DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
144th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
November 27, 2007

Building 31 C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 144th regular meeting on 27 November 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 27 November 2007, from 8:00 a.m. to 4:35 p.m. and closed to the public from 4:35 p.m. to 5:30 p.m. The NCAB Chair Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members
Dr. Carolyn D. Runowicz (Chair)
Dr. Anthony Atala
Dr. Bruce A. Chabner
Dr. Moon S. Chen, Jr.
Dr. Donald S. Coffey
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Dr. Lloyd K. Everson (absent)
Dr. Judah M. Folkman (absent)
Ms. Kathryn E. Giusti (absent)
Mr. Robert A. Ingram
Mr. David H. Koch (absent)
Dr. Diana M. Lopez
Dr. Karen Dow Meneses
Dr. Franklyn G. Prendergast (absent)
Ms. Lydia G. Ryan
Dr. Daniel D. Von Hoff

President's Cancer Panel
Dr. LaSalle D. Leffall, Jr. (Chairperson)
Mr. Lance E. Armstrong (absent)
Dr. Margaret L. Kripke (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC
Dr. Allen Dearry, NIEHS
Dr. Diane C. DiEuliis, OSTP (absent)
Dr. Michael Kelly, VA
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. John Krystal, VA
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Dori Reissman, NIOSH (absent)
Dr. Donald J. Wright, DOL (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Clinical Research
Ms. Kathy McBrien, Administrative Resource Center Manager
Mr. Lawrence Ray, Deputy Director for Management and Executive Officer
Dr. Alan Rabson, Deputy Director, Office of the Director
Dr. Craig Reynolds, Associate Director, NCI-Frederick
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Jaye Viner, Acting Director, Office of Centers, Training and Resources
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Eve I. Barak, National Science Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Ms. Suanna Bruinooge, American Society of Clinical Oncology
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Pamela K. Brown, Intercultural Cancer Council
Dr. Yvette Colon, National Cancer Institute, Director's Consumer Liaison Group
Mr. George Dahlman, Leukemia and Lymphoma Society
Ms. Georgia M. Decker, Oncology Nursing Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Leo Giambarresi, American Urological Association
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. David Lofye, Lance Armstrong Foundation
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 16–18 SEPTEMBER 2007 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, called to order the 144th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel (PCP), *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Dr. Runowicz expressed the Board's congratulations to Dr. John Niederhuber, Director, NCI, on his election to The American Association for the Advancement of Science (AAAS) for his pioneering research in major histocompatibility complex (MHC) immunology and cancer stem cells and for his outstanding leadership of the University of Wisconsin Cancer Center and the NCI.

Motion. A motion was made to approve the minutes of the 16-18 September 2007 NCAB meeting. The motion was seconded and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2009.

III. DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Dr. Niederhuber welcomed the Board and expressed appreciation to the members for taking the time to attend the NCAB meetings and provide input to the NCI. He said that today's meeting would discuss the NCI's intramural program. The leadership of the NCI, including the Executive Committee (EC), has continued to work collaboratively to make stronger both the NCI and the relationships between intramural and extramural communities. Dr. Niederhuber next provided an update on the NCI's FY 2007 and 2008 budgets and described the NCI leadership efforts at the NIH, as well as the NCI's commitment to translational research.

Fiscal Year (FY) 2007 Year-End Budget Summary. Dr. Niederhuber explained that research project grants (RPGs) were funded at more than the 15th percentile, and new investigator grants were funded at the 21st percentile (215 funded). In addition, 1,312 competing RPGs were funded in FY 2007, meeting the NIH-recommended target. Funding for the Specialized Programs of Research Excellence (SPORES) program, the Cancer Centers program, and the Community Clinical Oncology Programs (CCOPs) remained essentially level with FY 2006 rates. The NCI has funded two new cancer centers at the Baylor College of Medicine and Stanford University. Dr. Niederhuber expressed his appreciation to the NCI budget team, which succeeded in closing the FY 2007 budget with a $9,000 balance.

FY 2008 Appropriations and Operating Budget Development. Dr. Niederhuber told the Board that in mid-November, the President had vetoed the Congressional Appropriations Bill, which had allocated $4.925 B to the NCI. The President's Budget (PB) was lower, at $4.79 B for FY 2008. He said that the difference between the 2008 PB and the 2008 Congressional Appropriations was $128.101 M. The NCI's challenge is to address a 12 percent loss in purchasing power since 2004 caused by inflation. If

the appropriations accounted for inflation at a rate of 3.67 percent, the number would have been $177.513 M. Dr. Niederhuber described an FY 2008 operating budget based on the proposed Congressional Appropriations. The NIH taps and assessments are estimated to increase by $20 M, and the NCI requirements based on increases in competing RPGs, rents and utilities, small business program, and mandated salaries, as well as the NCI Director's Reserve of $25 M, provide an available subtotal of $15.6 M. The NCI intends to create a pool of $70 M for new initiatives, expansions, and restorations. The NCI planning also involves a 3 percent decrease in Division, Centers, and Office of the Director (OD) budgets to offset the estimated $54.4 M negative balance. There is great concern about how a flat budget will continue to affect the NCI's clinical research trials, including the discouragement that occurs across the cancer community and in private practice groups when faced with these budget reductions. The budget reductions are impacting individual investigators; funding of new and competing renewals grants is down 25 to 40 percent, which translates into at least one less specific aim on each application. Existing grants have experienced yearly reductions of about 3 percent, which translates into 6 percent when inflation is factored in. Laboratories are struggling across the country as a result of the continuing flat budget numbers, and the NCI clinical trials are being affected, particularly in Phases II and III. The CCOPs also have been affected by the funding shortage and could lose patients accrued to treatment and prevention trials.

Maintaining Momentum. Despite funding challenges, the NCI is facing the potential for more specific cancer treatment that requires a national clinical trials enterprise that integrates the knowledge, insights, and skills of multiple fields into a new kind of crossdisciplinary, scientifically driven, cooperative research endeavor. This potential is being tapped by the Coordinating Center for Clinical Trials (CCCT), with resources from the Clinical Trials Working Group (CTWG) and the Translational Research Working Group (TRWG). The TRWG integrates the NCI management to establish a refined coding system, implement the Special Translational Research Acceleration Project (STRAP) Awards, coordinate the TR Awards, establish a project management system, and coordinate activities with external constituents. Academia and the pharmaceutical and biotechnology industries collaborate through the TRWG with the NCI Cancer Centers Program, the CCOPs, and Community Cancer Centers. The NCI intramural program is clearly an outstanding program at the NIH and is responsible for leadership on the NIH campus in many scientific ways and in providing infrastructure research support to the Frederick and Bethesda campuses. Other examples of the NCI's leadership include the Chemical Biology Consortium (CBC) and the Life Sciences Consortium. The CBC complements the NCI's drug development platform. It is an integrated research cooperative at the interface of chemical biology and molecular oncology to establish a cancer drug discovery group on the scale of a small biotechnology concern and to focus on unmet therapeutic needs in oncology not currently addressed by the private sector. The Life Sciences Consortium, working in conjunction with the Clinical Trials Advisory Committee (CTAC) and members of the CEO Roundtable on Cancer, is addressing issues related to common language, intellectual property (IP), and antitrust.

Dr. Niederhuber shared an example of the unique role that the NCI plays in the world of drug development. He presented the results of a 26-year-old African-American female patient with cutaneous T-cell lymphoma who was successfully treated at the NIH Clinical Center with fenretinide (4-HPR), a synthetic drug related to vitamin A. Fenretinide was developed initially by Johnson & Johnson in the 1970s as a chemopreventive agent and was brought to the NCI's Rapid Access to Interventions Development (RAID) program by Dr. C. Patrick Reynolds of Children's Hospital in Los Angeles. Dr. Niederhuber said that a trial is underway to develop novel formulations of IV fenretinide. The RAID program is instrumental in bridging the gap between the lead discovery and drug delivery and provides the academic and small business communities with access to preclinical contract research resources.

Dr. Niederhuber described the NCI Centers of Excellence and Special Programs focusing on stem

cell biology, immunology, human genetics, lung cancer, the HIV and AIDS malignancies, neuroblastomas, core services, nanocharacterization, proteomics, and breast cancer. Many of the programs are trans-NIH efforts that benefit the entire NIH network and extramural science. The Tissue Array Research Program's (TARP) core laboratory provides standardization in the angiogenesis field and crosses many diseases, and is considered the central program for angiogenesis research across the country. The NCI SPORE program funds intramural research across the NIH and extramural scientists in support of our training program. The goal of the Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative is to develop molecular targets in pediatric cancer using current genomic technologies. The NCI also is involved with an advanced technology partnership initiative. New facilities will be built to co-locate advanced technologies, pool IP, and share selected resources. The facility will be home for the major portion of the NCI's drug development platform. It will serve as a coordinated think tank, providing for the strategic planning of research direction and priorities in conjunction with the private sector.

Questions and Answers

Dr. Runowicz asked about the future of the R01 mechanism in light of the emergence of new technologies and expressed a concern about the difficulties that clinician investigators face. Dr. Niederhuber said that the R01 mechanism will continue to be a significant instrument but that the state of science is driving change in many areas, including funding and the evaluation and promotion of new scientists. One of the challenges will be to balance the struggle between clinical time and laboratory time in support of research grants.

Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, and Chief of Hematology/Oncology, asked about the resources available to support each CBC project without losing funds for basic science through the R01s. Dr. James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), explained that the NCI is engaged in discussions with colleagues in academia regarding ways to support them clinically in early phase therapeutics using Roadmap resources. This support will help foster studies in areas and targets that are not in the interest of major pharmaceutical activities. Dr. Niederhuber added that the Roadmap has invested significantly to the National Genomics Center to help facilitate this process. This state-of-the-art facility incorporates robotics and industry professionals to conduct subcellular imaging that will impact future drug development; these resources will be available to academic investigators.

Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, complimented the NCI on its efforts in drug development, as seen by the example of the patient with cutaneous T-cell lymphoma; he noted that many pharmaceutical companies make significant programmatic changes that can be disruptive to drug discovery. Mr. Robert A. Ingram, Chairman of the OSI Pharmaceuticals Board, and Vice Chairman of Pharmaceuticals, GlaxoSmithKline, said that several pharmaceutical companies are restructuring and dismantling certain programs, and he felt that the industry should address inefficiencies in sales and marketing and increase its focus on research and development.

IV. PRESIDENT'S CANCER PANEL—DR. LASALLE D. LEFFALL, JR.

Dr. LaSalle D. Leffall, Chair of the President's Cancer Panel (PCP), showcased the Panel's 2006–2007 Annual Report, "Promoting Healthy Lifestyles: Policy, Program, and Personal Recommendations for Reducing Cancer Risk," which contains recommendations on physical activity, nutrition, obesity, and tobacco. The 2007–2008 meeting series of the PCP, Strategies for Maximizing the Nation's Investment in Cancer is examining the cancer enterprise as a whole. Discussion areas for the series include changes to

the current system to significantly impact cancer morbidity and mortality, applying business models to the cancer research enterprise as a means of optimizing the funding process, raising awareness of cancer funding needs at the legislative level, and balancing resources among basic, translational, clinical, and health services. The PCP is exploring ways to sustain the momentum of cancer care and research under the current fiscal circumstances and clarify the roles of the NCI and its constituencies in the prevention, detection, diagnosis, treatment, and survivorship of cancer. Additional areas of consideration include regulatory issues, collaboration and coordination, access to care, insurer reimbursement, and smoking. Additionally, it was noted that strong leadership is needed to gain the political will of legislators to succeed in the battle against cancer.

Questions and Answers

Dr. Runowicz pointed out that while the American public is willing to pay for more cancer research, there does not appear to be political will. Dr. Leffall agreed that there is not enough grassroots support currently, and urged members to contact their legislators to educate them about the need for increased funding. Dr. Runowicz asked what relationship existed between the PCP and the American Cancer Society (ACS) to increase political will. Dr. Leffall said that the PCP conducts outreach to several grassroots organizations, including the ACS and American Society of Clinical Oncology (ASCO), to work together as a unified force. Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, and Professor of Urology/Oncology/Pathology/ Pharmacology and Molecular Science, The Johns Hopkins University School of Medicine, mirrored the concern for lack of political will and the seeming lack of grassroots efforts to effect political will. He suggested that the PCP assess the ACS Ambassador Program, which was designed to build up grassroots support, to see if it is working. Dr. Runowicz added that mobilizing the ACS is important for moving the cause further, but the future also is very dependent on research and funding from the NCI. Mr. Ingram commended Dr. Runowicz for her past leadership of the ACS and agreed that local voices for cancer support can be effective for pushing legislation through.

Dr. Chabner requested clarification on recent epidemiologic studies suggesting that modest obesity is not associated with decreased longevity and may even lower the incidence of cancer. Dr. Leffall replied that these studies have been discussed at several PCP meetings, and the emerging research shows that being just a little bit overweight is not as detrimental to physical health as previously thought.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on the FY 2008 appropriations status and reviewed legislation of interest to the NCI.

FY 08 Appropriations. The PB of $4.78 B for the NCI was announced on February 5, 2007, and the House passed a bill in June allocating $4.87 B. The Senate passed a bill authorizing $4.91 B on October 23, and the NCI Conference Committee submitted a budget of $4.92 B in their November 1 report. The Conference Report was passed by both the Senate and the House, but it was vetoed by the President. The NCI currently is operating on a continuing resolution (CR) through December 14. If no appropriation is confirmed by that time, another CR will be proposed.

Legislation of Interest. Ms. Erickson provided an overview of the Conquer Childhood Cancer Act, the U.S. Food and Drug Administration (FDA) Amendments Act, in particular, the Clinical Trials Registry provision, and the Genetic Information Non-Discrimination Act. The Conquer Childhood Cancer Act was introduced by
Sen. Jack Reed (D-RI) to advance medical research and treatments into pediatric cancers, promote public

awareness of pediatric cancers, ensure patients and families have access to current treatments and information, and expand the National Childhood Cancer Registry. The Senate Committee on Health, Education, Labor, and Pensions (HELP) passed a replacement bill that calls for the expansion of pediatric cancer research programs and an award grant to track epidemiology of childhood cancer. The FDA Amendments Act (PL 110-85), introduced by Rep. John Dingell (D-MI), reauthorizes collection of prescription drug user fees and medical device user fees; requires manufacturers seeking new drug approvals or indications for pediatric use to complete studies in children requested by the FDA; and gives manufacturers a 6-month extension of market exclusivity if they conduct pediatric studies. Of particular interest to the NIH is the provision in the FDA Amendments Act that expands the Clinical Trials Registry, requiring registration of all phase II-IV intervention clinical trials for drugs and devices 90 days after enactment (December 26, 2007) and authorizes monetary penalties for noncompliance. In addition, the NIH will be required to create a basic results database, using a phased-in approach, for approved drugs and devices and make it available to the public through the Internet. The Genetic Information Non-Discrimination Act was introduced by Rep. Slaughter (D-NY) and Sen. Snowe (R-ME) in January 2007. This bill extends medical privacy and institutes confidentiality rules to the disclosure of genetic information. It also prohibits health insurance providers from denying enrollment, setting premiums based on genetic information, and requiring genetic testing of participants. It was passed by the House in April but has not been placed on the Senate calendar. The Senate Commerce, Science, and Transportation Committee conducted a hearing on the accuracy of the Federal Trade Commission's (FTC) tar and nicotine cigarette rating system. Dr. Cathy Backinger testified on behalf of the NCI that light and low-tar cigarettes do not reduce smokers' exposure to hazardous compounds and that these products do not reduce the risk for disease compared with regular cigarettes.

Questions and Answers

Dr. Niederhuber discussed the challenges involved with reporting clinical results. The NCI will have to work closely with the NIH to convince the NIH that the NCI has the mechanisms to report results. He noted that reporting will be highly problematic, however, in terms of managing the information and how the information will be received and used. Dr. Niederhuber also is concerned that posting clinical trial results, without the benefit of the internal review discussions, may lead the public to misinterpret results.

Dr. Chabner asked how financial penalties will be enforced for failure to report and suggested that this provision is impractical considering the fluidity of outcomes. Dr. Runowicz agreed and stressed the need for legislative guidance on how to interpret the details of the new reporting requirements. Dr. Jean B. deKernion, Chair, Department of Urology, University of California, Los Angeles, and The Fran and Ray Stark Professor of Urology, asked if reporting requirements apply to Phase I clinical trials, and Ms. Erickson clarified that the reporting requirements do not apply to Phase I clinical trials.

Dr. deKernion asked how long CRs could be extended. Ms. Erickson replied that the CRs can be extended to one full fiscal year. Dr. deKernion then asked if funding had been appropriated for the Childhood Cancer Act, and Ms. Erickson stated that authorization for appropriations has been received, but monies have not yet been appropriated.

VI. ENHANCING PEER REVIEW—DR. LAWRENCE A. TABAK

Dr. Lawrence A. Tabak, Director, National Institute of Dental and Craniofacial Research (NIDCR), described a self-study by the NIH to help it and its partners meet the increasing breadth, complexity, and interdisciplinary nature of the biomedical sciences, as well as ever-growing public health needs. Peer review is a key component of this system. These changes are creating new challenges for the

system used by the NIH to support biomedical and behavioral research, so the NIH must ensure that internal processes are adapted to support science as efficiently and effectively as possible. The NIH is seeking input from the external and internal scientific community, including investigators, scientific societies, grantee institutions, voluntary health organizations, and the NIH Institutes. The various phases of the study include a diagnostic phase, pilot phase, and implementation phase. The Steering Committee Ad Hoc Working Group is coordinating its efforts with those of the Center for Scientific Review (CSR). The CSR initiatives involve shortening of the review cycle, immediate assignment of applications to initial review groups, realignment of study sections, electronic reviews, and shortening the size of applications. Dr. Tabak noted the external and internal working group members and described selected activities of the diagnostic phase.

The NIH leadership will use input obtained through the diagnostic phase to determine the next steps, including the development and implementation of pilots. Pilot studies are expected to begin in March 2008. Final implementation will involve the expansion of successful pilots and the development of new NIH peer review policy. Briefings will be held for the NIH staff, the NIH Councils, scientific societies, advocacy organizations, legislative constituents, and the trade press.

Dr. Tabak described a number of ideas that have been shared by the community regarding the peer review process. These include review criteria, new models of review, maximization of reviewer quality, reviewer mechanisms, peer review culture, scoring, review system mechanisms, and other research support issues.

Questions and Answers

Dr. Runowicz thanked Dr. Tabak for his presentation and applauded his efforts. Dr. Moon S. Chen, Professor of Medicine, Internal Medicine, Oncology, and Hematology, University of California at Davis, also responded favorably to the ideas presented by Dr. Tabak and asked how the group would evaluate the public health impact of the project. Dr. Tabak envisioned a potential separate score for various dimensions, including one for public health impact.

Dr. Diana M. Lopez, Professor, Department of Microbiology and Immunology, University of Miami School of Medicine, thanked Dr. Tabak for his review of the process. She said that the lack of continuity of reviewers to the same application can be confusing for investigators and can have an impact on scoring. Dr. Tabak agreed that continuity is a very important element to the review process. Dr. deKernion questioned the feasibility of journal-type peer review, particularly for young investigators who are struggling to balance their time between clinical obligations and securing funding for their own grants. He suggested streamlining the process by having electronic review followed by a mini-panel and favored the use of multiple categories in the scoring process. Dr. Coffey agreed that it is time to revamp the system and asked if Dr. Tabak's group had researched the processes used by other countries. Dr. Tabak said there are certain elements that may be borrowed to enhance the system. Dr. Coffey suggested that young investigator grants be reviewed at their own institutions before being submitted for formal review at the NCI. Dr. Karen Dow Meneses, Professor and Associate Dean for Research, School of Nursing, University of Alabama at Birmingham, applauded Dr. Tabak's study and voiced her preference for the pre-application process in peer review. Dr. Daniel D. Von Hoff, Professor of Medicine and Molecular and Cellular Biology, University of Arizona, and Director, Arizona Cancer Center, inquired about privatization issues.

VII. THE NIH RESEARCH, CONDITION AND DISEASE CATEGORIZATION (RCDC) PROJECT—DR. TIMOTHY HAYS

Dr. Timothy Hays, Project Director, Research, Condition, and Disease Categorization (RCDC) Project, Chief, Portfolio Analysis and Scientific Opportunities Branch, Office of Portfolio Analysis and Strategic Initiatives (OPASI), OD, presented an overview of the RCDC project. NIH initiated the development of the RCDC project in 2005. Specifically, Congress mandated the system in the "National Institutes of Health Reform Act of 2006," which stated that the NIH "shall establish an electronic system to uniformly code research grants and activities of the Office of the Director and of all the national research institutes and national centers." Each year, the NIH reports to Congress and the public how much it spends on research. This information is intended to help Congress and the public better understand the NIH research spending and priorities. Prior to this initiative, the Institutes reported their data using differing definitions, methodologies, and parameters to the NIH OD for compilation.

Dr. Hays said that the RCDC provides an electronic categorization system designed to apply uniform NIH-wide definitions to all NIH-funded research projects to track spending across all 27 Institutes and Centers (ICs) of the NIH. The categories include approximately 360 research and disease areas to provide consistent, transparent, and efficient coding and reporting, as well as opportunities for further portfolio analyses. Each research project within each NIH grant, intramural project, or research and development contract will receive a project "fingerprint" based on the medical and research concepts in the research description. These concepts will be matched against a weighted list of concepts developed by experts drawn from the NIH Institutes to ensure that they are scientifically defensible. The NIH OPASI worked on a pilot tool for approximately 1 ½ years and presented it to Congress, who approved its use in 2006. The NIH expects to launch the RCDC tool by providing a complete list of projects funded in fiscal year 2008 for each category to the public in February 2009. Detailed information about how the tool works will be introduced in the summer of 2008.

Questions and Answers

Dr. Chen asked how the RCDC tool compares with the Computer Retrieval of Information on Scientific Projects (CRISP) system. Dr. Hays explained that CRISP is a database that can be searched by keywords to find the NIH-funded projects. The RCDC is expected to feed categorization data, accomplished using sophisticated text mining software, into a newer version of the CRISP tool that will offer the public more detailed searches, using concepts and keywords to search within categories and see resulting research as well as publications and patents associated with the projects. In addition, the new CRISP tool and RCDC project listings will be designed to offer data in downloadable format to certain software platforms such as Microsoft Excel.

Dr. Meneses asked if the RCDC tool will include past data like the CRISP database. Dr. Hays answered that the new CRISP tool will contain summaries or abstracts of past studies, as it does now, that are searchable by keyword, but the new functionality that includes category information as well as related publications and patents will apply only to projects from 2008 onward. There were multiple questions and concerns voiced regarding the categorization process and how it would impact the reporting of associated funds. Dr. Chabner asked for more explanation of the multiple-category reporting function of the RCDC tool regarding funding. He wondered how the funding would be reported in relation to each of the categories because research often falls under more than one category. For instance, a genetics project studying geographic or racial subgroups would fall under the categories of genetics and each of the subgroups. Dr. Kenneth H. Cowan, Director, Eppley Cancer Center and the Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, also asked for clarification about how the funding would be represented in such cases. Dr. Cowan wondered how this

accounting would meet the goal of being transparent and accurate. He asked also who would be assigning the categories for each project and if that person or persons were qualified to do so.

Dr. Hays stated that NIH, including NCI, has reported projects in multiple categories for many years, and that process will continue. Because research can have multiple applications, it is scientifically justifiable to have those projects appear in multiple relevant categories. Because the RCDC project listings will now be transparent, the public can identify which projects show up in multiple categories, something the public currently cannot do. Dr. Hays also noted that if a project falls in a category it will be reported at 100 percent of the funded amount for each project which differs from the current NIH process where some institutes like NCI pro-rate costs of projects within categories. Further, each project is assigned to the category in an automated fashion based on the category definition. Experts from the NIH ICs have defined these category definitions and the categorization process. NCI staff have been involved in the development of both the category definition process and the creation of definitions from the inception of the project. Dr. Cowan noted that it appears that the RCDC reporting system will be over-representing categories and wondered what the difference was between the old system and the new system. Dr. Chabner also noted that the new system will serve to confuse the public because there will now be two systems for tracking and reporting investment in various diseases and categories of cancer—total appropriations and now the categorized totals that will not match the total appropriations. Dr. Hays stated that the current cancer category does not match the NCI appropriation since nearly $600,000,000 worth of cancer research occurs in other NIH ICs.

Dr. Niederhuber shared his concerns about the RCDC project. This includes the decision to list AIDS and biodefense as separate categories, which have different reporting requirements mandated by government agencies outside of NIH, but not cancer. The NCI captures its research data and outcomes in its categorization database tool, The Cancer Biomedical Informatics Grid (caBIG™). The caBIG™ is used throughout the cancer community, particularly by advocacy groups that closely monitor the NCI activities. There is great concern about the NCI having to maintain two accounting systems.

Dr. Peter Kirchner, U.S. Department of Energy (DOE), Office of Biological and Environmental Research, voiced his concern about the fingerprinting system of the RCDC tool and how it would incorporate future technological advances that applied to more than one category. For instance, how would the system be programmed to categorize a new procedure that could be used to treat cancer, infection, or cardiac issues? Dr. Chabner asked if the new tool would cover cooperative group research that has multiple trials studying different diseases. Dr. Cowan asked if the projects tracked will include basic and clinical research. Dr. Hays said that the tool will track all NIH-funded research including basic, applied, and clinical research. Also, on a yearly basis, the category definitions will be updated as science advances.

Dr. Runowicz summarized the concerns of the Board as the worry of shifting authority for monitoring cancer research outside the NCI, but with the responsibility and accountability remaining within the NCI. Dr. Cowan asked if there will be a board to oversee the electronic categorization process. Dr. Hays said that the OPASI has a council of councils, with representation from the NCI council, to provide public oversight of portfolio analysis and the RCDC process. Dr. Cowan then asked what the budget was for the development of these categories and the processes and professionals involved. The estimate for developing each definition is about $10,000 and there are currently 360 definitions. Dr. Cowan wondered if the costs involved would be less than the current systems and also wondered if the one system will be sufficient and effective as a final product. Dr. Chabner was concerned that other Institutes were using different definitions of cancer for the purposes of categorizing, as opposed to the NCI's definition of cancer. Dr. Hays commented that NCI will continue to create the cancer-related definitions, but now they will be applied uniformly to all NIH projects, not just those of the NCI.

Dr. Coffey commented that he was not satisfied with the presentation, and requested a better explanation of the new tool and how it is a better system than the current one.

VIII. UPDATE: ROADMAP/COMMON FUND—DR. DINAH SINGER AND MS. ANNE TATEM

Ms. Anne Tatem, the NCI Roadmap Liaison, Division of Cancer Biology, NCI, presented an update of the NIH Roadmap for Medical Research, including information related to the Common Fund (CF) budget, Roadmap program areas approved for RM 1.5, current open Roadmap initiatives, and the NIH OPASI. The Roadmap was initiated in 2002 by Dr. Elias Zerhouni, Director of the NIH, to identify major opportunities and gaps in biomedical research that no IC could tackle alone. Three broad themes emerged: New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise. This initial phase of the Roadmap resulted in 38 solicitations issued in FY 2004–2005, resulting in the funding of 379 new grants.

Funding support for Roadmap programs has changed. Initially, the Roadmap program was supported through taps on the budgets of the NIH ICs (FY 2003–FY 2006). With the passage of the NIH Reform Act of 2006 and the subsequent passage of the FY 2007 Joint Resolution, funding for Roadmap initiatives is now covered through the CF. The FY 2007 CF budget was $483 M, and the FY 2008 President's CF budget is $486 M.

In the summer of 2006, the NIH embarked on a new process to solicit ideas for new Roadmap initiatives. This process involved the extramural and intramural scientific community, patient advocates, and the general public. The NIH anticipated spending $30 M to $50 M per year from within the existing Roadmap budget on these initiatives. More than 500 idea nominations were submitted, and five scientific areas were identified by the IC directors to be considered for further development as possible Roadmap 1.5 initiatives: the human microbiome program (HMP), epigenetics, protein capture, phenotyping, and inflammation. Working groups were formed around these topics and final concepts were presented to the NIH IC directors during their May 2007 retreat. The directors selected epigenetics and the HMP as major initiatives, and RFAs in these areas are being developed currently. The directors selected protein capture and phenotyping for future implementation. In addition to major Roadmap initiatives to move forward, the IC Directors selected broad areas that were to be pursued as either pilot studies (genetic connectivity map); coordination groups (regenerative medicine, pharmacogenomics, and bioinformatics); and strategic planning areas (health disparities, the science of science administration, and training/careers).

Recent Roadmap activities include the launching of the 2008 Pioneer and Innovator Awards application cycles and mid-course review of several initiatives initiated in Roadmap 1.0. The Molecular Libraries initiative underwent its review, and RFAs to further this initiative are in various stages of development. The National Centers for Biomedical Computing (NCBC) and Patient-Reported Outcomes Measurement Information System (PROMIS) were also approved for additional years of the CF funding. Modified proposals are under development for protein capture and phenotyping, and the connectivity map working group has planned a workshop to discuss scientific approaches. Regenerative medicine and bioinformatics are being led by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and National Library of Medicine (NLM), respectively. In addition, the health disparities group is planning to submit a proposal for consideration in February 2008.

Dr. Alan Krensky was appointed as the first director for the OPASI. OPASI's mission is to provide the NIH and its ICs with the methods and information necessary to manage their large and complex scientific portfolios; identify important areas of emerging scientific opportunities or rising public health challenges; assist in the acceleration of investments in these areas, focusing on multiple ICs; and

coordinate and make more effective use of the NIH-wide evaluation processes. NCI staff involvement in the NIH Roadmap has been significant. Approximately 40 NCI staff have been involved in Roadmap 1.0 and 1.5 activities and working groups during the past 5 years. Dr. Niederhuber, Dr. Singer, and Dr. Croyle have been involved actively in serving on Roadmap and OPASI steering committees, offering their leadership skills and scientific expertise.

Questions and Answers

Dr. Chabner asked for clarification on the facilities related to technology development that have been created for the Roadmap and how many exist. Dr. Dinah Singer, Director, Division of Cancer Biology, clarified that four or five screening centers were initially established related to the Molecular Libraries initiative, and these were awarded in response to an RFA. The NIH Chemical Genomics Center, awarded to the National Human Genome Research Institute (NHGRI), is up for recompetition. These molecular libraries screening centers perform high-throughput screening on assays provided by the research community against a large library of small molecules maintained in a central molecule repository. They also perform optimization chemistry required to produce useful *in vitro* chemical probes to modulate novel biological functions, which will lead to new ways of exploring gene functions and signaling pathways in health and disease. The data generated at these facilities will be compiled and made available to public sector biomedical researchers. Dr. Chabner asked if drug development is involved with these facilities, specifically in relationship to cancer drug discovery. Dr. Singer replied that the new facilities were not intended for drug development but a fraction of assays are targeted to cancer. Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives, added that the NCI set up a screening center at Harvard University prior to the development of the Roadmap, so potential screening assays may exist there.

Dr. Cowan asked if the results of the 3-year review process will be made public or if the Board could receive informal feedback from the NCI personnel who were involved with the review. Dr. Singer responded that some of the programs that have undergone mid-course reviews have posted executive summaries of these on the NIH Roadmap Web site and that she would inquire as to whether the detailed reviews were available for distribution.

Dr. Runowicz asked about the NCI funding contributions versus the return on cancer investment. Dr. Singer replied that during the timeframe when the ICs were tapped to contribute to the Roadmap, the NCI's return on investment in the Roadmap initiative was good, with cancer researchers being funded at a level higher than the NCI had contributed. Dr. Niederhuber agreed that the NCI competes very effectively for Roadmap dollars. Dr. deKernion requested clarification on the term limit for programs within the Roadmap. Dr. Singer explained that the Roadmap is designed to be an incubator space for new ideas to flourish and to develop new infrastructure within the Institutes. There is an ongoing controversy within the OPASI and the NIH as to whether or not a fraction of Roadmap funding should be set aside to continue long-term support of the Roadmap infrastructure.

IX. AMERICAN CANCER SOCIETY MEDAL OF HONOR: THE NCI RECIPIENTS—DRS. CAROLYN RUNOWICZ, DOUGLAS LOWY, AND MARK SCHIFFMAN

Dr. Runowicz introduced two recent NCI recipients of the ACS Medal of Honor: Drs. Douglas Lowy, Chief, Laboratory of Cellular Oncology, Signaling and Oncogenesis Section, and Mark Schiffman, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics (DCEG). The award is the highest honor given to distinguished scientists, physicians, or patient advocates in the areas of basic science, clinical research, and cancer control. The Board honored the two recipients by showing a video showcasing Drs. Lowy and Schiffman.

Basic and Translational Studies of HPV Infection. Dr. Lowy discussed public health issues for cervical cancer reduction. He described the characteristics and processes of the current L1 virus-like particle (VLP) vaccine, a second-generation LR vaccine, and a mouse cervico-vaginal human papillomavirus (HPV) challenge model, and presented an overview of basic and translational efforts in the HPV vaccine development. The HPV L1 vaccine provides systemic immunization with a noninfectious VLP. It induces high efficacy against mucosal and cutaneous infection caused by the HPV types in vaccine. Although current commercial vaccines can protect against 70 percent of cervical cancers and 90 percent of genital warts, there remain limitations. The vaccines protect only against new infections, not against established infections, and protection is type-restricted. In addition, vaccination is expensive, and vaccinated women must continue to receive regular cervical cancer screening. Dr. Lowy's outline of the public health considerations indicated that the research community must be committed to reducing the incidence of morbidity and mortality attributable to the HPV infection. Primary prevention is mainly for the next generation of women, as there is a long lead-time between vaccination and reducing the incidence of cancer, while secondary prevention can reduce the incidence of cancer in the current generation of women.

Next Steps in Epidemiologic and Prevention Research on the HPV Infection. Dr. Schiffman outlined the critical steps in cervical carcinogenesis, which begin with the HPV infection, and described recent efforts to distill the processes involved with the carcinogenic HPV genome. Ninety percent of carcinogenic HPV infections clear with time, but if infection persists, it can lead to cervical cancer. The HPV 16 and 18 are uniquely carcinogenic and may present scientists with biomarkers to predict progression. The HPV-related technology can greatly reduce the incidence of cervical cancer and the morbidity and mortality it causes, even in low-resource settings, where the problem is severe.

Dr. Schiffman suggested instituting screening with the HPV tests and begin treatment in developing countries. He also suggested vaccination of young women around the world and appropriate screening modalities for the last generations at risk over the range of settings around the world. Two examples of critical needs include incorporating new tests into the U.S. management guidelines, combining HPV testing, cytology, colposcopy, and age in risk prediction software; and adapting the HPV methods to reach low-resource regions that have a critical need for improved outpatient therapy. A low-cost, same-day HPV screening test has been already developed. Current cryotherapy is safe, but lesions can go down to 6 mm so we need to freeze them down to that level. Therefore, cryotherapy is effective in treating only one-half of the women we can identify with the precancerous stage of cervical intraepithelial neoplasia (CIN) 2-3. Improved outpatient treatment for an HPV infection would permit us to screen and treat, saving tens of thousands of lives per year. An important question remains as to who will lead the public health effort to increase the chance that the underserved are reached and to promote efficient use of resources and minimize iatrogenesis.

Questions and Answers

Dr. Coffey asked for clarification on the percentage of the HPV16 infections that develop into cervical cancer and if we could use the HPV 16 markers to predict cancer. Dr. Schiffman restated that about 20 percent of the HPV 16 infections develop precancer but there is no way to predict cancer risk by colposcopy or cytology at this time. Dr. Coffey asked about drug treatment. Dr. Schiffman explained that if we pursue a drug for treatment, it needs to be a very safe drug because cervical cancer is basically a skin lesion; it is not systemic. The challenge is to develop a simple, safe, and effective device for treating these lesions quickly in an outpatient setting.

Dr. Chabner wondered why the vaccine is not being targeted to young boys when we know that this disease is transmitted from men to women. In addition, there are the HPV infections in men that cause cancer as well. Dr. Schiffman said that the vaccine is not focused on boys currently because there is no evidence yet of protection in males. Dr. Lopez pointed out that the vaccine protects against *Condyloma accuminata,* so it would make sense to vaccine both genders. Dr. Lowy mentioned that an experimental vaccine against herpes simplex was partially effective in women but demonstrated no efficacy in men, so Dr. Chabner asked for more specifics about males' immunologic response to the HPV. Dr. Lowy explained that the rate of antibody development against the major capsid protein is about one-half as frequent in men as in women in response to natural HPV infection, but there was no difference in immunologic response to the vaccine in Dr. Lowy's studies. Dr. Niederhuber reminded Board members of the increasing evidence and incidence of head and neck and nasopharyngeal cancers attributable to the HPV 16. Dr. Chabner and Dr. Lowy agreed that a substantial proportion of these cancers are attributable to the HPV 16, perhaps more than cervical cancer.

Dr. Runowicz acknowledged Dr. Schiffman's team for a true example of translational research. Mr. Ingram congratulated Dr. Lowy and Dr. Schiffman for their recent awards and thanked them for their collaborative efforts with industry. He stated that Merck and GlaxoSmithKline are committed to working together to developing treatments that are affordable to all. Dr. Atala congratulated Dr. Lowy and Dr. Schiffman on their work and asked for elaboration on the idea of secondary prevention. Dr. Schiffman replied that secondary prevention refers to screening. Colposcopy is widely accepted as a screening tool in the United States, but it is only 55 percent sensitive in detecting incipient precancers. However, it can be used in conjunction with the HPV screening methods and computer models to help predict risk. Dr. Atala added that visuals on the pap smears have limitations. Dr. Schiffman stated that high-grade squamous intraepithelial lesions (HSIL), which are microscopic, are still very useful.

Dr. Coffey asked for clarification on Dr. Schiffman's specifications for cryoablation needs. He also offered that chemical and thermal ablation could be considered also as an option for cervical lesions and asked if there were current efforts into either of these. Dr. Schiffman answered that he was not aware of any studies presently. Dr. Lopez stated that she was surprised to learn that carrageenan was being used in translational efforts as a microbicidal agent. Dr. Lowy explained that carrageenans are sulfated polysaccharides that are widely used for their gelling properties as food additives and vaginal lubricants. Carrageenans of low molecular weight are known to induce inflammation and have been shown to induce gastrointestinal cancer in animal models when administered orally, but commercial use is limited to high-weight carrageenans. Although humans do not have enzymes to break down these substances, they have passed animal toxicity tests in the genital tract and are being tested in Phase III trials as a topical microbicide against the HIV. Carrageenans are about 1,000 times more sensitive against the HPV than against the HIV.

X. UPDATE: CENTER FOR CANCER RESEARCH—DRS. ROBERT WILTROUT, LEE HELMAN, MICHAEL GOTTESMAN, CAROLE PARENT, WILLIAM BONNER, YVES POMMIER, AND RAFFIT HASSAN

Introduction. Dr. Robert Wiltrout, Director, Center for Cancer Research (CCR), provided an overview of the CCR, which is an intramural division of the NCI that supports basic, translational, and clinical research. The Center was formed in 2001 as a means of uniting the NCI's intramural work in basic and clinical sciences to more rapidly capture translational opportunities and move research from the laboratory to the clinic and back to the laboratory. The CCR fosters a culture of collaboration, particularly with the sort of recent extensive discussions around team science and changed its review process in conjunction with the NCI's Board of Scientific Counselors (BSC) so that team science is appropriately

rewarded during the review process of the individual projects. Faculty and working groups facilitate crosscutting initiatives, and input from the community is most welcome. The CCR's mission is to make breakthrough discoveries in basic and clinical cancer research that are developed into novel therapeutic interventions for adults and children afflicted with cancer and the HIV. The CCR's clinical program supports concept-based, science-driven clinical trials that evaluate new therapies in most cases rather than test existing ones. It works to discover and develop molecular targeted agents and novel technologies, and to develop better preclinical models and methods to expedite development of novel interventions and shorten the drug evaluation timeline. During 2007 the CCR accrued almost 1,200 patients, most of whom are enrolled on early Phase 0, I, and II therapeutic trials. It is composed of 50 basic laboratories and/or clinical branches that include about 260 principal investigators (PIs). Centers of Excellence have been formed and focus on immunology, chromosome biology, the HIV and cancer virology, and molecular oncology. An additional center on molecular epidemiology is a partnership with the DCEG. Dr. Wiltrout told members that copies of the CCR's strategic plan and its second issue of its magazine, *Connections*, would be available at the next NCAB meeting. Dr. Wiltrout introduced the speakers: Dr. Michael Gottesman, Chief, Laboratory of Cell Biology, the CCR; Dr. Carole Parent, Principal Investigator, Laboratory of Cellular and Molecular Biology, the CCR; Dr. William Bonner, Senior Investigator, Chromatin Structure and Function Group, Laboratory of Molecular Pharmacology, the CCR; Dr. Yves Pommier, Chief, Laboratory of Molecular Pharmacology, the CCR; and Dr. Raffit Hassan, Chief, Solid Tumor Immunotherapy Section, Laboratory of Molecular Biology, the CCR.

New Tricks From a Multidrug Transporter. Dr. Gottesman said that mechanisms of drug resistance in cancer frequently involve decreased uptake or increased efflux of drugs. Other properties allowing survival include reduced apoptosis, altered cell-cycle checkpoints, or increased rates of repair of cellular damage. Molecular analysis of drug resistance in human cancers can be used to predict response to specific therapies, develop novel chemotherapies, and learn more about the cellular pharmacology and pharmacokinetics of drugs. The ABC transporters confer resistance to anti-cancer drugs. The multi-drug resistance 1 gene (MDR1) encodes an ABC transporter, P-glycoprotein (PgP). The PgP removes hydrophobic substrates, including some commonly used chemotherapy drugs such as vinblastine, taxol, and doxorubicin, from the plasma membrane. The major substrate/inhibitor binding site of the PgP is large, and substrates and inhibitors overlap.

The MDR1a/MDR1b knockout mice are viable but sensitive to toxic xenobiotics, especially neurotoxins. The pharmacokinetics of a number of the PgP substrates also are altered in these animals, with increased gastrointestinal absorption and decreased kidney and liver excretion observed. More than 50 single nucleotide polymorphisms (SNPs) have been reported in the human MDR1 gene and have been associated with different phenotypes. The C1236T, G2677T, C3435T haplotype has been linked to altered digoxin and fexofenadine pharmacokinetics, altered cyclosporine A and tacrilimus toxicity in transplant patients, and altered incidence of Crohn's disease, colon cancer, and Parkinson's disease.

Haplotypes carrying the synonymous C3435T SNP show differences in substrate specificity and inhibitor sensitivity compared to wild-type. Use of a conformation-sensitive antibody and differential trypsinization patterns suggested differences in conformation between the proteins encoded by the wild-type and the C3435T haplotype. The three polymorphisms in the haplotype replace relatively common codons with rarer ones that affect the PgP conformation and functions, possibly because they result in altered kinetics of translation due to requirements for rarer tRNAs. This situation could explain the conservation of the third position for many codons, might explain some forms of non-Mendelian inheritance, and might explain linkage of phenotypes to other synonymous polymorphisms. The C3435T haplotype could have selective advantages because it could affect the pattern of drug resistance and the ability to respond to specific inhibitors.

Questions and Answers

Dr. Coffey observed that pharmaceutical companies are testing new agents against the cells to determine if there is drug resistance, and that some analogs (e.g., taxanes) have reached the clinic. He asked about the regulation of translation by micro-RNAs. Dr. Gottesman indicated that this is being studied: the sites could be micro-RNA binding sites or binding sites of other regulatory proteins; there are no data available at this time.

Dr. Cowan wondered whether where the protein is located might influence the function of the protein, and whether this information might be useful for drug development. Dr. Gottesman agreed that minor nucleotide changes that lead to fairly significant conformational changes might affect where the protein is exactly in the cell. Thus, polymorphisms could affect interactions of cancer cells with membrane active agents such as VEGF inhibitors.

Signal Relay During Chemotaxis. Dr. Parent described research in understanding the mechanisms by which cells are able to sense and navigate directionally in response to chemoattractants, a phenomenon referred to as chemotaxis. Chemotaxis is important in many physiological processes and is equally important in pathological conditions such as cancer, cancer cell migration, and metastases. Neutrophils are good at chasing and capturing bacteria and phagocytosis by following an attractant that the bacteria secrete. This chemotaxis behavior also is essential for other types of organisms, such as the social amoeba *dictyostelium*. Cells have the ability to align in a fashion stream as well. *Dictyostelium* cells live in two independent states: in the presence of nutrients, they eat and divide; in the absence of nutrients, they enter a developmental program to survive after 5 hours of starvation by becoming very mobile and polarized and forming a stream of cells. After 6 to 7 hours, they form an aggregate that leads to a "fruiting body" that is comprised of spores on top of vacuolated cells. This process requires chemotaxis; the signaling pathway that the cells use to chemotax to form the structure are highly conserved with eukaryotes. The amoeba *dictyostelium* is amenable to genetic manipulation and has been very useful to study chemotaxis. Cells that are exposed to chemoattractant gradient are able to sense that gradient and to signal relay to neighboring cells. Most chemoattractants respond to signals that are binding to receptors that are members of the G protein coupled receptors.

Current chemotaxis research is studying how these biochemical responses lead to very spatially restricted responses in cell migration. Early studies showed that both receptors and the G protein remain uniformly distributed at the plasma membrane when cells are migrating. Dr. Parent's research has revealed that a subtype of a protein, called cytosolic regulator adenocyclase (CRAC) translates specifically at the leading edge of chemotaxis cells; it also has been found to act in the neutrophils. The cascade that leads to the activation of the CRAC includes the activated PI3 kinase, which was phosphorylated at the plasma membrane to make phosphatidylinositol phosphate (PIP)3, and the phosphatase and tensin homolog (PTEN) enzyme, which dephosphorylates phosphate everywhere except at the leading edge. The CRAC is essential in the *dictyostelium* to activate adenylcyclase, which generates cyclic adenosine monophosphate (cAMP), a chemoattractant that is integral to the aggregation of the cells.

Dr. Parent described her laboratory's work, particularly the protein that makes the cAMP gene. Adenylcyclase is enriched at the back of migrating cells. Cells without adenylcyclase were found in a micropipette assay to migrate directly into the pipette; the adenylcyclase chemotax is not needed for this process, but it is needed for the streaming behavior. Based on these and other findings, a model now suggests that the accumulation of the adenylcyclase at the back of the cell exists to generate a compartment where the cAMP will be secreted specifically to attract cells. A protein of transmembrane domain is able to accumulate because the adenylcyclase labels very dynamic intracellular vesicles.

Vesicle trafficking is involved in the accumulation at the back of the cell. The architectural cells show impressive microtubule networks that are involved in migrating and moving cargo in cells. The adenylcyclase vesicles in these cells co-localized on the microtubules, suggesting that the microtubules move the vesicles to the back of the cell and are required for chemotaxis. Cells treated with an agent that inhibits microtubule function lose their ability to align and form the stream; the adenylcyclase is not enriched at the back, the signal is not relayed to neighboring cells, and cells are unable to form chains. Another interesting finding was that migrating cells leave behind tracks that contain the adenylcyclase. Some of the components in the track actually signal transduction components. An isometric accumulation of new vesicles was found between cells. The adenylcyclase was found in highly dense intracellular pockets that are on vesicular components, called multivesicular bodies. An amazing activity of extracytosis of these vesicles has been seen. These vesicles also were contained as trails on the surface.

These findings have led to a model in which cells are sensing gradients and migrating and are expressing receptors across their surface. The CRAC protein has a strong cytosolic component and is located at the leading edge. Adenylcyclase is found at the plasma membrane and is highly enriched at the back vesicles; these vesicles are released and leave behind trails for cells to follow in the context of migration.

Signal type chemotaxis and migration is important in the subtype of cancer and has been shown to metastasize to specific tissues based on the fact that the cancer cells express specific chemokine receptors that migrate to tissue that will expose the corresponding chemokine. Dr. Peter Friedl proposed in 2004 that cells undergoing an epithelial transition might later undergo an amoeboid transition in metastases clusters. A model could look at the amoeboid type migration of metastasis to obtain the differentiation process. His research in cell migration in collagen found that the cells often left behind the vesicles; this was seen in the trails of cancer cells. Dr. Parent said that her laboratory will continue to study the mechanisms that *dictyostelium* cells use to follow each other and aggregate, particularly in the context of metastases and cancer cells migrate in the chemotaxin.

Questions and Answers

Dr. Niederhuber said that little is known about the process of metastases in the organism, and this gap in research knowledge has provided an impetus for the NCI to bring together experts from the theoretical physics and applied mathematics arenas to consider biologic problems, such as gradients and multiple dimensions, related to cancer. Dr. Parent added that physicists often indicate that gradients will disappear in seconds after a cell releases a chemoattractant; collaborations between the NCI and biophysicists are occurring to address this.

The H2AX Phosphorylation in Cancer and Drug Development. Dr. Bonner explained that the H2AX is an evolutionarily conserved histone protein that represents between 2 and 10 percent of total H2A in mammals. The H2AX becomes phosphorylated on serine 139 within minutes of the DNA double-stranded break (DSB) formation, in an almost immediate and highly amplified response. Antibodies to phosphorylated H2AX (γ-H2AX) show that foci of this protein form in interphase and mitotic cells after exposure to ionizing radiation at the DNA break sites; one γ-H2AX focus represents one DSB. These foci are detectable by 1 minute after exposure to ionizing radiation and reach maximum intensity after 30 minutes; foci decrease in number after 30 minutes. Some fragmented chromosomes have a γ-H2AX focus at one end.

The H2AX knockout mice have smaller testes that lack sperm. These mice also have incompetent class switch recombination, but competent V(D)J recombination. The mice show high levels of aberrant metaphases and chromosomes in the T cells, and the B cells that are deficient in foci formation for the

NBs1, 53bp1, and Brca1, but not the Rad51. The H2AX -/- mice also are sensitive to ionizing radiation and their cells lack the rapid phase of the DNA DSB rejoining.

The γ-H2AX foci numbers increase during human cell senescence *in vitro* and also during mouse tissue (somatic and germ) aging *in vivo*. This apparent increase in genome instability may be due to slow growth of the γ-H2AX foci and slow mobilization of the DSB repair proteins. Late passage normal human fibroblasts (NHF) have retarded mobilization of the Mre11, which participates in the repair of the DNA DSBs, to the γ-H2AX foci compared to early passage NHFs. Cells from patients with Werner syndrome, a disorder characterized by accelerated aging, also have extremely retarded mobilization of the Mre11 to the γ-H2AX foci. Mouse and human cells have similar numbers of the γ-H2AX foci at senescence, but the sources of these foci are different depending on telomere length. Two types of the DNA lesions, uncapped DNA ends, and the DNA DSBs are found in senescent cells and have equivalent involvement in cellular senescence. In addition to marking aging cells, the γ-H2AX could function as a biomarker for early cancer detection because increased DNA damage is a general characteristic of cancer development.

Dr. Pommier explained that the γ-H2AX could be used as a biomarker for topoisomerase 1 (Topo-1) inhibitor activity. Topoisomerases relieve the strain on the DNA that develops as the DNA is replicated. Topo-1 functions by binding the DNA, cutting one strand to relieve the strain, and then re-annealing the DNA. The Topo-1 inhibitor camptothecin binds at the cleavage site and prevents re-ligation, leading to a DSB, which in turn induces apoptosis. The camptothecin analogue topotecan, CPT11, is used clinically in the treatment of ovarian, lung, and some other cancers.

In the presence of camptothecin, the γ-H2AX colocalizes with the replication foci, indicative of damage at the foci. This damage persists for more than 4 hours after removal of the drug. The γ-H2AX foci also co-localize with the phosphorylated protein kinase ATM (ataxia telangiectasia mutated) and the Chk2 kinase. Persistent induction of the γ-H2AX thus can serve as a biomarker for the Topo-1 inhibitors. Work is in progress to develop non-camptothecin Topo-1 inhibitors. Camptothecin is chemically unstable; in contrast, the non-camptothecin Topo-1 inhibitors, called indenoisoquinoline are highly stable. Three of these compounds have been selected for clinical development. Two have been shown to induce the γ-H2AX as well as or better than camptothecin.

The availability of a well-defined biomarker with a persistent signal (i.e., the γ-H2AX foci) for these drugs will assist with translation to a clinical setting. To capitalize on use of this biomarker, a joint effort between Science Applications International Corporation (SAIC) and NCI is underway to develop a pharmacodynamic assay for the γ-H2AX. This immunofluorescence-based assay has been used to quantitate emergence of the γ-H2AX foci in a mouse xenograft after administration of idenoisoquinoline. The response can be quantitated and dose-response data generated.

Questions and Answers

Dr. Coffey noted that Dr. Mike Kastan reported research that swelling the chromatin would set off the ATM phosphorylation, suggesting a chemomechanical affect as well as DNA damage; he asked whether this could set off the H2AX. Dr. Bonner replied that investigators are hypothesizing that this is the process that occurs. The ATM is a dimer with inactive H2AX; damage from the DNA opens up the dimer, and it starts phosphorylating H2AX.

Dr. Chabner asked about the H2AX in terms of methylation sites. Dr. Bonner said that the H2AX has these sites, but they have not been well studied. There is one antibody— the acetylated lysine 5—to a modified H2A. Dr. Runowicz asked whether the H2AX has been sought in pre-invasive ductal carcinoma *in situ* (DCIS). Dr. Bonner indicated that this has been studied in European laboratories, and results show

some genome instability or other cause that moves the process toward cancer.

Dr. deKernion raised the issue of the development and commercialization of promising agents beyond early clinical trials. Dr. Pommier said that one parameter for agent transference to a company pipeline could be the agent's clinical activity. Dr. Chabner explained that licensing and Cooperative Research and Development Agreements (CRADAs) often are the vehicles used in the drug commercialization process.

Dr. Chabner asked about the drug's advantages in comparison to irenotecan. Dr. Pommier replied that it is chemically solid; camptotecins are alpha hydroxylactone. He noted that 90 percent of the cancers tested are inactivated immediately after administration. Other advantages include the number of studies on the MDR and the activity in the model system. Moreover, the genomic target in the topo cleavage complexes is in a different place.

Dr. Krystal wondered if the H2AX studies have examined the ATM/ATR inhibitors in relation to camptotecins and Topo1 inhibitors. Dr. Pommier said that this has not been studied, but more is being learned about the ATM inhibitors. Dr. Coffey asked about mitochondrial DNA. Dr. Pommier replied that mitochondria in the DNA are somewhat sheltered.

Dr. Atala added that this research provides a great example of the NCI's work in developing technologies that mitigate the risk to bring these discoveries faster to the patient.

Immunotherapy for Malignant Mesothelioma. Dr. Hassan said that mesothelioma is a relatively rare cancer, but its incidence continues to increase worldwide. Exposure to asbestos fibers is the principal risk factor for the disease, and there is a long latent period between exposure to asbestos fibers and development of mesothelioma, typically 30 to 40 years. It is an aggressive disease with poor prognosis; treatment with pemetrexed plus cisplatin is the only FDA-approved treatment, but the median survival of patients under this treatment is only 12 months. The underlying hypothesis of this research is that immunotherapy targeting mesothelioma tumor antigens, either alone or in combination with chemotherapy, can lead to effective therapy for the cancer. The tumor differentiation antigen mesothelin is the target for cancer therapy; mesothelin is a cell-surface glycoprotein that is highly expressed in many cancers, including ovarian, lung, and pancreatic. Recent studies have shown that mesothelin might play an important role in tumor metastases as it is a receptor for, and has high affinity and specificity for, the cell surface glycoprotein CA125 (now called the MUC-16). The CA125 present on tumor cells after binding to mesothelin that is present on the mesothelial cells, which line the pleura/peritoneal cavity, could lead to tumor and metastases.

Two approaches to target mesothelin for therapy are: recombinant immunotoxin (SS1P) and chimeric monoclonal antibody (MORAb-009). Recombinant immunotoxins are very potent and not toxic to the bone marrow, and resistance is infrequent; the disadvantage, however, is that these are immunogenic proteins and that patients can get one or two cycles of therapy, especially those with solid tumors. Studies have shown that the SS1P is cytotoxic to mesothelin expressing tumor cells obtained directly from patients with mesothelin in ovarian cancer, and it causes the regression of mesothelin positive tumors in mice. A Phase I clinical trial with the SS1P was conducted with 34 patients enrolled, 20 with mesothelioma, 12 with ovarian cancer, and 2 with pancreatic cancer. The maximum tolerated dose was 45 micrograms per kg, and the dose limiting toxicity was self-limiting pleuritis. The results were that 4 patients had objective minor response, 18 had stable disease (including complete resolution of ascites in two patients), and 11 patients had progressive disease. In a further study of whether SS1P in combination with chemotherapy (taxol, cisplatin, and gemcitabine) results in increased activity, a marked synergy in animal models between the SS1P and chemotherapy was seen. This increase in sensitivity is

caused because chemotherapy decreases the mesothelin concentration in the tumor extracellular fluid, allowing more SS1P to bind to the tumor cell and mediate cell kill. A future study will look at the SS1P plus pemetrexed and cisplatin for therapy of malignant pleural mesothelioma.

The MORAb-009 is an IgG1 antibody with the same Fv binding region as the SS1P. *In vitro*, the MORAb-009 kills mesothelin expressing cells by antibody dependent cellular cytotoxicity. Its advantages in cancer therapy are that it is less immunogenic so patients can receive multiple cycles and, more important, it has a novel mechanism of action in that it inhibits mesothelin CA-125 binding. A Phase I clinical trial was initiated in July 2007 to determine the safety and maximum tolerated dose of the MORAb-009. To date, 24 patients have been treated on this study, including 13 patients with mesothelioma, 7 with pancreatic cancer, and 4 with ovarian cancer; a wide range of dose levels was given, and the drug was well tolerated. The study has shown that treatment with the MORAb-009 resulted in a marked increase in serum CA-125 levels in patients; the CA-125 levels decreased to baseline values when treatment was stopped. Pharmacokinetic analysis shows dose-dependent increase in the MORAb-009 blood levels in patients. Results suggest that the increase in the serum CA-125 levels is a pharmacodynamic effect of antibody binding to mesothelin and evidence in patients that it can inhibit mesothelin CA-125 binding.

Dr. Hassan described a pleural/peritoneal cavity that contained mesothelial cells, which express mesothelin, and ovarian cancer or mesothelioma cells, which express both the CA-125 and mesothelin. The binding of the CA-125 on the tumor cells to mesothelin can lead to cell attachment and tumor metastases. Because normal mesothelial cells also express the CA-125, the binding of the CA-125 to mesothelial tumor cells can form a second anchor and lead to further tumor spread. There can be interactions between the tumor cells leading to homotypic adhesion and additional tumor metastases. For patients with mesothelioma and ovarian cancer, the MORAb-009 can interfere with attachment by inhibiting mesothelin and can inhibit this interaction by binding to the tumor cells.

Future work to exploit the MORAb-009 inhibition of mesothelin and the CA-125 binding for cancer therapy include the evaluation of other tumor types, further studies on models of tumor metastasis, and a clinical trial to prevent metastasis. Clinical trials of the MORAb-009 with chemotherapy have begun, and there are plans for a Phase II study of the agent in combination with pemetrexed and cisplatin for pleural mesothelioma. Dr. Hassan mentioned that a third agent, the CRS-207, also is being studied in the treatment of mesothelin-targeting tumors.

Questions and Answers

Dr. Runowicz asked whether the drug could have the same effect on the peritoneum or the mesothelium as surgery does, which is that of the release of the CA-125 rather than a binding activity. Dr. Hassan said that this is still being researched but that signs of inflammation have not been witnessed. There are plans to look at stored serum for the C reactive protein and to make certain that the antibody is not interfering with the CA-125 detection assay. Dr. Niederhuber suggested the possibility of using the antibody as a vehicle to carry radioactivity or toxin agents. Dr. Hassan replied that an imaging study to determine the antibody's localization has been initiated. Dr. Runowicz suggested that, because most ovarian tumors are chemosensitive and will go into remission, the MORAb linked to a beta emitter or other targeted therapy might be useful in a consolidation setting where a novel therapy is desperately needed.

Dr. deKernion asked about the anti-tumor efficacy of the naked antibody and commented on its infrequent success rate. Dr. Hassan said that *in vitro* it mediates antibody-dependent cellular cytotoxicity. It could have activity by the ADCC or other mechanisms; the ADCC activity may be increased when

combined with chemotherapy. He also noted the immunogeneity and tumor penetration issues in solid tumors. Dr. deKernion asked whether a combination with radiotherapy has the result of cell injury and disruption. Dr. Hassan responded that some preclinical work has been performed in this area, but there is a problem with bone marrow toxicity.

Dr. Cowan asked about the administration of the antibody; he also wondered about the effect of changing the sequencing of the agents (i.e., administering the antibody first, followed by the chemotherapy agent). Dr. Hassan confirmed that the antibody is given intravenously and said that more activity is seen in animal models when the chemotherapy drug is administered first. Dr. Cowan suggested that the sequencing issue for ovarian or interperitoneal antibodies warrants further study from acute and long-term perspectives.

XI. PROGRAM REVIEW OF THE DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS—DRS. JOSEPH F. FRAUMENI, JR., MARGARET A. TUCKER, AND STEPHEN CHANOCK

Introduction. Dr. Joseph F. Fraumeni, Jr., Director, the DCEG, said that there has been evidence from the global variation of cancer that environmental factors account for a large proportion of cancer incidence. Research priorities in cancer etiology have shifted through the decades from oncogenic viruses (1960s), chemical carcinogens from occupational and environmental exposure (1970s), to lifestyle practices (1980s), to the contribution of inherited genes (1990s). The recent completion of the human genome and haplotype mapping project has caused additional emphasis on genetic susceptibility. New genotyping platforms, particularly genome-wide association studies (GWAS), have made it possible for epidemiologists to identify the low and medium penetrance gene variants that are common in the general population and may have a substantial impact on the burden of cancer, especially through interactions with environmental factors. As a byproduct, the proportion of so-called “spontaneous” tumors that are thought to arise by random events or by chance is likely to shrink. Dr. Fraumeni introduced the speakers: Dr. Margaret A. Tucker, Director, Human Genetics Program and Chief, DCEG, and Dr. Stephen J. Chanock, Chief, Laboratory of Translational Genomics, DCEG.

Defining the Genetic Contribution to Cancer: Genome-Wide Association Studies and Follow-Up Opportunities. Dr. Tucker said that the NCI’s research on the genetic contributions of cancer causation started with Dr. Fraumeni and Dr. Fred Li’s studies of families with clusters of specific tumors in the 1960s. In evaluating a family with bladder cancer in the father and three sons, Dr. Fraumeni hypothesized that bladder tumors had both genetic and environmental components of causation. Drs. Li and Fraumeni also evaluated several families with an unusual constellation of tumors including soft tissue and bone sarcomas and breast carcinoma. The Li-Fraumeni syndrome is characterized by dominant inheritance, striking variety of early-onset tumors, predisposition to second primaries, and germline mutations of the *p53* gene. Since that time, a large number of high-risk susceptibility genes have been identified through various studies using linkage analyses, which tracks both genetic markers and cancers through families. DCEG investigators have been involved in the identification of at least eleven of these genes which confer high risk of developing cancer within specific families. Candidate gene studies take a different approach and look at common variations that are frequent in the general population; these genetic variations confer much lower risk. One example of this is the NCI’s study of the *NAT2* slow acetylation and the *GSTM1* null genotypes, and the risk of bladder cancer. The investigators were able to assess the contribution of both genetic variation and environmental exposures (cigarette smoking). They found a stronger effect of smoking on bladder cancer risk among the NAT2 slow acetylators, proving Dr. Fraumeni’s hypothesis that bladder cancer etiology has both genetic and environmental components.

The NCI's DCEG and the Division of Cancer Control and Population Sciences (DCCPS) have co-initiated a "cohort consortium" that includes 34 cohorts, many of which have biospecimens that were collected prospectively prior to diagnosis of cancer; they also have excellent epidemiologic variables and risk factors for multiple tumors. Because individual investigators in the cohort had been collaborating with each other, they were well poised to quickly take advantage of the opportunity to conduct GWAS when new technology made it feasible. These studies use genetic markers across the genome to assess association with common alleles in very large sample sizes. The NCI has worked closely with the NHGRI to establish the NIH-wide policies and procedures for handling these types of complex studies. The NCI's GWAS are conducted through the Cancer Genetic Markers of Susceptibility (CGEMS) project, which was initiated in 2005. It is a highly collaborative activity involving intramural and extramural investigators, including epidemiologists with prospective cohorts and molecular epidemiology studies, molecular geneticists at the Core Genotyping Facility, and an analytic team. Project data are posted quickly in the caBIG™. The initial selection of prostate and breast cancers for the CGEMS was based on available superb epidemiologic and phenotyping data, large public health impact, and consistent effect of genes in epidemiologic studies.

Dr. Chanock described some of the recent findings from the CGEMS' breast and prostate cancer studies. The assembly of dense markers is providing the opportunity for accelerating association to identify low to moderate penetrance alleles for cancer susceptibility. Replication of notable findings is key to ensure that findings of sufficient statistical significance occur in large datasets. Because of the challenge of false positive results, Dr. Chanock said that GWAS recently have identified a region in 8q24 that is important for more than one major cancer (in this instance, colon and prostate cancers), which is an exciting discovery for the field. GWAS can identify novel regions in the genome from which markers can be chosen to investigate risk and etiologic pathways. The CGEMS studies include three phases to establish loci: initial study, followup #1, and followup #2. The followup #1 phase has been completed for both breast and prostate studies, and the followup #2 phase has begun for prostate. The breast cancer scan was conducted through the Nurse's Health Study in partnership with Harvard investigators; it was focused on postmenopausal invasive breast cancer, and the replication strategy is designed to determine the largest and most comprehensive set of variants. So far, common genetic variants in the fibroblast growth factor receptor 2 gene (*FGFR2*) have been reported.

In the prostate cancer study, CGEMS has used the population-based Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial to oversample for aggressive (Gleason 7+ or beyond Stage 2) versus nonaggressive prostate cancer. The initial study tested 540,000 Tag SNPs and observed a series of signals in the 8q24 region; this was reduced to approximately 28,000 SNPs in followup study #1 and will involve 7,600 or more in followup study #2. Study #1 revealed 150 regions that are considered promising, 4 of which reached strong statistical significance. The fine mapping phase will look at regions achieving a high degree of statistical significance, and efforts are underway to investigate the gene-environment interaction. Approximately 10,000 SNPs have been identified that can effectively monitor possible population stratification. The PLCO samples were examined for admixture coefficient using two different techniques, structure and principal component analyses, to find a common set to monitor diseases while ensuring that subtle differences were considered. The CGEMS' work in the 8q24 region has identified the SNP rs6983267 as a second independent marker for prostate cancer; this is the same marker that four colorectal cancer scans have reported as their strongest finding as well. Replication studies of the SNPs in 8q24 also have been analyzed to estimate overall odds ratios for heterozygotes and homozygotes in populations. Results suggest that the SNPs rs6983267 and rs1447295 contribute substantially to the population burden of prostate cancer. Other studies also are looking at the 8q24 region as a possible master cancer region. To expedite access to this data and to be able to use it to test hypotheses and develop different methodological approaches, the CGEMS has posted the pre-computed

analyses on the caBIG™ with no restrictions, and the raw genotype or case control agent is available to those with registered access to accelerate their research with their particular studies.

Current GWAS activities are focused on five cancers: breast, prostate, pancreatic, bladder, and lung. Followup studies include these as well as colorectal, kidney, non-Hodgkin's lymphoma (NHL), and ovarian cancers. Many of these scans are conducted through collaborative efforts between investigators and among consortia and other extramural groups.

Dr. Tucker summarized the public benefits of the CGEMS, including the rapid public posting of summary SNP level data and the accessibility for investigators from commercial, academic, and government institutes to obtain individual-level data. An open-source toolbox of analytic software and accompanying tutorial will be released shortly to help manage the data and analyze GWAS studies. DCEG investigators also participate in the NIH Genes, Environment and Health Initiative (GEI) and have received funding for a GWAS in lung cancer. Concurrent analyses in GWAS include the primary main effects analyses of association with agnostic SNPs, candidate gene analyses, methodologic and epidemiologic analyses, and fine mapping/sequencing of regions. The Laboratory of Translational Genomics has been established at the NCI under the leadership of Dr. Chanock, and a search for tenure-track staff is underway. The laboratory is being established to pursue leads from GWAS or linkage studies for gene identification and functional studies. A Center of Excellence in Integrative Cancer Biology and Genomics in the Intramural Research Program also has been established and will encourage close collaboration between DCEG and CCR to identify genes, increase sequencing capacity, and build a molecular pathology capability, among other tasks.

Questions and Answers

Dr. John Krystal, Director, Clinical Neurosciences Division, National Center for Posttraumatic Disorder, the U.S. Department of Veterans Affairs, asked whether the CGEMS has looked at lymphoid tumors with the translocation of CMYC or their loci reproducibly being translocated with CMYC. Dr. Chanock said that the study has not yet had this opportunity but noted that colleagues in the extramural community are examining particular SNPs with specific somatic changes.

Dr. Chabner raised the issue of risk ratios compared to environmental and lifestyle issues or hormonal exposures. Dr. Chanock replied that it is too soon to have an answer to how much of the overall genetic contribution is attributable to common variants in populations. Dr. Cowan asked about the high-throughput sequencing studies on 8q24 in populations. Dr. Chanock indicated that work is underway in this area. Dr. Niederhuber said that the CGEMS is laying the foundation for cancer prevention in the future and that integration and collaboration among all parties, including the Cancer Centers, is important to accomplish this work.

A discussion ensued about the current emphasis in cancer placed on individualized medicine and on the R01 mechanism. Dr. Coffey said a balance is needed between team science and individual investigator approaches and made an analogy with the National Aeronautics and Space Administration's (NASA) and Guggenheim's separate efforts to develop a rocket to reach the moon; this goal would not have been accomplished without the efforts of both entities. Dr. Niederhuber said that the CGEMS work will empower the R01 community, and Dr. Barker and Dr. Atala agreed that the role of the R01 community should not be diminished. Dr. Barker said that the team science method promotes efficient research of genes that can be analyzed via algorithms by the R01 community to lead to personalized medicine. Dr. Cowan said that individual investigators will be important to study and validate potential phenotypes that appear to be associated with a specific gene, region, or marker. Dr. Fraumeni commented on the opportunities available for enthusiastic young scientists in this field.

Dr. Niederhuber asked about the integration of the whole genome scan with The Cancer Genome Atlas (TCGA) activities. Dr. Tucker described collaboration between the TCGA and the GEI in squamous cell lung tumors. It is hoped that research will advance based on the somatic mutation and expression data from tumors that have been collected already; there likely is genetic variation, for instance, that will determine how a patient metabolizes chemotherapy drugs.

XII. CLOSED SESSION—DR. CAROLYN D. RUNOWICZ

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552(b)(c)(6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Board would be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

There was a review of intramural site visits and tenured appointments, committee discussions, and recommendations. There also was a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was potential conflict of interest, real or apparent.

XIII. ADJOURNMENT—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz thanked all of the Board members, as well as all of the visitors and observers, for attending.

There being no further business, the 144th regular meeting of the NCAB was adjourned at 5:30 p.m. on Tuesday, November 27, 2007.

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Date Carolyn D. Runowicz, M.D., Chair

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Date Paulette S. Gray, Ph.D., Executive Secretary