NATIONAL CANCER INSTITUTE

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Meeting Report

Integrating and Leveraging the Physical Sciences to Open a New Frontier in Oncology

February 26-28, 2008 | The Ritz-Carlton | Pentagon City | Arlington, VA

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Executive Summary

The National Cancer Institute (NCI) is exploring new and innovative scientific approaches to better understand and control cancer. In that regard, the NCI is interested in engaging scientific teams and individual scientists from the fields of physics, mathematics, chemistry, and engineering to examine cancer using new, perhaps nontraditional, approaches. The NCI's goal is to join these often disparate areas of science through its various support mechanisms, including centers of excellence, to better understand the physical and chemical forces that shape and govern the emergence and behavior of cancer at all levels. The NCI anticipates that this initiative will foster the development of innovative ideas and new fields of study based on knowledge of the biological and physical laws and principles that define both normal and tumor systems. This is a new and exciting frontier for cancer research.

As a first step in the process of determining how the physical sciences may provide new fundamental knowledge and advance cancer research, the NCI convened a workshop at which leaders in the fields of cancer biology, physics, chemistry, mathematics, modeling, engineering, and nanotechnology discussed the state of the art in both cancer research and the physical sciences. Over 2½ days, the invited scientists listened to a few short plenary talks from thought leaders, heard the perspective of scientists working at the intersection of these fields, and were exposed to some examples of scientific areas in oncology, such as nanotechnology, where the physical and biological sciences are clearly converging. However, most of the facilitated workshop was spent brainstorming about target areas in the physical sciences and biology that will be critical to new thinking and future directions in cancer research.

Although a number of barriers to achieving progress in cancer research were highlighted in the brainstorming sessions of the think tank, one barrier to ultimately reaching NCI's overall goal (i.e., the effective convergence and integration of relevant areas of the physical sciences across the field of oncology) emerged during the discussions. This recurrent theme was the lack of a common language, which was felt to be required to unite and advance these innovative scientific efforts and create new opportunities for progress against cancer. Although viewed as a major challenge, it was the sense of the assembled group that we have reached a point in the development of these scientific disciplines when removing this barrier has become a tractable problem. The remarkable rate of development of advanced technologies is producing genetic, proteomic, and other molecular data at an unprecedented rate and, in parallel, driving remarkable advances in nearly all areas of physics, mathematics, physical chemistry, and engineering. It was the consensus of the group that the NCI could in fact now undertake initiatives to foster the transdisciplinary environments that would enable these disparate disciplines to develop and speak a common language. Overcoming this barrier would facilitate building the transdisciplinary teams, developing the advanced technologies and databases, and creating the standards and measurements from the physical sciences needed to truly ask and answer many seminal questions in oncology.

In regard to identifying some of the key scientific questions, as viewed through the lens of the physical sciences, four themes emerged which were major areas of focus for the discussions during the meeting. These four themes were as follows:

- Cancer is characterized by complexity and expertise is available in the physical sciences community that can help decipher this complexity and facilitate discovery. However, for this line of research to proceed, a sound mathematical foundation and standards will be required in areas such as language, quantitation, data representation, and others. Pioneering efforts in systems biology can be at the forefront of setting standards and creating a common language. The NCI's advanced technology initiatives are also well situated to provide the tools needed to better explore complexity in cancer.

- Cancer is not exempt from the physical laws that govern the behavior of all other matter. However, our knowledge of how the physical laws governing the short-range and other forces, energy flows, gradients, mechanics, and thermodynamics, among other properties, affect cancer cells versus normal cells is not well developed. Consequently there is a need and an opportunity to apply advanced technologies such as nanotechnology and mathematical models to make relevant measurements of the physics and mechanics of cancer cells.
- Cancer is an evolutionary process, and examining cancer from this perspective could open up new approaches to diagnosis, treatment, and, perhaps, prevention of cancer.
- Understanding information transfer in cancer is critically important. The information transferred within the cells that constitute a tumor, and the tumor with its microenvironment, is enormous; and it is imperative that we understand this information flow and how it differs from what occurs in normal cells and tissues. Engineers and physical scientists examine information flow in a much more sophisticated manner than employed in cancer biology to date, and it is essential that these advanced methods and models be applied in cancer research, especially at the molecular and submolecular levels.

Another near-universal theme to emerge from this meeting was that the physical sciences have unique knowledge and expertise that will be crucial in modeling and predictably understanding cancer's complexity and pursuing new research questions in information transfer and tumor cell evolution. Systems biology featured prominently in nearly all of the group's discussions as the future of how information about cancer from the myriad sources must be organized and interpreted. In that regard, the discussions also pointed specifically to the need for a theoretical basis for many of the major focus areas of cancer biology and a requirement for the significant engagement of mathematicians and theoretical physicists in the development of this field.

It was also clear that understanding how the range of physical laws and principles governing the behavior of all matter are operative in cancer at every scale will be critical to understanding and controlling cancer. New knowledge about how fundamental parameters such as energy and thermodynamics, gradients, electrostatic and other forces, and cancer in space and time are altered in cancer versus normal cells will provide opportunities to address practical challenges in cancer research. Information and knowledge from these new fields of integrative research offer significant potential to deal with problems such as the identification of drug targets, delivering drugs to the target, and perhaps most important, understanding and controlling metastasis. These new convergent fields show great promise for driving the development of new evidence-based early diagnostic technologies; systems cancer biology-based targeted therapies inclusive of the microenvironment; imaging and analytical tools for assessing therapeutic efficacy in days versus months; and, ultimately, with enough knowledge, the availability of preventive agents that can block both premalignancy and metastasis.

The think tank also focused on mechanisms that the NCI might use to catalyze cross-talk and the formation of transdisciplinary teams among researchers from these disparate fields – including new centers. For example, the NCI's Alliance for Nanotechnology in Cancer Centers, the Integrative Cancer Biology Program, and the National Science Foundation centers all strongly emphasize the development of transdisciplinary teams. Additionally, NCI should consider establishing smaller research initiatives that are dedicated to specific relevant focus areas in the physical sciences. New training grants and postdoctoral fellowships to provide multidisciplinary training to a new generation of scientists were also thought to be critical. To build on this meeting, NCI should convene a number of smaller meetings and establish this think tank as an annual event. Finally, NCI's leadership should and could encourage universities to support substantive collaborations among researchers from the physical and biological sciences, including an appropriate reward system.

Introduction

The National Cancer Institute (NCI) is exploring innovative scientific approaches to better understand and control cancer. In that regard, the NCI is interested in engaging scientific teams and individual scientists from the fields of physics, mathematics, chemistry, and engineering to examine cancer using new, perhaps nontraditional, approaches. The NCI's goal is to join these often disparate areas of science through its various support mechanisms, including centers of excellence, to better understand the physical and chemical forces that shape and govern the emergence and behavior of cancer at all levels. The NCI anticipates that this initiative will foster the development of innovative ideas and new fields of study based on knowledge of the biological and physical laws and principles that define both normal and tumor systems. This is a new and exciting frontier for cancer research.

As a first step in the process of determining how the physical sciences may provide new fundamental knowledge and advance cancer research, the NCI convened a workshop at which leaders in the fields of cancer biology, physics, chemistry, mathematics, modeling, bioengineering, and nanotechnology discussed the state of the art in both cancer research and the physical sciences. Over 2½ days, the invited scientists listened to a few short plenary talks from thought leaders, were exposed to perspectives from scientists working at the intersection of these fields, and heard a few examples of scientific areas in oncology, such as nanotechnology, where the physical and biological sciences are clearly converging. However, most of the facilitated workshop was spent brainstorming about target areas in the physical sciences and biology that will be critical to new thinking and future directions in cancer research.

The overall goal of this unprecedented forum was to converge on a few key scientific questions/areas that might represent potential focal areas for a new generation of teams and centers of excellence to ultimately accelerate progress in cancer research for the benefit of patients.

Day 1: Tuesday, February 26

The meeting began with a brief introduction by **Anna Barker, Ph.D.,** Deputy Director of the NCI. She noted that this meeting has been in planning for a long time and in many ways is unprecedented in the history of the NCI. Over 2 years ago, the NCI launched the Alliance for Nanotechnology in Cancer, an effort that engaged collaborative teams of leaders from the physical sciences with cancer biologists and oncologists. This experience, coupled with the creation of new centers in integrated cancer biology, set the stage for this meeting. However, this is likely the first time that leaders from physics, chemistry, mathematics, nanotechnology, and engineering have come together with cancer biologists and oncologists to discuss new physical sciences-based approaches to solving some of the most difficult problems in cancer research today. Dr. Barker also commented that the upcoming 2 days would not resemble the typical scientific meeting. It was not designed to be a series of PowerPoint-driven scientific talks; but rather a number of exploratory conversations designed to generate new ideas and concepts. Output from this meeting will enable the NCI to more clearly define the opportunities that will derive from enabling the convergence of the physical sciences with cancer biology.

After thanking the attendees for taking the time to participate in what she hoped would be a groundbreaking 2 days of discussion, Dr. Barker introduced the NCI Director and co-organizer for this meeting, Dr. John Niederhuber.

John Niederhuber, M.D., Director, NCI, welcomed the attendees by remarking that it was a good sign that he did not know most of the scientists at this meeting, which is not usually the case for an NCI-sponsored think tank. He felt that the assembled group of experts from the physical sciences, cancer

biology, and clinical oncology had significant potential to engage in an unprecedented discussion that would result in innovative ideas and directions for cancer research. Specifically, his hope was for convergence on a few new concepts that could inform the development of new collaborative transdisciplinary centers and other support mechanisms to enable this new frontier in oncology.

Dr. Niederhuber then presented the sobering statistics that represent the human and economic burden of cancer. Over 1.4 million Americans received a cancer diagnosis and an estimated 560,000 Americans died of cancer in 2007. In total, the United States spent over $200 billion on health care costs related to cancer in 2007, and, adding to the problem, 47 million Americans are uninsured. On a positive note, there are some 12 million cancer survivors today in the United States, thanks in large measure to progress in early detection and treatment. In 2003 and 2004, the death rate from cancer fell, only to increase again in 2006. This rise is likely a result of change in demographics, since cancer is primarily a disease of aging and the United States increasingly has an aging population. This demographic shift is projected to drive an increase in numbers of new cancer cases in the next 10-20 years, which will further weaken an already inadequate health care system.

Before introducing the evening's keynote speaker, Dr. Niederhuber quoted Carl Sagan, who wrote, "Biology is more like history than it is like physics. You have to know the past to understand the present. There is no predictive theory of biology, just as there is no predictive theory of history. The reason is the same; both subjects are too complicated for us." However, Dr. Niederhuber pointed out that the physical sciences have long dealt with complexity, and it is the NCI's hope that physics, physical chemistry, mathematics, and engineering can help to solve some of the most difficult and complex problems in cancer biology today. These solutions will help to enable what is surely a transformative era in medicine that is only just starting to unfold.

Keynote Presentation

Dr. Niederhuber introduced the evening's keynote speaker, Paul Davies, Ph.D., by first thanking him for his willingness to share his thoughts with us based on his experiences in theoretical physics, cosmology, and astrobiology. Dr. Niederhuber reasoned that there were few people in the world who could set the stage for this meeting, and from his vantage point, we could not have made a better choice. Dr. Davies is highly accomplished in his chosen areas of research in theoretical physics, specifically exploring some of the most profound questions in science such as the origin of life on earth and the nature of time. Dr. Davies has perhaps more than anyone else written for the public about the intriguing and visionary questions in the physical and biological sciences, authoring over 27 books. He has recently left his long-time home in Australia to head a new organizaion, the Beyond Institute at the Arizona State University, an institute that explores fundamental problems in science. Dr. Niederhuber speculated that cancer was one of those fundamental questions and looked forward to Dr. Davies' insights and ideas in that regard.

Confronting Complexity: Cancer at the Intersection of Physics and Biology

Paul Davies, Ph.D.

In preparation for this meeting, **Paul Davies, Ph.D.,** Professor and Director of the Beyond Institute at Arizona State University, began his talk by stating how surprised he was that so much is known about cancer biology, and yet cancer remains one of our major health care challenges. On that note, Dr. Davies said that he would discuss the frontiers of physics—the very large, the very small, the very complex—and the role that technology is playing in the advancement of these frontiers.

The physics of the very large is the subject of cosmology, the structure and evolution of the universe. Cosmology is a quantitative science that allows us to say so much more about the universe than that it began 13.7 billion years ago with a big bang. Much of the credit for this advance in knowledge comes from technology, specifically from a satellite known as WMAP. WMAP for the first time allowed cosmologists to generate a heat map of the cosmos, which, in turn, gave us a picture of what the universe was like a mere 380,000 years after the Big Bang. From this map, and associated advances in theoretical physics, we now know what happened back to about 1 billionth of a second after the Big Bang.

Another branch of what was originally theoretical physics, but is now applied cosmology, is the study of gravitational waves. A system of instruments, known as the Laser Interferometer Gravitational-Wave Observatory, or LIGO, is designed to detect these gravitational waves. The effects of gravitational waves on large masses are extremely small but should be measurable with an upgraded version of LIGO.

At the frontiers of the very small sits the Large Hadron Collider (LHC), which is a ring-shaped tube 27 km in circumference, built underground near the border between France and Switzerland, that is designed to accelerate protons to very near the speed of light. Once the LHC is online, researchers will examine billions of proton collisions in order to untangle the mix of particles that will be produced. Although a main task of LHC is to discover a hypothesized particle known as the Higgs boson, which may account for the origin of mass in the universe, the primary reason for building the LHC is to explore unknown physical processes at very high energies. Dr. Davies noted that it is incredible that this complicated technology actually works when it is activated.

Dr. Davies reflected on how physicists approach the enormity of the problems they tackle. In a phrase, physicists stand back and look at the whole problem. A star, for example, can be studied by a number of approaches: through nuclear physics, the thermodynamics of the star, the atomic physics of the corona, the electromagnetism controlling the flow of energy from the star, and so on. But despite the fact that all of these aspects of a star's physics are complex, the basic principles of the physics involved are elegantly simple. One elegantly simple equation, for example, describes the physics of a black hole—the final state of a star that has collapsed under its own gravity—and indeed, this theoretical description of a black hole agrees with observational measurements. And although the calculations are complicated, there is simplicity at the heart of the complexity.

On that note, Dr. Davies turned his attention to the third frontier of physics, complex systems. He explained that intrinsic complexity is not merely the complicated conjunction of many simple systems. The study of intrinsic complexity has given rise to diverse areas of study, such as nonlinear dynamics, systems theory, network theory, and ecosystems. Intrinsic complexity is also relevant to questions about life: What is life? How did it begin? Can we make it? What makes it tick? How can "stupid" atoms make such a thing as life happen? That transition from the components to the whole, from the relatively simple to the intrinsically complex, is something with which science struggles, especially in understanding living systems. As an example, he showed a slide of a metabolic map and asked how it would be possible to develop a theory to account for the level of complexity inherent in that map. One approach, he noted, is to look at a living organism as an integrated system, and recent efforts to study life in an integrated fashion has given rise to the field of systems biology.

To illustrate the value of understanding complex systems, Dr. Davies recounted a story about the famous Australian physicist Lawrence Bragg, who together with his father invented x-ray crystallography. During World War I, he was able to calculate where German artillery guns were located on the basis of the time delay between the pressure wave produced by an artillery gun firing and its sound. When the Germans began firing more than one gun at a time, Bragg turned this to the Allies' advantage by deconvolving the multiple signals and determining where each gun was located. Although

this appeared to be a complex system, it was, in fact, relatively simple.

Conversely, a living organism is a nonlinear system. It operates far from equilibrium and is adaptive and robust. Nonetheless, it is possible to derive clues about living systems from nonliving, coherent complex systems. One such system is typified by the Belousov-Zhabotinsky reaction, one of a class of chemical reactions that are a classic example of nonequilibrium thermodynamics, producing complex but stable visual patterns. Another example is the simple act of heating water very carefully, which will produce a hexagonal pattern of convection cells that form spontaneously in a manner impossible to predict in detail. These cells are a stable, self-organizing phenomenon. Hurricanes and other fluid vortices are another example of self-organizing systems, some of which, like the Great Red Spot of Jupiter, can persist for centuries. These are all self-organizing systems in which there is large-scale coherent cooperation among molecules.

However, Dr. Davies stated adamantly that life is not a self-organizing system. It is a supervised, organized system under software control. There is a blueprint, DNA, that directs development to unfold, and when the supervision of that development is flawed, problems such as cancer arise.

Life involves a complex web of information flow, but the information is not just "bits," but, rather, contextual. Contextual information is closely related to semantic information: genes are coded instructions that need "interpretation" by a molecular milieu. Otherwise, a genome is meaningless "noise"; in fact, there needs to be a context in which the genome is expressed. However, it is important to remember that cells, like molecules, do not think. Indeed, it is possible to think of life as a hardware-software entanglement, where information plays a different and more complex role than it does in a computer. In biology, information can produce both cause and effect. The physical components encode, transmit, and replicate information, but the information itself plays a role in this process. Biological systems harness physical forces to their own end to produce "emergence," a phenomenon in which new properties emerge when a system crosses a threshold of complexity.

Dr. Davies noted that physics has enjoyed great progress over the past few hundred years because simple underlying mathematical principles operate at both very large and very small scales. For biology, he noted, there is also an underlying operational principle: Darwin's Theory of Evolution. Evolution, Dr. Davies posited, may be a key to understanding cancer. He observed that cells in a multicellular organism live on a knife edge. Multicellularity involves joining a union, which means that cells give up their freedom to pursue a "selfish cell" singular agenda. In vertebrates, adult cells must proliferate, but they do so in a "unionized," or regulated, manner. With aging—and cancer is a disease primarily of aging—the delicate controls may fail because of a lack of selective pressure on regulatory systems, an idea that W.D. Hamilton first proposed in a seminal paper in the *Journal of Theoretical Biology* in 1966. When regulatory systems go awry, cells revert to a premulticellular, "selfish cell anarchy" that results in uncontrolled growth and tumor formation. Therefore, cancer can be thought of as a fine-tuning problem, one that may be tractable if we can understand where and how these breakdowns occur.

Dr. Davies mused that the notion that cancer and evolution are intertwined led him to the idea that life operates on the edge of chaos, being neither orderly nor chaotic. Life has a certain amount of freedom to explore new properties, but within a system of limits. If something tips this balance into the chaotic realm, cancer results. So how then can physics help tame cancer? One way, he said, would be to apply some of the new physics-based scanning techniques, such as terahertz radiation (T-rays), coherent anti-Stokes Raman scattering (CARS), and biophoton detection using ultra-low noise CCD cameras, to develop new methods for early detection of cancer.

It is also important that theoretical physics be brought to bear on some of the big questions in cancer. For example, physics could provide new conceptual insights into complex systems and undoubtedly contribute expertise in the modeling of cancer's complexity using computational techniques. Theoretical physics can also significantly improve the area of signal processing to more effectively extract biologically meaningful cancer signals from the confusing noise of normal cell function. More importantly, theoretical physicists may be able to stand back and see the system as a whole, and ask "stupid" questions seemingly without embarrassment. As an example of this, Dr. Davies asked what he considered two "stupid" questions:

- How do salamanders regenerate limbs, a process that obviously involves allowing cells to revert to a state of rapid growth and reproduction?
- How do cells stick together and why do metastasized cells come unstuck? There are obviously biophysical forces that keep cells

together, so what prevents those forces from continuing to work?

Also, physicists tolerate wild ideas. One such idea, he said, is wondering whether cells represent virtual "bags of quantum nanophysics." If so, quantum mechanics may play a role in life in two ways. First, on the negative side, life's efficiency is limited by quantum mechanics, so perhaps life tends to evolve only to the quantum edge. On the positive side, life harnesses quantum effects to improve its performance and improve certain tasks. Quantum tunneling, for example, occurs in certain enzymes and in the photosynthetic machinery that powers all of life. The question to be posed: Does quantum mechanics play a role in cancer?

Dr. Davies concluded his talk by noting that a class of problems exists that are computationally challenging, but not intractable, and may soon yield to the relentless improvement in computational power reflected in Moore's law. Cancer may be one of those problems. At the same time, it is important to consider that cancer, like life, can be understood only in the context of evolutionary biology as well as cell biology.

Discussion Highlights: As part of a lively discussion following Dr. Davies' talk, it was noted that if cancer is viewed from an evolutionary perspective, it is critical to put into context the fact that the process occurs when organisms react to their environments. It follows that cancer therapies that alter the local ecosystem of a tumor may represent some of the most effective approaches in the future.

Why, What, and How of This Think Tank

Dr. Barker and meeting facilitator **Robert Mittman** reiterated that although the next 2 days would focus on key areas of the physical sciences and their convergence with cancer biology and oncology, this forum was designed to be more of an orchestrated conversation. Mr. Mittman would help keep the conversations on track, while **Thomas Benthin,** a graphic recorder, would capture the key discussion points as this conversation unfolded. The goal was to have an opportunity to think and talk about key barriers and opportunities for solutions and then arrive at consensus on how the NCI might structure approaches to capitalize on these new directions. Dr. Barker noted that everyone had been invited for a reason, with each participant bringing unique expertise and perspectives to the discussion. In closing, Mr. Mittman asked participants to have an open mind about ideas and opportunities that would emerge over the next 2 days and, as Dr. Davies encouraged them to do, ask the "stupid" questions.

Day 2: Wednesday, February 27

Dr. Barker officially opened the meeting and thanked a number of people for their contributions to this unique forum. She explained that the attendees were assigned to specific small groups at the tables. Each table had one or more "voices" of cancer biology, in nearly every case an oncologist who would contribute the perspective of someone who sees patients and, of course, the mathematicians, physicists, and other physical scientists who would hopefully drive much of the discussion. The purpose of assembling these diverse groups of experts in their respective fields was to create an environment that would facilitate the development of non-obvious solutions to the problems that face cancer research and oncology overall. Dr. Barker then introduced the meeting facilitator, Mr. Mittman, who delineated the charge to the participants.

Mr. Mittman noted that although cancer researchers have made great strides in the past few years, the NCI believes that we have arrived a point in our efforts to unravel the complexity of cancer where the physical sciences can provide valuable contributions to removing long-standing barriers to progress. Specifically the leadership of the NCI is interested in guidance from this group of experts on how best to utilize its various support mechanisms to engage physicists, mathematicians, engineers, physical chemists, and so on to address difficult problems in cancer. One area of great interest is the development of a new generation of transdisciplinary centers to facilitate this convergence of fields. In this regard, the meeting objectives, outcomes, and ground rules were outlined.

Meeting Objectives

- Identify major barriers in cancer research that impede progress today.
- Identify major areas of the physical sciences that are critical to understanding cancer at the molecular and atomic levels with consideration given to the dimensions of space and time.
- Access the current "state of the art" in terms of the application of the physical sciences to problems in cancer research and clinical oncology.
- Explore physical sciences solutions to problems solved in other fields that may bear on similar barriers in oncology.
- Among other possible approaches, develop suggestions for a new generation of centers of excellence that integrate and leverage physics, chemistry, and mathematics to accelerate progress in cancer research and the conquest of cancer.

Expected Outcomes

- A meeting report that captures the major ideas and consensus suggestions and input from the participants.
- A short summary white paper (with potential for publication) that can serve to inform NCI's various communities on the promise and necessity of more fully engaging the physical sciences in achieving the Institute's mission.
- The development of new scientific collaborations stimulated by both formal and informal discussions among the attendees.
- Beyond this meeting, further definition of specific scientific focus areas and ideas that could shape a new generation of physical sciences-oncology centers of excellence, and offer opportunities for advances that leverage new forums for communications and access to resources.

Meeting Ground Rules

- Participate fully and be 100 percent engaged (cell phones or e-mail devices were turned off for the forum).
- Share "air time."
- Be brave and ask the "stupid" question.
- Be open to things you know being questioned and challenged.
- Be clear and do not descend into jargon.
- Avoid the swamps; issues that lack of clarity will be parked for later discussion.

Keynote Presentation

Dr. Barker then introduced the first Keynote Speaker for the day, John E. Niederhuber, M.D., Director of the NCI. Dr. Niederhuber is the 13th director of the NCI and served in an acting role before being named to the position by the President in August 2006. He also served as the Chairman of the National Cancer Advisory Board from 2002 until he joined the NCI in 2005. Prior to coming to the NCI, Dr. Niederhuber was a nationally recognized cancer surgeon and scientist and for several years served as the Director of the Comprehensive Cancer Center at the University of Wisconsin. His current scientific interests are focused primarily on questions related to the role of tissue stem cells in cancer. Dr. Niederhuber was challenged to set the stage for the think tank by summarizing the "state of the science" across the complex landscape of cancer research.

State of the Science in Cancer Research: Potential for the Physical Sciences To Remove Major Barriers
John E. Niederhuber, M.D.

Dr. Niederhuber's task was to set the stage for the day's discussions by delineating the current status of cancer research and offering his assessment of the remaining frontiers across the field of oncology. He reminded the group of the expected increases in the number of new cancer cases, resulting primarily from the aging of the U.S. population, and the often disproportionate economic and human burdens that the disease visits on underserved populations in this country and around the world.

Dr. Niederhuber's theme focused on the following question: "What can physics, physical chemistry, applied mathematics, and engineering bring to the study of cancer biology and control of cancer?" He reflected that although advanced technologies are impacting the study of cancer and other diseases in an unprecedented manner, cancer research overall has not engaged the fields of physics, chemistry, mathematics, and engineering very effectively to this point. Dr. Niederhuber made it clear that it was the NCI's desire and intent to reach out to these communities and create opportunities for active collaboration and synergy. In fact, the practice of medicine and our knowledge bases are likely to be radically different 10 years from now because of advances in technology and the inclusion of the physical sciences in biological and biomedical research. In that regard, he noted that cancer is well positioned to serve as a model for the study of other complex diseases.

In an overview of the state of cancer research, Dr. Niederhuber reiterated that cancer is a disease of the genome, arising from any number of different types of genetic and epigenetic changes that occur during an individual's lifetime. Cancer is genetically complex. In fact, the transformation of a normal cell to a cancerous state generally involves the accumulation of a number of genetic changes. Cancer's complexity also derives from the interacting molecular networks and redundant pathways that drive normal cell function at all levels. These major interactions include protein-protein interactions, protein-DNA interactions, and microRNA-mRNA interactions, to name a few. An obvious role for the physical sciences in cancer research is the application of knowledge from complex physical systems to better understand the normal and cancer "interactome."

Tumors can be viewed as organs composed of many interdependent cell types growing in a microenvironment that is now known to play an active role in the development of cancer. Research has shown clearly that there is a dynamic flow of information between the cells in a tumor and the cells in the surrounding microenvironment and

that some of the cells in the microenvironment are reprogrammed by the tumor. Therefore, an in-depth understanding of this relationship is a critical strategy for the future of cancer therapy. In fact, in the future, the microenvironment may become as much of a focus for the development of new cancer therapeutics as the tumor is today. In addition, increasingly it appears that tumors may contain a very small subpopulation of cancer stem cells that actually drive tumor growth and metastasis.

Given that cancer is a genetic disease, the completion of the Human Genome Project was a landmark for cancer research, much as the development of the periodic table was a landmark event in the history of chemistry. From the Human Genome Project came the HapMap project to search for SNPs (single nucleotide polymorphisms) and other germline changes to potentially gain a better understanding of an individual's cancer risk based on inherited mutations. Whole-genome scans of specific types of cancer are under way to determine whether there are SNPs that can predict risk of susceptibility to breast, prostate, lung, colon, and other cancers. In addition, the NCI and the National Human Genome Research Institute (NHGRI) have started a collaborative pilot project, known as The Cancer Genome Atlas (TCGA) Project. This pilot project has an overall goal of identifying all of the somatic genomic alterations initially in three cancers (brain, lung, and ovarian). If TCGA shows that the development of a complete multidimensional dataset on these cancers can be successfully achieved, the project would be scaled up to study other tumors. Dr. Niederhuber commented that this has been a fruitful collaboration with the development of a high-throughput network structure that may serve as a model for future multidisciplinary collaborations with multi-Institute support. TCGA will release its initial findings on glioblastoma in the next few months.

Projects such as HapMap and TCGA create major databases that drive new avenues of exploration. The need now is to build on this emerging basic genetic foundation by constructing a picture of the abnormal interactions that result from these changes in cancer genomes. Obviously, creating the network and standards for projects such as TCGA are major challenges, but the major challenges still lie before us, transforming that information into knowledge about how these alterations drive cancer. Dr. Niederhuber expressed his confidence that this information, and the new age of biologic discovery that it will drive, has the capacity to transform and individualize the diagnosis, treatment, and prevention of cancer. He also believes that cancer will lead as a model for the transformation of other diseases. Interestingly, it is the physical sciences that may contribute new and critical knowledge during the emergence of what is referred to as personalized medicine.

Dr. Niederhuber reviewed a few examples of cancer biology at the frontiers of cancer research. For example, stem cells, which represent a small percentage of cells in a tumor, have the ability to travel to other tissues; apparently they do not need to acquire this characteristic. They also exhibit drug resistance and naturally express high levels of drug transporters. Cancer stem cells also appear to exhibit many of the attributes uniquely present in embryonic stem cells. Currently, there are only crude markers for some cancer stem cells, most notably breast tumor stem-like cells that, unlike other cells from the tumor, can re-grow a new tumor. An important new avenue of research from these findings is to determine the role these stem-like cells play in metastasis and recurrence of cancer.

Another research frontier is the role of chemokines in premetastatic lesions. For example, VEGF produced by lung tumors triggers fibronectin recruitment over a chemical gradient. The result is the deposition of endothelial and hematopoietic cells in association with fibronectin, creating a microenvironment suitable for the development of metastasis. Indeed, blocking VEGF stops a site from becoming a home for metastasis.

While it is easy to create chemical gradients in a petri dish, it is much more difficult to study these gradients in vivo. Cells clearly migrate in these gradients, and they tend to form aggregates. Given that group cell migration is crucial to many cellular processes, including metastasis, the use of techniques from the physical sciences applicable to studying group dynamics could generate a global understanding of the molecular mechanisms and networked pathways involved in group migration and metastasis. Such techniques would include computational tools needed for the statistical analysis of complex behaviors and tracking software that could analyze image stacks and provide statistics on velocity, directionality, and cell shape.

The physical sciences can also help cancer biologists sort out the organization of the genome in three-dimensional space. The orientation of chromosomes within the nucleus is not random, and this parameter changes as cells progress from normal to premalignant to fully malignant. This raises the intriguing idea that changes in three-dimensional chromosomal organization could serve as a marker of premalignancy or very early tumor formation. New methods of measuring and analyzing the three-dimensional organization of the genome in vivo are needed to test this hypothesis.

Imaging and imaging research represent a major NCI focus that touches nearly all aspects of cancer research. For example, drug development increasingly must include a functional imaging component to track a drug molecule in vivo. We now need to extend imaging capabilities to the subcellular level in order to study protein-protein and protein-DNA interactions. The field also needs new methods that can merge imaging with mass spectroscopy in real time to gain insights into the molecular details of cancer.

Dr. Niederhuber closed his talk by noting that he hopes that bringing together the diverse talents, expertise, and tools of physical scientists and cancer researchers will provide new directions for investigation that will lead to new conceptual approaches to understanding the complexities of cancer. For example, by understanding the physics and energy constraints involved in the interactions between two or more proteins, it may be possible to identify ways of modifying those interactions and changing the course of cancer. New conceptual approaches will lead to new models that are more relevant to understanding the disease in humans.

There has never been a more exciting time in science. Advanced technologies are being created, maturing rapidly, and driving complex biomedical research; however, capitalizing on this momentum to defeat cancer will require transdisciplinary teams involving experts from physics, mathematics, physical chemistry, and engineering working side by side with cancer researchers.

Discussion Highlights: One participant noted that there were similarities between microbes and cancer stem cells and wondered whether antimicrobial agents might attack stem cells. Dr. Niederhuber remarked that this could indeed be a fruitful avenue of research, but he also cautioned that if this approach were viable, it would require a wide range of solutions, as is the case with the development of antimicrobials. Related to the question, he pointed out that there are also many connections and similarities between the inflammatory response to both infectious processes and cancer.

Finally, an attendee wondered whether mathematics could be used to understand the stochastic versus deterministic factors that control whether cancer develops. Such methods and models might also provide insights into how cells move from normal to premalignant to malignant, and from normal to stem-like cells.

Brainstorming Session I: Relevant Scientific Barriers Blocking Progress in Cancer Research

See Figure 1. Relevant Scientific Barriers in the Appendix at the end of this report.

At this point, the small groups engaged in a 25-minute conversation among themselves to identify the principal barriers and challenges in cancer biology and cancer research, adding to and embellishing those noted in the opening keynote presentation. The goal was to converge on a set of mutually exclusive barriers. Following the deliberations, Mr. Mittman proceeded around the room and solicited two barriers from each table. The long list of barriers generated by the groups is summarized (in no particular order) as follows:

- Lack of standard nomenclature across all of biomedical and cancer research, which makes it difficult to organize data in searchable databases derived from the different scales of biology and from different modalities. Common language and information management tools (algorithms, data interrogation software) could be very helpful.
- There are no conventions (or laws) of scalability in biology across the temporal or spatial realms. Biological (cancer) research today is focused on studying unimolecular events but is not good at moving from single molecules to the complex. In contrast, engineers have developed methods to go from simple systems to model systems as complex as turbulent flow over an airplane wing.
- Lack of tools to better co-represent imaging technologies, which could provide a more three-dimensional, and perhaps time-sensitive, view of tumors and their microenvironments.
- A need for new tools and technologies usable at the bedside that would provide the same type of information now generated in the laboratory.

- Normal tissues have not been thoroughly characterized for the areas of interest in disciplines such as genomics and proteomics, much less networks, to provide a basis for comparison studies.
- Lack of accessibility to patient materials – both normal and cancerous – collected in a standardized manner.
- Cancer and cancer processes are rare events; they are in the tail of a distribution from normal to cancerous. There is a need for statistical methods to understand the rare events occurring in these tails both to understand the distribution across normal and abnormal and to integrate those events across the tumor and its microenvironment.
- Given that cancer is an incredibly rare event, there is a need for high-throughput techniques that can identify rare cells and examine individual cells in ways that can ultimately represent the composition of a heterogeneous tumor.
- The intrinsic complexity of cancer is a significant barrier to understanding it, and we know from physics that complex events are highly sensitive to initial conditions. As a result, it is difficult to understand the initial conditions that lead to cancer when the starting point is often the conditions of end-stage disease.
- Cancer biology has only a limited understanding at the molecular level of the microenvironment that influences tumor growth, development, and metastasis.
- The heterogeneity of tumors and their microenvironment require quantitative measurements over many dimensions in order to generate the data needed to develop models for cancer based on systems biology.
- First principles and rules become distorted when trying to study the microenvironment without disturbing it; an in vivo Heisenberg uncertainty principle may well be relevant here.
- There is no field of theoretical cancer biology (or theoretical oncology). Therefore, there is a lack of models that can generate hypotheses and suggest new experimental approaches to studying cancer. Today's models are primarily focused on the explanation of existing data for end-stage disease.
- There are cultural barriers in the oncology community that make it difficult to find acceptance for modeling.
- Cancer biology (and cancer biologists) does not have a firm understanding of the differences between stochastic and deterministic events in cancer.
- There is a gap in understanding the spatial aspects of cancer, including how groups of cells interact and migrate.
- The lack of diagnostic tools for early detection and patient stratification makes it difficult to develop and test drugs for use in treating cancer at different stages.
- There is a lack of tools to study the natural history of the initiation and progression of cancer in humans; cancer has been cured too many times in mice, but not often enough in humans.
- Despite the large number of drugs available to treat cancer, the oncology community has a poor understanding of how best to use these drugs.
- The inability to study drug effects in real time using noninvasive tools is an impediment to drug development efforts.
- The fragmented nature of science makes it difficult to study cancer from a systems approach, highlighting the need for new team-based, collaborative research efforts that cross many disciplines.
- To make teams work, there is a need to understand differences in reward systems in different disciplines. Physics, for example, has adapted to large-scale projects by developing mechanisms to ensure that each contributor receives the appropriate reward.
- There are cultural and geographic barriers in academia that inhibit transdisciplinary approaches to research.
- Language barriers between physical scientists and oncologists impede progress.

Keynote Presentation

Dr. Niederhuber introduced the second keynote presentation for the day, given by Robert Austin, Ph.D. Dr. Austin is Professor of Biophysics at Princeton University, where he is actively engaged in a wide range of areas that utilize principles from physics to understand seminal questions in biology. Some of his interests include DNA-protein interactions, cell signaling, and cellular evolution. His charge was to review many of the key areas where 21st century physics intersects with, and has the potential to inform and enable, cancer biology. As Dr. Niederhuber remarked, he had no small task.

21st Century Physics – Relevant Intersections With Barriers in Oncology
Robert Austin, Ph.D.

Robert Austin, Ph.D., Professor of Biophysics at Princeton University, began his talk by commenting that the jargon of medicine is amazing and could represent a significant barrier to cross-disciplinary research. He also noted that he could not do justice in this talk to all of the advances that are occurring in physics that have potential applications in oncology, but he would try. He then launched into a discussion of a top-down approach to addressing some of the barriers in oncology using the tools of 21st century physics. For example, nanotechnology used in conjunction with various imaging platforms could provide the means to image tumors in tissues and then deliver interventions to kill the tumors. Of course, nanoparticles may exhibit complex toxicities, but we are beginning to understand the impact of these complex nanosystems when they are introduced into the body.

In addition to imaging modalities, such as MRI, nanoparticles can be combined with modern picosecond or femtosecond lasers, or perhaps more exotic up-conversion materials, to image tumors deep inside the body. As noted, it may be possible to use such optical methods to both image and destroy tumors. Up-conversion, he explained, means that the color of photon absorbed is changed through its interactions with a nonlinear material. This is a very interesting process to a physicist—a fundamental quantum mechanical property. Currently, up-conversion imaging technologies are expensive and require extremely high light intensities. However, there are examples of new materials being developed that need less energy to emit a bright signal using lower cost lasers, suggesting that advances in materials science will greatly benefit cancer biology. It appears that the way in which nanocrystals are structured in these materials plays a crucial role in the efficiency of the up-conversion process. For example, an investigator at Princeton has created a 50 nm "death-star" nanoparticle that contains an up-converting phosphor that transforms infrared light into visible light.

Physicists and engineers are also making significant progress in developing brighter, less expensive, light sources for imaging applications. New tunable and coherent light sources using free-electron lasers can produce coherent, narrow-band, tunable output in the x-ray region. Coherence affords the opportunity to create interference, the operating principle in x-ray crystallography, and therefore to create three-dimensional images. It is also possible to tune in to the edges of a coherent signal to produce contrast enhancement, which could improve the ability to generate sensitive, cancer-specific images. Coherent light can also serve as the basis for dynamic optical tweezers that would allow for the manipulation of individual cells or assembled groups of cells. In fact, tunable, coherent x-ray lasers should become available within the next decade.

To improve detection of metastasis, Dr. Austin speculated that one of the key challenges will be to find rare, circulating transformed cells as they leak from tumors, at a concentration of one cell in a billion or less. In a highly promising approach, researchers are using microfluidics, based on a deep understanding of hydrodynamics at the micro and nano scales, to find these cells. It is certain that understanding the mathematics of hydrodynamics is necessary to accomplish this task. Turning to anther physics-based opportunity, it is now possible to work with energies that impact the movement of cells in biological fluids in an asymmetric manner. When combined with new optical imaging methods that can analyze what is happening inside a cell, it may be possible to use microfluidics to develop insights into how one type of cell differs from another, irrespective of whether it is a comparison of healthy versus malignant cells or metastatic versus non-metastatic cells.

Dr. Austin reasoned that it is even possible today to give physics puzzles to cells, to confront them with various structures and barriers and determine how they solve these problems in terms of information content and information processing. It may be possible to use such tests as a means of

distinguishing between normal and metastatic cells and to better understand the dynamics of information transfer in metastasis. It is also possible to create microfluidic devices that can measure the force cells exert as they migrate, which could be useful in the study of invasive cells.

Next, Dr. Austin commented that he felt it was impossible to begin to understand the dynamics of cancer without a deep understanding of the ecology, evolution, and adaptation of cancer cells. He noted that from the perspective of a physicist, conventional Darwinian evolution theory and experimentation are fundamentally flawed because there is no mathematical model. He explained that he was not implying that he does not believe in Darwinian biology, merely that it lacks a basic model. Furthermore, Dr. Austin said he does not view mutations and evolution as random events. He said that he sees life as being "marooned on islands of fitness surrounded by huge areas of badness," and that this implies that there are deliberate mutations that involve moving from one "island" to another. One possibility, he said, is that there is a large distribution of mutations and genome changes that may represent the key mechanism for how the human species deals with stress.

Dr. Austin then turned his attention to what he believes are some of the most important unsolved questions in cancer research today. The first question involves the role that stress plays in the rate of adaptation and evolution of cells. He stated that he thinks that the accepted idea that random mutations are occurring at some universal rate is wrong. He described an experiment conducted in his laboratories that used nanotechnology to create complex nutrient landscapes to carry out evolution and adaptation studies in response to truly complex ecological situations. This experiment involved creating a landscape with good places and bad places by opening and closing nanochannels. When bacteria are added to this system, Dr. Austin and his colleagues found that the bacteria began to aggregate and associate with one another. These were collective dynamic processes that caused the bacteria to interact with one another, which may be analogous to the ways in which cells interact with one another in the human body.

On the basis of these studies and others, Dr. Austin proposed that game theory be applied to studies of the role of evolution in cancer in order to determine the "rules of engagement." He described an experiment involving mutant bacteria that do not power down metabolism when nutrients become limited. By exploiting resources, these bacteria operate much like cancer cells when they become disregulated and stop functioning as members of a collective of cells that work together to form an organ. Sequencing the genome of these "cheater" bacteria reveals that there is a genetic insertion that is reproducible. He showed in these studies that the cheaters versus the cooperators acquired the capacity to behave differently in terms of their ability to isolate themselves from one another. Using game theory and the prisoner's dilemma, it should be possible to model this behavior. Extending this idea to cancer, Dr. Austin said that malignant cheater cells must be metastatic because they can destroy their environment through resource overutilization and then move on to find new sources of nutrients. The challenge then is to adapt models such as he is developing to elucidate the behavior of the bacteria in his system to explain the metastatic behavior of eukaryotic cells. If that is possible, it would provide a means of developing the rules of engagement for cancer cells involved in development and metastasis.

In closing, Dr. Austin speculated that perhaps cancer is an inevitable part of evolution; i.e., it represents the ability of species to respond to the pressures of natural selection. If so, then the goal of killing cancer cells as embodied in current cancer therapeutic strategies may be the wrong experimental direction to take, and new approaches should aim toward understanding and controlling these evolutionary processes in order to control cancer.

Brainstorming Session II

Ideas/Concepts From the Physical Sciences That Represent Important Strategies To Address and Remove Barriers in Oncology

See Figure 2. Addressing Barriers in the Appendix at the end of this report.

The group then moved into a period of conversation in their small groups to identify some key ideas from the physical sciences that might address the major barriers and challenges in cancer biology and cancer research identified by the keynote speakers and the earlier small-group process. The goal of this discussion was to initiate a process that would allow the group to converge on a set of mutually exclusive strategies for overcoming the barriers. Following the deliberation period, Mr. Mittman proceeded around the room and solicited two strategies or concepts from each table, to create the following list:

- Develop theories of molecular ecology using nonequilibrium statistical mechanics in the same way that such methods have been used by scientists outside biology to explain the behavior of Internet networks and swarming/flocking behavior. Such an approach could produce a general theory of evolutionary dynamics that includes stochastic events.
- Apply game theory and evolutionary information exchange theories of cooperative and conflicting interactions, value creation, value exchange, and entropy maximization to the problem of cancer.
- Develop a data acquisition approach to make data ranging from the molecular to the histopathological available to scientists in many fields. This data acquisition style should be developed by the data users.
- Create opportunities for biologists to understand and utilize existing quantitative models. Mathematicians have developed a wide range of models that may be applicable to biology; however, biologists largely ignore these models—because either the mathematics is too complex or they believe the models are too "simple."
- Apply expertise in phase diagrams developed in soft nanophysics to cancer.
- Add energy landscapes to the theoretical framework of cancer.
- Enable studies that allow and encourage physical scientists to question the dogmas of cancer biology and biology in general.
- Develop probes that travel through the entire body that can be interrogated with short-wavelength radiation, to provide dynamic information with high resolution and without scatter.
- Use the tools of physics to reconstruct multidimensional data generated using the wealth of new analytical tools becoming available.
- Develop new technologies and analytic methods to measure heterogeneity, from the molecular to the cellular.
- Study the role of time dimensions in the development of cancer to determine whether the stages in cancer are reversible or reprogrammable.
- Use the principles of physics to determine the fundamental facts about the cancer state that are measurable. Use these facts to determine the threshold of changes that represent cancer and to develop the set of experimental facts that will be used to define a state of cancer and normal.
- Determine the specific levels of quantification that are necessary to apply physics to the problems of biology.
- Develop analytical tools capable of detecting one cell in a million and studying the interactions between these rare cells and their environment.
- Given that the signaling pathways involved in communication among different cells, and within individual cells, look much like nonlinear feedback systems, it may be

possible to use the same multispectral analysis techniques developed for the study of frequency information in physics to understand information flow in cancer.

- Apply information theory to help understand the genome and its relationship to healthy and disease states.
- Apply nonlinear dynamics to the analysis and modeling of pharmacokinetics.
- Develop high-throughput technology that couples biochemical and biophysical measures.
- Integrate experimental human data (therapeutic data) with models; data modeling should be about what a tumor actually does, not what a cell might do.
- Create an inventory of technologies and develop an infrastructure that makes these technologies available to the field.
- Apply the techniques of physics and chemistry that enable measurements at the single molecule or single cell level to the large scale in order to provide information across an entire system. Then use the data handling and analytic techniques developed by physicists to process all of these data.
- Create theoretic models that can move from simple to complex systems.
- Use data-mining techniques on existing biochemical, genetic, imaging, and clinical data to develop multiscale models of cancer.
- Use nanofluidic devices to decouple event-by-event cancer biology.
- Physicists take complexity and reduce it to simplicity in a way that is useful and testable; so use these methods to get at the physics of evolution; Darwin was right, but he presented a crude representation of evolution.

Panel Discussion I

Following the previous brainstorming session, Mr. Mittman introduced a panel of individuals whose job was to extend the discussion by considering specific perspectives from mathematics, physical chemistry, and cancer biology. Drs. DiBenedetto, Heath, and Bissell offered overview comments from their own experiences in working across disciplines, especially in their individual research efforts to address hypotheses in cancer. Mr. Mittman also posed questions for the panelists concerning the potential role and contributions of their specific disciplines, and how the NCI might assemble the teams needed to achieve the overall goal of this meeting.

Integrating Physical Chemistry, Mathematics, and Systems Models Into a Transdisciplinary Approach to Cancer Research

Each of the panel members gave a 5-minute talk and engaged in a lively discussion on questions posed by Mr. Mittman. **Emmanuele DiBenedetto, Ph.D.,** Professor of Mathematics at Vanderbilt University, began by noting that the field of mathematics is as diverse as biology, and so mathematicians as a group can approach problems in cancer biology from a wide range of perspectives. Coarse modeling of complex systems, he explained, assumes that conditions are uniform, or "well-stirred." In coarse-scale models, mathematicians use ordinary differential equations to express various relationships among the modeled elements. With models at this scale, you can ask questions about the physical laws governing how a moving boundary condition advances. This approach is ubiquitous in mathematically modeling physical problems with "free" boundaries or physical problems that have more than one phase.

Mathematical models can also involve homogenizing and bridging different scales. For example, it is possible to model individual elements of a system on the basis of its diffusion properties, how it reacts with other elements, and how it moves across various boundaries. However, while such a description of one element at one location is physically accurate, it is essentially useless for modeling complex

systems. Homogenization blends the components of a complex system into a "unified picture" using the language of partial differential equations.

Finally, variability and the suppression of variability must also be considered in modeling complex biological systems. For example, the activation and deactivation cascades of signal transduction are stochastic processes in which signal amplification by an enzyme introduces variability in the response of this system. Identifying such sources of variability, as well as factors that suppress variability, are essential to the development of useful mathematical models that describe biological systems.

Panel member **James Heath, Ph.D.,** Professor of Chemistry at the California Institute of Technology, spoke briefly about the different levels of analysis required to describe and analyze a complex system such as cancer. At one level, there is the biology of the genome and proteome. At another level there is the phenotype of an organism, and today we have significant difficulty moving from the genomics and proteomics levels to the phenotype. He added that understanding how emergent behavior, such as phenotype, arises from the interactions of cell-cell communication networks would provide vital advances in our understanding of cancer.

Mina Bissell, Ph.D., Distinguished Scientist at Lawrence Berkeley National Laboratory, then noted that defining the plasticity of the tumor microenvironment is, in her mind, the key to understanding cancer. The microenvironment may represent the best approach to defining what is normal and abnormal. Therefore, it may be possible to trick a malignant cell into returning to normal by changing conditions in the surrounding microenvironment. Form and function, she noted in closing, are associated through dynamic reciprocity.

Mr. Mittman then initiated a discussion by asking the panelists how mathematicians, physicists, and biologists differ in the way they think about and approach complex problems. Dr. DiBenedetto answered that mathematicians can state a few things with extreme precision, while biologists can state many things with limited precision. The precision required in mathematics means that the ability to describe large numbers of parameters is limited. Dr. Heath remarked that having only recently gotten into biology, he appreciates the different approaches inherent in both fields. He (and his research) has benefited signficantly from oncologists giving tutorials in the laboratory. He added that he and Dr. Hood, who are collaborators in one of the NCI Centers of Cancer Nanotechnology Excellence, perform very different types of experiments to attack the same problem. Dr. Bissell added that in her mind, the differences have more to do with creativity than other factors. She added that mathematicians and physicists do experiments or create models to find out what is possible, while biologists do experiments or create models to understand what actually happens.

Mr. Mittman then asked the three panelists how they would propose to apply a physical sciences perspective to create a more formal language for biology. Dr. Bissell commented that it is up to the biology community to first generate good, specific data that mathematicians and physicists can use to create models that the biologists can then test. Dr. Heath remarked that physical scientists sometimes do not appreciate that the problems they study do not exist in a vacuum. For example, the problems the NCI is interested in solving require solutions that can be translated to patients. On that note, Dr. DiBenedetto remarked that modeling a problem can be harder than solving it. In certain areas, such as drug development, creating perfect models is exceedingly challenging and time intensive.

Finally, Mr. Mittman asked the panel members for their insights into assembling transdisciplinary research teams. Dr. Heath said that it boils down to people, selecting individuals who not only have the right skills, but who also can buy into the notion that everyone has a particular, important part to play in attacking these complex, multidisciplinary problems. Dr. DiBenedetto added that for a mathematician or any other physical scientist, the key is to have problems that are challenging and that invite intellectual buy-in. Bringing in a mathematician merely to perform calculations that

a biologist does not know how to do is not a recipe for success. Dr. Bissell added that we need to understand the different rewards that motivate scientists from different disciplines.

Discussion Highlights: A participant observed that personal interactions are very important in multidisciplinary collaborations, but that often, because of clinical responsibilities, physicians find it difficult to commit enough time to create meaningful partnerships. It was also suggested that biologists need to employ language that is as precise as that used by physical scientists. This theme was reiterated by several participants, with the consensus being that there are many ways to overcome the language barrier, by both committing to the process of learning the languages and using students and postdoctoral fellows to bridge the gap between laboratories from disparate fields.

Keynote Address

In his introduction of the third keynote presentation of the day, Dr. Niederhuber commented that Leroy Hood, M.D., Ph.D., had most certainly pioneered the emerging and important field of systems biology. In addition, Dr. Hood's accomplishments in the development of advanced technologies such as the DNA sequencer represent seminal contributions to biomedical research overall – and particularly to cancer. He has driven the concept of transdisciplinary teams as the future paradigm for biomedical research and medicine, which is reflected in his most recent endeavor, the Institute for Systems Biology, where he serves as founder and president. Dr. Hood's presentation focused on employing systems thinking to drive the integration of the physical and biological sciences to speed progress in cancer research for patient benefit.

The Integration of Systems Thinking: Emerging Technologies, and the Biological, Physical, and Computational Sciences To Attack the Challenges of Cancer
Leroy Hood, M.D., Ph.D.

Leroy Hood, M.D., Ph.D., President of the Institute for Systems Biology, opened the afternoon sessions by giving his perspectives on how to build cross-disciplinary research teams to pursue systems biology. This perspective comes from his own sequential experiences of running a large laboratory engaged in biological research and technology development; as the founder and director of a National Science Foundation science and technology center; as founder of the first cross-disciplinary department at the University of Washington; and finally as cofounder and president of the Institute for Systems Biology. Dr. Hood noted that the next generation of cancer biology will require that physical scientists learn biology at more than a superficial level and cancer biologists appreciate and embrace the power of physics, mathematics, and chemistry to advance our knowledge of cancer. Physical scientists and biologists can use their respective understanding of biology and the physical sciences to create a new generation of teams with the capacity to solve biological problems, e.g., developing new measurement and visualization technologies and addressing questions of data capture, integration, mining, and modeling.

Understanding biological complexity, said Dr. Hood, will be the dominant scientific challenge for all scientific disciplines in the 21st century. Systems approaches will allow biology to systematically integrate new technologies for measurements and visualizations, which will solidify our thinking about biology as an information system. The tools developed for such an approach, along with integrated, information-based methods of looking at biological problems, will find applications in a wide variety of subjects and help solve a number of the major problems we face in creating 21st century medicine. Dr. Hood then commented that a reductionist approach to biology—looking at one gene and one protein in isolation—will not solve the complex problems associated with understanding normal, much less cancer, biology. For example, there is still no detailed explanation of the immune system, and it is clear today that we will never have a good model of the immune system by studying it one gene and one protein at a time.

Although the Human Genome Project was perhaps the seminal event for systems biology, the development of the new information technologies to analyze large-scale datasets and new instrumentation that facilitates gathering data at an ever-shrinking scale of resolution are equally important. Systems biology is fundamentally an

information science. The digital information of the genome and the environmental information that impinges upon and modifies the digital information represent the core "raw material" of systems biology. Biological information is also modulated by protein networks, genome-protein networks, and siRNA networks. Dr. Hood described the most sophisticated integrated biological network defined to date, one that accurately models sea urchin development. Using this network model, it is possible to use specific drugs to reengineer these systems, and as a result, the animal's development. But despite the success in modeling sea urchin development, Dr. Hood said he was skeptical that it is possible to develop such comprehensive models for higher order processes such as cancer because of the multiscalar level of the biological information. Indeed, he said that until we can integrate information from DNA and mRNA through individuals, populations, and ecologies, we will never truly understand the human system.

The Institute for Systems Biology studies dynamic networks made of elements or nodes – genes and proteins – and the interactions between the dynamic edges of these elements. The elements and their interactions are affected by the context of other interacting systems within cells and organisms, while the interactions between and among the elements give rise to a system's emergent properties. Six essential features set this type of view apart from the way biology has normally been studied:

- Quantitative measurements for all types of biological information.
- Global measurements that address dynamic changes in all genes, mRNAs, proteins, etc., across state changes.
- Computational and mathematical integration of different data types, including DNA, RNA, proteins, siRNA, and the interactions among these components, to capture distinct types of environmental information.
- Dynamic measurements across developmental, physiological, disease, or environmental exposure transitions.
- Utilization of carefully formulated systems perturbations.
- Integration of discovery-driven and hypothesis-driven measurements in a cycle of model development → hypothesis → perturbation → measurement → model development → hypothesis, and so on.

Overall, it is important that biology drive technology and computational tool development, with a focus on technologies that can make relevant measurements.

Taking a systems view of biology results in a relatively simple concept: that disease arises because one or more biological networks has been perturbed. In principle, then, we can understand disease by understanding the dynamics of network changes. As an example, Dr. Hood described a six-network system of genes, proteins, and the interactions among them to model prion disease. Studying the dynamics of the six networks involved explained the pathophysiology of the disease and led to the identification of key markers that previous research had missed.

Dr. Hood turned to the problem of finding diagnostic markers, one that he said is much like the problem of finding the needle in the proverbial haystack. The approach that he and his colleagues have taken has been to search for organ-specific secreted mRNAs, of which over 40 have been identified for individual organs in mice and humans. He believes that organ-specific blood proteins will provide a blood-based window into human health through "fingerprint proteins" that will give a status report on the health of each organ. Microfluidics and nanotechnology will be critical for developing the analytical tools needed to determine such fingerprints and for monitoring those fingerprints. So, too, will high-throughput DNA sequencing, new types of protein capture agents with improved specificity and sensitivity, single-cell analyses, and both in vivo and in vitro molecular imaging technologies. Together, the concerted application of these technologies combined with a systems biology approach should lead to what Dr. Hood referred to as P4 medicine – predictive, personalized, preventive, and participatory.

Discussion Highlights: A participant asked whether Dr. Hood thought that a systems biology approach could be employed to discover the origin of cancer. He replied that it should be possible to discover, at the least, the causative events that start a cell down the pathway toward malignancy. He also noted that new, powerful technologies are at hand for determining the originating events. He was asked whether systems biology had developed any new insights, and Dr. Hood replied with an emphatic yes, noting that as an example, work with prions identified new genes affecting previously undiscovered networks.

He was also asked whether he thought that small tumors would generate cancer-specific detectable molecules. He replied that he did not know, but he could imagine using various microfluidics-based concentrating technologies to locate and identify such molecules. He was also asked how systems biology might approach epigenetics, and he replied that cell lines will play a key role in understanding epigenetics. New cell-sorting technologies that could enable the study of multiple cell types clumped together in a manner that mimics a tumor and its microenvironment also promise to contribute to this area.

Brainstorming Session III

Framing and Prioritizing the Most Relevant Barriers in Cancer Research as Viewed From the Physical Sciences

The attendees reconvened in their small groups and engaged in a discussion aimed at finalizing and prioritizing key barriers blocking progress in cancer research, and identifying key areas of physics, mathematics, chemistry, and engineering that may contribute to removing these barriers. Given the discussions to this point, this closing session was far-ranging and spirited, with several innovative directions explored by the group. Ideas and questions that framed the discussion from each of the groups included:

Key Questions That Framed Most Relevant Barriers

- What role does evolutionary biology play in the development of cancer, drug resistance, and metastasis?
- Is it possible to define the physics of cellular evolution, and ultimately use these tools to differentiate between lethal and responsive cancers?
- How can we deal with heterogeneity within tumors?
- What makes just a few cells of the millions that a tumor sheds home to a tissue, become established, and create metastatic lesions?
- What drives this enormous degree of heterogeneity? How do cells communicate; overall, how do information transfer and management occur within and among cancer cells? Is it different from normal?
- How do we accurately distinguish the "abnormal-looking" that a pathologist observes in a tissue biopsy from truly malignant cells?
- Can engineering principles be used to examine the rare cell types present in tumors, that is, those that are in the "tails" of the distribution of cells in a tumor?
- How do we classify a tumor's phenotype using molecular markers and signatures?
- How do we classify the abnormal phenotype of the multiple cell types in a tumor's microenvironment? Are there overarching information and associated molecular principles that characterize the microenvironment?
- What are true measures of drug efficacy? Is a reduction of 50 percent in tumor volume really of value, or is a reduction in tumor growth rate (or some other critical measure) more appropriate?
- Can accurate measures of in vivo response to therapeutic interventions be developed?
- What role does energy use play in cancer development and metastasis? Are there markers of energy use that would help in diagnosing early-stage cancer or that could serve as an early indicator of disease and/or therapeutic efficacy? Can the metabolic state of a cell be measured with detailed molecular information?
- How do we train the next generation of scientists to be comfortable and conversant in these transdisciplinary fields?

Examples of Early Ideas for Solutions

- Examine cells from primary and malignant tumors and completely characterize their various physical and mechanical properties from a physics/engineering perspective. Such studies may well determine the role of hydrodynamic pressure in drug delivery and ultimately in drug resistance. This knowledge could lead to better therapeutic outcomes.
- Apply biomedical engineering to develop tractable in vitro systems that more closely reproduce in vivo systems.
- Define what happens from a physics/engineering perspective in cancer signaling pathways.
- Create a database of available devices and technologies from physics, mathematics, chemistry, and engineering that would be of value in addressing cancer barriers.
- Use information technologies and Web-based learning tools to enable the development of common language and facilitate communication among disciplines.
- Create summer school short courses to teach biology to physical scientists and the physical sciences to biologists.
- Develop formal opportunities for physical scientists to engage with pathologists and oncologists in order to develop more useful tools and diagnostic technologies that meet real needs.
- Engage physical scientists more fully to define the effects of radiation on tumor cells. There is a large volume of data on the variable response of tumors to what should be lethal doses of radiation that could be assembled.

Summary: Perspectives on Discussions

The session was closed first by Mr. Mittman, who recounted some of the themes that were woven through today's discussions that strongly supported the need for the physical sciences to become actively incorporated into the development of innovative approaches to controlling cancer. Although there was an agreement that an understanding of current cancer biology will be critical across new transdisciplinary efforts, he noted that some of the biggest "home runs" in biomedicine, such as x-rays, NMR, and PET imaging, occurred without a high level of participation by biologists in the early development of these technologies. This is a critical observation, as there is no need for either the physical scientists or cancer biologists to re-invent what the other community does well or has already discovered.

Dr. Barker then summarized what she felt were a few possible common integration points and overarching themes from the day's session. She also noted that these convergence areas could set the stage for the next day's discussions, which would attempt to identify key scientific focus areas and potential approaches for actively engaging physicists, mathematicians, physical chemists, and engineers in a new generation of cancer research.
The key points of convergence included the following:

- **The hallmark of cancer is complexity.** Complexity has long been the focus of the physical sciences, and there is broad and deep expertise that could be invaluable in simplifying and deciphering this complexity. In the day's discussions, it was clear that for these collaborations to be most fruitful, they will require that we set data, technology, and measurement standards and develop some common interface language. The day's deliberations also indicated that some of the pioneering efforts in systems biology could provide leadership in creating this common language but that it will take active buy-in and work by all of the participating disciplines. The NCI's advanced technology initiatives in nanotechnology, genomics and proteomics, and integrated cancer biology are also well situated to provide the tools needed to better explore the daunting complexity that in many ways defines cancer.

- Although hopefully not a revelation that occurred today, the discussion highlighted that **cancer is in fact not exempt from the physical laws that govern the behavior of all other matter in the universe.** However, we know very little about how these very basic physical laws such as short-range forces, hydrostatic forces, energy flows, gradients, mechanics, and thermodynamics, among other properties, are the same or different in cancer versus normal cells and tissues. We have a wide range of nanotechnology and other tools to make these measurements; these are solvable problems.
- **Cancer is an evolutionary process.** This has been a conversation that has waxed and waned in the field of cancer biology for a long time. However, data supporting any or all interpretations of what this might mean in cancer are sparse. From today's discussion, it is obvious that the physical scientists believe this is a critical concept that needs careful examination in terms of its role in transformation to cancer and what follows from these original changes. Evolutional cancer biology is clearly on the minds of this group.
- **Information transfer in cancer is not well understood but is critically important** to unraveling the complexity of cancer and designing innovative approaches for evidence-based treatment, prevention, and early detection. The information transferred between cells in both normal tissue and a tumor is massive, even compared to other complex systems that physicists are studying today. We need to understand this information flow. This is a critically important area for targeted collaboration with physical scientists, as there are well-developed approaches in these fields that may be invaluable in understanding cancer. It is imperative to bring these advanced methods and models into the study of cancer.

Day 3: Thursday, February 28

Robert Mittman reviewed the consensus points from yesterday and outlined the process for the final day of the meeting. He pointed out that the working groups that would convene later in the morning were critical to providing input to the NCI as the Institute considers the options for how best to accomplish its goal to enable integrative strategies that will effectively enable the entry of the physical sciences into cancer research to accelerate progress against the disease.

Keynote Presentation

Dr. Niederhuber then introduced the final keynote speaker for the meeting, Donald S. Coffey, Ph.D. Dr. Coffey, who is a Professor of Urology, Pathology, Oncology, and Pharmacology at Johns Hopkins University, has made seminal contributions in a number of fields, but is perhaps best known for his unparalleled accomplishments in the study of prostate cancer. He added that, if excellence is reflected in the students you train, then Dr. Coffey has exceeded all expectation, having trained several thought leaders in cancer research. However, while these numerous accomplishments should be enough to distinguish any scientific career, it is Dr. Coffey's untiring dedication to innovation, challenging assumptions and dogma, and asking the tough question that sets him apart. Dr. Niederhuber previewed Dr. Coffey's presentation by suggesting that there was no one better to capture these "glimpses across the frontier" and thanked him for his untiring dedication to changing the world.

The Physical Sciences and Cancer Biology: Early Glimpses Across the Frontier
Donald Coffey, Ph.D.

Donald Coffey, Ph.D., Professor of Urology at Johns Hopkins University, began his talk by stating that he is convinced that the cell is an oscillator and that comparing the harmonics of different types of cancer cells may be one way of distinguishing lethal from treatable cancers. Today, we mostly examine dead tissue and static cells, making it impossible to spot these types of dynamic patterns. He suggested that it may be possible to determine whether a cell can be "re-tuned" to revert to a normal metabolic and reproductive state.

Dr. Coffey's presentation then proceeded through a series of interesting observations and equally provocative questions that represented many glimpses across the frontiers of the physical sciences. He noted that life expectancy has increased by 1 year every 4 years over the past 160 years. Plots of male versus female life expectancy are linear with no inflections, even after the discovery of vaccines and antibiotics. He wondered what this observation means in terms of cancer, and he also wondered why female life expectancy has improved more than that for males.

He observed that certain aspects of selected physical parameters in cancer are quantifiable and measurable. For example, measuring the velocity of change in PSA levels among healthy controls, men with benign prostatic hyperplasia, local or regionally confined prostate cancer, and metastatic cancer is predictive of outcome. This argues for a more intensive study of the kinetics of cancer.

He highlighted the fact that in terms of cancer therapy, the academic and private sectors have produced 131 new cancer drugs over the past 26 years that have been clinically tested, FDA approved, and marketed. Nonetheless, we have made only limited progress in reducing the cancer death rate. Obviously, he noted, our current drug development paradigm is not working. In part this is likely because we are developing drugs that meet an endpoint defined by reducing tumor size by 50 percent.

He discussed the universal physical law that prescribes that entropy changes as a system, such as a healthy cell, goes from order to the chaos that is evident in a cancer cell. He then wondered whether this transition can yield some new insights into some of the characteristics that define cancer cells. For example, normal cells do not develop resistance to cytotoxic drugs, but some types of cancer cells develop resistance to all therapies. Research should focus on understanding these differences by studying systems entropy, information transfer, and reactivation and deactivation of evolution in cells. He added that such studies should also try to identify the two types of information flow in a cell: diffusional and vectoral.

Dr. Coffey reminded the attendees that most of the DNA in the human body is not human, but instead belongs to the bacteria in the gastrointestinal tract. These bacteria comprise a complex bioreactor that processes protective agents and carcinogens alike as they pass through the gut. Phytoestrogens, for example, are produced by the intestinal flora, and we have no idea of the role these bacterial metabolic products play in causing or preventing cancer.

He reminded the audience, too, that DNA is the coded range of possibilities for a cell. The structure of the nucleus organizes the decoder of this information, and as in the rest of the cell, there are domains in the nucleus that we do not understand in terms of their impact on mutation and repair, and the transformation of DNA into balanced or unbalanced rearrangement. He also cautioned that DNA is not the entire story, and indeed, RNA is the new frontier for cancer research. Noncoding regulatory RNA comprises 95 percent of the genetic information in a cell. He predicted that studies of RNA folding will provide valuable information, as will studies of DNA folding. Studying nucleic acid folding falls well within the realm of the physical sciences.

He then noted that the earliest premalignant changes leading to human prostate cancer involve dramatic changes in nuclear and cell structure. Indeed, the common denominator of all cancers is morphological change, although not all morphological changes lead to cancer, as evidenced by the fact that 90 percent of all breast and uterine tumors are benign.

Dr. Coffey then spent some time discussing the remarkable tissue specificity of cancer. Carcinogens, he said, are tissue specific, as are prevention and treatment. In fact, the occurrence of cancer is tissue specific; some tissues never develop cancer. Given that only 10 percent of the proteome distinguishes one tissue from another, studies of differential expression of proteins and RNA, as well as differential regulation of DNA expression through methylation and folding, could be fruitful avenues of research. He cautioned that although we are currently thinking of multiple aberrations and systems effects in cancer, we should not lose sight of the fact that a change in one gene can sometimes have a remarkably broad effect in the complex human system. As an example, he described a

medical condition that arises from the deletion of one gene for an androgen receptor; the effect of this one deletion is to produce an XY male with a female phenotype.

Finally, Dr. Coffey discussed the effect of temperature on development and epigenetics and speculated on its role in cancer. One straightforward example of the role that temperature plays on development can be seen in birds, where the male/female ratio is determined by nest incubation temperature. Temperature, he said, can serve as a stressor that changes the epigenetics of the local environment. The organization of chromatin, particularly DNA loop domain organization by the nuclear matrix, is very sensitive to slight changes in temperature. In fact, said Dr. Coffey, he believes that the reason why testicular cancer is so curable, and why Lance Armstrong is alive today, is that the testes themselves are very temperature sensitive, making it likely that testicular tumor cells are extremely temperature sensitive. It may be possible to use new methods to alter highly localized temperatures to develop a new therapeutic approach to treating cancer. He suggested that models such as understanding what triggers a temperature rise in women at the time of ovulation could yield ways of manipulating the temperature of a tumor's microenvironment.

Panel Discussion II

Dr. Coffey's presentation outlined a number of ideas, posed questions, and presented some provocative observations that demonstrated the criticality of engaging the physical sciences in cancer research to accelerate progress. This stage-setting exploration was followed by a panel of researchers who presented specific research from their laboratories that were representative of areas of cancer biology that are already progressing through the integration of aspects of physics and cellular mechanics, nanotechnology, and information theory. Drs. Manalis, Chambers, and Califano each gave insights and specific examples of ongoing research at the intersection of these disciplines that, while at the frontier, all offer a vision of the future.

Current Examples of Contributions of the Physical Sciences to Contemporary Oncology

To stimulate further group brainstorming, three participants each gave short talks on specific examples where the physical sciences are being clearly leveraged to understand and control cancer. **Scott Manalis, Ph.D.,** Professor of Biological Engineering at the Massachusetts Institute of Technology, began by describing a nanoscale cantilever device developed in his laboratory that may allow researchers to develop new cell-based assays that measure the growth of individual cells or organized groups of cells. He first reminded the audience that nanomechanical analysis of cells has already shown that metastatic cancer cells are 70 percent softer than normal cells. Could an understanding of how normal and malignant cells grow in terms of changes in physical properties, such as mass, prove to be diagnostic of early changes that trigger cancer? Dr. Manalis believes that the use of nanotechnology devices such as the one he is developing represents a unique opportunity to measure key parameters of cancer cells in new high-content assays. These approaches provide specificity and quantification missing in many of today's more anecdotal descriptions of cancer cells.

Cancer is posited to be a disease of the cell division cycle, but the relationship between cell growth and advancement through the division cycle is not well characterized or understood, largely because current methods for monitoring the growth of a single cell are not sufficiently precise to yield meaningful data. However, it is possible to measure biomolecules, single cells, and single nanoparticles with femtogram-level resolution in fluid by moving them through a hollow resonator – the nanoscale cantilever – that is suspended in a vacuum. As mammalian cells flow through the oscillator, histograms of their mass can be created with a precision of about 0.01 percent. Ultimately, cells can be recirculated through the nanocantilever, enabling measurement of their mass as they go through the cell cycle to be correlated with fluorescence from molecular reporters. It is also possible to measure cell density by tuning the resonator in an appropriate manner.

Measurements of single cells can sometimes reveal properties that cannot be observed by population-based measurements. For example, prior measurements based on whole cell populations suggest that the cell cycle starts close to the end of the G1 phase. However, measurements based on single cells made by the Zetterberg Laboratory show that the cell cycle starts early in the G1 phase and that there is a variable duration between the start of the cell cycle and the beginning of S phase. Results such as these suggest a number of important experimental questions related to distinguishing normal and abnormal cell growth that could be addressed through the nanotechnologies described:

- Does a single cell grow linearly or exponentially?
- Could such a system be used to determine the mechanisms that make a quiescent cell re-enter the cell cycle?
- Do protein networks that cause excessive tissue growth directly regulate both cell growth and division cycle? Or could size alone advance a cell into the cycle?
- Could tumor cell response to pathway-directed therapeutic agents be classified by measuring growth kinetics?

Ann Chambers, Ph.D., Professor of Oncology and Director of the Translational Breast Cancer Research Unit at the University of Western Ontario, then discussed the mechanics of metastasis. She began by noting that most cancer deaths result from metastasis, which can occur years after apparently successful primary treatment. The seriousness of metastatic cancer is compounded by the fact that nearly all drugs ultimately fail in the metastatic setting. To make real progress in the treatment of cancer, then, it is important to better understand metastasis from a number of standpoints:

- How does metastasis occur biologically, molecularly, and physically?
- What is responsible for tumor dormancy and "reawakening"?
- Can release from dormancy be prevented?
- Can metastasis be prevented or stopped?

Dr. Chambers' approach to studying metastasis is to put a window into the black box of metastasis by using in vivo video microscopy (IVVM) to observe the process as it occurs. The goal is to identify tumor cells and tumors, which are often rare or hidden; to observe the whole process over time to determine the dynamics and kinetics of both invasive and noninvasive metastasis; to characterize both the structure and function of cells and local microenvironments in the development of metastasis; to observe metastasis in multiple organs; and to characterize dormancy versus progressive growth in cancer cells.

Dr. Chambers and her collaborators have observed that metastatic cells get trapped in the smaller blood vessels in organs; indeed, the circulatory system's "wiring diagram" can explain much about which organs are most likely to be affected by metastases from specific cancers. Most circulating cancer cells are arrested in the first capillary bed encountered and do not circulate freely. However, not all filtered cancer cells develop into metastases. Indeed, using IVVM, Dr. Chambers and her collaborators have shown that metastases form from a small subset of cells delivered to a secondary site, while a larger population of potentially metastatic cells remain dormant in the same organ. In a second experiment, using MRI to follow the fate of breast cancer cells metastasizing to the brain, she showed that while many cells lodge in the brain immediately, many die quickly. Interestingly, of the cells that survive, the vast majority remained quiescent, with under 2 percent of the cells in a proliferating state.

Dr. Chambers described a test, known as the Luria-Delbruck fluctuation analysis, to determine what percentage of bacterial cells spontaneously mutate to become drug resistant, a situation analogous

to metastatic cells. The studies showed that highly metastatic cells had a higher rate of mutation than did poorly metastatic cells, which points to the need for further experimentation to discover what produces this higher degree of plasticity in cells that are highly metastatic. Dr. Chambers closed by highlighting a series of important research questions regarding metastasis:

- What affects the number of cells that are delivered to an organ?
- What affects the decision point percentages; that is, what cellular and host factors affect the percentage of cells that are metastatically active?
- What causes cells to become dormant and what affects the percentage of these cells in different models?
- What is required for re-activation of dormant cells?
- How can dormant cells be killed, and would that matter clinically?

In the final panel presentation, **Andrea Califano, Ph.D., Laureate in Physics,** Columbia University, discussed the use of information theory to dissect oncogenic pathways. He began by noting that living systems are close enough to equilibrium to make simulations possible. Indeed, it is now possible to use information theory to dissect transcriptional networks, including the *myc* proto-oncogene network, into a model known as a scale-free network. In this type of network, specific nodes act as highly connected hubs that influence the behavior of large parts of the network.

Dr. Califano described work using information theory to build a model of glioblastoma multiforme (GBM) that identified five transcription factors tied together in a tightly regulated network. This model also generated the hypothesis that two specific transcription factors are the master regulators of the mesenchymal signature of GBM, and co-expression of these two transcription factors reprograms mouse neural stem cells to become mesenchymal cells. Cells expressing these two transcription factors acquire all of the hallmarks of mesenchymal aggressiveness and tumorigenesis in both in vitro and in vivo experiments. Subsequent experiments showed that silencing these two transcription factors using siRNA produced an immediate transformation back to the normal phenotype, with a sixfold reduction in migration and invasiveness. Dr. Califano noted that expression of these two transcription factors correlates with the poorest outcome in human glioma patients.

Using another simulation approach, known as mean field theory approximation, Dr. Califano and his colleagues have also developed a complete interactome for B cells. This interactome provides a new means of interrogating the interaction among genes rather than just the genes themselves. Studies with this model have identified potential oncogenic lesions, perturbation targets, and master regulators. He closed by remarking that these maps can be used to take phenotypic data and discover potential targets for influencing that phenotype.

Brainstorming Session IV

Converging on the Major Areas of the Physical Sciences Critical to Addressing the Identified Barriers

Following the panel presentations, Mr. Mittman solicited additional comments from the group, and several were offered. Two oncologists (Drs. Agus and Kelloff) who are actively involved in clinical research and treating patients offered a list of barriers that they felt should be considered from the clinical perspective. They both expressed their belief that many of these problems can best be addressed through the creation of transdisciplinary teams that can leverage the unique technologies,

mathematical models, and expertise resident in the groups represented. This aggregated list represented strategic actions that might be valuable in discussions of how to remove barriers of clinical relevance in oncology:

- Standardize the collection of patient samples to use with advanced technologies.
- Amplify the target signal for both detection and therapy monitoring.
- Improve imaging to give clinicians better information on tumor size, shape, and growth rate.
- Combine optical imaging with interferometry to detect subtle changes in cells deep within the body.
- Develop and apply nanotechnology methods to overcome the hydrostatic pressure that blocks delivery of drugs to tumors.
- Develop methods to determine how much drug is getting into the target organ/tumor.
- Create new software algorithms to process imaging data to detect subtle changes in tumor activity in a therapeutic setting.
- Use new micro/nano-fluidic approaches to concentrate and identify rare tumor cells. Exploit the Warberg effect - apparent preference of cancer cells for low-efficiency metabolic pathways for energy utilization to improve therapy.
- Develop new methods to administer drugs other than intravenously.
- Determine how to measure blood flow to tumors, e.g., changes in VEGF therapy.
- Focus specifically on the development of technologies that can find tumors of 1,000 cells instead of a million to a billion cells.
- Determine the behavior of normal single cells compared with single cells from the bulk tumor.
- Use nanoparticles to study cell internalization pathways to improve drug delivery.
- Quantify the state of cells that transition from normal to premalignancy.

The Working Groups

In the final activity of the meeting, the attendees broke into four working groups focused on the following overarching emergent themes from the meeting:

Group 1: Cancer's Complexity
Group 2: Information Transfer and Cancer
Group 3: Universal Physical Laws and Principles in Cancer (1) (energy flows, signaling, cancer in space and time, role in evolutionary adaptation)
Group 4: Universal Physical Laws and Principles in Cancer (2) (forces, gradients, pressure, cancer in space and time)

The four working groups met and, under the leadership of a co-chairperson, considered their charge, which included detailing the specific barriers in the area considered; specific research questions of high importance; needed/required disciplines; required resources; and anticipated results. The reporter from each of the working groups summarized their consensus suggestions and ideas in each of the areas requested. These suggestions were presented and discussed in the final session of the meeting, which follows.

Brainstorming Session V

Report from the Working Groups: Bringing It All Together—Input on Specific Barriers, Scientific Focus and Problem Areas, Disciplines, Personnel and Other Resource Needs, and Anticipated Outcomes

Group 1 Report: Cancer's Complexity (Drs. Donald Coffey and Joseph DeSimone, Co-chairs)

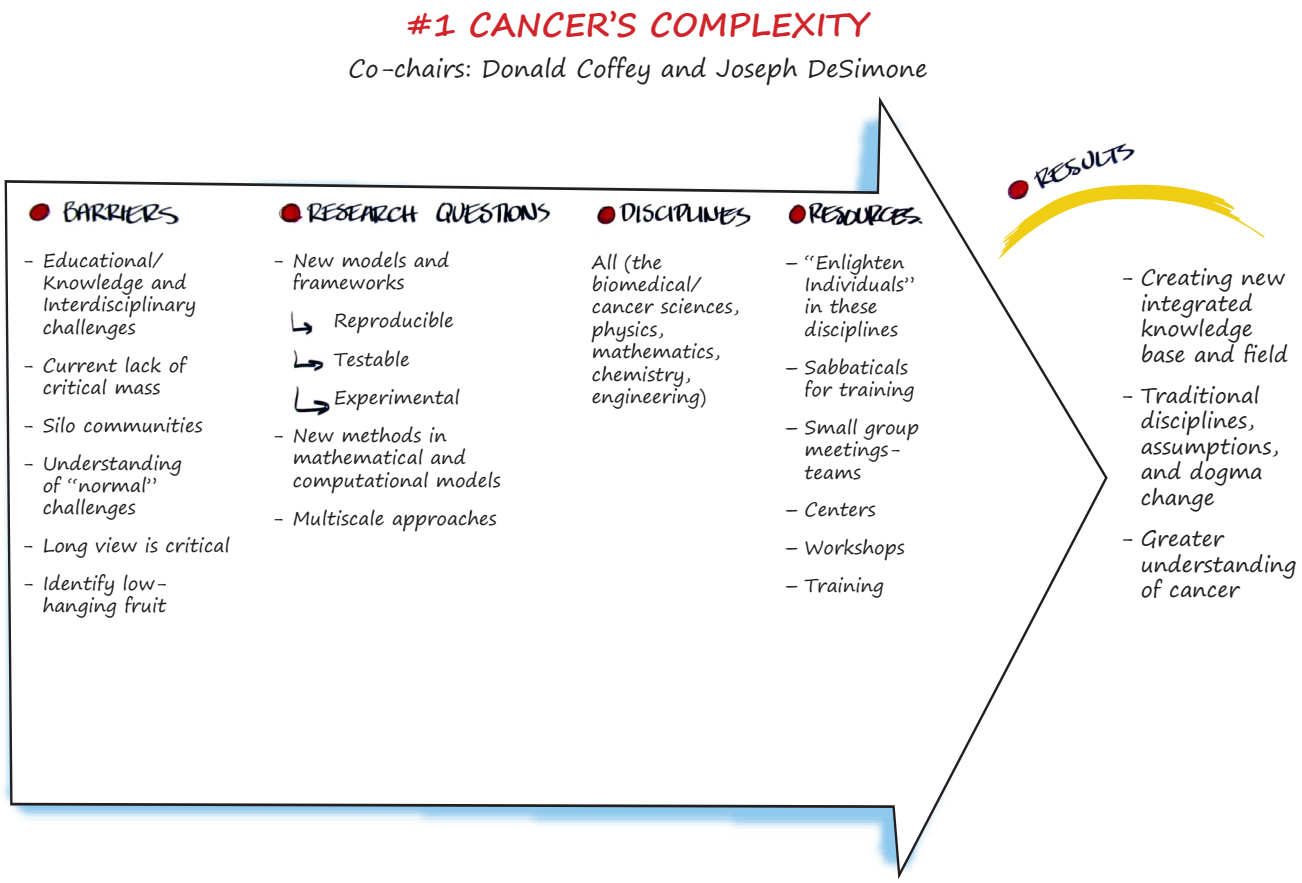
This group began by stating that its members found it almost impossible to describe what complexity is and what "normal" represents, but that even though they could not come to a consensus on what constitutes complexity in biological systems, there were plenty of opinions on how to tackle these intertwined problems. In its deliberations, the group agreed that understanding complexity and what constitutes a normal level of complexity versus the enormous complexity inherent in cancer will be addressed only through a sustained, multiyear effort involving the active participation of and interactions among researchers from a wide range of disciplines spanning the biological and physical sciences. This would be "big science." The fact that there are educational and language barriers among these groups and that they tend to work in silos today means that the NCI has a major challenge in supporting efforts to break down language and departmental barriers. Centers of Excellence would be one way of accomplishing this by institutionalizing transdisciplinary activities. Whatever mechanisms NCI uses to support such transdisciplinary activities, they should include provisions that emphasize short-term successes as proofs of principle for such an approach, as well as the longer term projects that are necessary to truly address the barriers of complexity in normal and cancerous states.

In terms of research questions, the working group voiced the opinion that there is a critical need for reproducible models and frameworks that can be tested and verified through experimentation. Given that mathematical modeling in cancer is early in its development, a major effort will be needed to recruit expertise from the physical sciences to advance modeling toward a firm theoretical and mathematical foundation. There is also a need to develop multiscale approaches, and given that multiscale systems are tough to tackle even in simpler materials science applications, let alone in biology, this represents a challenging endeavor that could attract top researchers from the physical sciences. The group also debated the difference between irreducible complexity and reducible complexity, and the need for good data to begin to define these two sides of the same coin.

In terms of resource needs, the working group felt that it was critical to let multidisciplinary research communities self-assemble around various aspects of these research questions. The working group offered that the opportunity to build centers, along the lines of the Centers of Cancer Nanotechnology Excellence (NCI Alliance for Nanotechnology in Cancer), that have some flexibility to recruit both permanent and visiting staff, may be a productive approach. The working group also recommended that there would be value in funding workshops to build relationships, seed new idea-focused groups, and develop grant mechanisms to support some smaller groups, as was done with the NCI's nanotechnology program. The working group also strongly supported the need to develop training programs that would create a new generation of researchers who could work across these disciplines. The bottom line is that such efforts will create a new field of research, one that will undoubtedly overturn some of today's dogma and generate new ideas that will enable every area of cancer research.

In the large-group discussion that followed, it was noted that there is no good resource available that could help senior faculty determine where to send postdoctoral fellows or graduate students for training in methods related to the study of complexity. One participant offered that the NCI's Integrative Cancer Biology Program (ICBP) does study complexity, but that the research funded by the ICBP should move beyond the current focus on conventional studies. The NCI was commended for its plans to create transdisciplinary teams and centers with a focus on applying principles and research strategies from the physical sciences to remove barriers in cancer. Although these new approaches

are likely to be productive and produce new opportunities for progress, the NCI will need to create a set of metrics for use by study sections to judge the productivity of these efforts. It was suggested by another contributor that California's Institute for Quantitative Biosciences could serve as an additional model for studying complexity in a transdisciplinary setting. Finally, it was noted that the complexity issue really revolves around subcellular measurements, for which there is a shortage of data that many new microfluidic and nanoscale imaging technologies may be able to address.



Group 2 Report: Information Transfer and Cancer (Drs. Robert Austin and Raju Kucherlapati, Co-chairs)

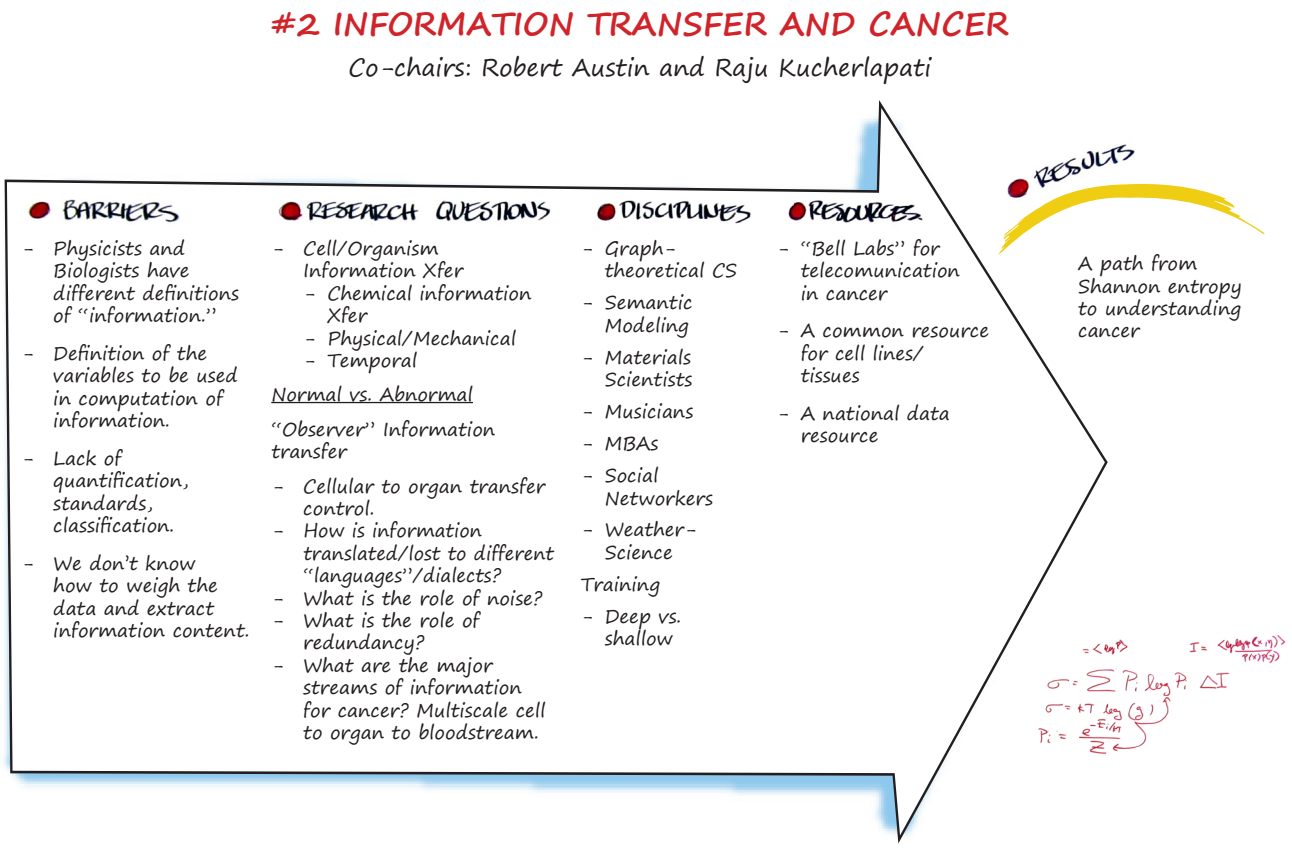
The second working group began its report by noting that physicists have one definition of information, while biologists have a much broader definition of information. The ensuing discussion reiterated the need for a common language at these emerging interfaces. Some of the definitional barriers include coming to an understanding as to the variables that need to be used in a computation and the data precision required to test computational models of information transfer. The lack of standards in data quality and data representation are also important barriers.

In terms of research ideas, the working group concluded that any model of information transfer will require accurate measures of chemical, physical, and mechanical information on multiple temporal and spatial scales, from both normal and malignant cells. Researchers from the different disciplines will need to determine how to measure information flow at the subcellular level and to develop techniques to monitor information flow control. The role of noise (what it is and what it means) in biological systems needs to be determined, as does the role of the redundancy present in mammalian information processing and control networks. Another important research focus must also involve identifying the major streams of information in cancer at all scales ranging from intracellular to multicellular to whole organs and even the bloodstream.

Addressing these research problems will require computer scientists with graph theory expertise, semantic modelers, engineers with expertise in materials science and condensed matter, and musicians; MBAs who learn how to manage projects and information flow, and social networking theorists; and meteorologists, who have learned how to process massive amounts of information efficiently. The working group also noted that training should involve depth in one discipline and opportunities and the resources to branch out into other areas; knowledge that is too shallow will not lead to new important insights.

In considering the resources needed to address these research problems, the working group suggested looking at the Bell Laboratory model that successfully tackled and solved many multidisciplinary problems. Beyond that, the group suggested that the NCI establish a national common oncology resource of cell lines and tissues as well as a national data resource. The results of this effort could be a path from Shannon's entropy – a measure of uncertainty – to a better understanding of cancer.

There was a lively discussion following this presentation. A few participants remarked that precise data are a key driver to the development of models of information flow and that standards are needed to ensure that data are usable in model testing activities. One attendee remarked that bacterial quorum sensing might serve as a useful model system for application to cancer, while another suggested that information flow might be modeled using coupled harmonic oscillators. In a final comment, one researcher noted that there is a difference between information and knowledge; that is, to be considered successful, any modeling effort must be able to shed light on how cancer functions.

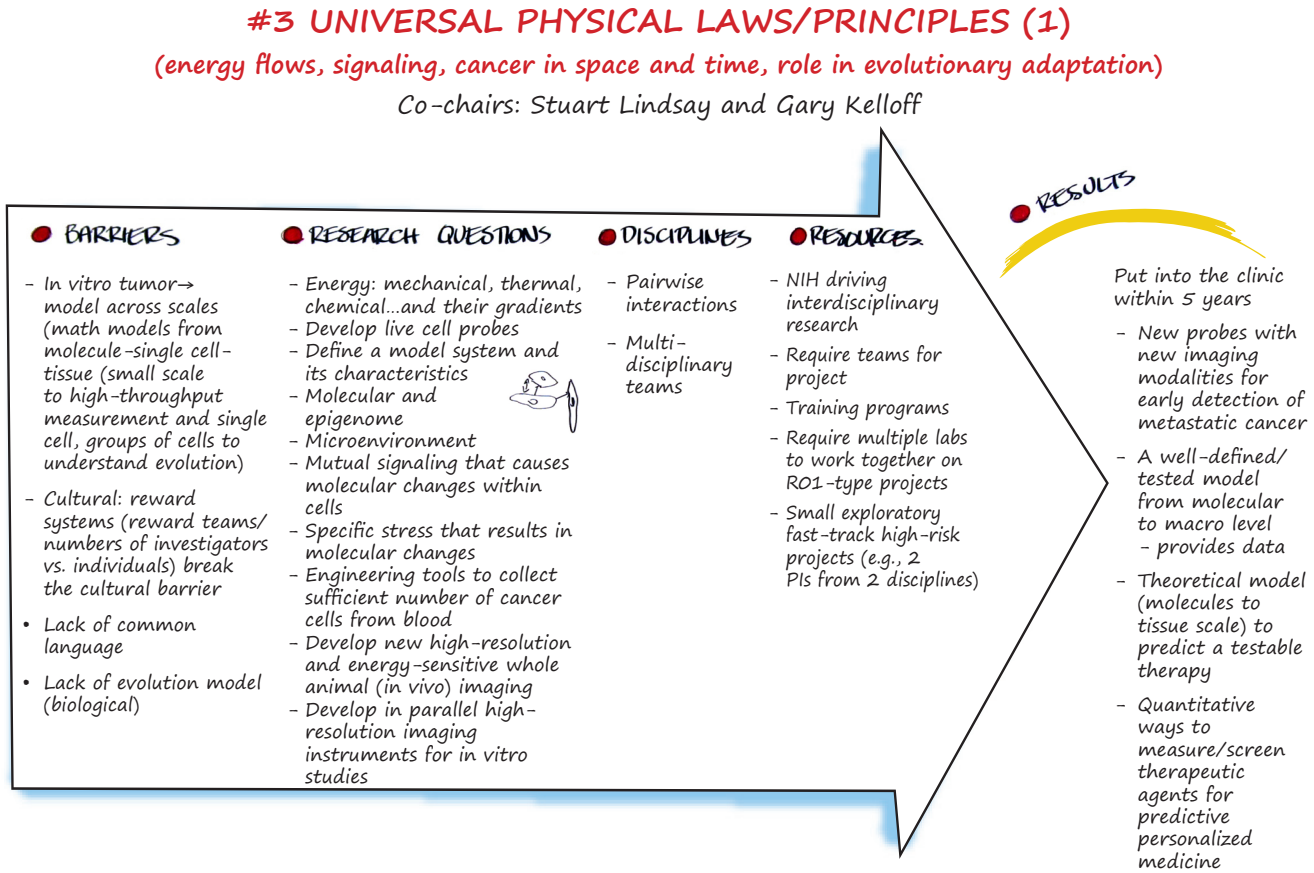


Group 3 Report: Universal Physical Laws and Principles (energy flows, signaling, cancer in space and time, role in evolutionary adaptation) (Drs. Stuart Lindsay and Gary Kelloff, Co-chairs)

Two groups divided the range of critical physical principles and laws that are undoubtedly important in understanding and controlling cancer. Group 3 identified two major barriers: (1) there currently are no model systems that contain enough complexity, perhaps on the order of a million cells, that can be interrogated simultaneously at the level of each individual cell, and so complexity is not yet reducible, and (2) cultural barriers represent significant impediments to progress.

This group identified a number of key research issues and questions. Specifically, they singled out the need for tools to measure energy flow in cells, and among collections of cells, at a variety of levels including mechanical, thermal, and chemical. To reduce this to a tractable problem, the working group suggested that well-defined model systems might help to establish baseline, universal characteristics of the different components of a tumor. There is also a need to measure energy flow over a relatively long time dimension to account for the slower growth of eukaryotic systems. Such extended temporal energy flows may be important in studying cancer from an evolutionary perspective.

To address fundamentals of signaling, there is a need for methods of collecting cancer cells from blood in order to study these rare cells for any differences that exist between those potentially metastatic cells, nonmetastatic malignant cells, and normal cells. There is also a need for three-dimensional, multicellular model systems that more accurately reflect the local signaling that is likely occurring between a malignant cell and its microenvironment. As an extension of this type of model, new methods are needed to image multiple cell types simultaneously in vivo in order to track signaling processes, energy flow, and temperature gradients in the heterogeneous tumor environment.



This working group felt that pair-wise interactions among different disciplines would be a good way to start attacking these problems. To foster such interactions, the NCI needs to more rigorously promote interdisciplinary and transdisciplinary, team-based science as a means of sending the various communities the message that such efforts are valued by funding agencies. Training grants to encourage cross-disciplinary education are also essential to expanding this new field and bridging communication gaps between laboratories now working in separate fields. It is important for the NCI to use a mix of grant mechanisms, ranging from centers to smaller seed grants, to team people who would not normally have a reason or the mechanisms to work together.

As far as results are concerned, the members of this working group felt that an early win could be the production of new imaging probes and imaging modalities that could enable early detection of cancer. The group also thought that it should be possible to develop well-defined and validated model systems of complexity that are addressable at the individual cell and even individual molecule levels. Such models could serve as test beds for cancer studies and provide predictive capabilities for treatment. The working group was also optimistic that multidisciplinary teams could develop assays that would provide quantitative measures of therapeutic efficacy, enabling oncologists to personalize therapy quickly.

The ensuing open discussion included a caution that there is a need to look beyond the atomic and molecular levels to the level of domains, which is where function and evolution occur. It was also suggested that the new genetically defined mouse models of human cancer could serve an important role in creating the models of cancer complexity. Another attendee suggested that the field might establish models using tissues that are normally resistant to cancer formation and determine what knowledge can be gained by attempting to induce tumor formation in those tissues.

Group 4 Report: Universal Physical Laws and Principles (forces, gradients, pressure, cancer in space and time) (Drs. Ken Dill and James Olson, Co-chairs)

The second working group that examined another group of physical laws and principles began by noting that we have a poor understanding of how an individual cell works at a fundamental, integrated level. However, the quest to remedy that knowledge deficit will certainly benefit from bringing new expertise to the table. Physical scientists can contribute technologies, data management expertise, new materials, and a variety of analytical techniques that could span both reductionist and systems-based approaches.

This working group spent time discussing how technology development could help address some of the barriers identified at the meeting. One approach would be to develop real-time remote sensing in multiple dimensions at a resolution of parts per billion or better. This effort could be aided by thinking about how electromagnetic energy interacts with matter, a focus for the physical scientists. Another approach would be to develop technologies that can measure the forces involved in cellular processes so that models could begin to measure and report the mechanics of living cells and organs. In the area of drug delivery, there is a need for new technology that can go beyond simple ligand binding assays and produce data on location, binding kinetics, cell uptake, and intracellular processing.

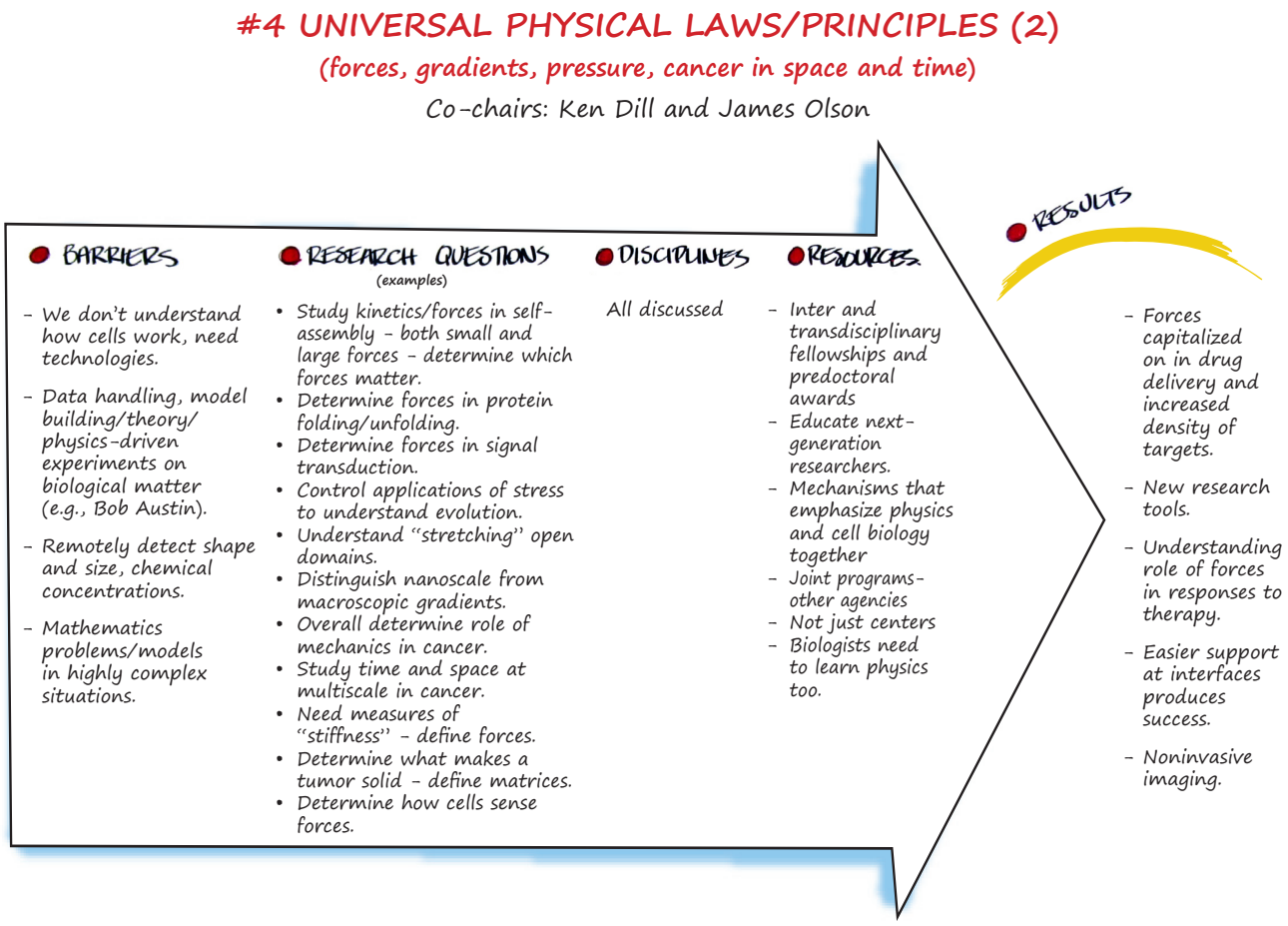
New areas of experimentation and nonequilibrium statistical analysis are needed to examine the tails of distributions of cellular events. By better understanding the rarer events represented by the distribution of responses observed in collections of cells, we may gain a better understanding of how heterogeneity impacts tumor development. Three-dimensional bioreactors, used in conjunction with new nanotechnology-based sensors and molecular beacons, may also help by affording the opportunity to monitor how cells function and respond to carefully controlled and varied conditions, both individually and as organized collections of cells.

This group commented that there was some concern in their discussions as to how to ensure that deep innovation could and would occur in transdisciplinary centers. The group voiced a need for also funding interdisciplinary and transdisciplinary fellowships for postdoctoral fellows and training grants for graduate students.

The working group members felt that addressing the major barriers highlighted would enable multidisciplinary teams to develop a compendium of first principles that would lead to mechanistic models of cancer. These models, in turn, could be used to better understand drug target selection, drug delivery, and drug resistance. Much of the data needed to build such complex models will come from long-term, stable research efforts that are not driven by the study of one disease. Results of these studies will create a foundation for advances in cancer management and detection.

In the discussion that followed, it was recommended that the NCI should work with the U.S. Department of Energy and U.S. Department of Defense laboratories to determine how technologies developed at those facilities could be brought to bear on the problems of cancer. Other comments supported the use of centers as places where technical expertise and tools can be used by researchers from multiple disciplines in an atmosphere that encourages out-of-the-box thinking. The general consensus seemed to be that centers are an important mechanism, but that they should not be the only one.

A number of participants offered that meetings such as this one could actually do a great deal to facilitate understanding across fields and stimulate new cross-disciplinary collaborations and suggested that the NCI should develop a meeting series from this inaugural meeting and continue both this think-tank format and smaller meetings that could focus on the major convergence areas



identified in this first forum. Meetings such as this are particularly important to "jump start" what amounts to a new field, and these types of opportunities raise awareness and encourage cross-talk among disciplines.

Summary and Next Steps

In closing, Dr. Barker thanked everyone for being active participants over the 2 days of deliberations and discussions. She noted that this was a landmark meeting in that it included leaders from the fields of physics, mathematics, physical chemistry, and engineering together with cancer biologists and oncologists. The immediate results are impressive, with the emergence of a number of innovative ideas and new directions for cancer research. In the longer term, this think tank has the potential to achieve the desired outcomes envisioned for the meeting and beyond. Dr. Barker noted that cancer biology has made enormous progress in the past few years, but the field may well be at a watershed moment, a point where overcoming major barriers to progress will require active engagement of the physical sciences. The cancer biology community by itself is unprepared to solve the difficult transdisciplinary problems such as biological complexity, information transfer, and tumor cell evolution identified in this meeting. In addition, cancer biology is at a point where we must look deep into the physical laws and principles that impact and control basic cancer processes.

Dr. Niederhuber also thanked the participants, telling them that he had learned a great deal about the relevance of the physical sciences to understanding the development of cancer and potentially more effective solutions. The group clearly converged on a number of very important areas with the potential to produce real progress against cancer. Although he could not say specifically how the NCI would leverage the information and ideas generated during this think tank, he pledged that indeed there would be followup. His thoughts were that the outcomes would be carefully considered and additional smaller workshops convened to further explore and define the major areas identified. He was confident that the NCI would rely on the output from the meeting and the assembled expertise for future guidance on how best to capitalize on the strategic research opportunities identified by this extraordinary group. He noted that the NCI will also look carefully at ways to leverage the wide range of government resources available to increase the participation of the physical sciences community in cancer biology and oncology. Cancer, he reiterated, is a model for all diseases, and if we can show that physics, chemistry, mathematics, and engineering can advance the field of cancer, then all areas of medicine will benefit.

The think tank concluded with a statement from Dr. Barker that a report would be forthcoming, and that the NCI would also develop a Web site to capture the major presentations and brainstorming sessions. The longer term intent is to utilize this Web site for communications on the follow-on activities that derive from this meeting.

Appendix

During the course of the think tank "Integrating and Leveraging the Physical Sciences to Open a New Frontier in Oncology," a graphic facilitator kept an ongoing graphic record of the deliberations in real time. These two figures reflect the richness of two of the brainstorming sessions: Session 1, where participants identified the barriers to progress that exist in cancer research today, and Session 2, which captured the range of ideas/concepts/approaches from the physical sciences with real promise to remove some of the barriers identified. If you are interested in other graphics from the meeting, you may view them at http://otir.cancer.gov/physicalsciences-oncology/.

Figure 1. Brainstorming Session I: Relevant Scientific Barriers Blocking Progress in Cancer Research

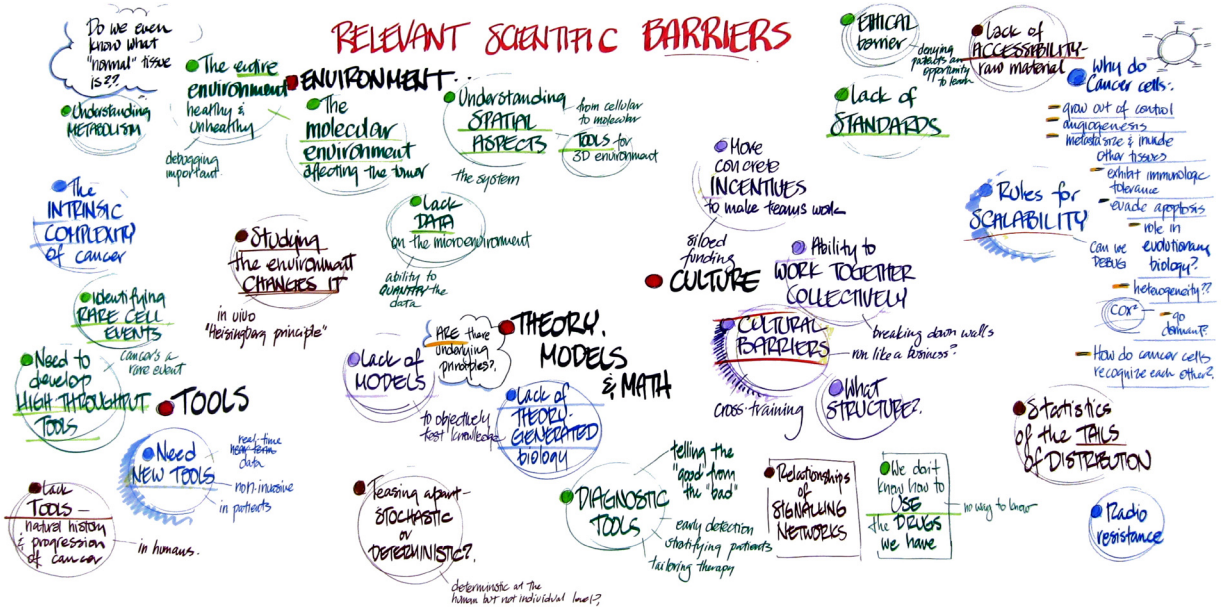
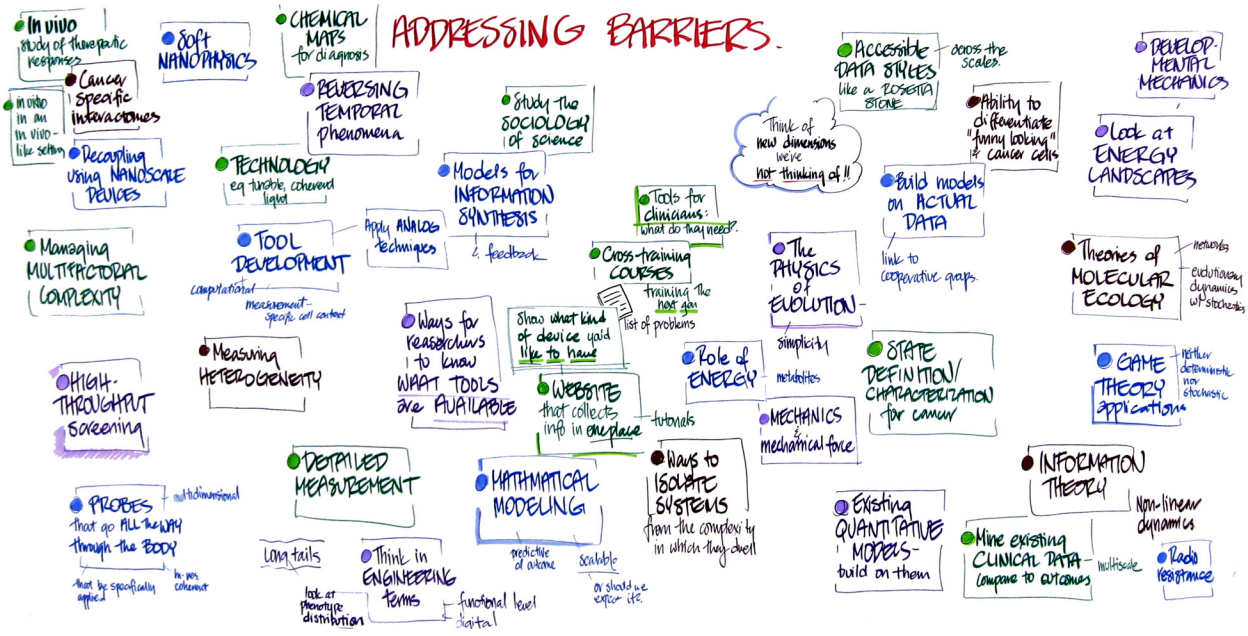


Figure 2. Brainstorming Session 2: Ideas/Concepts From the Physical Sciences That Represent Important Strategies to Address and Remove Barriers in Oncology



Meeting Agenda

Integrating and Leveraging the Physical Sciences to Open a New Frontier in Oncology

February 26-28, 2008

Tuesday, February 26, 2008

5:00 p.m. - 6:00 p.m.	**Registration**	
6:00 p.m. - 7:15 p.m.	**Reception and Buffet Dinner**	*Grand Ballroom Salon III*
7:15 p.m. - 7:25 p.m.	**Welcome and Introductions** Anna D. Barker, Ph.D. Deputy Director National Cancer Institute, NIH	*Grand Ballroom Salons I and II*
7:25 p.m. - 7:45 p.m.	**Background and Introduction of Keynote Speaker** John E. Niederhuber, M.D. Director National Cancer Institute, NIH	
7:45 p.m. - 8:45 p.m.	**Keynote Presentation** ***Confronting Complexity: Cancer at the Intersection of Physics and Biology*** Paul Davies, Ph.D. Professor of Physics Director, Beyond Institute Arizona State University ***Questions and Discussion***	
8:45 p.m. - 9:00 p.m.	**The Why, What, and How of the Think Tank—Introduction of Robert J. Mittman** Anna D. Barker, Ph.D. Deputy Director National Cancer Institute, NIH	
9:00 p.m. - 9:10 p.m.	**Expectations** Facilitator: Robert J. Mittman, M.S., M.P.P. Founder/President Facilitation, Foresight, Strategy	

Wednesday, February 27, 2007

7:00 a.m. - 8:00 a.m.	**Continental Breakfast**	
8:00 a.m. - 8:30 a.m.	**Introductions and Welcome** Anna D. Barker, Ph.D. Deputy Director National Cancer Institute, NIH	*Grand Ballroom Salons I and II*
	Process and Flow for the Think Tank Facilitator: Robert J. Mittman, M.S., M.P.P. Founder/President Facilitation, Foresight, Strategy	
	Introduction—Keynote Presentation	
8:30 a.m. - 9:15 a.m.	**Keynote Presentation** ***"State of the Science" in Cancer Research: Potential for the Physical Sciences to Remove Major Barriers*** John E. Niederhuber, M.D. Director National Cancer Institute, NIH	
9:15 a.m. - 10:15 a.m.	**Brainstorming Session and Group Discussion: Relevant Scientific Barriers Blocking Progress in Cancer Research** Facilitator: Robert J. Mittman, M.S., M.P.P. Founder/President Facilitation, Foresight, Strategy	
10:15 a.m. - 10:30 a.m.	**Break**	
10:30 a.m. - 11:15 a.m.	**Keynote Presentation** ***21st Century Physics—Relevant Intersections With Barriers in Oncology*** Robert H. Austin, Ph.D. Professor of Biophysics Department of Physics Princeton University	
11:15 a.m. - 12:15 p.m.	**Brainstorming Session and Group Discussion: Ideas/Concepts From the Physical Sciences That Represent Important Strategies to Address and Remove Barriers in Oncology (including solutions to nonbiologic problems that may be relevant)** Facilitator: Robert J. Mittman, M.S., M.P.P. Founder/President Facilitation, Foresight, Strategy	
12:15 p.m. - 1:15 p.m.	**Lunch**	

Wednesday, February 27, 2007 (continued)

1:15 p.m. - 2:15 p.m.	**Brainstorming Session and Group Discussion: Integrating Physical Chemistry, Mathematics, and Systems Models Into a Transdisciplinary Approach to Cancer Research** Emmanuele DiBenedetto, Ph.D. Centennial Professor of Mathematics Vanderbilt University James R. Heath, Ph.D. Elizabeth W. Gilloon Professor California Institute of Technology Mina J. Bissell, Ph.D. Distinguished Scientist Life Sciences Division Lawrence Berkeley National Laboratory	
2:15 p.m. - 3:00 p.m.	**Keynote Presentation** ***The Integration of Systems Thinking, Emerging Technologies, and the Biological, Physical, and Computational Sciences to Attack the Challenges of Cancer*** Leroy Hood, M.D., Ph.D. President Institute for Systems Biology	
3:00 p.m. - 3:30 p.m.	**Discussion: Role of Advanced Technologies in Enabling the Convergence of the Physical Sciences and Cancer Biology**	
3:30 p.m. - 3:45 p.m.	**Break**	
3:45 p.m. - 5:00 p.m.	**Framing and Prioritizing the Most Relevant Barriers in Cancer Research as Viewed From the Physical Sciences** ***Table Discussions: Finalizing and Prioritizing Key Barriers and Identifying Key Areas of Physics, Mathematics, and Chemistry to Meet Challenges Through Transdisciplinary Centers*** Facilitator: Robert J. Mittman, M.S., M.P.P. Founder/President Facilitation, Foresight, Strategy	
5:00 p.m. - 5:15 p.m.	**Perspective on Today's Discussions** Discussant TBA	
5:15 p.m. - 5:30 p.m.	**Plan for Tomorrow**	
6:30 p.m.	**Reception and Dinner**	*Ristorante Murali* *Pentagon City*

Thursday, February 28, 2008

7:00 a.m. - 8:00 a.m.	**Continental Breakfast**	
8:00 a.m. - 8:15 a.m.	**Review of Day 1** Facilitator: Robert J. Mittman, M.S., M.P.P. Founder/President Facilitation, Foresight, Strategy	*Grand Ballroom Salons I and II*
8:15 a.m. - 9:00 a.m.	**Keynote Presentation** ***The Physical Sciences and Cancer Biology—Early Glimpses Across the Frontier*** Donald S. Coffey, Ph.D. Distinguished Professor of Urology Johns Hopkins University	
9:00 a.m. - 10:30 a.m.	**Brainstorming Session and Panel Discussion: Current Examples of Contributions of the Physical Sciences to Contemporary Oncology** ***Nanotechnology: Capitalizing on the Physical Properties of Cancer Cells for New Intervention Strategies*** Scott R. Manalis, Ph.D. Professor Massachusetts Institute of Technology ***Questions and Answers*** ***Interrogating Cancer: The Mechanics of Metastasis*** Ann F. Chambers, Ph.D. Professor University of Western Ontario ***Questions and Answers*** ***Information Theoretic Approaches to the Dissection of Oncogenic Pathways*** Andrea Califano, Ph.D., Laureate in Physics Professor Columbia University	
10:30 a.m. - 10:45 a.m.	**Break**	
10:45 a.m. - 12:30 p.m.	**Converging on the Major Areas of the Physical Sciences Critical to Addressing the Identified Barriers** ***Group Discussions: Concept Development Group Input and Recommendations***	
12:30 p.m. - 1:30 p.m.	**Working Lunch** Work groups continue and prepare to report out.	

Thursday, February 28, 2008 (continued)

1:30 p.m. - 3:00 p.m.	**Brainstorming Session—Bringing It All Together: Input/Recommendations, Specific Scientific Focus and Problem Areas, Disciplines, Personnel and Other Resource Needs, and Key Specific Challenges for Transdisciplinary Physical Sciences-Oncology Centers**
3:00 p.m. - 3:15 p.m.	**Break**
3:15 p.m. - 3:30 p.m.	**Summary of Our Collective Thinking** Anna D. Barker, Ph.D. (Discussant) Deputy Director National Cancer Institute, NIH
3:30 p.m. - 4:00 p.m.	**Summary and Next Steps** John E. Niederhuber, M.D. Director National Cancer Institute, NIH

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