Testimony

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National Cancer Institute Research: Today's Progress; Tomorrow's Challenges

Statement of
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Good afternoon, Chairman Pallone and members of the Subcommittee. Thank you for the opportunity to testify this afternoon. I am Dr. Anna Barker, Deputy Director of the National Cancer Institute within the National Institutes of Health (NIH), an agency of the Department of Health and Human Services. I also serve as the NCI Deputy Director for Strategic Scientific Initiatives, a program focusing on trans-disciplinary programs in strategic areas of cancer research and advanced technologies including programs such as: the Nanotechnology Alliance for Cancer; The Cancer Genome Atlas (TCGA); the Clinical Proteomics Technologies Initiative for Cancer and Physical Sciences-Oncology Centers. It is my privilege to appear before you today to share some exciting new advances in our understanding of a disease that is tragically familiar to each of us.

Unfortunately nearly everyone has a personal story to tell of the toll taken by cancer. One out of every three women and one out of every two men in America will develop cancer over their lifetime. In addition to the enormous physical and emotional toll it takes, cancer represents a huge economic burden to the U.S., amounting to over $200 billion in total healthcare costs in 2004.[1] NCI's key challenge is to understand the changes in the genome and associated biology that ultimately cause cancer in order to enable the development of more effective diagnostics, therapies, and prevention strategies that can be delivered to cancer patients.

Cancer is an extraordinarily complex disease of uncontrolled cellular growth, proliferation, and spread beyond the original tumor. Cancer is also an integrated network of signaling pathways and chemical interactions between the cancer and its human host. In fact, cancer is a large number of different diseases – over 200 – and many of these cancers may be comprised of a number of different subtypes, depending on which pathways are altered by changes in the cancer genome. These changes result in uncontrolled growth, and once cancer spreads (metastasizes), it is extremely difficult to control.

In the 1980s, new tools in molecular biology led to the discovery that cancer is a disease of genetic alterations – some are inherited and others after birth due primarily to environmental exposures. Clearly the complex of environmental exposures that impact all of us plays a major role in who gets cancer and the mechanism by which it occurs. For example, environmental factors such as radiation can cause changes in genes (mutations) that increase cancer risk – and these changes, called somatic mutations, are responsible for most cancers. Some people inherit genes that may predispose them to cancer – but many people who inherit these genes never progress to cancer. Therefore, it is critical to systematically explore how environmental factors combine with genetic variants to produce cancer. For example, in one such study, researchers are assessing breast cancer risk during puberty following specific environmental exposures.

The current convergence of advances in molecular biology and advanced technologies is already beginning to transform our understanding of the mechanisms by which cancer arises in humans. Increasingly, knowledge of the genomic changes in selected cancers is beginning to allow oncologists to categorize cancers based on technologies that define these alterations These molecularly-based subclasses of cancers are beginning to support the development of more specific diagnostics through specific disease biomarkers – and drive the discovery of new cancer drug targets.

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[1] Smith BD, Smith, E, Hurria, A, et al: Future of Cancer Incidence in the United States: Burdens Upon an Aging, Changing Nation. J Clin Oncol published ahead of print on April 29, 2009 at http://jco.ascopubs.org/cgi/content/abstract/JCO.2008.20.8983v1

Ultimately, knowledge that is deriving from 21st century biomedical and cancer research will allow us to move from a "one size fits all" approach to disease – from a chemotherapeutic approach to cancer, for example – to safer and more effective interventions tailored to each individual's genetic makeup. NCI has developed a number of programs that are aimed at harnessing the power of molecularly-based interventions for cancer – ranging from studies that define specific changes in the genomes of cancer patients to nanotechnology-based diagnostics. As the cost of sequencing the human genome continues to fall and bioinformatics facilitates the availability of an electronic medical record that captures all of a patient's data, the next 10 to 20 years promises to transform the way cancer is diagnosed, treated, and prevented. The following is a brief sampling of recent advances in cancer research that highlights and supports the promise of personalized cancer medicine.

Recent Advances in Understanding the Genetics of Cancer

Well before the $1000 genome becomes a reality, advances from genome research are already leading to important new understanding of the role of genetic changes in a number of common cancers. For example, use of a technology called Genome-Wide Association Studies (GWAS) scans the genomes of many individuals to identify markers that may predict whether or not an individual may be susceptible to the development of a specific cancer. These studies have already shown that, generally, multiple genetic changes are required for an individual to be predisposed to developing cancer. GWAS also is proving invaluable in identifying genetic changes that are predictive for how an individual may metabolize a specific drug. This is proving especially valuable in reducing side effects in patients.

The Cancer Genome Atlas

In 2005, the National Cancer Institute and the National Human Genome Research Institute launched a groundbreaking collaboration called The Cancer Genome Atlas (TCGA) to ultimately identify and catalogue all of the relevant genomic alterations in most types of cancer. TCGA employs state of the art genomic characterization and sequencing technologies, engages a network of multidisciplinary centers that involve over 200 experts in genomics and cancer biology and all of the data is placed in a public database. TCGA is the largest and most comprehensive analysis of the molecular basis of cancer ever undertaken which has faced and overcome a large number of technical and scientific challenges in its three year pilot period. In addition to achieving the goal of establishing the network and supportive structure for this first-ever large-scale, high-throughput cancer genomic program –TCGA has already produced scientific advances in the most common form of adult brain cancer (glioblastoma multiforme, or GBM), ovarian and lung cancers.

Because of TCGA's enormous potential, NIH chose it as one of seven "signature projects" to receive special emphasis using American Recovery and Reinvestment Act of 2009 (ARRA) funds. Utilizing the latest technologies and molecular insights, TCGA is expanding its scope, to explore approximately 20 additional tumors over the next 5 years – 10 in the two years of the ARRA funding period. Results from TCGA will for the first time map the complex pathways involved in specific cancers which will re-define cancer targets and provide a rational basis for the development of new targeted diagnostics and therapeutics.

In 2008, the first major results of the TCGA pilot program produced a map of the three key pathways that are disrupted in glioblastoma – and defined the four specific molecular subtypes – paving the way for identifying the right patient for the right drug. Another exciting and unexpected finding points to a potential mechanism of resistance to a common chemotherapy drug used for brain cancer – which will influence clinical practice almost immediately. Although quite different from GBM, the TCGA team has discovered a large number of large scale genomic alterations called copy number changes in the DNA of patients with ovarian cancer. The value of TCGA will ultimately be measured in many advances – but perhaps one of the most striking is the value of the integration and analysis of multidimensional data to fully understand all of the genomic changes that impact the biology of specific cancers. We have seen unprecedented new investigations and interdisciplinary collaboration as these data become accessible to so many scientists. NCI has made a major commitment of ARRA funds to collect the tissues for TCGA sequence the genes and integrate and analyze the vast amount of data coming from the project. The rate-limiting step in TCGA is high quality samples; and NCI is working with survivors and advocates to ensure that cancers such as pancreas, melanoma, gastric cancer and other rare tumors are able to enter TCGA as soon as possible.

The Next Generation of Cancer Treatments

Prior to the emergence of the molecular diagnostic field, cancers were categorized solely by pathology, i.e., according to their appearance under a microscope. However, programs such as TCGA are changing this picture by producing molecular "maps" that allow scientists to determine how genes and proteins are interacting in a cell. This approach focuses upon patterns – gene and protein activity patterns – in different types of cancerous or precancerous cells. Molecular diagnostics uncovers these sets of changes and captures this information as expression patterns of the proteins that are coded for by the changes in DNA. Also called "molecular signatures," these expression patterns are improving clinicians' ability to diagnose cancer more specifically. This new approach extends to treatment as well as diagnosis, with the recent emergence of therapies specifically designed to hit a specific target defied by a molecular signature.

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. By focusing on molecular and cellular changes that are specific to cancer, targeted cancer therapies promise to be more effective than other types of treatment, including chemotherapy and radiation, and less harmful to normal cells. Molecularly-targeted cancer treatments are expected to yield the next generation of therapies that complement, or even replace, today's standard therapies for most cancers. The classic example is Gleevec, a small molecule drug that targets a class of overactive proteins formed due to a genetic change related to uncontrolled tumor growth. NCI-funded research on Gleevec has shown it to be highly effective for treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors.

A Coordinated Cancer Platform

NCI is initiating a number of key programs that will link the genomics of cancer with new ways to diagnose and treat the disease. The first step will be to ensure the availability of high-quality human biospecimens for cancer research, accomplished through the cancer human biobank (caHUB). TCGA and other high-tech initiatives demand the highest quality tissue, blood, and tumor samples, all rigorously and ethically collected, properly stored, and extensively annotated. caHUB, begun in 2009 after several years of work developing techniques and best practices, will be a national biobank: a repository for difficult-to-obtain biological materials and associated data that can be used for medical research and the sophisticated molecular assays necessary for identifying biomarkers that are key to understanding the biology of specific cancers.

Biomarkers and Proteomics

One of the key challenges in oncology is determining when and why cancer may recur in treated patients. Today, biomarkers, which are parameters that can be measured that reflect the biology of the disease, or in some cases the therapeutic effects of treatments, represent one of our best strategies to address these hurdles. These "biomarkers" of cancer can be measured through a variety of means, including dynamic imaging tests and laboratory tests on blood, tissue, and other biologic samples. The measurement of these parameters reflects changes in genes, proteins, or some combination that tell a story of the state of the cancer in a patient. The NCI is actively investigating biomarkers through TCGA, an initiative in clinical proteomics, and working with other sectors through several partnerships. One such unique collaboration is the Biomarkers Consortium, a public-private partnership organized and managed by the Foundation for the NIH (FNIH) with funding provided by philanthropic groups and industry. The Consortium is currently investigating fluorodexyglucose-positron emission tomography (FDG-PET) as a potential biomarker in clinical trials for lung cancer and lymphoma. These studies could have significant impact on patient management by validating a tool that can identify response to treatment and facilitate drug development.

A related area of examination involves determining what proteins are expressed in patients as a result of the various genetic changes identified by large-scale genomics programs such as TCGA. NCI has undertaken a program called the Clinical Proteomics Technology Initiative to develop needed standards for the discovery of proteins, so they can serve as biomarkers. There are clearly large numbers of proteins that are important in the development and maintenance of cancer, but the technologies, reagents and assays to measure them must be standardized and transferable across laboratories to maximize benefit to patients. Proteins are likely our best hope to identify cancer early from small amounts of blood – meaning they offer great hope to improve screening assays for a number of cancers. NCI is assembling new transdisciplinary teams to harvest the promise of biomarkers for both cancer diagnosis and new targeted drug development through a number of strategies – one of the most promising and exciting at the intersection of molecular biology and advanced technology is the area of nanotechnology for cancer. Cancer's complexity and the numbers of biomarkers that will be needed to diagnose and treat cancer will require new experimental platforms that can capture and multiplex large numbers of different parameters that define the state of the cancer.

Nanotechnology

Because of their small size, nanoscale devices can readily interact with biomolecules on both the surface and inside cells, giving them the capability to detect disease and deliver treatment in ways unimagined before now. Nanotechnology has the potential to enable all areas of cancer research including improving molecular imaging, early detection, cancer prevention, and treatment. In 2004, the National Cancer Institute established the NCI Alliance for Nanotechnology in Cancer program. The network is built on a strong foundation of superb science and technology development and is designed to accelerate the application of nanotechnology to remove some the major barriers in clinical oncology and basic cancer research.

One example of an exciting advance in nanotechnology involves the use of gold nanoparticles coded with "barcode" DNA to allow ultrasensitive detection of cancer biomarkers – six times greater than conventional assays. The technology has already been translated to bedside and has demonstrated preliminary success in clinical evaluations of the prostate cancer samples of approximately 400 patients, with a larger study currently being planned. Other advances that have derived from this multi-disciplinary program include a nanotechnology platform to detect multiple biomarkers of brain cancer and delivery of nanoparticles that contain a promising new cancer therapy called small interfering RNA (siRNA) directly to cancer cells. This type of drug delivery has already shown promising results in a small Phase I study of pancreatic cancer, a highly lethal type of cancer for which there are few treatment successes. The Alliance has placed significant emphasis on translating nanotechnology to patients, and as a result over 50 companies have been formed from these efforts over the past 5 years.

A New Framework of Physical Sciences

Understanding cancer at a fundamental level depends on more than just defining the genomic changes that characterize these diseases, as cancer occurs in space over time. To build a new framework for the advances and data that are deriving at a dizzying pace from present day cancer research, the NCI has created an unprecedented scientific network called the Physical Sciences-Oncology Centers (PS-OCs) program. These centers bring together teams of experts in the physical sciences with cancer biologists and oncologists to work together in innovative ways to understand how the physical forces in cells and organs impact on the expression of genomic changes that drive cancer biology. The fields of physics, mathematics, chemistry, engineering and biology are all working together to ask questions such as: How does evolution affect the way we look at cancer? How is information transferred and translated in cancer cells? What impact do the physical laws that govern the universe have across the scales ranging from molecules and atoms to whole organisms? It is anticipated that the PS-OCs will generate new bodies of knowledge that define the physical, chemical, and engineering processes that operate in cancer. Some examples of work already in progress at the POCs include examination of the physical dynamics of cancer progression, selective metastasis and specific mechanical properties of cancer cells. Studying cancer cells and tumors in terms of their physical properties will open new areas of research to drive the development of better diagnostic and treatment strategies for cancer (e.g., physical properties as potential cancer signatures).

We at NCI are proud of the progress we have made, excited by the opportunities that lie ahead, and challenged by the daunting amount of work that must yet be done. We are dedicated to achieving a future where the shadow of cancer is removed from our lives and those of our children and grandchildren. This increasingly seems like an achievable future - as thousands of dedicated intramural and extramural scientists work tirelessly to make personalized cancer medicine a reality for every American.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee might have.

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Dr. Barker serves as the Deputy Director of the National Cancer Institute (NCI) and as the Deputy Director for Strategic Scientific Initiatives. In this role she has developed and implemented multi/trans-disciplinary programs in strategic areas of cancer research and advanced technologies including: the Nanotechnology Alliance for Cancer; The Cancer Genome Atlas (TCGA); and the Clinical Proteomics Technologies Initiative for Cancer. She participates actively in these programs, and serves in a team leadership role for TCGA. Recently she led the development of a new initiative to develop a network of trans-disciplinary centers focused on the elucidation of the "physics" of cancer at all scales through the establishment of Physical Sciences-Oncology Centers. Dr. Barker has also led and collaborated on NCI's effort to develop contemporary resources for cancer research in the areas of biospecimens and bioinformatics (The Cancer Bioinformatics Grid) to support molecularly based personalized medicine. She serves as the co-chair of the NCI-FDA Interagency Task Force; the co-chair of the Cancer Steering Committee of the FNIH Biomarker Consortium; and oversees the NCI's pilot international cancer research programs in Latin America and China.

Dr. Barker has a long history in research and the leadership and management of research and development in the academic, non-profit and private sectors. She served as senior scientist and subsequently a senior executive at Battelle Memorial Institute for 18 years where she developed and led a large group of scientists working in drug discovery and development, pharmacology, and biotechnology, with a major focus in oncology and NCI supported programs. She co-founded and served as the CEO of a public biotechnology drug development company and founded a private cancer technology focused company. She has served in numerous volunteer capacities for cancer research and advocacy organizations including the AACR where she led the Legislative Affairs Committee for ten years and was a member of the Board of Directors. She has received a number of awards for her contributions to cancer research, cancer patients, professional and advocacy organizations and the ongoing national effort to prevent and cure cancer. Her research interests include small molecule experimental therapeutics, tumor immunology, and free-radical biochemistry in cancer etiology and treatment. Dr. Barker completed her M.A. and Ph.D. at the Ohio State University, where she trained in chemistry, immunology and microbiology.