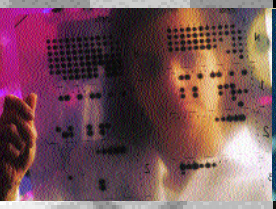
NATIONAL CANCER INSTITUTE

THE NATION'S PROGRESS IN CANCER RESEARCH: AN ANNUAL REPORT FOR 2003



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

NATIONAL
CANCER
INSTITUTE

PROGRESS BRINGS HOPE: AN ANNUAL REPORT FOR 2003

Director's Message

It has been two years since I joined the National Cancer Institute (NCI) as director, and I am extraordinarily proud of the many achievements NCI-supported researchers have made in the laboratory, at the patient bedside, and in the community.

We have set our sights on a major destination—the elimination of suffering and death due to cancer by 2015. The best scientists, our committed partners, and the patients and volunteers who participate in clinical studies are helping us focus to meet this ambitious Challenge Goal.

We move toward our goal in steps, each research finding is a milestone that informs the next study—sometimes moving us forward in a straight line, other times pointing us in unexpected directions. There is so much research being done and the pace is often so rapid, that it becomes too easy to move from one achievement to the next without pausing to take stock of where we have come and what each means. I have instituted this annual progress report to communicate the breadth and depth of accomplishments within cancer research, to share the commitment of the research community that I witness every day, and to convey the sense of hope that progress brings.

The research process spans a continuum from *discovery* of new knowledge about the process of cancer, to *development* of new interventions, to the ultimate *delivery* of new, more effective, and safer interventions to all who need them. This report contains examples of achievements that cross the discovery, development, and delivery continuum, and ends with a look at the infrastructure we have built to remove barriers to progress—forging partnerships, opening access to datasets and tissue resources, and more fully utilizing emerging technologies to apply them to our efforts in genomics, proteomics, communications, and delivery of clinical and public health interventions.

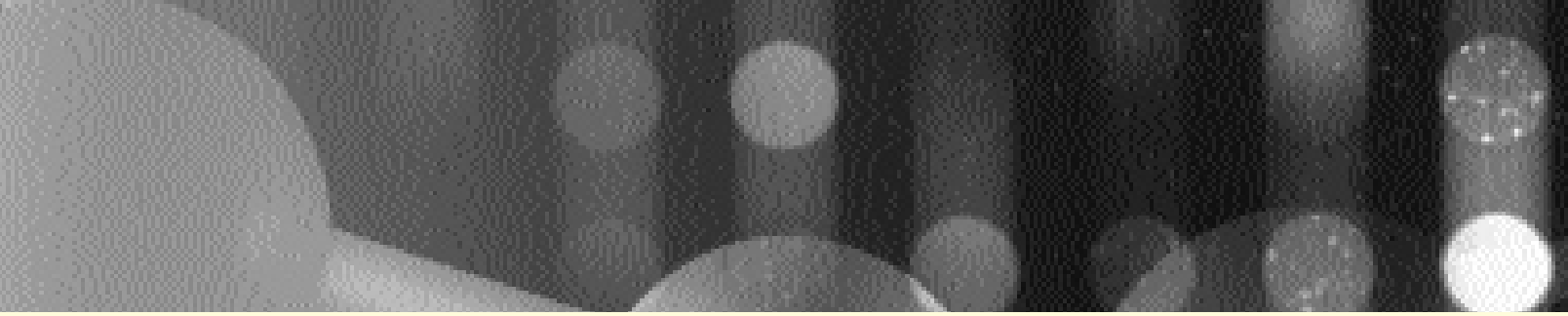
This is a time of great discovery in cancer research. Scientists are peering deep inside the cell, characterizing the many steps and complex mechanisms involved in the disease process called cancer. Researchers are beginning to unravel cancer's mysteries and use that new knowledge to develop ways to preempt cancer before it becomes life-threatening, or even prevent it altogether.

Because cancer research has been a vibrant, wide-ranging enterprise for decades now, cancer does not take the same toll it did 30 years ago. Now more people are living with cancer than dying from it. In 1976, half of all cancer patients survived more than five years after diagnosis. Today, closer to two thirds (63 percent) are alive five years after they learn they have cancer.

Last year, as we marked the 30th anniversary of NCI's Surveillance, Epidemiology, and End Results Program (SEER), we reported that death rates have declined from the four most common cancers—lung, breast, prostate, and colorectal. These examples of measurable progress mean that 10 million Americans alive today are survivors of cancer. Much more than dry statistics, these numbers reflect the lives of people who are counting on us to reduce the burden of cancer for them and future generations.

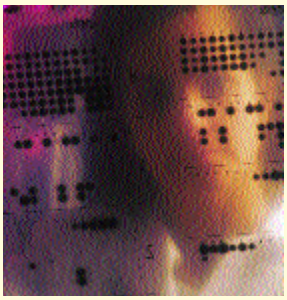
This report spotlights the achievements that define for me the excitement and potential for significant impact and real movement toward our Challenge Goal. The work described on these pages illustrates the innovation, focused energy, and collaborative spirit that is moving us forward.

Andrew von Eschenbach, M.D.
Director
National Cancer Institute



Discovery

The cell is no longer a complete mystery or "black box." Scientists have peered inside and shown it is a robust entity bombarded daily at its surface by hormones and chemicals, signals from neighboring cells, and nutrients.



Cancer is both a genetic disease and a cell-signaling failure. Genes that normally control orderly growth, differentiation, and proliferation become unregulated, allowing cells to reproduce without restraint. Altered genes produce defective proteins that do not function properly in the cell. With knowledge of the intricate biology of a cancer cell, scientists are designing interventions to preempt cancer's progression to uncontrolled growth at many stages along the disease process.

Scientists are using the latest technologies to scan a cancer's genetic signatures, manipulating cells to devise powerhouse cancer-fighting immune cells, investigating novel biochemical pathways to disarm the most resilient cancer cells, and using imaging probes to visualize a cancer's impact on the body without the need for invasive biopsies.

NCI researchers are using the latest tools in genetic epidemiology to study the relationship between cancer susceptibility genes and environmental factors in large groups of people prone to certain cancers. They are pinpointing genes involved in the more aggressive forms of certain cancers, genes that scientists can use to distinguish between a smoker who can quit successfully and a smoker who will have more difficulty and is more likely to relapse. They are scouring large data sets from long-running studies to find links between some commonly used vitamin supplements and a lower risk for certain cancers, as well as links between therapies for menopause and cancer risk. Each of these studies moves us closer to a time when physicians can rely on genetic, molecular, and environmental details about each patient to choose the intervention most likely to succeed.

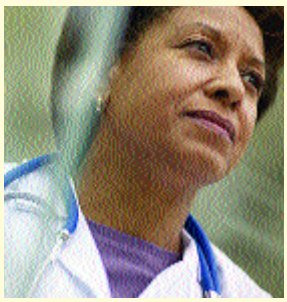
Development

The union of talent, scientific discovery, and advanced technology continues to expand our knowledge of the factors that increase cancer risk and of the processes within the cell that are disrupted in cancer's onset and progression. Our understanding of the molecular basis of cancer has led to more effective prevention strategies, improved tests for early detection, more precise diagnostic methods, and more powerful treatment approaches.

NCI-supported scientists are testing the ability of a well known drug to prevent prostate cancer and studying a vaccine that could have a significant impact in helping to eliminate cervical cancer. They are opening new vistas into the body, using a simple blood test to detect cancer, marrying imaging techniques with tracers that can track down the smallest cancer cells, and exploiting nanotechnology to access and interact with the tiniest domains of the cell. Some of this development work sounds like science fiction, but researchers aim to make them part of the realities of improved cancer diagnosis and treatment in the 21st century.

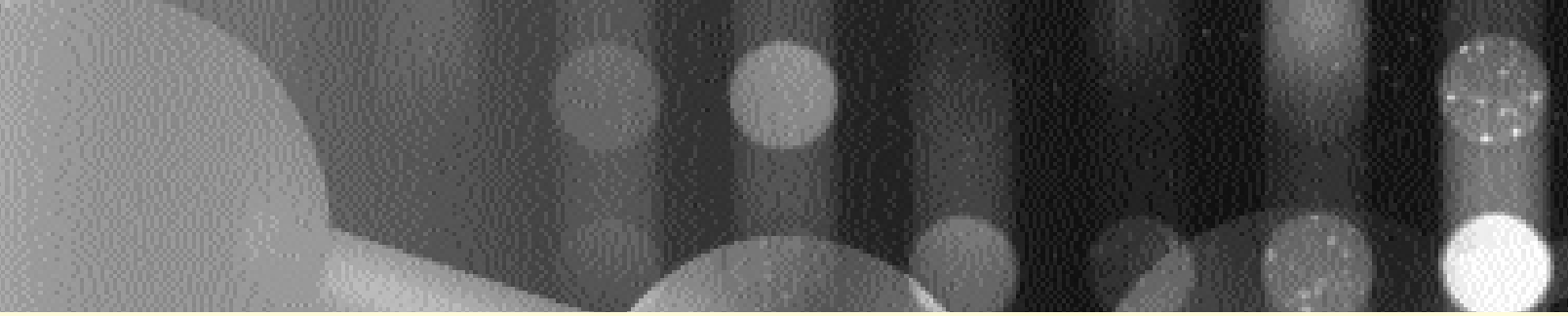
Delivery

The culmination of the cancer research continuum is the delivery of science-based, rigorously tested interventions—in cancer prevention, detection, treatment, as well as communications and education—to all patients and populations that need them.



Several of the achievements in this report are the results of clinical studies, or clinical trials—one of the last steps before delivery of new interventions to those who need them. NCI annually enrolls approximately 25,000 patients into treatment clinical trials conducted by 10,000 investigators at more than 3,300 sites across the country. These trials address important questions about cancer treatments. To learn better how to find cancers sooner, approximately 100,000 individuals at risk for either breast cancer or lung cancer are enrolled in NCI-sponsored early detection studies. In addition to examining whether spiral computed tomography reduces deaths from lung cancer compared with standard x-ray screening, the National Lung Cancer Screening Trial is studying biomarkers for early cancer detection. These studies are yielding the answers that will inform patient care for years to come, so it is critical that people continue to participate and that more join in the clinical trials process.

Our achievements in delivery are as diverse as completing the large-scale studies that prove an intervention's readiness for FDA approval, to showing a new use for an old drug, to disseminating proven communications interventions so that health professionals can design effective cancer control programs for their own communities, to reaching a specific audience with cancer prevention messages aimed at reducing their exceptionally high rates of cancer.



Infrastructure

Laboratory scientists and clinical researchers, epidemiologists and geneticists, cancer centers and community hospitals are generating an immense volume of valuable information. The potential power of these rich collections of information can be fully realized by enabling individual investigators and research teams to combine and leverage their findings and expertise across the cancer research community.

NCI has launched several programs to align resources, enabling new technologies and knowledge of cancer to speed research across the discovery, development, delivery continuum, and to more rapidly bring new interventions to the people who need them.

The Institute has made a significant commitment of resources to build a bioinformatics infrastructure to share data across miles and get tissue samples to the researchers asking important questions about cancer biology and tumor response to therapy. As NCI celebrated the 20-year anniversary of the Community Clinical Oncology Program, which brings clinical trials into local communities, it launched a consortium of large cohort studies to pool data and confirm findings on the relationship of genes and environment to cancer.

Effective collaborations across a diverse community will be central to many of these efforts. A partnership with the Food and Drug Administration, for example, will speed the process of developing and approving safe, more effective new cancer interventions.

The examples of infrastructure-building in this report are relatively new efforts designed to strengthen analysis, resource sharing, and dissemination of research findings. When fully realized, the scientific community will have the tools to integrate diverse data types, conduct analyses with accuracy and speed, and capture and share outcome data.

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OCEAN IS A TREASURE TROVE OF POSSIBLE ANTICANCER COMPOUNDS

Fifteen years of searching the ocean's mud for potential cancer-fighting compounds is paying off for William Fenical, Ph.D., and colleagues at the Scripps Institution for Oceanography at the University of California, San Diego.

They have discovered more than 2,500 new species of bacteria, which they have dubbed Salinospora. These new organisms are cousins of the land-based actinomycetes, which account for almost 70 percent of the world's naturally occurring antibiotics.

"The ocean muds are an extremely rich source of microbes that are different from anything we've seen on land," says Fenical. "The bottom of the ocean is the part that nobody cares about. We asked ourselves, if we go out and send down a sampler to 3,000 feet and bring back some mud, what's in there?"

The result? More than 80 percent of the Salinospora discovered by Fenical's team have shown activity against human cancer cell lines, and in extremely dilute concentrations.

In 2003, the group published its discovery of salinosporamide A, a proteasome inhibitor they isolated from a Salinospora species. The compound inhibits the enzymes that mop up old or malfunctioning proteins within a cell. As a result, the old proteins build up and the cell dies. Salinosporamide A is in preclinical development and should enter clinical trials in early 2005.

Along with the Salinospora, Fenical and colleagues have discovered several other new types of bacteria. The distinct genetics and chemistries of these bacteria may usher in a new era of anti-cancer drug development.

Mincer TJ, Jensen PR, Kauffman CA, Fenical W. Widespread and persistent populations of a major new marine actinomycete taxon in ocean sediments. *Applied and Environmental Microbiology*, October 2002; 68(10):5005–5011.

Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W. Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus salinospora. *Angewandte Chemie International Edition, English*, January 20, 2003; 42(3):355–357.

PROTEIN PUSHES BLOOD STEM CELLS TOWARD LEUKEMIA

Some B-cell precursor leukemias, the most common type of leukemia in children, are caused by a unique swapping of genetic material between two chromosomes, others by a mutation or change in a specific tumor suppressor gene—but both events never occur in the same patient. Scientists now know why and this has opened the door to developing more effective treatments for this disease.

The link between the two events is a key protein that can maintain a continuously dividing stem cell population and shut off critical tumor suppressor pathways.

NCI grantees at Stanford University and their colleagues at the Netherlands Cancer Institute in Amsterdam performed a series of laboratory experiments that provide compelling evidence of a role for the Bmi-1 protein in human cancer. Bmi-1 is important to stem cell function. Its levels are elevated in early blood stem cells and then decrease as the stem cells become differentiated and stop dividing.

In leukemias caused by chromosome translocation, a transcription factor called E2a-Pbx1 is produced, causing a cascade of events to maintain high levels of the Bmi-1 protein. Bmi-1 then represses expression of the tumor suppressor gene *INK4A-ARF* without mutating the gene. The result is continued proliferation of precursor leukemia cells.

INK4A-ARF normally suppresses tumor development by halting the cell cycle. About one third of children with leukemia have mutations in the *INK4A-ARF* gene that result in the gene's inability to suppress the cell cycle. Again, this allows unregulated production of precursor leukemia cells. Another 6 percent are due to the E2a-Pbx1 translocation and subsequent blockade of the tumor suppressor pathways, says Michael L. Cleary, M.D., senior author of the 2003 paper describing the work.

Because B-cell precursor leukemias can arise from these two distinct events, the treatments for these diseases may need to differ. Scientists hope to design a drug that targets the mutant transcription factor, E2a-Pbx1, that initiates the cancer and reactivate the tumor suppressor pathway. However, Cleary cautions, "for transcription factors it's been challenging to design a targeted agent. We're looking downstream in the transcription cascade to see if there's a more attractive target for molecular therapy."

Smith KS, Chanda SK, Lingbeek M, Ross DT, Botstein D, van Lohuizen M, Cleary ML. Bmi-1 regulation of INK4A-ARF is a downstream requirement for transformation of hematopoietic progenitors by E2a-Pbx1. *Molecular Cell*, August 2003; 12(2):393–400.

TUMOR CELL PROTEIN PREDICTS BREAST CANCER SURVIVAL

A newly identified molecular marker appears to be a powerful predictor of poor outcome in breast cancer patients. The presence of the protein, cyclin E, which scientists found in high levels in tumors that had recurred or spread, could indicate which patients are most likely to benefit from aggressive treatment, while sparing others from unnecessary, potentially toxic chemotherapy.

Low levels of cyclin E in cancer cells is apparently a much better predictor of survival than other commonly recognized predictors, such as lymph node status, according to an NCI-supported study by Khandan Keyomarsi, Ph.D., and colleagues at the M. D. Anderson Cancer Center. Their study found that cyclin E levels could help identify a patient whose prognosis is poor, even when her cancer has not spread to the lymph nodes.

In normal cells, cyclin E is an important regulator of the cell division cycle. In tumor cells, however, cyclin E is often overabundant. This over-expression is often associated with an aggressive form of cancer. In addition, the full-length form of cyclin E can generate low molecular weight versions of itself, found only in cancer cells, which are linked to even more rapid cell division. The presence of high levels of both forms of cyclin E is significantly associated with poor outcome in breast cancer patients.

Keyomarsi's retrospective study examined tumor tissues from 395 breast cancer patients. About 10 percent of women with stage I disease had high levels of cyclin E, and all of them died of recurrence within 5 years of diagnosis. None of the stage I patients with low cyclin E levels died within the same time period. The strong link between high cyclin E levels in stage I disease and poor prognosis suggests that these protein forms may play a specific role in the development of a malignant tumor.

"If this apparent correlation with aggressive breast cancer bears out, cyclin E analysis could provide a way to apply treatments and surveillance appropriately to the most at-risk patients," says Barbara Spalholz, Ph.D., chief of the Cancer Cell Biology Branch of NCI's Division of Cancer Biology.

A separate study suggests that cyclin E may be a marker for ovarian cancer, as well. Additional studies are under way including a prospective study of breast cancer patients to validate cyclin E's predictive value. Other research is focusing on the protein's unknown biological mechanisms to determine if cyclin E is a cause of, or merely correlated with, cancer's aggressiveness. If cyclin E is a direct cause of aggressive breast cancer, it could be a target for new treatments.

Keyomarsi K, Tucker SL, Buchholz TA, Callister M, Ding Y, Hortobagyi GN, Bedrosian I, Knickerbocker C, Toyofuku W, Lowe M, Herliczek TW, Bacus SS. Cyclin E and survival in patients with breast cancer. *New England Journal of Medicine*, November 14, 2002; 347(20):1566–1575.

PROTEASE INHIBITOR COULD FORESTALL BONE METASTASES

A study in mice has shown the potential for a protease inhibitor called maspin to prevent metastatic bone tumors in prostate cancer. The research by Wayne State University scientists, including NCI grant recipient Shijie Sheng, Ph.D., marks a promising advance toward preventing the spread of human prostate cancer to bone. Bone metastases are the primary cause of pain and death from this common cancer.

Protein-cleaving enzymes called proteases are important for normal cell development, but their presence in unhealthy cells can promote tumor growth and spread. Proteases are "major contributors to cancer's morbid effects," says Suresh Mohla, Ph.D., chief of the Tumor Biology and Metastasis Branch in NCI's Division of Cancer Biology. Many researchers have studied protease inhibitors as a means to block bone metastasis, but maspin is one of the few to live up to hopeful expectations.

In the Wayne State University study, tumor cells engineered to make maspin did not form invasive tumors in human bone fragments implanted in mice. In striking contrast, cells that did not create maspin formed large tumors that destroyed all bone tissue in the mice. While the exact mechanism by which maspin stops bone metastasis is not yet clear, maspin is known to be a potent inhibitor of urokinase-type plasminogen activator, or uPA, a protease that leads to bone deterioration and invasive tumor growth.

"Maspin presents an exciting therapeutic potential for treatment and prevention of metastases" in cancers that invade the bone, such as tumors of the breast and prostate, explains NCI's Mohla. He points out, however, that significant challenges remain in translating these mouse studies into human use. For example, implanting maspin-producing cells into rodents is much less complex than devising a method to target all prostate tumor cells throughout a patient's body to produce the metastasis suppressor.

Cher Cher ML, Biliran HR Jr, Bhagat S, Meng Y, Che M, Lockett J, Abrams J, Fridman R, Zachareas M, Sheng S. Maspin expression inhibits osteolysis, tumor growth, and angiogenesis in a model of prostate cancer bone metastasis. *Proceedings of the National Academy of Sciences*, June 24, 2003; 100(13):7847–7852. http://www.pnas.org/cgi/reprint/100/13/7847.pdf

SCIENTISTS MAY HAVE KEY TO CELL'S SWIFT RESPONSE TO DNA DAMAGE

DNA damage is the root cause of cancer and is responsible for the side effects caused by cancer treatments, such as hair loss, nausea, and bone marrow suppression. Yet DNA damage can also be used to kill tumor cells.

NCI-supported scientists at St. Jude's Children's Research Hospital in Memphis have discovered an early, critical process that helps cells respond to DNA damage. The finding opens exciting opportunities for cancer prevention, for enhancing radiation therapy, and for protecting healthy cells during cancer treatment. It also may lead to an assay for assessing exposure to toxins and other dangerous agents in the environment.

The process involves modifying an enzyme called ATM, which when activated sets off a cascade of reactions that halt the growth of a damaged cell and enable its repair and survival. The scientists developed an antibody that can specifically identify those ATM molecules that are responding to DNA damage. The antibody showed that damaged DNA signals the ATM to instigate repair within seconds of the damage occurring.

The scientists, led by Michael B. Kastan, M.D., Ph.D., envision several potential ways this new pathway could be manipulated. For example, ATM is central to a cell's response to radiation, so blocking its activity might make a tumor much more vulnerable to radiation therapy. Enhancing the repair process may prevent cancer development or help healthy cells in the body better tolerate exposure to cancer treatments. Kastan's group and several biotech companies are screening compounds to find those that can affect this pathway.

Among the proteins affected by activated ATM are BRCA1 and p53. These proteins play important roles in preventing cancer. When altered, they are responsible for inherited cancers, such as familial breast cancer. The new finding provides new insight into the way cells signal to BRCA1 and p53 following DNA damage.

Bakkenist CJ, Kastan MB. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. *Nature*, January 30, 2003; 421(6922):499–506.

HER2 RECEPTOR SHAPE ENCOURAGES TUMOR GROWTH

The family of proteins that serves as receptors for epidermal growth factor (EGF) is often involved with the aggressive growth and spread of a variety of cancers. The proteins sit in the cell membrane, with a portion jutting outside the cell to connect with growth factors or other chemicals, and a portion inside the cell to stimulate biochemical reactions caused by those external connections. They are named EGFR or HER1, and HER2, HER3, and HER4. Herceptin®, a drug that is effective against certain aggressive forms of breast cancer, targets the receptor called HER2.

Using a combination of techniques, including x-ray crystallography, Daniel Leahy, Ph.D., a Howard Hughes Medical Institute investigator at the Johns Hopkins University School of Medicine, and colleagues have determined the extracellular structure of several of these receptors, answering some fundamental questions about how the receptors operate. These structures suggest new approaches for interfering with their signals and may lead to the design of novel anticancer agents.

EGF receptors have a unique arm that remains folded when the receptor is inactive. The arm pivots open in a dramatic rearrangement when growth factors come to bind with it. The one receptor that stands out as different is HER2, which has its coupling arm always exposed, ready for action.

Over the past two years, groups in the United States, Japan, and Australia solved the crystal structures of different segments of these receptors. The groups came together to write a review article in September 2003, and "the picture that emerged was really very exciting," Leahy says. "The review was needed to fit all the puzzle pieces into the big picture."

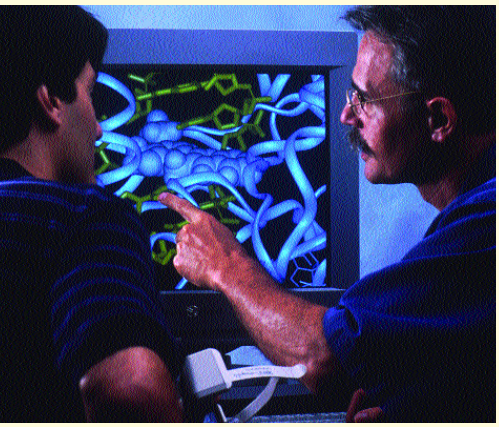
Today, they have seven different crystal structures, with distinct arrangements of the receptor domains, representing snapshots of both inactive and activated configurations. This wealth of data has revolutionized the view of how HER receptors are regulated.

"This explains a lot about HER2's unique properties," says Leahy. "It explains how HER2 is so promiscuous—readily partnering with each of the other EGF receptors—because it's always in the open state." When HER2 acts as a coreceptor to the other activated EGF receptors, growth signals are invariably enhanced, which likely underlies its role in several human cancers, he added.

Using the new information about the receptors' structures, researchers have begun work on new drugs that they hope will be more widely effective than Herceptin because they directly block the signaling between HER2 and its sister receptors.

Burgess AW, Cho HS, Eigenbrot C, Ferguson KM, Garrett TP, Leahy DJ, Lemmon MA, Sliwkowski MX, Ward CW, Yokoyama S. An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors. *Molecular Cell*, September 2003; 12(3):541–552.

NCI researcher Louis M. Staudt, M.D., Ph.D., has unveiled differences that help explain why one patient with a diffuse large B-cell lymphoma responds well to chemotherapy while another with the same disease can not be cured. On the surface both cancers appear the same, but a closer look at the molecular signature of the cancers reveals differences that could mean life or death.



Molecular characteristics seen when a tumor is first diagnosed dictate what happens years later, according to Staudt's work. A tumor's molecular profile predicts how it will respond to therapy, how aggressive it will be, and whether it will spread to other parts of the body. "Molecular wiring and the difference among patients is already there," says Staudt. "It's our job to use these signatures to make predictions and ultimately change therapy."

Staudt first developed this method of measuring DNA differences in diffuse large B-cell lymphoma, the most common type of non-Hodgkin's lymphoma, using a special DNA microarray. The "lymphochip" enabled him to analyze thousands of genes in lymphoma biopsy samples. It was the first example of taking samples from people with a clinical diagnosis of a cancer and splitting those samples into two groups that were different in the expression of genes and, more importantly, in the patients' ability to be cured by current therapies. Their first paper on the lymphochip was published in 2000.

Since then, Staudt's team of 14 researchers on the NIH campus has been using the latest genome technology to profile other lymphomas and leukemias while others study breast, lung, and other cancers. In 2003, his group reported exciting results in mantle cell lymphoma and chronic lymphocytic leukemia. They used molecular profiling to identify which mantle cell lymphoma patients will have a long survival following diagnosis and which will have aggressive disease. Patients in the most favorable group have a median survival of 6.7 years, whereas patients in the least favorable group survive less than 1 year after diagnosis. Knowing whose disease is slow-moving and whose is progressing rapidly should help determine who would do well with a watchful waiting approach and who may benefit from early and aggressive treatment, possibly with new therapeutic regimens, according to Staudt.

For chronic lymphocytic leukemia, scientists had shown several years ago that there were two types of this leukemia, but the means for telling the two apart and affecting treatment choices was complex and not available to most patients. Staudt's group showed that expression of a single gene, ZAP-70, is a surrogate for this distinction. "It lends itself to a rather easy clinical test that should be available to most patients within a year," says Staudt.

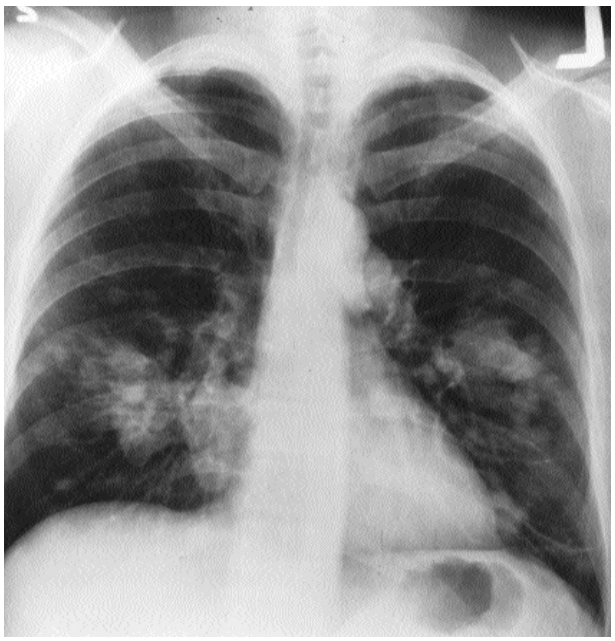
Improving diagnostic accuracy is only half of it. Staudt's group also probes the pathways within the cancer cell to see which ones are important for its growth and survival. They have clinical partners at NCI who can quickly move their findings into clinical studies and they look for partners within the pharmaceutical industry to develop drugs that will target the pathways they uncover, offering interventions targeted to each individual's cancer.

To speed molecular profiling research, NCI has formed the Lymphoma/Leukemia Molecular Profiling Project, an international consortium of eight institutions: University of Nebraska Medical Center, British Columbia Cancer Agency, Southwest Oncology Group, University of Wuerzburg in Germany, University of Barcelona in Spain, Norwegian Radium Hospital in Oslo, and St. Bartholomew's Hospital in London. Each institute sends its patients' tumor samples to Staudt's lab for his specialized molecular profiling.

Rosenwald A, Wright G, Wiestner A, Chan WC, Connors JM, Campo E, Gascoyne RD, Grogan TM, Muller-Hermelink HK, Smeland EB, Chiorazzi M, Giltnane JM, Hurt EM, Zhao H, Averett L, Henrickson S, Yang L, Powell J, Wilson WH, Jaffe ES, Simon R, Klausner RD, Montserrat E, Bosch F, Greiner TC, Weisenburger DD, Sanger WG, Dave BJ, Lynch JC, Vose J, Armitage JO, Fisher RI, Miller TP, LeBlanc M, Ott G, Kvaloy S, Holte H, Delabie J, Staudt LM. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. *Cancer Cell*, February 2003; 3(2):185–197.

MOLECULAR PROFILES MAY IMPROVE LUNG CANCER OUTCOMES

Lung cancer is the most frequent cause of cancer death in the United States. Even among patients whose cancer is diagnosed at an early stage, 40 percent will die from the disease. Scientists have been searching for a reliable way to identify those patients who need more than the standard treatment, which is surgery alone. Now, using molecular profiling, three groups of researchers have identified a subset of patients with a significantly worse outcome than the majority of stage I lung adenocarcinoma patients.



Scientists at the University of Michigan, Stanford University, and the Dana-Farber Cancer Center used various strategies for tumor selection and analysis, but each identified differences in the clinical behavior of tumors in a subset of early stage lung cancer patients whose tumors were indistinguishable using existing tests.

The results need to be confirmed in a larger data set, and NCI is already supporting that effort. To gain access to the numbers of specimens needed to confirm the initial results, the new study is being carried out. A data comparability study showed that the data from the study sites were of high quality and comparable, so a large study of 600 specimens is under way. Results are expected in late 2004.

If the combined study confirms that molecular profiles can predict patient outcome, physicians will have a new tool for selecting the most appropriate therapy for each patient. Those patients whose profiles predict a poor outcome might benefit from more aggressive treatment. The profiles may also identify new molecular changes that could be targets for novel therapies.

Bhattacharjee A, Richards WG, Staunton J, Li C, Monti S, Vasa P, Ladd C, Beheshti J, Bueno R, Gillette M, Loda M, Weber G, Mark EJ, Lander ES, Wong W, Johnson BE, Golub TR, Sugarbaker DJ, Meyerson M. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. *Proceedings of the-National Academy of-Sciences*,-November 20, 2001; 98(24):13790-13795.

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IMAGING PROVIDES A CLEARER PICTURE OF CANCER

Imaging scientists are testing molecular probes that can seek out specific proteins in a cancer cell and mark the cell for detection by standard imaging platforms such as magnetic resonance imaging (MRI) and positron emission tomography (PET). These new techniques—some tested in humans, others in animals—go beyond anatomical information to reveal biochemical events at the root of how cancers originate and spread. Researchers hope the new probes will detect cancers at ever-earlier stages and aid in personalizing medicine by quickly revealing whether a particular treatment is the best choice for an individual patient.

NCI-supported imaging researchers are studying a molecular imaging probe called fluorine-18 fluoroestradiol (FES) to help predict whether women diagnosed with advanced breast cancer will benefit from hormone therapy. The tracer points out breast cancer cells that have estrogen receptors and are most likely to respond to hormone therapy. This approach may help overcome the problems associated with using biopsies to determine estrogen receptor status in women with advanced cancer.

A second probe, fluorine-labeled thymidine (FLT), will soon enter NCI-funded clinical trials to measure how fast cancer cells are replicating. When used before treatment, then soon after treatment begins, it may help determine the extent to which a tumor's growth is being slowed.

"Within the next year we expect to start perhaps a half dozen clinical trials of molecular imaging agents to monitor patients' response to cancer treatment," says Daniel Sullivan, M.D., associate director of NCI's Cancer Imaging Program, "and within two to five years, we will have a much bigger body of evidence about how these agents can help in choosing the most appropriate treatment and monitoring patient response."

Two new imaging modes are well into NCI-supported human testing. The Digital Mammography Imaging Screening Trial is comparing the diagnostic power of digital mammography to conventional, film-based mammography, with results expected to be published in late 2004. The eight-year National Lung Screening Trial, launched in September 2002, is examining whether low-dose spiral computed tomography, used as a screening tool in people at high risk for lung cancer, reduces deaths from the disease compared with standard x-ray screening.

Feigal EG, Sullivan DC. National Cancer Institute and Imaging-Intersecting Scientific Opportunity with Clinical Need. *Journal of Biomedical Biotechnology*, 2004; 2004(1):3–4.

IMMUNE SYSTEM CAN BE ACTIVATED AGAINST MELANOMA

NCI scientists overcame a major hurdle in 2002 that enabled them to engineer a patient's own immune cells to attack and kill advanced melanoma. With a new method for growing T cells—the immune cells that recognize and kill foreign cells—they were able to boost the number of tumor-fighting cells in the body and keep them active long enough to beat back the tumor.

Thirteen patients with metastatic melanoma who had not responded to standard treatments underwent a process called adoptive transfer. They were given immune cells produced in the laboratory specifically to destroy their tumors. Six of the patients experienced at least 50 percent tumor shrinkage, with no new tumor growth. In four additional patients some cancer growths disappeared.

In previous studies, the T cells would last only a few days, not long enough to do their job, according to NCI's Steven A. Rosenberg, M.D., Ph.D., senior researcher of the study. Improvements in the way the immune cells are generated in the lab and in the way patients' bodies are prepared to receive them made all the difference.

The scientists use a small fragment of each patient's melanoma tumor to grow T cells in the lab, using T cells taken from the patients. Exposure to the tumor activates the T cells to recognize and attack cells from that specific cancer. As the T cells were growing, patients were given chemotherapy drugs to diminish their immune systems so that the new T cells would have the opportunity to rebuild the immune system. Once the T cells had multiplied to sufficient numbers in the lab, they were returned to the patients, who were also given a high dose of interleukin-2, a protein that stimulates continued T cell growth in the body.

The approach is still highly experimental, but Rosenberg and his colleagues are optimistic that adoptive transfer could be used to raise immune cells that will recognize and attack many tumor types, or to treat some infectious diseases, such as AIDS.

Dudley ME, Wunderlich JR, Robbins PF, Yang JC, Hwu P, Schwartzentruber DJ, Topalian SL, Sherry R, Restifo NP, Hubicki AM, Robinson MR, Raffeld M, Duray P, Seipp CA, Rogers-Freezer L, Morton KE, Mavroukakis SA, White DE, Rosenberg SA. Cancer regression and autoimmunity following clonal repopulation with anti-tumor lymphocytes and non-myeloablative conditioning. *Science,* October 25, 2002; 298(5594):850–854.

Dudley ME, Rosenberg SA. Adoptive-cell-transfer therapy for the treatment of patients with cancer. *Nature Reviews Cancer*, September 2003; 3(9):666–675.

DONATED IMMUNE CELLS CAN COMBAT BREAST CANCER

Using immune cells from a sibling, researchers were able to shrink tumors in patients with metastatic breast cancer. This is the first time researchers have clearly demonstrated that donated immune cells could act against breast cancer.

"The tumors were not completely eliminated, but the responses we saw provide hope that immunotherapies for breast cancer are worth pursuing," says the study's lead author Michael Bishop, M.D., of NCI's Center for Cancer Research.

Each of the 13 patients had already been through multiple treatments for metastatic breast cancer. At the beginning of this study, each patient's immune system was suppressed with chemotherapy drugs so that it would not reject the donated immune cells. Then stem cells from the blood of HLA-matched siblings were given to the patient. HLA-matched donor cells have the same set of proteins on their surface as the patient's own cells, so they are much more likely to be accepted by the patient's body. Once introduced into the patient, the stem cells begin to rebuild the patient's red blood cells, platelets, and white blood cells. A new immune system starts to develop.

Then the patient receives extra T cells from the sibling. T cells are specialized immune cells that recognize and kill foreign cells, such as cancer cells. This two-step approach—first stem cells, then T cells—was used for two reasons: The body is receptive to the T cells because it has already become used to the sibling's stem cells, and the researchers wanted to be able to distinguish any tumor regression due to the T cells rather than the chemotherapy.

The scientists will soon begin a study in up to 36 patients to see if they can go beyond tumor shrinkage to improve survival. Bishop's collaborator at NCI, Daniel Fowler, M.D., is manipulating T cells to reduce the likelihood that the patient's body will reject the T cells while maintaining their ability to kill tumors. This way, the T cells can be given immediately after the chemotherapy. The approach holds potential for other solid tumors as well.

Bishop MR, Marchigiani D, Grasmeder S, Steinberg S, Kasten-Sportes C, Chow C, Tamari M, Dean R, Gress R, Fowler D. Demonstration of clinical responses to adoptive cellular therapy using allogeneic T cells in metastatic breast cancer. Abstract #657. *Proceedings of the American Society of Clinical Oncology*. 2003.

DNA VACCINE READY FOR TESTING IN CERVICAL AND HEAD & NECK CANCER TRIALS

NCI-supported researchers are beginning clinical trials of DNA-based cancer vaccines for cervical cancer and for head and neck cancer. The DNA vaccine effort was spearheaded by T.-C. Wu, M.D., Ph.D., and Drew Pardoll, Ph.D., researchers at Johns Hopkins Medical Institutions. They focused on human papillomavirus-16 (HPV-16), a strain of HPV responsible for more than 20 percent of head and neck cancers and more than half of all cervical cancers.

The DNA in the vaccine codes for an altered form of the HPV's E7 protein, found in all HPV-16-infected tumor cells. The E7 protein is fused to a "heat-shock" protein, which helps boost the immune response by ferrying the E7 protein to the body's disease-fighting cells.

The vaccine will be used in at least three clinical trials at Hopkins in patients with preinvasive cervical cancer lesions or in patients with advanced head and neck cancer. Connie Trimble, M.D., assistant professor of obstetrics and gynecology at Johns Hopkins Medical Institutions, is the principal investigator on the cervical cancer vaccine trials. She and others designed a unique "pre-trial trial" to collect baseline data on the natural course of preinvasive cervical cancer lesions caused by HPV-16.

"We wanted to try and figure out what the natural immune response was to these lesions," said Trimble. The researchers collected tissue and lymphocytes over 15 weeks while monitoring the lesions. After 15 weeks, the women received state-of-the-art treatment. "People had never just watched in an organized way to see what would happen," she said, noting that while treatment would have been provided immediately if the lesions began to worsen, none worsened during the study period.

In fact, many women got better. "Thirty percent of the women resolved over 15 weeks, without any intervention," said Trimble. "So we started looking at the characteristics of lesions that resolve, and the characteristics of the women who resolve."

Women in the vaccine trial will receive three vaccinations four weeks apart, and will then be checked to see if the lesions have progressed. Seven weeks later, the women will receive standard treatment. "This study uses the same window [of time] as the previous study, so we'll be able to look at immune responses elicited by the vaccine and compare them to the natural immune responses," Trimble said.

"It's a unique situation because we can ask questions about what a successful immune response is against an established neoplastic process," she said. "That's the crux of the field of immunotherapy, but it isn't well understood in humans."

ESTROGEN THERAPY INCREASES OVARIAN CANCER RISK

Women in a large, long-term study who used estrogen-only menopausal hormone therapy had a 60 percent greater risk of developing ovarian cancer than postmenopausal women who did not use hormone therapy. The risk grew with increasing duration of use. Results from this and another large study of hormone therapy, published in 2002, have already had a marked impact on women's use of hormone therapy after menopause.

NCI scientists followed 44,241 women for about 20 years. The women were former participants in the Breast Cancer Detection Demonstration Project, a mammography screening program conducted between 1973 and 1980.

In the 1940s, women began using estrogens in high doses to counteract some of the discomforts of menopause such as hot flashes and vaginal dryness. After it became clear in the 1970s that women who took estrogen alone had a six to eight times higher risk of developing cancer of the lining of the uterus (endometrial cancer), doctors began prescribing progestin along with much lower doses of estrogen, which countered the endometrial cancer risk. Estrogens alone were limited to women who had undergone a hysterectomy.

Women in the 2002 study who took combination estrogen-progestin therapy were not at increased risk for ovarian cancer. However, says study author James V. Lacey, Jr., Ph.D., of NCI's Division of Cancer Epidemiology and Genetics, "there simply aren't enough data to say whether taking the combined therapy has an effect on ovarian cancer."

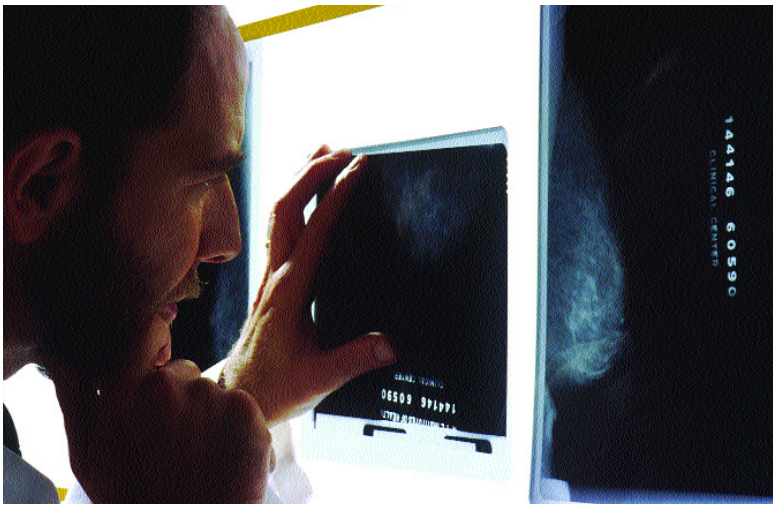
These data were published in conjunction with results of a large, multi-center clinical trial of the Women's Health Initiative, which showed increases in breast cancer, coronary heart disease, stroke, and blood clots in the lungs and legs for women who took combination estrogen-progestin therapy for an average of 5.2 years. Risk for hip factures and colon cancer decreased. Because the overall harm was greater than the benefit, that trial was stopped 3 years ahead of schedule.

Since these studies were published in 2002, use of menopausal hormone therapy among U.S. women has dropped dramatically, according to a study published in January 2004 in the *Journal of the American Medical Association*. Annual prescriptions plunged from 90 million during each year from 1999 through 2002 to 57 million in 2003.

Lacey JV, Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, Schatzkin A, Schairer C. Menopausal hormone replacement therapy and risk of ovarian cancer. *Journal of the American Medical Association*. July 17, 2002; 288(3):334–341.

THREE FACTORS AFFECT MAMMOGRAM RESULTS

According to a recent study conducted by a consortium of researchers from Dartmouth Medical School, NCI, and several other institutions, the density of a woman's breast tissue, her age, and whether she is using menopausal hormone therapy are important predictors of whether a screening mammogram will detect breast cancer.



The researchers reviewed about 463,000 mammograms performed on nearly 330,000 U.S. women aged 40 to 89. Breast cancer was eventually diagnosed in 2,223 of the women. The investigators analyzed the results of the mammograms, which were taken from 1996 through 1998, then looked at each mammogram's result and subsequent breast cancer diagnoses in relation to each woman's age, her breast density, and whether she was taking hormone therapy. With the large amount of data, the researchers were able to assess the individual and combined effects of the three factors.

The study showed that mammograms were more accurate for women whose breasts were less dense and more fatty, and were more accurate in older women. Of the factors examined, "breast density had the strongest association" with accurate mammograms, says study author Rachel Ballard-Barbash, M.D., M.P.H., associate director of the Applied Research Program in NCI's Division of Cancer Control and Population Sciences. Dense breast tissue may decrease mammography's accuracy by obscuring or mimicking tumors.

"The main thing we've discovered is that mammography performs differently among women with different characteristics," says the study's lead author, Dartmouth Medical School's Patricia A. Carney, Ph.D. "This finding is contrary to the popularly-held belief that mammography works the same for everyone."

Researchers are studying several approaches to improving mammography's accuracy. In the meantime, Carney and her colleagues recommend that women with dense breasts and those taking hormone therapy be told that increased breast density may obscure results and additional imaging may be needed to follow up on suspicious findings.

Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, Geller BM, Abraham LA, Taplin SH, Dignan M, Cutter G, Ballard- Barbash R. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography, *Annals of Internal Medicine*, 2003: 138:168-75.

A SINGLE GENE HELPS LIVER CANCER INVADE OTHER TISSUES

Scientists have found a gene that distinguishes between the deadliest liver cancers—those that will invade and spread to other tissues—and those that will not. This finding opens new diagnostic and treatment avenues for one of the most common and aggressive cancers worldwide.

The osteopontin gene may become a useful diagnostic tool for liver cancer's spread. And the protein it produces, called osteopontin, is a potential target for treatments for aggressive liver cancers.

"If we can identify in advance patients whose tumors are likely to metastasize, it will improve our ability to individualize treatment of their disease," says Xin Wei Wang, Ph.D., of NCI's Center for Cancer Research and the lead investigator of the study. The research was done in collaboration with surgeons at the Liver Cancer Institute of Fudan University in Shanghai.

To measure gene activity, the researchers used DNA microarrays—also known as DNA chips—glass slides that are coated with thousands of spots of DNA, each representing a different gene. The slide reacts with a sample of tumor tissue and the DNA spots on the chip corresponding to the active genes in the tumor light up.

After finding the gene, the researchers did additional experiments and showed that cells grown in the lab with high levels of osteopontin protein are more likely to invade neighboring tissue. Blocking the activity of the protein prevented tumor cells from spreading, both in mice and in cells grown in the lab. Thus, osteopontin may be a potential therapeutic target as well as a predictor of disease spread.

Ye QH, Qin LX, Forgues M, He P, Kim JW, Peng AC, Simon R, Li Y, Robles AI, Chen Y, Ma ZC, Wu ZQ, Ye SL, Liu YK, Tang ZY, Wang XW. Predicting hepatitis B virus-positive metastatic hepatocellular carcinomas using gene expression profiling and supervised machine learning. *Nature Medicine*, April 2003; 9(4):416–423.

BREAKING DOWN A CANCER CELL'S DEFENSES

NCI scientists are working on a way to deprive cancer cells of a key survival mechanism—the ability to thrive in a low-oxygen environment. Their systematic approach has generated several drugs that might be able to stop the most resilient cancer cells.

"Tumor hypoxia has become a major target in solid tumors," says Giovanni Melillo, M.D., of NCI's Developmental Therapeutics Program and SAIC-Frederick, Inc. "When cells lack oxygen—hypoxia—, the first thing they do is compensate, try to make new blood vessels. It's good for the tumor, bad for the patient. The cancer becomes more aggressive."

A transcription factor called HIF-1 (hypoxia-inducible factor) is essential for angiogenesis, the growth of new blood vessels. To find drugs that would block HIF-1, and ultimately starve tumors, Melillo and colleagues designed an assay and used it to screen one of NCI's chemical libraries. The high throughput screen uses automated equipment to screen thousands of compounds in a day.

They identified several potentially active compounds, some of which are already approved cancer drugs. Based on their research, however, those drugs would be used in a different way. Most anticancer drugs are given at high doses in cycles, one or a few days of drug followed by a three-week break, to let the bone marrow and other healthy cells recover. To disable HIF-1, a lower, daily dose would likely be more appropriate.

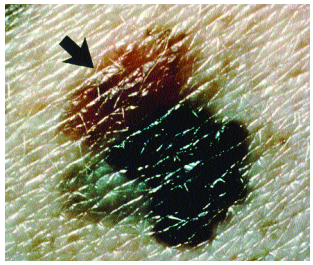
The researchers are studying these drugs in animals, to see if a low, continuous dose could sustain inhibition of HIF-1 while avoiding the harmful toxicities of standard chemotherapy.

Melillo says he hopes one day to see these drugs used in combination with drugs that block angiogenesis. "If one is able to shut down the blood supply to the tumor, the tumor—lacking oxygen—activates the HIF-1 response to survive," he explains. "If a second drug can block this compensatory response, the effect against the cancer cells can be much more pronounced. We'll be shutting down a response essential for cancer cells to survive."

Rapisarda A, Uranchimeg B, Scudiero DA, Selby M, Sausville EA, Shoemaker RH, Melillo G. Identification of small molecule inhibitors of hypoxia-inducible factor 1 transcriptional activation pathway. *Cancer Research*, August 1, 2002; 62(15):4316–4324.

IMPACT OF MELANOMA GENE VARIES BY GEOGRAPHIC LOCATION

2003 brought important news for people with a strong inherited susceptibility for melanoma. Whether they will actually develop this skin cancer varies by where they live, according to research led by Alisa Goldstein, Ph.D., and conducted by an international consortium including NCI scientists and researchers from Australia, France, Italy, the Netherlands, Sweden, and the United Kingdom.



"This result shows that factors other than genetics are important to the development of melanoma. Knowing this presents the opportunity to reduce risk in gene carriers," explains Margaret A. Tucker, M.D., chief of the Genetic Epidemiology Branch in NCI's Division of Cancer Epidemiology and Genetics.

Mutations or changes in the *CDKN2A* gene are an important factor in melanoma that runs in some families. So researchers in the NCI-supported Melanoma Genetics Consortium examined 80 melanoma-prone families with this gene mutation in Europe, Australia, and the United States.

Melanoma did not occur at a consistent rate across these families. Risks were lowest in Europe, higher in the United States, and highest in Australia. The researchers suggest that factors affecting melanoma occurrence in people in these geographic areas, perhaps sun exposure, also affect risk for melanoma among families that carry the *CDKN2A* mutation.

"Even when a strong susceptibility gene is identified, there are modifiers of that risk," says Margaret Tucker. "If we can identify the modifiers, we may be able to manipulate exposure or lifestyle factors and have a large impact on an individual's risk of eventually developing cancer."

The researchers are collecting new information on the 80 families and are expanding the number of families in the study. They plan to quantify sun exposure over time, and look at other risk factors, such as number of and types of moles, and will look for other genes that may play a role in risk.

Tucker's group has been working with the melanoma-prone families in the United States for 25 years, and has made sun protection an essential part of their care. When sun exposure is substantially reduced, risk of developing new melanomas drops. When melanomas do develop, they are very thin and curable.

Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, Chompret A, Ghiorzo P, Gruis N, Hansson J, Harland M, Hayward N, Holland EA, Mann GJ, Mantelli M, Nancarrow D, Platz A, Tucker MA. Geographical Variation in the Penetrance of CDKN2A Mutations for Melanoma. *Journal of the National Cancer Institute*, 2002; 94(12):894–903

NEW CLUES ON GENETIC SUSCEPTIBILITY FOR AGGRESSIVE PROSTATE CANCER

Results from several NCI-supported genetic epidemiology studies may help scientists better identify men at risk for aggressive prostate cancer. The studies, conducted at the Mayo Clinic, M. D. Anderson Cancer Center, and Wayne State University, also have important implications for improving prostate cancer diagnosis, treatment, and prevention.

Previous research suggested that chromosome 19q harbors a gene that codes for the aggressiveness of prostate cancer. A recent study by NCI grantees at the Mayo Clinic confirmed this finding. Mayo Clinic scientists analyzed genome scan data from men in 161 families with a history of prostate cancer. Along with strengthening the evidence about chromosome 19q, the study suggests that chromosome 4q may also be involved in tumor aggressiveness.

In another study, researchers at M. D. Anderson Cancer Center found a strong association between the presence of a certain allele—a mutational form of a gene—on chromosome 11 and a younger age at prostate cancer diagnosis. This allele, which is a form of the gene *cyclin D1*, is also linked with early-onset colorectal cancer and poorer prognosis for lung cancer. *Cyclin D1* helps regulate the cell cycle and is over-expressed in a wide variety of cancers.

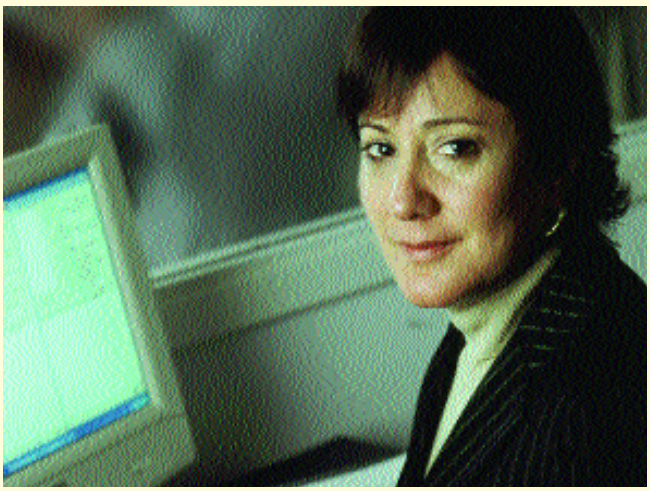
Finally, scientists at Wayne State University found that certain variations in the androgen receptor gene, as well as in genes that influence androgen metabolism, are associated with increased risk for prostate cancer, and for more aggressive prostate cancer.

Powell IJ, Land SJ, Zhou J, Sun Y, Dey J, Patel NP, Sakr WA, Hughes MR, Everson RB. Influence of androgen receptor and androgen metabolism polymorphisms on prostate cancer prognosis after prostatectomy in an ethnically diverse population. American Association for Cancer Research Proceedings. 2003.

Slager SL, Schaid DJ, Cunningham JM, McDonnell SK, Marks AF, Peterson BJ, Hebbring SJ, Anderson S, French AJ, Thibodeau SN. Confirmation of linkage of prostate cancer aggressiveness with chromosome 19q. *American Journal of Human Genetics*, 2003; 72(3):759–762.

Sanchez-Ortiz RF, Yamamura Y, Frazier ML, Babalan RJ, Troncoso P, Pettaway CA, Strom S. Relationship between cyclin D1 polymorphism and age at diagnosis of prostate cancer. Abstract #1090. American Association for Cancer Research Proceedings. 2003.

Smokers with certain genetic variants may be more likely to remain abstinent and less prone to relapse when trying to quit smoking, according to groundbreaking studies reported in 2002 and 2003 by NCI-supported researchers at the University of Pennsylvania's Abramson Cancer Center.



"Smoking cessation treatment may be much more effective if therapy could be tailored based on knowledge of the smoker's biological needs as well as his or her social needs," says Caryn Lerman, University of Pennsylvania, who found genetic variations that affect success in quitting smoking.

"Instead of using a standard, one-size-fits-all model of smoking treatment, we hope that, through genetics research, we can develop a more rational way of tailoring treatment to an individual's genetic profile," says Caryn Lerman, Ph.D., director of the University of Pennsylvania Transdisciplinary Tobacco Use Research Center (TTURC). NCI and the National Institute on Drug Abuse (NIDA) fund seven TTURCs at academic research centers to study various aspects of tobacco use and nicotine addiction—from genetics and pharmacology to communications and public policy. Additional support came from the Robert Wood Johnson Foundation. TTURC grants will be reissued in 2004 with funding from NCI, NIDA, and the National Institute on Alcohol Abuse and Alcoholism.

In 2002, Lerman's team reported on variations in CYP2B6, a gene that codes for an enzyme involved in brain metabolism of nicotine. Smokers who have one type of variation of the gene "experience greater increases in cravings for cigarettes and are about 1.5 times more likely to relapse during the treatment phase than smokers who do not have the variant." The study also showed that an antidepressant used to help smokers quit, bupropion, may lessen these effects, especially among women.

A study her group published in October 2003 added further evidence of genetic influences. Smokers with a specific combination of two genetic variants related to dopamine, a chemical in the brain that plays an important role in addiction, were more likely to remain abstinent and less prone to relapse when trying to quit smoking than those without the combination. This study provides the first evidence that genes that alter the activity of dopamine may influence success in smoking cessation.

"This research underscores the importance of not limiting genetic investigations of smoking behavior to single gene effects," Lerman says. She adds that any new findings related to the impact of genetics on tobacco use and medication effectiveness will need to be validated, and the roles of different genes, environment, and social factors need to be fleshed out. But she envisions a future when a smoker will go to the doctor for a panel of genetic tests and a psychosocial assessment and walk away with the treatment plan most likely to work for him or her.

Lerman C, Shields PG, Wileyto EP, Audrain J, Hawk LH, Pinto A, Kurcharski S, Krishnan S, Niaura R, Epstein LH. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. *Health Psychology*, 2003; 22(5):541–548.

BETA-CAROTENE SUPPLEMENTS NO GOOD FOR SMOKERS; VITAMIN E SHOWS PROMISE

Long-term follow up results from a study of vitamin E and beta-carotene supplements in smokers confirmed the detrimental impact of beta-carotene for this group and showed a potentially protective effect from vitamin E. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Trial was conducted by NCI and the National Public Health Institute of Finland from 1985 to 1993. Its aim was to determine if the two different supplements would prevent lung cancer and other malignancies in a group of 29,133 male smokers in Finland. Participants stopped taking the supplements in 1993, but the researchers followed them through 2001 to determine the long-term effects of the vitamins on cancer incidence and deaths.

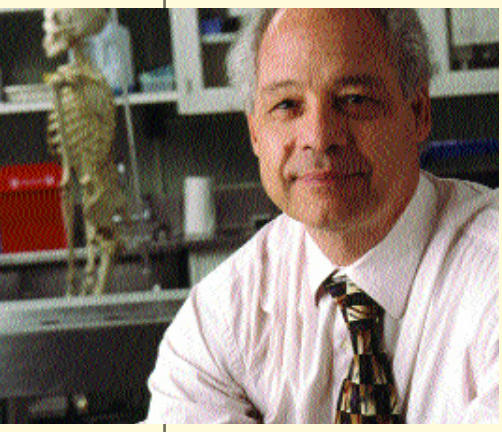
Men who took vitamin E had lower prostate cancer incidence while taking the supplement. Even after they stopped taking the vitamin, the men experienced slightly lower rates of prostate cancer than the placebo group, although the impact diminished as time went on.

The men taking beta-carotene had a higher mortality rate due to heart disease and lung cancer. The increased risk for lung cancer began to fall soon after the men stopped taking the supplements, but heart disease kept their mortality rate higher than the men who did not take beta-carotene. In both cases, the effects of the supplements began to disappear when supplementation was stopped.

The results confirm that smokers should avoid beta-carotene supplements. Vitamin E's protective effect against prostate cancer requires confirmation in other ongoing trials.

Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Malila N, Virtanen MJ, Albanes D, Taylor PR, Albert P. Incidence of cancer and mortality following ?-tocopherol and ?-carotene supplementation. *Journal of the American Medical Association*, July 23, 2003; 290(4):476–485.

Scientists may soon be able to obtain information about every tissue in the body from a finger prick's worth of blood. By looking for patterns of proteins in blood serum, NCI researchers, along with colleagues at the Food and Drug Administration (FDA), have developed a method to identify cancers at the earliest, most treatable stage. This work is likely to translate into better survival for patients with cancers that, like ovarian cancer, are usually diagnosed tragically late.



"If blood is coursing through every tissue of the body, remnants of what is happening within the tissues should be shed into the circulation," says NCI scientist Lance Liotta. He has turned his theory into a simple blood test that is winning attention for its ability to detect difficult cancers, such as ovarian cancer, at very early stages. The test also shows potential as a way to monitor therapy.

The NCI-FDA Clinical Proteomics Program has coupled the science of proteomics—the study of cell proteins—with sophisticated artificial intelligence programs. The scientists use a technique called mass spectroscopy to analyze serum protein patterns and software developed by partner Correlogic Systems, Inc. to sweep through thousands of protein fragments. The technique shows promise in lung, prostate, breast, and pancreatic cancers—with the most striking results in ovarian cancer.

In controlled experiments, proteomics was able to differentiate blood samples from patients with ovarian cancer, including early-stage cancer, with those from unaffected individuals. Currently, only 2 out of 10 ovarian cancers are diagnosed at an early stage, when prognosis is excellent. With an early-stage diagnosis, 95 percent of women are expected to live 5 years, compared with 20 percent or less of women diagnosed with late-stage disease.

The information-rich proteins represent "the underlying biological truth of what's going on in the patient's body," explains NCI's Lance Liotta, M.D., Ph.D., co-director of the proteomics program. "From a sample of blood, we can get a physiologic image of what's going on inside the body, and diagnose early-stage cancer while it's curable."

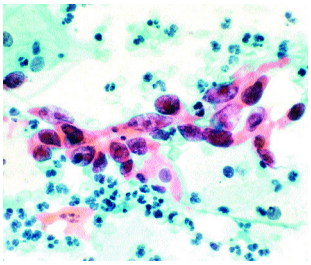
Proteomics is also showing an exciting potential to monitor a patient's response to a molecularly targeted cancer drug, which could prove useful in designing patient-tailored therapies.

Researchers are anxious to reap the clinical benefits of these discoveries. Says FDA co-director of the program, Emanuel Petricoin, Ph.D., "With our agencies' combined talents, we expect the new technologies under development to move quickly from bench to bedside."

Petricoin EF, Ornstein DK, Paweletz CP, Ardekani A, Hackett PS, Hitt BA, Velassco A, Trucco C, Wiegand L, Wood K, Simone CB, Levine PJ, Linehan WM, Emmert-Buck MR, Steinberg SM, Kohn EC, Liotta LA. Serum proteomic patterns for detection of prostate cancer. *Journal of the National Cancer Institute,* October 16, 2002; 94(20):1576–1578.

VACCINE PROMISES TO FEND OFF MOST CERVICAL CANCERS

A vaccine that is moving into large-scale clinical trials may one day prevent most cases of cervical cancer by protecting against the human papillomavirus, or HPV, an extremely common sexually transmitted disease that is the main cause of cancer of the cervix.



Early trials, funded by NCI with support from the NIH Office of Research on Women's Health, have indicated that the virus-like particle (VLP) vaccine is well tolerated and induces a strong protective response by the immune system. A large-scale efficacy trial in Costa Rica began in the spring of 2004, using the GlaxoSmithKline HPV 16/18 VLP vaccine. HPV 16 and 18—two common types of the virus—together account for an estimated 60 to 70 percent of cervical cancer cases worldwide.

In late 2002, Merck Research Laboratories reported exceptional efficacy of a similar experimental vaccine against HPV 16. None of the women in that placebo-controlled trial who received a series of three vaccine shots developed persistent HPV 16 infection.

NCI is also planning U.S. studies to evaluate another version of the HPV 16 VLP vaccine that, along with preventing infection with HPV 16, may also be able to fight an existing viral infection.

"Our hope and expectation is that we will soon have a vaccine in clinical use to prevent persistent infection with HPV 16 and 18, and cervical disease associated with these infections" says Allan Hildesheim, Ph.D., senior investigator in NCI's Division of Cancer Epidemiology and Genetics. "The vaccine could have tremendous public health implications. In the long term, if it cuts global incidence of cervical cancer in half, the vaccine could reduce the number of women affected by up to 250,000 per year."

DRUG IDENTIFIED TO PREVENT PROSTATE CANCERS

In 2003, the NCI-supported Prostate Cancer Prevention Trial (PCPT) identified the first-ever drug to reduce prostate cancer risk. Men in the study who took finasteride were 25 percent less likely to develop prostate cancer than men taking a placebo.

"From this study, we know we can eliminate the occurrence of prostate cancer in a substantial number of men," says the study's lead researcher, Ian Thompson, M.D., of the University of Texas Health Science Center at San Antonio. "I look at this as a huge first step in our journey away from the assumption that prostate cancer is an inevitable event in some men's lives."

He added one cautionary note: Men who did develop prostate cancer while taking finasteride were more likely than those on placebo to have high-grade tumors, which can spread quickly. The researchers are working to determine why.

Finasteride is approved by the Food and Drug Administration for treating a non-cancerous condition called benign prostatic hyperplasia and, at a much lower dose, for treating male pattern baldness. Its effectiveness in preventing prostate cancer appears to come from its ability to reduce levels of the male hormone dihydrotestosterone, which promotes growth of prostate cells and is involved in the development of prostate cancer.

Nearly 19,000 men ages 55 and older participated in the PCPT, which was supported by $73 million in NCI grants and coordinated by the Southwest Oncology Group. Although the 10-year trial was stopped ahead of schedule based on its striking results, researchers are following up on the PCPT findings to learn more about the molecular biology of prostate cancer and to determine who could maximally benefit from finasteride.

Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA. The influence of finasteride on the development of prostate cancer. *New England Journal of Medicine,* July 17, 2003; 349(3):215–224.

STEPS CLOSER TO COLORECTAL CANCER PREVENTION

Three NCI-supported studies giving new details about the interactions of several molecules that contribute to colorectal cancer growth are laying a solid foundation for targeted approaches to prevent the disease.

Raymond N. DuBois, M.D., Ph.D. and colleagues at the Vanderbilt-Ingram Cancer Center partnered with pharmaceutical and biotech firms to publish several papers in 2003 that have illuminated the pathways stimulated by cyclooxygenase-2 (COX-2).

DuBois, a long-time NCI grantee, was the first to report the role of the enzyme COX-2 in colon cancer. Since then, several COX-2 inhibitors, which suppress inflammation in the body, have been suggested as anti-cancer agents. One, celecoxib, was recently approved as an adjunct to traditional preventive measures in a group of patients genetically predisposed to colorectal cancer.

"It's looking more and more like mediators involved with chronic inflammation, such as COX-2 and prostaglandins, stimulate progression to cancer," says DuBois. "If we can target those, we should be able to inhibit progression of the tumor."

One study demonstrated a new pathway COX-2 uses to stimulate growth, migration, and invasiveness of colorectal cancer cells. The researchers found that prostaglandin E2, a product of COX-2 activity, triggers the epidermal growth factor receptor (EGFR), an important signaling molecule involved in the aggressive growth and spread of a variety of cancers. Several EGFR inhibitors exist, and DuBois says that early studies suggest that blocking both EGFR and COX-2 might have an additive effect.

In a second study, the team paired a COX-2 inhibitor with a matrix metalloproteinase (MMP) inhibitor in mice that are susceptible to colon cancer. The two drugs work on separate signaling pathways, and they did a better job in combination than either drug alone in reducing the number of adenomas in the mice. Importantly, the scientists were able to give the drugs at doses low enough to avoid side effects. The scientists wrote,"These compounds together could represent an easily tolerated chemopreventive regimen."

In a third study, the researchers explored how another signaling receptor, PPAR-gamma, blocks cancer cell growth and induces cell differentiation—two key steps in preventing cancer formation. This study opens the door to a potential new class of cancer prevention agents that activate PPAR-gamma specifically in epithelial cells in the colon.

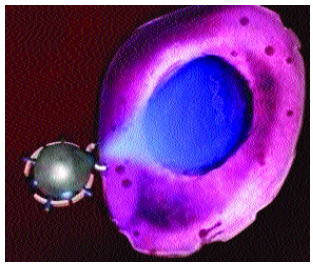
Buchanan FG, Wang D, Bargiacchi F, DuBois RN. Prostaglandin E2 regulates cell migration via the intracellular activation of the epidermal growth factor receptor. *Journal of Biological Chemistry*, September 12, 2003; 278(37):35451–35457.

Wagenaar-Miller RA, Hanley G, Shattuck-Brandt R, DuBois RN, Bell RL, Matrisian LM, Morgan DW. Cooperative effects of matrix metalloproteinase and cyclooxygenase-2 inhibition on intestinal adenoma reduction. *British Journal of Cancer*, May 6, 2003; 88(9):1445–1452.

Gupta RA, Sarraf P, Mueller E, Brockman JA, Prusakiewicz JJ, Eng C, Willson TM, DuBois RN. Peroxisome proliferator-activated receptor gamma-mediated differentiation: a mutation in colon cancer cells reveals divergent and cell type-specific mechanisms. *Journal of Biological Chemistry*, June 20, 2003; 278(25):22669–22677.

BIG PLANS FOR SMALL-SCALE SCIENCE

Researchers are pinning huge hopes on the science of tiny devices that could spot the earliest signs of cancer by interacting with the DNA, RNA, and proteins inside individual cells. Nanotechnology, the science of creating useful materials, devices, and systems by manipulating matter on the nanoscale (a nanometer is one billionth of a meter), has the potential to yield new tools that could transform cancer prevention, early detection, imaging, and treatment.



In 2003, nanoscience research was supported by three NCI programs managed by the Office of Technology and Industrial Relations: the Innovative Molecular Analysis Technologies program, the Fundamental Technologies for Biomolecular Sensors program, and the Unconventional Innovations program. These programs are producing notable achievements, including the development of targeted nanoparticles that enhance tumor imaging and the creation of molecular probes to predict the efficacy of treatments.

NCI-supported investigators are also creating nanotechnology platforms that could diagnose and treat cancer simultaneously. Scientists are currently evaluating these technologies in animals to determine if they are suitable for human clinical trials. Ultimately, this research aims to create targeted, multifunctional nanoparticles that circulate through the body, detect cancer-related molecular changes, release appropriate treatment compounds, and monitor a treatment's effectiveness.

Scientists predict that nanotechnology-based methods for cancer diagnosis and treatment could be available for clinical use within the next decade. In order to accelerate the application of nanotechnology tools to cancer biology, NCI is developing a Nanotechnology Plan under the leadership of Mauro Ferrari, Ph.D., Professor of Biomedical Engineering and Internal Medicine at Ohio State University. Dr. Ferrari, who is an expert in the field of biomedical nanotechnology, commenting on nanoscience's predicted impact said, "Great progress is already being made. Nanotechnology is expected to revolutionize the ways in which we diagnose and treat cancer."

http://otir.nci.nih.gov/brochure.pdf

SOPHISTICATED IMAGING ENHANCER STUDIED AS BIOPSY ALTERNATIVE

Nano-sized magnetic particles are enabling scientists to track down otherwise undetectable cancer cells in the lymph nodes of patients with prostate cancer. These virus-sized nanoparticles, which are injected into the body to accumulate in the lymph nodes, can be visualized with high-resolution magnetic resonance imaging (MRI).

NCI grant recipient Ralph Weissleder, M.D., Ph.D., and colleagues at the Massachusetts General Hospital, Harvard Medical School, and the Netherlands' University Medical Center reported in June 2003 that these nano-sized magnetic particles can enhance MRI enough to diagnose elusive lymph-node metastases in prostate cancer. The investigators correctly identified all 33 patients in their study whose prostate cancer had spread, or metastasized, to the lymph nodes.

Currently, determining whether prostate cancer has metastasized requires an invasive biopsy, in which lymph nodes near the prostate gland are removed and examined in the laboratory. That may change, however, if FDA approval is received for this MRI-enhancing agent known as Combidex®.

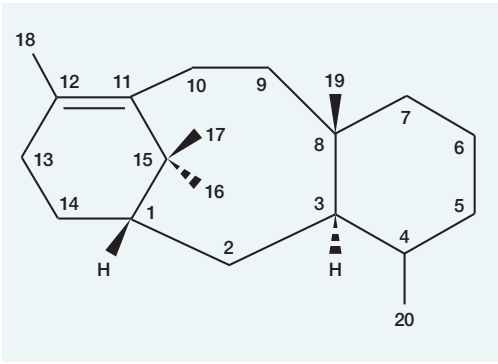
Accurate staging can dramatically affect treatment choices and outcome for many cancers, including prostate cancer and breast cancer, in which Combidex® is also being studied. When prostate cancer is still confined to the prostate, the disease is often treated with radical prostatectomy, watchful waiting, or radiation. When it has spread or metastized to lymph nodes, however, treatment typically includes more aggressive hormone therapy plus radiation.

If approved for clinical use, "Combidex® could improve cancer staging and thus change the management of the patient," says John M. Hoffman, M.D., chief of the Molecular Imaging Branch of NCI's Cancer Imaging Program. "Unnecessary surgeries could possibly be significantly reduced, and patients could get the most appropriate therapies for their stage of cancer."

Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, de la Rosette J, Weissleder R. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *New England Journal of Medicine*, June 19, 2003; 348(25):2491–2499.

TAXANE ALTERNATIVE MAY SIDE-STEP DRUG RESISTANCE

New drugs known as epothilones are being developed as hopefuls to join the taxane class of chemotherapy agents to treat various cancers, including metastatic breast cancer. Like Taxol® and other taxanes, epothilones fight cancer by halting cell replication. Unlike taxanes, epothilones appear able to evade the cancer cells' drug resistance mechanisms.



"The main advantage of the epothilones is they seem to be rather insensitive to multi-drug resistance, which in the end deprives many cancer therapies of their long-term effectiveness," says Samuel J. Danishefsky, Ph.D., Memorial Sloan-Kettering Cancer Center researcher and NCI grant recipient. "There is a good possibility that the epothilones could take over for Taxol when that treatment fails."

At Danishefsky's request, NCI's Rapid Access to Intervention Development (RAID) program helped initially in the preparation of an epothilone compound for mouse studies. In Danishefsky's NCI-funded studies, the mice tolerated the epothilone agent well and the drug was "virtually curative" against a variety of tumors, says Edward Sausville, M.D., Ph.D., former associate director of NCI's Developmental Therapeutics Program, which operates RAID. Follow up studies by NCI grantee Danishefsky in mice, rats, and dogs were encouraging in their results and set the stage for human trials.

Kosan Biosciences, Inc., in collaboration with Hoffmann-LaRoche, is developing epothilones commercially and has advanced the Danishefsky-studied epothilone D into three phase II clinical trials. Other companies with epothilone drugs in their development pipelines are Bristol-Myers Squibb and Novartis Oncology.

Drug companies are meanwhile exploring structural variations on epothilones that could prove less toxic or more potent than those currently in human studies, and are also seeking alternatives to current, costly production methods.

Promising second generation epothilones synthesized in Danishefsky's laboratory are undergoing pre-clinical evaluation.

Rivkin A, Yoshimura F, Gabarda AE, Chou TC, Dong H, Tong WP, Danishefsky SJ. Complex target-oriented total synthesis in the drug discovery process: the discovery of a highly promising family of second generation epothilones. *Journal of the American Chemical Society*, March 12, 2003; 125(10):2899–2901.

DRUG MAY MAKE SURGERY POSSIBLE FOR LIVER CANCER

Because liver cancer relies on the amino acid arginine for its growth, researchers have been searching for a way to prevent cancer cells from taking arginine from the blood. A drug called arginine deiminase (ADI) could do the job, but its effects alone are too short-lived, lasting only about an hour. Scientists overcame that problem by masking ADI in polyethylene glycol, or PEG, enabling the drug to stay in the bloodstream for about two weeks. In 1998, studies found that ADI-PEG killed liver cancer cells in mice.

More recently, NCI-funded scientists at the M. D. Anderson Cancer Center in Houston tested ADI-PEG in a small number of people with the most common liver cancer, hepatocellular carcinoma (HCC) and cirrhosis—with exciting results.

Most patients with HCC and cirrhosis live less than two months. When surgery is possible, the outlook improves, but a mere 6 percent of liver cancer patients are candidates for surgery. The ADI-PEG shrank tumors sufficiently so that two patients could undergo surgery. Larger trials to find the best treatment dose are now under way at the Pascale National Cancer Institute in Naples, Italy and at the M. D. Anderson Cancer Center, the latter with NCI support.

Some patients in the Italian study have been disease-free for more than two years. The numbers are small, but researchers are excited about the results because of the decrease in deaths and because the treatment produces few side effects and appears to be well tolerated. ADI-PEG does not damage normal, healthy cells.

Other types of cancer rely on arginine, notably melanoma. To a greater or lesser extent, sarcoma, leukemia, lymphoma, and cancers of the breast, brain, cervix, lung, and colon also are nourished by arginine. Researchers hope to study ADI-PEG's impact on these cancers as well.

Curley SA, Bomalaski JS, Ensor CM, Holtsberg FW, Clark MA. Regression of hepatocellular cancer in a patient treated with arginine deiminase. *Hepatogastroenterology*, September-October 2003; 50(53):1214–1216.

LETROZOLE REDUCES RECURRENCE OF BREAST CANCER

The long-term outlook for breast cancer survivors improved significantly with news of a study that revealed the benefits of a drug that inhibits the synthesis of the hormone estrogen. The large, international study of the drug letrozole was specific to postmenopausal women who had been treated for early stage breast cancer that was estrogen-receptor positive and had just completed a five-year course of tamoxifen.

Women who took letrozole (Femara®) were 43 percent less likely to experience a recurrence compared to women who took a placebo. The study, begun in 1998, was stopped ahead of schedule in 2003 when the positive effects became clear, so that the women taking a placebo could be offered the drug.

The Canadian-led study of more than 5,000 women was made possible by a public-private partnership between the Canadian Cancer Society, NCI, and Novartis Pharmaceuticals, the company that makes Femara.

These results have major implications. More than half of breast cancer survivors are postmenopausal and take a five-year course of tamoxifen after their initial treatment. The drug tamoxifen deprives breast cancer cells of estrogen and can reduce breast cancer recurrence by 47 percent. Unfortunately, resistance to tamoxifen develops over time, limiting the duration of tamoxifen's effectiveness to 5 years. Up until now, no treatment has been available for women after they complete the five-year course of tamoxifen.

"More than half of women who develop recurrent breast cancer do so more than five years after their original diagnosis," says Paul Goss, M.D., Ph.D., of Princess Margaret Hospital in Toronto. "For years, we have thought that we had reached the limit of what we could do to reduce the risk of recurrence with five years of tamoxifen. Our study ushers in a new era of hope by cutting these ongoing recurrences and deaths from breast cancer after tamoxifen by almost one half." Goss, a leading expert in novel hormone therapies for the treatment and prevention of breast cancer, conceived of and chaired the international trial with letrozole.

While both tamoxifen and letrozole block estrogen's growth-promoting action on tumor cells dependent on this hormone, they do so in different ways. Tamoxifen blocks estrogen from binding to cancer cells, whereas letrozole actually reduces the body's production of estrogen.

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ, Pater JL. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *New England Journal of Medicine*, November 6, 2003; 349(19):1793–1802.

ASPIRIN BENEFICIAL FOR THOSE AT RISK FOR COLON CANCER

Two recent randomized, placebo-controlled trials funded by NCI and a third study from France recently reported in Gastroenterology point to the benefit of aspirin against colon cancer and its recurrence. The results revolve around adenomas, non-cancerous growths in the colon that are a strong risk factor for colon cancer. Removing adenomas or preventing their recurrence significantly reduces the risk for colon cancer.

Researchers at Dartmouth University and colleagues around the country followed three groups of people who had recently had adenomas removed. One group took a placebo, a second group a "baby aspirin" (81 milligrams), and the third group a standard aspirin (325 milligrams). Compared to the group taking the placebo, those who took the "baby aspirin" were 19 percent less likely to develop another adenoma; those who took the standard-dose aspirin were 4 percent less likely to have another adenoma.

In the second study, done within the Cancer and Leukemia Group B and based at the University of North Carolina, researchers found a 35-percent reduction of adenomas in people who had already been treated for colorectal cancer. These people had taken the standard aspirin dose.

"Fortunately, aspirin seems to reduce the risk for adenoma when it is taken routinely at doses used in preventing heart disease or for arthritis," says Ernest Hawk, M.D., M.P.H., of NCI's Division of Cancer Prevention. "So patients using aspirin for these reasons may also be decreasing their risk for colon adenomas and cancer. Of course, aspirin—like any medicine—can cause serious side effects, such as stomach ulcers. It's important for people to carefully weigh the risks and benefits. Indeed, no one should take aspirin in an effort to prevent colon cancer without first consulting a doctor."

Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. *New England Journal of Medicine*, March 6, 2003; 348(10):891–899.

Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, Petrelli N, Pipas JM, Karp DD, Loprinzi CL, Steinbach G, Schilsky R. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *New England Journal of Medicine*, March 6, 2003; 348(10):883–890.

STUDIES EXPLAIN IMPACT OF SOCIAL SUPPORT ON OVARIAN CANCER PROGRESSION

Psychosocial factors, such as stress, depression, and social support, long known to affect the immune system, have been associated with cancer progression. But the biological basis of these relationships has been unclear. NCI grantees at the University of Iowa, Susan K. Lutgendorf, Ph.D., Anil K. Sood, M.D., (now at M. D. Anderson Cancer Center) and colleagues, have shed new light on how cancer cells respond to stress.

Lutgendorf and Sood's team drew a connection between social support, stress hormones, and a factor called vascular endothelial growth factor, or VEGF, that supports tumor progression. VEGF helps a tumor increase its blood supply and higher levels of VEGF are related to poor survival in women with ovarian cancer.

The researchers found that women with ovarian cancer who reported higher levels of social support had lower levels of VEGF. In contrast, individuals who reported greater distress—feelings of helplessness or worthlessness—had higher VEGF levels.

"This was one of the first clinical findings in humans indicating that behavioral factors may not only be related to the immune response, but also to substances produced by tumors and surrounding cells that promote tumor progression," Lutgendorf said.

The scientists went further and treated two ovarian cancer cell lines with stress hormones, including norepinephrine and epinephrine, at levels similar to those produced by the body during times of stress. The researchers saw a profound increase in VEGF production by the cancer cell lines. Conversely, when they added propranolol, a drug that blocks these stress hormones, VEGF levels did not increase.

The Iowa team has begun a larger prospective study to see if social support, distress, and VEGF levels are related to ovarian cancer recurrence. If this study supports earlier results, Lutgendorf envisions the use of behavioral interventions to reduce stress in patients in need. Further research may also lead to drugs that block the actions of stress hormones in cancer patients.

Lutgendorf SK, Johnsen EL, Cooper B, Anderson B, Sorosky JI, Buller RE, Sood AK. Vascular endothelial growth factor and social support in patients with ovarian carcinoma. *Cancer*. 2002; 95(4):808–815.

ZEROING IN ON COLON CANCER RISK FACTORS IN AFRICAN AMERICANS

African Americans have the highest incidence of colon cancer among U.S. racial-ethnic groups. Findings from the NCI-supported North Carolina Colon Cancer Study suggest that, while high calorie intake increases risk of colon cancer in both African Americans and Caucasians, some racial differences in incidence may be due to intake of fiber, fat, and certain micronutrients.

Jessie Satia-Abouta, Ph.D., Robert Sandler, M.D., M.P.H., and colleagues at the University of North Carolina, Chapel Hill, found that high total calories consumed was consistently associated with an increase colon cancer risk for both African Americans and Caucasians—a finding that is "in keeping with what we have long recognized as the association between obesity and colon cancer," says Sandler, principal investigator on the NCI-supported study.

Coupled with findings from a previous study, the North Carolina Colon Cancer Study also suggests that African Americans may decrease their risk for colon cancer by consuming a diet high in fiber and low in saturated fat. A high level of dietary fiber was associated with a statistically significant 50 percent to 60 percent risk reduction in African Americans. The risk reduction in Caucasians was substantially lower. Alcohol intake was not associated with colon cancer risk for either group.

In the study, which included 613 participants aged 40 to 80 with colon cancer (276 of them African American) and 996 matched controls (400 African American), researchers interviewed participants about their potential colon cancer risk factors, and assessed diet over a one-year period using a food frequency questionnaire.

A related analysis on the same study population suggests that high intakes of certain micronutrients in food sources—specifically, beta carotene, vitamin C, and calcium for Caucasians and vitamins C and E for African Americans—are independently associated with 30 percent to 70 percent reductions in colon cancer risk.

Satia-Abouta J, Galanko JA, Potter JD, Ammerman A, Martin CF, Sandler RS. Associations of total energy and macronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina colon cancer study. *American Journal of Epidemiology*, 2003; 158(10):951–962.

Satia-Abouta J, Galanko JA, Martin CF, Potter JD, Ammerman A, Sandler RS. Associations of micronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina colon cancer study. *Cancer Epidemiology, Biomarkers & Prevention*, 2003; 12(8):747–754.

NCI has long encouraged Americans to reduce their risk for cancer and other diseases by eating 5 to 9 servings of fruits and vegetables each day. In 2003, NCI began taking special steps to reach African American men with the 9 A Day message.

"What's critical here is that the right people give the right messages in the right places and to the right people," says Gary Dennis, M.D., chief of the Division of Neurosurgery at Howard University Hospital in Washington, D.C. "This is a powerful program." Dennis points to the Body and Soul effort: "We know, through research, that the church can be a vital ally. We did a small study, and we found that in churches that were not participating, nothing much happened, but among the congregations at participating churches, people did change their diets. They lost weight. They felt better."

African American men suffer a disproportionately high incidence of illness and death from chronic diseases related to diet, such as colon cancer. With the help of celebrities like radio personality Tom Joyner, basketball legend Clyde Drexler, and football star Kellon Winslow, NCI has launched a full-court press to persuade African American men between the ages of 35 and 54 to increase their intake of fruits and vegetables.

Communication efforts launched in 2003 included radio spots on ABC's Urban Advantage Network reaching more than 225 urban stations, and an Internet site featuring upbeat messages and tips for changing dietary habits, all especially geared towards African American men. A newly available NCI brochure, "Men Eat 9 A Day," is distributed by NCI's partners, including the National Association for the Advancement of Colored People and the National Medical Association (NMA). Through the National Newspaper Publishers Association, NCI collaborates with African American-owned newspapers across the country on a column, *Eat Better, Live Better*. Author Terry Mason, M.D., a leader in the NMA, gives readers practical health tips.

NCI's 9 A Day partnerships continue to dramatically extend the Institute's reach, taking the program to community organizations where it is likely to have the biggest impact. For example, NCI and the American Cancer Society are collaborating this year to disseminate *Body and Soul*, an evidence-based intervention put into practice by African American churches that have committed to spread the word and include more fruits and vegetables –and fewer fatty foods– at church functions.

www.9aday.cancer.gov

TAKING THE GUESSWORK OUT OF COMPREHENSIVE CANCER CONTROL

Cancer control planners and program staff all share the same goals—reducing cancer risk and deaths due to cancer and improving quality of life for survivors. Access to a new Internet portal for health professionals, called Cancer Control PLANET, will help them reach these important goals. The PLANET Internet portal is a collaboration among the NCI, the Agency for Healthcare Research and Quality (AHRQ), the American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), and the Substance Abuse and Mental Health Services Agency (SAMHSA).

It provides links to essential tools for designing systematic and evidence-based approaches to comprehensive cancer control. "Health professionals working in cancer control now have a one-stop shop for research-tested approaches and access to national and state data for designing effective and comprehensive cancer prevention and control programs," says Jon Kerner, Ph.D., director of NCI's development team.

At the heart of PLANET (***P***lan, ***L***ink, ***A***ct, ***N***etwork with ***E***vidence-based ***T***ools) is an interactive five-step approach to comprehensive cancer control program planning, implementation, and evaluation:

Assess program priorities by determining which populations in a state are at highest risk for certain cancers or certain behaviors, using data from the *State Cancer Profiles* Internet site, jointly developed by NCI and CDC.

Identify potential partners using a Internet site jointly developed by NCI, CDC, and ACS.

Determine the effectiveness of different approaches to reducing the cancer burden using the CDC-supported Internet site *Guide to Community Preventive Services* and the AHRQ Internet site *Guide to Clinical Preventive Services*.

Find research-tested intervention programs for immediate use through a Internet site jointly developed by NCI and SAMHSA.

Plan and evaluate your program using guidelines and tools on the Internet site, including CDC's *Guidance for Comprehensive Control Planning* and AHRQ's *Put Prevention into Practice*.

Cancer Control PLANET reflects NCI's commitment to interagency cooperation and collaboration from discovery through delivery. In addition to guiding users through the five program steps, PLANET also offers topic-specific guidance on cancer control programs designed for breast cancer, cervical cancer, diet and nutrition, physical activity, sun safety, and tobacco control, with more to come.

http://cancercontrolplanet.cancer.gov

CREATING A PARTNERSHIP TO ACCELERATE CANCER DRUG DEVELOPMENT

The National Cancer Institute and the Food and Drug Administration are sharing expertise and resources to streamline cancer drug development and bring safe, better medications and diagnostics to cancer patients more quickly.

The NCI/FDA Oncology Task Force, a group of senior staff from both agencies, will oversee implementation of the partnership, which announced two initiatives in November 2003:

Cancer fellowship training programs to develop a corps of physicians and scientists who are expert in clinical research and the regulatory approval process. Fellows will work in clinical oncology programs at NCI as well as in the technical and regulatory review programs at the FDA. Fellows will bring state-of-the-art knowledge to bear on the design, conduct, and review of clinical trials.

A new system for submitting investigational new drug (IND) applications electronically. The FDA must review IND applications before new drugs can be studied in humans. Electronic submission will lead to shorter FDA processing time, thereby giving cancer patients earlier access to clinical trials of new drugs. The system will be run through another new NCI program called caBIG (Cancer Biomedical Informatics Grid). caBIG will build a biomedical informatics network to connect teams of cancer investigators, their data, and their research tools. Fifty NCI-designated Cancer Centers are participating in a feasibility test of caBIG. This platform will allow research groups to tap into the rich collection of emerging cancer research data while supporting their individual investigations as well.

"The FDA is committed to finding better ways to get safe and effective treatments to patients with life-threatening diseases as quickly as possible," said former FDA Commissioner Mark McClellan, M.D., Ph.D. "At a time when the opportunities to reduce the burden of cancer are greater than ever, sharing tools and resources with our colleagues at the National Cancer Institute will help us fulfill that mission."

"The collaboration will help the two agencies take full advantage of their combined knowledge base at a time when many new kinds of anti-cancer agents are in the pipeline," said NCI Director Andrew von Eschenbach, M.D. "Molecularly targeted drugs and other novel agents offer great promise, but they also present new challenges that require more collaboration between those involved in their discovery and development."

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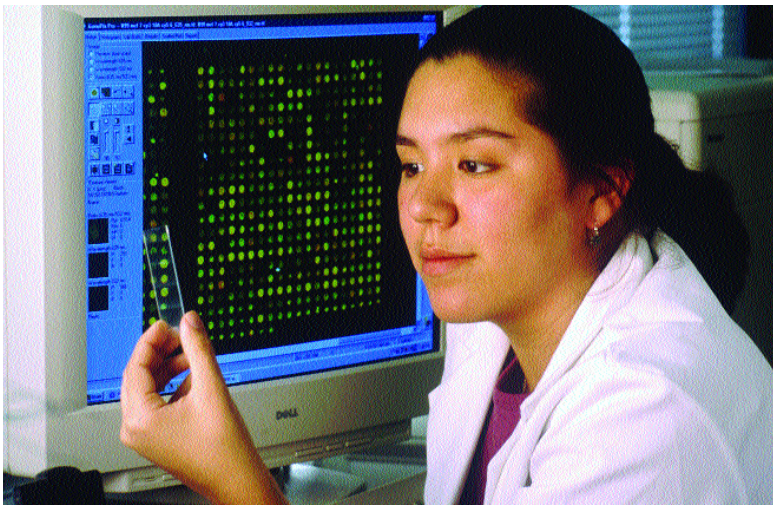
http://cabig.nci.nih.gov/

SPEEDING THE EVALUATION OF BIOMARKERS WITH TISSUE MICROARRAYS

Researchers need efficient, economical ways to analyze hundreds of tissue specimens to evaluate markers that will accurately predict a patient's prognosis and likely response to therapy. NCI's Cancer Diagnosis Program is working with clinical researchers around the world to make hundreds of specimens available on tissue microarrays.



Tissue microarrays are blocks of wax that contain large sets of tissue samples. Each block can contain hundreds of samples from different cancer cases—each just under a millimeter across. Tissue microarrays are designed to include enough samples of different tumors so that researchers can determine whether a particular marker is unique to a specific cancer site.

NCI is also creating tissue microarrays designed to give researchers enough statistical power to determine if specific markers change as the disease progresses. These arrays are specific to one type of cancer and contain tissue samples from patients diagnosed at different stages. Breast cancer tissue arrays are available from the NCI Cooperative Breast Cancer Tissue Resource.

NCI offers tissue microarrays for ovarian cancer, colon and rectal cancer, prostate cancer, and bladder cancer. The Cancer Diagnosis Program is working with NCI-supported Clinical Cooperative Groups to make arrays containing tissue samples from randomized clinical trials. Researchers will use these tissue microarrays to evaluate markers that can predict whether a patient is likely to respond to a particular therapy.

http://www.cancerdiagnosis.nci.nih.gov/

LOCATING HUMAN TISSUE SPECIMENS FOR RESEARCH

Hospitals are a treasure trove of tumor samples and related clinical data. NCI's Cancer Diagnosis Program is directing a feasibility study designed to help researchers access hospital electronic databases to locate human tissue specimens and associated clinical and pathologic data needed for cancer research—the Shared Pathology Informatics Network (SPIN).

SPIN will use Internet technology and peer-to-peer architecture to create a virtual database of archived specimens that exist at different hospitals. When fully developed, SPIN will allow approved researchers to conduct quick searches—not much longer than a Google™ search—of tissue specimen data from multiple hospitals while allowing those hospitals to maintain local control of their own data and samples.

There are several challenges to creating this resource: patient privacy must be protected, hospital computers operating on different software must be able to communicate with each other, and the same types of data in pathology reports must be coded the same way regardless of their hospital of origin.

NCI is addressing the technical challenges as it creates a test SPIN with hospitals in Boston, Indianapolis, Pittsburgh, and Los Angeles. To protect patient privacy, test records will not include patient identifiers. NCI will develop a tiered permission plan, designed to allow broad access to aggregate data, researcher access to de-identified data records, and access to summarized de-identified reports and even de-identified tissue blocks for researchers with Institutional Review Board approval to conduct SPIN collaborative projects.

If SPIN proves feasible, NCI hopes to expand the network, linking researchers with the rich resource of tissue samples located in hospitals around the country.

http://spin.nci.nih.gov/

COMBINING COHORTS FOR MAXIMUM IMPACT

Researchers conducting several large cohort studies are trying to find out what causes cancer, looking at heredity, diet, lifestyle, and other factors—but usually they are working in isolation. To tap the enormous potential of data combined from all the studies and to confirm findings from one study to another, NCI created the Cohort Consortium.

Cohorts are groups of individuals followed over time to track disease occurrence. Researchers periodically collect medical information and biological specimens from the participants. Because large cohort studies are expensive, few exist. NCI's Cohort Consortium brings 23 public and private cohort studies together to make the best use of the wealth of information available within each.

In 2003, the Consortium received approval to fund its first initiative, which is designed to do two things. First is to test feasibility—to learn whether independent investigators working with different cohorts can share data effectively to answer research questions and confirm findings from one cohort to another.

Second is to look at how genes interact with hormones, growth factors, and other risk factors in breast and prostate cancer development. Researchers will draw data from 897,000 people enrolled in 10 cohorts, 8,850 with prostate cancer and 6,160 with breast cancer. They will look for undiscovered inherited gene variants that may contribute to the development of these two cancers, perhaps through interactions with levels of hormones and growth factors, other risk factors such as family history and age at which a woman had her first child, environmental exposures, and health behaviors that work together to increase cancer risk. The two cancers were chosen because of similarities in the causal pathways for both. The large numbers of persons to be studied are necessary in order to tease out the associations among the various risk factors of potential interest. Only by combining data from many thousands of people will it be possible to begin to determine the role of interactions between genetic determinants and environmental factors in the development of human cancer.

Two of the cohorts are from NCI's Division of Epidemiology and Genetics. The others are the American Cancer Society/Cancer Prevention Study-II; the European Prospective Investigation into Cancer and Nutrition Study (EPIC) coordinated by the International Agency for Research on Cancer in Lyon, France; Harvard University's Nurses Health Study I and II, Physicians Health Study I and II, and Health Professional's Follow-up Study; and the Multiethnic Cohort Study conducted at the Universities of Hawaii and Southern California. The laboratory-based genetic component of the study is being led by the CEPH in Paris, France, the Whitehead Institute at the Massachusetts Institute of Technology and NCI's Core Genotyping Facility.

http://epi.grants.cancer.gov/Consortia/cohort.html

COMMUNITY CLINICAL ONCOLOGY PROGRAM—20 YEARS STRONG

To bring the benefits of clinical research to cancer patients in their own communities, NCI launched the Community Clinical Oncology Program (CCOP). The program celebrated its 20th anniversary in 2003 with a history that shows the wisdom of that decision.

Through 50 CCOPs and 11 Minority-Based CCOPs, more than 400 community hospitals in 36 states, Washington, D.C., and Puerto Rico participate with the Cooperative Groups and Cancer Centers in NCI-supported clinical trials. Today, one-third of all patients in NCI-sponsored prevention clinical trials and treatment trials come from the CCOPs and Minority-Based CCOPs. Community oncologists are able to stay involved in clinical research and their patients have access to state-of-the-art cancer care close to home.

CCOPs "have become the primary force behind prevention, cancer control, symptom management, and quality of life research," said Peter Greenwald, M.D., Dr.P.H., director of NCI's Division of Cancer Prevention, commemorating the program's 20-year history. "They are in the forefront of wide-scale testing of preventive interventions, and their research is conducted with exemplary quality and efficiency."

CCOPs made possible several large-scale cancer prevention trials supported by NCI. The Breast Cancer Prevention Trial tested the efficacy of tamoxifen in preventing breast cancer in women at high risk for the disease, and the Prostate Cancer Prevention Trial evaluated finasteride as a prostate cancer prevention drug.

The CCOPs network remains a strong partner in ongoing studies as well. The Study of Tamoxifen and Raloxifene (STAR) compares raloxifene with tamoxifen in breast cancer prevention and runs through 2010. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is evaluating the supplements to prevent prostate cancer. Results from SELECT are due in 2013.

http://www3.cancer.gov/prevention/ccop20th/

WORKING TOGETHER TO REDUCE HEALTH DISPARITIES

Responding to recent National Academy of Sciences reports recommending that health disparities—significant differences in the overall rate of disease or survival rate in a specific group of people, compared to the general population—be studied at the population and environment levels, rather than solely at the individual level, NCI is collaborating with the National Institute of Environmental Health Sciences (NIEHS), the National Institute on Aging (NIA), and the Office of Behavioral and Social Sciences Research (OBSSR) to fund eight Centers for Population Health and Health Disparities.

The eight centers form a network of research teams that will explore the complexity of health disparities, covering breast, prostate, and cervical cancer as well as obesity, cardiovascular disease, mental health, and other factors. Using a community-based participatory research approach, the centers will include community stakeholders in planning and implementing research into how the social and physical environment, behavior, and biology interact to determine health and disease in different populations, with the ultimate goal of reducing health disparities. The research communities will include low-income Caucasians, African Americans, Hispanics, and the elderly.

The centers are broadly based. Focusing solely on the centers that will research cancer, the University of Illinois at Chicago will look at the disconnect between the rates of mammography screening and stage of cancer at diagnosis experienced by African American and Hispanic women as compared with Caucasian women. African American and Hispanic women have higher breast cancer mortality rates than Caucasian women, even with similar screening rates. The Ohio State University and the University of Michigan will study high rates of cervical cancer incidence and mortality in Appalachian Ohio and University of Pennsylvania will examine the differences in outcomes between African American and Caucasian men with prostate cancer.

NCI will provide over half of the $60.5 million in grants that will be awarded to the centers over the next 5 years.

http://cancercontrol.cancer.gov/populationhealthcenters/

HARNESSING THE POWER OF COMMUNICATIONS

Communications has enormous power to improve health. Four NCI-funded Centers for Excellence in Cancer Communications Research (CECCR) are testing various approaches to harness that power. Housed at the universities of Michigan, Pennsylvania, and Wisconsin, and St. Louis University, each CECCR will investigate how communication and technology can be used in every aspect of cancer control—from prevention to survivorship.

Good health communications can raise awareness of health risks and solutions, motivate people, increase demand for appropriate health services, help people make complex health decisions, and influence public policy. Communications is critical in helping the public separate research-based findings from untested claims. The work done by the centers aims to make new scientific research useful to everyone, not just the scientific community.

The centers will explore both traditional (newspapers, radio, and television) and newer technologies (computerized information systems) to find the best mix of media and messages. The CECCR in Pennsylvania will look at how consumers' knowledge and behaviors are affected by the complex health information environment. In Wisconsin, researchers will explore helping cancer patients and their families using interactive computer systems. The center in Michigan will tailor health messages, using interactive computer technology, to match the information to the user's needs and background. St. Louis University will concentrate on communications and behavior change programs for African Americans. Each center will train students and young investigators in advanced cancer communication research skills.

The content areas the CECCRs will examine include anti-smoking media campaigns for adolescents, increasing fruit and vegetable consumption among African Americans, helping women at high risk for breast cancer decide whether to take the drug tamoxifen, and how the public looks for information about prostate, breast, and colorectal cancers.

Each project is funded for about $10 million over 5 years.

Glossary

adenoma – A non-cancerous tumor.

allele – Any of the alternative forms of a gene that are located together on a chromosome. For autosomal chromosomes, each allele will normally have two copies of the same gene, one inherited from the mother and one from the father.

angiogenesis – Growth of new blood vessels.

antibody – A type of protein made by certain white blood cells in response to a foreign substance (antigen). Antibodies bind to the antigen and either destroy the foreign substance directly or make it easier for the body to do so.

bioinformatics - the collection, classification, storage, and analysis of biochemical and biological information using computers especially as applied in molecular genetics and genomics.

biomarker – A substance sometimes found in the blood, other body fluids, or tissues that can be used to assess the presence of cancer.

cohort study – A research study that compares a particular outcome, such as lung cancer, in groups of individuals who are alike in many ways but differ by a certain characteristic – for example, female nurses who smoke compared with those who do not smoke.

enzyme – A protein that speeds up chemical reactions in the body.

epidemiology – The study of the patterns, causes, and control of disease in groups of people.

epithelium – The thin layer of tissue that covers organs, glands, and other structures within the body.

gene expression – The process by which a gene's coded information is converted into the structures present and operating in the cell.

genome – The complete genetic material of an organism.

hyperplasia – An abnormal increase in the number of cells in an organ or tissue.

hypoxia – A condition in which there is a decrease in the oxygen supply to a tissue. In cancer treatment, the level of hypoxia in a tumor may help predict the response of the tumor to the treatment.

immunotherapy – Treatment to stimulate or restore the ability of the immune system to fight infections and other diseases. Also used to lessen side effects that may be caused by some cancer treatments.

lymphochip – a microarray from lymphoma biopsy samples used to analyze DNA differences in large B-cell lymphoma.

magnetic resonance imaging (MRI) – A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue.

mass spectroscopy - a method used to identify the chemical make up of a substance by separating the gaseous ions according to their differing mass and charge.

metastasis – The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a "metastatic tumor" or a "metastasis." The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

microarray – A powerful technology that allows simultaneous measurement of expression levels for up to tens of thousands of genes.

molecular marker – A diagnostic indicator used to determine whether disease may develop.

molecular signature – Characteristic features of the molecular composition of a cell or its surroundings.

molecularly targeted therapy – In cancer treatment, substances that kill cancer cells by targeting key molecules involved in cancer cell growth.

mutation – A permanent change in the genetic material, usually in a single gene.

nanotechnology – Technology development at the atomic, molecular, or macromolecular range of approximately 1-100 nanometers to create and use structures, devices, and systems that have novel properties.

pharmacology – The study of the properties and reactions of drugs, especially with relation to their therapeutic value.

positron emission tomography (PET) scan – A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body.

precursor cells - cells that are in a period of rapid division but not yet fully differentiated cancer cells.

prostaglandin - fatty acids composed of a chain of 20 carbon atoms that perform a variety of hormone-like actions.

protease inhibitor – Drugs that block the action of proteasomes, cellular complexes that break down proteins.

retrospective study – A study that looks backward in time, usually using medical records and interviews with patients who already have or had a disease.

spiral computed tomography (spiral CT) – a scanning technique used to create a three-dimensional image from a series of computer images made by rotating a scanner around the body.

staging – Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.

stem cell – A cell from which other types of cells can develop.

T-cells – One type of white blood cell that attacks virus-infected cells, foreign cells, and cancer cells. T cells also produce a number of substances that regulate the immune response.

transcription factor – a protein that binds to DNA and plays a role in the regulation of gene expression by promoting transcription.

translocation - transfer of part of a chromosome to a different position especially on a nonhomologous chromosome.

tumor suppressor gene – Genes in the body that can suppress of block the development of cancer.

x-ray crystallography - an analytical technique in which X-ray diffraction is used to obtain information about the identity or structure of a crystalline substance.

Valuable World Wide Web Locations

National Cancer Institute **cancer.gov**
National Institutes of Health **www.nih.gov**
Department of Health and Human Services **www.hhs.gov**
Cancer Research Portfolio **researchportfolio.cancer.gov**
Cancer News **newscenter.cancer.gov**
Cancer Science **newscenter.cancer.gov/sciencebehind**

Cancer Information Service (CIS)

By phone **1-800-4-CANCER (1-800-422-6237)**
For deaf and hard-of-hearing **1-800-332-8615**
On the Internet **cis.nci.nih.gov**

NCI's Bypass Budget, "The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2005"
On the Internet **plan.cancer.gov**

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NIH Publication No. 04-5536
September 2004