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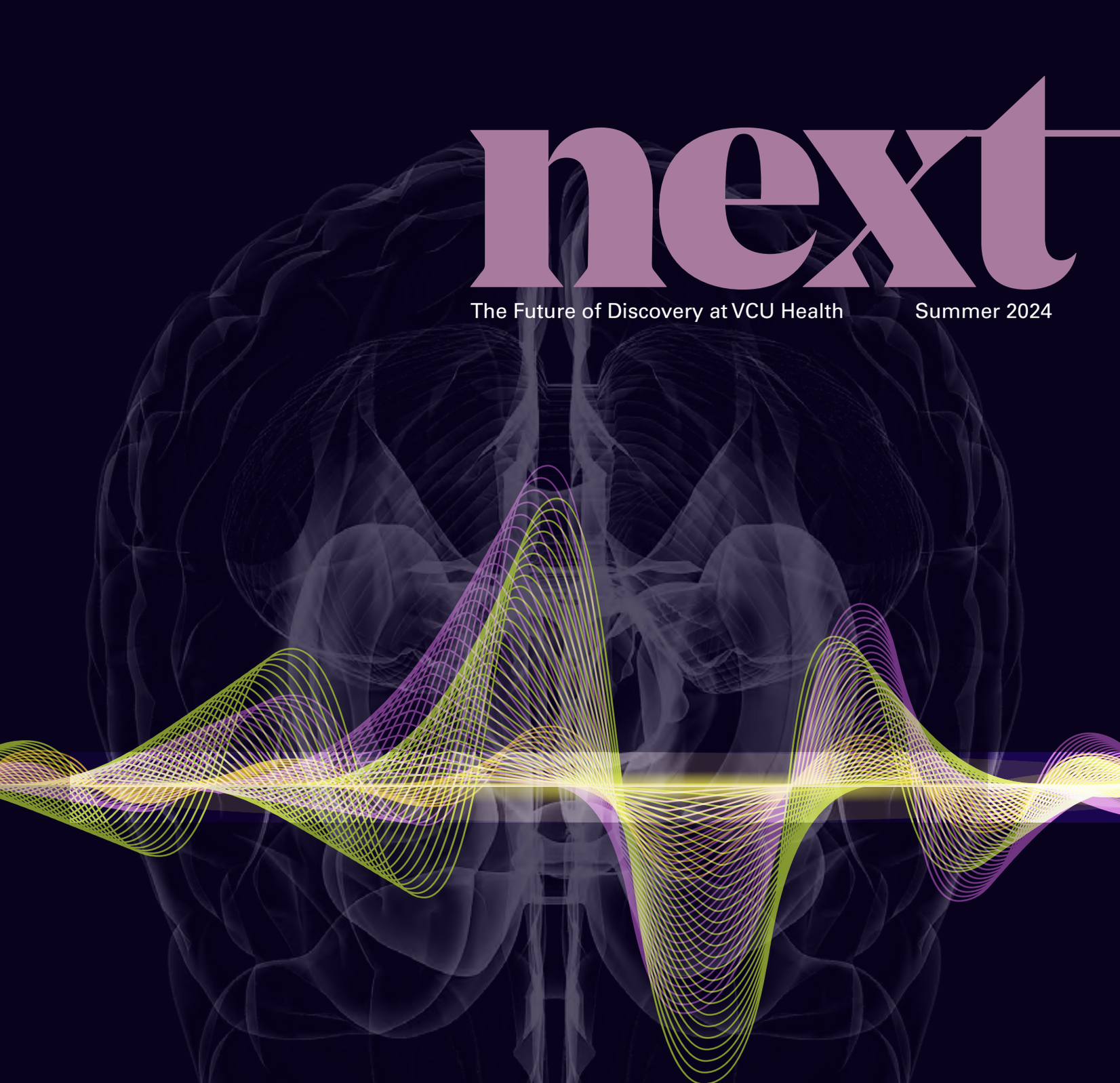
The Future of Discovery at VCU Health Summer 2024



SOUND THERAPY

New outpatient procedure offers quick relief for essential tremor

MCV Foundation
VCU Health

A Record-Breaking Year for Research

Dear Friends,

This publication reaches you at an important and exciting time for VCU and VCU Health. At no other point in their shared history have the university and the health system been as influential or grown more rapidly in the national research and innovation landscape than right now.

Over the last year, we've seen recognition and validation for some of what makes VCU — especially its MCV Campus — such an incredible place. In September, *U.S. News & World Report* ranked VCU as one of the 20 most innovative public universities in the country. Part of that ranking was due to faculty and staff filing 154 patents in FY23. Then, in December, VCU ranked 47th nationally in research expenditures among public research universities. VCU's overall research funding in FY23 was more than $460 million, marking a 71% increase since 2018. On the MCV Campus specifically, the health sciences schools and college received $266 million in new research and sponsored awards in FY23, raising the total MCV Campus sponsored research and award amount to more than $1 billion. Grants are an important piece of these totals, and in FY23, the MCV Foundation accepted 70 grant pledges on behalf of the university, totaling more than $74 million.

NEXT magazine is a fulfilling pursuit for us here at the MCV Foundation because it is our opportunity to tell the life-changing stories of perseverance, innovation and excellence that arise from the funding — and give rise to the rankings and accolades — that are highlighted above. In this issue, we explore focused ultrasound as a treatment for essential tremor, robot-supported understanding of concussions, findings on the ways in which food preparation affects cancer risk, a potential human vaccine for Lyme disease, and a possible cure for sickle cell disease.

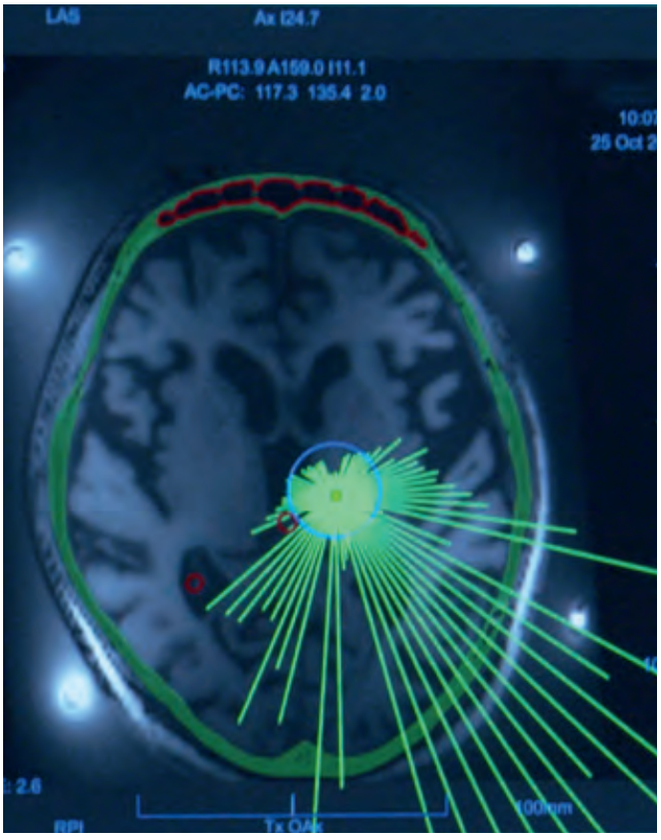
To see this amount of leadership in care delivery and research all in one magazine is awe-inspiring, and we hope you enjoy learning more about the critical health care resource that exists right here in Richmond. We look forward to telling you more of these amazing stories as VCU and VCU Health continue to grow, educate, treat and discover for many years to come.

Sincerely,

Darius A. Johnson
BOARD CHAIR

Margaret Ann Bollmeier
PRESIDENT AND CEO

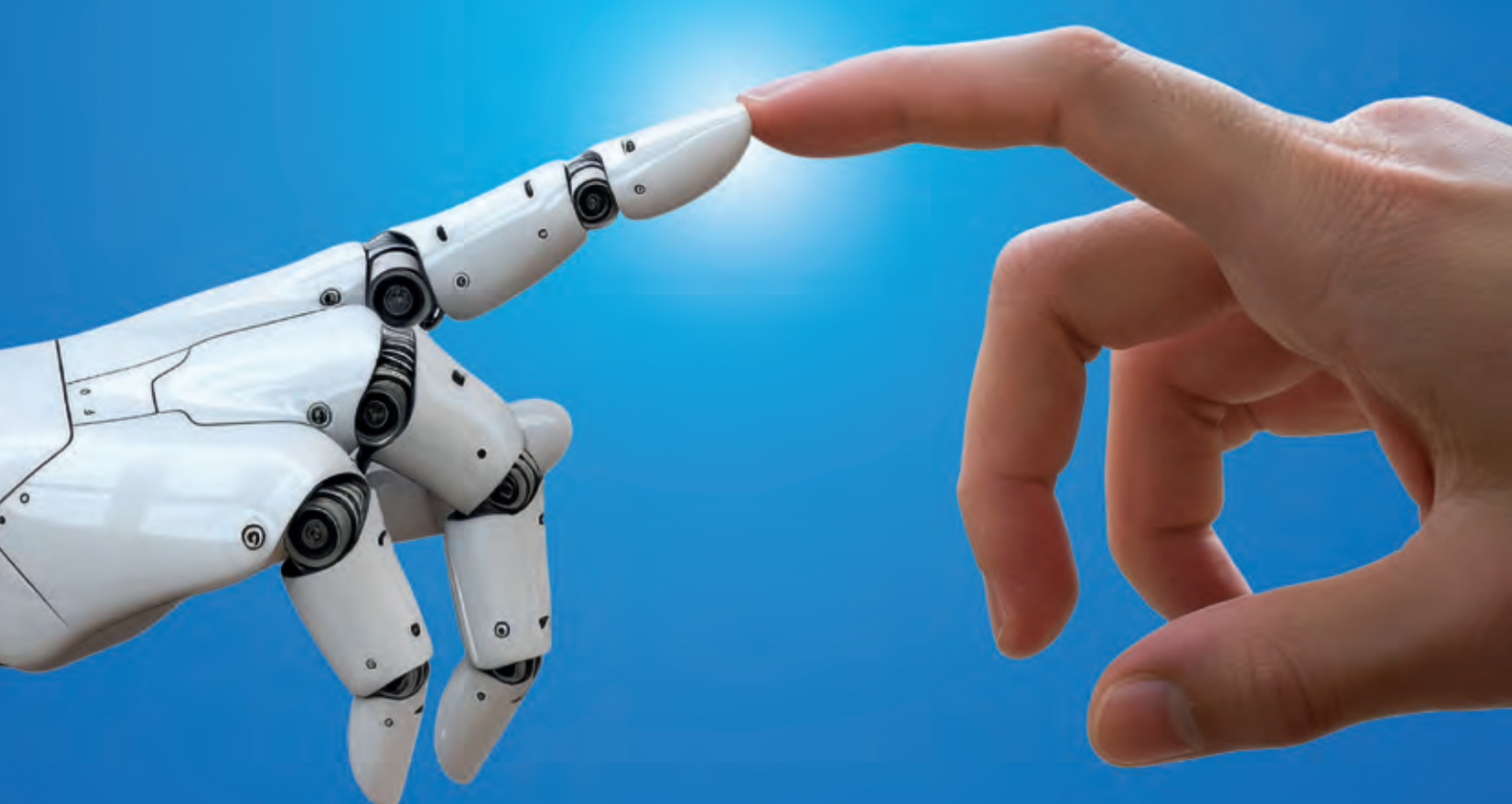
next SUMMER 2024



COVER STORY

Robotic Recovery Assistance

A transdisciplinary team of researchers is exploring how robot-supported measuring tools can help offer individualized understanding of the severity and recovery time for concussions.



By Olivia Trani, VCU Health
Photos by Daniel Sangjib Min, MCV Foundation

In the U.S., about 1 in 4 people are estimated to sustain a concussion in their lifetime. Some people who have a concussion fully recover in a matter of days, while others still experience symptoms for several weeks, months or even years following their injury.

A team of researchers at the VCU College of Health Professions and College of Engineering are using robotic technology to better understand the long-term impacts that concussions can have on patients. The goal of the project is to develop a model for assessing the level of physical impairment caused by a concussion and how long it takes to recover.

"From a therapeutic perspective, we hope that this technology can help health care professionals more accurately assess how quickly their patients are recovering from concussions," said Zach Moore, a master's degree student in the College of Engineering's Department of Biomedical Engineering, who is conducting this research as the basis for his thesis. "Collecting numerical data on a person's recovery gives the opportunity to better determine which treatments are effective for a patient."

Moore is working on this project with his advisor Peter Pidcoe, D.P.T., Ph.D., a professor at the College of Health Professions' Department of Physical Therapy.

REHABILITATION THROUGH ROBOTICS

A concussion can occur after a person experiences some form of trauma to the head, such as a bump, blow or jolt. Symptoms vary depending on the severity of the injury, but people commonly experience issues with their vestibulo-ocular reflex. This reflex stabilizes a person's gaze by moving the eye in the opposite direction from where the head moves. Disruption of this reflex can result in movement-related dizziness, blurry vision and difficulty maintaining balance.

"If you are focusing on a distant object and then move your head 10 degrees to your left, your eyes automatically will move 10 degrees in the opposite direction. This reflex keeps the object visually stable," Dr. Pidcoe said. "When this reflex isn't functioning properly, people often feel a sense of motion sickness and have degraded hand-eye coordination."

For this project, Moore and Dr. Pidcoe developed a robotic arm to help measure impairments to the vestibulo-ocular reflex in individuals who have sustained concussions at some point in their lives. Moore wrote the software that drives the robot based on algorithms provided by Dr. Pidcoe.

For this study, research participants are instructed to reach for a red square "target" on the tip of the robotic arm, kind of like giving the robot a high-five. The robotic arm is programmed to position this target at various static locations in front of participants.

"The robot is programmed to move to 27 different location points in total," Moore explained. "Some of them are high and some are low. Some are out to your right or left."

> "From a therapeutic perspective, we hope that this technology can help health care professionals more accurately assess how quickly their patients are recovering from concussions."
>
> Zach Moore, master's degree student in the VCU College of Engineering's Department of Biomedical Engineering

"My background in both engineering and physical therapy has often allowed me to act as a bridge in transdisciplinary research projects."

Peter Pidcoe, D.P.T., Ph.D., professor, Department of Physical Therapy, VCU College of Health Professions

At the same time, the participants wear glasses designed to switch quickly between transparent and opaque with the release of a button. In the experiment start position, participants place their hands on the button and the glasses become see-through, allowing them to see where the robotic arm positions the target.

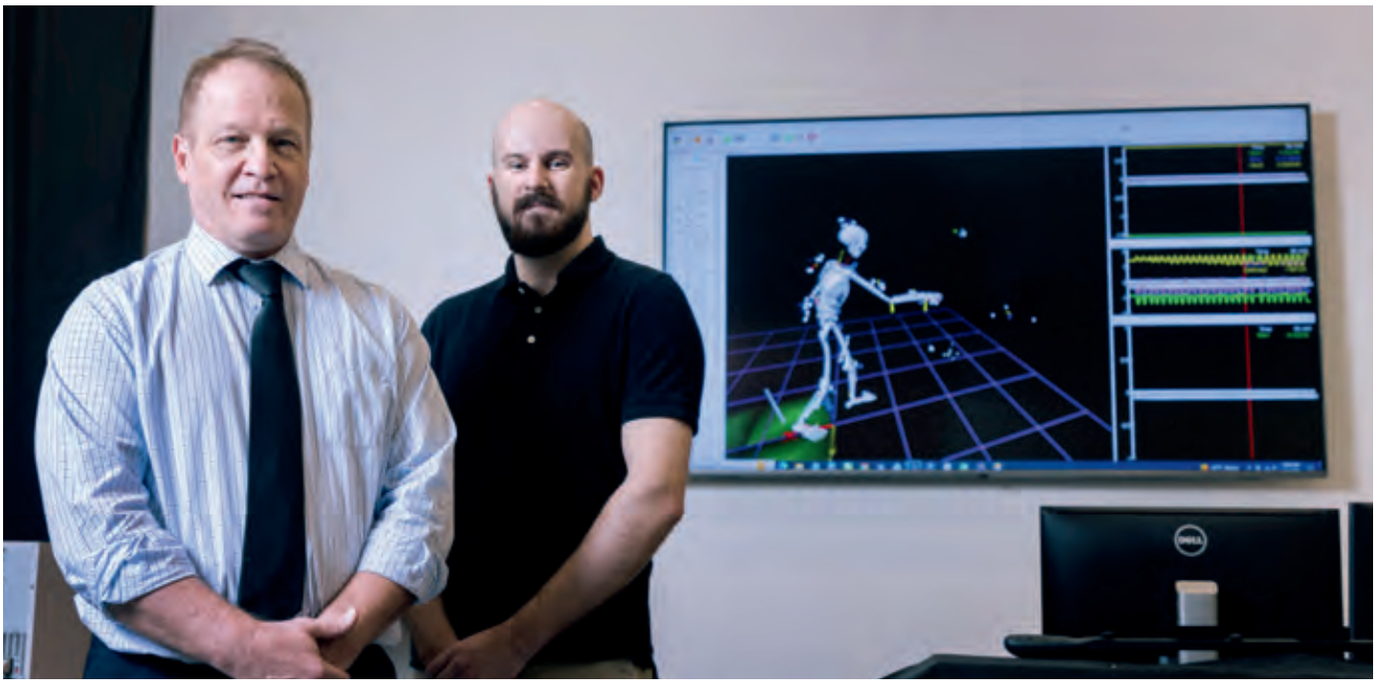
As soon as the participants release their hands from the button to reach for the target, the glasses become opaque, essentially acting as a blindfold. As they reach, the robotic arm also retracts. This means the participants have to use their memory of where the target is — rather than vision or touch — to complete the activity.

During the exercise, participants wear motion capture markers and their activity is recorded on cameras. Using this footage, the researchers can reconstruct the 3D skeleton of each participant on the computer and calculate the accuracy, speed, smoothness and path of their movements as they reach for the target.

"The locations of the targets are adjusted to match the body dimensions of each participant, so that everyone has targets scaled to their height and arm length," Dr. Pidcoe said. "This normalizes the data and allows a person-to-person comparison."

Preliminary data shows that participants who have not had concussions typically get within a quarter of an inch of the target positions, while people who previously have had a concussion don't have the same accuracy. The researchers hope to gain even more insights as they enroll more participants and collect more data for the study.

"We hope to not only capture data on how accurate people are when they reach for the targets, but also how long the process takes with each movement," Dr. Pidcoe said. "It's a simple experiment, but the data we're getting is very robust in terms of what it's telling us about how concussions influence the vestibulo-ocular reflex and hand-eye coordination."



TRANSDISCIPLINARY APPROACH TO PATIENT IMPACT

At the College of Health Professions, Dr. Pidcoe is the director of the Engineering and Biomechanics Lab, which is focused on identifying engineering solutions to address challenges facing patients in physical therapy. He says his work is made possible by the collaborative research culture fostered at VCU.

"One of the reasons I came to VCU was the opportunity to interlink with multiple schools," said Dr. Pidcoe, who was named a fellow of the National Academy of Inventors in 2020. "My background in both engineering and physical therapy has often allowed me to act as a bridge in transdisciplinary research projects."

Dr. Pidcoe oversees several projects in his lab that utilize robotic innovations to help with physical rehabilitation. These include using virtual reality technology as a therapeutic tool for concussion patients, developing modified elliptical exercise machines for stroke survivors, and building motorized devices to help children with movement disorders.

As a biomedical engineering student, Moore saw this lab as an opportunity to apply engineering principles learned from his classes to help patients improve their health.

"Biomedical engineers don't often get to interact with the patient population they are working for," Moore said, "and I thought this project would be a good opportunity for a more hands-on experience with direct clinical applications."

In addition to his studies and research, Moore works at Bon Secours as a rehabilitation tech. He plans to pursue a career in developing assistive technology after graduating from VCU, but he hopes future students continue to move this research forward.

"This thesis project is essentially laying the groundwork for others to expand upon," Moore said. "There are so many more factors to consider and questions to answer."

If you would like to support this research at the VCU College of Health Professions, please contact T. Greg Prince, Ed.D., the college's senior director of development, at 804-828-7247 or tgprince@vcu.edu.

Above: Peter Pidcoe, D.P.T., Ph.D. (left), a professor in the Department of Physical Therapy at the VCU College of Health Professions, is also a fellow of the National Academy of Inventors. He is advising a graduate project from Zach Moore to develop technology to help measure the severity of concussions and create individualized understanding of patient injuries and recovery time.

Opposite page: A VCU student and research participant wears a motion-capture suit as she reaches toward targets in front of a robotic arm. The exercise is part of a research project to better understand how concussions impact hand-eye coordination.

Boiling Down Dietary Cancer Risks

Researchers at VCU Massey Comprehensive Cancer Center are developing a deeper understanding of how individual food choice and preparation style affect inflammation and cancer risk.

By Paul Brockwell Jr., MCV Foundation

Food is more than just fuel for the body. It's often about the experience, the panoply of flavors and aromas — from the simple browning of a crispy slice of toast to the sweetness of caramelized onions. But behind the most delicious foods and flavors is a source of cellular inflammation that has led to growing concern among top cancer prevention researchers.

Nearly every food naturally contains what's known as advanced glycation end products (A.G.E.s). The amount of these metabolites can be supercharged depending on how food is processed and prepared. A raw apple, for example, contains 13 A.G.E.s. Cooking leads to the formation of new A.G.E.s, especially when food is cooked at higher temperatures for a long time. The amounts can increase depending on the method (see chart on page 10).

In addition to being consumed through food, A.G.E.s are formed within the body as sugar combines with fat, protein and even genetic material in a complex series of reactions known as glycation. Human bodies are only capable of eliminating a fraction of the A.G.E.s they consume. Over time, they accumulate in tissues and organs, causing increased oxidative stress and inflammation that research suggests contributes to chronic diseases throughout the body.

"Advanced glycation end-products" is hardly a household term ... yet. But a pair of researchers at VCU Massey Comprehensive Cancer Center are working to create greater awareness of the role they play in driving the body's inflammatory responses, more rapidly aging the body and increasing cancer risk.

Victoria Findlay, Ph.D., co-leader of the Cancer Prevention and Control Program at Massey, is the primary co-investigator along with her husband, David Turner, Ph.D., on a project funded by the National Cancer Institute that focuses on A.G.E.s and their negative impact on cancer risk. Both are associate professors in the Department of Surgery at the VCU School of Medicine.

Most people have not heard about A.G.E.s, but Drs. Findlay and Turner have been researching them for around a decade and building a better understanding of their connections with dietary lifestyle choices and increased cancer risks. What they've discovered has been motivating beyond the lab.

The pair were part of a four-person team that co-founded the Anti-A.G.E.s Foundation to promote understanding of A.G.E.s and to educate the general public about A.G.E.s and the keys to lowering consumption rates in one's diet. Both Dr. Findlay and Dr. Turner are currently rowing against the tide. Today, people consume A.G.E.s at an all-time high, thanks to the ubiquity of ultraprocessed, low-cost foods. An innocent-looking granola bar nets over 2,000 A.G.E.s. Three bacon slices contain a sizzling and crispy 91,577 A.G.E.s.

"The difficulty is that most people are unaware of the existence of A.G.E.s, let alone the damage that they cause," Dr. Findlay said. "Currently, there are no databases or resources detailing this information. This is where we hope the Anti-A.G.E.s Foundation can help. Our mission is to make the world more aware of A.G.E.s by creating dynamic educational resources that provide information on the links between modern nutritional habits, chronic diseases and A.G.E.s."

RAGING A.G.E.S

A diet high in A.G.E.s will, over time, slowly wreak havoc in the human body. A.G.E.s are a metabolic byproduct of complex interactions between sugars and fat, protein and genetic material. The body cannot fully process or eliminate A.G.E.s, and research strongly suggests that A.G.E. accumulation is connected with chronic inflammation.

"What's different about A.G.E.s is it's a spontaneous reaction. It's not a controlled reaction," Dr. Turner explained. "It's a bit like when two magnets come together, when a protein and a sugar come together, they're pulled together and form this A.G.E."

After A.G.E.s form, they can interact with receptors on the outside of cells, which are involved in controlling the body's immune response. When a person gets a cut or scrape on their skin, one of these receptors, called the receptor for A.G.E., or RAGE, helps to recruit immune cells to come fight any infection, creating the redness and telltale signs around a cut or scrape. If humans have too many A.G.E.s in their bodies, it can cause RAGE to recruit too many immune cells and can lead to inflammation in tissues. Ironically, the presence of inflammation can lead to the formation of more A.G.E.s and further RAGE activation, leading to persistent chronic inflammation.

"It's a complicated feed-forward loop," Dr. Turner said. "And we know that virtually all chronic diseases are driven by inflammation. It's central in cancer, diabetes, heart disease and Alzheimer's disease. Persistently causing chronic inflammation is where A.G.E.s really have an influence on most chronic diseases. Through their intrinsic ability to perpetuate immune-mediated inflammatory stress, A.G.E.s found in the diet represent an early life exposure that may influence the onset and/or severity of multiple chronic conditions when we grow older."

A.G.E.s also adhere to tissues and organs during these complex reactions in ways that are irreversible, according to Dr. Turner. "For example, over time when A.G.E.s accumulate and bind to the protein collagen in the skin,

A.G.E.s in Food per 100 Grams

Data Courtesy the Anti-A.G.E.s Foundation

White Rice

9 A.G.E.s

Raw Apple

13 A.G.E.s

Raw Cucumber

31 A.G.E.s

it can contribute to the formation of wrinkles in the skin as we grow older," Dr. Turner said. "If you can imagine the same thing happening to every organ in your body, A.G.E.s can make your organs grow older quicker. So you might be 35 years old, but if you've been exposed to a lot of A.G.E.s over your lifetime, the deterioration of your organs may reflect a 45-year-old."

A.G.E. INSIGHTS FUEL RECENT RESEARCH

A.G.E.s have been known for more than a century since French chemist Louis Maillard began studying the interactions between amino acids and sugars in 1912. In fact, the chemical reaction called the Maillard reaction, which can be seen when a slice of bread slowly transforms into a perfect golden-brown piece of toast, is named after him. But it was only in the last two decades that research on A.G.E.s and cancer really began.

"A scientist's journey is never one straight line," said Dr. Findlay. "You let the science take you wherever it guides you."

For her husband, Dr. Turner, the science started leading him toward A.G.E.s while at the Medical University of South Carolina. A research partnership with South Carolina State University, a historically Black university,

A.G.E.s have been known for more than a century since French chemist Louis Maillard began studying the interactions between amino acids and sugars in 1912. But it was only in the last two decades that research on A.G.E.s and cancer really began.

Kidney Beans

191 A.G.E.s

Potato Chips

2,883 A.G.E.s

Granola Bar

3,177 A.G.E.s

How Cooking Impacts A.G.E.s

The way food is prepared can dramatically increase the number of A.G.E.s in a dish. This is a product of both time and temperature. Broiling, grilling or frying foods will create higher amounts of A.G.E.s through the chemical reactions induced when food is exposed to higher temperatures over longer periods of time. One tip for preparing meats like chicken is marinating the meat in lemon juice, which reduces the amount of A.G.E.s created through the cooking process.

led him to some really astonishing insights about A.G.E.s that raised health equity concerns for communities with high cancer rates and where access to food is often limited to cheaper, ultraprocessed foods high in A.G.E.s.

"Fifteen years ago I'd never heard of A.G.E.s, so we had to do a lot of research on this," Dr. Turner said. "Once we found out what they were, we wondered, 'Why isn't everybody looking at these?' They just seem so important. Based on that alone, we both sort of changed our research direction."

At that time, there was one paper that looked at the role of these A.G.E.s in cancer development, Dr. Turner said. They seemed such an important area of inquiry for the duo since they're involved in all the foods people eat and the way they live their daily lives, and therefore can be part of understanding what lifestyle choices actually lead to cancer.

What they found set off some alarm bells. Data from several studies the pair have conducted have indicated that high-A.G.E. diets may cause prostate and breast tumors to grow faster. These studies provide evidence that consuming a diet high in A.G.E.s may create an environment around existing tumors that helps them to grow by causing RAGE activation. "We expected to see effects, but we didn't quite expect the extent of what we're seeing in our experiments," Dr. Findlay said. "Our study measured a three- to fourfold increase in tumor growth due to A.G.E.s in our experimental models, which is a lot."

"A.G.E.s are really understudied," Dr. Turner said. "And we're driving that forward especially when it comes to food and cancer. All of our data has indicated that A.G.E.s in the diet, especially the preformed A.G.E.s in food, seem to be making the cancers grow quicker and be more aggressive."

Further studies are required to support the experiments that Drs. Findlay and Turner have performed in the laboratory, and while this research continues, the pair have also explored potential interventions.

Dr. Findlay has examined how time-restricted eating can blunt the impact of high-A.G.E. diets by limiting eating from 10 a.m. to 4 p.m., for example. The results were compelling enough for her to adopt the practice into her own lifestyle. Collaborative studies between Drs. Findlay and Turner and other labs also support the theory that women who are consuming the most A.G.E.s may be at higher risk of being diagnosed with breast cancer.

"We never expected to see the magnitude of changes that we saw when we did dietary studies," Dr. Findlay said.

Associate professors David Turner, Ph.D., and his wife, Victoria Findlay, Ph.D., are co-leading research at VCU Massey Comprehensive Cancer Center that examines the negative effects of advanced glycation end products (A.G.E.s) on cancer risk. The duo also began an educational Anti-A.G.E.s Foundation to raise greater awareness about how diet choices can increase risk for cancer and other chronic diseases. *Photo: Daniel Sangjib Min, MCV Foundation*

"We're not genetically manipulating anything — it's literally just a diet. We truly believe that A.G.E.s within the food — and not just individual fat or sugar or protein — is really driving a lot of the chronic diseases that we're observing."

WHAT'S NEXT?

Drs. Findlay and Turner are enthusiastic about continuing this research and its potential for positive impact. They hope that by creating a better understanding of the role A.G.E.s play in chronic inflammation and diseases, they can help inform long overdue policy and regulatory discussions on food. They have enjoyed engaging with the community, especially in primary schools, because they believe that by educating children early, they can have a ripple effect with their parents at home around the dinner table.

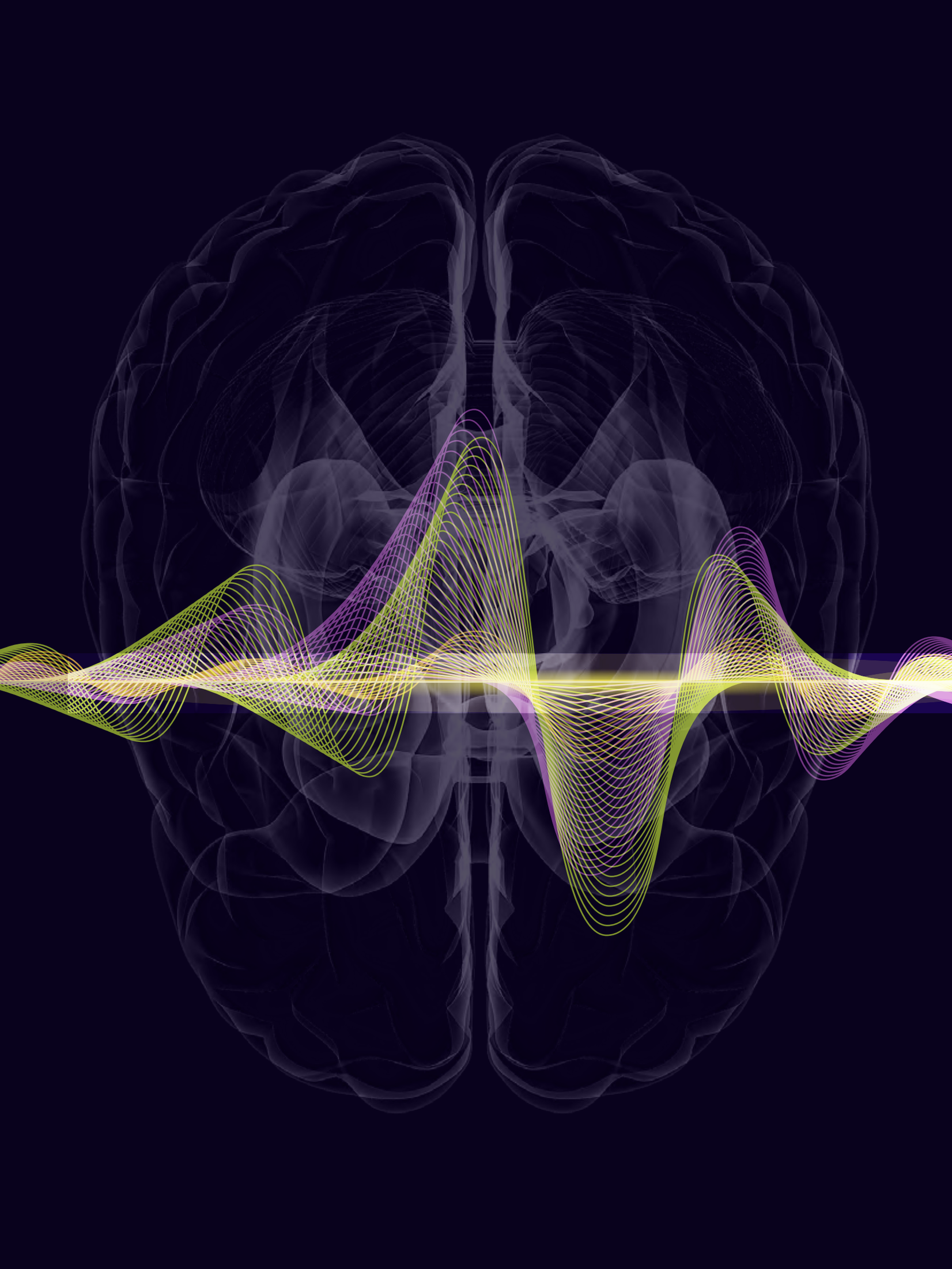
"We're about to put a list of 560 foods and their A.G.E. counts in various cooked formats on the website for the Anti-A.G.E.s Foundation," Dr. Turner said. The study was done by Jaime Uribarri, M.D., in New York. "I think that it would really help to get people to understand how many A.G.E.s they are consuming. Right now, few people know what A.G.E.s are, but if we educate people, they are then free to make their own decisions on A.G.E.s. They could totally ignore what we tell them, but if people aren't told, they can't make an informed decision about the foods that they're eating."

Initial studies in healthy individuals indicate that a consumption of between 15,000 to 20,000 A.G.E.s per day may be a healthy limit. However, Dr. Findlay is quick to share that further research is needed to definitively assign a recommended daily ceiling on the amount of A.G.E. consumption per day.

"The body can detoxify some, but not all A.G.E.s, and there is not yet enough research to show how much is truly too much," Dr. Findlay said. "There is no dietary requirement for A.G.E.s that we are aware of, thus 'less' is definitely better.

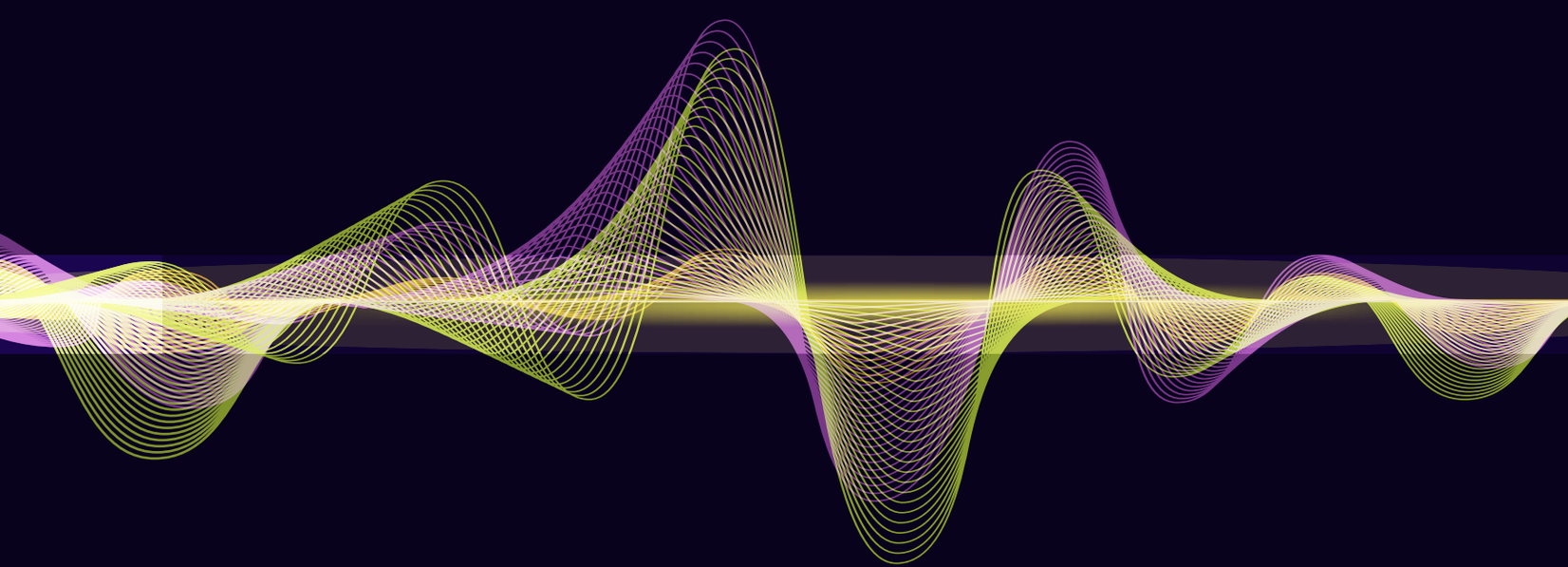
"We hope this research helps allow people to understand how their lifestyle choices can help reduce the risk of cancer and chronic diseases later in life," she continued. "People don't understand the power they have over their own bodies until it's often too late."

If you are interested in supporting research at VCU Massey Comprehensive Cancer Center, please contact Caitlin Doelp, Massey's executive director of development, at 609-432-6247 or doelpc@vcu.edu.



SOUND THERAPY

A new outpatient procedure offers quick relief for essential tremor.



By Holly Prestidge, MCV Foundation

"It was discovered that you could disrupt the tremor, either by putting a hole in the nodes in that circuit or stopping the transmission of communications by delivering electrical stimulation."

Paul Koch, M.D., neurosurgeon and director of VCU Health's focused ultrasound program

The gold standard for an established decades-old procedure that treats essential tremor faces competition from new technology and advancements that could upend the treatment of tremor-related conditions.

For the first time, last September, VCU Health performed a procedure called focused ultrasound to treat essential tremor, a neurological condition that causes one's hands, arms, head, legs or even their core to tremble uncontrollably. Tremors affect more than 10 million people and are about eight times more common than Parkinson's disease, a similar but different neurological disorder that affects movement and balance.

Where Parkinson's tremors are typically felt at rest and do not affect the voice box and speech, essential tremor causes shaking when an individual moves and can affect someone's ability to talk. Essential tremor worsens as people age. Minimal shaking might be annoying, but as the condition progresses, individuals lose their ability to function normally. Researchers and physicians do not know why tremors occur, but they do know how to reduce their severity to allow patients to lead fulfilling lives.

Paul Koch, M.D., a neurosurgeon and director of VCU Health's focused ultrasound program, led the health system's first procedure in September 2023 and has performed several since. Focused ultrasound creates a hole, or lesion, in a particular circuit in the brain that effectively disrupts the tremors' communication pathway.

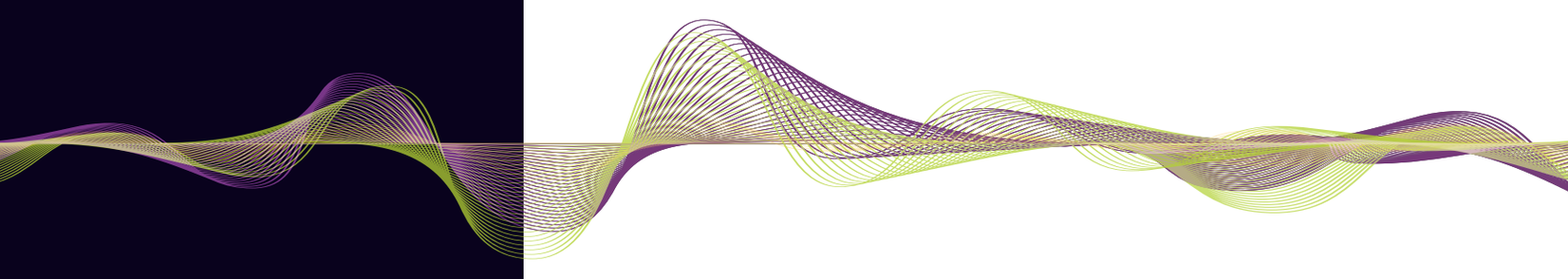
That lesion is created by small bursts of ultrasonic energy pinpointed to an exact location while the patient lies in an MRI machine.

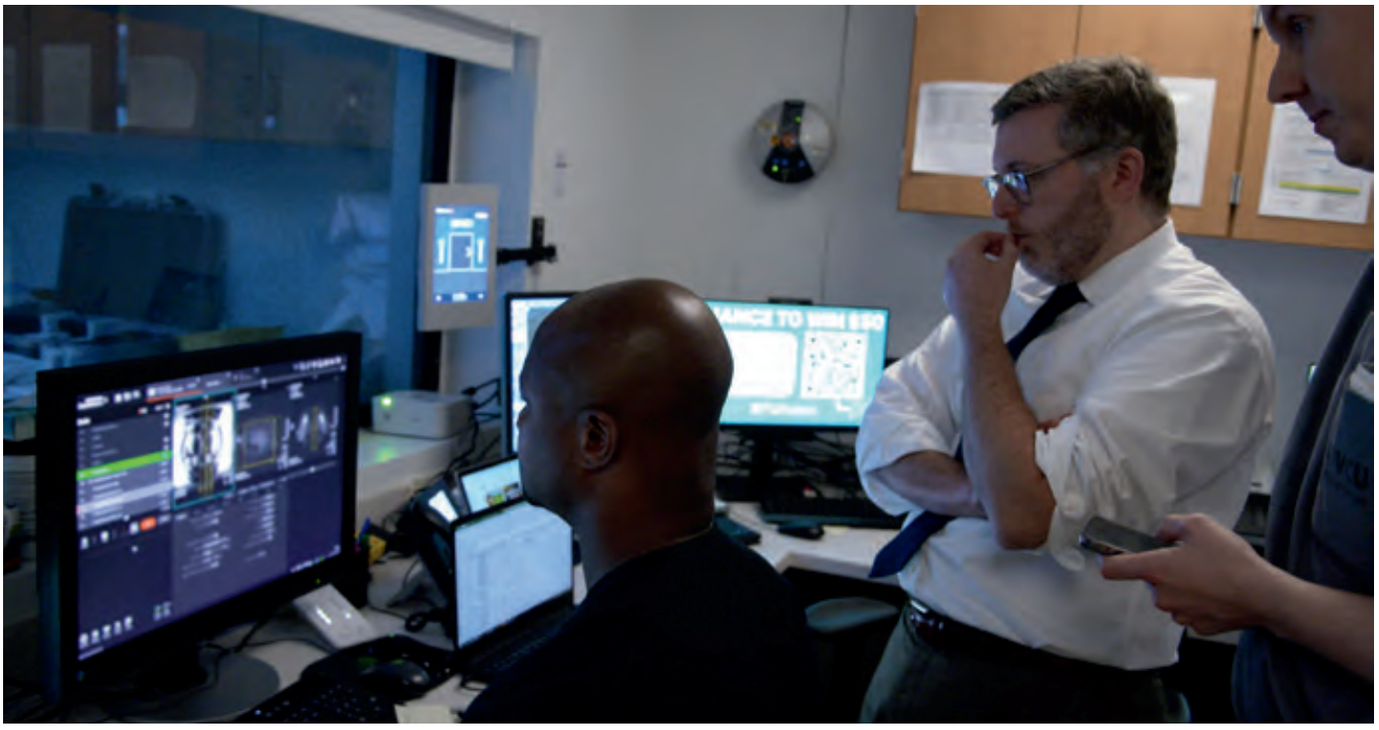
"It was discovered that you could disrupt the tremor, either by putting a hole in the nodes in that circuit or stopping the transmission of communications by delivering electrical stimulation," Dr. Koch said.

Each burst, called sonication, lasts about 10 to 12 seconds. The first one has the lowest amount of energy — like a test shot — followed by increased energy in subsequent bursts. Between each burst, patients are checked for potential side effects like slurred speech or tingling and numbness in their hands or other parts of their body.

As the procedure moves forward, patients and physicians detect whether tremors have already lessened by working through tasks that test fine motor skills. Patients typically receive about six to 10 bursts during the entire outpatient procedure, which only takes a matter of hours and for which general anesthesiais not necessary.

Relief can be felt very quickly.





VCU Health performed its first focused ultrasound procedure last September on a patient seeking relief from essential tremor, which impacts more than 10 million people. *Photo: VCU Enterprise Marketing and Communications*

"The most critical thing is, are the tremors significantly impacting their lives," Dr. Koch said. "It's all about improving people's functionality and quality of life."

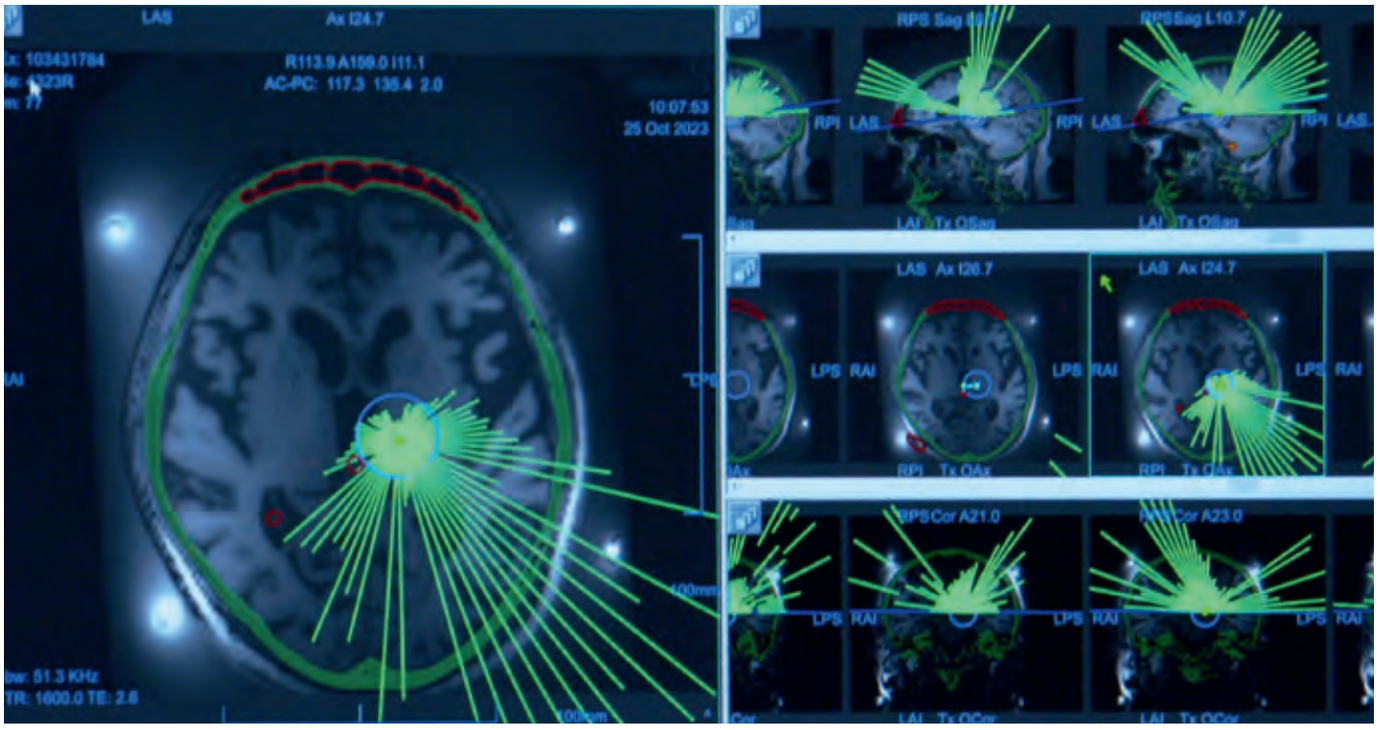
NEW TECHNOLOGY FOR AN ESTABLISHED PROCEDURE

For years, patients with tremors had been treated using deep brain stimulation, where electrodes are surgically implanted into the brain and act as a sort of switch that disrupts the tremors with electrical stimulation.

VCU Health has been a leader in deep brain stimulation for decades, thanks largely to Kathryn Holloway, M.D., a neurosurgeon and director of the deep brain stimulation program. Dr. Holloway has completed hundreds of DBS procedures, and she was part of a team that developed and researched frameless DBS technology.

Dr. Koch explained that both DBS and focused ultrasound disrupt the same circuitry in the brain, but there are differences between the two, and in some cases, focused ultrasound offers benefits both now and in the future. To start, DBS requires general anesthesia, which is high risk for some people. And patients who are on blood thinners are required to go off those medications for roughly two weeks before surgery, which could be risky for them.

Risks are inherent with any surgery, and for those undergoing DBS, the highest risks come during the procedure, from bleeding and infections. Following surgery, the electrodes are permanent, and need to be monitored and maintained regularly throughout the patients' lives, to address their condition.



A focused ultrasound procedure pinpoints thousands of ultrasound energy beams to one location on the brain to create a lesion that disrupts a tremor's communication pathway. *Photo: VCU Enterprise Marketing and Communications*

Focused ultrasound does not require permanent electrodes or general anesthesia. Similar to DBS, the procedure uses a localized anesthetic on the scalp when patients are fitted into a stabilizing apparatus before using MRI scans to map the brain and identify treatment targets. During this phase, patients in both procedures remain awake and alert, but DBS requires a second surgery under general anesthesia to implant a pulse generator in the chest wall that is connected subcutaneously to the permanently implanted electrodes.

Once doctors determine where the lesion will occur, they begin with several low-energy sonications to make sure the location is exact. If it is not, the target can be moved without any negative impact.

Unlike deep brain stimulation, the risks of focused ultrasound tend to be longer term, such as challenges with gait or lingering tingling and numbness in hands or mouth. While patients may experience those side effects for days or a few weeks, 90% of patients recover.

"Focused ultrasound is a new technology to do an old procedure, and it's more precise, more convenient and safer for the patient," Dr. Koch said. "For people who take medications and can't undergo general anesthesia or can't be in the hospital for days with a traditional surgical setting, this offers a significant advantage."

Dr. Koch explained that the FDA has approved focused ultrasound to treat essential tremor as well as tremor-dominant Parkinson's disease. It has also been

approved to treat both sides of the brain, though both sides can't be treated at the same time as surgeons need to determine if there are side effects after the initial procedure. If patients require a second procedure, the FDA requires a minimum wait time of nine months.

The data thus far, said Dr. Koch, shows that focused ultrasound can help ease essential tremor for about five years, though that varies by patient, as the treatment addresses only the symptoms of an underlying condition that will never go away.

Focused ultrasound has been approved for essential tremors in people ages 22 and older, while DBS is available for people ages 30 and up. Dr. Koch said the future of focused ultrasound includes treating patients not only with essential tremor and tremor-dominant Parkinson's, but also individuals with epilepsy.

While current clinical focused ultrasound uses high-frequency energy, low-frequency therapies are being studied as a means of temporarily opening what doctors call the blood-brain barrier.

The brain is a specialized compartment, and not everything that travels through the blood can easily get into the brain. This is a good thing when it comes to infections and toxins. However, it also means high concentrations of drugs such as chemotherapy are needed to get through that barrier, which can cause negative side effects in the body.

Low-frequency focused ultrasound could potentially open that barrier just enough in just the right place and for enough time that drugs are able to get through to targeted specific locations. Those abilities could change the landscape for chemotherapy or immunotherapies as well as gene delivery procedures, Dr. Koch said.

"What we do now with focused ultrasound is just the tip of the iceberg," he said. "This is a promising technology, both for high- and low-frequency focused ultrasound, and it's really positioning VCU Health to take the next steps in delivering truly personalized medicine."

If you would like to learn about opportunities and ways to support neurosciences at VCU Health, please contact Allie Betts, director of development for neurosciences and psychiatry in VCU's Office of Medical Philanthropy and Alumni Relations, at 804-828-3407 or bettsa@vcu.edu.

The FDA has approved focused ultrasound to treat essential tremor as well as tremor-dominant Parkinson's disease. The procedure has also been approved to treat both sides of the brain.

First VCU Health Focused Ultrasound Patient No Longer Held Back by Tremors

By Sara McCloskey, VCU Health News

Like clockwork, you can find Ross Southers at the gym on a treadmill several days a week. The Richmond firefighter didn't want to take retirement sitting down when he left the department nearly 25 years ago.

But Southers' routine started to change five years ago when his essential tremor, which had been diagnosed years before and at the time was very mild, got worse.

"I shook so bad that I could hardly function. My wife would fix my plate for me, and I would drop it all on my lap. I couldn't go to a restaurant anymore. It was very embarrassing," he said.

Southers was referred to VCU Health. His treatment journey led him to become the first VCU Health patient to receive an innovative surgery, called focused ultrasound, which had immediate results — helping him return to the gym and share meals more comfortably with loved ones.

When patients like Southers come to VCU Health's neurosurgery department, they're educated on a variety of treatment options. They also can expect to have a detailed conversation with their surgeon about what is important to them during their treatment journey.

"The sad fact is the medications typically do not work that well, and especially as the disease progresses," said Kathryn Holloway, M.D., director of VCU Health's deep brain stimulation program and one of Southers' surgeons. "If the patient is not responding to medication, then we consider a surgical procedure."

Essential tremor can typically be treated with focused ultrasound, or another procedure called deep brain stimulation, in which electrodes are surgically implanted onto the brain.

"VCU Health was one of the earliest sites in the country to do deep brain stimulation and to demonstrate that surgical intervention was a viable option for many of these patients," said Paul Koch, M.D., a VCU Health neurosurgeon who was part of Southers' care team. "Because of the comprehensive team involved, we have been treating these conditions surgically for a very long time."

After being reviewed by his care team, Southers found out he was not a good candidate for DBS due to fragile blood vessels. However, he was eligible for focused ultrasound.

> "The first time, I was coming off the pad and couldn't even make half a circle. After another 30 minutes, they handed it to me and everybody in there applauded because I made a perfect little circle."
>
> Ross Southers, VCU Health patient

During the focused ultrasound procedure, the patients are taken out of the MRI scanner about every 30 minutes to see if they are feeling side effects, like weakness or tingling in the hand, and to test for any improvements. To do this, they are asked to try to draw a circle on a piece of paper. The results are almost immediate.

"The first time, I was coming off the pad and couldn't even make half a circle," Southers said. "After another 30 minutes, they handed it to me and everybody in there applauded because I made a perfect little circle."

Being able to see a treatment work so quickly doesn't happen often in hospitals, making focused ultrasound different than other types of surgeries and procedures.

"For DBS, there's the procedure, there's the recovery, there's turning it on and there's titrating it," Dr. Koch said. "What makes focused ultrasound sort of more instantaneously gratifying is how immediately we see the effects and how little trouble the patient has had to go through to get to that point."

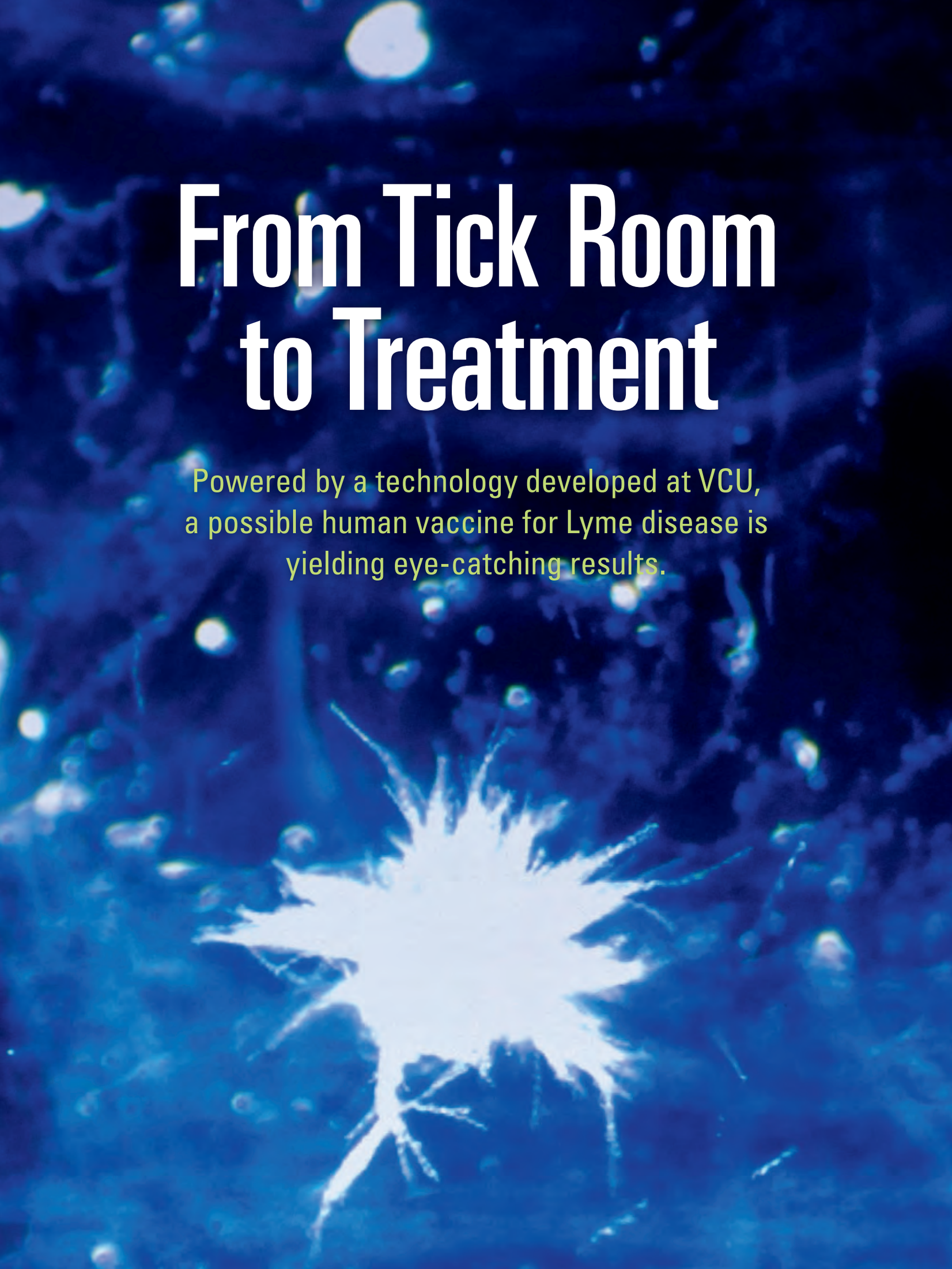
It takes a whole team to care for the patient, including neurosurgeons, neurologists, nurses, speech and physical therapists, and MRI technicians. Patients are checked by a physical therapist after this procedure due to potential balance issues. Southers immediately passed with flying colors.

"Our patients are reaping the benefit of this team approach that makes VCU Health so unique," Dr. Holloway said.

For Southers, tremors are no longer holding him back from his passions. With a speedy recovery, he is back at the gym three days a week, hitting the treadmill for an hour each day. The physical routine is important for Southers since he doesn't want to take retirement sitting down.

"I refuse to stop, but I'm a nut at it. Been doing it for 25 years," Southers said. "I won't quit till I can't move."

Ross Southers was the first patient at VCU Health to receive the focused ultrasound treatment for his essential tremor. *Photos: Taylor MacKillop*



From Tick Room to Treatment

Powered by a technology developed at VCU, a possible human vaccine for Lyme disease is yielding eye-catching results.

By Eric Peters, MCV Foundation
Photos by Daniel Sangjib Min, MCV Foundation

Tucked toward the back of a VCU School of Medicine research building, through a laboratory, around a couple of tight corners, just past pieces of equipment that accomplish tasks like "fast protein liquid chromatography," there is a door. It's nondescript, save for a small, lime-green, handwritten sign that reads: TICK ROOM.

Inside the broom-closet-sized room, researchers maintain live specimens of several species of ticks. Gathered from wild and domesticated animals such as deer and dogs from across the region, ticks are not hard to find — they are abundant in Virginia and can be found in any part of the state and across significant swaths of North America and Europe.

These parasitic arachnids are the reason scientists here in the lab of Richard T. Marconi, Ph.D., have been working for more than 30 years. They've been exploring and developing solutions to counteract the growing negative health outcomes related to the continent's steady increase in tick population.

The problem is, ticks can carry and transmit several debilitating diseases, including Lyme disease, which is a serious and difficult-to-diagnose illness that affects nearly half a million Americans every year. It is transmitted through the bite of an infected black-legged tick, and it is the most common vector-borne disease in the U.S. Early symptoms include a characteristic "bull's-eye" skin rash, fever, headache and fatigue. Early detection is difficult because these symptoms can easily be taken for any number of illnesses that general practitioners are more familiar with diagnosing.

And if left undiagnosed, long-term infection can be debilitating. It can affect the joints, the heart and the nervous system, resulting in severe fatigue, arthritis, facial palsy, muscle and joint pain, numbness, carditis, heart palpitations, dizziness, shortness of breath, memory loss, cognitive impairment, depression, anxiety, insomnia, psychosis and many other life-altering challenges.

In the U.S., the number of Lyme disease cases has doubled since 2000, and it is a serious concern across the rest of the continent and in Europe.

Facing the growing threat head-on, and with decades of experience, is Dr. Marconi's lab on the MCV Campus at VCU. There is no group anywhere in the world working harder or more effectively at the leading edge of the fight to detect and prevent Lyme disease.

In 2016, a novel, highly effective vaccine called Vanguard crLyme (Zoetis) that the team developed for dogs went to market. CrLyme is now the most widely used canine Lyme disease vaccine in North America. "The canine vaccine has taken the veterinary market by storm," said Magdalena Morgan, Ph.D., director of licensing at VCU Tech Transfer and Ventures. It's considered the best of several such vaccines available, thanks to its capability to fight different strains of the disease.

Dr. Marconi's team also developed a much-needed diagnostic for humans. This is hugely important because finding a diagnosis means finding the right care and, hopefully, some relief from symptoms. Just one example is Richmonder Craig Suro who, after searching for the cause of his unbearable and debilitating anxiety for six months, finally was given a Lyme disease diagnosis thanks to Dr. Marconi's lab. "When you hear the results, you literally stop what you're doing and just bawl," said Suro in 2017. "Not having a diagnosis is such torture. I don't think Dr. Marconi has any idea what he did for me."

To date, the Marconi Lab has enjoyed success and improved countless lives through its work, but they are not yet finished. The team now has its sights set on stopping Lyme disease in humans before it ever begins, and their initial research in developing a human vaccine has yielded eye-catching results: 100% effectiveness in a controlled lab environment.

THE MARCONI LAB EPIPHANY

Dr. Marconi is a professor in the Department of Microbiology and Immunology at the VCU School of Medicine. His busy lab employs 14 people today, but when he arrived at VCU in 1994 as a 34-year-old assistant professor interested in the basic science of Lyme disease, he had to build his team from scratch.

In those early days, creating vaccines based on research — which would be called translational science — was not in the plans. Basic science and understanding were the focus.

A cluster of *Borreliella burgdorferi* cells, the bacteria that cause Lyme disease.

Richard T. Marconi, Ph.D., in his lab on the MCV Campus at VCU.

"For the first 12 or 13 years I was here, we were studying what I refer to as the molecular pathogenesis of Lyme disease," Dr. Marconi said. "Our initial goals were to determine how the Lyme disease spirochetes persist in the body and cause disease. What are the proteins that are involved? How do the bacteria cause damage during infection?"

Lyme disease is caused by a bacterium named *Borreliella burgdorferi*, which belongs to a unique group of bacteria called spirochetes, and as the name implies, they have a spiral-corkscrew-like structure. The Lyme spirochetes can produce large numbers of outer surface proteins, which interface directly with the host immune system. The Lyme spirochetes switch the proteins they make as a means of adapting to different environments and protecting themselves.

By 2007, Dr. Marconi's team was very interested in one of these outer surface proteins — OspC. This protein is required for the bacteria to move from a tick to a mammal and cause an infection. Therefore, it is a perfect target for vaccines.

The challenge, however, in developing an OspC-based vaccine is that 30 distinct OspC variants have been identified worldwide, and any given strain of a Lyme disease bacteria only makes one version of it. Thus, using just one OspC in a vaccine wouldn't protect against all Lyme disease strains that are producing different OspC variants.

So the Marconi Lab began to ask, "How do we make one vaccine that works against all these different variants?"

Contemplating this challenge one day in his office, Dr. Marconi and his team had an epiphany of sorts. There might be a way, they surmised, to create a brand-new single protein to be used in a vaccine that includes segments of all the most important OspC variants.

And from that day on, the Marconi Lab became a translational science lab.

The team identified the piece of OspC, known as an epitope, that triggers the immune response and found that was the part that varies so widely worldwide. Based on the earlier epiphany in Dr. Marconi's lab, the team then invented a next-generation process they call chimeritope technology. Using this approach, they designed a DNA molecule comprising the epitope encoding sequences from several different variants of OspC. The word chimeritope is formed from the words chimeric — joining together parts of different organisms — and epitope.

"That was really the big breakthrough," Dr. Marconi said. "It wasn't a concept that was being pursued at the time. We were really at the lead of developing the concept of chimeritope proteins, but now it's widely used. It's really attracted a lot of attention."

It had been shown decades prior that the OspC protein is a potentially good vaccine candidate. But the problem was it didn't provide broad protection because of all the variants.

"For example, what everyone learned from COVID was that new strains can emerge and you need a new vaccine to address the new strains," Dr. Marconi said. "It's a little different with Lyme because new strains are not emerging,

"The importance of philanthropy can't be understated. Without it we would not have been able to make the key breakthroughs that have led to products that benefit patients."

Richard T. Marconi, Ph.D., professor,
Department of Microbiology and Immunology at the VCU School of Medicine

but there are many different strains that are stably maintained in nature — you need to make sure that you make a vaccine that can protect against all those different strains. The chimeritope approach is well-suited for achieving this goal."

While it wasn't what Dr. Marconi set out to do when he arrived in 1994, his basic benchside research built and accumulated over many years and directly led to vaccines, diagnostics and other health care tools. This is the definition of translational science: from the bench to the bedside. Or in this case, from the tick room to treatment.

An important piece of the foundation and the developments that follow, Dr. Marconi said, is philanthropic support. Private funding can quickly be put to use, and it provides resources to attract and retain skilled personnel, equipment and other tools. It also allows scientists to pursue new, unproven ideas. It enables them to explore — to be scientists. Oftentimes, donors provide seed funding for proof-of-concept studies that lead to larger funding from organizations like the National Institutes of Health.

"The importance of philanthropy can't be understated," Dr. Marconi said. "Without it we would not have been able to make the key breakthroughs that have led to products that benefit patients."

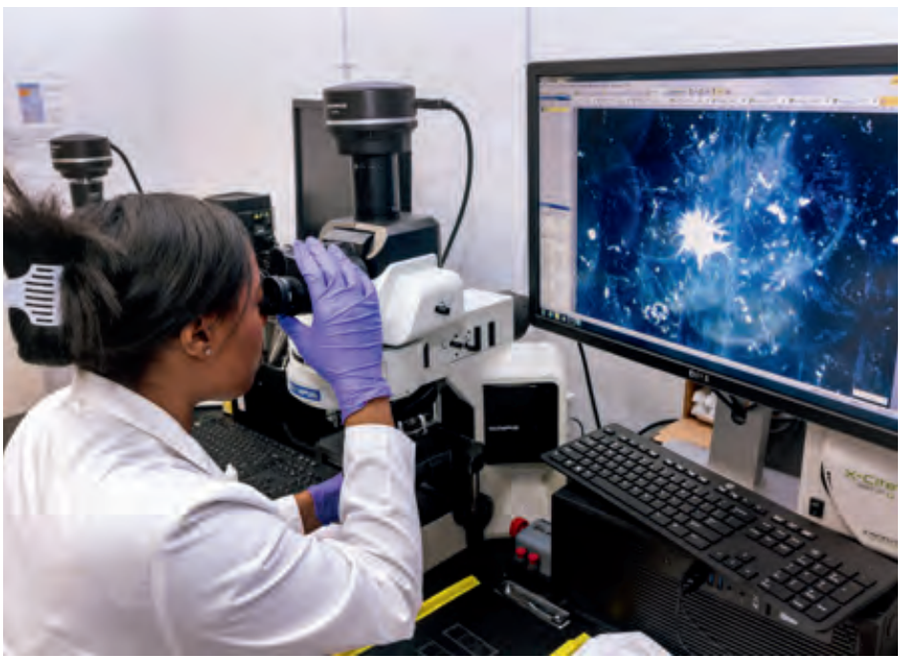
A HUMAN VACCINE AND NEW DIAGNOSTIC TEST

The lack of a human vaccine for Lyme disease has long plagued Dr. Marconi.

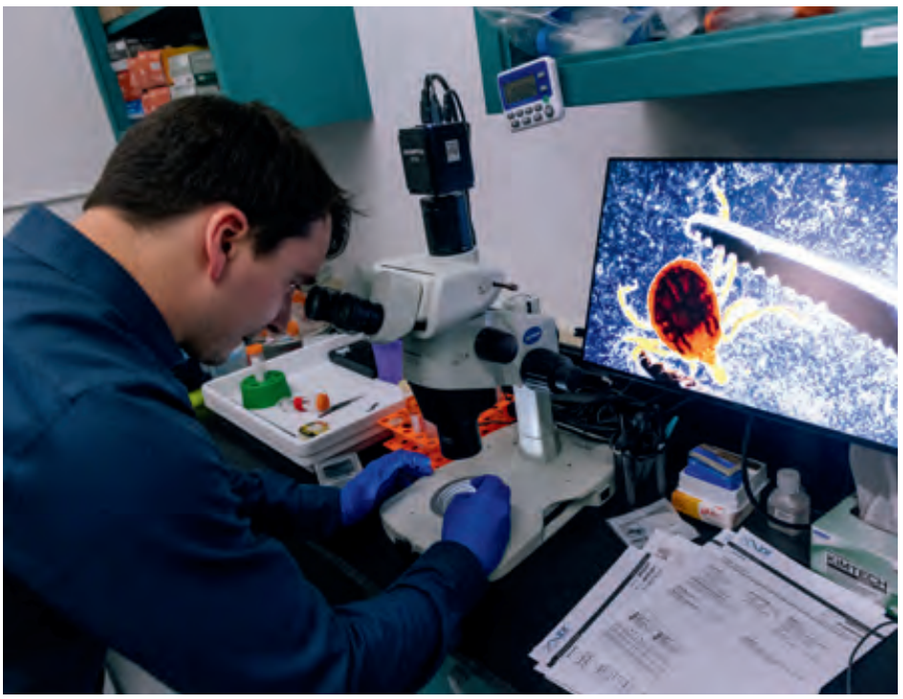
"What has consistently bothered me is the notion that the best we can do in terms of prevention after so many years of study is to tuck your pants into your socks, perform 'tick checks' and apply sprays containing permethrin," Dr. Marconi said. "With the increasing incidence of Lyme disease, I couldn't accept that this was the best we could do — I thought there's got to be a better way."

Building on his previous basic science work and its applications in the canine vaccine crLyme — and leveraging a $2.5 million grant from the National Institutes of Health in 2019 — Dr. Marconi and his team are close to solving the human vaccine puzzle.

They've developed a completely new Lyme disease vaccine that uses the same chimeritope technology as crLyme, but this time uses the OspC



Jade Smith, a Ph.D. student in the Marconi Lab, looks at a cluster of *Borreliella burgdorferi* cells.



Nick Cramer, a Ph.D. candidate at the VCU School of Medicine, examines a black-legged tick under a microscope in the lab of Richard T. Marconi, Ph.D. Cramer is working on a vaccine and diagnostic test for ehrlichiosis, a tick-transmitted bacterial disease.

variants that affect humans rather than the variants that affect dogs.

This past December, the team received word that the new vaccine formulation for humans yielded 100% efficacy in an elevated animal model.

"That's really exciting, particularly when you consider that the study closely mimics the way you or I might get Lyme disease in nature," Dr. Marconi said. "That's the optimal way to do a challenge study, and it provided complete protection."

Like the canine vaccine, the new human formulation incorporates an additional protein beyond the OspC chimeritope. Whereas OspC is active when the Lyme disease bacteria is inside a mammal, the OspA protein is active when the bacteria is still inside a tick. Thus, incorporating a chimeritope into the vaccine that is based on the OspA and two additional proteins that are primarily produced in ticks enables a vaccinated mammal's blood — full of antibodies activated by the vaccine — to go into the feeding tick and target the bacteria before it ever enters the mammal. This is known as a transmission-blocking vaccine.

Transmission-blocking vaccines aren't always effective, and focusing solely on this approach explains, in part, why previous Lyme disease vaccines have failed. When used together, however, the OspA and OspC chimeritopes developed in Dr. Marconi's lab provide a multilevel shield against the bacteria — inside the tick and then inside the human or other mammal.

Now that the multilevel shield specially formulated for humans is in place and has shown promising results, the next steps in the process are to optimize the dosage of the vaccine and identify the perfect ratio of the two chimeritopes to elicit the optimal immune response.

As the team finalizes the human vaccine, they are also developing a new diagnostic test. "Our strategy in the lab is that when we work on a vaccine, we simultaneously work on a diagnostic assay," Dr. Marconi said. "That's important because you want to make sure there is a diagnostic available that does not yield a false positive in someone who has been vaccinated."

The exciting development in this new diagnostic is that it is being designed to work as a lateral flow test. Examples of this type of test include pregnancy, drug or COVID-19 tests in which a sample is applied to a matrix and in a short time results can be seen on an indicator.

"That's a really nice kind of diagnostic test because it can be used by a clinician or a veterinarian in the office while that patient is there," Dr. Marconi said. Confirmation of results can then be obtained by diagnostic laboratories.

These diagnostic and vaccine developments are moving quickly, and Dr. Marconi expects clinical trials to begin within a few years. If he keeps up the current pace and optimism in being able to battle or prevent Lyme disease, that small TICK ROOM at the back of his lab might one day better serve as an actual broom closet.

If you would like to support VCU research on tick-related diseases and illnesses, please contact Brian Thomas, executive vice president and chief development officer at the MCV Foundation, at 804-828-0067 or brian.thomas@vcuhealth.org.

More Than Lyme Disease

The chimeritope technology developed in Dr. Marconi's lab is not just being applied to Lyme disease. His lab is full of students and postdoctoral researchers who are all working hard to develop vaccines and diagnostics for other important diseases.

"The approach that we're using can be applied to any infectious agent," Dr. Marconi said. "We see the potential to use this chimeritope technology to develop vaccines for many different pathogens."

Leptospirosis

Edward Schuler, Ph.D., is a postdoctoral fellow who graduated from the Marconi Lab in 2022 but has stayed on to finish the job he began as a student.

His sights are set on developing vaccines and diagnostics for leptospirosis, a bacterial disease that affects humans, livestock, companion animals and wildlife. It is not tick-borne but is found in and passed through urine and bodies of water contaminated by urine. Cases of leptospirosis are on the rise as outbreaks are associated with heavy rain, hurricanes or floods when people may have to wade through contaminated water or use it for drinking or bathing.

Without treatment, leptospirosis can lead to kidney damage, meningitis (inflammation of the membrane around the brain and spinal cord), liver failure, respiratory distress and even death.

An estimated 1 million cases occur globally each year, resulting in nearly 60,000 deaths. It also takes an economic toll on the livestock industry and companion animals.

Dr. Schuler is optimistic about his progress against leptrospirosis, and he credits much of that to working in Dr. Marconi's lab. "Rich is at the forefront of the institution-to-product pipeline. Other labs come up with the ideas, but there's not much infrastructure to generate a usable product. Here we have a proven process and pipeline demonstrated by the Lyme vaccine. And we're able to use the chimeric technology developed here to apply it to new challenges."

And it's vitally important, he said, to address these new challenges. "Leptospira are ubiquitous. No matter where you go, you're coming into contact with Leptospira. Significant numbers of serum samples from every species of mammal that we have screened have tested positive for exposure or active infection. In humans, many aseptic meningitis cases are actually leptospirosis. It's always out there."

Ehrlichiosis

Nick Cramer, a Ph.D. candidate, came to the Marconi Lab because he had a background in studying tick-borne diseases but wanted to find a lab focused on translational science so he could develop vaccines and other interventions for animals and humans.

When he arrived, he set out to find his own niche within the Marconi Lab umbrella, and he did so by studying ehrlichiosis.

Early signs and symptoms of ehrlichiosis, a tick-transmitted bacterial disease, include fever, chills, severe headache and muscle aches. If antibiotic treatment is delayed, ehrlichiosis can sometimes cause severe illness resulting in damage to the brain or nervous system, respiratory failure, uncontrolled bleeding, organ failure or death.

"This is important because tick populations and tick-borne diseases, already prevalent in Virginia, are spreading across the Northern Hemisphere," he said. "The problem is only getting worse."

He added that health care providers still don't have a great understanding of how big the problem actually is. "Ehrlichiosis cases are underreported because there are no rapid point-of-care diagnostic tests available for use in humans," he said. "For humans, really the only time they're tested is when they're already hospitalized, and the number of people hospitalized is going up year over year."

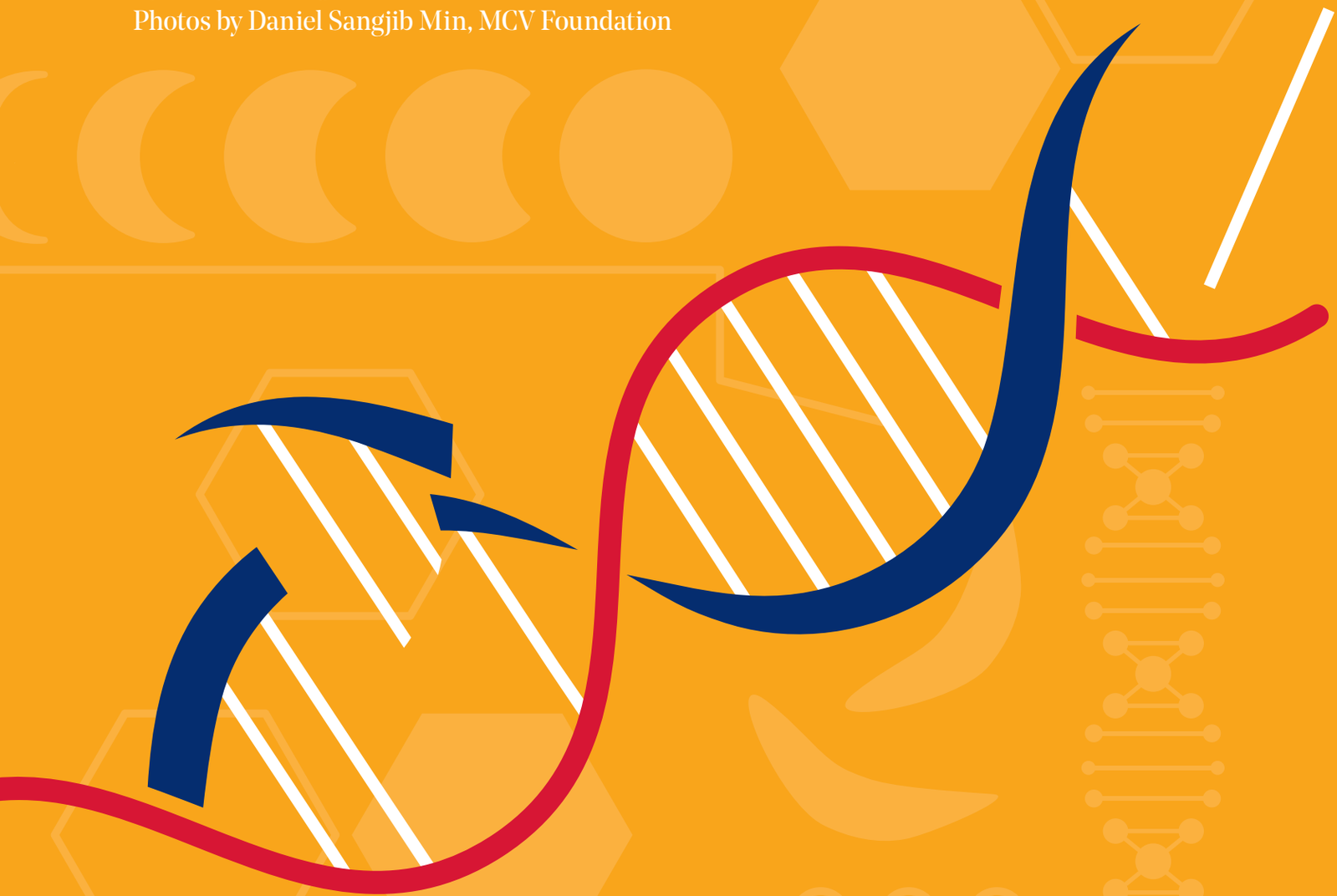
In addition to a vaccine, a rapid point-of-care test would help fight and monitor the disease. He's working on both — first for dogs, then using the lab's proven steps for transitioning into human applications.

"The prevalence of all tick-borne disease is increasing," Cramer said. "To mitigate this burden, the best thing we can do is get in front of it and prevent people from experiencing these terrible symptoms so they don't have to go through this, and so they can have a chance at a better quality of life."

The Gene Edit

A Virginia sickle cell patient is the first to receive a groundbreaking new gene therapy at VCU Health.

By Holly Prestidge, MCV Foundation
Photos by Daniel Sangjib Min, MCV Foundation



Walter Davis recalls few stretches throughout his 30 years on this earth when he did not measure the quality of his life on a pain scale.

Good days were 2s, maybe a 3. Life seemed almost normal. A heating pad's warmth soothed minor aches and pains.

An 8 or a 9, on the other hand, put him back in the hospital, in severe pain all over his body, his spirit falling deeper into a familiar darkness that he sometimes felt would swallow him.

Davis, who lives in Colonial Heights, was born with sickle cell disease, a genetic red blood cell disease that affects about 100,000 people annually in the U.S., predominantly African Americans.

Symptoms include anemia, debilitating pain, organ failure, strokes — the list goes on. Every patient experiences this disease differently. For decades, treatments have been only reactive, usually when the patient is already in a lot of pain. Preventive therapies that could shut down production of sickle cells at the start — considered the "holy grail" for sickle cell disease — were elusive.

But a successful clinical trial at VCU Health involving gene therapy has potentially broken through that barrier.

The Children's Hospital of Richmond at VCU and the VCU Medical Center are now the only qualified treatment centers in Virginia offering a newly approved sickle cell therapy that uses an individual's own stem cells with modified hemoglobin genes to produce healthy red blood cells.

The groundbreaking therapy, approved in late 2023 for patients 12 and older, was conducted as part of a clinical trial for which VCU Health was selected as a test site several years ago. Those involved say they were chosen thanks to the sophisticated, multifaceted collaboration that exists between ChoR's pediatric comprehensive sickle cell center and the adult program at VCU Medical Center that addresses every age and phase of sickle cell, from newborns and children through the transition to adulthood.

The therapy works like this: Patients are given medicine that effectively knocks out their bone marrow, which triggers the bone marrow's defense mechanisms to produce more stem cells as quickly as it can. Those extra stem cells are collected and sent to a partner company that specializes in gene modification. While there, the patients' genes — those that create hemoglobin — are modified via the introduction of a virus.

The gene modification allows the cells to produce a new kind of hemoglobin that allows the cells to function as a healthy red blood cells. Those cells are then returned to Richmond, where they are given back to the patient through an autologous stem cell transplant.

Groundbreaking, life-changing — the descriptors do not nearly come close to the feelings that physicians, researchers and countless others are experiencing as they now watch and study the therapy's effects.

In short, all eyes are on Davis.

At 28 years old, he was a willing, if not indifferent, participant. From his perspective, he recalled, it was just another clinical trial. Nothing had worked to that point, yet he continued to experience pain in new parts of his body. He felt defeated and he was tired.

Tired of pain, tired of hospitals, tired of living.

What was one more trial, he remembers thinking. He had nothing left to lose.

THE TURNING POINT

Red blood cells carry oxygen throughout the body. Sickle cell disease occurs when a mutation in the DNA that produces hemoglobin — one of the building blocks of red blood cells — causes those cells to be sickle-shaped, like a half-moon or a crescent.

The sticky, abnormally shaped cells don't carry oxygen efficiently and form blockages within the body. Over time, that lack of oxygen affects everything from the brain down to the toes.

Sickle cell can affect anyone, though it is most prevalent in African Americans. One in 13 African American babies is born with the sickle cell trait and 1 in 365 has the disease, according to the Centers for Disease Control and Prevention.

Individuals can be carriers of the sickle cell trait and never experience symptoms. But if two carriers have a baby, the chance of that baby having sickle cell disease rises to 1 in 4. Symptoms from the disease typically start early, sometimes in babies only a few months old. As the children grow, so does their pain.

As recently as the early 1970s, the lifespan for individuals with sickle cell disease was a painful 14 years. Those who made it to adulthood faced grim realities: eventual organ failure, strokes, infections and blindness. As a result, sickle cell research took an unusual path.

Walter Davis is the first sickle cell patient in Virginia to receive a groundbreaking new gene therapy at VCU Health that could alter the future of care for patients dealing with the debilitating disease.

"It's one of the only places in medicine where breakthroughs happen in pediatrics and then trickle into adult medicine," said India Sisler, M.D., interim division chief and clinic director of the Division of Hematology and Oncology and medical director of the pediatric sickle cell center at CHoR. "Typically, you're going to make sure something is safe in adults before testing on a child, but because historically there hasn't been adult sickle cell care, a lot of what we know about sickle cell started in pediatrics."

In addition, historically underrepresented populations with little or no access to medical care are those with the highest instances of sickle cell, and that underscores the importance of addressing sickle cell as a disparity disease, she said.

"There's still a lot of issues with health disparities around sickle cell because it's not a disease that communities openly talk about," Dr. Sisler said. "Even among health providers today there are discrepancies with regard to care and treatment."

Wally Smith, M.D., director of the VCU Adult Sickle Cell Program and the inaugural holder of the Florence Neal Cooper Smith Professorship in Sickle Cell Disease Research, echoed those remarks.

He explained that sickle cell was discovered in parts of the world where malaria was present. It was a survival advantage, as those who carried the trait were believed to be less susceptible to severe forms of malaria.

In the U.S., sickle cell care and awareness began changing in 1972 with the passing of legislation called the National Sickle Cell Anemia Control Act. The law put key measures into place, including required screenings for newborn babies.

That same year, the Virginia Sickle Cell Anemia Awareness Program was established on the MCV Campus. Efforts were led by Richmond's own Florence Neal Cooper Smith, affectionately known as the "mother of sickle cell" in Virginia for her advocacy.

"We did a lot in the U.S. to make it so children could live," Dr. Smith said about the years following the legislation. Screenings offered a clearer picture of just how many people were affected. Infants and children were given penicillin. By the 1980s, hydroxyurea, a drug still used today, could reduce the number of pain episodes in sickle cell patients. By 2000, vaccines existed to nullify infections from other diseases in people who were at greater risk due to sickle cell.

In the last decade, bone marrow transplants — where bone marrow is knocked out by chemotherapy and replaced by donated stem cells — have increasingly been successful in treating patients with sickle cell disease.

Today, 95% of individuals living with sickle cell disease survive into adulthood. Those positive outcomes are driven by better treatment of the symptoms, but gene therapy offers promising progress toward a longterm cure.

The new therapy in trials at VCU Health still doesn't completely eliminate the underlying genetic causes, but it is a therapy on the cusp of revolutionizing sickle cell care.

In 1972, the Virginia Sickle Cell Anemia Awareness Program was established on the MCV Campus. Efforts were led by Richmond's own Florence Neal Cooper Smith, affectionately known as the "mother of sickle cell" in Virginia for her advocacy that largely led to the sweeping national legislation.

"It's space-age," Dr. Smith boomed. "It is a landmark — a turning point for man."

The therapy has also been approved for patients with beta thalassemia, a red blood cell disease in which the body does not make enough red blood cells. In those cases, the therapy has been approved for ages 4 and up.

VCU Health is a leader in sickle cell research and care, Dr. Sisler said, because of the collaborative nature of robust teams that work across the pediatric and adult health spectrums. That's transplant specialists, oncologists and pathologists, as well as nurses, social workers and more.

"We take a lifespan approach to care," she said. "We are already recognized for our expertise in sickle cell care and research, and this is just the natural progression that leads to being on the forefront of transformational therapies for patients."

Dr. Smith went on to say that CHoR and the VCU Medical Center expect to be named as qualified treatment sites for a second and different gene therapy, possibly later this year.

For the current therapy, there are approximately 30 qualified trial sites nationally, but as Virginia's only site, Dr. Smith said there are already patient referrals coming in from neighboring states.

Beth Krieger, M.D., a pediatric hematology and oncology specialist at CHoR, said the therapy doesn't yet work for everyone with sickle cell. If comorbidities exist such as a previous stroke, or their symptoms aren't severe enough and they haven't had enough qualifying pain events, patients are not eligible for the therapy. Qualifying pain events are those that bring patients to the hospital for pain treatment, including emergency room visits, or more serious cases, like when they're having trouble breathing or need blood transfusions.

There are many patients with sickle cell but not many treatment centers yet — or even enough of the therapies from the drug companies to tackle the current need.

"Figuring out how to get the greatest number of patients who qualify and are interested in the therapy is what we're concentrating on right now," Dr. Krieger said, and not just from Virginia or neighboring states. "We're thinking globally because the vast majority of patients with red blood cell diseases don't live here in the United States."

"My hope," she added, "is that every child in the future whose parents are interested in a curative therapy will be able to get it."

'HE SHOWED US THE WAY'

Thokozeni Lipato, M.D., an assistant professor in the Division of General Internal Medicine at the VCU School of Medicine, first started working with Davis as a young adult about 10 years ago when Davis transitioned from pediatric care at CHoR to VCU Health's adult program.

While the therapy is administered by the pediatric team, the adult program encompasses everything that follows, from medical inpatient and outpatient treatment to support services for mental and social health. Today, the adult center serves about 1,200 individuals.

What struck Dr. Lipato was how diligently Davis followed his medical orders when he was a child. In fact, Davis was so dedicated that his red blood cell count at one point was better than some patients who had received blood transfusions.

Walter Davis jokes with his coach, Scott Brown, during a recent workout session. Boxing and fitness were activities Davis couldn't do for a long time as he struggled with sickle cell disease. Now that he's healthy, he's making up for lost time.

"There was this light in him," Dr. Lipato said. "He was fairly symptomatic, but he still had all of his hopes and dreams. He wanted to have a normal life and he truly believed that was still in his future."

That light, however, went out.

As Davis entered his early 20s, his pain became more frequent and more severe. He was in and out of the hospital. He couldn't hold a job. Davis loved working out and being fit, but he couldn't because he hurt all the time.

"I saw him slipping," Dr. Lipato said.

Davis had been on narcotics for pain since he was 11. By the time he reached adulthood, he was physically dependent on the drugs, and that dependency was another medical condition.

"When the medication runs out, when the stress goes up, that physical dependency plays a role in how the pain manifests," Dr. Lipato said, adding while Davis's dependency was deep, it never reached addiction levels.

"But this cycle began, and his mental health just took a nosedive," Dr. Lipato said. "I saw that light go out and what you're left with is this young man in the hospital all the time, on a lot of pain medication."

Adding to the downward spiral was faith lost. No treatment had worked. For all his compliance, his willingness, his trust in his doctors, nothing was making him better.

"To his credit, he did everything we asked him to do and still, he fell into this hole," Dr. Lipato said.

But when the gene therapy clinical trial became available, Dr. Lipato said he immediately thought of Davis, who fit the criteria: He was young enough and symptomatic enough. But more importantly, Davis had always trusted his doctors and followed their orders.

Dr. Lipato asked. After weeks of consideration, Davis agreed.

The trial took about a year. Davis's stem cells were collected and shipped off to the partner company. After several months, they came back, and Davis was back in the hospital last spring for the stem cell transplant. Little by little, his red blood cell counts improved.

By last fall, his blood counts looked like a patient with sickle cell trait but not the disease.

He will continue to be monitored at VCU Health.

"He always thanks me, but I thank him," Dr. Lipato said. "We could only do this because he basically stood up and said, 'I'll do it — I'll be the first one.' What this has afforded VCU, and me personally, is really being at the forefront of

this revolutionary medical treatment, and we learned how to do it because he showed us the way."

Davis grins as he talks about his life now. His body feels good. He can work out and he's taken up boxing for exercise. He's thankful for medical teams in his corner who saw something in him when he was ready to give up.

"This takes a toll on you and your family — physically, psychologically, spiritually," he said. "But they saw me trying to fight and they told me to trust them, and now I'm doing all the things I wanted to do, that I thought I could do."

Davis isn't ready to say he's cured.

"But it is the closest thing to a cure," he said. "I had to think of the bigger picture because this therapy, it could not only help me but also other people, too, and I'm happy and proud to be part of that."

If you would like to learn more about how you can support sickle cell research at VCU Health, or make a contribution to the Florence Neal Cooper Smith Professorship, please contact Brian Thomas, the MCV Foundation's executive vice president and chief development officer, at 804-828-0067 or brian.thomas@vcuhealth.org.

"This takes a toll on you and your family — physically, psychologically, spiritually. But they saw me trying to fight and they told me to trust them, and now I'm doing all the things I wanted to do, that I thought I could do."

Walter Davis

follow-ups

Checking in with researchers on the latest developments

VCU Researchers Developing Affordable, Noninvasive Treatment for RDS in Newborns

A VCU team received a $3 million grant last year from the Bill & Melinda Gates Foundation to help develop an affordable, noninvasive treatment for respiratory distress syndrome that can be delivered without the need for complex medical equipment.

RDS occurs in newborns who lack natural surfactants — materials that reduce liquid surface tension, enabling carbon dioxide and oxygen to easily exchange as lungs expand and contract, oxygenating blood and facilitating the body's natural functions. Though treatable through external therapy, the current procedure's cost, complexity and invasiveness make it inaccessible to many who require it, especially infants in low- and middle-income countries.

The VCU-led team is developing an aerosol drug formulation and delivery mechanism for a synthetic lung surfactant capable of being delivered anywhere, with minimal equipment and at a reasonable cost. The effort is led by Worth Longest, Ph.D., the Louis S. and Ruth S. Harris Exceptional Scholar Professor in the Department of Mechanical and Nuclear Engineering in the VCU College of Engineering; Michael Hindle, Ph.D., Peter R. Byron Distinguished Professor at the VCU School of Pharmacy; and Rob DiBlasi, leading clinical researcher and principal investigator at Seattle Children's Research Institute.

"Some physicians regard aerosolized surfactant delivery as an obvious need in neonatal respiratory care," Dr. Longest said. "It's been envisioned for many years but has not been realized due to a number of obstacles."

Among the challenges is how to deliver an effective dosage of the aerosol formulation. Current dry powder inhalers require more air to operate effectively than can be administered to infants based on their smaller lung capacities.

Work is underway to refine the delivery mechanism, followed by validation using computational fluid dynamics and concurrent lab testing to explore different design alternatives. The goal is a high-efficiency rapid aerosol delivery product that can fully restore an infant's blood gas levels and be administered as a stand-alone therapy in less than one minute, or simultaneously during nasal continuous positive airway pressure (CPAP) therapy.

The proposed devices, strategy and formulation are also based on earlier and ongoing work by Drs. Longest and Hindle funded by the National Institutes of Health and profiled in the inaugural issue of *NEXT* in 2017.

— Leila Ungincius, VCU News

Featured in the Inaugural issue of *NEXT*, Michael Hindle, Ph.D., a professor in the VCU School of Pharmacy (front), and Worth Longest, Ph.D., a professor in the VCU College of Engineering. *Photo: Steinbrenner Photography*

VCU Celebrates 'One of the Best' Years for Its Growing and Renowned Research Enterprise

Research and innovation at VCU are making a huge impact not only on students, faculty, researchers and staff, but also on the patients and communities VCU serves locally, regionally — and now nationally and internationally.

P. Srirama Rao, Ph.D., vice president for research and innovation at VCU, drew a detailed picture of the university's growing stature in the quest for discovery — as well as the goals and challenges surrounding VCU's research enterprise — during his 2024 State of the Research presentation in April.

"The last year has truly been one of the best for VCU," Dr. Rao said, noting record enrollment, high research rankings and recognition as one the nation's top 20 public universities for innovation.

Dr. Rao's presentation detailed how VCU research is innovative, collaborative, ambitious and impactful. He praised the growth of undergraduate students in research as well as the investment in shared facilities that propel research. He noted how the number of VCU startups exceeds the national average for universities.

VCU research highlights from fiscal year 2023 included a 71% growth in awards from 2018, from $271 million to $464 million, and a national top 50 ranking of 47 for public research universities. Dr. Rao also noted the $5.2 million invested into VCU's transdisciplinary research institutes and centers such as the Institute for Women's Health, Institute for Drug and Alcohol Studies, Humanities Research Center and VCU's Medicines for All Institute.

"Some of these societally important issues — for example, women's health, addiction or research in the humanities areas, or rehabilitation — are areas of research that cannot be solved by any one discipline," Dr. Rao said. "You really need to bring people from different disciplines together, and that is what our research institutes and centers do."

— Dina Weinstein, VCU News

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