

## In the Clinic

# Diagnosis: Skin Cancer Destination: Michigan

**WHEN ATHLETIC DIRECTOR BILL MARTIN** was diagnosed with melanoma a few years ago, it occurred to him that many of his staff members also spend a lot of time in the sun, which is one of the highest risk factors for the disease. And when, at Martin's request, Timothy M. Johnson, M.D., head of the U-M skin cancer program, performed screenings for the Athletic Department, he found some form of skin cancer or pre-cancerous lesions in nearly two dozen staff members.

Head hockey coach Red Berenson and former head football coach Lloyd Carr, now associate athletic director, also revealed recently that they were diagnosed and treated for melanoma, the deadliest form of skin cancer.

The three Michigan sports leaders are doing well — as are members of the Athletic Department staff — and screenings have continued; the third was held this summer. The most common type of cancer in the U.S., skin cancer is highly curable when caught early and treated properly. For Berenson, Carr and Martin, it wasn't just proximity that led them to the health system located in their own backyard for treatment; the U-M is a world leader in skin cancer diagnosis, treatment and research.

Carr has become an advocate after his diagnosis and treatment. "Do



**Former Head Football Coach Lloyd Carr advocates quick action when melanoma is suspected.**

something about it," he said during a recent television interview. "Don't wait and hope that it goes away, because it's not going away."

Melanoma is the most frequent type of cancer diagnosed and treated at the U-M Comprehensive Cancer Center, which has the largest multidisciplinary

## Gender and Depression

### THERE'S GOOD NEWS AND BAD NEWS ABOUT DEPRESSION

in women. The bad news is that women are twice as likely as men to develop depression. The good news is that women are 33 percent more likely to achieve complete remission of their symptoms when treated with a commonly used antidepressant.

The news about how men and women respond differently to antidepressants comes from a national, multi-year study of 2,876 men and women diagnosed with major depression and treated with citalopram, marketed as Celexa. Called STAR\*D, the study is funded by the National Institute of Mental Health. Elizabeth Young, M.D., a professor of psychiatry, was the study's lead author.

"Based on data from this large, well-controlled study, we are now confident there are true biological differences between how men and women respond to this antidepressant," Young says. Although the reasons for the difference are unclear, Young notes that animal studies have suggested that hormonal differences between males and females may be a factor.

Young cautioned that the study's results don't mean that citalopram should be used only in women, since up to 24 percent of men in the study responded well to the drug. Instead, it illustrates the point that people with depression often need to try several treatments to find one that works best for them. —SP

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melanoma program in the country and treats more skin cancer patients than nearly any other program. The U-M Health System also is leading the effort to find more effective treatments through an extensive, innovative and far-reaching program of skin cancer research.

Most skin cancers are non-melanoma of two primary types: basal cell carcinoma — slow-growing with a small likelihood of spreading to other parts of the body and accounting for 75 percent of all skin cancers; and squamous cell carcinoma — faster growing and potentially more invasive. A third type, Merkel cell carcinoma, is rare, but very deadly. The U-M program achieves a cure rate of approximately 90 percent to 99 percent for non-melanomas, even if other treatments have failed.

More than just high positive outcomes mark Michigan's multidisciplinary skin cancer program as one of the best in the nation. One phone call results in coordination of all the collaborative care the patient will require, across several specialties with prompt access and efficient scheduling to eliminate wait times.

Bill Martin and his staff certainly appreciate the work of Tim Johnson and the skin cancer program. Nationwide, athletics organizations are doing more to help raise awareness about skin cancer and its prevention.

"I'm so thankful to Bill that he had this screening," says Berenson, "because had he not had it, I probably would not have gone in. Had I not gone in, I would have been in serious trouble." —RICK KRUPINSKI



## In the Clinic

# Keeping an Eye on Diabetes

## Detecting signals from cells under stress

**NEARLY 24 MILLION AMERICANS** with diabetes have a higher-than-normal risk of losing their vision, but many of them don't know it.

According to the latest estimates from the U.S. Centers for Disease Control and Prevention, close to 8 percent of the U.S. population has diabetes. Early detection and treatment of diabetes is critical to preventing high levels of blood sugar from damaging cells in the retina — the thin layer of light-sensitive cells lining the back of the eye. This damage begins shortly after onset of the disease, but long before it can be detected during a routine eye exam.

Too often, patients aren't tested for diabetes until they experience complications. By that time, cells in the eye, as well as other organs, may already have suffered irreparable harm. Diabetic retinopathy is the leading cause of blindness among working-age adults and affects 4.1 million people over age 40.

Now, Victor Elnor, M.D., Ph.D., and Howard Petty, Ph.D. — researchers at the Kellogg Eye Center and professors of ophthalmology and visual sciences in the Medical School — have developed a noninvasive test that captures images of the eye and measures metabolic stress and tissue damage, two telltale signs of diabetes.

The computer imaging system Elnor and Petty developed detects a glowing



signal from flavoproteins in mitochondria, the energy factories in retinal cells. Flavoproteins are involved in many biological processes, including cell death. The glow, called flavoprotein autofluorescence or FA, occurs when retinal cells are in distress: The stronger the glow, the more severe the damage.

The new U-M imaging system can detect retinal dysfunction associated with disease several years before symptoms occur. Unlike glucose tolerance testing — the gold standard test for diabetes — patients don't need to fast or undergo multiple blood draws. The new test takes less than 10 minutes.

"Essentially the patient just sits in front of the instrument, the device

is focused on the eye, a specialized photograph is taken, and results are immediately available," says Elnor.

In a recent study, Elnor and Petty measured and compared FA levels of 21 people with diabetes and 21 people who were the same age, but did not have diabetes. They found that FA activity was significantly higher in diabetic patients, regardless of disease severity, compared with healthy controls.

The U-M scientists say the screening test could be given routinely by an optometrist, ophthalmologist or trained office staff. Abnormal test results would be due to diabetes about 90 percent of the time. In 10 percent of cases, elevated FA would likely

indicate other retinal diseases, such as glaucoma or age-related macular degeneration.

Elnor and Petty hope their imaging technology will be used not only to screen people at risk of developing diabetes, but also on an ongoing basis to monitor disease severity in those who already have been diagnosed. "When retinal metabolic analysis is used

routinely to help patients in the clinical setting," says Petty, "we'll know we've been successful."

The University of Michigan has applied for a patent on the imaging technology, and Petty and Elnor have formed a company called OcuSciences Inc. to develop and market it.

—KIMBERLEE ROTH

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## Gene Therapy to Fight Chronic Pain

**WHAT DOES THE HERPES SIMPLEX VIRUS (HSV), THE VIRUS THAT CAUSES cold sores, have to do with chronic pain?** Plenty, if you ask David Fink, M.D., the Robert Brear Professor of Neurology, who has been studying the use of a modified herpes virus to deliver genes for pain-killing molecules to the nervous system. Now, years of animal research conducted by Fink and his research colleagues have culminated in the first human clinical trial of a gene therapy for chronic pain in patients with intractable pain from cancer.

Gene therapy is an attractive alternative to conventional pain medications because it allows the therapy to be delivered directly to the pain pathways, according to Fink. "We hope selective targeting will result in pain-relieving effects that cannot be achieved by systemic administration of opiate drugs," he says.

In order to transform the virus into a gene delivery vehicle, or vector, Fink and his research colleagues removed genes that allow HSV to multiply and inserted the gene for enkephalin, one of the body's natural painkillers. Injected into the skin, the vector is taken up by sensory nerve fibers that then produce enkephalin. Release of enkephalin from the nerve fibers into the spinal cord selectively blocks the transmission of pain signals, thus relieving pain.

The clinical trial is the first trial of gene therapy for pain, and the first gene transfer trial to use HSV-based vectors in patients. If it is successful, Fink hopes to follow with HSV vectors carrying other genes for the treatment of different types of chronic pain. —CLE

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## Health Briefs

During the first six months of life, babies need to establish regular sleep-wake patterns, called circadian rhythms. But if Mom is depressed, it can interfere with this important milestone in a baby's life. A recent U-M study found that babies with mothers who suffered from depression had much more trouble falling asleep, woke more often during the night and had weaker circadian rhythms than babies born to mothers who did not have depression.

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The U.S. Centers for Medicare and Medicaid Services have recognized the U-M Faculty Group Practice for providing high-quality care for older patients with heart disease and diabetes, while reducing the cost of treating all Medicare patients at the same time. The group includes 1,500 physicians working at U-M hospitals and health centers.

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Almost half of 1,132 breast cancer patients surveyed by U-M researchers didn't know that their odds of surviving cancer, or having the cancer come back, were about the same whether they underwent a mastectomy or breast-conserving lumpectomy with radiation. African-American and Latina women were less likely to know than white women. U-M researchers say surgeons need to communicate more clearly and patients need to ask more questions. —SP

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## In the Lab

## MS: One Disease or Two?

### Research suggests need for individualized treatments

#### THERE ARE MANY MYSTERIES

surrounding multiple sclerosis, an unpredictable, degenerative disease that attacks the brain and spinal cord. Scientists don't understand why symptoms progress more rapidly in certain patients, or why some patients respond better than others to drugs used to treat MS.

Benjamin Segal, M.D., has devoted his career as a researcher and a physician to finding better ways to help people with multiple sclerosis. Fascinated by how the central nervous sys-

tem interacts with the immune system, Segal wants to understand the "why" of the body's abnormal response, what cells are involved, how they get into the central nervous system and what factors they produce that cause damage — all to develop new, more effective treatments for the disease.

Since joining the Medical School faculty in 2007, Segal has already made progress toward this goal. He and his colleagues recently discovered that two immune system T-helper cells, called Th1 and Th17, triggered clinically in-

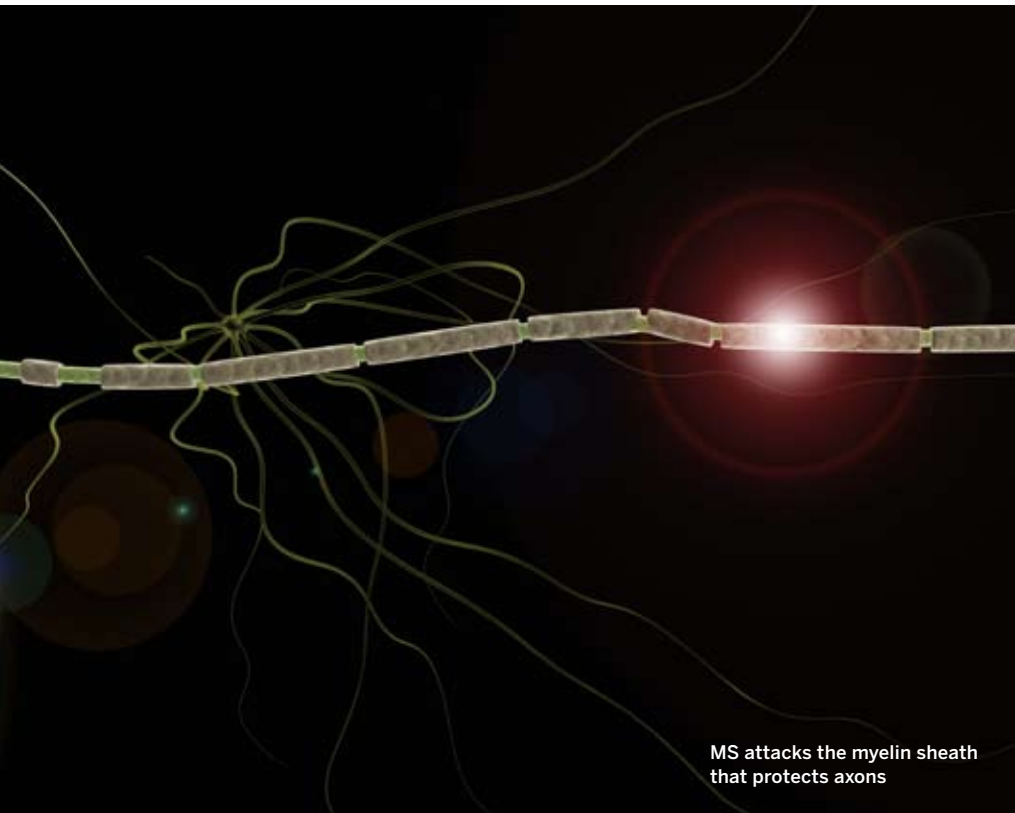
distinguishable symptoms in research mice with a form of MS.

Although their symptoms were the same, mice that were exposed to Th1 cells had different inflammatory agents in their central nervous system tissue than mice exposed to Th17 cells. The animals also responded differently to drugs intended to block the inflammatory response, suggesting there could be two different forms of multiple sclerosis. The research findings also might explain why some patients respond better to one medication than another — or don't respond at all.

As director of the U-M's new Multiple Sclerosis Center, Segal is all too familiar with the devastating effects MS can have on patients and their families.

"MS usually presents in young adults in their 20s and 30s," says Segal, the Holtom-Garrett Family Professor of Neurology. "They face living with a chronic, disabling disease that they will have for the rest of their lives." Segal also directs the Holtom-Garrett Program in Neuroimmunology.

Multiple sclerosis is believed to be an autoimmune disease that begins when cells in the body's immune system attack the central nervous system (CNS), specifically proteins in the myelin sheath surrounding axons — long filaments extending from nerve cells. The immune system's misguided attack disrupts the axons' ability to relay electrical impulses from cell to cell, leading to symptoms that include vertigo, balance and vision problems,



MS attacks the myelin sheath that protects axons

tremor, weakness, numbness, loss of bowel and bladder control, and cognitive difficulties.

In future studies, Segal hopes to learn how different T cells move from blood to the CNS and to devise strategies to block those pathways. “The more we understand, the more we can individualize therapies and make them more specific, so we don’t leave patients as vulnerable to side effects,” says Segal.

For patients, the Multiple Sclerosis Center means access to the newest therapies, as well as to specialists with extensive experience diagnosing and treating the disease over time, and staff

attuned to patient needs. Patients often need many types of support from a variety of professionals, explains Segal — including speech, occupational and physical therapists, as well as psychological support.

“Ultimately we want to provide care under one roof from all health providers concerned with the diagnosis and treatment of MS patients,” he says.

Segal knows there is a lot of work to do, but he remains driven and optimistic. “To offer patients reasons for hope, and to intervene in the disease process to improve their quality of life, is what it’s all about.”

—KIMBERLEE ROTH

## HIV’s Secret Weapon

**HIV, THE VIRUS THAT CAUSES AIDS,** is crafty and dangerous. Immune cells called cytotoxic T lymphocytes usually seek out and destroy cells infected by a virus, but HIV has a unique way of evading them. In recent research, U-M scientists led by Kathleen Collins, M.D., Ph.D., discovered how the virus uses an adaptable protein called Nef to short-circuit the body’s immune response.

Collins and her colleagues describe how Nef latches onto an important immune system molecule in infected cells — preventing it from moving to the cell’s surface where it could signal T lymphocytes to move in and kill the cell. This allows HIV to remain hidden and continue multiplying inside the cell.

“Anti-viral drugs protect new cells from infection, but have no effect on cells that are already infected and hidden from the immune system,” says Collins, an associate professor of internal medicine and of microbiology and immunology. She is now searching for new drug compounds capable of blocking Nef and targeting HIV inside infected cells. —SP [MORE ON THE WEB](#) ✦



Kathleen Collins

## Nano-Vaccine for Hepatitis B?

Animal tests of a new type of hepatitis B vaccine developed by scientists at the Michigan Nano-technology Institute for Medicine and Biological Sciences indicate that the vaccine is non-toxic and generates a strong, sustained immune response. The vaccine uses a nanoemulsion-based nasal spray to deliver a current hepatitis B antigen, which activates the body’s immune defenses against the hepatitis B virus. Positive results from animal testing mean researchers may soon begin the first human clinical trial of the vaccine. —SP

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## Gene Expression and Lung Cancer Survival

Research by Comprehensive Cancer Center scientists could one day help identify, in advance, patients with early-stage lung cancer who will need aggressive chemotherapy after surgery. Researchers identified genes active in 442 lung cancer tissue samples, and factored in clinical predictors like tumor stage, age and gender. They were able to divide the tumors into groups with better and worse survival outcomes, and hope this research will lead to diagnostic tools to help physicians determine individualized treatment plans for lung cancer patients. —SP

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## In the School

# Health Information, Wikipedia-style

### THE MEDICAL SCHOOL IS TAKING A

lead role in a global effort to create the most comprehensive and collaborative health and medical resource in the world. Modeled after Wikipedia, the highly successful online encyclopedia, Medpedia will launch at the end of 2008.

The ambitious Medpedia Project merges advances in information technology with the expertise of health professionals and organizations around the world to bring health care and medical information into the 21st century. The goal is to create a clearinghouse for medical information that cuts across disciplines, socio-economic status and geography to provide valuable health-related information to anyone, anywhere, at any time.

The University of Michigan Medical School, Harvard University Medical School, Stanford University School of Medicine and University of California, Berkeley School of Public Health are working together with other organizations, such as the American College of Physicians, to create the Internet-based learning tool. Gilbert S. Omenn, M.D., Ph.D., professor of molecular medicine and genetics, human genetics and internal medicine, is a member of Medpedia's board of advisers, and Robert Lash, M.D., associate professor of internal medicine, is a key adviser to the project.

The National Institutes of Health and the Centers for Disease Control and Prevention also are involved.



Gilbert Omenn and Robert Lash

"Medpedia is a great example of how Michigan can collaborate with our peer medical institutions to use the power of the Internet to disseminate medical information around the world," Lash says. "We hope this project will revolutionize access to health information for the public, as well as for health care professionals and students."

Unlike Wikipedia, which can be freely added to and edited by almost anyone, only rigorously vetted health professionals and organizations will be permitted to contribute content to Medpedia. Main topic pages will be written in language easily understood by lay users, while technical pages will provide more in-depth, clinical information intended for students,

physicians, nurses and other health care professionals.

The Medpedia.com Web site is maintained by Medpedia Inc., part of Ooga Labs — a technology incubator in San Francisco — and runs on Mediawiki, open source software which runs many wikis including Wikipedia. Like Wikipedia, Medpedia's content is freely licensable under the GNU Free Documentation License.

A wiki is a page or collection of Web pages designed to enable anyone to contribute or modify content, using a simplified markup language. Wikis are often used to create collaborative Web sites and to power community Web sites. "Wiki" is a Hawaiian word for "fast." —RICK KRUPINSKI

## New Chair for Molecular and Integrative Physiology

ON AUGUST 1, 2008, M. BISHR OMARY, M.D., PH.D., BECAME CHAIR of the Medical School's Department of Molecular and Integrative Physiology and the H. Marvin Pollard Professor of Gastroenterology. Before coming to U-M, Omary was a professor of internal medicine at the Stanford University School of Medicine and associate director of Stanford's Digestive Disease Center.

"Even with all of his impressive accomplishments," says James O. Woolliscroft, M.D., dean and Lyle C. Roll Professor of Medicine, "I have been particularly struck by his engaging, outgoing personality and his dedication to mentoring junior faculty and students."

Omary's research focuses on the function and regulation of keratins in digestive epithelia and their association with disease. He values translational research and has been an advocate for collaborations between the NIH, research institutions and industry. Omary served as director of an NIH training grant in academic gastroenterology at Stanford from 1999-2005. He is a regular speaker at the annual Academic Skills Workshop of the American Gastroenterological Association, and received a teaching award from Stanford in 2005. He serves as associate editor for the journals *Molecular Biology of the Cell* and *Gastroenterology*.

The Department of Molecular and Integrative Physiology dates back more than 125 years, making it one of the oldest departments of physiology in the U.S. The department works to understand the function of molecules, cells, tissues and organisms with an emphasis on their relation to human biology and medicine.

Says Omary, "I look forward to working to enhance departmental educational programs and existing collaborations with many areas of the University — including the Geriatrics Center, the Brehm Center for Type 1 Diabetes Research, the Gastrointestinal Peptide Research Center and the Center for Computational Medicine and Biology, among others."

—BS



LEFT: COURTESY OF M. BISHR OMARY;  
RIGHT: SCOTT SODERBERG, U-M PHOTO SERVICES



## The Dean Is In

Since starting his Office Hours program in early 2007, Dean Woolliscroft has met with approximately 125 faculty, staff and students who offer comments, suggestions and insights concerning the Medical School. Their input has led to a number of changes and innovations in the school.