

Super Small Science Holds Huge Potential

NEW NANOTECHNOLOGY INSTITUTE WILL DEVELOP AND MARKET BIOMEDICAL APPLICATIONS

Today's doctors can replace a worn-out hip or knee — even a damaged heart or kidney. But James R. Baker Jr., M.D., sees a future in which physicians will be able to replace defective genes or proteins, and design new therapies to fight disease from inside the cell.

It's all part of the rapidly advancing field of nanotechnology in medicine, and it's not just for science fiction anymore.

"Nanotechnology is changing how scientists work by giving them the ability to manipulate individual atoms and molecules in biological systems," says Baker, the U-M's Ruth Dow Doan Professor of Biologic Nanotechnology. "We are talking about materials that are thousands of times smaller than the smallest cell in the body. Applying nanotechnology to medicine will allow us to literally re-engineer how our cells work."

Nanotechnology deals with particles so small they can easily slip through tiny openings in cell membranes to get inside living cells. One nanometer equals one-billionth of a meter, which means it would take about 80,000 nanometers lined up side-by-side to equal the width of a human hair.

A pioneer in the field, Baker has been researching the biological applications of nanotechnology since the mid-1990s. He directs the Michigan Nanotechnology Institute for Medicine and Biological Sciences, which was established in April 2005. The institute's mission is to develop and market medical and biological applications of nanotechnology.

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research to develop what he calls the "nanotechnology equivalent of a Trojan horse."

It's a manmade nanoparticle less than five nanometers in diameter called a dendrimer, designed to smuggle a powerful anti-cancer drug inside tumor cells — increasing the drug's cancer-killing activity and reducing its toxic side effects.

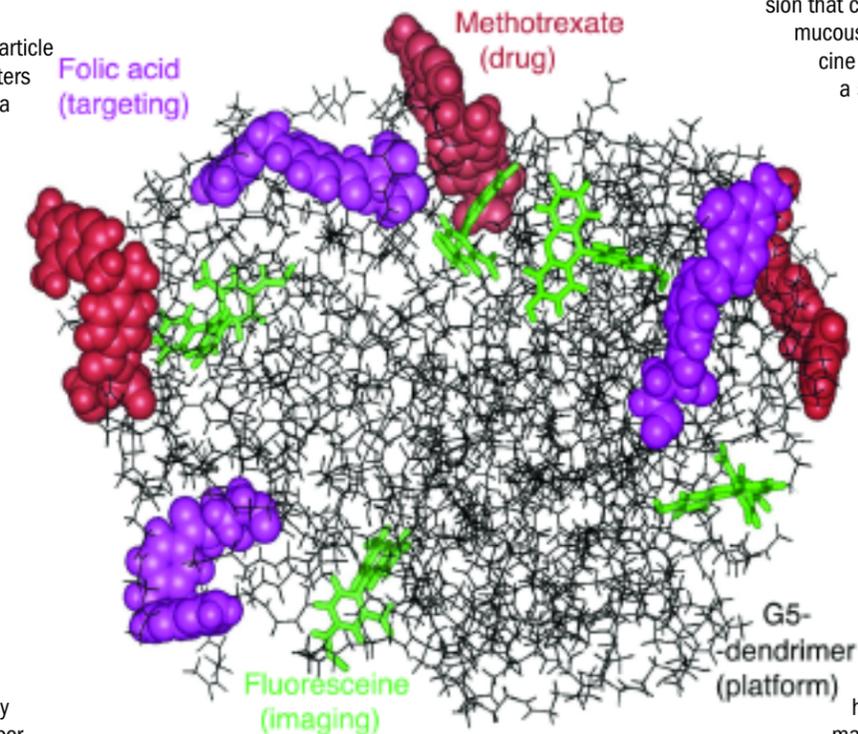
Dendrimers have a tree-like structure with many branches where scientists can attach drugs and molecules. U-M scientists attached methotrexate, a powerful anti-cancer drug, to one branch of the dendrimer. On another branch, they attached folic acid, an important vitamin required for the healthy functioning of all cells. But cancer cells, in particular, seem to need more than average amounts. By taking advantage of a cancer cell's appetite for folate, U-M scientists were able to concentrate more of the toxic drug in cancer cells, while reducing side effects on normal cells.

"The cancer cell thinks it's bringing in food," Baker explains. "But once inside, there's a poison on the nanoparticle that kills the cell."

When Jolanta Kukowska-Latallo, Ph.D., a research investigator at the Nanotechnology Institute, gave the nanoparticle-methotrexate combination to mice with tumors, she found it was more effective than giving the cancer-killing drug alone.

"Effectively, we delayed the growth of tumors in mice for 30 days," Kukowska-Latallo says. "Taking into account the length of a mouse's life, that is significant. One month for a mouse is about three years for a person."

The success of the Trojan horse approach led to a recent \$2.5 million, five-year Cancer



This simplified computer model of the U-M "Trojan horse" nanoparticle shows the dendrimer's branching structure and how molecules and drugs are attached.

Photo: Jolanta Kukowska-Latallo, Michigan Nanotechnology Institute for Medicine and Biological Sciences

Nanotechnology Platform Partnership grant from the National Cancer Institute. Baker will use the NCI funding to develop a modular dendrimer nanoparticle system that can be made-to-order using different drugs and imaging agents to create personalized cancer treatments tailored to each patient.

But the news isn't all about cancer. In June 2005, Baker learned that the Michigan Nanotechnology Institute was one of 43 institutions to receive a Grand Challenges in Global Health Initiative grant from the Bill and Melinda Gates Foundation, the Wellcome Trust and the Canadian Institutes of Health Research.

The \$6.3-million Grand Challenges grant will support development and clinical testing of a nanotechnology-based vaccine delivery system. To eliminate the need for injections and

refrigeration, hepatitis B vaccine will be suspended in an anti-microbial nanoemulsion that can penetrate the skin and mucous membranes, so the vaccine can be administered with a simple nasal swab.

"We believe this nanotechnology-based approach can revolutionize how vaccines are delivered and will be an important advance in the prevention of infectious diseases in developing countries," Baker says.

The next hurdle for researchers at the Michigan Nanotechnology Institute is to see if these nanotechnology-based treatments work as well in humans as they do in animals. Baker hopes to begin early human clinical trials of the nanoparticle cancer therapy and the hepatitis B nanoemulsion vaccine within a year.

Plans are already underway to jump-start the creation of new companies to market technologies developed at the institute, Baker adds. "We want to ensure that marketable technologies are transferred to the private sector as rapidly as possible," he says, "so they can be developed into new drugs and therapies for people who need them."

—SFP

For more information about nanotechnology: Michigan Nanotechnology Institute for Medicine and Biological Sciences www.nano.med.umich.edu

National Cancer Institute Alliance for Nanotechnology in Cancer <http://nano.cancer.gov>

Inflammation and Gastric Cancer: Connecting the Molecular Dots

When it comes to gastric cancer, too little stomach acid can be just as dangerous as too much, according to Juanita L. Merchant, M.D., Ph.D., U-M professor of internal medicine and of molecular and integrative physiology. Both extremes create inflammatory changes in the stomach lining and a condition called chronic atrophic gastritis, which over time often leads to cancer.

Most physicians are aware of the association between chronic inflammation and gastric cancer. They also know that infection with a bacterium called *Helicobacter pylori*, if left untreated, can cause stomach cancer. But the fact that lower-than-normal acidity can trigger pre-cancerous changes in the stomach lining is not well known.

“Our research shows that inflammation, regardless of the cause, is the key to the development of gastric cancer,” Merchant says. “We’re finding that there are many mechanisms, in addition to gastrin hypersecretion and *H. pylori* infection, capable of producing the chronic inflammatory changes that lead to cancer. Our goal is to identify genetic and molecular changes that occur early – for example, during the inflammatory process before cancer develops – and then see if it is possible to reverse those changes.”

—SFP

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

www.med.umich.edu/opm/newspage/stomachacid.htm

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



Juanita Merchant and research investigator Yana Zavros, Ph.D., a collaborator in the study of gastric cancer

“Our research shows that inflammation, regardless of the cause, is the key to the development of gastric cancer.”

—Juanita Merchant

Statins Cut Risk of Colon Cancer



Stephen Gruber

Taking cholesterol-lowering drugs called statins reduces the risk of colon cancer by nearly half, even in people with a family history of the disease or other risk factors, according to a study by researchers at the U-M Comprehensive Cancer Center and School of Public Health.

Statins have been shown to lower cholesterol and prevent heart disease, but scientists don't know why they also appear to have a protective effect against cancer, says Stephen Gruber, M.D., Ph.D., associate professor of internal medicine and human genetics at the Medical School and associate professor of epidemiology at the School of Public Health, who directed the research.

The study was based on interviews and analysis of medical records for nearly 4,000 people in northern Israel. About half the study participants had colorectal cancer and half did not. Those without colon cancer were nearly twice as likely to report taking statins for at least five years. Results were published May 26 in the *New England Journal of Medicine*.

—NF

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

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

Change of Heart

RESHAPING HELPS RESTORE LOST FUNCTION

A tiny titanium-and-silicone rubber ring co-invented by U-M cardiac surgeon Steven Bolling (M.D. 1979) helps patients with congestive heart failure regain lost heart function by changing the shape of the heart's main pumping chamber. This makes it possible to restore some of the heart's normal pumping ability, allowing many patients to live longer with fewer disabling symptoms.

Nearly 600,000 Americans are diagnosed with heart failure every year. About half of them also develop a leaky mitral valve as their heart enlarges and changes shape. The U-M device was designed to alter the shape of the left ventricle and allow the mitral valve to close properly.

Bolling developed the heart-valve ring with Ottavio Alfieri, a cardiac surgeon from Italy. Called GeoForm, the device is approved by the



Photo: Courtesy Edwards Lifesciences Corp.

U.S. Food and Drug Administration for use in mitral valve repair, and is marketed by Edwards Lifesciences Corp.

—KEG

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

For patient information on congestive heart failure:
www.med.umich.edu/cvc/lead/heartfailure.htm

Cardiac Stretch

CHEMICAL SEALANT RESTORES HEART MUSCLE CELLS' ABILITY TO LENGTHEN IN DYSTROPHIN-DEFICIENT MICE

U-M scientists have found a chemical "band-aid" that can repair damage to cardiac muscle cells and prevent heart failure in mice with the same genetic mutation that causes Duchenne muscular dystrophy in people.

This mutation in a gene called dystrophin causes skeletal muscle to deteriorate and affects cardiac muscle, too. Many people with Duchenne muscular dystrophy die in their 20s from heart failure caused by cardiomyopathy, a gradual weakening of the heart muscle.

"Our research found that mice with the dystrophin mutation have stiffer heart muscle cells, which don't relax and lengthen as readily as they do in normal mice," says Joseph M. Metzger, Ph.D., professor of molecular and integrative physiology and of internal medicine in the U-M Medical School. "This makes them vulnerable to damage when they must stretch to make room for blood flowing into the heart."

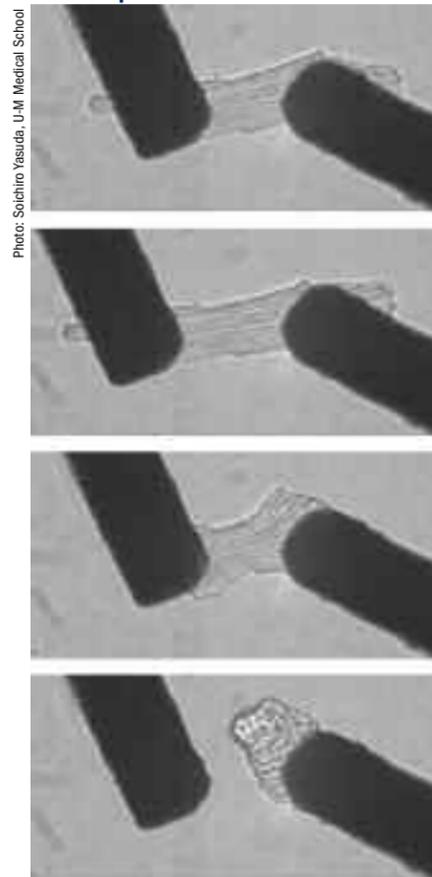
The U-M research team found that bathing heart muscle cells from dystrophin-deficient mice with poloxamer 188 — a chemical

sealant used in manufacturing and the pharmaceutical industry — restored the cells' ability to stretch without damage. And an infusion of P188 protected the mice from heart failure during a stress test.

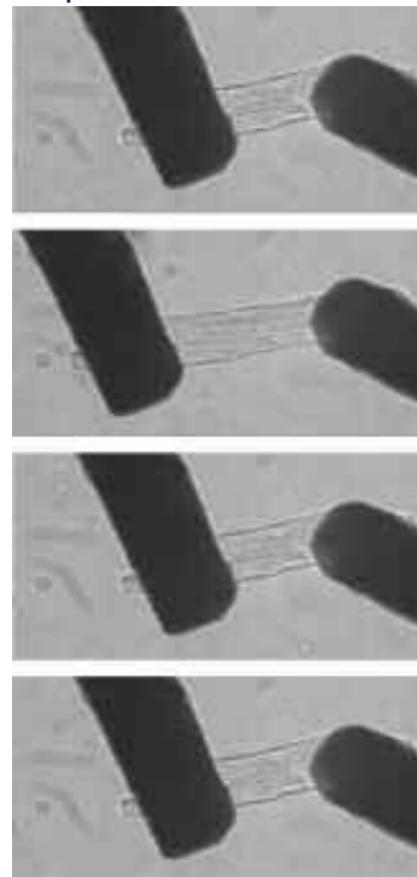
"If issues of dosing and long-term safety can be resolved, our research suggests that poloxamer 188 could be a new therapeutic agent for preventing or limiting progressive damage to the hearts of patients with muscular dystrophy," Metzger says.

—SFP

Without poloxamer 188



With poloxamer 188



The U-M research team found that bathing heart muscle cells from dystrophin-deficient mice with poloxamer 188 restored the cells' ability to stretch without damage.

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

Left column: This series of four images shows a cardiac muscle cell from a dystrophin-deficient mouse being stretched between microcarbon fibers. Untreated myocytes from these mice break and die after repeated 20 percent stretches.

Right column: This series of four images shows a cardiac muscle cell from a mouse that was treated with P188. Even though it has the same genetic defect, it survives 20 percent stretches without breaking.

Photo: Soichiro Yasuda, U-M Medical School

Photo: D.C. Goings



Effectiveness of Colon Cancer Screening Methods Differs between Genders

COLONOSCOPY BEST FOR WOMEN

Colonoscopy is the most effective method of detecting advanced pre-cancerous polyps in women, according to a new multi-center study directed by Philip Schoenfeld, M.D., associate professor of internal medicine in the Medical School.

The study, published in the *New England Journal of Medicine* in May, found that advanced pre-cancerous polyps tended to grow, in men, in the lower portion of the colon, while women's polyps developed deeper in the colon — beyond the reach of a flexible sigmoidoscopy exam. Previous colon cancer screening studies, which focused primarily on men, found that flexible sigmoidoscopy and occult blood testing can detect more than 70 percent of men with advanced pre-cancerous polyps. But the new study of 1,483 women showed that these two screening tests

would identify just 35 percent of women with the same type of polyps.

"With heart attacks and other diseases, we know that men and women develop symptoms differently and require different approaches," Schoenfeld says. "Colon cancer screening should be no exception."

—KH

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

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

Living with Polio

U-M CLINIC HELPS POST-POLIO SYNDROME PATIENTS MAINTAIN INDEPENDENCE AND MOBILITY

Fifty years after the University of Michigan's Thomas Francis Jr., M.D., announced that a new vaccine for one of the most virulent childhood diseases was "safe, effective and potent," the effects of polio still linger among the estimated 300,000 polio survivors in the United States.

Donald and Nancy Giroux from Davison, Michigan, are two of those survivors. Donald contracted polio in 1953 at age 8, and spent a year recovering in a Detroit hospital. Nancy was infected in 1949 when she was 3 years old. Both have worn leg braces and used crutches since childhood. Since their marriage in 1968, they have enjoyed a full and active life together — holding down jobs, raising their granddaughter, Donnajean, cutting and splitting firewood to heat their home, and going for long walks.

But a few years ago, Nancy noticed that her arms were getting weaker. Severe leg pain and flu-like symptoms were making it hard for Donald to keep working. After seeing several doctors, they were referred to the U-M Health System where they were diagnosed with post-polio syndrome.

Ten to 40 years after the initial onset of symptoms, polio survivors often begin to experience fatigue, muscle weakness, joint pain, and muscular atrophy caused by post-polio syndrome. Many polio survivors struggle with disability, pain and even limb deformity for years before seeking treatment, says Mark Taylor, director of clinical and technical services at the U-M Orthotics and Prosthetics Center.

"Post-polio syndrome creates challenges at work and in everyday life," says Taylor, a polio survivor who contracted the disease when he was 9

months old. "Polio patients strive to be normal, and at the clinic we work with them to create a treatment plan to help them maintain their independence and mobility."

The U-M Health System has one of only three clinics in the state focused on treating post-polio patients. Its team of physicians, orthotists and prosthetists come

mainly from the Medical School's Department of Physical Medicine and Rehabilitation. Together, they treat patients, study polio's long-term effects, and educate the next generation of health care providers.



Donald and Nancy Giroux

Photo: Marie Frost

Ten to 40 years after the initial onset of symptoms, polio survivors often begin to experience fatigue, muscle weakness, joint pain, and muscular atrophy caused by post-polio syndrome.

To maximize mobility and minimize stress on weight-bearing joints, Taylor fits many of the clinic's patients with custom leg braces and other orthotics, created by a team of experts at the Orthotics and Prosthetics Center using light-weight materials and the latest technology.



Ann Laidlaw and Mark Taylor

Photo: Martin Voet

"Mark [Taylor] made new braces for us that are lighter weight, more comfortable and provide more stability than the old ones," Nancy Giroux says. "It made a big difference in our walking. They sent us for physical therapy and gave Donald cortisone injections to help with his leg pain. Since Mark has polio himself, he knows how we feel and where we're coming from."

Photo: Scott Galvin

Patients come to the clinic from all over the United States, says Ann Laidlaw (M.D. 1996), a clinical lecturer in physical medicine and rehabilitation in the Medical School and director of the Post-Polio Clinic.

"Few clinics deal specifically with post-polio syndrome or other polio-related problems," says Laidlaw. "Patients are grateful we are here for them, and that we understand what they're going through."

Claire Kalpakjian, Ph.D., a research fellow in Physical Medicine and Rehabilitation, works with others in the department on research designed to learn more about polio's long-term effects.



Claire Kalpakjian

A recent nationwide study led by Kalpakjian examined the impact of menopause on women who are polio survivors, as well as the differences between men and women with post-polio syndrome. Kalpakjian will use the information for a collaborative study with Michigan State University that will focus on self-esteem and sexuality in post-polio women.

"Studying women with disabilities in general is so important because they have long been neglected in rehabilitation research," says Kalpakjian. "But learning and understanding how male and female polio survivors differ as they age will help us identify the best treatment and health management approaches for both groups."

—KH, SFP

For information on the U-M's Post-Polio Clinic and other services for patients with disabilities and injuries: www.med.umich.edu/pmr/clinical.htm

Insomnia and the Elderly

SLEEP AIDS MAY NOT BE RESPONSIBLE FOR PERILOUS FALLS

Insomnia in nursing home residents often goes untreated because doctors believe that sleeping pills increase the risk of falls — a frequent cause of serious injuries and major health crises in the elderly. Results from a new U-M Medical School study suggest that the real culprit may be the underlying insomnia, rather than the medications used to treat it.



make the patient more likely to fall and develop a hip fracture," says U-M sleep specialist Alon Avidan, M.D., M.P.H., assistant professor of neurology in the Medical School.

"But our findings suggest that people whose insomnia is treated effectively are less likely to fall than untreated insomniacs."

"Many physicians assume that if an older patient with insomnia is given a hypnotic drug to help induce sleep, the drug will

The study included more than 34,000 Michigan nursing home residents over age 65. Individuals with untreated insomnia at

the start of the six-month study period were 90 percent more likely to fall, compared to those without insomnia. In contrast, those who were taking hypnotic drugs to treat their insomnia were only 29 percent more likely to fall than those without insomnia.

—KEG

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

For patient information on insomnia: www.med.umich.edu/1libr/aha/aha_insomnia_crs.htm

Minimal Invasion, Maximum Benefit

NEW SURGICAL PROCEDURE FOR EARLY LUNG CANCER
REDUCES PAIN, RECOVERY TIME AND COSTS

A new surgical technique offered at the U-M Comprehensive Cancer Center is helping people with early stage lung cancer recover more quickly with less pain.

The new technique, called a thoracoscopic lobectomy, involves removing a portion of the lung without cutting large muscles or spreading the ribs. As a result, patients leave the hospital in half the time of conventional lung surgery, and can usually return to work in only two weeks. With traditional lung cancer surgery, patients remain in the hospital as long as a week.

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"It's a way of treating cancer with a less-invasive procedure that will get patients back to their regular activities sooner," says Allan Pickens, M.D. (Residency 2004), thoracic surgeon at the Cancer Center and lecturer in surgery at the Medical School. The U-M is one of a select few centers nationwide offering the new procedure.

Traditional lung cancer surgery is a thoracotomy, in which the surgeon cuts through the muscles into the chest and spreads open the ribs to access the lungs. The incision is large, about 20 centimeters, and recovery is slow and painful.

With the new technique the surgeon makes three small incisions of 2-4 centimeters each. A camera is inserted through a fourth small



Allan Pickens

incision and allows the surgeon to see inside the chest. Very little muscle is cut.

Surgeons are seeing better pulmonary function in patients who have the less invasive procedure, according to Pickens. In addition to going home sooner, recovery is easier and requires fewer narcotic painkillers. Initial research suggests cancer survival rates are similar for both procedures.

—NF

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

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

Photo: Scott Gavin

Free Drugs = Life + Cost Savings

Are some medicines so good they should be free? If we're talking about ACE inhibitors and the 8 million Americans over age 65 with diabetes, the answer appears to be yes.

A new U-M Health System cost-benefit analysis indicates these drugs are so beneficial to this group of patients that even giving them away would save both lives and money in the long run by preventing costly heart attacks, strokes and kidney failure.

Currently, more than half of these patients are not taking ACE inhibitors to lower blood pressure and reduce the risk of diabetes-related complications, says Allison Rosen, M.D., Sc.D., assistant professor of internal medicine in the Medical School and assistant professor in the School of Public Health, who directed the study.



The new Medicare prescription drug plan covers partial costs of medicines for people over age 65, and is expected to increase use of ACE inhibitors among seniors with diabetes. But under this plan, seniors will still pay part of their drug costs in the form of premiums, deductibles and co-pays.

"Out-of-pocket costs, such as co-pays, are designed to keep patients from over-using medications, but they also create barriers to the use of essential medications," Rosen says. "Our analysis shows that removing all patient costs for diabetes patients taking ACE inhibitors could save Medicare both lives and money."

—KEG

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

For patient information on type 2 diabetes: www.med.umich.edu/1libr/aha/aha_noninsul_crs.htm

The Wily Ways of Herpes Simplex

VIRUS MAY TRICK CELLS TO GAIN ENTRY

Millions of Americans know all too well that once you are infected with herpes simplex, you are infected for life. The virus can get inside almost any kind of human cell, reproduce in vast numbers, and linger for years in the body, causing everything from recurrent genital blisters to sores around the mouth. How does the virus do this?

That's what a team of Medical School researchers — led by A. Oveta Fuller, Ph.D., associate professor of microbiology and immunology — are trying to find out. They recently discovered a receptor called B5, which functions as a molecular "lock" in the outer

membrane of most human cells. Herpes simplex seems to have evolved a way to latch onto the receptor, and fool the cell into letting the virus inside.

"We can use the receptor molecule to try to understand the process, and perhaps combat infection at this vulnerable site," Fuller says. "While we're still a few years away from using this new knowledge to find and test effective antiviral drug candidates, this is an exciting first step."

—KEG



Photo: D.C. Gougeon

A. Oveta Fuller

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

For patient information on genital herpes: www.med.umich.edu/1libr/aha/aha_herpgeen_crs.htm

Blocking the Burn of Neuropathy

“Using the herpes vector to provide targeted gene delivery to the nervous system is a novel approach that shows tremendous promise for the treatment of neuropathic pain.”

—David Fink



David Fink, with study collaborators Marina Mata, M.D. (Residency 1981), and Shuanglin Hao, M.D., Ph.D.

Constant burning pain in the hands and feet is a common complication of many diseases, especially diabetes. Drugs have little effect on this type of neuropathic pain, which is caused by damage to sensory neurons that transmit pain, temperature and touch signals to and from the brain.

Now, scientists at the VA Ann Arbor Healthcare System and the University of Michigan Medical School have found a way to block the signals responsible for neuropathic pain. They use a genetically altered, non-infectious form of herpes simplex virus to deliver genes to the nucleus of neural cells near the spine.

“Patients with neuropathic pain suffer tremendously and the treatments available to us have limited effectiveness,” says David J. Fink, M.D., the Robert W. Brear Professor of Neurology in the U-M Medical School. “Using the herpes vector to provide targeted gene delivery to the nervous system is a novel approach that shows tremendous promise for the treatment of neuropathic pain.”

The herpes simplex virus has a natural ability to travel long distances along nerve fibers from the skin to the neural cell’s nucleus next to the

spinal cord. This makes it the perfect gene delivery vehicle for use in the nervous system.

In a study published in the June 2005 issue of the *Annals of Neurology*, Fink and his research colleagues described how laboratory rats with nerve damage showed much less pain-related behavior after receiving injections of the herpes simplex virus-based vector containing a gene that triggers production of an inhibitory neurotransmitter, which blocks the transmission of pain signals. The treatment’s pain-killing effect lasted up to six weeks, and even longer in rats that received additional injections.

In future research, the scientists plan to conduct the first phase I safety trial of a related vector in patients with pain caused by terminal metastatic cancer.

—SFP

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

For patient information on neuropathy:
www.med.umich.edu/1libr/aha/aha_perineur_crs.htm

U-M Expands Stem Cell Research Efforts

The University of Michigan will significantly expand its efforts in stem cell science with a new interdisciplinary center for stem cell research, to be based at the Life Sciences Institute.

The center for stem cell biology was established with \$10.5 million in funding provided by the Medical School, the Life Sciences Institute and the Molecular and Behavioral Neuroscience Institute.



life sciences institute

Under the leadership of Sean Morrison, Ph.D., associate professor of internal medicine and a Howard Hughes Medical Institute investigator, the center will emphasize

using stem cell science to answer the most pressing questions of fundamental human biology, such as how specific tissues in the body are formed and how cells communicate with one another.

M-CARE Medicaid HMO Ranks among Top 25

M-CARE, M-CARE’s Medicaid HMO, is ranked among the top 25 Medicaid health plans in the country, according to *U.S. News & World Report/NCQA America’s Best Health Plans 2005*. The list ranking America’s health plans appeared in the October 10 issue of *U.S. News & World Report*.

The Medicaid ranking includes measures for access to care and service, communication with doctors, staying healthy/preventive care, getting better/living with illness, and overall quality. The listing coincides with the release by the National Committee for Quality Assurance (NCQA) of its annual “State of Health Care Quality” report, an analysis and interpretation of major performance trends in health care over the past year. M-CARE’s Medicaid HMO ranked 21st out of all plans reviewed.



Medical Center Alumni Society board members, in Ann Arbor for their annual October meeting in conjunction with Reunion Weekend, take a guided tour through the Medical School’s nearly completed Biomedical Science Research Building. The BSRB, specifically designed to facilitate collaboration among scientists, will be the largest research facility on campus, occupying an entire city block. The building is scheduled to open in February.

Photo: D.C. Gaungs