MEETING SUMMARY
PRESIDENT'S CANCEL PANEL
TRANSLATING RESEARCH TO REDUCE THE BURDEN OF CANCER

January 24, 2005
New York, NY

OVERVIEW

The purpose of the meeting, the last of four regional meetings, was to examine barriers to progress in translating cancer research into reductions in suffering and death due to cancer. The President's Cancer Panel (PCP, the Panel) is seeking input to help develop its recommendations to the President of the United States, the U.S. Congress, the Secretary of Health and Human Services (HHS), and the broader community of researchers, policy makers, advocates, and others within the cancer community.

PARTICIPANTS

President's Cancer Panel (PCP)

LaSalle D. Leffall, Jr., M.D., F.A.C.S., Chair

Margaret Kripke, Ph.D.

National Cancer Institute (NCI), National Institutes of Health (NIH)

Maureen O. Wilson, Ph.D., Assistant Director, NCI, and Executive Secretary, PCP

Andrew C. von Eschenbach, M.D., Director, NCI

Sarah Birckhead, M.S.W., Special Assistant, Office of the Director, NCI

Andrea Collins, Deputy Committee Management Officer, NCI

Claire Harris, Committee Management Officer, NCI

Heather Kapp, M.P.H., M.S.W., NCI

Karen Parker, M.S.W., Special Assistant, PCP, NCI

David Pugach, J.D., Legislative Analyst, NCI

Abby Sandler, Ph.D., Institute Review Office (IRO), NCI

Doug Ulman, Director's Consumer Liaison Group, NCI

Speakers

Karen Antman, Ph.D., Deputy Director, Translational and Clinical Science, NCI

Wendy Chung, M.D., Ph.D., Irving Assistant Professor of Pediatrics and Medicine, Columbia University Medical School

Carolyn Clancy, M.D., Director, Agency for Healthcare Research and Quality

Ethan Dmitrovsky, M.D., Chairman and Andrew G. Wallace Professor, Department of Pharmacology and Toxicology, Dartmouth Medical School

Harold P. Freeman, M.D., Director, The Ralph Lauren Center for Cancer Care Prevention

William N. Hait, M.D., Ph.D., Director, The Cancer Institute of New Jersey; Associate Dean of Oncology Programs, UMDNJ–Robert Wood Johnson Medical School*

Robert A. Ingram, Vice Chairman, Pharmaceuticals, GlaxoSmithKline*

Kathie-Ann Joseph, M.D., M.P.H., Assistant Professor of Surgery, Columbia University College of Physicians and Surgeons

Howard Koh, M.D., M.P.H., Associate Dean for Public Health Practice
Professor of Health Policy and Management, Harvard School of Public Health*

Kitta MacPherson, Science Writer, *The Star-Ledger**

William G. Nelson, M.D., Ph.D., Professor, The Johns Hopkins University School of Medicine

Larry Norton, M.D., Deputy Physician-in-Chief and Director of Breast Cancer Programs, Memorial Sloan-Kettering Cancer Center

Kenneth Olden, Ph.D., Sc.D., L.H.D., Director, National Toxicology Program,
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Drew M. Pardoll, M.D., Ph.D., Director, Division of Immunology and Hematopoiesis, Sidney Kimmel Cancer Center, The Johns Hopkins University School of Medicine

Gary M. Reedy, Worldwide Vice President, Biopharmaceutical Public Policy, Johnson & Johnson

Barbara Rimer, Dr.P.H., Alumni Distinguished Professor, School of Public Health; Deputy Director for Population Sciences, UNC Lineberger Comprehensive Cancer Center*

Richard L. Schilsky, M.D., Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago*

Joseph V. Simone, M.D., President, Simone Consulting

Ralph M. Steinman, M.D., Henry G. Kunkel Professor and Senior Physician, The Rockefeller University

Bruce Stillman, Ph.D., President and CEO, Cold Spring Harbor Laboratory

Lawrence Sturman, M.D., Ph.D., Director, Wadsworth Center Laboratories, New York State Department of Health*

Selwyn M. Vickers, M.D., Senior Scientist, UAB Cancer Center; Professor of Surgery, Birmingham School of Medicine, University of Alabama*

Susan L. Weiner, Ph.D., President and Founder, The Children's Cause for Cancer Advocacy

Peter H. Wiernik, M.D., Director, Comprehensive Cancer Center, Our Lady of Mercy Medical Center, New York Medical College

Robert E. Wittes, M.D., Physician-in-Chief, Memorial Hospital, Memorial Sloan-Kettering Cancer Center

Jerome W. Yates, M.D., M.P.H., National Vice President of Research, American Cancer Society

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* Unable to attend due to weather-related circumstances. The speaker's submitted written testimony is summarized in this document.

OPENING REMARKS—DR. LaSALLE D. LEFFALL, JR.

On behalf of the PCP, Dr. Leffall welcomed invited participants and the public. He provided a brief overview of the history and purpose of the Panel and the aims of the current series of meetings on translating research to reduce the burden of cancer. Dr. Leffall explained that the meeting would consist of three panel discussions, each addressing a unique aspect of translating research. Abstracts submitted in advance by the speakers were made available during the meeting.

WELCOME—DR. ROBERT E. WITTES

Background

Dr. Wittes graduated from Harvard College in 1964 and from the Harvard Medical School in 1968 and received his training in Medical Oncology at Memorial Sloan-Kettering Cancer Center (MSKCC). Following 10 years at MSKCC as a clinician and clinical investigator, he joined NCI as Associate Director of the Division of Cancer Treatment in the Cancer Therapy Evaluation Program (CTEP) and later served the Bristol-Myers Company as Senior Vice President for Cancer Research. From 1990 to 2002, he served in many roles at the NCI, including Chief of the Medicine Branch in the Division of Cancer Treatment, Director of the Division of Cancer Treatment and Diagnosis, and Deputy Director of Extramural Science. He returned to MSKCC as Physician-in-Chief in 2002. Dr. Wittes was awarded the United States Public Health Service Distinguished Service Medal in June 2000.

Key Points

- Through much of the 20th Century, the medical community has been practicing translational research. Some products of this research include Banting and Best's discovery of insulin and demonstration of its efficacy in type 1 diabetes, the work of Brown and Goldstein, allogeneic bone marrow transplantation, and immense advances in diagnostic radiology. Perhaps nowhere in medicine is the value of translational research better shown than in the application of concepts from applied physics, engineering, and high-performance computing to human health. Diagnostic radiology has begun to revolutionize a variety of medical subspecialties, including cardiology, gastroenterology, surgery, and clinical oncology.
- There is new urgency surrounding translational research because persistent need and rich scientific opportunity have created optimism that exploitation of such scientific opportunity is possible. Impediments to translation include developmental barriers; barriers within the interaction of business, academia, and the Government; intellectual property barriers; and societal barriers.

PANEL DISCUSSION I—BARRIERS TO TRANSLATING RESEARCH INTO REDUCTIONS IN THE BURDEN OF CANCER

INTRODUCTION—DR. KAREN ANTMAN

Background

Dr. Antman is currently the Deputy Director of Translational and Clinical Sciences at the National Cancer Institute (NCI). She was previously the Wu Professor of Medicine and Chief of the Division of Medical Oncology at Columbia University and the Director of Columbia's Herbert Irving Comprehensive Cancer Center. Dr. Antman received her M.D. from the Columbia University College of Physicians and Surgeons. She joined the Harvard Medical School faculty in 1979 and served as Clinical Director of the Dana-Farber Cancer Institute Solid Tumor

Autologous Marrow Program and the Sarcoma and Mesothelioma Clinical Research and Treatment Programs until July 1993, when she returned to Columbia. Dr. Antman has served as President of the American Society of Clinical Oncology (ASCO), the American Society of Blood and Marrow Transplant, and the American Association for Cancer Research (AACR).

Dr. Antman introduced the panel members and noted that Mr. Ingram, Dr. Schilsky, and Ms. MacPherson were unable to attend due to inclement weather.

MR. ROBERT INGRAM

Background

Mr. Ingram is Vice Chairman, Pharmaceuticals, at GlaxoSmithKline (GSK). In this role, he represents GSK as a member of the Executive Committee and Board of the Pharmaceutical Research and Manufacturers of America (PhRMA). He began his career in the pharmaceutical industry as a professional sales representative and ultimately became CEO/Chairman of Glaxo Wellcome. He co-led the merger and integration that formed GSK. Mr. Ingram also serves as Chairman of OSI Pharmaceuticals, Inc., and is on the Boards of Directors of Edwards Lifesciences Corporation; Lowe's Companies, Inc.; Misys plc.; Nortel Networks; VALEANT Pharmaceuticals International; and Wachovia Corporation. He is currently Chairman of the Board of Trustees of the American Cancer Society (ACS) Foundation. In January 2004, Mr. Ingram was awarded the Martin Luther King, Jr., Legacy Award for International Service. Mr. Ingram was appointed by President George H. W. Bush to form and chair the CEO Roundtable on Cancer.

[Mr. Ingram was unable to present due to inclement weather; the following is a summary of his submitted written testimony.]

Key Points

< Chartered as a 501(c)(3) nonprofit corporation, the CEO Roundtable is composed of corporate executives from more than 40 major American companies representing diverse industries, as well as state Governors. The Roundtable's mission is to provide hope to cancer patients and their loved ones by making continual progress toward the elimination of cancer as both a personal disease and a public health problem. Members of the CEO Roundtable have pledged to develop and implement initiatives that reduce the risk of cancer, enable early diagnosis, facilitate access to the best available treatments, and hasten the discovery of novel and more effective diagnostic tools and anticancer therapies.

< The *CEO Cancer Gold Standard*™ is a powerful initiative that encourages state-of-the-science prevention, diagnosis, and treatment. It consists of a series of cancer-related priorities that address three specific goals: risk reduction, early detection, and quality care. The initiative focuses on five critical areas, the "pillars" of the *Gold Standard*: Tobacco Use, Diet and Nutrition, Physical Activity, Screening and Early Detection, and Access to Quality Treatment and Clinical Trials. Organizations that adopt the *Gold Standard* maintain a culture that encourages healthy lifestyles and provides support when a diagnosis of cancer becomes a reality. In addition, they offer benefits and programs that lower the risk of cancer, detect it earlier, and provide access to the best available care.

  - The Tobacco Use pillar requires organizations to establish and enforce tobacco-free worksite policies; ensure that health benefit plans include coverage at no cost for evidence-based tobacco treatments, including counseling and medications; and establish workplace-based tobacco cessation initiatives.
  - The Diet and Nutrition pillar requires organizations to sustain a culture that supports healthy food choices and provide access to nutrition/weight control programs.

- The Physical Activity pillar requires organizations to sustain a culture that promotes physical activity and demonstrate commitment to eliminating barriers to active lifestyles.
- The Screening and Early Detection pillar requires organizations to sustain a culture that promotes appropriate cancer screening behaviors; ensure that health benefit plans include cancer screening provisions that adhere to ACS or U.S. Preventive Services Task Force Guidelines; and offer health benefit plans that eliminate cost as a barrier to accessing preventive/screening tests and exams.
- The Access to Quality Treatment and Clinical Trials pillar requires organizations to provide education about and promotion of cancer clinical trials; offer health benefit plans that eliminate cost as a barrier to accessing cancer clinical trials; and ensure that health benefit plans provide access to cancer care at Commission on Cancer-approved facilities and/or NCI-approved Cancer Centers.

< Organizations that become accredited as "*CEO Cancer Gold Standard*™ companies" must satisfy the comprehensive and rigorous requirements of all five pillars. For example, organizations must establish and enforce tobacco-free worksite policies. A "no tobacco use" employment policy must extend to all U.S.-based employees in all locations, in all facilities, indoors and out, whether owned, leased, or shared. The *Gold Standard* also requires that organizations provide coverage for evidence-based tobacco cessation medications and counseling—at no cost to the employee. This approach allows *Gold Standard* employers to send a clear message to their employees: "We care about your health; we want you to stop using tobacco; and we will do what it takes to help you quit." CEO Roundtable Members believe that this nonpunitive approach will make a difference.

< CEO Roundtable members are implementing the *Gold Standard* within their respective organizations during 2005 and will encourage adoption of the *Gold Standard* by other organizations beginning in 2006. While the design of the *CEO Cancer Gold Standard*™ is the result of the collaborative leadership of all member companies, the CEO Roundtable intends to partner with key cancer organizations to hasten its deployment. The CEO Roundtable welcomes the opportunity to explore ways in which to partner with the Government to support the national cancer agenda.

DR. CAROLYN M. CLANCY

Background

Dr. Clancy currently serves as Director of the Agency for Healthcare Research and Quality (AHRQ). Prior to her appointment, Dr. Clancy was the Director of AHRQ's Center for Outcomes and Effectiveness Research (COER). She has also served as an Assistant Professor in the Department of Internal Medicine at the Medical College of Virginia and Director of the Center for Primary Care Research. Dr. Clancy holds an academic appointment at the George Washington University School of Medicine and serves as Senior Associate Editor of *Health Services Research*. She is a graduate of Boston College and the University of Massachusetts Medical School.

Key Points

< AHRQ's mission is to improve the quality, safety, efficiency, and effectiveness of health care for all Americans. AHRQ does not concentrate exclusively on cancer; its work is patient-focused rather than disease-focused. However, it has supported a body of research related to cancer detection, alleviation of pain, and treatment and currently participates in a number of collaborations with the NCI. AHRQ research also focuses on the intersection of individual disease management strategies for patients with multiple chronic conditions and examines the

intersection of the clinical content of care with the delivery system in which that care is provided.

< It is difficult to gain access to relevant useful scientific information and clinical practices. As a result, clinicians and patients face uncertainty about their options for intervention and treatment. Because the scientific community, collectively, has neither the time, the money, nor the ability to address all areas of practice, it faces three challenges:

  - Priorities must be set for addressing the most important gaps in both biomedical and health care effectiveness research.
  - When a randomized trial is not possible or feasible, other options must be made available.
  - Tools and knowledge must be provided to guide decision making in the midst of scientific uncertainty.

< Even if these challenges are overcome, the process of determining effectiveness in daily practice is accelerated, and information is widely disseminated, barriers will still exist. Clinicians are reluctant to change their current practice patterns. The practice environment needs to better support the use of evidence-based interventions; tools such as decision support systems, incentives, and even the design of the physical space of the practice setting lead clinicians to use evidence-based interventions.

< For the last 10 years, AHRQ has had in place a mechanism for the development of systematic review of existing scientific evidence, beginning with a rigorous assessment of each study's design and methodological rigor. AHRQ has funded a number of reports for the NCI, including *Efficacy of Interventions to Modify Dietary Behavior Related to Cancer Risk*, *Impact of Cancer-Related Decision Aids*, and *Management of Cancer Pain*. In the past, these reports have identified what is known using conventional scientific thresholds for certainty, leaving others to assess research that did not rise to that level of certainty. AHRQ can and must do better: While certainty should not be attributed where it does not exist, clinicians cannot always wait for the completion of research in order to make decisions concerning their patients.

< AHRQ is working with NCI and other Federal agencies on a series of three reports: *Cancer Care Quality Measures for Breast Cancer*, *Colorectal Cancer*, and *Cancer at the End of Life*; these measures will be submitted for endorsement by the National Quality Forum. These reports and others are available at the AHRQ Web site: www.AHRQ.gov.

< The Medicare Prescription Drug, Improvement, and Modernization Act (MMA) is shifting AHRQ efforts in two ways: It broadens the scope of clinical practice being addressed, and it mandates updates of reviews as new findings warrant. The MMA mandates that AHRQ conduct research relevant to individuals receiving services through Medicare, Medicaid, and the State Children's Health Insurance Program. The bill also directs AHRQ to develop a list of ten priority areas; cancer is one of these areas.

< The MMA poses two challenges to AHRQ: Research findings must be understandable and useful to those served by the programs, and AHRQ must use health information technology to ensure widespread availability and use of these findings. Congress envisions that findings will be provided in formats that can be rapidly incorporated into electronic health records, computerized physician order-entry systems, programs for personal digital assistants, clinical and consumer Web sites, and other innovative venues. This will require a fairly substantial shift from simply posting new information on Web sites to customizing delivery of information to the point of care. Publishing an article or a systematic review alone will not transform practice; resources are being shifted to expand support for alternative approaches to implementing effective and generalizable interventions.

- AHRQ supports several practice-based research networks connected with integrated delivery systems, primary care, and HIV/AIDS care and has developed a new collaborative with the largest health plans in the country to test initiatives to reduce racial and ethnic disparities in health care. These programs are being explored as ways to better support rapid-cycle research that will speed implementation of proven interventions. Specifically, the growth of health information technology systems is being linked to real-time clinical research as part of the recently announced $139 million multiyear initiative in health information technology.
- One of the biggest areas of discussion and debate is how to improve quality of care. The community agrees that physicians and organizations that consistently provide high-quality care should be rewarded through the reimbursement mechanism. The challenge lies in ensuring that the reward system does not create any unintended or perverse incentives but actually promotes the highest-quality care.
- Another challenge in translating research relates to health literacy. What may be suitable, comprehensible information for one group of patients may be completely unusable by other populations. Self-efficacy, or the belief that what one does makes a difference, is perhaps the strongest component of improving care.
- A problem faced by the clinical research enterprise concerns generalizability: If a clinical trial shows that an intervention is effective for a select group of patients, the question becomes how generalizable the findings are to other groups of patients. There is currently a strong interest in developing a process by which, if an intervention seems effective for some patients but has not been generalized in a large trial, clinicians can provide that intervention to their patients. Through the use of registries and other strategies to gather evidence, the community may learn while providing care.

DR. ETHAN DMITROVSKY

Background

Dr. Dmitrovsky is a physician-scientist and practicing oncologist. He completed his undergraduate studies at Harvard College and received his medical degree from Cornell University Medical College. After training in Medical Oncology at the NCI, he joined the faculty at MSKCC in the Department of Medicine and the Molecular Pharmacology and Therapeutics Program. At MSKCC, he headed the Laboratory of Molecular Medicine while directing the NIH-funded Clinical and Molecular Cancer Research Training Program. In 1998, Dr. Dmitrovsky became the Andrew G. Wallace Professor and Chairman of the Department of Pharmacology and Toxicology at Dartmouth Medical School. He also served a term as Acting Dean of Dartmouth Medical School before assuming his current role as the Senior Advisor to the President of Dartmouth College for Science and Technology.

Key Points

- This is an exciting moment in the history of translational research. Decades of basic science have led to the uncovering of molecular targets for cancer therapy and chemoprevention. A tenet of cancer biology is that carcinogenesis is a chronic and multistep process occurring over decades. The scientific community now stands ready to target and even prevent the causes of cancer. However, barriers to cancer chemoprevention exist and must be overcome.
- Barriers to chemoprevention include scientific barriers. Cancer chemoprevention and cancer therapy have been thought of as distinct, but each is part of a continuum: the process of carcinogenesis. Postgenomic tools should uncover rate-limiting steps in carcinogenesis. However, clinical cancer chemoprevention trials are long and expensive. Changes in

validated biomarkers can be intermediate endpoints for these trials, helping to obtain valuable early evidence of clinical response. A biomarker also can be a chemoprevention target.

- Another barrier is that chemoprevention agents are often studied based on their activity in overt cancers. They may be rate-limiting in the maintenance of an overt malignancy but have a very different role in a premalignant state. Agents developed specifically for cancer chemoprevention are needed.
- Disincentives for industrial partners exist. The biotechnology and pharmaceutical industries often are reluctant to develop chemopreventive agents when chronic toxicities may limit clinical use or even raise concerns about litigation. Also, not all desired chemopreventive agents exist in the portfolio of a single company. The industrial community must overcome barriers to combining agents from different companies early in development.
- Creative incentives are needed to encourage discovery and development of chemopreventive agents. Lengthening protection time for such agents by using validated biomarkers on a provisional basis for Food and Drug Administration (FDA) approval should be carefully considered.
- Perhaps the greatest barrier is how science is conducted. Cancer research has been the enterprise of creative and talented individuals who have often worked alone or in small, isolated groups; future advances will come from the efforts of interdisciplinary teams. Discoveries will be made at the edges between disciplines, where distinctions between fields become blurred. Examples of this are evident in postgenomic research in the proteomic and genomic arenas.

MS. KITTA MacPHERSON

Background

Ms. MacPherson has been *The Star-Ledger*'s (Newark, NJ) Science Writer since 1983. She is fascinated by the convergence of science, medicine, and business. In a series of award-winning pieces, she chronicled advances in cancer research, attempting to provide a glimpse of what it was like to be a "foot soldier"—patient, scientist, physician—at the front lines of the "War on Cancer" during a period of breakthroughs. Ms. MacPherson has written about the public health response to bioterrorism and, before that, West Nile virus. She has also studied the interplay of science and public perceptions, especially as it has been reflected in health concerns emanating from the long-simmering debate over the safety of genetically engineered food and questions over global warming. Ms. MacPherson won the Science in Society Award from the National Association of Science Writers.

[Ms. MacPherson was unable to present due to inclement weather; the following is a summary of her submitted written testimony.]

Key Points

- Doctors are learning that they must speak with patients, but many of them still do not appear to enjoy it very much, and many do not understand the notion of context. Even patients who may be getting excellent treatment are left in a state of anxiety if they are not properly informed. Better communications could make a difference in cancer research and in getting results to patients. Improvements are needed in communications between Government agencies, from Government agencies to research scientists, between research scientists, between corporate and academic scientists, between scientists and physicians, and between physicians and patients.
- Activists are beginning to raise questions about the direction of research and, more troubling, whether extensive fundraising efforts are making a difference. This was evident in October

2004, during Breast Cancer Awareness Month, when the advocacy group Breast Cancer Action launched an offensive against the pink-ribbon campaign that has become a hallmark of the breast cancer advocacy movement. The San Francisco-based group launched a national e-mail campaign urging women to "Think Before You Pink." The group faulted a lack of coordination among the dozens of Federal agencies, private foundations, and pharmaceutical companies that fund breast cancer research. No one knows exactly how much money is being raised and spent every year, nor where all the money is going.

< To a large degree, the differences in opinion among breast cancer activists about how to eliminate the disease stem from their perceptions of the relative success being achieved in the War Against Cancer. The discussion raises the larger question of who or what organization is maintaining the "big picture" in the "War": Which agency is the lead, and which person or persons are the thought leaders? Scientists at the NCI may have an answer for this, but it is not meaningful when the rest of the community does not know.

< If average, intelligent people had a sense of context about the scale and scope of research and its directions and possibilities, they would be far more inclined to embrace information about their own treatment and about clinical trials. To be successful at this, scientists—particularly corporate scientists—will have to undergo a change in culture. Many companies are secretive about early-phase trials and about the entire research process. One cannot be secretive about the process and then convince people to participate in something they know nothing about. In addition, such secrecy leads people to speculate that the process is probably dangerous. That is not a positive mindset in which to cultivate participation.

< One of the best ways to encourage transparency in the clinical trials process is to allow press coverage. This has been done already, and it is extremely useful. In 1998, *The Star-Ledger* ran a piece following patients going through Phase I of a cancer drug trial at Johnson & Johnson. There was an enormous, positive reaction from readers, who reported that they learned much from the piece. Though the purpose of the piece was purely informative, readers came away with a broader, deeper sense and appreciation of the risks and rewards of clinical trials for both patients and researchers.

MR. GARY M. REEDY

Background

Mr. Reedy serves as Worldwide Vice President for Biopharmaceutical Public Policy at Johnson & Johnson. He is responsible for spearheading initiatives to influence global health policy for the company's biopharmaceuticals business. Mr. Reedy has over 26 years of domestic and international experience in the pharmaceutical and biotechnology industries. Prior to joining Johnson & Johnson, he held positions at SmithKline Beecham, Centocor, and Ortho Biotech. He also serves as Vice Chairman of the Executive Committee of the ACS Foundation and is a member of its Nominating Committee. Mr. Reedy is a charter member of the CEO Roundtable on Cancer and serves as Chair of the *CEO Cancer Gold Standard™* Task Force.

Key Points

< Development of biomarkers must be encouraged. The research community is beginning to see how much more efficient clinical trials and treatment can be with the use of biomarkers. As a result, diagnostic tools to identify patients who are most likely to respond are being developed. As clinical trial criteria and treatments become more targeted, the number of patients eligible to enroll will decrease; once a drug is on the market, it will be used in smaller, more targeted patient populations. If investigators are able to enroll patients who are more likely to benefit from a specific drug, the size of the Phase III registration trials could be greatly reduced, and potentially, they could be completed more quickly.

- Regulatory requirements regarding clinical trial size need to be more flexible. Increased utilization in the target population will compensate for decreased use in the broader patient population, but even without biomarker-selected patients, it is a challenge to enroll sufficient numbers of patients in clinical trials. Unless requirements for clinical trial size and endpoints change, recruitment will absorb a disproportionate share of the research budget. If patients in a trial are known to have a higher likelihood of response, the risk-benefit ratio could change drastically.
- Traditional clinical trial endpoints should be modified to take into account therapies that halt the progression of the tumor or have other effects on the disease, much as reduced viral load has become a surrogate marker of HIV drug efficacy.
- Over the years, pharmaceutical companies have funded many landmark public education programs promoting such messages as HIV testing, breast cancer detection, and organ donation. In cooperation with oncologists and academic medical centers, pharmaceutical companies must provide marketing support to encourage enrollment in clinical trials.
- The continuum of drug discovery, development, marketing, and real-world experience functions optimally as a closed loop rather than a linear process. This is critical in oncology because of the complexity and diversity of both cancers and drugs and the willingness of oncologists to explore new options for their seriously ill patients. The most beneficial uses for new agents are generally discovered after the FDA has approved them. The outcomes of clinical experience beyond approved indications can be extremely instructive; oncologists and researchers must be able to share this information at symposia and other educational programs and should be able to do so with the support of the pharmaceutical companies, which have vast knowledge concerning their products. In the current regulatory environment, however, these discussions have been increasingly curtailed due to evolving regulatory and enforcement developments. Pharmaceutical companies are currently unsure what they can and cannot do concerning data/information sharing. Ideally, the vast knowledge that pharmaceutical and biotechnology companies have would be shared seamlessly and transparently with researchers and investigators. Closing the loop from real-world experience back to discovery and development can help resolve some of the complexities of cancer therapy.
- Better channels are needed to enable postmarketing clinical feedback to influence preclinical research. Surrogate markers, nontraditional endpoints, and flexible enrollment numbers in clinical trials need to be accepted more widely. Public awareness of the importance of clinical trials must be heightened and enrollment increased. Also necessary is more regulatory clarity around the role pharmaceutical companies should play in furthering scientific exchange and supporting medical education.
- Pharmaceutical companies need to collaborate more freely to share information and data on their products. Mr. Ingram is leading a group of industry representatives (the CEO Roundtable); this group is working to address the issues of intellectual property so that pharmaceutical companies can better work together to combine their reagents.

DR. RICHARD L. SCHILSKY

Background

Dr. Schilsky earned his M.D. from the University of Chicago Pritzker School of Medicine. Following a residency in Internal Medicine at the University of Texas Southwestern Medical Center and Parkland Memorial Hospital, he received training in Medical Oncology and Clinical Pharmacology at the NCI. He then served as Assistant Professor of Medicine at the University of Missouri–Columbia School of Medicine, where he was awarded the Outstanding Teacher Award

by the Department of Medicine. He returned to the University of Chicago in 1984 and, in the ensuing years, has served as Associate Director of the Section of Hematology-Oncology, Director of the Cancer Research Center, and Associate Dean for Clinical Research, as well as the Chair of the Cancer and Leukemia Group B. Dr. Schilsky has published more than 220 articles and book chapters in the medical literature and is the editor of 4 books.

[Dr. Schilsky was unable to present due to inclement weather; the following is a summary of his submitted written testimony.]

Key Points

< A fundamental and pervasive barrier to translating research to reduce the burden of cancer is a culture of "protectionism" in Government, academia, and the private sector that leads to undesirable and often unnecessary regulations and practices that stifle collaboration and slow progress. Specific steps that could be taken to alleviate "protectionism" include:

- Making the NIH Clinical Center accessible to investigators across the country as a site at which to conduct novel translational research studies that require intensive and sophisticated patient monitoring. Funding for studies of proprietary agents could be derived from user fees charged to the sponsor.
- Encouraging national laboratories to collaborate with clinical research programs to apply novel technologies that assess treatment-induced changes in host and tumor biology and to develop biomarkers that predict response to treatment.
- Working to coordinate biomarker discovery and development across all units of NCI so that it proceeds in an efficient and strategic fashion, even if it requires some programs to cede authority or resources. FDA should require development of molecular diagnostics in concert with targeted therapeutics to facilitate drug development and identify patients most likely to benefit from a novel therapy. Drug companies should be rewarded with accelerated drug approvals for developing valid surrogate endpoints.
- Establishing a national registry of cancer clinical trials so that all investigators can access information regarding ongoing studies and patients can access information about study outcomes, as well as developing a national inventory of specimens collected as part of these trials.
- Harmonizing the review of NCI-sponsored trials to streamline the process. Right now, a Phase III Cooperative Group trial conducted under an investigator-initiated Investigational New Drug Application (IND) requires review by the NCI CTEP, Cancer Trials Support Unit, Central Internal Review Board (IRB), company sponsor, FDA, and hundreds of local IRBs. Steps must be taken to replace this process with a single scientific review and a single IRB review that meet the needs of all stakeholders.
- Addressing intellectual property barriers by developing financial incentives for companies to collaborate in developing targeted therapies, biomarkers, and reagents, perhaps by extending patent life for new chemical entities registered based on a successful collaboration.
- Continuing the work of the NCI-FDA and NCI-Centers for Medicare & Medicaid Services (CMS) Task Forces and involving extramural investigators and industry representatives, as appropriate, in these activities.
- Creating demand for participation in clinical trials by recognizing oncologists who actively participate in clinical trials and encouraging patients to see only physicians with such credentials, as well as reimbursing such physicians at a higher rate for care delivered in an approved clinical trial.

- Providing financial support to successful Community Clinical Oncology Programs (CCOPs) to provide mentoring to other physicians who wish to establish a clinical trials program as part of their practice.

DR. BRUCE STILLMAN

Background

Dr. Stillman is President and CEO of Cold Spring Harbor Laboratory. A native of Australia, he obtained a Bachelor of Science degree from Sydney University and a Ph.D. from the John Curtin School of Medical Research at the Australian National University. In 1979, he moved to Cold Spring Harbor Laboratory as a Postdoctoral Fellow. In 1992, he was appointed Director of the Cancer Center; in 1994, he became Director of Cold Spring Harbor Laboratory; and in 2003, he was appointed President. In 2004, Dr. Stillman was awarded the Alfred P. Sloan, Jr. Prize from the General Motors Cancer Research Foundation.

Key Points

< The National Cancer Policy Board (NCPB) Subcommittee on Advanced Technologies in Cancer Research has made a recommendation to the NCI to support a human cancer genome project with the specific goal of identifying all of the major genetic lesions in the approximately 40 major human cancer types. This would include oncogenes, tumor-suppressor genes, predisposition genes, modifier genes, and survival genes. The President's Cancer Panel should endorse this project.

< In cancer, the ultimate biomarkers are the genetic alterations that occur in tumors; these can be identified using existing technologies in as few as ten cells and even from cancer cells in circulating blood. The identification of a suite of cancer genes will be important in prognosis, linking existing cancer therapies to the underlying genetics of the tumor and linking future cancer therapies to specific genes.

< An immediate product of this genome project could be diagnostic and prognostic tests; there are many molecular approaches to establishing such tests. These approaches need to be properly validated, but there is not yet a systematic effort to evaluate them. Once tests are validated, they need to be introduced into clinical practice—e.g., through commercial avenues. With the accumulation of genomic and proteomic approaches to diagnosis and prognosis, caution will be necessary to avoid public confusion over the plethora of tests available. There should be regulation of these tests; however, conducting clinical trials before they are introduced to the market is costly. To keep costs down, there should be a mechanism to monitor commercial progress wherein the suppliers of those tests would be required to submit data further down the road to ensure efficacy. This could be similar to the way the FDA treats drugs that are approved based on surrogate markers but which require a follow-up study to demonstrate efficacy with survival.

< The targets for cancer therapy used by the pharmaceutical industry are not validated. The proposed human cancer genome project would lead to ideas about validated targets. Currently available validated targets are linked to genetic alteration in human tumors.

< If funding were available for this project, whole-genome scans of patients' cancers might be available within 2 to 3 years. If tissue samples were available for which there is a known clinical outcome, patient profiles could be available within 3 to 4 years; those patients could then be linked to existing therapeutic targets.

< Biomarkers used for early tumor detection will come from the detection of proteins that are present on the surface of the cancer cells circulating in the blood. It could be possible to scan

the entire genome on as few as 100 cells. Early-detection tests using the genome could be as close as 5 years away.

< The genetic instability that is a hallmark of cancer might create more complexity when one looks at cancer tissue and at the end product of carcinogenesis. However, when considering a large number of cancers, common genes modified in a particular cancer type will become evident.

< The proposed human cancer genome project might cost one-tenth to one-fifth of the cost of the Human Genome Project, which was originally proposed because it was known that cancer is a genetic disease and that the underlying causes need to be understood before it can be rationally approached.

< Consideration needs to be given to combination therapies. Traditionally, cancer therapies have been directed at single therapeutic targets and have not been based on the underlying genetics of the tumor.

DR. JEROME W. YATES

Background

Dr. Yates is National Vice President for Research at the ACS, supervising the Extramural Grants Program, Behavioral Research Center, and Epidemiology and Surveillance Department. Previously, Dr. Yates worked at the Roswell Park Cancer Institute as Senior Vice President for Population Sciences and at the NCI as the Associate Director for Centers and Community Oncology. NCI honored Dr. Yates for 3 consecutive years with the Outstanding Work Performance Award. Dr. Yates received his M.D. from the University of Illinois and completed his residency at Marquette University in Milwaukee, Wisconsin. He received an M.P.H. from Harvard in 1981, with an emphasis in Epidemiology and Biostatistics.

Key Points

< A manpower shortage is occurring at all levels, from basic laboratory science through health care delivery. As NCI and NIH funding have become more limited, administrators and institutions squeeze time allocations for research and force investigators to identify sources of income to help pay their salaries. As a result, the research environment has become more competitive. There are fewer young researchers being funded through the R01 mechanism; this is likely to reach crisis proportions unless funds are redirected in a way that supports young investigators. Many leave the field to work for industry, which can protect their time and provide a salary. ACS spends the majority of its extramural grant money supporting young scientists who are out less than 8 years from their final formal training.

< A major change in cancer classifications is also occurring. Subclasses of cancers are arising—for example, within breast and prostate cancer—that are specifically amenable to new therapeutic agents. While allowing for a targeted approach to treatment, this "fragmenting" of disease targets will make it more difficult for industry to support drug development activities. It is commonly estimated that drug companies must recover $500 million from the market in order to support a drug's development. As few agents meet this standard, the research community needs to address how to develop small-market agents that have potential benefit while protecting companies' investments. Models such as the Drug Development Program might be useful in developing new ways to deal with these agents; unfortunately, ACS does not have the funding available for this kind of project; however, the NCI could be a significant force. Changing patent laws also might help solve this problem, and developing models for dealing with intellectual property laws would save time and effort spent deliberating over how the laws should be applied.

- A better system is needed for tracking outcomes and patterns of care. Tumor registries are mostly hospital-based; there is no good outpatient management information. As classification of cancer as a disease changes, there will be serious limitations to the current registries. Administrative data sets should be constructed. If CMS and private insurers had a standardized set of definitions for reimbursement, administrative data sets could generate patterns-of-care information. Tumor registry data and laboratory data could be linked with administrative data sets to generate timely cancer care information. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) needs to be modified to allow maximum use of available science.
- The growing elderly population will require improved methods for early detection. The most common cancers that occur in the elderly are best treated surgically—if they are identified early. Those who are eligible for Medicaid are looking at Federal and state cuts across the country; Medicare and Social Security are also under financial stress. How will care be provided for this population in the future? The two biggest risk factors for cancer are older age and a previous cancer. As the number of cancer survivors doubles in the next 10 years, the surveillance system for cancer survivors will require new approaches to early detection in the elderly population.

DISCUSSION: PANEL I—BARRIERS TO TRANSLATING RESEARCH INTO REDUCTIONS IN THE BURDEN OF CANCER

Key Points

- While there have been and are a number of individual efforts to identify mutations associated with genes in cancer, there has not been a concerted or systematic approach in this regard. Individual efforts are not addressing the entire potential of genetic alterations, and many researchers are sequencing candidate genes in cell lines rather than looking at primary human tissue samples. The proposed human cancer genome project would incorporate many technologies in addition to DNA sequencing.
- Patient research currently makes up 35 percent of the ACS research portfolio; ACS is moving toward making 50 percent of the portfolio translational rather than conventional laboratory research. Lack of available funding is an obstacle; there is simply not enough money to fund all of the researchers who are interested in conducting patient research.
- To address the problem of small markets and the cost of drug development, the pharmaceutical industry is examining how to share information in a commercially viable way while protecting intellectual property rights. Revisiting orphan drug regulation and extending patents may prove helpful as well. As biomarkers are validated and surrogate endpoints are used, the possibility of patient benefit rises, which may make small-market drugs more commercially viable. However, this will not be a standalone solution.
- The elderly population is the largest group of cancer patients, yet most clinical trial protocols preclude this population through age cutoffs. Progress cannot be made in clinical trials with the largest group of patients if they are not allowed to participate.
- The value of clinical trials must be better communicated to patients so that when they are presented with the opportunity to be in trials, they will be more disposed to participate.
- There is a need to translate research advances from academic centers to the community; for example, breast conservation surgery is practiced much more widely in academic centers than in the community. Radical mastectomy commands a considerably higher fee than lumpectomy, and this reimbursement inequality plays a role in treatment decisions. Some have suggested that CMS be made aware of the ramifications of reimbursement inequality and make changes so that fee levels will no longer be a factor in treatment decision making.

Informing the public about advances would also be helpful. A study in the *Journal of the American Medical Association* showed that there was a significant increase in modified radical mastectomies after several well-known public figures with breast cancer chose that treatment option—even though lumpectomy/radiation is the more technologically advanced option.

< Using health information technology to transform health care has enormous potential to both advance clinical trial enrollment and disseminate results, bringing them to the point of care in a much more rapid fashion than is currently possible.

< Science is changing; there are many examples of interdisciplinary collaborations, including the Human Genome Project, which has spawned a new discipline in bioinformatics. If a human cancer genome project were to go forward, it would be necessary to understand the clinical significance of the information gleaned and how best to use it. To this end, an interdisciplinary approach would be necessary, with population biologists and medical economists playing a role.

< The scientific community needs to begin using humans as model organisms and analyzing human tumors if it is to understand human cancers. The proposed human cancer genome project would drive other studies on diagnosis and prognosis; thus, the project would be a beginning, not an end.

< Each day in the United States, 1,500 people die from cancer. Cancer is now the major cause of death in Americans under age 85. The cancer community must work to change paradigms in order to meet the NCI Director's goal to eliminate the suffering and death due to cancer by 2015.

< It is becoming necessary to link data systems, including outpatient physician systems, in order to fully understand the state of patient care. While the hospital has been the point at which most data are gathered, much patient care is taking place outside of the hospital setting. It is likely that suboptimal treatment related to the administration of radiation and/or chemotherapy is occurring in the outpatient office, where physicians operate with maximum autonomy. Most physicians would respond appropriately to useful information, but without better knowledge of what is happening, little can be done to improve quality of care.

PANEL DISCUSSION II—THE ROLE OF ACADEMIC MEDICAL CENTERS IN TRANSLATING RESEARCH INTO CLINICAL PRACTICE

INTRODUCTION—DR. LARRY NORTON

Background

Dr. Norton is Deputy Physician-in-Chief and Director of Breast Cancer Programs at MSKCC. He is also Scientific Director of the Breast Cancer Research Foundation (BCRF) and has served as Chair of the BCRF Medical Advisory Board since its inception in 1993. Dr. Norton is a past President of ASCO and Chair of the ASCO Foundation. A presidential appointee to the National Cancer Advisory Board (NCAB) of the NCI (1998–2004), he is the first incumbent of the Norna S. Sarofim Chair in Clinical Oncology at MSKCC and recipient of ASCO's 2004 David A. Karnofsky Memorial Award. He is the coauthor of the *Norton-Simon Model*, which has broadly influenced cancer treatment and research for over 25 years. Dr. Norton received his M.D. from the Columbia University College of Physicians and Surgeons.

Dr. Norton introduced the panel members and noted that Drs. Hait and Koh were unable to attend due to inclement weather.

DR. WENDY CHUNG

Background

Dr. Chung began her career in human genetics after working at the NIH with Dr. Seymour Kaufman on phenylketonuria, a genetic disorder that can be effectively cured by dietary manipulation. She received her Ph.D. in Genetics from the Rockefeller University and her M.D. from Cornell University. Dr. Chung served her residency in Pediatrics at Columbia University and completed her training with a fellowship in Clinical Genetics at Columbia University. She remained at Columbia as the Herbert Irving Assistant Professor of Pediatrics and Medicine and is currently Director of the Clinical Genetics and Oncogenetics programs. She has published more than 40 papers and several reviews on oncogenetics and obesity and is the recipient of numerous awards for her research, including the Louis Gibofsky Memorial Prize, Dean's Research Award, and the American Academy of Pediatrics Young Investigator Award.

Key Points

- In the future, patient health care and oncology, in particular, are going to be individualized in terms of determining risk, treatment, and prognosis using biomarkers and tumor profiles. The difficulty lies in translating basic discoveries into practical and approachable solutions for patients.
- Pharmacogenetics and pharmacogenomics will play an increasingly important role in therapy. While developments in these areas may fragment target populations into smaller subsets (a concern of pharmaceutical companies), more targeted therapy may enhance clinical utility by removing the subset of patients who would have had adverse reactions to prescribed medications. In addition, by using biomarkers to refine treatment profiles, researchers can design better, shorter clinical trials to identify efficacious compounds, as well as specific, smaller clinical trials to identify those patients mostly likely to benefit.
- Many oncogenomic and pharmacogenomic systems are going to involve complex interactions—not just as single genes, but also in gene pathways—some of which relate to cancer but may also intersect with other diseases. When considering how to design these programs, researchers must take into account the number of subjects needed in order to detect modifier gene effects and gene-environment interactions.
- In order to rapidly translate advances, the research community needs to think ahead about technology and what will be possible in the next 5 or 10 years in terms of metabolomics, proteomics, and genomics. Biological resources should be stored in biorepositories so that outcomes data will be available.
- As clinical trials and treatments are individualized, populations need to be equally represented. Minority populations are already less likely to enter clinical trials and, from a genetic or genomic point of view, may have different susceptibilities and profiles.
- Patients at highest genetic risk for cancer and other diseases should be identified for the general practitioner. Barriers to genetic testing, including prohibitively high costs, need to be removed, and education among patients and health care providers should be expanded. Augmenting the population of genetic professionals, including genetic counselors and genetic physicians, will ease the burden of providing these services and disseminating genetic information.
- Patients also have concerns about genetic privacy; Federal legislation should be passed to protect privacy. One difficulty with protecting privacy is that researchers do not always know all of the future uses of a sample when asking a patient for informed consent. IRBs differ in their leniency regarding anticipated future uses of samples.

< The HIPAA legislation, while well intentioned, is somewhat restrictive. However, researchers have found ways to work within its confines.

DR. WILLIAM N. HAIT

Background

Dr. Hait has been Director of The Cancer Institute of New Jersey and Professor of Medicine and Pharmacology and Associate Dean for Oncology Programs at the University of Medicine and Dentistry of New Jersey (UMDNJ)–Robert Wood Johnson Medical School since January 1993. Dr. Hait received his M.D. and Ph.D. (Pharmacology) degrees from the Medical College of Pennsylvania. He joined the Yale University School of Medicine faculty in 1984 and was promoted to Associate Professor of Medicine and Pharmacology. Dr. Hait served as Associate Director of the Yale University Comprehensive Cancer Center and Director of the Breast Cancer Unit and Co-Director of the Lung Cancer Unit at the Yale University School of Medicine. He was appointed Chief of Medical Oncology at the Yale University School of Medicine in 1988. Dr. Hait is a prolific author with more than 200 articles, chapters, and abstracts to his credit.

[Dr. Hait was unable to present due to inclement weather; the following is a summary of his submitted written testimony.]

Key Points

< Translational research is difficult to define but recognizable to all who engage in it. Academic medical centers struggle to participate effectively, in contrast to the biotechnology and pharmaceutical industries, which are designed for nothing else. The process of translational research can be viewed as a cycle with defined phases and identifiable checkpoints. At a recent retreat of the Clinical Translational Research Committee of the AACR, many of the issues facing academic centers were discussed.

< Several important advances have been made that ease the movement of research from the preclinical to clinical stages, including the creation of Specialized Programs of Research Excellence (SPOREs), formation of clinical study sections, improvement in training—or K—awards, and the recently announced Paul Calabresi Award for Clinical Oncology (K12).

< Translational research should not end with a clinical trial. Rather, the initial clinical experiment should be viewed as the first of a series of experiments designed to test an important hypothesis—the reentry point into the "resting phase," where data can be evaluated and new ideas generated. Many investigators/companies, caught up in the excitement of moving into the clinic, become convinced that their new treatment will actually work—a phenomenon known as "blockbuster blindness." In fact, most targets for anticancer drugs are present in most tumors, yet the drugs that target these molecules are inactive in most patients. If, before designing a clinical trial, researchers define the most likely reasons the drug will not work, they will be better prepared to design rational, informative, early-phase clinical experiments with realistic expectations and open-mindedness toward unexpected results.

< The translational research cycle has identifiable activators, including committed mentors, protected time, a critical mass of scientifically sophisticated physicians, and medically sophisticated scientists, nurses, and advocates who share interests, goals, rewards, venues, seminars, retreats, societies, and resources. The AACR working group drafted recommendations for alleviating four major barriers:

  • Culture. Mechanisms should be established for people from various disciplines to work together effectively. This process can be expedited by identifying models used by others that reward a team approach to science; exploring innovative mechanisms/relationships among academia, industry, and Government; funding "Genius Grants" designed to