

In the Lab

Skinny Worms
Live Longer

EAT LESS, LIVE LONGER! THAT'S NOT A rallying cry for the latest fad diet; it's the conclusion from decades of solid scientific research. Study after study has demonstrated that drastically reducing food intake lengthens the lifespan of laboratory animals from roundworms to rhesus monkeys and often delays the onset of age-related diseases.

The catch is that calorie consumption must be cut by 30 to 40 percent. That may be OK for roundworms, but it's unappealing and downright impractical for most of us, so U-M scientists like Ao-Lin Hsu, Ph.D., are trying to find other ways to achieve the same effects in humans.

"The ultimate goal is to find something that can fool our body into thinking we are being restricted, but without the actual restriction," says Hsu — an assistant professor of internal medicine and of molecular and integrative physiology.

To do this, Hsu and his team are studying a gene called *drr-2* and trying to understand how it affects longevity. In recent research, they found that making *drr-2* underactive or overactive was enough to lengthen or shorten the lifespan of *Caenorhabditis elegans* — a tiny roundworm often used in aging research because it shows many of the same age-associated changes seen in higher organisms, but lives for just two weeks.

According to Hsu, the roundworm gene *drr-2* is analogous to the human gene *eIF4H*, which holds the genetic instructions to make a small protein that

stimulates overall protein production. This similarity suggests that whatever scientists learn about how *drr-2* works in roundworms may apply to the human version of the gene as well.

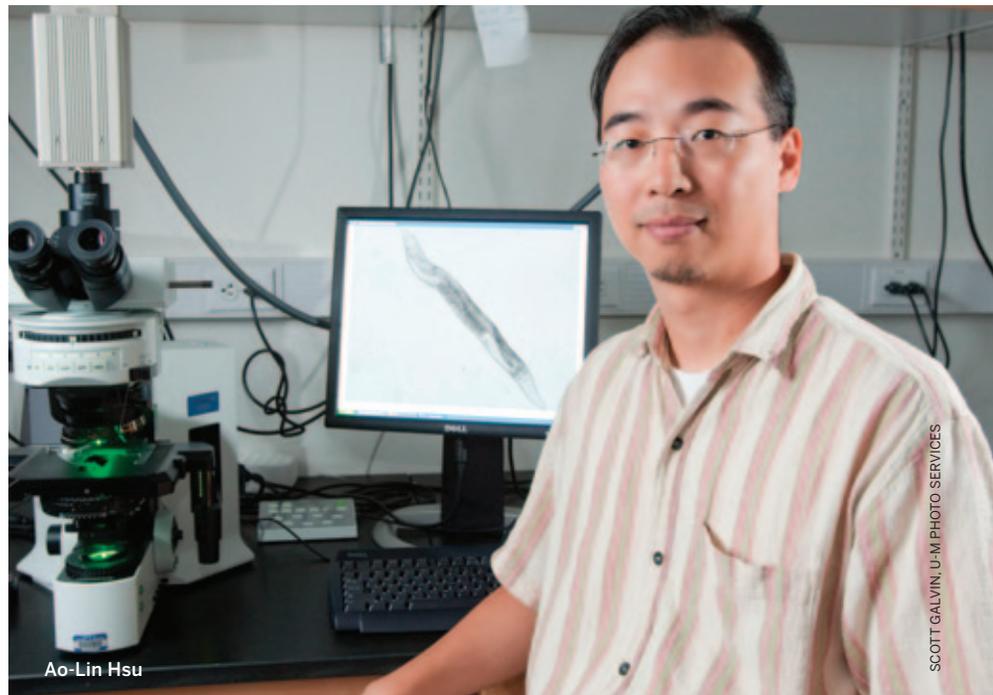
Both genes function in a signaling pathway called the TOR pathway that senses nutrient levels in cells and is believed to mediate the anti-aging effect of dietary restriction.

"In the mammalian system, TOR senses the level of amino acids in a cell, and the cell makes changes in response," Hsu explains. "If nutrients are low, TOR initiates a cascade of signaling events that eventually turns off protein synthesis, so non-essential proteins are not produced when energy is low." At the same time, maintenance and repair mechanisms are ramped up to keep existing proteins working properly. In addition to making these energy-saving

shifts, the cell may respond in other lifespan-extending ways.

Hsu and his colleagues found that *drr-2* plays a key role in protein synthesis, and that reducing the gene's activity slowed down protein production. What's more, simply silencing the gene was enough to increase lifespan in roundworms. Taken together, these results suggest that *drr-2* plays an essential role in the TOR pathway, controlling both protein synthesis and longevity.

"We've shown that genes involved in initiating protein synthesis are important," Hsu says. "The next step is to learn exactly how genes control longevity by manipulating protein synthesis. Eventually, we hope to discover or develop drugs that target key points in the TOR pathway, so we can all live longer without having to eat less." —NANCY ROSS-FLANIGAN [MORE ON THE WEB](#) ✦

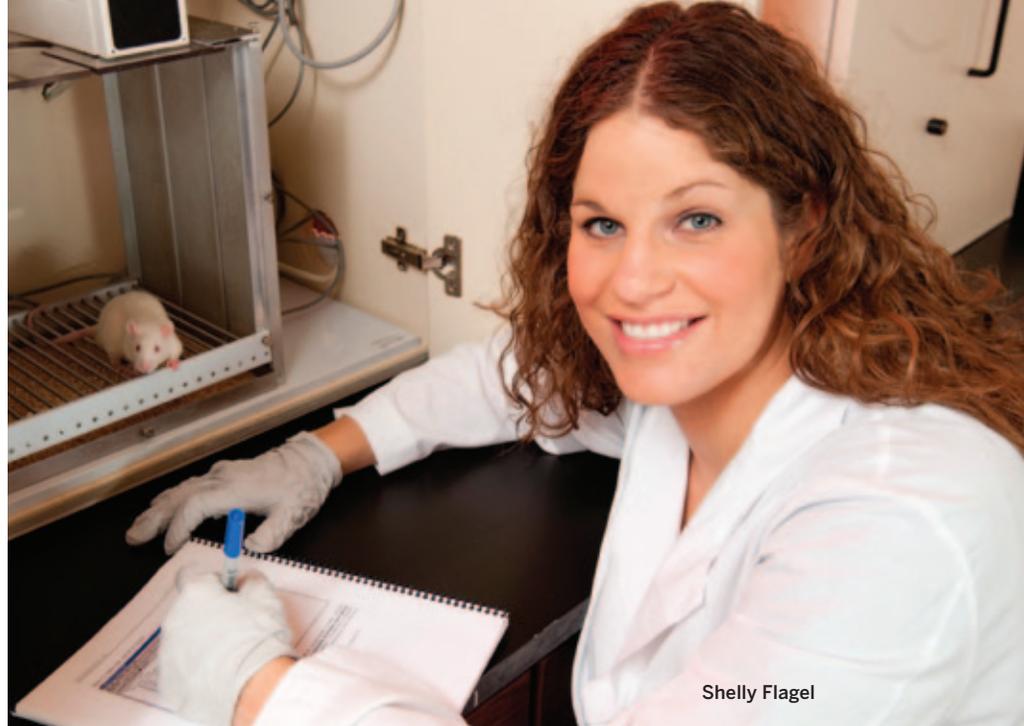


The Pull of Pleasure

KNOW SOMEONE WHO CAN'T SEEM to resist temptation? Maybe a friend who's trying to quit smoking, but still reaches for a cigarette with her morning coffee? A new study by scientists in the U-M's Molecular and Behavioral Neuroscience Institute and at the University of Washington suggests why some people find it easier to overcome addiction than others.

Shelly Fligel (Ph.D. 2003), an MBNI research investigator, and her colleagues used rats to study impulse control and its relationship to brain levels of dopamine, a chemical that signals pleasure. The brain releases dopamine when we experience something rewarding (delicious food) or an environmental cue that predicts the reward (smells in Grandma's kitchen).

Fligel and her colleagues designed an experiment where, during a train-



Shelly Fligel

ing session, rats were repeatedly presented with a lever, immediately followed by a banana-flavored food pellet.

"The rats didn't have to do anything to receive the food reward, it simply always followed the lever," Fligel explains. "Some rats attributed motivational value to the lever and approached and manipulated it as if it were the food itself; while others simply treated the lever as a predictor of reward and immediately approached the food tray upon being presented with the lever."

Using microsensors implanted in the rats' brains, the scientists monitored dopamine production. Rats that were attracted to the lever experienced an extra surge of dopamine, while rats that just hung around the food tray did not.

If human brains respond similarly, the study could explain why people who experience pleasure from an environmental cue find it harder to resist temptation, and why addicts or people with brain disorders have more trouble controlling impulsive behavior. —CMW [MORE ON THE WEB](#) ↗

PREDICTING PROTEINS

HERE'S A FUN BRAIN TEASER FOR YOU:

What is the three-dimensional shape and function of a protein made up of these amino acids?

**MVLSEGEWQLVLHVWAKVEADVAGHGQD
ILIRLFKSHPETLEKFDREVKHLKTEAE**

**MKASEDLKKHGVTVLTALGAILKKKGHHE
AELKPLAQSHATKHKIPIKYLEFISE**

**AIIHVLHSRHPGNFGADAQGAMNKALEL
FRKDIAAKYKELGYQG**

Most of us wouldn't even understand the question. But Yang Zhang, Ph.D., associate professor of computational medicine and bioinformatics, tackles problems like this every day. Zhang and his associates are so good at predicting protein structure and function, they've placed first in three worldwide scientific competitions.

Zhang and colleagues create computer algorithms to translate strings of amino acid sequence code into three-dimensional protein structures. It's more than an academic exercise. A protein's shape determines its function in cells, so the ability to predict structure from sequence is important for drug discovery and biomedical research. Approximately 15,000 scientists from 89 countries use Zhang's algorithms in their research. —SP [MORE ON THE WEB](#) ↗

In the School

Bisiklet for Haiti

ON APRIL 4, U-M MEDICAL STUDENT

Jeff Crawford dipped the rear tire of his bike in the Pacific Ocean. Then he began a 2,965-mile ride eastward.

Motivated by his previous work in Haiti and the tragedies that have recently befallen the Caribbean island nation — including an earthquake, hurricane, and ensuing cholera outbreak — Crawford, from Northville, Michigan, is spending five weeks cycling across the country to raise money and awareness for the Cloud Forest Medical Clinic in Seguin (say-GEN). His trip takes place during a period when all fourth-year students get

time off prior to graduating and beginning their medical careers.

So why embark on such an ambitious endeavor when many of his classmates will be taking a much-needed break? Crawford, who plans to specialize in general surgery, explains, “Two of my biggest passions are working to provide medical care in Haiti and cycling. I’ve volunteered at Cloud Forest for the past 8 years and I’ve fallen in love with the people of Haiti.”

Access to Western medicine for the roughly 40,000 people of Seguin would be extremely challenging without the clinic. Though located only about 20 miles from the capital of Port-au-Prince, the city sits atop a plateau in an agricultural mountainous region, and the only

means of travel for many of its poverty-stricken residents is by foot.

A Christian mission organization opened the first incarnation of the clinic in 2002, but it closed in 2008 due to lack of funding and leadership. Humanity First, a human development and disaster relief organization headquartered in London, England, reopened the clinic shortly after the 2010 earthquake and renamed it Cloud Forest Medical Clinic for the unique beauty of its location. Since then, an average of 50 patients per day seek care at the clinic for conditions such as hypertension, upper respiratory infections, intestinal parasites, diarrheal illnesses and urinary tract infections. A majority of patients are children younger than age 9.

“My goal is to raise \$30,000 for Humanity First,” Crawford says, “to maintain the clinic for another year and improve health care in Seguin.”

Crawford’s journey, which he calls “Bisiklet for Haiti” (bisiklet is the Creole word for bicycle), has him pedaling an average of 80 miles per day, though he takes occasional days off to rest. He plans to camp along the way, but has also gratefully accepted a few offers of beds and couches to crash on in the cities he’s passing through. His trip began in Huntington Beach, California, and concludes on May 10 in Charleston, South Carolina, where he’ll dip his front tire in the Atlantic. Three days later, he’ll receive his M.D. —CLAIRE NORTHWAY WITH MARIE FROST

To view Crawford’s route and stories and photos from the road, or to learn how you can get involved, visit www.BisikletHaiti.com, or follow him on Twitter @BisikletHaiti.



Jeff Crawford on a previous bike trip in Colorado

Connecting Galens Alumni

YOU MAY HAVE SEEN THEM IN THEIR red ponchos on Ann Arbor sidewalks in early December, handing out colorful tags in exchange for donations to C.S. Mott Children's Hospital and local charities, but how much do you know about U-M Galens Medical Society members? In addition to raising approximately \$65,000 annually during Tag Days, the student service and social organization also produces the Smoker play each spring, provides loans to help defray residency interviewing costs for students, and organizes events to facilitate interaction between students and faculty.

Now Galens members have another project ahead of them: Planning events and activities to celebrate the group's centennial anniversary in 2014. The first step is reaching out to alumni members.

Fourth-year student and current Galens president Isabel Abella is working to collect contact information from former Galens members to create a directory which will keep them connected. "Through the years, the alumni information was lost as graduating presidents left for residency," she explains. "I want to ensure Galens alumni know about the events we're planning for the centennial."

Galens alumni can reconnect by visiting www.umich.edu/~galens/alumni.shtml. —MF

The Hippo

A LIVELY AND PROVOCATIVE STUDENT-RUN LITERARY AND VISUAL ARTS

magazine is providing U-M medical students with a creative outlet for original works of fiction, nonfiction, art, photography and humor.

The Hippo, whose name is derived from the Hippocratic Oath, is now entering its third year of publication under founding editors-in-chief Owen Albin and Priya Rajdev, both second-year students.

From gripping accounts of medical missions to humorous sketches to high quality photography, *The Hippo* serves up the "other side" of budding clinicians and researchers. Sponsored by the U-M Center for the History of Medicine and the Medical School's Office of Student Programs, *The Hippo* can be found at www.the-hippo.com. —RK



NIH Funds at Record High

U-M MEDICAL SCHOOL PHYSICIANS AND SCIENTISTS ARE REACHING NEW

heights in funding from the National Institutes of Health. According to recent data, during federal fiscal year 2010 the school's faculty brought in a record \$368.7 million in NIH funds. The figure places U-M ninth on the national list of medical schools to receive NIH funding, and fourth among medical schools affiliated with public universities.

Additionally, the U-M Comprehensive Cancer Center received the most grant funding from the NIH National Cancer Institute, among all medical schools in the country. U-M cancer researchers received \$87.5 million in grants from the NCI in the 2010 fiscal year.

"We are pleased to announce that each year our faculty and researchers attract significant funding for this important work. This achievement reflects incredible effort by thousands of faculty, staff, trainees and students," says Medical School Dean James O. Woolliscroft, M.D. (Residency 1980). "We are especially pleased to be able to bring significant funding to Michigan to help build the foundation for the state's long-term economic growth." —MF

In the Clinic

Changing the Face of Cancer Research

SOCIETY'S ATTITUDE TOWARD

breast cancer has changed significantly since 1974 when then-First Lady Betty Ford announced that she'd had a mastectomy. Before then, the words "breast" and "cancer" were rarely spoken in polite society. "Saying you had breast cancer then was a matter of shame," says Daniel F. Hayes, M.D., the Stuart B. Padnos Professor of Breast Cancer Research and director of the U-M Breast Oncology Clinic.

Today, many former patients identify themselves proudly as breast cancer survivors, and are active in peer support, fundraising and patient advocacy.

Patient advocates have even changed how breast cancer research is conducted in the U.S. Not only do they raise

money for research, they want a say in how that money is spent. At the National Cancer Institute, patient advocates work alongside physicians and scientists on study committees to review grant proposals and decide which get funded.

Members of the Breast Cancer Advocacy and Advisory Committee (BCAAC) play a similar role in the U-M Comprehensive Cancer Center. The committee's main job is "to help us design and conduct clinical trials in a way that fits the priorities of people who participate in and benefit from them," says Hayes, who established the committee in 2004.

"Our research role is to represent the patients who will participate in these studies," says Jane Perlmutter, a 25-year breast cancer survivor and committee

member. "We try to ensure that studies are patient-focused and that the needs and issues of patients come first. Most of our concerns involve informed consent, ethical questions and limiting the burden on patients who volunteer for studies."

"We talk about the 'shell-shocked look' of the newly diagnosed who often are overwhelmed with information," says Ruth Freedman, another 25-year survivor who co-chairs the committee and volunteers as a peer counselor. "We can offer personal experience, hope and support."

Anyone is welcome to attend monthly committee meetings at the Cancer Center, says Freedman. But regular participation in meetings and education programs are required to become a full-fledged member of the group. To facilitate their continuing education, Hayes pays travel expenses for full-fledged committee members to attend one scientific conference on breast cancer research each year.

As patient advocates assumed more responsibility for funding decisions, some scientists worried that the scientific quality of research would suffer. "There was this huge fear that we'd be studying whether boysenberry jam cures cancer," Hayes says. "But women were sensitive to this criticism and established training programs and rules for legitimacy for advocates.

"It's a pretty sophisticated group," Hayes adds. "I've found their input to be legitimate and rigorously scientifically based. In fact, I've been on committees where the advocate knew more than I did." —SALLY POBOJEWSKI



Ruth Freedman and Daniel Hayes

An Antibiotic for IBS

THIRTY MILLION AMERICANS LIVE

with the abdominal pain, bloating, diarrhea or constipation of irritable bowel syndrome. Changing diet or taking fiber supplements often doesn't provide relief.

Now IBS patients may have another option: an antibiotic called rifaximin. In recent randomized, controlled clinical trials, taking rifaximin for two weeks relieved symptoms for about 40 percent of 1,260 IBS patients enrolled in the study. Symptom relief continued for up to 10 weeks after taking the medication.

Although the cause of IBS remains unknown, many researchers believe that bacteria in the gut play an important role. Since antibiotics kill gut bacteria, the new research findings support this idea.

"It represents a big change in the way we think about and treat IBS," adds



William Chey, M.D. (Fellowship 1993), a professor of internal medicine and one of several researchers who participated in the study.

Rifaximin is a minimally absorbed antibiotic that stays in the gut. It's approved by the FDA to treat travelers' diarrhea and hepatic encephalopathy. Rifaximin is marketed by Salix Pharmaceuticals Inc., which funded the clinical trials. —SP [MORE ON THE WEB](#) ↗

When Less is More

DIAGNOSTIC IMAGING TESTS ARE AN IMPORTANT PART OF TODAY'S MEDICAL care, but Adam L. Dorfman (M.D. 1988), clinical assistant professor of pediatrics and of radiology, cautions about using these tests too often with children.

Dorfman led a study that tracked how often imaging procedures are used in children and explains that children and infants are more susceptible to the long-term risks of radiation exposure. "There is often a chance to reduce the dose of radiation given to children, particularly from CT scans," he says.

Researchers examined records from 355,088 children younger than age 18 in five large U.S. health care markets. The research team found that more than 400,000 imaging procedures were performed in just three years; 42.5 percent of the children received at least one procedure and many underwent multiple tests. Based on this data, the average child would receive more than seven imaging procedures by age 18. "Our goal is to raise awareness and start a national dialogue by identifying the overall scope of the problem," says Dorfman. —SP

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Health Briefs

Here's one way to slash \$35 million from the annual U.S. health care budget: Stop the common practice of sending excised tonsils to a pathologist for examination. Analyzing data from 5,235 U-M tonsillectomies, U-M investigators found that pathologists detected just 18 cases of cancer or other diseases in the tonsils — all of which were suspected before surgery. Precious health care dollars might be better spent elsewhere, suggests Marc Thorne, M.D. (Residency 2006), who led the study.

[MORE ON THE WEB](#) ↗

In 2008, the FDA recommended that over-the-counter cough and cold products not be used by infants and children younger than age 2. But a recent Health System poll found that 61 percent of parents reported giving them to their young children within the last 12 months. Surprisingly, half the parents said their child's doctor told them OTC cough and cold products were safe and effective. Matthew Davis, M.D., a U-M physician and children's health expert, says health care providers must give clear and consistent information about the dangers of OTC products when used by young children. —SP

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In the Clinic

One Donor Saves Two Lives

TWO MICHIGAN MEN WERE SAVED BY A SINGLE ORGAN DONOR ON JANUARY 3 when Health System Transplant Center surgeons performed, almost simultaneously, the center's 499th and 500th lung transplants. Jack Wagner received the 499th lung transplant in a procedure performed by Rishindra M. Reddy, M.D., assistant professor of surgery. Dan Roy received the 500th lung transplant. Roy's surgeon was Jules Lin, M.D. (Residency 2006), assistant professor of thoracic surgery.

Both Wagner and Roy had Idiopathic Pulmonary Fibrosis — a fatal lung disease for which there is no treatment. The average survival time after being diagnosed with IPF is less than three years.

The two men met when they arrived at the Health System after being notified that a lung was available. Roy told Wagner he was there to get a new left lung. Surprised, Wagner replied that he was getting a right lung. They have since discovered that they share many things in common — they are both Vietnam veterans and auto industry retirees. Both are 64, have three children and have been married more than 40 years.

Kevin Chan, M.D., medical director of lung transplantation, stressed the important role of the donor's family, whose generosity in a time of tragedy gave Wagner and Roy a second chance at life.

"Thanks shouldn't go to us, but to the family who made it possible to save two lives," he says. "They are the true heroes of this story."

The U-M Health System transplants more lungs than any other hospital in Michigan and is ranked in the top third of national lung transplant programs based on number of operations. —SP

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Rishindra Reddy, Jack Wagner,
Dan Roy and Jules Lin



Egg allergies?
No problem.

THERE'S NO NEED TO GIVE preliminary skin tests or divided doses of H1N1 flu vaccine to children with egg allergies, according to a recent U-M study. The study included 19 non-egg-allergic patients and 105 egg-allergic pediatric patients — including 25 with a history of egg-induced anaphylaxis — a potentially life-threatening allergic reaction.

People with egg allergies often avoid the H1N1 or seasonal flu vaccines because they contain egg protein, but none of the 124 study participants who received the H1N1 vaccine developed an immediate or serious reaction. "Our study offers good evidence that administering H1N1 vaccine as a single, full dose without pretesting or graded challenge is safe and well tolerated in any type of egg-allergic patient," says Matthew J. Greenhawt, M.D., assistant professor of internal medicine.

—SP

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