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

identify and develop innovative partnerships; offering fellowships/sabbaticals to individuals in academia who wish to spend time in industry; and writing a "white paper" on the barriers to translational research present within academic institutions.

- Human Resources/Education. A stable, effective "army/orchestra" of translational researchers should be created to better link biology and medicine by making the AACR national meeting attractive to the best and brightest translational researchers; exploring ways to influence medical school curricula to develop pathways for training translational scientists outside of the traditional M.D. and Ph.D. programs; creating educational series at AACR meetings; and producing a handbook on the fundamentals of clinical translational research.
- Infrastructure. Best practices that are known, approved, and implemented should be designed. Many of the shared resources that make up the infrastructure of clinical translational research may not be available to some investigators wishing to enter the field. An electronic clearinghouse would help identify where these resources exist and how they can be accessed. In addition, AACR could publish guidelines that attempt to define standards for developing and reporting clinical/translational research for publications or presentations at national meetings and to regulatory agencies.
- Regulatory. Simple, streamlined, efficient processes should be created to protect patients and promote research. Some ways to effect these include convening a working group to share or create best-practice guidelines; involving international FDA representatives through AACR meetings; supporting a national IRB to expedite institutional approval of national Cooperative Group protocols; educating the public on the negative impact of overregulation on the development of effective new treatments; engaging advocates to help combat the media-driven image that clinical trials and clinical researchers are "evil"; and stressing to the press the importance of balanced reporting on the successes and mishaps of clinical research.

DR. KATHIE-ANN JOSEPH

Background

Dr. Joseph holds a joint M.D./M.P.H. from the Columbia Medical School and its School of Public Health. She completed her General Surgery residency and a research fellowship in Surgical Oncology at the New York University (NYU) Medical Center, after which she returned to Columbia to complete a Breast Surgical Oncology fellowship. Currently, Dr. Joseph is an Assistant Professor of Surgery in the Department of Surgery at Columbia University Medical Center. She is a member of several professional societies, including the AACR, ASCO, and the Association for Academic Surgery. Dr. Joseph has received several grants to pursue basic science research related to breast cancer and is the recipient of the Joanne Masin Breast Cancer Alliance Young Investigator Award. She was recently selected as a Southwest Oncology Group Young Investigator and the recipient of the 2004 Minority Scholar Award in Cancer Research.

Key Points

< Conducting translational research is challenging in this era of managed care. It is extremely important for clinicians to work in an environment where there is active collaboration with basic scientists. By sharing ideas, both clinicians and basic scientists can be more successful than either would be separately.

< Grants are helpful in providing partial support to carry out research, as they provide salary support and support for supplies; however, they do not provide funding for data managers, equipment, ancillary staff, or other important aspects of the research process. It is important

to consider other avenues of support for the young clinician-researcher. Cancer centers and Government institutions might provide more support by sponsoring postresidency fellowships. Government funding for cancer centers to partially or completely fund young researcher salaries and research expenses for the first 3 to 5 years would be ideal. This would relieve the clinical departments of some financial burden while allowing researchers time to cultivate their research and work within the cancer center.

< It is extremely important to share new and potentially effective treatments with not only patients being treated at a cancer center, but also those being treated in the community. It is those patients who may stand to gain the most from these treatments. When and if these patients finally present at the academic institutions, it is generally at an advanced stage of disease. In an effort to recruit patients from underrepresented minorities into clinical trials, Columbia University Medical Center's recruitment core has reached out to other community hospitals, such as Harlem Hospital. However, conducting clinical trials at multiple institutions requires obtaining IRB approval for each participating institution, which is a major impediment to moving a trial forward. Having a centralized IRB for multi-institutional studies would make this process considerably more efficient.

< Conducting clinical trials through large Cooperative Groups has the benefit of providing principal investigators with manpower and access to a large number of patients. However, the establishment of smaller consortia should be explored in an effort to move translational research into the community. For example, the Melanoma Consortium involving Columbia, MSKCC, and NYU allows patients to get needed care at multiple institutions, taking advantage of the individual strengths of each institution. Collaboration among medical centers also offers the opportunity for clinical and basic scientists to work together.

< Having protected time to conduct research is important for the young clinician-scientist. Often, researchers coming out of training are eager to practice their clinical skills by seeing patients, and research is left behind. If young researchers work in a clinical setting, they will have less protected time to conduct research.

DR. HOWARD KOH

Background

Dr. Koh is Associate Dean for Public Health Practice, Director of the Division of Public Health Practice, and Professor of Health Policy and Management at the Harvard School of Public Health. He also serves as Director of the Harvard School of Public Health Center for Public Health Preparedness. Dr. Koh graduated from Yale College and the Yale University School of Medicine. After training at Boston City Hospital and Massachusetts General Hospital (MGH) and serving as Chief Resident at both institutions, he joined the faculty of the Boston University Schools of Medicine and Public Health. There, he also became Director of Cancer Prevention and Control and Professor of Dermatology, Medicine, and Public Health. From 1997 to 2003, Dr. Koh served as Commissioner of Public Health for the Commonwealth of Massachusetts. He has earned board certification in Internal Medicine, Hematology, Medical Oncology, and Dermatology, as well as a Master of Public Health degree.

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

Key Points

< Translating research into practice to reduce the burden of cancer necessitates a transdisciplinary systems approach. Traditionally, the academic medical center has focused primarily on the biology of disease in individuals. The 2003 Institute of Medicine (IOM)

report, *The Future of the Public's Health in the 21st Century,* underscores the need to build further on this foundation by addressing the multiple determinants of population health. The IOM report reemphasizes that the health of populations is determined not only by biology of disease, but also by multiple levels of determinants affecting each individual. Such determinants include individual behavior; social/family and community networks; living and working conditions, including employment status, socioeconomic status, and public health services; broad social, economic, cultural, health, and environmental conditions; and policies at the local, state, national, and global levels. In this model, both "micro-level" determinants (such as the virulence of a disease agent) and "macro-level" determinants (such as policies and social norms) interact to affect health and disease in populations.

< Academic medical centers can build on this model by helping to create systems of care and prevention. In such systems, academic medical centers act as members of a broad societal partnership committed to reducing the burden of cancer.

DR. WILLIAM G. NELSON

Background

Dr. Nelson is a Professor of Oncology, Urology, Pharmacology, Medicine, Pathology, and Radiation Oncology at the Johns Hopkins University (JHU) School of Medicine, with a joint appointment in Environmental Health Sciences at the JHU Bloomberg School of Public Health. Dr. Nelson also directs a research laboratory focused on discovering new strategies for prostate cancer treatment and prevention and manages a clinical practice focused on developing these new treatment and prevention approaches in early proof-of-principle prostate clinical trials. He is Co-Director of the Prostate Cancer Program at the Sidney Kimmel Comprehensive Cancer Center and also serves in a leadership role in the National Cancer Institute-funded Molecular Targets Training Program and in the Howard University Cancer Center-Sidney Kimmel Comprehensive Cancer Center Partnership Program. Dr. Nelson completed his M.D. and Ph.D. training at the JHU School of Medicine.

Key Points

< The association between inflammation and cancer has been long recognized, but in the last few years, basic research in this area has intensified as understanding of the immune system has advanced.

< The activated immune system by itself can cause a cancer. The propensity of carcinogens to cause cancer is greatly amplified in the setting of inflammation. In the absence of an inflammatory response, genes that might otherwise cause rapidly growing cancers do not invade normal tissues or metastasize to other sites. Epidemiology studies have associated symptomatic prostatitis, or inflammation of the prostate gland, which occurs in 9 percent of American men, with risk for prostate cancer. Pathologists now recognize an inflammatory lesion called proliferative inflammatory atrophy as a precursor to cancer. Genetics, however, has provided a different story for prostate cancer risk: Inherited prostate cancer susceptibility genes that cluster in families encode proteins that function in host responses to promote infection and inflammation.

< Antioxidants, which can attenuate the damage caused by the immune system, and anti-inflammatory drugs may protect against cancer development. Transdisciplinary research teams must be brought together to conduct the translational research necessary to understand the relationship between inflammation and cancer.

< There are tremendous barriers to chemoprevention for cancer. To date, there has not been a single drug discovered, developed, and FDA-approved specifically for cancer prevention. Of

the six drugs that have had some success (tamoxifen, raloxifene, finasteride, dutasteride, rofecoxib, and celecoxib), none was tested for chemoprevention ability until it was already generating revenues in excess of $1 billion.

- There are great disincentives to the pharmaceutical industry to engage in cancer prevention, including long pathways to development and the absence of surrogate and strategic markers.
- Forty years ago, physicians and scientists came together with regulatory agencies and decided that two biomarkers, elevated blood pressure and elevated serum cholesterol, were so convincingly associated with risk for heart attack and stroke that they could be used to target pharmaceutical development. The same model needs to be applied to presence of inflammation.
- The evidence used to remove rofecoxib from the market resulted from adverse events in cancer prevention trials; this may have added a significant disincentive for future such trials. In the case of rofecoxib, the drug was used chronically. Intermittent, long-term use might have yielded a different result.
- C-reactive protein, which is associated with inflammation of the center of the prostate, seems to correlate in some preliminary epidemiology studies with a propensity for benign prostate enlargement. There is a growing sense that inflammation that affects the middle of the prostate gland, whether chronic or recurrent, may lead to benign prostatic enlargement, and inflammation that affects the periphery of the gland may lead to prostate cancer.
- The terms *infection* and *inflammation* should not necessarily be used interchangeably. There are cancers, such as those of the stomach and liver, that are associated with specific infectious organisms; for the colon, prostate, and lung, there is as yet no such clear association. However, the immune system is clearly activated. It is possible that it is a "hit-and-run" infection—an infection that activates the immune system—but for whatever reason, the immune system encounters an autoimmune pattern after the infection is subdued. Inflammation is the key effector, but infection may be what starts the process.

DR. DREW M. PARDOLL

Background

Dr. Pardoll received his B.S., M.D., and Ph.D. from JHU. Except for a fellowship at the National Institute of Allergy and Infectious Diseases (NIAID), he has remained at JHU as a resident, fellow, and faculty member. Currently, Dr. Pardoll is Professor of Medicine, Oncology, Pathology, and Molecular Biology and Genetics and Co-Director of the Division of Immunology/Hematopoiesis at the Sidney Kimmel Cancer Center at the JHU School of Medicine. Dr. Pardoll has received many honors—most recently, the Seraph Chair in Oncology at JHU. He serves as Associate Editor of the *Journal of the National Cancer Institute, Cancer Research, Molecular Therapy,* and *Cancer Cell* and is the co-inventor on 23 patents in molecular medicine and anticancer vaccines as well as the author of more than 180 scientific papers in basic and applied genetics and immunology.

Key Points

- Effective integration of the academic and private sectors is crucial to the translation of science into patient benefit. The immune system possesses powerful anticancer potential; the wrong kinds of immune responses can have procarcinogenic activity. In no other form of cancer therapeutics is the empowerment of the academic sector to partner effectively with the corporate sector more critical. For the most part, this partnership is not now happening and will not happen without active assistance from both the NCI and FDA.

- The potency of the immune system as an anticancer weapon has been validated in a number of situations. Antibodies like Herceptin and Rituxan are the most rapidly expanding forms of therapeutics today. The capacity of T cells to target cancer has been demonstrated in chronic myelogenous leukemia (CML): The T-cell component of bone marrow transplants cures CML in over 60 percent of cases. As dramatic as these examples are, it is the revolution of cellular and molecular immunology that gives cancer immunotherapists the power to distinguish between cancer-promoting and cancer-fighting mechanisms in the immune system and, therefore, gives them unprecedented power to manipulate the immune system. These new tools and knowledge could transform cancer therapy in the next decade.
- There is a disconnect between immunology research and cancer research at the NIH level; immunology's home is the NIAID, not the NCI. Immunologists believe that cancer provides a great opportunity to try innovative immunotherapies because of the severity of the disease, yet the cancer research community has put immunology "in the corner." The immune system is a crucial part of cancer's microenvironment, and the tools now exist to understand this dynamic. The NCI needs to increase its advocacy of immunology.
- Regulatory barriers cause serious problems for translational research. Without leadership and support, the FDA will not be able to keep pace with the evolving frontiers of complex immunotherapeutic agents. The fact that there has been a permanent FDA commissioner for only 15 months of the last 4 years concerns investigators, universities, and companies alike regarding the Administration's commitment to a robust, informed FDA. When regulatory barriers become unreasonable, the greatest threat to innovation is at the level of the translational investigator, who typically has little or no infrastructural support to address regulatory affairs.
- FDA workers are committed to greater levels of bidirectional education between the agency and investigators to ensure that regulatory assurances are appropriate and not unnecessarily burdensome. This endeavor should be strongly advocated and supported.
- Perhaps the biggest barrier to the development of successful cancer immunotherapy is that promising agents are retained by companies that do not test them in the most effective fashion—and often, not at all. Individual academic investigators have little or no leverage to mobilize these agents into the right patient populations and in the most effective combinations. NCI's partial response to empower investigators has been the Rapid Access to Intervention Development (RAID) program, which uses the Biological Resources Branch to produce clinical-grade biologic agents for academic investigators. The concept is excellent, but in reality, the program is extremely slow. The program needs a complete overhaul and greater resources. This overhaul needs to utilize a mechanism that prioritizes the therapeutics that are not being developed adequately in the private sector and then, together with the FDA and NCI, proactively work with investigators and companies to mobilize these agents.
- The recent controversy over COX-2 inhibitors raises concern that the industry and the FDA will become defensive. The FDA must be empowered to work with the NCI and investigators to be proactive—particularly in the area of cancer—where there are tremendous unmet needs in order to move experimental agents more quickly into patient testing. FDA staff are committed to this but feel they are "forgotten" when drugs do well and are "blamed" when drugs do not. There also needs to be systematic liability protection for companies in order to encourage them to transfer to other investigators agents that they are not actively testing.

DR. RALPH M. STEINMAN

Background

Dr. Steinman heads the Laboratory of Cellular Physiology and Immunology at The Rockefeller University; he is also a senior physician at The Rockefeller University Hospital. He received his B.S. from McGill University and his M.D. from Harvard Medical School. After completing an internship and residency at MGH, he joined The Rockefeller University in 1970 as a postdoctoral fellow in the Laboratory of Cellular Physiology and Immunology. He became a Professor in 1988 and was named Henry G. Kunkel Professor in 1995 and Director of the Chris Browne Center for Immunology and Immune Diseases in 1998.

Key Points

- Immune therapies now represent the major form of significant new cancer therapy approved by the FDA in the last 5 to 10 years. In spite of these advances in basic science, there are only 70 IND protocols funded by the NCI to develop vaccines and therapies. That is less than one per medical school and represents a huge deficiency.
- Human researchers need to be trained early in medical school rather than at the fellowship stage, where most such training currently takes place. If students are exposed to human research early on, they will develop the necessary commitment and scientific experience to be more productive and tenacious as their careers advance.
- Scientists in academic medical centers must be provided the required professional teams and infrastructure to study humans. Patient-oriented researchers now spend endless hours with essential but non-research-related tasks.
- There must be more open peer review of grant applications. The system seems to insist that scientists who study animals act as arbiters for scientists who study humans.
- Manufacturing facilities need to produce both newly conceived and existing clinical-grade reagents. Currently, the demands and delays in obtaining these reagents are formidable: at least 1 to 3 years.
- More funds must be dedicated to research on patients, particularly research that fosters collaboration between clinical and preclinical investigators in academic medical centers. Funding for Phase I/ II studies is currently very difficult to obtain. However, funding is more available for large-scale trials of clinical efficacy.
- NIAID has directed $140 million over several years to transferring the biology of tolerance to autoimmune diseases and related matters, such as transplantation. NIAID's Immune Tolerance Network is a dedicated network of scientists that assesses proposed studies in humans and then brings together available resources to accelerate these studies. While it has been a slow, hard task, the Network is meeting the demands and needs of investigators. This could be a model for cancer-related research coordination.
- Clinical departments encourage their investigators to conduct basic research to compete with preclinical scientists. It would be better if clinical departments were the leaders for Phase I and II human research studies. SPOREs are not producing many Phase I/II human studies. A better mechanism is needed. Perhaps if clinical departments had incentives and funding to collaborate with preclinical investigators, more Phase I/II human studies would exist.
- If human research is going to become a major part of the research enterprise, more than RAID is needed. It is up to individual regions to develop facilities to manufacture needed reagents.
- Regarding animal model vs. human research, there are certain areas where there simply is no mouse model that can replicate the human host. For immunotherapy, many of the molecules

being tested as well as many of the approaches deal with natural responses in the body; these can be tested in humans in an appropriate dose-escalation fashion.

< Many in basic science feel that human research is applied science and not the authentic discovery process that is associated with simpler systems; this is a culture that needs to change. Human research is basic research; it is the careful, systematic study of a particular problem. Balance must be brought to the research enterprise, and incentives, training, and resources must be available for human researchers and those interested in conducting human research.

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

Key Points

< Barriers exist in training specialists to translate genetic knowledge into the community. Approximately 180 genetic counselors are being trained in New York State each year, most of whom do not go into cancer genetic counseling. The numbers of physicians who become board-certified in medical genetics and the numbers of genetic counselors who become board-certified are declining. The solution may lie in disseminating information to health professionals, such as nurse practitioners, nurses, and physician assistants, as well as physicians and genetic counselors. Genetic counselors also need to be able to be licensed and autonomous in order to practice and act effectively as information disseminators.

< One of the factors slowing technology transfer is the regulatory mess that now exists. Patient safety is important, but regulatory overattention is counterproductive. Bidirectional education is important. The FDA needs experts to educate it about new classes of agents that may not have significant toxicity profiles, for example, and clinical investigators in cancer centers need to be educated about FDA regulatory processes.

< Only about half of patients receive treatments that are known to be effective. How can treatments proven to be effective in academic settings in increasing survival be translated to the community? Increased participation in clinical trials is one way to better disseminate state of the art care.

< Proof-of-principle trials are needed to determine whether molecularly targeted therapy actually "hits" the expected target.

< It will take the study of human biology to meet the challenge of understanding the connections among cancer, inflammation, and the immune system. Most human biology research takes place in academic medical centers. Also, the academic medical center is an ideal place in which to bring together disparate specialists, from basic informaticians to basic scientists to human clinicians. Current culture, the question of responsibility, and the amount of training needed act as impediments to this process. Possible solutions include training physician-scientists beginning in college and medical school; educating students about how clinical trials are conducted; and informing students about the academic medical environment. Both the curricula of medical schools and the culture of the academic medical center would need to change.

< The concept of interactive teams should go beyond groups within the academic medical center to include the relationships among groups in academic medical centers, companies, and Government agencies such as the NCI and FDA. That kind of empowerment is necessary to drive the translation of science into patient benefit.

PANEL DISCUSSION III—BEST MECHANISMS FOR MOVING RESEARCH INTO COMMUNITIES

INTRODUCTION—DR. JOSEPH V. SIMONE

Background

Dr. Simone is the President of Simone Consulting Company, which advises organizations on cancer program quality and development. He is Clinical Director Emeritus of the Huntsman Cancer Institute and Professor Emeritus of Pediatrics and Medicine at the University of Utah School of Medicine. From 1992 to 1996, he served as Physician-in-Chief at MSKCC. Prior to that, he spent virtually his entire medical career at St. Jude Children's Research Hospital in Memphis, where he joined the staff in 1967 and served as its Director from 1983 to 1992. Dr. Simone is Chair of the NCPB of the IOM, which has published several reports on the quality of cancer care. He was the founding Medical Director and Chair of the National Comprehensive Cancer Network and served on the NCI Board of Scientific Advisors from 1996 to 2002. He currently serves on the external advisory committees of 12 NCI-designated Cancer Centers.

Dr. Simone introduced the panel members and noted that Drs. Sturman, Olden, Rimer, and Vickers were unable to attend due to inclement weather.

DR. LAWRENCE STURMAN

Background

Dr. Sturman is Director of the Wadsworth Center for Laboratories and Research, New York State's Public Health Laboratory. Wadsworth provides laboratory services, conducts biomedical and environmental research, and ensures the quality of clinical and environmental laboratory services for state residents through its licensure program. Dr. Sturman received his medical training at Northwestern University Medical School and the Hospital of the University of Pennsylvania. After earning a doctorate in Virology from The Rockefeller University, he worked in the Laboratory of Viral Diseases at the NIH, joining the New York State Health Department in 1970 as a research physician. Dr. Sturman became the Wadsworth Center's Director in 1992.

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

Key Points

- The Federal Government has a process in place for review and approval of clinical laboratory tests sold as kits. However, clinical tests developed by laboratories for their own use and sold as services rather than kits are not evaluated by the Federal Government.
- The New York State Department of Health is charged with ensuring that all clinical laboratory tests performed are acceptable to the scientific community. Any laboratory seeking to offer a new assay must submit for evaluation and approval its standard operating procedures and test-validation data. Only after thorough review of the assay's sensitivity, specificity, and reproducibility data is approval granted.
- Of more than 400 applications reviewed in the past year for in-house-developed laboratory assays in 26 testing categories, 100 were in genetics and nearly 50 in molecular oncology.
- As valuable as this process is, it cannot adequately ensure a new test's clinical validity once it is employed in a wider population. In many instances, assays proven to have analytical validity and thought to have clinical validity have been found inadequate after several years of general use. The ultimate goal is clinical utility. Does the test help avoid unnecessary

treatment? Does the laboratory result affect patient management? Does it impact morbidity and mortality?

< To determine whether the potential of a test has been realized will require close cooperation among the medical community to amass the necessary data for evaluating the clinical validity and utility of new laboratory assays.

< Laboratory scientists, physicians, patients, insurers, and government health agencies all have a stake in this process. Once they are in wide use, new tests need to be assessed for clinical validity and utility. It is only necessary to look at recent reports of negative outcomes from widely used therapeutics to understand the importance of collecting retrospective population-wide data. This undertaking presents both a challenge and an opportunity.

DR. KENNETH OLDEN

Background

Dr. Olden was named Director of the National Institute of Environmental Health Sciences (NIEHS) and Director of the National Toxicology Program (NTP) in 1991. He is a cell biologist and biochemist by training and has been active in cancer research for almost three decades. Previously, Dr. Olden served as Director of the Howard University Cancer Center and Professor and Chair of the Department of Oncology at Howard University Medical School. He has also served in the NCI Division of Cancer Biology and Diagnosis (now the Division of Cancer Epidemiology and Genetics) as a senior staff fellow, expert, and research biologist.

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

Key Points

< There is a disconnect between the nation's capacity to deliver quality health care and the actual health outcomes for the average American. This point was reinforced by a recent World Health Organization survey of 191 countries in which the U.S. health care system was ranked 37th while also ranking first in terms of expenditures. Unfortunately, Americans are no healthier than people in many countries that spend far less on health care.

< The nation's investment and scientific leadership in medical research are not being translated into improved health for millions of Americans. The poor quality of health care experienced by millions of Americans will not be significantly improved—irrespective of any efficiency in translation—unless the health care enterprise itself, from research to delivery, is reformed. It is difficult to justify the nation's research priorities and health care system given that more than 80 million Americans are among the ranks of the un- and underinsured are denied access to medical knowledge and technologies that already exist.

< As a result of recent gene discovery efforts, the public and scientific communities are inundated with the message that genetic defects and damage to DNA and protein alone cause chronic diseases and that genetic screening and gene therapy will lead to cures and improvement in population health. However, a single risk factor is rarely responsible for the development of most chronic diseases; in fact, substantial data now exist showing that most chronic diseases are caused by interactions among genetic, environmental, and behavioral risk factors rather than "bad genes" alone. Understanding the development and progression of cancer and other chronic diseases will require knowledge of how genetic, environmental, and behavioral factors interact at the molecular level.

< A better understanding of genetic variation can result in a more refined understanding of critical gene-environment interactions. While most of the polymorphisms that exist in the human genome are neutral, a fraction are functional and may influence disease susceptibility

and response to environmental toxicants. The discovery of polymorphisms in genes involved in the metabolism of carcinogens has led to the hypothesis that these variations account for the high degree of individual variability in cancer susceptibility. For most genes, there is more variation within groups (e.g., races) than between groups, although some differences in allelic frequencies may alter susceptibility to disease or to environmental exposures. Estimation of allelic sharing among different populations and racial and ethnic groups is important for the development of public health disease-prevention/intervention strategies.

< Understanding gene-environment interactions is important for promoting health and preventing disease. While behavior and lifestyle factors, nutrition, and access to health care services are important contributors to health disparities among socioeconomically disadvantaged populations, environmental and occupational exposures are likely to play a prominent role. In cases where disadvantaged groups have a greater genetic susceptibility to toxic environmental agents, the problem is compounded.

< The health care delivery system must be rethought with respect to strategies and investment priorities. The current health care system was developed with a focus on the individual patient, which systematically excludes overall population health and dilutes the planning and infrastructural development needed to improve the system. For example, investment in disease prevention and health promotion has largely been ignored in favor of research to develop more sophisticated and costly therapeutic interventions that are unlikely to be accessible to millions of Americans.

< A health care system is needed that provides the most protection for the largest number of people based on predetermined standards of care, which should be decided by an independent body such as the National Academy of Sciences and with considerable public input. Once developed, these standards should be applied equitably, without regard to race, ethnicity, gender, or socioeconomic status. Such a community- or population-based health care system would greatly improve the overall health status of the U.S. population and would not prevent individuals or households from independently purchasing additional health care.

DR. BARBARA K. RIMER

Background

Dr. Rimer received an M.P.H. from the University of Michigan in 1973, with joint majors in Health Education and Medical Care Organization. She earned her Dr.P.H. in Health Education from the Johns Hopkins School of Hygiene and Public Health in 1981. She is currently Alumni Distinguished Professor of Health Behavior and Health Education at the University of North Carolina School of Public Health and Deputy Director for Population Sciences at the Lineberger Comprehensive Cancer Center. Previously, she served for 5 years as Director of the NCI Division of Cancer Control and Population Sciences (DCCPS). Dr. Rimer was the first woman and behavioral scientist to lead the NCI's NCAB. She is currently Vice-Chair of the Center for Disease Control and Prevention's (CDC) Task Force on Community Preventive Services.

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

Key Points

< It is possible that more lives could be saved today by successful translation of proven interventions than by most new treatments. New treatments are needed, but evidenced-based prevention, early detection, and treatment interventions also need to be disseminated to people who can apply them. It currently takes 17 years to disseminate about 14 percent of what is learned through research.

- One of the reasons translation fails is lack of infrastructure. Too often, the person with a demonstrated effective, evidence-based intervention has to create a way to disseminate his or her program, especially if it is in areas that are not likely to produce quick profits, such as behavioral interventions. If each investigator has to create his or her own distribution system, the result can be too time-consuming and expensive to produce dependable results.
- There have been positive steps. One is the CDC-NCI partnership to create the Cancer Prevention and Control Research Network, which has as its mission examining evidence-based recommendations produced by the CDC's *Guide to Community Preventive Services*, conducting dissemination research where there are evidence-based programs and pursuing further research where there is insufficient evidence. A special focus is on underserved populations, which suffer most from failure to translate discovery to delivery.
- A second crucial step is recognition of the important role of Comprehensive Cancer Centers in dissemination research and research dissemination and the recent revision of the P30/50 guidelines to permit Centers to create core dissemination resources. The PCP should commend the NCI's Centers program for this revision and track progress in this area. The Panel should also encourage C-Change to take on dissemination as an important focus area; commend the NCI-CDC partnerships for their emphasis on dissemination; and recommend that additional resources be created to facilitate dissemination.
- Because dissemination has not received sufficient emphasis, too little is known about how to do it well. Thus, providing support for the important work of dissemination research is inseparable from creating and maintaining working systems. Something as straightforward as providing a fifth year of funding to investigators who can show evidence that their interventions are efficacious and who have peer-reviewed dissemination plans—as is being done through DCCPS—can make a large difference.
- Some of the expertise needed for dissemination may exist outside academic medical centers and cancer centers—perhaps in business schools. Partnerships are needed to stimulate discussions between developers of effective interventions and those with expertise in marketing and dissemination.
- Academic researchers are concerned that dissemination efforts will detract and distract from their academic efforts and will not bring them academic and professional recognition. There must be acknowledgment that this is an important area of inquiry that deserves funding and attention and that it is a worthy pursuit for investigators. Public universities, in particular, should be provided funds for their role in dissemination—and they should be held accountable for results.
- Another important incentive is the potential for reimbursement. For example, the recent major announcement by CMS that it would reimburse smoking cessation counseling by health providers will exert a powerful force for translation. The PCP should examine other areas where changes in reimbursement might facilitate dissemination of evidence-based interventions.
- The Panel should call for a review of policies that act as disincentives to dissemination, such as the restriction on Small Business Innovation Research grants forbidding the use of funds for marketing.
- Dissemination is taught in only the most cursory way in schools of public health. M.P.H. students should know more about dissemination, and new types of professionals with specific expertise in the dissemination of health innovations may need to be trained.

DR. HAROLD P. FREEMAN

Background

Dr. Freeman is an Associate Director of the NCI and Director of the NCI Center to Reduce Cancer Health Disparities (CRCHD). He is also the Medical Director of the Ralph Lauren Center for Cancer Care and Prevention and holds the academic position of Professor of Clinical Surgery at Columbia University College of Physicians and Surgeons. He is a past Chair of the President's Cancer Panel. Dr. Freeman has been Medical Director of the Breast Examination Center of Harlem, a program of MSKCC, since 1979. He served as National President of the ACS from 1988 to 1989 and is the chief architect of the ACS's Initiative on Cancer in the Poor. Dr. Freeman received his M.D. from Howard University Medical School.

Key Points

< The single most effective way to reduce disparities in cancer is to provide everything that is known to all of the American population; this would result in a 10 to 15 percent increase in survival from cancer. Paradoxically, when advances in discovery are made, the typical result is greater disparities unless a way is found to make the new discoveries available to everyone. Discovery and development should continue, but what is already known needs to be applied as well.

< Poor cancer outcomes cannot be separated from poor living conditions, low education levels, and diminished access to standard care. The poorer the community, the worse the cancer outcome, irrespective of race and culture. There is a need to look at geographic areas of excess mortality and create interventions that could be applied in those communities. However, many residents in those communities are skeptical, having seen programs begin, conduct their research, and then leave. If research is to be done in these areas, a different approach must be taken. The communities must believe that researchers are there to help them. Involving community researchers and empowering people in their own communities to participate in the research process helps. The NCI's CRCHD has initiated some major research projects around the country over the last 5 years with great success—in no small part because community-based members were brought in to connect with and involve their communities.

< Research can be conducted that studies the community, involves it, and helps it at the same time. The Patient Navigation Program in Harlem created Patient Navigators whose responsibility is to eliminate any barrier the patient may encounter when seeking diagnosis and treatment. The Program uses people from the community to help others in the community, which helps build trust in local systems. This was done in a research setting in which information was collected about the Patient Navigators, the encounters between them and the patients, and the barriers they faced. After the Program was instituted, the 5-year survival rate for breast cancer in Harlem rose from 39 to 70 percent.

< The Patient Navigation Act of 2004 was introduced into and passed the U.S. House of Representatives; however, it has not yet come out of the Senate committee that is overseeing it, so the Senate has not been able to consider it. It will be reintroduced in the current legislative year.

< There should not be a contest between investment in research and applying discoveries to benefit communities; both should be supported. The NCI and NIH are funded to be institutions of discovery, but paradoxically, they are measured as research institutes by the results and outcomes of research delivery—i.e., decreased mortality and increased survival. The research enterprise must address the spectrum of discovery, development, and delivery and remain connected to the communities where people live.

DR. SELWYN M. VICKERS

Background

Dr. Vickers received his M.D. from the JHU School of Medicine. Dr. Vickers is an Associate Professor in the Department of General Surgery and Chief of Gastrointestinal Surgery at the University of Alabama at Birmingham (UAB) and UAB Co-Director of The Pancreaticobiliary Center. Previously, he served as an Instructor in Surgery in the Department of Surgery at JHU. He is actively involved in research involving pancreatic cancer, chronic and acute pancreatitis, cholangiocarcinoma, and liver cancer.

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

Key Points

< The U.S. health system has made significant strides in improving the technology of care, which has increased the number of available drugs and devices to address cancer. However, whether these drugs and devices truly impact a community will be determined by many factors. Most recently, an article published by Woolf and Satcher demonstrated that new technology may not be the most significant means of reducing deaths attributable to cancer or other medical illnesses. Were disparities in care eliminated, the number of averted deaths could increase significantly. Thus, achieving true implementation of new devices and drugs will require cancer centers and communities to act in combination in order to deliver these therapies to populations where they are truly needed.

< Many technological advances target cancers that will produce a high monetary return to the companies that invest in the development of those technologies. "Orphan" diseases, such as pancreatic cancer, may be significant killers, but drug and technology development targeting these diseases is stagnant. Much of the lack of development is due to both an inconsistent level of funding from Federal sources and a lack of ability to achieve a monetary return on the millions of dollars invested in a compound or drug to treat these illnesses.

< In order for the latest research to fully impact communities, there must be a significant partnership between academic medical centers and those communities, particularly those with a history of distrust and inequity in care. Many of the billions of dollars spent to improve health outcomes are directed toward technology; thus, there is competition in private industry and academia to develop better drugs, devices, and procedures to attack cancer. Far less money and infrastructure is devoted to improving health by partnering with communities to deliver new drugs and devices in an equitable fashion.

< One potential mechanism for bridging the gaps among academia, pharmaceutical companies, and communities is the implementation of community health associates/advisors (CHAs), trusted community members who establish vital links between health providers and the community. Centers or programs that employ CHAs to advance and implement new therapies in the community have three interrelated goals: to build a stronger relationship between health care professionals, improve appropriate health care utilization, and reduce health care risks. The strength of a therapeutic alliance that is supported by appropriate health beliefs and provider-patient trust can improve health care utilization, risk reduction, and clinical trial enrollment.

DR. SUSAN L. WEINER

Background

Dr. Weiner is President and Founder of the Children's Cause for Cancer Advocacy, a Washington, DC-based organization dedicated to accelerating the discovery of effective treatments for childhood cancers and ensuring ready access to quality services for patients, families, and survivors. She received her Ph.D. in Cognitive Developmental Psychology from Columbia University and completed a National Institute of Mental Health (NIMH) postdoctoral fellowship. Following a diagnosis of brain tumor in her infant son and throughout his 13 years of life, Dr. Weiner started and worked for programs for children with disabilities and their families in New York City. She also served as the first Executive Director and is a continuing board member of the Children's Brain Tumor Foundation and serves with the North American Brain Tumor Coalition. She is the founder of the Mary McDowell Center for Learning, a 20-year-old independent school for children with learning disabilities.

Key Points

- The Children's Cause for Cancer Advocacy comprises survivors and family members who work nationally to stimulate drug discovery and development for childhood cancers, expand resources for research and treatment, and ensure follow-up care for survivors.
- Prior to 1990, most agents used to treat childhood cancers were developed to treat adults; about 50 percent were approved prior to 1980. Successful treatment in children has been the result of combined drug regimens with increasing dose intensity and interactions with technological improvements in surgery and radiation. While newer regimens improve outcomes and reduce adverse effects, intensifying therapy with the same drugs is not likely to result in major increases in survival.
- Pharmaceutical and biotechnology companies typically do not screen their agents for pediatric activity. Their goal is to find treatments for high-incidence adult cancers, such as breast and prostate cancers. There is little, if any, economic incentive for industry to screen for pediatric activity. Also, some companies are reluctant to conduct pediatric testing of agents early in adult drug development programs. They are concerned about possible unexpected adverse events in children that might result in negative publicity and jeopardize FDA approval (despite assurances to the contrary from the FDA, researchers, and advocates). As a result, companies typically delay evaluating drugs in children, sometimes waiting until after the FDA approves them for adult indications.
- Congress recently passed the Best Pharmaceuticals for Children Act of 2002, which offers 6-month marketing exclusivity for all uses of an agent if the company conducts FDA-requested pediatric studies, and the Pediatric Research Equity Act of 2003, with gives the FDA authority to mandate that companies conduct pediatric studies. These laws depend on agents having the same indications for diseases that are the same in children as in adults. However, most pediatric malignancies are different from those found in adults, and the relationship of pediatric to adult disease is currently a matter of scientific debate. The application of these laws has been neither straightforward nor especially effective in stimulating more rapid pediatric access to new cancer agents.
- Another barrier relates to the relatively small number of children with cancer compared to adults, even though a much higher proportion of children than adults participate in cancer clinical trials. The decision to evaluate an agent in children can limit testing of other, potentially more valuable therapies because of the need to enroll a sufficient number of patients to reach a reliable scientific conclusion.

< At present, there is no systematic, coordinated way to discover drugs that may be valuable for the treatment of uniquely pediatric malignancies. Companies have large libraries of compounds and screening capabilities, but it will require creative entrepreneurship to absorb economic and publicity risks so that companies will allow screening of their compounds for pediatric potential.

< The Children's Cause recommends:

- Formation of a new public-private, independent, nonprofit organization with representation and resources from Government, academia, industry, philanthropic sources, and advocates to stimulate, coordinate, monitor, and lead pediatric oncology drug discovery and development.
- Creation of legislative provisions that stimulate industry investment in pediatric oncology drug development. One idea is to have transferable exclusivity within the same therapeutic class: If a company conducted pediatric studies early in drug development, exclusivity could be transferred to another agent within cancer therapeutics.
- Formation of an NCI-created public database for researchers that collates information on genetic and molecular characterization of pediatric malignancies, compounds of interest, preclinical models, and Phase I trials. Trials are being conducted in other countries that repeat what has been done in the United States. While the database would be limited to what is in the public domain, even a Web link to PubMed for publication of Phase I trails in children could reduce redundancy.
- Vigorous efforts by NIH and FDA to increase the numbers of children participating in clinical trials by removing regulatory barriers that impede collaboration among international pediatric oncology research groups.

DR. PETER H. WIERNIK

Background

Dr. Wiernik is Director of the Comprehensive Cancer Center at Our Lady of Mercy Medical Center of New York Medical College. He received his medical degree from the University of Virginia, followed by an internship and assistant residency at Cleveland Metropolitan General Hospital, Case Western Reserve University. He also completed a senior residency at JHU Hospital and a fellowship in Medical Oncology at the NCI. Dr. Wiernik is an active member in many professional societies, including the AACR, American College of Clinical Pharmacology, American Federation for Clinical Research, and American Society of Clinical Investigation. He reviews manuscripts for numerous journals, including the *Journal of Clinical Oncology, New England Journal of Medicine,* and *Blood.*

Key Points

< The Governor of New York has proposed substantial, if not fatal, cuts in the Medicaid program, and the President has proposed significant cuts in Medicare and Medicaid. If these cuts are enacted, the question will be not how to get more patients on clinical trials, but how to get the majority of patients served by cancer centers treated at all. These cuts should not be enacted.

< The FDA should establish an editorial board, much like the NCI's PDQ editorial board, composed of academicians, FDA staff, pharmaceutical industry representatives, and community physicians engaged in clinical trials and have as its chief responsibility editing and updating package inserts for approved cancer drugs. This would allow for the package insert to always include the latest indications for and adverse reactions to cancer drugs, saving FDA staff time and pharmaceutical companies millions of dollars on new indication

applications. Package insert changes would be based on the available medical literature as well as unpublished FDA and pharmaceutical company data. Reduced administrative costs for the pharmaceutical industry could result in lower drug prices.

< Medicare and Medicaid should reimburse institutions for cancer treatment in a different manner. The Federal Government should establish an overhead rate for each institution similar to the mechanism used for grants and contracts. That rate should include the cost of supplies, nurses, pharmacists, and administrative personnel and should be applied to the institution's cost for cancer drugs and other agents. The institution's reimbursement for treating a cancer patient would then be the invoiced cost of a drug plus the overhead rate applied to that cost. Similar arrangements could be worked out for surgical and radiation treatment. Private practices could be treated as small businesses, with similar arrangements made.

< For patients enrolled in clinical trials, the overhead rate should include the costs of clinical research at the institution, including data managers, research nurses, record keeping, and audits. Incentives such as travel reimbursement could be built into the system to encourage physicians to enroll and encourage patients to participate in clinical trials.

< This method of reimbursement would save Medicare and Medicaid administrative dollars, the NCI and other governmental and private funding agencies research dollars, and the pharmaceutical industry drug development dollars, which would result in lower drug costs.

DISCUSSION: PANEL III—BEST MECHANISMS FOR MOVING RESEARCH INTO COMMUNITIES

Key Points

< If learning institutes receive Federal money, they also must be mandated to reach out to the community. A collaborative effort and partnership will help ensure that when the research funds come in, grassroots groups are in place that can participate in community-based research. There is considerable distrust in communities because research institutes receive funding, but the grassroots organizations do not, even though they are committed to translating the research.

< The CDC and public health departments play an important role in providing access to screening and treatment for breast and cervical cancers throughout the nation. Also, individual states are developing and implementing cancer plans, some of which are being organized through the NCI.

< Many patients who participate in clinical trials do not live close to an academic cancer center. They would like to receive care in their communities, but often, HIPAA rules and IRBs will not allow their medical information to be sent to community hospitals. There is currently no good way to involve community physicians in the clinical trials process, especially physicians whose offices and equipment do not fulfill trial requirements; however, their patients are often those who most need access to trials.

< Often, when regulations are "simplified," they actually become more complicated. HIPAA problems vary from who pays for paper shredders to how to obtain research material from deceased patients who, when alive, gave consent but whose consent was worded incorrectly.

< The critical challenge is to connect the discovery system with the delivery system. The principal problem in the poor communities of America is that they have neither knowledge of nor access to early diagnosis and treatment. Almost all people with cancer ultimately are treated; however, the current systems do not allow people to be treated early enough to be

cured. There is a need for serious dialogue on this disconnect between the discovery and delivery systems.

< Dr. Philip Van Der Gann [sp.?] has been working actively to set up Centers of Excellence across New York State between environmental health and pediatrics. Networks of Centers of Excellence would empower rural communities, and researchers could collect data about physical and environmental health.

< There need to be more options for patients looking for information about state-of-the-art care. Many currently seek third and fourth opinions on treatment options; this is an inefficient way to determine whether the best care is being given. NCI's PDQ Web site is a good, nonpartisan resource for obtaining information about state-of-the-art treatments for various malignancies. The Cancer Information Service is also a resource for both patients and professionals seeking information about treatments and clinical trials.

< America spends more on health care and health care administration than any other country in the world and has poorer outcomes than most industrialized nations. Major health care reform is needed; better cancer research is not going to resolve the problem of millions of un- and underinsured Americans.

NCI DIRECTOR'S REMARKS—DR. ANDREW C. von ESCHENBACH

< Dr. von Eschenbach began by thanking the members of the Panel for their leadership and efforts in bringing forth from the community the insights being shared. Dr. von Eschenbach also thanked MSKCC for its hospitality.

< The National Cancer Act of 1971 not only created the President's Cancer Panel and the NCAB, but it charged the NCI with conquering cancer. The Act began a process in which, over the past 30 years, the scientific community has learned a great deal about cancer as a disease and a disease process. The cancer community can now envision a time when this knowledge can be used in a way that will definitely and truly affect the outcome of this disease. The opportunity now exists not only for further discovery, but also for the development of interventions based on those discoveries that will be delivered to everyone in need. Cancer is a systems problem, and the solution to cancer must be a systems solution.

< The National Cancer Act also gave the NCI legislative authority to create and oversee the National Cancer Program, a term used to encompass the entire spectrum of public and private efforts to reduce the burden of cancer. While this authority has since been modified, the NCI has retained many core authorities related to creating programs such as the National Cancer Center Program, training programs, and international programs. In the near future, Congress will be addressing not only appropriations and NCI resources, but also the question of the NCI's authority over the National Cancer Program.

< The integration and coordination of the nation's cancer efforts is a critical element in the fight against cancer. The enterprise has grown over the past three decades by virtue of NCI-provided resources; the creation of infrastructure; the commitment and investment of other partners, including advocacy groups and private foundations; and most recently, the powerful biotechnology, pharmaceutical, and device industries. How these resources are integrated and leveraged is one of the critical elements of success.

< The NCI provides leadership both formally and informally. The NCI recently created joint task forces with the FDA, CDC, and CMS to address research and regulatory barriers.

< The current information systems are elegant when it comes to billing and collection but woefully inadequate when it comes to determining best practices and quality improvements. That gap must be closed, and the NCI is committed to working toward that goal.

< The NCI is committed to doing what is necessary to eliminate the suffering and death due to cancer by the year 2015.

REPORT BACK—DIALOGUE ON KEY BARRIERS AND AVENUES FOR CHANGE: INNOVATION, AFFORDABILITY, AND PRACTICABILITY

INTRODUCTION—DR. LaSALLE D. LEFFALL, JR.

The discussion panel leaders were asked to summarize what was said in their panels and add anything else they would like to express based on their experience and expertise.

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

Key Points

< The ACS and the NCI are putting considerable thought into protecting young investigators, particularly at this time of lean funding for new investigators and training grants.

< A common information infrastructure would be beneficial for improved research decisions. This infrastructure could include information about clinical trials, treatments, and pediatric concerns—particularly regarding late effects.

< There are a number of models for resolving intellectual property conflicts, particularly as they pertain to collaboration among pharmaceutical companies and academic medical centers. Perhaps a "beta-test" for a model legal agreement within cancer research would provide information and experience that could then be more broadly applied.

< Orphan diseases—those diseases with prevalence under 200,000—are a concern. There is a question as to whether development and application of more targeted markers will create numerous subsets of orphan cancers. For example, 20 percent of breast cancers are known to overexpress Her2. Does this make Her2-positive breast cancer an orphan disease?

< Concurrent biomarker and drug development need to proceed. Postmarketing clinical feedback should be improved so that companies can modify drugs that become problematic.

< Access to state-of-the-art care is a large concern. A substantial portion of insured patients does not receive standard therapies; a third of insured patients over 65 do not receive state-of-the-art treatment. About half of patients do not receive appropriate treatment, and even when insured, minorities do not receive state-of-the-art care and have poorer outcomes. Minorities without insurance have even greater difficulties.

< Public mistrust of the cancer industry and the lack of transparency of pharmaceutical industry clinical trials are other barriers to treatment.

< Central IRBs would decrease the cost and time involved in opening clinical trials. There is also an attitude of protectionism with multiple levels of review that is interfering with clinical trials.

< Regulatory harmonization and collaboration among academics, payers, industry, and Government are needed.

< Chemoprevention needs to become a focus; a shift is needed from diagnosis and treatment to prediction and prevention. There exist major disincentives for the pharmaceutical industry to develop preventive agents.

< A human cancer genome project would lead to new pathways and therapeutic targets.

DISCUSSION PANEL II: THE ROLE OF ACADEMIC MEDICAL CENTERS IN TRANSLATING RESEARCH INTO CLINICAL PRACTICE—DR. LARRY NORTON

Key Points

- It is not enough to make scientific advances; something must be done with those advances. The answer to cancer lies as much in sociology as in the "hard" sciences. There is a strong need to create multidisciplinary teams and borrow expertise from colleagues; provide better training that starts earlier in the career process; protect time for young and established investigators alike; and reexamine issues surrounding promotion within academic medical centers.
- New molecular targets are needed for prevention, therapy, and diagnosis. An increase in the number of targets, however, means increasingly fragmented markets; it is not currently economically feasible to develop drugs for such small percentages of the population. This is especially true in developing prevention drugs.
- Broad-based human studies are using samples derived from many different diseases and many different backgrounds. Researchers are attempting to attack the heterogeneity of cancer by obtaining large collections of samples.
- Human researchers do not receive the same recognition and promotion as other researchers.
- HIPAA represents the fundamental conflict between the need for confidentiality and autonomy and the need for progress and civic responsibility.
- There is a good deal of quality research being conducted outside the United States as a result of other countries' greater ability to obtain genetic material.
- A central IRB is a double-edged sword: In theory, it increases approval speed and decreases costs, but it also places more power in fewer hands.
- More early-phase trials are needed to delineate the relationship between cancer and the immune system and further explore immunocausation and immunotherapy.
- There is a need to define clinical trials for adults with cancer as the standard of care, as has been done with pediatric cancer. However, there is much work to be done to make the clinical trials system more efficient, larger, more responsive to translational scientists, and more conducive to collaboration.
- While desirable, collaboration among academics, industry, advocates, and regulatory experts to better the system is hampered by economic constraints and intellectual property rights.
- The NCI is addressing or has already addressed many of these issues. Communication within the cancer community about what is being done already and what some of the unmet needs are would be appropriate.

DISCUSSION PANEL III: BEST MECHANISMS FOR MOVING RESEARCH INTO COMMUNITIES—DR. JOSEPH V. SIMONE

Key Points

- A large portion of the population does not receive what is considered established standard care, particularly related to cancer care. There are a series of reasons for this. One example is a Medicare and Medicaid reimbursement system that is counterproductive to encouraging the delivery of high-quality medical care. The health care delivery system is left to find ways around this reimbursement system. This is a bigger problem for smaller community providers.

- There is a lack of political will to repair the cancer care delivery system. A large number of the poor do not vote or are otherwise disenfranchised; these groups have no political clout. It is up to society to develop the political will to repair the system on behalf of all people.
- No one knows how to mend the health care system. Focusing on geographical areas with major problems in cancer is one practical approach. The fundamental problem with that approach, however, is the lack of good outcome information. The most important thing that can be done to improve quality and delivery of care is to ensure transparency of good clinical outcome information.
- Pediatric oncology has had many "firsts." The first use of adjuvant chemotherapy was in children; the first systematic use of combination chemotherapy was in children; the first use of multimodal therapy combining radiation, chemotherapy, and surgery was in children. The first time chemotherapy was sent to home doctors to give between chemotherapy administrations on protocol was in pediatrics. The first therapy that successfully cured a common cancer was in pediatrics. The first biological prognostic factor was described in childhood leukemia; the first genetic prognostic determination in cancer was in childhood disease. If those in pediatric oncology could attain those "firsts," they should be trusted to appropriately apply drugs that are at the beginning of their entry into the system.

REPORT BACK—DISCUSSION

- Oncology teams caring for patients must have access to all records for those patients.
- The NCI budget should be doubled. The American tobacco industry spent $12 billion in 2003; adding another $5 billion to the NCI budget is realistic and reasonable, considering the outcome for the public good.
- CMS should make the information system on cancer patients more robust.
- Expanding the SEER-Medicare system to include 50 percent of the population, as opposed to the current 15 percent, would greatly improve the system as a research tool.
- Health policy should be considered a tool to reducing health disparities.

CLOSING REMARKS—DRS. KRIPKE, WILSON, AND LEFFALL

- Dr. Leffall acknowledged Dr. Maureen Wilson, who is ending her term as the Panel's Executive Secretary. Dr. Abby Sandler will be the new Executive Secretary.

CERTIFICATION OF MEETING SUMMARY

I certify that this summary of the President's Cancer Panel meeting, *Translating Research to Reduce the Burden of Cancer*, held January 24, 2005, is accurate and complete.

Certified by: LaSalle D. Leffall, Jr. Date: 5/25/05

LaSalle D. Leffall, Jr., M.D.
Chair
President's Cancer Panel