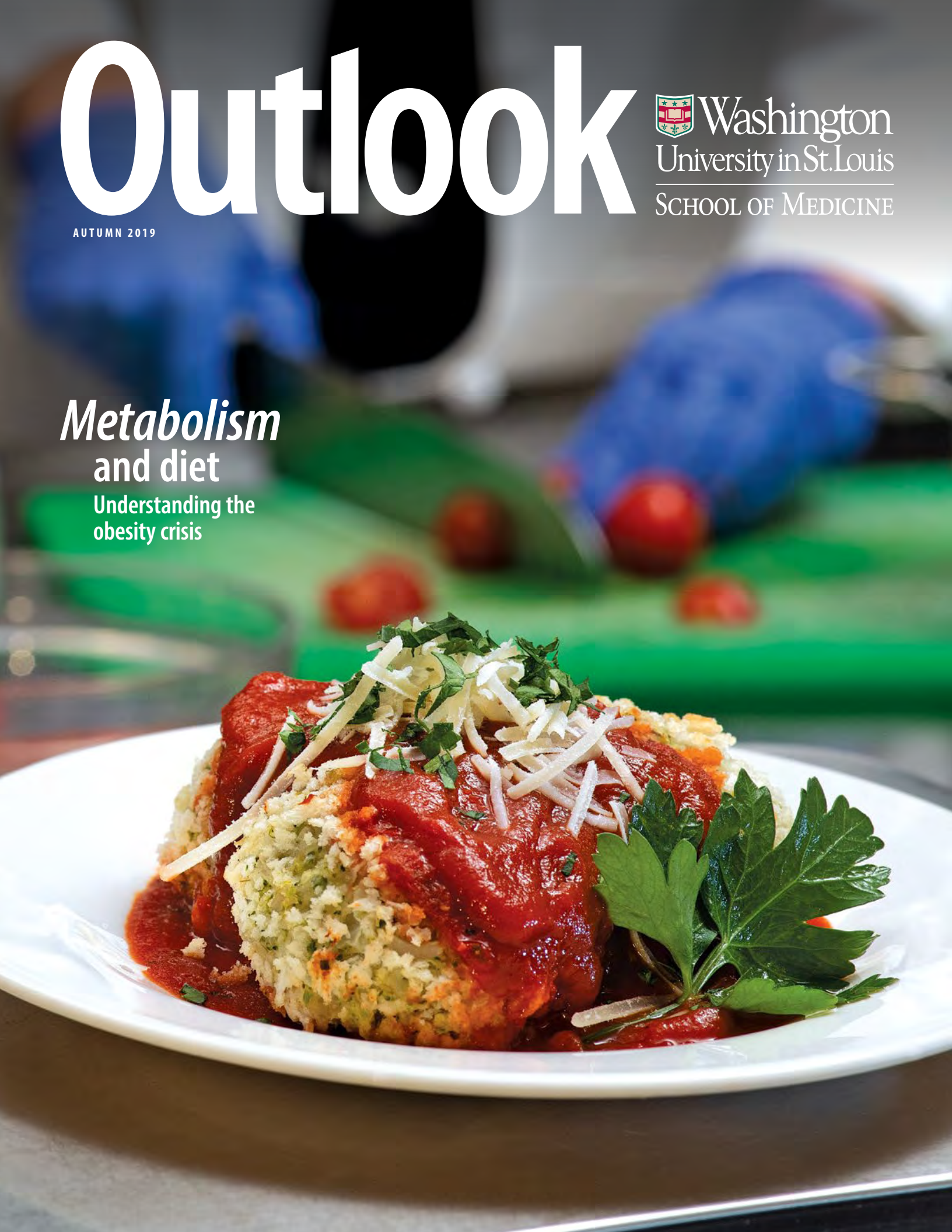
Outlook

AUTUMN 2019

Washington University in St. Louis
SCHOOL OF MEDICINE

Metabolism and diet

Understanding the obesity crisis



The School of Medicine is committing $100 million to scholarships and curriculum revision. Increased community engagement is a critical part of the revised curriculum. Above: Trauma surgeon Laurie Punch, MD, (speaking) discusses gun violence prevention efforts, as part of a curriculum retreat involving more than 200 faculty, medical students and trainees. See page 8.

MATT MILLER

COVER Meals like this one are carefully planned and packaged for metabolically unhealthy people enrolled in a study led by Sam Klein, MD. Researchers are controlling participants' food intake and evaluating biological function in multiple organs in a comprehensive, evidence-based approach to understanding obesity. See page 12. Recipe on back cover.

FEATURES

MATT MILLER

Outlook

Washington University School of Medicine

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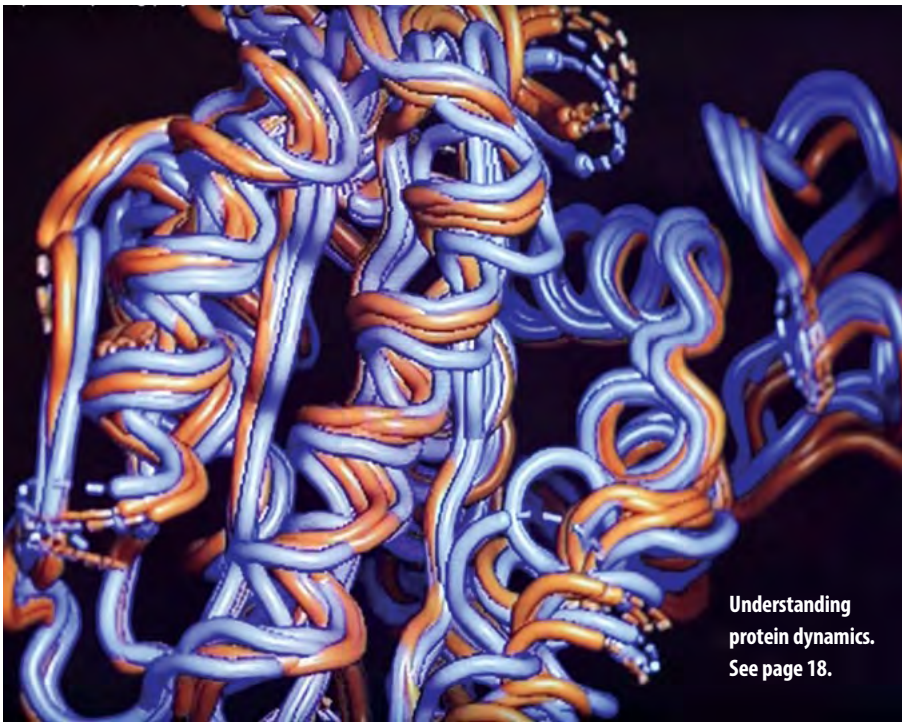

Understanding protein dynamics. See page 18.

DEPARTMENTS

MARK BEAVEN

Medical school alumni reconnected with peers during Reunion 2019. **See page 26.**

STAFF:

MANAGING EDITOR **DEB PARKER**
DESIGNER **SARA MOSER**
ART DIRECTOR **ERIC YOUNG**
EXECUTIVE EDITOR **VIRGIL TIPTON**
PHOTOGRAPHER **MATT MILLER**
CIRCULATION **THERESA HOWARD**

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PHONE **(314) 286-0100** EMAIL **mpa@wustl.edu**

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Researchers report that they can measure levels of the Alzheimer's protein amyloid beta in the blood and use such levels to predict whether the protein has accumulated in the brain.

One step closer

Blood test is highly accurate at identifying Alzheimer's before symptoms arise

Up to two decades before people develop the characteristic memory loss and confusion of Alzheimer's disease, damaging protein clumps start to build up in their brains. A blood test to detect such early brain changes has moved one step closer to clinical use.

School of Medicine researchers report that they can measure levels of the Alzheimer's protein amyloid beta in the blood and use such levels to predict whether the protein has accumulated in the brain. When blood amyloid levels are combined with two other major Alzheimer's risk factors — age and the presence of the genetic variant APOE4 — people with early Alzheimer's brain changes can be identified with 94% accuracy, the study found.

The findings were published Aug. 1 in the journal Neurology. Surprisingly, the test may be even more sensitive than the gold standard — a PET brain scan — at detecting the beginnings of amyloid deposition in the brain.

Such a test may become available at doctors' offices within a few years, but its benefits will be much greater once there are treatments to halt the disease process and forestall dementia. Clinical trials of preventive drug candidates have been hampered by the difficulty of identifying participants who have Alzheimer's brain changes but no cognitive problems. The blood test could provide a way to efficiently screen for people with early signs of disease so they can participate in clinical trials evaluating preventative treatments.

"Right now we screen people for clinical trials with brain scans, which is time-consuming and expensive, and enrolling participants takes years," said senior author Randall J. Bateman, MD, the Charles F. and Joanne Knight Distinguished Professor of Neurology. "But with a blood test, we could potentially screen thousands of people a month. That means we can more efficiently enroll participants in clinical trials, which will help us find treatments faster, and could have an enormous impact on the cost of the disease as well as the human suffering that goes with it."

There is growing consensus among neurologists that Alzheimer's treatment needs to begin as early as possible, ideally before any cognitive symptoms arise.

Home pregnancy tests can return false negatives

Each year, women in the U.S. rely on some 20 million home pregnancy tests to learn potentially life-altering news. Despite marketing claims that such tests are 99% accurate, research has shown that up to 5% of pregnancy tests return false negatives.

Makers of pregnancy tests advise that tests taken in the first week or two after conception could be inaccurate because pregnancy hormones may not have risen high enough to be detected. But Ann Gronowski, PhD, a professor of pathology and immunology and of obstetrics and gynecology and medical director of core laboratory services at Barnes-Jewish Hospital, discovered that pregnancy tests also can give incorrect results to women five weeks or more into their pregnancies, when hormone levels tend to be very high.

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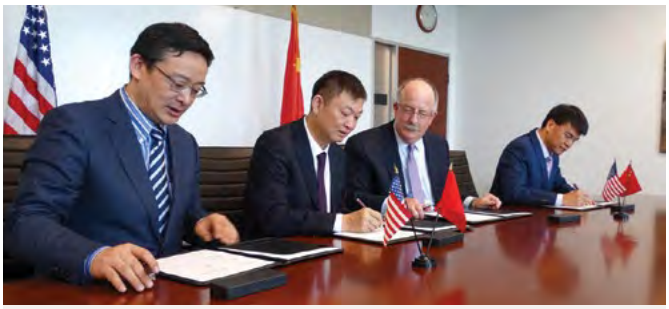
Gronowski first published on this problem in 2009, and has continued studying and raising the alarm on this under-recognized issue. Recently, she and colleagues published a paper in the journal Clinical Chemistry, in which they evaluated how likely several pregnancy devices were to give false negative results.

The team researched 11 of the most commonly used pregnancy tests to see if they were susceptible to false negatives. Seven were somewhat susceptible, two were highly susceptible, and only two tests were not susceptible. The worst one gave false negatives in 5% of the urine samples of pregnant women tested.

Gronowski said the best test to detect pregnancy is a blood test. If there's any doubt, women are urged to talk to their physicians.

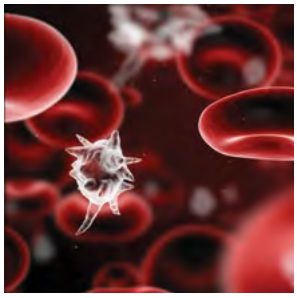
To learn more about stories in Pulse, go to **medicine.wustl.edu/news**


WORLD TRADE CENTER ST. LOUIS

LEARNING OPPORTUNITIES Collaborating with China-based Huici Health Management Co., the School of Medicine is helping to train physicians and design a 1,000-bed medical center in Suzhou. Washington University medical students, residents and fellows also will have opportunities to train at the center. From left: Eric Tong Jiang, vice president, and Lyu Chengli, president, of Huici Health Management Co.; Paul Scheel, MD, CEO of Washington University Physicians; and Wang Haitao, dean of the Chinese Academy of Medical Sciences/Peking Union Medical College.

Genes linked to sepsis found in mice

Sepsis is a life-threatening condition that occurs when the body's immune response to infection spirals out of control. Bacteria in the bloodstream trigger immune cells to release powerful molecules called cytokines to quickly activate the body's defenses. Sometimes the response goes overboard, creating a so-called "cytokine storm" that leaves people feverish or chilled, disoriented and in pain. In severe cases, it can lead to multi-organ failure and death.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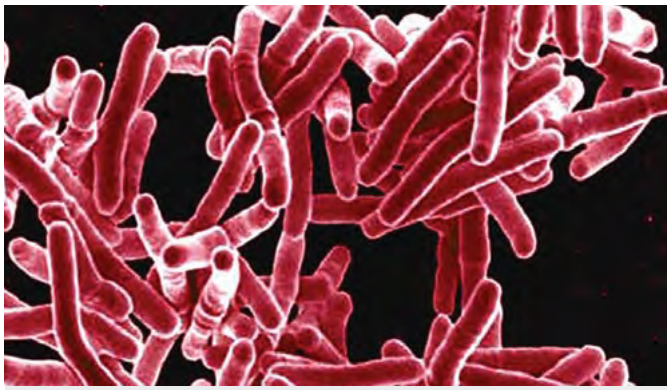
Now, researchers have found genes that help cells survive exposure to cytokines. The genes are involved in disposing of cellular waste, a process known as autophagy. Mice that lack key autophagy genes are more likely to die from sepsis, the study shows. The findings raise the possibility that enhancing autophagy could potentially lead to treatments for the deadly condition.

"When we recognize signs of sepsis in patients, we prescribe antibiotics and fluids, but we lack therapies to protect patients from the direct effects of the cytokine storm," said first author Anthony Orvedahl, MD, PhD, an instructor in pediatric infectious diseases. "Our research indicates that if we could modulate autophagy levels in cells, we might be able to promote cell survival and resistance to the cytokine storm, which may ultimately help people survive sepsis."

The study was published online the week of July 22 in Proceedings of the National Academy of Sciences.



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Drug-resistant TB reversed in lab

About 1.5 million people died of tuberculosis (TB) in 2017, making it the most lethal infectious disease worldwide. A growing rise in drug-resistant TB is a major obstacle to successfully treating the illness.

Now, researchers at the School of Medicine and Umea University in Sweden have found a compound that prevents and even reverses resistance to isoniazid, the most widely used antibiotic for treating tuberculosis.

The research, published the week of May 6 in Proceedings of the National Academy of Sciences, was conducted in bacteria growing in the lab, setting the stage for future studies in animals and people.

Using the compound, called C10, in conjunction with isoniazid potentially could restore the antibiotic's effectiveness in people with drug-resistant tuberculosis. The compound also may bolster the antibiotic's power to kill TB bacteria, which means doctors could start thinking about cutting down the onerous six-month treatment regimen they prescribe today.

"It is very hard for people to comply with such a long regimen," said co-senior author Christina Stallings, PhD, an associate professor of molecular microbiology at the School of Medicine. "It's four drugs. They have side effects. It's no fun. The longer people have to be on antibiotics, the more issues with patient compliance you get, and that can lead to drug resistance and treatment failure.

"Here, we've found a compound that sensitizes bacteria to an antibiotic, prevents drug resistance from arising, and even reverses drug resistance — at least in the lab. If we can turn this compound into a drug for people, it could make our current therapies more effective and be really beneficial for fighting this pandemic."

Antibiotics may treat endometriosis

Researchers have found, in mice, that treatment with an antibiotic reduces the size of lesions caused by endometriosis.

The researchers are planning a large, multicenter clinical trial to test the drug metronidazole in women who have the painful condition.

The study is published online April 30 in the journal Human Reproduction.

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The condition results from uterine cells migrating upward into the stomach area, where those cells clump together to form lesions. In addition to pain, endometriosis often contributes to fertility problems. Current treatment strategies include hormone therapy and surgery, but both approaches involve significant side effects and recurrence after treatment.

The researchers found that treating mice with metronidazole reduced the size of endometriosis-related lesions in the gut. That was true whether treatment was started before the lesions began forming or after endometriosis already was well-established. Interestingly, other antibiotics tested in the study — ampicillin, neomycin and vancomycin — did not lessen inflammation or shrink lesions.

The findings also suggest that gut bacteria may help drive, or prevent, progression of the disease, said principal investigator Ramakrishna Kommagani, PhD, an assistant professor of obstetrics and gynecology at Washington University's Center for Reproductive Health Sciences.

Kommagani's team found that levels of a protective type of gut bacteria were very low in the mice with endometriosis, so they believe that in addition to antibiotics, it may be possible to use probiotics to boost levels of protective bacteria.

"This study is exciting as it opens new frontiers in identifying bacterial candidates that can promote endometriosis in reproductive-age women, and it enables us to conduct future studies aimed at developing simpler ways to diagnose endometriosis," said co-author Indira Mysorekar, PhD, the James P. Crane Professor of Obstetrics and Gynecology and a professor of pathology and immunology.

GETTY IMAGES

$9.5 million aimed at detecting autism earlier in childhood

A multicenter research team led by the School of Medicine and the University of North Carolina at Chapel Hill has received a five-year, $9.5 million grant to further evaluate whether brain imaging can help detect high risk of autism spectrum disorder in early infancy. Researchers believe if the condition can be detected earlier, behavioral interventions can begin sooner, potentially improving outcomes for affected children.

The new grant, from the National Institute of Mental Health of the National Institutes of Health (NIH), funds the continued efforts of researchers in the Infant Brain Imaging Study (IBIS) network.

IBIS network researchers will conduct MRI brain-imaging studies on infant siblings of children with autism diagnoses. Such children are known to have a 20% chance of developing autism spectrum disorder. Previously, IBIS researchers demonstrated that specific findings on MRI scans in children as young as 6 months of age can accurately predict which children later will be diagnosed with autism. They also have identified behaviors that indicate a high risk for a later autism diagnosis.

Learn more at ibis-network.org.

Young mouse blood delays aging in older mice

New research has identified a novel approach to staving off the detrimental effects of aging.

A protein that is abundant in the blood of young mice plays a vital role in keeping mice healthy, the study suggests. With age, levels of this protein decline in mice and people, while health problems such as insulin resistance, weight gain, cognitive decline and vision loss increase. Supplementing older mice with the protein obtained from younger mice appears to slow this decline in health and extend the life spans of older mice by about 16 percent.

The study was published June 13 in the journal Cell Metabolism.

The circulating protein is an enzyme called eNAMPT, which is known to orchestrate a key step in the process cells use to make energy. Over time, the body's cells become less efficient at producing this fuel — called NAD — which is required to keep the body healthy. Washington University researchers have shown that supplementing eNAMPT in older mice with that of younger mice appears to be one route to boosting NAD fuel production.

Senior author Shin-ichiro Imai, MD, PhD, a professor of developmental biology, has long studied aging, using mice as stand-ins for people. Unlike other studies focused on transfusing whole blood from young mice to old mice, Imai's group increased levels of a single blood component, eNAMPT, and showed its far-reaching effects, including improved insulin production, sleep quality, function of photoreceptors in the eye, and cognitive function in performance on memory tests, as well as increased running on a wheel.

MITSUKUNI YOSHIDA

Supplementing older mice with an enzyme called eNAMPT from younger mice extends life spans in the older mice.

Imai's group also has shown other ways to boost NAD levels in tissues throughout the body. Most notably, the researchers have studied the effects of giving oral doses of a molecule called NMN, the chemical eNAMPT produces. NMN is being tested in human clinical trials.

Leadership changes announced

Head of Anesthesiology

Michael S. Avidan, MBBCh, is head of the Department of Anesthesiology. He also is anesthesiologist-in-chief at Barnes-Jewish Hospital. He succeeds Alex S. Evers, MD, who became interim head of anesthesiology in 1992 and assumed the permanent post in 1994.

Avidan, the Dr. Seymour and Rose T. Brown Professor of Anesthesiology, has investigated the effectiveness of interventions to prevent neurologic complications associated with surgery and general anesthesia. From 2006-2012, he led three large clinical trials in the U.S. and Canada focusing on the prevention of intraoperative awareness, when patients regain consciousness and retain memories of surgery. The widely disseminated study findings (including in two highly cited papers in The New England Journal of Medicine) have had a major impact on monitoring techniques employed during surgery.

Director of ICTS

William G. Powderly, MD, the Dr. J. William Campbell Professor of Medicine, has been named director of the university's Institute of Clinical and Translational Sciences (ICTS).

He succeeds Bradley A. Evanoff, MD, the Richard A. and Elizabeth Henby Sutter Professor of Occupational, Industrial and Environmental Medicine. Evanoff will remain involved with the ICTS and continue his roles as a principal investigator researching work-related injuries and workplace health, and as director of the Division of General Medical Sciences.

Powderly, the Larry J. Shapiro Director of the Institute for Public Health, also co-directs the Division of Infectious Diseases at the School of Medicine.

Chief Information Officer

Maria Russo is now chief information officer at the School of Medicine. In the newly created position, Russo will serve as the university's assistant vice chancellor and deputy university chief information officer. She will work closely with Chris Kielt, the university's vice chancellor and chief information officer.

Russo previously served as executive director for Systems Integration in Kaiser Permanente's Washington Region. She led a team that supported the hospital and health plan's electronic medical records in Kaiser Permanente's Northern California region.

Among other clinical practice initiatives, Russo will oversee implementation of electronic medical record software across the faculty practice plan. She also will lead IT service delivery in the school's academic, clinical and business units and support growing research computing needs.

Head of Molecular Microbiology

Noted virologist **Sean Whelan, PhD,** has been named head of the Department of Molecular Microbiology and the Marvin A. Brennecke Distinguished Professor of Microbiology, effective Jan. 1. He studies how deadly viruses such as Ebola and rabies enter cells and multiply, a key step to finding targets for new antiviral drugs.

Whelan comes from Harvard Medical School, where he is a professor of microbiology and of immunobiology, and head of the virology program.

Whelan succeeds interim head Shabaana Abdul Khader, PhD, and former head Stephen Beverley, PhD, who stepped down after 21 years. Beverley is continuing his research on the parasite Leishmania.

Head of Neurosurgery

Gregory J. Zipfel, MD, a professor and vice chair of the Department of Neurosurgery, has been named the new head of the Department of Neurosurgery. He also is neurosurgeon-in-chief at Barnes-Jewish Hospital.

Zipfel is known for surgically correcting aneurysms and other blood vessel malformations in the brain; removing complicated tumors near the skull base; and creating surgical bypasses around blocked or diseased arteries of the brain to increase blood supply.

Zipfel succeeds Ralph G. Dacey Jr., MD, who has led the department since 1989. Dacey is renowned for his accomplishments in cerebrovascular research, his myriad contributions to the clinical practice of neurosurgery and his unwavering leadership in resident training and education.

GETTY IMAGES

Early antibiotic treatment could have potentially harmful effects on the gut microbiome, a study suggests.

Evaluating antibiotic use in preemies

Drug resistance, unhealthy bacteria persist in gut microbiome

Nearly all premature babies receive antibiotics in their first weeks of life to ward off or treat potentially deadly bacterial infections. Such drugs are lifesavers, but they also cause long-lasting collateral damage to the developing microbial communities in the babies' intestinal tracts, according to research.

A year and a half after babies leave the neonatal intensive care unit (NICU), the consequences of early antibiotic exposure remain, the study showed. Compared to healthy full-term babies in the study who had not received antibiotics, preemies' microbiomes contained more bacteria associated with disease, fewer species linked to good health, and more bacteria with the ability to withstand antibiotics.

The findings, published Sept. 9 in Nature Microbiology, suggest that antibiotic use in preemies should be carefully tailored to minimize disruptions to the gut microbiome – and that doing so might reduce the risk of health problems later in life.

"The type of microbes most likely to survive antibiotic treatment are not the ones we typically associate with a healthy gut," said senior author Gautam Dantas, PhD, a professor of pathology and immunology, of molecular microbiology, and of biomedical engineering.

"The makeup of your gut microbiome is pretty much set by age 3, and then it stays pretty stable," he added. "So if unhealthy microbes get a foothold early in life, they could stick around for a very long time. One or two rounds of antibiotics in the first couple weeks of life might still matter when you're 40."

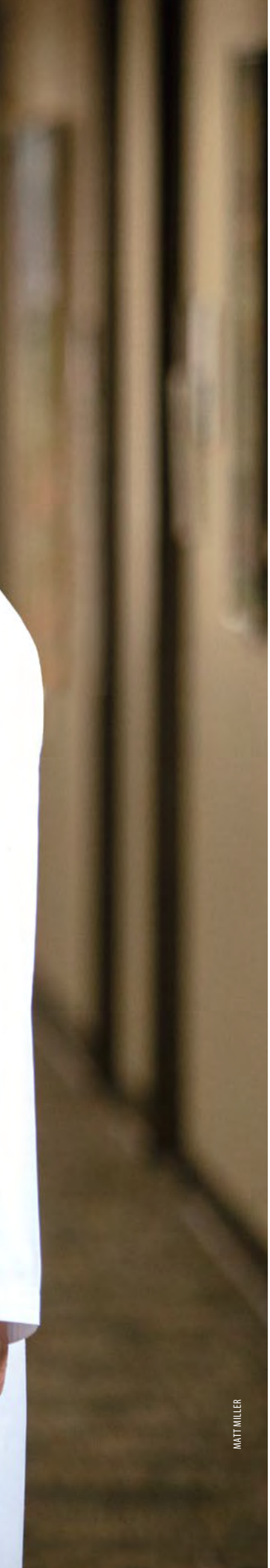
The researchers analyzed 437 fecal samples collected from 58 infants, ages birth to 21 months. Forty-one of the infants were born around 2 ½ months premature, and the remainder were born at full term.

The preemies who had been heavily treated with antibiotics (an average of eight courses) carried significantly more drug-resistant bacteria in their gut microbiomes at 21 months of age than preemies who had received just one course of antibiotics, or full-term infants who had not received antibiotics.

The findings already have led neonatalogists at St. Louis Children's Hospital to scale down their use of antibiotics.

"We're being much more judicious about initiating antibiotic use, and when we do start babies on antibiotics, we take them off as soon as the bacteria are cleared," said study researcher Barbara Warner, MD, director of the Division of Newborn Medicine. "We still have to use antibiotics – there's no question that they save lives – but we've been able to reduce antibiotic use significantly with no increase in adverse outcomes for the children."

Valerie Ratts, MD, left, and Eva Aagaard, MD



MATT MILLER

Reflection of values

School of Medicine pledges $100 million to provide free or reduced tuition

A Q&A with Eva Aagaard, MD, and Valerie Ratts, MD

On a crisp autumn Saturday two years ago, the newly appointed senior associate dean for education began getting ready for an important finance meeting with the medical school's senior leaders. That's when a crazy idea struck her.

"I was thinking about ways to reduce medical school debt and, on a broader level, my overall purpose here, when it suddenly occurred to me that it would be a good idea to become a free medical school," recalled Eva Aagaard, MD, also the Carol B. and Jerome T. Loeb Professor of Medical Education. "I seriously thought I would be laughed out of the board room."

But David H. Perlmutter, MD, executive vice chancellor for medical affairs and the George and Carol Bauer Dean of the School of Medicine, didn't laugh. Neither did Richard Stanton, associate vice chancellor and associate dean for administration and finance, nor did Valerie S. Ratts, MD, associate dean for admissions and a professor of obstetrics and gynecology.

In fact, Ratts found herself nodding in agreement. The medical student admissions office was thinking along similar lines.

Dozens of meetings later, the crazy idea evolved into a serious scholarship program, and its announcement made headlines last April. The School of Medicine would commit $100 million to scholarship and education over the next decade — allowing as many as half of its medical students to attend tuition-free and many others to receive partial support. The funding also underpins curriculum revision efforts.

Washington University is one of a growing number of medical schools instituting steep tuition-reduction programs. The program took effect in the 2019-20 academic year.

How did the conversation about free and reduced tuition evolve?

Aagaard: It grew out of a real concern about the amount of debt medical students were acquiring, and how that is influencing career choices, and, specifically, how educational costs might be pushing people out of careers in academic medicine.

What I love about my job is that you can have a crazy idea and people here won't laugh. Instead, they'll ask about the reasoning behind the idea.

We went through many iterations about what we were trying to accomplish. We want to minimize debt and increase people's freedom to pursue the medical specialties they're most passionate about, instead of selecting the ones that will pay off debt more quickly. We want to train academic physicians — those who work at teaching hospitals and instruct medical trainees, those who pursue research, and those who lead improvements in the health-care system. One of the biggest barriers to pursuing academic medicine is leaner earnings compared with private practices.

All of the qualities dovetail with our new curriculum's emphasis on academic medicine and community health care. The new curriculum will debut in the 2020-21 school year.

Ratts: Dean Perlmutter and Rick Stanton recognized that if we are going to remain a top-10 medical school, we had to address medical school debt. The vast majority of our students, if not 100 percent, factor in finances when selecting medical schools. We don't want money to be a reason why a highly qualified student selects another medical school.

It always has been a top priority to graduate physicians with as little debt as possible. In four of the past five years, the School of Medicine has ranked second-lowest nationally in average medical school debt. This new scholarship program expands upon these existing efforts to reduce medical student debt.

Where does the money come from to support the $100 million investment?

Aagaard: The funding for the scholarship program and revised curriculum comes primarily from the School of Medicine, through new funding from its departments, and the university's affiliated training hospitals, Barnes-Jewish Hospital and St. Louis Children's Hospital. It comes from the operational funds of each entity and represents a commitment to support our academic mission.

It's different than the other medical schools that procured funding from a major donor. It's a statement about the values of the School of Medicine and its partner hospitals. That's not to say we don't want donors to commit to it, because we do.

How is this scholarship program sustainable in years to come?

Aagaard: Dean Perlmutter is committed to it over a 10-year period without knowing what the program's outcomes are. A decade provides an idea of the program's impact. We don't feel like we can judge its impact in a shorter time frame. But we will examine it closely.

We'll look at the students, both those who receive full or partial scholarships and those who do not. How does it influence student well-being? How does it affect career choices?

How have alumni reacted?

Ratts: Alumni cheered when we announced it at events. Medical student debt is a primary concern among alumni. Many of them have children pursuing medical careers who are facing extreme debt. They also mentor a huge number of medical students all around the country, and they feel strongly that we need to do something.

What has been the student response?

Aagaard: The incoming students are thrilled. The existing students have had a mixed response. There were a number of students who appreciate that the school is investing in students and addressing this problem. A number of students were personally disappointed

"Our intention is to recruit the best and brightest students who are passionate about improving health care in the community and across the globe."

– Valerie Ratts, MD

but understood. And then a group of students felt like we didn't factor their debt into the equation, and we've been looking at that.

Note that we just announced a one-time $3 million investment in current students to reduce debt. The program will provide scholarships to those students who are expected to graduate with greater than $150,000 debt and who have been identified to have financial need based on FAFSA.

How do you hope the scholarship program will affect student diversity?

Ratts: The program is being used to recruit the entire medical school class. A scholarship committee will award scholarships based on several factors, including financial need, merit or a combination of the two.

Our intention is to recruit the best and brightest students who are passionate about improving health care in the community and across the globe. We want to attract students who represent a diversity of racial, ethnic and socioeconomic status.

But we also value diversity of experience, for instance, non-traditional medical students. We want people who we think have the potential to change the face of medicine.

The scholarship program allocates $25 million to curriculum revision. How does tuition fit into the broader picture?

Aagaard: Curriculum renewal allows us to create a state-of-the-art curriculum that not only trains outstanding physicians, but also trains people in the skills they need to pursue their passions in science, education and advocacy.

We already have an outstanding curriculum in science. We are one of the best schools in the country at training physician-scientists in basic science, translational science and clinical science. We're building on that, thinking about other kinds of academic physicians, such as outstanding clinicians, physician-educators and physician-advocates.

The new curriculum encourages us to do creative things concerning community engagement, which is something that we feel has been lacking in our current curriculum. Community medicine and outreach have been considered more extracurricular activities. We plan to embed it in the curriculum to give it the importance it deserves, which allows us to do a better, more consistent job of teaching about social determinants of health and other critical topics. This will impact positively the kinds of students who may choose to come here.

Ratts: Curriculum renewal is looking at how we're going to educate the physician of the future. How they will practice medicine is going to be very different.

Previously, a medical student went to school and did two years of basic sciences. And why did they do that? To learn all the basic science you'd ever need to be a physician. That model doesn't work anymore.

All the information we need as physicians is truly at our fingertips, and we have to learn how to better access and apply it. The field's changing every day, and the knowledge is exploding. We're thinking about what students need to be successful 20, 30, 40 and 50 years from now. What is that skill set that will make them successful for what's coming in the future? And nobody completely knows, but we have ideas and we need to prepare students.

Aagaard: At no time in the past has there ever been so much knowledge accumulating so quickly. Physicians need to know how to integrate the technology into the medical practice. A big part of the physician's job has transitioned to translator of that information. This involves helping them to curate information sources, understand how the information applies to them and their unique situation, as well as helping to determine decisions that are right for them based on their values.

We've moved from a much more paternalistic model of care to a much more engaged, patient-centered one. That is a big part of what's different now, and it's a whole skill set medical trainees need to learn.

Interview condensed and edited by Kristina Sauerwein, senior medical sciences writer.

Staff members in a special metabolic kitchen prepare meals for patients enrolled in a diet and metabolism study.

MATT MILLER PHOTOS

Food *for* thought

Understanding obesity by examining nutrition and metabolism

BY GAIA REMEROWSKI

At nearly 250 pounds, Linda DeCosta had tried everything — and failed — to lose weight: prescription drugs, exercise programs, dieting. She had even considered bariatric surgery, but insurance wouldn't cover it.

"I was almost starving myself," DeCosta said. "Our family doesn't eat out a lot. I don't cook a lot of fried foods. I didn't know what I was doing wrong."

Diagnosed with asthma and high blood pressure, her health was suffering. Even the short walk to the bus stop was a struggle.

By the time DeCosta saw the recruitment email for an obesity study looking at metabolism and diet, she had about given up. Motivated by her husband and three children, she decided to enroll. "I figured I won't be long for this world unless I do something to change this."

Intensive effort

"Obesity is a major public health problem," said Samuel Klein, MD, the study's principal investigator. "It's abnormal to be lean in this country."

Klein, the William H. Danforth Professor of Medicine and Nutritional Science, is an internationally renowned expert with more than 30 years of experience studying nutrition, metabolism, obesity and weight loss.

Obesity is linked to a slew of metabolic problems, such as high blood triglycerides, high blood pressure and insulin resistance. Many people with obesity develop chronic conditions such as diabetes, heart disease, fatty liver disease, arthritis, cancer and lung disease.

"Obesity is caused by eating more calories than you expend over a long period of time and storing those excess calories as body fat; excess body fat causes dysfunction in nearly every organ system in the body," said Klein, who also directs the Center for Human Nutrition at Washington University.

Klein's research program combines basic and clinical science to examine multiple organ systems simultaneously. Because obesity affects biological function in so many different organs, his group is one of the most collaborative on campus — joining together molecular biologists, physiologists, endocrinologists, cardiologists, immunologists, neurologists, radiologists and psychologists. Nearly 50 clinicians, researchers, technicians, nurses and recruiters collaborate on the team. (For a list of primary collaborators, see outlook.wustl.edu/foodforthought.)

Samuel Klein, MD, (right) watches as Adewole Okunade, PhD, performs a chromatography analysis of blood plasma. Klein's lab studies nutrition and metabolism in health and disease.

"To address the complex issues of obesity, you need to conduct research that involves a multi-organ system approach, which requires collaboration among investigators with different expertise," Klein said. "This kind of research is possible at Washington University because of the collegiality of our faculty and breadth of scientific expertise. I am fortunate to be able to work with so many talented people."

Losing weight comes down to simple math: people must burn more calories than they consume, so that their bodies use the excess fat as fuel. But it's not as easy as it sounds, Klein said, because weight loss is influenced by many complex factors, including genetics, birth weight, brain chemicals, cultural and work environment, food availability and marketing, physical activity, stress and the pleasure of eating.

For a person who is obese and consuming 3,000 calories a day, that may mean cutting daily intake to 1,500 calories indefinitely. "How do you get people to eat fewer calories than they normally consume and maintain that low-calorie intake for the rest of their lives? Weight loss maintenance is the Achilles' heel of weight management," Klein said.

Also, eating a healthy diet is complicated because different people respond differently to the same food. A serving of potato chips may cause blood sugar to spike in one person, and not another. There is likely no "one-size-fits-all diet." While the total calories consumed still matters, the composition of those calories may need to vary by individual. This is why personalizing nutrition is the logical next step in fighting obesity and its complications, Klein said. But more research is needed before useful recommendations can be made.

Approximately 10% of those who are obese do not develop metabolic abnormalities. Klein is seeking to understand why some people with obesity are protected from the adverse health effects of excessive body fat. In one study, Klein found that people with metabolically healthy obesity remained healthy even after gaining 6% body weight, whereas those who already had metabolic problems got worse.

The metabolically healthy participants were able to store fat in a healthier way, without impairing their metabolism, unlike in the metabolically unhealthy individuals.

Klein's current diet and metabolism study is comparing three groups: metabolically healthy people who are lean; metabolically healthy people with obesity; and metabolically

unhealthy people with obesity (those with issues such as insulin resistance, high liver fat and high blood triglycerides).

Klein and his collaborators will follow these individuals for several years, particularly those who are obese and metabolically normal, to see if their metabolism remains normal.

The metabolically unhealthy individuals with obesity are randomized to follow one of three popular diets: the low-carb ketogenic or "Keto" diet; the Mediterranean diet, emphasizing fruits and vegetables, whole grains and fish; or a very low-fat, plant-based diet. The plan is to see if these diets have different effects on metabolic and health outcomes.

This research is labor-intensive and involves a team of skilled research coordinators, research nurses and nurse practitioners, dietitians and recruiters. Every week, staff members working in a special metabolic kitchen at the Medical Center's Clinical and Translational Research Unit carefully plan, prepare and package meals for the metabolically unhealthy participants.

The diet phase of the study lasts over a year and requires a big commitment from participants, who undergo weekly visits with occasional overnight stays. Tests include assessing insulin action; examining cell metabolism and inflammation from fat and muscle biopsies; measuring body fat content and distribution, as well as brain function through MRI and PET scans; studying the gut microbiome from stool samples; profiling the blood's metabolites over 24 hours and assessing cardiorespiratory fitness.

Following individuals for long time periods with controlled dietary intake, evaluating biological function in multiple organs, and involving so many collaborators is unique in the nutritional research field.

"Sam Klein is one of the finest clinical and translational investigators in the country, and has built a unique, multidisciplinary obesity research program at Washington University," said David Brenner, MD, vice chancellor for health sciences at the University of California, San Diego, where Klein has a joint appointment. "He has made seminal contributions to our understanding of the mechanisms responsible for the metabolic abnormalities associated with obesity and the profound therapeutic effects of decreasing body fat in people with obesity."

This kind of intensive research is also costly. "Sophisticated translational research conducted in people is expensive and requires substantial resources and personnel," Klein said. "We are

Obesity and the body

Obesity affects the entire body. Klein's group is studying many aspects of this process.

BRAIN

The "reward" system in the brain is likely altered in many people with obesity, which can lead to increased food intake to get a pleasure response.

HEART

Heart blood vessel health is often compromised in those with obesity, leading to an increased risk of cardiovascular disease.

LIVER

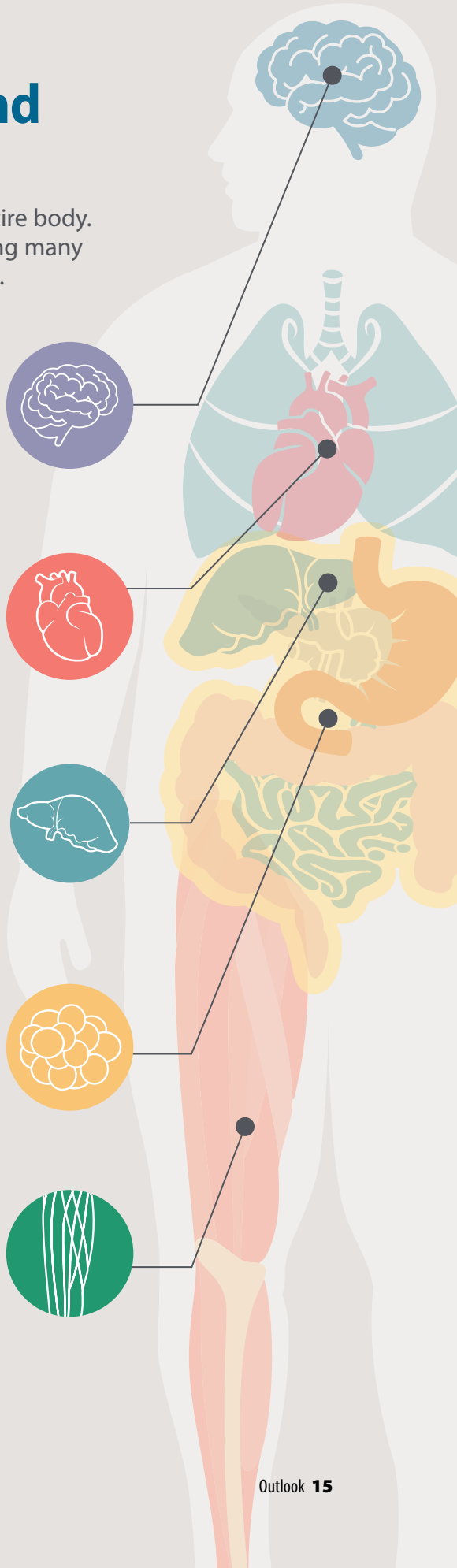
Increased fat inside of liver cells is common in those with obesity and is associated with metabolic abnormalities, such as insulin resistance and heart disease, and can progress to cirrhosis.

FAT

The increased distribution of fat in the abdomen, increased inflammation in adipose tissue and increased adipose tissue fibrosis are associated with poor metabolic health.

MUSCLE

Muscle helps clear glucose from the blood, a process that often goes awry in obesity and leads to high blood sugar.



Liquid nitrogen is used to preserve a fat biopsy sample from a study participant. Klein's group studies the role of fat, a highly metabolically active organ, in obesity.

fortunate that Washington University has made the commitment to advance this kind of translational research that begins in cell systems but must ultimately lead to costly but necessary human studies."

Philanthropy is also crucial, he adds, as government agencies do not provide adequate funding for expensive clinical research. The Pershing Square Foundation has made a commitment to advancing research in obesity and funded the study looking at diet and metabolism. Klein also receives funding from other private organizations, including the Robert C. and Veronica Atkins Foundation. In 2003, Klein led the first randomized, controlled trial demonstrating that the Atkins diet produces greater short-term weight loss than conventional diets in those with obesity.

A broad range of research

One-third of U.S. adults and nearly three-quarters of people with obesity have nonalcoholic fatty liver disease, defined as an increase in liver triglycerides, which can progress to cirrhosis and is a leading cause of liver transplantation. Klein's group is examining the connection between excess fat in the liver and the metabolic abnormalities associated with liver fat accumulation.

Once considered to be an inert tissue, fat is now known to be a highly active organ that secretes proteins and lipids, affecting metabolic function in other organs. To assess fat distribution in the liver and around internal organs, the Center for Clinical Imaging Research assists with MRI scans. Pear-shaped people with fat accumulation in the lower body tend to have fewer metabolic abnormalities than apple-shaped individuals, who carry the majority of their fat in their abdomens. Klein's group is trying to understand why these differences occur.

To study the growth of fat cells, participants in some of Klein's studies drink heavy water containing deuterium, an isotope that is twice as heavy as hydrogen. Researchers track the heavy water molecules as they are incorporated into newly made fat cells and into fat cell lipids. This allows the team to evaluate the rate at which new fat cells are made and the importance of fat cell dynamics in regulating metabolic health.

Metabolically abnormal individuals with obesity tend to have more inflammation in their fat tissue than people with obesity who are metabolically healthy. This chronic inflammation is believed to increase the risk of cardiovascular disease and diabetes. Immunologists are looking at fat tissue gene expression and tracking inflammatory cells to understand how inflammation in obesity contributes to chronic diseases.

Interested in becoming a study participant?

CALL 314-273-0300 or 314-747-2627 or **EMAIL** ashley.roberts@wustl.edu or j.sonnenschein@wustl.edu.

In people with obesity, the structure and function of certain brain areas differ from people who are lean. And people with obesity and insulin resistance are at increased risk of developing Alzheimer's disease. Radiologists and psychologists are using functional MRI and PET scanning to study the effects of diet and weight loss on brain structure and the pleasure-inducing dopamine response to food.

As obesity is known to increase heart disease risk, Klein is partnering with cardiologists to look at the health of the blood vessels, as well as the effects of diet on the heart. In collaboration with neurologists, he is also looking at the link between sleep deprivation and sleep quality on body metabolism.

One of Klein's most seminal findings provides hope for those struggling with weight loss: Losing even 5% of one's body weight can significantly improve metabolic health. "Moderate weight loss is achievable in many people and is clinically important," Klein said. "It is important to realize that obesity is a chronic, lifelong disease, so helping patients make small, progressive changes in eating behavior for life is the goal."

How did we get here?

Unhealthy lifestyle behaviors are the underlying reason for more than half of chronic diseases, such as obesity, diabetes, heart disease and cancer, Klein points out. But willpower, he said, is often not the issue and cannot solve this problem.

"Many highly motivated people who are obese are successful in their professional lives, but they are unable to make the lifestyle changes needed to lose weight and maintain that loss," he said.

The human race has undergone dramatic changes in lifestyle in a very short time, Klein said. We evolved to avoid starvation by storing the excess calories we consume as fat. But we no longer have to burn energy to find food — we have easy access to a large variety of palatable foods and we have developed many labor-saving devices that contribute to a sedentary lifestyle.

It is now very easy to consume more calories than we need to maintain a healthy weight. "Within a blink of time in Earth's history, modern society has completely overcome our evolutionary biology," Klein said. "We have not adequately adapted to this dramatic change in our environment." The genes once meant to help us survive are now working against us, he added.

Primary care changes

When agreeing to participate in the study, DeCosta figured she would end up in the metabolically normal obese group. After all, her yearly blood work had never revealed elevated blood glucose or blood lipid levels. Klein's screening showed otherwise.

"I found out I had a predisposition for type 2 diabetes and I was showing signs of fatty liver disease," DeCosta said. By not doing more in-depth testing, DeCosta said she felt primary care doctors are doing patients a disservice.

Most primary care physicians rely on an A1C test, an indicator of blood glucose levels over time, to determine a patient's risk of developing diabetes. A better predictor is an oral glucose tolerance test, where the patient drinks a glucose solution and has a blood test two hours later. While not costly, the test is time-consuming and not often prescribed.

Doctors need to become more involved in preventing excessive weight gain and initiating effective obesity strategies for their patients, Klein said. This is where things like medication, tailored diets and even bariatric surgery can come in.

"Less than 2% of patients who are eligible for prescription weight-loss drugs actually receive them," Klein said. Bariatric surgery is the most effective available therapy for treating obesity and its complications but it is infrequently recommended by doctors.

Ultimately, we need more research to better understand why obesity causes so many diseases and how we can individualize diet therapy for each patient to get the best health outcomes.

After three months on the Keto diet, DeCosta is down more than 30 pounds.

DeCosta says she is now losing weight for herself. Recently, on her way to catch the bus to one of her study visits, she realized she was no longer out of breath.

Gaia Remerowski is a senior content strategist in Medical Public Affairs.

Gordon Smith, PhD, measures study participant Linda DeCosta's resting metabolic rate. DeCosta is participating in one of Klein's diet and metabolism studies.

MATT MILLER

Collective power

Through a crowd-sourced network, Bowman seeks cures for diseases — including his own

BY JULIA EVANGELOU STRAIT

When Greg Bowman was in second grade, he began to have trouble reading the board in his classroom. Playing goalie for his soccer team also became difficult. Over the following year, he lost most of his central vision due to an inherited genetic disorder, a form of juvenile macular degeneration.

"It gradually dawned on me that this would have a severe impact on my future life, with where I should live and work," Bowman said. "But in retrospect, my parents handled it extremely well. I never felt like damaged goods or like I shouldn't push myself to achieve as much as I could."

Passionate about science, Bowman realized that experimental biology is not very accessible to those who are visually impaired. "Essentially, I see at low resolution, mostly with my peripheral vision," he said. "I can navigate hallways and laboratories, but I can't read the small dial on a pipette."

So, Bowman found another route into the field: Computer science could be applied to biological problems and, with computers, he could zoom in to 16 times magnification.

Bowman, PhD, now an associate professor of biochemistry and molecular biophysics at the School of Medicine, is legally blind; he leads one of the largest crowd-sourced computational biology projects in the world.

Though legally blind, Greg Bowman, PhD, can see with his peripheral vision and is able to read computer screens at high magnification. "One of the things that draws me to studying protein dynamics is that it's something nobody can see," said Greg Bowman, PhD, "so in some ways the playing field is a little leveled for me."

The effort is aimed at understanding how proteins — the raw materials that make up our bodies — fold into their proper shapes to keep our bodies running properly. Proteins are vital cellular machinery, and understanding how they assemble and function — or malfunction — could shed light on many of the most vexing problems in medical science.

The project is called Folding@home. It relies on the power of tens of thousands of home computers to perform the complex calculations required to simulate protein dynamics. Volunteers from all over the world install a program that runs those calculations when a computer otherwise would sit idle. Often motivated by personal interest, the participants get to select their area of contribution, whether it's boosting cancer understanding, preventing Alzheimer's disease or fighting antibiotic resistance, among others.

With this networked computing power, Folding@home is, essentially, one of the world's largest supercomputers.

"There are some traditional supercomputing folks who might take issue with that characterization," Bowman said with a laugh. "Rather than a single massive machine, Folding@home is a distributed computing network. But in terms of raw computing power — the sheer number of calculations it can perform per second — it's on par with the world's biggest supercomputers."

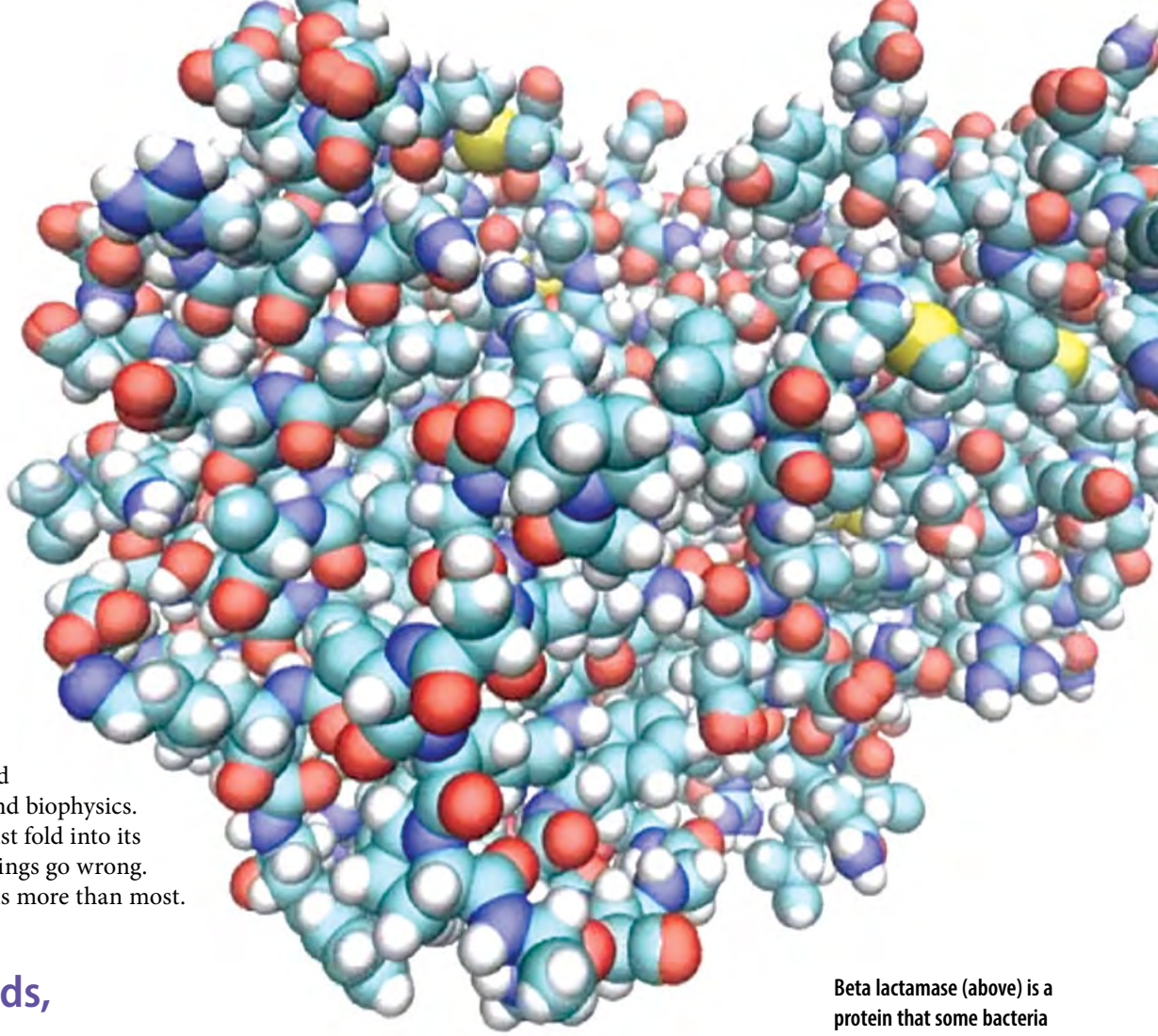
With Folding@home, Bowman and his colleagues are zooming in on proteins much more than 16 times. Indeed, they are getting as close as physically possible — down to the atomic level. Many important biological processes that proteins perform take place over milliseconds to a few seconds.

"To model just one millisecond of folding, even for an average-size protein, on a top-of-the-line MacBook Pro, it would take something like 500 years," Bowman said. "But with Folding@home, we can split these problems into many independent chunks. We can send them to 1,000 people at the same time. Running those calculations in parallel, we can take these problems that would have taken 500 years and instead solve them in six months."

Bowman got started on this work in the lab of Folding@home founder Vijay Pande, PhD, of Stanford University. After heading the project for 18 years, Pande chose Bowman, who completed a doctoral degree and postdoctoral research at Stanford, to take over leadership.

MATT MILLER

Greg Bowman's team listens to a presentation at their lab meeting. The team is trying to unravel the role of protein dynamics in health and disease.



Beta lactamase (above) is a protein that some bacteria deploy to protect themselves from antibiotics. By watching beta lactamase in motion, researchers have found "cryptic pockets," weak points in the protein that could be targeted by drugs. Cryptic pockets only reveal themselves when the protein is moving.

"Greg has a unique combination of skills," Pande said. "He has the technical chops to lead this complex project, and he has the people skills to manage the distributed nature of it, especially the fact that it involves so many different kinds of people — scientists and nonscientists alike. Greg also has great vision for the future of this project."

Folding@home's massive computing capacity is crucial to understanding protein behavior, a problem Bowman calls a classic grand challenge in biochemistry and biophysics. To do its work, a protein must fold into its proper form. If it doesn't, things go wrong.

Bowman understands this more than most.

A protein misfolds, then blindness

In childhood, Bowman's vision loss was attributed to Stargardt disease, a form of juvenile macular degeneration caused when a protein that removes waste from retina cells doesn't fold properly and can't do its job. As a result, light-sensing cells in the retina become overwhelmed with waste and die, causing loss of central vision.

Later, with the advent of genetic testing, a basic microarray test did not find mutations in either of Bowman's two copies of the gene that causes Stargardt's disease — called ABCA4.

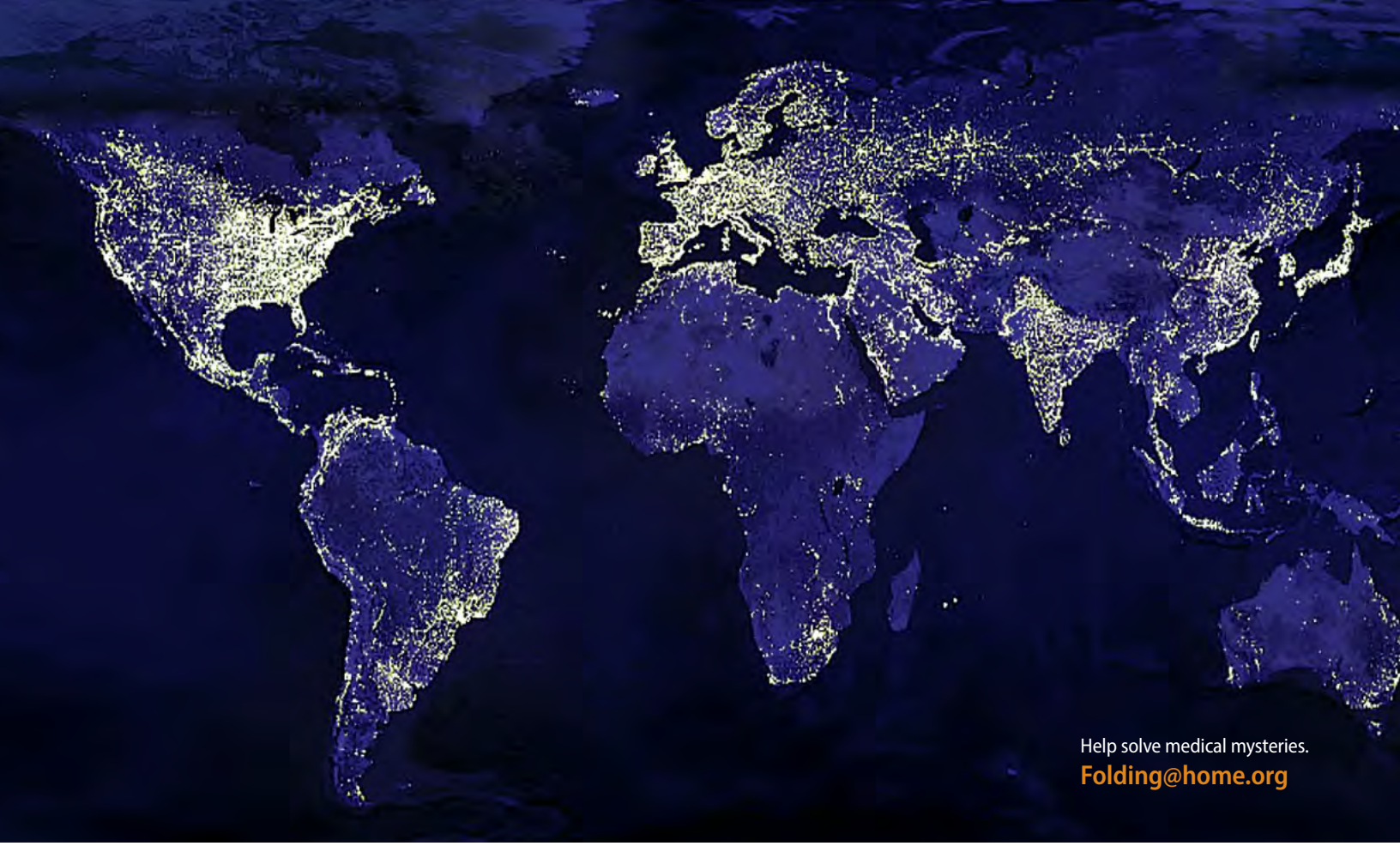
"As we've learned to classify diseases based on genetics rather than symptoms, my doctors backed off that diagnosis, no longer sure it was appropriate," he said. "But it was an obvious candidate gene. Mutations in the protein ABCA4 are likely to interfere with its job pumping waste products out of retinal cells. We did sequencing at the time to look for mutations but didn't find anything."

More recently, sequencing technology has improved. New vision-related sequencing panels can identify mutations in what are called splice sites of the genes, which are difficult to analyze due to their repeating sequence patterns.

"In a new sequencing panel, three of the four mutations that popped up were in ABCA4," Bowman said. "So, these are smoking guns, if you will. We are now looking into having sequencing done for my parents and my brother. Neither of our parents has any vision issues, but my brother and I do. We should be able to see what mutations we have in common and where we differ."

Now that Bowman has a lead on what mutations are likely to have caused his own vision loss, he is interested in harnessing Folding@home to see what is going wrong with the protein and whether there is some route to fix it. Currently, there is no available structural information about ABCA4.

"We have found some related proteins that we hope to use as a template for trying to guess the structure of ABCA4, and then we can run simulations of both the normal protein and the mutated forms of the protein to see how they change," he said. "Even if I can't fix my own vision issue, it would be really cool to contribute to the fundamental base of knowledge that could help researchers do that for future people who come along with these genetic mutations."



This map shows active Folding@home users at a single point in time.

Studying at the atomic level

Because Bowman studies proteins at their most elemental level — looking at changes in individual atoms — his team can study a surprisingly wide array of biological problems. In addition to the early work on ABCA4, his lab also has well-established projects looking at antibiotic resistance in bacteria, proteins that contribute to Alzheimer's disease and molecules involved in the extreme virulence of the Ebola virus.

"We're in the nice position of having, essentially, a very rare microscope," Bowman said. "Folding@home and all of the simulation tools and analysis tools that we've developed let us jump into a lot of different areas at once. We're asking a lot of very basic science questions — how do things work in general, and those answers apply in many different contexts."

Bowman envisions a future where Folding@home serves as a starting point for precision medicine, studying specific mutations in proteins and developing therapies to fix them. Right now, scientists often have only one structure of any given protein to study, if any structural information is available at all.

Proteins largely have been studied using X-ray crystallography. In this technique, proteins are treated with chemicals, artificially freezing them into a particular shape, and then viewed by bouncing an X-ray beam off of them. However, this only gives static pictures of proteins in their "crystal" form. For example, beta lactamase, a protein that some bacteria deploy to protect themselves from antibiotics such as penicillin, has a well-documented, long-studied crystal structure. But that structure only represents a single snapshot of beta-lactamase at one moment in time.

Proteins often consist of hundreds or thousands of amino acids forming long chains that continuously bounce around in all directions.

"That snapshot contains valuable information," Bowman said. "But it's kind of like seeing a picture of a construction vehicle in a parking lot and trying to guess what it does. Really, what you would like is to watch this thing move around and see how it works together with other machinery to, say, build a building. We're interested in watching how every atom in a protein moves — as it's being assembled for the first time and as it goes about its jobs. And one genetic mutation changes maybe a dozen atoms out of thousands. We want to understand what that does to the entire protein."

Fixing misfolds with new drugs

Among several projects, Bowman's lab is using Folding@home to seek new drugs to combat antibiotic resistance. Watching the movement of beta lactamase, for example, already has revealed what Bowman calls "cryptic pockets," weak points in the protein that could be targeted by drugs but that are not visible in the long-studied snapshot of this protein. The cryptic pockets only reveal themselves when the protein is moving.

Bowman also is using this rare microscope to study Alzheimer's disease. A protein called APOE is responsible for transporting cholesterol through the body. The normal version of this protein is called APOE3. For reasons not yet known, a variant called APOE4 is associated with an increased risk of developing Alzheimer's disease with age.

"Having one or two copies of APOE4 increases a person's risk of developing Alzheimer's anywhere from 3- to 15-fold," Bowman said. "But APOE3 and APOE4 differ by only one amino acid — one protein building block out of 300 that make up the entire protein. We are trying to understand why one version of the protein is normal and the other is neurotoxic even though their structures are so similar. It's a challenging problem to study because APOE is an extremely dynamic, floppy protein. It's been hard to identify its structure using typical techniques, such as crystallography.

"If we can understand these structural differences, hypothetically, we can start developing small molecules that push neurotoxic APOE4, nudging it to look more like the neutral APOE3 variant," he said. "And if we succeed in doing that, we might have a useful therapeutic. Rather than a typical 'inhibitor' drug, this would be a new type of compound that some people are calling a structure-corrector."

Building on the discovery of cryptic pockets in beta lactamase, the researchers also are looking for weak points in Ebola virus, a deadly viral infection that causes vomiting, diarrhea and internal bleeding. On average, the disease is fatal in about half of all cases, with death rates ranging from 25 to 90% in past outbreaks.

Researchers are working to develop an Ebola vaccine or other therapies, but so far, the best treatment is intensive hospital care, including intravenous fluids and oxygen.

"Despite its virulence, Ebola has only seven proteins in its genome," Bowman said. "These proteins interact with each other and with the molecules in our cells to hijack the infected person's cellular machinery to reproduce the virus and suppress the immune response."

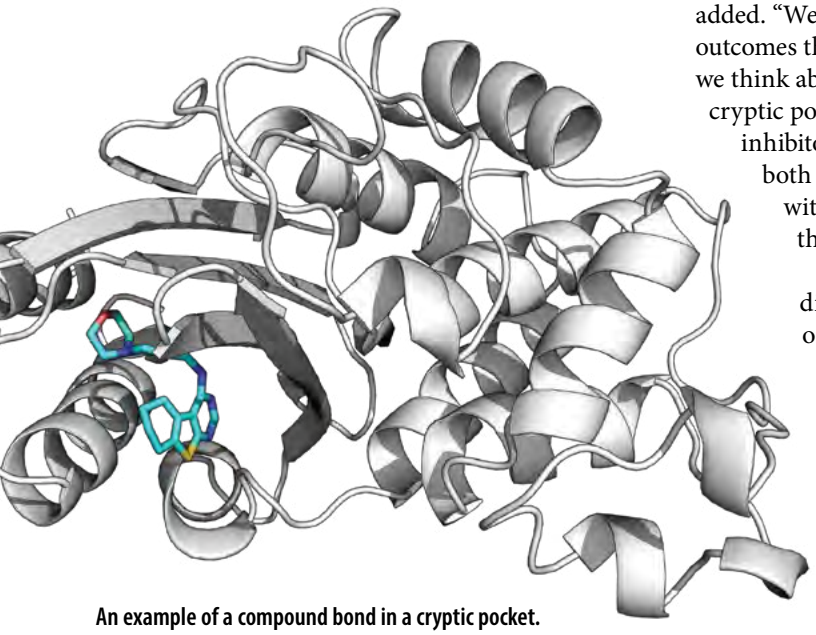
Conventional wisdom says these types of protein and RNA interactions can't be targeted with conventional drugs because they don't offer deep pockets where a small molecule inhibitor would fit to block their activity.

"If we could knock out some of these protein-protein interactions, how devastating would that be for the virus? That's the kind of question we're interested in," Bowman said.

"I think this is a really exciting time," Bowman added. "We're starting to see some tangible outcomes that have the potential to impact how we think about diseases. We've already identified cryptic pockets and developed small molecule inhibitors for those pockets that interfere with both beta lactamase antibiotic resistance and with one of the protein-protein interactions that makes Ebola so deadly."

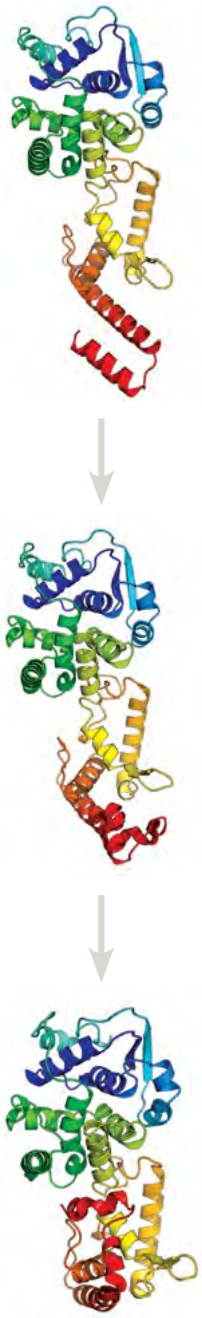
As Bowman sees the world a bit differently than most, Folding@home offers scientists a different look at long-studied proteins, revealing solutions to biological problems that might otherwise remain hidden from view.

Julia Evangelou Strait is a senior medical sciences writer in Medical Public Affairs.



FOLDING@HOME

An example of a compound bond in a cryptic pocket.



Nucleoprotein from Ebola virus in motion.

Servant leader

Native St. Louisan Lee Kling is thinking about his city's needs now and in the future.

BY CHANNING SUHL

Throughout the St. Louis region, underserved and low-income patients cannot obtain quality health care. Many live in poverty without access to medical services, or even food. Dedicated community leader Lee Kling has seen firsthand how economic disparities create lifelong challenges for so many people.

In response to those challenges, Kling, a St. Louis native and president of The Kling Company, has committed a multimillion personal bequest to the Department of Medicine toward research, teaching and patient care, specifically to benefit the underserved.

While a board member on The Foundation for Barnes-Jewish Hospital, Kling learned that many gifts and grants are restricted for research or other specific purposes. He also heard from doctors about the myriad unmet societal needs. Important community programs often go unfunded and, as a result, must be sidelined. Kling felt compelled by family tradition and the example of others to help address those needs.

"It's an obligation I have. Life's been good to me, and I want to give back," Kling said. "I'm passionate about addressing health-care disparities in the St. Louis community."

The Department of Medicine was a natural choice for Kling, who has a trusted friendship with Victoria J. Fraser, MD, department chair and the Adolphus Busch Professor of Medicine.

"Lee and his family members are incredibly charitable and caring," Fraser said. "They have been fascinated by the breadth and depth of diseases addressed by internal medicine. This gift will accelerate and improve treatments for those who don't have access to health care and modern research."

MATT MILLER

Lee Kling and Victoria Fraser, MD

Humanitarian legacy

Kling is the son of the late philanthropist and community leader S. Lee Kling and Rosie Kling. His parents set a strong model for and a high value on supporting the community. S. Lee Kling was a civic, philanthropic and community leader. As board chairman of The Foundation for Barnes-Jewish Hospital, he helped fund the Goldfarb School of Nursing and the Kling Center for Proton Therapy.

Lee Kling, 55, wanted to contribute expressly to the programs Fraser highlighted that help the underserved and secure those programs for the future. While somewhat atypical for people in their 50s to make estate bequests, planned giving advisers say that today's donors are trending younger.

This bequest is the latest in a series of significant gifts from his family foundation or from broader contribution efforts spearheaded by Kling. "I've been privileged to see tremendous generosity from others; I want to emulate that spirit," Kling noted. Previously, he has donated expendable research funds to Fraser and Anthony Lubniewski, MD, in the Department of Ophthalmology and Visual Sciences and fellowships for the Department of Medicine.

Kling's history of volunteerism includes serving on the St. Louis Lambert Airport Commission, as well as stints as a National Council Member for the School of Medicine, board president at Food Outreach, board member at Variety, the Children's Charity of St. Louis, and trustee of the Wyman Center, which empowers teens from economically disadvantaged circumstances to lead successful lives and build strong communities, among many other volunteer roles.

"This gift will accelerate and improve treatments for those who don't have access to health care and modern research."

– Victoria J. Fraser, MD

"Like any city, St. Louis has challenges. Unlike some, St. Louis also has the strength, energy and human capital to address those challenges," Kling said. "Our city has a rich culture and history combined with tremendous leadership in science and business. In particular, people come from all over the world to access our outstanding medical experts.

"I believe in this city and I want to do what I can to ensure a healthy future for all."

Student guide Tanvi Subramanian, MD '19, far right, leads Class of 1999 members and guests on a Medical Campus tour.

Home again

Rediscovering campus, renewing friendships

BY CHANNING SUHL

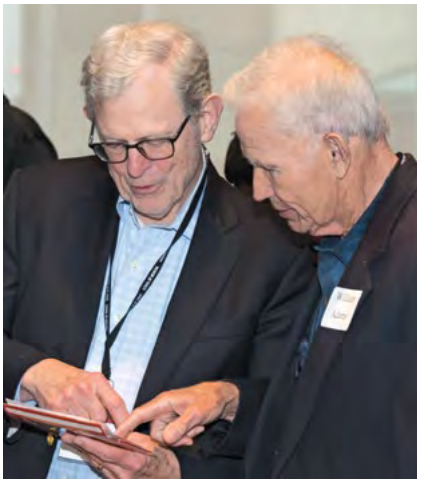
Medical school alumni came back to campus April 4–7 for Reunion 2019 — a chance to celebrate milestones, see the growing campus and enjoy St. Louis attractions.

The annual spring event pays tribute to the school's storied history, while providing an up-close look at the innovation shaping medicine.

David H. Perlmutter, MD, executive vice chancellor for medical affairs and George and Carol Bauer Dean of the School of Medicine, outlined initiatives to modernize the curriculum and reduce student debt. The dean also discussed research on personalized medicine and aging.

The weekend culminated with a dinner honoring the 2019 Reunion Award recipients (see page 32) and the newest alumni, the Class of 2019.

Four attending members from the Class of 1954: Norman Leffler, Bob Parsons, Robert Mendelsohn and Donald Rucknagel.



Class of 1969 members Richard Wyatt and William Adams look at photographs together.

Pat Penkoske, Natalia Kozak and Margaret Kitchell, all members of the Class of 1974, mingle at the class dinner.

Andrew B. Landes, MD '88, Felice Heller, MD '89, and Rebecca Walker, MD '89, at the Friday class dinner.

From left to right: Adewale Adeniran, Daniel Wattson and Monique Farrow, all MD '09.

Dean David Perlmutter, MD, greets Chuck Norland, MD '59.

Reunion by the numbers

- **38 states**
  Alumni traveled from 38 states and Puerto Rico
- **523 guests**
  (alumni, guests, students and faculty) joined the celebration
- **46% attendance**
  The Class of 1969 had the highest percentage with 32 attendees
- **57% class giving**
  The Class of 1954 had the highest giving: more than $3.2 million dollars
- **Record setters**
  The Class of 1974 set a record for 45th Reunion attendance with 31 classmates

View more Reunion photos at outlook.wustl.edu/2019galleries.

SAVE THE DATE

Reunion 2020

April 30–May 3

The following classes will celebrate in 2020:

Emeritus	1985
1955	1990
1960	1995
1965	2000
1970	2005
1975	2010
1980	2015

Front row, from left: Ann Randolph Flipse, Kimberly S. Quayle and Diana L. Gray. Back row: Andrew C. Chan, David A. Hunstad, Mary V. Mason and William E. Klunk.

Alumni Association honors faculty, graduates, former house staff

The Washington University Medical Center Alumni Association annually honors a select group of alumni, faculty members and former residents and fellows for professional achievements, community service and dedication to the School of Medicine. The four awards — Alumni Achievement, Faculty Achievement, Resident/Fellow Alumni Achievement and Distinguished Service — are presented at Reunion each April.

The 2019 honorees

Alumni Achievement Award

Andrew C. Chan, MD/PhD '86, HS '89 (reunion year '84)

Ann Randolph Flipse, MD '59, HS '61

Gurjit K. Khurana Hershey, MD/PhD '92, HS '97 (reunion year '89) — deferred acceptance until 2020

William E. Klunk, MD/PhD '84

Mary V. Mason, MD '94, HS '98, MBA '99

Faculty Achievement Awards

David A. Hunstad, MD '95, HS '03

Kimberly S. Quayle, MD '88, HS '94

Distinguished Service Award

Diana L. Gray, MD, HS '90

To submit nominees for the 2020 awards: outlook.wustl.edu/2020awards.

1950s

William Brydon, MD '56, and **Doris Ann Weaver Brydon, PT '55,** celebrated their 65th wedding anniversary June 27, 2019.

Sidney Richman, MD '58, is working part time as a cardiac consultant after a successful career. He was among the very first cardiologists at Harvard Medical Service to perform coronary angiography. Later, he was in private practice for many years in Connecticut, followed by serving as chief of cardiology at Mt. Sinai Hospital in Hartford, and then as chief of cardiology at West Palm Beach VA Medical Center in Riviera Beach, Fla. After retirement, he joined a cardiology group in Palm Beach County, Fla.

1960s

Martin Fischer, MD '61, and his wife, Mary Jean, celebrated their 60th wedding anniversary in June.

Hunter Heath, MD '68, moved with his wife, Glenna, to Indianapolis in summer 2019. Retired 12 years, he enjoys charitable work with a social service agency, spends one day per week at Indiana University School of Medicine, continues to improve his guitar skills, and publishes aviation articles after deciding to no longer fly. He reports "gratitude for the experiences and accomplishments undreamed of in youth."

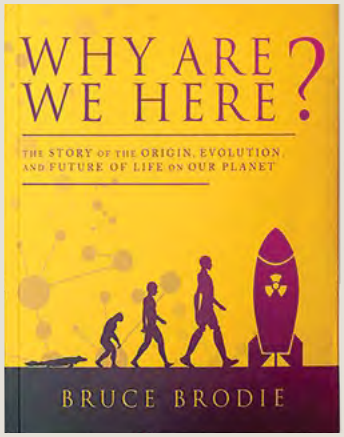
1970s

Toby Simon, MD '70, recently became a senior medical director for CSL Plasma, a subsidiary of the global biopharmaceutical company, CSL Behring. His home is in Albuquerque, N.M.

Lincoln L. Berland, MD, '75, is a radiologist and professor emeritus at the University of Alabama at Birmingham and is on the American College of Radiology Board of Chancellors. He was awarded a Gold Medal in March 2019 from the Society of Abdominal Radiology. He and **Nancy Berland, PhD, '75,** have been married for 47 years.

Charles Carrasco, MD '77, has retired and enjoys travel, fly fishing, golf and gardening. He also works several days per month at a free clinic.

Marcy Hipskind, MD '78, was named Family Physician of the Year for 2019 by the Washington Academy of Family Physicians. The award is given annually to a family physician who exemplifies a compassionate commitment to improving the health and well-being of people and communities throughout Washington state. Hipskind recently retired as president and CEO of Family Care Network, the largest single-specialty group practice in Whatcom County, Wash. She resides in Bellingham, Wash.



Bruce Brodie, MD '70, recently published a book, titled "Why Are We Here: The Story of the Origin, Evolution and Future of Life on Our Planet." He began the project after retiring in 2011 from a busy cardiology practice in Greensboro, N.C. He also was a clinical professor of medicine at the University of North Carolina, an interventional cardiologist and co-founder and past chairman of the LeBauer-Brodie Center for Cardiovascular Research and Education. The book culminates a journey that attempts to understand how we got here, how our evolutionary past has shaped the way we are, and where we might be headed. More information at brucerogersbrodie.com.

1980s

Edward Fry, MD '83, serves many roles: as a cardiologist at St. Vincent Medical Group in Indianapolis; as chair of the Cardiovascular Service Line, St. Vincent Health, a statewide, 20-hospital system in Indiana that is part of Ascension Health; as chair of the National Cardiovascular Service Line, Ascension Health, a 154-hospital, not-for-profit Catholic health system in 18 states; and as trustee for the American College of Cardiology.

Heather Gantzer, MD '85, became chair-elect, Board of Regents, American College of Physicians (ACP), in April 2019. ACP is the professional medical society of internists with more than 164,000 members worldwide.

M. Victoria Marx, HS '88, serves on the American Board of Radiology Board of Trustees and was president of the Society for Interventional Radiology in 2018-19. She is also on the faculty at Keck Medicine of the University of Southern California and maintains an active clinical practice in addition to administrative and educational roles.

1990s

Grant Hoekzema, MD '92, FAAFP, Department of Family Medicine chairman of Mercy Hospital St. Louis, has been named chair-elect of the Accreditation Council for Graduate Medical Education Review Committee for Family Medicine.

Capt. Gregory Gorman, MD '97, member of the Medical Corps, U.S. Navy, was named executive director of the Defense Health Board, a federal advisory committee to the Secretary of Defense on policies, programs and quality of care pertaining to the Military Health System. He continues part-time clinical work in pediatric nephrology at Walter Reed Medical Center and the National Institutes of Health (NIH) Clinical Center. Greg and his wife, **Elizabeth "Beth" Hisle-Gorman, SW '97,** also are Washington University parents with their son, John, enrolled as an undergraduate.

Michael Finley, PhD '98, recently was promoted to senior principal scientist at Janssen Research & Development. He heads a team of assay development and screening scientists, identifying new small molecule leads for a variety of therapeutic indications, including oncology, immunology, metabolism and neuroscience.

Amanda F. Cashen, MD '99, associate professor of medicine at WUSM, has been named executive chair of the university's Institutional Review Board, the multidisciplinary group that reviews and approves protocols for research studies that involve human subjects. The group is responsible for protecting the rights and welfare of anyone participating in a research study conducted by Washington University investigators.

2000s

Kimberly Dache Masker, OT '00, was named education division director of the American Society of Hand Therapists in October 2018. She is serving a two-year term.

Julie K. Schwarz, MD/PhD '04, HS '09, has been appointed vice chair for research in the WUSM Department of Radiation Oncology.

Andwele Jolly, LA '02, PT '05, a business director in the Department of Medicine, has been named vice chairperson for the Missouri Foundation for Health. Jolly will serve as the vice chairperson for the foundation's Board of Directors' Executive Committee.

Jimmy Kimmel officiates the wedding as David Spade offers a toast.

Celebrities crash alumna's wedding

Kate Baker, OT '10, got the surprise of a lifetime when the Jimmy Kimmel Live! show — joined by celebrities David Spade and Celine Dion — crashed her April 5 wedding to Jason Brosseau.

Celine Dion serenades the couple.

It all started when Baker and Brousseau — both Colorado-based Air Force majors — learned that friends had submitted their names into a drawing to win a Las Vegas wedding. Planet Hollywood Resort & Casino called to say the couple won — and that the wedding would take place in five days.

The wedding began in traditional fashion: Baker's dad walked her down the aisle and the couple exchanged rings. Then, Jimmy Kimmel spontaneously video-conferenced into the ceremony, taking over for the officiant, and ultimately pronouncing them husband and wife. David Spade showed up, offering a toast to the couple.

"Things seemed to finally be winding down when the chapel doors busted open and standing there in a sea of dry fog was Celine Dion," Baker said. "My jaw literally hit the floor and I started what I can only describe as an out-of-body experience." Dion serenaded them with her 1996 ballad "Because You Loved Me."

From there, the crew ushered friends and family to the nearby Jimmy Kimmel set. "While waiting to walk out on stage, I felt a tugging on my dress and turned around to see Celine Dion holding onto it. 'I'll take care of this,' she said, and we stood like that for several minutes waiting to go out. During this time I just kept looking behind me and staring … mumbling things to her like, 'Is this for real,' 'I love you,' 'Thank you so much,' 'You are so amazing,' and then back to 'I love you.' What other celebrity would have held my dress like that? She also offered up some solid marriage advice."

The newlyweds watched the rest of the show seated up front with friends and family. "This whole experience has been surreal," Baker said. "I am just so appreciative of this amazing day and all of those involved in making it happen. What a story!"

Julie Margenthaler, MD, HS '05, professor of surgery at WUSM, has been named president-elect of the American Society of Breast Surgeons. She will serve in the role until 2020, when she becomes president of the organization.

Christopher R. Carpenter, MD, GM '07, professor of emergency medicine at WUSM, has been elected to the Society for Academic Emergency Medicine (SAEM) Board of Directors. The board establishes SAEM's mission, purpose, values and direction.

John "Keoni" S.K. Kauwe, PhD '07, recently was appointed dean of graduate studies at Brigham Young University. He began serving a five-year term as dean this past summer.

Seth Goldberg, MD, HS '09, received the inaugural Nathan Hellman Teaching Award in WUSM's Division of Nephrology. He is an associate professor of medicine. **Patricia and Richard Hellman, HS '79,** established the award in honor of their late son, **Nathan Hellman, MD/PhD '03.** The award will be given annually to a faculty member in nephrology, as selected by division fellows.

Jaclyn Stephens, OT '09, recently gave a TEDx talk at Colorado State University that describes her research on athletes with concussion. Video of the presentation is available on YouTube.

2010s

Craig Press, MD/PhD '10, is director of pediatric neurocritical care at Children's Hospital Colorado. After completing additional neurocritical care and epilepsy training, he is focusing on the treatment of children with acute neurological injury through a newly developed multidisciplinary NeuroRecovery Program.

Ryan Duncan, DPT '12, MSCI '19, recently graduated with a Master of Science in Clinical Investigation. He will continue as assistant professor of physical therapy and neurology within the WUSM Program in Physical Therapy.

Lauren Stone, OT '12, was hired as an assistant professor for the 2019-20 academic year in the developing Master of Occupational Therapy program at North Central College in Naperville, Ill. Her research platform will focus on pediatric neuro-oncology rehabilitation.

Jennie H. Kwon, DO, MSCI '16, assistant professor of medicine at WUSM, has been named a member of the National Academy of Medicine's Health Policy Fellowships and Leadership Programs (HPFLP) Advisory Committee. As a committee member, she will provide perspective and insight to the HPFLP director and staff on current fellowship and leadership programs, and assist in the exploration of new programs and strategic initiatives.

Austin Wesevich, LA '11, SW '16, MD '17, and Megan Lynch were married by Fr. Gary Braun at the Washington University Catholic Student Center on Oct. 13, 2018.

George J. Broze Jr., MD, a well-known leader in the field of hematology and a professor of medicine at the School of Medicine, died of a heart attack Wednesday, June 19, 2019, at his home in St. Louis County. He was 72.

Broze, also a professor of cell biology and physiology, was an expert in the management of blood clotting and bleeding. He came to Washington University in 1976 as a clinical fellow in hematology and remained at the school for his career.

Beginning in 1980, Broze served as an attending physician and as director of the transfusion unit at Jewish Hospital, while teaching hematology to medical students. From 1987 to 1996, he was an attending physician at Barnes Hospital. Further, he was part of the hematology consult service at Barnes-Jewish Hospital, where he had been caring for patients since 1997.

Broze's research focused on the role of blood coagulation factors in the inflammatory response and in vascular disease, with his most recent work focused on an inhibitor of coagulation called tissue factor pathway inhibitor (TFPI). His research with TFPI, Protein Z and human tissue factor pathway inhibitor earned him 17 patents.

"He was a superb clinician whose advice often was sought in the most difficult bleeding and blood-clotting cases," said Stuart Kornfeld, MD, the David C. and Betty Farrell Distinguished Professor of Medicine and a professor of biochemistry and molecular biophysics.

"He was a world leader in the field of blood coagulation and best known for the discovery of a protein in plasma that he called TFPI. He established that TFPI plays a central role in regulating the extent of coagulation and preventing thrombosis, and his work provided the field with an integrated pathway of blood coagulation."

Born in Seattle in 1946, Broze earned a bachelor's degree in physics from the University of Washington (UW) and a medical degree from the UW School of Medicine. He completed his internship and residency at North Carolina Memorial Hospital in Chapel Hill, N.C.

He is survived by his wife, Jilla; his sons George John "Yuri" Broze III and Charles "Chip" Broze Belpedio (Tony Belpedio); and his brother, Greg Broze.

The family requests letters with anecdotes and memories be mailed to his home at 15 West Point Lane, St. Louis, Mo., 63131.

Susan Jo Kemmer Keating, a former project manager in the Department of Psychiatry, died Thursday, June 20, 2019, in Cary, N.C. She was 75. Her husband, James P. Keating, a meticulous physician who served 44 years at the university and St. Louis Children's Hospital, preceded her in death.

She was born July 15, 1943, in Chestnut Hill, Pa., to Frank Nelson Kemmer and Carol Pancost Kemmer. A 1965 graduate of the University of North Carolina-Chapel Hill School of Nursing, she served as a pediatric registered nurse at Massachusetts General Hospital and as a nurse practitioner at St. Louis Childrens' Hospital. Later, she worked as a project manager in the Washington University psychiatry department.

Susan also volunteered for the Sierra Club, Blue Star Mothers of America, the ASPCA, and the Litzsinger Road Ecology Center. A lover of wild places, from the Grand Canyon to the Appalachian Trail, Susan was a passionate student of the natural world and a committed advocate for nature conservation. She was a competitive runner and an enthusiastic hiker who instilled a love of sports and the outdoors in her children.

She is survived by her son, Thomas Peter Keating, daughter, Amy Keating Foote (Christopher), sisters Gretchen Kemmer, Molly Roberts (Christopher), and Carolyn Oliver (Kenneth Anderson). An infant son, Matthew Anthony Keating, preceded her in death.

Jerome Fred Levy, MD, a distinguished surgeon and emeritus professor at the School of Medicine, died Wednesday, June 12, 2019, of pancreatic cancer at home in St. Louis. He was 84.

A Washington University alumnus, Levy earned a bachelor's degree in chemistry in 1954 and a medical degree in 1958. Levy's passion for arts compelled him to earn a master of liberal arts degree from University College in Arts & Sciences in 2010.

A native St. Louisan, Levy began his professional career at Washington University. He started as a surgical resident at Barnes Hospital, rising to become an associate professor in clinical surgery before retiring from his surgical practice in 2002.

Early in his medical practice, Levy was drafted during the Vietnam War to serve as a captain in the U.S. Army, primarily with the 101st Airborne at Fort Campbell, Ky.

He trained as a vascular surgeon and eventually focused on treating patients with breast cancer, becoming one of the region's first surgeons to perform immediate reconstruction following a mastectomy.

"Jerry was loved by his patients and was an early pioneer of breast conservation and immediate reconstruction," said Timothy J. Eberlein, MD, the Bixby Professor of Surgery, head of the Department of Surgery and director of the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine.

Levy is survived by his wife of 33 years, Judith Weiss Levy; and six children, Rebecca Levy Williams (Seth Williams, DVM), JoAnne Levy (Jim Thomeczek), the Hon. Ellen Levy (Carl Desenberg), Jerry Lundsgaard, Nancy Levy, and David Levy (Stephanie Kurtzman); 12 grandchildren; and three great-grandchildren. He was preceded in death by his brother Monroe Levy (Constance).

Kelley Ann Mullen, senior director of scheduling services and service quality for the School of Medicine's faculty practice, died at her home Tuesday, May 21, 2019, after a brief illness. She was 57.

Mullen joined the School of Medicine in 1995 as nursing and clinical administrator for the Department of Neurosurgery. She moved to the faculty practice in 1998, where she had worked since.

"Kelley was a remarkable person — a gifted nurse-clinician and highly experienced administrator," said James P. Crane, MD, who was head of Washington University Physicians during most of Mullen's tenure. "I feel so fortunate that we were able to recruit her to join the faculty practice plan during its formative years. Kelley was among the most selfless, genuine and caring individuals I have ever known."

1940s

Caroline Beard, NU '46; Dec. '18
Margaret Bubolz, NU '45; Dec. '18
Rufus S. Cooper, DE '42; Feb. '19
Corinne Cullen, NU '47; May '19
Dottie Herweg, NU '47; April '19
Donald J. Stallard, MD '47; April '19
James M. Stokes, MD '48; Feb. '19
Humbert M. Valenti, DE '49; April '19
Charles Rex Witherspoon, DE '46; Jan. '19

1950s

Charles F. Bahn, MD '52; April '19
Ronald B. Burt, DE '56; April '19
Milton J. Deitch, MD '59; May '19
Morton H. Field, MD '56; March '19
R. G. Funderburg, DE '55; Dec. '18
Virginia H. Granger, NU '52; Jan. '19
Richard C. Holmes, DE '55; Dec. '18
Frederick T. Kraus, MD '55, HS; Aug. '19
Ansel R. Marks, LA '49, MD '53; Jan. '19
James T. McDonald Jr., DE '54, GD '58; Jan. '19
Sally Francis McMillen, NU '56; March '19
William E. Mundt, MD '59; Feb. '19
Kenna Kelley Shean, NU '52; Dec. '18
Mary A. Soest, NU '51; April '19
James L. Wellhouse, MD '52; May '18
Mary Margaret Wilkinson, NU '57; Feb. '19

1960s

Arthur M. Clements, MD '61; March '19
Harold K. Kanagawa, MD '65; April '19
David J. Krutchkoff, DE '64; April '19
O. Lamar Majure, HS '67; Jan. '19
Robert H. Shidler, DE '60; March '19
James E. Standefer, HS; Dec. '18
Gary A. Storey, MD '61; March '19
George L. Tucker, HS '63, EMBA '91; Feb. '19
Addie Wiggins, NU '66; March '19
Morris F. Wise, MD '64, HS; March '19
Gerald Wool, MD '62; May '19

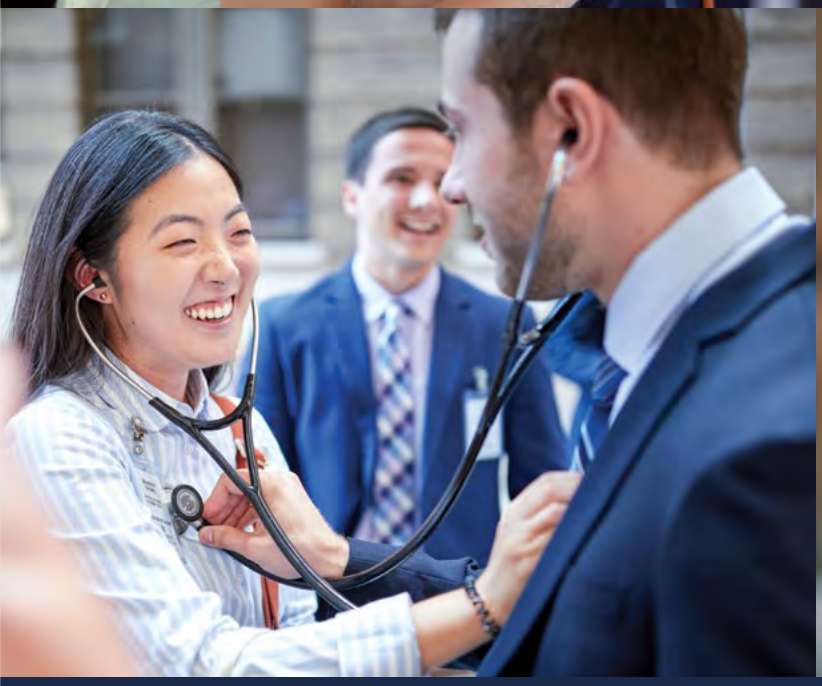
1970s

Meryl K. Abensohn, LA '72, MD '78, HS '84; Feb. '19
Wallace P. Berkowitz, HS; Jan. '19
Joan Blondin, HS '74; March '19
Gregory L. Johnson, MD '71; Jan. '19
Robert P. Rothenberg, DE '73; April '19
James D. Torghele, DE '72; Feb. '19

1980s

Stephen J. Barenkamp, HS '82; March '19
Daniel T. Sargeant Jr., HS '80; April '19

For full obituaries, visit:
outlook.wustl.edu/obits



Back to school shopping: **MD STYLE.**

During orientation, first-year medical students carefully test and select their clinical gear for the school year.

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A SAMPLE RECIPE FROM THE SCHOOL OF MEDICINE METABOLIC KITCHEN:

Mediterranean Baked Arancini

(makes 4 servings)

INGREDIENTS

½ cup	brown rice, cooked
1½ cups	broccoli, cooked
¼ cup	onion, diced
1 tsp.	minced garlic
1	large egg
1½ tsp.	parsley, dried
1 tsp.	lemon rind, fresh or dried
1½ tbsp.	olive oil
½ cup	parmesan cheese, fresh, diced into small pieces
¾ cup	Panko bread crumbs
2 cups	pasta sauce (homemade or your favorite premade)

NUTRITION

Cal	400
Carb	53g
Total Fat	15g
Sat Fat	5g
Protein	15g
Sodium	870mg

DIRECTIONS

Pre-heat oven to 400 degrees F.

Heat a small pot on the stove with 1 cup of water until boiling. Add brown rice and reduce to a simmer for 10-15 minutes or until tender.

Microwave broccoli until tender, 3-5 minutes.

Set aside Panko bread crumbs in a separate bowl.

In a food processor, add cooked brown rice, cooked broccoli, onion, egg, garlic, parsley, lemon rind, and olive oil. Pulse to blend; take care not to make it into a paste.

Divide the rice mixture into 8 portions and roll each into a ball. Create a hole in the center of the ball and stuff with parmesan cheese. After stuffing the rice ball with cheese use your hands to seal the hole.

Take the stuffed ball and roll in Panko bread crumbs, covering lightly. Place on a foil-lined baking sheet sprayed with non-stick cooking spray.

Bake for 15 minutes. Flip, and bake for another 15 minutes.

Top two arancini balls with ½ cup of pasta sauce for each serving.