Canine CONNECTION

People and dogs with cancer may benefit from similar therapies.
Perfectly matched

Justin Krogue brought along his son, 1-year-old Miles (dressed in baby-sized scrubs), and wife, Marissa, to Match Day festivities March 20 in the Eric P. Newman Education Center. The envelope contained big news: The family will relocate to the University of California, San Francisco, where Justin will train in orthopedic surgery. To learn the fate of more than 120 transitioning School of Medicine students, see page 24.
Cover Researchers at the School of Medicine and the Auburn University College of Veterinary Medicine in Alabama are working together to develop cancer therapies for people and their animal companions. The researchers have collaborated for 20 years in an effort to make viral-based cancer treatments a reality for both dogs and people. To learn more about this human-animal connection, see page 12.

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Every mosquito season brings with it the fear that these annoying insects could arrive carrying a dangerous disease. One such infection has recently been detected in the U.S.

Known as Chikungunya, an African word for “that which bends up,” this mosquito-borne virus causes arthritis-like symptoms. The virus is mainly spread by the tropical *Aedes aegypti* mosquito and first was identified 60 years ago in eastern Africa. Since then, it has spread across the world.

In 2014, more than 2,000 people in the U.S. developed the infection after traveling abroad, mostly to the Caribbean. That same year, 11 cases of Chikungunya infection were reported among people living in Florida who had not traveled outside the U.S., suggesting that mosquitoes in that state were spreading the virus.

In most patients, the infection causes a fever, rash and severe joint pain. The fever and rash typically subside in seven to 10 days, but symptoms of arthritis may persist in up to 60 percent of patients for a year or longer.

Researchers at Washington University School of Medicine have found that blood tests of patients carrying the Chikungunya virus and those with rheumatoid arthritis can produce similar results. This may lead to the misdiagnosis of some patients with the virus.

The findings underscore the need for doctors to obtain detailed travel and medical histories from patients being evaluated for rheumatoid arthritis. Such details could help distinguish between the two conditions.

The global spread of the Chikungunya virus suggests that the disease is likely to provide a diagnostic challenge in the years ahead. Physicians treat rheumatoid arthritis with drugs that suppress the immune system, but it’s not yet known whether that approach will help or harm patients with Chikungunya virus.

“We’re anticipating that Chikungunya virus will spread broadly in the U.S., so it’s important to develop better tools for diagnosis, prevention and treatment,” said Deborah J. Lenschow, MD, PhD, a rheumatologist involved in the research. Researchers here have established an online Chikungunya registry.
Larry J. Shapiro, MD, has announced he will step down as executive vice chancellor for medical affairs and dean of the School of Medicine.

Shapiro, who has led the school for nearly 12 years, will continue at the helm until a national search is conducted and his replacement found.

Chancellor Mark S. Wrighton is chairing the search committee, which includes the provost, university trustees, School of Medicine department heads and others.

Wrighton, referring to Shapiro as “St. Louis’ physician-in-chief” and a leader devoted to the university and medical school, said it is impossible to recount all of Shapiro’s achievements.

“Larry has done a terrific job in every respect: The school has never been stronger, and he has done fabulously well in recruiting outstanding department heads and faculty; recruiting the most outstanding medical students; and building an outstanding and large clinical program, including development of the Alvin J. Siteman Cancer Center.

“He was instrumental in launching the Institute for Public Health and supporting its development, and he played a lead role in enhancing the school’s educational mission and in strengthening the quality and impact of research.”

Shapiro said his leadership role at the university “has been the utmost privilege of my professional career and has provided me with challenges, great satisfaction and much happiness.”

A pediatric geneticist by training, Shapiro is a Washington University legacy. He first arrived in St. Louis 50 years ago as an undergraduate student in Arts & Sciences. He then pursued his medical degree at the School of Medicine and completed his residency at St. Louis Children’s Hospital in 1973.

Afterward, he embarked on a medical career at the National Institutes of Health (NIH) and then at the University of California, Los Angeles, and the University of California, San Francisco. He returned to St. Louis in 2003 as a renowned genetics researcher, administrator and pediatrician. That year, he took on the roles of executive vice chancellor for medical affairs, dean of the School of Medicine and the Spencer T. and Ann W. Olin Distinguished Professor.

He is also president of Washington University Medical Center, which includes the School of Medicine, Barnes-Jewish Hospital and St. Louis Children’s Hospital.

Study may aid stroke recovery

Stroke can lead to a wide range of problems such as depression and difficulty moving, speaking and paying attention. Scientists have thought these issues were caused by damage to the brain’s “computer processors” — cells in the brain’s outer layer that do much of the work involved in higher brain functions.

But a new study by School of Medicine researchers has found compelling evidence that stroke damage to “cables” buried inside the brain plays an important role in these impairments. The cables connect cells on the brain’s surface to each other, to other cells deep in the brain and to cells in the spinal cord that link the brain to the rest of the body.

“This study provides a new framework to think about the damage caused by stroke,” said senior author Maurizio Corbetta, MD, the Norman J. Stupp Professor of Neurology. “A more complete and accurate description of the most common anatomical damage and deficits after a stroke will help us understand how the brain can adapt to recover lost functions and potentially lead to new rehabilitation strategies.”

To get a better sense of how stroke damages the brain, Corbetta and his colleagues initiated a study of 132 patients who had just suffered first-time strokes. The results appeared online March 4 in Neuron.
Antibiotic resistance is poised to spread globally among bacteria implicated in respiratory and urinary infections in hospital settings, according to new research. Two genes that confer resistance against a particularly strong class of antibiotics can be shared among a family of bacteria responsible for a significant portion of hospital-associated infections, the study shows.

Drug-resistant germs recently infected several patients at two Los Angeles hospitals. The infections have been linked to medical scopes possibly contaminated with bacteria resistant to carbapenems, potent antibiotics for use only in gravely ill patients or those infected by resistant bacteria.

“Carbapenems are one of our last resorts for treating bacterial infections, what we use when nothing else works,” said senior author Gautam Dantas, PhD, associate professor of pathology and immunology. “Given what we know now, I don’t think it’s overstating the case to say that for certain types of infections, we may be looking at the start of the post-antibiotic era, a time when most of the antibiotics we rely on to treat bacterial infections are no longer effective.”

Dantas and others recommend limiting the usage of carbapenems to cases in which no other treatments can help. The study, conducted by researchers at Washington University, Barnes-Jewish Hospital and the National University of Sciences and Technology in Pakistan, is available online in Emerging Infectious Diseases.

School of Medicine researchers have developed a noninvasive method to screen for kidney cancer that involves measuring the presence of proteins in the urine. The findings are reported March 19 in the journal JAMA Oncology.

The researchers found that the protein biomarkers were more than 95 percent accurate in identifying early-stage kidney cancers. In addition, there were no false positives caused by non-cancerous kidney disease.

“These biomarkers are very sensitive and specific to kidney cancer,” said senior author Evan D. Kharasch, MD, PhD.

Like most cancers, kidney tumors are easier to treat when diagnosed early. But symptoms of the disease, such as blood in the urine and abdominal pain, often don’t develop until later, making early diagnosis difficult.

“The most common way that we find kidney cancer is as an incidental, fortuitous finding when someone has a CT or MRI scan,” said Kharasch, the Russell D. and Mary B. Shelden Professor of Anesthesiology. “It’s not affordable to use such scans as a screening method, so our goal has been to develop a urine test to identify kidney cancer early.”

With researchers from the Alvin J. Siteman Cancer Center, the Mallinckrodt Institute of Radiology and the Division of Urologic Surgery, Kharasch and principal investigator Jeremiah J. Morrissey, PhD, professor of anesthesiology, analyzed urine samples from 720 patients at Barnes-Jewish Hospital who were about to undergo abdominal CT scans for reasons unrelated to suspicion of kidney cancer.

Results of the scans let the investigators determine whether patients might have kidney cancer. As a comparison, they also analyzed samples from 80 healthy people and 19 patients previously diagnosed with kidney cancer.

The researchers measured levels of two proteins in the urine — aquaporin-1 (AQP1) and perilipin-2 (PLIN2). None of the healthy people had elevated levels of either protein, but patients with kidney cancer had elevated levels of both proteins.

About 15 percent of kidney masses found by CT scans are not malignant. The only way to know definitively is to operate. Kharasch and Morrissey are using the findings to develop an easy-to-use, more widely available screening test.
It’s a firmly established fact straight from Biology 101: Traits such as eye color and height are passed from one generation to the next through the parents’ DNA. But now, a new study in mice by School of Medicine researchers has shown that the DNA of bacteria in the body can pass a trait to offspring in a way similar to the parents’ own DNA. According to the authors, the discovery means scientists need to consider a significant new factor – the DNA of microbes passed from mother to child – in their efforts to understand how genes influence illness and health. The study appeared online Feb. 16 in Nature.

“We have kept bacteria on one side of a line separating the factors that shape our development — the environmental side of that line, not the genetic side,” said co-senior author Herbert W. Virgin IV, MD, PhD. “But our results show bacteria stepping over the line. This suggests we may need to substantially expand our thinking about their contributions, and perhaps the contributions of other microorganisms, to genetics and heredity.”

Bacteria are known for their roles in harmful infections. But scientists have realized that such bacteria are only a tiny fraction of the bacterial communities that live in and on our bodies. Most bacteria are commensal, which means they do not cause harm and often confer benefits. Commensal bacteria influence traits such as weight and behavior. But until now, researchers thought the bacteria that exerted these effects were acquired during a person’s life. The study is the first to show that bacterial DNA can pass from parent to offspring in a manner that affects specific traits such as immunity and inflammation.

The researchers linked commensal bacteria in mice to gut injury susceptibility. Mice with certain inherited bacteria are susceptible to the injury, which is caused by exposure to a chemical. Female mice pass the bacteria to their offspring, making them vulnerable to the injury. Others carrying different bacteria are less susceptible.

In the short term, the findings may help scientists eliminate a significant “bug” in studies of genetically engineered mice. In several fields of research, scientists have been confronted intermittently with the sudden, unexplained appearance of new or altered traits in mice. The traits often spread from one mouse habitat to the next, suggesting a spreading microbial infection is responsible. But the traits also consistently pass from mother to offspring, suggesting a genetic cause.

In the long term, Virgin expects the expanded model of heredity to produce a more complicated but also much more insightful picture of how human, bacterial and viral genes influence human health.
In the spotlight  Recipients of the 2014 2nd Century Awards: (from left) Scott J. Hultgren, PhD, Carol B. Loeb and F. Sessions Cole, MD. The 2nd Century Awards recognize those whose long-term commitment and participation have helped the School of Medicine enter its second century with strength and confidence. Hultgren was honored for research focused on microbial-host interactions and his work on how infectious diseases are diagnosed, treated and prevented. Loeb was honored for personal and professional dedication to the advancement of education. Cole was honored for achievements in improving outcomes for newborns.

Evaluating long-acting birth control

New research indicates that hormonal intrauterine devices (IUDs) and contraceptive implants remain highly effective one year beyond their approved duration of use, according to a School of Medicine study. The preliminary findings are reported in Obstetrics & Gynecology.

Researchers are evaluating whether such long-acting forms of birth control are effective for up to three years past the length of use approved by the Food and Drug Administration (FDA). Contraceptive implants — matchstick-sized rods inserted into the arm — are approved for three years, and hormonal IUDs are approved for five years. Extended use of these devices reduces cost to individuals and insurers, said first author Colleen McNicholas, DO, assistant professor of obstetrics and gynecology.

These long-acting contraceptive methods are garnering renewed attention in the U.S. because of their superior effectiveness over other forms of birth control. The study aims to enroll a total of 800 women.

“In the long term, this work has the potential to change how we provide contraceptive methods around the world and can enable women to control their reproductive health and family size,” said senior author Jeffrey Peipert, MD, PhD, the Robert J. Terry Professor of Obstetrics and Gynecology.

Respiratory gamut

Targetings colds, COPD and more

A Washington University drug discovery program has received three grants totaling more than $5 million from the National Institutes of Health (NIH) to develop new therapeutics for respiratory diseases. The target illnesses range from the common cold to life-threatening lung disease.

The projects include designing next-generation drugs to open the airway passages by controlling mucus production, as well as new agents to fight off respiratory infections by boosting the immune system. The program, based in the Division of Pulmonary and Critical Care Medicine in the Department of Medicine, is led by pulmonologist and principal investigator Michael J. Holtzman, MD, the Selma and Herman Seldin Professor of Medicine.

“Chronic respiratory disease is the third-leading cause of death in the U.S. and the fifth worldwide, and these deaths are linked most strongly to overproduction of inflammatory mucus that blocks the airways,” he said. “The pathway to mucus production is invariably activated in respiratory viral infections, and the same process drives exacerbations and progression of chronic respiratory diseases like asthma and COPD, yet there are no drugs that effectively control this pathway.”

The largest award, totaling just over $3 million, will support a project focused on optimizing a chemical compound Holtzman’s group developed to block a key checkpoint in the mucus pathway.

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Two other awards totaling $2.5 million will address the need to control viruses that drive acute and chronic respiratory disease. These awards are designed to develop the next generation of antiviral drugs. There is a crucial need for drugs that battle common viruses that cause respiratory illness. To address this issue, Holtzman’s group came up with a strategy to improve the body’s interferon signaling pathway, the main means for antiviral defense.

The Drug Discovery Program, in its fourth year of operation, is envisioned as a model for academic development of new therapeutics.
WARNING LIGHTS

Clinical studies begin on a tiny technology that could pinpoint arterial disease risks

BY JULIA EVANGELOU STRAIT
In patients with atherosclerosis, plaque accumulates on the inner walls of arteries, which deliver blood to the body. In many cases, the accumulated plaque causes no symptoms and remains undiagnosed by physicians. Plaque accumulation eventually can narrow an artery enough to cause chest pain or mild symptoms. But, for some, this plaque suddenly can rupture without warning, create blockages and cause a heart attack or stroke.

“Plaque is a complex structure, made up of cholesterol, calcified deposits and other substances, all of which can cause plaque instability,” said Woodard, also director of the Center for Clinical Imaging Research (CCIR) at the Mallinckrodt Institute of Radiology at Washington University.

“This imaging agent targets a specific receptor that is present in more vulnerable complex plaque, thereby identifying which plaques might rupture in the patient, leading to stroke or heart attack.”

Past research shows most patients with plaque narrowing a carotid artery will not go on to have a stroke.

Distinguishing high-risk patients

“With current technology, such as ultrasound, we can’t tell whether the plaque is vulnerable or stable,” she said. “So we can’t distinguish the high-risk patients who need surgery from low-risk patients who can be treated with medication alone.

“We designed this nanoparticle agent to develop a test that can detect these vulnerable plaques and identify those patients at highest risk of stroke and in need of surgery to remove the plaque.”

Gregorio A. Sicard, MD, vascular surgeon and professor of surgery and of radiology, said specialists who treat carotid artery disease have been seeking a diagnostic test that could identify extracranial carotid artery disease, which is more prone to embolize, rupture or occlude the carotid artery. These types of vulnerable plaques are more likely to cause an embolic cerebral vascular event with devastating effects. In many cases, these patients are asymptomatic.

“This exciting work by Dr. Woodard and collaborators may provide a screening imaging study that will identify, in asymptomatic patients, those that have a vulnerable plaque and are therefore more likely to have a cerebral vascular event,” Sicard said. “This cutting-edge diagnostic study hopefully will revolutionize the management of patients with asymptomatic carotid plaque and plaque in other arterial beds.”
How it works

The nanoparticle is unique in how it is targeted, according to Yongjian Liu, PhD, assistant professor of radiology and co-investigator on the project. Previous research demonstrated that a receptor called NPR-C is present on the surface of cells that line blood vessels and is increased in plaque associated with atherosclerosis. So the investigators added a small peptide to the nanoparticle. That peptide seeks out and binds to NPR-C, specifically targeting the particle to potentially dangerous plaque.

The nanoparticle also carries copper atoms, making it visible with a standard positron emission tomography (PET) scanner. Similarly, small amounts of copper-64 are used in PET scans for cancer detection and therapy and neurologic imaging. Once injected, this nanoparticle agent can illuminate potentially vulnerable plaque in the body’s arteries.

The carrier nanoparticle was crafted in the lab of Craig J. Hawker, PhD, professor and director of the California Nanosystems Institute at the University of California, Santa Barbara. “We couldn’t carry out the research without his contributions,” Woodard said.

Following successful tests in animal models, researchers recently began testing the safety of the nanoparticle in healthy individuals. Next, they will focus on patients with atherosclerosis who already are scheduled to undergo surgery to remove plaque from their carotid arteries.

Testing of these patients will begin in a novel PET-MR system housed in the CCIR, so that the researchers can look at plaque anatomy on MRI and PET signals from the new agent concurrently.

“We’ll be able to see whether the areas that light up in the image because of our nanoparticles are the same areas that contain vulnerable plaque, as assessed from the surgeries,” Woodard said.

Once the investigators demonstrate success imaging the carotid arteries, they will evaluate the nanoparticle agent in other vessels such as the coronary arteries, which represent a greater challenge because of their smaller size and complex motion.

“Given the clinical success of this agent, with the assistance of the Office of Technology Management, we have begun seeking to advance this imaging agent into a commercial product,” Woodard said.

“We have been able to develop this highly receptor-specific imaging technology because of the generous support from the National Heart, Lung and Blood Institute, our diverse and dedicated team of investigators and our extensive facilities at Washington University,” she added.
Celebrating differences

Kids with hearing loss must overcome obstacles beyond the usual struggles growing up. One impassioned alumna is providing an uplifting resource worldwide.

Today, as a result of newborn hearing screenings, advanced technologies and early intervention programs, more and more children with hearing loss are being mainstreamed into classrooms alongside hearing peers. With individualized support and assistive devices, such as cochlear implants, these children thrive academically. But, though they may excel in speech and listening, often, they feel socially isolated. Alumna Melanie Paticoff is working to help them combat these feelings, providing a point of connection for kids and teens with hearing loss around the world. Last year, she launched Hearing Our Way, the only such magazine for children and teens. The goal: Bring hearing-impaired young people together through shared experiences.
Closing a gap

Growing up in Long Island, New York, Paticoff was inspired by her cousin Julie, now 19. As Paticoff explains, Julie listens to her iPod, attends concerts and is a member of a dance team. She also is profoundly deaf. Bilateral cochlear implants give her complete access to sound.

“There are 3 million other kids in the U.S. just like Julie and millions more around the world,” Paticoff said. “They attend school with their friends, join clubs and play sports, but they are usually the only ones with hearing loss in their entire school district.”

Often, these children haven’t spent any time in schools for the deaf and have had little exposure to other kids with hearing loss.

While pursuing degrees in deaf education, Paticoff witnessed a gap in social and emotional support for children with hearing loss. She noticed, for example, that children’s literature rarely depicts characters with hearing loss. This inspired her to write and self-publish two award-winning children’s books featuring Sophie, a fictional dog with a cochlear implant — “Sophie’s Tales: Learning to Listen” (2010) and “Sophie’s Tales: Overcoming Obstacles” (2012).

In 2011, Paticoff earned a bachelor’s degree in deaf education from Fontbonne University and, in 2013, a master’s degree from Washington University’s Program in Audiology and Communication Sciences (PACS), where she received the Max A. Goldstein Award for outstanding academic achievement and professional promise.

“Melanie was a special student from the very beginning,” said Paticoff’s mentor Heather Hayes, PhD, director of deaf education studies. “Her drive to help children who are deaf and who learn to listen and talk was unparalleled. It was my distinct pleasure to be one of her mentors, and I take great pride in it still.”

Reaching out

After graduating in May 2013, Paticoff began developing the magazine that summer. The first issue arrived in homes a year later, and a successful crowdfunding campaign followed.

The quarterly magazine, which includes inspirational stories, language tips and tricks, self-advocacy skills and interviews with teens who have faced similar obstacles, is offered free.

“The magazine teaches kids and teens to celebrate their differences and provides vital social and emotional support to young people during their formative years,” Paticoff said.

Filled with positivity and pop culture references, a recent issue contained song lyrics from the Jonas Brothers and advice on hairstyles that work well with cochlear implants.

Five thousand subscribers signed up in the first two months — with readers across the U.S. and as far away as Australia and Italy. Now, there are 10,000 subscribers.

“Melanie is reaching out to children across the country (and the world) with her publication,” Hayes said. “Most importantly, she’s also reaching families, audiologists and physicians who might not even realize how valuable a magazine like this can be to young children and adolescents. Just simply seeing images of children with devices like hearing aids and cochlear implants in a fun publication can mean the world to a child.

“Deafness is a low-incidence disability and, thus, many children and parents struggle to find common experiences with others.

“Additionally, Mel is bringing awareness to others about how children who are deaf can learn to listen and talk. This is invaluable.”

The partnership between the magazine and the medical school is still strong nearly two years post-graduation. PACS is a magazine sponsor, and every issue spotlights a current deaf education or audiology student at the medical school. A recent issue featuring a graduate student with hearing loss helped further illustrate that those with hearing impairment can go on to become audiologists, teachers or leaders in other fields.

Paticoff resides in St. Louis as editor-in-chief of Hearing Our Way and chief executive officer of Sophie’s Tales LLC.

Sophie, a spunky Maltipoo that proudly wears a purple cochlear implant, is based on Paticoff’s real-life pet, a certified therapy dog.

LEARN MORE
HearingOurWay.com
Humans and dogs have lived alongside one another for millennia. Dogs have provided protection and companionship, labor and love. They have worked our farms, hunted our food, guarded our livestock, played with our kids and evolved with us. It’s a unique relationship, unrivaled by any other set of species. And while we may recognize many of the mutually beneficial aspects of this bond, a new paradigm is emerging between man and his best friend: shared medicine.

It’s no secret that animals and people share many of the same diseases. Testing possible treatments for people on animals, especially laboratory mice, is a mainstay of medical research and the origin of most modern therapies. But physicians are realizing how much stands to be learned by collaborating with veterinarians and designing clinical trials for animals — to treat their naturally occurring diseases — just as we do in people.

The lesson has been embraced by Washington University’s David T. Curiel, MD, PhD, a professor of radiation oncology and of cancer biology. Much of Curiel’s research focuses on the use of engineered viruses to treat disease, especially cancer. He and veterinarians at Auburn University in Alabama are cultivating partnerships they hope will speed the development of cancer therapies for people and their animal companions.

“People love their pets and want to treat them when they get cancer,” Curiel said. “And dogs get cancers that are very similar to human cancers.”
It started with a limp.

At first, Dawn Oravetz thought her rescue greyhound Gary had simply tripped and bruised his right rear leg. Or, at age 10, perhaps some arthritis was developing in his joints, especially since Gary had spent his early life sprinting around racetracks at 40 miles per hour. Oravetz hoped it was just a bruise, but she had good reason to worry.

Greyhounds, especially those bred for racing, and other large-breed dogs are at above average risk of developing a type of bone cancer called osteosarcoma. Osteosarcoma is also one of the more common cancers of human adolescence, emerging with teenage growth spurts. In dogs, the tumor tends to be particularly aggressive. Standard treatment is amputation of the affected leg followed by several rounds of chemotherapy. The tumor often spreads to the lungs. Even with aggressive treatment, prognosis is poor. Greyhounds survive an average of only nine months after diagnosis.

Oravetz and her husband, Bill, understood this better than most, already having lost two adopted greyhounds to the disease.

Through contacts in a local greyhound rescue organization, Oravetz learned of a clinical trial at Auburn’s College of Veterinary Medicine, about a four-hour drive from their home in Navarre, Florida.

“We learned from past experience that you don’t put it off,” Dawn Oravetz said. “We found out about Gary’s tumor on a Saturday. And by Thursday, we were at Auburn.”

The director of Auburn’s cancer research initiative, Bruce F. Smith, VMD, PhD, has been collaborating with Curiel for more than 20 years, in an effort to make virus-based cancer treatments a reality for both dogs and people.

A major barrier to research and development of viral cancer treatments is that they cannot be tested in traditional mouse models.

“Human adenoviruses don’t replicate in mice,” Curiel said. “But we thought, what if we take a virus that normally infects dogs and use it to treat dog tumors? Now you have a virus that can replicate in the tumor. The animals have working immune systems and are genetically diverse. In theory, this fully mimics what we want to do in humans. It’s a more stringent test of the system. And you may end up with a new therapy for dogs in the process.”

Curiel and Smith emphasize that Gary and dogs like him are not experimental animals. As in people, their cancers develop spontaneously, probably due to some interaction between genes and environment. They don’t live in controlled laboratory settings with identical diets. These dogs live at home with their families. And perhaps most importantly for this particular kind of trial, they have intact immune systems, unlike mice so commonly used in cancer research. In short, if a clinical trial of an investigational therapy works in dogs living in the real world, it may be more likely to work in the people who live with them.
Building viral-based therapies

Making custom cancer-destroying viruses requires meticulous teamwork. In the Curiel lab, that collaboration is fostered by two husband-and-wife partnerships: Igor Dmitriev (1) and Elena Kashentseva (3), and Sergey Kaliberov (2) and Lyudmila Kaliberova (4), all Russian émigrés who brought their scientific skills to Washington University School of Medicine.

The process begins with a procedure that reprograms viral DNA so it can target cancer cells.

A whirl in the centrifuge separates the virus from the packaging cells. Testing reveals bands of pure virus (see arrows at edge of this page).

Specialized packaging cells house the virus, supply necessary cellular functions and allow the virus to grow and multiply.

Finally, the scientists verify that the new batch of virus will spare healthy cells and kill tumor cells when used in clinical trials.
As with clinical trials for people, which are voluntary, participation in this trial is at the discretion of the pet owners. Similar to human trials, clinical trials involving animals are overseen and approved by an independent committee that reviews the protocol and decides whether all requirements for ethical disclosure are met.

While the concept of uniting human and veterinary medicine is not new — most recently dubbed the One Health or One Medicine movement — it is beginning to gain new traction in the human medical community. The initiative received a boost in 2012 with the publication of The New York Times bestselling book “Zoobiquity: The Astonishing Connection Between Human and Animal Health.” In it, Barbara Natterson-Horowitz, MD, and co-author Kathryn Bowers argue for increased collaboration between physicians and veterinarians.

Natterson-Horowitz, a cardiologist at the University of California, Los Angeles, noted that veterinary colleagues at the Los Angeles Zoo often consult human doctors and the medical literature for insights into how best to treat their animal patients. But the reverse — human doctors seeking the collective wisdom of animal doctors and their flagship journals — is a rarity, the authors observed.

In the spirit of shared medicine, Curiel and Smith have developed a trial using a modified version of a common canine virus to treat canine osteosarcoma. Curiel, who also directs Washington University’s Biologic Therapeutics Center, and his team in St. Louis manufacture the viral vectors, freeze them and ship them to Smith.

The therapeutic virus can infect any cell in the body, but it is engineered to replicate in bone tumor cells. Curiel explains bone tumor cells contain a genetic “on” switch required to set the altered virus’s replication machinery into action. Once the virus infects a bone tumor cell, which flips the switch, the virus begins replicating, filling up the cell and causing it to explode.

“‘We turn the cancer cell into a factory of its own destruction,’” Smith said. “Rupturing the cell also sets loose more viruses that are now free to infect other cells.”

To determine if the virus is working as designed, the researchers plan to involve 20 dogs, including Gary, in the current trial. Four dogs participated in a previous, smaller trial to test the safety of the viral treatment, much like human clinical trials start with a phase 1 safety trial. According to Smith, the experience of one dog in particular laid the groundwork for the current trial.

In late 2006, Nancy Hunter noticed the telltale limp in her rescue greyhound, Pretty. After receiving the osteosarcoma diagnosis, Hunter scoured the Internet and found information about racing greyhounds are at greater risk for osteosarcoma, a fast-moving bone cancer that often strikes human adolescents.
the investigational viral treatment available at Auburn. Pretty had the affected leg amputated, received the viral treatment and later underwent chemotherapy.

“She handled the treatment really well,” Hunter said. “After recovering from the surgery, she went back to digging in her sand pile, running around the yard and taking long walks. She got around great on three legs.”

At one year, when Hunter took Pretty for follow-up X-rays, the vets saw two spots on her lungs and suspected the cancer had spread. Upon further analysis, the lesions were determined to be scar tissue. Most significantly, these lesions were possible evidence of an acquired immune response to the tumor.

In addition to rupturing tumor cells with replicating viruses, the treatment may prime the dogs’ immune systems to recognize and attack the virus-infected cells.

“If that is the case, we may be creating an environment that could allow the immune system to start recognizing tumor cells and mount an anti-tumor immune response,” Smith said. “In other words, we’re trying to find out if the dogs become vaccinated against a recurrence of the tumor. That’s the question we want to answer in the current, larger trial.”

Pretty ultimately lived two years and four months after diagnosis, more than twice as long as the average. Smith said there’s no way to know if the experimental treatment was responsible for this. But Pretty’s experience and that of the other three dogs in the first trial allowed them to get funding for the current one.

Very early evidence suggests that a subset of dogs responds well to the treatment. The rest follow the average course. Curiel compares this to human treatments in which only a subset of patients responds well, pointing to the importance of personalized or precision medicine.

“W

We all want the silver bullet,” Smith said. “But the reality is that cancer is very diverse. This is another reason clinical trials in dogs are excellent models for human studies. All the dogs have different immune systems. They all respond to the world in different ways, just as people do.”

According to Curiel, several other cancers in dogs are excellent mimics of human disease, including melanoma, lymphoma and prostate cancer. Partnering with more veterinarians, including some at the University of Missouri-Columbia, Curiel is working to begin canine trials to test viral therapies in canine melanoma and lymphoma. He is also working with breast cancer researchers to look for ways to improve an investigational vaccine against human breast cancer.

As for Gary, he finished chemotherapy Jan. 30 and is doing well. Four months post-diagnosis, his chest X-rays were clear of signs of tumor spreading. It’s too early to say whether this new treatment has helped, but the Oravetzes are optimistic.

“He’s doing so well, there are times when I forget he has cancer,” Dawn Oravetz said. “I just see my loving, energetic, three-legged greyhound.

“With osteosarcoma so common in the greyhound community, I think a lot of owners are willing to participate in trials like this,” she added. “But what really geared me toward wanting to do the study was the idea that what they learn from the greyhounds could potentially help kids with osteosarcoma. If what they learn from Gary could help children with this cancer, I just think that’s an awesome thing.”

Beyond osteosarcoma, other cancers in dogs mimic human disease. These also could point toward improved therapies.

David T. Curiel, MD, PhD
Surgery’s seismic shift from time-to competency-based training
FOR 100 YEARS, general surgeons have learned their craft in exactly the same way. As residents, they spent most of their waking (and non-waking) hours in the hospital, shadowing more experienced surgeons and jockeying for time in the O.R. There was no academic curriculum per se; the patient mix dictated the day’s lesson plan. The “apprentice” model has remained largely unchanged.

This broad-based surgical field and its proliferation of increasingly sophisticated tools and techniques — combined with a U.S. mandate for reduced residency training hours — is making learning by osmosis all the more challenging. The ever-expanding body of knowledge is staggering; the time to learn it has shrunk.

As a result, nationally, general surgical education is in the midst of transformation. “The next five years will look nothing like the last 50,” explained Michael M. Awad, MD, PhD, assistant professor of surgery and associate dean for medical student education.

At the institutional and national levels, Washington University educators are devising improved methods to teach surgical skills. Consistently, School of Medicine faculty members have been ahead of the curve in surgical education — crafting a curriculum, employing skills labs outside the O.R., implementing quantitative evaluation measures and designing customized experiences for residents.
FEWER training hours

A number of factors over the past 10 to 15 years have altered the training landscape. Declining clinical reimbursements require doctors to see more patients to make the bottom line, allowing less time to teach. And residents are spending much less time in the hospital.

In 2003, the Accreditation Council for Graduate Medical Education (ACGME) limited the resident workweek to 80 hours. This mandate, a response to patient advocacy groups, was an effort to reduce medical errors.

“Now that residents are in the hospital less, the ‘education-by-accident’ model doesn’t work as well,” Awad said. “We have to do education by intention.”

The reduction affects all medical residents, but surgical training programs, in particular, had difficulty making the switch. Research indicates a strong link between a surgeon’s operative skill, the number of operations performed and patient outcomes.

“Resident graduates today voice a concern about their lack of preparedness for independence,” said Timothy J. Eberlein, MD, chair of the Department of Surgery and surgeon-in-chief at Barnes-Jewish Hospital. “Not long after the introduction of an 80-hour workweek, there was a national increase in the percent of residents failing the certifying examination of the American Board of Surgery.”

Due to medicolegal concerns, the ACGME restrictions tightened again in 2010, calling for greater supervision of physicians-in-training. Interns now must be directly supervised when performing a critical portion of any procedure.

In the past, surgical trainees became increasingly autonomous during residency, gaining the necessary expertise for independent practice. “Before, you could do five years of residency and hang your shingle,” Awad explained.

Today, however, most aspiring general surgeons undertake one to three years of post-residency fellowship training to strengthen skills and specialize.
GENERAL gets specialized

“General surgery” and “specialization” might seem like a contradiction in terms, but the field’s scope is so wide, it’s virtually impossible to master all aspects.

General surgery encompasses the abdomen, breast, skin and soft tissue, the endocrine system, transplants, pediatric surgery, critical care, surgical oncology (including head and neck surgery), emergency surgery, the alimentary tract (including bariatric surgery) and vascular surgery.

“The public also drives the push for specialization,” Awad said. “If you’re getting your hiatal hernia repaired, do you want to go to someone who does two or three a year, along with thyroid and gallbladder procedures, or do you want to go to someone who does 100 of these operations a year?”

Additional, specialized training time is needed, according to a 2013 study in the Annals of Surgery. Awad partnered on the multi-institutional study in which U.S. fellowship directors assessed the preparedness of general surgery residents after completing nine years of training (medical school and residency).

The result: 30 percent of fellowship directors felt that those entering fellowship could not independently perform a gallbladder removal, 19 percent felt that incoming fellows could not sufficiently operate laparoscopic tools and 56 percent felt they could not perform laparoscopic suture techniques.

TECHNOLOGY revolution

These percentages perhaps further underscore the breadth of general surgery and the dizzying array of laparoscopic, endovascular and robotic techniques.

The push for better patient outcomes has fostered ever-more-minimally invasive procedures. There used to be one way to remove a gallbladder — through a five-inch abdominal incision; now there are at least three ways.

At a recent Washington University Mini-Medical School session geared for the general public, audience members gasped in unison as they watched a video of a surgeon removing an appendix — through the patient’s mouth. By passing surgical instruments and a tiny camera through a natural opening in the body, the surgeon is able to perform incisionless procedures.

However, it’s not entirely out-with-the-old and in-with-the new. Surgeons must be prepared to operate the old-fashioned way if complications develop, despite less practice with these procedures.

CRITICAL shortage

The complexity and added debt and training time have made general surgery a less attractive career option for medical students, who may prefer to match to a non-surgical specialty right out of school. “The average medical student is no longer the single male who spends 168 hours a week at the hospital,” Awad said. “People want a life and families. Arguably, that makes for a more well-rounded person and doctor.”

In 2003, general surgery nationally had a number of unfilled residency positions in the Main Residency Match; this, combined with unfilled spots in 2002, served as a wake-up call. The country continues to face a general surgeon shortage, particularly in rural areas. Almost half of U.S. counties have no general surgeons.

“It was of concern,” said Mary E. Klingensmith, MD, the Department of Surgery’s vice chair for education and the Mary Culver Distinguished Professor of Surgery. “We realized that change was needed to bring the best and brightest to our field to ensure a stable workforce for the future.”

Nationally, schools are moving away from “one-size-fits-all” programs, instead customizing for individual aspirations.
TIME for change

Anticipating many of these pressures, Washington University leaders have been retooling the training regimen and implemented an 80-hour workweek at the medical school before the mandate.

“The ACGME adjusts its rules frequently, often giving advance notice of planned changes,” explained Paul Wise, MD, general surgery residency program director. “Here, we use ‘future’ regulations as our guide. We are a very proactive, progressive, almost risk-taking program as opposed to many more conservative programs that wait to let others sort out what will and won’t work.”

With prototype programs in place, the medical school is well poised to lead the national discussion about how best to train future surgeons. Klingensmith directs a consortium of eight U.S. surgical organizations, known as SCORE, which collaborate to develop a unified training curriculum, something that previously did not exist.

The web-based curriculum is updated annually. “We look at the technological advances and ask, ‘Is that a standard we want to make sure every resident is learning?’” Klingensmith explained.

Nearly two decades ago, Klingensmith, a fledgling resident herself, observed as the attending physician performed a mastectomy. Suddenly, the attending turned to Klingensmith and said, “OK. Close it up,” before promptly exiting the room.

“As I looked down at this young patient, I thought, ‘You’ve got to be kidding me. I’m learning right now,’” Klingensmith recalled. “I felt enormous pressure to make the incision look as nice as I could. I thought if I’m ever in a position to change surgical education, I’m going to do something about this.”

GAINING proficiency

Klingensmith, who began directing the general surgery residency at Washington University in 2001, made good on her promise, developing a skills training lab outside the O.R. that would expose residents to graduated levels of experience and provide practice opportunities in a low-stress environment.

A novel concept at the time, only two other institutions offered such labs: Southern Illinois University-Springfield and the University of Toronto.

Washington University has made major investments in the lab, formally the WUSM Institute for Surgical Education, accredited as a Level 1 (top) institute by the American College of Surgeons in 2012. Awad, nurse coordinator Debbie Tiemann, RN, and surgical technician Angelia DeClue, RST, now administer the lab.
Tools range from low-tech plastic body parts to highly realistic computer simulators. Students and residents can remove a virtual gallbladder before ever putting scalpel to flesh. Laparoscopic box trainers test precision and speed as residents transfer rows of pegs using a video monitor as a guide. Trainees also perform progressively challenging procedures in animal models and human cadavers.

“There isn’t any question that working on fundamental skills translates to the operating room,” said L. Michael Brunt, MD, professor of surgery and chief of the Section of Minimally Invasive Surgery and president of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES).

**INDIVIDUAL experience**

Traditionally, surgical residents have received little formalized performance feedback. Washington University is piloting an “academy model” that outlines core competencies and key milestones for several general surgery sections. “We are moving toward competency-based rather than time-based training,” Awad said.

The model stipulates that residents discuss learning objectives with faculty as they begin a rotation, receive mid-term feedback and undergo formal assessment at the end.

To more accurately gauge trainee performance, input is collected from nurses and technicians, as well as faculty. Awad then meets personally with the resident. If a resident is struggling in a particular area, he or she is paired up with a senior resident for as long as it takes to refine the skill.

“The academy model has revolutionized my education,” said fifth-year surgical resident Ashley M. Holder, MD, who began training at the medical school before the model was introduced. “I have witnessed that I can achieve the same competencies much more quickly in this streamlined and personalized approach.”

Another significant change nationally is a shift away from “one-size-fits-all” programs requiring residents to complete identical training modules across five years.

“As medical care becomes increasingly complex, it’s evident that not every individual needs to learn the entire breadth of surgery,” Klingensmith said. “For instance, do trainees going into heart surgery ever need to do pancreas surgery? Right now, that is a requirement. But it may not make a lot of sense in the big picture.”

Customizing residency training to individual aspirations could maximize the experience — reinforcing select skill sets while decreasing the dependency on fellowships.

Klingensmith is leading a nine-institution consortium examining flexibility in surgical training. At participating institutions, residents in their third, fourth or fifth years may spend 12 months in specialized rotations that will better prepare them for their intended areas of practice. The institutions are evaluating the effectiveness of such a model and collecting data on resident performance.

Washington University’s general surgery residency was one of the earliest to develop a “fast track” in cardiothoracic (2005) and vascular (2006) surgery, allowing senior residents to focus on these areas. The vascular surgery section took it a step further in 2013; trainees do not enter a general surgery residency, but rather spend five years learning vascular surgery almost exclusively, with some general surgical skills taught early in the program.

“Training the next generation of surgeons will require the types of programs we are developing, which are intentional, structured, rigorous and customized,” Awad said. “We no longer can rely on whatever happens to come through the operating room doors.”
Doctors learn their futures

THE FIRST DAY OF SPRING, MARCH 20, also was the day medical students across the country found out where they will head for their residency programs, the next stage in their medical careers.

School of Medicine students gathered at the Eric P. Newman Education Center for the much-awaited delivery of envelopes containing news of where the soon-to-be graduates had matched.

As students approached the microphone one-by-one to announce their specialties and where they had matched, they each placed $1 in a bin. Tradition has it that the cash goes to the student whose name is called last. The students are called randomly, so the loot goes to the person who had to wait the longest for such big news.

Overall, 123 medical students matched in 22 specialties in a total of 23 states. Top specialties included internal medicine, pediatrics, obstetrics-gynecology, orthopaedic surgery and anesthesiology.

C A L I F O R N I A
Los Angeles
University of California, Los Angeles
OPHTHALMOLOGY
Kirk Hou
RADIATION ONCOLOGY
Naomi Jiang

Riverside
University of California, Riverside, School of Medicine
PSYCHIATRY
Kazuo Omi

Sacramento
University of California, Davis Medical Center
INTERNAL MEDICINE
Vivian Tien

San Diego
University of California, San Diego
DERMATOLOGY
David Cotter
OBSTETRICS-GYNECOLOGY
Sarah Lederhandler
ORTHOPAEDIC SURGERY
Dylan Kluck
PEDiATRICS
Leslie Chiang

San Francisco
California Pacific Medical Center
OPHTHALMOLOGY
Ann Thomas
University of California, San Francisco
INTERNAL MEDICINE
Hailyn Nielsen
ORTHOPAEDIC SURGERY
Justin Krogue

S a n J o s e
O’Connor Hospital
FAMILY MEDICINE
Lawrence Zieske

Stanford
Stanford University Programs
EMERGENCY MEDICINE
Alexander Zorula
INTERNAL MEDICINE
Madeleine Chollet
OToLARYNGOLOGY
Varun Chalivendra
PEDiATRICS/RESEARCH TRACK
Susan Canny

Whittier
Presbyterian Intercommunity Hospital
FAMILY MEDiCiNe/TOpICAL MEDiCiNe
Amber Lin

C O L O R A D O
Aurora
University of Colorado
DERMATOLOGY
Jennifer Barkhund

C O N N E C T I C U T
Farmington
University of Connecticut
School of Medicine
OBSTETRICS-GYNECOLOGY
Stephanie Higgins

New Haven
Yale-New Haven Hospital
INTERNAL MEDiCiNe/PHiSiCAl SCIenTIST
Sandra Williams

D E L A W A R E
Newark
Christiana Care
OBSTETRICS-GYNECOLOGY
Kristen Kapalka
Chelsea Kebodeaux

D I S T R I C T O F C O L U M B I A
Washington
Children’s National Medical Center
PEDiATRICS
Angelica Wong

F L O R I D A
Miami
Jackson Memorial Hospital
PEDiATRICS
Temidayo Adebiyi

G E O R G I A
Atlanta
Emory University
School of Medicine
INTERNAL MEDiCiNe
Amirhossein Esmaceli

I L L I N O I S
Chicago
Northwestern McGaw Medical Center
INTERNAL MEDiCiNe
Lindsay Forbes
INTERNAL MEDiCiNe/DERMATOLOGY
Lida Zheng

K E N T U C K Y
Lexington
University of Kentucky Medical Center
DIAGNOSTIC RADiOLOGY
Leanne Lin

M A R Y L A N D
Baltimore
Johns Hopkins Hospital
INTERNAL MEDiCiNe
Stephanie Wang

M A S S A C H U S E T T S
Boston
Beth Israel Deaconess Medical Center
INTERNAL MEDiCiNe
Pankaj Pal

M I C H I G A N
Ann Arbor
University of Michigan Hospitals
EMERGENCY MEDiCiNe
Alexander Beyer
OToLARYNGOLOGY
Michael Wilson
PEDiATRICS
Michael Trreibwasser

Detroit
Children’s Hospital of Michigan
PEDiATRICS
Tamara Cooks
Wayne State University/Detroit Medical Center
OBSTETRICS-GYNECOLOGY
Sarah Cortez

Royal Oak
Beaumont Health System
ORTHOPAEDIC SURGERY
Kevin Park
Jonathan Wright

M I S S O U R I
St. Louis
Barnes-Jewish Hospital
ANEsTHESIOLOGY
Kristina Escallier
Bradley Fritz
Maxim Wolfson
DermAtolOgy
Leonid Shmuylovich
Christian Wichterman
EMERGENCY MEDiCiNe
Kevin Baumgartner
Jarrod Dornfeld
GERIATRIC SURGERY – PRELIMINARY
Gregory Ebersole
INTERNAL MEDICINE
Jordan Atkins
Stephen Chi
Christopher Chung
Nihla Jagadeesan
Joyce Ji
Ramon Jin
Jimmy Ma
Arvind Renganarajan
Anjali Rohatgi
Stephanie Vellozo
Peter Zhao

NEUROLOGICAL SURGERY
Jacob Greenberg
Bhuvic Patel

NEUROLOGY
Elyse Everett
Alan Plotzker

OBSTETRICS/GYNECOLOGY
Chelsea Bayer
Katherine Smith
Jennifer Traverso

ORTHOPAEDIC SURGERY
Zachary Meyer

PATHOLOGY
Brianna Kolody
Stephen Persaud

PSYCHIATRY
Desiree Baumgartner
Marie Bosch
Allan Jiang
Lauren Marks
Alexander Rose
Max Rosen

St. Louis Children’s Hospital

PEDIATRICS
Cori DeSanto
Sarah Ihnen
Natalie Macaruso
Drew Schwartz
Miriam Steinberg
Jessica Tsai
Annie Wang
Julia Warren
Elizabeth Wright-Jin

St. Louis University
School of Medicine

ORTHOPAEDIC SURGERY
Kelsey Rebhn
Washington University

OPHTHALMOLOGY
Han Li
James Liu

NEW MEXICO
Albuquerque

University of New Mexico
School of Medicine

PATHOLOGY
Samuel Anderson

NEW YORK
Bronx

Einstein/Montefiore Medical Center

GENERAL SURGERY
Faye Yu
New York Hospital for Special Surgery

ORTHOPAEDIC SURGERY
Lauren Wessel

New York

New York Presbyterian Hospital-Columbia

INTERNAL MEDICINE
John Blackett
Judith Kim

Rochester

University of Rochester/Strong Memorial

ORTHOPAEDIC SURGERY
Wajeeh Baksh

NORTH CAROLINA
Chapel Hill

University of North Carolina Hospitals

FAMILY MEDICINE
Alvin Powell

DURHAM
Duke University Medical Center

ORTHOPAEDIC SURGERY
Gerald Aggrey

OHIO
Cincinnati

Cincinnati Children’s Hospital

CHILD NEUROLOGY
Adrienne Brower-Lingsch
University of Cincinnati

ORTHOPAEDIC SURGERY
Carl Bruce

Cleveland

Cleveland Clinic-Cole Eye Institute

ORTHOPAEDIC SURGERY
Robert Purgert

COLUMBUS
Ohio State University Medical Center

ORTHOPAEDIC SURGERY
Rahel Ghenbot

OKLAHOMA
Oklahoma City

University of Oklahoma College of Medicine

ORTHOPAEDIC SURGERY
Emily Zantow

PHILADELPHIA
Philadelphia

Hospital of the University of Pennsylvania

NEUROLOGY
Nicole Shin
INTERNATIONAL MEDICINE-RESEARCH
Wumesh K.C.
Jonathan Lake

NEUROLOGY
Neena Cherayil

PITTSBURGH
University of Pittsburgh Medical Center

ORTHOPAEDIC SURGERY
Wajeeh Bakhsh

WASHINGTON
Seattle

University of Washington Affiliated Hospitals

ORTHOPAEDIC SURGERY
Adam Aronson

PROVIDENCE
Rhode Island Hospital/Brown University

ORTHOPAEDIC SURGERY
Steven Bokshan

TAMPA
University of South Florida

ORTHOPAEDIC SURGERY
Stephen Persaud

TEXAS
Edinburgh

University of Texas Health Science Center

ORTHOPAEDIC SURGERY
Chi Lun Pui

Choosing to defer residency:
Carolyn Purgert
NEW NAME, NEW ERA

The Elizabeth H. and James S. McDonnell III Genome Institute
GENOMICS-BASED RESEARCH is opening the door to more precise diagnoses, new disease treatments, and the ability to understand people’s health needs based on their genetic makeup. In the future, individualized DNA analysis will lead to a powerful form of preventive medicine.

To help support this paradigm shift in medicine, civic leaders and longtime philanthropists Elizabeth H. and James S. McDonnell III pledged $25 million to The Genome Institute, which will be renamed the Elizabeth H. and James S. McDonnell III Genome Institute at Washington University.

“This extraordinary gift will enable our top-line researchers to set more ambitious goals and step up discoveries in the fast-paced world of genomics,” said Washington University Chancellor Mark S. Wrighton.
Tracing the roots of disease

Under the leadership of Director Richard K. Wilson, PhD, the Alan A. and Edith L. Wolff Distinguished Professor of Medicine, and Co-director Elaine Mardis, PhD, the Robert E. and Louise F. Dunn Distinguished Professor of Medicine, the institute is helping to transform medicine using genomics.

Founded in 1993, the institute played a key role in the Human Genome Project, an international effort to decode all 6 billion letters of our genetic blueprint. It ultimately helped decode, or sequence, 25 percent of the genome by the project’s completion in 2003. The institute also has pioneered whole genome sequencing as a way to study cancer and other diseases.

In 2008, using private funds, institute researchers became the first to decode the whole genomes of both healthy and tumor cells from a leukemia patient — tracing the disease to its genetic roots. This potent mix of technology and ingenuity ushered in a new era, enabling researchers to search the entire genome to identify possible cancer-causing mutations.

Even though the institute is one of only three National Institutes of Health (NIH)-funded, large-scale sequencing centers in the U.S., it has struggled to find funding for some...
of its riskier projects. Sequencing the first whole cancer genome was a tough sell, as it was thought to be too expensive and too risky, possibly without much immediate benefit.

The McDonnells, who lost their daughter, Peggy, at age 2 of neuroblastoma, a common cancer in children, have long supported pediatric cancer research. “What appeals to us about the institute is its collaboration with St. Louis Children’s Hospital, Washington University School of Medicine’s Department of Pediatrics and others in the application of genomics to pediatric cancers,” said James McDonnell III.

In 2010, to better understand the genetic origins of pediatric cancer, the institute launched the St. Jude Children’s Research Hospital-Washington University Pediatric Cancer Genome Project. The project has led to the whole genome sequencing of more than 1,000 childhood cancer patients, helping to pinpoint a variety of mutations, including a key mutation in pediatric neuroblastoma.

Over the past six years, cancer genomics studies at the institute have compared the tumor and normal genomes in patients with breast, liver, kidney, brain, lung, skin and blood cancers, among others.

“At some point, we’ll be able to look at many different patients with the same type of disease and start to understand what’s genetically similar about all these people’s diseases and what’s different,” Wilson said. “That information eventually will lead to the development of new treatments. But even in the short term we can use that information to more effectively utilize the drugs we already have on the shelf right now.”

**Precision therapy**

In one clinical study, Lukas Wartman, MD, a patient with leukemia, had relapsed twice and run out of options. Institute researchers sequenced his genome and discovered a mutation that might be treatable instead with a kidney cancer drug already on the market. Wartman, who is now an assistant professor in the Department of Medicine and an assistant director at the institute, took the drug and was able to attain remission, allowing him to receive a stem cell transplant. Without the sequencing data, Wartman’s doctors say he likely would not have survived.

“Soon, we’re going to see an era where patients are monitored much more closely, their diagnoses are much more precise and individualized and, hopefully, their outcomes are much better,” Mardis said. “Side effects will be diminished. The days of one-size-fits-all therapeutics will be gone.”

To fulfill the promise of putting genomics into clinical practice, Wilson said, philanthropy is crucial.

“There is not a lot of support at this time for clinical genomic testing of cancers because it’s still in its infancy,” he said. “To take it to the next level and really touch more patients, we’ve got to have gifts like the McDonnells bring.”

Elizabeth H. and James S. McDonnell III have championed research efforts at the School of Medicine for many years.

In 2000, together with Anne, AB ’64, and John F. McDonnell and the JSM Charitable Trust, they funded the construction of the McDonnell Pediatric Research Building. The building was dedicated in memory of their daughter, Peggy, who died of cancer in 1972 at age 2.

In 2009, they endowed the Elizabeth H. and James S. McDonnell III Distinguished Professorship, which was instrumental in bringing Dennis Hallahan, MD, a preeminent figure in the study of cancers of the brain and central nervous system, to Washington University.

“Libby and Jim’s philanthropy has spawned scientific discoveries in nearly every pediatric discipline,” said Larry J. Shapiro, MD, executive vice chancellor and dean of the School of Medicine. “They have championed the medical school for many years, and this gift demonstrates their exceptional dedication to ensuring success in many key areas.”

McDonnell’s father, James S. McDonnell Jr., made a gift in the 1960s to establish the McDonnell Medical Sciences Building. In 1968, he endowed the James S. McDonnell Professorship in Genetics. And, in 1975, he made a gift to create the James S. McDonnell Department of Genetics, one of the first genetics departments within a U.S. medical school.
The promise of tomorrow

With support from generous alumni, Washington University is helping a new generation of aspiring medical professionals minimize student debt.

More than 80 percent of its medical students receive financial aid, primarily in the form of scholarships.

“We’ve always tried to see that anyone who has the ability and the desire to be a student at Washington University is given the opportunity,” said Larry J. Shapiro, MD, executive vice chancellor for medical affairs and dean of the School of Medicine. “We’re proud of the fact that our medical students have among the lowest debt of any medical students in the country,” he said.
Psychology of scholarships
Scholarships are a top priority for Gammon Earhart, PT, PhD, director of the Program in Physical Therapy.

“We want to continue to attract the best and the brightest physical therapy students, and to do that we need to be sure that they have the support they need,” she said. “That includes support from our faculty and staff for academic endeavors, but also financial support so they know that they can graduate with a manageable debt load,” she said.

Scholarships also have psychological benefits, Earhart said. “Students who receive scholarships feel welcomed. They feel like we have identified them as the best of the best and that we really want them to be here.”

Matthew Mastenbrook, DPT ’17, would agree. “I really want to work hard to show that I deserve the scholarship, and that I can make the person who gave it proud,” he said.

Shirley Sahrmann, PT, PhD, professor emerita of physical therapy, has created two scholarships, including the one awarded to Mastenbrook, and plans to create more as she leads fundraising efforts among alumni.

Sahrmann wants to help talented students “be at peace” with the choices they have made, and live their lives without the worry of student debt.

Sahrmann said that the program’s strong research component, an outgrowth of collaborations with the medical school, offers students the opportunity to “do incredible things.” “Students are exposed in every which way to people who are on the cutting edge.”

Such a dynamic environment can’t help but produce top practitioners and leaders, she said. “I get to travel around the country, and I’m always so pleased when I hear from clinicians saying, ‘Oh, we hired one of your amazing graduates,’” Sahrmann said.

“To think I can play some little role in helping people get on with their lives not only as professionals, but also in their personal lives, is really important to me.”

Reasons for giving
Retired Col. William P. Wiesmann, MD ’72, president and CEO of bioSTAR Inc., created scholarships because he wants others to “experience the wonderful things” he experienced at Washington University.

“When I came as a freshman I could get into a laboratory right away and start doing research with some very wonderful people,” he said.

“I had the chance to do some really fundamental basic science. I was able to write papers in medical school, which was a fantastic opportunity for me. It set me on my career path at that point.”

Wiesmann spent the majority of his career as a research scientist for government organizations such as NASA, and later became an entrepreneur.

“I’ve been looking back and thinking, ‘What were the things that made a difference in my life, and allowed me to get to where I am?’” Wiesmann said. “Some of those things have to do with being free to do what you want to do — being free to be passionate about what you love to do.”

A full-tuition scholarship enabled Vernetta Harris, MD ’04, to graduate from the School of Medicine with relatively little debt. Harris began practicing medicine in Atlanta, and eventually became a medical director of an emergency department in Tennessee. Being on sound financial footing allowed her to make the move, she said. “I felt like I was empowered to make changes, some call it risk, without thinking of the financial consequences.”

Harris also took some time off from clinical practice to participate in relief efforts in Ghana and Jamaica. “I would not have been able to do that so early in my career if I had had a large amount of financial stress.”

Harris funds scholarships to help others in the way she was helped.

“I know how big a boost and blessing it was to me, and I wanted to provide that to other students. Hardworking, talented students should be rewarded.”

Degrees of debt
Scholarships and financial aid help Washington University School of Medicine students graduate with far less debt on average compared to students at other medical schools.

<table>
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Scholarship support helps deserving students succeed.

LEARN MORE (314) 935-9691

LEARN MORE (314) 935-9691
Rodger and Paula Riney know all too well the devastating effects of Alzheimer’s disease. “My mother struggled with it for quite a long time,” said Rodger Riney, the founder and CEO of Scottrade, a nationwide discount retail brokerage firm. “It was just the most awful thing to watch.” Paula Riney has a similar story. “My dad passed away just over three years ago after battling Alzheimer’s for 12 to 13 years,” she said. “It was one of the saddest things I’ve ever experienced.”

The couple became involved with the Alzheimer’s Association, St. Louis chapter, and ultimately decided to make a significant investment toward research. “We felt that we wanted to do something a little more substantive,” Rodger Riney said. “Certainly something needs to happen because the cost of Alzheimer’s on society is just devastating and it doesn’t get the attention of other diseases.” “We just felt like we needed to do more,” added Paula Riney.

The couple discussed various initiatives of the university’s Charles F. and Joanne Knight Alzheimer’s Disease Research Center (Knight ADRC) with its director, John C. Morris, MD, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology. The Rineys decided to support School of Medicine researcher Beau Ances, MD, PhD, who they previously had met at an Alzheimer’s Association event. “We thought he was a terrific guy,” said Rodger Riney.

Ances, an associate professor of neurology affiliated with the Knight ADRC, is seeking biomarkers and developing imaging techniques to help researchers visualize amyloid and tau deposits in the brain. These protein deposits are hallmarks of Alzheimer’s. Amyloids form clumps outside of brain cells that disrupt neural networks, Ances said, while tau deposits form “tangles,” which twist and destroy communication pathways.

Studies by the Knight ADRC have shown that tau and amyloid can start to show up in the brain 15 to 20 years before symptoms manifest. “A lot of changes go on in this early preclinical phase,” Ances said. “Even though the individual is very normal, he or she already has pathology.”

While amyloid imaging has been used extensively in Alzheimer’s research studies, Washington University is one of the few sites worldwide that can image tau. These tau deposits can be viewed with labeled radioisotopes and a PET scanner, Ances explained.

Better imaging techniques will help researchers pinpoint the disease mechanisms, he added, and identify therapies that could stop the disease or delay onset. “My biggest hope is that we could find something to stop it in its tracks,” said Paula Riney.
1940s

Elliot Luby, MD 49, received a Distinguished Service Award from Wayne State University School of Medicine in Detroit for his 60 years of training, research and clinical care at the institution.

1960s

George Bohigian, HS 69, LA 61, gave the Charles A. Snyder Lecture at the annual meeting of the Cogan Ophthalmic History Society in Monterey, Calif. He is a professor of clinical ophthalmology and visual sciences at WUSM.

1970s

Susan Cigelman, PT 76, recently retired as vice president for academic affairs at AIB College of Business in Des Moines, Iowa. Prior to this position, she served as director of the physical therapy program at Des Moines University from 1987 to 2003.

David Dooley, MD 79, continues his responsibility with resident, fellow and medical student education at the South Texas VA and University Hospital. He also teaches internal medicine and infectious diseases to trainees.

1980s

Gina Musolino, PT 87, was re-elected to a second term as Florida chief delegate to the American Physical Therapy Association, House of Delegates.

John Constantino, MD 88, was awarded the 2014 Irving Phillips Award for Prevention from the American Academy of Child & Adolescent Psychiatry for significant contributions to the prevention of mental illness in children and adolescents. He is the Blanche F. Ittleson Professor of Psychiatry and Pediatrics at WUSM.

Andrew Sonin, MD 88, LA 84, was inducted as a fellow in the American College of Radiology. He is a diagnostic radiologist and a clinical assistant professor of radiology at the University of Colorado.

1990s

Dale Horne, MD 90, LA 82, recently accepted a position with the Mayfield Clinic & Spine Institute in Cincinnati. He is a board member and past president of the Ohio State Neurosurgical Society, secretary of the Northwest Quadrant of the Council of State Neurosurgical Societies, and a fellow of the American College of Surgeons.

Jeff Boris, MD 91, is a clinical professor of pediatrics at the University of Pennsylvania and a pediatric cardiologist in the outpatient clinic and director of the Postural Orthostatic Tachycardia Syndrome Program at Children’s Hospital of Philadelphia. He also chairs the American College of Cardiology Foundation/ American Heart Association Task Force for Data Standards for the Electronic Health Record, specific to pediatric and congenital cardiology.

Grant Hoekzema, MD 92, was named chair of the Council of Academic Family Medicine in 2013-14 and recently completed a term as president of the Association of Family Medicine Residency Directors. He is program director for Mercy Family Medicine-St. Louis.

2000s

Stefan Schulz, PT 01, is lead ergonomist with Briotix, a workforce performance company.

Laura VanZandt, OT 08, was married Aug. 30, 2014.

In Memory

Edna Dependahl, NU 45

Dependahl died Tuesday, Dec. 9, 2014. She was 91. Dependahl worked at Normandy Osteopathic Hospital for many years. An avid gardener, she was a docent at the Missouri Botanical Garden for 45 years. She was married to the late Eugene Dependahl for 50 years. Dependahl is survived by children Deborah, Frances and Carol; and three grandchildren.

Birkie Eck, MD 42, LA 38

Eck died Wednesday, Sept. 17, 2014. He was 97. During undergraduate study at Washington University, he served as class president and did so again while at WUSM. After finishing a medical degree, Eck joined the U.S. Army, serving in Africa, Italy and Japan and achieving the rank of major before leaving active duty service in 1945. He served a residency at the VA Medical Center at Jefferson Barracks. He later opened a private practice in Clayton, Mo., and served on the Deaconess Hospital staff. The last 10 years of his career were spent as medical director at Mari de Villa Retirement Center. He is survived by his wife of nearly 53 years, Mary Lea Eck.

Albert Eisenstein, MD 44

Eisenstein died Thursday, Dec. 18, 2014. He earned a bachelor’s degree from the University of Missouri before attending WUSM. During World War II, he was a U.S. Army captain. Before moving to New York in 1968, Eisenstein served as professor of medicine at Washington University and chief of internal medicine at Jewish Hospital. In New York, he served as professor of medicine at Downstate Medical School and chief of internal medicine at Gouverneur Hospital. After retiring to Florida, he became volunteer physician and medical director of the Senior Friendship Center for about 30 years. Eisenstein is survived by his wife of 73 years, Barbara; five children, Robert, Sylvia, Lesley, James and Richard; and 11 grandchildren and 17 great-grandchildren.

Harry Allen Fozzard, MD

Fozzard, a pioneer in the study of cardiac muscle activity and the Otho S.A. Sprague Distinguished Professor Emeritus in the Department of Medicine at the University of Chicago, died Tuesday, Dec. 9, 2014. He was 83. He attended Washington & Lee University and WUSM and interned at Yale University. He served in the U.S. Navy Corps at Camp Lejeune in 1957-59 and remained in the reserves, retiring in 1969.
Guy Harper, MD 52

Harper died Sunday, Aug. 24, 2014. He was 91. Born in Steele, Mo., Harper served in the European Theater from 1943 to 1945 during World War II. He graduated from the University of Missouri before attending WUSM. Harper completed an internship and residency at Methodist Hospital of Indianapolis, Ind., before beginning a private practice as a family physician in Charleston, Ill. He is survived by his wife of 62 years, Dorothy; children, Chrys, Robin, Reg, Jill and Roy; 10 grandchildren; and brother, Bobby Joe.

Betty Owen Knoblock, NU 51

Knoblock died Saturday, Oct. 25, 2014. She was 85. Born in St. Louis, she attended Iowa State University before achieving a nursing degree at Washington University. She was a head nurse at Barnes Hospital and met future husband, Dr. James Owen Jr. After the couple moved to Oklahoma, Knoblock suspended her nursing career to be a full-time mother and volunteer. She was president of the Service League and a longtime member of First Presbyterian Church of Bartlesville. Several years after the death of her husband, she married Richard Knoblock, who also preceded her in death. Knoblock is survived by her three sons, Jim, John and David; three daughters from her second marriage, Jane, Susan, and Trish; and nine grandchildren, as well as many nieces and nephews.

Edgar Nathaniel Lockett Jr., MD 45

Lockett died Monday, Oct. 20, 2014. He was 93. Lockett served as medical officer in the U.S. Navy during World War II. He later was a surgeon at the VA Hospital in Marion, Ill., and practiced internal medicine at the VA Hospital in Lake City, Fla. He was proud to serve as chairman of the deacons and Sunday school director at his church. His wife of 56 years, Helen, preceded him in death. He is survived by his sister, Kathryn; sons, Edgar, John, David and Jerry; nine grandchildren and 12 great-grandchildren.

In Memory

Herman Eisen, MD

Eisen, head of the Department of Molecular Microbiology at WUSM from 1961-1973, died Sunday, Nov. 2, 2014. He was 96. Eisen earned a medical degree from New York University in 1943 and was a member of its faculty from 1950-55. He came to Washington University in 1955 as a professor of medicine in the Division of Dermatology. Eisen authored the immunology section of an influential 1970s textbook on microbiology for medical students. He retired in 1989 from Massachusetts Institute of Technology, but, as a professor emeritus of biology, maintained an active lab at the university. As head of the Department of Molecular Microbiology at Washington University, Eisen oversaw the recruitment of several faculty members and supervised the department’s move to the McDonnell Medical Sciences Building in 1970. Among his survivors is his wife, Natalie.

John “Jack” Gilster, DE 44

Gilster, professor emeritus of pediatric dentistry at Washington University School of Dentistry, died Wednesday, Aug. 6, 2014. He was 92. Born in Chester, Ill., Gilster graduated from the University of Illinois in 1940 and the Washington University School of Dentistry in 1944.
He served two years in the U.S. Army and three years in a general practice in Illinois before establishing a private practice in pediatric dentistry. He joined the Washington University faculty in 1950 and taught pediatric dentistry until his retirement in 1987. During that time, he also served on the American Board of Pediatric Dentistry, as president of the North District of the St. Louis Dental Society and as president of the Missouri Society of Dentistry for Children. He was named a Distinguished Alumnus of Washington University in 1987. After retirement, he moved to Albuquerque, N.M. Gilster is survived by his children, John, Norman and Elisabeth, and six grandchildren.

David B. Gray, PhD
Gray, a professor of occupational therapy and neurology who worked tirelessly to improve the lives of people with disabilities, died Thursday, Feb. 12, 2015. He was 71. Gray became motivated to change what it means to be disabled after he was paralyzed in 1976 in a fall from a roof that broke his neck. He went on to work for several agencies at the National Institutes of Health (NIH), was appointed director of the National Institute on Disability and Rehabilitation Research by President Ronald Reagan and was an important advocate for the Americans with Disabilities Act of 1990. He was present when President George H.W. Bush signed the bill into law. Gray joined the School of Medicine faculty in 1995 to conduct research and teach courses on social issues and disability. He was the visionary behind the internationally recognized Enabling Mobility Center, now called the Health and Wellness Center, located at Paraquad, an independent living center in St. Louis. Gray was passionate about developing personalized interventions to help individuals fully participate in their everyday life activities. His work on the role that the environment can play in determining whether a person with disabilities can fully participate in an activity is internationally recognized. Realizing unemployment was a major problem for people with mobility limitations, he developed a program to study people with disabilities who had been successfully employed for two years. He created videos to tell their stories and made the videos available to potential employers. Additionally, Gray developed programs for parents with mobility limitations. Gray was born in Grand Rapids, Mich. He graduated from Lawrence University in 1962 with a bachelor’s degree in psychology. Gray later earned a master’s degree in experimental psychology from Western Michigan University, in 1970, and a doctorate in psychology and genetics from the University of Minnesota, in 1974. Survivors include his wife of 47 years, Margaret “Margy”; his son, David; two daughters, Elizabeth and Polly; a sister, Priscilla; two brothers, Fred and William; and two grandchildren.

James P. Keating, MD
Keating, a meticulous physician who helped mold hundreds of medical residents, organized the first pediatric intensive care unit west of the Mississippi and was sought for his ability to solve mystery illnesses, died Thursday, Dec. 25, 2014, in Cary, N.C. He was 76. Keating, a professor emeritus of pediatrics at WUSM and the inaugural W. McKim Marriott, MD, Chair in Pediatrics at St. Louis Children’s Hospital, died from a pulmonary embolism. In a career spanning 44 years at the university and St. Louis Children’s Hospital, Keating’s impact was far-ranging. In 1971, he established the pediatric gastroenterology and nutrition division in the Department of Pediatrics and served as its director until 1992. Recognized as one of that field’s founders, Keating helped develop many new-standard approaches to patient care. As an early proponent of pediatric intensive care, Keating shaped the first pediatric intensive care unit in St. Louis and was its director from 1980-1992. Keating also pioneered the concept of pediatric diagnostic medicine, founded such a division in 1992 and served as its director until his retirement. Digging for elusive answers in medicine was a passion. Keating and his colleagues discovered a significant cause of water intoxication — a potentially fatal condition — in infants. They found that 3- to 6-month-olds living in poverty suffered the illness disproportionately because their caretakers were more likely to run out of formula and instead feed infants water. Keating’s position as director of the pediatric residency program, which he held from 1969-2002, was among the roles he loved most. A demanding teacher, he was both feared and revered by the legions of residents he trained. Keating was born in Braddock, Pa. His father was killed in a military accident when Keating was 11, leaving his mother to raise four children. Keating earned an academic scholarship to Harvard, where he went on to receive an undergraduate degree and attend Harvard Medical School. He worked at Massachusetts General Hospital and then served as a U.S. Navy lieutenant at a civilian hospital in Vietnam during the Vietnam War. Among other honors, he received the Navy Commendation for Valor. After retiring in 2012, Keating moved to North Carolina. His survivors include his wife, Susan; daughter, Amy; son, Thomas; sister, Mary; and brothers, Larry and Jerry.

Herbert Rosenbaum, HS 51
Rosenbaum, professor emeritus of neurology at WUSM, died Wednesday, Dec. 10, 2014. He was 90. Distinguished as a clinical neurologist, diagnostician, outstanding teacher and dedicated supporter of Washington University and Barnes-Jewish Hospital, Rosenbaum was widely respected for his contributions to students and trainees. He taught the Practice of Medicine course for 61 years and mentored many residents during his tenure. Rosenbaum attended the University of Oregon for bachelor’s and medical degrees before completing residency and training at Barnes Hospital. He served for two years as a neurologist in the U.S. Air Force during the Korean War before joining WUSM faculty in 1954. Rosenbaum was a member of the American Academy of Neurologists and the Clinical Society of Neurology. He was awarded the Distinguished Service Award by the Washington University Medical Alumni Association in April 2014. Survivors include his wife, Velma; children, Robert, Barbara and Nancy; stepdaughter, Diana; and several grandchildren and step-grandchildren.
John C. Morris, MD
Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology; Director, Charles F. and Joanne Knight Alzheimer’s Disease Research Center

Childhood dream:
To play for the Cleveland Browns in the National Football League

Guess that didn’t work out. What did?
Wrestling — Athletic Hall of Fame inductee, Ohio Wesleyan University

What are you most grateful for?
After my family, it is all the talented faculty, staff and dedicated volunteers of the Knight ADRC!

Favorite honor:
One award with great personal significance is the Dr. Neville Grant Award for Clinical Excellence from Barnes-Jewish Hospital and Washington University Physicians. It means my peers consider me a good doctor!

Proudest moment:
Most recently it is the birth of my first grandchild, Jack, as he represents the next generation of what is most important — my family.

I support the School of Medicine because:
Washington University has been so supportive of me, and I am most pleased to give back.

Like Dr. Morris, consider supporting Washington University School of Medicine through an estate gift, life income plan or other planned gift.

To learn more, visit plannedgiving.wustl.edu or call 800.835.3503.
Dissecting Vesalius

Marking 500 years since the birth of Andreas Vesalius, the father of modern anatomy, Washington University and Saint Louis University co-hosted an interdisciplinary symposium. The three-day event included a roster of internationally renowned speakers and a dramatic re-creation in the Eric P. Newman Center — complete with an actor in a cadaver suit. Above, performers portray the intellectual struggle between 25-year-old Vesalius and aged professor Mattheus Curtius. Authorities such as Curtius revered the writings of ancient Greek physician Galen. Vesalius instead championed “the body over the book.” His inquiring mind would come to define a new era of anatomical exploration.

Online exhibit: beckerexhibits.wustl.edu/vesalius

Video — Faculty discuss Vesalius’ lasting impact: wumcnews.org/vesalius
Voices heard  First- and second-year medical students recently met with legislators at the Missouri State Capitol in Jefferson City. The cohort discussed issues of importance to the next generation of doctors.