next

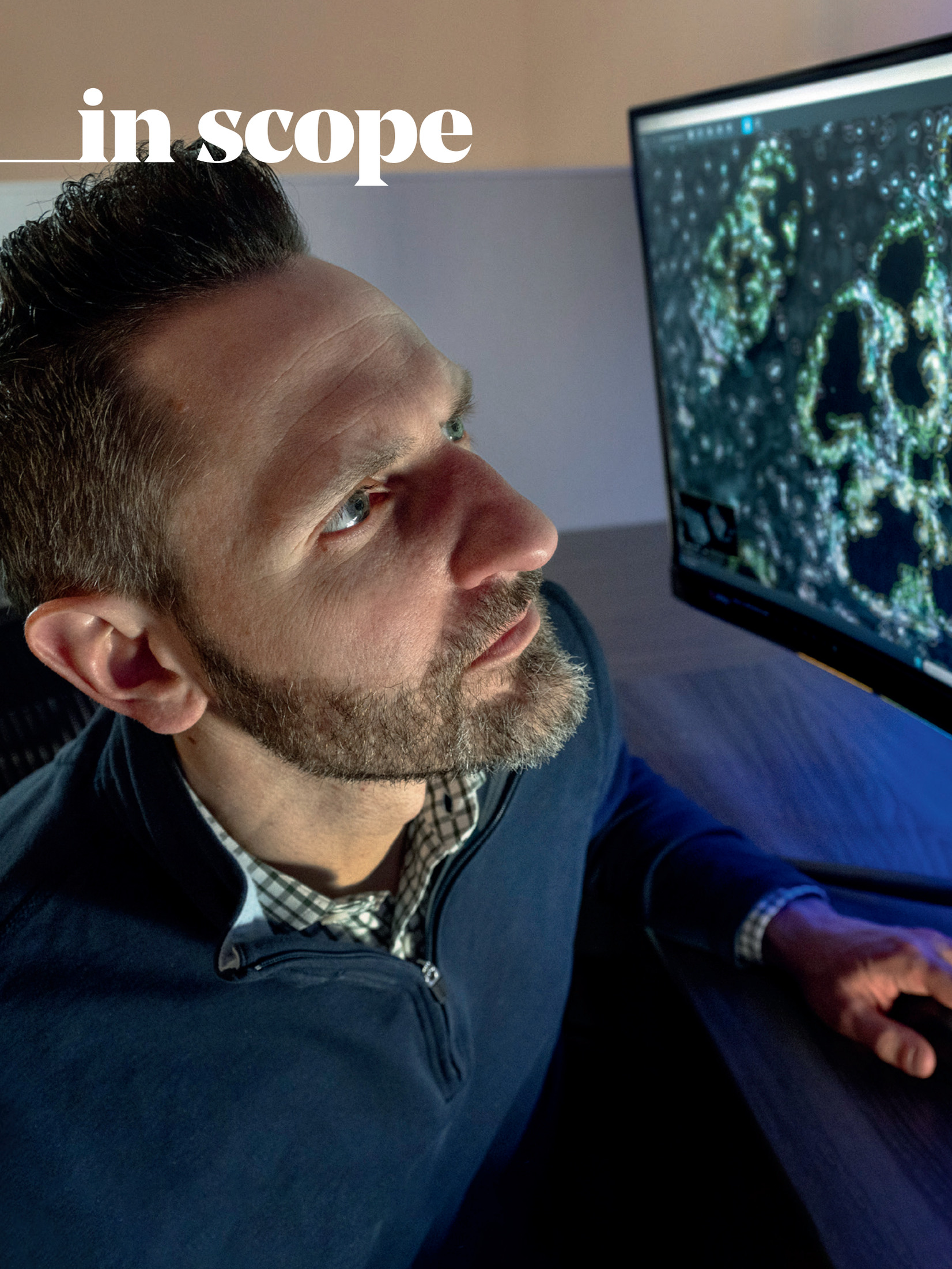
The Future of Discovery at VCU Health

Fall 2025

Gaining Ground Against Alzheimer's

The Small Molecules That Could Make a Big Impact

in scope



A Global Atlas

Researchers at the VCU School of Dentistry are part of a multinational effort to map the millions of cells that make up respiratory systems in children, who can be more vulnerable than adults to airborne pathogens since their immune and respiratory systems are still developing.

"The lungs, oral cavity and nasal space are essentially one interconnected cul-de-sac of breathing," said Kevin Matthew Byrd, D.D.S., Ph.D., a leader of the project and an assistant professor at the VCU School of Dentistry's Philips Institute for Oral Health Research. "This includes all the tissues and fluids that interact with the air you breathe."

It's not the first time Dr. Byrd has led oral health research with wide-ranging import. Earlier this year, he received the prestigious 2025 World Perio Research Award for a project studying how COVID-19 interacts with cells lining the oral cavity in ways that make it easier for the virus to infect salivary glands and soft tissue in the mouth.

Photo: Kevin Morley, VCU

MCV Foundation
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A New Era for Research

Dear Friends,

There has never been a more vital moment for medical research. While funding challenges and hurdles evolve, the possibilities for improving and saving lives have never been greater. We stand at the intersection of discovery and transformation, where bold ideas are changing the future of health. In an era marked by rapid scientific advancement, medical research is not only a tool of progress — it is a lifeline. It extends hope and creates possibilities where none existed before.

In this issue of *NEXT* magazine, we explore some of the projects that are generating those possibilities, ranging from new approaches for treating dementia to reversing liver disease and inventing nonaddictive painkillers.

We can all be part of securing the future for these types of discoveries by coming together through a powerful catalyst: philanthropy.

Gifts of all sizes help accelerate innovation. Whether by funding early-stage ideas that need proof of concept or by supporting ambitious, high-impact research with the potential to redefine care, philanthropy empowers researchers to ask bold questions, take risks and pursue answers that might otherwise go unexplored.

The stories in this magazine remind us of what's possible when research, passion and partnership come together.

Thank you for believing in the power of discovery and for being a part of this important journey. Together, we can shape a healthier future for all, because research saves lives.

Sincerely,

Brian S. Thomas
INTERIM PRESIDENT AND CEO

Stephen J. Gaidos
BOARD CHAIR

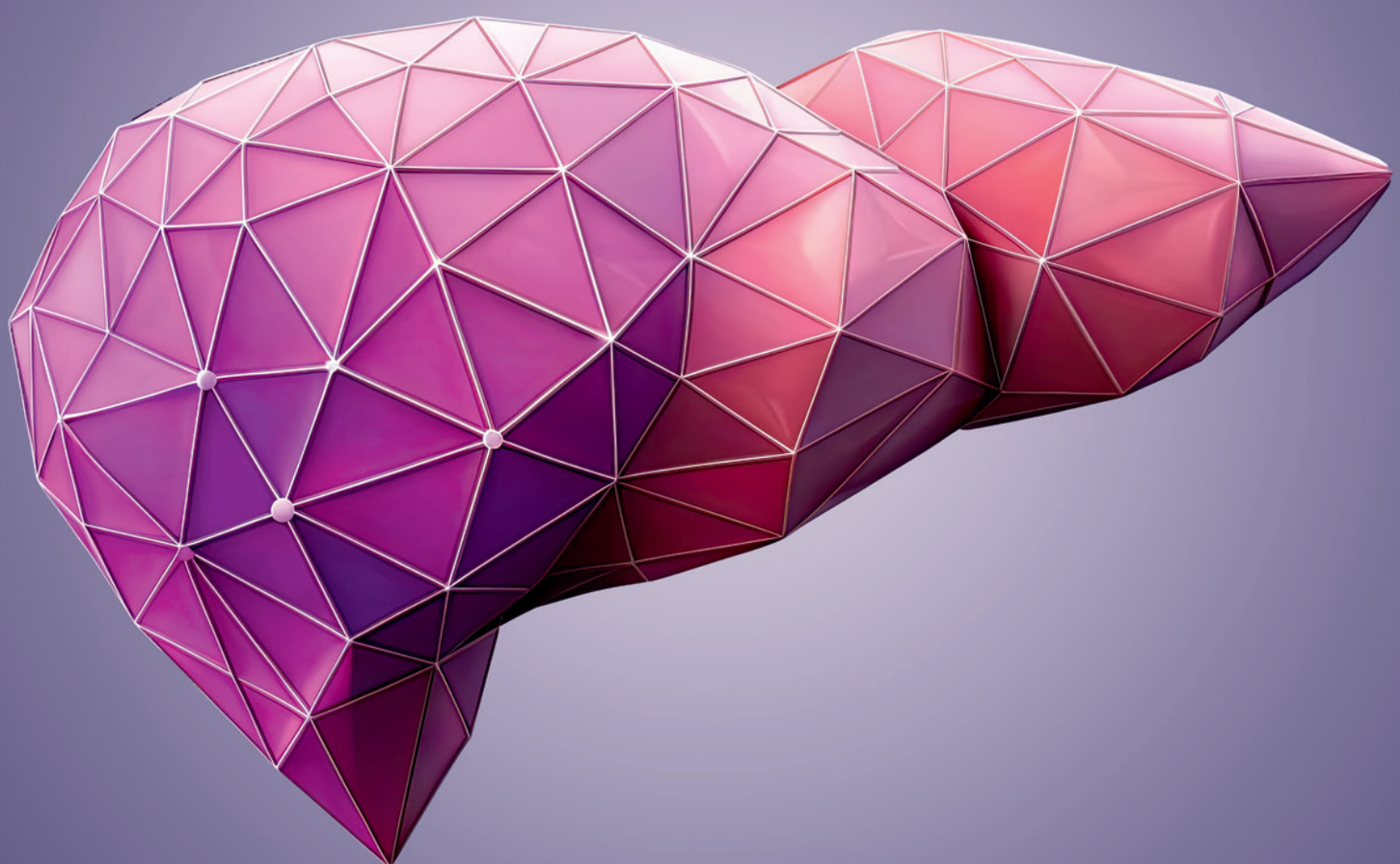
next FALL 2025

COVER STORY

Reversing Liver Damage

The main ingredient in Ozempic has been found in landmark VCU-led clinical trials to stop and reverse fatty liver disease.

By A.J. Hostetler, VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health



The lifesaving answer for tens of millions of people around the world who suffer from liver disease may have been hiding in plain sight for years.

In 2017, the U.S. Food and Drug Administration approved semaglutide — the main ingredient in drugs like Wegovy and Ozempic — to treat type 2 diabetes, reduce the risk of major cardiovascular events and manage weight in adults with obesity.

The treatment's success, especially as a weight loss tool, has fueled an explosion in media coverage and popularity over the past eight years, and some have even hailed it as a miracle drug.

Now, researchers at VCU have discovered a possible new use: The drug may stop a common liver disease in its tracks — and amazingly, it might even reverse it.

The findings from a Phase 3 clinical trial were published this year in the *New England Journal of Medicine* and provide the most comprehensive data yet on semaglutide's effectiveness in targeting the liver disease known as metabolic dysfunction-associated steatohepatitis (MASH).

MASH affects around 15 million Americans, and currently there is only one FDA-approved treatment available, increasing the urgency for effective therapeutic options. Phase 3 clinical trials are an important step to prove a drug's efficacy and safety before the FDA grants regulatory approval to new treatments or uses of existing medications, and the company that makes semaglutide now plans to seek approval this year following these recent studies.

"This is very exciting for people like me, who have spent 20 to 30 years taking care of patients with this condition," said Arun Sanyal, M.D., director of the VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health. "It's incredibly gratifying to see the results and to be able to have something, hopefully down the road, that we will be able to offer to all our patients who need it."

"The results from this landmark study across 37 countries provide strong evidence that semaglutide can help patients with MASH by not only improving liver health, but also addressing the underlying metabolic issues that contribute to the disease," said Dr. Sanyal, the lead author on the new paper and chief of the Division of Gastroenterology at the VCU School of Medicine. "Once approved, this could offer an additional therapeutic option for patients with MASH and fibrosis. This is crucial, given the strong link between MASH and cardiovascular, metabolic and renal conditions where semaglutide has already shown established health benefits."

MASH is closely linked to metabolic risk factors like obesity, type 2 diabetes and high blood pressure. Over time, MASH can lead to liver fibrosis, cirrhosis and even liver failure that requires a liver transplant, making it a major public health concern.

"The results from this landmark study across 37 countries provide strong evidence that semaglutide can help patients with MASH by not only improving liver health, but also addressing the underlying metabolic issues that contribute to the disease."

Arun Sanyal, M.D., chief of the Division of Gastroenterology, Hepatology and Nutrition and director of the VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

"By treating both liver disease and its metabolic causes, semaglutide offers a promising new approach for millions of patients."

Arun Sanyal, M.D.

MASH

Metabolic dysfunction-associated steatohepatitis (MASH) is a serious liver disease that develops when fat builds in the liver causing inflammation. This condition was previously known as nonalcoholic steatohepatitis (NASH).

Of the 800 participants in the "Effect of Semaglutide in Subjects with Non-cirrhotic Nonalcoholic Steatohepatitis" (ESSENCE) trial, 534 were assigned to take semaglutide and 266 were in a placebo group. The results were promising:

- About 63% of semaglutide users experienced a reduction in liver inflammation without worsening scarring, compared to only 34% of the placebo group.
- Almost 37% of those on semaglutide showed less liver scarring, compared to nearly 23% in the placebo group.
- About a third of semaglutide users achieved both inflammation reduction and scarring improvement, more than double compared to those taking the placebo.

The drug also helped participants with weight loss, improved liver markers and boosted overall heart health — with no major differences in serious side effects compared to those not taking it.

The ultimate goal for researchers in the ESSENCE trial was to find the right balance of semaglutide to resolve the damage caused by fat buildup in the liver (steatohepatitis) while at the same time to reduce scarring (fibrosis). Both are crucial for improving liver health in patients with MASH.

Semaglutide belongs to a class of drugs known as GLP-1 receptor agonists as they resemble a hormone called glucagon-like peptide 1, which stimulates insulin production, helps to lower blood sugar levels and, due to those metabolic effects, often results in weight loss. Semaglutide was developed based on research into the venom of a Gila monster, a near-threatened species of lizard native to the Southwestern U.S. Researchers isolated a hormone called exendin-4 from the lizard's venom that can help regulate blood sugar and appetite in humans.

Dr. Sanyal and other researchers are studying several GLP-1 receptor agonists and related drugs as potential treatments that might help, halt, improve or even reverse the damage caused by MASH.

"The ESSENCE data may represent key findings for patients in the treatment of MASH, which is estimated to affect about one in 20 adults in the U.S.," Dr. Sanyal said. "By treating both liver disease and its metabolic causes, semaglutide offers a promising new approach for millions of patients."

The clinical trial involved participants with moderate to advanced liver scarring who were treated for 72 weeks with either a 2.4-milligram weekly injection of semaglutide or a placebo. Most participants tolerated semaglutide well. Nearly 90% of participants remained on the medication after 72 weeks. The most common side effects were mild digestive issues, such as nausea.

Arun Sanyal, M.D., director of the VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, co-led a landmark international study exploring how semaglutide may halt or even reverse metabolic dysfunction-associated steatohepatitis, a common and serious liver disease affecting millions worldwide. *Photo: Tom Kojcsich, VCU*

In the second part of this clinical trial, researchers led by Dr. Sanyal will follow nearly 1,200 participants from 37 countries for up to five years to gather data on semaglutide's impact on long-term liver complications.

WHAT'S NEXT?

Semaglutide, manufactured by Novo Nordisk, was approved by the FDA in August for treating MASH, but it is only one type of GLP-1 agonist receptor that could provide treatment options.

Dr. Sanyal is already working to evaluate multiple potential next-generation GLP-1 agonist therapies that pharmacological researchers are enhancing with additional agonists that can act directly on the liver. He is studying two additional drugs now in Phase 3 clinical trials. They are drug retatrutide, made by Eli Lilly and Co. for the treatment of obesity and type 2 diabetes, and survodutide, a glucagon/GLP-1 receptor agonist made by Boehringer Ingelheim. Both show strong potential. Dr. Sanyal called survodutide a game-changer for people living with MASH. Up to 83% of participants on survodutide had measurable improvement of their disease: lower levels of liver fat, inflammation and no worsening of the fibrosis. In 75% of patients treated, the disease resolved, meaning their livers were significantly less inflamed, fatty and scarred. Dr. Sanyal also published his analysis of retatrutide in the *New England Journal of Medicine* and found more than 85% of obese participants with fatty liver disease taking retatrutide reduced their liver fat to the point where they would no longer be classified as having fatty liver disease.

"The implications of these additional trials mean that we could wipe out the fat very early in the course of this disease before it becomes a real threat to the liver and, potentially, reduce the long-term cardiac, metabolic, renal and liver-related harm from obesity," Dr. Sanyal said.

If you would like to support research at the VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, please contact Nathan Bick, executive director of development in the VCU Office of Medical Philanthropy and Alumni Relations, at 804-827-0387 or ngbick@vcu.edu.

15 million

MASH affects around 15 million Americans.

TWO

There are only two FDA-approved treatments available, increasing the urgency for effective therapeutic options.

Gaining Ground Against Alzheimer's

Novel molecules discovered and built by VCU School of Pharmacy researchers may hold the key to new and more effective treatments for Alzheimer's disease.

By Paul Brockwell Jr., MCV Foundation
Photos by Daniel Sangjib Min, MCV Foundation

Millions of families say a long and gut-wrenching goodbye to a loved one with Alzheimer's disease. Over time, the brain of the once vibrant person they know and love will succumb to the telltale deterioration. People whose lives lit up rooms will fade into unrecognizable versions of themselves. They may even forget the ones they love the most.

What scientists know today is that the disease appears strongly linked to inflammation responses in the brain that cause a build-up of protein clumps and tangles that accumulate over time and begin to disrupt healthy function between nerve cells. The disease, which can progress for years before outward behavioral symptoms develop, robs its victims of the very thoughts and memories that make up their identity. The good days and bad days are marked by the ebb and flow of emotional suffering that some families and caregivers experience.

Shijun Zhang, Ph.D., knows that anguish well. He witnessed it when hearing heartbreaking stories from families of patients while serving as a member of the board of the Greater Richmond Chapter Alzheimer's Association. And he's lived it in the two years since his mother-in-law received a dementia diagnosis.

Since 2008, that agony has helped fuel his work to engineer new drugs that stop the vicious cycle of inflammation, and he's more optimistic than ever for a breakthrough that can give hope to both patients and families whose lives are often upended by the demands of caring for their loved one around the clock.

"There is a huge burden on caregivers," said Dr. Zhang, professor and graduate program director in the VCU School of Pharmacy's Department of Medicinal Chemistry. "We need to have something that is more effective not only at treating this disease, but also to help reduce the emotional and financial burden on the caregivers."

Nearly 7 million Americans are living with Alzheimer's disease today. By 2050, that number is expected to double to 14 million, according to the Centers for Disease Control and Prevention. Globally that patient population is around 55 million, and it's expected to double every 20 years, according to Alzheimer's Disease International. By their estimate, someone around the world develops dementia every 3 seconds.

The need for a medical breakthrough has never been more urgent. In 2021, the FDA approved aducanumab, the first new drug in nearly two decades to treat Alzheimer's. But that decision was contentious, and the results have been marginal. Since then, the FDA has approved additional drugs including lecanemab in 2023 and donanemab in 2024. The approved treatments are monoclonal antibodies, or lab-produced proteins designed to mirror the body's immune response. In Alzheimer's drugs, the antibodies are designed to target amyloid deposits, a key pathology of the disease long suspected of playing a role in its development.

The available treatments themselves are incredibly costly, and they require additional costs for regular follow-up MRI imaging to monitor risks such as hemorrhaging and cerebral edema. Monoclonal antibody treatments for Alzheimer's have only achieved between 27% and 30% improvement in patients when it comes to regaining cognitive function, said Dr. Zhang.

"We need something more effective, and I think a small molecule solution could be a preferred way to pursue treatments," he said.

Tucked in a lab space in downtown Richmond, Va., he's been making remarkable progress on that challenge by building and testing small molecules that could be the key to disabling the body's internal alarm system that drives chronic inflammation.

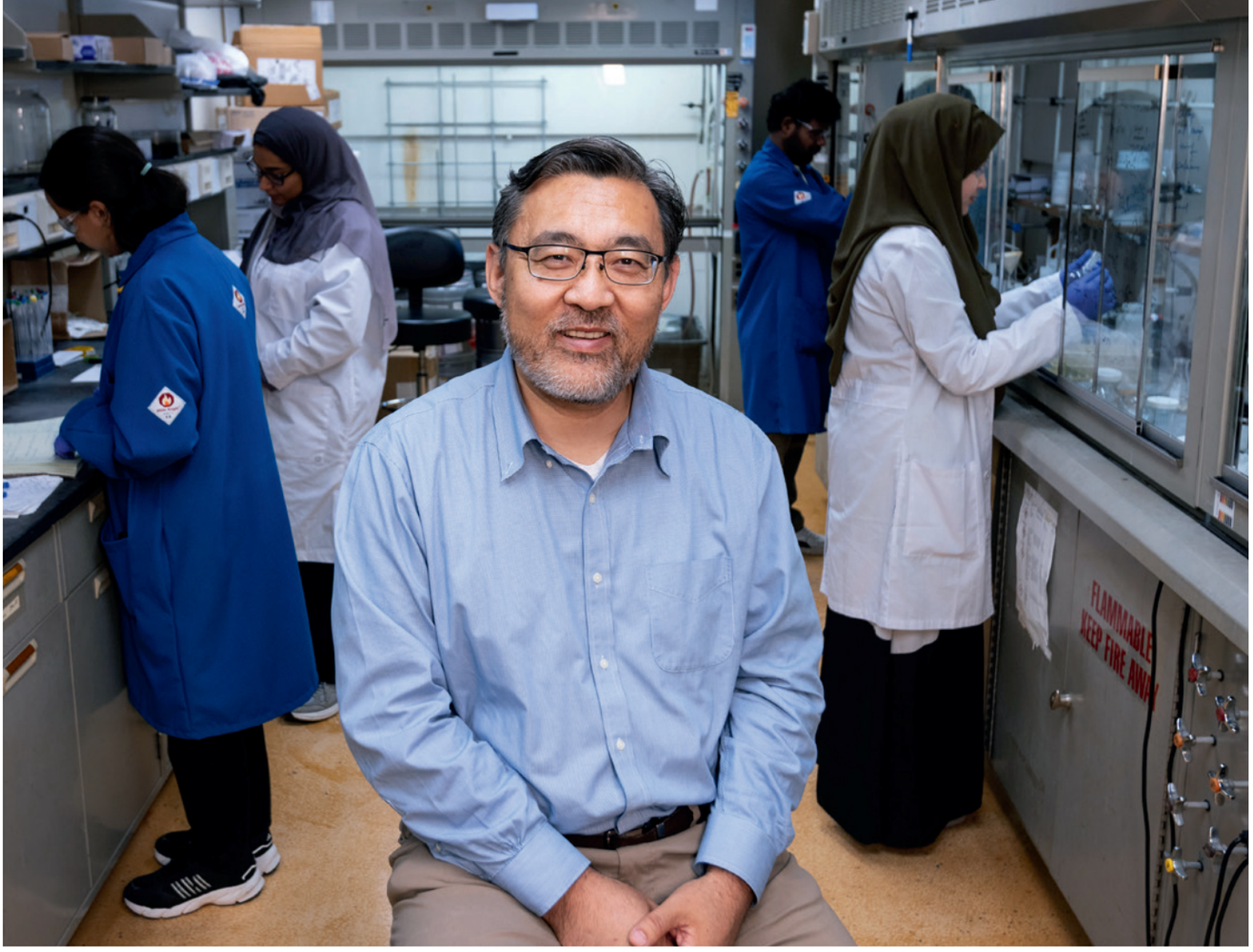
FROM BASIC SCIENCE TO NEW TREATMENTS

Scientific consensus recognizes that neuroinflammation plays a role in the development and progression of Alzheimer's disease. To address that pathology, Dr. Zhang and his lab have focused on engineering molecules that can help tamp down inflammation associated with Alzheimer's disease. In particular, he has been working to identify drugs that target a particular inflammasome, NLRP3, a group of proteins that behave like a home security system for the body's innate immune response. When NLRP3 detects danger signals in a cell, it triggers additional inflammation response through signaling.

The type of small molecules that Dr. Zhang is testing would inhibit the inflammasome response in the brain. The active agents in this potential treatment are small molecules that Dr. Zhang and his team, including research assistant professor Yiming Xu, Ph.D., design and build at the bench through an iterative process, synthesizing and testing how efficient and effective the candidates are for suppressing the inflammasome. From there, additional testing and imaging is done in animal models to ensure effectiveness. One of the agents he has developed shows great promise as a potential treatment and has achieved more than 50% suppression of the target inflammasome at a dose of 5 mg/kg in preclinical animal models.

Delivery of New Treatments

It's a challenge to design drugs with the right qualities of movement through the body that can ensure the medicine can get to the area of the body where it's most needed. Solving that challenge can make the difference between a treatment that requires regular injections for delivery or oral tablets. From a patient perspective, a tablet taken orally presents fewer barriers to access and compliance with a treatment than more involved delivery mechanisms.



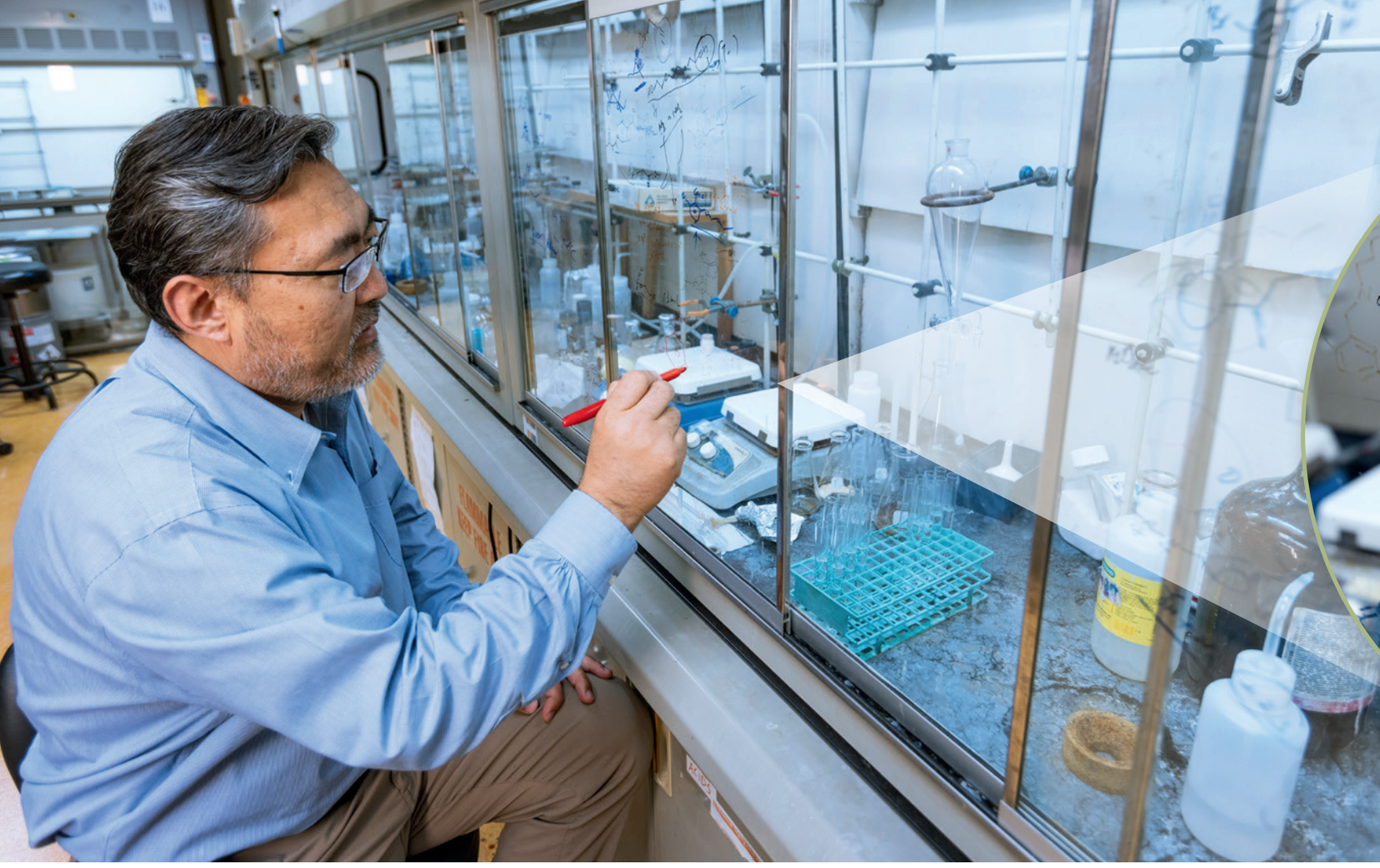
Shijun Zhang, Ph.D., professor and graduate program director in the VCU School of Pharmacy's Department of Medicinal Chemistry, has been researching and testing novel treatment options for Alzheimer's disease. *Photo: Daniel Sangjib Min, MCV Foundation*

Some of the biggest challenges for drug discovery are finding solutions that can cross the blood-brain barrier, a selective semi-permeable membrane that allows cerebral blood vessels to regulate molecule and ion movement between the blood and the brain. It's a challenge to design drugs with the right qualities of movement through the body, or pharmacokinetic properties, that can ensure the medicine can get to the area of the body where it's most needed. Solving that challenge can make the difference between a treatment that requires regular injections for delivery or oral tablets. From a patient perspective, a tablet taken orally presents fewer barriers to access and compliance with a treatment than more involved delivery mechanisms.

"We have reached the third generation of molecules and, in some of them, the potency is very promising," Dr. Zhang said. "With some of them we have observed significant suppression of the targeted inflammasome by the molecules, which is really quite good. We've also been able to achieve brain penetration and are reaching the point for a suitable oral pharmacokinetic property, which will be critical for the clinical studies."

"We have reached the third generation of molecules and in some of them, the potency is very promising. With some of them we have observed significant suppression of the targeted inflammasome."

Shijun Zhang, Ph.D., professor and graduate program director, VCU School of Pharmacy's Department of Medicinal Chemistry



Dr. Zhang's team has also been exploring ways to address mitochondrial dysfunction, another source behind Alzheimer's.

In a separate research project, Dr. Zhang's team has been exploring ways to address mitochondrial dysfunction, another source behind Alzheimer's. When mitochondria, the powerhouses of cells, are not functioning normally, they are linked to oxidative stress and inflammatory responses as well as other pathologies of Alzheimer's. The theory is that by helping address mitochondrial dysfunction as a driver of multiple Alzheimer's pathologies, treatments could reduce root causes to provide more effective treatments for Alzheimer's and other dementia types.

"Initially when we started these two projects, they were unrelated," Dr. Zhang said. "But with further studies, we realized these are not two isolated targets, which has made this research more exciting. They are actually closely interconnected."

Dr. Zhang and his team have connected the two projects to the same common treatment pathway, which is regulating the immune responses. He believes that ultimately researchers may discover that combining effective therapies may be the key to a long-term treatment, a theory that underlies his work targeting both the inflammasome and the mitochondrial dysfunction in order to provide a one-two punch toward addressing the pathology of Alzheimer's disease development.

What are small molecules?

Dr. Zhang and his lab focus on small molecule drug discovery and development for neurodegenerative diseases and inflammatory diseases by rational design and medicinal chemistry. He works to engineer and test small molecules, which are organic compounds with a molecular weight usually less than 900 Daltons. Often a pathway for new treatments, small molecules can be used to inhibit the function of a particular protein complex and have the ability to rapidly diffuse across cell membranes to reach intracellular action sites.

IMAGING PROJECT PROVIDES KEY INSIGHTS

Developing a drug is its own iterative process, but so is the challenge of proving the efficacy of potential candidates. In 2022 and 2023, Dr. Zhang and his team received grants from the Commonwealth of Virginia's Center on Aging, National Institute on Aging and the Alzheimer's Drug Discovery Foundation to build and test radiotracers for using positron emission tomography (PET) by targeting the NLRP3 inflammasome to prove the efficacy of future drug candidates. The new PET imaging tools are also aimed at identifying good biomarkers and ways of imaging neuroinflammation.

"The PET imagining tools will help us test whether neuroinflammation is a good biomarker for Alzheimer's disease," Dr. Zhang explained. "They also will make it possible to image the progression of neuroinflammation. Not only would these tracers help us in the future clinical evaluation of potential drug candidates, but they also can become useful diagnostics in the future when neuroinflammation is accepted as a biomarker."

Neuroinflammation likely begins much earlier than the plaque and tangle pathology associated with advanced disease. His hope is that some combination of therapies and the PET imaging could help physicians provide the best available interventions earlier for those at risk of developing severe disease. Emerging research suggests that the disease can begin developing 20 years before symptoms become clear in patients.

The imaging and diagnostic project is the third leg of the stool when it comes to Dr. Zhang's research. He said progress is possible when combining the imaging with his projects aimed at stopping inflammation by inhibiting the NLRP3 protein as well as taming mitochondrial dysfunction as a driver of other pathologies linked to disease progression.

WHAT'S NEXT?

Dr. Zhang and his team are working toward the goal of conducting enabling studies to investigate a new drug next year. Enabling studies are a critical step that bridges the gap between preclinical and clinical research. During this phase, Dr. Zhang and his team will seek to prove both the efficacy and safety of potential drug candidates. Once his lab can prove the effectiveness of a drug candidate and that the drug itself is not harmful or toxic in preclinical animal models, investigatory phases involving clinical trials will become possible.

"We never imagined we could end up where we are now," Dr. Zhang said. "With the support of the university and these grants, we can do some real drug discovery and maintain full-speed ahead on identifying drug candidates with good pharmacokinetic properties and efficacy."

In February, the team received commercialization funding from VCU TechTransfer and Ventures, which will help advance their research. While Dr. Zhang remains focused on the Alzheimer's drug development project, he's also quick to point out that inhibiting the NLRP3 inflammasome has exciting potential application to other disorders associated with inflammation, from chronic pain to autoimmune disorders and chronic gastrointestinal diseases.

"The commercialization funds were a great addition to this project and will allow us to pursue pharmacokinetic studies to help speed the process," Dr. Zhang said. "It's also exciting to see how this research could grow to have an impact on other chronic inflammation-driven diseases."

If you are interested in learning more about how to support Dr. Zhang's research on Alzheimer's disease, please contact Louie Correa, senior director of development at VCU School of Pharmacy, at 804-828-3016 or lacorrea@vcu.edu.

Graduate students in Dr. Zhang's lab help develop and test various iterations of small molecules that could be developed into drug candidates based on their efficacy.

Alzheimer's Disease Facts and Figures

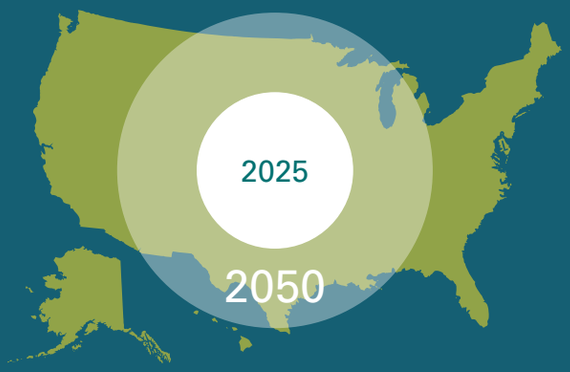
Data from the Alzheimer's Association helps to illustrate the growing prevalence of Alzheimer's in America as well as the scope of emotional and financial costs faced by caregivers.

Around **1 IN 9** people age 65 or older has Alzheimer's.

The lifetime risk for Alzheimer's at age 45:

1 IN 5 for women

1 IN 10 for men



MORE THAN

7 million

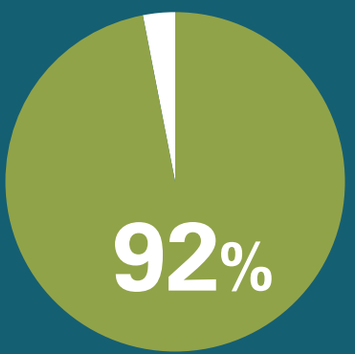
Americans are living with Alzheimer's. By 2050, this number is expected to nearly double.

NEARLY 12 MILLION

Americans provide unpaid care for people with Alzheimer's or other dementias.

Those caregivers provide more than 19 billion hours valued at nearly

$413 BILLION.



of Americans would want a medication to slow the progression of Alzheimer's disease following a diagnosis.

Source: Alzheimer's Association
2025 Alzheimer's Disease Facts and Figures

RETHINKING PAINKILLERS

VCU research is developing new nonaddictive painkillers and re-engineering treatments to better care for opioid users.

By Olivia Trani, VCU Health

People don't ask to descend into opioid addiction. They don't ask for the physical dependence — the cravings and the sweating. They don't ask for it to control and affect every moment of their lives.

It could happen to any of us.

Dispensed for prescriptions approximately 125 million times in 2023 to manage chronic pain or pain following surgery, physical trauma, and cancer diagnosis, opioids do work — but their risks are significant.

In 2023, nearly 8.6 million Americans reported misusing prescription opioids in the previous year, and from 1999 to 2022, approximately 294,000 people died from overdoses involving prescription opioids. Compounding the problem is that in many cases, misuse of prescriptions leads to use of illegal drugs such as heroin and fentanyl.

So, as more than 50 million people in the U.S. suffer from chronic pain and millions more face surgeries, trauma and cancer diagnoses, what is the safe answer? Is there a safe answer?

The answer is that a reliable, nonaddictive drug to ease suffering remains out of reach. However, researchers at VCU are leading successful pursuits to create new, nonaddictive painkilling agents and re-engineer available treatments for opioid use disorder that work better.

They are working with teams from the University of Texas at Austin and the University of Virginia to develop a novel drug candidate for treating chronic pain more safely that works by turning off the body's inflammation. In their most recent study, published in *Proceedings of the National Academy of Sciences*, the researchers found that the drug candidate was able to effectively trick immune systems in such a way as to shut off an inflammatory response, thereby alleviating pain. While this research is currently at the preclinical stage, the ultimate goal is to make an effective and targeted treatment for people suffering from chronic pain.

PROMISING DRUG CANDIDATE SPARKS COLLABORATION

Immune cells in the human body produce compounds called endocannabinoids which, among other things, regulate inflammation. In a healthy person, inflammation is a process that helps the body heal from infections or injuries. But the downside is that it also causes swelling and buildup of tissue that presses on nerve endings and causes persistent pain.

"When the endocannabinoids in our bodies cause inflammation, our nerves become sensitized. They react more rapidly with less stimulation than is normally needed. This causes things that normally wouldn't hurt to suddenly become extremely painful, similar to how we feel when we have a bad sunburn," said Aron Lichtman, Ph.D., a professor in the VCU School of Medicine's Department of Pharmacology and Toxicology.

In this study, the researchers analyzed an inhibitor called KT109 that blocks the activity of an endocannabinoid-producing enzyme in immune cells called DAGLß.

Ken Hsu, Ph.D., an associate professor in the Department of Chemistry at UT Austin, developed the inhibitor as a postdoctoral fellow at The Scripps Research Institute. He has since fostered a long-term collaboration with Dr. Lichtman and Hamid Akbarali, Ph.D., also a professor in VCU's Department of Pharmacology and Toxicology, to better understand how inhibiting DAGLß reduces inflammation and the associated pain.

Dr. Akbarali's expertise is investigating how inflammation impacts the nervous system at the cellular level. His research team examined how the drug candidate interfered with pain-transmitting neurons in mouse models.

"In our lab, we look at the speed and strength of the pain signals that neurons send to the brain, and for this particular project, we analyzed how the drug candidate weakened these signals as they traveled through the nervous system," he said.

Dr. Lichtman's research team focused on understanding how these cellular processes then impact the behavior and function of chronic pain in animal models.

"Our process has really been a bottom-up discovery," Dr. Lichtman said. "This research originally started with understanding the inhibitor at the molecular level, while this new study aimed to better understand how the inhibitor has an impact at the cellular and behavioral levels."

UNCOVERING THE PATHWAY TO PAIN RELIEF

Previous work demonstrated how KT109 controls inflammation via inhibiting endocannabinoids and prostaglandins, which are a type of lipid, or fatty acid, that plays a significant role in pain perception by modulating the activity of receptors in the sensory nerve endings that detect pain. But in this latest study, the researchers were surprised to discover that KT109 also controls inflammation through an additional pathway, which helps explain why the inhibitor is effective in treating different types of pain.

Hamid Akbarali, Ph.D., a professor of pharmacology and toxicology, helped develop an understanding of how inhibiting a specific enzyme reduces inflammation and the associated pain. Dr. Akbarali's expertise is investigating how inflammation impacts the nervous system at the cellular level. His research team examined how a drug candidate interfered with pain-transmitting neurons in animal models. *Photo: Thomas Kojcsich, VCU*

294,000

From 1999 to 2022, approximately 294,000 people died from overdoses involving prescription opioids.

"When you inhibit DAGLß, your immune cells are tricked into thinking they are starving," Dr. Hsu said. "Changes in energy metabolism in the immune system can turn off inflammatory signaling and be effective in pain management." One example is the drug metformin, which is commonly used to treat diabetes but also has been found effective in treating pain.

The team's inhibitor targets DAGLß, which is mainly present and active in immune cells, thereby avoiding any unnecessary reaction with other cells that might lead to side effects.

"You're going to affect these pathways where it matters, where the inflammation is happening," Dr. Hsu said.

The researchers don't believe this drug inhibitor acts in the brain, thereby avoiding the potential alteration of reward pathways in the brain that might lead to substance abuse.

The research team has so far only studied the effects of the inhibitor through injection, but the goal is to develop a pill that can be swallowed. To avoid internal toxicity, the researchers will aim to refine the chemistry and reduce the number of times the medicine needs to be taken while maintaining the same pain-easing effect.

The findings are helpful for pharmaceutical companies considering the development of medicines that target DAGLß in people experiencing chronic pain.

RE-ENGINEERING TREATMENTS FOR OPIOID USE DISORDER

As the U.S. continues to grapple with the unrelenting opioid crisis, researchers at VCU have also reformulated an opioid use disorder medication in a way that could extend its therapeutic effects. With a new formulation of one drug, they hope to offer a longer-lasting therapy for patients with opioid use disorder that addresses long-term challenges around treatment access and compliance.

In 2023, more than 150 people died every day on average from opioid overdose in the U.S., according to the Centers for Disease Control and Prevention. A number of medications help curb opioid addiction, but several barriers can interfere with a patient's path to recovery, such as strict regulations, adverse side effects and limited access to treatment clinics.

In hope of providing more treatment options for opioid use disorder, the VCU research team reworked levo-alpha-acetylmethadol, also known as LAAM, a metabolite of a previous FDA-approved opiate dependence medication, into a new formulation that could be used to help patients with opioid addiction.

Their latest study, published in the *Journal of Controlled Release*, showed that the reformulated medication

The researchers don't believe this drug inhibitor acts in the brain, thereby avoiding the potential alteration of reward pathways in the brain that might lead to substance abuse.

significantly reduced opioid use and withdrawal symptoms in animal models. The researchers say these findings have promising implications for ultimately expanding the range of medicinal therapies available for treating opioid addiction.

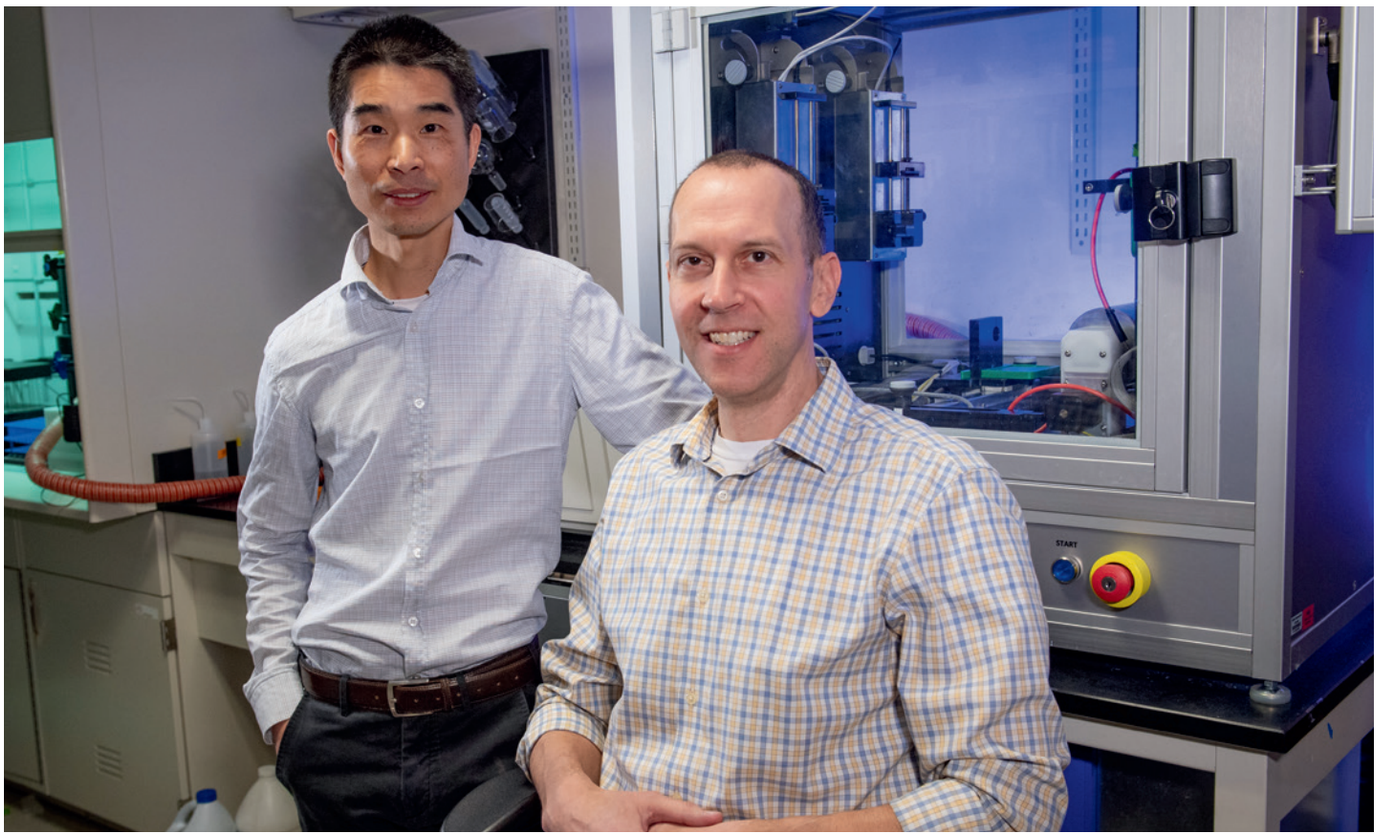
"There is an urgent need to develop more therapeutic strategies for enhancing the effectiveness of our interventions and the overall well-being of patients with opioid use disorder. Our goal is to give physicians another tool in their toolbox to help patients overcome addiction," said Qingguo Xu, Ph.D., an associate professor in the VCU School of Pharmacy's Department of Pharmaceutics. He co-led the new study with Matthew Banks, Ph.D., a professor in the VCU School of Medicine's Department of Pharmacology and Toxicology.

There are currently three FDA-approved medications used to treat opioid use disorder: methadone, buprenorphine and naltrexone. Despite their effectiveness in helping patients curb addiction, barriers to access and other challenges persist.

"Part of the issue is that each of these medications comes with their own set of regulatory hurdles. In particular, methadone is very effective at decreasing illicit drug-taking behavior, but there are a lot of regulatory restrictions and stigma around its use," Dr. Banks said. "Another challenge is that some patients are unresponsive to the current medications or experience undesirable side effects."

"Some patients also have a hard time managing the dose requirements of the current medications," Dr. Xu added. "Methadone treatment requires daily visits to an approved methadone clinic, which can be a huge burden for patients, especially if they live in rural areas with limited access to clinics. Since the pandemic, government officials have been working to loosen those restrictions."

Research to develop nonaddictive painkillers received essential help from VCU faculty like Aron Lichtman, Ph.D., a professor in the VCU School of Medicine's Department of Pharmacology and Toxicology. Dr. Lichtman and his team focused on understanding how the cellular processes that drive pain sensation impact the behavior and function of animal models with chronic pain. *Photo: Allen Jones, VCU*



Qingguo Xu, Ph.D., an associate professor in the VCU School of Pharmacy's Department of Pharmaceutics, co-led a new study with Matthew Banks, Ph.D., a professor in the VCU School of Medicine's Department of Pharmacology and Toxicology. The pair have created a safer and more effective medication for opioid use disorder patients. *Photo: Tom Kojcsich, VCU*

"We hope that expanding the medicinal options for opioid use disorder helps with increasing patient retention to their treatments, gives them a better chance to overcome addiction and ultimately gives them back their lives."

Qingguo Xu, Ph.D., associate professor,
VCU School of Pharmacy's
Department of Pharmaceutics

Previous research had shown LAAM was more effective than methadone in suppressing opioid use, but it was taken off the market in 2003 due to concerns about cardiac effects and declining sales after buprenorphine's introduction as a prescription treatment. Drs. Xu and Banks saw an opportunity to reformulate LAAM to address safety concerns while also making treatment more accessible for patients.

The team's research findings have demonstrated their new formulation of the medication, which they call nor-LAAM, could be a safer, more potent alternative to LAAM and existing drugs. Their goal is to give pharmaceutical companies a reason to bring back the medication as an additional option for reducing opioid cravings and preventing relapse. In this new formulation, the researchers also developed a novel drug-loading system that packs a high dose of nor-LAAM into biodegradable microparticles, which in turn releases a steady level of medication over a long period of time. While current medications for opioid use disorder often require daily doses, nor-LAAM is designed to be taken once a month, or potentially even less frequently.

"This is an important benefit since reducing the frequency of doses can make it easier for patients to comply with their treatment plans," Dr. Banks said.

He and Dr. Xu have since been leading preclinical studies to better understand nor-LAAM's potential for treating opioid use disorder. In their latest study, the researchers examined the behavior of fentanyl-dependent rodents when treated with either nor-LAAM or a placebo. They specifically looked into how the medication impacted the subjects' preferences when given the option to either self-administer fentanyl or receive food.

Their study revealed that subjects treated with nor-LAAM significantly reduced their preference for fentanyl over food over the course of four weeks. Additionally, subjects treated with nor-LAAM exhibited fewer signs of opioid withdrawal over time.

While this project is still in the preliminary stages and it may be a few more years until this medication is ready for human clinical trials, the researchers say these findings give promising insights into nor-LAAM's potential as a long-acting strategy for treating opioid addiction. Looking ahead, Drs. Xu and Banks will continue to develop nor-LAAM formulations and assess its effectiveness for therapeutic use.

"We hope that expanding the medicinal options for opioid use disorder helps with increasing patient retention to their treatments, gives them a better chance to overcome addiction and ultimately gives them back their lives," Dr. Xu said.

If you would like to support addiction research on the MCV Campus, please contact Nate Bick, executive director of development in the Office of Medical Philanthropy and Alumni Relations, at 804-827-0387 or ngbick@vcu.edu.

The Next Generation

VCU is committed to training future leaders who can help end addiction.

The project to develop nonaddictive painkillers has received significant support from the Central Virginia Center on Drug Abuse Research, an interdisciplinary research center based at VCU that is focused on addiction to opioids and other drugs of abuse.

Fueled by a $6.8 million grant from the National Institute on Drug Abuse, the center provides funds and resources to advance promising research aimed at addressing addiction. Drs. Lichtman and Akbarali credit this grant with helping VCU be a leader in training the next generation of scientists to tackle drug abuse.

At VCU, students and trainees are given opportunities to join cutting-edge projects that build their knowledge on addiction research and other subjects. Many of the graduate students and postdoctoral researchers who contributed to this study are funded through the NIDA grant. VCU's Department of Pharmacology and Toxicology initially secured the federal grant in 1976 to provide tuition, equipment and supplies to those training to be addiction researchers. The grant has been renewed every five years ever since, providing roughly $24 million in support to more than 600 students and trainees over the past 50 years.

"Our studies benefit from student involvement because they are the conduits of research and collaboration," Dr. Lichtman added. "They are the ones actually at the bench doing this important work."

In recent years, the university has expanded learning opportunities for students. In 2020, Omar Abubaker, D.M.D., Ph.D., made a lead gift to establish the Adam Abubaker Memorial Lectureship at the VCU School of Medicine. Dr. Abubaker, who holds the S. Elmer Bear Chair in Oral and Maxillofacial Surgery at the VCU School of Dentistry, wanted the lectureship to honor the memory of his son, Adam, who died from an opioid overdose in 2014.

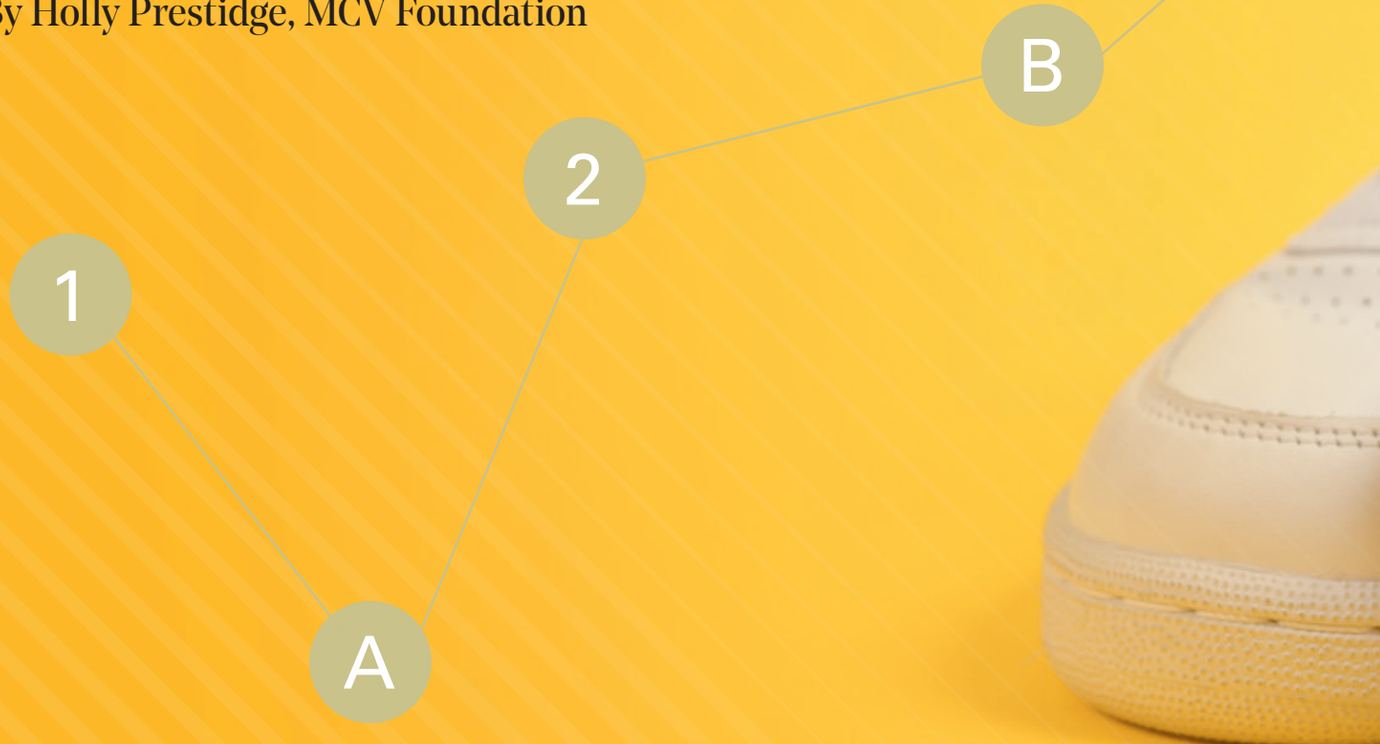
The lectureship provides students in medicine and dentistry with opportunities to learn from national experts in addiction medicine on topics including prevention, treatment, community health, and understanding the science of addiction and substance use disorders.

"No parent should have to endure the hardship of a loss this great," Dr. Abubaker said. "Doctors, including myself, were part of this opioid epidemic. I have made it my personal mission to be a part of the solution and to educate other health care providers on the dangers that opioid prescriptions pose and safe prescribing practices."

Predicting Dementia

Through brain games, surveys and wearable technology, the VCU School of Nursing is studying how physical movement could be an indicator of dementia and serve as a roadmap for earlier interventions.

By Holly Prestidge, MCV Foundation

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Maurice Henderson stood in front of dozens of his fellow senior congregants at Fifth Street Baptist Church in Richmond's historic Highland Park in early 2025 and introduced a topic that stirs all sorts of emotions for older people: dementia.

Flanking him on both sides were members of various VCU Health and VCU Health Sciences teams who are working to figure out if changes in physical abilities are an indicator of dementia's onset. They were also there to support Henderson, who does not have dementia but has decided that while he's healthy, he's going to do all he can for those who are not.

Henderson is one of 150 people participating in a VCU School of Nursing study that aims to identify physical markers of cognitive decline. These markers can be shared with providers who can intervene early in the disease's progression and potentially delay the onset of dementia and other cognitive diseases. The five-year, $3.1 million study, funded by the National Institutes of Health, began in 2022 and particularly targets medically vulnerable and underserved communities.

Changes in one's physical abilities over time, especially changes within daily functions, could indicate a risk of dementia. The study looks at the physical abilities of people ages 65 and older who do not have dementia. By establishing a baseline of physical markers within healthy individuals, researchers can intervene earlier when they detect changes and offer lifestyle modifications to ward off those risks.

The study, called Life-Space and Activity Digital Markers for Detection of Cognitive Decline in Community-Dwelling Older Adults, works like this: Participants visit VCU about every six months over three years, and during those visits, they complete a series of brain games. The games test memory and recall through exercises involving numbers and words. Participants also fill out surveys, which dive deeply into their lives, revealing everything from how many times they leave their bedroom, their home or their town, to the number of people within their social circles.

Before they leave those visits, participants are outfitted with a wearable device like a fitness tracker that is worn for a week. They also carry a GPS locator. Over a week's time, the devices record individuals' activity levels, while GPS shows their physical locations.

Henderson, a retired engineer whose career has taken him and his family all over the world, knows his community well. He knows they need the facts about dementia and Alzheimer's now, because the likelihood of experiencing it themselves — or knowing someone with it — is high and increasing every year.

He knows it runs in his family.

Henderson also knows that VCU needs healthy people like him to participate. It's why he stood before his church friends and neighbors earlier this year and encouraged them to join him. Because for too many, he knows, it is already too late.

A GROWING PROBLEM

Dementia is an umbrella term for symptoms related to brain disease that result in impairments in cognitive function and particularly affect one's daily life. While many think dementia is a normal part of aging, it's not.

Nearly 10% of adults ages 65 or older in the U.S. have dementia. Another 22% have some degree of mild cognitive impairment. The estimated number of people who have Alzheimer's disease — the most widely recognized type of dementia — is about 7 million, and that number is expected to nearly double by 2050.

Dementia isn't just memory loss. The disease manifests in other ways, including loss of communication and language, the inability to focus and pay attention, trouble

Maurice Henderson works brain teasers during his session with VCU School of Nursing's Hannah Khan, RN, a research nurse. He is one of 150 participants in a VCU study looking at physical indicators of dementia that could lead to earlier detection and personalized interventions. *Photo: Daniel Sangjib Min, MCV Foundation*

with visual perception and lack of reasoning and judgment, as well as functional abilities of daily life.

In addition to Alzheimer's, which collectively kills more people across the U.S. than breast and prostate cancer combined, there are several other types of dementia, including frontotemporal, Lewy body and vascular dementia.

Co-leading VCU's study are Lana Sargent, Ph.D., associate dean for practice and community engagement at the School of Nursing, and Jane Chung, Ph.D., a former VCU associate professor who remains involved. The study also involves the VCU Mobile Health and Wellness Program and VCU's Convergence Lab: Health and Wellness Across the Lifespan. They are also partnered with the Osher Lifelong Learning Institute at the University of Richmond.

"People know the importance of physical activity, but they don't know the connection between mobility and the prevention of dementia."

Jane Chung, Ph.D., co-leader of the study

"We wanted to look at how people moved within their home and their spaces and how all of that could potentially change if they're developing these cognitive declines, and then look at ways we may be able to intervene early to improve people's physical functions."

Lana Sargent, Ph.D., associate dean for practice and community engagement, VCU School of Nursing

Lana Sargent, Ph.D., associate dean for practice and community engagement, VCU School of Nursing. *Photo: VCU*

Dr. Sargent said one of the ways this study differs from others is that it tracks people within their daily lives versus participants who come to VCU to be observed in a clinical setting, which is not where people spend the majority of their time.

"We wanted to look at how people moved within their home and their spaces and how all of that could potentially change if they're developing these cognitive declines," she said, "and then look at ways we may be able to intervene early to improve people's physical functions."

While the data looks at physical movement, Dr. Sargent said those markers can point to larger issues within the participant's environment, social circles and overall health, and ultimately, reveal their risk of dementia. For example, if someone does not feel safe leaving the house, the ability to interact with other people lessens, which can lead to loneliness and depression — important factors that have been proved to impact cognitive function.

The devices capture an individual's movements, including the amount of time the person is physically active and the intensity of their movements. GPS tracks the geographic area covered while the person is mobile. In all, researchers are hoping to identify as many as 20 indicators from physical activity that they can use to detect cognitive changes.

Dr. Chung, the study's co-leader, explained that traditional methods of dementia diagnosis include blood biomarkers and imaging biomarkers from MRI or PET scans, which are often expensive and therefore out of reach for many people. By contrast, this study provides data through research using equipment that's more accessible and affordable to more people.

VCU specifically chose the wearable devices, called Real-Life Activity and Life-Space Mobility Monitoring Solution, or RAMS, for their convenience. Unlike many fitness trackers today that require users to have smartphones and then download apps to get their personal health data, RAMS devices gather data on their own without the use of complicated and often costly technology.

"Translating mobility science into brain health is going to be really important for preventing dementia because there's a gap in that understanding," Dr. Chung said. "People know the importance of physical activity, but they don't know the connection between mobility and the prevention of dementia."

Data from this study can open conversations between clinicians and patients about lifestyle modifications much earlier in patients' lives.

In all, over the five-year study, participants will have roughly seven visits at VCU. Dr. Sargent said they continue to recruit study participants, with the goal of enrolling at least another 150 people.

They're looking for people 65 and older, in relatively good health, who do not currently take prescriptions for dementia.

AN EASY LIFT

Henderson, 72, chuckled as he shared that he learned about the VCU study when he saw a magazine story about it last year in his doctor's office. It piqued his interest.

The chuckle is because he took the magazine. (Not just for the study information; his daughter Leah, an author, had a book listed in the magazine's summer reading list.)

"It's clear that we all need to know more," Henderson said earlier this spring. He had just finished his second two-hour stint with Hannah Khan, RN, a research nurse with the School of Nursing. The brain teasers, he noted, were a mental workout. For a week, he would wear the device on his wrist, giving researchers glimpses into his life.

Just two sessions in, he's already learned a few things.

"I'm maintaining a mental yardstick on my performance," he said. "The experience has raised my awareness of lifestyle options I can choose for my own health."

He also understands and appreciates the broad network of support available at VCU for people experiencing cognitive impairments and their caregivers. He hopes others will join him in the study.

"We need a rich and diverse population to achieve the best possible findings from this study," he said. "We cannot achieve any measure of success if we hide the disease."

Henderson's family is his inspiration, but countless others will benefit.

"We seek to give a little helping hand whenever we can," he said, "and this one is an easy lift."

If you would like to support dementia-related studies at the VCU School of Nursing, please contact Jess Sorensen, the school's senior director of development, at 804-615-5877 or jlsorensen@vcu.edu. If you would like to learn more about the RAMS study or be a participant, please contact the RAMS study team at sonramsstudy@vcu.edu.

TRACKING MOVEMENT

Participants are outfitted with a wearable device that is worn during waking hours for a week. They also carry a GPS locator. Over a week's time, the devices record the individuals' activity levels, while the GPS shows their physical locations.

follow-ups

Checking in with researchers on the latest developments

22 VCU Health Sciences Schools and Departments Rank in Top 50 for NIH Research Funding for Public Institutions

New rankings from the Blue Ridge Institute for Medical Research include the VCU School of Dentistry and the VCU Department of Family Medicine in the top 10.

Five of VCU's health sciences schools and departments rank in the top 15 for National Institutes of Health research funding in their fields among public institutions, according to new rankings from the Blue Ridge Institute for Medical Research. Overall, six VCU health sciences schools/colleges and 16 departments placed in the top 50 among public institutions for fiscal year 2024.

The Blue Ridge Institute is an independent, nonprofit organization that compiles annual rankings of NIH research funding to individual researchers and academic institutions.

VCU's School of Dentistry entered the top 10 in the Blue Ridge ranking of public institutions, while the VCU School of Medicine's Department of Family Medicine is at No. 4. Three more School of Medicine departments —pharmacology and toxicology, psychiatry, and human and molecular genetics — also ranked in the top 15 for fiscal year 2024, all driven by significant increases in NIH funding.

The National Science Foundation classifies VCU as one of the country's top 50 public universities for research expenditures. VCU surpassed $500 million in sponsored research funding for the first time in 2024, representing a 9% increase from 2023, and the university's research funding has grown by 86% since 2018.

"Our Blue Ridge rankings across all of our health sciences and increased NIH funding are a testament to our faculty and team members' commitment to advancing our mission through research," said Marlon Levy, M.D., senior vice president for VCU Health Sciences and CEO of VCU Health. "The impact of their research and discoveries makes VCU and VCU Health a destination for our patients and communities, giving them access to the future of health care today."

— Madeline Reinsel, VCU Enterprise Marketing and Communications

Early Detection of Freezing Gait in Parkinson's Disease Patients

Freezing of gait is a sudden inability to walk. It presents a significant challenge for many living with Parkinson's disease.

Ingrid Pretzer-Aboff, Ph.D., a nurse researcher and professor at the VCU School of Nursing, has been working to address this challenge with Leslie Cloud, M.D., a professor who holds the Rogliano Family Endowed Chair in the Department of Neurology at the VCU School of Medicine. The pair collaborated to create a wearable device that detects freezing of gait in people with Parkinson's disease and delivers vibration impulses to stop the freezing. They recently concluded a four-year study that was supported by a $1.2 million grant from the Smart and Connected Health program — a partnership between the National Institutes of Health and the National Science Foundation.

NEXT covered Dr. PretzerzAboff in 2020, shortly after she and several VCU colleagues — including Dr. Cloud, who serves as director of the Parkinson's Disease Program at the VCU Parkinson's and Movement Disorders Clinic — received a grant from the Michael J. Fox Foundation. The grant allowed the team to explore gait data from a vibrating device worn on the feet.

After recording users walking through controlled settings to trigger freezing, the team hand-annotated the video data to note when freezing started and stopped in relation to the environmental stimuli. This information was used to train an AI system to build an algorithm. The algorithm helped the team design a closed-loop, nonintrusive and real-time treatment system that detects and treats freezing of gait with a small vibrating device that creates a localized sensation on the body.

With this recent grant, the device was updated for comfort to allow patients to wear it outside of controlled lab settings like parks or malls. Data collected from this study measured the gait more accurately and identified the freeze of gait in a nanosecond.

Dr. Pretzer-Aboff and her team are applying to secure additional grant funding to continue working on the wearable device. While the research has helped her identify triggers in early detection, the next goal is to predict freezing of gait before it happens and develop interventions to mitigate it. If funding is approved, she can continue to work with researchers across VCU and at other universities, which, according to Dr. Pretzer-Aboff, has been a cornerstone of her research's success.

"Connecting clinicians with technically minded individuals across the campus is the sweet spot," Dr. Pretzer-Aboff said. "It allows for a merging of minds between those who are interested in a subject and innovative enough to build tools from a 'What if' question."

— Zaynah Qutubuddin, MCV Foundation

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NEXT is published by the MCV Foundation to share the latest breakthroughs at VCU Health and the positive impact these exciting innovations have on patients.

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