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
OPENING REMARKS—DR. L aSALLE 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 rethink 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: nanotherapeutics, 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.
An example of this is the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a randomized clinical trial designed to determine whether certain screening tests can save lives. In addition to the important information gained about the benefits of screening, biospecimens collected from PLCO participants are being used to conduct observational studies and molecular characterization of tumors that arise in this cohort.

Lessons can be learned from groups that have successfully conducted population-based research, including Scandinavian countries, health maintenance organizations, the Veteran’s Administration, and the U.S. Armed Forces. Many of these groups have access to closed populations, which is conducive to research.

In addition to limited access to tissue samples, long startup times are a major hurdle to population-based research that needs to be addressed.

More rigorous case-control studies that compare patients with a certain cancer or one of a group of closely related cancers with people who are at risk but did not develop cancer are needed to elucidate the factors that contribute to cancer.

Epidemiologists also need to conduct studies nested in routine medical care settings.

There is an explosion of information available on genes and proteins. Large data sets—including those from GWAS—should be available to scientists around the world to enable the pursuit of diverse research questions. For example, the results of the pancreatic cancer GWAS study are available to qualified scientists via the NIH database of Genotypes and Phenotypes (dbGaP).

Epidemiologists need to develop creative methods to monitor exposure that go beyond questionnaires. For example, there has been innovation in the development of handheld devices that can measure substances of interest. Future innovations in epidemiology will stem not from nanotechnology but from microtechnology.

A guiding philosophy for future measurements of the genetic, behavioral, and environmental influences of cancer should be to scan widely and drill deeply. GWAS illustrate this philosophy for genomics; GWAS have generated hundreds of leads that should be studied in more detail. High-throughput studies in the areas of proteomics and metabolomics should also yield important leads. The idea of an exposome—a comprehensive readout of an individual’s lifetime exposures—is attractive but is not yet achievable.

Epidemiologists need to refine their definitions of “outcomes” and focus more on survival following a cancer diagnosis. Information can also be gained from the study of well-defined cancer precursors (e.g., colon polyps).

Cancer surveillance must be continued and improved as health information technologies create new opportunities to collect and link data. Cancer surveillance should follow the model of infectious disease surveillance.

DR. PETER ALPERIN:

INDIVIDUALIZED CANCER GUIDELINES: A METHOD FOR ADDRESSING THE COMPLEXITY OF CARE

Background

Dr. Alperin is Vice President of Medicine at Archimedes, Inc. His responsibilities include implementing mathematics-based simulations of physiology and the health care system with industry clients, voluntary health organizations, and health plans. He is also deeply involved in product strategy and ongoing development of the Archimedes Model. Prior to joining Archimedes, Dr. Alperin was Director of Medical Informatics at Brown and Toland Medical Group, where he was charged with implementing an electronic
health record system for a group of 1,600 physicians. Before that, he was a Director at ePocrates, a privately held health care technology company based in San Carlos, where he was responsible for developing the most widely used handheld formulary support tool for physicians. He is an Assistant Clinical Professor of Medicine at University of California, San Francisco and has authored several papers and book chapters. He continues to practice medicine at the San Francisco VA Medical Center. Dr. Alperin received his medical degree from the University of Texas Southwestern Medical School and his undergraduate degree in biochemistry from University of California, Berkeley.

Key Points

- Archimedes is a privately owned health care modeling company that is headquartered in San Francisco, California. Archimedes was founded by noted health economist David Eddy and is now a subsidiary of Kaiser Permanente.

- Archimedes’ core technology is the Archimedes Model, a highly detailed and rigorously validated mathematical model of human physiology, disease interventions, and the health care system. The idea behind the Archimedes Model is to integrate a wide variety of relatively disparate pieces of information and put them into a clinically useful format so that clinicians, policy makers, and researchers can examine data like never before. The Model is specifically built to be useful to clinicians.

- The Archimedes Model includes information related to a number of diseases, including cardiovascular disease, asthma, obesity, hypertension, metabolic disease, and cancers of the breast, colon, and lung. These disease-related factors are applied to virtual people within the Model. As a virtual biomarker progresses on a continuous basis within the simulation, it integrates with the different downstream models. The virtual people then interact with the health care system in a “Sim City” fashion.

- Although most of Archimedes’ work has been focused on population-level simulations, over the past several years the company has worked extensively to build tools to help translate data gathered by scientists and national research organizations and bring it to the point of care.

- Recent technological advances have generated an enormous amount of data for each patient. It has become very difficult for health care professionals to integrate all of these data at the point of care in a systematic fashion. This challenge will become even more complex in the future, particularly given the flood of additional information that will accompany implementation of electronic health records.

- Patient care is currently driven by population-level guidelines. These guidelines take a one-size-fits-all approach to cancer care and are inherently limited in their ability to address the increasing levels of data available about individuals’ cancers. For example, current cancer guidelines from the United States Preventive Services Task Force recommend that colon cancer screening cease after 75 years of age; however, there is no reason to stop screening a healthy 75-year-old. Many clinicians do continue to screen past this age, though it goes against guideline-based care.

- Thus, the risk-benefit estimates that are generated based on systematic reviews of clinical trials that inform these guidelines do not necessarily apply to individual patients. This is particularly true for patients who are older and relatively poorly represented in clinical trials.

- Archimedes operates on the premise that next-generation guidelines should take into account a much more diverse set of information about individual patients and recognize the continuous nature of most risk factors and biological variables. This would result in customized treatment recommendations based on each patient’s characteristics and needs.

- The development of individualized guidelines has several key requirements. First, access to patient-specific information will be necessary to generate individualized guidelines and facilitate model building. Second, quantitative models must be developed that analyze patient-specific information and evaluate the outcomes and tradeoffs for each management option. Third, an effective interface
must be developed to deliver expected outcomes of each option to physicians and patients for discussion and decision-making.

- Individualized guidelines have been developed for cardiovascular disease and diabetes, both of which have yielded favorable results.

- Archimedes piloted a model at Kaiser Permanente called Individualized Guidelines and Outcomes, or IndiGO. The tool was embedded inside the Kaiser electronic health record system. Information generated by the tool was presented to patients to help convey how their risk of cardiovascular disease and diabetes would vary by making lifestyle changes, as well as if they were to undergo a variety of different treatments for the diseases. The results from the pilot were favorable; among other things it improved patient compliance and physician performance, as well as reduced LDL cholesterol, blood pressure, and other risk factors. There was also a decrease in the expected number of cardiovascular events, such as myocardial infarctions and strokes. Plans are under way to conduct a longer-term study of the benefits of IndiGO.

- Several things are necessary to continue progress in the area of developing individualized guidelines. In the long term, the availability of patient-specific information must be increased; increased collaboration among cancer modelers is needed; and standards for the documentation and validation of models must be developed. In the short term, models for calculating individualized guidelines for a select number of specific cancer decisions (e.g., PSA testing) must be developed. The use of these models must be demonstrated and evaluated in a clinical setting, and formal comparisons between individualized guidelines and traditional guidelines must be drawn to quantify the differences in performance between the two.

DR. CAROLYN COMPTON:

THE ESSENTIAL ROLE OF HUMAN BIOSPECIMENS IN THE FUTURE OF CANCER RESEARCH

Background

Dr. Compton is the Director of the Office of Biorepositories and Biospecimen Research (OBBR) at the National Cancer Institute. In this capacity, she has leadership responsibility for strategic initiatives that include the Cancer Human Biobank (caHUB) project, the Innovative Molecular Analysis Technologies for Cancer program, and the NCI Community Cancer Centers project. She is an adjunct Professor of Pathology at the Johns Hopkins School of Medicine. Dr. Compton received her M.D. and Ph.D. from Harvard Medical School and the Harvard Graduate School of Arts and Sciences. She is trained and boarded in both anatomic pathology and clinical pathology at Harvard’s Brigham and Women’s Hospital. She came to NCI from McGill University, where she had been the Strathcona Professor and Chair of Pathology and the Pathologist-in-Chief of McGill University Health Center from 2000 through 2005. Prior to that, she had been Professor of Pathology at Harvard Medical School and the Massachusetts General Hospital, where she was the Director of Gastrointestinal Pathology for 15 years. Dr. Compton has held many national and international leadership positions in pathology- and cancer-related professional organizations. Currently, she is the Chair of the American Joint Committee on Cancer and a member of the Executive Committee of the Commission on Cancer. She has published more than 500 original scientific papers, reports, review articles, books, and abstracts.

Key Points

- Tissue banking is essential to innovation in cancer research and progress against cancer.

- Personalized medicine has the potential to transform medical practice. This approach moves from the one-size-fits-all way in which medicine has traditionally been practiced—the generic approach that treats tumors that look alike in a standard way—to a more customized approach. It involves
performing molecular analyses on individuals’ tumors and classifying them based on specific molecular features. From there, therapeutic approaches will be designed that specifically target these molecular features, leading to higher efficacy, less toxicity, and greater cost savings in the way medicine is practiced. Biospecimens are at the core of this approach.

- High-quality human biospecimens are critical to elucidate molecular mechanisms of neoplasia; identify targets for drug development for cancer treatment and prevention; define markers for risk assessment, screening, and recurrence; develop molecular taxonomies; identify genetic variations in humans that determine drug efficacy and/or toxicity; and develop diagnostics and therapeutics.

- The lack of high-quality, clinically annotated human specimens is the most important limiting factor of translational research in the world. For example, despite significant investment of resources and advanced planning, only a minority of biospecimens collected for The Cancer Genome Atlas project (TCGA) have been of high enough quality to use. Today, biospecimen collection is TCGA’s primary bottleneck.

- Today’s technologies afford tremendous advances. In 1990, whole-genome sequencing would have taken eight years and cost $3 billion. Today, whole-genome sequencing takes three to four months and costs $100,000. It is believed that as early as next year whole-genome sequencing will take as little as 24 hours and cost only $1000; the cost could drop to as low as $100 within a few years. Whole-genome sequencing could be part of the standard of care for all patients in the very near future and yet it is unknown how to care for biospecimens so these technological advances can be leveraged.

- With poor-quality samples comes great risk. Perhaps the greatest risk is the potential for incorrect treatment as the move is made toward targeted therapies (e.g., administration of Herceptin is based on the results of HER2 testing).

- The reason it is difficult to access high-quality biospecimens in the United States is that biobanks within the currently siloed system do not share standards by which they routinely operate. Collection, processing, and storage procedures differ among sites, as do the degree and type of data annotation and the scope and type of patient consent. Supporting IT structures also differ in capacity and functionality so that even if biobanks want to exchange data, they often are unable to do so. Access policies are often lacking or unknown to potential users. Perhaps most importantly, the quality of the samples in those banks is unknown.

- Standards in biobanking are critically needed. To this end, NCI has produced a state-of-the-science document entitled Best Practices for Biospecimen Resources. This publication is available to the community, but NCI is not a regulatory agency and cannot enforce its recommendations.

- NCI aims to bring to the biobanking arena a more scientific understanding of what constitutes a high-quality specimen and to develop new technologies that address challenges in biobanking. This is the focus of NCI’s Biospecimen Research Network and its Innovative Molecular Analysis Technology for Cancer. NCI also needs to provide to the research community the extremely high-quality human samples that are needed as reference samples but are currently unavailable.

- Most investigators think of biospecimens as a “mini-me” of the patient when, in fact, each biospecimen is a viable, living entity that reacts to environmental stresses it encounters when being removed from the patient and manipulated in the biobank. These induced molecular changes are not well understood and vary among different types of biospecimens and different types of stresses. There is thus a need to scientifically study biospecimens.

- NCI is in the process of building the novel National Human Biobank to provide scientists with standardized human specimens for research and product development. This biobank will follow standardized guidelines for collection, transportation, processing, annotation, and storage of all biospecimens.
- Data from these biospecimens will be made publicly available via a shared database. Users will be required to redeposit information based on their analyses; thus, over time, the value of this database will expand beyond the provision of biospecimens.

**DR. LOUISE M. PERKINS:**

**MMRF/MMRC MODEL**

**Background**

Dr. Perkins is the Chief Scientific Officer of the Multiple Myeloma Research Foundation (MMRF), where she is responsible for strategic development and execution of the Foundation’s research agenda. Dr. Perkins brings to MMRF more than 16 years of pharmaceutical research experience from two pharmaceutical companies. Prior to joining MMRF, she was the Director of Cancer Research at Bayer Pharmaceuticals. Previous to that, she led a cancer research group at the Schering Plough Research Institute. She graduated from the University of Michigan with a Ph.D. and M.S. in biological chemistry and conducted postdoctoral studies at Princeton University in the Department of Molecular Biology. She earned her B.S. in zoology from the University of North Carolina at Chapel Hill.

**Key Points**

- MMRF aims to accelerate the development of new treatments for patients with multiple myeloma and, ultimately, find a cure for the disease.
- Multiple myeloma is a cancer of plasma cells. There are 20,000 newly diagnosed cases expected this year in the United States and approximately 10,500 people are expected to die from the disease.
- One of multiple myeloma’s seminal features is that it causes bone loss and can be a very painful and debilitating disease. Patients diagnosed with multiple myeloma are faced with about a five- to seven-year survival—a rate that has nearly doubled in recent years with the advent of new treatments approved since 2003. However, the disease remains uniformly fatal and many patients exhaust their treatment options.
- MMRF’s sister organization, the Multiple Myeloma Research Consortium (MMRC), was founded in 2004 to accelerate early-stage clinical research. To this end, the MMRC focuses on facilitating the launch of Phase I and II clinical trials. The MMRC also conducts basic science research, including a genomics initiative.
- MMRF and MMRC set themselves apart from some other advocacy organizations with their senior leadership, all of whom have backgrounds in the pharmaceutical industry, which results in a business approach to science.
- Since MMRF was founded in 1998 and MMRC was founded in 2004, the organizations have gone through several phases—from building a community of researchers and patients and creating more awareness of the disease to funding research, building a tissue bank, and developing a genomics initiative to understand the heterogeneity of the disease—without losing focus on the overall mission.
- From these efforts, it is now understood that multiple myeloma likely encompasses seven to eight different unique subdiseases.
- MMRC brings together 13 academic institutions across North America to facilitate tissue banking and speed Phase I and II clinical trials. These institutions are legally bound by a membership agreement that delineates roles and responsibilities for everything from tissue banking to the execution of MMRC-facilitated Phase I and II clinical trials.
- MMRC member institutions’ progress is tracked to ensure that milestones—such as the number of clinical trials opened, how quickly these trials opened and closed, and the number of tissue samples...
To date, MMRC has facilitated the launch of 26 clinical trials through its clinical trials network. These trials were opened approximately 60 percent faster than the industry standard in oncology, allowing patients to access these trials almost 100 days earlier. This was accomplished through the implementation of business solutions, such as standardized contracts and protocols, as well as dedicated clinical trials coordinators.

The MMRC Tissue Bank was established in 2004 as a centralized facility to process tissue and matched peripheral samples collected at each member institution. Samples are processed following standard operating procedures that meet good laboratory practice standards. Associated clinical data are collected via a tracking system. The MMRC Tissue Bank currently houses a total of 2,800 purified multiple myeloma samples and approximately 2,100 matched peripheral blood samples.

In 2007, MMRF and MMRC launched the Multiple Myeloma Genomics Initiative (MMGI). Samples from the MMRC Tissue Bank, particularly the matched peripheral blood samples, have proven extremely valuable for MMGI. To date, MMGI has analyzed 250 patient samples using array comparative genomic hybridization and gene expression profiling. Efforts to conduct whole-genome sequencing on some of these samples are under way, with the goal of sequencing 100 samples using a combination of whole-genome and whole-exome sequencing.

All data from these studies are posted in a publicly available portal established and supported by MMRF and MMRC. The portal is the world’s only myeloma-specific repository of genomic information. The data sets are posted in the portal in near real time.

MMRC presented findings from a study conducted as part of MMGI at the annual American Association for Cancer Research meeting in April 2010. This included data on 23 whole-genome sequences of purified myeloma tumor cells and corresponding matched normal whole-genome sequences. In addition, the team presented data on 16 whole-exome sequences.

From these analyses, researchers found several genetic mutations (e.g., p53, NRAS, KRAS) present in multiple myeloma that have also been linked to several cancers. The data also revealed a mutation in FAM46C, which, to date, is a poorly characterized target. Links have also been identified with BRAF, a target for which several new drugs are already being developed, and histone methyltransferases (HMTs). HMTs are of particular interest because at least one HMT gene is affected by chromosomal translocations observed in multiple myeloma. A number of companies were established as early as 2008 to pursue HMTs as targets, and MMRF and MMRC are actively engaged in discussions with companies who are pursuing HMTs as drug targets to encourage them to consider applications in multiple myeloma.

A manuscript detailing outputs from MMGI has been submitted for publication and is expected to be published in the next couple of months.

There is a perfect storm of new technology, new communications approaches, and new data collection and analysis techniques that places MMRF and MMRC—as well as other groups focused on ‘omics with clinical networks in place—in a position to make personalized medicine a reality.

The landscape of multiple myeloma is changing. Despite the fact that myeloma remains a heterogeneous disease, it is now understood to be amenable to molecular profiling. In the future, detailed profiling may inform clinical management of individual patients. At present, there is a great need to characterize many more samples to identify new hypotheses and new targets that can drive development of the next treatment strategies and biomarkers.

Epigenetic studies are a focus of MMRF and MMRC. So, too, are next-generation ‘omics studies to elucidate and validate new biomarkers and treatments. In addition, MMRF and MMRC are developing a longitudinal study of newly diagnosed patients that will not only capture clinical data
but also tissues profiled at the time of patients’ diagnosis and relapse. Finally, as patients become more engaged in their own care, MMRF and MMRC are focused on mobilizing the multiple myeloma community to participate in the research process.

DR. TOMASZ M. BEER:

HIGH-INTENSITY COLLABORATION: AN ESSENTIAL CATALYST FOR RAPID DEVELOPMENT OF NOVEL CANCER THERAPIES

Background

Dr. Beer serves as Grover C. Bagby Endowed Chair for Prostate Cancer Research, Professor of Medicine in the Division of Hematology and Medical Oncology, and Deputy Director at the Oregon Health & Science University (OHSU) Knight Cancer Institute. An internationally renowned prostate cancer researcher and clinician, Dr. Beer leads Knight’s horizontally integrated, multidisciplinary program in prostate cancer. He received his medical degree from Johns Hopkins School of Medicine in 1991 and then moved to OHSU, where he completed his internship, residency, and chief residency in internal medicine and his fellowship in hematology and medical oncology. Currently, Dr. Beer is a fellow of the American College of Physicians and a member of other professional societies including the American Society of Clinical Oncology, the American Urologic Association, the American Association for Cancer Research, and the Southwest Oncology Group, where he has led a number of clinical trials. Dr. Beer has served on numerous national committees related to prostate cancer research and care. Among these activities are his contributions to clinical trial guidelines published by the Prostate Cancer Working Group, his role as Chair of the 2010 Prostate Cancer Foundation–National Cancer Institute Treatment Sciences Symposium, and his service as Chair of the Genitourinary Oncology section of the American Society for Clinical Oncology 2011 Annual Meeting Scientific Program Committee. Dr. Beer has authored and coauthored more than 250 articles and abstracts on prostate cancer, largely with a focus on the development of novel therapies through clinical and translational investigation. Dr. Beer is passionate about advancing the care of prostate cancer patients through research. He is currently working on a book designed to demystify clinical research for patients and their loved ones.

Key Points

- The current focus on personalized medicine influences early-stage drug development and clinical research. Identifying strategies to take advantage of new opportunities to accelerate the delivery of new therapeutics to patients is critical.
- The idea that the sequencing or genotyping of tumors will guide selection of therapies is not an idea for the future; it is already a reality. Gleevec, for example, was developed based on the understanding of a molecular defect in cancer and how it might be exploited. This drug is an example of how genotypic information—in this case for gastrointestinal stromal tumors (GIST) with a c-Kit-activating mutation—can be used not only to select therapy, but to select the appropriate dose of the drug.
- The Knight Cancer Institute has assessed the presence of 500 known gene mutations in each of nearly 1,000 melanoma specimens. The genes in the mutation panel were selected based on their perceived biological importance and the likelihood that it will be feasible to develop drugs targeting them now or in the near future.
- Sequencing data revealed the expected BRAF mutation in about 43 percent of patients. Rare mutations, such as in AKT, that are likely to be druggable, were also identified in some of these melanoma patients; mutations such as these would never be exploited therapeutically in individual patients were this kind of genomic data not accessible.
Molecular information about cancers will increasingly direct cancer therapy. In fact, the proposed $100 genome sequencing allows one to contemplate a future in which comprehensive understanding of what drives each individual cancer can influence therapy.

Efforts to describe the cancer genome, epigenome, and transcriptome are accelerating and are becoming a reality at NCI and in various private venues around the country. From these efforts, it is now understood that very complex and difficult-to-treat cancers have a finite number of defects. For example, an average pancreatic tumor has about 60 genetic defects that can be assigned to approximately 12 cancer-driving pathways.

Until recently, the predominant approach to drug development has been, by and large, to knock out one pathway with a single drug. This strategy has been successful in some cases (e.g., Gleevec in chronic myeloid leukemia, GIST, and melanoma), but in many cases the benefits of targeting a single pathway are transient because of redundant signaling by the other pathways.

Understanding the complexities of redundant signaling and developing targeted therapies that knock out enough pathways to induce a durable response in individual cancers are critical. Doing so will require a shift from today’s therapeutic paradigm—a standard one-size-fits-all approach—to one in which a comprehensive diagnostic effort occurs before treatment is initiated.

Clinical research must be adapted to fit into and inform this new paradigm, which will result in the fragmentation of cancer into molecularly defined subdiseases. Even small clinical studies will need access to large numbers of patients so that the subsets with relevant molecular characteristics can be identified. Tight links to sophisticated laboratory specimen collection efforts are going to be a prerequisite for early-stage drug development.

The Prostate Cancer Clinical Trials Consortium (PCCTC) was established in 2006 through a competitive grant process issued by the Department of Defense and the Prostate Cancer Foundation. The mission of the PCCTC is to design, implement, and complete hypothesis-driven Phase I and II clinical trials of novel agents and combinations that could prolong the lives of patients with prostate cancer.

PCCTC utilizes the expertise of its members in the areas of basic science, preclinical correlative studies, and biomarkers to design trials that have clinically meaningful endpoints and also yield molecular and mechanistic information necessary to advance research.

PCCTC has participated in approximately one quarter of the Phase I and II clinical trials in prostate cancer in the United States in the last five years. PCCTC has activated 103 trials and completed 45. In addition, PCCTC has helped advance eight therapeutic candidates into Phase III studies and, just as importantly, determined that 15 agents are ineffective in prostate cancer. Resources that would have been used to further study these agents can now be applied to more promising studies.

Many factors contribute to PCCTC’s success. It is a model of a public-private partnership that is both federally funded and supported by a highly respected advocacy group. It utilizes incentives and a high level of accountability among all partners to ensure robust individual contributions and collaboration. It focuses specifically on early-stage drug development—the phase of drug development where there is the greatest opportunity to accelerate progress. It includes high-performing, tightly focused organizations and has access to laboratory expertise. Finally, it is a training ground for young investigators.
DR. NINA WALLERSTEIN:

COMMUNITY-BASED PARTICIPATORY RESEARCH AND ITS ROLE IN CANCER RESEARCH

Background

Dr. Wallerstein is Director of the Center for Participatory Research in the Office of Community Health, Director of the new Community Engagement and Research component of the Clinical Translational Science Center, and a Professor in the Department of Family and Community Medicine at the University of New Mexico (UNM). She was the founding Director of UNM’s Master's in Public Health Program until 2007. For over 25 years, Dr. Wallerstein has conducted research in both North American and Latin American settings, in healthy city initiatives, in adolescent and women’s health intervention research, and in community health development. She has directed youth policy and women’s empowerment research programs and was Principal Investigator of an R01 for a National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded youth empowerment intervention as well as the NIAAA-funded Southwest Addictions Research Group, the purpose of which was to train junior faculty of color in research to reduce alcohol-related disparities among Native American and Hispanic communities. Since 1999, Dr. Wallerstein has been funded by the Centers for Disease Control and Prevention and Native American Research Centers for Health (NARCH)/NIH grants to work in collaboration with Native American tribes, developing understandings and assessment tools for tribal community capacity and social capital, including through a cervical and breast cancer screening grant. This work also includes translational community-based participatory research (CPBR) to develop, implement, and evaluate family/youth/elder culturally based interventions with diverse tribes. She is a coeditor of the first national textbook of CBPR, Community Based Participatory Research for Health: From Process to Outcomes, and author of other books, book chapters, and over 100 articles in public health and education. Dr. Wallerstein was principal investigator of a national grant funded by the National Center on Minority Health and Health Disparities (NCMHD) to identify research strategies to assess facilitators and barriers of community-academic research partnerships. She is currently co-principal investigator, with the National Congress of American Indians Policy Research Center and the University of Washington, on an NARCH effort to conduct a mixed-methods study of CBPR partnerships nationwide on the correlations between CBPR processes and outcomes to reduce health disparities. Her research focuses on community capacity and health development, culturally appropriate translational intervention research, participatory evaluation, and CBPR processes and outcomes to further enhance the science of CBPR.

Key Points

- The majority of states in the United States face widening socioeconomic and racial/ethnic disparities and chasms in health care access, screening, and treatment. In the field of CBPR, the challenge is not debating whether these disparities exist but determining what should be done to improve health status to reduce health disparities.

- There are many challenges of intervention research that CBPR can address. In intervention research, moving from efficacy to effectiveness trials has been a challenge. Internal validity is not sufficient; external validity and contextualization must also be considered. Cookie-cutter interventions—the same interventions used for differing racial/ethnic groups—are no longer acceptable; interventions must be culturally and linguistically tailored.

- Within the field of intervention research, there is a need for bidirectional communication and input so that research takes into account not just the opinions and experiences of academics and scientists but of advocacy groups and community members.

- Other challenges of intervention research include a lack of accountability to the communities, a lack of sustainability once the funding period is over, and, particularly among communities of color,
suspicion of research abuses and a lack of public trust. These challenges make it difficult to recruit diverse populations to research efforts and to procure biospecimens.

- CBPR is increasingly gaining recognition as being critical to interventional research. For example, the Institute of Medicine has recommended that CBPR be one of the eight competencies taught to all health science students. Special issues of journals and NIH Requests for Applications have been devoted to CBPR. Advocacy organizations are also increasingly involved in cancer research with Federal agencies.

- Rather than stemming from academic literature or gaps in the literature, or being generated in a research lab, CBPR ideas are generated by community members based on issues that most concern them. Many of their research topics could be explored in the research lab as well.

- CBPR is not a research method. Epidemiologists can use CBPR. Qualitative researchers can use CBPR. Molecular researchers can also use CBPR if they consider the constituents and stakeholders with which they will be developing research questions and designing research.

- Although there are certain defined principles of CBPR, it is often necessary to take into consideration cultural beliefs and practices. For instance, in working with Native American communities, it is necessary to follow tribal customs and regulations that at this time forbid genetic research for any of their people.

- Much CBPR research is already ongoing within the cancer community. A search of NIH-funded CBPR research studies identified 87 focused on cancer, 54 of which are funded by NCI. In addition, the NCI’s Center to Reduce Cancer Health Disparities Community Networks Program has already created an opportunity for engaging diverse populations. Examples include “Messengers for Health,” a partnership between Montana State University and the Crow Tribe, and “Cancer 101,” a partnership between the University of New Mexico and various Hispanic and Native American communities.

- Cancer 101 offers culturally appropriate cancer education in Hispanic communities through the work of Latino Promotoras and by training Native community outreach and education workers. With a network of people now built, the partnerships are defining research questions for which funding will be pursued.

- A team of CBPR researchers from the National Congress of American Indians Policy Research Center, University of Washington, and UNM have a grant to identify facilitators and barriers to effective CBPR across diverse populations and settings and to advance the science of CBPR in order to reduce health disparities. The specific aims of the project are to: (1) identify differences and commonalities of CBPR processes and outcomes across partnerships, (2) describe and assess the impact of governance structures within American Indian/Alaskan Native communities and other communities of color on CBPR, (3) examine associations among group dynamic processes and CBPR outcomes, and (4) identify promising practices, assessment tools, and a future research agenda for the field of CBPR.

- If recruitment of minorities into clinical trials and procurement of biospecimens from minorities are key barriers to research, NCI should develop a research initiative in which partnerships that include community representatives explore how to best address community mistrust.

**DISCUSSION AND CONCLUDING COMMENTS:**

**PANEL II**

**Key Points**

- The development and adoption of data standards and data sharing are critical for progress in cancer research. Data sharing will help the research community gain the most value possible from participating patients and the tissues they have contributed.
Archimedes, Inc. attempts to integrate medical knowledge using common data standards to generate clinical treatment plans based on an individual’s characteristics.

Biobanking research and standardization are important for all uses of human tissues, including research and clinical management. Standardization of tissue collection and storage will not address all of the challenges surrounding biospecimen use. Standardization merely ensures that tissues are treated according to a defined protocol. Adhering to standards decreases the likelihood that outcomes are the result of differences in tissue handling rather than biological differences among specimens.

It is recognized that not all current standards regarding specimen banking are evidence based; many are based on the experience and preferences of experts in the field. These standards may not be optimal for certain types of analyses. However, as the field of biospecimen research advances, insights will be gained regarding the effects of different processes, and information will be generated to create data-driven methodologies.

Innovation in biobanking—and many other areas—will require changes in the behaviors of many within the clinical and research workforce. There are at least three options for promoting behavior change. The first is to pay people to do things differently. For example, creating reimbursement codes for standardized banking of human specimens would likely encourage this behavior; however, it is unlikely that this will happen. The second option is to encourage people and institutions to modify their behaviors by adopting licensing and accreditation processes. The disadvantage of this approach is that resources are needed to enforce compliance with these processes. The third option is to educate the workforce to increase understanding of the importance of adhering to these standards so that physicians and researchers will spontaneously change their behavior. This third option has the potential to make a large impact; however, it was pointed out that it is very difficult to accomplish behavior change, particularly within institutions. One discussant felt strongly that incentives are needed to promote behavior change. For example, incentives are needed to encourage collaborative research that reflects the priorities of the communities being served. Research should be done to determine which kinds of incentives are effective for various purposes.

In addition to the tissue quality issues that surround biospecimen use in research, investigators must consider the biological relevance of the specimens they use. Some issues stem from tissue sampling; there are molecular differences within primary tumors as well as among primary tumors and metastases to various body sites. In addition, tissues collected at one stage of disease may not be relevant for different disease stages (e.g., tissue collected at the time of prostate cancer diagnosis is often early-stage cancer, which may not be relevant for development of drugs to treat late-stage disease). In order to address some of the challenges associated with biospecimens, PCCTC is working to standardize image-directed bone marrow sampling of metastases and assess the utility of circulating cancer cells for research.

In addition to its work on the technical aspects of biospecimen collection, the Office of Biorepositories and Biospecimen Research has done considerable work on the ethical, legal, and social issues surrounding biospecimens. The Office has worked closely with the NCI Center to Reduce Cancer Health Disparities and with various advocacy groups to identify factors, including cultural concerns, surrounding issues such as consenting to biospecimen donation for unspecified research, specimen collection from pediatric patients, and the need to return specimens so that they can be buried with their Native American donors upon death. The findings from these efforts are being incorporated into the best practices for biospecimen resources that are being developed by the Office.

The Multiple Myeloma Research Foundation project utilizes a central site for tissue storage and analysis. Specific standards for tissue collection were developed based on the goals of the project. These standards were adjusted when the project was expanded to include DNA sequencing in addition to RNA analysis. It was noted that the tissue collection effort was successful because
multiple myeloma patients were excited about taking part in a flagship genomics project to enhance understanding of the disease.

- Cancer develops in an environment that includes other cells and is influenced by systemic host factors. These extracellular factors must be taken into consideration in order to understand the disease. However, cancer is a disease of the genome, meaning that cancer cells transmit their aberrations to their progeny. Thus, much can be learned from looking at the genomic changes that underlie cancer, although it must be recognized that these observations do not necessarily provide insight into the biology of cancer.

- Developing ways to determine people’s exposome would benefit cancer research, but this concept has not yet been realized on a large scale. For some substances, such as those that are fat soluble (e.g., polychlorinated biphenyls), there may be biological indicators of exposure that can be evaluated. Exposures can also be estimated by linking information about where individuals lived and worked with data from environmental samples taken during the same time period. There have been some innovations that can help determine exposure to certain substances (e.g., radon).

- The Love/Avon Army of Women represents a new, patient-centered paradigm of research. These women want to participate in research but also want to ensure that the research agenda meets their needs. The Army of Women has a contract with NCI’s caHUB to conduct the biobanking component of the research effort, which illustrates how the creation of national infrastructure can support patient-driven research.

- Intervention research is different from laboratory research. Research is ongoing across the nation to gain insight into how to adapt interventions for various communities. Much of this work is being done in the areas of prevention, early detection, and early intervention.

- Laboratory- and community-based research are generally conducted by separate groups of investigators, with little interaction between them. However, it is important to integrate these different approaches to research. Community-based researchers frequently adapt their research to the needs and interests of the communities with which they are working. This is often difficult for basic and clinical researchers, who are accustomed to standardized protocols. Community-based researchers can help basic and clinical researchers understand how to negotiate research methodologies and designs with communities. They can also help other researchers engage communities and address key concerns that communities may have.

- Researchers should view their engagement with research participants as a social contract. The research community has an obligation to wisely utilize the contributions of participants, including the biospecimens they donate, in ways that will benefit patients. This includes consideration of cultural issues. However, current processes related to clinical research—including informed consent and institutional review boards—focus more on patient safety than on the concept of a social contract. Investigators need to consider the social contract paradigm when designing and implementing their research.

- The HHS Office for Human Research Protections (OHRP) does not have a budget to support research, but is interested in practical information about many issues relevant to the concept of the social contract. OHRP is hoping to gain insights through its partnership with the NCI OBBR, but it might be helpful if OHRP could support research directly.

- The Specialized Programs of Research Excellence (SPORE) program and the Prostate Cancer Clinical Trials Consortium are complementary. SPOREs tend to focus on translational research projects rather than on clinical research. On the other hand, the PCCTC conducts clinical research, some of which is the continuation of SPORE projects.

- It is unlikely that the NCP will have the resources to invest in many large new initiatives but it seems that there are common tools and resources—particularly in the area of emerging technologies—that will benefit many across the NCP and warrant support.
There are many innovative solutions for the challenges facing the NCP. The NCP should consider how unconventional funding sources can be used to support multiple alternative approaches to addressing these challenges.

PUBLIC COMMENT

Key Points

- It seems that many innovative early-phase clinical trials are being conducted at universities and/or are being supported by philanthropic organizations rather than by large pharmaceutical companies. It can be a challenge to attract patients to these trials, in part because many patients prefer to receive care at community-based centers close to home. To address this challenge, MMRF is undertaking an initiative to create community-based centers across the country capable of conducting early-phase trials. The NCI Community Cancer Center Program is also working to help institutions that specialize in care delivery in various geographic settings to create the infrastructure to support participation in national clinical trials.

- Substantial work has been done to elucidate molecular pathways involved in cancer; however, it does not seem that there has been systematic work to determine how exposures to specific chemicals may influence these pathways. A project funded through the NIH Common Fund is investigating how single-nucleotide polymorphisms influence tissue-specific gene expression. The biological insights gained through this project may be relevant to the study of how certain chemicals selectively cause cancer in certain organs.

CLOSING REMARKS—DR. LASALLE D. LEFFALL

- Dr. Leffall thanked the speakers for their excellent presentations and their participation in the meeting.

CERTIFICATION OF MEETING SUMMARY

I certify that this summary of the President’s Cancer Panel meeting, *The Future of Cancer Research: Accelerating Scientific Innovation*, held October 26, 2010, is accurate and complete.

Certified by: LaSalle D. Leffall, Jr., M.D.
Chair
President’s Cancer Panel

Date: February 18, 2011