In the Lab

Good Bug/Bad Bug

The two faces of *Helicobacter pylori*

A FUNNY THING HAPPENED TO *Helicobacter pylori*, the bacterium that causes gastric cancer or peptic ulcers in up to 15 percent of the people it infects. After decades of work to develop a vaccine and plans for a global vaccination campaign, scientists now have evidence that it might not be such a bad bug, after all. In fact, for most people, there could be benefits to having *H. pylori* living in your stomach.

"Until recently the consensus was that the only good *H. pylori* are dead *H. pylori*," says John Y. Kao, M.D., a U-M gastroenterologist and assistant professor of internal medicine. "But 85 percent of infected individuals have no symptoms and never develop cancer or ulcers. We want to know if there's anything good about these bacteria before we talk about wiping them out."

More than half the world's population is infected with *H. pylori*. Most people are infected early in childhood, especially among families living in crowded, unsanitary conditions. The bug spreads via fecal-oral, oral-oral or gastric-oral transmission.

"The global incidence of *H. pylori* infection has been declining for the last two decades," says Kao. "The decline has been attributed to a cleaner environment, testing and treatment, but as the rate of *H. pylori* infection goes down, rates of chronic inflammatory diseases like asthma, allergies and inflammatory bowel disease are going up."

Kao and his team discovered there's a connection between *H. pylori* and the immune system. They found that *H. pylori* down-regulates inflammation in its human host by causing certain immune cells to shut down production of pro-inflammatory molecules called cytokines. Suppressing the immune system helps the bacteria avoid the body's normal attack-and-kill response to bacterial infection.

Kao wondered if the bug's innate ability to dampen down the immune system could explain why cases of inflammatory bowel disease (IBD) like ulcerative colitis or Crohn's disease increased as cases of *H. pylori* infection went down. He assigned three researchers from his lab to work on the problem.

One was Jay Luther, M.D., then a second-year resident in internal medicine who had received an NIH grant to do research in basic science. The second, Stephanie Owyang, was an Ann Arbor high school student who had received an award from the American Gastroenterological Association to work in Kao's lab during the summers. Min Zhang, M.D., a research specialist in Kao's lab, assisted with the project.

Luther and Owyang analyzed DNA from different strains of *H. pylori*, *E. coli* and other bacteria. They found that DNA from *H. pylori* contained more regulatory sequences known to reduce an inflammatory response. DNA from *E. coli* and other pathogens had more DNA sequences known to stimulate an inflammatory response. When added to

Jay Luther, John Kao, Min Zhang and Stephanie Owyang

ERIC BRONSON, U-M PHOTO SERVICES

cultures of dendritic cells grown in the laboratory, *H. pylori* DNA suppressed production of pro-inflammatory cytokines.

The next step was to determine if *H. pylori* DNA could suppress inflammation in laboratory mice with colitis, an acute inflammation of the colon. The researchers fed *H. pylori* DNA to one group of mice with colitis and *E. coli* DNA to a second group. Mice given *H. pylori* DNA had significantly less diarrhea, bleeding and inflammatory changes in the colon than mice in the control group or mice given *E. coli* DNA.

As a final step, the researchers measured levels of type 1 interferon, an inflammatory cytokine, in blood serum from 46 healthy men. The 22 men who were infected with *H. pylori* had lower levels of this pro-inflammatory molecule in their system than men without *H. pylori*.

Kao emphasizes that he's not suggesting physicians start infecting their patients with *H. pylori*. He hopes this research will highlight the potential negative consequences of global vaccination programs against *H. pylori* and support the current practice of treating only people with symptoms. He hopes to identify the *H. pylori* DNA sequences with potent anti-inflammatory effects and use them to develop a new therapy for patients with IBD and other chronic inflammatory diseases.

"This could be a way to give patients the beneficial effects of *H. pylori* without causing any of its complications," Kao says. "If you give only these genetic sequences, the bug cannot colonize the stomach, so there's no concern about cancer or ulcers." —SALLY POBOJEWSKI

MORE ON THE WEB

AUSTIN THOMASON, U-M PHOTO SERVICES

Focus: Fucose

PANCREATIC CANCER IS A LEADING cause of cancer deaths in the U.S., and it has the worst prognosis of any type of cancer. It's difficult to diagnose in its early stages and hard to distinguish from other non-malignant conditions. But the outlook is not completely bleak. Scientists in the U-M Cancer Center are developing a new way to detect pancreatic cancer earlier with a simple blood test.

The key is a sugar called fucose, says David Lubman, Ph.D., the Maude T. Lane Professor of Surgical Immunology. Fucose attaches to cellular proteins in groups to form specific patterns, which are different in cancer cells than in normal cells.

Lubman's research group obtained blood samples from healthy humans and patients with chronic pancreatitis, type 2 diabetes, and various stages of pancreatic cancer. They isolated a protein called haptoglobin from these samples, and analyzed the structure of its sugar groups.

The investigators found that haptoglobin from almost all the cancer patients — some with very early stages of disease — had extra fucose groups, particularly in two specific locations. By analyzing fucose patterns, the scientists could discriminate accurately between cancer and other conditions.

"We're hopeful that this technique can eventually be applied to other cancers," says Lubman. —CMW

MORE ON THE WEB


David Lubman

The Fruit Fly Shuffle

How do you get a fruit fly to exercise? To study the long-term effects of exercise on geriatric flies, Robert Wessells, Ph.D., an assistant professor of internal medicine, had to find a way. Nicole Piazza, his former lab technician and a recent U-M grad, came up with the solution: A device that takes advantage of flies' natural instinct to climb up vertical surfaces. Someday, Wessells' research could help people stay healthier and more active as they age. —SP

MORE ON THE WEB *Video: fruit flies exercising*

In the School

Training Agents of Change

Leadership paths for students will develop focused expertise

IN TODAY'S WORLD — AND MORE importantly, tomorrow's — it isn't always enough for physicians to be highly skilled clinicians, dedicated medical educators or tenacious biomedical researchers. The University of Michigan Medical School is committed to training outstanding future physicians who also will serve as leaders in the ever-changing field of health care.

Brent Williams

Paths of Excellence will offer a self-directed, flexible program of study for medical students to develop the skills to become change agents in a domain of their choosing. The first of several anticipated paths will begin this September, in the domain of global health and disparities.

"Students choosing to focus on disparities in health care will be assigned to a faculty member who will help them develop and implement their course of study and clinical experiences throughout their medical training," says Brent Williams, M.D., associate professor of internal medicine and director of the U-M Global Health and Disparities Path of Excellence.

Students will build foundational knowledge on determinants of health disparities and sustainable methods to address them, and apply this knowledge in clinical settings domestically and internationally. Students will meet regularly with their mentor throughout their four years of medical education to monitor progress and refine their course of study.

The choice of global health and disparities as the first Path of Excellence to be implemented "reflects the school's larger commitment to address the profound inequalities in health status and health care encountered by patients in the U.S. and throughout the world," Williams says. —RICK KRUPINSKI

Former Dean Giles G. Bole Dies at 82

GILES G. BOLE (M.D. 1953, RESIDENCY 1956), former dean of the U-M Medical School, died June 8 at University Hospital. He was 82.

Bole served as dean from 1990-96, during which time the Medical School moved from 16th to 9th in the nation among research-intensive medical schools, according to *U.S. News & World Report*. In 1992, he led a redesign of the medical curriculum, the first such change in 23 years. He advocated for cultural diversity and commissioned an audit to help the school develop new ways to integrate the values of diversity.

During Bole's tenure, construction of Medical Science Research Building III and renovation and remodeling of Medical Science Buildings I and II were completed; the Cancer-Geriatric Center and East Medical Campus construction projects were begun.

Prior to serving as dean, Bole, who specialized in rheumatology and arthritis research, directed the Rackham Arthritis Research Unit and served as chief of the U-M Division of Rheumatology, and as senior associate dean and executive associate dean. In 2003, he retired from the U-M after spending nearly his entire academic career here.

"We are still benefiting from the leadership of Dean Bole, whose commitment to research helped lead to our current success as a top academic medical center," says James O. Woolliscroft, M.D. (Residency 1980), dean of the Medical School and Lyle C. Roll Professor of Medicine. "He will be

MARTIN VLOET, U-M PHOTO SERVICES

remembered for his exemplary work as a clinician, educator, leader and administrator."

Memorial contributions may be designated for the Giles G. Bole, M.D., Professorship in Rheumatology at the U-M and sent to Internal Medicine Development, 1000 Oakbrook Dr., Suite 100, Ann Arbor, MI 48104. —MM

Giles Bole

Student Earns AMA Leadership Award

MEGAN ALYSSA GAYESKI, A FOURTH-year U-M medical student, is one of 24 U.S. medical students to receive the American Medical Association Foundation's 2011 Leadership Award. The award provides medical students, residents and early career physicians with special training to develop their skills as future leaders in organized medicine and community affairs. [M]

Medical Students Place Third in International Writing Competition

A GROUP OF U-M MEDICAL STUDENTS WON THIRD PLACE IN THE 2011 NextBillion Case Writing Competition, an international business-writing contest.

The students' entry, "Catch a Falling STAR: Sustainable Financing for a Base of Pyramid Hospital (BoP)," was written by Shilpa Gulati, Gopal Pai, Dave Seo and Alice Zheng, working under the supervision of Paul Clyde, an adjunct professor of business economics and public policy at the U-M Stephen M. Ross School of Business.

Clyde says the students' work is "a concise description of some of the key challenges of health care delivery in emerging markets."

STAR, a comprehensive mission hospital in India, is facing an impending decrease in donations, which currently comprise nearly 50 percent of the mission's total funding. The hospital's founder must consider shifting its business model to adopt more sustainable financing mechanisms.

"This was a great way to put together our interests and combine our different backgrounds to look at emerging market health care issues," says Alice Zheng, a third-year medical student. "We have experience in different sectors spanning business and public health, which helped us have a multi-disciplinary approach in writing a case."

The William Davidson Institute at the U-M was one of the sponsors of the competition. The 2011 winning submissions have been published by GlobaLens, a publishing division of the William Davidson Institute. GlobaLens features one of the largest collections of BoP and Social Enterprise teaching cases available from any publisher.

The NextBillion Case Writing Competition, now in its second year, recognizes and publishes the best new business cases on social enterprise or BoP topics. The goal of the annual competition is to engage students and faculty on campuses globally in the emerging field of social enterprise. —IH

Gulati

Pai

Seo

Zheng

In the Clinic

The Hurt Blockers

U-M researchers test gene therapy for pain

MEDICINE HAS COME A LONG WAY since the days when a shot of whiskey was the best painkiller doctors had to offer. Today's physicians use morphine and other analgesic drugs to control acute pain in their patients after surgery or traumatic injury. But when it comes to severe chronic pain, it's a different story.

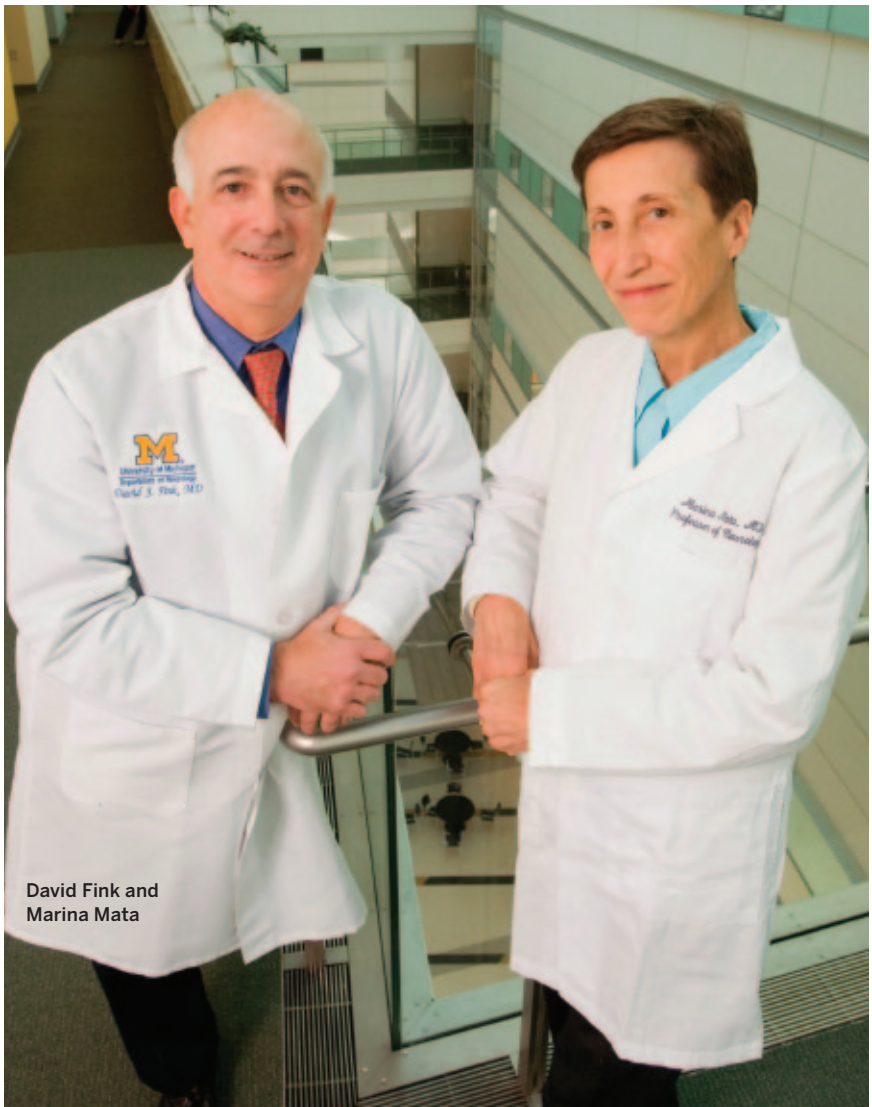
For many patients, even high doses of painkilling drugs cannot relieve the agony of advanced bone cancer or dull the constant burning pain of diabetic neuropathy. Opiate drugs like morphine act inside the central nervous system — the brain and spinal cord — to block the perception of pain. But these drugs have systemic side effects that limit the amount patients can take safely.

U-M researchers David Fink, M.D., and Marina Mata, M.D. (Residency 1981), believe they have a better idea: using targeted gene therapy technology to block pain signals before they reach the central nervous system. They have constructed a non-infectious form of the herpes simplex virus (HSV) — the same virus that causes cold sores — to deliver genes for natural painkilling opioids directly to the nucleus of sensory nerve cells near the spinal cord. The genes that control replication of the virus are inactivated, so it's impossible for the virus to reproduce and spread in the body.

"HSV is the perfect gene delivery vector for sensory nerves, because the virus moves naturally from the skin into sensory nerve fibers," says Fink, the Robert Brear Professor of Neurology and chair of the Department of Neurology.

After the HSV vector is injected into the skin, it travels up the long projecting axon of the sensory nerve cell until it reaches the cell's nucleus located in the dorsal root ganglion, or DRG, just outside the spinal cord. When the vector reaches the nucleus, the gene it carries is activated and begins to express the natural painkilling peptide that has been inserted in the vector. Since pain signals pass through the DRG before entering the spinal cord to reach the brain, it is an ideal site to interrupt the transmission of pain sensations.

Another advantage of gene therapy is its specificity. "Because gene delivery can be targeted to specific sensory nerves, it allows us to block incoming pain signals from just one part of the body," explains Mata, a U-M professor of neurology.



David Fink and Marina Mata

SCOTT GALVIN, U-M PHOTO SERVICES

Fink and Mata worked with co-inventor Joseph Glorioso, Ph.D., and colleagues at the University of Pittsburgh to develop the gene therapy technology while Fink was a professor of neurology at Pitt. Since joining the U-M faculty in 2004, Fink and Mata have continued their research here. After 20 years of work to develop the technology and test it in research animals, Fink and Mata were able to celebrate the completion, early in 2011, of the first human clinical trial of their gene therapy technology. It was a small phase 1 trial of 10 patients with intractable severe pain from cancer. Each patient received 10 injections in one sitting of an HSV-based vector called NP2, which contains a gene for a natural pain-inhibiting endorphin.

"Patients who received low doses of the vector reported little change in pain levels, but patients receiving higher doses reported more than an 80 percent reduction in pain over the four weeks following treatment," says Fink. "No serious adverse effects related to treatment were reported during the four-month follow-up period of the study."

Diamyd Medical, the Swedish biotechnology company that sponsored the phase 1 trial, has initiated a phase 2 trial to compare pain levels in cancer patients who receive gene therapy to those of patients receiving a placebo. Diamyd Medical holds exclusive licensing rights to patents for the technology. Other vectors developed by the group for other types of pain, including neuropathic pain caused by diabetes and nerve injuries, are being prepared for additional clinical trials. —SALLY POBOJEWSKI

MORE ON THE WEB

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Warning Signs for Heart Disease in Kids

RESEARCH FROM THE U-M CARDIO-vascular Center suggests that low levels of high density lipoprotein (HDL) cholesterol — so-called "good" cholesterol — could be a warning sign of future heart disease in children, just as it is in adults.

"There may be factors that could help us identify young people who might be at increased risk for developing health problems later on," says Elizabeth Jackson, M.D., M.P.H., a U-M preventive cardiologist and assistant professor of internal medicine.

U-M medical students collected and analyzed data from more than 1,100 sixth-graders enrolled in Project Healthy Schools, a school-based intervention program in southeast Michigan. The data included lipid and glucose levels, body mass index (BMI), blood pressure, heart rate and a standardized questionnaire assessing diet and exercise.

Jackson and her co-researchers compared results from two groups — those with HDL below 40 mg/dL and those with HDL greater than 40 mg/dL. Students with low HDL were much more likely to be overweight and physically inactive, and have higher blood pressure and triglyceride levels, than children with higher levels of HDL.

They also found that students whose heart rates were still elevated one minute after completing a three-minute step test were more likely to be obese, have higher cholesterol levels and other cardiovascular risk factors. Jackson says this simple test could be a practical way to assess cardiovascular fitness in children. —SP

MORE ON THE WEB

Glaucoma Risk and Asian Americans

ASIAN AMERICANS NEED TO KNOW THAT THEY FACE A SIGNIFICANT RISK OF developing glaucoma as they get older, says Joshua Stein, M.D., an assistant professor of ophthalmology. Stein and other Kellogg Eye Center researchers reviewed insurance records of more than 44,000 Asian Americans over age 40. They found that Asian Americans had a 51 percent increased risk of open-angle glaucoma and a 123 percent increased risk of narrow-angle glaucoma compared to non-Hispanic whites. "Eye care providers should be aware that their Asian American patients are at increased risk for glaucoma and monitor them carefully after age 40 for signs of the disease," he says. —SP

MORE ON THE WEB

In the Clinic

Older, but Stronger

GROWING OLDER DOESN'T HAVE TO MEAN GETTING WEAKER. U-M RESEARCHERS say that progressive resistance training can build muscle and increase strength in all adults — no matter what their age.

"People can significantly improve strength with progressive resistance exercise, even into the eighth and ninth decades of life," says Mark Peterson, Ph.D., a physical medicine and rehabilitation research fellow.

Peterson and Paul M. Gordon, Ph.D., M.P.H., an associate professor of physical medicine and rehabilitation and director of the Laboratory for Physical Activity and Exercise Intervention Research, have conducted multiple studies pertaining to resistance exercise in older adults. They found that after 18-20 weeks of progressive resistance training, healthy older adults can add as much as 2.42 pounds of lean muscle to their body mass and increase overall strength by 25 percent to 30 percent.

They suggest that people over 50, especially those who are sedentary, should first check with their doctor to see if it's safe to start a resistance training program. A good way to begin is to use body mass as a load for simple exercises like squats, modified push-ups and lying hip bridges. Non-traditional exercises that progress through a full range of motion, such as tai chi, Pilates and yoga, can also be effective.

Once accustomed to these activities, older adults can progress to more advanced resistance training in an exercise and fitness facility. A certified trainer or fitness professional who has experience working with older adults can help with the transition.

"Working out at age 20 is not the same as at age 70," Peterson says. "A fitness professional who understands the difference can help you plan a safe training regimen and adjust it based on how you respond." —SP

MORE ON THE WEB

Mark Peterson and Paul Gordon

AUSTIN THOMASON, U-M PHOTO SERVICES

Health Briefs

Millions of women take bisphosphonates to help prevent bone loss after menopause. A new U-M study found that women who took these bone-strengthening drugs for more than one year had a 50 percent reduction in relative risk for development of post-menopausal colorectal cancer. If results are confirmed in clinical trials, researchers say bisphosphonates could become an important cancer prevention drug.

MORE ON THE WEB

If you're a middle-aged adult with diabetes, your risk of developing common geriatric conditions before age 80 is nearly twice as high as it is for adults without diabetes. In an analysis of data from the U-M Health and Retirement Study, researchers found that adults aged 51-70 who had diabetes developed ailments like incontinence, falls, dizziness, or chronic pain faster and earlier than adults in the same age range who did not have diabetes.

MORE ON THE WEB

U-M's C.S. Mott Children's Hospital has once again earned top rankings from *U.S. News & World Report*. In the publication's annual evaluation of the top 50 children's hospitals in the nation, Mott had the highest rankings in the state of Michigan and was nationally ranked in all 10 evaluated pediatric specialties, including third in heart care and heart surgery. —SP

MORE ON THE WEB