National Cancer Institute

The Nation's Investment in Cancer Research

AN ANNUAL PLAN AND BUDGET PROPOSAL FISCAL YEAR 2011

Connecting the Nation's Cancer Community

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

On the Cover
Peter A. Pinto, M.D., NCI Urologic Oncology Branch

Carole A. Parent, Ph.D., NCI Laboratory of
Cellular and Molecular Biology

Melanoma cell observed under ion-abrasion scanning electron microscopy, a strategy for 3D imaging of biological specimens/Credit: Donald Bliss (National Library of Medicine) and Sriram Subramaniam (NCI)

Director's Message

Grasping opportunity is rarely easy and never simple. Nor is it for the timid, requiring wisdom and forethought, grounded in a keen sense of the possible. Opportunity always involves some risk-taking. For those of us at the National Cancer Institute, it is also built on an abiding sense of duty, of responsibility to every cancer patient.

Indeed, cancer remains a scientific and medical challenge of singular difficulty. For everyone who comes to work at NCI, the urgency of our mission is ever present. Each day in our clinical center, we see the anguished faces of those who suffer from this disease. We understand the sting of cancer that grips far, far too many of our fellow citizens. We know that cancer's losses sometimes seem unbearable — at a family dinner table where an empty place setting is the reminder of a loved one taken away, or in the laugh of a lost child now consigned to an increasingly distant memory. We dedicate our work to those who have faced cancer, to those who will face cancer, and to those who hold tight to their loved ones at the most vulnerable of moments.

It is, thus, with the greatest sense of mission that NCI can report real progress against many forms of cancer and, even more importantly, exciting opportunities that lie ahead. Biomedical science's understandings of the inner workings of the cancerous cell and the host tissue in which it resides are accelerating at an unprecedented pace. Genomic research is contributing — virtually on a daily basis, it often seems — to our catalogue of knowledge about the mutations, genomic alterations, and processes of cancer. In an era when targeted cancer therapies are no longer a prediction but an accumulating reality, the challenge we face is to continue to turn groundbreaking science into lifesaving care, at an even greater speed.

This document is the story of opportunity: how NCI is exploiting the confluence of unexpected new financial resources and a steady stream of scientific and technological advances, in order to make strides in cancer risk reduction, early detection, patient care, and survivorship.

NCI has a vision for a unified, comprehensive system of cancer research and care, in which every new cancer patient is part of a nationwide research cohort — genomically characterized, tracked, secured, and linked through an electronic cancer health record. We see a future in which new therapies are tested more efficiently, beginning with evidence of efficacy, viewed from inside the tumor. We envision a care system where access to science and cancer treatment of the highest caliber are available to all patients, in our major university-based cancer centers and in the communities where they live. We are working for a day when the American story of all forms of cancer will be about survivorship, about a once-fatal disease — a disease that is cured or a disease turned into a chronic one. And we are committed to the kind of medical diplomacy that helps all nations of the world achieve greater success against their cancer burdens.

This document is about the initiatives NCI has begun or strengthened, to guide cancer research through the remaining years of the 21st century. These plans and programs, if nurtured in the years ahead, hold great promise of unprecedented progress. They also remind us of the economic force that is cancer research, bringing and sustaining quality jobs in communities across the nation.

Over my career — as a physician-researcher, surgeon, professor, medical school administrator, NIH advisor, and cancer center director — I have been privileged to work with outstanding professionals deeply committed to cancer research and care. As National Cancer Institute director, I come to work each day with a dedicated group of individuals who are the envy of the world. Together we work to support the nation's investment in cancer research, a workforce thousands strong and unflinchingly dedicated to a common purpose. It is an honor to lead them, both intramural and extramural, to represent their achievements, and to boldly promise that NCI recognizes, and will firmly grasp, every opportunity for continued progress. Our country and our patients are counting on it.

John E. Niederhuber, M.D.
Director, National Cancer Institute

Introduction

In early February 2009, just weeks into President Obama's administration, the National Cancer Institute was poised for positive news. Congress appeared to be heading toward an omnibus spending bill for the 2009 fiscal year that would give NCI a budget increase of just over 2 percent. While still somewhat lower than the biomedical research inflation rate, such a potential raise — NCI's first budget increase in four years — was a most welcome possibility, especially during a difficult economic downturn. Also that February, rumblings from Capitol Hill suggested that the Institute might receive as much as $125 million, to be spread across two years, through an economic stimulus package. It was clear that these two potential infusions of resources would require careful planning and coordination, to make sure every dollar had the greatest possible impact on the nation's cancer research infrastructure.

A month later, everything changed.

It began February 17, at the Denver Museum of Nature and Science, where President Obama — sitting at a desk in front of a row of American flags, with Vice President Biden looking over his shoulder — put pen to paper and, four days after Congress' passage, signed the American Recovery and Reinvestment Act into law. At its core, the $787 billion legislation was about jobs and the American

President Obama signs ARRA into law in Denver, Colorado
Credit: Official White House Photo by Pete Souza

economy: creating and preserving employment and spurring economic activity. "It's about rising to the moment when the moment is hard, converting crisis into opportunity, and seeing to it that we emerge from whatever trials we face stronger than we were before," the President said at the signing ceremony.

This economic stimulus package — ARRA, as it became widely known — turned out to be much more. The law allocated $10.4 billion to the National Institutes of Health for biomedical research and support. President Obama expressed his hope that "this investment will ignite our imagination once more, spurring new discoveries and breakthroughs in science, in medicine, in energy, to make our economy stronger and our nation more secure and our planet safer for our children."

Ultimately, ARRA brought $1.26 billion in new funds to NCI, to be obligated in the remaining seven months of the 2009 fiscal year and in 2010. But the news of 2009 did not end there.

On March 10, Congress completed action on the Omnibus Appropriations Act of 2009. Signed by the President the next day, this legislation brought NCI a budget increase of approximately $138 million, or 2.9 percent. With the enactment of that second bill, the careful planning and coordination NCI had begun a month before took on a new sense of urgency — and the air of a once-in-a-lifetime opportunity.

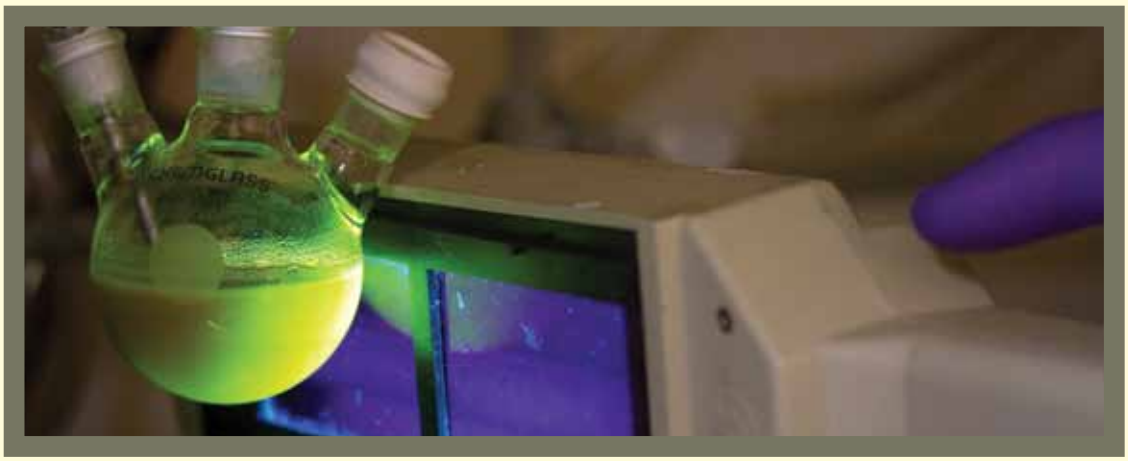
Opportunity, however, is not created by dollars alone. It is the confluence of unexpected funding with progress in the nation's outstanding cancer research laboratories that creates exceptional potential. Yet, at the NCI, our hopes for progress in the very fundamental aspects of scientific discovery are always balanced against human need. Cancer, we know all too well, remains a very complex and formidable foe. A recent study predicted that if more progress against the disease is not forthcoming, the number of cancer cases in the United States could reach 2.3 million by the year 2030, a 45 percent increase from the 1.6 million estimated new cases predicted in 2010.

Management of an institute as large as NCI cannot ever be a static process. America's cancer research enterprise is continually growing, as it should be, and at the same time, it is becoming more technologically intricate and sophisticated. Virtually any budgetary increase will quickly be overtaken by demand, particularly in an era of complex and expensive genomic research. In any year, NCI leadership must carefully look at the Institute's

entire portfolio, carefully considering where programs can be eliminated or curtailed, in order to redirect resources to pressing and emerging areas of research opportunity. That managerial process was no different for 2009, even with the increase to NCI's appropriated budget. Increase or not, funding the best science requires clear-eyed analysis and foresight.

The unexpected fiscal infusion from ARRA presented a unique set of challenges. First was the ever-present reminder that this was about employment. (As of January 2010, ARRA had created or saved about two million jobs). But it was also about the President's challenge to advance science. ARRA came with unprecedented requirements for reporting — about dollars spent, jobs created, and the status of projects — all to be publicly available. In addition, it was mandated that ARRA funds and appropriated funds could not be mingled in any way, as if they were different colors of money. The hurdles of process and review for NCI were well-defined; in the months that followed, the staff of the Institute showed it was more than up to the challenge.

Setting clear priorities. Individual investigators conducting hypothesis-driven science remain the lifeblood of NCI. It was clear, from the beginning of NCI's planning, that the majority of ARRA dollars would go to supporting their work.



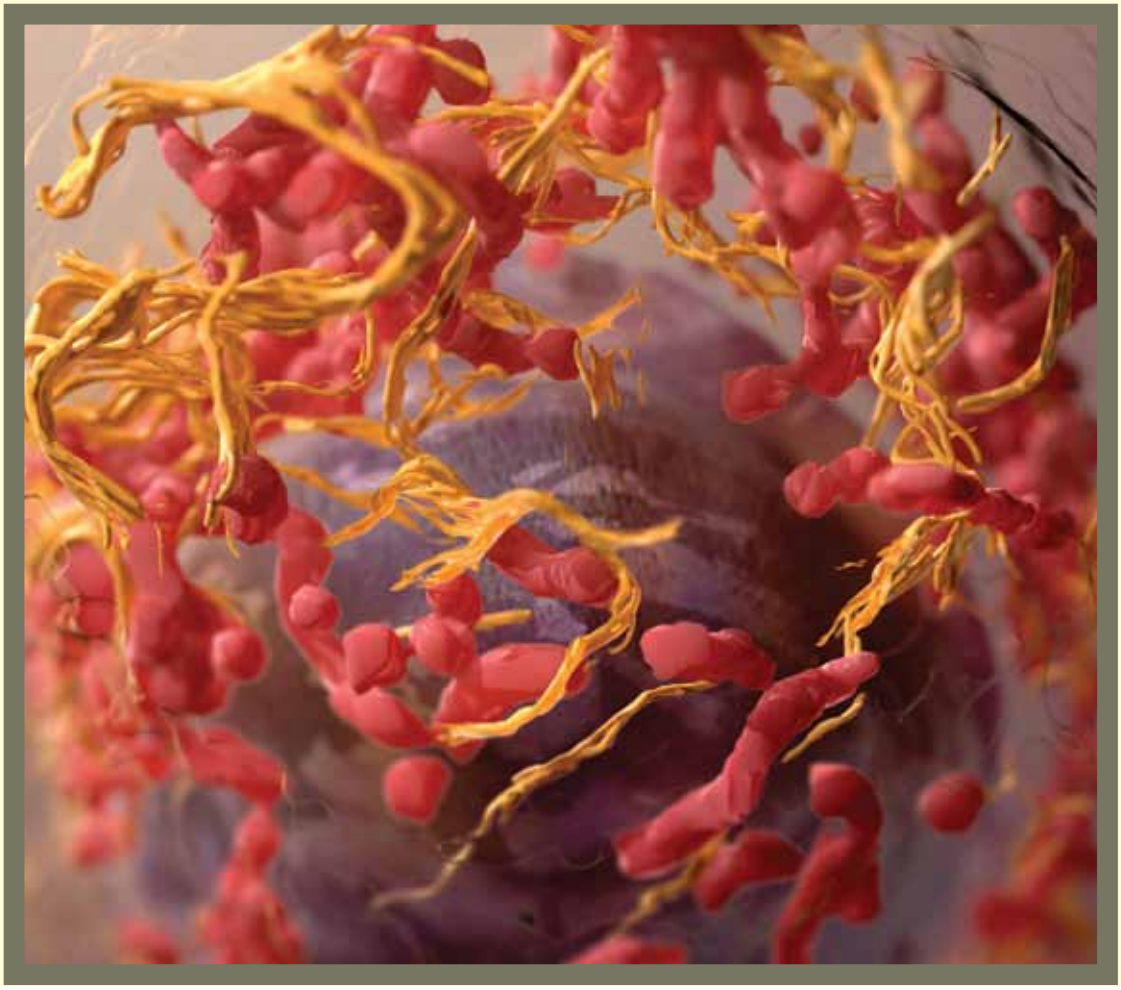
Quantum dots used to detect cancer shown in laboratory flask at the Johns Hopkins Engineering in Oncology Center

"This investment will ignite our imagination once more, spurring new discoveries and breakthroughs in science, in medicine, in energy, to make our economy stronger and our nation more secure and our planet safer for our children." —President Barack Obama

During deliberations on ARRA priorities, NCI's executive leadership came to believe that these dollars could also be used to launch new initiatives that hold immense potential to alter the future of biomedical research: programs and projects of great magnitude with large-scale resource requirements that otherwise would have taken many years to begin.

Among those initiatives, NCI is committed to even more deeply studying the human genome and the genetics of cancer; developing a manifest vision for the development of new, targeted therapies; devising streamlined and innovative approaches to clinical research and clinical trials; bringing the fruits of our science to patients in the communities where they live; eliminating the all too common inequities of cancer care; and investing in supporting technologies and infrastructure that will make it possible to enter this new era of personalized, highly prescriptive cancer medicine.

It is our hope that this document will help you better understand the science — and the scientific careers — that ARRA has made possible and, in the end, the progress that we can more rapidly attain, if these initiatives see continued and robust financial support. It is truly a story of progress for cancer patients.



Melanoma cell observed under ion-abrasion scanning microscopy, a strategy used for 3-D imaging of biological specimens
Credit: Donald Bliss, National Library of Medicine, and Sriram Subramaniam, NCI

Supporting Individual Investigators

Biomedical science clearly depends on ideas and on the researchers who pursue them: individual scientists, driven by hypotheses and dedicated to rigorous research methods that, over the course of time, lead to scientific discovery. These are dedicated women and men who work at the laboratory bench or in the clinic (or, in some cases, both), in the belief that intense investigation will make a life altering difference for cancer patients. At NCI, the RPG, or Research Project Grant, has long been the mainstay of scientific investment and progress. The researchers NCI supports, the majority of whom work in our country's great research universities, are also the professors who nurture, develop, and mentor new, young scientists. Those scientific careers — both established and emerging — have been of great concern during the past five years. As budgets remained flat, when adjusted for medical inflation, NCI was required to reduce spending by up to $175 million per year, in order to redirect or reprogram funds to be able to fund new initiatives. Over the past decade, anecdotes of dwindling laboratory staffs and young scientists turning away from biomedical research have echoed more and more frequently through the cancer community.

Mindful of the clear and present need, it was NCI's top priority in 2009 to bolster support of individual investigators. Using appropriated dollars, we were able to increase funds for established investigators and new grantees, the associate and assistant professors whose professional development and hopes for academic tenure are frequently hinged to an NIH grant. Using separate infusions of ARRA funds, we were able to fund even more investigators, although in many cases for just two years. All told, NCI awarded 5,461 RPGs in fiscal year 2009 (4,918 grants funded with appropriated dollars, bolstered by 543 ARRA grants), a 5.5 percent increase over fiscal year 2008.

Additional ARRA resources have been dedicated to supplementing existing grants. NCI has also developed recruitment packages that assist new faculty members, and the universities for which they work, in starting their research programs; incentives to help bring established investigators back to cancer research; and methods of support designed to draw together as diverse a research community as possible.

The mere possibility of ARRA support led to a groundswell of applications, particularly through two trans-NIH opportunities: Challenge Grants, which address specific scientific and health research challenges in biomedical and behavioral research that will benefit from significant two year jumpstart funds, and Grand Opportunities grants, which are being used to support high impact ideas that lend themselves to short-term funding and may lay the foundation for new fields of scientific inquiry. While great care was taken to ensure that the finest science was funded, many meritorious proposals still went unsupported. Hence, NCI expects that many of those unsuccessful applica-

tions may come back as applications for RPG support in the 2011 fiscal year.

THE BOTTOM LINE. Laboratory research is an iterative process that does not lend itself to showing progress according to a date on the calendar. Consequently, after ARRA funds are expended, there is no doubt that many investigators will return to NCI, seeking continued support. In order to continue funding promising research, and maintain the RPG success rates that ARRA made possible, NCI would require an additional $310 million in the 2011 fiscal year.

Advancing Genomic Science

Cancer is an extraordinarily complex disease of uncontrolled cellular growth, proliferation, and spread, combined with very unique networks of chemical interactions between the tumor and its host.

The disease is not singular in definition, but differs according to the organ site of origin; it often has important genetic and phenotypic subtype differences within the same site — breast or lymphoma, for example — and differences between primary and metastatic sites, as well as between young patients and older patients. Cancer relies on many communication pathways in the cell, and it utilizes the seemingly normal microenvironment of the tumor for nourishment and support. Yet, cancer begins in our DNA. Its origins may come from the genes we inherit from our parents; it may arise from the changes to our genes that accumulate over a lifetime — or to the regulatory systems within the genome that control how the genes code for and assemble their specific proteins. Environmental factors, from tobacco use to pollutants in the air we breathe, to chemicals and infectious agents, may play roles as well. All of these areas clearly demonstrate the importance of studying the genome, both of healthy people and of the cancers they develop.

Without any doubt, the completion of the Human Genome Project in 2003 opened a new era of science. That landmark effort completed a catalogue of the thousands of protein-encoding genes in the human genome. The challenge of cancer science is to apply that knowledge to the treatment of disease.

In 2005, NCI and the National Human Genome Research Institute launched what has rapidly become one of the most significant efforts in genomic science: The Cancer Genome Atlas. TCGA is a large-scale, high-throughput, multi-institutional effort to sequence and characterize the genetic and epigenetic changes associated with the development of cancer. It is an enterprise born of technological advances but sustained by scientific prowess. TCGA is this nation's largest comprehensive effort to apply our knowledge of the normal human genome sequence to a very complex disease.

Because of the investment in the Human Genome Project, today's sequencing technology has greatly increased capacity and speed, with rapidly falling costs. What once took tens of millions of dollars and years to accomplish can now be done in about a week for $10,000 or less, thanks to next-generation sequencing technology. The day of the $1,000 genome, sequenced nearly in real time, is no longer a futurist's vision.

In its pilot phase, TCGA set out to sequence the genomes of three cancers: glioblastoma, lung cancer, and ovarian cancer. As important as sequencing — creating the catalogue, if you will — is genomic characterization. Such analysis takes huge volumes of raw sequencing data, from the hundreds of tumors sequenced, and documents the mutations, changes in gene copy number (duplications of the same gene), translocations, and other alterations of the genome and epigenome that are associated with the particular cancer under study.

In glioblastoma, TCGA has identified four distinct subtypes of the disease that will help to stratify patients into different treatment regimens — to make clear what therapies would have greater or equally important benefit for certain patients.

As will be discussed later in this document, TCGA will be a key driver of future research, as scientists translate this new knowledge into targeted therapies.

Because of TCGA's enormous potential, the National Institutes of Health chose it as one of seven Signature Projects to get special emphasis under ARRA. Utilizing the latest technologies and techniques, TCGA is expanding to probe 20 or so additional tumors in the next two years.

NCI has, in the past, also supported a similar program directed at the genomic characterization of pediatric cancer known as Therapeutically Applicable Research to Generate Effective Treatments, or TARGET. The TARGET initiative utilizes the power of modern genomics research technologies to identify new therapeutic targets for childhood cancers. The success of this pediatric project and TCGA led to assigning $25 million in ARRA funding to TARGET, which will enable expanding the research scope from a current focus on acute lymphoblastic leukemia and neuroblastoma, to at least five more pediatric cancers for which current treatments are deemed inadequate. NCI is merging our efforts in pediatric tumor sequencing and genomic characterization to maximize the ability to bring the best minds and experience to work in this field, across the spectrum of all cancers — pediatric and adult — so that the knowledge gained can have optimal impact.

THE BOTTOM LINE. The genomic analysis of all major tumors, along with a host of rarer types, will be critical to continued research progress against cancer and will continue long after ARRA funds are expended. NCI will be pushing the TCGA project to complete sequencing with FY 2011 funds of 2,400 cancer genomes and matched normal tissues from 17 tumor types. Continuing to support NCI's activities in TCGA and TARGET would require an additional $27.5 million in the 2011 fiscal year.

Ronald DePinho, M.D., Dana-Farber Comprehensive Cancer Institute

"Generals and soldiers" and "enemies and holding the line" sound like battle paradigms for the Army or Navy, but in the eyes of Ronald DePinho, M.D., professor of medicine at Dana-Farber Cancer Institute in Boston, these are perfect analogies for how TCGA is approaching cancer and its genetic underpinnings. "For the past several decades, we knew where 5 to 10 percent of the enemy troops were, meaning we had discovered about 5 to 10 percent of the genes responsible for cancer. Soon, TCGA will provide us with full visibility of the enemy troops, along with strong strategy opportunities and points of attack."

Many new genetic aberrations have come to light in just the few years that the TCGA project has been up and running — more than had been previously thought possible. Recent research at Dana-Farber demonstrates the progress that has been made in the area of genes and cancer causation. For example, the ALK (anaplastic lymphoma kinase) pathway has been identified as a significant target for intervention. A new investigational drug, developed to selectively attack the ALK mutation in lymphoma may also be a viable treatment option for people suffering from another form of cancer, non-small cell lung cancer, because researchers have found that this disease also demonstrates an aberrant ALK pathway alteration and activation.

Although TCGA is providing a treasure trove of data, it is still a first step. The next step is to understand the functional relevance of these mutations. Moreover, said DePinho, "Cancer is not a simple collection of a few genetic alterations, occurring in a monotonous collection of tumor cells, but an intricate organ system with cellular complexities including interactions with surrounding host cells."

We now know that an increasing number of tumor genes will need to be identified in order to develop effective, targeted therapeutic agents for cancer. Scientists must first identify "driver" genes and distinguish these from irrelevant "bystander" genes. Then, those hundreds to several thousands of genetic elements of interest must be functionally analyzed to determine the mission critical events, which perhaps boil down to a few dozen genes that are driving the biology of these cancers and their response to therapies, DePinho added. "Moreover, we need to further distinguish those genes that initiate the cancer processes from those that are responsible for the maintenance of established tumors. These tumor maintenance events will represent the best strategic points of attack, leading to more durable responses."

Returning to his battlefield analogy, DePinho said that maintenance genes are the generals — their extinction will stop most tumors — but some genes develop bypass mechanisms. Investigators must identify how this bypass happens and combat these rogue genes with new combination drug therapies for cancer, similar to the multi-drug strategy that is often employed against bacterial infections.

Today, DePinho continues to work in his lab discovering the underpinnings of cancer by using TCGA-generated data in conjunction with mouse models of human cancer. These studies evaluate the roles played by growth-promoting oncogenes and tumor suppressor genes that

Ronald DePinho, M.D., Dana-Farber Cancer Institute/
Credit: Sam Ogden, Dana-Farber

constrain growth and/or stimulate differentiation. In recent work, with collaborators Samir M. Hanash, M.D., Ph.D., of the Fred Hutchinson Cancer Research Center in Seattle, and Nabeel Bardeesy, Ph.D., from the Massachusetts General Hospital in Boston, a panel of proteins linked to early development of pancreatic cancer in mice was identified that also applies to early stages of pancreatic cancer in humans. This is a breakthrough that brings scientists a significant step closer to developing a blood test to detect the disease early, when cure rates are highest.

Facilitating Genomic Study

The Cancer Genome Atlas — in addition to NCI's other major efforts at whole genome scanning, such as the Cancer Genetic Markers of Susceptibility (CGEMS) program — is continually contributing more and more volumes to the catalogue of cancer information. NCI has established a data sharing policy to ensure that de-identified human genomic data are available to the entire cancer research community. Genome-wide association studies of cancer risk, conducted through CGEMS and other closely related programs, have identified more than 400 loci, or locations along the genome, that indicate an association with predetermined cancer risk. These regions will need further study to determine the biologic significance of their increased risk and prognosis, as well. These discoveries should point to genetic regions that are most susceptible to alteration and the interacting environmental exposures that drive later carcinogenic changes over the course of a person's life. The next generation of genome-wide association studies will be conducted in conjunction with clinical studies, with the aid of comprehensive treatment and survival data, in order to assess determinants of tumor progression, therapy response, and late effects of treatment.

One of NCI's responsibilities will be to provide leadership and coordination of the many projects underway now and planned in the future in this field of study. TCGA, CGEMS, and other projects directly sponsored by federal dollars

should be coordinated, as much as possible, with similar projects supported by foundations, private resources, and by other governments. We must lead the way in knowledge sharing, through publicly accessible databases, and we must strive to ensure, as best possible, that our efforts are complementary, representing the best use of precious resources: dollars and patient tissues.

In the years ahead, there is no question that NCI's most pressing challenge will be to take the information from that catalogue and turn it into a cancer repair manual. This will not be easy; many are concerned about expectations being created by our efforts. Translation of this new, and certainly empowering, knowledge will require diligence as scientists work toward understanding how that knowledge can ultimately be used in making a difference for patients. Many coordinated steps will be involved, from understanding the biological function to chemistry to drug development to first-in-human testing. A common starting point among them all will be the management of information.

The cancer Biomedical Informatics Grid. caBIG® has a deceptively simple mission: electronically connecting the cancer research community. It begins with information from genomic and other research, measured by the petabyte (10^9 megabytes) that is safely and securely stored and accessible. Data are also annotated with clinical information and protected. caBIG connects scientists, in the laboratory and the clinic, through a single infrastructure, with standard rules and common language developed for information sharing. caBIG builds and develops tools for collecting, analyzing, and disseminating information associated with cancer research and care. caBIG also is the information backbone of TCGA, providing tools and connectivity to collect, organize, share and analyze its data. Developing the new age of analytical tools and mathematical models needed to maximally utilize such large and varied sets of information will require a significant investment in the years ahead. The magnitude of this is yet to be well realized. As discoveries move toward the clinic, caBIG also provides tools for the management of clinical trials and specimen acquisition — and most importantly, a pace-setting initiative to implement the use of the electronic health records. The knowledge gained through caBIG will benefit not only cancer research, but the entire biomedical research enterprise.

THE BOTTOM LINE. ARRA funding is enabling the expansion of caBIG, both in scope and mission, particularly toward its goal of developing an interactive online knowledge base of all-important cancer information. Continuing support of caBIG would require an additional $103 million in the 2011 fiscal year.

The cancer Human Biobank. Inasmuch as caBIG relies on rigorously collected, carefully protected and stored data, genomic studies through TCGA and other initiatives demand the highest quality tissue, blood, and tumor samples, rigorously and ethically collected, properly stored, and extensively annotated. In short, that is the message of one of NCI's new initiatives, the cancer Human Biobank, or caHUB.

Brian Henderson, M.D., USC Norris Comprehensive Cancer Center

Twenty years of planning, cajoling, meeting, and organizing are now paying off in big ways for NCI's cohort consortium, an effort to link many individual groups of research subjects into a more informative whole. NCI's wide-ranging research cohorts, along with the extremely large amounts of resources and data they collectively make available, will help the Institute rapidly advance its understanding of genomic changes and environmental influences in cancer across large, ethnically diverse populations.

One of the deans of these efforts is Brian Henderson, M.D., from the USC Norris Comprehensive Cancer Center in Los Angeles who, for the past 15 years, has headed up a multi-ethnic cohort with Laurence Kolonel, M.D., Ph.D., of the Cancer Research Center of Hawaii. By pooling biospecimens from 10 large study populations, investigative teams now have a much better understanding of the relationship between genes and environmental influences that play a role in prostate, colorectal, and breast cancer for native Hawaiians, Japanese, African-Americans, and Latinos.

Brian Henderson, M.D., University of Southern California Norris Comprehensive Cancer Center/ Credit: USC Norris

Prior to these studies, most cohort gene studies were done in homogenous European populations. One of the least studied populations, at least from a genetic variant perspective, is Native Americans. "Because Latino populations, particularly in Mexico, have up to 50 percent Native American ancestry, the cohorts we've assembled there will be most useful in helping us elucidate some of the genetic variants and risk factors for Native Americans," said Henderson. Individual cohort studies alone seldom gave us sufficient power to obtain highly reliable data, he noted. "Because we're all now using just a couple of the same gene analyzer machines with the same basic chips, some of which will soon be able to store five million samples per chip, we expect to rapidly accelerate our ability to collect and analyze specimens so that we can apply those findings to prevention and treatment modalities for some of the most prevalent cancers."

One of the key understandings to come out of the consortia research is that prostate cancer has virtually no environmental variables associated with it. Thus, through deep re-sequencing, the multi-ethnic consortia are looking for rare functional variants in high-risk populations, such as African-Americans, to try to find those inherited variants that may confer greatest risk.

The cohort consortia effort has been a truly collaborative one, involving many NCI-sponsored research institutes, such as the Broad Institute of MIT and Harvard in Cambridge, Mass., among others. The consortium now includes more than 20 cohorts and is facilitating almost instantaneous replication of each other's findings, giving a high degree of confidence in findings that show a strong association between gene variants, hormones, and growth factors that can all influence the risk of cancer. "We've now assembled truly global consortia, as we know we can't do these studies on our own, and I expect that future cohort studies will be quite collegial and fruitful," said Henderson.

Susan Love, M.D., Dr. Susan Love Research Foundation

A unique collaboration is using the tools of caBIG to help bring together a million women to participate in breast cancer research. The Army of Women initiative, launched in October 2008, is the brainchild of the Dr. Susan Love Research Foundation.

The Army of Women had recruited over 320,000 women for 18 different studies by the beginning of 2010. The Dr. Susan Love Research Foundation in Santa Monica, Calif., working in concert with City of Hope's Beckman Research Institute in Duarte, Calif., and NCI, will now be recruiting women (and men) of all ages and ethnicities for the Health of Women study, which will follow long-term cancer survivors to identify both predictors of longevity and consequences of therapy. It will also look at healthy women in order to develop a better understanding of potential new risk factors for breast cancer.

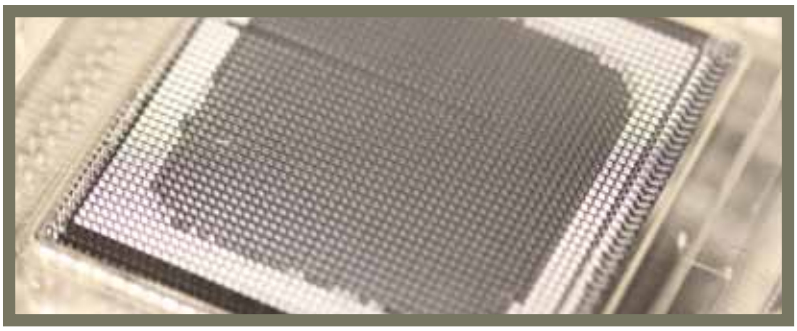
"Women have repeatedly demonstrated through fundraising and advocacy their personal dedication to ending this disease," said Susan Love, M.D., the foundation's president. "This initiative gives women the opportunity to take the next steps and be part of the research itself."

caBIG tools are enabling the secure online submission and handling of data for the study. Using web technology, women can respond to periodic short questionnaires or modules about their personal or family health history, reproductive health, breast cancer (for those with the disease) experiences, and much more. Because fewer than 20 percent of women who get the disease demonstrate any of the known risk factors for breast cancer, information gathered in this study should provide valuable insight for researchers in the field.

Additionally, the Health of Women study allows researchers to rapidly pose questions, using a larger sample population than has ever been feasible. That, in turn, will make research more dynamic and let investigators be more flexible in their studies. The hope is that research studies that used to take months or years can be done in days or weeks, as data become more accessible.

"Many of the researchers using the Army of Women have recruited everyone they needed for their studies within 24 hours. In many cases, we even recruited more people than they needed. This has amazed the research community and pleased all of us," said Love. The collaboration also has the potential to empower participants to feel involved in research while they are healthy or if they are diagnosed with the disease.

Susan Love, M.D., (second from right)
Dr. Susan Love Research Foundation
Credit: Dr. Susan Love Research Foundation



A microarray at NCI's Core Genotyping Facility, capable of over 2,000 high-throughput assays at a time.

Begun in 2009, as the culmination of several years of work in developing techniques and best practices, caHUB will be a national biobank, a repository of biological materials and associated data, acquired within an ethical framework, that can be used for medical research. caHUB will help ensure that a continuous supply of biospecimens is available to the cancer research community. caHUB is also advancing technology development to support biobanking practices.

caHUB will, on one hand, help solve the longstanding problem of many scientists who face great obstacles in obtaining high-quality research samples; on the other hand, this initiative will also advance science in its own right, through connections to caBIG, which will enable the combination of biospecimens with data derived from research on those specimens at the molecular level. Each specimen, then, will be the source of a uniquely rich data profile.

THE BOTTOM LINE. An ARRA investment of $60 million has helped caHUB become an established program ahead of its original timetable. Because of the critical importance of biospecimens to leading-edge cancer research, to maintain caHUB as a first-class resource, would require an additional $60 million in the 2011 fiscal year.

Patient Characterization Center. As genomic science rapidly moves forward, cancer science is pushing toward an era when the molecular characteristics of patients and their tumors (primary and metastatic) will be more clinically significant than the organ site where the cancer originated. Consequently, the need for characterization of individual cancer patients will grow in significance — and likely quite soon. NCI's proposed model to support that future is its Molecular Characterization/Clinical Assay Development Center, which will include a Patient Characterization Center.

This center will be a model for the development of personalized, highly prescriptive cancer care, based on traditional epidemiological and risk-factor analysis combined with molecular characterization of a patient's tumor as well as the pharmacogenetics and pharmacogenomics of the patient. Ultimately, the center will have the capacity to perform complete genomic characterization of patient specimens (normal and tumor). This characterization will evolve, as technology and cost permit, to include proteomic and metabolomic key information relevant to the patient's tumor process. While NCI has responsibility for innovative technology development and proof-of-principle standards, it also must lead the way in distribution of this science to appropriate sites across the country. In the end, all patients must have access to characterization technologies to inform personalized care.

THE BOTTOM LINE. ARRA funds have made possible the launch of an initiative that might otherwise have taken years to move forward. Continuing development of the Patient Characterization Center would require an additional $12 million in the 2011 fiscal year.

Taking the Genome to the Clinic

The results of genomic studies, as previously discussed, are extremely important science. Yet they remain, for the time being, largely fascinating information which we must further refine, in order to turn them into new therapies. The reason, simply stated, is that genes do not have an active role in disease. Rather, genes "express" themselves by initiating the deeply complex process of creating the cell's functional molecules: proteins. The intricacy of such processes is, in fact, where cancer research is finding important opportunities. But the process begins with knowledge of a gene gone awry. For example, in a non-invasive breast cancer known as ductal carcinoma *in situ*, or DCIS, cases of DCIS were highly correlated with mutations in the gene p53.

Turning information about genomic and genetic aberrations into knowledge of biologic function — about proteins and pathways that control cancer's development and growth — is becoming an ever more crucial role of NCI. New knowledge from programs like TCGA is spurring laboratory research to turn cancer cell signaling pathways and epigenetic regulatory mechanisms, once considered too complex and difficult to hit, into targets for new therapies. NCI is using ARRA resources to bolster a platform of initiatives designed to take knowledge of function derived from genomic discoveries and turn that knowledge into therapies. However, the mechanisms used to drive these initiatives forward are somewhat unique and thus optimally will involve numerous university-based researchers, who will be joined into several consortia, to tackle specific tasks. This will bring to bear greater amounts of resources — including teams of scientists — than any one institution could bring together. These coordinated programs are doing important work today that will help NCI continue to play a unique role as a facilitating institution.

Chemical Biology Consortium. Probing cancer's complex networks of signaling pathways requires cutting-edge chemical tools, which often exceed the capacity of an individual laboratory or, for that matter, an individual research university. Along with NCI's functional biology efforts, NCI's Chemical Biology Consortium (CBC), which sits at the intersection of chemical biology and molecular oncology, is designed to be a flexible network of hundreds of scientists working to increase the flow of early-stage drug candidates into the developmental pipeline. By establishing this network — including government, academia, and industry — the CBC will focus on the chemistry needed to optimize compounds or small molecules and to improve efficacy and reduce toxicity in pre-clinical assays and animal models prior to first-in-human testing.

The CBC will revolve around task-oriented science, involving projects with clear objectives, deadlines, and milestones. Of vital importance to this initiative will be the selection of projects. Without question, there is great demand for refinement and definition of potential targets and targeted agents; consequently, we must carefully prioritize those efforts in order to push the most promising concepts more rapidly toward the clinic. That is why the CBC is employing a Special Emphasis Panel: outside experts who will meet periodically to recommend which projects the consortium should focus on. Their

approximately 70 percent do not advance, often because of a lack of efficacy. NExT is designed to address many of these problems earlier in the drug development process and to continue to evolve the process, always striving to decrease cost and time.

NExT includes toxicology testing and drug manufacturing (when there is no commercially produced option), along with early phase clinical trials, including Phase 0 trials, in which non-toxic doses of an agent are tested in a small number of patients, utilizing advanced imaging to determine in weeks, not years, whether a drug is reaching its intended target and having its intended biologic effects.

Specifically, a Phase 0 clinical trial is designed to study the pharmacodynamic and pharmacokinetic properties of a drug. Pharmacodynamics describes the biochemical and physiological effects of a drug on the body, including how the drug binds to various structures, and interacts with certain molecules within target tissues. Pharmacokinetics describes the activity of a drug in the body over a period of time. This includes the process by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted. Considered together, data from pharmacodynamic and pharmacokinetic studies help researchers determine a rational dosage regimen for testing in subsequent clinical trials.

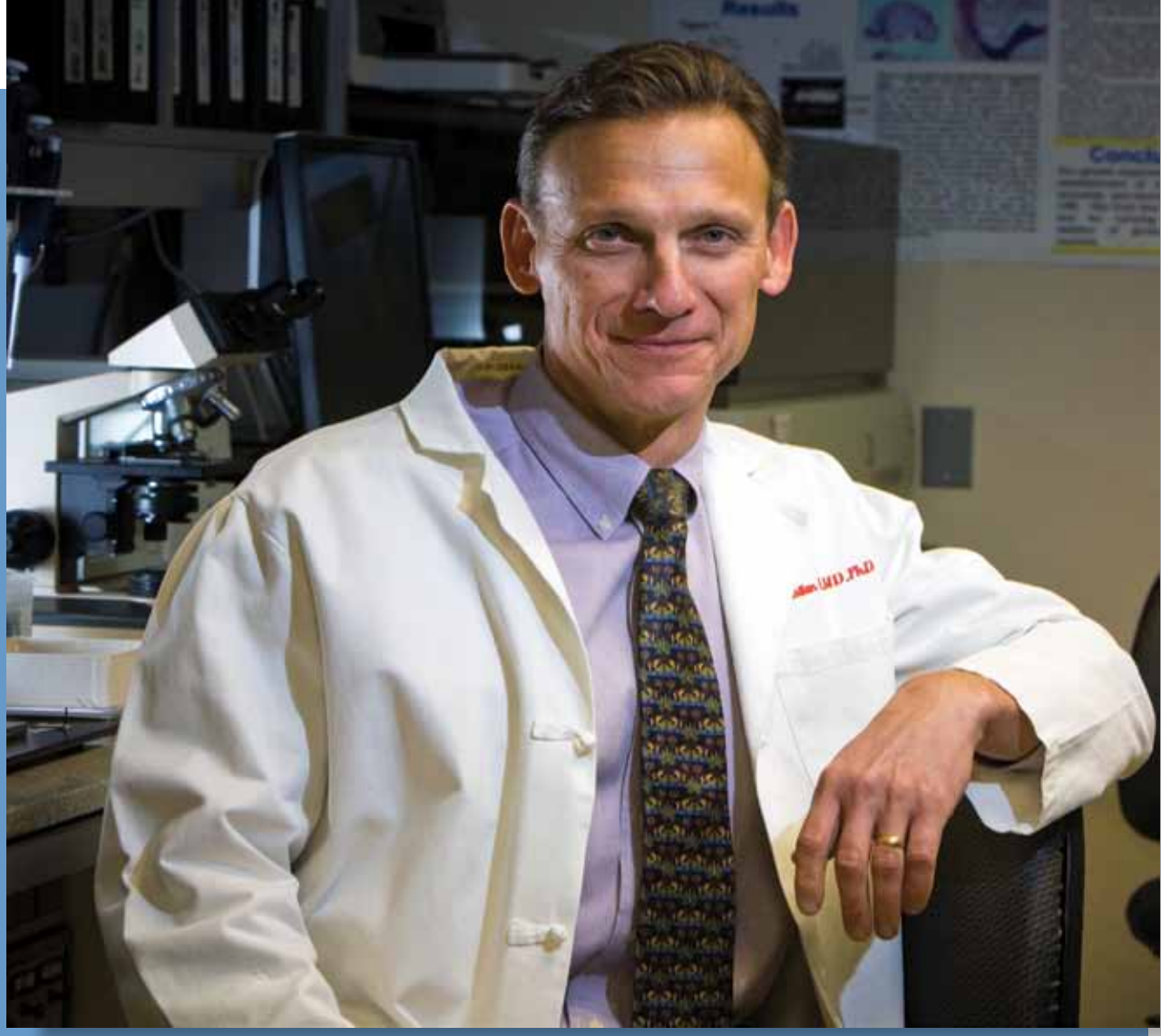
In a Phase 0 trial, a limited number of doses and much lower concentrations of the drug are administered, therefore there is little risk to the participant. Fewer patients are needed (about 10 to 12, on average, in a Phase 0 study compared to about 20 to 25 in a Phase 1 trial). By studying pharmacodynamics and pharmacokinetics, researchers can determine which agents are hitting their targets and weed out the drugs that are not producing the desired effects much

John Reed, M.D., Ph.D., Burnham Institute for Medical Research

For a quarter of a century, NCI has acquired, through its Natural Products branch, plants and marine organisms from more than 25 tropical and subtropical countries worldwide, including Africa, Madagascar, Central and South America, and Southeast Asia. During the same period, over 10,000 marine invertebrates and marine algae have been collected, mainly from the Indo-Pacific region. Important drugs, such as taxol, which comes from the bark of the Pacific Yew tree, were developed based on these collection efforts. But many drugs that have already been developed were based upon cell culture toxicities, which would be considered a rather crude marker today compared to more modern molecularly targeted therapies. Thanks to the establishment of the NCI-sponsored Chemical Biology Consortium, newly discovered or synthesized compounds will now be screened with highly specialized techniques to see if the drugs can be directed at carefully validated biological targets.

"One of the more interesting series of compounds that we're looking at are those that neutralize apoptotic, or cell death, targets," said John C. Reed, M.D., Ph.D., president of the Burnham Institute for Medical Research in La Jolla, Calif. "Some marine species can't outrun their predators so they use chemicals to ward them off, and it turns out that these chemicals have properties that can induce tumor cell death by neutralizing cell survival gene products that are over-produced in malignant cells, which is a very common event in cancer." Burnham is at the forefront of screening these types of natural products using high throughput technology and advancing translational research to optimize development of these agents into highly targeted therapies.

Eight years ago Burnham put a plan in place to transition the institute from a primarily basic science institution to one that had an active translational mission



John Reed, M.D., Ph.D., Burnham Institute for Medical Research/ Credit: Nadia Borowski Scott

as well, and chemical biology research is one of the key elements in this new mission. Reed notes that they have 80 researchers in both La Jolla and their campus in Orlando, Fla., working in this area. Between the two locations combined, Burnham has high throughput robots that are capable of screening nearly three million compounds per day. "Because a lot of biotechnology companies are no longer doing early stage discovery research, we feel that we're filling that void quite well — we are going after the more difficult and challenging targets, such as protein-protein interactions," Reed said. "Funding is a major issue; venture capitalists these days are primarily interested in funding product opportunities that have reached Phase II trials, so the Chemical Biology Consortium plays a vital role in early discovery."

In particular, Reed noted, scientists at Burnham are looking intensively at cellular processes like autophagy, or the breakdown of a cell. Autophagy has recently been implicated as a possible agent of cancer causation, and trying to find valid targets that affect this process is going to be one of the important consortium projects done at Burnham.

more quickly, and they can avoid moving those drugs into further trials.

By conducting a Phase 0 trial on a particular drug, the process for Phase I and II trials on that drug is accelerated. Additionally, because Phase 0 trials study how the body reacts to the drug and how the drug acts in the body, if a drug is found to react poorly or to have serious side effects, the testing for that drug can be stopped sooner, without the additional expense of further trials.

ACTNOW. NCI is using ARRA resources to fund 37 new Phase I and Phase II cancer treatment trials to test the effectiveness of molecularly-targeted cancer therapies. The program, Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW) has a goal of shortening the time it takes to move new cancer therapies from discovery, to development, to approval and safe use by adult and pediatric cancer patients.

The program has dedicated $31 million for early phase trials, plus $5 million for support contracts, including those to assist investigators with data monitoring and statistical analysis. This is money that is paying compound dividends in health care and jobs for physician-scientists, oncology nurses, clinical research coordinators, statisticians, medical assistants, and other staff members who are helping administer ACTNOW trials at institutions all over the country.

Importantly, all of the ACTNOW studies are designed to integrate the latest imaging technologies and correlative laboratory research studies to help us understand the underlying biological mechanisms of action.

ACTNOW awards are also contingent on a very strict, accelerated timeline. Study investigators were required to finalize institutional review board approval and begin enrolling patients within 90 days, and enrollment must be completed within the two-year ARRA timeline. Investigators are also required to submit quarterly metrics related to the economic impact of their project throughout the funding period.

DRUG DEVELOPMENT: THE BOTTOM LINE. As activities and initiatives across NCI's drug development pipeline mature and become more successful, the need for modern, efficient clinical trials to test those new agents will increase proportionally. The success of the ACTNOW program under ARRA — in terms of greatly accelerating the process of trial initiation and significantly increasing the number of new drugs that could be tested in patients — has moved NCI to plan to award a similar number of ACTNOW trials in FY 2011. Adequately supporting NCI's early phase drug testing and development efforts designed to shorten the time from discovery to patient use would require an additional $69 million in the 2011 fiscal year.

NCI-designated Cancer Centers. The National Cancer Act of 1971 brought strong change to the operations of NCI, designating it as the leader of the National Cancer Program, making its director a Presidential appointee, and establishing the National Cancer Advisory Board and the President's Cancer Panel, with members of both bodies also appointed by the President. The cancer act also provided NCI other important special authorities, including the NCI director's capacity to "provide for the establishment of fifteen new centers for clinical research, training, and demonstration of advanced diagnostic and treatment methods relating to cancer."

Today, those centers number 65, and they can be found in 33 states plus the District of Columbia. These are places of great research, home to the majority of the individual investigators

NCI supports. One would have a difficult time finding any major NCI initiative — from TCGA to the Chemical Biology Consortium to ACTNOW trials — that does not involve Cancer Centers and their faculty members. They are places sought by cancer patients for the latest advances in treatment and by young scientists and clinician-scientists dedicated to solving the mysteries of cancer; they are places that provide the best cancer care anywhere, that train the next generation. Cancer Centers, located at the country's major academic health centers, are also strong forces in their communities, providing care to underserved patients, providing leadership in the healthcare field, educating the community, and providing many health care, technical, or other support staff jobs.

Through ARRA, NCI-designated Cancer Centers received $63 million to supplement their core grants. Additional ARRA funding was awarded to specific research investigators within Cancer Centers through other mechanisms at NCI and NIH, including Challenge Grants, Grand Opportunity Grants, comparative effectiveness research funds, and others. ARRA funding has allowed the Centers to hire and retain faculty and staff, purchase equipment for new and existing labs, increase their investment in information technology, and initiate developmental projects focused on clinical trials, personalized medicine, and health disparities, among other areas.

The majority of Centers receiving ARRA funds were able to hire or retain between one and five new faculty, scientists, research coordinators, radiologists, research physicians, nurses, statisticians, post doctoral students, and laboratory technicians. Additional funding in FY 2010 is contributing to the hiring and retention of new faculty and other workers to support existing and new research opportunities. Through ARRA funds, Cancer Centers will also enhance current research facilities by purchasing additional large equipment, replacing older equipment, and, in some instances, constructing new facilities and renovating existing space.

THE BOTTOM LINE. Cancer Centers are key participants — the linchpin, some might say — across virtually every NCI initiative. Their support needs will certainly never diminish, and there is a list of strong contenders that have been actively planning, with the strong backing of their universities, to prepare to apply for their Cancer Center Support Grant. Sustaining ARRA momentum at Cancer Centers and adding two new Centers would require an additional $50 million in the 2011 fiscal year.

The NCI Community Cancer Centers Program. The NCCCP originated from a simple statistic: Approximately 85 percent of cancer patients in the United States receive their cancer care in the community where they live. For the complex, multispecialty care of cancer patients required today, community health systems and private practice cancer physicians have made great strides. Cancers, however, are not all common forms, and in some cases, simply diagnosing the correct disease can be a daunting process. In such cases, the NCI-designated Cancer Centers have long been the places patients seek out. For many, however, that is simply not possible. These patients may lack the strength, financial resources, insurance, language capacity, education, or family support system to seek out a large university health care system or NCI-designated Cancer Center.

With those reasons — and those patients — in mind, NCI created the NCCCP pilot to test the concept of a national network of community cancer centers to expand cancer research and deliver the latest, most advanced cancer care to a greater number of Americans in the communities in which they live. The principle was to give every cancer patient in the United States access to NCI — its science, its technology, and the latest guides to care. The NCCCP, through its current 16 sites, extends the reach of NCI research into

Mark Krasna, M.D., Cancer Institute at St. Joseph Medical Center

Best practices. Those are the two words that the director of the NCI Community Cancer Centers Program's (NCCCP) facility in Towson, Md., constantly espouses. "On an almost daily basis we assemble a team of physicians and other specialists from our facility and get them together with private practice doctors in the area and discuss everyone's most challenging patient caseloads. We arrive at a solution that takes into account a far wider range of opinion than we could ever hope to assemble on our own," said Mark Krasna, M.D., medical director of the Cancer Institute at St. Joseph Medical Center in Towson. "By assembling such a broad range of community expertise, patients essentially get a second and third opinion instantaneously, and for free."

As an NCI community cancer center, Dr. Krasna's team is often able to offer a more personalized sense of care than some larger facilities. St. Joseph's 6 percent clinical trials accrual rate, which he hopes to get to 10 percent by the end of 2010, is a testament to Krasna's efforts, as the average adult accrual rate to cancer clinical trials is about 3 percent. Additionally, Krasna notes, what had been a three month course of treatment for many advanced cancers now only takes about two weeks, on average. "Most of our achievements have been based on the trust factor — we bring outsiders to us to see how we manage patients and offer them the opportunity to share their successes and failures with us, and by dint of that sharing, we're all able to learn and benefit."

As an NCI community cancer center, St. Joseph's doesn't try to do what Krasna feels NCI-designated, university-based cancer centers already do extremely well, and that is discovery and early phase research. Rather, they tend to deal with later phase trials and more advanced disease and are eager to rapidly incorporate the important research findings developed by academic centers into their trials and patient care.

St. Joseph's is also part of the Catholic Health Initiative (CHI) chain of 70 hospitals and care facilities nationwide. Dr. Krasna notes that CHI is a microcosm of health care in America as it represents all ethnicities, geographies, and age ranges, and as a bonus to NCI and the NCCCP, many of its hospitals are in locations without NCCCP or NCI-designated Cancer Centers.

"NCI is certainly getting a good bang for its buck, because the best practices in cancer care being developed at St. Joseph's and other such facilities are being rapidly disseminated to other CHI

Mark Krasna, M.D., Cancer Institute at St. Joseph Medical Center

more U.S. states, cities, and towns, including rural areas and inner cities.

The NCCCP sites are working to draw more patients into clinical trials in community-based settings, reduce cancer health disparities, prepare sites for standardized collection and storage of biological specimens for cancer research under caHUB, and link all of the information gathered at these sites together with the national computer networks and electronic cancer health records made possible through caBIG.

In just a little over two years, NCCCP sites have increased outreach staff and forged new community partnerships. They have instituted cancer screening initiatives, new survivorship programs and, importantly, have dedicated resources to reducing

hospitals in addition to NCCCP sites," said Krasna. As a prime example, he noted that 90 percent of breast, lung and colorectal cancer patients are now getting multi-modality care, with routine prospective case presentation, which a center such as St. Joseph's or other CHI hospitals can now easily handle. "This is a huge paradigm shift from just three years ago."

inequalities of care. Close to half of the NCCCP sites have also developed relationships with academic medical institutions.

NCI, with the use of ARRA funds, plans to add approximately 14 competitively chosen NCCCP sites. We are also allocating funds to current NCCCP hospitals for two years, again competitively awarded, for 18 specific projects encompassing clinical trials, disparities, community outreach, biospecimen collection, electronic health records, quality of care, partnerships with state cancer plans, communications, survivorship, and palliative care.

THE BOTTOM LINE. Sustaining NCCCP as a community project, as it moves to the end of its pilot phase and becomes a permanent NCI program, would require $56 million in the 2011 fiscal year.

Areas of Intensified Scientific Investigation

One important subtext to everything discussed in this document is the fact that science thrives on ideas. It is often said that every truly successful experiment leads to 10 new questions to be studied. Thus, we face the obligation to look just over the horizon, to consider important new concepts at their earliest stages of intellectual development. Science most often can benefit from utterly unique viewpoints — from the unanticipated, and from creating opportunities for research at the crossroads of scientific disciplines.

Physical Science-Oncology Centers. In early 2008, NCI commenced a series of meetings designed to elicit views of cancer from scientific disciplines that have traditionally not been involved in its study: physics, physical chemistry, engineering, and theoretical mathematics. The physicists, in particular, brought to the table a list of concepts more foreign to cancer biologists, including the influences on cells of heat, pressure, time, and evolution. Out of this series of three workshops came the realization and confirmation that the germ of an idea was a good one, and

Franziska Michor, Ph.D., Memorial Sloan-Kettering Cancer Center

The mental image of a cancer researcher is more likely to involve a lab coat than an equation. Yet, because of NCI's Physical Science-Oncology Centers initiative, the picture is changing.

"I'm trying to use techniques from applied math and statistics to answer questions in cancer research," said Franziska Michor, Ph.D., principal investigator of the PS-OC at New York's Memorial Sloan-Kettering Cancer Center. "We try to come up with a mathematical representation of a particular situation in cancer and then use mathematical techniques to solve it and make some useful predictions."

One of the projects Michor's group is pursuing is the identification of the sequence in which genetic alterations arise on the road to cancer. "If you look at the cancer genome of a patient, you see hundreds to thousands of mutations. The question is, which of those mutations are necessary and sufficient to cause cancer and which are just bystanders? And also, what's the order, the temporal sequence, in which they arise?" It could be, Michor says, that there is no sequence — that cancer development simply involves the accumulation of a critical mass of mutations in any order — but she suspects otherwise. "This is such an important question because if we know what the sequence of mutations is, we can better design treatments. Those mutations that come up early during tumorigenesis are more likely to be homogeneous in the tumor. Whatever comes up late can probably be found in only a small subset of the cancer cells." Michor's PS-OC is working to develop mathematical and statistical techniques that parse out the temporal sequence of mutations.

Michor is quick to point out that mathematics, physical sciences, and biological sciences depend on each other, and that the interactions will benefit all of the disciplines. Her mathematical models, for example, may be validated or modified by biological studies.

Bringing disciplines together in the pursuit of cancer also requires a degree of cultural acclimation. "If you meet a researcher trained in pure mathematics who wants to collaborate, it's actually very difficult, because their language is different from that of biologists," says Michor. "Biology is intrinsically very complex. It's not clear that if you've shown something in one situation it's going to be true in all situations, like it is in math. There are a lot of conceptual differences between these disciplines, and also differences in expectation. That's why the PS-OC initiative is such a great idea. It's a strong incentive to bring people of different disciplines together."

The Memorial Sloan-Kettering PS-OC is also working to identify the cell of origin of tumors, which may be "stem-like" cells, progenitor cells, or more differentiated cells. Additionally, Michor's group is working on mathematical models for optimally dosing chemotherapeutics, to avoid — or at least postpone — the emergence of drug resistance.

Franziska Michor, Ph.D., Memorial Sloan-Kettering Comprehensive Cancer Center

One intriguing question is why a mathematician would want to participate in cancer research. The chance to impact a devastating disease, Michor says, is never far from her mind. So, too, is an intriguing intellectual quandary. "As an evolutionary theorist, it's a very interesting case. Cancer is something that goes wrong, even though there are no external causes, such as an infection, in many cases. It's an evolutionary system that goes wrong even though it's designed to prevent exactly that case."

this idea became reality with the funding of 12 Physical Science-Oncology Centers and a five-year initiative to better understand the laws and principles that shape and govern the emergence and behavior of cancer.

Given the complexity of cancer, it is becoming increasingly clear that external forces and physical laws have profound influences on cancer initiation and progression, and upon the behavior of the host as it deals with the abnormal growth process. The Physical Science-Oncology Centers will probe those forces, through understanding the physics of cancer by studying how energy flows, gradients, mechanics, and thermodynamics affect cancer cells versus normal cells and contribute to the complexity of cancer; exploring and understanding evolutionary theory and evolutionary processes of cancer from a physics perspective; and understanding the coding, decoding, and transfer of information in cancer at the molecular and submolecular levels, particularly in the tumor microenvironment.

THE BOTTOM LINE. NCI established the Physical Science-Oncology Centers as a five-year initiative. Through funding of an additional $9 million in the 2011 fiscal year, NCI could expand the centers' areas of investigation.

Infectious agents and cancer prevention. Current evidence indicates that as many as one in five cancers have an infectious cause. With an increased effort, research addressing how viruses or bacteria can impact cancer causation may continue to give us significant opportunities to reduce incidence and mortality.

Researchers are still learning how a cell that is infected with a virus becomes a cancer cell. Hepatitis B and C have been linked to liver cancer conclusively and there are several cancers, including cervical cancer, as well as a subtype of upper-airways cancer, that are associated with the human papillomavirus (HPV).

Additionally, the bacteria, *Helicobacter pylori,* has been linked to stomach cancer and several viruses have been associated with leukemia, lymphoma, and Kaposi sarcoma. Scientists are currently examining potential connections between some viruses and brain, colon, breast, and prostate cancers, although no definitive associations have been established yet for these diseases.

Identifying, treating, and even possibly preventing cancers caused by infectious agents such as retroviruses are ongoing challenges, because each agent causes cancer through a different process and some cause cancer indirectly. Each day we are gaining a better understanding of the relationship between infection, immunity, and genetics. With this new understanding, we are beginning to develop new therapies and novel vaccines that target these agents, which could help to significantly prevent the number of cancers that are associated with infections.

THE BOTTOM LINE. These efforts received $20 million in ARRA funds to study possible viral genomic fingerprints associated with cancer. Expanding the infectious agents and cancer prevention effort would require an additional $30 million in the 2011 fiscal year.

Cancer stem cells. A growing body of evidence suggests that some tumors are driven by a small number of cells that have properties similar to those of embryonic stem cells. The cancer stem cell hypothesis suggests that these rare cells are the only cells within a tumor that can self-renew and give rise to diverse progeny. It is also theorized that in cancer, stem cells or their near descendants, with their longevity and proliferative ability, must be the cells co-opted by the genetic alterations associated with the disease in order to lead to malignancy. These cells are known, therefore, as cancer stem cells or tumor-initiating cells. Unlike the bulk of tumor cells, tumor-initiating cells may be able to endure hostile environments by entering a state of dormancy. This hypothesis, if confirmed, could help explain why many patients with cancer unfortunately relapse after apparently successful treatments.

This area of study, while still relatively new, is growing at a tremendous rate. The study of stem cells can yield enormous gains in treatment of diseases where the replacement of these damaged cells would be effective. In addition, insights into cell proliferation and differentiation can be gained from studying the exact means of control utilized by stem cells. Such insights would prove invaluable in the development of therapies for cancer, in which differentiation and proliferation are often deranged.

THE BOTTOM LINE. NCI is taking steps to build a nationally recognized cancer stem cell biology program. It will provide scientific discoveries in understanding cellular development and proliferation in support of strategic approaches in early drug development, and serve as an important focal point for cancer-related research. Expanding that effort would require an additional $40 million in the 2011 fiscal year.

Cathy Backinger, Ph.D., NCI

Despite significant progress in reducing smoking in the U.S., nearly 20 percent of Americans smoke, and tobacco use remains the leading preventable cause of death in the United States. A new era is at hand, however, now that the U.S. Food and Drug Administration has the authority to regulate tobacco products. "NCI-supported science will be crucial to informing FDA as it moves forward to implement its new authority," said Cathy L. Backinger, Ph.D., chief of NCI's Tobacco Control Research Branch. "We are committed to working with FDA to ensure that scientific research continues to help advance tobacco control policies and interventions."

Backinger's branch funds a broad spectrum of basic and applied tobacco control, prevention, and cessation research. The branch has recently co-sponsored several scientific meetings, including a workshop focused on the use of graphic images on cigarette package warning labels, and a conference examining the health implications of menthol in cigarettes. "These activities help build our research base and provide critical forums for scientific discussions," she noted.

Research related to light cigarettes is a particularly important example. NCI-supported research helped determine that light cigarettes are not less hazardous than other cigarettes, and have not contributed to reducing the enormous health risks of smoking. Backinger notes that "NCI helped provide the scientific evidence supporting FDA's efforts to ban the use of misleading terms such as 'light' and 'low,' on cigarette packaging."

Then there is smokeless tobacco. "Traditionally our research portfolio focused primarily on smoked tobacco products. But, last year we issued a request for applications to jump-start research on smokeless tobacco products, including studying patterns of use and smokers' perceptions about the products," said Backinger. The results of this research should be of great help and interest to the FDA.

Tobacco use by young people remains a particular concern for NCI. "We need to focus efforts to look at products like bidis, which are small hand-rolled cigarettes, and hookahs, both trendy products that appeal to adolescents and young adults. A recent NCI funded study found higher nicotine and carbon monoxide levels, and dramatically more smoke exposure, in hookah smokers compared to cigarette smokers. More research is required to get a better handle on these products," said Backinger.

Cathy Backinger, Ph.D., NCI

Supporting FDA regulation of tobacco products. The Family Smoking Prevention and Tobacco Control Act, signed into law June 22, 2009, gave the U.S. Food and Drug Administration new authority to regulate tobacco products. Already the FDA has banned candy-flavored and fruit-flavored cigarettes; in the months ahead, it is slated to require brand-specific disclosure of ingredients; restrict marketing and sales to youth; and ban misleading descriptors, including "light," "mild," and "low tar."

In addition, the bill gives the FDA other authorities that will require resources from NCI. For example, FDA will be able to establish product standards, to remove or reduce harmful ingredients, and will be able to reduce — but not eliminate — nicotine. FDA will be able to require enlarged warning labels and graphic images on smokeless tobacco and cigarettes. It is clear, though, that research will be necessary to determine the impact of new warning labels; understand effects of changing marketing practices; develop methods and measures for determining the impact of product ingredient changes; monitor how exposures change over time, as a result of product changes, and determine long-term effects. NCI is preparing for what will most certainly be requests to help the FDA implement this sweeping public health law.

THE BOTTOM LINE. NCI has issued administrative supplements to existing grants to expand the science base to more effectively inform FDA efforts to design and implement tobacco product standards, regulations, and criteria for product-related review. In the 2011 fiscal year, an additional $20 million would be required to maintain and expand these efforts.

Comparative Effectiveness Research. During the debate over health care reform, one oft-used phrase has been "comparative effectiveness," sometimes referred to as research into "what works." Comparative effectiveness research, or CER, is about using tools such as clinical trials; observational studies and population modeling; and secondary data analysis to compare the benefits and harms of different interventions and strategies in real world settings. Ultimately, CER is about improving patient outcomes by developing and disseminating evidence-based information. CER is not a new concept to NCI; however, ARRA funds have opened up new areas of investigation.

Using CER dollars allocated under ARRA, NCI is conducting smoking cessation trials; studying risk behavior interventions in health care settings; comparing surgical treatment options for prostate cancer; and studying colon cancer screening methods, just to highlight a few examples.

NCI's ongoing CER efforts cover numerous programs and initiatives, including the Cancer Intervention and Surveillance Modeling Network (CISNET) and HMO Cancer Research Network.

THE BOTTOM LINE. A total of $40 million would be required to maintain and expand the CER effort in fiscal year 2011.

Muin Khoury, M.D., Ph.D., Centers for Disease Control and Prevention

Given the many recent advances in genomics and personalized medicine, do we currently have the evidence to prove that applying new genetic screening and testing modalities in clinical and public health practice will lead to better health outcomes than our current practice? "There is what I call an 'evidence dilemma' in genomic medicine," said Muin Khoury, M.D., Ph.D., director of the Office of Public Health Genomics at the Centers for Disease Control and Prevention in Atlanta, and a senior consultant to the NCI. "There are many basic science discoveries that make biologic sense, but they haven't really been explored in the real world to see, if you compare them to standard practice, whether they would lead to better outcomes and less harms."

Khoury is working with the NCI's Division of Cancer Control and Population Sciences to develop a collaborative network to advance comparative effectiveness research in genomics, in order to develop a roadmap for genomics and personalized medicine for the 21st century. Comparative effectiveness research, including some of the projects being funded by ARRA, can help assess the utility of genome-based medical applications and facilitate the progress toward personalized medicine.

Muin Khoury, M.D., Ph.D., Centers for Disease Control and Prevention

ARRA funds are supporting seven institutions that will be part of this network, each studying a different aspect of the field. They will develop and apply methods to analyze and synthesize existing knowledge about genetics and cancer, gained from basic, clinical, and population sciences. This research will be genome based, but will study not only genes but also proteins, biomarkers and tissues, all of which present more complex scientific challenges that must be faced.

The traditional clinical trials model used to study efficacy, Khoury says, needs to be adapted when trying to study the effectiveness of new personalized genomic tests, because clinical trials are costly and time consuming. "People often ask, 'How much evidence is enough?' I don't think we know the answer to this question," said Khoury. "It's easy to be seduced by the allure of the technology, but when you start using it in people, sometimes you need clinical trials, other times you can start using it while you are conducting the research. This is why we need CER in this area."

CER can be utilized not only to compare new technologies to standard practice, but also as a means of comparing competing technologies currently accepted by the medical community. When looking at an area like colorectal cancer screening, where there are several different screening modalities available, CER can be used to determine which of the technologies is truly more effective.

"Performance in the real world is a combination of the effectiveness of the intervention plus the uptake of the intervention. If you have something that is less effective with better uptake, you might be saving more lives. That is why CER as a form of translational research is so important," said Khoury.

Presidential Recognition

On a warm autumn morning, President Obama stepped onto the stage in a crowded auditorium on the campus of the National Institutes of Health. He had come to Bethesda, Md., along with Health and Human Services Secretary Kathleen Sebelius to say thank you — and to recognize the work and long hours staff members at all of the NIH institutes and centers had put into implementation of the American Recovery and Reinvestment Act."The work you do is not easy," the President said. "It takes a great deal of patience and persistence. But it holds incredible promise for the health of our people and the future of our nation and our world. That's why I'm here today."

President Obama went on to praise the work of The Cancer Genome Atlas, which, by that day, had been selected as one of seven ARRA Signature Projects of the NIH. "In cancer, we're beginning to see treatments based on our knowledge of genetic changes that cause the disease and the genetic predispositions that many of us carry that make us more susceptible to the disease. But we've only scratched the surface of these kinds of treatments, because we've only begun to understand the relationship between our environment and genetics in causing and promoting cancer."

As part of the President's NIH visit, he and others got to see cancer cells close up under a microscope, as NIH Director Francis Collins, M.D., Ph.D., led the President and Secretary Sebelius on a tour of the laboratory of W. Marston Linehan, M.D., in NCI's Urologic Oncology Branch, a component of its Center for Cancer Research.

Indeed, we do have much left to accomplish. President Obama's visit was an affirmation of the lifesaving work that is symbolized by TCGA but that is also realized in thousands of labs and clinics in Bethesda and across the United States.

The work that we do at NCI is paying dividends. The Annual Report to the Nation released in December 2009, shows that the incidence and mortality rates for most cancers continue to decline. But that progress is not sufficient. The very word "cancer" still engenders fear. For too many of our fellow citizens, it elicits images of suffering and of death. NCI's true cause for celebration will come when all cancer patients are free of those bonds, whether envisioned or experienced. None of us will rest until we get there.

Official White House Photo by Lawrence Jackson

"The work you do is not easy," the President said. "It takes a great deal of patience and persistence. But it holds incredible promise for the health of our people and the future of our nation and our world. That's why I'm here today."

Documents like this one are, by nature, selective and not encyclopedic. The examples cited in the preceding pages discuss the progress begun with the unanticipated but needed funds from American Reinvestment and Recovery Act and how it could be financially sustained. ARRA allowed NCI to put into action most of the plans contained in last year's Bypass Budget request. This year's document request includes resources that would allow NCI to further cultivate and mature the initiatives originated with ARRA funding.

There are, however, hundreds of NCI programs that remain extremely valuable, even though they have not been discussed in detail on these pages. From systems biology to efforts to reduce cancer risk for all patients, from NCI's proud intramural science program to every effort to end inequities in cancer diagnosis and treatment, the Institute remains committed to every avenue of research, be it laboratory, clinical, or behavioral. The final three items in the new investments table reflect budgetary requests for some of these areas.

The numbers that follow represent the NCI's professional judgment on potential budget increases that could hasten our research progress against cancer, bringing new therapies, earlier detection and better prevention techniques to all people.

National Cancer Institute

New Investments

(dollars in millions)

Supporting Individual Investigators	$ 310
TCGA and TARGET	$ 28
caBIG	$ 103
caHUB	$ 60
Patient Characterization Center	$ 12
Chemical Biology Consortium	$ 11
Drug Development	$ 69
Cancer Centers	$ 50
NCI Community Cancer Centers Program	$ 56
Physical Science-Oncology Centers	$ 9
Infectious Agents and Cancer Prevention	$ 30
Cancer Stem Cells	$ 40
Support FDA Regulation of Tobacco Products	$ 20
Comparative Effectiveness Research	$ 40
Expand Training and Career Development	$ 40
Invest in Intramural Research Program	$ 75
Strengthen Scientific Infrastructure	$ 145
Total Annual Increased Investment	**$ 1,098**

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