

Outlook



Washington
University in St. Louis

SCHOOL OF MEDICINE

WINTER 2021-22

Fighting
cancer
before it starts



MD/PhD student Rita Chen (left) and postdoctoral researcher Brett Case, PhD, conduct COVID-19 research in this biosafety level 3 lab. See page 22.



COVER Surgeon Andrea R. Hagemann, MD, removes a patient's ovaries and fallopian tubes to mitigate cancer risk. With the aid of genetic testing, genetic counselors increasingly are able to identify cancer-causing variants and inherited risk patterns. Armed with this knowledge, patients can undertake a number of options to potentially avoid certain types of cancers. See page 16.

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A conversation with two scientists who are taking part in the global effort



MATT MILLER

Outlook

Washington University School of Medicine

OUTLOOK.WUSTL.EDU WINTER 2021-22



MATT MILLER

C. elegans (nematode roundworms), just about 1 mm in length, share many genes in their genome with humans, making them useful models for human diseases. See page 10.

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BERNARD BECKER MEDICAL LIBRARY

P. Roy Vagelos, MD (right), founder of the Division of Biology & Biomedical Sciences (DBBS), at the School of Medicine in 1973. See page 28.

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Photos of unmasked people in this magazine were taken prior to the COVID-19 pandemic or in accordance with School of Medicine masking protocols at that time.

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Lab space expansion

School adds 6 floors to BJC Institute of Health building

The School of Medicine will begin construction this spring on a six-floor expansion on top of the Steven & Susan Lipstein BJC Institute of Health building. The addition, estimated to cost \$150 million, will include 160,000 square feet of lab space.

The expansion will house a 7,900-square-foot biosafety level 3 (BSL-3), or high-containment, laboratory to support research on infectious viruses such as SARS-CoV-2 and tuberculosis. Specialized ventilation and other systems in BSL-3 labs

enable scientists to safely study viruses that spread through

the air, so that diagnostic tools, treatments and vaccines can be developed.

The building expansion also will include: a 5,100-square-foot Biologic Therapy Core Facility for developing cellular therapies to treat cancer (following Current Good Manufacturing Practice regulations enforced by the Food and Drug Administration); 103,000 square feet of expanded laboratory space; and about 44,000 square feet of mechanical building-support areas.

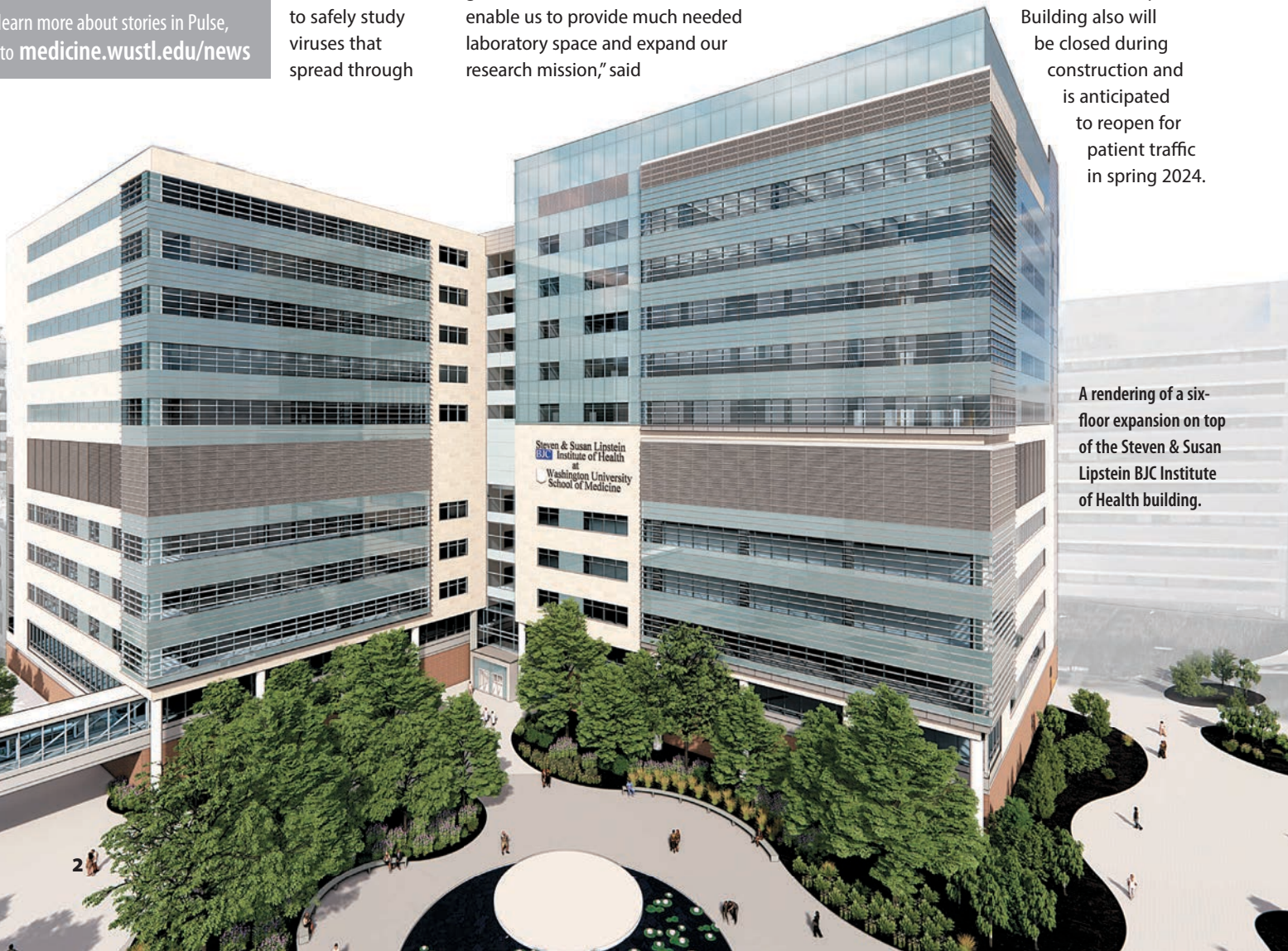
“This building addition is a very exciting and critically important next step in the growth of the medical school and will enable us to provide much needed laboratory space and expand our research mission,” said

David H. Perlmutter, MD, the George and Carol Bauer Endowed Dean of the School of Medicine, executive vice chancellor for medical affairs, and the Spencer T. and Ann W. Olin Distinguished Professor.

The BJC Institute of Health building faces Ellen S. Clark Hope Plaza, which will be closed during construction. Until the plaza reopens in winter 2024, pedestrians will be routed to the plaza’s perimeter and will use a covered walkway to reach the front door of the BJC Institute of Health building. A portion of Wohl Circle Drive in

front of Wohl Hospital Building also will be closed during construction and is anticipated to reopen for patient traffic in spring 2024.

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



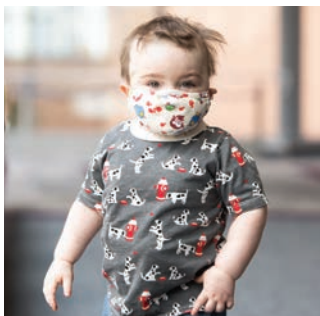
A rendering of a six-floor expansion on top of the Steven & Susan Lipstein BJC Institute of Health building.

Immunotherapy could help young patients with AML

An immunotherapy harnessing the immune system's "natural killer" cells has proven effective in treating acute myeloid leukemia (AML) in some adults whose cancers return. Now, researchers have shown in a small clinical trial that the same natural killer cells also can help some children and young adults with recurrent AML.

The journal *Blood* published online results from the phase 1 trial, which included eight patients ages 1 to 30 years.

"All of the patients enrolled in this study had very aggressive AML," said first author Jeffrey J. Bednarski, MD, PhD, an assistant professor of pediatrics. "For all of them, their leukemia recurred after stem cell transplantation and was not responsive to several treatment regimens before they were referred to this study. This is a very challenging disease to treat — none of the patients had any curative options. The survival expectation for these patients was essentially zero. That three patients are still alive is very encouraging for this really challenging disease."



GARA ELIZABETH PHOTOGRAPHY

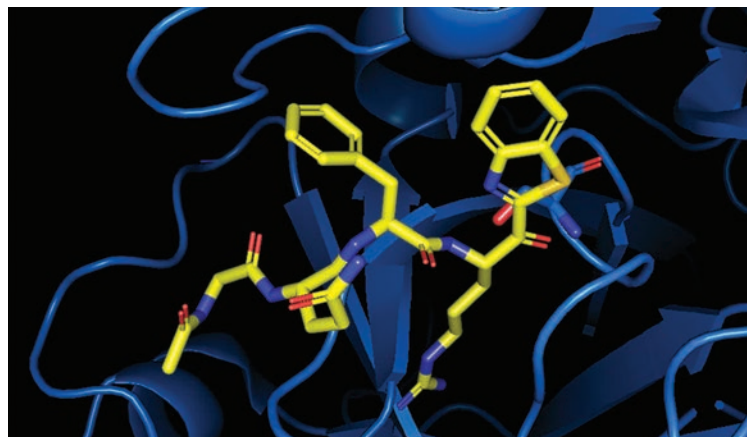
Past work from Washington University researchers has shown that natural killer cells' ability to attack cancer cells can be enhanced by exposing them to a specific cocktail of chemicals called cytokines. When such "cytokine-induced memory-like" natural killer cells are given to the patient, they are more aggressive in attacking the cancer because of this pre-activation.

"A unique angle to this study is that we're using the patient's original stem cell donor's cells to generate the memory-like natural killer cells, so the cells won't be rejected by the patient's immune system but are still able to fight the leukemia," said senior author Todd A. Fehniger, MD, PhD, professor of medicine. Fehniger's lab developed the methods for producing the cytokine-induced memory-like natural killer cells and led the original clinical trial of these cells in adults with AML.



MINI-MEDICAL SCHOOL GOES ONLINE

Attend WashU's popular, long-running Mini-Medical School on Zoom. Spring registration is underway soon. Learn more at minimed.wustl.edu.



JAMES JANETKA

This compound (in yellow) blocks the active site of a human protein that the virus hijacks to enter human cells.

Antiviral compound blocks SARS-CoV-2

Scientists have developed a chemical compound that interferes with a key viral feature that allows the viruses to invade human cells. The compound, MM3122, was studied in cells and in mice and holds promise as a way to prevent COVID-19 infection or reduce its severity if given early in the course of an infection. The *Proceedings of the National Academy of Sciences* published the study online Oct. 11.

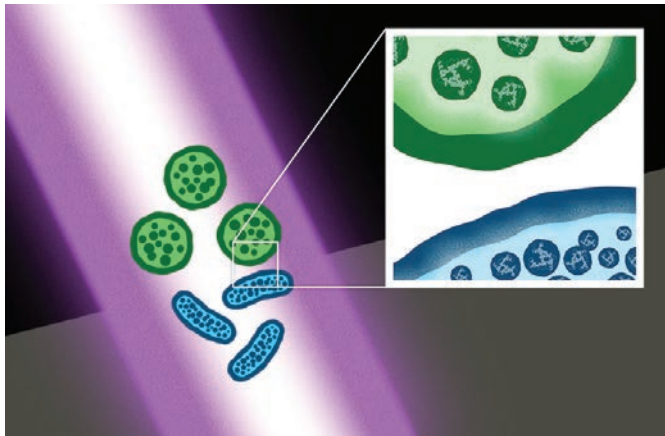
The compound targets a key human protein, transmembrane serine protease 2 (TMPRSS2), that coronaviruses harness to enter human cells.

"The compound we're developing prevents the virus from entering cells," said senior author James W. Janetka, PhD, a professor of biochemistry & molecular biophysics. "Our ultimate goal is to advance the molecules into an inhibitor that can be taken by mouth and that could become an effective part of our armamentarium of inhibitors of COVID-19."

MM3122 protected cells in the lab that were infected with SARS-CoV-2 from viral damage much better than remdesivir, a COVID-19 treatment approved by the Food and Drug Administration. An acute safety test in mice showed that large doses of the compound given for seven days did not cause any noticeable problems. The compound also was as effective against the original Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV).

Janetka and his colleagues are collaborating with researchers at the National Institutes of Health (NIH) to test the effectiveness of MM3122 in treating and preventing COVID-19 in animal models. Working with Washington University's Office of Technology Management, Janetka co-founded a biotechnology startup company called ProteXase Therapeutics, which has licensed the technology.

MIKE WOLFUL



The ultrashort-pulse lasers could destroy bacteria that are hard to kill by other means.

Lasers kill bacterial superbugs, spores

Lasers that emit ultrashort pulses of light can kill multidrug-resistant bacteria and hardy bacterial spores, WashU Med researchers have found. The findings, available online in the *Journal of Biophotonics*, open up the possibility of using such lasers to destroy bacteria that are hard to kill by other means. The researchers previously have shown that such lasers don't damage human cells, making it possible to envision using the lasers to sterilize wounds or disinfect blood products.

"Imagine if, prior to closing a surgical wound, we could scan a laser beam across the site and further reduce the chances of infection," said first author Shaw-Wei (David) Tsen, MD, PhD, an instructor of radiology at Washington University's Mallinckrodt Institute of Radiology (MIR). "I can see this technology being used soon to disinfect biological products in vitro, and even to treat bloodstream infections in the future by putting patients on dialysis and passing the blood through a laser treatment device."

Tsen and senior author Samuel Achilefu, PhD, until recently, the Michel M. Ter-Pogossian Professor of Radiology, have been exploring the germicidal properties of ultrashort-pulse lasers for years.

In the new study involving methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* (*E. coli*) and spores of *Bacillus cereus*, the lasers killed more than 99.9% of the target organisms, reducing their numbers by more than 1,000 times.

Asthma may lower brain tumor risk — but how?

There's not much good that can be said about asthma, a breathing disease in which the airways become narrowed and inflamed. But there's this: People with asthma seem to be less likely to develop brain tumors than others. And now, researchers believe they have discovered why.

It comes down to the behavior of T cells, a type of immune cell. When a person — or a mouse — develops asthma, their T cells become activated. In a new mouse study, researchers discovered that asthma causes the T cells to behave in a way that induces lung inflammation but prevents the growth of brain tumors. What's bad news for the airways may be good news for the brain.

The findings, available online in *Nature Communications*, suggest that reprogramming T cells in brain tumor patients

GETTY IMAGES



to act more like T cells in asthma patients could be a new approach to treating brain tumors.

"Of course, we're not going to start inducing asthma in anyone; asthma can be a lethal disease,"

said senior author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology. "But what if we could trick the T cells into thinking they're asthma T cells when they enter the brain, so they no longer support brain tumor formation and growth? These findings open the door to new kinds of therapies targeting T cells and their interactions with cells in the brain."



SHOW ME THE SCIENCE

TO LEARN MORE about how WashU Med scientists and clinicians are confronting the COVID-19 pandemic, listen to the "Show Me the Science" podcast, produced by the Office of Medical Public Affairs. Find the podcast on Apple Podcasts, Spotify or wherever you listen to podcasts.

Time until dementia predicted by amyloid levels

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positron emission tomography (PET) to gauge brain levels of the Alzheimer's protein amyloid beta.

In those who eventually develop Alzheimer's dementia, amyloid silently builds up in the brain for up to two decades before the first signs of confusion and forgetfulness appear. Using a person's age and data from a single amyloid PET scan, the algorithm

yields an estimate of how far a person has progressed toward dementia — and how much time is left before cognitive impairment sets in.

Suzanne E. Schindler, MD, PhD, an assistant professor of neurology, spent years trying to figure out how to use the data in amyloid PET scans to estimate the age at which symptoms would appear.

The breakthrough came when she realized that amyloid accumulation has a tipping point and that each individual hits that tipping point at a different age. After this tipping point, amyloid accumulation follows a reliable trajectory.

People in the study who reached the tipping point at younger ages took longer to develop cognitive symptoms than those who reached it later in life. Participants who hit the tipping point at age 50 typically took nearly 20 years to develop symptoms; those who hit it at age 80 took less than 10 years.

The power of this new technique is that it requires just one brain scan, plus the person's age. With that data, the model can estimate the time to symptom onset, plus or minus several years. In this study, the correlation between the expected age of symptom onset and the true age at diagnosis was better than 0.9 on a scale of 0 (no correlation) to 1 (perfect correlation).

WashU Med researchers have developed an approach to estimating when a person who is likely to develop Alzheimer's disease, but has no cognitive symptoms, will start showing signs of Alzheimer's dementia.

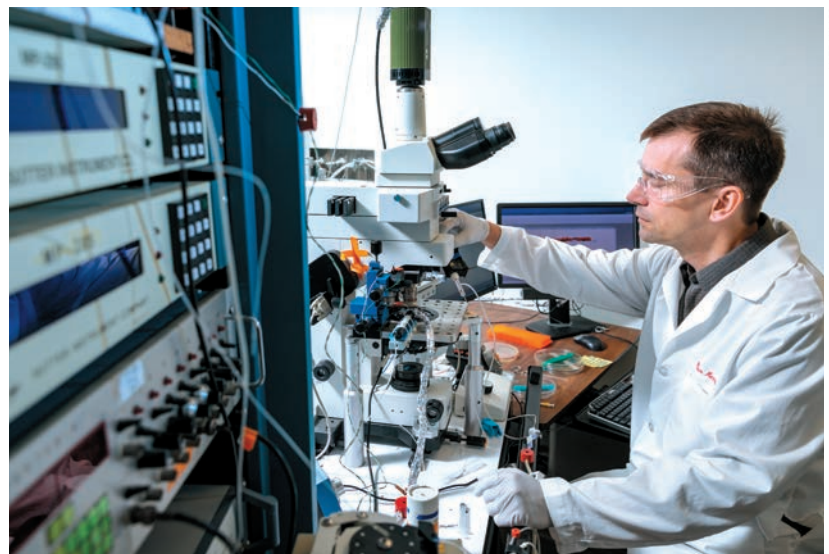
The algorithm, available online in the journal *Neurology*, uses data from amyloid

Center to study treatments for psychiatric disorders

The National Institute of Mental Health (NIMH) has awarded the School of Medicine a five-year, \$12.2 million grant to create a center aimed at advancing research into neurosteroids as treatments for depression and other psychiatric disorders.

The new Silvio O. Conte Center for Basic Neuroscience Research is one of only 15 Conte Centers funded by the NIMH, of the National Institutes of Health (NIH). The center's research focus complements work performed at Washington University's Taylor Family Institute for Innovative Psychiatric Research, where scientists have focused since 2013 on the potential of neuroactive steroids to be used to treat psychiatric problems.

In addition to tapping psychiatrists, neuroscientists, anesthesiologists and chemists at the School of Medicine, the new Conte Center also will involve researchers at Tufts University, Duke University and the University of Colorado. The overall goal is to identify pathways and receptors in the brain that interact with neuroactive steroids.



MATT MILLER

Steven J. Menerick, PhD, works in his laboratory, where he studies neurosteroids and their potential as antidepressants.



All-time high

NIH funding to medical school continues explosive expansion

Regional pandemic stay-at-home orders in 2020 temporarily halted all biomedical research unrelated to COVID-19 at the School of Medicine. But as COVID-19 restrictions were lifted, the school bounced back, and researchers returned to their benches. Despite pandemic challenges, 2021 proved to be yet another year of remarkable accomplishments as the school exhibited dramatic growth.

The National Institutes of Health (NIH) awarded School of Medicine researchers \$575.8 million in funding in 2021, an increase of nearly \$88 million over the previous year. This is an all-time high for the school and the sixth consecutive year of growth in NIH grant awards. Research grants to the School of Medicine from all sources reached close to \$750 million in 2021. Together with increased institutional support, the total annual investment in research has reached more than \$1 billion.



David H. Perlmutter, MD, executive vice chancellor for medical affairs, George and Carol Bauer Endowed Dean of the School of Medicine and Spencer T. and Ann W. Olin Distinguished Professor, talks about the exciting research that has fueled this growth and expansion.

Outlook: Since 2016, NIH funding has grown by more than \$200 million, an increase of 54% that corresponds to a compound annual growth rate of over 9%. What do these numbers tell you about the School of Medicine?

Perlmutter: The increase in grant awards from the NIH, as well as other funding sources, is a reflection of the remarkable depth and breadth of talent here at the School of Medicine. Even with the challenges and disruptions of the COVID-19 pandemic, the commitment of WashU Medicine faculty and staff to our missions has been breathtaking. We care for patients with deep

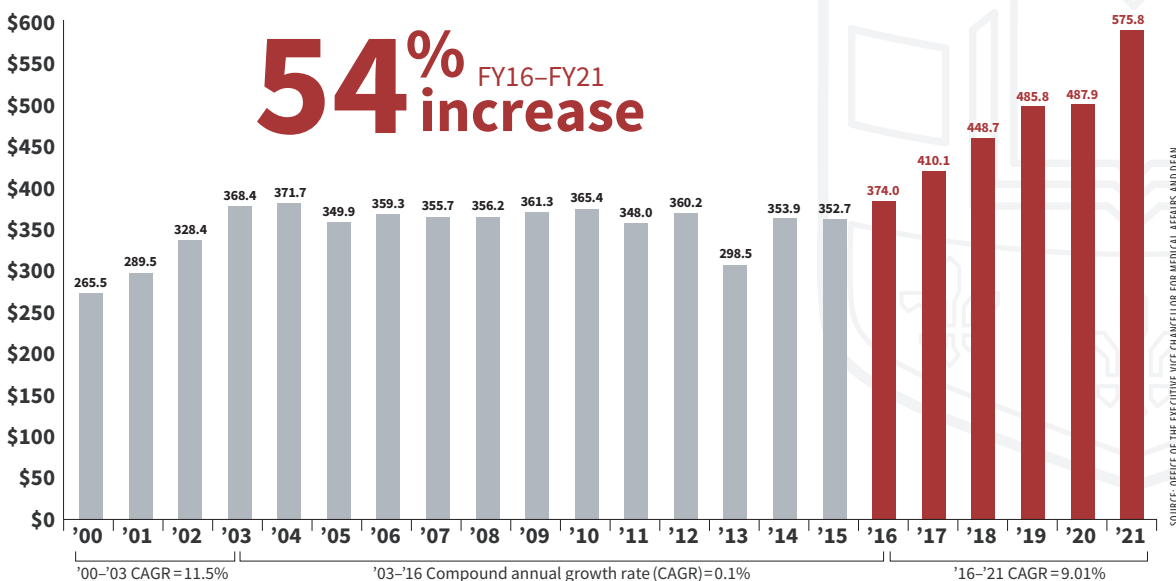
compassion and the highest standards of quality possible today, while also carrying out research that will allow us to enhance that care and the outcomes for tomorrow and well into the future.

Our goal has never been getting grants just for the sake of getting grants or because it's prestigious. Our holy grail has always been curing disease and improving human health. We do this in large part through our discovery capabilities — through knowledge that advances in the lab and leads to new therapies and innovations for improving patient care. And grants allow us to do more of this work and to do it at the level of excellence that everyone has come to expect from WashU. That is why this news is so incredibly exciting and gratifying.

I track our NIH funding very closely, and I knew we had great momentum over these past few years, but it still was completely astonishing to see the total number of \$575.8 million for federal fiscal year 2021, particularly when I realized that we had surpassed other top-notch academic medical centers with whom we collaborate and whom we deeply respect like the University of Pennsylvania, Stanford University and Johns Hopkins University. As an institution, we cannot be humble about this — it is a spectacular achievement.

WashU Medicine: NIH awards

Total dollars in millions, 2000–2021



The growth in our research base has included new recruits, the evolution of our junior faculty to independent funding, and new grants from long-standing members of our faculty. Some of the newer grants — like the Center for Perioperative Mental Health, the Conte Center for Basic Neuroscience Research, which will work on new drugs for psychiatric disease, and the Long Life Family Study — and new projects using the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) represent existing strengths across several departments and are responsive to key areas for the future of biomedicine. We also have seen wonderful and complementary growth in our clinical and educational programs over the last five years. There’s been so much growth that we now are scrounging around for space and counting the days until major construction projects are done, including the Neuroscience Research Building, the vertical, six-floor expansion of the BJC Institute of Health and the Ambulatory Cancer Building.

Outlook: How has the School of Medicine achieved such strong growth in NIH support?

Perlmutter: The School of Medicine has been investing in research for decades — long before I became dean — and that investment has paid off in the form of a strong track record of groundbreaking publications and successful NIH

funding. We continue to build on that foundation, thanks to the leadership of the Executive Faculty and the power of its shared governance model. Each of our department heads has figured out ways to invest more in the research and clinical programs of their departments, to bring in new recruits and to explore new research areas. We also have benefited from the BJC Investigators Program, which has added six brilliant leaders in science to our faculty and will bring in four more BJC Investigators in the coming years.

This kind of long-term and stable investment has led to an exceptional standard for the quality of science that is baked into the culture of this community. Every project and every initiative is conceptualized to address an extremely important goal using the best possible scientific approach no matter how daunting the challenges. You can observe it in work from our most distinguished faculty to the students even as they start their first research projects.

Outlook: Why is the amount of NIH funding particularly significant?

Perlmutter: NIH funding is an objective measure of scientific competitiveness and undergoes extremely rigorous peer review. We and many of our peer institutions consider this funding the most useful in setting strategic goals and measuring our success because it is

MATT MILLER



David H. Perlmutter, MD

2016 top 5 in funding compared to 2021

	2016	2021
UCSF	\$518,037,400	\$626,297,281
Hopkins	\$456,734,343	\$566,302,205
Penn	\$392,015,147	\$529,569,145
Stanford	\$381,724,197	\$524,214,470
WashU	\$374,029,188	\$575,870,613

SOURCE: OFFICE OF THE EXECUTIVE VICE CHANCELLOR FOR MEDICAL AFFAIRS AND DEAN

publicly available and can be validated. Other ranking metrics, such as those of U.S. News & World Report, include data that is not verifiable and, because of that, often generate relatively inexplicable rankings. But more than being the gold standard, NIH funding also provides partial funding for facilities and infrastructure that supports the research, and that obviously helps us a great deal as we try to get more and more lifesaving therapeutics and techniques out into the world.

Outlook: Can you comment on the research expansion as it relates to what you have articulated about the “virtuous cycle” of academic medicine?

Perlmutter: We invest in education and research to improve clinical care and create better outcomes for patients and better health for the community. In turn, our clinicians identify important areas for study. This culture of academic improvement also draws more patient referrals and clinical research studies that elevate us as a clinical provider. This is what distinguishes an academic medical center from other hospitals and clinics, and we strongly believe that it is the best way to advance human health for everyone. Yes, we’re doing the best we can to take care of patients today, but we aspire to do even more — we are compelled to do even more for the people of our city and the region.

Outlook: In the School of Medicine’s 2021 State of the School Report, you noted other growth metrics. Can you elaborate?

Perlmutter: Every way you look at it, the school is thriving. Successes over the past five years include: curriculum modernization and major increases in scholarships; increased support to expand the number of graduate students in the Division of Biology & Biomedical Sciences; an increase in the number and diversity of medical school faculty; an increase in clinical activity, in terms of patient visits and in the number of staff available to support that care; and substantial new investments in research, ambulatory clinic space and research and clinical programmatic initiatives. In total, the number of medical school faculty has increased by 29% since 2016. Patient visits have increased by 51% during that same time period, and that is a reflection of our success in providing better access to care for our community.

2021 NIH funding to medical schools

NYU*	\$807,641,873
UCSF	\$626,297,281
Duke*	\$608,276,422
WashU	\$575,870,613
Hopkins	\$566,302,205
Penn	\$529,569,145
Stanford	\$524,214,470
Yale	\$505,425,019
UCLA	\$493,820,803
Columbia	\$497,122,157

*Funding to NYU and Duke include short-term grants for coordinating large national multicenter clinical research projects related to COVID-19 of \$448 million and \$115 million, respectively.

SOURCE: OFFICE OF THE EXECUTIVE DEAN/CANCELLOR FOR MEDICAL AFFAIRS AND DEAN

Outlook: Where do you see the School of Medicine going in the next few years?

Perlmutter: We are having a positive impact in so many ways here at WashU. We are home to great talent and are succeeding in attracting new recruits as well. It is inspiring to see how our strategic plans have led to growth in all of our missions: research, education and clinical care. Looking to the future, we can’t help but think big. Our primary goals are: How can we change the way we fight disease and meet medicine’s most enduring challenges, including prevention and lowering cost of health care? How can we make sure that everyone in our region, urban and rural, benefits from the work we’re doing here? What can we do to improve the economy in our city and the region since we know that economic status plays such an important role in health outcomes? Yes, these are big challenges, but we can tackle them at WashU Medicine. I cannot imagine anything I would rather do with my life right now. Nor can I think of a community, a team, with whom I would rather do it. ☐

A man with a beard and a baseball cap stands in a field, looking off to the side. He is wearing a blue t-shirt with a logo that says "Destin ORIGINAL CLASSIC" and "EST. 1950". He is also wearing blue jeans. In the background, there is a red utility vehicle, possibly a golf cart or a small truck, and some trees. The overall scene is outdoors and appears to be a rural or recreational area.

Diagnostic odyssey

Undiagnosed Diseases Network seeks to explain mysterious medical conditions

BY GAIA REMEROWSKI

When you seek medical care, you expect a diagnosis. You may need to answer a lot of questions and undergo tests, but usually doctors can figure out the root of the problem.

This is not the case for a surprisingly large group of patients. According to the National Institutes of Health (NIH), 25 million to 30 million Americans live with rare diseases that sometimes require years to diagnose.

Funded by the NIH, the Undiagnosed Diseases Network (UDN) collaborates on hard-to-diagnose conditions in patients of all ages. With 12 clinical sites, including a coordinating site at Harvard University, the UDN joins together clinicians, researchers and physician-scientists from around the country who use advanced technologies in a way that would not be possible outside of this network.

The School of Medicine, an international leader in genome sequencing, is bringing its unique strengths to the UDN, helping to solve some of today's most challenging medical mysteries.



Jason and Amy Lair with their son, James, 8, on the family farm near Alexis, Ill. The Undiagnosed Diseases Network discovered a genetic variant that inhibits James' growth.

In search of answers

When Amy Lair gave birth to her son, James, six weeks early, he weighed in at a healthy 8 pounds. But his growth slowed as months passed.

“He just never did really take off, as far as eating or motor skills like crawling around,” said James’ father, Jason Lair. “He was 3 years old before he walked.”

“We went through a lot of referrals from different doctors, but every test we ever did was normal,” Amy added. “Everybody said, ‘Oh, he’s fine. He’s just going to be little. He’s just a slow grower.’ As parents, we knew something was definitely wrong.”

The Lairs spent countless nights Googling symptoms and possible conditions they thought might apply to James. That’s how they came upon the UDN.

By the time families like the Lairs find out about the UDN, they have been through a “diagnostic odyssey,” said Patricia Dickson, MD, head of the Washington University UDN clinical site and the Centennial Professor of Pediatrics and professor of genetics. They have often been referred to multiple specialists who evaluate each symptom independently and try to come up with a diagnosis. But this approach often fails to explain all the patient’s underlying symptoms and issues.

“The Undiagnosed Diseases Network either gives families a way to end their diagnostic odyssey because they find an answer, or because

they can be satisfied that they’ve done everything that they can and there’s nothing else left,” said Dickson, who also leads the Division of Genetics and Genomic Medicine in the Department of Pediatrics. This form of closure “is an incredibly powerful gift to families that the network provides,” she said.

Uniquely positioned

Neonatologist F. Sessions Cole, MD, led the way for Washington University’s acceptance into the UDN in 2018. Cole, the Park J. White, MD, Professor of Pediatrics, already was working on diagnosing mysterious diseases in infants. He co-leads a lab with Jennifer A. Wambach, MD, associate professor of pediatrics. This lab often is the first stop when patients from Washington University’s UDN clinical site need genetic sequencing and data analysis.

As a leader in genome sequencing since the start of the Human Genome Project, which aimed to sequence every letter of our DNA, Washington University has remained a powerhouse in the field, going on to sequence the first cancer genome and provide exceptional clinical genetics care through its pediatric and adult genetics clinics.

Washington University also is home to one of the largest physician-scientist training programs in the country, another boon for the UDN. “We have the ability to call on clinicians from a variety of different specialties, all of whom have a research background or are actively engaged in research,” Dickson said. “They can bring both their knowledge of research and their clinical knowledge to each and every case.”

One of the UDN’s greatest assets is also one of its simplest ideas: Doctors who talk to each other, Dickson added. It’s often hard for diverse specialists to find the time and opportunity to discuss patients’ cases. But this is one of the most valuable parts of the network, said Stephen I. Stone, MD, an endocrinologist who helped with James Lair’s case.

“Collaboration is paramount in the Undiagnosed Diseases Network. Our guiding principle is solving medical mysteries through team science,” said Stone, an instructor in pediatrics, endocrinology and diabetes. After examining James, Stone was able to consult with the boy’s geneticist, Dorothy K. Grange, MD, at a UDN meeting that was set up to discuss the case. The two physicians spoke about trying growth hormone to address James’ slow growth and agreed it was the best next course of action.



Pediatric endocrinologist
Stephen I. Stone, MD, examines
James in the clinic at St. Louis
Children’s Hospital.

JUDY MACCH



A genetic coincidence

It turns out Grange, who is a professor of pediatrics in the Division of Genetics and Genomic Medicine, had another patient with the same exceptionally rare genetic change that James Lair has. This change, or variant, is in *MAP2K1*, a gene that makes an enzyme that is important in cell signaling. Disruption of this gene can lead to problems with cellular growth and development. The variant was not found after a genetic analysis of James' parents, so it likely arose spontaneously in James.

When Grange first examined James, she asked Daniel J. Wegner, a lab manager in the Cole-Wambach lab, to reanalyze James' exome sequence, which contains the sequencing data for all the protein-coding regions of the genome. After analyzing the data within their research pipeline, Wegner discovered the variant in *MAP2K1*, as well as two other patients with the same variant.

"By coincidence, it turned out that one of those patients was my patient that I've been following here at Washington University for the past 20 years," Grange said. "I've been seeing her for a long, long time, trying to figure out what her diagnosis is. Without the UDN, we would not have figured this out."

The third patient lives on the west coast and is not treated at Washington University. All three

patients shared similar symptoms, with the major one being slow growth. "Finding more patients with variants in the same gene is usually the best way to solve these cases," Wegner said.

Given these similarities in cases, Stone decided to prescribe growth hormone for James. Even though growth hormone has some risks, without it, "we're looking at someone who could potentially be so short that they would have trouble living independently or without assistance," Stone said.

James' geneticist, Dorothy K. Grange, MD, a professor of pediatrics, and bioinformatics researcher Daniel J. Wegner consult on the case. Grange asked Wegner to reanalyze James' exome sequence.

"We have the ability to call on clinicians from a variety of different specialties."

— Patricia Dickson, MD



Gregory P. Van Stavern, MD, professor of ophthalmology and visual sciences, and resident Kelly Kiser, MD, examine patient William Spinks during a neuro-ophthalmology appointment at the Center for Outpatient Health. Spinks had five physician exams and a number of tests over a three-day period as the UDN worked to find the cause of his balance issues.

One day, soon after being accepted into the UDN, Amy and Jason Lair were working on their farm with the tractor running. Amy’s phone rang. It was nurse practitioner Kathleen A. Sisco, Washington University’s UDN clinical site coordinator. She told Amy the team may have figured out what was going

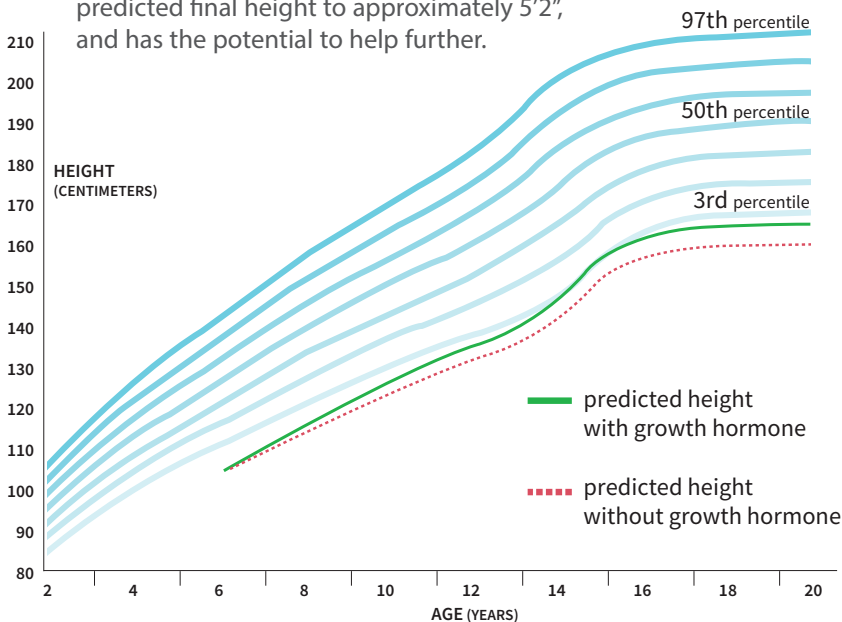
on with James. Amy told Jason to shut off the tractor and asked Sisco to repeat the news. “It was just a relief — instant relief,” Amy said.

“To get that news that you’ve been waiting seven years to hear — that someone has actually found something that they think is wrong with your child,” she added. “It was an amazing phone call.”

Stone added that over the past few months of being on growth hormone, James’ growth rate has been increasing quickly, and he is starting to get closer to a more normal growth curve for his age. Stone and Grange will continue to follow up with James, who is now 8 years old, and monitor his progress while he takes growth hormone.

Predicted height

The figure below maps James’ height with and without growth hormone therapy on an average growth chart. Adding growth hormone has increased James’ predicted final height to approximately 5’2”, and has the potential to help further.



Above and beyond

Jorge L. Granadillo, MD, an assistant professor in pediatrics for the Division of Genetics and Genomic Medicine, had a particularly tough case. Based on the symptoms he was seeing in his 7-year-old patient, it seemed very likely the boy had a genetic disorder called CHARGE syndrome. The syndrome is characterized by growth delay, hearing and vision loss and trouble communicating. But nothing in the patient’s genetic profile indicated a change in the *CHD7* gene, which is known to be associated with CHARGE syndrome.

Granadillo recommended the patient apply for the UDN. Once the patient was accepted, the team got to work.

MODEL ORGANISMS

help researchers understand rare diseases

The *CHD7* gene is known to play a role in epigenetics. This process regulates gene expression without modifying the gene itself. This led Granadillo's team to do a less commonly performed epigenetic analysis called genomewide methylation analysis. The results showed methylation patterns typical of someone with CHARGE syndrome.

The team then performed whole genome sequencing, a more costly form of sequencing that is not done in a typical genetics clinic. The more detailed sequencing data further revealed a variant that was missed by traditional exome sequencing (which looks only at the protein coding regions of the genome). With some additional testing, the group demonstrated this was a new, unreported gene variant associated with CHARGE syndrome. They published their findings last year in the *American Journal of Medical Genetics*.

"There's no way we could do this with all of our patients," Granadillo said. "It requires a lot of time and resources. Resources that wouldn't be available in a typical genetics clinic and are not covered by insurance. All of this is a clear benefit of the UDN," he added.

Unfortunately, not all families leave with answers, said Sisco, who helps coordinate care for UDN patients. The team does make sure patients know that the UDN will continue to research their cases, particularly as new information and research findings come to light. It also provides patients with resources, such as genetic counseling, and often connects patients with other families in similar situations. "We continue to interact with these families and have ongoing relationships with them even after they leave." □

► To watch more of the Lair's story, visit outlook.wustl.edu/udn.

► For more information on the Undiagnosed Diseases Network, visit undiagnoseddiseases.wustl.edu.

Many of the UDN cases are solved through genetic sequencing. But some cases need more investigation. The UDN has Model Organisms Screening Centers (MOSCs) that use simple organisms, such as nematode worms (*C. elegans*), fruit flies and zebrafish, to study complicated genetics associated with rare diseases. Washington University is home to both worm and zebrafish MOSCs.

Washington University has the only dedicated *C. elegans* modeling center in the country, which is co-led by Stephen C. Pak, PhD, associate professor of pediatrics, and Tim Schedl, PhD, professor of genetics. The university also is home to one of the largest zebrafish model facilities in the country, led by Lila Solnica-Krezel, PhD, who also heads the Department of Developmental Biology.

When UDN clinical team members pinpoint a genetic change or variant that potentially is causing a patient's disease, they may send that information to the MOSCs for further study — particularly if the candidate gene is not known to cause disease.

The MOSC bioinformatics team, co-led by Dustin M. Baldridge, MD, PhD, instructor of pediatrics, determines if the candidate gene variant is appropriate for modeling by the MOSC. If so, the model organism teams decide which organism is best suited for the work.

Once the model system is determined, MOSC team members quickly learn all they can about the gene and the disease it may cause. The group often collaborates with clinicians and researchers who know about the disease or gene to better understand its mode of action.

The MOSC groups typically use advanced gene editing technology to replicate the patient's gene variant in the model organism. The goal of the studies is to provide data in the model organism that supports the hypothesis that the candidate gene variant is indeed causing the patient's disease. So far, the *C. elegans* team has provided functional support that helped diagnose 16 UDN patients, while the zebrafish team has provided support for 13 UDN diagnoses.

The MOSC team then may look for treatment strategies in that same model organism, including identifying possible drugs that might act on the gene. "These models can both provide evidence of pathogenicity and potentially be used for future studies for therapies as well," said Angela Bowman, PhD, associate professor of developmental biology and MOSC administrative core lead.

All this work happens in a matter of months. "The team works very hard to generate the data as quickly as possible," said Pak, the co-leader of the *C. elegans* core. "It's extremely gratifying to be part of a team that helps bring diagnoses to patients and families with previously undiagnosed diseases."

Washington University has the only dedicated *C. elegans* (nematode roundworms) modeling center in the country.

MATT MILLER



Patient Bridget O'Malley decorates for the holidays in her Central West End home after undergoing proactive surgery to reduce her cancer risk.



Calculating cancer risks

Genetic counseling empowers families

BY CONNIE MITCHELL

Only a couple decades ago, physicians and their patients faced many uncertainties when it came to hereditary health risks. Some diseases were clearly genetic, so even one diagnosis in a family set off alarm bells. But many cancer types, neurological illnesses and other disorders with potential genetic components were like wild cards for people who worried about their own future health when a family member got sick.

Even today, 18 years after scientists mapped the entire human genome, physicians may not have definitive answers, but they are increasingly able to help patients discern health risks with the aid of genetic testing. For patients such as Bridget O'Malley, the information revealed and interpreted by a genetic counselor could make the difference between a cancer diagnosis or avoiding certain types of cancer.

“Having an expert available who can explain the nuances of a genetic result in an objective, unbiased way is crucial,” said Timothy J. Eberlein, MD, director of the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. “It takes time and expertise to help patients understand risk calculations and the resulting options. The genetic counselors on staff with Siteman are important members of our multidisciplinary teams.”



Susan Jones, a certified genetic counselor, helps patients understand hereditary cancer risk.

Setting off the cascade

O'Malley first met Susan Jones, a certified genetic counselor, during a Zoom meeting with multiple family members concerned about possibly carrying a variant in the *BRCA2* gene. A normal *BRCA2* instructs cells to manufacture a protein needed for tumor suppression by repairing cellular DNA. *BRCA2* variants disrupt the production of this protein, increasing the risk of breast, ovarian and prostate cancers as well as melanoma.

At 51, O'Malley had never been diagnosed with cancer — and she wanted to keep it that way. “My mom was diagnosed with breast cancer in 2015, when she was 75. It was very treatable, and at the time no one really thought about it being *BRCA*-related,” O'Malley said. But when her mother, Noreen Kelly, faced a pancreatic cancer diagnosis in late 2019, Kelly's doctor noted her prior cancer history and suggested testing.

Jones often works with patients who seek testing, not just to understand why they developed cancer or other diseases, but for the sake of their families. “They want to know if their families need to be concerned,” she said. “When we're looking for familial gene mutations, we hope individuals don't have it, but if they do, most consider it better to know so they can do something about it.”

The results indicated that Kelly had a pathogenic *BRCA2* variant. Awareness of that variant resulted in adjustments to Kelly's cancer treatment because *BRCA2*-positive pancreatic cancer is more receptive to specific types of chemotherapy. Kelly, however, died Sept. 28, 2021.

Kelly had been deeply concerned about her six children, all of whom had a 50% chance of a *BRCA2* variant. The decision for multiple family members to seek testing when a relative is found to have a variant is known as cascade genetic testing. “Mom wanted us to have knowledge so we can make good choices and take the best care of ourselves,” O'Malley said.

The advent of telemedicine has made it even more convenient for family members from anywhere in the country to gather together and access genetic counseling. Not all institutions offer this benefit, but Washington University has embraced it. “The first step is to talk about the testing itself and provide background on why specific genes affect cancer risk,” Jones said. “This first appointment is informational, and I make sure to address concerns and questions before making any decisions about testing.”

Based on the information an individual or family provides, Jones draws a three-generation family tree to illustrate risk and make sure the resulting testing panel covers all concerns. Family histories containing multiple cancer diagnoses may lead to a multi-gene panel. Jones provides testing kits to family members who want them. The tests, which use saliva samples, are mailed to a lab and offer the same accuracy as blood tests, with only about a 4% sample failure rate.

Jones pointed out that she and her colleagues always respect individual decisions regarding testing. “It's a very personal decision,” she said. “We try to share in that decision-making process by offering the facts and discussing when or how a person wants that kind of information.”

O'Malley noted that not all her relatives were interested in testing. For instance, an older uncle who had no children decided against testing. However, several men in the family proceeded with testing for their own knowledge and to help inform their children of potential risk.

Providing the option to undergo genetic testing and having genetic counselors available to help families sort through the complicated physical and psychological issues was important to Patricia Dickson, MD, chief of the Division of Genetics and Genomics and the Centennial Professor of Pediatrics and professor of genetics. “When she was hired in 2018, she made it a part of her mission to bring cancer genetics back to Washington University and Siteman Cancer Center,” Jones said.

Eberlein, also the William K. Bixby Professor and Spencer T. and Ann W. Olin Distinguished Professor and chair of the Department of Surgery, fully supported the decision. “Genetic counselors are the best people on the team to discuss all those complexities with the patient.”

By the time most people talk with Jones, they are seriously interested in pursuing genetic testing. Jones explains how testing helps determine treatments for existing cancers, what types of cancer could be associated with a variant and family risk levels.

“It’s important to spread the word among family members, but it can be difficult for a family member to know how to broach the subject and suggest a relative consider testing. We can help with that, too, to make the process less stressful,” Jones said. She offers template letters and emails, among other resources, that help explain the situation and urge relatives to talk with their doctors about testing.

Results point to options

Genetic test results do not mean a cancer diagnosis is imminent, which is one of the common fears that cause some people to avoid testing. Instead, uncovering a genetic variant means an individual’s risk for cancer is different than it would be without it. A risk analysis can direct patients to options for managing that risk.

Scientists are working to expand and enhance genetic testing abilities and resulting clinical decision making by sequencing hundreds of patients with colorectal cancer, multiple myeloma and cholangiocarcinoma, a rare bile duct cancer. Li Ding, PhD, a professor of medicine in the Division of Oncology and professor of genetics, is part of a research program known as the Washington University Participant Engagement and Cancer Genomic Sequencing Center, which received a \$17 million grant from the National Institutes of Health. “The goal of our current study is to conduct large-scale genomic sequencing in people with these three types of cancer to create a broad data platform on which we can identify the best actionable events in the clinical setting,” she said.

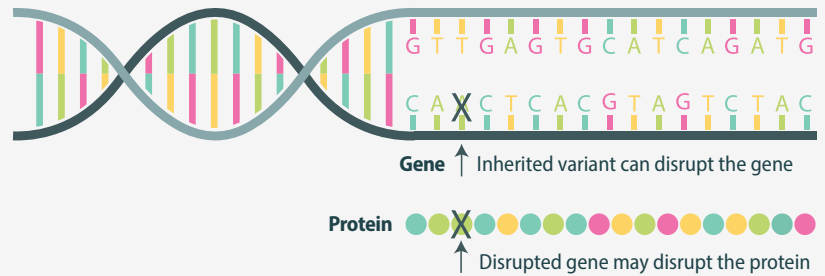
By referencing more genomic data, genetic counselors can compare individual findings with a broader baseline to identify specific

Understanding cancer genetics

Genetic counselors help families navigate hereditary cancer risk, prevention and early detection. These diagrams are a sampling of what a counselor might share with patients to explain their genetic risk of developing cancer.

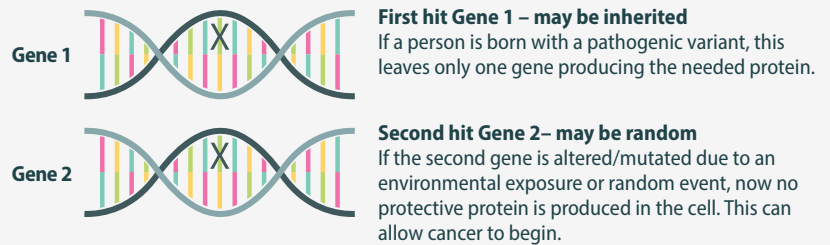
How gene variants cause cancer

BRCA1 and *BRCA2* normally act as tumor suppressor genes, producing proteins that help repair damaged DNA. Inherited variants in these genes can prevent proteins from working properly, increasing the risk of several cancers.






Knudson’s two-hit hypothesis

Everyone has two copies of each gene — one copy inherited from each parent. For a protein to be disrupted and cause cancer, variants are needed in both genes. This is the principle behind Knudson’s two-hit hypothesis.



Variant classification

A variant in the *BRCA1* or *BRCA2* genes doesn’t automatically mean cancer. There are thousands of known variants, which are classified based on their likelihood of pathogenicity.

	Pathogenic or likely pathogenic	Actionable variants. Recommendations can be made. Family members may be tested for their cancer risk.
	Variant of uncertain significance (VUS)	Unknown variants. Not yet known to affect cancer risk. Still being researched. Will be reclassified later.
	Likely benign or benign	Harmless variants. Considered part of normal human variation.

treatments known to be most effective in patients with similar genetic profiles. “Genetic counselors are an integral part of this work,” Ding said. “When we use this data to identify clinically relevant information, the counselors and clinicians are the people who will deliver that information to patients and help them understand it.

“In this way, scientists in the lab and genetic counselors and clinicians who work directly with patients are incredibly important to each other,” she added. “Genetic testing is already important for many kinds of cancer, and we believe the ability to use genetic information to make significant clinical decisions about more types of disease will increase greatly in coming years.”

Once results arrive, genetic counselors interpret and discuss them with patients such as O’Malley. In the case of *BRCA2*-positive women, Jones recommends appointments at the high-risk Gynecologic Oncology Clinic, where breast and ovarian cancer risks can be monitored on an

“Finding out I was positive ... I was just in shock,” O’Malley recalled. “I was upset, but not like I would be if I had a cancer diagnosis. It was more a question of, ‘Now what?’”

After receiving their results, O’Malley and her sister made an appointment with gynecologic oncology surgeon Andrea R. Hagemann, MD, as a result of Jones’ referral. An associate professor of obstetrics and gynecology, Hagemann said that knowledge of *BRCA* and other high-risk gene variants are essential when considering screening and surgical recommendations.

O’Malley opted to have her uterus, cervix, ovaries and fallopian tubes removed to mitigate her ovarian and fallopian tube cancer risk and undergo close breast surveillance via mammograms and breast MRIs. “It was a relatively easy decision to have a hysterectomy because I knew I wasn’t going to be having children,” she said.

A personal choice

Treatment is highly personalized to each patient’s risk level, stage of life and future goals. For example, some women may opt to keep their ovaries — to preserve fertility via egg harvesting or to prevent triggering premature menopause — and have only the fallopian tubes removed. Patients at menopausal age may prefer uterine removal to reduce endometrial and cervical cancer risk and help ease hormonal replacement management.

“We want patients to know that there are choices,” Hagemann said. “There’s not just one way to go if you have a *BRCA2* mutation.

In the case of a *BRCA2* mutation, some patients opt for both ovary removal and prophylactic double mastectomy with breast reconstruction. Because of Siteman’s multidisciplinary and collaborative approach, all of this can be performed in a single surgery, reducing exposure to anesthesia and other surgical risks. Many of the team’s specialists participate in expert panels that set and refine National Comprehensive Cancer Network guidelines, and are uniquely suited to ensure that patients receive precision care, taking into account all factors.

O’Malley’s aunt, Julie Childress, who had a hysterectomy before learning she had the *BRCA2* variant, chose not to have a mastectomy at this time. Instead, she is participating in more frequent screenings for breast cancer, pancreatic cancer and melanoma, which provide a sense of control regarding her health and future. “As hard as it



Gynecologic oncology surgeon Andrea R. Hagemann, MD, meets with Bridget O’Malley prior to surgery. O’Malley opted to have her uterus, cervix, ovaries and fallopian tubes removed to mitigate her cancer risk.

ongoing basis. Specialists available to help patients at higher risk of breast cancer include surgeons, medical oncologists, radiation oncologists, radiologists and psychologists.

BRCA2-positive patients also are advised to see a dermatologist due to their higher risk of melanoma, which is 3% to 5% compared to the average 1% to 2% lifetime risk. In all cases, the center’s collaborative multidisciplinary approach is a win-win for clinicians who can plan coordinated care and patients who receive a complete picture of their risk with the assurance that all aspects are being addressed.

was to hear this news, it's been an impetus for me to be more vigilant about my health," she said.

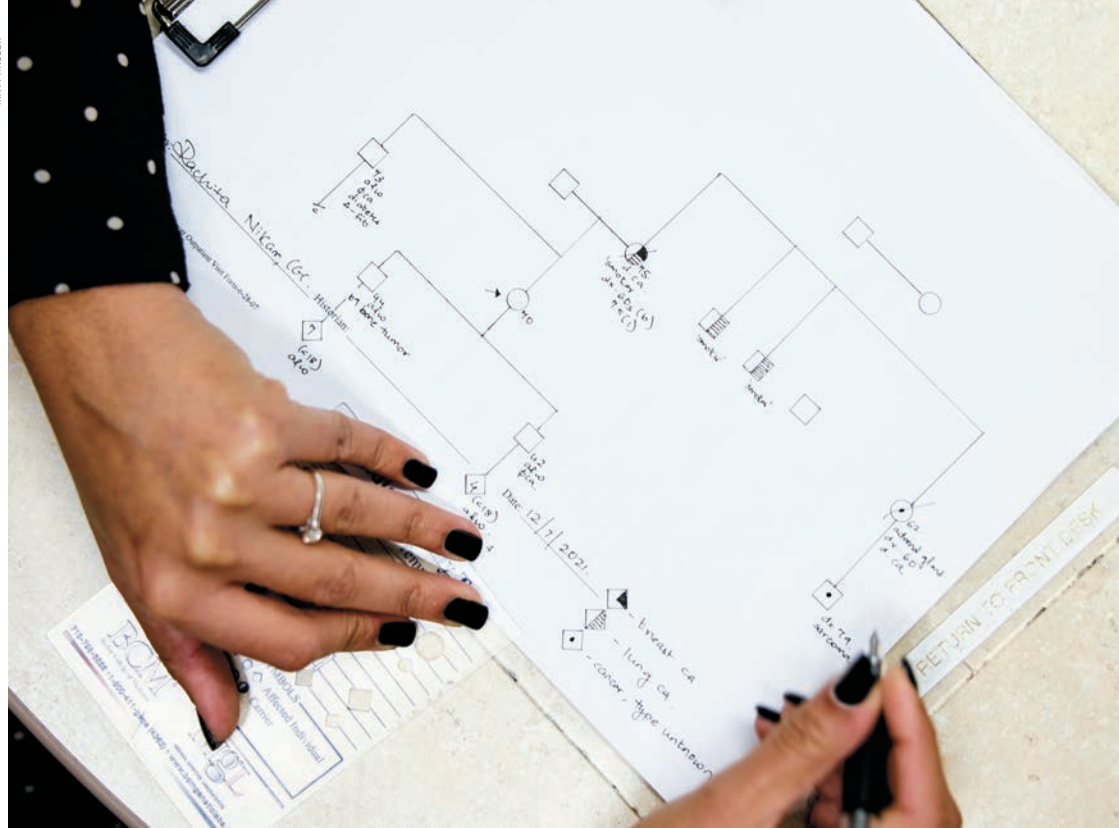
Screening is vitally important for early detection in many types of cancer. Ovarian cancer, however, often presents with subtle symptoms and is diagnosed at late, metastatic stages. This makes genetic testing all the more beneficial as it alerts practitioners and patients to risk probability before a diagnosis is made.

Up to 25% of women diagnosed with ovarian cancer are found to carry a high-risk mutation. "If we had known they had the variant, we potentially could have prevented that diagnosis by being proactive," Hagemann said. Finding these mutations early and reducing risk via surgery after genetic counseling is still key for ovarian cancer prevention.

Certain cancer diagnoses automatically flag a referral for genetic counseling and testing. In particular, ovarian, pancreatic, metastatic prostate, colon and endometrial cancers are known to have possible genetic links. These cancers often involve point-of-care genetic testing and brief counseling in on-campus clinics at time of diagnosis and then a referral to further counseling with one of the certified genetic counselors when variants are found.

Women who have a strong family history of breast cancer, diagnosis before the age of 50, or have been diagnosed with triple-negative breast cancer are also candidates for genetic testing. However, anyone with concerns about family health history can self-refer to Jones or her colleagues for consultation and testing. Jones notes that about half her patients are referred from oncologists and half from their primary-care physicians or via self-referral.

With the knowledge provided by the genetic information, patients can take important steps to enhance their health and reduce cancer risk via lifestyle changes and noninvasive treatments. Health preservation planning includes consideration of diet, exercise, stress management, screening schedules and preventive medications. For instance, those at higher risk of colon cancer could benefit from more frequent colonoscopies, which can prevent cancers by removing precancerous polyps.



Responding to increased demand

As more people realize the benefits of genetic testing, Washington University is poised to be on the forefront of ensuring testing is easily accessible. Eberlein saw demand increasing and knew the trend would continue, especially in the age of personalized medicine based on genetic information. "Nationally, the shortage of certified genetic counselors can increase patients' wait time to get an appointment," he noted. "And as clinicians, we also need genetic counselors on the patient care team because they provide a really important service to patients with complex medical histories and issues."

One solution for Washington University and its associated clinical institutions was to establish a new 21-month master's degree program in genetic counseling, which is accredited by the Accreditation Council for Genetic Counseling. "Through this program, we're helping to provide more certified genetic counselors, some of whom we hope will stay here and work with us," Eberlein said.

Jones noted that she and her colleague, Rachita Nikam, stay busy with in-person and telehealth clinics, and added that working with Noreen Kelly and her family is an example of the ideal situation. "When a diagnosis and subsequent genetic test result lead to a family cascade so that many others can understand their risk and manage it for a healthier future, that's exactly what we want — keeping people as safe and healthy as possible." □

Based on a family's medical history, genetic counselor Rachita Nikam draws a pedigree showing cancer inheritance patterns.

► Learn more about the new master's degree program: geneticcounseling.wustl.edu



MD/PhD student Rita Chen (left) and Brett Case, PhD, a postdoctoral researcher, work with SARS-CoV-2 under strict biosafety conditions in Michael Diamond's biosafety level 3 lab.

The race for COVID-19 vaccines

A conversation with two scientists who took part in the global effort

BY TAMARA BHANDARI

As the COVID-19 pandemic began to take shape in the first weeks of 2020, viral immunologist **Michael S. Diamond, MD, PhD**, and immunologist **Ali H. Ellebedy, PhD**, dove into the global race to develop vaccines and therapeutics against COVID-19. Years of training and experience had prepared each for just such a crisis.

The two quickly pivoted to studying how SARS-CoV-2, the virus that causes COVID-19, infects people and how the immune system fights back. Ellebedy investigated what a protective immune response looks like and whether natural infection and vaccination effectively induce such a response. Diamond developed a mouse model and with colleagues at Washington University created two vaccine candidates, one an inhalable nasal vaccine that is in advanced clinical trials in India.

Here, they reflect on the international effort to develop COVID-19 vaccines, the state of vaccine science, and how the field has changed under the extraordinary pressures — and opportunities — of a once-in-a-lifetime pandemic.

2020 started with vague reports that a new member of the coronavirus family was making people sick, and ended with health-care workers rolling up their sleeves to get their shots. Designing, testing and authorizing a vaccine against a novel virus — in under a year — was an extraordinary triumph of modern science. How did it happen?

Diamond: We weren't starting from scratch. There already was a body of research on the related coronaviruses SARS-CoV-1 (the original SARS) and MERS (the Middle Eastern Respiratory Syndrome virus). There were vaccines for SARS-CoV-1 in animal testing and vaccines for MERS-CoV in animal testing and in early-phase clinical trials. These vaccines all targeted the same viral protein: spike, which the viruses use to get inside cells. And they worked in animals. So that told us, right away, that spike was probably a good target for a SARS-CoV-2 vaccine.

Another important advantage is that we knew the structure of the spike protein. Sometimes, a virus emerges from a family that we just don't have a lot of information about. Here, we had a very high-resolution structure of spike from related coronaviruses. We also knew how to mutate the spike in such a way to produce the best antibodies. Scientists quickly figured out that SARS-CoV-2 uses the same human receptor to get into cells as SARS-CoV-1; MERS, in contrast, uses a different one. This allowed us to take all of that information we already had on how antibodies block SARS-CoV-1 binding to the receptor and translate that to SARS-CoV-2. And finally, of course, the messenger ribonucleic acid (mRNA) vaccine platform already was under development.

Ellebedy: We knew that most successful vaccines for viral infections work by eliciting high levels of neutralizing antibodies, so that's where we started. Then, we learned from early studies of people who



Ali H. Ellebedy, PhD (right), talks in his lab with instructor Jackson Turner, PhD.

were infected with SARS-CoV-2 that many of them developed potentially neutralizing antibodies upon natural infection. That was a very good sign. If natural infection induces a good immune response, then all you have to do is mimic that natural response. Those early studies told us that it should be possible to make a successful vaccine, and what that successful vaccine should target.

A pandemic is a catastrophe, of course, but it's also an opportunity for people in your field. What have vaccine scientists learned from this pandemic?

Ellebedy: The main thing we learned is that, in the past, we took far too long to make new vaccines.

Diamond: The shortest one before was measles, at four years. Most vaccines have taken the better part of a decade, and some were 20, 30 years in the making. We learned by use of new vaccine platforms that as soon as we

had the genetic sequence of the virus we could make a vaccine as long as we understood some of its biology. Before, we didn't think developing a vaccine for humans in this time frame was possible.

Ellebedy: Ten years, 15 years from now, when we look back at this time, I think we'll see that one of the silver linings of this pandemic is that it provided the opportunity for the mRNA platform to be utilized on a global scale. I wasn't here in St. Louis when the work was done on the Zika mRNA vaccine in Mike's lab, but I saw the preclinical data and it was very impressive. But luckily we did not need to deploy that vaccine globally. A major advantage of the mRNA platform is that it can be adapted quickly. I think it's definitely going to be used against other viruses like influenza, where you really need the ability to make changes quickly. And the ability to include multiple mRNAs against multiple strains in one shot is certainly a plus.

Diamond: And also, we've learned a lot about B cell responses, which are the group of cell types that produce antibodies. We knew some of it from flu and other viruses before. But during this pandemic we've learned about how B cell responses occur in individuals infected or vaccinated for the first time, individuals infected after vaccination, individuals vaccinated after infection. We've learned about the B cell response to viral variants. Those are all important points that will translate to other pathogens as well.

A lot of people hoped that vaccines would be a silver bullet and stop the COVID-19 pandemic in its tracks. They've helped, but the pandemic is still going. Why?

Ellebedy: This pandemic revealed the huge disparity between developed and developing countries in terms of vaccine access. After this pandemic, as a global population, we really need to take a look at how we can fix

that because we've learned that you cannot just vaccinate your population and expect that things will be fine. A variant can come from an under-vaccinated area where the virus is circulating and basically nullify all your efforts to control the virus. We should care about the pandemic situation in places where vaccination coverage remains poor like Egypt, India, South Africa and many others.

Diamond: Part of that is financial, but part of that is there just wasn't the infrastructure to deliver these high-efficacy vaccines. There were worldwide cold-chain issues, meaning that it was hard to ensure that the vaccines stayed at the proper temperature from the time they left the factory to the time they were injected. Vaccines will not end a pandemic alone; you need other public-health measures, including testing. Ali mentioned earlier the situation in Egypt, where people don't bother to try to get tested because it's not reliable or they can't get tests or the

test doesn't come back in time. There are many places in the world where testing is still a problem nearly two years into this pandemic. That's another huge inequity that we need to solve.

Has the global race to develop vaccines for SARS-CoV-2 revealed any blind spots or weaknesses in the field of vaccine science?

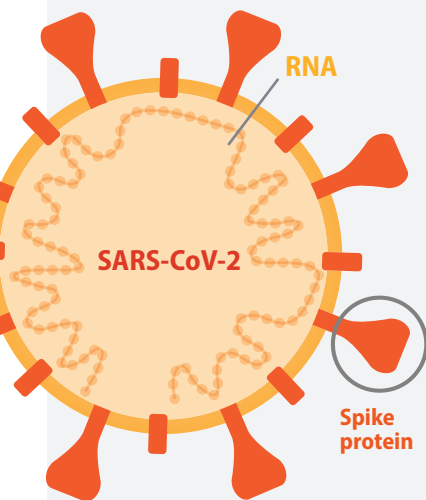
Ellebedy: The vaccines that were created were amazing, but we probably needed a mucosal vaccine that can elicit a strong immune response at mucosal surfaces. It is almost impossible to control transmission of a respiratory virus without having a really strong, very solid immune response at the site of entry: the nose. The problem is that we don't really have many successful examples of good mucosal vaccines. Historically, most vaccines are injected, and we measure their immunogenicity by assessing antibody levels in the blood.

Antibodies in the blood prevent the virus from spreading from the upper airways through the blood to other parts of the body, like the lungs, where it can cause more severe disease. Early COVID-19 vaccines do induce a strong antibody response in the blood, which is why they have been very effective at preventing severe disease, hospitalization and death. But they don't do a great job of preventing infection, and that's because we don't really know much about antibody responses in the nose. We don't know how to tell if we have enough antibody there for protection or how long those antibodies will last.

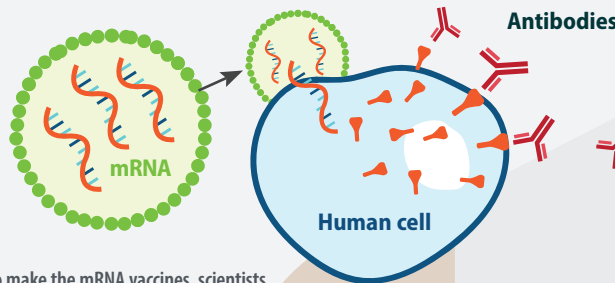
Diamond: The first goal was to get people out of the hospitals, stop people from dying, and get back to some sense of normalcy and any vaccine that did that reasonably well was a success. The fact that the mRNA vaccines were 90% to 95% efficacious was beyond our wildest dreams. But we designed the vaccines based on

What is an mRNA vaccine?

Many vaccines work by putting weakened or inactivated germs, or pieces of germs, into our bodies to trigger an immune response. mRNA vaccines are different because they put the instructions for making a protein into our bodies. Our cells then produce that protein and trigger an immune response.



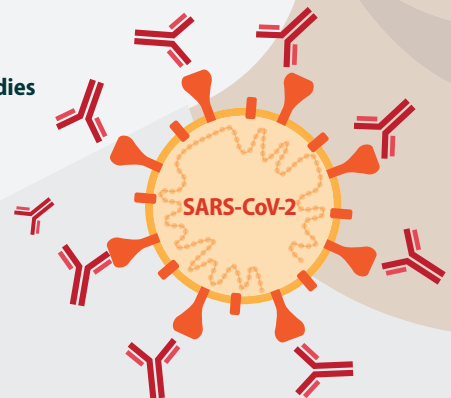
Scientists quickly identified the spike protein (circled) as the key to the virus's ability to invade cells, and located the gene for spike.



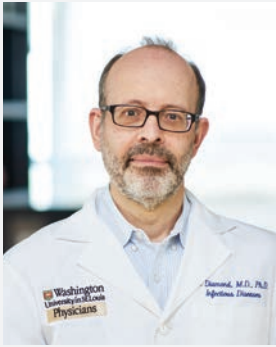
To make the mRNA vaccines, scientists created mRNA molecules carrying the genetic instructions for spike and encased them in a protective coating that helps them get inside cells.

Protein translation

The cell reads the mRNA instructions, builds spike proteins and places them on its outer surface. The immune system detects the spike proteins and creates antibodies against them.



After a few days, the body breaks down the instructions and stops making the spike protein. But the immune response continues to develop, providing lasting defense against the virus.



Michael S. Diamond, MD, PhD, the Herbert S. Gasser Professor and a professor of medicine, of molecular microbiology and of pathology & immunology, is a veteran of battles against West Nile virus, which emerged in the U.S. in 1999, and Zika virus, which caused an epidemic that rocked Brazil in 2015 and 2016. Diamond, with Moderna, helped to develop an experimental mRNA vaccine for Zika that performed well in animal testing. That vaccine candidate is still in clinical trials.



Ali H. Ellebedy, PhD, an associate professor of pathology & immunology, of medicine and of molecular microbiology, has spent the past several years unraveling the complex immune response to influenza infection with the goal of creating a better flu vaccine. He developed a new technique to assess whether a vaccine activates the kind of immune cells needed for long-lasting immunity, and identified antibodies effective against a wide range of lethal influenza strains.

assumptions about human behavior that turned out not to be true. We had an expectation that if we had an effective vaccine, everybody would get it. Like last century, everybody got the smallpox vaccine. That's how we got rid of smallpox. Same for polio. But here, in the U.S., and especially in Missouri, you have swaths of the population that remain unvaccinated and therefore vulnerable to infection. Where you have so many people that remain susceptible, a regular vaccine that prevents severe disease will not break the cycle of transmission. You need to have a vaccine that stops transmission. That's the only solution to it. And that would be a mucosal vaccine ... that people take.

Ellebedy: Another thing we learned during this pandemic was that speed matters. Not only do you need to be fast in developing a vaccine, but also fast in advancing it through clinical testing. Academic research centers like this one have historically not been set up to rapidly move a vaccine candidate from the lab to clinical trials.

Diamond: Ali and I, along with Rachel Presti, the director of the Infectious Disease Clinical Research Unit, have established a Vaccine Research Center here at WashU. The plan is to take advantage of our outstanding community here to develop a pipeline of vaccine discovery — starting from the most basic aspects of vaccine science, going through small animal studies and then into phase 1 clinical trials through the center. And then we'd help advance the candidates that are the most successful through later-stage clinical trials and, ultimately, ideally, get FDA approval. The center will be not just for viruses, but also for bacteria, parasites, fungi, any pathogen that could be targeted with a vaccine, especially those for which there are currently no good vaccines or therapies. We have a huge amount of expertise at WashU in microbiology, immunology, infectious diseases, as well as other relevant areas such as pediatrics, emergency medicine and nuclear medicine, that we can tap into to design vaccines, evaluate them and get them into people. □



Research technician Mahima Thapa (left) and visiting researcher Shaza Ahmed collaborate in Ali Ellebedy's lab.

MATT MILLER

Enduring connections

In the 1970s, P. Roy Vagelos, MD, imagined life science training programs that would transcend boundaries. With unwavering support from then-Chancellor William H. Danforth, Vagelos founded the Division of Biology & Biomedical Sciences (DBBS) and the Medical Scientist Training Program (MSTP).

One of the first MSTP graduates, Roger M. Perlmutter, MD, PhD, who describes his training experiences as transformational, went on to create revolutionary cancer drugs at Merck & Co.

Read more about the lasting impact of these programs and how they continue to generate connections that strengthen the medical school's efforts to advance human health.

P. Roy Vagelos, MD, lecturing at the School of Medicine in 1973.

Fifty years after its founding, the Roy and Diana Vagelos Division of Biology & Biomedical Sciences remains a nexus for pathbreaking science. Here, Carolina B. López, PhD (right), a professor of molecular microbiology and BJC Investigator, and graduate student Lavinia Gonzalez Aparicio talk about ongoing research in the lab.

DBBS named after Vageloses



\$15 million gift to strengthen life science research, education across university

BY KRISTINA SAUERWEIN

D deep discussions about enzyme chemistry, fatty acids, lipids and cardiac metabolism revealed a scientific kismet of sorts between William H. Danforth, MD, chancellor emeritus of Washington University, and renowned biochemist P. Roy Vagelos, MD.

This shared devotion to basic science would lead to a decades-long friendship and the 1973 formation of one of the university's most integral programs, the Division of Biology & Biomedical Sciences (DBBS).

To honor Danforth, who died in 2020 at age 94, Vagelos and his wife, Diana Vagelos, made a \$15 million gift to DBBS. The gift will fund graduate student fellowships, particularly in novel research areas, and bolster undergraduate programming.

The university has renamed DBBS the Roy and Diana Vagelos Division of Biology & Biomedical Sciences in recognition of the couple's generosity.

An intellectual kinship

Before moving into administration, Danforth, a biochemist, conducted basic science research in the laboratory of Washington University Nobel laureates Carl and Gerty Cori. In the mid-1960s, Danforth, then-vice chancellor for medical affairs at the School of Medicine, recruited Vagelos, who was working at the National Institutes of Health (NIH), to succeed Carl Cori as head of the WashU Department of Biological Chemistry.

From their first meeting, Vagelos recalled, the physicians bonded over basic science research.

"Bill Danforth was convinced that the improvement of human health would depend on good doctors as well as new knowledge emerging from biomedical research," said Vagelos, chairman of the board at Regeneron Pharmaceuticals since 1995. "He strongly felt that a great university medical school would be rooted in science. We shared this belief."

Danforth and Vagelos could talk for hours about basic science — the intricacies, the possibilities — but when it came to enhancing the university's training in the life sciences, their discussions were brief and their decision-making quick and decisive. "When I explained to Bill what I was trying to do in creating DBBS, he became excited and immediately suggested funding sources," Vagelos recalled with a chuckle. "I didn't even have to ask for the money. He offered it. It was incredible."

With Danforth's unwavering support, Vagelos transformed undergraduate and graduate education in the biosciences at Washington University and, by extension, across university campuses nationwide.

The 'WashU model'

A pioneering model for interdisciplinary education in the life sciences, DBBS united basic science departments from the School of Medicine with the Department of Biology in Arts & Sciences to offer unparalleled training and research opportunities for undergraduate, graduate and medical students. The division served as a bridge across Forest Park by joining the university's two geographically separate academic campuses.

Such collaborations elevated the caliber of the university's life sciences curriculum while also advancing scientific discovery and innovation.

Known in academic circles as the "WashU model," DBBS has been emulated by top biomedical centers, including the NIH.

Since its creation, DBBS has ranked as one of the best U.S. doctoral programs. Today, the division comprises about 600 graduate students and 13 doctoral training programs. Faculty members from 30-plus departments, including those at the School of Medicine, the McKelvey School of Engineering and Arts & Sciences, contribute to the admission, teaching and research training of the division's students.

"In founding DBBS, Roy forged unprecedented connections between academic departments, Washington University's main campuses, and undergraduate students and medical school faculty," Chancellor Andrew Martin said. "Fifty years later, the division remains a nexus for pathbreaking science conducted at the university. This gift will raise DBBS to even greater heights and expand its reach to more aspiring physicians and scientists."

The Vageloses' gift will increase fellowship opportunities, easing stress and reducing time spent applying for grants, so students can more easily focus on research itself. It also is a testament to Washington University as a major research powerhouse that continues to grow.

"Research is ultimately the expression of how we improve at treating diseases," said David H. Perlmutter, MD, executive vice chancellor for medical affairs, the George and Carol Bauer Endowed Dean of the School of Medicine, and the Spencer T. and Ann W. Olin Distinguished Professor. "Roy and Diana's generous endowment will allow us to strengthen research enterprises on both campuses by leveraging the last five years' remarkable growth in research technologies to enhance science education across the university."

"The gift also speaks to Washington University's supportive, tight-knit community, where lifelong professional partnerships and personal relationships are formed," Perlmutter added. "Roy conceived of DBBS, and Bill Danforth brought it to life."

Vagelos and Danforth formed a close friendship, as did their wives, Diana Vagelos and Elizabeth "Ibby" Danforth (who died at age 75 in 2005). During a trip to Greece, the couples



P. Roy Vagelos, MD, and Diana Vagelos

toured an archeological site on the island of Ithaca, believed to be the castle of Odysseus, hero in Homer's epic poem "The Odyssey." "That trip was one of our most memorable," Diana Vagelos said. "For Ibbey and Bill, there was no hill too high to climb, no ancient ruin too insignificant to bypass, no myth too wild to believe, no beach too stony to swim and no meal too exotic to enjoy."

Indeed, the founding of DBBS is rooted in their friendship and shared conviction that basic science can improve human health and better the world. Both Vagelos and Danforth have cited the division's formation as a point-of-pride achievement.

A forward thinker

Vagelos' vision for DBBS proved prescient. "It's mind-blowing to me that 50 years ago, Roy Vagelos recognized the importance of breaking down administrative barriers and disciplinary silos to help provide cutting-edge training for undergraduate, graduate and medical students," said Feng Sheng

Hu, PhD, dean of the faculty of Arts & Sciences, the Lucille P. Markey Distinguished Professor in Arts & Sciences and professor of biology and of earth and planetary sciences.

"I'm particularly delighted that this gift includes a focus on undergraduate programs," he added. "It will unlock exciting opportunities for our students, and investing in their careers at an early, formative stage will ultimately advance both research and medicine."

During his tenure, Vagelos also recruited leading scientists to the faculty and founded the university's highly regarded Medical Scientist Training Program, which offers students the opportunity to earn doctoral and medical degrees simultaneously and is considered among the top MD/PhD programs in the country.

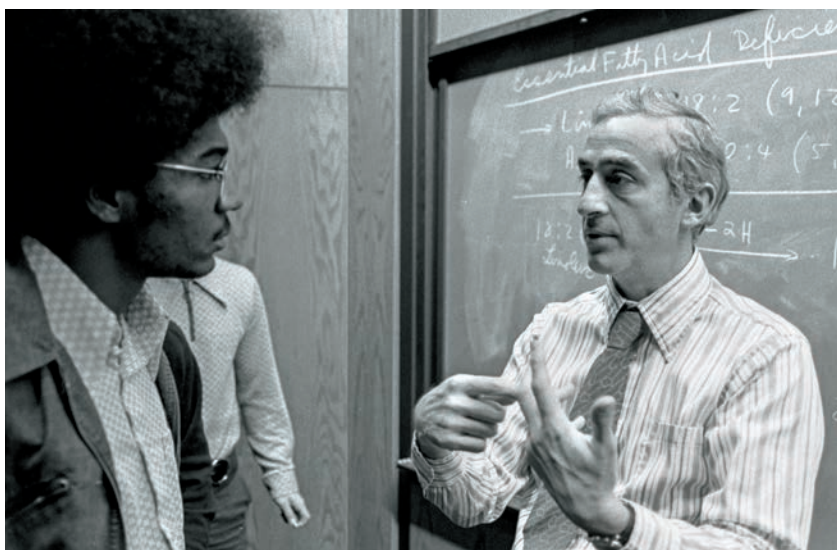
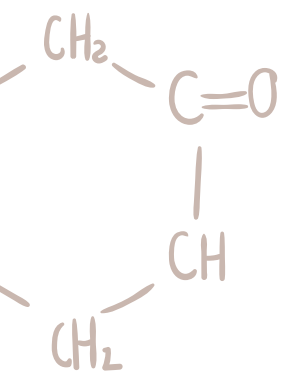
"Roy was the best department head I saw while I was at Washington U," Danforth said during a 2007 interview for Becker Medical Library's Oral History Project. "He was incredible. ... Roy was so imaginative. He went out of his way to get good people and make sure things worked well."

Steven J. Mennerick, PhD, the DBBS interim associate dean of graduate studies and the John P. Feighner Professor of Neuropsychopharmacology, said Vagelos unified diverse stakeholders in a schoolwide vision of biosciences training. "The vision recognized that the best science is done at the boundaries between departments and disciplines," he said.

In 1975, Vagelos left the university to join Merck & Co., where he directed the discovery of the statin drugs Mevacor and Zocor for reducing blood cholesterol. There, he ascended to CEO and chair. After retiring from Merck, Vagelos joined the board of directors as chair of Regeneron Pharmaceuticals.

At Danforth's invitation, Vagelos served on the boards of the Danforth Foundation and the Donald Danforth Plant Science Center. Additionally, the Vageloses, who reside in Far Hills, N.J., have continued their support of the university over the years by funding a professorship and a fellowship. To their delight, their granddaughter Emma is a second-year undergraduate.

"Washington University is one of the world's great academic and research institutions," Roy Vagelos said. "Bill Danforth devoted his life to the university because he knew that knowledge and research, ultimately, could better humanity. DBBS is a source of pride for both Diana and me, and we want to honor Bill's legacy by further elevating an already stellar program."



P. Roy Vagelos, MD (right), visits with students on the Medical Campus in 1973.

Former Chancellor William H. Danforth, MD (right), presents Vagelos with the 2010 Danforth Distinguished Service Award at the Donald Danforth Plant Science Center Plantasia gala.





Roger M. Perlmutter, MD, PhD, a graduate of the Medical Scientist Training Program and, later, head of research and development at Merck & Co.

Rather than teaching from a textbook, Vagelos and Glaser assigned primary literature to their students. Each week, Perlmutter and his classmates pored over scientific papers, interpreting and interrogating their findings. The course was an exercise in critical analysis and an effective introduction into the rigorous training Perlmutter would receive over the next six years.

The training ably prepared Perlmutter for a distinguished career in pharmaceutical research and development, notably at Merck & Co., from which he recently retired. The Merck Foundation is honoring Perlmutter's tenure with a \$2 million commitment to the medical school for career development assistant professorships. Perlmutter views the gift as an opportunity to acknowledge the place where it all began for him.

A foundation for success

At the medical school, Perlmutter found "an extraordinary group of faculty and fellow students who were focused on asking important questions about biomedical research and developing the ability to answer those questions." One of those faculty members was Joseph M. Davie, MD, PhD, his dissertation adviser and then-head of the Department of Microbiology and Immunology. "I simply could not have had a more supportive, thoughtful or humane mentor," Perlmutter said of Davie.

David M. Kipnis, MD, also left a lasting impression on Perlmutter. Kipnis, a pioneering physician-scientist who led the Department of Medicine, strongly advocated for research partnerships between medicine and the basic sciences. Together, Davie, Kipnis and others profoundly shaped Perlmutter's approach to science and medicine. He learned that basic scientific research was much too important to be left to the basic scientists alone, as Carl V. Moore, AB '28, MD '32, founder of the

'How I got my start'

Merck tribute funds rising physician-scientists

BY EMMA DENT

Roger M. Perlmutter, MD/PhD '79, entered the Medical Scientist Training Program (MSTP) at the School of Medicine in 1973. Although the program was just four years old, its renowned faculty and unique pedagogy were firmly in place. Perlmutter found himself learning biochemistry from P. Roy Vagelos, MD, one of MSTP's founders, and Luis Glaser, PhD '56, head of the biological chemistry department and a former student of Nobel laureates Carl and Gerty Cori.

P. Roy Vagelos, MD, who founded the university's Medical Scientist Training Program before becoming CEO and chair of Merck & Co., delivered an Assembly Series lecture on the Danforth Campus in March 1991. The talk focused on management strategies behind Merck's success.



BERNARD BECKER MEDICAL LIBRARY



Dean Y. Li, MD/PhD '90, succeeded Perlmutter as president of Merck Research Laboratories.



Monica Chang-Panesso, MD, is the first recipient of a Perlmutter Career Development Professorship.

medical school's hematology division, often argued. "Clinicians needed to understand that work and to make use of it in their clinical practice," Perlmutter said. "This understanding informed everything I did in my career thereafter."

Perlmutter began his professional life in academic medicine at the University of Washington, Seattle, where he was a professor of medicine and biochemistry and the founding chair of the immunology department. He then became executive vice president of worldwide basic research and preclinical development at Merck before moving to Amgen Inc., where he was the executive vice president of research and development for more than a decade.

In 2013, he returned to Merck as executive vice president and president of Merck Research Laboratories, where he reinvigorated drug discovery and development. Under his watch, the company earned more than 100 global regulatory approvals for vaccines and treatments targeting cancer, diabetes, Ebola and HIV, among other diseases. Perlmutter's greatest legacy at Merck is arguably his

work in cancer immunology, which yielded the revolutionary cancer immunotherapy Keytruda.

Alumnus Dean Y. Li, MD/PhD '90, succeeded Perlmutter as president of Merck Research Laboratories in January 2021. "Roger Perlmutter saw data that shook his view of cancer biology," Li said, "and he took risks to prove his point. Because of his work and the team he assembled, Merck has redefined cancer treatment. He helped change the trajectory of medicine."

A dynamic legacy

The Merck Foundation wished to pay tribute to Perlmutter's impact by making a gift to an organization with personal meaning. For Perlmutter, that place was the medical school. The gift establishes two Roger M. Perlmutter Career Development Professorships to support promising young physicians and scientists from populations that are historically underrepresented in medicine and biomedical sciences. Monica Chang-Panesso, MD, an assistant professor of medicine in the Division of Nephrology, was awarded the first of the two professorships.

"Our student body at the School of Medicine is incredibly diverse," said David H. Perlmutter, MD, executive vice chancellor for medical affairs and the George and Carol Bauer Endowed Dean of the School of Medicine. "This generous funding will help us foster greater diversity within our faculty and, ultimately, the fields of science and medicine by supporting physicians and scientists at a pivotal professional time."

The gift also pays tribute to the rich, shared history between Merck and the medical school. Over more than 40 years, alumni and faculty have left their mark on Merck. Among the group are Vagelos, who oversaw the company's research division before becoming its CEO, and Joe Miletich, MD/PhD '79, now a senior scientific adviser to the CEO and a former classmate of Roger Perlmutter.

These long-standing connections do not surprise Perlmutter. "Washington University Medical Center exemplifies the fundamental mission of the academic medical center, which is to translate advanced research into clinical improvements that really matter," he said.

Perlmutter hopes the recipients achieve their own scientific breakthroughs and are able to one day say, "This is how I got my start."

1950s

Emil Louis Mantini, MD '58, and his wife, **Mary Jane, NU '57**, have moved to Tampa, Fla., to live closer to their younger son and his family. They are happy to report that they are vaccinated and no one in their independent living facility has gotten COVID to date. He says hello to all his classmates and hopes they are doing well and misses those who are no longer living.

1960s



Gordon Schaye, MD '63, stopped practicing medicine two years ago. He is happy to report that he is having a lot of fun acting in various films in Hollywood and producing short independent films.



Donald Marler, DE '66, served as a captain and executive officer of the 17th Dental Company in the U.S. Marine Corps and had his own dental clinic at San Mateo on

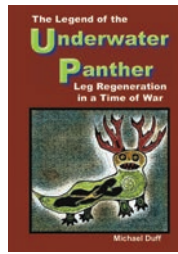
Camp Pendleton in California. He then worked privately as a general practitioner in Wichita, Kan., for 40 years, building his own dental clinic. After retiring in 2008, Marler became a professional author and has published and sold worldwide on Amazon. He became a professional photographer, and his 2021 Wichita Wings Autograph Book is for sale through Marler directly. He would love to hear from any fellow classmates of



1966 to hear how they are doing.
Clifton Smith, MD '69, retired from the practice of dermatology after more than 48 years in the field.

1970s

Wm. Michael Duff, MD '73, has been researching the early hospitals and medical care in the Ozarks. Several years ago, he published a book called "The Legend of



the Underwater Panther: Leg Regeneration in a Time of War." The title of the book came from his interest in Native American folklore, the underwater panther and Picture Cave in Warrenton, Mo.



Robert Schmidt, MD '76, PhD '76, professor of pathology & immunology at WashU Med, has received the Meritorious Contributions to Neuropathology Award from the American Association of Neuropathologists. The award recognizes Schmidt's contributions to the advancement of knowledge of diseases that affect the nervous system.

Fred Horowitz, LA '76, DE '79, is a contributing author to "CDT 2021 Coding Companion," published by the American Dental Association in 2021. He also is a member of the executive steering committee, Culinary Health Center, Las Vegas; board of directors, PrimeCare Benefits Inc., Las Vegas; and board of directors, Paragon National Supply, Chicago.

Barry Wershil, LA '75, MD '79, received the 2021 Margaret Stallings Distinguished Service Award from the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN). Presented to members of NASPGHAN, the award honors excellence, service and achieving national and/or international recognition in the field.

1980s

Mark Mintun, MD '81, HS '85, is senior vice president of neuroscience R&D for Eli Lilly and Co. He also is the president of Eli Lilly unit Avid Radiopharmaceuticals.

David W. Moskowitz, HS '83, recently added COVID-19 to the list of diseases he has published on. He also has published on acute and chronic kidney failure, chronic obstructive pulmonary disease and sickle cell, among other conditions.



Robin Womeodu, MD '83, was named by Methodist Le Bonheur Healthcare as senior vice president and chief academic officer to lead the system's office of Medical Education

and Academic Affairs. She will strengthen academic partnerships, as well as medical student, residency and fellowship programs. Womeodu currently serves as chief medical officer for Methodist University Hospital. Womeodu also will oversee the organization's collaboration with the University of Tennessee Health Science Center, the University of Memphis and Meharry Medical College to expand statewide education, training and research opportunities for medical trainees, including medical students and residents. She is a board-certified internist and fellow in the American College of Physicians-American Society of Internal Medicine.



Cheryl Parsons, PT '85, now works for the Missouri Department of Health as a senior regulatory auditor for long-term care facilities.

Theodore Washburne, PT '85, is a 15-year cancer survivor. Though diagnosed with Parkinson's disease in 2019, he is pleased to report that he feels well and has been helped by physical and speech therapies. Washburne finds enjoyment in teaching Sun-style Tai Chi.

Jeffrey Barteau, EN '82, MD '86, HS '93, retired from positions as general surgeon and regional director of specialty practices at OSF-Rockford in November 2020. He reports that he is now catching up on 30 years of sleep deprivation. Barteau and his wife, Dawn, have enjoyed visiting children (and first grandchild) from coast to coast, as time and vaccination have allowed.

1990s

Sam Stokes III, MD '92, was re-elected trustee of the Illinois State Medical Society (ISMS) during its 2021 Annual Meeting. ISMS is a professional membership association

representing Illinois physicians in all medical specialties, and their patients statewide. A board-certified urologist, he is on staff with Memorial Hospital of Carbondale and Chester, St. Joseph's Hospital in Murphysboro and Herrin Hospital in Herrin. Stokes' current practice is with Southern Illinois Healthcare Urology Group. He is a member of the American Urological Association, American Association of Clinical Urologists and the National Medical Association. He is a fellow of the American College of Surgeons. His term as ISMS trustee will run through April 2024.

Leonard White, PhD '92, received the 2021 Alpha Omega Alpha Robert J. Glaser Distinguished Teacher Award from the American Association of Medical Colleges. As associate professor in neurology at Duke, White has set the bar for medical education through impressive foresight, anticipating student needs and pioneering new approaches ahead of others in the field. He helped establish team-based learning at Duke, developed the first modular videos for hybrid flipped-classroom learning and integrated humanities into medical education — long before these strategies became well-known and adopted across the country.



Scott Markowitz, MD '93, has returned to Washington University as the inaugural vice-chair for professional development and diversity, equity and inclusion in the

Department of Anesthesiology. He is excited to return in this role and reports that it is a great privilege to be back and to participate in this work.

Douglas Schulte, MD '95, reports that he has repurposed his life after 20 years in private practice. In March 2021, he joined the Mercy Ships organization as a full-time volunteer head and neck surgeon. This comes after serving on the Africa Mercy hospital ship in Madagascar, Benin, Cameroon, Guinea and Senegal. Currently serving in Monrovia, Liberia, he has no plans to retire. For more information on the organization, visit Mercyships.org.

Shannon M. Tharp, MSOT '97, resigned after 17 years at TCC Rehab/Tiffany Care Centers working as an occupational therapist, therapy manager and clinical trainer. She is currently enjoying travel with her husband, Brian. Their two children, Gretchen and Fischer, are in college.

Mary Lou Meier, MSOT '98, continues to work as the lead occupational therapist for the Saint Joseph School District and recently accepted an adjunct professor teaching position at Missouri Western State University Department of Nursing and Allied Health Physical Therapy Assistant Program.

2000s

Jason Stephenson, MD '04, HS, was appointed as the associate dean of multicultural affairs for health professions learners at the University of Wisconsin School of Medicine and Public Health. In this role, he is responsible for promoting equity and inclusion by supporting student recruitment, retention and engagement in the MD, PA, PT, MPH, medical genetics, and UWH residency programs. Stephenson reports that he is excited to begin this new stage of his career and hopes to emulate the success of role model and mentor **Will Ross, MD '84, HS '91**.



Kara Barnett, LA '01, MD '05, was promoted to associate attending at Memorial Sloan Kettering Cancer Center. She is also director of anesthesia services at their Monmouth site in Middletown, N.J.



Timothy Loftus, MD '06, graduated in May 2021 from the University of Miami School of Law, obtaining a juris doctorate. He recently joined the University

of Miami faculty as the Fredman Family Foundation Health Disparities Project's practitioner-in-residence and lecturer. The project is a collaboration among the schools of law and medicine and the Sylvester Cancer Center.

2010s

Tassy Hayden, LA '07, MD '11, began work at Total Access Urgent Care at locations in and around St. Louis in August 2021.

Erin McDuff Roades, GM '11, earned a PhD from the University of Missouri-St. Louis in teaching and learning processes.

Jackie Goff, MSOT '12, received a high-performer award from Christian Hospital, where she has worked for eight years in acute care and inpatient rehabilitation. Goff has worked with many patients with COVID-19 in the past 18 months, and participated in the turn team to assist with proning intubated patients. She is happy to report that she recently purchased a house.



Latrell Evans Selvaratnam, MSOT '18, and **Arun Selvaratnam, MSOT '18**, are pleased to announce they were married in Richmond, Va., May 14, 2021.

2020s



Samantha Lund, MD '21, married Warren Rixon May 29, 2021, in St. Louis. They were joined by many WUSM alumni and current students.

First row, left to right: Tamara Sanchez Ortiz, '22; Celia Cubitt, MSTP; Iris Kuo, '22; Samantha Lund, '21; Connie Gan, '21; and Priscilla Stecher, '22. Second row, left to right: Sean Terada, '21; Timothy Rooney, '21; Carly O'Donnell, '21; Cory French, '21; and Jason Morris, '21. Not pictured: Kaitlin McCallum, '21; Herluf Lund, '85; Greg Finn, '92; and Allen Baudendistel, '85.



Paula Jean Clayton, MD, 86, a psychiatrist who helped destigmatize depression and suicide, died peacefully surrounded by loved ones Saturday, Sept. 4, 2021, joining her

beloved parents, Dorothea Pflasterer and Oscar Limberg, and sisters, Betty Cisco and Dorothea Wolfgram. Clayton was born and raised in St. Louis. She graduated from the University of Michigan in 1956 and from Washington University School of Medicine in 1960. She did her psychiatric residency there and joined the faculty in 1965, becoming a full professor in 1976. Her leading-edge research on mood disorders and bereavement conducted at Washington University achieved international recognition. During this busy period, she married Charles Clayton and had three children, Clarissa, Matthew and Andrew.

In 1980, Clayton became the first woman in the U.S. to chair a psychiatry department, joining the University of Minnesota School of Medicine, where she served until 1999. She subsequently became a professor of psychiatry at the University of New Mexico School of Medicine from 2001 to 2005. In 2006, Clayton moved to New York City to become the medical director of the American Foundation for Suicide Prevention.

Clayton remained committed to advancing the field of psychiatry, conducting research, teaching students and residents, mentoring young doctors and seeing patients. She published four books, including "Manic Depressive Illness" and "The Medical Basis of Psychiatry," more than 180 papers and 20 book chapters.

Clayton is survived by her three children, Clarissa Weirick (Brad), Matthew Clayton and Andrew Clayton (Jojo), and seven grandchildren: Austin Clayton, Andrew Clayton, Catherine Weirick, Clayton Weirick, Madeline Weirick, Sophia Clayton and Chelsea Clayton.

Donations may be made in her memory to the Paula J. Clayton MD Endowment Fund at Washington University in St. Louis or the American Foundation for Suicide Prevention.



Colin Eugene Kluender, a graduate student in his fourth year of the Biochemistry, Biophysics, and Structural Biology Program in the Roy and Diana Vagelos Division of Biology & Biomedical Sciences, died unexpectedly Thursday, Nov. 4, 2021, in his hometown, Milwaukee. He was 26.

Kluender came to the university in 2018, after graduating from the University of Wisconsin-Madison with bachelor's degrees in microbiology and Spanish.

As a DBBS student, he worked in the lab of Jennifer M. Alexander-Brett, MD, PhD, assistant professor of medicine. His focus was on the contribution of cellular chaperones to inflammatory signaling pathways in chronic respiratory disease. His work recently was published in the journal *JCI Insight*, and he had been working toward an exciting follow-up publication.

"Colin was a brilliant scientist, performed impeccable work, and was a trusted colleague and loyal friend to many," Alexander-Brett said. "We shared a passion for cool science, nature, social justice and local politics; he poured himself into each with unmatched intensity. I've never known a more kind and selfless person as Colin. I could always count on him to make a new addition to the group feel immediately at home, and he was always the first to volunteer to help someone in need. He will be so greatly missed by his research family."

He is survived by his parents, Steven and Shirley Kluender of Milwaukee; his brother, Chad, of Boise, Idaho; and several aunts, uncles, cousins, other relatives and friends.



Michael M. Mueckler, PhD, professor emeritus of cell biology and physiology, died Wednesday, July 14, 2021, of natural causes at his home in Creve Coeur, Mo. He was 67.

Mueckler studied how the body regulates blood sugar and how this regulation goes awry in diabetes. His focus was on how sugar is transported into cells. He identified and studied several glucose transporter molecules, uncovering key insights into glucose homeostasis and insulin resistance. Among other accomplishments, he led breakthrough studies of insulin resistance caused by HIV protease inhibitor therapy.

Mueckler served as the associate director of the university's Diabetes Research Center for a decade. During that time, he encouraged the diabetes research community to adopt genomics techniques that enhanced understanding of the disease. In 1998, he received the Lilly Award for Outstanding Scientific Achievement from the American Diabetes Association, the highest accolade given by the association.

Mueckler earned a bachelor's degree in microbiology in 1976 and doctoral degree in oncology in 1983 from the University of Wisconsin-Madison. After postdoctoral training at Massachusetts Institute of Technology, he joined Washington University School of Medicine in 1986 as assistant professor of cell biology and physiology. He retired in 2019 as professor emeritus.

Mueckler is survived by his daughter, Sita Upadhyay; former spouse and good friend, Paula Hartman; a nephew, a niece and their families.

Memorial contributions may be made in his memory to the Juvenile Diabetes Research Foundation.



Allen Sclaroff, DDS, professor of clinical otolaryngology, died Wednesday, Aug. 18, 2021, in St. Louis, following complications of multiple myeloma. He was 75.

Sclaroff was an oral and maxillofacial surgeon who cared for patients — adults and children — with a variety of diseases, from oral cancers to temporomandibular joint disorders (TMJ). He was a sought-after speaker, giving grand rounds lectures on his areas of expertise, including TMJ surgery and reconstruction, surgical treatment of maxillofacial injuries, dental implants, treatment of cleft palate, oral and dental care for patients undergoing chemotherapy, oral care for patients undergoing radiation for head and neck cancer, and oral considerations in sleep apnea.

Also dedicated to teaching, Sclaroff led graduate education in the Department of Oral & Maxillofacial Surgery from the time he joined the faculty of what was then the School of Dental Medicine in 1978 until the dental school closed in 1991. Sclaroff then served as a professor and director of the Division of Oral & Maxillofacial Surgery in the Department of Otolaryngology-Head & Neck Surgery until his retirement in June 2020.

He is survived by his wife, Jan Sclaroff; two daughters, Megan Katz and Lindsey Creech; their spouses; and five grandchildren.

Memorial contributions may be made to Siteman Cancer Center, MSC 1204, 7425 Forsyth Blvd., St. Louis, Mo., 63105 or online at siteman.wustl.edu/tribute.



George Dubar Wilner, MD, a hematologist-pathologist, died peacefully Friday, Feb. 19, 2021, at Jersey Shore University Medical Center in Neptune, N.J., following complications from COVID-19 and an underlying neurological disease. He was 80 years old.

Wilner's research included pioneering publications on fibrinogen derivatives such as thrombin and collagen in hematology, immunology and chemotaxis. Many of these have been cited in top journals over 100 times and are standards of the field.

Wilner loved his country and served in the U.S. Army during the Vietnam War. He left the reserves as a lieutenant colonel in 2003.

Wilner earned a doctor of medicine from Northwestern University in Chicago. He served his residency at New York Presbyterian-Columbia University Medical Center and Montefiore Medical Center, in pathology and hematology. For nine years, Wilner was a physician at Columbia Presbyterian Hospital.

Wilner spent 10 years at Washington University Medical Center. There, he served as a professor of medicine and director of blood banks at the university and Jewish Hospital. While in St. Louis, he worked in conjunction with Monsanto Co., where he developed recombinant blood products, which Monsanto still holds many patents on to this day.

Wilner spent over 30 years at Albany Medical Center, from which he retired. During his time, he served as medical director of the northeast region of the American Red Cross, the Albany Medical Blood Bank and as director of labs at Albany Medical College.

He is survived by his wife, Judy; his son, Michael Wilner (and his wife, Alexa); his daughters, Jessica Pollard and Marissa Mandell (and her husband, David); eight grandchildren; and two stepsons, Gary Bickham and Steven Bickham. He was predeceased by his brother, Harvey Wilner, and his sister, Helene Wilner.

1950s

- James H. Dunlevy**, MD '51; April '21
- Nancy K. Elsea**, PT '59; July '21
- Wilbur H. Gearhart**, HS; July '21
- Betty Castleman Gilbert**, NU '50; May '21
- Marshall Greenman**, HS '52; May '21
- Jere P. McClure**, MD '53; April '21
- William A. Reynolds**, MD '56; Aug. '21
- Gerald S. Spear**, HS '53; April '21
- David S. Taylor**, DE '57; July '21
- Dolores P. Wolff**, LA '54, MD '59; May '21

1960s

- Gloria Doll Gottschalk**, GN '62; May '21
- Marjorie D. Head**, PT '61; April '21
- Floyd G. Johnson**, MD '60; June '21
- Marjorie A. McCown Moore**, PT '62; May '21
- Manzar Rad**, HS '60; April '21
- Harry E. Reynolds**, MD '60; June '20
- Ronald E. Rosenthal**, MD '61, HS '66; Aug. '21
- Bernard Schaaf**, MD '62; April '21
- Ruth Shulman**, OT '65; June '21
- Donald W. Turner**, DE '60; April '21

1970s

- Jeffrey David Barnett**, HS '75; May '21
- Robert L. Bartlett**, DE '70; April '21
- Arthur J. Elman**, HS; April '21
- Diana S. Lassen**, PT '72; Oct. '20
- Patricia Ann Newton**, MD '75; Sept. '20
- William Stanton III**, MD '70; June '21
- Albert Joseph Tahmoush**, HS '70; April '21
- Richard A. Weisiger**, HS '76; April '21
- James R. Wiant**, HS '74; Aug. '21

1990s

- Karen Ann Donahue**, PT '90; Aug. '21

In Memoriam

To read full obituaries on any of the alumni listed on this page or to submit an obituary for publication in a future issue of Outlook magazine, visit medicalalumni.wustl.edu/alumni.

M CENTRAL WEST END

Improving rider safety

A \$7.5 million redesign of the Central West End MetroLink Station on the Medical Campus is reducing pedestrian congestion and improving safety and convenience for riders. More than 4,300 people board trains at the station each weekday, making it the busiest station on the MetroLink light rail system. Washington University and BJC HealthCare, in partnership with Metro Transit, funded the improvements. The university also played a significant role in the station's redesign, which includes a welcome center staffed by medical school employees.

Above: A new entrance/exit monitored by contract security officers at peak travel times is one of the features of the redesigned Central West End MetroLink Station.

Left: Upgraded platform lighting, including LED lighting on the canopy, can change colors to celebrate different campus initiatives or events. The much larger canopy provides better shelter.



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First impressions Second-year medical student Kristine “MaeMae” Huang (right) performs an otolaryngology checkup on a baby at St. Louis Children’s Hospital. As part of the Gateway Curriculum, medical students at Washington University now undertake clinical immersion rotations earlier in training. Huang is working under the direct supervision of Katherine Dunsky, MD (observing, but not shown), assistant professor of otolaryngology-head and neck surgery.



MATT MILLER