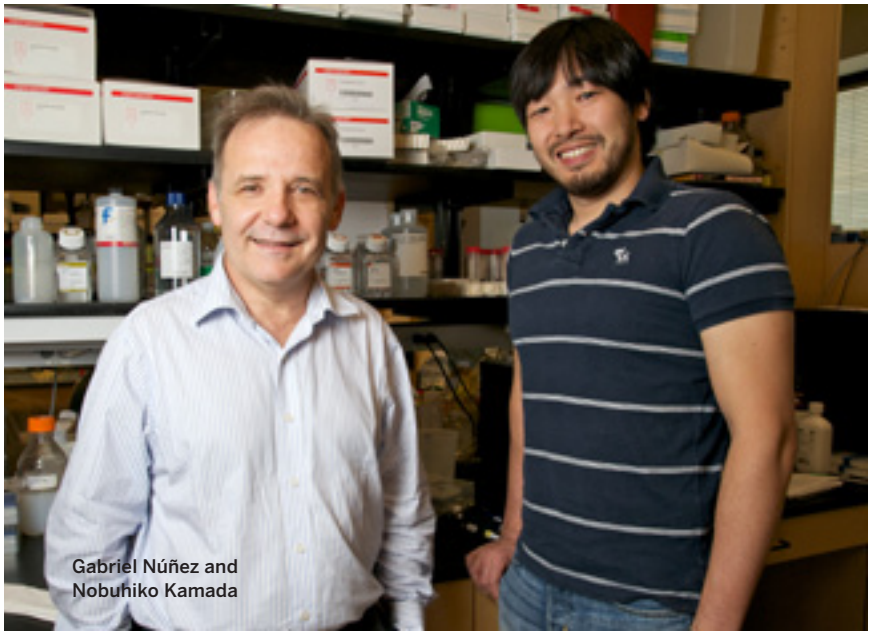
In the Lab

Cracking the Virulence Code

U-M research makes strides in fight against major worldwide killer



Gabriel Núñez and Nobuhiko Kamada

WHILE *ESCHERICHIA COLI* BACTERIA are part of the normal flora of the human digestive system, harmful strains of *E. coli* kill 1 million people worldwide each year and sicken 160 million more. Children in the developing world are hit hardest, though Western, industrialized countries also experience outbreaks — a particularly virulent strain traced to bean sprouts killed dozens of people in Germany last year.

"Most bacterial infections are controlled by antibiotics, but with severe *E. coli* infections the patients actually do worse. Typically you take them to the hospital, put them on IV fluids and just pray for the best," says Gabriel Núñez, M.D., the Paul H. de Kruif Professor of Pathology in the Medical School.

Núñez and postdoctoral fellow Nobuhiko Kamada, Ph.D., are helping to unravel fundamental questions about how infectious *E. coli* interacts with non-pathogenic *E. coli* and other microbes inside the gut — which, in turn, may lay the groundwork for new clinical approaches.

"On one side you have basic questions about how the microbiota in the gut and the pathogen try to control each other, but we're also gaining insights into fighting these infections," says Núñez. Research led by the U-M duo was recently published in *Science* magazine.

The scientists compared the response of conventionally raised mice and germ-free mice — which do not have normal, "good" bacteria living in their digestive systems — to *Citrobacter rodentium*, which serves as a model for human infections of enterohemorrhagic and enteropathogenic *E. coli*.

For both types of mice, the *C. rodentium* load rises dramatically over the first seven days. In those with normal flora, known as commensals, the infections drop until they are eliminated by day 21, while the germ-free mice maintain a steady, high load — indicating healthy gut bacteria are necessary for the eradication of the pathogen. But something left the scientists scratching their heads.

"We expected the germ-free mice to be overwhelmed by the infections," Núñez says. "That all the mice survived was very shocking to us, but it was good because it showed us that there was something important that we didn't understand."

The key lay in an island of genes whose expression regulates the bacteria's virulence. Early expression of virulence genes helps the pathogen out-compete the existing microbiota and establish itself on the intestinal lining. Then, after about a week, virulence expression is down-regulated and the bacteria move to the open center of the intestine, where they are eventually competed into extinction — but not before the diarrhea they cause provides an escape route for some of them, allowing them to leave the body and seek new hosts.

"From the point of view of evolution, the pathogen and host shake hands in a very important agreement. The patho-

ELIZABETH WALKER

gen is allowed to multiply, but eventually virulence gets turned off, which allows both to survive," Núñez says.

The researchers found that changing the balance of dietary sugars can help tip the scales against the invaders. They also discovered that when a factor activating the expression of virulence genes was missing, commensals could out-compete and decimate the invading pathogen in the early days of an infection — suggesting it may be possible to greatly lessen the effects in humans by tricking virulence genes into turning off early.

"We are very optimistic. The drugs would simply need to mimic what nature does," Núñez adds, noting that his lab is continuing to study the mechanisms underlying virulence regulation, and collaborating with others at the U-M to identify potential therapeutic agents. —IAN DEMSKY

MORE ON THE WEB

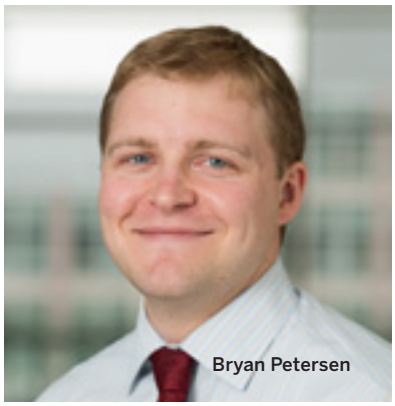
New Cell Linked to Treatment-Resistant Asthma

STUDYING THE ROLE OF A SIGNALING MOLECULE ASSOCIATED WITH asthma known as interleukin 25 (IL-25), a research team led by pathology professor Nicholas Lukacs, Ph.D., and Medical Scientist Training Program student Bryan Petersen has uncovered a new type of cell — dubbed T2M — which, in a mouse model, continued to produce inflammation-promoting cytokines in the presence of steroid medication.

Partnering with U-M allergy specialist Alan Baptist, M.D. (Fellowship 2005), an assistant professor of internal medicine, the researchers also discovered T2M-like cells in humans — with higher numbers in those with asthma. Future research will determine whether the cells are more prevalent in those with more severe, treatment-resistant forms of the disease. The team hopes that the findings, published in *Nature Medicine*, may aid in the development of new therapies and better ways of identifying patients at risk for becoming steroid-resistant. —ID

MORE ON THE WEB

Nicholas Lukacs



Bryan Petersen

AUSTIN THOMASON, MICHIGAN PHOTOGRAPHY

Protein Implicated in Insulin Resistance

YOU MIGHT WANT TO THINK twice before you cuddle up to that tub of ice cream: U-M researchers have found new clues to how overindulging in fat can lead to the insulin resistance seen in diabetes and related metabolic problems.

By tracing the health-damaging molecular changes set in motion by the wrong kind of treats, they found that a protein known as Bcl10 plays a key role in the ability of free fatty acids — found in high-fat foods and stored in body fat — to impair insulin action, leading to potentially dangerous elevations of blood sugar. The results, published in *Cell Reports*, also revealed that mice deficient in Bcl10 were protected from developing insulin resistance.

"We were surprised to learn that Bcl10, a protein previously known for its critical role in immune cell response to infection, also plays a critical role in the liver's response to fatty acid," says senior study author Peter C. Lucas, M.D., Ph.D. (Residency 2001), associate professor of pathology. "The study underscores how very short-term changes in diet can induce a state of insulin resistance." The findings could lead to novel ideas for treating the increasing number of patients with metabolic syndrome and type 2 diabetes. —SK

MORE ON THE WEB

In the School

App-lied Technology

Mobile apps aid learning and practicing medicine

ONE OF THE GREAT CHALLENGES of medical education is imparting a level of practical skills that equals and complements the strong didactic learning students get during medical school. Clinical rotations, patient simulators, patient "actors" — even anatomical dissection — are among many methods of teaching these sensory skills, yet graduating U-M Medical School students have reported in exit interviews that they lack full confidence in their hands-on abilities.

Now mobile apps have joined the skill-based educational arsenal, merging learning with convenience as technology continues to provide new avenues for reaching students and maximizing learning opportunities. Waiting for a bus? Why not challenge yourself to learning heart sounds? Your smart phone is probably in your hand anyway.

Professor Emeritus of Cardiology Richard Judge (M.D. 1951, Residency 1957) and Medical School Media Services Manager Chris Chapman have collaborated on several projects that use technology to improve learning and skill acquisition. One of those projects included a Web-based interface for learning heart sounds, providing 24 well-known variations to help students learn to distinguish among them.

The heart sound challenge was widely used but not very portable. With the iPhone, the smart phone of choice for a majority of students, Chapman saw the opportunity to bring portability to the challenge, and at the same time ramp up student engagement by adding game-like qualities — a technological world it's safe to call familiar to most students.

Learning to distinguish among the different sounds the heart makes is difficult to master. "We needed to create an environment where someone would listen to something over and over, and not make it boring," Chapman says. With the help of Bruce Maxim, associate professor of computer and information science at U-M Dearborn, who teaches a course in game development — and his students — Chapman, Judge and colleagues worked out an initial design. Maxim's students did the programming. "We performed usability testing throughout the process," Chapman adds. "Students liked it, and they kept going until they could identify the sounds and get a perfect score."

The Heart Sounds Challenge app was released on iTunes in August 2011. "We've learned that we're good at teaching science, but less good at teaching skills," Judge says. But given the success of the Web-based version at the U-M, now also in use at Dartmouth Medical School, Chapman and Judge are excited about the possibilities of the app for anywhere, anytime skill-building.

"Using a program like this helped me gain confidence in my ability to use my stethoscope," says Erin Strong. "As a third-year student who sees patients, I know I'm being judged by the residents on my skills as well as the confidence I project."

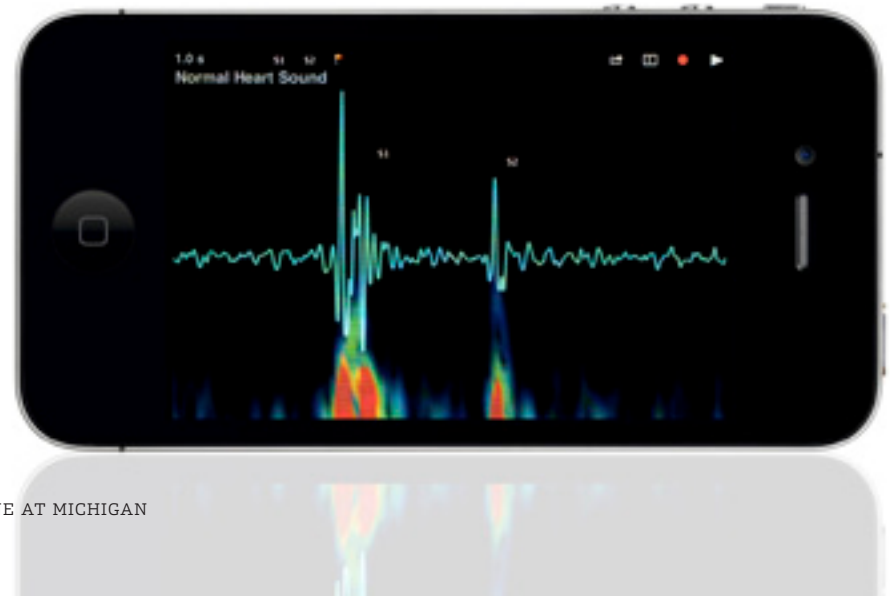
The iPhone's younger sibling, the iPad, provides residents the essentials needed for education, patient care and other functions in the Department of Anesthesiology — the first residency program to use a paperless environment.

There are apps for patients, too. UMSkinCheck allows users to complete and store a full body photographic library, track detected moles and lesions, access informational videos and literature, and fill out a melanoma risk calculator.

—SUSAN TOPOL

For a complete list of U-M mobile apps, visit mobileapps.its.umich.edu/apps.

MORE ON THE WEB



MUTLU KURTBAS/ISTOCKPHOTO.COM


Sujal Parikh

The first annual **Sujal Parikh Memorial Symposium for Health and Social Justice** was a global event, drawing speakers and presenters from around the world on March 26 to discuss such topics as curricula as an agent of social change, the concept of health equity, and innovations in global engagement. The symposium, co-sponsored by the Medical School and the national organization Physicians for Human Rights, honors Parikh, a U-M medical student who was killed in a motor vehicle accident in Uganda in 2011 while on a Fogarty Fellowship. —RK

New Leadership for Emergency Medicine

ROBERT W. NEUMAR, M.D., PH.D., A RENOWNED EXPERT IN BRAIN damage after cardiac arrest or head trauma, is the new chair of the Medical School Department of Emergency Medicine, effective July 1. Neumar succeeds William Barsan, M.D., who led the department since its establishment in 1999 and remains on the U-M faculty.

Neumar comes to the U-M from the University of Pennsylvania Perelman School of Medicine, where he was an associate professor of emergency medicine and associate director of the Center for Resuscitation Science. Along with maintaining an active clinical practice at the Hospital of the University of Pennsylvania, Neumar conducted extensive research focused on understanding the mechanisms of brain injury, and developing therapies to minimize brain damage and improve brain recovery after cardiac arrest or traumatic brain injury.

Neumar has a 17-year track record of continuous NIH funding and is certified by the American Board of Emergency Medicine. A fellow of the American College of Emergency Physicians, he is a recipient of ACEP's Award for Outstanding Contribution in Research.

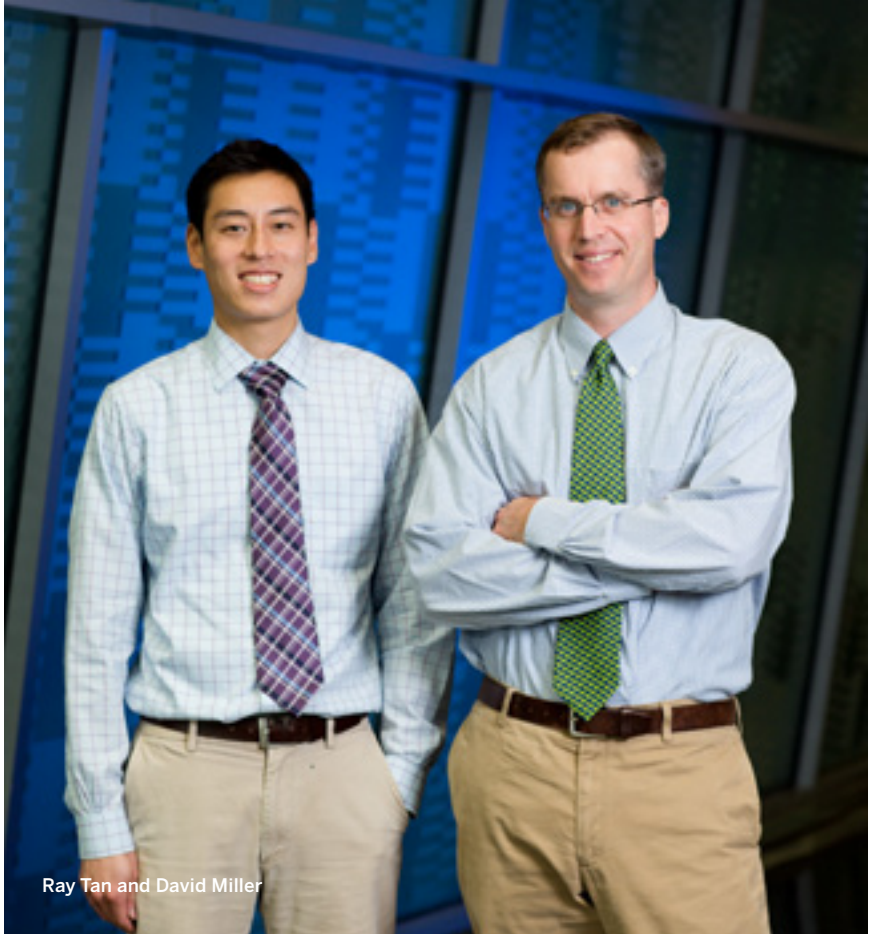
His appointment brings Neumar back to the state of Michigan where he received his Ph.D. in physiology from Wayne State University. He received his M.D. from the University of Pittsburgh School of Medicine, and completed his internship and residency at the University of Pittsburgh, as well as research fellowships at Pitt and Wayne State. —KG


Robert Neumar

In the Clinic

Improving Kidney Cancer Survival

Partial nephrectomy may increase odds



Ray Tan and David Miller

ERIC BRONSON, MICHIGAN PHOTOGRAPHY

KIDNEY CANCER RATES ARE steadily rising, but research results have been mixed regarding whether it's best to remove the whole kidney or, when possible, just the tumor. Now a U-M study, published in the *Journal of the American Medical Association*, provides new evidence that a partial nephrectomy in those with early-stage cancer may offer the better possibility for long-term survival.

According to the American Cancer Society, nearly 60,000 people will be diagnosed with kidney cancer this year, a majority of them with localized or early-stage tumors. David Miller, M.D., M.P.H. (Residency 2005), assistant professor of urology and the senior study author, says that beginning in the 1990s data increasingly suggested that for some patients, removal of the tumor alone could achieve the same cure rates as radical nephrectomy, or removal of the entire kidney. That led researchers to consider whether the procedure should be used even when the remaining kidney is healthy, since those undergoing radical nephrectomy may end up with worse kidney function in the long run. In 2009, the American Urological Association recommended partial nephrectomy as the preferred treatment for most patients with small kidney cancers.

That recommendation was called into question, however, by a study published in *European Urology* at the end of 2010. The randomized control trial showed a slight survival benefit with radical nephrectomy, but Miller and his team felt the study had limitations. Since previous observational studies produced one result and the randomized trial showed the opposite — and represented a significant change from the literature — there was an interest in exploring the issue further, says urology resident Hung-Jui "Ray" Tan (M.D. 2007), the U-M study's first author.

U-M researchers undertook an observational study, but made efforts to reduce sampling bias and thereby come closer to replicating a randomized study. In a unique partnership, they collaborated with health economist Edward Norton, Ph.D., from the U-M School of Public Health, who developed statistical models that helped balance the characteristics of patients in the treatment groups. In so doing, the models provided less biased insight than a typical observational study about the relative benefits of the two surgical treatments.

Findings from the U-M study ran counter to those of the 2010 study, showing patients with small tumors undergoing partial nephrectomies had better survival rates: After an average of five years, 42 percent of those having their entire kidney removed had died compared to just 25 percent of patients who had a partial nephrectomy. "Adjusting for differences in patient groups, these data suggest that for every seven patients we treat with a partial (rather than radical) nephrectomy, we could avoid the loss of one more life," says Tan.

Miller acknowledges that partial nephrectomy is a more complex procedure, with a higher risk of complications, but notes the effects are manageable and typically resolve within a few weeks. "If patients can accept the slightly higher risk of short-term complications, we think there could be a bigger pay-off in the long-term with partial nephrectomy," Miller says. —JULIE HALPERT

Honesty is the Best Policy

ONCE AGAIN, INNOVATIONS developed at the U-M are helping to change medicine across the country. In April, seven major Massachusetts hospitals, along with the state's medical society, announced they will emulate an approach pioneered at the U-M for dealing with unexpected medical outcomes — one that focuses on honesty, transparency and prevention of future errors.

A roadmap to the U-M model of addressing mistakes was also recently laid out in *Frontiers of Health Service Management*, published by the American College of Healthcare Executives. The authors — who include Health System Chief Medical Officer Darrell "Skip" Campbell Jr., M.D. (Residency 1978), and Chief Risk Officer Rick Boothman, J.D. — emphasize that the approach goes far beyond "apology" policies that have been advocated elsewhere, and replace the "deny and defend" approach still in place at most hospitals.

When a U-M doctor acknowledges a mistake, it's the outward sign of a deeper culture shift "that seeks to elevate patient safety to the foreground and relegate claims considerations to the background," they note. Since implementing the approach in the early 2000s and continuing to refine it, the Health System has seen a drop in claims filed against it and improvements in other metrics, such as time taken to processes claims, defense costs, and average settlement amounts. —KG

MORE ON THE WEB

An Ounce of Prevention

A U-M-LED TEAM OF RESEARCHERS HAS SHOWN THAT A SINGLE DOSE of anti-inflammatory medication costing less than $3 can help eliminate a disabling and occasionally deadly complication from a common gastrointestinal procedure.

Despite decades of research, the trial, published in the *New England Journal of Medicine*, was the first to convincingly demonstrate an effective means of preventing pancreatitis after a procedure known as ERCP. Endoscopic retrograde cholangiopancreatography is performed on hundreds of thousands of patients each year and involves inserting a lighted scope through the mouth, in order to diagnose and treat disorders of the bile and pancreatic ducts, including blockages and leaks.

Only 9.2 percent of patients who were given indomethacin developed post-ERCP pancreatitis compared to 16.9 percent of those who received a placebo — a 46 percent drop in relative risk, the study found. Post-ERCP pancreatitis costs an estimated $150 million annually to treat and affects up to 1 in 4 high-risk patients.

"Health care costs in the U.S. are soaring, so it's important for the scientific community to find innovative, low-cost ways to improve health," says lead study author and gastroenterologist B. Joseph Elmunzer, M.D., assistant professor of internal medicine. "This is a perfect example of a widely available, inexpensive, easily administered drug that does exactly that." —ID

MORE ON THE WEB

DAVID GALLAHER/DREAMSTIME.COM

In the Clinic

IPF Standard of Care Raises Concerns


Fernando Martinez

RESEARCHERS ARE CALLING ON DOCTORS around the world to cease using a three-drug combination to treat patients with idiopathic pulmonary fibrosis. A 25-center research trial found the therapy for the deadly lung disease resulted in far more hospitalizations and deaths than did a placebo, says pulmonologist Fernando Martinez, M.D., a professor of internal medicine at the U-M who presented the results at the annual American Thoracic Society meeting in May.

"The findings show the importance of testing even those treatments that doctors give routinely for any type of condition — to see if they truly help, and don't harm, patients," Martinez says.

The National Heart, Lung, and Blood Institute-funded research, conducted by the IPF Clinical Research Network, was stopped early when an interim analysis raised concerns about the regimen of prednisone, azathioprine and N-acetylcysteine. Eight patients in a group of 77 assigned to the three-drug combination died and 23 were hospitalized, compared with one death and seven hospitalizations in the placebo group. The treatment, which had been the standard of care, additionally did not appear to improve lung function, nor slow the disease's progression. The unexpected results were also published in the *New England Journal of Medicine*.

IPF affects nearly 100,000 Americans, slowly robbing them of their ability to breathe. In addition to investigating treatments, U-M researchers are also working to illuminate the biological factors driving the disease. —ID

MORE ON THE WEB

A Michigan First: The U-M Neuroscience Hospital

THE GLEAMING NEW HOME OF THE C.S. MOTT CHILDREN'S HOSPITAL AND Von Voigtlander Women's Hospital won't be the new kid on the block for long. The former Mott space freed up by the move will allow the U-M to create the state's first neuroscience hospital. It will also pave the way for much needed expansion of adult inpatient capacity.

In April, the U-M Board of Regents approved a $163 million expansion and renovation project that will include the establishment of a new hospital offering advanced treatments and therapies, including those emerging from U-M research. The project will also result in 120 new beds and eight more operating rooms. Completion has been targeted for the end of 2014. —ID

MORE ON THE WEB

Health Briefs

As use and abuse of prescription painkillers like OxyContin and Vicodin have skyrocketed in the last decade, the number of babies across the country born suffering the effects of drug withdrawal has almost tripled, according to U-M research. By 2009, roughly one baby was born per hour with neonatal abstinence syndrome, which often leads to longer, costlier hospitalizations.

MORE ON THE WEB

Following the rapid adoption of intensity-modulated radiotherapy (IMRT) to treat prostate cancer, a team of U-M researchers found that men with low-risk disease were nearly as likely as high-risk patients to receive it, raising some concerns about overtreatment. Although evidence is accumulating in support of IMRT, it comes at a price — up to $20,000 more than surgical or other radiation options — and raises questions about the costs to achieve small improvements in outcomes.

MORE ON THE WEB

The antidepressant drug duloxetine, or Cymbalta, helped relieve painful tingling caused by chemotherapy in 59 percent of patients who took it, a U-M study found. This is the first clinical trial to find an effective treatment for this chemo side effect. Duloxetine has previously been shown to help relieve painful diabetic neuropathy. It is believed to work on pain by increasing neurotransmitters that interrupt pain signals to the brain. —ID

MORE ON THE WEB

AUSTIN THOMASON, MICHIGAN PHOTOGRAPHY