Division of Cancer Biology's (DCB) Request for Application (RFA) entitled "Erythropoietic Stimulating Agents (ESAs) and Tumor Growth" was approved unanimously. A BSA subcommittee (Schilsky (chair), Caliguiri, Allen, and R. Schreiber) was formed to work with DCB program staff to restructure the concept. An e-mail vote by the full Board will be taken.

Division of Cancer Control and Population Sciences (DCCPS)

Transdisciplinary Cancer Genomics Research: Translation of Genome-Wide Association Studies (GWAS) (RFA/Coop. Agr.)

Dr. Daniela Seminara, Program Director, Epidemiology and

Genetics Research Program (EGRP), DCCPS, said that the goals of the RFA are to accelerate and coordinate post-GWAS research by identifying and validating genetic variants that are associated with increased cancer risk and gaining insights on underlying mechanisms from targeted functional studies. Dr. Seminara reported that GWAS has identified new variants and potential pathways in cancer etiology for breast, colon, melanoma, and prostate. Interestingly, the most robust association in cancer GWAS has not been within candidate genes/pathways and some associations have been in regions not even known to harbor genes.

She stated that the areas to be studied include robust associations within candidate genes and pathways, associations in regions that are not known to harbor genes, and validation of results and identification of disease causal variants. Successful GWAS translation requires a population-health approach that includes evidence-based guidelines, cancer practice and control programs, discovery, and promising applications to reduce the burden of cancer. The RFA can support the establishment of integrated research teams, expedite trials, accelerate discovery, and build the foundation for translational results.

The grant mechanism is a multiple PI cooperative agreement (U01) that allows credit and leadership for all investigators, provides programmatic input in coordination, and allows for collaboration with other intra- and extramural researchers.

Subcommittee Review. Dr. Todd R. Golub, Director, Cancer Program, Broad Institute of MIT and Harvard, was enthusiastic about the success of GWAS in identifying variants that were significantly associated with cancer. The proposed RFA is the next body of work that needs to occur, but questions were raised about the amount of funding. The Subcommittee recommended that the RFA be flexible regarding the number of areas that applications are required to cover. Concerns also were expressed about the inclusion of replication studies in GWAS; the nexus of analysis, modeling, and functional studies; and the breadth of the RFA.

The first year cost is estimated at $24 M for 5-8 U01awards and a total cost of $96 M for 4 years.

In the discussion, the following points were made:

- Members were concerned that the investigators doing GWAS studies may not be the appropriate investigators to also identify genes and conduct functional studies. New methods are needed to study the functions of the loci.
- Gene-environment interactions should be an important focus, including gene-diet, health disparities, and influences ranging from structural and contextual to biological influences and their interactions.
- The development of benchmarks and a monitoring and evaluation strategy at the onset of the project is important to ensure a successful investment.
- One concern is the research focuses on low penetrance alleles that are very common; scientifically valid biological functional studies and gene-environment studies will be difficult.

Motion. A motion to concur with re-issuance of the Division of Cancer Control and Population Sciences= (DCCPS) RFA/ Cooperative Agreement entitled "Transdisciplinary Cancer Genomics Research: Translation of Genome-wide Association Studies" and amended to state that the RFA should emphasize gene-environment interactions was approved with 22 yeas, 3 nays, and 0 abstentions.

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Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)
(Letter RFA/ Coop. Agr. Reissuance)

Dr. Steven B. Clauser, Chief, Outcomes Research Branch, Applied Research Program, DCCPS, explained that CanCORS established seven centers in 2001. The original aims were to determine how patients, physicians, and characteristics of health care organizations influence treatments and outcomes and to evaluate the effects of care delivery on patients= survival, quality of life, and satisfaction with care. Dr. Clauser stated that the Consortium has been successful in recruiting 5,000 patients each for lung and colorectal

cancer, creating a prospective cohort starting at 3-4 months after diagnosis, and following patients through 1 year of treatment. One goal of the reissuance is to assess outcomes beyond one year, including the variation in outcomes of post-treatment surveillance and the variation in receiving targeted molecular therapies. Another goal is to investigate post-treatment survivor issues, particularly continuity and coordination of care. Issues of surveillance, recurrence, occurrence of metastatic disease, and the transition from curative therapy to end-of-life care have been vastly understudied.

The RFA reissuance creates an open research resource available to non-CanCORS investigators. The Consortium intends to concentrate on intervention research using CanCORS tools and findings. Final phase project enhancements consist of: creating a scientific chair position; streamlining data collection strategies; and focusing medical record abstraction on recurrence, surveillance, and followup care. Collaborations include a Veterans Administration component adding additional study centers in 2003, and CDC support for Medicare claims linkage. The CanCORS RFA presents an opportunity for leveraging the data resources created in the initial phase to comprehensively evaluate the quality of care delivered to and health outcomes experienced by longer term survivors of colorectal and lung cancers.

Subcommittee Review. Dr. Kathleen Foley, Pain and Palliative Care Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center, informed members that the subcommittee supported the reissuance. Dr. Foley stated that the five recent Institute of Medicine reports on quality of cancer care have called attention to the need for this type of research. She noted that the CanCORS has framed a methodology to link data systems and directly evaluate patients= and caregivers= needs within a useful public health perspective.

The first year cost is estimated at $3.7 M for 7 U01 awards and a total cost of $11 M for 3 years.

In the discussion, the following points were made:

- ? A priority is to promote the CanCORS database so that investigators will use the resource. The Statistical

Coordinating Center will be instrumental in outreach efforts and developing educational interventions.

Motion. A motion to concur with the re-issuance of the DCCPS= letter RFA entitled "Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)" was approved with 21 yeas, 0 nays, and 2 abstentions.

Centers for Population Health and Health Disparities (CPHHD) (RFA Reissuance)

Dr. Robert Croyle, Director, DCCPS, introduced the CPHHD by stating that the focus is broader than cancer, with some of the programs being cancer related. The National Institute for Environmental Health Sciences (NIEHS), the original lead institute for the RFA, will not participate in this reissuance, but new NIH partners have been identified. Dr. Shobha Srinivasan, Health Disparities Research Coordinator and CPHHD Program Director, DCCPS, described the CPHHD's mission to integrate basic, clinical, and population science to provide novel insights about health disparities and to develop innovate new models that can simultaneously account for multiple factors/levels.

The original CPHHD RFA established Centers across the United States to investigate racial/ethnic and socioeconomic factors, such as rural or inner city residence, and breast, prostate, and cervical cancer-related outcomes. By studying the simultaneous effects of neighborhood, community, and social and behavioral factors in three localities (low-income Philadelphia, inner city Chicago, and Appalachian Ohio), the CPHHD studies found that social isolation significantly impacted cancer outcome at the genetic, biological, and clinical levels.

Dr. Srinivasan indicated that the Centers had been able to leverage funds, spin off grants, and contribute to more than 230 publications. Goals for the next round of funding include the addition of a training component and developing interventions as well as testing multilevel hypotheses. Trans-NIH collaborations will be encouraged to promote a unique, transdisciplinary scientific agenda. Each Center must incorporate basic science (including

biology and genetics); social, behavioral, and population sciences; and clinical sciences. The P50 Centers will promote transdisciplinary team science, facilitate examination of complex research questions, and train the next generation in health disparities research.

Subcommittee Review. Dr. Kathleen Mooney, Professor, University of Utah College of Nursing, informed members that the subcommittee is very supportive of this reissuance, which is a fully open recompetition. Dr. Mooney noted that the program has demonstrated the complexity of the factors implicated in disparities, and the P50 centers mechanism is appropriate. The training component is a noteworthy addition, as is the requirement that at least one project address an intervention on a multilevel basis. The Subcommittee encouraged more gene-environment interaction and fewer social-social interaction studies. Stronger mechanistic models could support real interventions.

The first year cost for NCI funded Centers is estimated at $10 M for 5 P50 awards and total costs over 5 years of $50 M. The total NIH estimated commitment is 8-10 centers (including those funded by NCI).

In the discussion, the following points were made:

- The model should include factors within the health care system, such as chemotherapy and surgery, clinical scientists= involvement, and more emphasis on potentially alterable mediators of disparities, such as access to screening facilities and transportation.
- There appears to be a disconnect between CanCORs and CPHHD, or programs with and without clinical focus. This will be addressed in the reissuance.
- This RFA should accept multiple Principal Investigator applications since the research could involve scientists in genetics, epidemiology, sociology, behavioral medicine, and clinicians.

Motion. A motion to concur with the re-issuance of the DCCPS= RFA entitled "Centers for Population Health and Health Disparities (CPHHD)" was approved with 19 yeas, 0 nays, and 4 abstentions.

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Office of the Director

Comprehensive Minority Institution Cancer Center Partnership (MI/CCP) (Letter RFA/ Coop. Agr. Reissuance)

Dr. Nelson Aguila, Acting Branch Chief, Diversity Training Branch, Center to Reduce Health Disparities (CRCHD) described the MI/CCP as a synergistic model where the strengths of the minority serving institution (MSI) and the cancer center are brought together to build research capacity and create stable and long-term collaborations in research, training, career development, and outreach in underserved communities. The existing partnership includes three funding mechanisms: 1) P20 or feasibility studies; 2) U56 or cooperative planning grants, which are phasing out; and 3) U54 or larger comprehensive partnerships, which are being requested in this RFA reissuance.

Dr. Aguila highlighted accomplishments in research, training, outreach and education of the current 170 U54 and U56 research projects. Since 2001, MI/CCP has had over 300 publications and a 56 percent success rate for grants, with 78 funded grants. The program has supported 881 trainees, 70 new faculty members at MSIs, and 13 new faculty or investigators have been employed at the cancer centers. Recent achievements in outreach include the development of several cancer control and prevention programs for Native Americans, Pacific Islanders, and Hispanic communities. An ongoing activity of note is the U54 partnership between the University of Puerto Rico Cancer Center and M.D. Anderson Cancer.

Subcommittee Review. Dr. Hoda Anton-Culver, Chair, Department of Epidemiology, University of California at Irvine, expressed the Subcommittee's support for the reissuance and funding. She commended the project staff on the progress made and noted that program objectives are being met. There were

questions about the phase-out process of the U56 grants, and bridge funding was encouraged. The hands-on approach in working with grantees was an important component of the program's success and should be continued.

The first year cost is estimated at $5 M to support 2 U54 partnerships (4 awards) for 5 years for a total cost of $25 M.

Motion. A motion to concur with the re-issuance of the Office of the Director's Letter RFA entitled "Comprehensive Minority Institution Cancer Center Partnership (MI/CCP)" was approved with 20 yeas, 0 nays, and 2 abstentions.

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Division of Cancer Treatment and Diagnosis

Cancer Disparities Research Partnership Program (RFA/Coop. Agr. Reissuance)

As chair of the Subcommittee, Dr. Kirby Bland, Professor and Chairman, Department of Surgery, University of Alabama at Birmingham, reminded members that the reissuance of the Cancer Disparities Research Partnership (CDRP) Program that had been previously presented to the Board in February 2008. He noted the Board had previously expressed concern about disparate accrual rates and performance across sites, lack of sustained relationships between PIs and mentors, need for diverse clinical trials beyond radiation therapy, and the need to develop strategies to transfer the patient navigation system to community doctors.

Dr. C. Norman Coleman, Radiation Research Program, Division of Cancer Treatment and Diagnosis, (DCTD), described the CDRP Program as a unique pilot program through which health disparities community-based institutions can participate in NCI clinical research through collaborations with cancer centers or cooperative groups. Evaluation metrics include: the development of a clinical trials program; accrual in clinical studies; mechanisms of

recruitment; success of partnership, whether a research culture could be established; and the potential impact on communities.

Dr. Coleman reviewed the CDRP research currently underway. Aggregate data from all CDRP sites show that the cumulative number of patients accrued is rising and that multimodality trials have increased. Future goals are to: continue increasing clinical trial accrual; ensure sustainability by requiring PIs to apply for grants; and encourage investigators to become independent grantees through other NCI mechanisms.

Subcommittee Review. Dr. Bland said that the Subcommittee supported the CDRP reissuance as a letter RFA so that the pilot program could be completed. He indicated that the Subcommittee encouraged the development of additional treatment modalities beyond radiation therapy and complimented the use of Telesynergy7. Dr. Bland stated that additional strategies should be considered to overcome accrual to clinical trials barriers in the next 5 years. The mentors at NCI-designated centers or other partners should be more visible, and NCI's commitment to the program should be maintained.

The first year cost is estimated at $4.2 M for 5 U56 awards and a total cost of $14.5 M for 5 years.

In the discussion, the following points were made:

- The CDRP should consider dissemination of tools or developing a generic blueprint outlining how community hospitals can self-generate this kind of program. Several sites might share their best models to help build capacity elsewhere.
- An optimal exit strategy might be to encourage sites to develop the resources necessary to participate in the CCOP over the next 5 years.

Motion. A motion to concur with the re-issuance of the Division of Cancer Treatment and Diagnosis (DCTD's) RFA entitled "Cancer Disparities Research Partnership Program" was approved with 13 yeas, 7 nays, and 1 abstention.

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Pediatric Preclinical Testing Program (RFP Reissuance)

Dr. Smith informed members that the Pediatric Preclinical Testing Program is a research contract for testing new agents using in vitro and in vivo panels of childhood cancers. He stated that there is an in vivo panel of more than 60 xenografts and an in vitro panel of 27 cell lines; the activity is able to test 10 to 12 new agents per year against the childhood cancer panels. A panel of preclinical models was carefully selected based on molecular characterization, standard transcriptomic, and genomic profiling to recapitulate basic characteristics of the clinical specimens. A two-stage process for drug evaluation involves testing at the maximum tolerated dose (MTD) against the entire panel, a report of the results, additional testing by a pharmaceutical company, and a final report followed by publication and presentation of results. Examples of agents studied include: Millennium compound MLN8237, an Aurora A kinase inhibitor, with activity against neuroblastoma and ALL xenografts; and SVV-002 (NTX-010), an oncolytic virus, with activity against alveolar rhabdomyosarcoma xenografts.

The program has established molecularly characterized pediatric preclinical panels that recapitulate basic biological characteristics of the corresponding clinical histotypes, established successful collaborations with over 20 pharmaceutical companies for agent testing, and demonstrated the capacity to screen 12 agents per year. The PPTP has rapidly disseminated testing results through publications and six clinical trials are ongoing or being planned as a result of findings to date.

Subcommittee Review. Dr. Richard L. Schilsky, Professor of Medicine, Pritzker School of Medicine, University of Chicago, stated that the Subcommittee supported reissuance of the RFA. Dr. Schilsky noted that the xenografts seem to be well characterized genetically and representative of the pediatric tumors, and the screens can identify known active drugs and identify new and interesting agents. When questioned about the use of the cell lines, Dr. Smith explained that they provide an additional data set to be correlated with clinical observations and in vivo findings. Each of

the six sites works on one cancer type, and the work is centrally coordinated with standard methods for reporting.

The first year cost is estimated at $2.7 M for 1 RFP award and a total cost of $14.5 M for 5 years.

In the discussion, the following points were made:

- A concern was raised about how much could be learned from expensive xenograft studies as compared to cell lines in culture. Staff indicated that ALL provides an example where in vitro selection pressure better mimics the clinical condition.
- A member expressed the concern that xenograft screening has not proven to be effective for adult tumors. Program staff noted that pediatric tumors appear to be genetically less diverse and more responsive to chemotherapy. The multiple pediatric xenograft models are better characterized and inclusion of PK comparison studies is an additional strength.

Motion.A motion to concur with the re-issuance of DCTD's RFP entitled "Pediatric Preclinical Testing Program" was approved with 16 yeas, 2 nays, and 2 abstentions.

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Division of Cancer Control and Population Sciences

Replication and Fine-Mapping Studies for the Genes, Environment, and Health Initiative (RFA)

Dr. Elizabeth Gillanders, Program Director, Host Susceptibility Factors Branch, EGRP, DCCPS, updated members about NCI's involvement in the Genes, Environment and Health Initiative (GEI), a 4-year NIH-wide program. The overall goal of the initiative is to accelerate understanding of both the genetic and environmental contributions to health and disease.

The GEI is composed of an Exposure Biology Program and a Genetics Program. The Genetics Program identifies genetic susceptibility factors for diseases that have a high public health impact, focusing on common diseases that have well-established environmental risk factors, such as lung cancer. The Replication and Fine-Mapping Studies RFA is among 12 RFAs being issued between 2007 and 2011. NCI has agreed to be the lead IC for this RFA. Each RFA focuses on an individual step in the continuum between the initial GWAS studies and clinical translation.

The NCI has led the scientific community in advocating for the need for replication and fine-mapping studies to validate and replicate initial GWAS findings, which will eliminate false positives, narrow the association intervals of interest, and extend the findings to diverse populations. For FY2008, the NCI is managing the solicitation and review of GEI administrative supplements.

The budget for the Replication and Fine-Mapping Studies RFA is comprised of a $2 M NIH/GEI set aside for FY 2009 and $3 M set aside for FY 2010 for 4 to 6 R01 awards each year.

In the discussion, the following points were made:

- The NIH-wide GEI Coordinating Committee does not have a preset prioritization of diseases beyond having a significant public health impact and environmental exposure causality.

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X. UPDATE: THE CANCER GENOME ATLAS (TCGA) - DRS. ANNA D. BARKER, ERIC LANDER, CAMERON BRENNAN, STEPHEN BAYLIN, RICHARD K. WILSON, AND CHARLES PEROU

Introduction - Dr. Anna Barker

Dr. Barker introduced the TCGA project and described the progress made in developing an effective infrastructure, determining which technologies are most useful for its purposes, and collecting high-quality biospecimens, as well as in genomic analyses. Dr. Barker introduced the presenters: Drs. Eric Lander, Professor of Biology, Director, Broad Institute of M.I.T. and Harvard University; Cameron Brennan, Assistant Professor, Department of Neurosurgery, Memorial Sloan-Kettering Cancer Center; Stephen Baylin, Professor of Oncology, Johns Hopkins University School of Medicine; Richard K. Wilson, Director, Genome Sequencing Center, Professor of Genetics and Molecular Microbiology, Washington University School of Medicine; and Charles Perou, Associate Professor, Departments of Genetics and Pathology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill.

TCGA: Current Status - Dr. Eric Lander

Dr. Lander explained that the goal of TCGA is to develop a comprehensive public catalog of genomic alterations that occur with significant frequency in all major cancer types. The catalog will include copy number alterations, amplifications and deletions, translocations, gene expression differences, coding mutations, and methylation differences. The initial goals are to assemble a high-quality sample collection, characterize the tumor genome using various approaches, share the data with the scientific community, improve technologies used to characterize genomic alterations in tumors, and integrate the data to help understand the basis of different cancers.

The TCGA has focused on three cancer types. Data currently are available for the projects focused on glioblastoma multiforme (GBM). The GBM sample collection criteria included: 1) greater than 80 percent tumor content; 2) less than 40 percent necrosis; 3) matched normal DNA samples; 4) clinical annotation; and 5) appropriate informed consent. Approximately 225 samples meeting these criteria have been obtained and analyzed for genomic characterization; approximately 120 samples have entered the sequencing pipeline, and data for these samples is becoming available. Analysis of previous studies of GBMs found a lack of concordance, but analysis of larger numbers of samples will permit

researchers to distinguish between meaningful and background mutations.

Glioblastoma Multiforme (GBM) and Genome Characterization - Dr. Cameron Brennan

Dr. Brennan described GBM genomic characterization efforts and noted that data was retrieved from public Web sites and integrated toward classifying GBMs. Analyzing U133 expression data in 205 GBMs resulted in at least three defined subclasses of tumors. Integration of exon expression, copy number, and sequencing information defined an Epidermal Growth Factor Receptor (EGFR) subclass of tumors characterized by EGFR alteration. Sixty-five percent of the tumors had amplification or mutation of EGFR, a small percentage had ERBB2 or MET mutations, and 20 percent remain to be sequenced.

A second GBM subclass is characterized by amplifications and/or mutations in PDGF receptor A. Some tumors in this class also were found to have amplification of EGFR. However, a significant proportion of this subclass of GBMs has elevated PDGF ligand, rather than receptor amplification; PDGF signaling has recently been reported in EGFR-amplified tumors. Thus, tumors may appear similar at the level of expression, but differ with respect to post-translational regulation.

The third GBM subclass identified through this approach is characterized by deletions or mutations in NF1. These tumors have uniformly low expression of NF1 and a high preponderance of deletions. Sixty-three percent of samples in the NF1-associated group had deletions or mutations in NF1; 40 percent remain to be sequenced.

These preliminary analyses have defined at least three subclasses of GBM with associated mutations. The data will permit analysis of mutation patterns and interaction among signaling molecules that will be useful for the development of therapies. These subclasses also mirror existing genetically defined mouse models, giving these models new relevance for biological and preclinical studies.

In the discussion, the following points were made:

- No correlations between GBM molecular subtype and survival have been observed, although the proneural class of GBMs appears to occur more often in younger patients.

The GBM Epigenome - Dr. Stephen Baylin

Dr. Baylin described work to characterize the GBM epigenome. Analysis of epigenomic changes in tumors may help with tumor classification and the development of treatments. The first part of the project was to perform high- throughput analysis of changes in DNA methylation in GBM specimens. DNA hypermethylation, and associated transcriptional repression, is, perhaps, the leading mechanism for loss of gene function in cancer. Initial results have shown that primary tumors have DNA methylation changes that differ for each allele. The density of methylation also can vary within the tumor, and because methylation density at CpG islands can correlate with the degree of repression of transcription, gene dosage will have a significant effect.

DNA hypermethylation of DNA repair genes accounts for the majority of mutations in approximately 30 percent of GBMs sequenced. Analyses of hypermethylation patterns have identified nearly 300 genes with cancer-specific hypermethylation of the CpG islands located within promoters; these patterns define subgroups of GBM which may have important biological and clinical implications. Analysis of nine tumors from patients who had been treated found a significantly high number of mutations. Nearly all of these tumors had loss of function of either 06 MGMT, a gene involved in repair of alkylating changes, or another mismatch repair gene through mutation or methylation or both.

The search for cancer-specific DNA hypermethylation at CpG islands will be expanded. Global histone modifications also should be analyzed relative to levels in embryonic cells and stem cells, which may be informative regarding tumor maturation. Emerging platforms that would allow all patterns of DNA methylation and chromatin structure to be monitored also will be investigated.

GBM Mutation Analysis and New Sequencing - Dr. Richard K. Wilson

Dr. Wilson described the sequencing component of TCGA, which involves targeted resequencing of approximately 1,500 genes in an initial sample of 200 GBMs plus matching normal samples. At the current time, a total of 90 million bases have been sequenced. A total of 454 somatic nonsynonymous mutations in coding sequences have been identified and validated. Ninety-four glioblastoma tumors have been sequenced for an initial 601candidate genes, and mutations have been found in 85 of these tumors. Mutations have been found in 233 of the initial 601 candidate genes.

Significantly mutated genes in GBM included novel mutations in ERBB2, PIK3R1, and NF1. Both EGFR and TP53 had a large number of mutations. Mapping of EGFR mutations in GBM showed differences compared to the location of EGFR mutations in other cancers. In lung adenocarcinoma, mutations occur primarily in the tyrosine kinase domain, whereas most of the EGFR mutations in GBM are found in the extracellular and ligand binding domains. One area of interest for TCGA is the extent to which mutations overlap across different cancer types. The three sequencing centers have participated in a project to examine mutations in lung adenocarcinoma samples. Comparisons of these mutations and those observed in GBM show some overlap that may have implications for several signaling pathways.

New sequencing technologies have been developed and are being evaluated at the genome centers. Using one of these technologies, the entire genome of an AML patient was sequenced and 3.7 million sequence variants relative to the reference genome were found, which is in line with the number of SNPs found in two other individual human genomes. Using this approach, it was possible to discover and validate eight somatic mutations in the patient's genome. The Steering Committee has agreed that three GBM samples will be selected for whole genome sequencing using the new technologies.

The Challenges of Integrative Analysis Technologies - Dr. Charles Perou

Dr. Charles Perou described integrative analysis of TCGA data and analysis of gene expression patterns and micro-RNA (miRNA). Dr. Perou stated that analysis of gene expression patterns has defined four different molecular GBM subtypes which are the: 1) proneural group characterized by high expression of genes involved in neural development and differentiation; 2) normal-like group with changes in nucleotide metabolic processes and neurological system processes; 3) EGFR group which has high expression of EGFR and also upregulation of PDGF alpha; and 4) mesenchymal group with alterations in expression of mesenchymal genes and in genes involved in apoptosis via the NFkB pathway. Analysis of these subtypes in conjunction with clinical data found no survival differences between the groups. Analysis of tumor histology found correlates between age and subtype; proneural-type tumors tended to occur in younger patients. Cellularity and necrosis was lowest in the normal-like group, and necrosis was highest in the mesenchymal group. Analysis of public-domain data on expression patterns in 174 samples found the same expression subtypes using the genes and predictors developed on the TCGA data.

Analysis of miRNA expression patterns found a proneural group similar to that defined by gene expression data and another miRNA group that shared similarities with the mesenchymal group. A third group contained EGFR and mesenchymal subtype GBMs. Analysis of clinical correlates found that the tumors expressing miRNA miR630 in the mesenchymal group had the worst prognosis.

Integration of data across data types is the next challenge. Specific correlations between mutations, gene expression, and molecular subtype have been observed. These analyses have found mutations in the p53, RB, and RTK signaling pathways in most or all GBMs. Information on when and where a pathway is mutated will translate into clinical implications.

TCGA Summary of Progress - Dr. Eric Lander

Dr. Lander informed members that the program has involved

collaboration among at least 250 investigators across 14 different institutions. TCGA is performing well as a mechanism to integrate researchers across different types of institutions and data across different types of analysis platforms. He acknowledged the leadership of the NCI and the NHGRI in developing and implementing the TCGA.

In the discussion, the following points were raised:

- Information gained in the GBM sequencing project should help determine the most optimal platform for full genome sequencing and provide cost information.
- Because most common brain tumors do not have precursors, determining associations of molecular subtypes with progression could be difficult.
- The strict selection criteria for GBMs being analyzed will change in the future when analyses can be done on single molecules with the next generation technologies.
- Analysis of benign brain tumors is currently not part of TCGA, but work done by TCGA would provide the capability to analyze many more types of tumors.
- The existence of GBM mouse models that, to some extent, recapitulate the three molecular subtypes has implications for translational research to develop new therapies.

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XI. UPDATE: INTEGRATIVE CANCER BIOLOGY PROGRAM (ICBP)
DRS. DINAH SINGER, DAN GALLAHAN, JOE W. GRAY, VITO QUARANTA, DOUGLAS LAUFFENBURGER, AND LOURDES ESTRADA

Introductions - Drs. Dinah Singer and Dan Gallahan

Dr. Dinah Singer, Director, DCB, stated that the ICBP was created 4 years ago to bring together cancer biologists, engineers, computational biologists, mathematicians, and physicists to research cancer's complex cell biology. Dr. Daniel Gallahan,

Deputy Director, DCB, indicated that the goals of the ICBP are to: 1) develop an integrative approach to the understanding of cancer through the development of multidisciplinary research teams; 2) create predictive in silico models to aid the understanding and management of the disease; 3) integrate the multidimensionality of large "omic" datasets as well as quantitative and descriptive data; and 4) enrich the community and the developing field though shared resources and educational/outreach efforts. The nine ICBP centers are diverse in their research approaches but share the mission of using computational approaches to find answers to critical questions in cancer biology. Dr. Gallahan introduced the speakers: Drs. Joe W. Gray, Director, Division of Life Sciences, Lawrence Berkeley National Laboratory; Vito Quaranta, Vanderbilt Integrative Cancer Biology Center; Douglas Lauffenburger, Professor of Bioengineering and Chemical Engineering, Massachusetts Institute of Technology; and Lourdes Estrada, Assistant Professor, Vanderbilt-Ingram Cancer Center.

Modeling Molecular Diversity in Cancer - Dr. Joe W. Gray

Dr. Gray reported that his ICBP multidisciplinary team developed experimental and computational models that will allow them to test how genomic data may inform pathophysiology and response to therapeutics. They assembled a collection of 50 breast cancer cell lines that retain important transcriptional and genomic features of primary tumors and have sufficient diversity so that statistical analyses can identify molecular features associated with drug response. Dr. Gray described their work in testing whether a six-gene predictor could predict response to the drug lapatinib within the HER2-positive population. In a randomized Phase III study, the researchers demonstrated that molecular markers could predict response to chemotherapy including lapatinib in HER2 positive patients. The team explored the epidermal growth factor receptor signaling pathway using a pathway logic model and concluded that the PAK1 gene was required for network activation of mitogen-activated protein kinase (MEK)/ERK signaling in luminal cell lines. Another project used Bayesian network analysis to study AKT signaling. The researchers found that AKT pathway inhibitors, such as lapatinib and paclitaxel, showed strong luminal subtype specificity, whereas mitotic apparatus drugs showed basal specificity. P13 kinase pathway mutations were found to be

preferentially located in the luminal subtype, predicting strong responsiveness to AKT pathway inhibitor drugs.

Predictive Mathematical Models of Tumor Growth in Distinct Microenvironments - Dr. Vito Quaranta

Dr. Quaranta explained that taking a biological systems approach to cancer means breaking down complex variables and then reconstructing using mathematics. Three mathematical models are currently being used to describe cancer at the molecular/cellular, cellular, and tissue scales. The goal of these models is to predict the dynamics of tumor growth and progression.

Computer simulations can measure the complex interactions between the cancer cell and its microenvironment and quantitatively predict tumor progression or treatment response. The simulations indicate that mitogen deprivation and space barriers in the microenvironment favor the emergence of aggressive cancer cell clones. This observation supports the hypothesis that the tumor's adaptation to a competitive microenvironment underlies cancer invasion. If personalized data from individual patients were used, the simulations could dramatically improve cancer treatment. Introducing actual patient data into mathematical models remains a challenge, largely dependent on researcher’s success in connecting cancer cell genotype to phenotype.

Regulatory Networks in Cancer Initiation and Progression - Dr. Douglas Lauffenburger

Dr. Lauffenburger noted that models for cell behavior need to factor in the extracellular context (growth factors, cytokines, matrix, drugs); intracellular networks (regulatory circuits); and cell phenotypic responses (death, proliferation, migration) to elucidate how cell behavior arises from both genomic and environmental influences. The researchers studied the impact of mutations on EGFR signaling network dysregulation to help understand why Gefinitib (Iressa), an inhibitor of EGFR signaling, only works on select patients and to identify those most likely to respond to this

drug. Mathematical modeling indicated that "Iressa-sensitive" EGFR mutations had lower receptor-binding affinity for ATP and reduced endocytic internalization rates. These findings may enable extension of Iressa treatment to more patients.

The ICPB team also investigated why certain patients are unresponsive to trastuzumab (Herceptin7), an inhibitor of HER2 signaling. Their mathematical model predicted the effects of HER2 overexpression on cell proliferation and migration. These models hold exciting potential for providing mechanistic explanations for tumor cell behavior and for predicting the effects of mutations or interventions.

Education, Training, and Outreach in Integrated Cancer Biology - Dr. Lourdes Estrada

Dr. Estrada stressed how important educational, training, and outreach efforts have been to the success of ICBP. The ICBP seeks to motivate a new generation of scientists to integrate research approaches from diverse disciplines. He reported that the undergraduate summer program allows young investigators to conduct hands-on experimentation with interdisciplinary teams under the guidance of a faculty mentor. The program also includes faculty lectures, seminars, discussions, and web-conferences. The postdoctoral exchange program allows junior investigators to spend time at another ICBP Center to master and exchange techniques; enables them to carry out analyses that would not be possible in their home laboratory setting; and fosters the cross-fertilization of ideas. Junior investigator meetings have allowed scientists to share current science, form collaborations, and enhance their career development. Numerous ICBP workshops and symposia have resulted in the establishment of collaborations within the ICBP Centers. Dr. Estrada concluded by noting that "integration" of people and expertise is at the core of the ICBP education, training, and outreach component.

In the discussion, the following points were raised:

- In response to a member's question on undergraduate programs in systems biology, it was indicated that M.I.T.

has developed a new biological engineering major and Princeton University has added a quantitative biology field of study. There is a shortage of mathematical biologists in the United States.

- With computational mathematical modeling, it may be feasible to predict the effects of combinatorial drugs by driving cellular models under different contexts and types of matrices or growth factors.

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XII. ADJOURNMENT—DR. ROBERT C. YOUNG

There being no further business, the 40th regular meeting of the Board of Scientific Advisors was adjourned at 11:40 a.m. on Tuesday, 24 June 2008.

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