

News

Digitized Serum Mass Spectrometry Peaks Diagnostic of Prostate Cancer

For more information, contact: Michael Cohen; Tel.: 508.856.2000; Email: michael.cohen@umassmed.edu



Shuk-Mei Ho, Ph.D.

A prostate cancer screening test developed at the University of Massachusetts Medical School achieved a 94 percent success rate in a blinded study of serum samples from healthy men and those who had been diagnosed with prostate cancer through a traditional biopsy.

The results of the study are published in the July 2004 issue of *The Journal of Urology* and indicate this technology may eventually yield a rapid, highly accurate, clinical screening test to replace the current PSA test for prostate cancer. "Not only did we detect the cancer with a high degree of

known clinical profiles and outcomes of the patients. "Instead of using only PSA level, the combination of changes in the abundance of multiple proteins are used to predict cancer for each patient and classify their disease stage. That allows us to not only identify prostate cancer with a higher level of accuracy, but also to identify subtypes of prostate cancer," Ho said.

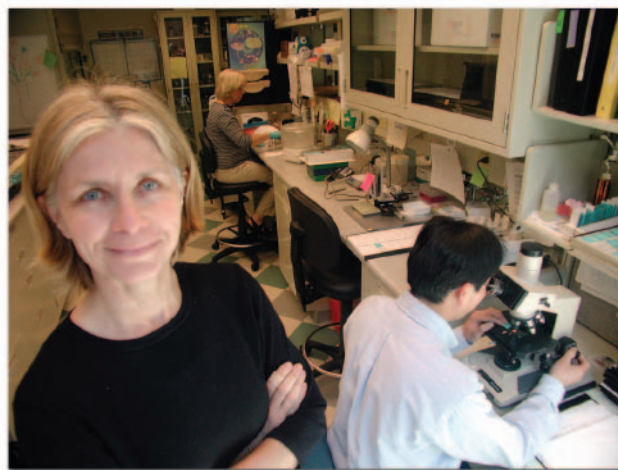
In the study published in the *Journal of Urology*, Ho's lab focused on 36 "protein peaks" in the sera that characterized the presence of prostate cancer. The first tests were done on 48 serum samples, where the diagnoses of the patients were known up front. Those 48 samples were used to refine and "train" the computer model used to analyze the protein data from the serum. Following that, Ho's team tested 168 blind serum samples, meaning the researchers did not know which samples came from healthy men versus those taken from men diagnosed with prostate cancer via biopsy. In that second set, the testing platform accurately diagnosed the cancer, or lack thereof, in 158 cases—a 94% success rate. Of the remaining 10 cases, one was a false positive, four were false negatives and five were inconclusive.

Ho's team is now testing the new process on a much larger scale, using hundreds of serum samples from labs across the country. If the process continues to perform well, Ho expects the research will lead to a more reliable and informative clinical prostate screening that will help catch the disease earlier and target the most effective treatment. "Eventually, we hope this test can be refined so it is a very simple, inexpensive blood test, perhaps even a urine analysis test," Ho said. "We've got more work to do, but so far, we're pleased with the progress."

In addition to her own lab work, Dr. Ho is co-director of the Genitourinary Oncology Program at the UMass Memorial Cancer Center, which brings together researchers and clinicians to help translate basic science advances into clinical applications for cancer treatment.

Cell Cycle Abnormalities May Be Key to Aggressive Breast Cancers in African-American Women

For more information, contact: Kristen Woodward; Tel.: 206.667.5095; Email: kwoodwar@fhrc.org



Peggy Porter, M.D.

A new study led by investigators at Fred Hutchinson Cancer Research Center may help explain why African-American women with breast cancer are more likely to be diagnosed with advanced disease and are less likely to survive the disease than white women.

"So we're hopeful this screening technology will have important clinical uses in the future, both by catching the cancer early, and helping to identify which cancers are more aggressive,"
— Dr. Shuk-Mei Ho

accuracy, we're able to differentiate between subtypes of tumors," said Shuk-Mei Ho, PhD, professor of Surgery, Cell Biology and Physiology and Director of Urologic Research and Translational Research for the Department of Surgery at UMMS, whose lab developed the screening technology. "Early detection of prostate cancer is important because when it's caught early the survival rate is almost 15 years. But when the disease is caught in the advanced stage and has spread beyond the prostate, the survival rate is very poor. So we're hopeful this screening technology will have important clinical uses in the future, both by catching the cancer early, and helping to identify which cancers are more aggressive," Dr. Ho said.

Prostate cancer is now the most frequently diagnosed malignancy in American men, with 220,000 new cases and nearly 30,000 deaths in 2003. As baby boomers age, those numbers are expected to increase. Currently, there is just one marker used to test men for prostate cancer—prostate specific antigen (PSA). A rising PSA level in the blood stream can indicate cancer, but the PSA test has high false-positive and high false-negative rates, so significant efforts are underway at UMMS and other institutions to develop a more accurate test to detect prostate cancer.

The new screening platform developed at UMMS uses mass spectrometry—a process that measures the mass and electrical charges of molecules in a sample to identify unknown substances and quantify known substances. With mass spectrometry, Ho's team determined the mass-to-charge ratios of hundreds of proteins that are found in the sera of men diagnosed with prostate cancer. The mass spectra of the sera samples were then digitized and processed by software package Ho's team configured for the screening process. The results of the computer analysis were then correlated with the

"A major benefit of focusing on women in a clinical trial is that we know that all of them received similar treatment, ...That will enable us to more directly evaluate the correlation between tumor characteristics and survival." — Dr. Peggy Porter

In a large study of young African-American and white women in Atlanta, researchers at Fred Hutchinson and collaborators at Emory University and the Centers for Disease Control and Prevention have found that breast tumors from black women are more likely to be fast-growing and aggressive than those from white women. The findings, to be published in the June 15 issue of *Cancer*, hold true even for breast tumors of equally advanced stages in the two groups of women.

"One of the important conclusions from this study is that even when you correct for stage—that is, look at tumors of the same stage from white women and black women—tumors from the African-American women tend to have features characteristic of more aggressive and rapidly growing cancers," said Peggy Porter, M.D., lead author of the study and an associate member of Fred Hutchinson's Human Biology and Public Health Sciences divisions. "If their tumors tend to grow more quickly, this may help to explain why their cancers are being diagnosed at later stages, which can lead to poorer outcomes," Porter said.

Other studies have reported similar findings, but the Fred Hutchinson analysis, funded by the National Cancer Institute and the Avon Foundation, is the first to examine tumors for a full array of proteins that control how quickly a cancer cell divides. Porter and colleagues found that tumors from African-American women were more likely to contain abnormal amounts of several cell cycle regulatory proteins compared to tumors from white women. While the researchers do not yet know if these differences affect a woman's survival from cancer, cancers that lose control of these cell cycle proteins tend to be more aggressive and harder to cure.

For nearly all factors analyzed, the researchers identified race-specific differences among the cancers, and tumors from African-American women almost always exhibited more aggressive characteristics than those from whites. For example, 13 percent of white women had stage III or higher disease, while nearly 20 percent of African-American women had this level of advanced disease. The odds of having a high-grade tumor, an indication of aggressiveness as judged by microscopic examination of the cells, was more than five times higher for black women than for white women.

Multiple studies have identified social, economic and cultural factors that contribute to later-stage diagnosis and poorer survival of breast cancer among African-Americans, but less is understood about differences in tumor biology that factor into this health disparity. The findings from the Fred Hutchinson study lay the groundwork for future studies to identify the specific risk factors that cause tumors from African-American women to develop dangerous characteristics, which could lead to new strategies to prevent and treat the disease.

"We know that African-American women with breast cancer are diagnosed at later stages, which is undoubtedly due in large part to socioeconomic factors, such as access to medical care. What we don't know is how much tumor biology contributes to diagnosis at later stages," Porter said. "We've just begun to tease out the biological factors that might contribute to late-stage diagnosis."

Study co-author Ralph Coates, Ph.D., associate director for science in the Division of Cancer Prevention and Control at the Centers for Disease Control and Prevention (CDC) in Atlanta, said that the research provides unique new knowledge about the abnormal cell cycle and greater loss of cycle control in breast cancers of African-American women compared with such cancers in white women.

"These new findings can guide further research to identify potentially modifiable risk factors that contribute to the increased risk in African-American women of more aggressive breast cancer," Coates said.

The study involved 124 African-American women and 397 white women aged 20 to 54 who had been diagnosed with breast cancer. The researchers obtained information on each woman's age, race, marital status and the stage of their cancer at diagnosis, which indicates whether the cancer is localized (confined to the breast) or has spread to nearby or distant parts of the body.

Researchers also obtained tissue samples from each woman's tumor, which Porter analyzed for 17 different characteristics that provide information about a tumor's aggressiveness or a patient's prognosis.

Aggressive tumor characteristics more common among African-American women than white women included:

Estrogen- and Progesterone-Receptor Status (Positive or Negative): A marker that has been tested and used to assess the likelihood of outcome regarding survival or cancer recurrence. Loss of estrogen and progesterone receptors on tumor cells (such as ER-negative or PR-negative status) is associated with poor clinical outcome. The odds of having ER-negative tumors were nearly three times greater for African-American women than for white women. The odds of having a PR-negative tumor were more than three times greater for African-American women than for white women.

Mitosis: Active cell division as determined by looking at the cancer cells under a microscope. Tumors with a high mitotic count are more aggressive. The odds of having a tumor with a high mitotic count were three times greater for African-American women than for white women.

p53: A protein product made by the p53 tumor-suppressor gene. When detected in large amounts, it is often associated with abnormal function of p53 and loss of cell cycle control, which can lead to cancer. The odds of having a tumor with high p53 levels were twice as great for African-American women than for white women.

Cyclin E: A protein important for proper control of cell division. High levels of cyclin E can cause unrestrained cell division and are associated with poorer survival. The odds of having a tumor with high levels of cyclin E were four times greater for African-American women than for white women.

Cyclin D: A protein important for proper control of cell division. High levels of cyclin D in many studies are associated with a better chance of survival. The odds of having a tumor with high cyclin D levels were half as great for African-American as for white women.

When researchers reanalyzed these characteristics by comparing tumors from the same stage or from women diagnosed at the same age, many of these aggressive characteristics were still more common among African-American women.

Porter suggested several possible explanations for why tumors from the African-American women exhibit these differences, most of which affect a woman's exposure to the steroid hormones estrogen and progesterone. "One important factor may be differences between the racial groups with respect to reproductive experiences," she said. "The age at which a woman has children and how many children she has could be a factor. Pregnancy results in very high levels of circulating hormones. The question is whether many pregnancies, and therefore extended periods of high hormone levels, at a relatively young age increase the risk for onset of cancer with aggressive characteristics."

Among women aged 45 or younger, African-Americans have a higher risk of developing breast cancer than white women. Yet among older women, whites are more likely than African-Americans to develop breast cancer.

Porter said that one aspect not addressed in this study was whether the aggressive tumor biology they identified in African-American women contributes to poorer survival. Analyses in this group of Atlanta women are under way to determine the relationship of tumor characteristics and survival. Additionally, she and colleagues in the Southwest Oncology Group, a nationwide network of researchers that conducts clinical trials, are beginning a study to address this. Porter will examine many of the cell cycle-related tumor characteristics analyzed in this study and the survival outcome of black and white breast-cancer patients enrolled in a clinical trial.

"A major benefit of focusing on women in a clinical trial is that we know that all of them received similar treatment," Porter said. "That will enable us to more directly evaluate the correlation between tumor characteristics and survival."

HIF-1 Blockade Inhibits Gastric Cancer Growth in Mice

For more information, please contact: Dr. Lee Ellis; Email: lellis@notes.mdacc.tmc.edu



Lee Ellis, M.D.

Targeting a master molecule that helps cancer cells survive when blood oxygen levels are low may offer a potentially powerful strategy for blocking tumor growth, say researchers at The University of Texas M.D. Anderson Cancer Center.

The molecule, “hypoxia-inducible factor 1,” or HIF-1, controls production of a number of other proteins, such as vascular endothelial growth factor (VEGF), which work in concert to help nurture these stressed cancer cells. Researchers show

“We have shown, genetically, that inhibiting HIF-1 significantly impairs tumor growth, so it seems that targeting HIF-1 might offer a great deal of promise in regulating the growth of solid tumors,” – Dr. Lee Ellis

that genetically jamming HIF-1 damages the vascular microenvironment and impairs tumor growth, according to the study, published in the June 16th issue of *Journal of the National Cancer Institute*.

The researchers found, for example, that while new blood vessels still grow in tumors when HIF-1 is blocked, the blood vessels were small, with thin walls, and no lumen—the passage through which blood flows. The tumors were only about 1/10th the size of cancerous masses seen in a group of control mice.

Although the researchers caution that their study was conducted only in animals, they say the findings are of note because HIF-1, as a master molecule, could prove to be a target for anti-cancer drugs.

“We have shown, genetically, that inhibiting HIF-1 significantly impairs tumor growth, so it seems that targeting HIF-1 might offer a great deal of promise in regulating the growth of solid tumors,” says the study’s senior author, Lee Ellis, M.D., a professor in the Departments of Surgical Oncology and Cancer Biology at M.D. Anderson.

The value of inhibiting this “angiogenic” pathway has already been shown in federal approval of the drug Avastin, an antibody that binds VEGF and prevents its effect on angiogenesis. But there are no drugs currently available or in testing that specifically target HIF-1, Ellis says, so clinical validation of these findings in patients will probably be years away.

“The next step in the process is to seek or develop agents that specifically target HIF-1; until then, this work is limited to animal models,” he says.

The study focused on HIF-1’s role in gastric (stomach) cancer, but the master molecule is believed to play a role in growth and metastasis of colon, pancreatic and other cancers, and is directly associated with development of renal cell carcinoma, says Ellis.

Cells continually produce HIF-1 proteins, but they are quickly degraded if the cell is healthy, receiving a sufficient supply of oxygen. If the cell become hypoxic (lacking oxygen), HIF-1 is not destroyed. It binds with a partner protein and moves into the cell’s nucleus, where it turns on a large number of genes that help support the cell in a relatively caustic environment “of low oxygen and nutrients, and increased acidity,” says Ellis. “When cells grow faster than blood vessels, such as when cancer develops and there is not enough oxygen and glucose around, HIF-1 becomes active, pushing the growth of new blood vessels.”

In the study, the researchers conducted a series of both cell culture and mouse experiments; previous studies conducted in one or the other system have been contradictory. They transferred a gene into human gastric cancer cells that would not allow HIF-1 to initiate gene activation in the cell nucleus, and then found that in hypoxic conditions, VEGF secretion was not increased, showing that HIF-1 controlled VEGF levels.

They then conducted animal studies, including one in which the altered cancer cells were injected into the stomach wall. Gastric tumors grew in both a control group and in the experimental group of animals. At 22 days, tumors growing in the experimental group, in cells that expressed low levels of HIF-1, were significantly smaller than those growing in the control group.

“We were able to markedly inhibit tumor growth, and we also found something interesting,” says Ellis. “The number of blood vessels between the groups was unchanged, yet in experimental mice, the vessels were smaller, and without a lumen. They didn’t appear to be able to remain open. They were not ‘good’ vessels.”

The investigators evaluated the structure of these altered vessels and found they didn’t contain many pericytes. Normal blood vessels have endothelial cells surrounded by pericytes, which provide structural rigidity and also modulate endothelial cell survival. “We found that the endothelial cells had little pericyte coverage in tumors with decreased HIF-1 activity, suggesting that HIF-1 not only regulates molecules that mediate endothelial cell function, but also pericyte function,” Ellis says.

These results suggest that HIF-1 not only regulates VEGF expression in cancer cells, he says, “but also contributes to the formation of a complex proangiogenic microenvironment in tumors, affecting both the structure and function of blood vessels.”

The study was supported by grants from the National Institutes of Health. Co-authors include, from M.D. Anderson’s Department of Cancer Biology: Oliver Stoeltzing, M.D., Fan Fan, BS, Weinbiao Liu, M.D., and Anna Belcheva, M.D.; from M.D. Anderson’s Department of Surgical Oncology: Marya McCarty, Ph.D., and Jane Wey, M.D. Another co-author, Gregg Semenza, M.D., Ph.D., at the Johns Hopkins University School of Medicine, is a leading expert on HIF-1 research.

Overexpressed DLC1 as Target for Breast Cancer Cell Shape and Survival

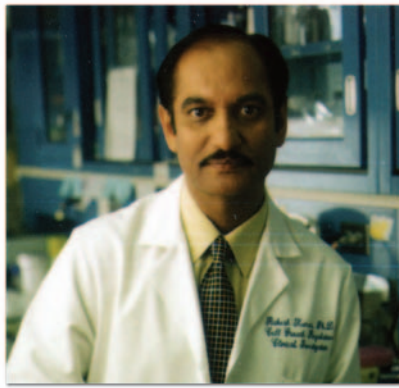
For more information, please contact: Dr. Rakesh Kumar; Email: rkumar@mdanderson.org

Two proteins that normally help cells move from place to place and are made in large quantities in breast cancer cells work together to promote the survival and spread of breast cancer, according to a new study by scientists at The University of Texas M.D. Anderson Cancer Center.

The finding, which appears in the June 2004 issue of the journal *Cancer Cell*, links together for the first time two proteins known to influence cell shape and survival of cancer cells. What’s more, when the scientists created a single change in a small 19-amino acid portion of one of the proteins, it stopped tumor formation. The results may lead to new strategies to trigger cell death in cancer cells, the scientists say.

“We can now target these 19 amino acids,” says Rakesh Kumar, Ph.D., Professor of Cellular and Molecular Oncology and the study’s lead investigator. “We might be able to develop a small molecule, a drug that could target the business end of this protein to interfere with the transformation process.”

The National Cancer Institute estimates that nearly 13 percent, about 1 in 8, of all women in the United States will develop breast cancer. It is the most commonly diagnosed malignancy among women. The proteins that



Rakesh Kumar, Ph.D.

Kumar and his research team studied appear to be involved in the process of transforming normal breast cells into cancer cells in the majority of breast cancer cases.

The research team discovered that when the two proteins, Pak1 and DLC1 (dynein light chain 1) interact, Pak1 chemically modifies DLC1 at a single site and changes the cell's ability to respond to cell death signals. When DLC1

Clinical Targeting of VEGF and EGFR Effective in Non-Small Cell Lung Cancer

For more information, please contact: Dr. Alan Sandler; Email: alan.sandler@vanderbilt.edu

Results of the first clinical trial to combine two new targeted cancer drugs suggest that the combination may provide a powerful "one-two punch" against lung cancer, the nation's leading cancer killer.

The work, led by researchers at the Vanderbilt-Ingram Cancer Center in Nashville, Tenn., and The University of Texas M.D. Anderson Cancer Center in Houston, was presented June 5, 2004, at the 40th annual meeting of the American Society of Clinical Oncology in New Orleans.

Tumors were controlled among 85 percent of the 40 patients with advanced non-small cell lung cancer (NSCLC) who entered the Phase I/II trial of a combined regimen of bevacizumab (Avastin™) and erlotinib (Tarceva™).

The response rate—proportion of patients whose tumors shrank in size by more than half—was about 20 percent, while median survival was 12.5 months. This compares to about 10 percent response and between six and eight months median survival with traditional therapy or erlotinib alone, said Alan Sandler, M.D., associate professor of Medicine and director of the lung cancer clinical program at Vanderbilt-Ingram.

The treatment resulted in only mild side effects, including rash and diarrhea, and the drugs did not appear to interact adversely with one another, the investigators report.

"The anti-tumor activity was encouraging" said Sandler, who presented the research at the meeting. "These findings suggest not only that combining these two agents is feasible, but that this approach may provide a one-two punch against tumors that should be further examined in larger clinical trials."

Lung cancer is the leading cause of cancer death in the United States, killing more than 157,000 people each year, more than the next four leading cancers (colorectal, breast, prostate and pancreas) combined. About 85 percent of all lung cancers are non-small cell cancers, and nearly half of these patients are diagnosed with advanced disease and receive only chemotherapy or supportive care, the investigators say.

Despite newer third-generation chemotherapies, most of these patients become resistant to treatment or develop side effects so severe that they cannot continue treatment. "Less toxic and more effective treatments are clearly needed," Sandler said.

The two drugs are among newer so-called targeted cancer agents that focus on specific molecular features of cancer cells. Because they potentially target cancer cells while sparing healthy cells, the hope for these new agents is more effective cancer therapy with fewer side effects.

Bevacizumab blocks the vascular endothelial growth factor (VEGF), which is involved in making new blood vessels (a process called angiogenesis) that help feed tumor growth and spread. Erlotinib inhibits the epidermal growth factor receptor (EGFR), a key player in delivery of signals that prompt the runaway cell growth that characterizes cancers.

Increased activity of the EGFR pathway, as well as increased number of tumor blood vessels resulting from VEGF expression, are associated with poorer outcomes for patients with NSCLC, the investigators note.

Other research has suggested that activities of EGFR and VEGF are related—EGFR appears to play a role in angiogenesis, while blocking VEGF appears to interrupt EGFR signaling. As a result, the researchers suspect that a dual blockade of these targets may be synergistic.

Interim results from this research were presented at last year's ASCO meeting in Chicago, prompting other investigators across the country to examine this combination in other tumor types as well as combine other targeted agents in clinical trials, Sandler said.

"Taken together, these studies show cells that overexpress DLC1 have enhanced cell survival and blockage of death signals, all of the characteristics required for successful tumor formation." — Dr. Rakesh Kumar

is modified it interferes with the cell death signaling pathway. As a result, cells no longer respond to death signals and instead continue to survive, multiply and spread. The loss of ability to respond to cell death signals is a hallmark of cancer.

When the scientists looked for DLC1 in breast cancer tumors, they found 54 out of 60 had elevated levels of DLC1. When they examined some of the tumors in greater detail, they found five out of six tumor samples studied had increased levels of the modified DLC1 that does not respond to cell death signals.

The scientists then used genetic methods to test the breast cancer cells in a mouse model that the scientists genetically altered to increase or over-express levels of DLC1. These mice developed tumors, and when they examined the cells that over-express DLC1, they also discovered that the cells could move faster than normal cells, they reproduced faster, and could grow without normal cell contacts—what is called anchorage independence.

"Taken together, these studies show cells that overexpress DLC1 have enhanced cell survival and blockage of death signals, all of the characteristics required for successful tumor formation," says Kumar.

But when the research team engineered a form of the DLC1 protein missing the crucial modification site, the protein could no longer block cell death signals and could no longer form tumors.

Kumar says that since DLC1 is a small protein and the research team has identified exactly how it becomes modified by Pak1, it may be possible in the future to block its activity through the use of drugs designed to inhibit its activity. Such inhibitors might restore the cell's normal recognition of cell death signals, Kumar says.

However, he adds that more work needs to be done to understand how over-expression of DLC1 contributes to the development of breast cancer.

M. D. Anderson scientists Ratna Vadlamudi, Ph.D., Rozita Bagheri-Yarmand, Ph.D., Zhibo Yang, Ph.D., Seetharaman Balasenthil, Ph.D., Diep Nguyen, Aysegul Sahin, M.D., and Petra den Hollander, contributed to the study. The research was supported by NIH grants.

At the time the study was launched, it was the first time two drugs that had not yet been approved by the U.S. Food and Drug Administration were combined in a trial. Since that time, bevacizumab has been approved for use in advanced colorectal cancer in combination with chemotherapy. Erlotinib is pending FDA approval.

Co-investigators include Roy Herbst, Eric Mininberg, Ted Henderson, Edward Kim, George Blumenschein Jr., Jack Lee, Mylene Truong, and Waun Hong of M.D. Anderson; David Johnson and David Carbone of Vanderbilt-Ingram; Ben Garcia of the University of Texas Southwestern Medical Center; and Dong Xie and Sean Kelley of Genentech Inc., which makes both drugs and funded the clinical trial.

Knudson Wins 2004 Kyoto prize

For more information, visit the Center's web site at www.fccc.edu or call 1-888-FOX CHASE.



Alfred G. Knudson Jr., M.D., Ph.D.

Cancer researcher Alfred G. Knudson Jr., M.D., Ph.D. of Fox Chase Cancer Center, Philadelphia, Pa., has been named winner of a prestigious Kyoto Prize for 2004. The Kyoto Prize is considered among the world's leading awards for lifetime achievement and is given to those who have "contributed significantly to mankind's betterment." Knudson will receive a cash gift of about \$450,000 (50 million yen), the 20 karat gold Kyoto Prize Medal and a diploma at the Kyoto Prize Ceremony in Kyoto, Japan on November 10, 2004.

The Inamori Foundation selects three Kyoto Prize laureates annually for significant contributions to the scientific, cultural and spiritual development of mankind in the fields of advanced technology, basic sciences, arts and philosophy.

Knudson will receive the basic sciences prize for his role in establishing the theory of tumor suppressor genes, which opened a new horizon in modern cancer genetics, and made a pivotal contribution to major subsequent research developments in understanding human cancer.

"Today, we are rushing ahead with incredible scientific and technological achievements, while inquiry into our spiritual nature lags deplorably," said Dr. Kazuo Inamori, founder and president of the Inamori Foundation. "It is my hope that the Kyoto Prize will encourage balanced development of both our scientific and our spiritual sides, and hence provide impetus toward the structuring of new philosophical paradigms."

This year's other Kyoto Prize laureates will be:

- Dr. Alan Curtis Kay, a computer scientist and senior fellow at Hewlett-Packard Co., whose work at Stanford University and the Xerox Palo Alto Research Center in the 1960s and '70s led the paradigm shift away from mainframe computing and opened the door for the personal computer revolution; and
- Prof. Jurgen Habermas, a philosopher at the University of Frankfurt and permanent visiting professor at Northwestern University, whose communicative action theory and discourse ethics support a commitment to the elimination of discrimination and violence in human society, and the establishment of relationships of coexistence among all free and autonomous people.

Knudson has been a senior member of the scientific research staff at Fox Chase Cancer Center since 1976. A geneticist and physician, Knudson is internationally recognized for his "two-hit" theory of cancer causation,

which explained the relationship between the hereditary and non-hereditary forms of a cancer and predicted the existence of tumor-suppressor genes that can suppress cancer cell growth. This now-confirmed theory has advanced understanding of errors in the genetic program that turn normal cells into cancer cells.

Knudson's powerful insights into the development of cancer hold implications for both treatment and prevention. Tumor-suppressor genes, in particular, are important targets for prevention research since they normally function to apply the brakes to cellular growth. This is a topic of Knudson's current research.

Defects in tumor-suppressor genes permit abnormal, cancerous growth, so devising ways to remedy such flaws or replace the gene's missing product through medication are of interest to researchers.

The Inamori Foundation was established in 1984 by Kazuo Inamori, founder and chairman emeritus of Kyocera Corporation. The Kyoto Prizes were founded in 1985 in line with Inamori's belief that "man has no higher calling than to strive for the greater good of society, and that mankind's future can be assured only when there is a balance between our scientific progress and our spiritual depth." It is characteristic of the Kyoto Prizes that they are presented to individuals or groups in appreciation not only of their outstanding achievements but also of the excellence of the personal characteristics on which they have built their contributions to mankind. The laureates are selected through a strict and fair process considering candidates recommended from around the world.

As of January 2004, the Kyoto Prize has been awarded to 63 laureates from 12 nations-ranging from scientists, engineers and researchers to architects, sculptors and film directors. The United States has produced the most recipients with 27 laureates, followed by the United Kingdom (nine), France (eight) and Japan (seven).

Knudson was born in Los Angeles in 1922. He received his B.S. from California Institute of Technology in 1944, his M.D. from Columbia University in 1947 and his Ph.D. from California Institute of Technology in 1956. He held a Guggenheim fellowship from 1953 to 1954.

Knudson came to Fox Chase Cancer Center in 1976 after serving as a member of its scientific advisory committee for seven years. Knudson was named a Fox Chase Distinguished Scientist and senior advisor to the Fox Chase president in 1992. Previously, Knudson served as director of Fox Chase's Institute for Cancer Research from 1976 until 1982, Center president from 1980 to 1982 and scientific director from 1982 to 1983.

Before coming to Fox Chase, Knudson was dean of the University of Texas Graduate School of Biomedical Sciences and researcher at the M.D. Anderson Hospital and Tumor Institute in Houston, Texas, where he specialized in pediatrics and biology. Prior to that, Knudson served as associate dean for basic sciences at the State University of New York at Stony Brook from 1966 to 1969.

In 1995, Knudson was appointed as special advisor to Richard Klausner, director of the National Cancer Institute. While continuing his work at Fox Chase, Knudson also worked closely with Joseph Fraumeni in the NCI's Division of Cancer Epidemiology and Genetics. Knudson served as acting director of its new human genetics program until September 1999, when he returned to Fox Chase full-time.

Among Knudson's many professional distinctions, he received the 1998 Albert Lasker Award for Clinical Medical Research, one of seven Lasker Awards presented that year. Considered "America's Nobels," Lasker Awards rank among the highest recognition for careers of distinguished work because of the extremely rigorous process of nomination and selection conducted by a jury of the world's top scientists.

In 1999, Knudson received the international John Scott Award from the City of Philadelphia. In addition, Knudson has received the 1988 Charles S. Mott Prize of the General Motors Cancer Research Foundation; Canada's 1997 Gairdner Foundation International Award; Switzerland's 1995 Charles Rodolphe Brupbacher Foundation Award; the 1996 Robert J. and Claire Pasarow Foundation Award; and the American Cancer Society's 1989 Medal of Honor.

Knudson is married to Anna T. Meadows, M.D., a pediatric oncologist at Children's Hospital of Philadelphia.

Kelly, Langer, Sherr and Stillman Win 2004 GM Awards

For more information, please visit the company's corporate website at <http://www.gm.com>

Four world-renowned scientists have been recognized by the General Motors Cancer Research Foundation (GMCRCF) for their seminal contributions to cancer research.

The award recipients are:

- Dr. Thomas Kelly, director, Sloan-Kettering Institute in New York
- Robert Langer, professor of Chemical and Biomedical Engineering at the Massachusetts Institute of Technology (MIT) in Cambridge, Mass.
- Dr. Charles J. Sherr, Herrick Foundation co-chair of Genetics and Tumor Cell Biology at St. Jude Children's Research Hospital in Memphis, Tenn.
- Bruce Stillman, president and CEO, Cold Spring Harbor Laboratory in Cold Spring Harbor, N.Y.

GMCRCF has previously awarded nearly \$14 million to 105 scientists in an effort to focus worldwide scientific and public attention on cancer research. Twelve previous winners have subsequently won Nobel Prizes.

GM has made cancer research a key philanthropic priority, and this year marks the 26th anniversary of the GMCRCF Awards. GM has given more than \$50 million to the cause, and is committed to helping eradicate cancer and supporting cancer research until the battle is won.

Alfred P. Sloan, Jr. Prize

Kelly and Stillman have been awarded the Alfred P. Sloan, Jr. Prize for their major contributions to our understanding of the biochemistry and regulation of DNA replication. The Sloan Prize recognizes the most outstanding recent contribution in basic science related to cancer research.

In the late 1970s and 1980s, Kelly was the first to establish cell-free systems for *in vitro* replication of DNA in extracts derived from human cells. The development of these systems made it possible to study the molecular machinery that duplicates the human genome.

"Cancer is a genetic disease, characterized by the uncontrolled growth of cells, so if we understand the mechanisms that control DNA replication, we may be able to develop new drugs that target key aspects of the replication machinery," Kelly said.

Studying DNA replication in both human cells and yeast extracts, Stillman made two significant discoveries. In the 1980s, he and Dr. Kelly discovered the protein machinery that enables chromosomes to be copied. In 1992, Stillman discovered a protein complex (the Origin of Recognition Complex, or ORC) that regulates the copying process.

"Understanding the process of DNA replication in normal cells has been important for us to understand what goes wrong in cancer cells," Stillman said. "We've learned so much about the process of chromosome duplication and how it integrates into the biochemical pathways that are defective in cancer cells."

Kelly and Stillman's discoveries have significant implications for cancer research. Kelly provided a first look into how DNA replication works in human cells and Stillman demonstrated that entire chromosomes need to be copied accurately and just once in the cell division process or abnormalities can occur in the number of genes copied, a characteristic of cancer cells.

A graduate of the Johns Hopkins University, Kelly received his M.D. and Ph.D. in Biophysics. He is a member of the National Academy of Sciences.

A native of Sydney, Australia, Stillman is a graduate of the University of Sydney and earned his doctorate from the John Curtin School of Medical Research at the Australian National University. He is a member of the National Academy of Sciences and a Fellow of the Royal Society (London). Both Kelly and Stillman have received several awards for their work.

Charles F. Kettering Prize

Langer has been honored with the Charles F. Kettering Prize for pioneering the development of sustained-release drug delivery systems for the treatment of cancer. The Kettering Prize recognizes the most outstanding recent contribution to the diagnosis or treatment of cancer.

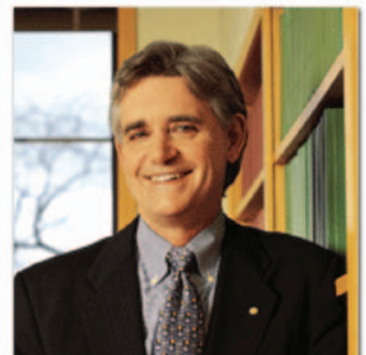
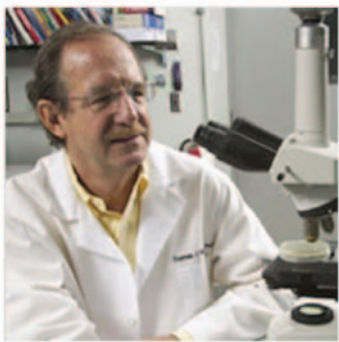
Langer's achievements have had a profound impact on the field of cancer research. When he began working in the field of cancer research in 1974, the scientific community at that time believed that only small molecules could pass through a plastic drug delivery system in a controlled manner.

However, Langer went on to develop polymer materials that allowed large molecules to pass through plastic membranes to inhibit angiogenesis, the process by which tumors recruit blood vessels. Blocking angiogenesis in the case of cancer is critical because during the development of the new blood vessels, tumor cells escape into the circulation and lodge in other organs.

In addition, this discovery led to his work on biodegradable polymers that pharmaceutical companies later used for treating men with advanced prostate cancer. Langer's subsequent research on biodegradable polymers with Dr. Henry Brem of the Johns Hopkins University School of Medicine led to new treatments for patients with brain cancer.

"In a general sense, I think the significance of our discovery is that it opened up the field of controlled drug delivery systems, allowing for treatments with molecules of varying sizes that could be delivered over a broad range of time—from days to months," Langer said. "Specific to cancer research, I think it helped in three areas: the angiogenesis field, the development of new treatments, and the introduction of local chemotherapies."

A graduate of Cornell University with a bachelor's degree in Chemical Engineering and an Sc.D. in Chemical Engineering from MIT, Langer is a member of the National Academy of Sciences and the recipient of several awards for his work.



From left to right: Thomas Kelly, Robert Langer, Charles J. Sherr and Bruce Stillman.

Charles S. Mott Prize

Sherr was honored with the Charles S. Mott Prize for the discovery and characterization of key genes and proteins that control cell division and are frequently involved in the development of cancer. The Mott Prize honors the most recent outstanding contribution related to the cause or prevention of cancer.

Sherr has worked in the field of cancer research for more than 30 years and is a pioneer in understanding the complex biochemical pathways that cause tumors. In the 1990s, Sherr defined two major biochemical pathways that sense signals arising outside the cell and translate them into information that drives cell division.

The components of these pathways include cancer-causing genes (oncogenes, such as cyclin D and CDK4), and genes that prevent cancer (tumor-suppressor genes, such as ARF). According to Sherr, genetic alterations in these pathways occur frequently in most, if not all, forms of human cancer.

Sherr's work has had a significant impact on the field of cancer research. His discoveries provide a basis for the development of new and improved diagnostic and therapeutic tools for human cancers.

"Cancer is a genetic disease and is one of the major medical problems we face today," Sherr said. "If we can understand the genetic framework of cancer, then we can develop drugs that would cure this disease."

Sherr is a graduate of Oberlin College (Ohio) with a bachelor's degree in Biology. He earned both Ph.D. in Immunology and M.D. degrees from New York University. He is a member of the National Academy of Sciences and has received many awards.

Dr. Samuel A. Wells, Jr., president of the GMCRCF, praised the award winners and cited their major contributions to combating this deadly disease. He noted that the laureates were chosen through a rigorous review process conducted by distinguished international scientists who served on the Foundation's Selection Committees and Awards Assembly.

"Cancer research is crucial, because the effects of the disease are so far-reaching," said GMCRCF Chairman Harry J. Pearce. Pearce, a cancer survivor, has indicated on many occasions that he credits cancer research with saving his life. "Over 10,600 GM employees, retirees and their family members were treated for cancer in just the past year alone."

"Through these awards, GM supports some of the world's most gifted scientists, who have made highly important discoveries leading to the diagnosis, prevention and treatment of cancer," Wells said. "Research is the basis for all cancer breakthroughs, and we must do everything we can to support and nurture that spirit of discovery."

The GMCRCF Annual Scientific Conference, held at the National Institutes of Health on June 8 and 9, focused on "Genome Integrity and Cancer" and included lectures by the laureates describing their research. GM is presenting the prizes to the laureates during an awards ceremony at the U.S. Department of State on the evening of June 9.

Folkman, Hunter, Massagué, Vogelstein and Weinberg Win 2004 Prince of Asturias Awards

For more information please see: <http://www.fpa.es/ing/index.html>

Judah Folkman, Tony Hunter, Joan Massagué, Bert Vogelstein and Robert A. Weinberg, researchers at the forefront of the fight against cancer, have won the 2004 Prince of Asturias Award for Scientific and Technical Research. The decision was announced by the Jury in Oviedo today.

The minutes of the Jury are read from the Hotel de la Reconquista in Oviedo. The jury for the award—convened by the Prince of Asturias Foundation—was chaired by Julio Rodríguez Villanueva, and comprised of

José Luis Álvarez Margaride, José Baselga, Antonio Fernández-Rañada Menéndez de Luarda, Luis Fernández-Vega Sanz, Santiago Grisolia, Juan José López Ibor, Emilio Lora Tamayo, María del Carmen Maroto Vela, Enrique Moreno, Rafael Nájera Morrondo, César Nombela Cano, Fernando Ortiz Maslloréns, Miguel Ángel Pesquera, Rafael Puyol, Rafael Sariego García, Guillermo Suárez Fernández and José Antonio Martínez-Álvarez (secretary).

Dr. Judah Folkman was born in Cleveland (USA) in 1933 and graduated in Medicine at Harvard University in 1957. He now heads the Department of Surgical Research at Boston's Children's Hospital and is Professor of Cellular Biology at Harvard Medical School. Angiogenesis, for which he devised a theory in the sixties, and of which he is considered the father figure, is now one of the major research lines in the fight against cancer. It is a process whereby tumors generate their own vascular system, allowing them to receive nutrients and to develop. Doctor Folkman discovered that tumor angiogenesis can be kept at bay for a considerable length of time, and even rendered dormant indefinitely, when tumors produce high levels of certain protein factors, yet regain their angiogenic capacity and ability to become invasive when these levels dwindle. This has triggered new lines of oncological research into the synthesis of angiogenesis inhibitors, some of which—endostatin and angiostatin, for example—were discovered by Folkman himself. Doctor Folkman is a member of the American National Academy of Science, and holds honoris causa doctorates from fifteen universities.

Tony Hunter was born in Kent (United Kingdom) in 1943. He earned his doctorate from Cambridge University (1969), and at present pursues his research interests at the laboratory for molecular and cellular biology at the Salk Institute, in La Jolla, California. Considered to be one of the world's top experts in the study of cell growth-regulating genes, in 1979 Doctor Hunter discovered the phosphorylation of tyrosine kinase, which led the way towards research into these enzymes and the role they play in the transduction, development and growth of cancer-causing cells. Knowledge of tyrosine kinase has been a determining factor in the development of a new generation of drugs to treat oncological conditions. Doctor Hunter is a member of the European Molecular Biology Organisation, of the American Academy of Arts and Sciences and of the Royal Society of London. He was awarded the Medal of Honour of the American Cancer Society last February.

Joan Massagué Solé was born in Barcelona in 1953. He holds a doctorate in Pharmacy (Biochemistry) from the University of Barcelona (1978). He joined Brown University, Rhode Island, in 1982, where he discovered the structure of the insulin receptor. He lectured as Professor of Biochemistry at the University of Massachusetts. In 1989, he joined New York's Memorial Sloan-Kettering Cancer Center to head their Department of Cell Biology and Genetics, where he is director of the Programme for Cancer Biology and Genetics. He also researches at the Howard Hughes Medical Institute. His work has mainly targeted the study of the various glycoproteins that trigger cell transformation. In 1993 he published his studies on the working mechanisms of two of the three factors that check the uncontrolled multiplication of cancer-producing cells: the p27 peptide and the tumor growth factor beta. The identification of TGF- β , one of the most powerful inhibitors of cell proliferation, figures outstandingly amongst his work. His team has defined FoxG1 and PI3K-AKT, new targets for future drugs. He is a member of the National Academy of Sciences of USA, the American Academy of Arts and Sciences and the European Molecular Biology Organization.

Bert Vogelstein was born in Baltimore (USA) in 1949. He is Professor at the Faculty of Medicine Johns Hopkins University and research fellow at the Howard Hughes Medical Centre. As a result of his work to identify and characterise gene changes leading to colon cancer, he is now considered one of the benchmark figures in oncological research. He discovered the APC gene—which controls cell growth in the colon—and has also made major contributions to our understanding of the role of the p53 gene in the tumor-producing process, and of other p53-linked genes such as PUMA and PRL-3. The Medal of Honour of the American Cancer Society (1992), the Pezcoller Foundation Award (1993), the Clowes Memorial, awarded by the American Association of Cancer Research and the acknowledgements of a

number of universities around the world figure amongst Bert Vogelstein's distinctions. He is also a member of the American Academy of Arts and Sciences.

Robert A. Weinberg was born in Pittsburg (USA) en 1942. He is a founder member of the Whitehead Institute for Biomedical Research and Professor of Biology at the Massachusetts Institute of Technology (MIT), where he earned his doctorate in 1969. He is considered to be one of the pioneers in the understanding of the genetics of cancer, and is a specialist in the study of human oncogenes and in tumor suppressor genes. He isolated the first carcinogenic gene, the Ras oncogene, and the first tumor suppressor gene, rb, the retinoblastoma gene. His most recent research is focused on new development models, breast cancer and cancer telomerase. The U.S. National Medal for Science (1997) figures amongst his distinctions; he is also a member of the U.S. National Academy of Science.

This candidature was proposed by Cesar Nombela, a member of the Jury.

The Prince of Asturias Foundation's statutes establish that the aim of the Awards is to acknowledge and extol 'scientific, technical, cultural, social and humanistic work carried out by individuals, groups or institutions world-wide'. Consonant with this spirit, the Prince of Asturias Award for Technical and Scientific Research 'will be bestowed upon the individual, working group or institution whose discoveries or research represent a significant contribution to the progress of humanity in the fields of Mathematics, Physics, Chemistry, Biology, Medicine, Earth and Space Science, as well as their related technical aspects and technologies.'

This year a total of 45 candidatures from Brazil, Costa Rica, Egypt, Germany, Italy, Japan, Mexico, Portugal, Puerto Rico, Rumania, United Kingdom, United States, Venezuela and Spain ran for the award.

This is the second of the eight Prince of Asturias Awards to be bestowed in what is their twenty-fourth edition. Claudio Magris, the Italian writer, has recently been given the Award for Letters. In the upcoming weeks, Awards in the following categories will be announced: Social Sciences, Communication and Humanities, International Co-operation, and the Arts, with the Sports and Concord awards being announced in September.

Each of the Prince of Asturias Awards, which date back to 1981, is endowed with 50,000 Euros, a commissioned sculpture donated by Joan Miró, a diploma and an insignia. The awards will be presented in the autumn in Oviedo at a grand ceremony chaired by H.R.H. the Prince of Asturias.
