ABOVE THE HURON
News and research from the Medical School

Photo: Martin Vloet

Diane Simeone and Mark Prince

Kill the Stem Cell — Kill the Tumor

U-M scientists are on the front lines of a revolution in cancer therapy

Since 1971, when President Richard M. Nixon declared a national "war on cancer," billions of federal tax dollars have been spent on research to find out what causes the disease and how to cure it. But 36 years later, it remains the second-most-common cause of death in the United States.

Early detection and more effective treatments can cure or control some types of cancer for long periods of time. But too often, the cancer eventually returns – stronger and more aggressive.

Now scientists are beginning to consider the intriguing possibility that current therapies might be aiming at the wrong target. Instead of carpet bombing all the cells in a tumor with chemotherapy or radiation, it may be more effective to use a strategic strike aimed at one specific type of cell called the cancer stem cell.

While an ordinary cancer cell divides a certain number of times and then dies, a cancer stem cell can multiply indefinitely. Every time a cancer cell divides, it makes one exact copy of itself and one cell capable of morphing into all the different types of cells found in the original tumor. So if even one cancer stem cell remains alive, the cancer can return.

Two research teams affiliated with the Cancer Center have discovered evidence for stem cells in two particularly deadly forms of the disease – cancers of the pancreas and cancers of the head and neck.

Cancer stem cells were first discovered in the 1990s in a type of leukemia. Since then, scientists at the University of Michigan Comprehensive Cancer Center and other leading medical centers have been searching for these rare, elusive cells in different types of cancer.

In 2003, Max S. Wicha, M.D., Distinguished Professor of Oncology and director of the Cancer Center, and other U-M scientists were the first to discover stem cells in human breast cancers. They found that stem cells have a specific pattern of proteins on their surface membranes. To identify stem cells among all the other cells in a tumor, scientists look for their unique protein marker fingerprint.

In 2006, U-M scientists led by Sean Morrison, Ph.D., a professor of internal medicine who directs the Center for Stem Cell Biology, found a way to kill cancer stem cells in mouse tumors without harming the normal stem cells in the same tissue.

Now two other research teams affiliated with the Cancer Center have discovered evidence for stem cells in two particularly deadly forms of the disease – cancers of the pancreas and cancers of the head and neck.

Mark Prince, M.D., an assistant professor of otolaryngology in the Medical School and section chief of otolaryngology at the VA Ann Arbor Healthcare System, led a Stanford/U-M research team that identified stem cell markers on cells from human cancers of the tongue, larynx, throat and sinus.

Diane Simeone, M.D., an associate professor of surgery and of molecular and integrative physiology, directed a study that found stem

Speeding the Search for Bipolar Genes

Depression Center, Johns Hopkins join forces to increase sample size

For the 5.7 million Americans with bipolar disorder, the manic "highs" and the deep depressed "lows" they experience are bad enough. But they also live with the knowledge that their loved ones, especially their children, are at risk of developing the disease. Although no single gene causes bipolar disorder, the disease has its roots in genetic vulnerabilities that run in families.

A new cooperative effort by scientists at the U-M Depression Center and Johns Hopkins University will accelerate the search for these genetic underpinnings of the disease. The two universities are combining research efforts and stockpiles of biological samples from bipolar patients and their families. The sample collection also will be available to other researchers who study the genetics of bipolar disorder.

Photo: Martin Vloet

Robert Thompson, Ph.D. (left), an assistant professor of psychiatry and research assistant professor in the Molecular and Behavioral Neuroscience Institute, manages the laboratory for the Prechter Bipolar Genetics Repository. Thompson works closely with Melvin McInnis, seen here holding a DNA microarray slide containing small points of genetic variation called single nucleotide polymorphisms in human DNA. Modern laboratory analytical systems like the ones in Thompson's lab are helping scientists identify genes that may predispose people to bipolar disorder.

The U-M/Hopkins collaboration will expand the Prechter Bipolar Genetics Repository, which has been used by U-M researchers and colleagues at Stanford University and Cornell University since 2005. The repository is funded by the U-M Heinz C. Prechter Bipolar Research Fund, founded by Waltraud "Wally" Prechter in an ongoing effort to conquer the disease that led to her husband's suicide in 2001.

"Cooperation means acceleration in genetics research, because the more samples we can study from more families, the faster we can get to definitive answers about the genes involved in bipolar," says Melvin McInnis, M.D., the Upjohn Woodworth Professor of Bipolar Disorder and Depression in the U-M Medical School Department of Psychiatry, and director of Depression Center psychiatry programs.

McInnis and his colleagues have used genetic scans to identify a particular region of chromosome 8, which appears to contain areas of major variation between people with bipolar disorder and those without the disease. Now, the combined genetic repository will allow scientists to narrow their search for the genes and individual nucleotides that lie at the heart of that variation.

More than 1,500 blood and cell samples from 140 families affected by bipolar disorder are being shipped from the Hopkins campus in Baltimore, Maryland, to be stored with hundreds of samples collected since 2005 by U-M researchers. The Hopkins repository includes samples collected since the late 1980s. U-M scientists will prepare DNA samples from the Hopkins blood and cell samples, which then will be studied at both institutions.

U-M researchers will continue adding new samples from additional patients and their relatives to the repository.

For more information on the Prechter Bipolar Genetics Repository, and the need for more patients and families to volunteer samples of their blood and DNA, call (877) 864-3637 or e-mail bpresearch@umich.edu.

—Kara Gavin

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

For patient information on bipolar disorder:
www.med.umich.edu/depression/bipolar.htm

cells in tumors removed from patients with pancreatic cancer. Any progress in pancreatic cancer is significant, according to Simeone, because it has the worst survival rate of any major type of cancer.

Prince and Simeone emphasize that the field is new and much additional research will be needed before new therapies aimed at cancer stem cells will be possible. But as scientists continue to find stem cells in more and more types of cancer — including brain, colon, prostate and ovarian — Simeone is sure of one thing:

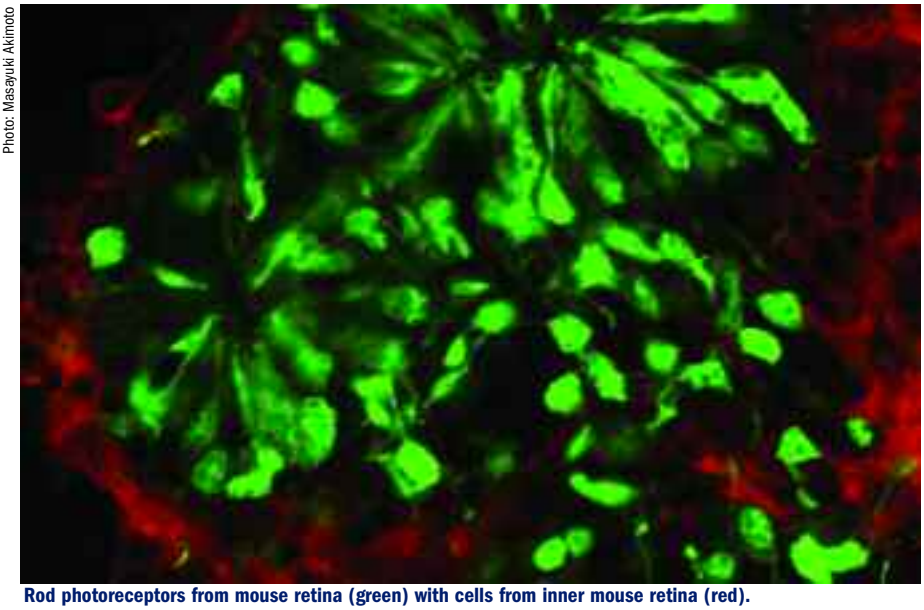
"Stem cells are going to radically change how we treat cancer," she says.

—Sally Pobojewski

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2007/headneckcancer.htm

www.med.umich.edu/opm/newspage/2007/pancancer.htm

Photo: Masayuki Akimoto



Rod photoreceptors from mouse retina (green) with cells from inner mouse retina (red).

New Promise for Restoring Vision

Successful cell transplants in mice could benefit humans

Using new technology developed at the U-M Kellogg Eye Center, scientists at the London Institute of Ophthalmology have transplanted light-sensing cells called photoreceptors directly into the retinas of blind mice to restore their visual function.

According to Anand Swaroop, Ph.D. — the Harold F. Falls Collegiate Professor of Ophthalmology and Visual Sciences in the Medical School — who developed the technology, the key to its success is transplanting photoreceptor cells at a particular stage in their early development. Called precursors, they are immature cells that are "programmed" to be, but have not yet become, functionally mature photoreceptors — the light-sensitive cells in the retina that are essential for sight.

Photoreceptors are part of a complex sensory system that delivers visual signals to the brain. They consist of rods and cones, highly specialized cells that capture light and convert it into chemical signals that travel through the retina and optic nerve to the brain where signals are converted to the images we see. In most macular and retinal degenerative diseases, such as age-related macular degeneration and retinitis pigmentosa, it is the loss of photoreceptors that leads to blindness.

"One of our critical discoveries," Swaroop says, "is that there is a window of opportunity during which a cell has committed itself to becoming a rod, but has not yet started to function as such."

Successful transplantation requires that cells reach a certain level of maturity before being transplanted into the eye, Swaroop explains. When cells are transplanted at a very early stage, they survive, but fail to integrate into the mature retina.

Robin R. Ali, Ph.D., and colleagues at the Institute of Ophthalmology transplanted photoreceptor precursor cells into mice with retinal degeneration caused by genetic defects. The transplanted cells survived and were functional for the duration of the study. Scientists observed improvements, including pupil response to light and response to light stimuli from ganglion cells, which form the circuitry to the brain. Results of the study were published in *Nature*.

Although the experiment has implications for human eye diseases, Swaroop anticipates that several years of additional research will be needed before transplantation can be tested in humans.

But after almost two decades of directing fundamental research on retinal development and degenerative diseases, Swaroop believes scientists are at last entering a period of rapid discovery. "We now have proof of principle that our approach to repairing damaged retina by transplantation of appropriate cells can be successful," he says.

—Betsy Nisbet

For an expanded version of the story:
www.kellogg.umich.edu/news/20061108_visionRestored.html

For patient information on retinal degenerative diseases:
www.kellogg.umich.edu/research/crmd.fop.html

Photo: Martin Vloet

Anand Swaroop

Photo: ©iStockphoto.com/Christine Balderas

Stroke Costs Expected to Soar

Price tag could reach $2.2 trillion by 2050

Unless Americans do more to lower their risk of stroke and improve stroke care, the United States will pay $2.2 trillion by the year 2050 to care for people who suffer the most common form of the disorder, according to a U-M study.

A disproportionate share of the bill will be for young and middle-aged black and Latino stroke patients, because they tend to have strokes at younger ages than other ethnic groups and receive poorer-quality preventive care.

"Doing the right thing now could be cost-saving in the future, but we have a long way to go before all Americans receive adequate stroke prevention and emergency stroke care," says Devin Brown, M.D., an assistant professor of neurology and a member of the U-M Stroke Program, which is part of the Cardiovascular Center.

The $2.2 trillion price tag includes the cost of everything from ambulances and hospital stays to medications, nursing home care, at-home care and doctors' visits. It also includes lost earnings for stroke survivors under age 65.

Brown and colleagues maintain their estimate is extremely conservative, because it is based on current rates of the conditions that put people at higher risk of stroke — such as diabetes, cardiovascular disease and obesity. These conditions are projected to become more common in the future.

What can Americans do to decrease this looming bill? No matter their age or ethnicity, individuals can cut their own stroke risk by quitting smoking, losing weight, eating healthy, exercising, and keeping their blood pressure, cholesterol levels and any heart-rhythm problems under control, Brown says.

Meanwhile, doctors and hospitals can do a better job of providing preventive care and screening to patients with high blood pressure, clogged arteries and heart-rhythm problems. And they can improve their use of a post-stroke drug called tPA, which breaks up blood clots.

—Kara Gavin

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

For patient information on stroke:
www.med.umich.edu/1libr/aha/aha_strnos_crs.htm

U-M Boasts Top-10 Medical School

The University of Michigan Medical School has been recognized as one of the best in the country with a top-10 ranking in the annual *U.S. News & World Report* "Best Graduate School" listings.

The U-M tied for 10th overall among the nation's 125 fully accredited research-oriented medical schools and placed highly in five specialties: family medicine (4), geriatrics (5), women's health (6), internal medicine (8) and pediatrics (12).

Last year, U-M ranked 11th overall.

"Our excellent national reputation is a testament to the breadth and depth of the work our faculty, staff and students accomplish every day at the University of Michigan Medical School," says Interim Dean James O. Woolliscroft, M.D. (Residency 1980).

The rankings of research medical schools are based on several factors, with the most weight given to a quality assessment determined by input from medical school leaders around the country. Other factors are a school's level of research activity, student selectivity and faculty resources.

—Katie Gazella

Photo: Martin Vloet

Maria Soengas

Many Moles Do Not Make Melanomas

Skin cells block cancer-causing mutations

Everyone has moles. Most of the time, they are nothing but a cosmetic nuisance. But sometimes pigment-producing cells called melanocytes in moles start dividing abnormally to form a deadly form of skin cancer called melanoma.

Scientists know that 30 percent of all melanomas begin in a mole. They also know that 90 percent of moles contain cancer-causing mutations. So what stops most of these mutations from triggering the development of skin cancer?

Maria S. Soengas, Ph.D., and other scientists in the Multidisciplinary Melanoma Clinic at the U-M Comprehensive Cancer Center, found the answer to this important question in an unexpected place — a structure called the endoplasmic reticulum, which is the cell's protein production factory.

According to Soengas, the endoplasmic reticulum induces a mechanism called premature senescence in melanocytes with cancer-causing mutations. It's a form of "suspended animation" that stops the cell cycle and keeps cells from dividing, but doesn't kill them.

"The cells are held in check — they don't die, but they don't proliferate, either," explains Soengas, an assistant professor of dermatology in the Medical School. "Melanocytes can stay this way for 20 to 40 years or even your whole life. For most of us, just holding cells in an arrested state is sufficient to prevent the development of cancer. That's why so many people have moles, but few have melanoma."

—Sally Pobojewski

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

For patient information on melanoma:
www.cancer.med.umich.edu/cancertreat/skincancer/index.shtml

Hope for a Devastating Disease

While search for a cure progresses, U-M scientists hope to slow damage

Idiopathic pulmonary fibrosis, or IPF, is a disease that affects hundreds of thousands of Americans, and kills 40,000 of them every year. In a process scientists don't understand, the disease gradually destroys air sacs in the lung and replaces them with scar tissue, making it difficult and eventually impossible for patients to breathe. In most cases, the cause of IPF remains a mystery.

At the University of Michigan, clinicians and scientists are working together to unravel the mysteries surrounding IPF. They hope their research will lead to therapeutic drugs to block the scar-forming process or diagnostic tests that could make early detection possible.

"IPF is very hard to diagnose, and the diagnosis is often missed for months, and sometimes years, before it is recognized,"

Illustration: Lisa Zador/Photodisc Green/Getty Images

Too Much Treatment?

Patients with prostate cancer often treated aggressively

When it comes to some types of prostate cancer, taking a wait-and-see approach may be the best option, according to physicians at the U-M Comprehensive Cancer Center.

For men with less aggressive prostate cancers, the balance between the risks and benefits of immediate treatment are not always well-defined. Surgery or radiation can lead to complications such as erectile dysfunction, urinary incontinence and bowel difficulties. And older men with lower-risk prostate cancer are likely to die from something else during the 20 years after they are diagnosed with cancer.

"For some men with early-stage prostate cancer, surgery or radiation therapy may result in substantial negative effects without a survival benefit," says John T. Wei, M.D., an associate professor of urology in the Medical School.

Wei and his research collaborators used a National Cancer Institute database to survey medical records from 64,112 men diagnosed with early-stage prostate cancer. Men were divided into high-risk or low-risk categories, based on characteristics of their tumors.

Among the 24,835 men with lower-risk cancers, 55 percent were treated with initial surgery or radiation, suggesting that aggressive treatment is quite common even among men where a more conservative approach with frequent monitoring of the tumor could be a viable option.

"Based on data from this study, it is clear that the number of lower-risk patients who receive initial aggressive therapy is not trivial, and we have to ask the question whether this is too much treatment for some of these men," says lead study author David C. Miller, M.D., an adjunct lecturer in the Medical School and health services research and oncology fellow at the UCLA David Geffen School of Medicine.

—Nicole Fawcett

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

For patient information on prostate cancer:
www.cancer.med.umich.edu/cancertreat/urologiconcology/prostate_cancer.shtml

Photo: Martin Vloet

John Wei

says Kevin R. Flaherty, M.D., an assistant professor of internal medicine in the Medical School, noting that early diagnosis is important in the management of IPF.

Most people believe IPF is the result of injury to the lung, followed by an abnormal healing process, Flaherty says. Exposure to toxic environmental agents like beryllium and silica dust can trigger IPF, and smoking is probably a related factor in many cases. Genetics almost certainly plays a role, as the disease tends to run in families.

Once diagnosed, there are no effective treatments. Flaherty says lung transplantation is an option for some patients, but many have other diseases that make a transplant impossible. And there simply aren't enough donated lungs for everyone who needs one.

Bethany B. Moore, Ph.D., an assistant professor of internal medicine, and Galen B. Toews, M.D., professor of internal medicine and chief of pulmonary and critical care medicine, have identified biochemical signals that attract cells called fibrocytes to damaged lung tissue — one of the first steps in a chain of events leading to the formation of scar tissue in the lungs.

"We may not be able to stop the initial disease process, but perhaps we could keep it from progressing so rapidly," Moore adds. "It's a first step, but an important one, in solving the mystery of this disease. Right now, research is the only hope we can offer IPF patients."

—Katie Gazella and Sally Pobojewski

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

For patient information on IPF:
www.med.umich.edu/intmed/pulmonary/patients/fibrosis.htm