Outlook

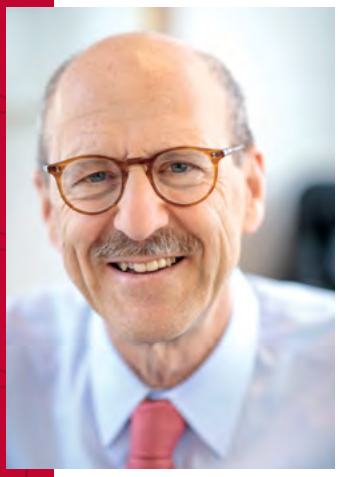
Washington University in St. Louis
School of Medicine

WINTER 2018-19

Together we heal

How the *Leading Together* campaign is turning hope into reality

A letter from the dean



When I came to Washington University School of Medicine as executive vice chancellor and dean in 2015, *Leading Together* was charging full steam ahead. It was inspiring to see philanthropic support for the school, already at a remarkable level, soar to even greater heights. I am deeply grateful to everyone involved in the campaign for joining with us to pursue the vision of advancing human health.

I'd like to take a moment to thank members of the Washington University Board of Trustees, the School of Medicine National Council, the School of Medicine campaign committee, our Eliot Society committee, the Washington University Medical Center Alumni Association executive council, and the many other alumni volunteers who provided crucial leadership during the campaign. You helped steer the School of Medicine through the campaign's goals and successful conclusion.

We face clear challenges as we look to the future of medicine. However, we also are poised to continue exceptional work and to make bold moves that will keep the School of Medicine at the forefront of biomedicine and health care. Many, many donors — from our loyal annual fund supporters, to those who invest in the leaders of tomorrow through scholarships, to those who have made a significant impact on faculty by funding research, professorships, facilities and centers — have made this possible. These individuals have helped position us to explore new partnerships, rethink our curriculum for new generations, build our excellent faculty practice, enhance and improve diversity, develop physician-scientists, and improve the already extraordinary breadth and depth of our collaborative research. This will translate into discoveries that will ultimately benefit patients here and around the world.

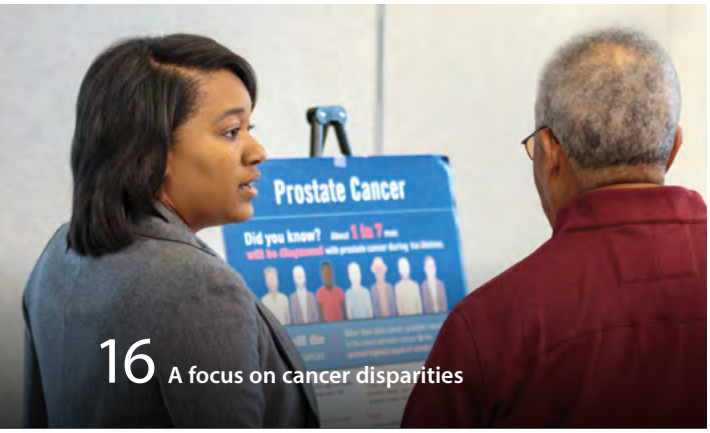
Together, we can pursue a future in which discoveries reach patients sooner. Together, we can realize the dream of personalized medicine. Together, we can continue to generate the resources needed to transform health care. Thank you for giving us the momentum to aim for the highest of ideals at Washington University School of Medicine. It's an amazing place to be, and I'm so excited and fortunate to be a part of it.

Sincerely,

David H. Perlmutter, MD

George and Carol Bauer Dean, School of Medicine
Spencer T. and Ann W. Olin Distinguished Professor
Executive Vice Chancellor for Medical Affairs

10 New drugs for mental illness



16 A focus on cancer disparities

24 The microbiome's secrets

Outlook

Washington University School of Medicine

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FEATURES

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BOB SHENCO SHENCO PHOTOGRAPHY

Together, we heal.

This issue of Outlook is a special one. It documents the conclusion of *Leading Together: The Campaign for Washington University.*

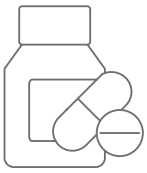
The campaign, which ended this summer, raised an unprecedented $1.85 billion for the School of Medicine in the most successful campaign in school history. The campaign has established 281 endowed scholarships, produced 73 named professorships, and generated $1.34 billion for research.

These contributions have huge real-life import. They allow gifted students to attend a world-class medical school and learn from extraordinary faculty. And they allow leading researchers to find solutions for some of medicine's most intractable problems. Those things are happening now, and, because of the generosity of donors, will continue to happen.

In this issue, we'll look at four areas of research the campaign has significantly advanced. They are:

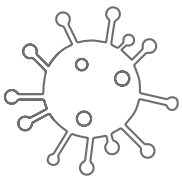
Alzheimer's

Prevention, early diagnosis and treatment of Alzheimer's disease



Mental illness

New medications for mental illnesses, such as depression, anxiety and schizophrenia



Cancer

Targeted therapies that harness the patient's own immune system to fight cancer

Microbiome

Improved understanding of the human microbiome to address a host of health problems

We'll introduce you to the researchers who are advancing medicine in these areas, and, because the campaign was about looking forward, we'll show you what the future holds.

New hope for old disease

Doctors may soon be able to predict, prevent Alzheimer's disease

BY TAMARA BHANDARI

Caring for an aging relative with Alzheimer's disease, watching memories slowly slip away, is an exhausting and heartbreaking ordeal. For those with the condition, modern medicine can offer little in the way of treatment as the disease inexorably strips away their ability to recognize and understand the world around them.

Finding solutions can't happen soon enough. The American population is rapidly graying, and the risk of developing the disease rises with advancing age. The Alzheimer's Association predicts that 16 million Americans will be living with the disease by 2050.

A large, dedicated team at Washington University School of Medicine has been working for 40 years to brighten this bleak outlook, and the investigators may be on the cusp of succeeding. They have traced the natural history of the disease, studied the molecular and cellular changes that occur in the brain, designed and tested investigational drugs aimed at slowing or stopping the disease, and developed imaging techniques to detect toxic proteins in the brain. Now, they are on the brink of finding ways to predict who will get the disease and when; they may even determine how to prevent it entirely.

An Alzheimer's-free future has never looked more likely.

Randall J. Bateman, MD, examines Taylor Hutton, a participant in a global multicenter study testing drugs that may delay or prevent Alzheimer's onset. An active Alzheimer's advocate, Hutton attends and speaks at awareness events and wears an Alzheimer's awareness tattoo on her foot.

Step one: diagnosis

The first sign is usually forgetfulness — a forgotten conversation, a misplaced item, a question asked and answered and asked again. Until a few decades ago, such lapses might have been chalked up to the normal effects of aging. But Leonard Berg, MD, a professor of neurology at Washington University, was concerned that the distinction between normal aging and dementia was poorly understood, so in 1972 he started a faculty lunch group to discuss how to distinguish the two processes.

"At the time, there was no standard method to distinguish normal aging from very mild dementia," said John C. Morris, MD, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology and professor of pathology and immunology. "So Leonard and his colleagues developed a clinical tool to diagnose dementia and to determine its severity."

That tool, the Clinical Dementia Rating Scale, later revised by Morris, is now used worldwide to identify people with dementia. Berg died in 2007; but the work he started has since grown into Washington University's Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC), a network, directed by Morris, of faculty members, trainees and staff dedicated to understanding, treating and preventing the No. 1 cause of cognitive decline in older people.

Today, we know that memory lapses could be caused by many things: lack of sleep, medications, vitamin deficiencies, brain tumors or neurological diseases other than Alzheimer's, such as Parkinson's disease or frontotemporal dementia.

"When people come in and they're clearly impaired but we don't know what the cause is, that's when biomarkers can be really useful," said Anne Fagan, PhD, a professor of neurology and head of the biomarker research unit at the Knight ADRC. Biomarkers are proteins or other biomolecules that indicate the presence of disease.

Research by Fagan and others has established that two proteins linked to Alzheimer's disease — amyloid beta and tau — can be detected in the cerebrospinal fluid that bathes the brain and spinal cord. Neurologists can resolve a difficult diagnosis by taking a spinal tap and measuring levels of the two proteins.

"I use the results of these biomarker tests to inform the care of my patients," said Gregory S. Day, MD, an assistant professor of neurology. "A few decades ago, Alzheimer's was formally diagnosed only on autopsy. Now using biomarkers or imaging, we can tell people what is going on very early in the process."

Research by David M. Holtzman, MD, has focused on how levels of the Alzheimer's proteins amyloid beta and tau in the brain and spinal fluid are linked to risk for and progression of the disease.

MARK KATZMAN

Stopping the disease in its tracks

Early detection allows physicians to discuss lifestyle modifications and financial arrangements with patients. It does not, however, allow them to offer any medications to slow or stop the disease. The Food and Drug Administration has not yet approved any such drugs.

Tammie L.S. Benzinger, MD, PhD, prepares to scan a patient with PET imaging. She and colleagues pioneered the use of PET to detect Alzheimer's.

David M. Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor, head of the Department of Neurology and professor of developmental biology, is trying to change that. He studies the basic biology underlying Alzheimer's disease — how amyloid beta and tau build up in the brain, why clumps of such proteins cause brain cells to die, and how drugs can be designed to interrupt the process. The research of Holtzman and colleagues at Eli Lilly and Company led to the development of solanezumab, a drug designed to counter amyloid beta's toxic effects. Solanezumab and another drug, gantenerumab, are now being evaluated in the first-ever Alzheimer's disease prevention trial, at the School of Medicine and elsewhere.

Other drugs — targeting amyloid beta or tau — also are being tested, and researchers are hopeful that some will prove effective.

In the past, drug trials were complicated by a lack of accurate disease detection methods.

Then in the early 2000s, Tammie L.S. Benzinger, MD, PhD, the Knight ADRC's director of imaging studies, and others pioneered the use of positron emission tomography (PET) brain scans targeted against amyloid beta as a tool for detecting Alzheimer's.

"When people started using amyloid PET to assess trial participants, they discovered that only about 80 percent of the participants actually had Alzheimer's," said Benzinger, a professor of radiology and of neurological surgery. "If you treat someone whose dementia is not related to amyloid with an amyloid drug, of course it's not going to work."

Now, clinical trials routinely screen for misdiagnosed participants using amyloid PET scans or biomarker analysis.

In addition, researchers are expanding the basic science foundation upon which drug development rests. But much of what we know about Alzheimer's disease has been learned from studying only one part of the American population.

"There is a lot of mistrust in the African-American community because of a history of

"Researchers here are pursuing treatments that could one day dramatically improve the lives of millions of individuals worldwide. We want to do our part to fulfill that goal."

— the late Charles F. Knight, former Trustee

Charles F. and Joanne Knight's extraordinary campaign support included a major commitment to name The Charles F. and Joanne Knight Alzheimer's Disease Research Center.

Anne Fagan, PhD, observes staff scientist Matthew R. Amos as he processes samples in her lab. Fagan has identified a number of biomarkers for Alzheimer's disease.

medical exploitation," said Myrtis E. Spencer, who leads the Knight ADRC's African-American outreach program. "But they are twice as likely to get the disease compared with non-Hispanic whites. We don't know why. We don't have the full scientific picture because research historically hasn't been inclusive."

Through the efforts of Spencer, Morris and others, African-American participation in Alzheimer's studies at the School of Medicine has risen to 18 percent, comparable with the African-American population in the St. Louis area and significantly higher than the national average for Alzheimer's studies.

"We've found that the concentration of tau protein is significantly lower in African-Americans than in non-Hispanic whites," Morris said. "What does that mean in terms of the pathology of the disease? I don't know. But I do know it means that we can't just take everybody and lump them together. The disease may develop and progress differently in different populations. We are not going to find treatments that work for all people if we don't understand how the disease behaves in all people."

Detecting the silent phase

Although treatment is important for the estimated 5 million Americans already living with Alzheimer's, it won't lead to a future free of Alzheimer's. By the time people show up in doctors' offices complaining of forgetfulness, their brains already have begun to atrophy. And while some of the drugs currently in trials may be able to prevent more brain cells from dying, nothing will bring back the cells already lost.

To truly stop Alzheimer's, doctors must catch people heading down the path to Alzheimer's dementia and redirect them, much as physicians today measure blood cholesterol levels and, if necessary, prescribe cholesterol-lowering drugs to avert a heart attack.

Since the early 1990s, Washington University researchers have been collecting evidence that memory loss and confusion show up very late in the game, after years of toxic protein accumulation in the brain and corresponding tissue damage. Two major studies led by Washington University have used imaging and biomarker analysis to trace the natural history of the disease: the Adult Children Study, which follows people with at least one parent diagnosed with Alzheimer's, and the Dominantly Inherited Alzheimer Network (DIAN), which studies people genetically predisposed to develop the disease at a young age. These two studies, and others conducted at Washington University and elsewhere, have allowed researchers to develop a rough timeline of what happens in the brain in the years before symptoms appear: Amyloid plaques appear first, then tau tangles, followed by brain atrophy.

"This silent phase may last two decades, which gives us a chance to intervene," Morris said.

Spinal taps and PET scans can reliably detect signs of disease before dementia, but neither is ideal for widespread screening. A single PET scan

One day, Alzheimer's disease will be treatable or even preventable. Researchers at Washington University are leading the way to making that bright future real."

— David C. Farrell, Trustee Emeritus

David C. Farrell and his late wife, Betty, made major commitments to establish and enhance the Farrell Family Alzheimer's Disease Research Fund, supporting the research of David M. Holtzman, MD.

costs approximately $5,000 and requires equipment and expertise difficult to find outside of research settings. Spinal taps have an undeserved reputation for being painful and dangerous, so some patients are reluctant to undergo the procedures.

MRI scans, though, are already a routine part of neurological care, available in most clinics. Benzinger and colleagues have shown that a characteristic pattern of brain atrophy is visible in an MRI scan before symptoms appear. They are developing an MRI scan to diagnose Alzheimer's in its pre-symptomatic phase.

A blood test is also on the horizon. "Last year my lab reported the first highly specific blood test for amyloid," said Randall J. Bateman, MD, the Charles F. and Joanne Knight Distinguished Professor of Neurology. "Since then, other groups have replicated and expanded on it. I think we'll see that test in use in doctor's offices in the next three to five years."

Rajendra S. Apte, MD, PhD, the Paul A. Cibis Distinguished Professor of Ophthalmology and Visual Sciences, and Gregory P. Van Stavern, MD, a professor of ophthalmology and visual sciences, recently have reported a small study that suggests that signs of Alzheimer's might be detectable through a specialized, noninvasive eye exam.

No longer inevitable

But finding people on the path to dementia is only half the battle. We also need to find a way to get them off the path.

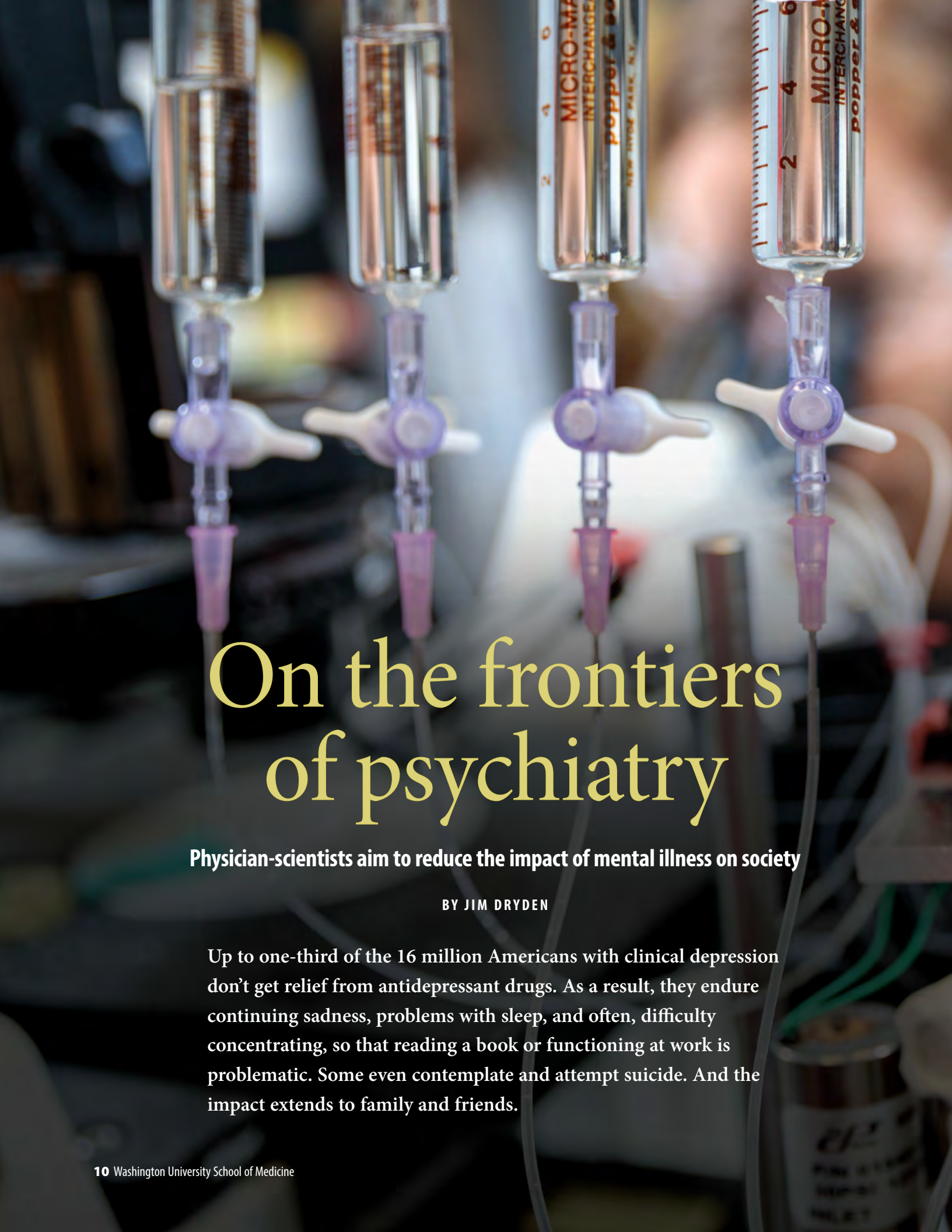
Bateman directs the DIAN Trials Unit (DIAN-TU), an international clinical trial designed to find drugs that prevent Alzheimer's dementia. The trial involves people from DIAN families; family members who inherit a faulty gene variant are all but guaranteed to develop Alzheimer's dementia at about the same age their parent did, typically in their 50s, 40s or even 30s. Participants enroll in the trial while their minds are still sharp but their brains show some amyloid accumulation. Two drugs are being tested — the trial of a third was stopped due to safety issues — to determine whether they can slow amyloid plaque buildup. The final report is due out in a year.

Although DIAN-TU involves people with rare mutations, treatments that are successful in this population could also help people with the more common forms of the disease, which strike older adults. It is thought that the destructive processes in the brain are much the same for both types of the disease.

Other prevention trials involving people with genetic forms of Alzheimer's are in the works. A few prevention trials are underway in people without genetic forms of the disease, and more could be launched once screening tests are more fully developed. There are plenty of experimental drugs to try.

Shakespeare lamented the coming of the "second childishness." We may be able to elude it.

Myrtis E. Spencer, conferring here with pioneering Alzheimer's researcher John C. Morris, MD, leads an outreach effort dedicated to ensuring that African-Americans are appropriately represented in Alzheimer's research.

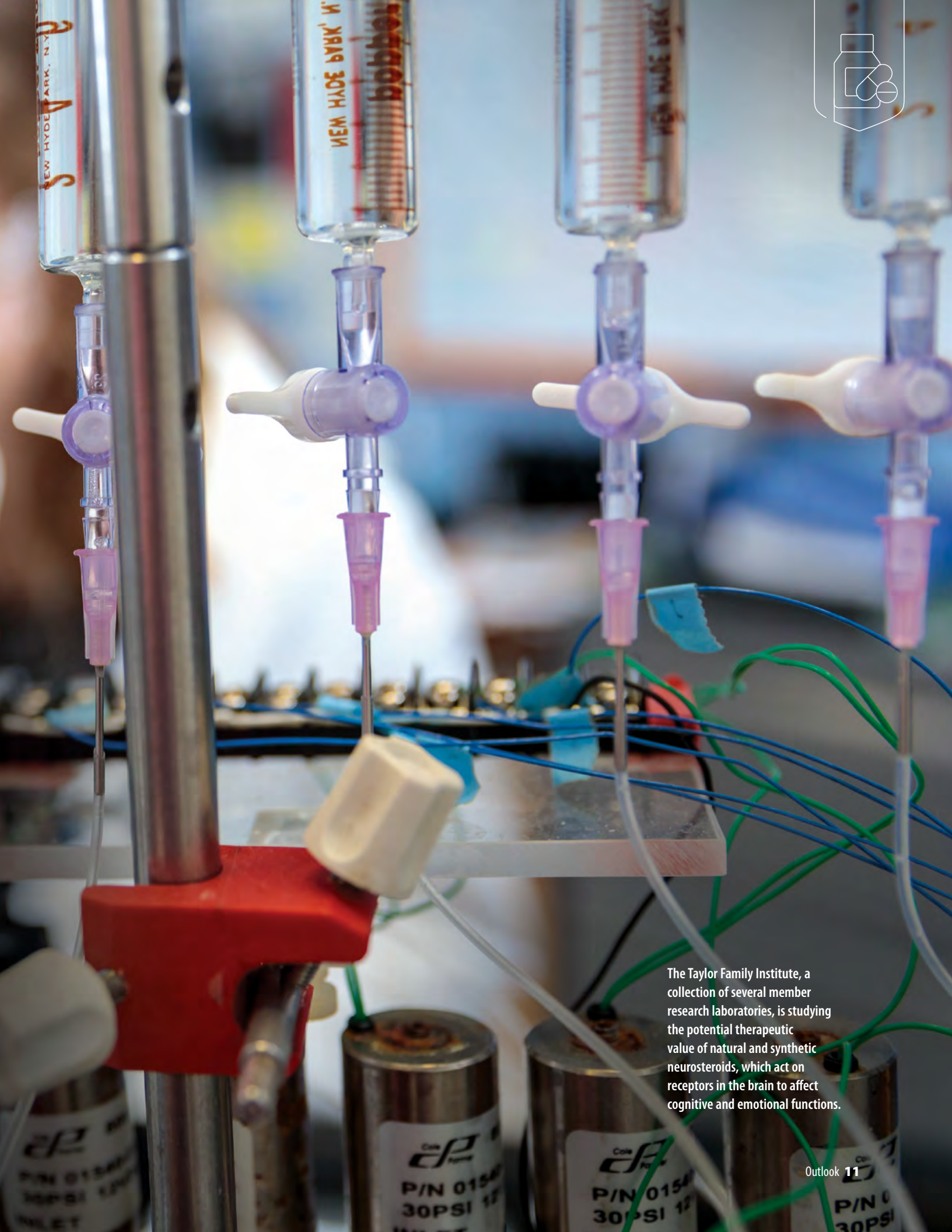


On the frontiers of psychiatry

Physician-scientists aim to reduce the impact of mental illness on society

BY JIM DRYDEN

Up to one-third of the 16 million Americans with clinical depression don't get relief from antidepressant drugs. As a result, they endure continuing sadness, problems with sleep, and often, difficulty concentrating, so that reading a book or functioning at work is problematic. Some even contemplate and attempt suicide. And the impact extends to family and friends.



The Taylor Family Institute, a collection of several member research laboratories, is studying the potential therapeutic value of natural and synthetic neurosteroids, which act on receptors in the brain to affect cognitive and emotional functions.

Steven J. Mennerick, PhD, prepares to use a collection of technology — including a microscope and amplifiers — to measure the tiny electrical impulses between brain cells. The equipment helps him assess how the electrical conversations of neurons are influenced by therapeutic drugs.

For doctors treating patients with depression and other psychiatric disorders, the reality is that many of the therapeutic drugs at their disposal have major limitations — both in terms of effectiveness and potential adverse side effects. Not only that, but the last new class of antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs) such as Paxil, Zoloft, Lexapro and Prozac, hit the market 30 years ago.

At Washington University's Taylor Family Institute for Innovative Psychiatric Research, investigators are looking for new solutions. Their ultimate goal: Reduce suffering and diminish the impact of psychiatric illnesses on society.

Institute investigators are exploring receptors in the brain to identify new targets for therapy, developing potential drug candidates, and partnering with industry to speed progress. The institute is on the verge of helping get two investigational antidepressant drugs to the market, and there could be other promising compounds in the pipeline, too.

Private funding = fast progress

The institute was created in 2012 through private funding from the university's *Leading Together* campaign. Its founding mission: to provide flexible funding to foster and streamline efforts in basic research, clinical research and drug development as scientists work across disciplines to uncover new ways to treat psychiatric illness. Members of the institute collaborate among several departments, including psychiatry, anesthesiology, developmental biology, radiology and neurology.

"The institute really was founded on the premise that we need flexible funding to support pipelines of research development, rather than focusing on individual projects in specific departments," said Steven J. Mennerick, PhD, a professor of psychiatry and of neuroscience and the institute's scientific director. "Government grants tend to be very specific, so to take a project to the next step, you need another grant, and then another. But with flexible funding through the institute, we can partner — quickly — with people who have expertise in other areas of science or

drug development, and we can make progress faster than is possible with traditional grants."

Their work starts with understanding the genetics and biology of psychiatric illness, as well as the brain circuits involved. Then, when basic science reveals a potential new therapeutic approach, institute investigators can get their findings into the hands of collaborators in private industry very quickly, especially through the institute's close relationship with Massachusetts-based biopharmaceutical company Sage Therapeutics.

A new treatment target

Much of the focus at the institute today is directed toward a class of compounds called neurosteroids — chemicals that occur naturally in the brain and are involved in brain networks used for cognition, emotion and motivation. Disruptions in neurosteroid levels can contribute to mood disorders such as depression, anxiety disorders, schizophrenia, alcoholism, sleep disorders, chronic pain, epilepsy and neurodegenerative illnesses such as Alzheimer's disease.

Current evidence suggests that stress and disorders such as depression affect neurosteroid production in the brain, so institute scientists believe that replacing or enhancing these depleted steroids may alleviate that stress response to make the brain function more normally.

Although the institute only has been around for a handful of years, some of its members have been studying natural and synthetic neurosteroids for several decades. That work began in 1993, when Douglas F. Covey, PhD, then a professor of molecular biology and pharmacology, and Charles F. Zorumski, MD, then an associate professor of psychiatry, were part of a Program Project Grant from the National Institutes of Health (NIH) to study neurosteroids for their anesthetic effects. Their process: Covey's lab synthesized neurosteroid molecules, and Zorumski tested them in brain cells.

"In those early days, we mostly were trying to learn about whether these molecules had anesthetic effects, and if so, how they might work," said Covey, a professor of developmental biology, of anesthesiology and of psychiatry. They discovered that neurosteroids weren't working through serotonin receptors the way SSRIs did. Instead, many were influencing gamma-aminobutyric acid (GABA) receptors, the same neuronal receptors affected by anesthetics.

Fast-forward about 20 years. By the spring of 2012, Covey had made hundreds of synthetic neurosteroids, some of which seemed to have the potential to alleviate symptoms of depression. And Zorumski, now the Samuel B. Guze Professor, head of the Department of Psychiatry and professor of neuroscience, believed that after years of making and testing neurosteroids, they had a good handle on how the molecules interacted with two types of receptors in the brain: GABA receptors and excitatory glutamate receptors. They could, he thought, be on the verge of identifying neurosteroids to alleviate depression and other psychiatric disorders.

"Some of these neuroactive steroids were potent anesthetics, but we believed others were going to prove to be useful for treating several psychiatric disorders," Covey said.

But at just about that time, a letter arrived from NIH announcing that the program project group was about to lose its funding.

Within a day or two of receiving the bad news, Zorumski started drafting a new white paper, attempting to explain the importance and potential impact of the project he'd been involved in for two decades.

"It was written around the time that Doug Covey and I were just starting to interact with Sage Therapeutics, and it was built around the idea that we could take neurosteroids — as well as the

> *"I have received notes from people around the country who have been impacted by mental illness. They now have a sense of hope; someone is paying attention. I want many people to pay attention, because I think awareness promotes momentum."*
>
> — *Andrew C. Taylor, Life Trustee; Chair,* Leading Together *campaign*
>
> Andrew C. and Barbara Taylor, and the family's Crawford Taylor Foundation, made major commitments to establish and enhance the Taylor Family Institute for Innovative Psychiatric Research.

Douglas F. Covey, PhD, left, Charles F. Zorumski, MD, and colleagues have spent decades conducting groundbreaking research on the therapeutic potential of neurosteroids.

synthetic molecules that had been developed here at Washington University — and turn them into therapies," he said. "We weren't entirely sure what these molecules actually would treat, but epilepsy was a clear target, so was insomnia, and so was postpartum depression."

The proposals in the white paper eventually received funding, and the Taylor Family Institute for Innovative Psychiatric Research was born.

On the verge

The results are impressive.

"We're literally only about six years from when the institute was created, and there already could be new drugs coming to market just several months from now," said Zorumski, now the director of the institute.

Sage is seeking Food and Drug Administration approval of two neurosteroids that it developed based on Washington University research: an IV drug called brexanalone to treat post-partum depression, and an oral drug known as Sage 217 for clinical depression in men and women.

During the Taylor Institute's first half decade of existence, its scientists have published more than 60 scientific papers. They have continued to prepare new compounds to enlarge the original set of over 700 compounds, and multiple U.S. and foreign patents are pending. In collaboration, investigators at Taylor Institute and Sage are discovering and applying ways to optimize these neurosteroids for therapeutic use in humans.

Covey, who has patented many of the molecules developed in his lab, served for a time as a partner at Sage, and Zorumski serves on the company's scientific advisory board. As a result, much care has been taken to avoid conflicts of interest, so a good deal of the clinical testing of neurosteroid molecules has occurred at other centers.

But other clinical research is underway at the institute. For example, institute researchers have been involved in clinical testing of anesthetic drugs, such as ketamine and nitrous oxide, as treatments for depression. Their common goal, one way or another, is to find new ways to provide relief to the many individuals, families and friends living with the effects of psychiatric illnesses.

"The success of the Taylor Family Institute demonstrates the critical impact of private philanthropy on Washington University's efforts to improve human health," said David H. Perlmutter, MD, executive vice chancellor for medical affairs and the George and Carol Bauer Dean at the School of Medicine. "The investment to launch the institute was instrumental in helping our scientists make discoveries that hold great promise for ameliorating the burden of mental illness, and their continued support will bolster our ability to work on the therapeutic frontiers of psychiatry."

Charles F. Zorumski, MD, is a scientific advisor for Sage Therapeutics and receives compensation and stock equity from the company for this role. Research partnerships between Sage Therapeutics and Washington University are managed in accordance with applicable conflict-of-interest policies and regulations. Douglas F. Covey, PhD, has an issued patent and pending patents for jointly invented intellectual property assigned to Washington University and Sage Therapeutics.

ADVANCES IN TREATING
mental illness

Taylor Family Institute investigators are setting their sights on a new set of therapeutic targets in the brain. Their goal: Develop drugs that engage these new targets and better address depression and other mental illnesses.

Then

Target serotonin receptors.

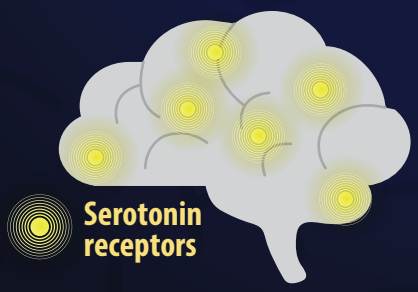
Administer selective serotonin reuptake inhibitors (SSRIs) and tricyclic drugs, which increase brain levels of serotonin and promote feelings of well-being.

PROS

Existing SSRIs and tricyclics are effective for many people.

CONS

Drugs can have undesirable side effects. Up to one-third of patients are not helped by these drugs.



Now

Target GABA and glutamate receptors.

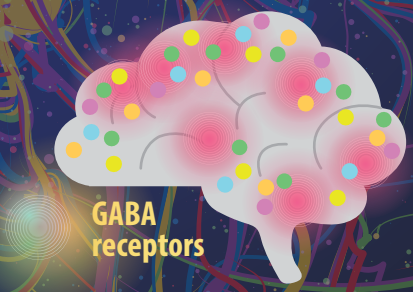
Generate and test compounds that augment the action of gamma-aminobutyric acid (GABA), which calms key brain cells, and glutamate, which excites key brain cells. Seek ways to balance their activities to achieve well-being.

PROS

The prevalence of, and variations in, GABA and glutamate receptors may facilitate targeting specific receptor classes for more effective therapies.

CONS

The landscape is complex and not thoroughly understood. Defining a "normal" balance may be difficult.



The warrior within

The future of cancer treatment

BY GAIA REMEROWSKI

A few short decades ago, cancer treatment consisted mainly of three pillars: surgery, radiation and chemotherapy. Although each has earned its place as a valuable option, more precise alternatives have long been the oncologist's dream.

Now, a deeper understanding of the way our bodies fight disease is launching a promising new era in which cancer's worst enemy may be the warrior within: our own immune system. By determining the characteristics of individual tumors at the genetic and molecular levels, researchers are tailoring treatment to each patient, aiming the built-in destructive power of the immune system directly at cancer.

Robert D. Schreiber, PhD, right, consults with doctoral student Samuel O. Ameh. Their work exploring the immune system's role in controlling cancer is fueling development of a range of approaches to cancer immunotherapy.

A seismic shift

Until the early 2000s, researchers only dreamed that the immune system could be capable of keeping cancer at bay. Then research at Washington University and elsewhere began uncovering evidence that made the dream seem possible.

The shift began in 2001, when Washington University's Robert D. Schreiber, PhD, and colleagues published a landmark paper in Nature concerning the adaptive immune system — the part of the immune system that recognizes and destroys specific disease-causing agents. They showed that mice lacking adaptive immunity developed more tumors, showing that conversely, healthy adaptive immunity restrains cancer development.

His subsequent work demonstrated that tumors can evolve to evade and resist the adaptive immune response, which is why cancer can form in people with intact immunity. So, Schreiber surmised, if we could retrain the immune system to see cancer, we might have a new targeted tool to fight the disease. This research has advanced the latest frontier in cancer treatment: immunotherapy.

Schreiber leads the Andrew M. and Jane M. Bursky Center for Human Immunology and Immunotherapy Programs, where he and many others are dedicated to translating human immunology research from the bench to the bedside. Much of their work has started in animal models. As he put it: "We've cured a lot of mice of their cancers." But it's not only mice who benefit from the center's work.

"One of the things that's been so exciting is that for the first time we have an opportunity to take what we're learning at the bench level and see it applied to human disease," said Schreiber, the Andrew M. and Jane M. Bursky Distinguished Professor. "That's what's so amazing about the Bursky Center."

While Schreiber focuses on cancer, others at the center are applying findings about the immune system to autoimmune and infectious diseases, such as diabetes and the flu.

The center's seminal cancer immunology research is beginning to move from the lab into the clinic, thanks to collaborations across the School of Medicine — and particularly with the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, where clinical researchers are working on a variety of ways to harness the immune system to fight cancer.

"Figuring out how to use the immune system to target cancer cells and not normal cells is something many of us have worked on for the last three or four decades," said Timothy J. Eberlein, MD, the Spencer T. and Ann W. Olin Distinguished Professor, chair of the Department of Surgery and director of Siteman Cancer Center. "Now something we only dreamed about is becoming a reality."

Personalized vaccines

One way to train the immune system to recognize cancer cells is by using a vaccine. Vaccines work by injecting parts of the foreign invader — in this case, cancer cells — into patients. The vaccine then prompts the immune system to mount an attack on that invader.

William E. Gillanders, MD, professor of surgery and Siteman Cancer Center research member, led one of the earliest human breast cancer vaccine trials. The vaccine contained a protein called mammaglobin-A, which is found at abnormally high levels in almost all breast cancer cells, making it an easy target for the immune system. Gillanders and Washington University

"The speed at which the center is translating groundbreaking discovery into new modalities of personalized treatment is incredibly exciting."

— Andrew M. Bursky, Trustee

Andrew M. Bursky and his wife, Jane M. Bursky, made a significant commitment to name the Andrew M. and Jane M. Bursky Center for Human Immunology and Immunotherapy Programs.

colleagues were the first to study the protein in breast cancer and elicit an immune response to it, then developed the vaccine based on that work.

The trial results were promising, but mammaglobin-A also is made by certain normal cells and can generate an autoimmune response to them. So Gillanders, Schreiber and others began searching for other, more tumor-specific vaccine targets.

They found a candidate in proteins called neoantigens that exist on the surface of cancer cells. Neoantigens, which Schreiber was among the first researchers to recognize, are unique to each patient's tumor but, importantly, are not present on normal cells. He and Gillanders reasoned that the immune system could be trained to recognize neoantigens as foreign and to destroy cancer cells without harming normal ones. But the challenge, said Schreiber, was how to identify each patient's unique neoantigens and determine which were most likely to be recognized by the immune system.

This is where genome sequencing comes in. By sequencing patients' cancer cell genomes and comparing them to their normal cell genomes, researchers can determine which neoantigens are unique to each patient's tumor and which generate the strongest immune response. They can then use those neoantigens to make a personalized vaccine.

Gillanders' group is testing neoantigen vaccines in patients with triple negative breast cancer, a form that is difficult to treat. They are conducting trials that combine the current standard of care — surgery, radiation and chemotherapy — with a vaccine in the hope of preventing recurrence.

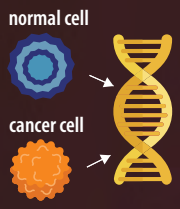
"Finding the right way to combine traditional therapies with immune therapies such as vaccines, that's where things are moving," said Gillanders.

Neoantigen cancer vaccines represent a truly personalized treatment approach; neoantigens vary from patient to patient and from tumor to tumor, so each patient's vaccine must be made from scratch. That can present challenges with production.

William E. Gillanders, MD, senior scientist Xiuli Zhang, MD, and colleagues have developed breast cancer vaccines now in clinical trials. Here, they examine blood test results indicating study participants' response to a vaccine.

HOW TO MAKE A cancer vaccine

Vaccines work by co-opting a disease-causing agent to generate or rev up an immune response against that disease. To avoid harming healthy tissue, a cancer vaccine must be generated from an agent unique to cancer cells. Among the promising candidates are neoantigens — proteins present only on tumor cells, in combinations unique to each patient.



1. Sequence

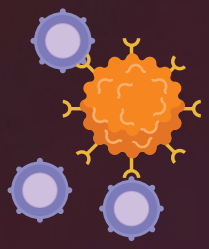
Sequence the genomes of the patient's normal and cancer cells.

2. Identify

Using sequencing data, identify cancer cell neoantigens unique to the patient.

3. Prepare vaccine

Make a vaccine with the neoantigens and inject into the patient.



4. Vaccinate & monitor

Immune cells now see tumor cells as foreign and attack the cancer.

More ways to treat cancer

CAR-T cell therapy
Collect patient's T cells and engineer them to recognize and kill cancer.

Checkpoint inhibitors
Use antibodies that block cell interactions to restore immune destruction of tumors.

Monoclonal antibodies
Use antibodies that attach to cancer cells to make them visible to the immune system.

NK cell therapy
Expose patient's NK immune cells to chemicals called interleukins to help them better fight cancer.

"The research being conducted at the Siteman Cancer Center is transforming the way the disease is treated."

— Alvin J. Siteman, Trustee Emeritus

During *Leading Together*, Alvin J. and Ruth Siteman continued their transformative support for the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, which was named in 1999 in honor of their generosity.

"There aren't many places that can generate these products under the kinds of conditions that you need to make a vaccine," said Schreiber.

Fortunately, the School of Medicine and Siteman Cancer Center are home to a Good Manufacturing Practice (GMP) lab, where immunotherapies such as cancer vaccines can be made and tested in clinical trials. Such facilities, which meet exceedingly high standards for consistency and quality, are not typical in most academic medical centers and help keep costs down when producing such expensive individualized treatments.

Deploying T cells

Another form of immunotherapy under investigation at the School of Medicine uses a patient's T cells to target certain blood cancers, such as leukemia, lymphoma and multiple myeloma. T cells typically fight off disease. But in some cancer patients, these cells lose the ability to recognize and attack cancer cells.

"The immune system can't always see cancer cells as threats; the T cells are sometimes blind to them," said John F. DiPersio, MD, PhD, the Virginia E. and Sam J. Golman Professor of Medicine in Oncology and deputy director of Siteman Cancer Center. "By modifying T cells, we tell them what to look for so they can go right to the leukemia or lymphoma and eliminate the cancerous cells."

Like the cancer vaccines, this therapy is individualized for each patient and each tumor. The T cells, known as Chimeric Antigen Receptor, or CAR-T cells, are produced in the same GMP facility where the vaccines are made. They are designed and tested by the Center for Gene and Cellular Immunotherapy (CGCI) in the Department of Medicine's Division of Oncology.

DiPersio and colleagues were involved in clinical trials that led to the Food and Drug Administration's approval of CAR-T cell therapy, and Siteman Cancer Center is now among the first centers nationwide to offer it to patients. DiPersio's team is now working on a way to make a universal form of CAR-T cells that can come from a donor rather than the patient. Such an approach could be faster, less costly and more effective for patients with rapidly progressing blood cancers. DiPersio and the CGCI team are attempting to expand application of current CAR-T to other diseases, such as T-cell leukemias and lymphomas, acute myelogenous leukemia and solid tumors.

Also entering the clinic is a new form of immunotherapy called checkpoint inhibitors. Checkpoints are proteins on the surface of T cells that survey proteins on other cells to determine whether they are normal or diseased. Normal cells are left alone, and diseased cells are flagged for destruction. Unfortunately, cancer cells can display proteins that bind to T cell checkpoints and trick the T cells so they do not see the cancer as foreign. Researchers are now devising antibodies that block the T cell-cancer cell interactions, making the cancer once again visible to the immune system.

The 2018 Nobel Prize in Physiology or Medicine went to James P. Allison, PhD, of the United States and Tasuku Honjo, MD, PhD, of Japan, who independently discovered two separate checkpoint inhibitor pathways. At Washington University, researchers are using checkpoint inhibitors in combination with traditional therapies as well as neoantigen vaccines in trials for breast, lung and other cancer types.

Bettina Drake, PhD, MPH, discusses cancer prevention at a health fair in East St. Louis.

A FOCUS ON cancer disparities

One of the best ways to fight cancer is to stop it before it starts, and, failing that, make sure everyone has access to the best possible care. Siteman Cancer Center is working with the community in and around St. Louis to improve prevention and screening programs and to reduce cancer care disparities.

At the forefront of these efforts is Bettina Drake, PhD, MPH, associate director of cancer health equity for Siteman Cancer Center.

Drake, an associate professor of surgery in the Division of Public Health Sciences, began researching prostate cancer as a doctoral student at the University of South Carolina, in a state where African-American men are almost three times more likely to die of prostate cancer than white men — often due to missed diagnoses. The survival rate for prostate cancer, if caught early, is normally 95-100 percent.

Soon after her father was diagnosed with prostate cancer, Drake got involved in community outreach with area churches, providing educational materials about prevention and screening for those at risk of getting cancer. "The combination of my outreach experiences and my father's diagnosis fueled my interest and passion in disparities research," said Drake.

In St. Louis, Drake now leads the Prostate Cancer Community Partnership, part of the Program for the Elimination of Cancer Disparities at Siteman Cancer Center. The program seeks to eliminate screening and treatment barriers to improve patient outcomes. Drake works with community leaders and colleagues such as Lannis Hall, MD, MPH, Arnold D. Bullock, MD, and Aimee S. James, PhD, MPH, to develop public awareness campaigns and refine identification of high-risk groups. She is also focused on recruiting a more diverse patient population for Siteman clinical trials.

"When we do research, we want our patient population to resemble the people who will be receiving the treatment in the future," said Drake.

A new standard

Much of the work on targeted cancer immunotherapies could not have been done without the Elizabeth H. and James S. McDonnell III Genome Institute (MGI). In 2008, the institute led a historic effort to sequence the first entire cancer genome, of a woman with leukemia, and helped identify the genetic errors that contributed to her disease. Though it was an uncertain endeavor at the time, St. Louis philanthropist Alvin J. Siteman agreed to fund the project. That work has since established Washington University as a national leader in the field of cancer genomics and prompted many clinicians to add cancer genome sequencing to their standard of care.

A case in point: Nearly every patient with lung cancer who sees Ramaswamy Govindan, MD, the Anheuser-Busch Endowed Chair in Medical Oncology, gets some or all of their genome sequenced.

"We no longer stop at the microscopic level when diagnosing cancer," said Govindan, co-leader of Siteman Cancer Center's solid tumor program and a leader in lung cancer clinical trials and translational research. "Now we do molecular profiling and study the genes that are altered to see whether we can use targeted therapies." Depending on the situation, that might involve using a targeted chemotherapy or customized tumor vaccine, either as part of a clinical trial or as a standard of care.

Govindan's group is trying to understand the reasons why cancer cells metastasize or become unresponsive to medical therapies. He also is using sequencing to develop a neoantigen vaccine that he is testing in a trial for patients with non-small cell lung cancer, the most common form of the disease.

"With the research that is being done, we are getting so close. The future looks brighter than ever before."

— Rodger O. Riney

Paula C. and Rodger O. Riney made a major commitment to establish the Paula C. and Rodger O. Riney Blood Cancer Research Initiative Fund for multiple myeloma research.

What appeals to us about the institute is its collaboration with St. Louis Children's Hospital and the School of Medicine's Department of Pediatrics in the application of genomics to pediatric cancers."

— James S. McDonnell III

Elizabeth H. and James S. McDonnell III and the JSM Charitable Trust made an extraordinary commitment to name the Elizabeth H. and James S. McDonnell III Genome Institute.

Researchers at MGI and elsewhere at the School of Medicine are making key discoveries in a number of other cancer types, including leukemia, aggressive prostate cancer and estrogen receptor positive breast cancer, one of the most common forms of that disease. This work is helping to guide treatment decisions such as choosing the appropriate chemotherapy or determining who may be a good candidate for certain immunotherapies, such as vaccines.

MGI's sequencing advances, the Bursky Center's immunology discoveries and Siteman Cancer Center's clinical prowess make for a powerful combination.

"The next frontier in cancer research is to apply our skills in genomics to better characterize the tumor, its environment and its interaction with the immune system," said DiPersio. "That will be a huge help in understanding the relapsing and remitting of cancers."

"The future is going to be pretty amazing for cancer patients. They'll have more effective treatments with fewer side effects, more targeted therapies, early diagnosis and even ways to prevent the disease," said Eberlein. "We've been fortunate to have the partnership of so many donors, patients and their families, who have recognized that investing in innovation and research is the future of cancer care."

Oncologist John F. DiPersio, MD, PhD, meets with cancer patient Stephen Brown.

Jeffrey I. Gordon, MD, the founder of microbiome research, is also known as a dedicated and very influential mentor who has trained a next generation of leaders in this field. Carrie A. Cowardin, PhD, left, and Vanderlene L. Kung, MD, PhD, are postdoctoral researchers in Gordon's lab.

Probing the microbiome

Studies of people and their companion microbes shed light on health and disease

BY JULIA EVANGELOU STRAIT

Even in our most solitary moments, we humans are never alone. On us and within us, tens of trillions of microbes live and thrive — not as passive hitchhikers, but as interactive, symbiotic shapers of our biology. From the time of our births, these microbes are at work, establishing distinct communities in many regions of our bodies.

In recent decades, scientists at Washington University have led the way in exploring how these microbial communities impact human health. Their work has shaped a new area of study that is revolutionizing our understanding of normal human physiology, metabolism, immunity, growth and neurodevelopment, as well as the roots of many diseases.

David Wang, PhD, right, and PhD student Luis Sandoval are studying viruses in the gut to learn more about their impact on health and disease.

A new field emerges

Using the gene sequencing technology of the genome revolution, along with many other experimental and computational methods and tools, researchers worldwide are studying our microbial companions — considering them not in isolation, but rather in the context of the complex communities in which they dwell. Scientists are learning which microbial members exist in a given area of the body, what genes they collectively possess, what their genes do, how community membership varies from person to person, and ultimately, how these communities influence health and disease.

The work has emerged as a new field called microbiome research, founded by Jeffrey I. Gordon, MD, the Dr. Robert J. Glaser Distinguished University Professor and director of the Edison Family Center for Genome Sciences & Systems Biology at Washington University School of Medicine.

Microbiome is the term given to the collective repertoire of genes possessed by microbes in a given community. Microbiomes are massive; the gut microbiome alone is made up of more than 100 times the number of genes in the human genome. In 30 years of seminal research, Gordon has revealed the fundamentals of how these communities first assemble, how they adapt, how community members cooperate and compete with one another, and how they interact with the human body. What's more, he and his students were the first to link the gut microbiome to two of the world's most vexing global health problems — childhood malnutrition and obesity.

"For human societies to flourish, our challenge is to do everything in our power to promote the healthy development of children so that they may realize their full potential," said Gordon, also professor of pathology and immunology, of developmental biology, of medicine and of molecular microbiology. "There are dramatic disparities in the abilities of children in different

"The Edison family greatly respects Dr. Gordon's sound thinking and innovative research. His work has global importance and appears to be critical to helping malnourished children throughout the world."

— Andrew E. Newman, Life Trustee and Edison family member

The Harry Edison Foundation and the Edison family made a major commitment to name the Edison Family Center for Genome Sciences & Systems Biology.

parts of the world to live healthy lives. And somewhere in the midst of this challenge to promote healthy development sits the gut microbiome."

Healthy communities

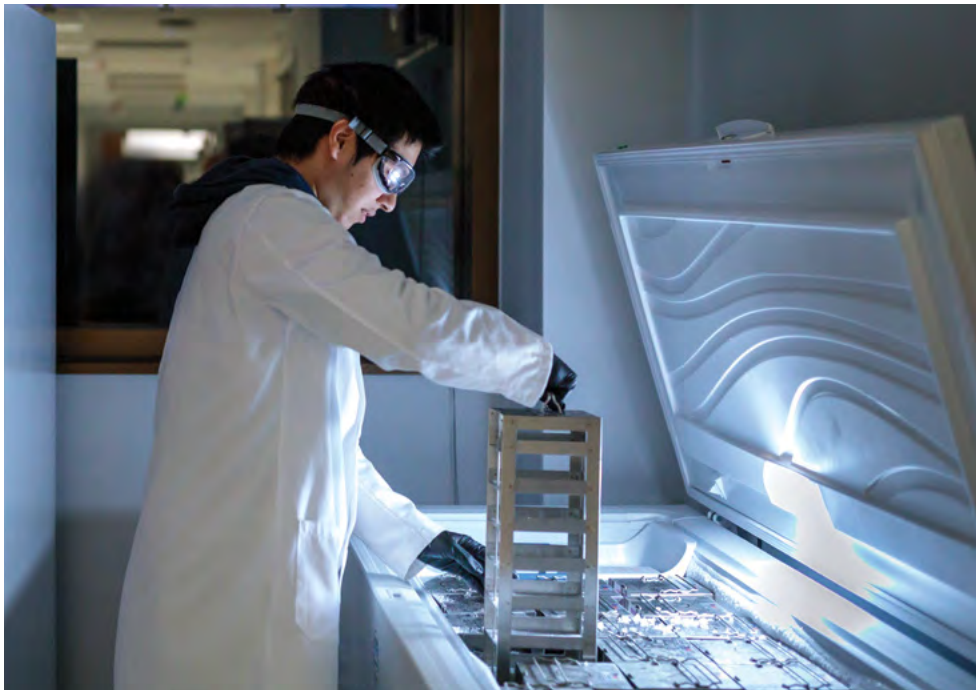
"No one else was doing this work when Jeff first started, and he was alone in the wilderness for a long time. Now, myriad microbiome projects at Washington University and around the world have built on Jeff's science, in part because he has trained many of the next generation of leaders in this field," said Phillip I. Tarr, MD, the Melvin E. Carnahan Professor of Pediatrics and professor of molecular microbiology.

Central to the field is learning how to nurture microbial communities in ways that enhance human health — much as one would cultivate the natural flora and fauna common to a forest or wetland to support a healthy, diverse and robust ecosystem. That ability could have massive public health implications, including checking infectious disease, resolving chronic inflammatory conditions, correcting metabolic dysfunction, and tackling the global problems related to the quality of our diets and nutrition — all at a time of rapid population expansion and challenges to environmental sustainability.

"This is a new frontier," said Tarr, also director of the Division of Pediatric Gastroenterology, Hepatology, and Nutrition. "The rules are now just beginning to be written."

Therapeutic foods

Central to Gordon's current work is addressing malnutrition. He and his collaborators at the International Centre for Diarrhoeal Disease Research in Bangladesh have shown that children with malnutrition possess gut microbial communities that fail to develop normally, leaving them with communities that appear younger, or less mature, than those of healthy children. Moreover, current therapeutic foods do not repair this immaturity or correct the long-term effects of malnutrition, including impaired growth, metabolism, immunity and brain development. These findings have led his team to develop new therapeutic foods, composed of affordable,



Medical student researcher I-Ling Chiang pulls bacterial cultures from a freezer in the lab of Thaddeus S. Stappenbeck, MD, PhD.

culturally acceptable components that advance development of immature gut communities and improve the health status of malnourished children.

Their work is not only establishing a vital link between formation of healthy microbial communities and healthy growth, but also is revealing how microbial communities transform components of the foods we consume into products that influence numerous features of human postnatal development. At the same time, food science is revealing more about the components of various food staples and how plant genetics and food processing technologies and consumers' microbiomes influence the nutritional content and value of those foods. Together, these advances should enable discovery, development and deployment of entirely new health-promoting foods and better dietary recommendations for children and their parents, Gordon said.

Preventing disease

Beyond Gordon's lab, Washington University microbiome researchers are addressing other topics.

Tarr and colleagues Barbara B. Warner, MD, professor of pediatrics, and Gautam Dantas, PhD, professor of pathology and immunology and of molecular microbiology, for example, are studying the gut microbiomes of babies born prematurely. These babies are at risk of developing a potentially deadly condition called necrotizing enterocolitis, a progressive inflammatory process that begins inside the gut and causes tissue death. Sometimes antibiotics are an effective treatment, but some babies need surgery to remove dead tissue. Even with these aggressive therapies, about 30 percent of babies who develop the disease die from this catastrophic event.

Tarr and Warner have shown that babies who develop necrotizing enterocolitis have a different mix of microbes in their intestines than babies who never develop the disease.

"We're still in the earliest stages of defining which microbes are good and which are bad," Tarr said. "But broadly, we want to find out what factors make it likely for good microbes to get into the gut and stay and, similarly, what factors help the body get rid of bad microbes. The hope is to ultimately protect premature infants from ever developing this terrible disease."

Thaddeus S. Stappenbeck, MD, PhD, right, reviews slides with postdoctoral fellow Umang Jain, PhD.

The virus hunters

Tarr and his colleagues — including David Wang, PhD, professor of molecular microbiology and of pathology and immunology, and Lori R. Holtz, MD, MSPH, associate professor of pediatrics — also have studied viruses living in the guts of healthy newborns. The viruses' collective genetic material is called the virome.

"Not only are there many viruses in the digestive systems of infants that we had no idea were present, there are viruses that infect the bacteria in great numbers," Tarr said. "And this almost certainly plays a role in how the bacterial community develops."

Indeed, the bacteria, viruses and other microbes in the intestine together offer a picture of the gut environment that metaphorically resembles a backcountry wilderness.

And as they explore that wilderness, Wang and his team have viruses in their sights. Wang seeks out previously unstudied viruses to understand how they function and to learn more about how viruses cause disease.

"We want to understand the nature of the whole virome and how it may be associated with health or disease," Wang said. "We've done this in the context of a number of diseases, including acute diarrhea, HIV/AIDS, type 1 diabetes and

Barbara B. Warner, MD, left, Lori R. Holtz, MD, MSPH, and Phillip I. Tarr, MD, discuss their research on gut microbial communities in premature and healthy newborns.

inflammatory bowel disease. This has been fascinating because we had no idea what to expect."

Working with Thaddeus S. Stappenbeck, MD, PhD, the Conan Professor of Laboratory and Genomic Medicine, Wang and colleagues found that the virome in patients with inflammatory bowel disease is different than the virome of healthy people, suggesting viruses may play a role in the development of this condition.

Guardians of the gut

Stappenbeck's work examines the interaction of gut microbes and human gut tissues, including agents he calls "guardians of the gut." One such agent is an antibody called immunoglobulin A, or IgA. IgA coats gut microbes and may well calm the response of our immune system to the microbiome. Another is a cell type in the gut lining known as Paneth cells.

"These cells protect the inner lining of the gastrointestinal tract by making a variety of antimicrobial proteins," said Stappenbeck, also a professor of developmental biology and a former postdoctoral fellow in Gordon's lab. "In doing so, they help shape the microbiome present in the gut. We know that mice with defective Paneth cells can develop worsened gut inflammation. This suggests that we can use the genetics of the abnormal Paneth cells to diagnose the type of inflammatory bowel disease a patient might have."

A better understanding of these guardians and others may contribute to better ways to diagnose, treat or prevent inflammatory diseases of the gut.

As scientists study the gut microbiome, additional complexity reveals itself. But if researchers can navigate that complexity to understand and promote a healthy gut ecosystem, their work may save preemies from a deadly inflammatory disease, prevent the complications of obesity, or protect children from the ravages of malnutrition. Nurturing a healthy gut may be the next public health revolution.

"If we are able to help mitigate suffering in any way, that's a larger contribution to humanity than Debra and I ever envisioned we would have. We feel very fortunate that we can do something that has such potential to help others."

— George W. Couch III, Trustee

Debra and George W. Couch III provided significant campaign support for research in personalized medicine; in their honor, the university named the Debra and George W. Couch III Biomedical Research Building.

Research technician Ira Wight, left, and PhD student Arielle Homayouni examine microscopic samples related to autophagy, a natural cell recycling process.

Emerging areas

New centers address personalized medicine and aging

BY CHANNING SUHL

Three newly established research centers will strengthen the School of Medicine's commitment to advancing two of the institution's major research priorities: personalized medicine and aging. Investigators in these centers will undertake multidisciplinary work with implications for addressing a broad range of major health issues.

Personalized cardiovascular care

Despite years of advances in the treatment and prevention of cardiovascular disease, it remains the leading cause of death worldwide. Now, personalized medicine — an innovative approach based on individual genetics and biomarkers — has the potential to change the standard of care.

Alumnus Kim D. Kuehner, MBA '77, has committed $15 million to establish and endow the **Kim D. Kuehner Program for Personalized Cardiovascular Medicine** in the School of Medicine. The program will fund competitive research grants within the school, providing a permanent source of funding for research aimed at improving the prevention, diagnosis and treatment of heart disease.

The complexities of cardiovascular diseases such as heart failure, atherosclerosis and cardiomyopathy make developing personalized medicine approaches challenging. At the center, researchers hope to elucidate the mechanisms behind each disease to enable development of therapies tailored for certain patient subgroups — ending the approach of treating the "average patient." Ultimately, clinicians will address the cause of the disease rather than the presenting clinical symptoms.

"Individualized patient care strategies have transformed the care of patients with cancer," said Douglas L. Mann, MD, the Tobias and Hortense Lewin Professor of Medicine and chief of the Cardiovascular Division. "Thanks to Kim Kuehner, investigators involved in cardiovascular disease at Washington University will now have the opportunity to transform the care of patients afflicted with heart disease."

The Kuehner program comes at the perfect time, as the School of Medicine ushers in the next phase of its personalized medicine initiative.

"This new program will allow us to leverage our leadership in personalized medicine to develop tailored approaches to cardiovascular disease," said David H. Perlmutter, MD, executive vice chancellor for medical affairs and the George and Carol Bauer Dean of the School of Medicine. "Mr. Kuehner's exceptional generosity and deep interest in addressing a significant health challenge will benefit patients around the globe."

Aging and age–dependent degenerative diseases

Sima Needleman and Philip Needleman, PhD, former chair of the Department of Pharmacology, have committed $15 million to establish the **Sima and Philip Needleman Center for Autophagy Therapeutics and Research** and the **Philip and Sima Needleman Center for Neurometabolism and Axonal Therapeutics.** The combined research efforts are expected to foster development of novel therapies for multiple diseases and impact neurodegenerative diseases of aging such as Alzheimer's.

"Part of my vision for this school is to have a major impact on aging. It touches research underway in every department," said Perlmutter. "These centers will support us in advancing shared priorities and making progress towards real, measurable outcomes."

The Center for Autophagy Therapeutics and Research, led by Perlmutter, will focus its efforts on autophagy — the mechanism by which cells break down and recycle their contents. Recent studies show that exercise and caloric restriction promote autophagy, resulting in better health and increased longevity. But when the process becomes impaired, which is increasingly likely with age, abnormal cellular activity can lead to cancer, diabetes and neurological disorders.

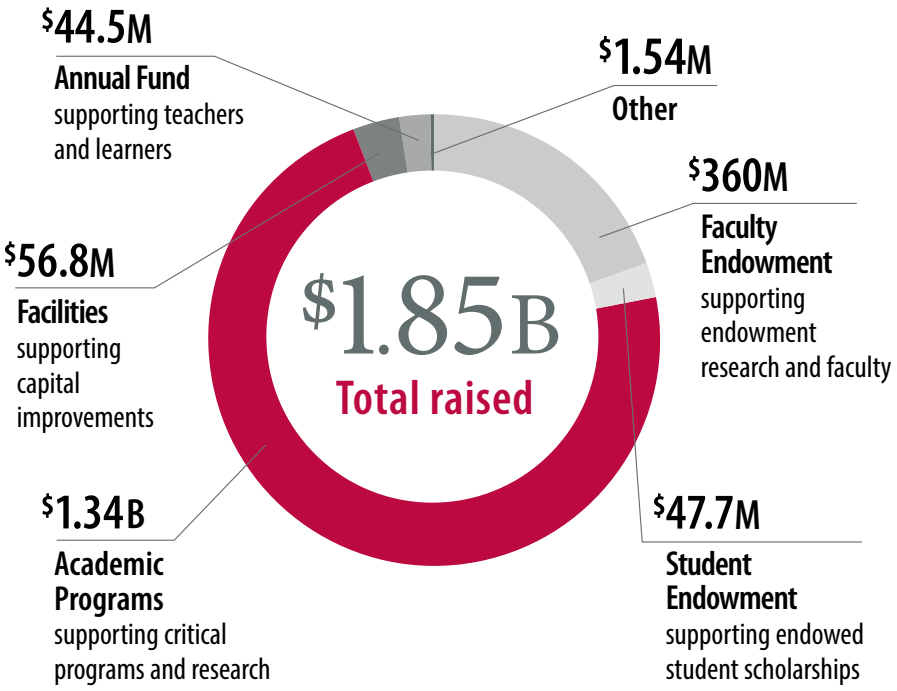
"These centers will support us in advancing shared priorities and making progress towards real, measurable outcomes." — *David H. Perlmutter, MD*

The Center for Neurometabolism and Axonal Therapeutics will be led by Jeffrey Milbrandt, MD, PhD, James S. McDonnell Professor and head of the Department of Genetics, and Aaron DiAntonio, MD, PhD, Alan A. and Edith L. Wolff Professor of Developmental Biology. Building on recent breakthroughs in understanding how nerves degenerate, the center will explore the intersection of metabolism, inflammation and degeneration in the nervous system in order to develop novel therapies for neurological diseases.

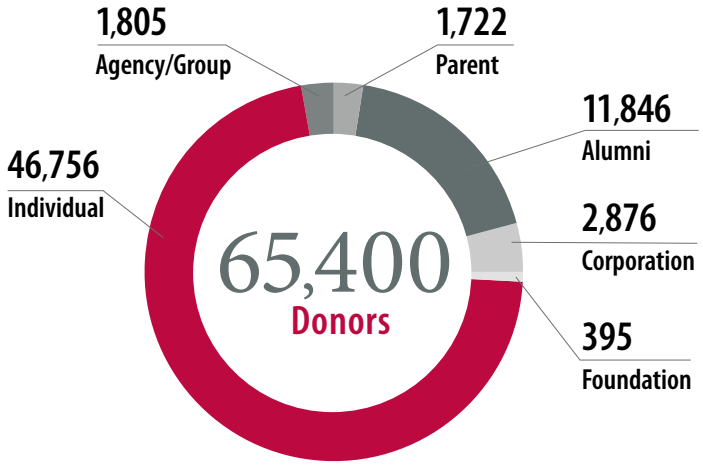
Needleman began his career at the School of Medicine in 1964 as a postdoctoral fellow and later held several pivotal roles there. He spent 14 years at Monsanto, later Pharmacia LLC, heading pharmaceutical research and development. Building on research begun at Washington University, he led the development of the arthritis drug Celebrex.

Campaign summary

A successful campaign is supporting scientists, teachers and learners as they change the future of medicine locally and around the globe.



RESEARCH The Debra and George W. Couch III Biomedical Research Building, named in recognition of significant campaign support from Debra and George W. Couch III, is home to numerous research initiatives and centers, including the Edison Family Center for Genome Sciences & Systems Biology, the Center for Cellular Imaging, the Center for Multiple Myeloma Nanotherapy, the Optical Radiology Lab and the Molecular Imaging Center.



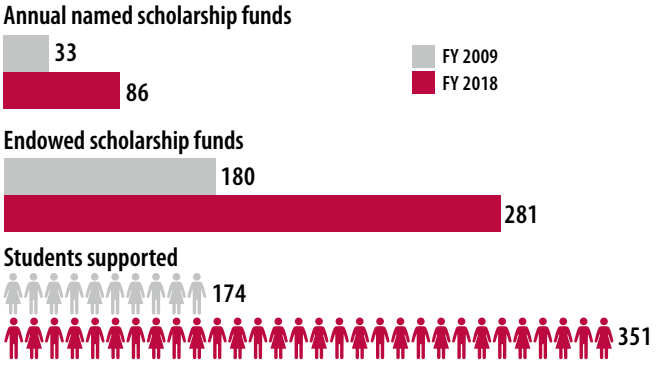
73
Endowed professorships

Endowed professorships established during the campaign included a named deanship, making David H. Perlmutter, MD, the inaugural George and Carol Bauer Dean of the School of Medicine.

JANA HOLSTEIN

EDUCATION Medical students Tiffany J. Wu, Jason A. Morris, Jae Lee and Jane M. Hayes, all Distinguished Alumni Scholarship recipients, are among hundreds of graduate students at the School of Medicine supported by scholarship donations.

$67M Scholarship funds raised



PATIENT CARE The School of Medicine's patient care mission has flourished during the 10-year campaign period, which ended in summer 2018. The number of clinical practice sites grew from 35 to 49, clinical revenues nearly doubled, and two 12-story towers — carefully designed to support patient comfort and optimal care — opened on the Medical Campus, offering facilities for patients of Siteman Cancer Center and the Women & Infants Center. Here, Alison Cahill, MD, visits patient Susan Zeid.

1960s

Harvey Michael "Mike" Jones, MD '66, was elected vice president of the American Osler Society and will serve a three-year term, including one year as president. The American Osler Society is a history of medicine organization that seeks to advance a humanistic approach to medicine. A retired clinical professor of pathology and laboratory medicine at the University of North Carolina at Chapel Hill, Jones also recently was selected by high school classmates in Winters, Texas, as a distinguished alumnus.

1970s

Marilyn Escobedo, MD '70, stepped down after nearly 40 years as a division chief of neonatal perinatal medicine at the University of Texas, San Antonio, and then at the University of Oklahoma. She became professor emeritus in fall 2017. Escobedo was named a 2018 Distinguished Alumnus at Baylor University, where she completed her undergraduate study. Escobedo spends summers in East Hampton, N.Y., and winters in San Antonio.

Barbara Seaworth, MD '77, a professor of medicine at The University of Texas at Tyler, has been awarded grants exceeding $30 million in the last 10 years, the most recent from the Centers for Disease Control and Prevention (CDC) in 2018. She is director of the Heartland National Tuberculosis Center in San Antonio, Texas. The CDC recognized Seaworth as a 2018 National Physician TB Champion for treating patients and providing education programs to caregivers who treat the disease. She was named by the San Antonio Business Journal as a 2018 Health Care Hero. Seaworth was in the Marshall Islands during summer 2018 to screen for and treat tuberculosis in that island nation. She also runs marathons and tries to keep up with her six children and husband, **John Seaworth, MD '76,** as well as their six grandchildren.

Gregorio A. Sicard, MD, HS '78, professor emeritus of surgery at WUSM, was awarded the Lifetime Achievement Award from the Society for Vascular Surgery in 2018. Sicard was on the WUSM faculty for more than three decades and started the vascular surgery section in 1983, the first year the American Board of Surgery certification in vascular surgery became available. Under Sicard's leadership, the section grew from performing fewer than 300 procedures annually to becoming a globally recognized center in endovascular patient care and research. He retired in 2015.

Richard L. Wahl, MD '78, HS '83, received the 2018 Georg Charles de Hevesy Award from the Society of Nuclear Medicine and Molecular Imaging. The award recognizes researchers whose groundbreaking discoveries have advanced nuclear medicine.

1980s

Nancy L. Bartlett, MD '86, the Koman Chair in Medical Oncology at WUSM, has been named a 2018 Legacy Leadership Award honoree by the Gateway Chapter of the Leukemia & Lymphoma Society.

1990s

Bradley L. Schlaggar, MD/PhD '94, HS '96, HS '99, has been named president and CEO of the Kennedy Krieger Institute in Baltimore, Md. The institute works to improve the lives of children and adolescents with disorders and injuries of the brain, spinal cord and musculoskeletal system. He spent 19 years on the WUSM faculty; during his tenure, he served as director of the pediatric neurology residency program, division head of pediatric and developmental neurology, neurologist-in-chief at St. Louis Children's Hospital, and co-director of the Intellectual and Developmental Disabilities Research Center.

Julie Miller, MD '96, has been living in Melbourne, Australia, since finishing surgical training in 2001. Miller, an academic endocrine surgeon, recently was elected president of Australian and New Zealand Endocrine Surgeons, and also the Asian Association of Endocrine Surgeons. This is the first time a woman has led either organization. She is married with three children, ages 12, 14 and 15.

Jamey Gordon, PT '97, DPT '07, is director of athlete development and a partner at Pro X Athlete Development in Westfield, Ind. Pro X specializes in sports performance training, skill development, rehabilitation and recovery in all sports. The partners planned to open a 55,000-plus-square-foot facility in late 2018 in Westfield, Ind. Gordon will continue to serve as a clinical instructor and fellowship mentor for the Program in Physical Therapy at WUSM.

2000s

Armand Antommaria, MD '00, was promoted to professor in the Department of Pediatrics at Cincinnati Children's Hospital Medical Center and the University of Cincinnati School of Medicine. He is the director of the Ethics Center at Children's.

Emily Bannister, LA '96, MD '01, and her husband, David, welcomed twins Abigail and David to their family in April 2017. They join big sister, Lucy, born in July 2015. Bannister is an attending in the HealthPartners Occupational Medicine residency program in St. Paul, Minn., and serves as medical liaison for laboratory biosafety at the University of Minnesota.

Katie Grover, DOT '03, and her husband, Ben, welcomed a child, Mason, Jan. 6, 2018.

Brian J. DeBosch, MD/PhD '08, is one of five faculty members at the School of Medicine elected to the Society for Pediatric Research, which aims to improve child health through research, professional collaboration and advocacy.

2010s

Kristin Haider Chumbley, AuD '10, was married June 22, 2018.

Danielle Doria Braman, OT '11, announces the birth of her first daughter, Elliana, on March 15, 2018. Braman is working at Children's Hospital Colorado.

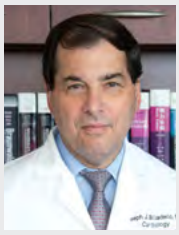
Ian Glenn, MD '12, and **Tara Glenn, MD '12,** welcomed a daughter, Nora Mary, on July 14, 2018.

Jennifer Yu, EN '08, MD '12, MPHS '15, a general surgery resident at WUSM and Barnes-Jewish Hospital, has received a 2018 Outstanding Resident Teacher Award from the Association for Surgical Education. Yu's award recognizes her enthusiasm, effectiveness and commitment to teaching surgical skills to medical students and other residents.

Samuel Nemanich, MS/PhD '16, is listed as co-principal investigator on a grant awarded from the National Center of Neuromodulation for Rehabilitation, a National Institutes of Health (NIH)-funded project. Nemanich and his wife, **Sarah Wahlstrom Helgren, PhD '16,** also welcomed their second child, Lucille, on July 25, 2018.

Brandon Holmes, MD/PhD '17, married **Diane Snyder, OT '10,** on April 14, 2018. Both work at the University of California, San Francisco, where Brandon is a neurology resident physician and Diane is a practicing occupational therapist.

Matthew McCoy, PhD '18, and **Amy Herbert, PhD '18,** were married June 30, 2018. The couple met at Washington University while working on PhDs in biology and biomedical sciences. They are Grass Fellows in Neuroscience at the Marine Biological Laboratory in Woods Hole, Mass., and will be moving to Stanford University in fall 2018 as postdoctoral researchers.



Joseph J. Billadello, MD, a professor of medicine and director of the Adult Congenital Heart Disease Center, died Wednesday, Aug. 8, 2018, following a long battle with multiple myeloma. He was 65.

Billadello came to Washington University in 1981 as a cardiology fellow and joined the School of Medicine faculty, where, over his long career, he cared for patients with heart disease, especially adults living with congenital heart disease. He also helped lead several organizations focused on treating individuals born with heart defects who survive to adulthood and require specialized care.

"Joe's leadership of the Adult Congenital Heart Disease Program culminated in the designation of the Washington University program as an accredited comprehensive care center by the Adult Congenital Heart Association, one of only a few such centers in the nation," said Victoria J. Fraser, MD, the Adolphus Busch Professor and head of the Department of Medicine. "Joe was passionate about patient care, and that is reflected in the quality of care he and his colleagues provided."

Billadello earned a medical degree from Georgetown University School of Medicine in 1978. He completed an internship and residency in internal medicine at Duke University before coming to Washington University for fellowship training.

He is survived by his wife, Guadalupe Sanchez, MD; mother, Julia "Peggy" Billadello; sister, Joan Quinn; daughter, Laura Billadello, MD; and son-in-law, Michael DeVita, MD.

John O. Holloszy, MD, whose research led to advances in the understanding of the body's response to exercise, died Wednesday, July 18, 2018, in Town and Country, Mo., following a long battle with kidney disease. He was 85.

A 1957 alumnus of the School of Medicine, Holloszy went on to train as a postdoc at the school under Nobel laureate Carl F. Cori, MD. In 1973, Holloszy became the director of the school's Division of Applied Physiology in the Department of Preventive Medicine, and later served as director of the Division of Geriatrics and Gerontology in the Department of Medicine. He retired from the university in 2017.

Holloszy's studies of aerobic exercise, nutrition and muscle development changed the way elite athletes train and helped others better cope with heart disease, diabetes, obesity and aging.

Holloszy also discovered that exercise improved insulin sensitivity in patients with type 2 diabetes, and that exercise training could reverse some of the damage in patients with coronary heart disease. In key animal studies, Holloszy found that calorie restriction lengthened the animals' lives even more than exercise.

"John Holloszy is considered the father of modern exercise biochemistry," said Samuel Klein, MD, the William H. Danforth Professor of Medicine and Nutritional Science and director of the Division of Geriatrics and Nutritional Science.

In 2000 at the Olympic Games in Sydney, the International Olympic Committee presented Holloszy with a gold medal, the IOC Olympic Prize in Sports Medicine, for his contributions to understanding the science behind enhanced athletic performance and disease state management.

Born in Vienna, Holloszy earned a bachelor's degree in 1953 at Oregon State University.

Holloszy is survived by his wife, Violetta, and a brother, Fred.

J. Russell Little, MD, professor emeritus of medicine, died Saturday, Aug. 18, 2018, in St. Louis following a long illness. He was 87.

Little served on the School of Medicine faculty from 1964 to 2005 and as chief of infectious diseases at Jewish Hospital from 1967 to 1996.

He was known for his dedication to teaching, mentoring and patient care. In 2017, the Division of Infectious Diseases established the J. Russell Little Award for Excellence in Teaching in his honor.

"His compassion and expertise were remarkable, and he was a significant reason why the infectious diseases program here is one of the best in the country," said William G. Powderly, MD, the Larry J. Shapiro Director of the Institute of Public Health and co-director of the Division of Infectious Diseases.

Little helped characterize the structure of antibodies and contributed to an understanding of how they recognize their targets. He also studied how the fungus Histoplasma survives inside immune cells, and showed that the antifungal medication amphotericin B changes the behavior of the immune system.

He earned a medical degree from the University of Rochester and completed a medical residency at Barnes Hospital in 1957. Following a research appointment at the National Institutes of Health (NIH), he returned to St. Louis as chief resident at Barnes Hospital.

He is survived by his daughters, Nancy Little and Susan Little; son, Bryan Little; and four grandchildren.

Necita Llorin-Roa, MD, a practicing anesthesiologist in St. Louis for nearly 50 years, died of natural causes Sunday, May 27, 2018, at St. Luke's Hospital in Chesterfield, Mo. She was 74.

After graduating from the University of the Philippines Manila College of Medicine in 1969, she completed an anesthesia residency and fellowship at Barnes-Jewish Hospital and the School of Medicine in 1973-1974.

A renowned educator and clinician and a beloved colleague, Roa was an associate professor of anesthesiology and served on the Washington University faculty for 42 years. She endowed the Necita Roa Award for the best graduating anesthesiology resident as well as a fund to support global health programs for anesthesiology trainees. Since 2014, Roa was president of the Philippine Medical Association of the Greater St. Louis Medical Foundation Inc., leading six annual medical and surgical missions to underprivileged communities in her home country of the Philippines.

The widow of the late microbiologist Renan C. Roa, who immigrated with her from the Philippines to the U.S. in 1969, Roa is survived by her brothers Carlos Llorin Jr. and Manuel Llorin and sister Marilu Arellano.

James C. Warren, MD, professor emeritus and former head of the Department of Obstetrics and Gynecology, died Saturday, July 21, 2018, at his home in Mobile, Ala. He was 88.

Warren, a renowned researcher, clinician and teacher, was noted for his work in the endocrinology and biochemistry of reproduction. One of Warren's most important research contributions was identifying and determining the significance of progesterone, a hormone that is an essential part of birth control pills.

Warren earned a medical degree from the University of Kansas in 1954. Following an internship at the University of Kansas Medical Center, he served as a physician in the U.S. Navy for two years. Warren then completed a residency in obstetrics and gynecology and a doctorate in biochemistry, both at the University of Nebraska. For 10 years, he served as a professor of obstetrics and gynecology and of biochemistry at the University of Kansas School of Medicine. He joined the School of Medicine faculty in 1971 and served as a department head until 1989.

He is survived by his wife, Margie; his sister, Kay Ross; three children, Jamie Warren Corkran, James Douglas Warren and Allison Warren; and nine grandchildren.

1940s

Richard Bell, DE '46; July '18
Martha Benedict, OT '47; June '18
Virginia P. Hagemann, NU '48; July '18
Homer H. Hanson, HS; Apr. '18
Richard C. Lyon, DE '47; Apr. '18
Ruth Portman Steele, OT '48; Aug. '18

1950s

David J. Edwards, MD '57; July '18
Stephen M. Harris, HS '54; Apr. '18
Frank A. Howard, MD '50; Apr. '18
Daniel B. Lowrey, MD '50; June '18
Muriel MacKallor, OT '53; Apr. '18
Morris Reichlin, LA '55, MD '59; July '18
Joseph Sanker, DE '55; Apr. '18
Richard L. Swarm, LA '49, MD '50; June '18
Paul D. Tinnin, DE '54; July '18
Milton M. Tofle, LA '51, DE '55; Aug. '18
Stephen L. Washburn, MD '52; June '18

1960s

Ray Bowman Duncan, HS '65; June '18
Darlene A. Feser, NU '64, GN '66; July '18
Cleveland M. McCarty, DE '61; July '18
Paul K. Orsay, HS '67; May '18
Robert E. Smith, DE '63; June '18

1970s

Clinton N. Corder, MD '71; Apr. '18
Steven Levitt, LA '66, DE '70; June '18
Michael O. Williams, MD '74; Aug. '18

1990s

Darlene Eyster, LA '75, HS '95; June '18
David M. Peeples, HS; June '18

For full obituaries, visit:
wumcnews.org/obits

Correction: Jacquelyn Carter Kremer, OT '97, was incorrectly listed among the deceased in the Fall 2018 Outlook issue.

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