next

The Future of Discovery at VCU Health Winter 2023–24

Remote Control

VCU Health Surgeons Bring Robotic Surgery to Living Donors

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Transforming the Future of Medicine

Dear Friends,

As we write this note, the new year is on the horizon, and this is the perfect time for reflection, giving thanks and looking ahead with purpose and optimism.

We can think about the incredible work that researchers and care providers have accomplished to change health care, and we can look forward to the impact this work will make. Most of all, we can be thankful for how the work highlighted in this publication is making our communities and our world healthier places to live and thrive.

In this issue of *NEXT*, you can explore VCU Health's leadership in fully robotic transplant surgery. VCU Health is one of only three institutions in the country using the technique, and as its Hume-Lee Transplant Center applies the tool in living liver donation procedures, the VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health is working to extinguish the need for ever resorting to liver transplants in the future.

This issue also will open your eyes to incredible work being done here in Richmond that may stop metastases from occurring in cancer patients. It can show you how a new drug delivery method using nanoparticles can help corneal transplant patients avoid rejection and reduce the possibility of losing their eyes. And it will explore a seemingly ordinary tape patented at VCU that has created a new standard of care by binding and healing nerve damage using microhooks.

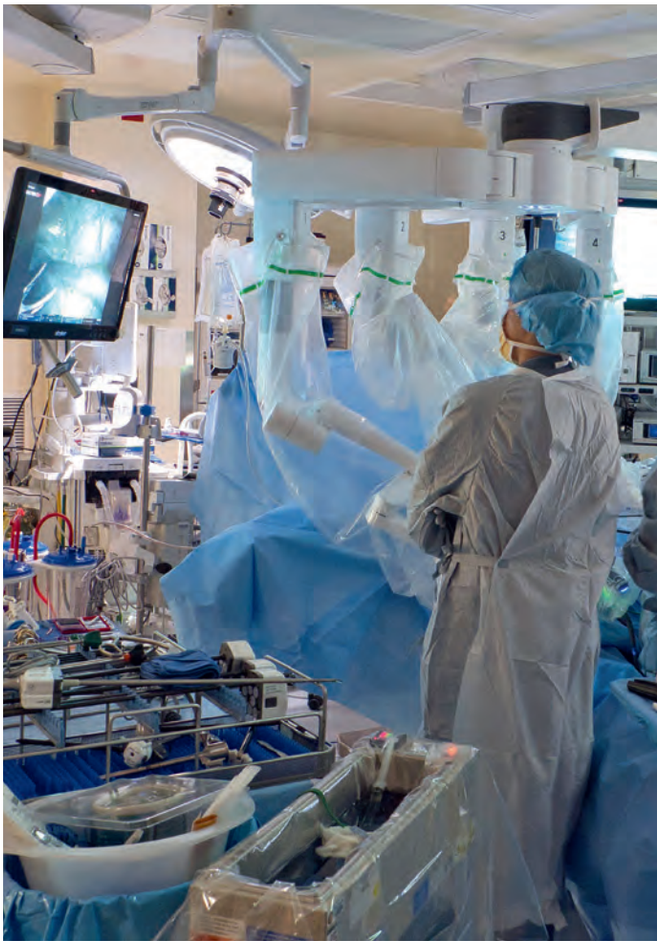
These incredible advances in science and medicine are changing the way people heal and receive care. We are proud to share these stories because we know and see every day that VCU Health is an invaluable engine for improving health for us all. Thank you for reading.

Sincerely,

Darius A. Johnson
BOARD CHAIR

Margaret Ann Bollmeier
PRESIDENT AND CEO

next WINTER 2023–24



COVER STORY

Redefining Metabolic Health

Early successes at VCU's Stravitz-Sanyal Institute for Liver Disease and Metabolic Health will help millions of patients who suffer from health issues related to the liver.

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

The liver is a powerhouse. The low-key, often overlooked organ handles essential functions such as detoxification, metabolism and nutrient storage. It breaks down toxins, aids digestion and produces bile to help absorb fats and fat-soluble vitamins. In short, the liver ensures the healthy functioning of other vital organs, like the heart, the brain and kidneys.

Although resilient, the liver is susceptible to various diseases, including fatty liver disease. Often, the warning signs come too late to reverse damage. As fat builds up in the liver, inflammation and scarring, or fibrosis, affect the liver's function in myriad processes for the body.

Left unaddressed, the scarring and inflammation progress to cirrhosis, making organ transplant the only option for patients. Transplantation is not a realistic solution to this issue because demand for liver transplants has grown steadily since 2012, outpacing the supply of available livers. Moreover, the prevalence of fatty liver disease, propelled by the increase in obesity and diabetes, also dwarfs the supply of liver donations, even with the ability to transplant a portion of a liver from a living donor. As many as 15 million people in the U.S. are affected by this form of advanced liver disease, and there are no approved treatments.

On the MCV Campus, clinician-researcher Arun J. Sanyal, M.D., has focused his career on better understanding and developing ways to address the growing problem of liver health. Dr. Sanyal is a professor in the VCU School of Medicine and director of the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health. Dr. Sanyal is internationally known for his work in the development of therapeutics for reducing liver disease around the globe. For years he has led a program in gastroenterology and hepatology that is ranked 17th in the world by *U.S. News & World Report*. He has won multiple national awards, such as the 2018 Distinguished Achievement Award from the American Association for the Study of Liver Diseases. He also founded the Liver Forum, which brings the U.S. Food and Drug Administration and European Medicines Agency together with academics and industry to facilitate drug development.

In September, ScholarGPS, which analyzes researchers and their publications worldwide based on productivity, impact and quality, gave a lifetime ranking to Dr. Sanyal as fifth among hepatologists overall. He was also ranked No. 2 among those specializing in liver disease. The ScholarGPS database covers more than 30 million scholars in more than 200 countries, and, according to the company, Dr. Sanyal has published 935 publications and been cited by other researchers more than 104,566 times. Dr. Sanyal's vision for the liver institute was a key inspiration for its creation in February 2022 following a historic and transformational gift from the Barbara Brunckhorst Foundation. A longtime friend and colleague, R. Todd Stravitz, M.D., gave $104 million through his family's foundation to fast-track Dr. Sanyal's vision for the liver institute. That funding will fuel research activity and treatment, as well as provide training for a future global network of liver health researchers and clinicians.

"The heart of this is the ability to transform the lives of people with liver disease around the world," Dr. Sanyal said. "With every new finding, you can impact a million people. That's what makes research so powerful."

A NEW NOMENCLATURE

Earlier this year, at an international liver conference in Vienna, Dr. Sanyal helped introduce a newly established naming and classification system for fatty liver disease. Over the years, this disease has been defined and classified by various terms, leading to confusion among health care providers, researchers and patients. This hindered effective communication and even research efforts to address complex liver disease comprehensively.

In 2020, multinational liver associations and patient advocacy groups convened a group to review naming and definition options for the stages of fatty liver disease. The names adopted in summer 2023 emphasize the metabolic underpinnings of the liver condition, aligning it more closely with its root causes, such as obesity or diabetes.

Fatty liver disease, now called steatotic liver disease, can progress to a more severe form, which involves liver inflammation and potential scarring, which can worsen into cirrhosis and perhaps lead to a liver transplant.

What was previously called nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (MASLD). The NIH estimates around a quarter of the U.S. population has both the hepatic steatosis and at least one of five cardiometabolic risk factors that define this condition. Similarly, metabolic dysfunction-associated steatohepatitis (MASH) replaces nonalcoholic steatohepatitis (NASH).

With clearer communication, tailored treatment plans and patient empowerment, health care providers, patients and the public can work together toward fostering a healthy future for all. The nomenclature also aims to remove perceived connections or stigma related to liver disease and alcoholism.

A NIMBLE, NONINVASIVE APPROACH TO SCREENING

The Stravitz-Sanyal Institute is leading a critical effort to develop noninvasive screening tests that would allow physicians to assess a patient's liver health without the invasive, surgical requirements of a biopsy.

MASH is often called a silent disease because patients do not display symptoms until later stages of the condition, when they develop cirrhosis. There are no FDA-approved treatments for the disease, which affects about 6% of the U.S. population, or around 20 million people. About 20% of those patients with MASH progress to cirrhosis.

Dr. Sanyal is leading a global consortium studying and developing noninvasive tests for liver disease, and his group has successfully demonstrated the effectiveness of five noninvasive tests, a significant milestone on the path to regulatory approval. In an article published this fall in the journal *Nature Medicine*, Dr. Sanyal and colleagues report on five biomarker tests that potentially could be given to patients who may have MASH.

The research to evaluate blood and imaging biomarker tests for liver disease is part of NIMBLE — the Noninvasive Biomarkers of Metabolic Liver Disease project, a public-private partnership involving the Foundation for the National Institutes of Health, the Food and Drug Administration, academic researchers and industry partners. Dr. Sanyal, who is the first author of the *Nature Medicine* paper, chairs the FNIH Biomarkers Consortium NIMBLE program.

Although several companies have developed such tests, none has yet met the requirements for FDA regulatory approval. Finding alternatives to liver biopsy is critical.

"Currently, diagnosing early-stage MASH requires a liver biopsy, which is a painful, invasive and expensive process for patients," Dr. Sanyal said. "MASH is a serious disease,

Arun J. Sanyal, M.D., is a professor in the VCU School of Medicine and director of the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health. Dr. Sanyal is internationally known for his work in the development of therapeutics for reducing liver disease around the globe. *Photo courtesy of the Stravitz-Sanyal Institute*

and once the liver starts to scar up, the risk of cirrhosis, liver cancer and death rises, often leaving transplant the only treatment option for patients."

The NIMBLE biomarker tests were compared to standard measures, such as the FIB-4, an index used to gauge liver health developed by Richard Sterling, M.D., clinical director at the liver institute and a professor of medicine in the School of Medicine's Division of Gastroenterology, Hepatology and Nutrition and its Division of Infectious Diseases. Each biomarker test that met or exceeded the performance of current lab tests was evaluated for use in diagnosing MASH and related conditions among the more than 1,000 patients who participated in the newly published research.

"This brings us a step closer to having simple blood-based tests that can be ordered in virtually any clinical setting and will provide access to care to patients," Dr. Sanyal said. "Such a step will facilitate our ability to identify those most at risk of outcomes and target them for therapy. It will also serve as a foundation for prognostic, disease monitoring and treatment-response biomarker development."

Having accurate biomarker tests for MASH is expected to encourage patients to participate in future clinical trials, which would otherwise require liver biopsies. Using noninvasive blood tests may also significantly reduce costs of such studies, increasing interest in drug development. Equally important, the tests could be easily ordered in a doctor's office.

"Dr. Sanyal's leadership of the NIMBLE project has been invaluable as we move toward our goal of fully qualifying noninvasive biomarkers through the FDA," said Tania Kamphaus, Ph.D., a co-author of the paper and leader of

"We are helping create a global community to shift the paradigm for liver health, so that our patients, both in Virginia and beyond, can get the care they need faster."

Arun J. Sanyal, M.D., professor, VCU School of Medicine, and director of the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

FNIH's metabolic disorders and patient engagement efforts. "The initial study findings demonstrate that these tests have the potential to enable breakthrough discoveries in developing new treatments for patients with liver disease."

WHAT'S NEXT?

Therapeutic interventions are an area of intense focused inquiry for Dr. Sanyal. There is a desperate need for treatments that can stop or reverse the progression of scarring in patients with metabolic dysfunction-associated steatotic liver disease. The FDA has begun considering potential approval for drugs to treat MASLD, and many investigators, including Dr. Sanyal, have been thinking beyond diagnosis, interventions and disease regression toward future therapies.

"There are a number of different approaches," Dr. Sanyal explained. "We are looking at the other recent drugs that target the same receptors of bile acids to improve the body's metabolic state. We're also working on very cheap, simple solutions, such as vitamin E. We published a paper 10 years ago in showing that vitamin E can reverse the disease in a significant proportion of patients. And we are now working with the NIH to do additional studies to make sure we get the dosing correct, which we plan to follow with a more definitive study."

In June 2023, he co-authored a paper with researchers at University of California San Diego regarding a drug called pegozafermin that mimics a hormone secreted in the body and showed that it could improve both liver scarring and inflammation in patients. Additional trials are anticipated for this drug. He also continues to work on clinical trials investigating resmetirom, a therapy that mimics a thyroid hormone receptor critical in healthy liver function and has shown the potential to reduce inflammatory liver fat and fibrosis while lowering cholesterol and other atherogenic lipids. Dr. Sanyal oversees one of the clinical trial sites evaluating the drug's effects.

"I'm incredibly proud of what we have accomplished, and we're only just getting started," Dr. Sanyal said. "We are helping create a global community to shift the paradigm for liver health, so that our patients, both in Virginia and beyond, can get the care they need faster."

If you would like to support Stravitz-Sanyal Institute research, please contact Niles Eggleston, VCU's senior associate vice president for medical philanthropy and alumni relations, at egglestonn@vcu.edu or 804-828-2112.

The Stravitz-Sanyal Liver Institute is building a global biorepository of liver samples that will enable researchers around the world to access and study liver case samples in collaboration. Michigan-based Cirius Therapeutics co-founder Jerry Colca, Ph.D., donated nearly 8,000 samples to build the institute's biorepository core. Jennifer Saynes, Ph.D., the repository manager, predicts it will quickly become one of the largest in the world.
Photo: Tyler Trumbo, MCV Foundation

Turning Off the Engines of Metastatic Growth

VCU Health researchers identify promising potential therapies for stopping the growth of metastasis in cancer patients.

By Paul Brockwell Jr.

Metastasis starts with a cancer cell's escape from a primary tumor and into the bloodstream. Over time, tumor cells land in other locations and form a cluster of new cells. Dysregulated cells continue to grow and wreak additional havoc by branching out, invading organs and tissues throughout the body.

The spread of cancer through metastases accounts for an estimated 90% of cancer deaths in patients with solid cancers, a grim statistic that has changed very little over the past 50 years.[1] The process almost always worsens a patient's prognosis because once cancer has embedded throughout the body, detection and treatment become inefficient and ineffective.

VCU researchers are working to understand the complicated protein interactions that drive tumor cell growth, and they've invented a molecule that shows great potential for stopping metastatic growth in its tracks. That goal has been the focus of research teams at the VCU Institute of Molecular Medicine (VIMM) and VCU Massey Comprehensive Cancer Center, which are developing novel ways of targeting the processes that fuel such unregulated cell growth and stopping the expansion of cancer cells before they take root in other parts of the body.

"Our interest and focus over the years have been to comprehend and define ways to attack metastases," said Paul B. Fisher, M.Ph., Ph.D., professor and previous chair in the Department of Human and Molecular Genetics at the VCU School of Medicine. "Achieving success in this quest has potential to directly translate into therapies for multiple types of advanced aggressive cancers."

Dr. Fisher holds the Thelma Newmeyer Corman Chair in Cancer Research at Massey. He founded the VIMM at the School of Medicine and has served as its director since 2008. He co-founded the Cancer Molecular Genetics research program at Massey and helped lead it for nine years. In 2017, Dr. Fisher was named a fellow of the National Academy of Inventors.

Along with Swadesh K. Das, Ph.D., an associate professor and key VIMM member, Dr. Fisher and the team have been exploring ways to interrupt the processes that drive metastatic tumor growth through inhibiting a specific pro-metastatic gene called melanoma differentiation associated gene-9, or MDA-9. When active, this protein plays a key role in driving metastatic growth.

"An intriguing and important property of MDA-9 is its ability to regulate many of the critical steps of metastasis in an expansive array of metastases originating from different organ sites in the body," Dr. Fisher said. "This property suggests that inhibiting the activity of this protein could in principle have broad applications in the therapy of multiple metastasizing cancers."

Drs. Fisher and Das noticed additional benefits to blocking MDA-9 in metastatic cells — doing so makes tumor cells more sensitive to a second therapeutic agent and makes the cellular environment more hostile to cancer growth.

"What's most exciting is that our preclinical studies confirm that inhibiting MDA-9 either genetically or pharmacologically can profoundly suppress metastasis," Dr. Das said. "Unraveling the mechanisms of this complicated process continues, but our ability to effectively target and treat metastasis to decrease patient morbidity and mortality has found a potentially powerful tool when targeting and inhibiting this gene."

Additionally, they were able to show that the MDA-9 gene regulates key components of the immune system and blocking MDA-9 increases sensitivity of cancers to immune destruction. This key research was done in collaboration with fellow faculty in the Department of Human and Molecular Genetics and VIMM: Xiang-Yang (Shawn) Wang, Ph.D., professor, associate director of immunology at VIMM and co-leader of Massey's Developmental Therapeutics Program, and Devanand Sarkar, M.B.B.S., Ph.D., professor, associate director of cancer therapeutics at the VIMM and Massey's associate director for cancer research training and education coordination.

ISOLATING A KEY METASTASIS PROTEIN

Dr. Fisher's team needed to find ways to effectively disrupt the cellular processes driving metastasis. They examined

By examining the genes and proteins mapped in the Human Genome Project and through direct laboratory and preclinical animal studies, the team established that MDA-9 is a critical protein in cancer progression and can affect a broad spectrum of different cancers.

the genetic information produced in growing metastatic melanoma cells vs. metastatic melanoma cells chemically induced to stop growing and revert to a noncancerous state, a form of cancer differentiation therapy. A molecular approach called subtraction hybridization identified the MDA-9 protein as an upregulated molecule associated with melanoma metastasis. By examining the genes and proteins mapped in the Human Genome Project and through direct laboratory and preclinical animal studies, the team established that MDA-9 is a critical protein in cancer progression and can affect a broad spectrum of different cancers.

"We proposed two simple hypotheses: first, could we identify the genes and proteins that might be critical in regulating various stages in the metastatic process?" Dr. Fisher said. "Most approaches have focused on one or at most a few of the key steps. However, in many instances, tumor cells may develop compensatory mechanisms avoiding single-agent therapies. By blocking multiple stages simultaneously, the tumor cells may fail to overcome inhibition. Accordingly, our second hypothesis was that we should look for proteins that regulate the metastatic process at multiple steps, thinking that if we simultaneously inhibit several key regulatory pathways, we could cut off multiple avenues controlling tumor cell progression to metastasis."

Metastasis is a multistep process involving several critical stages. First, a cancer cell must leave the primary tumor (intravasation), survive in a patient's bloodstream and begin to invade new tissues or organs (extravasation) before it grows and builds the cellular infrastructure to support the new tumor cell growth. An essential component of continued tumor growth and expansion is angiogenesis, or the development of new blood vessels.

A key to why targeting MDA-9 might be a more feasible approach to block metastasis than trying to block only one or a few of the stages comes from research indicating that MDA-9 is active in most, if not all, of the major stages of metastasis. Since one of its major functions is invasion, MDA-9 was considered a prime target for therapeutic interventions.

BLOCKING MDA-9 PROTEIN INTERACTIONS INHIBITS METASTASIS

The MDA-9 protein contains two similar PDZ domains, PDZ1 and PDZ2. PDZ domains are commonly found amino acid structures that play a key role as signaling proteins. These domains are essentially the temporary staging areas for organizing and maintaining complicated protein interactions that are needed to initiate transcription of the genetic code required for both normal and abnormal cell physiology. In a cell, they are construction sites for new growth and transformed properties of a cell. For a cancer cell, the problem is that these signaling domains are working from corrupted blueprints. Interrupting their functionality helps shut down the work site and inhibit cancer-associated and metastasis-associated processes.

Since PDZ domains with similar sequences are found in a vast number of proteins, it was considered unlikely that specific inhibitors of the MDA-9 PDZ domains could be identified. Put more simply, this protein was considered "undruggable." In collaboration, Drs. Fisher and Maurizio Pellecchia, professor of medicinal chemistry at the Sanford Burnham Prebys Medical Discovery Institute, La Jolla, Calif., where Dr. Fisher is a visiting professor, proved the protein was, in fact, druggable.

They employed a novel strategy, called fragment-based drug discovery (FBDD) informed by nuclear magnetic resonance (NMR), to identify small molecules that could bind specifically to the PDZ domains of MDA-9, but not similar PDZ domains in other proteins. This work resulted

in the identification of a first-in-class inhibitor of the MDA-9 PDZ1 domain, called PDZ1i (IVMT-Rx-1).[2]

When initially tested in brain tumor models, PDZ1i inhibited invasion of glioblastoma, prolonging survival, which was enhanced even further when combined with the standard-of-care radiation. It is worth noting the inhibitor identified by Dr. Fisher was included in studies published in *Proceedings of the National Academy of Sciences* and highlighted in the journal *Science* as a potential future drug for brain cancer treatment.

"The exciting part of identifying a potential small molecule inhibitor is that you can directly evaluate its biological and pharmacological properties to determine the possibility that this molecule might be progressed as a therapeutic agent," Dr. Fisher said. "After examining these aspects, our first-in-class PDZ inhibitor looked promising. The molecule was bioactive, nontoxic and had a long half-life in serum; it did not disappear after eight hours. Unfortunately, it was poorly soluble, suggesting that it could not be formulated without further modification to be used in a patient."

In preclinical animal modeling, PDZ1i was shown to be very active in inhibiting invasion and metastasis in a broad spectrum of cancers, including brain (glioblastoma), neuroblastoma, prostate, breast, liver and pancreas. The team's initial PDZ1 inhibitor looked promising and provided a proof of principle for drugging a specific MDA-9 PDZ domain; however, they needed to make it more soluble in order to be able to deliver the molecules where needed and to allow for detailed toxicology testing prior to human use.

Luckily, they had been introduced to a wet milling technique where ground up a large molecule with zirconium beads to make nano crystals with the same properties as the original inhibitor. The result was smaller and soluble molecules that could be used in an intravenous solution for human patients, with the hope of achieving the same results observed in preclinical animal models.

CREATING A DUAL INHIBITOR

Previous studies in the Fisher and Das laboratories suggested that both PDZ domains are necessary in defining the many attributes of MDA-9's role in metastatic cell growth. To address this challenge, the team created a novel hybrid molecule called IVMT-Rx-3 that binds to both domains and effectively blocks interactions with relevant cancer partner proteins.

"In principle, we hypothesized that this molecule might prove more active than a single PDZ domain inhibitor in maximizing disruption of MDA-9 protein signaling and many of MDA-9's pro-metastatic activities," Dr. Fisher said.

Stopping Metastasis by Blocking Protein Interactions with MDA-9

With robust expression in cancer cells and physical interaction with partner proteins, MDA-9 maintains activation of signaling pathways critical for multiple steps in metastasis. These include EMT (epithelial to mesenchymal transition), matrix degradation (secreted enzymes essential for cell invasion), migration, invasion, angiogenesis (new blood vessel formation), survival in circulation, adhesion to new cells/tissues, and immune escape. Collectively, these multi-signaling pathway activations result in metastases that are responsible for cancer-associated mortality. A novel molecule developed in the VIMM at VCU School of Medicine can help.

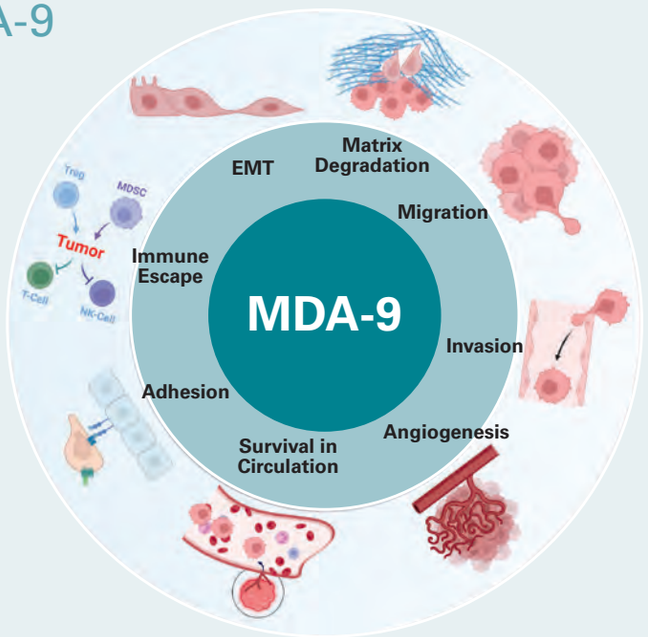


Illustration courtesy of the VCU Institute of Molecular Medicine

To test their solution and prediction, the team picked the gnarliest and most aggressive metastatic melanoma models that do not respond to the most advanced immunotherapies.

IVMT-Rx-3 has good pharmacological properties, does not show toxicity toward normal pigmented skin cells, blocks invasion of metastatic melanoma cells and is well tolerated and clinically effective in a preclinical animal model. An added advantage of IVMT-Rx-3 is its solubility in solutions that could potentially allow formulation for use in patients. By itself, IVMT-Rx-3 inhibited development of lung metastases by the aggressive and immune therapy-resistant B16 metastatic melanoma cells.

To further enhance therapeutic outcomes, IVMT-Rx-3 was combined with an immune checkpoint inhibitor, a type of immunotherapy that helps maximize the host's natural immune system activity by preventing, blunting or negating the immunological impact of the novel therapeutic molecules. This solution worked, allowing immunotherapy to be effective and eliminating metastatic growth in animal models with these more soluble molecules, resulting in repression of melanoma metastasis. But the benefits did not end there.

"In new follow-up studies, we noticed that blocking the MDA-9 gene or protein inhibits the ability to transport chemotherapy out of cancer cells," Drs. Fisher and Das said. "Accordingly, physicians may be able to use lower chemotherapy doses and combine them with MDA-9 PDZ inhibitor treatment, which retains the therapy in the tumor cell. These molecules synergize with existing standards of care and can effectively block metastatic growth by causing tumor cell death."

WHAT'S NEXT?

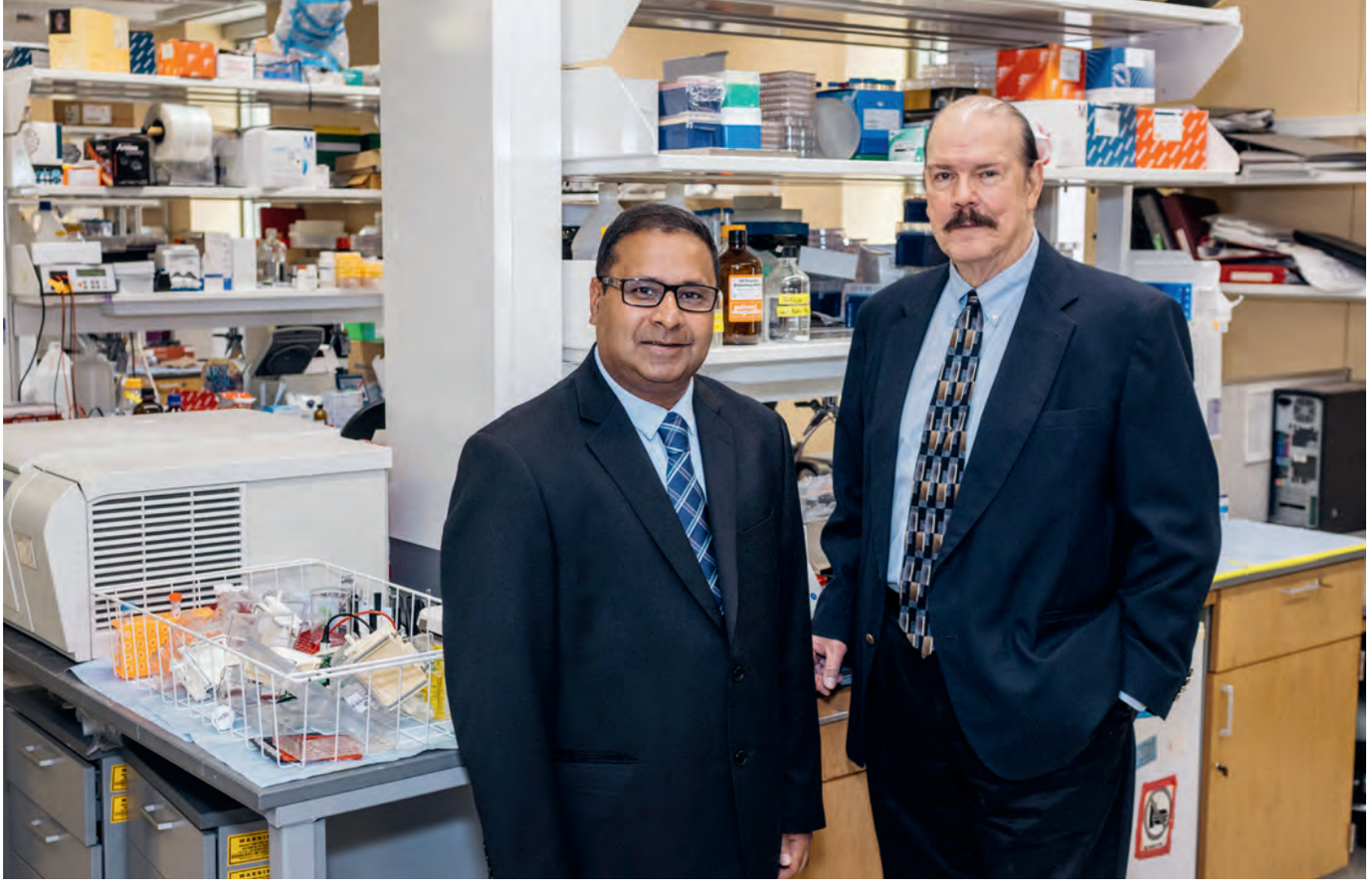
Dr. Fisher and his team hope to move this MDA-9 inhibitor treatment through toxicology studies to show that the biochemical properties are not harmful to patients and can be adjusted and translated into a clinical model.

The road to the clinic will ultimately involve detailed toxicology to define the safety of the small molecule and to identify combination strategies that can be translated into effective therapies for patients with advanced and aggressive metastatic and invasive cancers.

"We hope to advance specific MDA-9 PDZ inhibitors from bench to bedside to prevent and treat patients with metastatic cancers. The biggest gap in advancing small molecules is always doing this last part," Dr. Fisher said. "We're at a point where we do not think our treatments are toxic since they kill cancer cells indirectly through the immune system and by inhibiting other components of metastasis, but they need to undergo rigorous testing to ensure they're safe before early-stage clinical safety and future therapeutic trials can be performed with MDA-9 PDZ inhibitors in human subjects."

Additional limiting factors in advancing promising technologies into the clinic involve the costs associated with detailed toxicology, making patient-ready small molecules and performing the actual clinical trials. For the latter challenge, the team continues to work with VCU's Molecules to Medicine program, the VIMM and a biotechnology company, InVaMet Therapeutics Inc. (IVMT), to create and develop the molecules needed to continue their research. To accelerate the MDA-9 PDZ inhibitor program from bench to bedside, Drs. Fisher and Webster K. Cavenee formed IVMT with funding from

> "Combined with other available standard-of-care and new innovative therapies, we hope to provide powerful tools for stopping the spread of cancer as patients receive other treatments and a strategy that also attacks resident metastatic tumor cells."
>
> Paul B. Fisher, M.Ph., Ph.D., professor and previous chair in the Department of Human and Molecular Genetics at the VCU School of Medicine, and director of the VCU Institute of Molecular Medicine



VCU researchers Swadesh K. Das, Ph.D., and Paul B. Fisher, M.Ph., Ph.D., are leading teams that hope to create and test a theoretical universal inhibitor for the key steps of metastasis that would complement other standards of care to ensure better patient outcomes. *Photo: Daniel Sangjib Min, MCV Foundation*

private philanthropy and the National Foundation for Cancer Research. The current PDZ inhibitors, including IVMT-Rx-1 and IVMT-Rx-3, are exclusively licensed to IVMT to expedite translation of these small molecules from the laboratory into the clinic to treat patients with aggressive advanced cancers.

Their work with the new chimeric inhibitor IVMT-Rx-3 is gaining the notice of researchers around the world. *Molecular Cancer Therapeutics*, an American Association for Cancer Research journal of cancer drug discovery and preclinical research, highlighted this new compound as a "First Disclosure" of a novel therapeutic agent and also featured the lab's model for IVMT-Rx-3 mode of action on the cover of its October 2023 issue.[3]

"In principle, our new results support the feasibility of engineering MDA-9, dual-PDZ inhibitors with enhanced antimetastatic activities and applications of our novel molecule to a broader array of human cancer metastasis caused by an overexpression of this particular pro-metastatic gene," Dr. Fisher said.

Such a treatment could turn off the engines of metastasis and inhibit the ability of tumor cells to grow and spread throughout the body. With more research, Drs. Fisher and Das hope their teams may be able to test a theoretical universal inhibitor for the key steps of metastasis that would complement other standards of care to ensure better patient outcomes.

"We believe our small molecule inhibitors could be incorporated to help treat many different types of cancers," Dr. Fisher said. "Combined with other available standard-of-care and new innovative therapies, we hope to provide powerful tools for stopping the spread of cancer as patients receive other treatments and a strategy that also attacks resident metastatic tumor cells."

If you are interested in supporting this research effort at VCU Massey Comprehensive Cancer Center, please contact Jasmine J. Davis, senior director of development in the Office of Medical Philanthropy and Alumni Relations, at 804-484-4903 or jjdavis3@vcu.edu.

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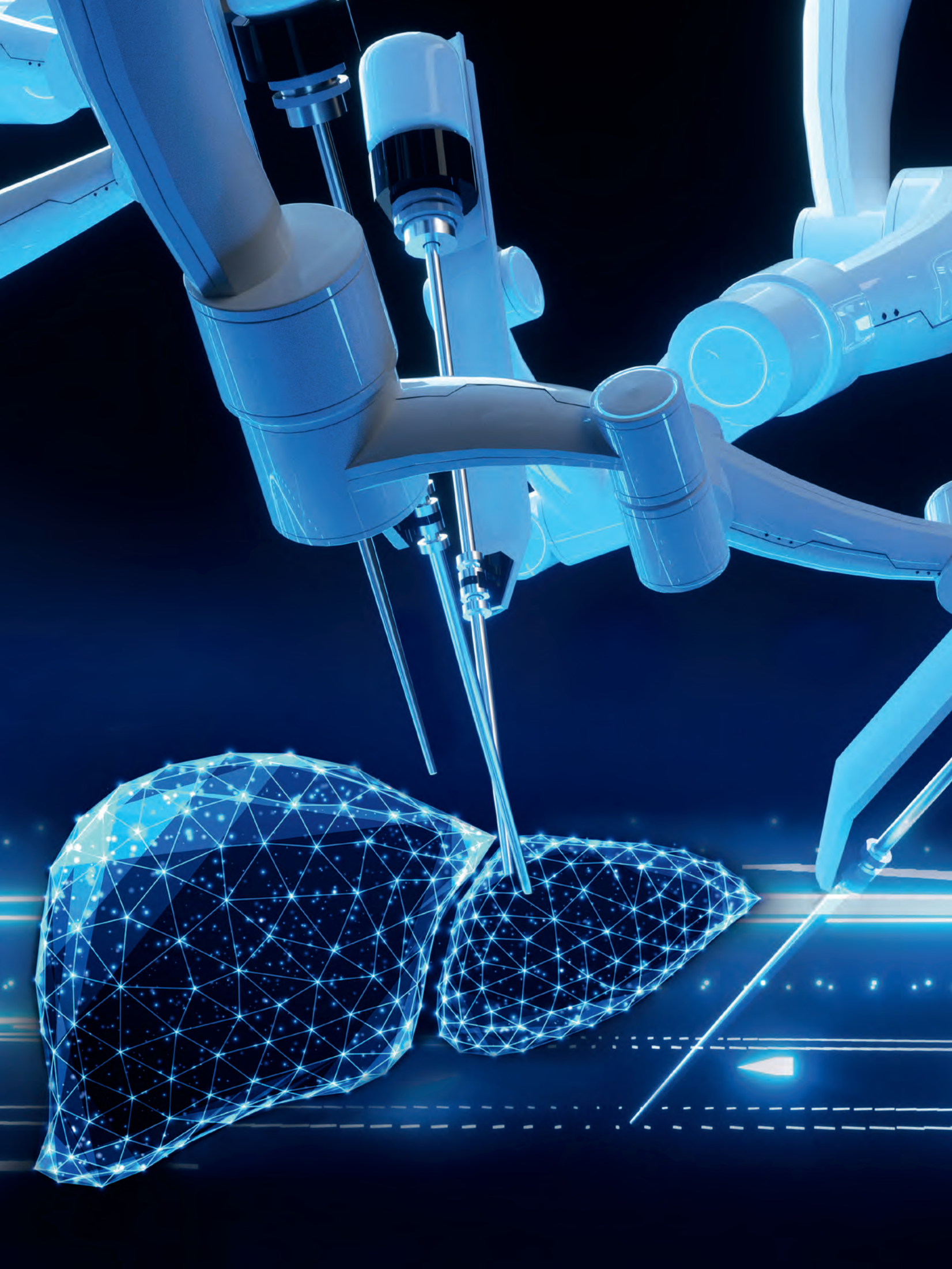
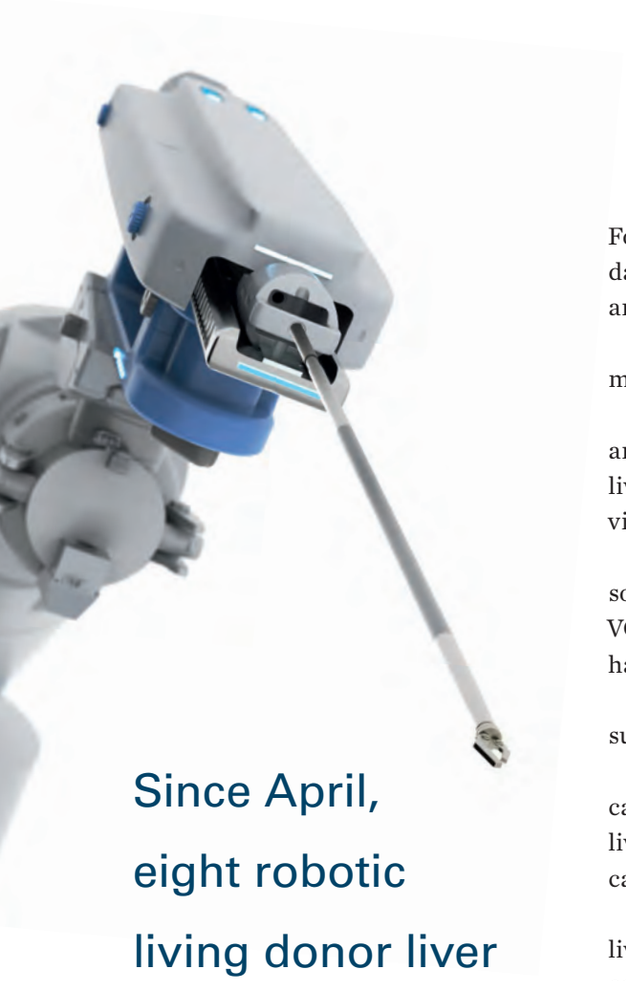


Remote Control

VCU Health surgeons bring robotic surgery to living donors.

By Holly Prestidge



Since April, eight robotic living donor liver transplants have been performed, making Hume-Lee one of only three centers nationally to perform such procedures and the only such center on the East Coast.

Four robotic arms extend like metal tentacles over the operating table inside a darkened operating room at VCU Health's Main Hospital, moving ever so slightly and seemingly at will.

The arms are fitted with thin removable rods, the tips of which hold tiny medical instruments — graspers, suction aids, needle drivers, even a camera.

Their insertion into a living human body via four small punctures initiates an hours-long removal of part of a healthy liver — the first step in a living donor liver transplant. And all of it is captured, thanks to that tiny camera, in wildly vivid, magnified detail on screens all around the room.

Remarkable in their complexity and dexterity, the robot arms are sleek and sophisticated, and their potential impact on living donor liver transplants at VCU Health — not just the critical care but also future research and education — has yet to be fully realized.

Still, the robots are nothing without a human touch, and the VCU Health surgeons leading this procedure are among the most highly skilled in the world.

VCU Health's Hume-Lee Transplant Center has reached the apex of clinical care for living donor liver transplants thanks to a relentless drive to treat more liver transplant patients, particularly those who historically have not been ideal candidates for liver transplants.

It is using robotic technology to do that. Since April, eight robotic living donor liver transplants have been performed, making Hume-Lee one of only three centers nationally to perform such procedures and the only such center on the East Coast.

"Robotic surgery" means surgeons control the robotic arms and their instruments to perform the partial hepatectomy, or removal of the right side of the liver. They manipulate the arms with incredible precision and accuracy from a console on the other side of the operating room.

Compared to traditional open surgeries, robotic procedures cut recovery time nearly in half, and result in fewer complication risks for patients. At an academic health system, the robot also serves as a powerful teaching tool. Add it all up, and VCU stands to offer liver transplants to a wider range of patients with better outcomes than ever before.

Fully robotic living donor liver transplants are the future. At VCU and Hume-Lee, the future is happening right now.

REINVIGORATING THE LIVING DONOR PROGRAM

The liver is the largest solid organ in the body, and its varied functions, from managing blood clotting and filtering toxins from the blood to helping with digestion, are crucial to good health. Liver disease encompasses a variety of conditions, including hepatitis viruses, autoimmune diseases, cancer and more.

The American Liver Foundation estimates that upward of 100 million people have some degree of liver disease, but many do not know they have it. An estimated 4.5 million people are diagnosed annually. Roughly 10,000 people with the worst cases of end-stage liver disease await liver transplants each year around the U.S.

In 2022, Hume-Lee performed nearly 170 liver transplants and it expects to surpass that number in 2023 with 180. The vast majority will be open surgeries and not robotic, but the goal — 100% robotic living donor liver transplants — is within sight.

VCU Health Hume-Lee Transplant Center team members watch on screens as robotic arms are used during a living donor liver transplant. The arms are controlled by surgeons at consoles nearby. *Photo: VCU Health Hume-Lee Transplant Center*

It is not a stretch for a health system that has led the transplantation field for decades.

David Bruno, M.D., interim chair of both Hume-Lee and the VCU School of Medicine's Division of Transplant Surgery, flashed a grin as he recalled stories of VCU's renowned transplant history.

He was recruited to VCU in 2019 but is quick to sing its praises as an institution with an illustrious, decades-long past, one that largely started with the transplant center's namesake, David M. Hume, M.D.

Dr. Hume successfully performed the first kidney transplant in 1957, and in the early 1960s, laid the foundation for VCU's current transplant program. Dr. Hume was later joined by Hyong Mo Lee, M.D., who added liver, pancreas and liver cell transplantation to the center's capabilities.

Decades later, in 1984, Dr. Lee, then president of the American Society of Transplant Surgeons, pushed for the signing into federal law of the National Organ Transplant Act. The law effectively outlawed the sale of human organs and established the basis for a national registry for organ matching, allocation and distribution.

The robotic elements of surgery came after human mastery of the field. In 2014, Hume-Lee launched a robotic surgeries system, using the technology to perform transplants for kidneys and other organs. By 2019, VCU Health had hit the gas pedal when it came to liver transplants. Hume-Lee established a minimally invasive surgery division with a goal of specializing in kidney, liver and pancreas transplants using robot-assisted and laparoscopic procedures.

The underlying intent was to jump-start what had become a stagnant living donor liver transplant program. The efforts were led by Marlon F. Levy. M.D., then the chair of the Division of Transplant Surgery and director of Hume-Lee, and now the interim senior vice president for health sciences at VCU and the interim CEO of VCU Health.

In addition to hiring Dr. Bruno, a noted pediatric transplant surgeon, the transplant center hired Vinay Kumaran, M.D., Hume-Lee's living liver donor surgical director, whose career includes more than 800 living donor transplant

Compared to traditional open surgeries, robotic procedures cut recovery time nearly in half, and result in fewer complication risks for patients.

surgeries. It also hired Seung Duk Lee, M.D., Hume-Lee's associate surgical director of liver transplants, who previously served as a living donor liver transplant surgeon in South Korea. There, such transplants are common.

The team got to work. To prepare for a 2023 launch of the newly invigorated living donor program, Dr. Lee and Dr. Kumaran traveled to South Korea in 2022. There, they observed surgeries performed by the world's preeminent liver transplant pioneer, Gi Hong Choi, M.D., of Yonsei University College of Medicine's Division of Hepatopancreatobiliary Surgery, who has performed more than 150 robotic surgeries.

Dr. Lee and Dr. Kumaran brought that knowledge back to the MCV Campus, where they successfully performed VCU's first and second robotic living donor liver transplants in spring of 2023. Their third and fourth surgeries, however, proved challenging. The physical size of one individual was a concern, and the other had prior surgeries. The team once again reached out to Dr. Choi in South Korea.

That summer, Dr. Choi visited Hume-Lee to aid doctors during those two procedures.

"It's very complicated and very difficult," Dr. Lee said of robotic liver transplants, noting that surgeons need to be highly skilled in open liver transplants before they can begin to train with a robot. "Our plan was to start very slowly and very safely."

His team spent months preparing to use the robots, and they started by performing hybrid procedures in which the healthy liver was cut both by robots and through open surgeries. Eventually the team advanced into using primarily robot-assisted procedures whenever possible.

"You're operating on a perfectly healthy patient, so the expectation is that they'll do well," Dr. Bruno said. "The most important thing about how we developed this program is that it's very measured and the patient safety comes first — there's zero room for error."

Robots offer benefits that open surgeries do not. Unlike human hands, which need to be steady, robots are tremor-

Doctors manipulate the robotic arms by consoles in the operating room during a living donor liver transplant at VCU Health Hume-Lee Transplant Center. *Photo: VCU Health Hume-Lee Transplant Center.*

"The most important thing about how we developed this program is that it's very measured and the patient safety comes first — there's zero room for error."

David Bruno, M.D., interim chair of Hume-Lee and VCU School of Medicine's Division of Transplant Surgery

free. The visualization from the camera allows images within the body to be magnified up to 10 times what the human eye can see.

"The camera can see around corners, and you can see up close and then zoom back out and see a larger perspective," Dr. Bruno said.

Unlike robotic surgeries, open transplant surgeries require large incisions to allow doctors to reach the liver with enough space to work to retrieve it. These larger incisions take longer to heal. Additionally, with open surgeries, cutting through layers of the main muscles in the abdomen — including accessory muscles for actions like breathing — means patients are put at risk for pneumonia and other infections.

But with robots, the four arms enter the body through four small punctures rather than a large incision. When the liver portion needs to be extracted, an incision is made that resembles a pregnancy C-section, just below the waistline. Patients report less pain, and scars below the waistline heal in about four to six weeks versus eight to 10 weeks. The smaller incisions also allow for minimal incision scars.

"The difference in the incision is so remarkable," Dr. Bruno said. "Less scarring means less injury and risk of infection, which ultimately means less morbidity."

But the robotic benefits do not end there. For academic surgeons, the new technology is the perfect teaching tool.

"These robots have side-by-side consoles so a student can watch as the doctor works at their console to control the robots," Dr. Bruno said. "In contrast, when I am teaching a fellow during an open surgery, I am not always sure they're seeing what I'm seeing. But with the robots, the views are the same — they are seeing the same views that I see during an operation."

Dr. Bruno said for now, robots are used only on donors. The recipients of a new liver are still treated through open surgeries. But the potential is there to eventually reach completely robotic liver transplants.

"The robot provides for all these things," he said, "innovation, apex clinical care and an outstanding educational component."

THE FUTURE OF SURGERY

Back in the operating room, Dr. Lee turns away from the console for a moment, stretching his arms over his head.

In all, he spends more than five hours peering into that console, which offers him a 360-degree view of the liver and the surrounding organs. With his hands, he deftly maneuvers joysticks while pushing pedals with his feet — each tap of his foot or turn of his wrist or push of a finger sends commands to the four robotic arms and tiny instruments.

Next to him, at a second identical console, is Dr. Kumaran, who watches from the same vantage point as his trusted colleague. They are not alone. For hours, physicians stand by the operating table as Dr. Lee sits at the console. The attending surgeons remove and reinsert the rods with the medical instruments as needed, sometimes every minute or so, per Dr. Lee's orders.

Not far away in another operating room, physicians and hospital staff prepare the transplant recipient to receive their new liver.

To support the VCU Health Hume-Lee Transplant Center, please contact Andrew Hartley, director of development in the Office of Medical Philanthropy and Alumni Relations, at 804-305-3055 or aphartley@vcu.edu.

Fiancée Becomes Living Liver Donor to Her Beloved Husband-to-Be

Shannon "Christ" (pronounced Chris) Harris' abdominal pain reached the point in November 2022 where he couldn't bend down to put on shoes. He and his fiancée, Jessica Garrett, thought it was a good idea to get checked out at a nearby Atlanta emergency room.

Once there, he was admitted overnight, and scans the next day revealed a likely diagnosis of hepatocellular carcinoma (HCC), the most common form of liver cancer.

"They said, 'You can't leave this floor,'" Harris said. He remained in the hospital and a week later, surgeons removed 75% of his liver in a procedure called a resection, in hope of removing the cancer along with the organ. The liver grows back within a few weeks.

The couple figured the worst was behind them. But a follow-up scan in March showed the cancer had returned.

"They told me the only way out was a liver transplant," Harris said. "They immediately referred us to VCU Health."

Shannon "Christ" Harris is an abstract artist. This artwork, titled GRAF, is the only painting Harris says he has completed since being diagnosed. *Photo courtesy Shannon "Christ" Harris*

Harris' diagnosis was later upgraded to fibrolamellar HCC, an ultra-rare form of cancer primarily occurring in young adults. Though transplantation is a method of treatment — due to a national waiting list of over 10,000 patients, a scoring system putting the sickest candidates at the top of the list and the fact he'd already undergone a resection — Harris would die waiting.

For Harris, a musician and abstract artist, the only viable transplant option was to find a living donor. Lucky for him, he didn't have to go far to find one.

"The second they said he could get a living donor," his fiancée, Garrett, said, "I wanted to go get tested."

A week after learning the cancer had returned, the couple made the eight-hour drive from Atlanta to VCU Health Hume-Lee Transplant Center in Richmond, where Garrett — despite having an incompatible blood type — was ruled a healthy living donor candidate for a partner she's known for a decade.

"The fact that she wanted to do the surgery is really the starting criteria for finding a liver donor," said Joel Wedd, M.D., Hume-Lee's medical director of liver transplant. "The matching process for livers is much less rigorous from a biochemical perspective than it is in other organs because the liver is a relatively immune-tolerant organ when transplanted. It still has risk of rejection, but it's not as high."

While the donor was lined up, the question of who would pay for the complicated surgery was not.

"This was a difficult, apex-level transplant case. We just don't see cases like Christ. His surgery was

Atlanta residents Shannon "Christ" Harris and his fiancée, Jessica Garrett, are all smiles following his liver transplant earlier in 2023 at VCU Health Hume-Lee Transplant Center. In helping her fiancé, Garrett was the fifth living donor to participate in a robotic liver transplant since April, making Hume-Lee the only center on the East Coast to perform such transplants. *Photo: VCU Health Hume-Lee Transplant Center*

so on the extreme edge of what we do — you typically don't transplant people who have had a resection, or recurrence after a resection," said David Bruno, M.D., interim chair and surgical director of liver transplant at Hume-Lee. "But from the moment I met him, I knew I was going to figure out a way to get this transplant done."

For almost two months, the couple and the Hume-Lee team went back and forth with Harris' insurance to make the case for covering the transplant. At this point, he was planning to move forward with radiofrequency ablation, a minimally invasive procedure that shrinks the size of tumors or other growths in the body, when Bruno received news that changed the trajectory of Harris' treatment plan.

Dr. Bruno's phone rang on a Friday afternoon when he was at a farm-supply store buying grease for his tractor. It was the medical director from the insurance company. With patient privacy in mind, he popped into an empty office at the store to take the call.

"I was anxious because we had gotten some denials. But I talked to the medical director, and he said he was approving it," said Dr. Bruno, his eyes welling up. "I remember getting really emotional about it. Being able to help someone like that is the greatest."

Since the June transplant, Harris and Garrett have remained in Central Virginia, renting an apartment in Old Towne Petersburg. He typically has follow-up appointments in Richmond on Thursdays.

Today, Harris is considered cancer-free. He'll be scanned every three months for the foreseeable future.

"It's kind of ridiculous how fast VCU Health got everything done," Harris said. "I don't think there's anywhere else in the world where we could have gotten that turnaround. Three months for a liver transplant is unheard of."

Father and son James (left) and Jim Busic benefited from the first robotic living donor liver transplant surgery at VCU Health Hume-Lee Transplant Center. *Photo: VCU*

A Son's Living Liver Donation Saves Father's Life

James "Jim" Busic and his wife, Michele, were awaiting the birth of their son last year.

But as a new life drew near, another life — that of the Long Island, New York, man's father, also named James — was at risk of being lost because of liver cancer.

Word came from doctors that James would need a new liver, and in November 2022 he joined a national waiting list where demand for organs outweighs supply.

People die every day waiting for livers, kidneys and other critical organs. But there is a way to avoid competing with the more than 10,000 patients on the national waiting list in need of a liver: find a living person willing to donate the organ.

With these statistics in mind, Jim immediately began the process of learning whether he could give his dad part of his own liver. Their blood types matched, which helps, but the same blood isn't required nor is it the defining factor for matching. After a series of tests — psychological exam included — specialists cleared him for living donation in March.

And not only did he save his father's life a few weeks later, but Jim also became the first patient at VCU Health

James Busic meets his newborn grandson, James. *Photo courtesy Busic family*

> "This was a journey, but it was a good journey. My future looks bright."
>
> James Busic
> liver transplant recipient

Hume-Lee Transplant Center to undergo surgery to donate a portion of his liver that was assisted by robotic technology.

THE ROAD TO RICHMOND

A Florida resident, James was diagnosed with cirrhosis in the early 1990s, and has lived with the stabilized condition since. But a diagnosis of liver cancer nearly three years ago compounded the condition.

By mid-2022, James' liver cancer was getting worse, and it was clear he would need a transplant.

On April 18, James was transplanted by David Bruno, M.D., interim chair of Hume-Lee and VCU School of Medicine's Division of Transplant Surgery.

Without a living donor, Dr. Bruno says, the 68-year-old would have been on the list for a long time, with risk of getting sicker growing daily.

"A living donor was the safest way to cure him from his cancer," Dr. Bruno said. "We're really embracing living donor surgery and looking for ways to extend it to everyone, regardless of how sick they are, or how old, or how many surgeries they've had prior — even if they've had a prior liver transplant. This is a surgery that saves lives."

Jim had his liver removed by the team of Vinay Kumaran, M.D., and Seung Duk Lee, M.D. Dr. Kumaran is director of living donor liver surgeries, and Dr. Lee, associate surgical director of liver transplant, has been working as a robotic surgeon for the last 10 years.

Jim found out only a few days prior to surgery that his procedure would be robotic, thanks to a slim build and healthy liver.

"I first met my surgeons, and as soon as you speak to these gentlemen — incredibly bright, incredibly professional — and you know they've done hundreds of these things, the confidence instantly puts you at ease," Jim said. "Whatever hesitations I had, they quelled it."

A 'RETURN ON MY INVESTMENT'

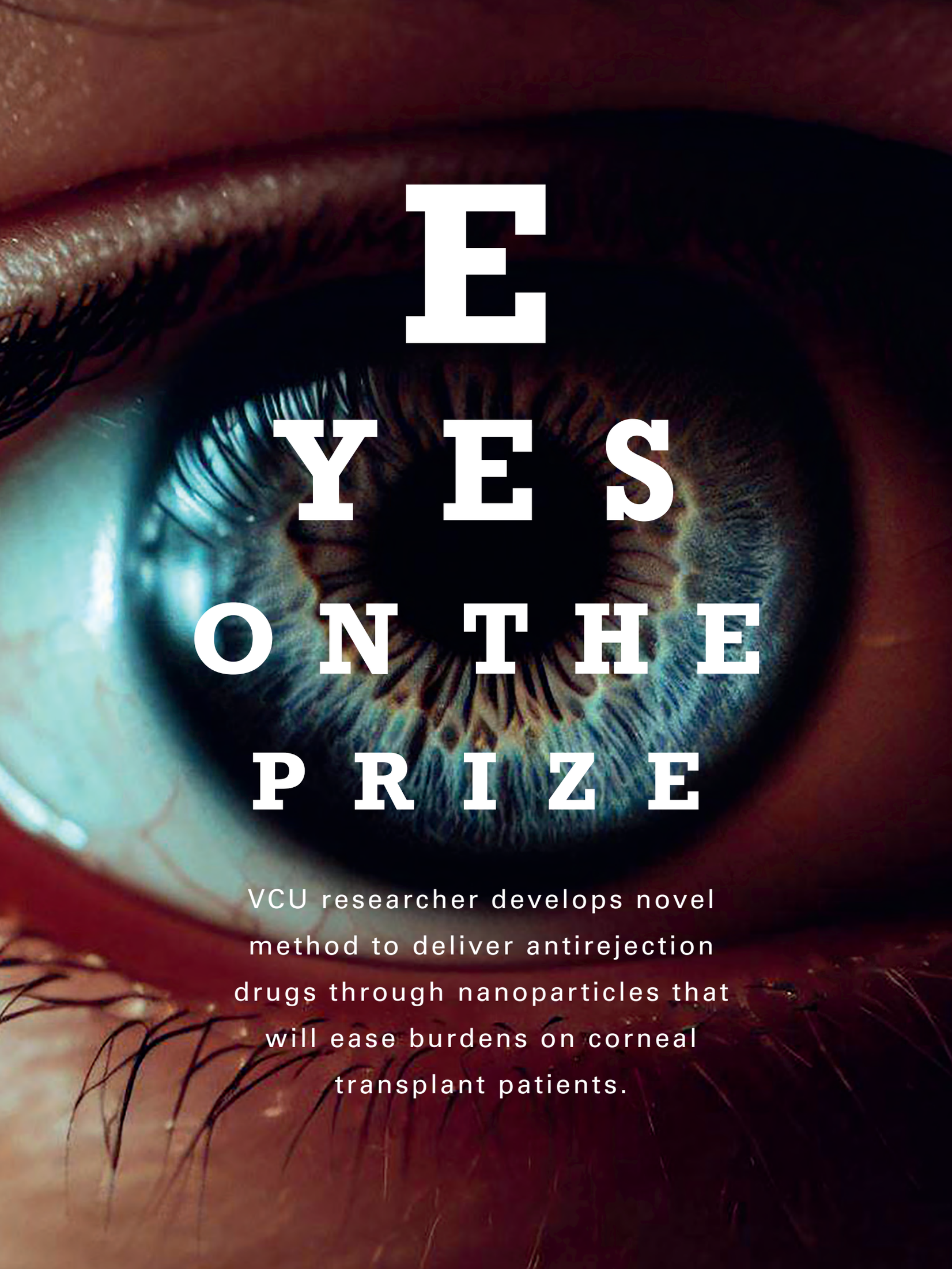
Jim and his wife, Michele, welcomed their son, also named James, in February 2023. The baby wasn't home long before Jim came to Richmond in March for a battery of tests that ultimately cleared him for surgery, and he was back at VCU for the surgery in mid-April. He stayed in Richmond for a month before heading home to Long Island.

Even with the demands of a newborn, "There was never a question of whether I'd do it," he said. "And my wife was supportive of everything."

Dr. Kumaran says long-term outcomes for the transplant look positive and that James' body likely won't reject the organ, in part because his donor is a family member.

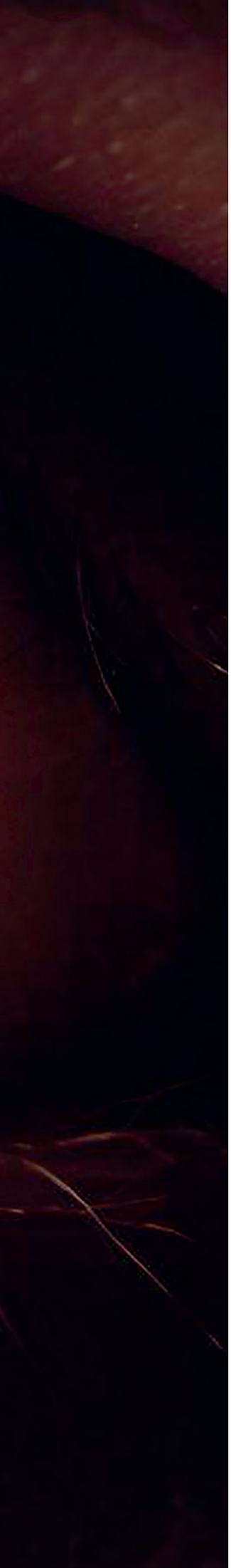
"Like I told everyone" James said, "expect me around for another 20 or 25 years."

"At least 20," Jim added. "I want a return on my investment."



EYES ON THE PRIZE

VCU researcher develops novel method to deliver antirejection drugs through nanoparticles that will ease burdens on corneal transplant patients.



By Holly Prestidge

The human eye is often called a window into one's soul. It's a miraculous organ that detects light wavelengths through tiny rods and cones and translates them into images that the brain processes via the optic nerve.

But sometimes, those windows get dry, dirty or damaged. And while eye drops often provide some relief, half of those drops will inevitably roll down our cheeks, across our eyelids — essentially, anywhere but our eyes.

It is a common annoyance for many people, but for corneal transplant recipients — who rely on eye drops following surgery — wayward drops are not just irksome, they could mean the difference between one transplant or two, maybe even three. With each rejected cornea, there are significantly higher rejection risks for the next transplant.

Through his now-patented delivery method, one VCU researcher aims to reduce the risk of corneal transplant rejection via nanoparticle injections that could dramatically increase transplant success rates.

Qingguo Xu, D.Phil., is an associate professor of pharmaceutics and ophthalmology at the VCU School of Pharmacy who specializes in nanotechnology drug delivery and eye diseases. He is the principal investigator of a study that uses an injection of nanoparticles to slowly release corticosteroids into the eye after corneal transplant surgery.

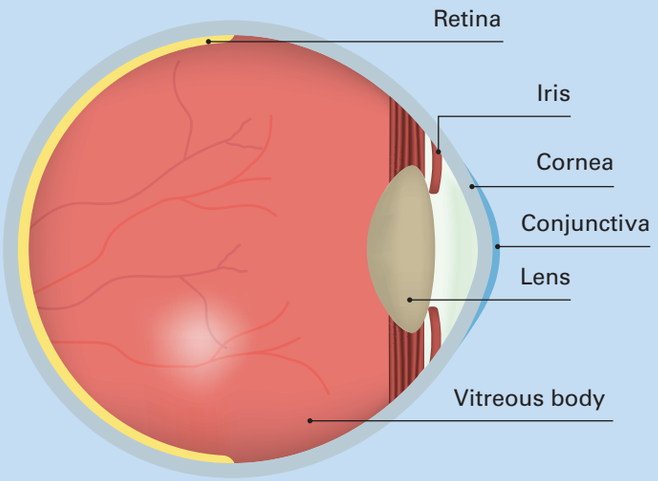
Dr. Xu, who was recognized for his exceptional early career work in 2019 with VCU's Blick Scholars award, collaborated with researchers in the U.S. and around the world, including Justin Hanes, Ph.D., of Johns Hopkins University, and collectively the team published a 2023 paper in *Science Advances* called "Six-Month Effective Treatment of Corneal Graft Rejection."

Corneal transplants are common, with more than 80,000 performed in the U.S. annually. The cornea is the clear, dome-shaped surface of the eye that is largely responsible for bending light into the retinas at the back of the eyes and supporting the eyes' ability to focus.

Transplants are needed when diseased corneas are no longer functioning properly. Depending on the severity and type of the cornea disease, a surgeon can replace a layer of the cornea or the entire cornea.

From a global perspective, the U.S. performs the most corneal transplants, thanks to an abundance of donated corneas and a well-established eye bank that offer them for both transplants and research. Today's transplant outcomes are largely successful for normal-risk corneal transplants, but a small number — roughly 5% to 10% of patients — experience rejections.

How It Works



Nanoparticles of antirejection medicine are injected between the clear outer membrane of the eye (conjunctiva) and the cornea. Dr. Xu's novel approach eliminates the need for repetitive doses of eye drops and reduces the risk of corneal transplant rejection.

Early signs of rejection can stem from the intense burden on patients following surgery. Normal treatment following a corneal transplant involves repeated eye drop dosing. For some, that means six to eight times daily, for weeks or months at a time. Others with a higher risk of rejection may need eye drops hourly during that same span.

Therein lies the problem, Dr. Xu said. Eye drops are challenging for many patients. Countless amounts of medicine are wasted when patients can't get enough of the drops into their eyes. But without the drops, their risk of corneal graft rejection increases.

"For some people, it's very difficult to use eye drops," Dr. Xu said, "And at six to eight times per day after transplantation, that's a huge burden."

Corneal transplants, while generally successful, do come with some risks, including infections, bleeding, even issues with the sutures used to secure the donated cornea. If the first transplant is rejected and a second is needed, the risk of rejection rises sharply to about 50% for that second procedure.

"That's a high-risk situation," Dr. Xu said. "If you have to get a second transplant, there is a good chance you might need a third, and eventually, you could lose the eye altogether."

Dr. Xu's novel approach cuts out the hassle of eye drops by injecting the medicine between the clear outer membrane of the eye (conjunctiva) and the cornea, an area, which can hold critical amounts of medicine.

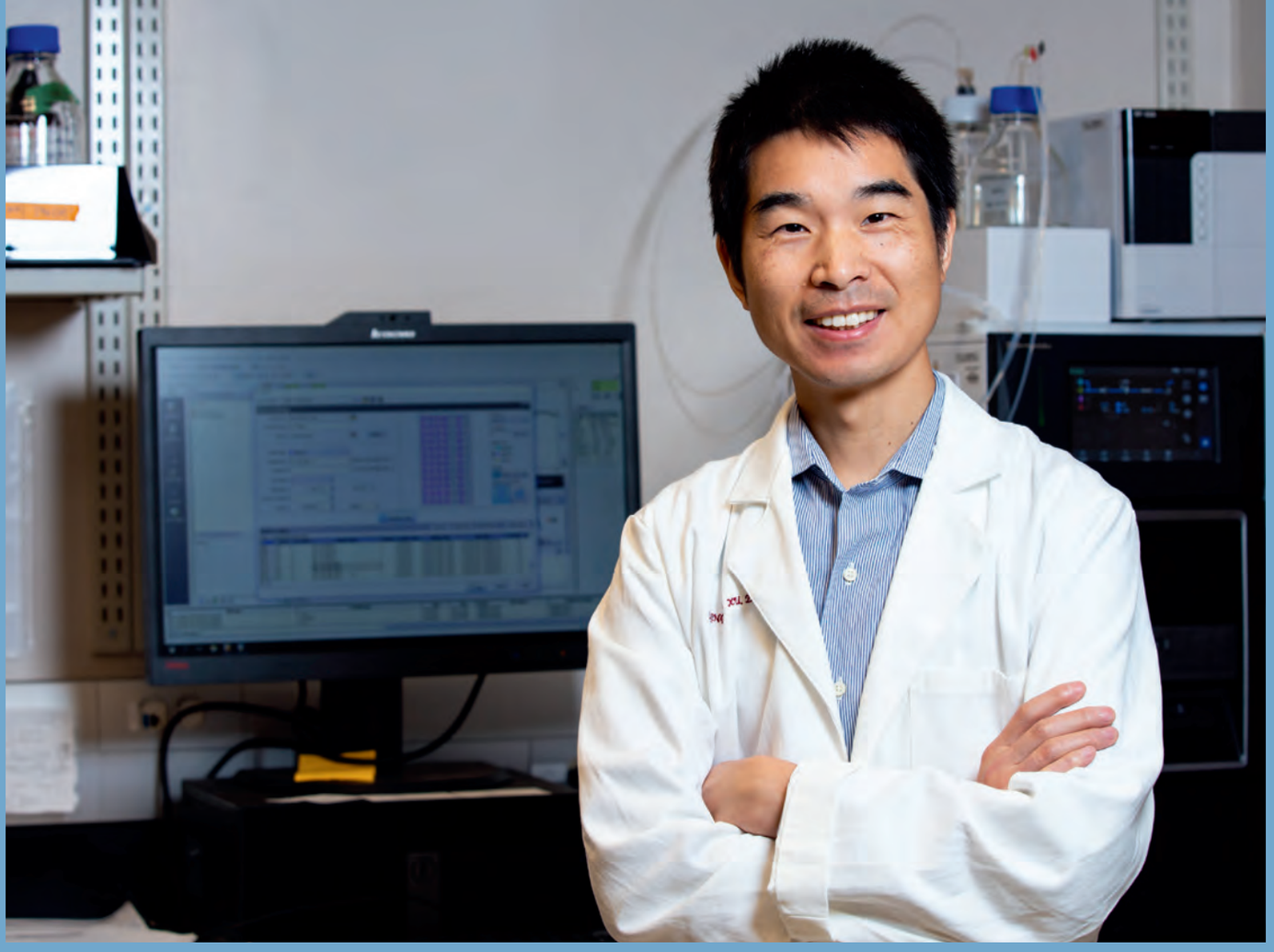
Thus far, he is seeing good preclinical results, which have shown six-month efficacy through using only a single subconjunctival injection next to the cornea. The slow release of the corticosteroids, combined with getting the medicine exactly where it is needed, effectively eliminates the need for frequent eye drop dosages.

The medicines used are already available and safe, he said. His study simply changes the delivery of the medicine to the eyes by encapsulating the antirejection drugs in nanoparticles, which help control the release of a commonly used corticosteroid over time. The benefit of this approach is that one injection is provided after the transplant surgery compared to several doses of eye drops a day.

"An easier treatment plan means higher success rates for patients," Dr. Xu said, "and fewer transplants overall."

The project is supported by $2 million in research project grants from the National Eye Institute, part of the National Institutes of Health. Dr. Xu also received VCU commercialization funding earlier this year to support the future clinical translation of ocular drug delivery systems for treating various eye diseases.

If you would like to support research at the VCU School of Pharmacy, please contact Louie Correa, the school's senior director of development, at lacorrea@vcu.edu or 804-828-3016.



Qingguo Xu, D.Phil., associate professor of pharmaceutics at the VCU School of Pharmacy, patented an approach to more effective and efficient post-surgical care for corneal transplant recipients. Dr. Xu is a former Blick Scholar. *Photo: Danny Tiet*

Fueling Innovation Through Junior Faculty Research

"The Blick Scholar award is a premier recognition for those junior faculty members who have been exceptionally successful in research."

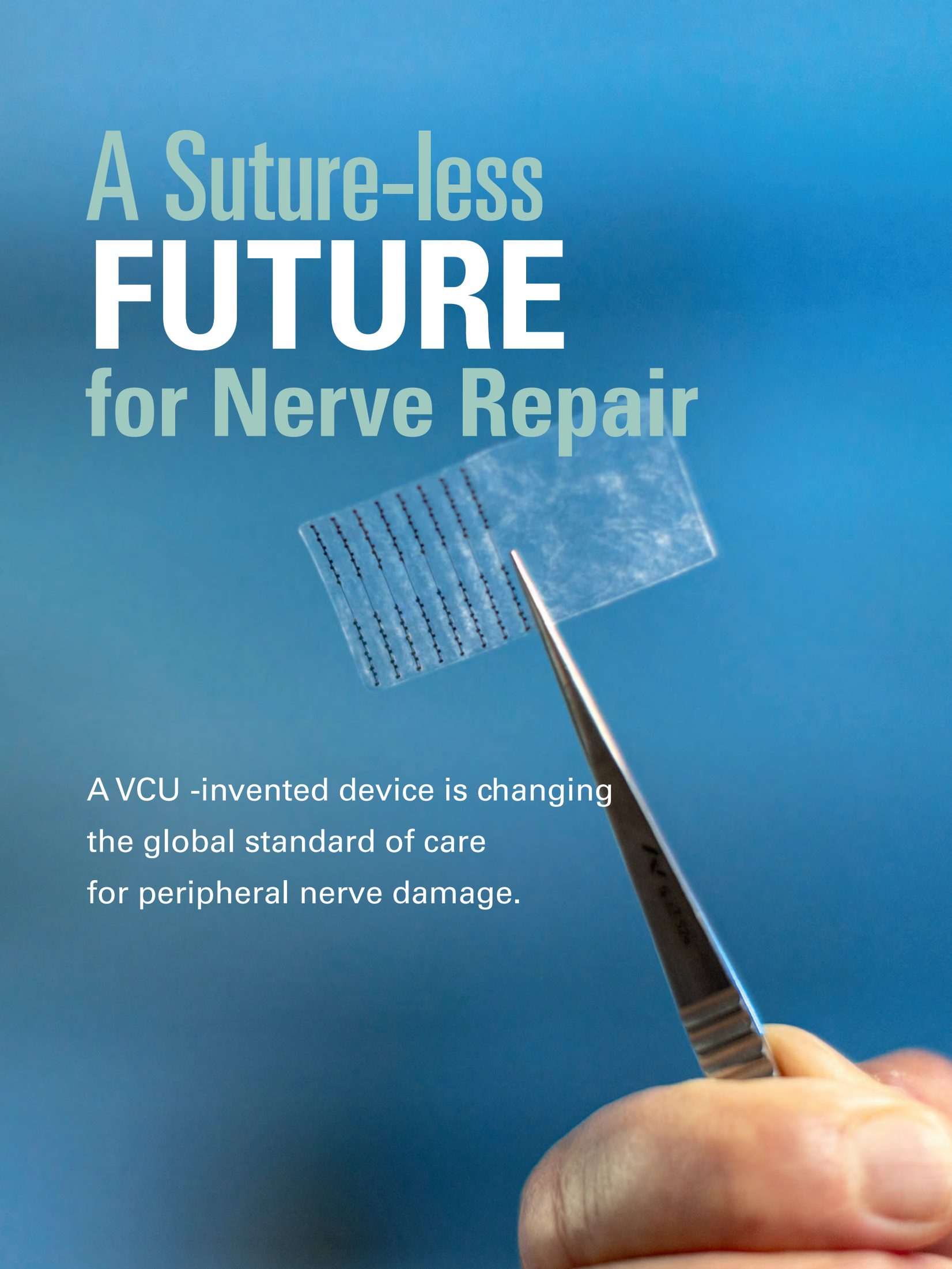
Marlon Levy, M.D., interim senior vice president for VCU Health Sciences and interim CEO of VCU Health System

Every four years, VCU Health Sciences selects four to six junior faculty members to become Blick Scholars, a prestigious award that honors and invests in their promising research.

The George and Lavinia Blick Research Fund was established in 2009 through a $2 million gift dedicated to research on the MCV Campus. Inspired by the care that her father and other loved ones had received at MCV and, later, VCU Medical Center, Lavinia Blick made the gift specifically to advance research across the academic health system.

"The Blick Scholar award is a premier recognition for those junior faculty members who have been exceptionally successful in research," said Marlon Levy, M.D., interim senior vice president for VCU Health Sciences and interim CEO of VCU Health System. "They are an extraordinary group. Without question, we are extremely grateful for the foresight of George and Lavinia Blick to establish this fund."

A Suture-less FUTURE for Nerve Repair



A VCU -invented device is changing
the global standard of care
for peripheral nerve damage.

By Zaynah Qutubuddin

One of America's favorite fruits is the culprit for sending more people to the emergency room than one might expect: the avocado.

Avocado hand, as it is aptly named, happens when a person holds an avocado to slice it and accidentally cuts through to the palm. In many cases, individuals end up cutting into nerves and other structures. Nerve injuries in general can result in degrees of disability ranging from isolated numbness in a single finger to devastating loss of function. In many situations, one might even lose all sensation in the fingers and thereby the ability to detect the temperature of a pot or use a smartphone.

Nerve damage can affect complicated environments throughout the body depending on the site of injury. But as one example, nerves in the hand are particularly difficult to repair. Three major nerves are woven through more than 30 muscles, 27 bones, and various tendons, ligaments and blood vessels. Each finger alone is supplied by four bundles of nerves and blood vessels.

An injury like avocado hand involves peripheral nerve damage, which can affect any nerves in the body that branch out from the brain and spinal cord. Repairing the damage requires the right combination of microsurgical skill and precise alignment of the cut nerve ends. Both are difficult to achieve, and good recovery following major peripheral nerve repair is just 50%. One VCU researcher is working to change that.

Jonathan Isaacs, M.D., a VCU School of Medicine professor and chair of the Division of Hand Surgery, set out 10 years ago to improve outcomes for nerve repair. His research has led to the invention of Nerve Tape, a patented device with microscopic hooks that creates a tube around nerve ends. The device allows for more precise alignment of nerve ends and mechanical repair strength equal or greater to clinical microsuture repairs. The result is an improved recovery for peripheral nerve injuries over the current standard of care.

"Microsutures are the conventional gold standard way to fix nerves, so we knew Nerve Tape had to be at least as good as that," Dr. Isaacs said. "And now, after all our testing and research, we know that Nerve Tape is a lot better."

The invention has received clearance from the U.S. Food and Drug Administration, meaning that its development partner, Atlanta-based BioCircuit Technologies, can market the product in anticipation of the first human use in the coming months.

Repairing the damage requires the right combination of microsurgical skill and precise alignment of the cut nerve ends. Good recovery following major peripheral nerve repair is just 50%. One VCU researcher is working to change that.

Nerve Tape (left) is a suture-less solution to repair transected nerves. The tape is wrapped around two nerve ends and the hooks bind to the nerve's outer connective tissues to align peripheral nerves with the goal of better nerve regeneration and clinical recovery.
Photo: Tyler Trumbo, MCV Foundation

"The development and clearance of Nerve Tape represent a significant advancement in the treatment of nerve injuries. This product has the potential to offer surgeons a faster, simpler method for achieving a precise, reliable repair of injured nerves."

Jonathan Isaacs, M.D., VCU School of Medicine professor and the chair of the Division of Hand Surgery at VCU Health Medical Center

"The development and clearance of Nerve Tape represent a significant advancement in the treatment of nerve injuries," Dr. Isaacs said. "This product has the potential to offer surgeons a faster, simpler method for achieving a precise, reliable repair of injured nerves."

RETHINKING THE GOLD STANDARD

Peripheral nerve injuries make up many of the more than 2 million upper extremity injuries reported in the U.S. each year. These injuries occur when there is damage or disruption to nerves that extend from the spinal cord and brain to the rest of the body outside of the central nervous system. They are often caused by trauma, compression, disease or inflammation.

When it comes to recovery of peripheral nerve lacerations, a patient typically has a 50% chance of limited or no return to normal function with conventional microsuture surgery.

"Even in the best-case scenarios, nerve injuries often don't do well," Dr. Isaacs said. "Despite our best efforts, we only have positive results half of the time, and this is after decades and decades of research in trying to understand how nerves heal."

Subpar outcomes are due to a multitude of reasons.

First, time. Nerves take a long time to heal at about a millimeter per day or an inch per month.

Second, the type of cut. The cleaner and more direct the cut, the better the repair. But a clean cut, like with avocado hand, is the rare, "ideal" scenario.

Third, the location of the injury. The farther the injury is from the site of the movement, the longer the healing process will take. In the case of muscles in the hand, a nerve injury at the wrist does better than one near the shoulder. The nerves at the wrist are closer to the hand and require less distance for the signal to travel from the injured location.

Finally, the surgery itself is complicated and challenging. Microsutures, the current gold standard of care, are thinner than human hair. They require steady hands to place precise stitches and properly aligned nerve ends, and a small number of surgeons have the specialized training necessary to perform such surgeries.

Properly aligned nerves are essential. Suturing nerves with too much of a gap allows for tissue growth between nerve stumps. Suturing too tight can result in nerves growing over each other. Both cause misalignment.

INVENTING A FASTER, BETTER STANDARD

In March 2023, Dr. Isaacs conducted a usability study of Nerve Tape at Massachusetts General Hospital in collaboration with Harvard Medical School in Boston. The study included some of the top microsurgeons in the country and six trainees ranging from mid-year orthopaedic residents to hand surgery fellows.

The group was tasked with completing a series of nerve repairs with microsutures that mimicked clinical scenarios while Dr. Isaacs and his team blind-judged the repairs based on alignment and time. For both groups of participants, the judges found that many of the microsuture repairs were suboptimally aligned, meaning that many of the nerve fascicles were overlapping or pointing in the wrong direction. This observation tracked with current data on outcomes. The microsurgeons had 60% acceptable suture repairs and trainees had 30% acceptable suture repairs.

The group then completed repairs using Nerve Tape for the first time. For both the advanced surgeons and the trainees, 97% of all repairs were deemed technically well aligned and acceptable. Timewise, the microsuture repairs took up to 15 to 20 minutes while Nerve Tape typically took about one to two minutes to apply. In the final phase of testing, the Nerve Tape proved to be two to three times stronger in repair. The study was submitted for publication and will be presented at the American Association for Hand Surgery meeting in January, where it has already been selected as the "Best Scientific Abstract."

"It's very promising data and this was the kind of study that gets us most excited that we are headed for success," said Dr. Isaacs, whose team worked through VCU Innovation Gateway to initially license the hooks to a company that specializes in making microneedles on metal discs that could be implanted into the muscle.

Nerve Tape's success is based on the microhooks made of nitinol, an alloy of nickel and titanium, which is super elastic — nitinol is flexible and prevents metal crimping that could affect or compress the underlying nerve tissue when used in Nerve Tape.

The nitinol hooks are attached to a biological backing that minimizes tissue adhesions, protects the repair site and prevents misalignment of nerve ends. During the procedure, the nerve stumps are placed on the microhooks that engage the outermost layer of a peripheral nerve. The tape is then wrapped around the nerve ends to allow for additional microhook engagement as it creates a secure tube that acts as a guide for nerve fibers to grow in the correct direction and in proper alignment.

Geetanjali Bendale, Ph.D., joined Dr. Isaacs' team at the time that Nerve Tape's ultimate design was

THE STATS

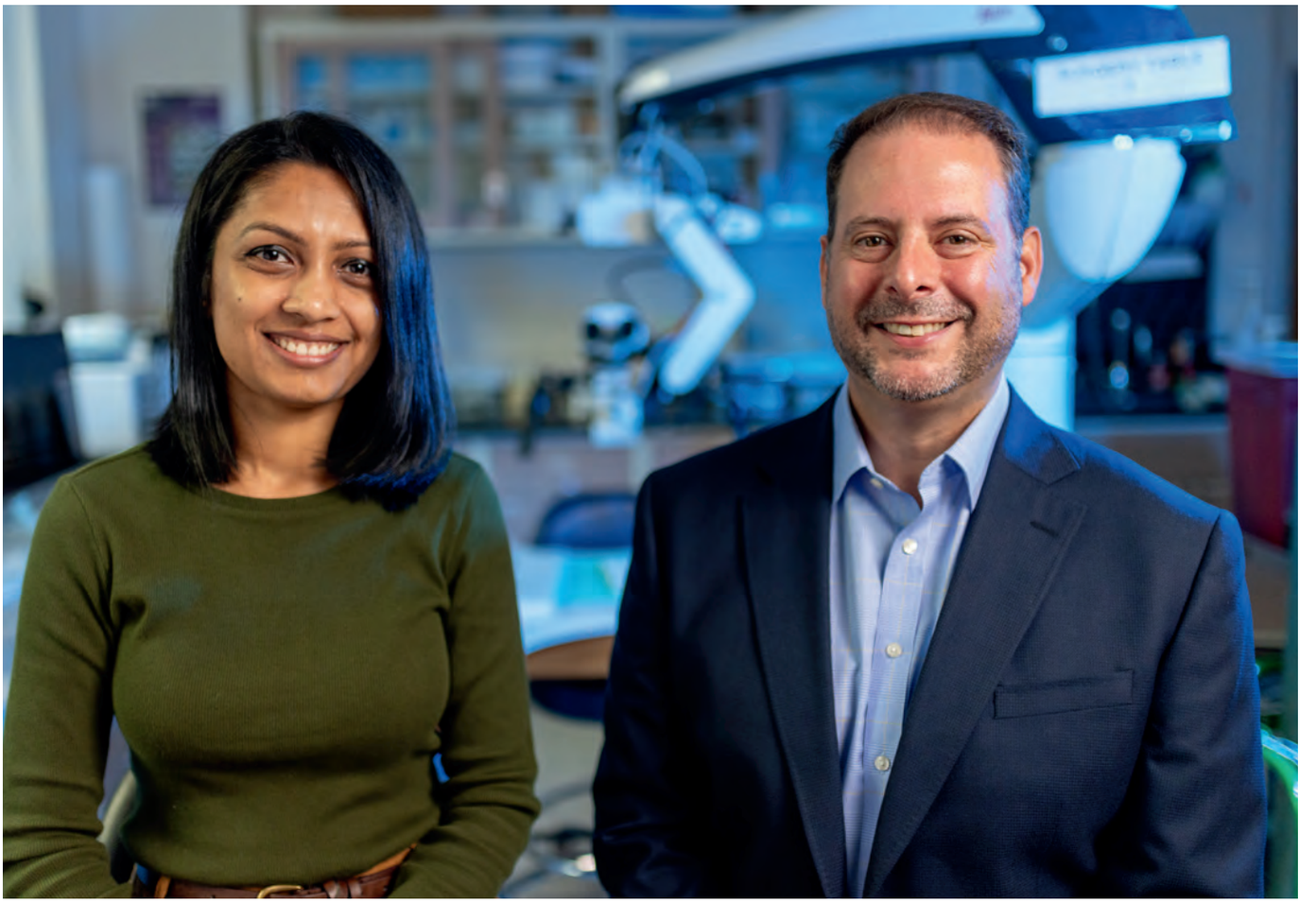
Preclinical study results showed a marked improvement in nerve repair outcomes.

60%

Acceptable repair rate by microsurgeons using microsutures

97%

Acceptable repair rate when using Nerve Tape



Nerve Tape was invented by Jonathan Isaacs, M.D. (above right), a VCU School of Medicine professor, orthopaedic surgeon and the chair of the Division of Hand Surgery at VCU Health Medical Center. His lab team includes Geetanjali Bendale, Ph.D. (left), a research scientist in the VCU Department of Orthopaedic Surgery. *Photo: Tyler Trumbo, MCV Foundation*

being finalized. As a research scientist and the main surgeon for Nerve Tape, she sets up experiments; analyzes data, histology and pathology; and writes papers to present.

Dr. Bendale said the most important element of nerve repairs is that the nerve ends should be well aligned, and any tension be distributed along the length of the repair. While the microhooks seemed to do this, it was also critical that the microhooks did not damage the underlying nerve fibers. She has completed countless suture repairs in the lab, and three out of 10 times is unhappy with the results despite having so much practice.

"With Nerve Tape, it's just quicker, easier and gives me more satisfaction," Dr. Bendale said. "I now think of repair success in terms of surgeon satisfaction. Surgeons who end up using Nerve Tape will hopefully have greater satisfaction in their repair."

WHAT'S NEXT?

Nerve Tape is just a few months shy of being available on the market and accessible to surgeons for clinical use. A soft launch is planned for early 2024 to include the Mayo Clinic and about 10 major academic medical centers around the U.S.

Once implemented, the hope is that Nerve Tape will be considered a tool that will not only allow for better results on nerve repairs, but also speed up surgeries, which will open operating room capacities for other surgeries. Because of its ease

of use, non-nerve specialists will be able to repair nerves without transferring to specialized centers. This will be particularly helpful in rural areas where there are no trauma hospitals nearby and could have potential future uses in military trauma care.

The research team has a grant from the Department of Defense for an ongoing research project to modify Nerve Tape to facilitate other treatments that might improve nerve regeneration. Additional research will continue to define repair parameters and determine different ways to apply Nerve Tape.

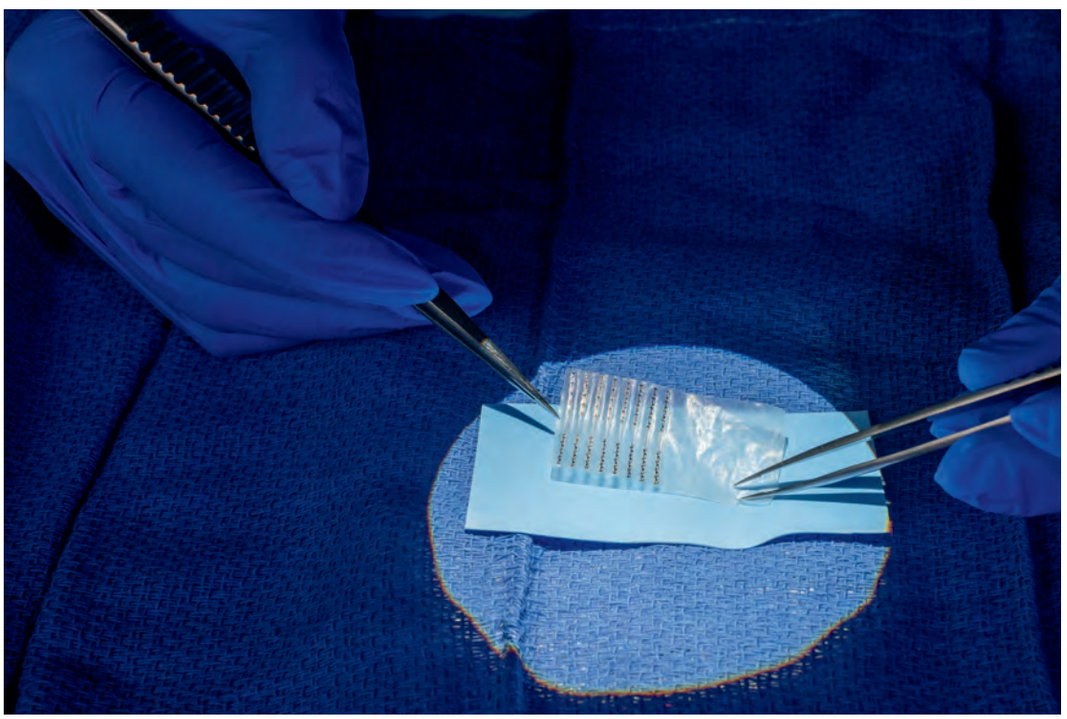
"People have talked about it before, but nobody has ever made something similar to the prototypes we have," Dr. Isaacs said. "Once we started thinking about it, we realized that there are many different ways to use microhook technology inside the human body to fix all sorts of injuries and improve patient recovery."

The myriad possibilities for Nerve Tape's application beyond nerve repairs are a sure sign this invention will be sticking around for a long time. Dr. Isaacs is confident that Nerve Tape can be used for a host of other nerve surgeries beyond the extremities such as maxillofacial surgeries and breast reconstruction surgeries for patients recovering from breast cancer.

"Nerves are my passion and will continue to be," Dr. Isaacs said. "And if this is as successful as I believe it will be, then this will certainly be impactful to patients around the world and VCU's national reputation."

If you would like to support this research, please contact Andrew Hartley, director of development with VCU's Office of Medical Philanthropy and Alumni Relations, at 804-628-5312 or aphartle@vcu.edu.

A soft launch is planned for early 2024 to include the Mayo Clinic and about 10 major academic medical centers around the U.S.



follow-ups

Checking in with researchers on the latest developments

VCU Sets Record for Sponsored Research Funding

Funding totaled $464 million in FY23, which is an increase of 71% over five years ago.

VCU announced the highest sponsored research funding in its history this fall, continuing its growing national distinction as a top urban, public research university. The latest institutional record of $464.6 million total sponsored funding for fiscal year 2023 marks a 71% increase over five years ago and a 14% increase since last year.

"I'm proud that research is one of the fastest areas of growth and impact at VCU. Thanks to our faculty and supportive leaders, we continue to set new records for our sponsored research funding and have risen in the national rankings as a top public research university," said VCU President Michael Rao, Ph.D. "Research is one of the most important ways that VCU as a public institution truly serves the public good. Research is a priority in every school — we're asking questions that vex society and finding answers that improve and lift lives."

In addition to more state funding for VCU's research portfolio, federal funding, in particular from the National Institutes of Health, has grown exponentially since last year, preliminary analyses show. Research funding grew in nearly every college and school on the MCV, Monroe Park and Qatar campuses.

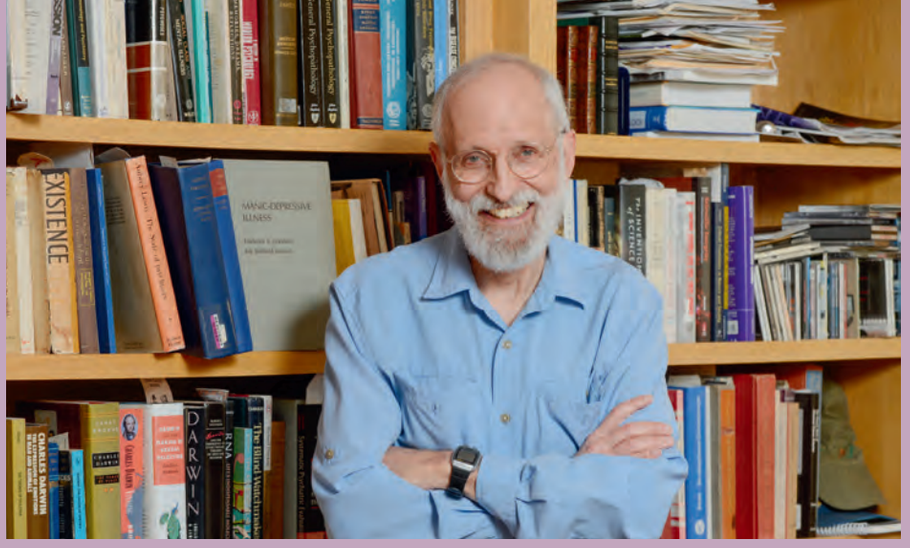
"In addition to the record sponsored research funding, our impact continues to grow at a rapid pace, reflecting VCU's deep commitment to knowledge creation and ability to conduct transformative research and innovation," said P. Srirama Rao, Ph.D., vice president for research and innovation.

The increase underscores the university's commitment to its One VCU Research Strategic Priorities Plan and its investments into four key research initiatives led by innovative and high-impact teams across its three campuses, which are designed to capitalize on VCU's growing national leadership in many fields of research and scholarship and accelerate transformative innovation.

"This increased funding and impactful research span the arts, humanities, social sciences as well as the STEM and health fields and will further allow our dedicated and talented faculty, fellows, staff and students to take creative inventions, ideas and innovations into the public domain — whether it is the community marketplace or from the bench to the bedside — to make a difference locally, nationally and globally," Dr. S. Rao said.

In September, the National Academy of Inventors announced that VCU ranked among the top 100 universities in the U.S. (86th) for utility patents granted, reflecting VCU's excellence in innovation and research. Last year, the National Science Foundation ranked VCU 50th among public universities nationwide for federally funded research expenditures.

— Mike Porter, VCU Enterprise Marketing and Communications



VCU's Kenneth Kendler Achieves No. 1 Lifetime Ranking Among Published Psychiatry Scholars

Analytics site ScholarGPS, which tracks more than 30 million scholars worldwide, says Dr. Kendler's work has been cited more than 125,000 times.

Kenneth Kendler, M.D., doesn't love attention — he says he finds it "a little embarrassing." But as a world-renowned researcher from his pioneering studies in psychiatric genetics, the VCU School of Medicine professor has continued to rake in the accolades throughout his decades-long career. The latest speaks to his legacy.

Dr. Kendler has long been among the top five most-cited researchers in the field, and in September 2023, he achieved the No. 1 lifetime ranking from ScholarGPS, which analyzes researchers and their publications based on productivity, impact and quality. The ScholarGPS database covers more than 30 million scholars in more than 200 countries, and the company said Dr. Kendler has published 1,299 works and been cited more than 125,000 times.

News of the No. 1 ranking did not come as a surprise, Dr. Kendler said, but it did mark an opportunity to share credit with the many collaborators who helped him achieve it.

"As is often the case with science, there is someone who gets to stand in the spotlight," Dr. Kendler said. "But there were many other people throughout my career who helped me get here, and I am so grateful to each and every one of them."

Throughout his 40 years at VCU, Dr. Kendler and his co-investigators have researched how molecular genetics, coupled with environmental factors, lead to psychiatric disorders such as depression, anxiety, eating disorders and substance use disorders. *NEXT* covered his research on identifying risk genes for depression in the inaugural issue. His collaborators include multidisciplinary colleagues at the School of Medicine, where Dr. Kendler is the Rachel Brown Banks Distinguished Professor of Psychiatry, and across the campus, including dozens of graduate students and postdoctoral fellows as well as scientists around the globe.

— Anthony DePalma, VCU School of Medicine

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