MEETING SUMMARY

PRESIDENT'S CANCER PANEL

THE FUTURE OF CANCER RESEARCH: ACCELERATING SCIENTIFIC INNOVATION

October 26, 2010
Philadelphia, Pennsylvania

OVERVIEW

This meeting was the second in the President's Cancer Panel's (PCP, the Panel) 2010-2011 series, *The Future of Cancer Research: Accelerating Scientific Innovation*. During this meeting, the Panel heard expert testimony regarding new technologies, models of research, collaborations, funding strategies, and ways of communicating toward the goal of accelerating the pace of scientific progress within the National Cancer Program (NCP) in coming years. The agenda for the meeting was organized into two discussion panels.

PARTICIPANTS

President's Cancer Panel

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

Margaret Kripke, Ph.D.

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

Abby Sandler, Ph.D., Executive Secretary, PCP

Gwen Darien, Chair, Director's Consumer Liaison Group

Speakers

David Agus, M.D., Director, Center for Applied Molecular Medicine, Keck School of Medicine of the University of Southern California

Peter Alperin, M.D., Vice President of Medicine, Archimedes, Inc.

Margaret Anderson, M.S., Executive Director, FasterCures/The Center for Accelerating Medical Solutions

Tomasz M. Beer, M.D., F.A.C.P., Deputy Director, Oregon Health & Science University Knight Cancer Institute

Carolyn Compton, M.D., Ph.D., Director, Office of Biorepositories and Biospecimen Research, National Cancer Institute

Ronald F. Dixon, M.D., Director, Virtual Practice Project at Massachusetts General Hospital Department of Medicine

Charles Friedman, Ph.D., Chief Scientific Officer, Office of the National Coordinator for Health IT, Office of the Secretary, Department of Health and Human Services

Patricia Hartge, Sc.D., Deputy Director, Epidemiology and Biostatistics Program, National Cancer Institute

Bernard Munos, M.S., M.B.A., Advisor, Corporate Strategy, Eli Lilly and Company (Retired)

Louise M. Perkins, Ph.D., Chief Scientific Officer, Multiple Myeloma Research Foundation

Robert G. Urban, Ph.D., Executive Director, David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology

Nina Wallerstein, Dr.P.H., Director, Center for Participatory Research, University of New Mexico School of Medicine

OPENING REMARKS—DR. LaSALLE D. LEFFALL

On behalf of the Panel, Dr. Leffall welcomed invited participants and the public to the meeting. He introduced Dr. Thomas Tritton, President of the Chemical Heritage Foundation (CHF), who welcomed everyone to CHF and provided a brief overview of the Foundation's purpose. Dr. Leffall then introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings.

Dr. Kripke reported that the Panel held a Working Group meeting on September 24, 2010, to discuss policy, research, and program recommendations for the 2010-2011 Annual Report to the President. Dr. Kripke's motion to accept the Working Group recommendations was unanimously passed.

PANEL I

DR. DAVID B. AGUS:

COMPLEX SYSTEMS, PROTEOMICS, AND CANCER THERAPY

Background

Dr. Agus is a Professor of Medicine at the University of Southern California (USC) Keck School of Medicine and heads USC's Westside Cancer Center and the Center for Applied Molecular Medicine. His research focuses on the application of proteomics and genomics for the study of cancer and the development of new therapeutics for cancer. Dr. Agus' clinical responsibilities include the development of clinical trials for new drugs and treatments for cancer that are supported by the National Cancer Institute and private foundations. A research project principal investigator, Dr. Agus serves on the executive committee of the Stanford Center for Cancer Nanotechnology Excellence and, together with Danny Hillis, is co-Director of the newly funded USC-NCI Physical Sciences in Oncology Center.

Key Points

- One problem with cancer drugs is that they are evaluated based on one metric—the percentage by which they can reduce the size of a tumor. This approach does not take into account the fact that the tumor exists within the complex system of the patient. There are currently no metrics to measure how a drug might be benefiting a patient even in the absence of tumor shrinkage. In some cases, a drug that did not reduce tumor size has extended patient survival.
- The cancer field has erroneously followed the model of infectious disease since the 1920s. Infectious disease is characterized and treated according to diagnostic criteria, and the treatment of cancer has followed suit. However, human diseases, such as cancer, cannot be categorized or treated like bacterial infections.
- The dictionary of terms for describing cancer is currently very poor, consisting of only about 100-120 adjectives. The vocabulary focuses mainly on symptoms. Efforts such as The Cancer Genome Atlas will allow cancer researchers to apply more precision when describing the disease and enhance their ability to categorize what they are treating.
- As the cancer field moves forward, clinicians and researchers need to view the patient as a system and overall health, not merely a 50 percent reduction in cancer, as the goal. The patient is a system in which the inputs are interactions with the environment (diet, stress, genes, and disease treatment) and the outputs are disease symptoms. This view contrasts with current methods to diagnose cancer,

which mainly consist of taking a biopsy and conducting pattern recognition (e.g., Do the cells look normal?).

- Biomarkers are already utilized for early disease risk assessment and detection, but should also be developed as indicators of health. For example, in the treatment of diabetes, glycosylated hemoglobin is a biomarker that is used to reveal the status of glucose in the body over a 90-day period. Cancer researchers need to focus on new biomarkers to better understand the state of the patient system.
- Three control systems are involved with cancer treatment: (1) the patient's body; (2) the cancer; and (3) the patient/treatment loop, which helps control system one overcome control system two.
- Treatments are controllable variables in the patient system. Each treatment given is a variable that can be controlled to change the system in a positive direction towards overall health. Time is an integral component to the system approach to cancer. Currently, there is no mechanism to understand the kinetics of the disease—cancer is assessed only within a finite moment in time.
- The NCI Web site states that cancer is a disease of the genes; however, this statement may not be accurate. Evolution selects phenotypes, not genotypes, as diseases. When pathologists look under the microscope, they are identifying a biologic mass that looks like ovarian cancer, prostate cancer, and so forth (i.e., the phenotype); they are not identifying specific gene mutations. At the most basic level, cancer diagnosis is simply pattern recognition, and phenotype is an important lens through which to view all cancers.
- NCI is exploring new and innovative approaches to better understand and control cancer through initiatives that enable the convergence of the physical sciences with cancer biology. The Physical Sciences in Oncology Program was developed to address cancer diagnosis and treatment through a new systems approach involving physicists and mathematicians. The presenter—along with Murray Gell-Mann, who won the Nobel Prize in 1969 for his work on quark and string theory, and Danny Hillis, who pioneered supercomputing—received funding through this program to bring a novel approach to cancer research. This new approach will utilize technology and algorithms similar to those used to predict weather.
- Technology, and the cost of utilizing it, has changed dramatically over the past 36 years. By one report, it cost $150 million to sequence one gene in 1974; in 2008, the cost was 70 cents.
- The presenter's laboratory uses mass spectrometry to generate profiles of all the proteins in the blood of a patient. This profile is influenced by what the patient ate, events in tissues and the blood, and how fast a cancer is growing. This is one of the first examples of cancer researchers looking at the whole-body system of a patient. Coupling this approach with clinical annotation in electronic health records will yield information that will help model and treat cancer in new ways.
- A mathematician was given histopathology samples of 20 different brain cancers and asked to devise a formula to predict patient prognosis. The variables in this formula included the blood supply, nuclear atypia, rate of cell growth, and gene mutations. The mathematician and a neuro-oncologist at Duke University were then each given MRIs of 100 brain cancers and asked to predict the prognoses of the patients; the mathematician, who had never actually seen a brain cancer patient, was better at predicting outcome.
- Clinicians and researchers do not need to fully understand cancer in order to treat it. Cancer is a robust system that is difficult to understand in detail but can still be controlled. This concept is illustrated by the many examples of drugs, not necessarily thought to directly target cancer, that improve patient outcomes by changing the microenvironment of the tumor.
- A dramatic example of such a drug was published in the *New England Journal of Medicine* (*NEJM*) last year. In this study, 1,800 women with premenopausal breast cancer were randomized after chemotherapy to receive hormone therapy alone or hormone therapy in combination with a drug that

promotes bone growth. The drug combination reduced disease recurrence by 36 percent and decreased the incidence of new primary tumors by 30 percent.

- The reasons why some drugs are effective for treating cancer and others are not are poorly understood at present. This is illustrated with the example of a 46-year-old woman with stage IV lung cancer. This patient underwent two brain surgeries and three radiation therapies for recurrent brain metastases and was also given several chemotherapeutic drugs, all without positive results. The patient was then given a single pill a day with the only side effect being acne, and her tumor disappeared. Her doctors had no idea why her tumor was more sensitive than the tumors of 98 percent of the other patients who are given this drug.
- The presenter serves as a scientific advisor to a brain cancer foundation called Accelerate Brain Cancer Cure. Several years ago, the foundation received a call from a doctor who had a patient with advanced glioblastoma. If the patient failed chemotherapy, he would have only weeks to live. The patient requested to be put on the drug bevacizumab, which at the time was approved by the U.S. Food and Drug Administration (FDA) only for the treatment of colon cancer. The patient had a complete response, which astounded the doctor. Accelerate Brain Cancer Cure then funded a clinical trial to treat 40 patients with this drug and witnessed an 80-percent response rate. The United States excels at reporting adverse responses to drugs, but there is no national mechanism to report positive events such as the unusual drug response witnessed by the oncologist with the advanced glioblastoma patient.

MR. BERNARD MUNOS:

BRINGING BREAKTHROUGH INNOVATION BACK TO ONCOLOGY

Background

Mr. Munos is the founder of InnoThink, a partnership aimed at achieving a deeper understanding of breakthrough innovation and bringing new evidence-based innovation models to the pharmaceutical industry and its stakeholders. He previously spent nearly 30 years with Eli Lilly and Company. While at Lilly, he noticed how little was known about what causes innovation, despite the huge sums invested each year in research and development by pharmaceutical companies and publicly financed research institutions. This caused him to shift his focus to the study of innovation. With the encouragement of the late Armen Tashjian, Professor at the Harvard Medical School and the Harvard School of Public Health, he went on to publish a series of papers in *Nature* and *Science* that have helped stimulate a broad rethinking of the pharmaceutical business model by the industry, investors, policymakers, regulators, and patient advocates.

Key Points

- The United States currently spends about $95 billion each year on drug development and produces only about 20 new drugs annually.
- Despite a surge of new drugs currently in development for the treatment of cancer, the future of cancer therapy looks grim. Last year the pharmaceutical industry counted 861 cancer treatments as being in various stages of development. However, the output of new drugs is flat or declining. According to data from the FDA, over the last 7 years, each of the top 13 pharmaceutical companies has produced only an average of 0.6 new drugs per year, and the trend is flat. This year will be an all-time low for the number of new cancer drugs approved.
- In 2009, 98 percent of large pharmaceutical companies' ("big pharma") sales were from drugs five years and older. This has two implications. First, in an industry with an average patent life of 11 years, most of the drugs generating that 98 percent of sales will face competition with generics within

the next 5 years. Second, the drugs that have been produced within the past 5 years and have captured only 2 percent of sales are likely small in number and not very effective.

- Last year, almost 75 percent of American's pharmaceutical needs were met with yesterday's innovation—generic drugs. Once the majority of big pharma sales have fallen to generics, one must begin to question the relevance of the pharmaceutical industry.
- The inefficient output of the pharmaceutical industry implies the failing of its business model, which is unable to produce affordable innovation. The model first failed 10 years ago with antibiotics, when most of the industry stopped developing new anti-infectives. More recently, the model failed again when it deprioritized drugs for mental illnesses and cardiovascular disease. The retrenchment of the industry into fewer therapeutic areas that it thinks can carry its enormous costs reflects companies' failures to produce affordable innovation. As research and development costs continue to rise, even oncology may no longer be viable.
- Research has shown that of the 300 or so biomedical breakthroughs of the 20th century, nearly all have been a result of engaging in high-risk and unconventional research. For most of the past century, the pharmaceutical industry's research model has followed this approach, allowing its leaders to evolve into what has become big pharma. In the last 15 years, however, pharmaceutical innovation has changed under a new generation of CEOs, many of whom were not scientifically trained. They destroyed scientific innovation in the industry by reorganizing research and development to mirror an assembly line. They tried to optimize production to predict blockbusters in the market (i.e., drugs for which sales are $1 billion or more per year). Instead of allowing scientists to follow their intuition, they were directed to produce drugs predicted to be sure sellers. However, this strategy has failed. The prediction of blockbusters is an impossible task; it fails 80 percent of the time. This approach to research and development has had a disastrous impact on innovation. This will cause the demise of this business model but not innovation because society will continue to demand novel therapies.
- There is a better way to organize research and development—the evidence-based innovation model. Biomedical companies and research organizations should stop chasing blockbusters and focus on producing scientific breakthroughs. The blockbuster-driven model focuses on sales irrespective of novelty; the breakthrough-driven model focuses on therapeutic innovation and patient needs irrespective of commercial potential. Breakthroughs represent momentous advances in therapy and, generally, a universal consensus quickly develops around their transformational character. An example is Gleevec (imatinib), which in one of its earliest clinical studies brought remission to 53 of 54 patients with chronic myeloid leukemia. Its sales, first predicted to peak at $50 million, yielded $4 billion in revenue in 2009.
- Currently, the pharmaceutical industry avoids anything deemed high risk. A mechanism is needed to foster high-risk, unconventional ideas and research.
- Innovation does not increase in proportion with funding. Some of the most innovative research organizations are those that are small and run on minuscule budgets. The Rockefeller University is the archetype of such an organization. It was the first institution in the United States devoted solely to biomedical research, and it continues to pursue this mission with 250 employees on a budget of only $250 million per year. Despite this small budget, the scientists at this institution have been awarded an average of one Nobel Prize every three years for the past six decades.
- Historically, the majority of innovation has not come from laboratories or pharmaceutical companies but, rather, from physicians trying to help patients for whom standard therapy has failed.
- Experience suggests that marginal innovation is costly because a complicated clinical trial must be conducted in order to establish and demonstrate superiority to existing treatment options; however, breakthrough innovation is much less expensive. Therefore, the question arises: Why does the pharmaceutical industry insist on developing marginal innovation?

- Breakthroughs do not need to be predicted because they stand out in the very early stages of clinical trials. They are cheaper and faster to develop because large patient populations are not required to demonstrate superiority. They also make irrelevant the industry strategy of developing multiple compounds for one indication, in case one fails.
- A concern is that there may not be enough breakthroughs to support a large industry. This overlooks the fact that if breakthroughs are the only way to get funding, supply will expand to meet demand.
- A quick review of the scientific literature reveals that breakthroughs may be more common than anticipated. Examples of some recent breakthroughs include a compound that clears malaria with a single application; a cancer drug capable of bringing HIV out of dormancy, making it susceptible to treatments against the active virus; and a drug that causes a response in 81 percent of patients with a mutation responsible for half of melanoma cases.
- The accumulation of knowledge fosters innovation and breakthroughs and should be encouraged from a policy standpoint. For example, all new drug applications approved by the FDA should be shared with the entire scientific community to move understanding of a disease forward. Additionally, data on all abandoned investigational new drug applications should be released so industry does not repeat mistakes.
- Other polices that promote accumulation and sharing of knowledge are encouraging pharmaceutical companies to collaborate at the precompetitive level by supporting the creation of open research consortia dedicated to increasing foundational knowledge about basic biology or pathology.
- About 40 percent of the human genome (8,000 genes) still has no known function. It is impossible to do predictive biological modeling if 40 percent of the system to be modeled is unknown. A broad, collaborative effort to complete annotation of the human genome should be one of the highest research priorities.
- Assembling a large database of wholly sequenced genomes (over 10,000) should be considered. The cost of sequencing the genome may drop from $3,000 to below $100 within the next five years. The genotyping of the entire U.S. population should be considered and the resulting data made readily available to the scientific community.

MS. MARGARET ANDERSON:

PAVING THE PATH TO A MORE EFFECTIVE AND EFFICIENT RESEARCH ENTERPRISE

Background

Ms. Anderson is Executive Director of *FasterCures/The Center for Accelerating Medical Solutions*, a role that involves defining the organization's strategic priorities and positions on key issues, developing its programmatic portfolio, and managing its operations. Prior to her appointment as Executive Director, she was *FasterCures*' COO for five years. Ms. Anderson previously served as deputy director of the Academy for Educational Development (AED), where she was also a team leader in the Center on AIDS & Community Health. Prior to AED, she led programs and studies at the Society for Women's Health Research, the American Public Health Association, and the Congressional Office of Technology Assessment. She serves on the boards of the Alliance for a Stronger FDA and the Council for American Medical Innovation, and has held numerous committee and coalition memberships for Federal agencies and professional associations in the biomedical and public health arena.

Key Points

- *FasterCures* is a nonprofit think tank and catalyst for action that works across research sectors and diseases to transform the medical research enterprise to become more effective and efficient. The

mission of *FasterCures*, a center of the Milken Institute, is to accelerate the process of discovery and development of new medical solutions for deadly and debilitating diseases.

- *FasterCures* has a three-pronged strategic plan that includes fostering innovation and accountability across research organizations, improving and continuously modernizing the medical research environment, and maximizing the development and use of research resources. Most importantly, *FasterCures* keeps a patient-centered focus in their work by determining whether opportunities for patients to participate in clinical trials are being maximized.
- In order to accelerate medical solutions and save more lives, the research enterprise must save time—time in discovering breakthrough ideas, time in pursuing those ideas and turning them into therapies, and time in bringing those therapies to patients.
- Medical research is an investment, and a robust life sciences infrastructure is necessary to the nation's wellbeing, economic standing, and global leadership. In order for the investment to pay off from a monetary and therapeutic benefit standpoint, research must be outcomes oriented. This is not a very popular idea in some scientific communities; however, a medical research enterprise in which the central organizing principle is improving patient outcomes needs to be created.
- *FasterCures* tries to accelerate medical solutions and foster innovation within the research enterprise by creating opportunities to convene, connect, cultivate, and catalyze. An example of these opportunities is the Partnering for Cures series of meetings. This effort brings together and provides a forum for discussion among medical research leaders and decision-makers, innovators, and advocates from across sectors who share the goal of getting therapies to patients faster.
- In spite of efforts such as Partnering for Cures, patients are still paying the price of delays in development of efficient therapies. This is due to a combination of factors, which includes lack of medical breakthroughs, limited resources, and restrictive policies that stall progress. Developing a new medicine takes an average of 10-15 years, and according to the Congressional Budget Office relatively few drugs survive the clinical trial process. The costs of developing a new drug are also too high; in 1979, it cost $100 million to develop a drug and in 2005 it cost $1.3 billion, on average.
- Researchers must address the changing demographics of the U.S. population. The number of adults older than 65 years of age is steadily increasing. When treating aging populations, clinicians interact with patients who are often diagnosed with more than one condition, which can complicate therapy options.
- Despite the current state of the medical research enterprise, transformation is happening. A large investment is being made in health information technology (IT), which has the potential to greatly change clinical research. Other examples of transformation include the Human Genome Project, personalized medicine, and new entrepreneurial business models.
- There is an educated and increasingly engaged patient community. *FasterCures* is looking to ACT UP as a model patient organization to understand the community's ideas to change the medical enterprise. ACT UP, or AIDS Coalition to Unleash Power, is a diverse, nonpartisan group of individuals committed to direct action to end the AIDS crisis.
- NCI has a unique opportunity to serve as the pathfinder for an outcomes-oriented biomedical research enterprise. NIH is already starting on this path with the Cures Acceleration Network (CAN), which will work to reduce the time it takes to move new drugs and therapies from the laboratory to the clinician's office. CAN will be established within the NIH Office of the Director and will authorize grants expected to quickly move discoveries from the laboratory through the development, testing, and regulatory review processes and into the hands of the patients who need them.
- New business models are needed to address the challenges within the traditional research system. An example of this is the venture philanthropy groups involved with The Research Acceleration and

Innovation Network (TRAIN). TRAIN was established to create opportunities for medical research innovators to discuss and tackle challenges that cut across diseases.

- Philanthropic priorities are shifting to respond to patient demand. Some of the innovative practices involved in the ventures of philanthropic foundations include strategically using capital, building collaborations, streamlining the grant-making process, and sharing information. These foundations, such as the Multiple Myeloma Research Foundation and the Cystic Fibrosis Foundation, are unique in that they offer the possibility of true access to patients in the form of robust patient registries and large tissue banks.
- The recipe for successful innovation in disease research includes research resources, infrastructure, and environment. Human capital—a highly-skilled, diverse pipeline of scientists—is key. Also important are novel ingredients such as risk-sharing on precompetitive tools and increased awareness of the importance of translational research programs.
- The research enterprise is starting to see pockets of innovation, best practices, and glimpses of progress and it needs to continue to the next level of transformational change. In order for this to happen, academia, the pharmaceutical industry, venture capital and philanthropic foundations, government, and patient advocacy groups must all efficiently work together.

DR. ROBERT G. URBAN:

DAVID H. KOCH INSTITUTE FOR INTEGRATIVE CANCER RESEARCH AT MIT

Background

Dr. Urban received both an undergraduate and a doctoral degree from the University of Texas system. After graduation, he moved to Cambridge to become an Irvington Institute fellow at Harvard College, where his research involved structural immunology. The research conducted during his time at Harvard led to the formation of a Harvard startup biotechnology company called Pangaea Pharmaceuticals. Over time, Pangaea evolved into a company called ZYCOS and the related oncology products moved into clinical trials. After ZYCOS, Dr. Urban became President and CEO of Acretia, a privately held drug development company based in Boston. While he was at Acretia, the company invested in a portfolio of oncology, dermatology, and pain products. Dr. Urban remains on the Board of Acretia and is a cofounder and board member of BBI, a company developing synthetic glycosylated peptide-based drugs for use in treating neuropathic pain. In 2007, Dr. Urban was recruited to join the Massachusetts Institute of Technology's (MIT) leadership team in the kickoff of the Koch Institute.

Key Points

- Cancer is the most feared of human diseases, not because of the possibility of death after diagnosis, but because of the prospect of having to undergo aggressive treatments such as surgery, chemotherapy, or radiation therapy. A real benefit can be imparted by simply providing new ways in which patients can be treated—by reducing toxicity and minimizing the number of needed surgical procedures.
- Oftentimes, cancer is not viewed from a global perspective; it is seen as a disease of the developed world. The truth is that cancer kills more people globally than HIV/AIDS, malaria, and tuberculosis combined. The World Health Organization projects that the global cancer burden will increase to about 15 million new cases per year by 2020.
- The National Cancer Act was established in 1971 and MIT was one of the first institutions to receive funding to focus on basic cancer research. Scientists who, at the time, were not particularly recognized or celebrated were recruited to work at the MIT Center for Cancer Research and went on to win four Nobel Prizes over the next 30 years. Some of the discoveries they made were that of the

first oncogene and validation of the role of chromosomal abnormalities in cancer, which led to the development of effective cancer treatments like Herceptin and Gleevec.

- MIT has three institutional priorities, areas in which incentives are created for people from different areas within the Institute to come together and conduct team science. The first priority is education, second is energy, and the third priority is cancer. The Koch Institute (KI) has five cancer research priorities: nanotherapuetics, devices and monitoring, metastasis, pathways and resistance, and cancer immunology.
- For the first time, MIT faculty and students are being told that they should measure themselves by the impact of their research on the lives of people. The only way to make an impact is through extensive and productive collaboration.
- Cancer is most often a disease of later life. MIT is dedicated to uncovering what can be done from a technology standpoint to improve the detection and screening of patients. Being able to intervene earlier can greatly improve cancer prognosis. MIT is not looking to merely add another layer of cost when implementing improved technology; the health care system is already burdened with existing costs. Technology must be applied in a way that is mindful of existing financial problems.
- The idea of the KI was born when Susan Hockfield joined MIT as the Institute's first-ever life science president. Together with Tyler Jacks, the Director of the MIT Cancer Center, she concluded that a mechanism was needed to translate basic science research into commercially viable therapies for patients. Thus, the KI was created to bring together life sciences researchers with an equivalent number of engineering faculty across the MIT campus—an interdisciplinary workforce working in a targeted manner to accelerate medical innovation.
- The building that will house KI is almost complete and was designed to drive faculty interaction. Half of every floor of the building is designed to host the resources required of engineering faculty, and the other half comprises laboratories devoted to basic life science research. However, all of the shared employee spaces—offices, conference rooms, restrooms, etc.—are in the center of the building, connected from top floor to bottom with a continuous stairwell.
- Laboratory spaces on every floor of the Institute are reserved for a new set of investigators—incredibly gifted scientists who are also practicing oncologists willing to see patients up to 50 percent of their time. These individuals will serve as a link to the unmet therapeutic needs of oncologists.
- There is specialized unit within KI called the Swanson Biotechnology Center. It is named after Bob Swanson, an MIT alumnus and founder of Genentech. The Center has one of the world's most sophisticated small-animal preclinical testing capabilities, embedded with magnetic resonance imagers (MRIs) and microcomputer tomography scanners (micro-CTs), and other imaging capabilities that work with mouse models at very high resolution. All KI faculty and collaborators can be trained on and use these resources at a remarkably discounted price.
- The Frontier Research Program provides novel funding sources for the KI community. Capital is collected through largely philanthropic efforts and made readily available to faculty for difficult-to-fund and potentially disruptive cancer research projects in a manner that drives sustained program growth. Frontier Research Grants range from as little as $50,000 for project startup (Seed grants) to $250,000 for Transcend grants, which provide access to capital and infrastructure resources available within pharmaceutical companies.
- A significant number of KI faculty is devoted to the study of nanotherapeutics. Nanoparticles are typically around 1,000 times smaller than a cancer cell, which means they can readily enter the bloodstream, but can also be rapidly cleared from the body. Chemical manipulation enables the particles to stick to chemical determinants present on the membrane of cancer cells, then release a chemotherapeutic embedded within the nanoparticle. This mechanism should facilitate increased potency and decreased toxicity of cancer treatments.

- Another example of the nanotherapeutic technology resulting from KI funding and resources is an implantable sensor to detect cancer occurrence or relapse much earlier than traditional techniques. Ferric (iron-based) nanoparticles are coated on their outer surface with molecules that can recognize a tumor biomarker. The presence of this biomarker causes the nanoparticles to aggregate, which changes their interaction with water molecules and allows for quantitative measurement by applying a magnetic field. The efficacy of these sensors has already been proven in animal models.
- Researchers working closely with clinicians questioned whether a similar implantable sensor could be developed for real time use alongside treatments to measure the efficacy of drugs. Research efforts are swiftly being directed to investigate the potential of this nanotherapeutic opportunity.
- KI is also working on uncovering the biology of metastasis. Nine out of ten cancer patients die as a consequence of their cancer spreading, and too little is known about the biology of this phenomenon. One research team has discovered that the presence of a form of the Mena protein resulting from alternative gene splicing allows tumor cells to interact with migratory macrophages and facilitates their movement into and out of the bloodstream. This form of the protein can be used as a biomarker to accurately determine whether or not a breast cancer patient is at high risk for relapse.
- Cancer cells are immunosuppressive—turning off the killer function of the immune system. Yet, the body's immune system cells are incredibly efficient at finding cancer cells anywhere in the body. KI researchers have attached nanotherapeutic particles to tumor-specific T cells—a type of immune system cell—to harness the honing precision of the T cells and effectively deliver cancer drugs. This has been tested in mouse models and a 400-fold improvement in the delivery of the drug to the tumor was observed.

DR. RONALD F. DIXON:

THE VIRTUALIZATION OF HEALTH CARE DELIVERY

Background

Dr. Dixon is the Associate Medical Director at Massachusetts General Hospital (MGH) Beacon Hill Internal Medicine Associates and the Director of the Virtual Practice Project at MGH. Dr. Dixon's interests are in alternative methods of health care delivery, specifically relating to general internal medicine. Dr. Dixon sits on a number of committees designed to make care delivery more efficient and effective for patients and physicians. He is actively pursuing clinical-practice-based research in this domain that is supported by MGH and the Center for the Integration of Medicine and Innovative Technology. His current projects include "Virtual Visits in General Medicine," "Primary Care Kiosks," "Low Acuity Clinics," and "Remote Physiological Monitoring in Patients at Risk for Chronic Disease."

Key Points

- Funding for the MGH Virtual Practice Project is provided by the Center for Integration of Medicine and Innovative Technology (CIMIT), a nonprofit consortium of Boston teaching hospitals and engineering schools. CIMIT fosters interdisciplinary collaboration among experts in medicine, science, and engineering in concert with industry and government to rapidly improve patient care. CIMIT does this by providing small seed grants of $25,000 to $50,000 for early-stage, collaborative research projects aimed at improving patient care, with an emphasis on devices, procedures, diagnosis, and clinical systems.
- Readily available technologies, such as telephones, email, and videoconferencing, have the capability to transform health care delivery. Other possible transformative technologies include cell phone applications, SMS messaging, kiosks, social networks, home monitoring, and electronic health records. Three out of five face-to-face physician appointments in the general medicine environment could be virtual. These virtual appointments could have a particular impact on patients with chronic

disease (e.g., diabetes, depression); patients with acute, one-time illness; and caregivers or those managing elderly patients.

- The presenter provided an example of the utility of using communication technologies to connect with patients on a virtual basis. While out of the hospital, the presenter received a call from a 55-year-old male patient with a history of cutaneous T-cell lymphoma. The patient called the presenter complaining of a rash on his back associated with pain that had lasted for two days. He was unable to accurately describe the rash, so he emailed a photo of it to the presenter, who was able to view this photo on his phone. From the photo, the presenter accurately diagnosed the rash as a case of shingles and faxed a prescription for antiviral medication to the patient's pharmacy.
- Many patient stories have inspired the development of the Virtual Practice Project. One story is that of an 80-year-old woman with a significant history of congestive heart failure. She was admitted to the hospital for congestive heart failure complications six times in a period of three months. Doctors tried to communicate to her the importance of managing diet, etc., yet she would continually end up back in the hospital. After the sixth hospital discharge, a nurse took the patient's phone number and instructed her to set a scale near her bed. Each morning the nurse called the patient and had her weigh herself—the patient's treatment (diuretics) was then adjusted based on the recorded weight. By doing this, the patient was not admitted to the hospital again for an entire year. A simple daily telephone call to a patient can improve health outcomes and significantly reduce costs.
- Another story involves a 60-year-old male patient with newly diagnosed non-small cell lung cancer. The diagnosis was metastatic stage IV and after a few months the patient was in palliative care; the patient wanted to continue his end-of-life care with the presenter, his general physician. Every week, the presenter and the patient communicated via Skype to manage his pain regimen and handle secretions. However, the patient's medical record does not include evidence of these interactions because of their nontraditional nature.
- A study supported by MGH and the Massachusetts General Physicians Organization was conducted to examine the feasibility, effectiveness, and acceptability of virtual (videoconferenced) physician visits. The study included 152 patients who were randomized to compare the effectiveness of virtual visits (using Skype) with that of face-to-face visits. Each patient came into the office and interacted with one physician via Skype and a second physician via face-to-face visit. The order of the two visit types varied among patients. Patients were very satisfied with videoconferencing as a way to interact with their physicians. No difference was found in terms of attention given to patients or the quality of physician explanations. There was a slight difference in the overall rating of the virtual visits compared with the face-to-face visits, but the virtual visit rating was nonetheless high. Physicians were not as satisfied with the virtual visits due to the inability to conduct physical examinations.
- A second virtual communication modality—templated electronic visits—was also tested for feasibility, effectiveness, and acceptability. The templated electronic visit is part a commercial Web portal aimed at providing patients with an alternative way to asynchronously interact with physicians for evaluation and management of nonurgent medical problems. For example, if a patient is experiencing back pain, he or she fills out a template that asks questions relevant to back pain. The questions are the same as those a physician would ask if presented with the complaint in an in-person visit. The physician receives the completed template via email and sends back an evaluation and management decision response within 24 hours. About 70 percent of the MGH patient population are currently using the Web portal.
- The feasibility study showed that patients view the Web portal as an acceptable alternative to face-to-face visits for nonurgent concerns. Web portal features liked best by the 362 patients enrolled in the study included: prevention of unnecessary trips to the doctor's office, direct access to a physician, and elimination of phone calls. The top-ranked barrier to the Web portal was the site's graphic user interface.

- The Virtual Practice Project is working on developing a tool that captures nontraditional patient-physician interactions, such as asynchronous communication with a patient at home, communication using a cell phone, or synchronous videoconference communication. The tool would capture all communication modalities and be recorded in the patient's medical record.
- With the help of engineers from CIMIT, the Virtual Practice Project is also developing a chronic disease management kiosk. Patients could visit the kiosk for self-service evaluation and management issues. One of the kiosks currently in development is for diabetes management; it conducts a hemoglobin A1c test to assess blood sugar control for patients.
- Some of the applications of virtual technology for cancer include virtual videoconferences post-chemotherapy for acute side-effect follow-up, asynchronous evaluation of systems and progress, and virtual discussion of oncology cases among physicians (i.e., virtual clinical rounds).
- Better delivery of general care results in better cancer prevention. Significant medical funding is currently devoted to the management of acute and chronic care, and the focus needs to shift to cancer prevention as a priority for the health care delivery system.

DR. CHARLES FRIEDMAN:

TRANSFORMATIONAL CHANGE AND THE RAPID LEARNING HEALTH SYSTEM

Background

Dr. Friedman is the Chief Scientific Officer for the Office of the National Coordinator for Health Information Technology (ONC) in the U.S. Department of Health and Human Services (HHS). As ONC's chief scientist, he leads a group responsible for the tracking and promotion of innovation in health IT, research programs to improve technology, applications of health IT that support basic and clinical research, evaluation of all of ONC's programs, programs to develop the health IT workforce, and activities supporting global eHealth. Dr. Friedman served as ONC Deputy National Coordinator for two years prior to assuming his current position. He was lead author of the national Health IT Strategic Plan released in June 2008.

Key Points

- In order for health information technology to succeed on the national level, its development must support the health system of the future, not the current system. During his first radio address to the nation, President Obama stated that the United States would computerize its health records within five years—half the time in which his predecessor wished to achieve this goal. It is fundamental to have the support of the President for this endeavor, but much work must be done to implement a functional, national electronic health record (EHR) system in only five years.
- In 2009, only 6.3 percent of U.S. office-based physicians had fully functional (capacity to carry out 10-15 specific functions) EHR systems in place. About 20 percent had a basic EHR system (able to carry out approximately four specific functions), and 43.9 percent had any type of EHR system in place (i.e., some kind of computer in the office).
- The utilization of EHRs in hospitals is further along than in physician offices. According to the *New England Journal of Medicine*, about 2 percent of hospitals have comprehensive EHR systems and about 9 percent have basic systems. By *NEJM* definition, comprehensive systems are able to carry out all 24 functions on which they are surveyed. Seventy-five percent of hospitals in the United States have electronic laboratory and radiology reporting capabilities, about half have computerized medication lists, and approximately 50 percent have active reporting systems for drug allergies and drug interactions. Hospitals vary in their progress, but the majority are on their way towards adoption of complete EHR systems.

- The Health Information Technology for Economic and Clinical Health (HITECH) Act, enacted as part of the American Recovery and Reinvestment Act, was signed into law in February 2009 to promote the adoption and meaningful use of health information technology. HITECH provides payment incentives through the Centers for Medicare and Medicaid Services (CMS) to providers and hospitals who achieve meaningful use of certified EHRs. A separate part of HITECH appropriated $2 billion to ONC to develop a program supportive of the movement toward meaningful use of health information technology. However, estimates of the net cost to implement a complete national EHR are around $17 billion.
- There are also three supportive grant programs and enhanced privacy, security, and access provisions of the HITECH Act.
- Meaningful use should be understood as those uses of health IT that will improve the quality, efficiency, and safety of health care, as well as support quality improvement studies, research, and population health. More simply stated, it is the pursuit of transformation. Meaningful use has been rigorously defined through a formal rule-making process. Final rules for the CMS incentives program and ONC standards for EHRs were issued on July 13, 2010. Stage 1 of meaningful use entails 15 core objectives and an additional menu set of 10 objectives from which any 5 can be selected that all eligible providers and hospitals must achieve.
- ONC efforts to promote meaningful use will work toward increased transparency and efficiency, improved individual and population health outcomes, and improved ability to study and improve care delivery. Two programs are of central importance to these efforts. The Strategic Health IT Advanced Research Project will support research to enhance health IT. The Beacon Community program will demonstrate what is possible in terms of the ability of meaningful use to affect the health of individuals and populations in defined geographic areas.
- Currently, the nation does not have the health IT capabilities needed to achieve the end goals of the ONC program. The health IT needed to support transformation must match the way users think, be safe and usable, make location irrelevant (for patients and providers), assemble relevant data and apply “best practice” knowledge to decisions, and enable a real-time learning health system.
- The highest-level goal of the ONC program is to have a federated, integrated learning system for health care quality improvement and population health research by 2015. Having a learning system in place will enable many new health IT possibilities. For example, an authorized person could broadcast a research question that is applied to relevant data distributed across the nation. From a public health perspective, a learning system could allow an epidemic to be tracked almost automatically as new cases are reported in EHRs. The system could also work in reverse, with care outcomes data feeding the national knowledge library.
- A learning system cannot be built on centralized databases, but should be built upon many “islands of excellence” that exist, such as the NCI caBIG program. Implementation of a learning system will need strong policy and governance.
- The first step toward realizing a federated learning system took place in the form of multistakeholder workshops convened by the Institute of Medicine (IOM) in July, September, and October 2010. Results from these workshops will be summarized in a report on an electronic infrastructure for a learning system that will be released by IOM by December 31, 2010.
- The learning system will be a tremendous exercise in coordination and leverage. Most of the system can be built from meaningful use, governance of the Nationwide Health Information Network, agency-specific “learning health system” efforts and policy initiatives, and “islands of excellence” outside the government.

DISCUSSION AND CONCLUDING COMMENTS:

PANEL I

Key Points

- Tumor shrinkage is commonly used as an endpoint in clinical trials, but there is some question as to whether this outcome is a good surrogate for patient survival. It would be more desirable to identify biomarkers—preferably measurable within the blood—that provide information about if and how a tumor is being altered by an intervention. However, there is currently no clear regulatory process for the use of biomarkers, which likely discourages innovators and investors from devoting resources to this area. FDA regulatory processes have not kept pace with advances in science and technology. FDA and others have begun to develop ideas for these processes, and FDA leadership appears to be committed to making improvements in this area but nothing has yet been put in place.
- FDA faces serious challenges with respect to its budget. Salary support for its highly trained workforce comprises a substantial portion of the FDA budget. FDA has good intentions to work with other agencies, but is often limited because of financial challenges.
- Although industry has suffered from lack of leadership and subsequent lack of innovation, it is clear that innovative efforts are ongoing in other sectors. Much of this innovation is being driven by the involvement of scientists from disciplines that have not historically participated in biomedical research.
- Incremental innovation and disruptive innovation cannot coexist. There is always a tendency for incremental innovation to encroach upon, and eventually completely overtake, disruptive innovation because the former is easier, cheaper, and often easier to evaluate. The only successful models that have produced disruptive innovation on a consistent basis are those that focus exclusively on disruptive innovation. One good example is the Defense Advanced Research Projects Agency (DARPA), which only funds ideas with disruptive potential. However, it was pointed out that, unlike some other fields, innovation in medicine is often driven by reimbursement trends.
- The scientists of the world need to be encouraged to foster disruptive ideas and conduct innovative science. Cutting-edge science and transformative ideas can take place anywhere in the world. Unlimited funding should be provided to support unconventional ideas with potential to lead to breakthroughs. Additionally, the NCP needs to support spontaneity in research. Current grant funding mechanisms force investigators to wait months before they can secure funding to pursue ideas.
- The MIT Koch Institute attempts to provide opportunities for investigators to pursue creative ideas and collect enough data to determine whether a project should be further pursued. The seed money the Koch Institute uses to fund innovative research projects comes primarily from philanthropic donations from individuals who have a strong interest in supporting cutting-edge research. Resources are also sometimes secured through partnerships with pharmaceutical companies. These funding streams are used to support promising science that is not likely to receive traditional grant support from NIH or other government sponsors. While most of its research laboratories rely heavily on NIH funding, the Institute has recognized the value of providing its researchers access to alternative sources of support.
- The cancer research community has the benefit of a large and enthusiastic workforce and substantial financial resources. Because of this, cancer researchers, and in particular NCI, have the opportunity to set an example within the broader realm of biomedical research. NCI should carefully consider how it can use its funding mechanisms to promote innovation and flexibility in science. It should also invest in team science and provide evidence for the utility of this approach in addressing research questions. It is often difficult to implement change within the scientific community, but NCI has the opportunity to drive constructive transformation.

- Much of the funding from foundations and other nongovernmental organizations focuses on specific tissues of origin (e.g., breast cancer). This approach often fails to support more generalized research that may be beneficial to multiple cancer types.
- It was noted that as the primary funding source for cancer research, NCI has historically been in a position to ensure that funding is devoted to various disease sites and areas and to facilitate the dissemination of research results across these areas. The increasing support of research through philanthropy and by advocacy groups may result in less cross-talk across fields and more silos. However, it was pointed out that NCI does not fund all disease sites in proportion to the burden they cause; advocacy and the stigma associated with some cancers have influenced funding trends.
- There is a lack of standards for data reporting; investigators can store and present their data in any format they choose. The government should help establish standards. This would facilitate the exchange of information within the research community. One speaker warned that research results can be uninformative if the data are not standardized and the analysis is not done by knowledgeable researchers. A balance will need to be achieved in which standards are sufficient to support cohesion without stifling innovation.
- It was suggested that if data were made publicly available, researchers would analyze it to answer interesting scientific questions, sometimes even if they had little or no funding to do so (i.e., they would do this research in addition to their grant-funded research).
- Technology can bring together researchers from different institutions and from around the world. The Center for Integration of Medicine and Innovative Technology is a venue through which researchers at various hospitals and universities in Boston can communicate and collaborate. The Council of Scientific and Industrial Research in India recently launched an online platform that allows scientists around the world to collaborate to study tuberculosis. Thousands of scientists around the world have contributed their expertise and the initiative has made significant advances with relatively modest financial resources.
- The current approach in which virtual interactions with patients are not captured in medical records and are not reimbursed is not sustainable within the fee-for-service model of health care delivery. However, these types of interactions may be better supported in different reimbursement models, such as the medical home and accountable care organizations. Careful consideration must be given to how these types of interactions will be captured in electronic health records. Decisions will need to be made about which data should be captured in structured formats and when it is more appropriate to use unstructured formats.
- In order for electronic health record systems to make contributions to public health and research, individual patients and institutions will need to be willing to share their medical data. A climate of trust will need to be created to ensure that patients feel comfortable consenting to making their data available. Policies will need to be put in place to encourage institutions to share their data; for example, certain benefits of EHR systems should be dependent on institutions making their data available.
- There is some concern that emerging health care delivery technologies and EHR systems will not benefit underserved populations such as the elderly and some minority groups. However, it was noted that most populations have or are adopting technologies that can be used to facilitate interactions with health care providers. In some cases, technologies as widespread as cell phones can be effectively used. In addition, it should be recognized that there will likely be increased utilization of technologies in the future, including among Baby Boomers and older Americans. Rather than assuming certain populations will be unwilling or unable to use technology to access health care, processes should be developed to build on the technologies being used in these populations. For example, text message reminders have been successfully used to increase the proportion of young women who return for the

necessary second dose of the HPV vaccine. With regard to the spread and use of EHRs, it will undoubtedly be necessary to conduct targeted programs to prevent and/or alleviate disparities.

- Technology should not be viewed as a barrier to relationship building between patients and providers. On the contrary, technology can enable and foster these relationships, which are critical to health care delivery, particularly general medical care.
- Researchers are striving to develop cures for cancer but patient-centered research is also looking for ways to improve the quality of life of cancer patients and survivors (e.g., identifying minimally toxic treatments that reduce the likelihood of long-term effects). Some of the approaches described by the presenters may be very helpful in serving the health care needs of cancer survivors as they address and are being monitored for long-term effects.
- In order to make a difference, advocates must be well informed and prepared to make contributions and offer solutions to pressing problems. Some people have suggested that cancer advocates should model their activities after those of the HIV/AIDS advocates. However, it was pointed out that there are several differences between cancer and HIV/AIDS. One of these differences is the availability of a clinically important biomarker for HIV/AIDS (i.e., viral load). Also, the cancer advocacy community is somewhat splintered, which differs from the unified efforts that have characterized AIDS activism.
- The NCP has an obligation to allocate resources in a way that will benefit cancer patients. The primary goal of the NCP should not be to understand cancer but to help people. Progress in this regard will require investment in team science. The most significant innovations of the future will come from teams, not from individual investigators. Emerging health information technologies will facilitate team science on a national scale.
- The NCP should fully utilize the spirit of volunteerism among cancer patients and the general public. It is somewhat paternalistic to assume that certain segments of the population will not want to participate in cancer research or utilize health information technologies. Most patients who participate in research report having a very positive experience and appreciate the opportunity to contribute to future advances, even if they will not personally benefit.
- The NCP needs to ensure that there are viable career opportunities in cancer research for young investigators. Currently, many trainees are unsure about their futures and the sustainability of research careers.

PUBLIC COMMENT

Key Points

- The Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) initiative, which is funded by various NIH Institutes, including NCI, supports the type of nonincremental research that some foundations and research organizations are trying to foster.
- Members of the general public and the patient community often do not have a strong understanding of the research process. It is important to communicate that innovative research may not always progress in the originally predicted direction. Some people may view this as failure, but it must be recognized that important things can be learned from so-called failures.
- The peer-review process for cancer research has not historically involved experts from diverse disciplines, such as physics and mathematics. The peer-review process would be strengthened by the participation of those with expertise in all of the areas relevant to cutting-edge research.
- Thoughtful evaluation and modification of the NCP based on past successes and failures and the challenges of the present and future are essential for creating a supportive environment for young investigators and future cancer patients.

PANEL II

DR. PATRICIA HARTGE:

ACCELERATING INNOVATION IN CANCER RESEARCH THROUGH EPIDEMIOLOGY

Background

Dr. Hartge is the Deputy Director of the NCI Epidemiology and Biostatistics Program. She has conducted epidemiologic research at NCI since 1977 and has published 250 scientific reports. Dr. Hartge received her B.A. from Radcliffe College, her M.A. in economics from Yale University, and her Sc.D. in epidemiology from the Harvard School of Public Health. She studies the etiology of lymphoma and cancers of the pancreas, ovary, breast, and brain, and has published extensively on epidemiologic methods. She cofounded the lymphoma consortium, InterLymph, in 2001. She previously served as the assistant editor of the *American Journal of Public Health*, on the editorial board of *Epidemiology*, on the Governing Council of the American Public Health Association, and on the Board of Directors of the American College of Epidemiology. She now serves on the editorial board of the *American Journal of Epidemiology* and as an adjunct professor at George Washington University. She chaired the NCI Cohort Consortium from 2006 through 2009.

Key Points

- A Norwegian study of the effects of screening mammography on breast cancer mortality was made possible by the fact that cancer incidence data can be accurately linked to the availability of screening. This type of study would not be possible in the United States at this time. Widespread adoption of EHRs would facilitate these types of population-based studies. Epidemiologists need to capitalize on the opportunities provided by EHRs.
- The field of epidemiology is benefiting from the fact that researchers in past decades collected blood and other types of tissues from healthy cohorts of patients, although it is sometimes difficult to decide how these valuable tissues should be used.
- A genome-wide association study (GWAS) of 2,000 people with pancreatic cancer and 2,000 healthy controls revealed an association between polymorphisms in a gene that determines ABO blood type and risk of pancreatic cancer. Interestingly, a connection between blood type and pancreatic cancer was noted in the clinic 30 years ago, but there was little follow-up on this observation. This study was a breakthrough for the disease made possible by collaboration among researchers from 12 cohort studies and 8 case-control studies.
- In another GWAS, researchers identified common genetic variants linked to breast cancer; however, it is unknown if and how the presence of these variants should inform clinical management of patients (e.g., frequency of mammography, benefit of chemoprevention). This illustrates the challenge of communicating these kinds of discoveries, particularly to patients.
- The Cohort Consortium is an extramural-intramural partnership formed by NCI to address the need for large-scale collaborations to pool the large quantities of data and biospecimens necessary to conduct a wide range of cancer studies. Through its collaborative network of investigators, the Consortium provides a coordinated, interdisciplinary approach to tackling important scientific questions, creating economies of scale, and quickening the pace of research.
- The studies conducted by individual members of the Cohort Consortium have yielded important information, but combining the data from these studies has facilitated more powerful studies and led to an improved understanding of the many forms of cancer. Researchers must consider how each of their trials can continue to yield important information long after that trial is completed.