

When Good Genes Go Bad

NEW EVIDENCE TIES GENE FUSION TO PROSTATE CANCER

Could scrambled genes cause prostate cancer? Arul M. Chinnaiyan (M.D. and Ph.D. 1999), the S.P. Hicks Collegiate Professor of Pathology in the U-M Medical School, thinks so.

In a research study published in the October 28, 2005, issue of *Science*, scientists in Chinnaiyan's laboratory reported a recurring pattern of mixed-up chromosomes and abnormal gene activity that was found only in prostate cancer. The rearranged chromosomes caused specific genes to merge, creating what scientists call a gene fusion.

"We found tantalizing evidence that gene fusion is the causative agent – the initiating event – in prostate cancer," says Chinnaiyan. "It's what drives the aberrant over-expression of cancer-causing genes and is the first step in the progression of tissue changes leading to prostate cancer."

Because this particular gene fusion occurs only in prostate cancer, a diagnostic test to detect the fused genes or their protein products in a patient's blood or urine would be specific for prostate cancer and far more accurate than current screening tests. And if scientists could find a way to block the fused genes, it could be the basis for a new, effective treatment for prostate cancer.

Every year, more American men are diagnosed with prostate cancer than with any other type of cancer. The American Cancer Society estimated that, in 2005, 232,000 men in the United States would be diagnosed with prostate cancer and 30,350 men would die from the disease. It is the second-most common cause of cancer-related deaths in men.

While similar rearrangements in chromosomes and fused genes have been detected in blood



Arul Chinnaiyan and Scott Tomlins

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cell cancers like leukemia and lymphoma, and in Ewing's sarcoma, this is the first time they have been found in a common solid tumor like prostate cancer, which develops in epithelial cells lining the prostate gland.

"It is a paradigm shift for all epithelial tumors – such as cancers of the lung, breast, colon, ovary, liver and prostate – which are the most common types of cancer and account for most deaths due to cancer," says Chinnaiyan,

who directs the Bioinformatics Core at the U-M Comprehensive Cancer Center. "We knew gene rearrangements were involved in hematologic malignancies and sarcomas. But finding this recurrent pattern in prostate cancer suggests that other common epithelial cancers have their own recurrent chromosomal rearrangements. We just haven't found them yet."

A bioinformatics analysis method called the Cancer Outlier Profile Analysis developed by Scott A. Tomlins and Daniel R. Rhodes, U-M graduate students working in Chinnaiyan's laboratory, made it possible for the research team to detect the signature of fused genes in prostate tissue.

"We are especially excited by the profound implications these findings have for the treat-

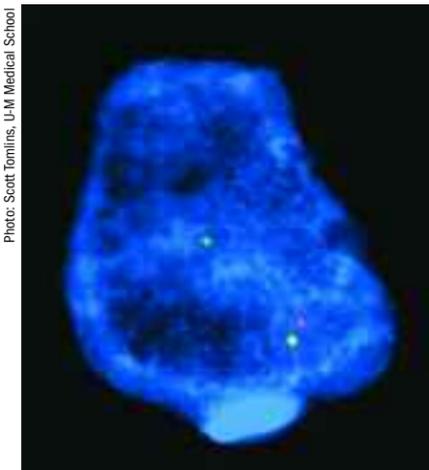


Photo: Scott Tomlins, U-M Medical School

This FISH (fluorescence in situ hybridization) image shows fused genes in prostate cancer cells. Fusion is indicated by the yellow signal indicating gene overlap.

ment of prostate cancer," Chinnaiyan says. "It will allow us to categorize prostate tumors by molecular sub-type, which could help determine the most effective treatment for each patient."

Research leading to the gene fusion discovery was supported by the National Cancer Institute.

—Sally Pobojewski

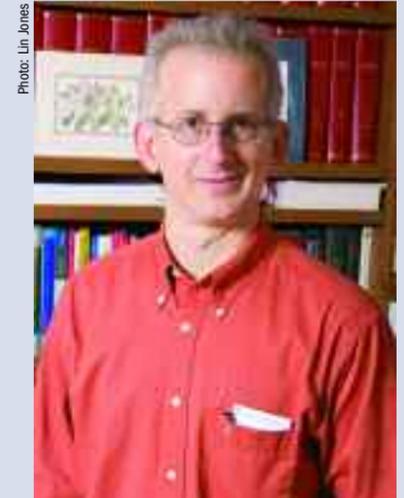
For an expanded version of the story:
www.med.umich.edu/opm/newspage/2005/fusedgene.htm

For patient information on prostate cancer:
www.cancer.med.umich.edu/learn/prostate.htm

Expanded Criteria Yield Larger Pool of Kidneys for Transplant

'A GOOD SOLUTION IN CERTAIN SITUATIONS'

More than 64,000 people in the United States today are waiting for a kidney transplant. The need for donated kidneys is growing much faster than the current supply, so some people have to wait for years before a healthy kidney is available. Unfortunately, many can't afford to wait.



Robert Merion

So instead of remaining on kidney dialysis and continuing to wait, more patients are accepting kidneys from expanded criteria donors (ECD). These are older donors and those with pre-existing kidney or medical problems whose kidneys were often not used for transplants in the past.

Even though organs from expanded criteria donors have a higher risk of organ failure, their growing use is adding to the pool of kidneys available for transplantation, and increasing the chances for survival in certain patients with end-stage renal disease.

Robert M. Merion (M.D. 1979, Residency 1986), professor of surgery in the Medical School, directed a nationwide Scientific Registry of Transplant Recipients study to determine which patients would benefit most by taking the ECD kidney now and which patients would be better off waiting for a healthier kidney. Results of the study were published in the December 7, 2005, issue of the *Journal of the American Medical Association*.

Merion and his colleagues measured the outcomes of patients on dialysis from the day they were placed on the organ wait list. The study looked at all patients in the United States – a total of 109,127 people – who were on dialysis for kidney failure and were added to an organ wait-list between 1995 and 2002, and then followed their progress through July 2004.

In terms of survival, ECD kidneys were shown to have the greatest benefits for patients over the age of 40 and those who would have to wait more than 44 months before a non-ECD kidney was available. Only diabetic patients were found to benefit from ECD kidneys in areas where wait times were shorter. For patients younger than 40, there was no significant advantage to accepting an ECD kidney.

"ECD kidneys are clearly a good solution in certain situations," says Merion. "This study's results allow us, with greater clarity than before, to maximize the benefits of ECD kidneys for patients and to match patients with a transplant option that will offer them the best chance for survival."

—Krista Hopson

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2005/kidneytransplant.htm

For patient information on chronic kidney failure:
www.med.umich.edu/1libr/aha/aha_kdnyfail_sha.htm

The Miracle of Maia

ROBOTIC-ASSISTED TECHNOLOGY HELPS CANCER SURVIVOR BECOME A MOTHER



Arnold Advincula with the da Vinci surgical robot

“Women who want to preserve their fertility have more options today than ever before.”

—Arnold Advincula

Brad and Carrie Lintner of Climax, Michigan, had a special reason to celebrate on February 25. It was their daughter Maia's first birthday — a happy event that Carrie Lintner thought she'd never see when she was diagnosed, for the second time, with a type of cancer called Hodgkin's lymphoma.

This time, it was stage III Hodgkin's lymphoma and far more advanced than the stage I Hodgkin's she had conquered years earlier. When doctors told her she needed pelvic radiation treatment to fight the cancer, her first thought was: “If I have to undergo radiation, what about a family?” says Lintner, a dentist in Kalamazoo. “It was always one of my hopes to have kids.”

The Lintners came to the University of Michigan Health System to discuss their options with Arnold Advincula, M.D., clinical assistant pro-

fessor and director of minimally invasive surgery in the Medical School's Department of Obstetrics and Gynecology.

“Advances in technology and medicine have made it possible for physicians to offer new



Carrie, Maia and Brad Lintner

fertility-preserving treatments to patients with cancer and other medical conditions,” Advincula says. “Women who want to preserve their fertility have more options today than ever before.”

The option Advincula suggested to the Lintners was ovarian transposition, a procedure that moves the ovaries to a more protected location. In Carrie's case, the ovaries were moved behind the uterus, allowing the uterus to act as a shield against tissue-damaging radiation. Advincula used robotic-assisted technology to perform the delicate surgical procedure through several small incisions in Carrie's abdomen.

All of this was done in the hope that she would be able to conceive a child. There was no guarantee it would work, but Advincula hoped it would at least preserve Carrie's ovarian func-

tion and prevent her from going into menopause at an early age.

But would the procedure allow her to conceive? Only time would tell — and, as it turned out, not much time was needed. Shortly after the surgery, the Lintners learned that Carrie was pregnant. After a normal pregnancy and an easy labor, Maia Lintner was born on February 25, 2005.

“The first thing I said to her after she was born was, ‘Are you OK?’” says Carrie Lintner. “She is an absolute joy. She is the light of my life. I feel like it's a miracle.”

Advincula is thrilled for the Lintners, and he believes that advances in robotic-assisted technology will help more women in the future. University Hospital was one of the first hospitals in the United States to offer robotic-assisted surgery. In the area of gynecological surgery, the U-M Health System is a leader in robotic myomectomy — a procedure that removes fibroid tumors from the uterus and makes it possible for women to preserve their fertility and avoid invasive surgery.

—Katie Gazella and Sally Pobojewski

For an expanded version of the story: www.med.umich.edu/opm/newspage/2005/hmfertility.htm

For patient information on preserving fertility during cancer treatment: www.cancer.med.umich.edu/clinic/fertilityclinic.htm

For patient information on the UMHS Minimally Invasive Surgery Program in Obstetrics and Gynecology: www2.med.umich.edu/departments/obgyn/index.cfm?fuseaction=Obgyn.MISP

Getting the Skinny on Fat

RESEARCHERS AT NEW U-M CENTER INVESTIGATE THE SCIENCE OF WEIGHT

Two-thirds of Americans, including an increasing number of children, are overweight or obese — setting the stage for a lifetime of obesity-related illnesses like diabetes, heart disease, stroke, cancer, and bone and joint problems. We know we need to exercise more and eat a healthy diet. So why is it so difficult for many of us to lose weight?

Researchers at the University of Michigan's new Metabolomics and Obesity Center are looking for answers. Using molecular-level research on how the body breaks down and uses food, and how metabolism varies among individuals, they will explore the science behind weight gain and loss.

“Obesity is a huge public health challenge, but also a major scientific challenge,” says center director Charles Burant, M.D., Ph.D., associate professor of internal medicine in the Medical School who studies how the body processes sugars and fats. “We still don't understand why the same food intake can lead to weight gain in one person but not another, nor why diabetes develops in some overweight people but not others. We hope to accelerate progress in understanding weight gain, weight loss and metabolism at the most basic levels, and to help translate that understanding to clinical practice.”

The center was created with a \$1 million grant from the Medical School's Endowment for the Basic Sciences. Established in 2002, the endowment supports interdisciplinary research programs and facilities that benefit scientists across the Medical School.

—Kara Gavin

For an expanded version of the story: www.med.umich.edu/opm/newspage/2005/obesitymetabolism.htm



Charles Burant

Genetic Test Helps Zero in on Eye Disease



Photo: Martin Voet
John Heckenlively and Radha Ayyagari

Rapid genetic testing for eye disease is becoming a reality, thanks to a microchip developed at the U-M Kellogg Eye Center which can screen simultaneously for mutations in multiple genes. The screening technique has proven to be reliable and cost-effective.

Scientists in the Medical School's Department of Ophthalmology and Visual Sciences created the first-of-its-kind test on a microchip array to help physicians diagnose patients with the blinding disease known as retinitis pigmentosa. RP is a group of diseases, affecting one in every 3,500 individuals, in which retinal degeneration leads to blindness or severe vision loss.

"For diseases associated with multiple genes, like RP, we now have a new and faster method for identifying the underlying genetic basis," says Radha Ayyagari, Ph.D., assistant professor of ophthalmology and visual sciences.

It is nearly impossible to identify which form of the disease a patient has through a clinical examination alone, according to John R. Heckenlively, M.D., professor of ophthalmology and visual sciences.

"Identifying the precise genetic mutation responsible for an individual's disease will allow us to provide a precise diagnosis and more accurate prognosis, and also we will know which patients will be eligible for genetic therapies as they are developed," Heckenlively says.

Studies to design these chips and provide molecular diagnostic testing to patients are funded by the National Eye Institute and the Foundation Fighting Blindness.

—Betsy Nisbet

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2005/arrp.htm

For patient information on RP:
www.kellogg.umich.edu/patientcare/conditions/pigmentosa.html

The Effects of the Unmentionable

INCONTINENCE CAN SIGNIFICANTLY DIMINISH THE QUALITY OF WOMEN'S LIVES

It's discussed so infrequently that it may seem it isn't much of a problem. But a U-M survey of 6,000 U.S. women found that 7.2 percent of them, especially older women, had regular episodes of fecal incontinence.

Many women in the study who had fecal incontinence also had another medical condition, such as major depression or diabetes, and often also experienced urinary incontinence, according to Dee E. Fenner, M.D. (Residency 1989), associate professor of obstetrics and gynecology in the Medical School.



Photo: Scott Galvin
Dee Fenner

The impact of incontinence on the quality of life was significant, says Fenner, who directed the study. "Half of the women with fecal incontinence reported that bowel symptoms had a large impact on their quality of life."

Treatments are available to help women manage this condition, says Fenner, but physicians need to take an active role and ask their patients about it. While it is most often present in elderly women, it should not be considered a normal part of aging.

—Katie Gazella

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2006/fecal.htm

For patient information on the Michigan Bowel Control Program:
www.med.umich.edu/bowelcontrol

How We Die

CULTURAL BELIEFS AND VALUES VARY

Americans have different ideas about how and where they want to die. Preferences on end-of-life issues tend to vary along racial, ethnic and gender lines, according to a focus group study conducted by researchers in the U-M Medical School.

For example, many Arab Americans would prefer not to go to a nursing home as they near the end of their lives, but many African Americans are comfortable with nursing homes and hospitals. Many Hispanic people are strongly concerned about dying with dignity. Many white people don't want their families to take care of them, but they — like members of other racial and ethnic groups — want their families nearby as they live out their last days. Hispanic men, in general, wanted little medical intervention at the end of life, while Hispanic women tended to favor extensive medical intervention. The split

was similar between African American men and women.

"Our country's medical system is based on Western values, and those values may not translate to other cultures," says Sonia A. Duffy, Ph.D., R.N., a research investigator in otolaryngology and psychiatry at the Medical School who directed the study. "Deeply rooted cultural beliefs and values are difficult to influence."

The 10 focus groups included 73 people who identified themselves as Arab Muslim, Arab Christian, Hispanic, black or white. They were all 50 years and older. They participated in exercises, scenarios and discussions about



end-of-life issues, and they completed questionnaires that, among other things, helped measure how closely they were connected with their cultural group.

"One of the most important findings in our study is that there are so many different points of view, it is important for health care providers to treat everyone as an individual," adds Duffy, who conducted the study with colleagues in the Center for Practice Management and Outcomes Research at the VA Ann Arbor Healthcare System.

The research was jointly funded by the Michigan Department of Community Health, Blue Cross Blue Shield of Michigan, and the Department of Veterans Affairs.

—Katie Gazella

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2006/endoflife.htm

A comprehensive list of resources and information about end-of-life issues:
www.nlm.nih.gov/medlineplus/endoflifeissues.html

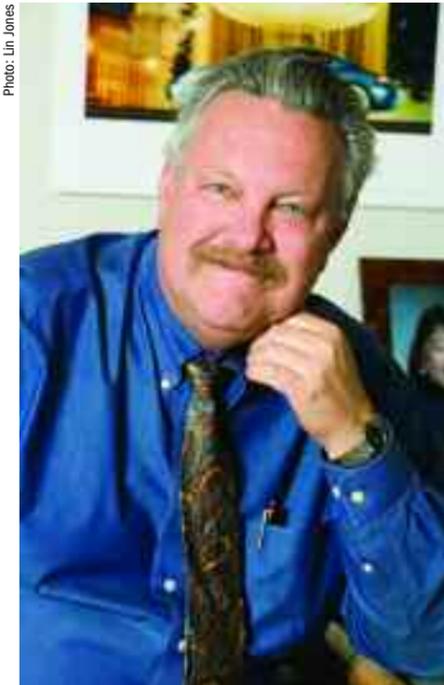
"One of the most important findings in our study is that there are so many different points of view, it is important for health care providers to treat everyone as an individual."

—Sonia Duffy



Photo: Lin Jones
Sonia Duffy

Tracking the Elusive Stem Cell



Douglas Engel

An international team of scientists led by Douglas Engel, Ph.D., the Medical School's G. Carl Huber Professor of Developmental Biology and chair of the Department of Cell and Developmental Biology, has found a way to see rare blood-forming adult stem cells, called hematopoietic stem cells, living in their natural environment.

Until now, scientists didn't know exactly where to find these elusive stem cells — the only ones capable of forming all the different types of blood and immune cells found in mammals. Most scientists believed they clustered together somewhere in bone marrow, but no one knew for sure.

"We took time-lapse movies of sections from mouse leg bone as seen under a fluorescent microscope," says Engel. "They clearly showed individual, isolated hematopoietic stem cells at the edge of the bone marrow."

According to Engel, the discovery will make it possible to study these stem cells undisturbed and in their natural environment. That's important, he says, because when stem cells are

removed from bone marrow, they either die or start differentiating — changing into different types of specialized blood cells.

Scientists currently identify a hematopoietic stem cell by looking for a unique pattern of protein markers on the cell's surface. The process is complicated and the flow cytometry equipment used to sort the cells is expensive. Plus the sorting process removes stem cells from bone marrow, which changes their properties in fundamental ways.

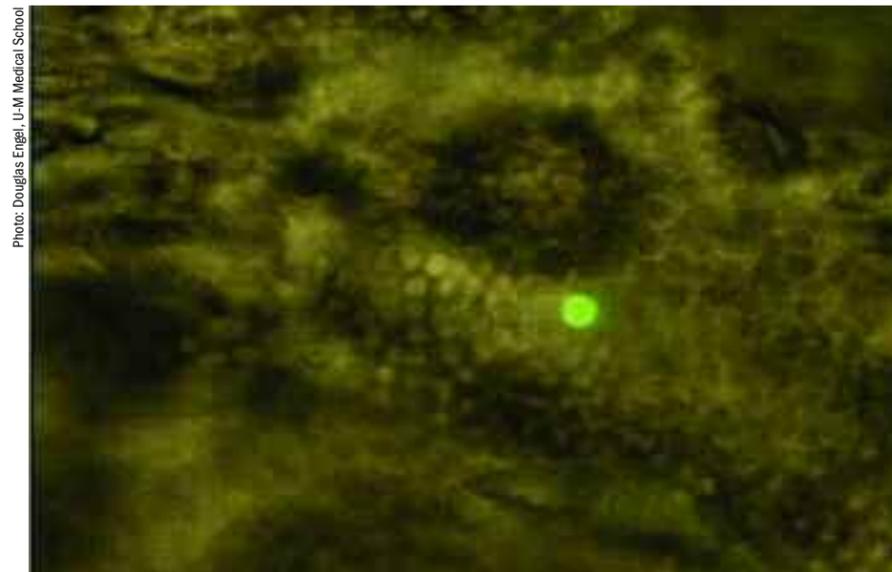
"There's something about the physical location and cellular environment surrounding stem cells in their bone marrow niche that is at least partly responsible for their ability to remain in a primitive state," Engel says. "Now that we can visualize them, we are in a better position to find out how they do it."

—Sally Pobojewski

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2006/stemcells.htm

"There's something about the physical location and cellular environment surrounding stem cells in their bone marrow niche that is at least partly responsible for their ability to remain in a primitive state."

—Douglas Engel



A single glowing blood-forming stem cell is visible among living mouse bone marrow cells.

Photo: Douglas Engel, U-M Medical School

Photo: Lin Jones

Surgery or Chemo?

DETERMINING THE BEST TREATMENT EARLY IMPROVES SURVIVAL RATES FOR LARYNGEAL CANCER PATIENTS

In the past, treating cancer of the larynx, or voice box, usually meant disfiguring surgery to remove the larynx. Chemotherapy with radiation can be an effective alternative for many patients, but it doesn't work for everyone.

In a new study conducted at the U-M's Comprehensive Cancer Center, researchers found that determining early in treatment which patients would benefit from chemo-radiation treatment, and which would be better off

"The excellent survival rates in our study may be a result of identifying patients earlier for surgery, if they are likely to fail the chemo-radiation treatment."

—Susan Urba



Gregory Wolf and Susan Urba with Kathleen Glaser, a patient who participated in the study

Photo: Lin Jones

with surgery to remove the larynx, led to better survival rates than typically expected for this type of cancer.

"Approximately 30 to 40 percent of patients with advanced laryngeal cancer will not be cured with chemotherapy and radiation, and survival rates have traditionally been poor," says study author Gregory Wolf (M.D. 1973), professor and chair of otolaryngology at the U-M Medical School. "That's why these patients should be identified and treated with surgery as early as possible."

In this study of 97 patients with advanced-stage laryngeal cancer, patients had six days of chemotherapy, after which they were examined to see whether the cancer had shrunk. Tumors shrank by more than half in three-quarters of the patients. These patients then went on to

receive radiation therapy for six to seven weeks, with additional chemotherapy. The 25 percent of patients whose cancer did not respond to the initial chemotherapy were immediately considered for surgery.

Three years later, 85 percent of all patients in the study were still alive, and 70 percent still had their larynx. Traditional survival rates for advanced laryngeal cancer are usually less than 60 percent. Patients in the study who had early surgery had similar survival to patients receiving chemo-radiation treatment.

"One cycle of chemotherapy can identify patients whose cancer is likely to be successfully treated with chemotherapy and radiation," says Susan Urba (M.D. 1983), associate professor of internal medicine. "The excellent sur-

vival rates in our study may be a result of identifying patients earlier for surgery, if they are likely to fail the chemo-radiation treatment."

—Nicole Fawcett

Read an expanded version of the story:
www.med.umich.edu/opm/newspage/2006/laryngeal.htm

For patient information on laryngeal cancer:
www.cancer.med.umich.edu/learn/voicebox.htm