Board of Scientific Advisors

Meeting Minutes

November 2-3, 2006

Building 31C, Conference Room 10
Bethesda, Maryland

Quick Links

Members

Agenda & Future Meetings

Meeting Minutes

BSA: Page 1

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 35th meeting on Thursday, 2 November 2006, at 8:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Robert C. Young, President, Fox Chase Cancer Center, presided as Chair. The meeting was open to the public from 8:00 a.m. until 5:00 p.m. on 2 November for the NCI Director's report, the NCI Legislative update, an overview of the Foundation for the NIH (FNIH), ongoing and new business, a Nanotechnology Symposium, the annual Request for Applications (RFA) Concepts Review Report, an update on genetic profiling of cancer, consideration of RFA concepts presented by NCI program staff, and a report on the NCI community-based cancer centers pilot program. The meeting was open to the public from 8:00 a.m. on 3 November until adjournment at 12:00 noon for the Cancer Centers Directors' report, a mid-course update on the Centers of Excellence in Cancer Communication Research initiative, reports from the Investigational Drug and Phase III Disease-Specific Steering Committees, and a report on the Genes and Environment Initiative.

Board Members Present:
Dr. Robert C. Young (Chair)
Dr. Paul M. Allen
Dr. Hoda Anton-Culver
Dr. Kirby I. Bland
Dr. Susan J. Curry
Dr. Raymond N. Dubois
Dr. H. Shelton Earp III
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Dr. Patricia A. Ganz
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. William N. Hait
Dr. Leland H. Hartwell
Dr. James R. Heath
Dr. Mary J. Hendrix
Dr. Hedvig Hricak
Dr. Eric Hunter

Board Members Present:
Ms. Paula Kim
Dr. Michael P. Link
Dr. Kathleen H. Mooney
Dr. Richard L. Schilsky
Dr. Robert D. Schreiber
Dr. Margaret Ruth Spitz
Dr. Jean Y. J. Wang
Dr. Jane Weeks
Dr. James K. Willson

Board Members Absent:
Dr. William S. Dalton
Dr. Leroy Hood
Dr. Christopher J. Logothetis
Dr. Lynn McCormick Matrisian
Dr. Edith A. Perez
Dr. Mack Roach III
Dr. Ellen V. Sigal
Dr. Robert A. Weinberg

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

TABLE OF CONTENTS

VIII. Annual RFA Concept Report; Dr. Paulette Gray

IX. Genetic Profiling of Cancer; Dr. Louis Staudt

X. RFA/Cooperative Agreements New Concepts; Presented by NCI Program Staff
Division of Cancer Biology
The Biology of Breast Pre-Malignancy
Lung Cancer and Inflammation

XI. NCI Community-Based Cancer Centers Pilot Program; Dr. John Niederhuber

XII. Cancer Centers Director's Report; Dr. John Mendelsohn

XIII. Centers of Excellence in Cancer Communication Research Initiative: Mid-Course Update; Drs. Robert Croyle, Brad Hesse, Victor J. Strecher, Matthew W. Kreuter, and K. Viswanath

XIV. Investigational Drug and Phase III Disease-Specific Steering Committees; Drs. James Doroshow and Sheila Prindiville

XV. RFA/Cooperative Concept; Presented by NCI Program Staff
Division of Cancer Control and Population Sciences
Genes and Environment Initiative; Drs. Robert Croyle, Teri Manolio, and Amy Subar

XVI. Adjournment; Dr. Robert C. Young

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

Dr. Young called to order the 35th regular meeting of the BSA and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. New members to the Board were introduced, including Drs. Paul M. Allen, Robert L. Kroc Professor of Pathology & Immunology, Washington University School of Medicine; Todd R. Golub, Director, Cancer Program, Broad Institute of Massachusetts Institute of Technology and Harvard University; Leland H. Hartwell, President and Director, Fred Hutchinson Cancer Research Center; Jean Y. J. Wang, Professor and Associate Director, Moores Cancer Center, University of California, San Diego; and James K. Willson, Director, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center. Dr. Young reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. He

called attention to confirmed meeting dates through 2008 and the annual joint board retreat scheduled for 8 January 2007. 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.

top

II. CONSIDERATION OF THE JUNE 29-30, 2006, MEETING MINUTES - Dr. Robert C. Young

Motion: The minutes of the 29-30 June, 2006, meeting were approved unanimously.

top

III. DIRECTOR'S REPORT - Dr. John Niederhuber

Dr. Niederhuber welcomed the new BSA members and expressed appreciation to Drs. Richard Schilsky, Professor of Medicine, University of Chicago, Pritzker School of Medicine, and Hoda Anton-Culver, Professor and Chief, Epidemiology Division, Department of Medicine, University of California, Irvine, for agreeing to extend their terms.

Closing Out Fiscal Year (FY) 2006 Budget. Dr. Niederhuber reviewed the status of various grant mechanisms at the close of FY 2006: 1) the R01 and *R01 (for new investigators) paylines increased to the 12th and 18th percentile, respectively; 2) 15 percent of the competing pool was used for exceptions; 3) Type 5 grants were generally 2.35 percent below the commitment; 4) Special Programs of Research Excellence (SPOREs) were about 6.1 percent below FY 2005; 5) Cancer Centers increased by 3.9 percent above FY 2005; and 6) Training increased by 1 percent above the FY 2005 level. Members were informed that the NCI had experienced a mid-year increase of almost $4 M in taps for utility costs.

FY 2007 Operating Budget Development. Dr. Niederhuber

reminded members that the NCI currently is operating on a continuing resolution and at about 80 percent of the FY 2006 level of $4.79 B pending passage of the FY 2007 appropriations legislation. Factors that will influence the development of an operating budget, including: 1) the decrease of $36.5 M from FY 2006 if the FY 2007 President's Budget is enacted with $4.754 B for the NCI; 2) transfers estimated at $20 M that could be exercised by the Director, NIH, and Secretary, Department of Health and Human Service (DHHS), 3) an increase by $14.5 M in NCI's NIH Roadmap contribution; 4) NCI-wide requirements for mandated salary increases estimated at $7 M and rent/lease/utility increases estimated at $10 M; 5) Trans-NIH FY 2007 initiatives, Genes and the Environment and the Pathways to Independence Career Program, estimated at $7.8 M and $1.8 M, respectively; and 6) the NCI Director's Reserve of $25 M. The FY 2007 appropriations, therefore, would be reduced by approximately $122.6 M at the outset. Members were told that NCI leadership were involved in an intensive examination to identify programs and projects that could be phased out or reduced to produce approximately $175 M in funding to cover the projected shortfall and make approximately $50 M available for new initiatives and expansions. One further consideration is the potential for a further reduction by $4.866 M if Congress applies a 1 percent across-the-board reduction of the discretionary budget.

Dr. Niederhuber briefly reviewed the status of FY 2007 appropriations. He also reviewed several factors that have helped to produce some of the current budgetary stress, such as doubling of the NIH budget and increase by 80 percent of the NCI budget over the 5-year period from 1998 to 2003; expansion of medical facilities and faculties; and essentially flat budgets since FY 2004. He noted that the growth in number of applications continues, with more than 7,000 projected in FY 2007

Members were given a fiscal-year-end summary of NCI FY 2006 allocations and actions compared with previous years: 1) 1,280 competing research project grants (RPGs) were awarded, down from 1,492 in FY 2004; 2) 5,172 RPGs were awarded, up from 5,070 in FY 2004; 3) average cost per competing grant was $324 K, down from $346 K in FY 2003; 4) 7 percent of the competing pool went to RFAs, down from 9 percent in 2004; 5) 5,679 individual investigators were supported, up from 5,636 in FY 2004; and 6) $42.8 M was allocated to the Roadmap Initiative, up from

$16.2 M in FY 2004. The NCI was able to create a pool of about $60 M in FY 2006 to recognize specific projects and opportunities within the portfolio, compared with $108 M in FY 2005.

Roadmap 1.5 Planning Process. Dr. Niederhuber presented an update on the progress in developing and identifying a new cohort of trans-NIH Roadmap initiatives. Via a "common fund," up to $50 M per year of the current Roadmap funding will be allocated for these initiatives. Growth of the "common fund" in future years will not exceed the real growth of the NIH.

Ongoing Scientific Initiatives

The Biomarkers Consortium. Members were reminded that the Biomarkers Consortium is an outgrowth at the NIH level of the Oncology Biomarkers Qualification Initiative (OBQI). The OBQI was initiated in February 2006 as an NCI collaboration with the Food and Drug Administration (FDA) and the Center for Medicare and Medicaid Services (CMS) to develop biomarker technologies, develop guidance for the use of biomarkers, and make decisions about reimbursement for new or existing cancer treatment regimens based on biomarker-guided knowledge. The Consortium was announced on October 5 as a public-private partnership, which includes representatives from the NIH, FDA, CMS, Foundation of the National Institutes of Health (FNIH), and the pharmaceutical industry. The two initial projects, which will be conducted by the NCI, are focused on imaging-based biomarkers: 1) fluorodeoxyglucose (FDG)-positron emission tomography (PET) for prediction of tumor response and patient survival during treatment of lymphoma; and 2) Phase II study of FDG-PET/ computed tomography (CT) as a predictive marker of tumor response and patient outcome, with prospective validation in non-small-cell lung cancer.

The Cancer Genome Atlas Project (TCGA). In collaboration with the National Human Genome Research Institute (NHGRI), TCGA was launched in December 2005 as a 3-year, $100 M pilot project. On 13 September, lung cancer, glioblastoma, and ovarian cancer were announced as the first three tumor types to be studied. Dr. Niederhuber noted that an initiative entitled ***Therapeutically Applicable Research to Generate Effective Treatments (TARGET)*** represents an effort to move the public/private partnership approach into the pediatric arena.

Bringing Science to Patients. Dr. Niederhuber explained that conversations with patients and their families, academic scientists, and industry have led to the characterization of cancer research needs in a continuum of science that comprises three areas: chemical, biological, and translational. In the chemical space, the focus should be on a molecular targets development program, connectivity mapping, development of a complete chemical library, and development of a chemistry resource for reengineering molecules. To address biologic research needs, the effort should focus on signal pathways that become abnormal, tissue microenvironment, angiogenesis, cancer-activated fibroblasts, and cancer stem cell biology and the stem cell "niche." In regard to the later, a Stem Cell Mini Retreat was sponsored by the NCI on 1 November 2006 in which 21 intramural and extramural scientists presented their research on the breadth of the science, from yeast genetics to animal models. A need was identified for unified definitions, characterization of cells, markers, assays, and the role of the microenvironment. Dr. Niederhuber noted that the meeting results suggest that the NIH Clinical Center could be a resource for helping to influence clinical trial design, especially the very earliest phase trials. In the translational space, research efforts should focus on animal models, first-in-human studies where targets and biomarkers inform drug development, and molecular imaging. Here again, the Clinical Center can be a resource for the entire community. As an example of this, a pilot program is bringing extramural investigators to the Clinical Center for work in advanced medullary thyroid cancer in children. Another example is the recent meeting on campus to focus on IL-15 development. Resources are being devoted to the effort to develop IL-15 in the intramural program; production is underway for first-in-human studies in the Clinical Center.

Members were reminded of other scientific initiatives that are being implemented on a trans-NCI basis and extend into other Institutes and the extramural research community, such as computational biology, cancer stem cells, the lung cancer program, population science research, the Breast Cancer Stamp pre-malignancy program, and the Trans-Institute Angiogenesis Research Program (TARP).

In discussion, the following point was made:

- In the effort to identify $175 M to compensate for the projected shortfall in FY 2007 and provide monies for new opportunities, a rigorous process has been implemented across the NCI, which includes reviewing infrastructure, each project or program, the research project grants (RPG) portfolio, and special initiatives. The NCAB will be given a report at the end of the process.

top

IV. NCI/CONGRESSIONAL RELATIONS - Ms. Susan Erickson

Ms. Susan Erickson, Director, Office of Policy Analysis and Response (OPAR), reviewed the status of NCI appropriations. Members were told that, in the House bill, which was passed by Committee on 13 June included language that commended the NCI in the areas of the American-Russian Cancer Alliance, Cancer Centers program, TCGA, and community cancer centers. The NCI was encouraged to include gynecologic cancer in the TCGA pilots, coordinate the federal effort in lung cancer, add a minority institution to the Cancer Centers program, and fund the SPOREs at the FY 2004 level. In addition, all Institutes were asked to tie strategic plans to specific programs in their Congressional justification documents for the benefit of new committee staff. The Senate bill language contained NCI commendations in the areas of Cancer Centers, TCGA, prostate cancer, and antimicrobial resistance research, encouragement in a number of areas, and specific recommendations, e.g., the development of a strategic plan in the area of melanoma.

Ms. Erickson brought the Board up to date on the status and provisions of the NIH Reform Act (HR 6164). She noted that key provisions of the bill which passed the House were: 1) authorization of overall funding levels for the NIH with a 5 percent increase for FY 2007; 2) establishment of the Common Fund as a permanent funding mechanism to be administered by the Director, NIH; 3) establishment of a Division of Program Coordination, Planning and Strategic Initiatives; and 4) a periodic organizational review. Members were told that the recently established NIH Office of Program Analysis and Strategic Initiatives (OPASI)

satisfies the third provision.

In discussion, the following point were made:

- The Common Fund should be structured in such a way to ensure that it is scientifically and not resource driven.
- Members queried whether the Institute or Center (IC) allocations to the Common Fund can be increased without the passage of the NIH Reauthorization Bill.

top

V. OVERVIEW: NIH FOUNDATION - Ms. Amy McGuire

Ms. Amy McGuire, Executive Director, Foundation of the National Institutes of Health (FNIH), presented an overview of the Foundation's mission, organization, topical focuses, revenue sources, operational characteristics, and the status of current public-private partnerships. FNIH was created by Congress to support the mission of the NIH and its ICs by working with partners from all sectors. In the 10 years since authorization by Congress as a 501C3 nonprofit, the FNIH has been recognized as successful in facilitating public-private partnerships to support biomedical research. Foundation partnerships have focused on topics such as global health, genomics, and biomarker research. Examples of FNIH-mentored activities are the Alzheimer's Disease Neuro-imaging and Osteoarthritis Initiatives, the Edmond J. Saffra Family Lodge, which was opened in 2005 to provide free lodging for families of adult patients at the Clinical Center. Program and FNIH agency revenue has risen over the past 10 years to a projected $90 M in 2006. A $200 M grant from the Bill and Melinda Gates Foundation for the Grand Challenges in Global Health initiative is being factored in over a period of years.

Ms. McGuire noted that the value added of FNIH to partnerships include: 1) acting as a neutral convener in bringing the partnerships together; 2) ensuring the correct players are selected for successful program design and implementation; 3) making it possible for industry and donors to participate in concept development and other activities; 4) creating innovative and flexible funding models; and 5) ensuring that private funds received for partnership are spent

appropriately and in alignment with donors' initial intentions. Keys to partnership success include: 1) leadership by decisionmakers; 2) public and private sector involvement; 3) input from all sectors; and 4) communication between the partners and with the stakeholders. Currently, NCI public-private partnerships have led to the funding of educational initiatives and fellowships (such as the Sallie Rosen Kaplan fellowship for Women Scientists in Cancer Research); research initiatives such as the Human Papilloma Virus Clinical Trial; and special events. NCI public-private partnerships in most active development are the Biomarkers Consortium, FDG-PET Lymphoma and Lung Initiatives, and the Childhood Cancer (TARGET) Initiative. Others in early development are the Cancer Expert Corps, Cancer Information Service (CIS) Initiative, and the Tobacco Quitlines Research Database. Ms. McGuire concluded the overview with a request for help from BSA members in identifying potential projects the Foundation could facilitate and by sharing the names of possible partners, which would include anyone interested in advancing medical research to support the NIH and its mission. In recognition of its 10th anniversary, the Foundation has created an entity called the Discovery Society to comprise individuals who make annual unrestricted gifts of $1,000 or more. Annual gatherings are planned to bring together Society members for recognition of singular achievements and contributions.

In discussion, the following points were made:

- Donor involvement in projects initiated and funded through the Foundation varies from none to supplemental. Projects can come together in different ways and on a case-by-case basis. Any FNIH project that involves the NCI with the private sector is reviewed by NCI's general counsel to ensure the absence of undue influence. All activities undergo peer review.

- The FNIH is supported by a fee in the 3-7 percent range; about 96 cents of every dollar received goes into research or projects. The FNIH is attractive to donors because of lower fees; the opportunity for close and appropriate interactions with the NIH; continuity of relationships that are not possible with the NIH itself because of inevitable changes in leadership; worldwide reputation of the NIH and NCI as leaders in biomedical research; the availability of a rigorous peer review; and the flexibility that enables the FNIH to

negotiate with institutions for the best combined overhead rate.

top

VI. ONGOING AND NEW BUSINESS - Drs. Robert C. Young and Malcom Smith

Dr. Young explained that the BSA request for information about the FNIH evolved from the request received by the BSA to create an oversight subcommittee for the Childhood Cancer TARGET Initiative, a collaborative project of the NCI and FNIH. He introduced Dr. Malcolm Smith, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), to introduce and describe the initiative.

BSA Subcommittee: The Childhood Cancer (TARGET) Initative

Dr. Smith, Program Director, Clinical Investigations Branch, Division of Cancer Treatment and Diagnosis, and Subcommittee Executive Secretary, informed members that a concerted effort is required so that children can benefit as rapidly as possible from the molecular revolution in cancer therapy, i.e., improvements in pediatric patient outcome have slowed; current treatment approaches have reached maximum tolerable intensity; validated therapeutic targets for pediatric cancers are scarce; and the financial incentive to spur pharmaceutical investment is lacking. In the current funding environment, a public-private partnership was deemed necessary if a major new project were to be started. The TARGET initiative builds on recommendations from a meeting sponsored in May 2005 by the NCI and American Cancer Society (ACS) and capitalizes on the NCI/NHGRI experience in establishing TCGA.

Three areas for TARGET initiative research focus are: 1) high-throughput, array-based technologies to comprehensively characterize genomic and transcriptomic profiles; 2) gene resequencing to identify genes that are consistently altered in specific childhood cancers; and 3) high-throughput RNA interference (RNAi) to identify and validate therapeutic targets.

Acute lymphoblastic leukemia (ALL) has been chosen as the pilot TARGET project in a collaborative effort by the Children's Oncology Group (COG), St. Jude Children's Research Hospital, and the NCI. Current activity on the project is the analysis of high-resolution genomic and transcriptomic profiles for about 240 leukemia cases. Upon completion of this analysis, approximately 200 genes will be selected for resequencing. Experience gained from the pilot project will inform similar efforts for the overall initiative.

General principles guiding implementation of this initiative are: 1) move quickly to begin TARGET research projects; 2) leverage with ongoing NCI activities, including TCGA, COG, and Strategic Partnering to Evaluate Cancer Signatures (SPECS); 3) leverage with ongoing industry and research activities through "in kind" support; and 4) receive advice and oversight from the BSA ad hoc Subcommittee, which includes, in addition to BSA members, ad hoc scientific members and advocacy representatives, FNIH Board members, FDA representatives, and FNIH and NCI staff. TARGET Initiative awards are anticipated in four research areas: tumor/ sample component with associated disease expertise, genomic and transcriptomic characterization, DNA sequencing, and RNAi and small molecule screens. It is anticipated that awards generally will be cooperative agreements or contracts and that the data-sharing policy will be similar to that used for TCGA. Dr. Smith noted that the FNIH is committing approximately $9 M over 3-years towards focusing on two cancer types.

In summary, the TARGET initiative seeks to exploit opportunities for rapid advances in target identification and validation for childhood cancers through coordinated research efforts applying state-of-the-art technologies. The goal is to achieve major advances in target identification for two or more childhood cancers within 2 years of project initiation.

In discussion, the following points were made:

- In addition to the study of bulk leukemic cells, biological analysis or construction of new models of ALL stem cells should be considered. Data on the heterogeneity that can be introduced during expansion could be useful for target selection.

- There's the potential that TCGA and TARGET could eventually merge as the two projects go forward and that both pediatric and adult cancer data would be included in the database.

- Criteria for choosing cancer types for the pilot are availability of tumor and normal tissue and the prognosis of the particular population with a focus on those at highest risk. Benchmarks for measuring progress in 2 years are the successful acquisition of data about the genes that are consistently mutated and initial consideration of some of the therapeutic implications.

- There will be a solicitation for the two additional cancers to be studied following the pilot project, through either an RFA or administrative supplements to existing awards.

top

VII. NANOTECHNOLOGY SYMPOSIUM - Drs. Anna Barker, Gregory Downing, Jonathan W. Simons, Joseph M. DeSimone, Chad A. Mirkin, David Cheresh, and Michael E. Phelps

Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnerships, NCI, informed members that the speakers would present information on advances in nanotechnology supported by the NCI. She noted that the Nanotechnology Initiative brings together molecular diagnostics, target therapies, and imaging technologies, and intersects with the fields of proteomics, genomics, physics, chemistry, mathematics, and other related fields. Approximately 200 people attended the first meeting of investigators involved in this initiative.

Dr. Downing, Director, Office of Technology and Industrial Relations, NCI, introduced the speakers and informed members that in 2003, a planning process to develop this initiative was started, based on two existing programs, the Fundamental Unconventional Innovations Program, and the Fundamental Biosensors for Medical Technologies Program. In 2005, RFAs for training initiatives using the F32/F33 mechanism, R01-based platform development, and a U54 mechanism for the Centers for

Excellence in Cancer Nanotechnology (CECN) were initiated.

In the past year, Dr. Downing informed members that an infrastructure had been developed that includes the Nano-Characterization Laboratory based in Frederick, MD, which provides an interface for product development. A number of collaborations with the intramural program and international collaborators have been established. An annual reporting process based on performance milestones for the CECNs and individual investigator laboratories has been established, and site visits to all of the CECNs and many of the individual investigators have been completed. Additionally, a team involved in intellectual property management to facilitate the exchange of nano-materials across different laboratories has been established, a number of training programs developed, a number of standards established in partnership with the FDA and the National Institutes of Standards and Technology (NIST), and a number of important tools for sharing and disseminating information from the laboratories will be available next month through partnerships with the Cancer Bioinformatics Grid (caBIG^{TM}).

Nano-Molding of Organic Delivery Vehicles for Probing and Treating Biological Systems. Dr. Jonathan W. Simons, Georgia Institute of Technology, explained that engineering techniques used in the electronics industry to create computer chips can be used to make organic-based particles upon which can be loaded a wide range of substance for applications in nano-medicine. Photolithography, which has been used to create smaller and smaller computer chips and transistors, can be adapted for use with organic carriers. The Particle Replication in Non-Wetting Templates (PRINT) technique has been used to create molds for fabrication of organic particles. PRINT will allow the clinician to define the particle cargo as well as the release mechanism and release profile necessary for treatment. Particles can be loaded to conform to desired dosage form, administration route, and biodistribution profile. The mesh density of the particle can be varied to control diffusion of the cargo, for example, doxorubicin, out of the particle. A tight mesh density results in slow or no release, and variation of mesh density allows precise control of the release profile of the doxorubicin. So-called “Trojan horse particles” prevent release of the cargo until the particle reaches the cell of interest.

A wide range of cargo types have been loaded onto these particles, including plasmid DNA, antisense oligonucleotides, and virus particles. Transport by particles has been shown to be an effective technique for delivering antisense oligonucleotides and silencing RNA (siRNA) to cells. The particles also can be coated with avidin to allow conjugation of a wide range of biotinylated reagents directly on the particle; this can permit multiplexed delivery of target anticancer agents. The particles physical and mechanical properties can be readily manipulated. The ability to create particles in a range of precise, defined sizes and shapes allows studies of biodistribution as a function of size. PRINT makes rigid particles, but poragens can be incorporated into the particles, resulting in mechanical proprieties similar to those of red blood cells. Imaging agents such as magnesium and magnitype for magnetic resonance imaging (MRI) also can be attached to the particles. Collaborations to develop such particles have begun with Dr. Phelps and colleagues at the California Institute of Technology and the UCLA.

The Nanoparticle-Based Bio-Barcode Assay: A New Paradigm in Molecular Diagnostics and Cancer Research. Dr. Chad A. Mirkin, Northwestern University, informed members that nanotechnology is being used to develop PCR-type assays with greater sensitivity and selectivity and that also can be applied to protein detection. Nano-materials have properties that provide major advantages for technology development. When nanoparticles are chemically modified with oligonucleotides and proteins, the resulting structures exhibit highly cooperative binding, which translates into very high selectivity in a diagnostic setting. These structures also have catalytic properties that allow amplification of signal, resulting in very high sensitivity. If the compositions of these structures are chosen properly, they are environmentally benign. This technology also allows for use of many different types of readout mechanism. Because nanoparticles are larger compared to their molecular counterparts, they provide a scaffold onto which can be added different types of molecules needed for various diagnostic applications. Gold nanoparticle probes in particular have been used in the development of diagnostic tools during the last decade. A number of these systems currently are being commercialized and should be on the market within the next few years.

A system currently in development for detection is based on

microarray formats. Oligonucelotides are used to probe a particular solution for a target and then immobilize the target on the microarray. A nanoparticle with an oligonucleotide complementary to another portion of the target binds to form a sandwich structure. This interaction results in a signal, but the catalytic properties of these types of structures can be used to increase the signal by a factor of 105. This is a nonenzymatic system that can compete with PCR in many detection settings and is simpler and has more multiplexing capabilities than traditional PCR. Nanoparticle probes also have different properties than fluorophor probes, allowing better detection. Molecular fluorophors have very broad transitions compared to nanoparticle-based systems, which can be a diagnostic disadvantage; sharper transitions permit greater selectivity. The sharp transition of nanoparticles-based probes allows selective detection of targets at 100 attomolar (100 x 10-18 molar target concentration). This system is being commercialized under the name Verigene System.

This technology may be useful for development of a similar system for detection of proteins. Commonly used protein diction assays such as ELISAs have a limit in the low picomolar to high femtomolar target concentration range. This system provides detection at up to six orders of magnitude more sensitivity than a standard ELISA; single cell protein expression experiments may be possible. The technology will allow evaluation of new biomarkers that currently cannot be used because of the low sensitivity of conventional detection tools.

The Bio-Barcode assay may be useful for prostate-specific antigen (PSA) screening, especially to detect recurrence, because when the prostate is removed, PSA drops to levels below the sensitivity limit of current detection technologies; in a commercial setting, this technology can detect PSA at 30 attomolar. The technology also allows for multiplexing, which will permit simultaneous detection of a number of different proteins in the same sample. Two clinical trials are underway using the Bio-Barcode assay to detect diagnostic markers of ovarian and prostate cancer present at very low levels.

Selective Ablation of Metastatic Disease by Nanoparticle-Targeted Drug Delivery to the Neovasculature. Dr. David Cheresh, University of California at San Diego, explained that tumor endothelium and neovascular tissue represent important

chemotherapeutic targets. Tumors develop in response to an angiogenic stimulus that recruits blood vessel to produce both growth at the primary site and provide a conduit for metastatic tumor cells to travel to other sites. Attacking the tumor blood supply is a useful strategy, because tumor cells metastasize by entering the bloodstream.

Compared to normal blood vessels, endothelial cells of tumor blood vessels have high levels of the integrin ___3 which is a good marker for the invasive process of tumor growth. The growth inhibitor vitaxin, a humanized antibody to ___3, has shown promise for increasing survival from some cancers, particularly melanoma. To deliver vitaxin directly to the tumor neovasculature, lipid-based nanoparticles with a linker group bound to ___3 targeting ligands were designed. Delivery of the drug directly to the tumor vasculature could impart a significant antitumor effect while preventing systemic toxicity.

Nanoparticle delivery systems also may be useful for delivering smaller, yet still effective chemotherapy drugs. Preliminary experiments using a pancreatic cancer model involving both primary pancreatic cancer and metastatic cancer showed that delivery of doxorubicin using the ???3 targeting nanoparticle had a modest, yet significant impact on the primary tumor and a very significant impact on metastatic disease. The apoptotic effect of doxorubicin on the vasculature ultimately eliminates the tumor by producing a second wave of apoptosis attributable to the dramatic lowering of oxygen and reduction of nutrient supplies.

Targeting of chemotherapeutics using nanoparticles has promise for approaches, including the targeting of therapies to circulating cancer stem cells, or identifying signatures of specific metastatic disease sites and delivering particles to these sites. The particles could deliver RNAi to suppress oncogene expression, or pro-apoptotic genes, as well as chemotherapeutics.

PET Imaging and Use of Microfluidics for Rapid Synthesis of Radiolabeled Molecular Imaging Probes. Dr. Michael E. Phelps, University of California at Los Angeles (UCLA) School of Medicine, began with the idea that imaging biomarkers and surrogate markers should provide a number of direct measures, such as the biology of the disease and the impact of a drug on the disease. Such markers should enable investigators and clinicians to

stratify patients into treatment responders and nonresponders as determined by biological response; measure drug interaction with a given target and other systems throughout the body; perform pharmacokinetic and pharmacodynamic analyses using labeled drugs and drug analogs; and measure drug targets with molecular probes and segregate patients by whether or not they have the drug target. Ultimately, molecular diagnosis and drug treatment should be packaged together to provide the right drug for the right patient.

PET is a technique used to make quantitative measures of a labeled molecule's concentration over time. PET can be used to measure metabolic rates, determine KeB Vmax ratios of a ligand for a receptor in patients, measure enzyme activity, and analyze DNA replication. The sensitivity of PET is high. The concentrations of PET labels and the tracers themselves are considered generally safe and effective by the FDA. Quantitative assays performed using PET are based on well-established cancer biology and biochemistry. FDG-PET has been used to diagnose, stage, detect recurrence, and measure therapeutic response; FDG-PET is 9 to 43 percent more accurate than computed tomography or magnetic resonance imaging. The ability to quickly assess response, or lack thereof, to a therapeutic means the patient will receive the appropriate treatment more quickly.

Integrated microfluidics chips are in development for synthesis and labeling of PET biomarkers and to measure their membrane transport, biochemical reaction rates (such as phosphorylation), and affinity for a protein target. The goal is to use micro- to nanoliter volumes and digital control of physical and chemical parameters to simplify production procedures in PC-based devices. Chips made of PDMS (silicone) have been used to produce F-18 FDG and to synthesize F-18 FLT. Experiments also are underway to produce alternative sources of inert materials suitable for performing organic chemistry on a chip. An integrated circuit-based total device for building labeled molecules, such as biomarkers, nanoparticles, and drugs also is in production, which should reduce the cost of materials substantially. The goal of this work is to provide PET radiopharmacies with chips that will allow each facility to synthesize the compounds it needs and to exponentially enlarge the capability to use these labeled biomarkers in pharmaceutical research and clinical practice.

In discussion, the following points were made:

- Nanoparticle technology appears to present promising uses, but translational issues must be considered to effectively use this technology for diagnosis in a clinical setting.

- A significant hurdle to protein-based diagnostics is the availability of useful antibodies. During the Roadmap 1.5 discussions, it was suggested that a library of antibodies to all proteins and all variations of those proteins be created as an enabling infrastructure for the scientific community.

- Nanoparticles could potentially be used to clear or inhibit cytotoxic or cancer-promoting molecules.

top

VIII. ANNUAL RFA CONCEPT REPORT - Dr. Paulette S. Gray

Dr. Gray presented the annual RFA concepts report. She reminded members that the report includes RFA and RFP concepts that have been reviewed by the Board since its establishment in 1996. Information is reported initially by the date the concept was presented to the Board and by the Division in which the concept originated. As requested by the Board, a history of concept re-issuances, which are brought to the Board for concurrence, were now included. Dr. Gray briefly explained how the report information was organized and the rationale or impetus for including certain categories. Members were invited to submit ideas for additional information to include or clarification of existing information.

In discussion, the following points were made:

- If the quality of applications received in response to an RFA is not acceptable, the funds set aside for that particular RFA revert to the RPG pool.

- When the decision has been made to fund an RFA, a funding plan is developed and presented for EC approval; if a particularly attractive group of proposals are received, a case can be made for requesting additional funding.

top

IX. GENETIC PROFILING OF CANCER - Dr. Louis Staudt

Dr. Louis Staudt, Head, Molecular Biology of Lymphoid Malignancies Section, Center for Cancer Research (CCR), informed members that gene expression profiling is a platform that currently is available for obtaining high-content molecular information from tumors, such as breast and the diversity of human lymphomas. Dr. Staudt told members pathologists over the years have classified and sub-classified human lymphomas as follicular, mantle cell, Hodgkin, diffuse large B cell, primary mediastinal B cell, and Burkitt. This diagnosis influences treatment choice. Some are curable with various chemotherapy and radiation regimens, and some are responsive to symptomatic chemotherapy interventions, which may have an impact on overall survival but have not been shown to mediate a cure.

Board members were reminded that, in 2000, the NCI established a cooperative group, the Lymphoma/Leukemia Molecular Profiling Project (LLMPP). The goals were to establish a molecular classification of human lymphoid malignancies and define molecular correlates of clinical parameters that were useful in prognosis and the choice of optimal therapy. Collaborators with the NCI include experts in lymphoma in academic institutions and hospitals nation- and worldwide, as well as the Southwest Oncology Group (SWOG). Over the years, lymphoma biopsies have been saved and frozen so they are available now for profiling by gene expression.

Dr. Staudt described various studies in his laboratory:

1) Improving the Accuracy and Reproducibility of Diagnosis Using Gene Expression Profiling - The study compared the accuracy of the molecular predictor and current means of pathological diagnoses in differentiating Burkitt lymphoma from all subgroups of diffuse large B cell lymphoma (DLBCL). Conclusions from the work were that: 1) Burkitt lymphoma has a distinct molecular profile that can reliably distinguish it from all forms of DLBCL; 2) current pathological methods for the diagnosis

of Burkitt lymphoma disagree with the molecular diagnosis of Burkitt lymphoma in 17 percent of cases; and 3) the distinction between Burkitt lymphoma and DLBCL is critical because of significant differences in treatment. Molecular diagnosis of Burkitt lymphoma, therefore, will improve patient outcome.

2) Gene Expression Profiling To Clarify the Diagnosis of Problematic Cases. In another study, gene expression profiling was applied to clarify the diagnosis of problematic cases of lymphoma with mantle cell lymphoma (MCL) morphology but without the hallmark translocation of the cyclin D1 gene (i.e., cyclin D1-negative MCL) as specified in World Health Organization (WHO) guidelines. Conclusions were that diffuse large B cell lymphoma can be thought of as an amalgam of at least three molecularly distinct diseases with differences in both gene expression and clinical outcomes. Dr. Staudt noted that his laboratory has been working to show that a signaling pathway, the NF kappa B pathway, is differentially utilized in these lymphomas. They have shown that a small molecule inhibitor of the I kappa B kinase that targets the NF kappa B pathway will kill in a dose-dependent fashion the ABC type of lymphoma cell lines but not the GCB cell lines. The hope is that, when various pharmaceutical companies release the NF kappa B inhibitors they have developed, a clinical trial can be conducted to determine whether diffuse lymphomas of different types would respond differentially. The public health significance of these findings relates to the fact that cases of diffuse large B cell lymphoma constitute 40 percent of the non-Hodgkin lymphomas, with about 23,000 new diagnoses annually, a cure rate of about 40 percent, and about 10,000 deaths per year.

3) Molecular Predictors of Outcome in Cancer Using Gene Expression Profiling - A study develop a survival prediction score based on the gene expression profile of the diagnostic biopsy. He noted that within a current diagnostic category, gene expression profiling can identify: 1) heterogeneity in the cell of origin; 2) heterogeneity in oncogenic pathways; and 3) heterogeneity in common cellular functions such as proliferation, survival, and cell-cell interactions. This heterogeneity is believed to be present in the tumor at the time of diagnosis. In both follicular lymphoma and diffuse lymphoma, these studies have shown that the infiltrating cells are a major predictor of outcome.

4) Routine Molecular Diagnosis of Cancer in Clinical Oncology: Development of a Lymphoma Diagnostic Microarray. In an effort to deliver these diagnoses to cancer patients, scientists in the Metabolism Branch, LLMPP, and Affymetrix collaborated to develop a lymphoma diagnostic microarray. On a microarray of about 2,600 human genes, they showed they were able to make a molecular diagnosis, that is, identify differentially expressed genes in about 500 specimens of different types of lymphomas, including benign conditions. This study is being expanded through the NCI-sponsored SPECS with the goal of implementing a gene expression-based molecular diagnosis of lymphoma in routine clinical practice. In the first phase, a custom diagnostic microarray will be designed. In the second phase, data will be generated for FDA approval.

5) Evolving Molecular Diagnosis To Match Changes in Cancer Treatment. Dr. Staudt briefly described how an iterative molecular diagnosis cycle can be used to subdivide patients in a clinical trial to match changes in cancer treatment. He noted that gene expression profiling analysis has been incorporated into the Cancer and Leukemia Group B (CALGB) Phase III randomized clinical trial of CHOP-Rituximab versus dose-adjusted EPOCH-Rituximab in untreated DLBCL, which opened for accrual in May 2005.

In summary, Dr. Staudt expressed the view that gene expression profiling, if it could be delivered to all cancer patients, would be one way to make diagnoses reproducible and quantitative, clarify the edges of diagnoses that are currently made wrong, and ensure that patients are getting optimal therapy.

In discussion, the following point was made:

- The possibility of making a larger scale, full diagnostic array available, as opposed to reducing the feature set to focused arrays, should be considered.

top

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

Division of Cancer Biology (DCB)

The Biology of Breast Pre-Malignancy

Dr. Dinah Singer, Director, DCB, informed members that the NCI Breast Pre-Malignancy Program will be funded from the surcharge on the special issue postage stamp authorized by Congress in the 1997 Stamp-out Breast Cancer Stamp Act and recently reauthorized through 2007. Seventy percent of the donated funds are allocated to the NCI and 30 percent to the Department of Defense (DoD) Breast Cancer Research Program. As of FY 2006, the NCI has received a total of $35.2 M for support of breast cancer research. Until now, the funds have supported two major programs: Insight Awards to Stamp Out Breast Cancer (44 R21 grants for high-risk research) and the Breast Cancer Research Stamp Act Awards (R01 proposals focused exclusively on breast cancer but outside the pay line). For FY 2007, the NCI has $8.3 M from the fund to support additional research, and breast pre-malignancy research was identified by the EC and Divisions as the target area for use of the new funds. A Trans-NCI Steering Committee was formed to provide oversight and integration to the Program. In addition to the biology of breast pre-malignancy, the components are: molecular epidemiology and mammographic density; evaluation of decision-making approaches used by women recruited to chemoprevention trials for breast cancer; evaluation strategies to improve accuracy of mammography interpretation; MRI-guided therapy with targeted SPIO carbon nanostructure; and isolation, propagation, characterization, and imaging of breast cancer stem cells to improve early diagnosis and therapy of breast cancer. Funding for this effort will come entirely out of the earmarked Breast Cancer Stamp Act Fund.

Dr. Cheryl Marks, Associate Director, DCB, informed members that the intent of the RFA concept entitled “The Biology of Breast Pre-Malignancy” is to assemble multidisciplinary research teams to characterize the genetic, molecular, cellular, or functional biology of pre-malignant states in human breast cancer, in contrast to high-risk normal breast tissue and the earliest identifiable breast cancer lesions. Dr. Marks stated that the project will take advantage of existing and available research resources, including: 1) large collections of clinically annotated breast tissues from normal, high-

risk normal, and sporadic cases; 2) large cohorts of breast cancer families and controls; 3) substantial data about pre-malignant lesions from a variety of valid animal models; 4) new tools for analysis of human specimens; and 5) a highly motivated research community. Possible research topics include, but are not limited to: characterizing the differences among the various types of breast tissue; defining the functions of epithelial and stromal cell types; isolating stem cells and defining their role as cells of origin; using advanced technologies to distinguish pre-malignancies with the ability to progress; applying functional or other imaging approaches to distinguish normal, high-risk normal, and pre-malignancies; and identifying metabolic or physiologic or structural distinctions among histologically defined pre-malignancies. Public sharing of resources, technologies, and data will be required, the latter through caBIGTM.

Estimated first year set aside from the Breast Cancer Stamp Fund is $4.5 M for two or three R0l grants.

In discussion, the following points were raised:

- The scope of the program as described may be too broad to address the key issue, what happens during pre-malignancy that might predict malignant transformation and dissemination of the cancer? The program would be strengthened by a tighter focus.

- The RFA should include the requirement for investigators to identify sources of well-defined, well characterized tissue that can be accessed and should emphasize the multi-investigator, multi- disciplinary nature of the project. Additionally, the RFA should include a list of known NCI-supported tissue resources to stimulate participation by outside collaborators. Applicants should have the flexibility to propose research that calls merely for blood and DNA specimens, not access to large tissue banks.

Motion: A motion to approve the RFA entitled “The Biology of Breast Pre-Malignancy” was unanimously approve.

Lung Cancer and Inflammation (RFA)

As background for this concept, Dr. Singer reminded members that trans-Divisional Integration and Implementation (I2) teams had been formed to advise the NCI EC on trans-NCI scientific opportunities in the areas of lung cancer, bioinformatics, imaging, and health disparities. Major opportunities in the area of lung cancer were seen to be: early detection and treatment, novel targeted therapies based on close coordination with ongoing or planned cancer biology initiatives, and more effective tobacco control to reduce the risk of lung cancer. As recommended by the Lung I2 Team, a Strategic Plan for Lung Cancer was established and a search was initiated for a senior Scientific Leader. Components of the Program that are currently being implemented are: the Lung Cancer and Inflammation RFA; supplements to Cancer Intervention and Surveillance Modeling Network (CISNET) to improve understanding of the impact of cancer control interventions; supplemental funding of National Lung Screening Trial (NLST) tissue collection, processing, and database; and collaboration with the FDA and CMS on molecular targets—a Critical Path initiative. Other current projects that are being done under the aegis of the Lung Cancer Program are the Phase 0/1 trial targeting DNA methylation, the FNIH Biomarkers Consortium, and TCGA.

Dr. R. Allan Mufson, Chief, Cancer Immunology and Hematology Branch, DCB, informed members that the proposed RFA is intended to stimulate research that will promote a better understanding of the biological mechanisms underlying the development of lung cancer in non-smokers. Dr. Mufson noted that this research would aid in identifying targets for prevention and treatment of lung cancer as well as markers for early detection. Existing data suggest strong links between chronic inflammatory disease in the lung and the subsequent development of lung tumors. These linkages include: 1) the correlation of lung cancer in non-smokers with pulmonary inflammation such as that associated with chronic obstructive pulmonary disease; 2) the finding that mouse models of pulmonary inflammation show a progression from granulomatous lesions to adeno and squamous cell carcinoma in the lung; and 3) the finding that the lung microenvironment is altered by pulmonary inflammation. Moreover, emerging lines of research suggest that both normal tissue stem cells, putative tumor stem cells, and their microenvironmental niches may be important targets for inflammatory molecules in the development of lung cancer. Emerging opportunities to facilitate lung cancer and

inflammation research include the availability of cycloxygenase knock-out mice, groups of markers for tumor stem cells, developments in in vivo imaging technologies, and manipulable genetically engineered mouse models of lung cancer.

Estimated cost for the 5-year project period is $10 M, with a first year set-aside of $2 M for the funding of four or five R01 grants.

In discussion, the following points were raised:

- Because lung cancer is one of the top three mortality solid tumors, the research proposed to address the profile of correlates of carcinogenesis from an environmental or exposure standpoint is vital.
- In addition to targets for treatment and prevention, the focus should be broadened to include novel targets for inhibition of progression or metastases. A molecular epidemiologic approach also should be considered as responsive to the proposed RFA.
- Because emphysema, a chronic inflammatory disease, is the second most important risk factor after cigarette smoking, answers could come from studying smokers as well as non-smokers.
- Because of the inflammatory element in lung cancer associated with occupational groups like silica-exposed workers, co-funding could be sought from another Institute such as the National Institute of Environmental Health Sciences (NIEHS).

Motion: A motion to approve the RFA entitled “Lung Cancer and Inflammation” was approved unanimously.

top

XI. NCI COMMUNITY-BASED CANCER CENTERS PILOT PROGRAM — Dr. John Niederhuber

Dr. Niederhuber provided an update of the NCI Community-based Cancer Centers Pilot Program (NCCCP). He noted that the 61 NCI-

designated cancer centers make significant contributions to the understanding, prevention, and treatment of cancer. The realities of cancer care in the United States are that more than 85 percent of individuals with cancer receive care in their local communities rather than through NCI-supported cancer centers.

During the past year, the NCI has worked collectively to develop the NCCCP to better connect the cancer centers program with the community environment. The NCCCP's purpose is to enable the provision of state-of-the-art multi-specialty care and early phase clinical research in community-based locations to bring the science and meet the needs of the people where they live. An estimated six pilot sites will be sponsored for 3 years to identify critical factors to be incorporated into a future RFA. The NCI needs to conduct research about some of the issues related to health care, such as better health care delivery, health care disparity issues, navigation issues, and other problems that people living in the communities face. The House Appropriations Subcommittee 2007 report commended the "NCI for its foresight in developing the community cancer centers program, which is a direct mechanism to translate the most promising advances in cancer treatment...to community hospitals around the country."

The pilot program is considering a number of research questions, including: What are the necessary components to ensure a comprehensive approach to cancer care in the community setting? What methods are effective to increase the accrual of patients into clinical trials, particularly in early phase trials? How can the benefits of a multi-disciplinary model of cancer care best be demonstrated? Can the NCCCP model improve quality of care? What approaches can reduce health care disparities? How can NCI's biorepository guidelines be implemented in a community hospital-based cancer program? How can community-based cancer programs effectively participate in caBIG™? How can a Knowledge Exchange Network support the advancement of goals for the NCI and NCCCP program? It is important to connect research activities addressing these questions to the cancer centers program; this is possible through the use of electronic media, such as telecommunication concerning images, participation from the local community through university tumor boards, and interactions between university experts and local physicians. Moreover, specimens can be transported across the United States through commercial delivery systems, such as Federal Express (FedEx) and

United Postal Service (UPS).

NCCCP components include a community cancer program, clinical trials experience, disparities and community outreach, information technology and the ability to work on electronic medical records, biospecimen initiatives, and hospice and palliative care. The NCI is interested in sites with programs that have an organized cancer center concept with multi-specialty involvement (such as medical, surgical, and radiation oncology) and an existing administrative and medical program structure. It also should include a physician director with cancer expertise, patient navigation support, and the development of multi-disciplinary or multi-specialty disease specific planning and review committees within that structure. To encourage an organized and sustainable approach to community health outreach, relationships should be formed with other community-based organizations, and resources should be found to provide care for the uninsured and underinsured. To leverage the investment in the community aspect of cancer care, a track record of public-private partnership development is preferred, as well as partnerships with national, regional, and state public health departments.

Special areas of interest during the pilot include linkages with NCI-designated cancer centers; new community-based models to address health care disparities; a national health system model in multiple markets to study knowledge transfer methods, rapid replication capability, or rapid diffusion of best practices; state-funded cancer initiatives; and special locations with high incidence of cancer or lack of services. State or regional health information technology initiatives, survivorship plans, experience with payer-supported clinical initiatives, and supplemental funding models also are important.

An external and independent program evaluation during the first year will address infrastructure development and refinement of the pilot program and research questions. Evaluations in the second and third years will focus on the implementation of the model and further evaluation of the metrics and research questions.

The NCCCP is intended to support multiple sites for a total of $9 M for 3 years, along with supplemental funding models, such as matching funds from local institutions, to leverage NCI’s investment in health care disparities, information technology,

biospecimen initiatives, and clinical trials. The RFP was posted on http://www.fedbizopps.gov, and responses were due 9 January 2007. Pilot selections will be announced in March 2007, and the NCCCP is expected to be launched in late spring.

In discussion, the following points were raised:

- Ground rules should be established to include more nonprofit groups from the local communities to help address health care disparity issues. National organizations that are involved in quality of care and the delivery of health care, such as Joint Commission on Accreditation of Healthcare Organizations (JCAHO), also could be involved.
- To better reach into communities where robust cancer programs do not exist, the pilot program includes community hospitals with existing review boards.
- NCCCP is a mechanism that aims to provide service to the local community "rim" of the cancer family and is not intended to replicate the work of the NCI Cancer Centers or the Community Clinical Oncology Program.
- A concern was raised about the incentives to the Cancer Centers to assist with technology transfer issues.

top

XII. CANCER CENTERS DIRECTOR'S REPORT — Dr. John Mendelsohn

Dr. John Mendelsohn, President, The University of Texas M. D. Anderson Cancer Center, presented highlights of the report drafted by cancer center directors. The report was conceptualized at a meeting about the expectations of the 2015 goal between the cancer center directors and NCI senior management. The Cancer Center directors sought a way to express what they felt was possible to achieve despite the reduction in the NCI funding at a time of great opportunity for increased successes. The directors also felt that the centers, which have the dual missions of research and dissemination of improved care, could assume a greater leadership role in translational research.

The report addressed six areas: (1) Prevention, (2) Early Detection, (3) Treatment, (4) Survivorship, (5) Collaborations, and (6) Dissemination. It emphasized the progress made in cancer prevention and alleviation to date, including that a midpoint analysis of the ACS' goal of 50 percent reduction in cancer deaths between 1990 and 2015 affirmed an estimated success of 23 percent (Cancer, Byers, et al., July 2006). Additionally, the decrease in deaths from breast, male lung, and colon cancers is tracking at 50 percent, with success more attributable to prevention and early detection than treatment.

Following a brief overview of each area of the report, Dr. Mendelsohn noted that the report emphasizes the benefits of collaboration of cancer centers with each other and with other stakeholders. The report is available online: http://www3.cancer.gov/cancercenters/Accelerating_Successes_Against_Cancer_Report.pdf.

In discussion, the following points were raised:

- Following a discussion of the relationship between the cancer center support grants and the NIH's Clinical and Translational Science Awards (CTSA) initiative, several members indicated there is a need for systems integration.
- The NCI can play an important role in introducing standards and developing databases, such as in the identification and validation of large panels of biomarkers. Standardization with internal review board (IRB) issues and studies also would streamline the process.

top

XIII. CENTERS OF EXCELLENCE IN CANCER COMMUNICATION RESEARCH INITIATIVE: MID-COURSE UPDATE — Drs. Robert Croyle, Brad Hesse, Victor J. Strecher, Matthew W. Kreuter, and K. Viswanath

Introduction. Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences, introduced the midcourse update

of the Centers of Excellence in Cancer Communication Research (CECCR) Initiative. Dr. Croyle noted that the challenge of how to communicate about science and how to build communication about science concerns three domains: geographic information systems (GIS) science, value-add initiatives, and information that elucidates intervention approaches. Dr. Croyle introduced the speakers: Drs. Brad Hesse, Chief, Health Communication and Informatics Research Branch, DCCPS; Victor J. Strecher, Principal Investigator, Center for Health Communications Research, University of Michigan; Matthew W. Kreuter, Center for Cultural Cancer Communication, School of Public Health, Saint Louis University; and K. Viswanath, Dana-Farber Cancer Institute, Harvard School of Public Health.

Why Communication Science Is Vital To Progress Against Cancer in the 21st Century. Dr. Hesse informed members that there are four areas in which communication science can assist with the battle against cancer: (1) biomedical advances, (2) smarter communications, (3) informatics support, and (4) overcoming disparities. Members were told that communication technology began with the widespread use of the personal computer in the early 1980s, advanced with the introduction of html and the Internet in the 1990s, and continues to evolve as the media environment changes. The revolution in the digital market and the increasing use of personalized information delivery formats, such as that found on Amazon.com, continue to push these advances. In a crowded information environment, it is important to impart a clear and effective message; private companies develop creative advertisements to have such an effect, including promoting tobacco use. The NCI and cancer community, however, must face the issue of how to advocate smoking cessation and counter clever tobacco advertisements.

The Health Communication and Information Research Branch was created in 1999 to accelerate cancer and informatics research related to the use of informatics. During the period from 2000-2002, the CECCR initiative was formed and subsequently launched Health Information National Trends Survey (HINTS), in 2003, as a general population tool to assess cancer communication success. The four centers currently awarded to assist with CECCR are the University of Michigan, University of Wisconsin, St. Louis University, and University of Pennsylvania.

CECCR aims to develop cancer communication science by generating basic research evidence; supporting novel, interdisciplinary research; and increasing peer-reviewed publications. Effective interventions also will be developed to produce evidence-based interventions and increase the coverage in understudied areas. CECCR works to train and attract investigators, thus increasing the number of researchers from relevant disciplines; it emphasizes interdisciplinary training to ensure that scientists are capable of conducting cutting-edge communications research. Overarching communication themes include extending reach and improving effectiveness and efficiency.

Customizing Cancer Communication for Increased Effectiveness. Dr. Strecher explained that the CECCR centers intend to reach a large number of the population with effective communications delivered at a low cost. Current tools range in cost, from group therapy programs (limited reach and costly) and tele-counseling (good reach but costly) to self-help guides and booklets (broad reach and inexpensive but low efficacy). A potential solution is provided by "eHealth," which is interactive health communication based on information technology and the interest in personalized health care. One popular eHealth intervention is the Internet. It is reported that more than 10 million people use the Internet for help in quitting smoking. Much online information, however, is dated or ineffective.

Tailored health communications should parallel advances made in biomedically based tailoring. Messages might target specific demographics, social environments, motives, barriers, or coping strategies. Based on smokers' stories developed in a tailor-focused randomized trial, this added depth to tailoring appears to be effective. Six-month results showed that low-tailored stories produced a 31 percent rate of smoking cessation and the high-tailored programming yielded a 44 percent success rate. The study also examined why this tailoring depth seemed to have an influence. To determine whether the high-tailored messages activated a specific part of the brain, Dr. Strecher's group is exploring neural activation. This involved 60 tailored message snippets, comprised of both low and high tailored messages, which were distributed during a 40-minute period of time. The study has found that the prefrontal cortex, which is related to self-referential activities and personal relevance, is stimulated as a result of higher tailored messages.

Building a highly tailored program requires an interactive, collaborative, and transdisciplinary effort from many schools: medicine, public health, art, nursing, social work, dentistry, statistics, psychology, and information. The immediate dissemination route is through health maintenance organizations (HMOs) and NCI's Cancer Research Network. Moreover, tremendous interest has been expressed during the past 2 years by other institutions, including the National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), Occupational Safety & Health Administration (OSHA), and the Robert Wood Johnson Foundation (RWJF), as well as global groups, such as Singapore Health Care-National Health Care Group, Health Canada, and Intel. JCAHO and Institute of Medicine (IOM) could be helpful in reaching low-literate populations. A workshop on tailoring content is in the planning stage, and an elaborately packaged tailoring engine eventually will be available as shareware; the new methods of eHealth will remain an important topic for future training.

Communication-based Strategies To Eliminate Cancer Disparities. Dr. Kreuter described the work of the Center for Cultural Cancer Communication, a collaboration of scientists from the School of Public Health at St. Louis University, the Siteman Cancer Center at Washington University, and the School of Journalism at the University of Missouri. The collaboration aims to identify and apply communication-based strategies to eliminate cancer disparities, specifically in African American populations. Dr. Kreuter shared several data maps of St. Louis, MO, showing where, based on 2000 census records, the largest percentage of African Americans reside; where the greatest incidence of late-stage breast cancer occurs; and the locale of neighborhood health centers serving predominantly African American populations.

The study hoped to provide tailored information to African American women in these clinics to increase their use of mammography by determining whether the effects of tailored communication can be enhanced by tailoring on cultural values. More than 1,200 African American women, ages 18 to 65, were enrolled and randomly assigned to a usual care group or to three groups that received different levels of tailored messages based on behavioral determinants (such as beliefs, barriers, and readiness to get a mammogram); cultural values (i.e., spirituality, family, racial

pride, and time orientation); or a mixture of behavioral determinants and cultural values. During 18 months, the women received six magazines tailored to their particular characteristics. More than 54 percent of the women in the usual care group reported having a mammogram during the last 12 months; more than 64 percent of the behavioral group; more than 63 percent of the cultural group; and more that 75 percent of the behavioral and cultural group.

To help disseminate information and overcome problems with digital access, a computer kiosk called “Reflections of You Kiosk” was created and placed throughout the community, including laundromats, beauty salons, churches, health centers, public libraries, and social service agencies. The kiosk prints a full-color tailored magazine based on answers given to questions. Kiosk placement sites were identified based on community settings with the highest rates of kiosk use, community settings that reached users with the highest need for information about breast cancer and mammography, and the settings with the greatest geographically localized reach. Four kiosks have been installed throughout the community; they have been used 13,000 times during the past 3 years, with highest rate of use in laundromats (almost 19 times per day), followed by health centers, libraries, churches, and beauty salons. Only 33 percent of women over the age of 40 who used the kiosk in a laundromat have had a mammogram. A GIS analysis approach was used to calculate the mean distance in miles between where kiosk users lived and where they used the kiosk. Additional GIS analyses could help develop an outreach approach to reach those with limited access to technology or the greatest need for information. The GIS approach can be adapted to national data. Preliminary results suggest that readers are being affected.

Communication and Cancer Control: Where Do We Go From Here? Dr. Viswanath provided a context of what CECCR-related research means to the larger world of cancer communications and cancer control, the effectiveness of using a center approach, and how to incorporate it into the larger cancer enterprise. Cancer-related communication, whether positive or negative, is everywhere, including television, the Internet, and the print and digital media. People can suffer, however, from information overload. A HINTS study revealed that more than 50 percent of the people agree with the statement that “everything causes cancer,” but more than 70 percent of the people admit that they do not know

which of the many available recommendations to follow. This suggests that, despite the cascading information around cancer, communication is not fully effective.

A multi-level, multi-disciplinary, and multi-pronged approach is needed to address problems at various levels of analysis and at individual, group, institutional, social, and community levels. Moreover, to ensure that cancer communication is evidence based, efficient, and effective, different stages of cancer control continuum and different types of audiences must be targeted. Reaching multiple audiences requires a variety of channels or information delivery systems, messages, and formats of messages, including genres such as news or soap operas. Innovative methods must be employed to deliver information and collect data. CECCR helps address these challenges because individual centers working under a larger umbrella pursue research in different stages of the cancer control continuum: prevention, detection, treatment, survivorship, and end of life. This structure also allows more than 25 academic areas to work together.

In cancer communication, it is important to connect the biomedical and communication revolutions. CECCR is using complex algorithms to personalize communications to patients. Sophisticated methods, such as fMRI, are used to understand audience reactions to media and communication messages. In other instances, new and innovative information delivery systems, such as electronic kiosks, intranet, or Internet, are being adopted. The center approach allows the NCI to capture the synergy evident among the disciplines that could not be achieved through a standard R01 mechanism. The development of projects is a part of the center that encourages innovative work. Finally, CECCR can train and nurture future cancer communication researchers and allow for the study of multiple channels, formats, strategies and stages of continuum simultaneously as opposed to performing it one piece at a time.

It is important to connect successful communications research to the larger cancer enterprise, including other NCI entities (e.g., comprehensive cancer centers, the Office of Communications and Education, CIS, etc.) and DHHS agencies, such as the CDC, which is spearheading numerous outreach programs. Hospitals, HMOs, medical and public health schools, and mass media also should be involved. Drawing from evidence-based communications will help

demonstrate to the public the value of supporting biomedical research and contribute to the reduction of morbidity and mortality related to cancer.

In discussion, the following points were raised:

- Targeting communication campaigns toward the internal cancer community (e.g., scientists, cancer center directors, and patients) is as important as focusing on the general public.

- Regarding primary prevention and behavior modification for children, CECCR has brought together African American teenagers, Hollywood Screenwriter Guild writers, computer information experts and graphic designers, and physicians and behavioral scientists to create interactive and entertaining educational programs, including those about healthy eating and physical activity.

- The strategies used by CECCR differ from the advertising industry not only with regard to cost sensitivity, but also by the leveraging of collaboration, including with the CDC.

- Internet penetration and access will improve for poor and underserved populations, but the right kinds of cancer communication interventions need to be developed to help the public process and act on information and bridge the digital divide.

- A request for information recently was published in The Federal Register for improving health and accelerating personalized health care through health information technology and genomic information and population and community-based health care delivery systems. Initiated in collaboration with the NHGRI, the pilot project focuses on communications targeting the introduction of technologies in health care delivery settings, particularly for multiplexed, multi-disease test results, marker test results to physicians and patients in primary care settings.

top

XIV. INVESTIGATIONAL DRUG AND PHASE III DISEASE-SPECIFIC STEERING COMMITTEES — Drs. James Doroshow and Sheila Prindiville

Drs. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), and Sheila Prindiville, Director, Coordinating Center for Clinical Trials, provided an update of Clinical Trials Working Group (CTWG), with a focus on the work of the Investigational Drug and the Disease-Specific steering committees. Members were reminded that the overall themes of the CTWG's restructuring plan center around an integrated management, enterprise-wide series of recommendations; prioritization and scientific quality issues; coordination and standardization; and operational efficiency. The CTWG recommends that all stakeholders should be involved in the design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology.

The Investigational Drug Steering Committee is looking at prioritization issues in early phase trials. The committee provides strategic input into the clinical development plans for new agents, addresses critical scientific issues in early phase trials, and links developmental therapeutics activities with disease-specific clinical trial prioritization. It also assists in dispute resolution and enhances the transparency of NCI's drug development process. Five task forces (clinical trial design, biomarkers in early therapeutics, pharmacology, signal transduction, and angiogenesis) and two working groups (conflict of interest and meeting planning) have been established.

The Investigational Drug Steering Committee has developed and implemented a conflict-of-interest policy and reviewed current and proposed development plans for specific agents. The Biomarker Task Force is developing benchmarks for correlative markers in early phase therapeutics. The Pharmacology Task Force is evaluating the logistics required to expand pharmacogenetic studies during the conduct of early phase trials. The Clinical Trial Design Task Force is focusing on new endpoints and the use of randomized Phase II trial designs earlier in drug development. In terms of prioritization, the committee has improved transparency in the NCI drug development process. It also will continue assisting with the coordination of NCI's activities and providing enhanced scientific input for novel therapeutics. There is now a mechanism

to provide a smooth transition for the early therapeutic agents into NCI's Phase III studies, a process which is facilitated by designated liaisons.

The Disease-Specific Steering Committees are mandated to prioritize Phase III concepts for therapeutic clinical trials, convene state-of-the-science meetings to identify critical questions to prioritize key strategies and future concepts for NCI-supported clinical trials, develop Phase III concepts for new clinical trials using Task Forces, and periodically review accrual and unforeseen implementation issues. Currently, there are four subcommittees:

1) **The Gastrointestinal Steering Committee** has established six disease task forces (colon, esophagogastric, pancreas, rectal-anal, hepatobiliary, and neuroendocrine) are now in place. To date, the committee has reviewed four Phase III concepts and approved one pending revisions. The Pancreas Task Force is planning a state-of-the-science meeting.

2) **The Gynecologic Steering Committee** will establish task forces to focus on ovarian, cervical, and uterine cancers. The committee will review both Phase III and large, randomized Phase II concepts. Three concepts and protocols have been reviewed; one was approved pending revisions. An endometrial cancer state-of-the-science meeting is planned for November 2006.

3) **The Head and Neck Steering Committee's** first meeting will be held in December 2006. The co-chairs include surgical, medical and radiation oncologist.

4) **Symptom Management and Health Related Quality of Life Steering Committee** (in formation) will review symptom management intervention studies conducted in the Community Clinical Oncology Program, as well as develop and review studies with quality of life secondary endpoints in the Cooperative Group treatment studies.

In summary, the formation of Disease-Specific Steering Committees has ensured that community oncologists and patient advocates are now an integral part of the prioritization process. The full spectrum of NCI clinical trials funding mechanisms is represented, and translational scientists are actively participating. A

more rigorous scientific review process also has resulted in substantial changes to trial design, as well as the evaluation of the priority of concepts.

Future goals for the steering committees include the plan for other disease-specific steering committees, the initiation of a community oncologist and patient advocate steering committee, a baseline evaluation of the current prioritization process, and a plan to evaluate the initial four steering committees. More information about these committees, including the Investigational Drug Steering Committee, is available on the Coordinating Center for Clinical Trials Web site (http://ccct.nci.nih.gov).

In discussion, the following points were raised:

- The CTWG Steering Committees reflect a new way of conducting business in that, for the first time, the committees: (1) are given the authority to turn down weak trial designs, and (2) are comprised of researchers who actually perform trial work and enroll patients in the trials.
- It was suggested that the Symptom Management and Health Related Quality of Life Steering Committee should consider barriers to the field, such as the assignment of the value of symptom management compared to other research topics.
- In addition to quality of life, other endpoints such as correlative science could be taken into account for clinical trials. In particular, NCI-supported trials could support economic endpoints.
- Present information gained by the Committees that are implementing CTWG recommendations related to balancing the knowledge base and conflict-of-interest considerations.

top

XV. RFA/COOPERATIVE AGREEMENT CONCEPT — Presented by NCI Program Staff

Division of Cancer Control and Population Sciences

Genes and Environment Initiative

Drs. Croyle, Teri A. Manolio, Senior Advisor, NHGRI, and Amy Subar, DCCPS, provided information about the Genes and Environment Initiative, a program proposed by the DHHS Secretary. The Genes and Environment Initiative is co-led by the NHGRI and the NIEHS. The opportunities for conducting genome-wide association studies have increased significantly. At the same time as the accuracy and coverage of the genome has increased, there has been a significant decrease in costs associated with genotyping, making the gene side of the genes-and-environment interaction quite tractable; environmental technologies require improved specificity and accuracy.

The Genes and Environment Initiative is comprised of an exposure biology program and a genetics program, each guided by subcommittees. The exposure biology program examines diet and physical activity, environmental exposures, and psychosocial stress and addictive substances. In addition to genome-wide association studies, the genetics program includes data analysis, replication, sequencing, database, function, and translation. There are three RFAs for genotyping facilities, a coordinating center, and investigators to submit samples and data for the genome-wide association studies. The solicitations aim to support initial genome-wide association genotyping for approximately 15 complex diseases or traits as well as genotyping of strongly associated variants in replication samples. Investigators may apply for initial discovery genotyping, replication genotyping, or both. In addition, the RFAs promote standardization and harmonization of phenotypic and environmental exposure data to permit cross-study analyses and support analysis efforts within and across studies.

Once approved by peer review, investigators will provide study protocols and the genotype data and phenotype the data to a repository managed by the National Center for Biotechnology Information (NCBI). Two levels of access will be in place: (1) public access for study protocols and descriptive information; and (2) more limited access to coded genotype and phenotype data. There will be a login control for this, as well as a controlled access process.

The goal of the environmental exposure biology program is to link personal exposures to disease, integrating the genetic and exposure sides. The genetic side will give priority to selecting the studies for the genome-wide genotyping with historic biospecimens and provide high-quality environmental exposure data. The exposure side will give priority to develop novel assessment technologies for substances with presumed proximity to the genetic effects while focusing on public health problems. Finally, the new biomarkers that are developed through the initiative will be applied to stored specimens in the initiative's genome-wide association studies.

The exposure biology program is developing an RFA to improve measures of diet and physical activity (http://www.gei.nih.gov/exposurebiology). The intent of the RFA is to move the diet and physical activity field forward by developing new or refining existing technologies to measure dietary intake, physical activity, or both. A limited or minimal amount of validation is expected, and multidisciplinary research is encouraged. The diet component will focus on technologies and biomarkers. The physical activity will involve motion or physiologic sensors and monitors, imaging methods, cellular telephone and wireless technologies, bioinformatics tools and database solutions, and ecological assessments.

In discussion, the following points were raised:

- The NCI has been collaborating with the National Heart, Lung, and Blood Institute (NHLBI) on applying biotechnology to the issue of assessing diet and physical activity related to the trans-NIH obesity initiative.
- Further budget clarification of the RFA entitled "Improved Measures of Diet and Physical Activity for the Genes and Environment Initiative (GEI)" was requested.

top

XVI. ADJOURNMENT - Dr. Robert C. Young

There being no further business, the 35th regular meeting of the Board of Scientific Advisors was adjourned at 12:00 noon on Friday, 3 November 2006.