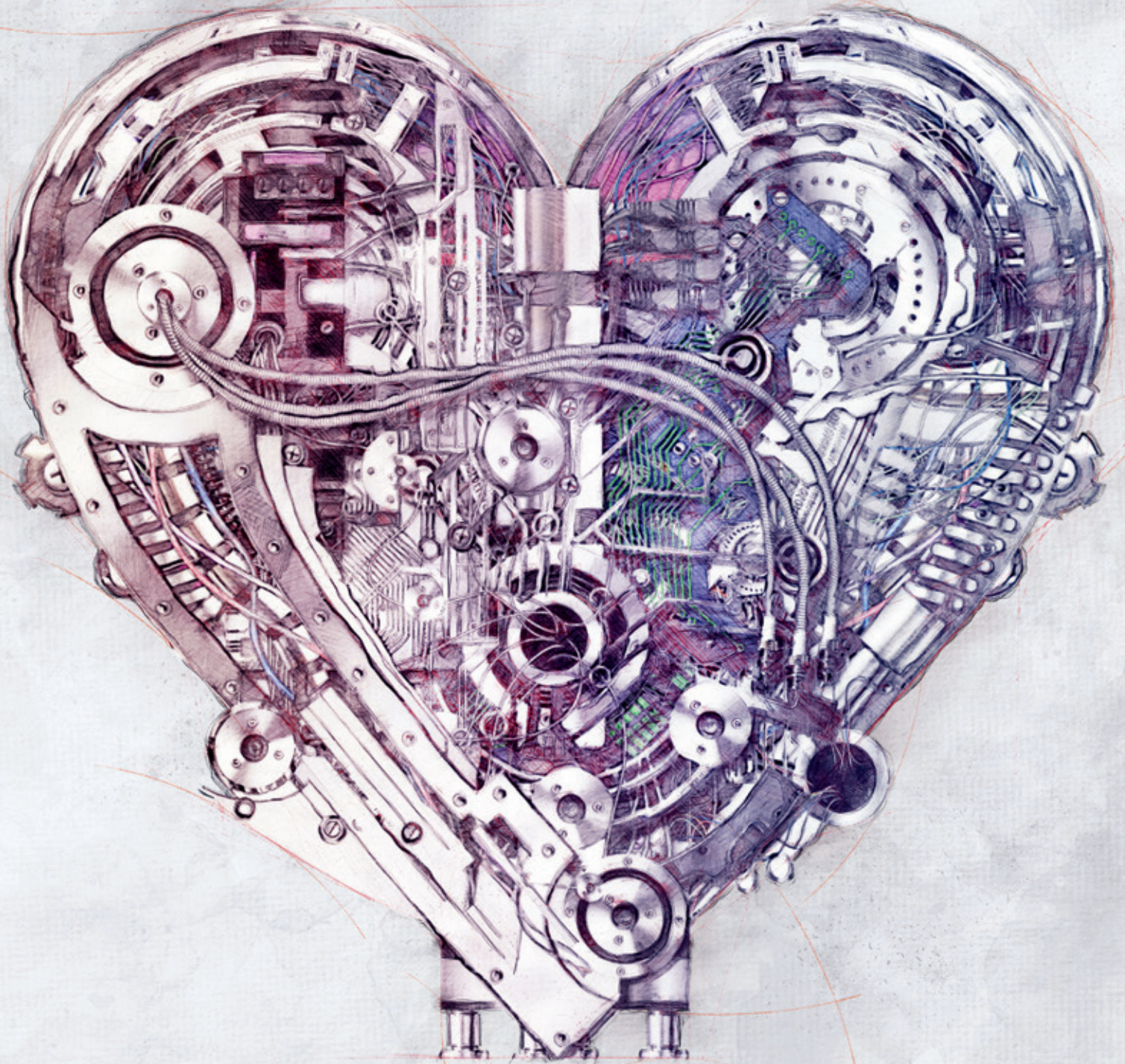


next

The Future of Discovery at VCU Health

Summer 2021



The Artificial Heart

A BRIDGE TO TRANSPLANT



Emerging from Crisis Stronger

Dear Friends,

Spring's arrival this year carried new hope and robust growth in research activity on the MCV Campus. As we began to emerge from the pandemic, many clinicians and researchers continued to advance their work in VCU Health's areas of strength. We're pleased to share some of those stories in our fifth issue of NEXT, and to highlight the innovative research that is changing the future of medicine here in Richmond and in the wider world.



Our cover story features groundbreaking advances in artificial heart technology and covers VCU Health's leadership in this area over the last 15 years under the guidance of Dr. Vigneshwar Kasirajan. We also explore exciting research at the VCU Massey Cancer Center from Dr. Saïd Sebt, associate director of basic research, whose lab is discovering and developing drugs to treat pancreatic cancers. Another researcher is working to commercialize a solution that helps buy critical time by stabilizing patients suffering from traumatic shock, and VCU's Pauley Heart Center is leading a global trial that gives patients with atrial fibrillation the ability to reduce dependency on blood thinners to manage their care.

A deep and authentic commitment to health equity runs throughout our efforts on the MCV Campus. VCU Health continues to be a leader in patient care and treatment development for sickle cell disease, a condition that disproportionately affects Black Americans. This record of support goes back 50 years and continues today with innovations in patient care through an adult medical home for patients and new drug discoveries that can help treat a disease which too many have forgotten.

Much of our early-stage research is made possible through the generosity of donors and friends who have experienced the benefits of a world-class academic health center in their community. In fact, we follow up on an article about Parkinson's disease research from the Spring 2020 issue. Initially supported by private foundation giving, the project has recently received funding from the National Institutes of Health to expand a study exploring how wearable technology can help reduce a common symptom that affects mobility and quality of life.

We hope the research and patient stories in this issue leave you inspired by the work of many to advance new knowledge and treatment in Central Virginia and beyond to ensure a healthier future for all. And if you do feel so inspired, we hope you will join us in the future to learn more about these discoveries through programs and opportunities to support the MCV Campus.

Wyatt S. Beazley IV
BOARD CHAIR, MCV FOUNDATION

Margaret Ann Bollmeier
PRESIDENT AND CEO, MCV FOUNDATION



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An abstract graphic on a dark blue background. It features a stylized human figure composed of glowing blue lines and dots, suggesting a network or molecular structure. A red ECG line runs horizontally across the middle. In the center-right, there is a glowing red heart shape, also composed of a network of lines and dots. The overall theme is medical technology and research.

Buying Time

One VCU researcher has discovered a solution that stabilizes patients experiencing traumatic shock and is pursuing commercialization of the lifesaving compound.



By Mary Kate Brogan

Untangling the effects of trauma on the body takes time, a precious commodity in short supply in the minutes after a car crash or a battlefield injury. In those harrowing moments, preventing the body from the ravages of traumatic shock is often the first major hope for survival. Keeping at bay the body's unfettered inflammation response is critical to ensuring patients do not deteriorate before receiving acute care — whether a few exits down the interstate or a flight through remote and mountainous areas across the world.

Time may not be often on the patient's side in these serious cases, but a solution discovered by one VCU Health researcher is showing promise for helping stabilize trauma victims after those harrowing moments and allowing them to be transported to the critical care they need.

When Martin Mangino, Ph.D., and his colleagues discovered a chemical compound while seeking a way to better preserve organs for transplants, he quickly recognized its potential to have other lifesaving uses.

Dr. Mangino, a professor in the Department of Surgery at the VCU School of Medicine, realized the synthetic solution that his team created using this chemical compound could help stabilize people in shock who are suffering from dangerously low circulation, whether it's from loss of blood, illness or another injury. The U.S. military, seeking ways to improve outcomes for soldiers facing battlefield trauma, quickly became interested in the solution's possible applications in the field.

This solution can help the body increase tissue perfusion — the microscopic distribution of blood flow into the body's tissues, including its vital organs, which enables oxygen exchange — in situations where a person is bleeding profusely or has a low volume of blood.

"When you lose a lot of blood, if you're out on a battlefield or you're on I-95 and you're bleeding out, you don't have blood flow getting to your tissues where oxygen exchange can occur," Dr. Mangino said. "What this compound does is, even under very low volume conditions, it pulls water out of the cells and puts it back into the capillary spaces, which increases tissue perfusion."

This stable, crystallized solution that Mangino's team discovered is called polyethylene glycol-20k IV solution or "PEG-20k." It's intended to be more portable, when used in small volumes, and stable so military field medics and emergency medical technicians can use it without refrigeration, unlike blood products. What laxatives do for the intestines — pulling water back to speed up the body's intestinal transit while keeping pressure stable inside the body — this solution could do for the bloodstream.

BETTER THAN BLOOD

When Dr. Mangino began developing PEG-20k for the U.S. Department of Defense, he expected it could work as well as whole blood. But in a paper published in 2020 in the *Annals of Surgery*,¹ lead authors Jad Khoraki, M.D., a VCU Department of Surgery

Photo: Allen Jones, VCU University Marketing

“PEG-20k buys you time, and it also increases the quality of the patient so that they’re in better shape when you deliver definitive care.”

Martin Mangino, M.D.
Professor, Department of Surgery
VCU School of Medicine

postdoctoral fellow, and Niluka Wickramaratne, M.D., a VCU Health surgery resident, found that PEG-20k significantly increased the rate of survival.

Dr. Mangino, a senior co-author on the paper, said that while the solution is not a blood substitute, it could significantly enhance the effectiveness of whole blood transfusions and help patients in life-threatening situations survive longer. As a result, a patient is likely to survive transport and arrive in better condition at a medical facility for definitive medical or surgical treatment. For armed forces members, where a field hospital could be hundreds of miles away, this could mean the difference between life and death.

“This buys you tremendous amounts of time,” Dr. Mangino said. “Instead of hours, it now buys you maybe close to a day to get somebody off that mountaintop [where they’ve been injured] and to get them to definitive care where they can undergo surgery and other resuscitation. So this buys you time, and it also increases the quality of the patient so that they’re in better shape when you deliver definitive care.”

Dr. Mangino has received more than \$12 million in funding from the Department of Defense since 2012 to conduct this research and is currently doing further studies on the solution’s potential uses for critical illness in the intensive care unit and for spinal cord injuries and traumatic brain injuries. The National Institute of General Medical Sciences, a division of the National Institutes of Health, has also contributed funding to his research projects on the basic microcirculatory mechanisms of action of PEG-20k.

HOW PEG-20K WORKS

When the solution is administered to a person in shock, it prevents oxygen-deprived cells from swelling by pulling water from the body’s cells back into the blood vessels to increase circulation. This helps the circulatory system deliver enough oxygen to the major organs when someone has lost a lot of blood.

On top of helping patients in shock, Dr. Mangino said the solution could have potential uses for patients with several other conditions, such as compartment syndrome, ICU care or other traumatic injuries.

When a limb is traumatized or crushed, it can cause dangerously low blood flow to that limb, followed by massive swelling that causes very high pressure in the sheaths that wrap the muscles together. The high pressure further prevents adequate circulation in the limb. This is called compartment syndrome, and it’s treated by cutting open the sheaths that bundle muscles together to relieve the pressure. In rare cases, if the pressure isn’t relieved, amputation may be necessary.

“The IV solution will draw the water out of the tissue and prevent the swelling without the need for an invasive surgical treatment,” Dr. Mangino said.

For people who have a traumatic injury to their spinal cord or brain, the solution can pull water out of the area that is swelling to reduce the likelihood of paralysis in spinal cord injuries and of lasting brain damage in traumatic brain injuries.

Sometimes, hospitalized patients can experience critical illness and septic shock from severe injuries and infections. In these situations, their blood has difficulty delivering oxygen to tissues, even when blood loss is not

a problem. Dr. Mangino said PEG-20k could help the body deliver oxygen to tissues more efficiently and improve patients' outcomes.

Loren Liebrecht, M.D., a postdoctoral scholar in the Mangino lab working on the project, developed the concept called "PEG-first," where a medic could give a patient polyethylene glycol solution first, and then the amount of whole blood the patient would need afterward is considerably less, Dr. Mangino explained.

"We see all sorts of uses for it," Dr. Mangino said of PEG-20k. "It can expand the blood supply so you don't need a lot of red blood cell products when you use it first. We need to do more experiments to actually determine the exact magnitude of the savings, but we can probably cut red blood cell product use in half by using polyethylene glycol first in certain settings."

'SEEMINGLY SIMPLE SOLUTION' COULD SAVE MILLIONS

When Dr. Mangino decided he wanted to pursue getting this solution into the hands of doctors and patients as soon as he could, he approached VCU's Innovation Gateway, a division of the Office of the Vice President for Research and Innovation, to help bring his solution to the public. Innovation Gateway decided the best path was to find an experienced entrepreneur to serve as an executive-in-residence to commercialize the product.

"VCU Innovation Gateway worked with Dr. Mangino for over eight years to find the right partner to commercialize this technology," said Magdalena Morgan, Ph.D., assistant director of Innovation Gateway. "To see this project licensed to a company and on the path to commercialization is deeply moving. Such a seemingly simple solution could save the lives of millions of people."

Now, Mangino and his business partner Gerard Eldering, a Virginia-based entrepreneur, have collaborated, creating Perfusion Medical LLC to bring the solution to market. Their company is starting the process of conducting trials necessary to get FDA approval for the solution to be available to patients.

"This solution has the potential to revolutionize trauma medicine, assisting in emergency situations where blood products are scarce," said Peter Buckley, M.D., dean of the VCU School of Medicine. "We are grateful for Dr. Mangino



A new synthetic solution, developed by Professor Martin Mangino, M.D., and VCU School of Medicine researchers, has the potential to help people in shock who are experiencing blood loss and other traumatic injuries. Photo: Allen Jones, VCU University Marketing

and his team's efforts over the past decade to engage in research that could help health professionals stabilize patients in shock."

Dr. Mangino said he's gotten feedback from surgeons who are eager to use the solution, once the FDA gives the go-ahead.

"It has such profound physiological effects that it can actually be better than blood," Dr. Mangino said, "because it attacks this basic molecular mechanism of what goes wrong during shock that even blood doesn't do."

If you would like to support Dr. Mangino's research, please contact Brian Thomas, vice president and chief development officer for the MCV Foundation, at 804-828-0067 or brian.thomas@vcuhealth.org.

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1. Khoraki, Jad; Wickramaratne, Niluka; Kang, Hae Sung; Xu, Haoxuan; Archambault, Caitlin; Blocher, Charles; Li, Ru; Liebrecht, Loren; Aboutanos, Michel and Mangino, Martin J. "Superior Survival Outcomes of a Polyethylene Glycol-20k Based Resuscitation Solution in a Preclinical Porcine Model of Lethal Hemorrhagic Shock." *Annals of Surgery*, July 2020; PMID: 32773641



Orphans

VCU Health's leadership in sickle cell disease care and research provides a national model for how to address disparities and quality of care.

in Need

By Paul Brockwell Jr.

“In November 2020, the National Academies of Science, Engineering, and Medicine formally declared sickle cell disease as a disparities disease.”

Wally Smith, M.D.
Professor and Scientific Director
VCU Center on Health Disparities



Wally Smith, M.D., professor and scientific director of the VCU Center on Health Disparities, directs VCU's Adult Sickle Cell Medical Home.
Photo courtesy VCU Public Affairs

The trouble usually starts around six months after birth. By that point, children born with sickle cell disease have stopped producing fetal hemoglobin, and the first symptoms begin. Hemoglobin is the oxygen-carrying protein inside red blood cells. In sickle cell disease, a minor DNA mutation produces red blood cells that have sickle hemoglobin, an abnormal hemoglobin that cannot carry oxygen as well as regular hemoglobin. When it releases oxygen, sickle hemoglobin proteins link together to form long, unbendable polymers inside the red blood cell. These polymers stretch the red blood cells out of their usual donut shape into abnormal sickle or crescent-shaped cells that no longer move through the body's blood vessels, slowing and stopping blood flow.

Chaos ensues all over the body. Organs no longer receive oxygen. Pain begins, and sickled red blood cells break open and die, spilling poisonous waste into the body. This vicious cycle continues. Less oxygen means more hemoglobin polymers, and in turn more clogged blood vessels, more red blood cell death, more pain and more anemia. Eventually, massive tissue and organ damage and a weakened immune

system shorten the lifespan of many patients who experience painful crises that become chronic, with frequent emergency room visits, failing organs and a sense of helplessness.

For too many years, the medical community and society abandoned these patients who, in the U.S., are predominately Black. Many doctors threw up their hands and told children and parents not to worry about making life plans or attending school, since they likely would not live long past their 20th birthday. Those lucky enough to survive were told there was little to do for them other than to give them opioids. And doctors were also stingy with opioids, leaving patients in pain for fear of turning them into addicts. Similarly, most researchers overlooked the disease. Almost all of society stigmatized patients with the condition.

The exact prevalence of SCD remains unknown. The Centers for Disease Control and Prevention estimates that it occurs in approximately one out of every 365 births of Black or African American individuals in the U.S. Researchers estimate around 100,000 individuals suffer

from SCD in the U.S., making it the most common inherited blood disorder. Millions worldwide are born with SCD.¹ Even so, patients with hemophilia and cystic fibrosis, which when combined are still less common than SCD, have far more access to comprehensive care. SCD is thus the paragon of a disparities disease. For comparison, cystic fibrosis affects fewer than half the number of persons but receives 3.5 times the funding from the National Institutes of Health and 440 times the funding from national foundations.²

“In November 2020 the National Academies of Science, Engineering, and Medicine (NASEM) formally declared sickle cell disease as a disparities disease, in an exhaustive 500-page report filled with recommendations for federal funders, foundations, industry and private philanthropy,” said Wally Smith, M.D., professor and scientific director of the VCU Center on Health Disparities. “The NASEM report is the bible we’ve been waiting for to outline how the U.S. should treat SCD patients equitably.”

Since the 1970s, research and clinical advances no longer make SCD a death sentence. On the MCV Campus, a strong, five-decade-long history of outreach and research has made VCU Health a leader. It started in 1972, when Congress passed the National Sickle Cell Disease Control Act. The law provided the first-ever authority to set up education,

screening, research and treatment programs for SCD.³

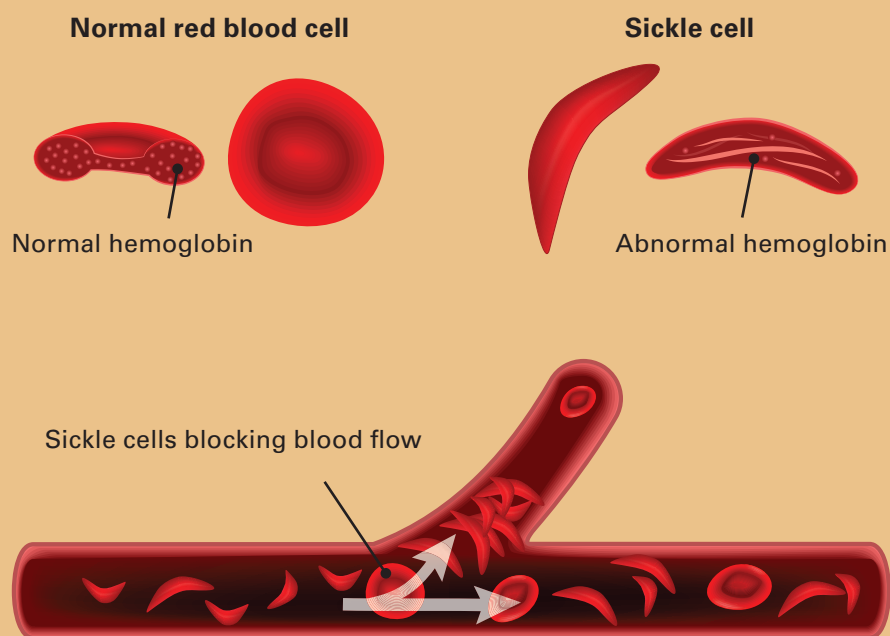
VCU started one of the first efforts to screen all newborns in Virginia for sickle cell disease, thanks to the leadership of Robert Scott, M.D., and Florence Neal Cooper Smith.

“VCU was in the unique position of being one of the first 19 institutions to have a sickle cell disease outreach program in 1972,” Dr. Smith said. “Florence Neal Cooper Smith and Dr. Robert Scott started the clinic in the face of overwhelming opposition. They were swimming upstream the whole time. Now people look to us as authorities in this area. We are clearly one of the top 10 centers in the country — whether you measure by number of patients, funding from the federal government or industry, or research productivity.”

Thanks to groundbreaking research and advances in care, children with SCD are now surviving well into adulthood. The resulting adult population growth underscores the need for new investment in research and patient care for this expanding patient population. Dr. Smith directs VCU’s Adult Sickle Cell Medical Program, which now cares for nearly 700 patients, three times as many as when he arrived on the MCV Campus in 1991. VCU Health currently serves SCD patients from across Virginia, intentionally reaching and educating patients and providers as far away as the Eastern Shore.

Sickle Cell Disease

When it releases oxygen, sickle hemoglobin proteins link together to form long, unbendable polymers inside the red blood cell. These polymers stretch the red blood cells out of their usual donut shape into sickle or crescent-shaped cells that carry oxygen less efficiently and no longer move through the body’s blood vessels, slowing and stopping blood flow.



Family Care for All Life's Stages



Photo: Paul Brockwell Jr.

Jennifer Folsom was six months old when doctors diagnosed her with sickle cell disease. Since receiving that life-changing news, she has grown up knowing that her condition requires caution and careful monitoring. As a kid, she would always think twice before engaging in team sports for fear the strenuous activity could potentially cause complications, and she often had to educate adults around her about sickle cell disease and how it affects her.

Originally from Delaware, Folsom and her family moved to Virginia after her father's death when she was in elementary school. Since then, she's been a patient in VCU Health's sickle cell programs, transitioning at 19 from the pediatric care team to the adult sickle cell program led by Wally Smith, M.D. Dr. Smith and his patient navigators count nearly 700 patients in the adult sickle cell program.

The transition from pediatric to adult sickle cell care can be rough. Research shows persistent challenges with adequate access to treatment, especially to physicians who understand and can treat patients with the condition. Thankfully, Folsom says her experience at VCU Health has been overwhelmingly positive.

"My transition was smooth," Folsom said. "My pain changed as I grew older, and finding the right medication was a concern, but it wasn't a hard transition."

Access to health care professionals who understand her condition and advocate for her health has been

a hallmark of Folsom's experience, including after-hours calls and quick efforts to ensure key prescriptions are available to manage her disease and reduce emergency room visits and hospital stays.

"I have never felt like I was alone," Folsom said.

"My care team has always had my back. If I had to reach out to someone, even before the patient portal was operational, I could contact them directly. It feels more like a family — everyone knows everyone, and they ask how we're doing to make sure we are doing OK."

Folsom, a parent of two, considers herself fortunate because the reality for too many sickle cell adult patients remains more challenging. Growing up, she said people didn't understand what sickle cell was and how it affects people with recurring pain and other complications. She has lost jobs due to the chronic nature of her condition, but she also has a hopeful outlook when sharing challenges she's faced. At VCU Health, she says she feels seen and heard for who she is as a patient, and the care received has enabled her to live her life and enjoy her career as an aesthetician as she hopes, one day, for a cure through research.

"Not every day is going to be sunshine and rainbows," Folsom said, "but my doctors and nurses are working to make sure I am able to do what I want to do, and their investment in my progress means a lot."

The advances in pediatric SCD care have largely not translated to advances and better outcomes for adults with sickle cell disease. Care remains poor in many parts of the U.S., which in turn leads to a higher need for acute care and hospitalizations, and paradoxically worsening mortality for patients.⁴ That's the professional challenge and calling that Dr. Smith has been pursuing since 1984.

"I saw orphans needing a home," Dr. Smith said. "There's a whole generation of Americans who don't remember the days when sickle cell patients were not living to adulthood. They don't understand how much we have had to go through to get care to where it is today."

His efforts fall into three major categories: developing and testing new treatments, understanding and removing barriers to care in order to improve health outcomes for patients, and advocating with policymakers at the local, state and national level to achieve equity in funding and equitable lifespans for adults with SCD.

RESEARCH AND TREATMENT DEVELOPMENT

In addition to his clinical duties, Dr. Smith consults on a drug development project based at the VCU School of Pharmacy. He's working with Martin K. Safo, Ph.D., professor in the school's Department of Medicinal Chemistry, to develop compounds that help improve the oxygen-carrying capacity of red blood cells in sickle cell patients and destabilize the polymers from causing further sickling, which in turn instigates the pain and other chronic and potentially life-threatening issues experienced by patients.

"This is a team effort," said Dr. Safo, who is affiliated with the School of Pharmacy's Institute for Structural Biology, Drug Discovery and Development. "We have spearheaded global efforts over the past four years to develop new compounds to treat sickle cell disease with partners like Dr. Osheiza Abdulmalik at the Children's Hospital of Philadelphia and King Abdulaziz University in Jeddah, Saudi Arabia."

Dr. Safo has been working on drug discovery for sickle cell for almost 30 years. Originally from Ghana, he knows firsthand how the disease can affect people. Two of his cousins were born with sickle cell, and one has already died from the disease. He earned his doctorate in inorganic chemistry before being inspired to pursue sickle cell research with the late Donald Abraham, Ph.D., who was the Alfred and Francis Burger Emeritus Professor of Medicinal Chemistry and Biological Chemistry, and Emeritus Director of the Institute for Structural Biology and Drug Discovery at VCU. Dr. Abraham died in April.

Their early efforts explored the potential of vanillin, an aromatic aldehyde, which is the primary component of vanilla extract. Early studies were promising, but ultimately the naturally occurring compound was not potent enough and lacked the pharmacokinetic properties to make an impact in patients. Dr. Safo's independent research also found promise in the byproduct of a sugar molecule named 5-HMF. In studies, this compound was five times more potent than vanillin at increasing the concentration of the non-polymerizing oxygenated sickle hemoglobin. Dr. Safo and his team took the research far enough to license the compound to a pharmaceutical company to produce for clinical trials. That company, unfortunately, went bankrupt and future studies stalled, but Dr. Safo and his team had managed to change the paradigm on exploring potential therapies.

Additional research on potential compounds put VCU Health at the forefront of sickle cell disease drug discovery among aromatic aldehydes.⁵ During this time, a private company, Global Blood Therapeutics, built off of VCU researchers' published compounds to produce a similar compound that they tested and brought to market. That drug, voxelotor, was approved in 2019 as only the second new therapeutic authorized for use in SCD patients in the 21 years since hydroxyurea, an antimetabolite used to slow the growth of certain types of cancer, was authorized by the FDA for treatment of SCD.

The VCU Health team continues to explore and improve potential treatments. Their latest promising work is a compound named VZHE-039, a novel anti-sickling agent that the team hopes to advance for clinical trials in the next year. Unlike therapies currently on the market, this new compound designed on the MCV Campus works on two levels: first, it increases the concentration of the non-polymerizing sickle hemoglobin; second and uniquely, it directly destabilizes the sickle hemoglobin from forming polymers, thus preventing further sickling and reducing the risk of pain and organ damage downstream.⁶ The candidate is rapidly advancing toward Phase I/II clinical trials.

"Our compound is rather unique," Dr. Safo said, "The dual anti-sickling activities of VZHE-039 would be critical to successfully ameliorate the disease phenotype in areas of severe hypoxia. For instance, voxelotor-bound sickle hemoglobin may still be incorporated into fibers, whereas VZHE039-bound sickle hemoglobin would destabilize polymer formation."



Martin Safo, Ph.D., professor in the VCU School of Pharmacy's Department of Medicinal Chemistry, has been leading efforts on the MCV Campus to develop new treatments for sickle cell disease. Photo courtesy VCU Public Affairs

"Our compound is rather unique. The dual anti-sickling activities of VZHE-039 would be critical to successfully ameliorate the disease phenotype in areas of severe hypoxia."

Martin Safo, Ph.D.
Professor, Department of Medicinal Chemistry
VCU School of Pharmacy

This spring, the team received funding from the National Institutes of Health to continue the effort to develop this new treatment. One thing has changed, however. After their earlier experiences with licensing to a company stalled progress, the researchers formed their own company, IllExcor Therapeutics, to develop the compounds coming from research being conducted at VCU for the treatment of SCD. The name is a combination of the word "ill" and a shortening of the word exorcism, a clarion statement of the company's purpose.

"We have a lot of hope that these therapies will be a huge benefit," Dr. Smith said of the team's efforts. "And that this compound can be added to the arsenal of potential tools. It's very encouraging. I would say that the future is bright right now. Our biggest challenge remains awareness."

If you would like to support sickle cell disease research and care on the MCV Campus, please consider making a gift to the Florence Neal Cooper Smith Professorship by contacting Brian Thomas, MCV Foundation vice president and chief development officer, at 804-828-0067 or brian.thomas@vcuhealth.org.

1. Centers for Disease Control and Prevention. "What is Sickle Cell Disease?" www.cdc.gov/ncbddd/sicklecell/facts.html
2. Lee, L.; Smith-Whitley, K.; et al. "Reducing Health Care Disparities in Sickle Cell Disease: A Review." *Public Health Reports*, Nov./Dec. 2019; PMID: 31600481
3. Manley, A.F. "Legislation and funding for sickle cell services, 1972-1982." *American Journal of Pediatric Hematology/Oncology*, Spring 1984. PMID: 6711766
4. Kanter, J., Smith, Wally R., et al.; "Building access to care in adult sickle cell disease: defining models of care, essential components, and economic aspect." *Blood Advances*, Aug. 2020; PMID: 32785684
5. Pagare, P.P.; Ghatge, M.S.; Chen, Q.; Musayev, F.N.; Venitz, J.; Abdulmalik, O.; Zhang, Y. and Safo, M. "Exploration of Structure-Activity Relationship of Aromatic Aldehydes Bearing Pyridinylmethoxy-Methyl Esters as Novel Antisickling Agents." *Journal of Medicinal Chemistry*, Dec. 2020; PMID: 33205981
6. Abdulmalik, O.; Pagare, P.P.; Huang, B.; Safo, M. et al. "VZHE-039, a novel antisickling agent that prevents erythrocyte sickling under both hypoxic and anoxic conditions." *Scientific Reports*, Nov. 2020; PMID: 33219275

FINDING A HOME:

VCU Health's National Leadership on Sickle Cell Outreach and Innovation in Care

VCU Health's strength in sickle cell research and care grew from decades of intentional outreach and efforts of several key individuals. Florence Neal Cooper Smith remains a tireless leader in the effort to raise awareness of sickle cell disease, both on a regional and national level. She is a graduate of Virginia Union University and completed graduate studies in pathology on the MCV Campus.

In 1969, she organized Richmond's first city-wide survey to determine the extent of sickle cell awareness in surrounding areas and, in 1972, she founded the Virginia Sickle Cell Anemia Awareness Program at MCV with Dr. Robert B. Scott Sr. This ambitious campaign sought to educate the public about sickle cell anemia. Because of her efforts, Virginia now screens all newborns at birth for sickle cell disease, and it was one of the first states to do so.

Since coming to VCU in the early 1990s, Dr. Wally Smith has continued efforts to define optimal care models for adults while advocating for better policies and new treatment discovery. Under his leadership, the health system has seen several breakthroughs in designing how systems of care can better handle adults living with SCD. Today, Dr. Smith is recognized as a national and international expert in this area.

The initiative he is proudest of is the launch of the Adult Sickle Cell Medical Home in 2018 to address a steady increase in emergency department visits and hospital admissions among adult SCD patients. The goal was to design a system of care that provided patients with navigators, social workers and a team of specialists to understand the barriers to access and how to build the best care possible for adult patients who often lack the resources to adhere to the care needs of a chronic disease like SCD. Additionally, the team partners with physicians and staff in the hospital to ensure open dialogue about SCD cases and patient needs.

"It's like a calling, and you can't turn your back on it," said Shirley Johnson, who is the adult program manager of the Sickle Cell Disease Adult Medical Home and supervises the team of patient navigators. "These are genuinely ill people through no fault of their own, and they have not been treated well by society or the health care system."



Florence Neal Cooper Smith (left) is a pioneer in early outreach efforts related to sickle cell disease. She is pictured with Shirley Johnson, who helps manage the adult sickle cell medical home for VCU Health, at an event to raise awareness and funds for sickle cell care and research on the MCV Campus. Photo: Thomas Kojcsich, VCU University Marketing

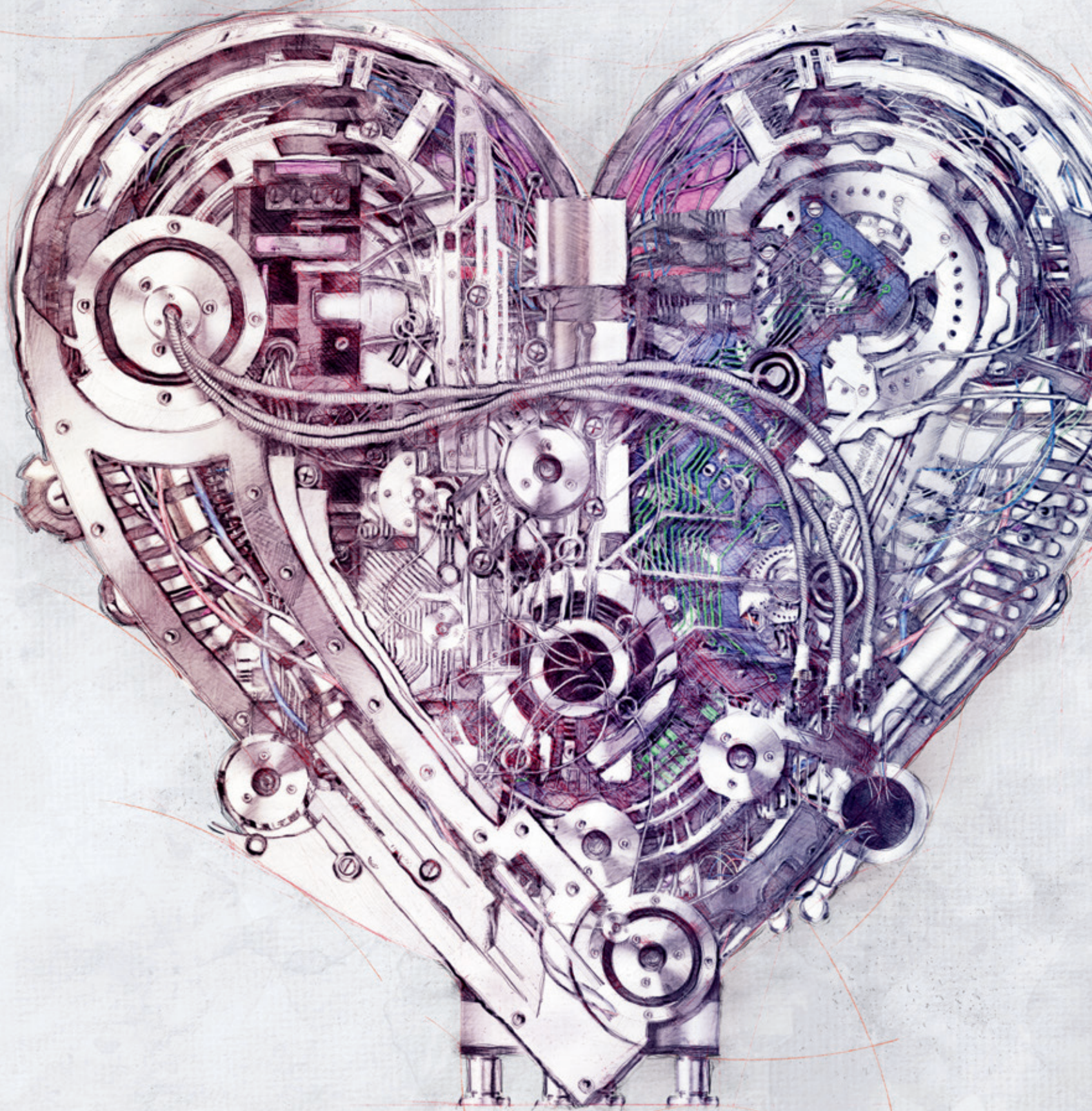
Johnson has worked with the adult sickle cell program for 12 years and said she misses her day-to-day care role now that she helps manage the 15-person team at the medical home, but it has been exciting to see how VCU has become a national leader in designing a system of care that shows results and offers training to fellow health care professionals through programs like the Sickle Cell Care Coordination for Achieving Patient Empowerment Conference (SCCAPE), which VCU began hosting in 2019 to provide training to professionals across the country in best practices for SCD patient navigators and care delivery.

The adult medical home has been noteworthy for its effectiveness. Among the entire adult SCD population, the initiative managed to reduce the number of inpatient days from SCD patients by 1,096 in 2019. Additionally, the readmission rate dropped 10%. Ultimately, this model of care saved around \$1.18 million in charges for patients and the health system, a figure that doubles when you look at the 50 patients who were among the highest utilizers of the health system.¹ But the proof is not just in the numbers. The quality of life for these patients increases when the whole team works together to stabilize housing, ensure ideal care is adhered to, and emergent needs are averted. Reducing emergency department visits and inpatient stays became even more critical once the pandemic hit in 2020.

Since then, the program adapted to ensure patients still received the resources they needed. Staff screened patients for depression and anxiety, and conducted COVID-19 surveillance among residents, given their higher vulnerability.

"I didn't realize we would see the results we have so quickly," said Johnson. "We still have work to do, but it has been a very rewarding team effort when it comes to improving the quality of life for people who too often have had no one in their corner."

1. 2019 Annual Report of the VCU Health SCD Adult Medical Home



A Bridge to Transplant

VCU Health continues its national and global leadership in implanting and researching total artificial heart technology.

By Eric Peters and VCU News Center Staff

In 2006, a man named Cecil Nester lived for nearly two months at VCU Medical Center with no biological heart in his body. At the end of those two months, he received a new heart via transplant and returned home to New Castle, Virginia.

Those two months he waited for a transplant were made possible thanks to a new technology approved by the FDA in 2004 — the SynCardia total artificial heart. It was the first time any health system on the East Coast had implanted the device into a patient.

Artificial hearts provide total biventricular replacement therapy, which means they replace both ventricles of diseased or dying hearts to improve circulation throughout the body and rejuvenate vital organs that have suffered due to poor circulation. The SynCardia device was designed to act as a bridge to transplantation for some of the sickest people any hospital will see.

More than 300,000 people in the U.S. die every year as a result of heart failure,¹ and a number of them could benefit from a heart transplant. However, the total number of heart transplants completed annually is only about 3,500. For those with no other option as they wait to move up the transplant list, artificial hearts can provide additional months and even years to their lives.

Most people who receive total artificial hearts are not candidates for the more widely used left ventricular assist device, or LVAD, which is a pump that helps the left ventricle, the main pumping chamber of the heart, pump blood to the rest of the body. Artificial heart recipients need more help because they usually face serious problems with both ventricles, abnormally thick hearts or irregular heart rhythms.

“These are some of the sickest patients in the hospital,” said Vigneshwar Kasirajan, M.D., chair of the VCU Health Department of Surgery. “They are in dire need of help because their hearts simply cannot pump enough blood to the rest of the body, which slowly suffocates every other organ.”

Dr. Kasirajan led the interdisciplinary team of physicians, nurses, perfusionists and medical technicians that completed Nester’s implant in 2006. In the 15 years since, VCU Health has become the most prolific total artificial heart program in the U.S., and perhaps one of the top five in the world, according to Dr. Kasirajan. More than 110 artificial hearts have been implanted at VCU Health, and the health system has remained at the forefront as technology has evolved.

In 2010, for example, VCU Health was the lead institution in a national clinical trial of portable technology that allows SynCardia total artificial heart patients to detach from the 418-pound console previously used to power the devices. This enables patients to recuperate, rehabilitate and wait in the comfort of their own homes until donor hearts becomes available for transplant.

The leadership in this field that VCU Health has exhibited over more than a decade is the reason Dr. Kasirajan is the principal investigator of a new device that could transform the way total artificial heart recipients live. And the hope is that one day this type of technology can evolve beyond serving as a temporary bridge to transplant to become a permanent alternative to transplant.



Vigneshwar Kasirajan, M.D., led the team in 2006 that, for the first time on the East Coast, implanted a total artificial heart into a human. VCU Health has maintained its leadership in this area and is now leading a clinical trial to test the newest artificial heart, which could provide more freedom and normalcy for those who receive the device. *Photo: Kevin Schindler*

CARMAT TRIAL

The newest version of the total artificial heart that Dr. Kasirajan and his team, along with seven other centers across the country, will test is called the CARMAT. Like current artificial hearts, this device replaces both of the lower pumping chambers of the heart, but there are some significant differences.

“Our current artificial heart is pneumatically powered through a console the patient wears in a backpack,” Dr. Kasirajan said. “The new heart features two small motors tucked inside the device. It’s powered by external, wearable batteries that can be hidden underneath a jacket. It’s totally implantable, with only a small driveline. It’s also quite a bit quieter — nearly silent.”

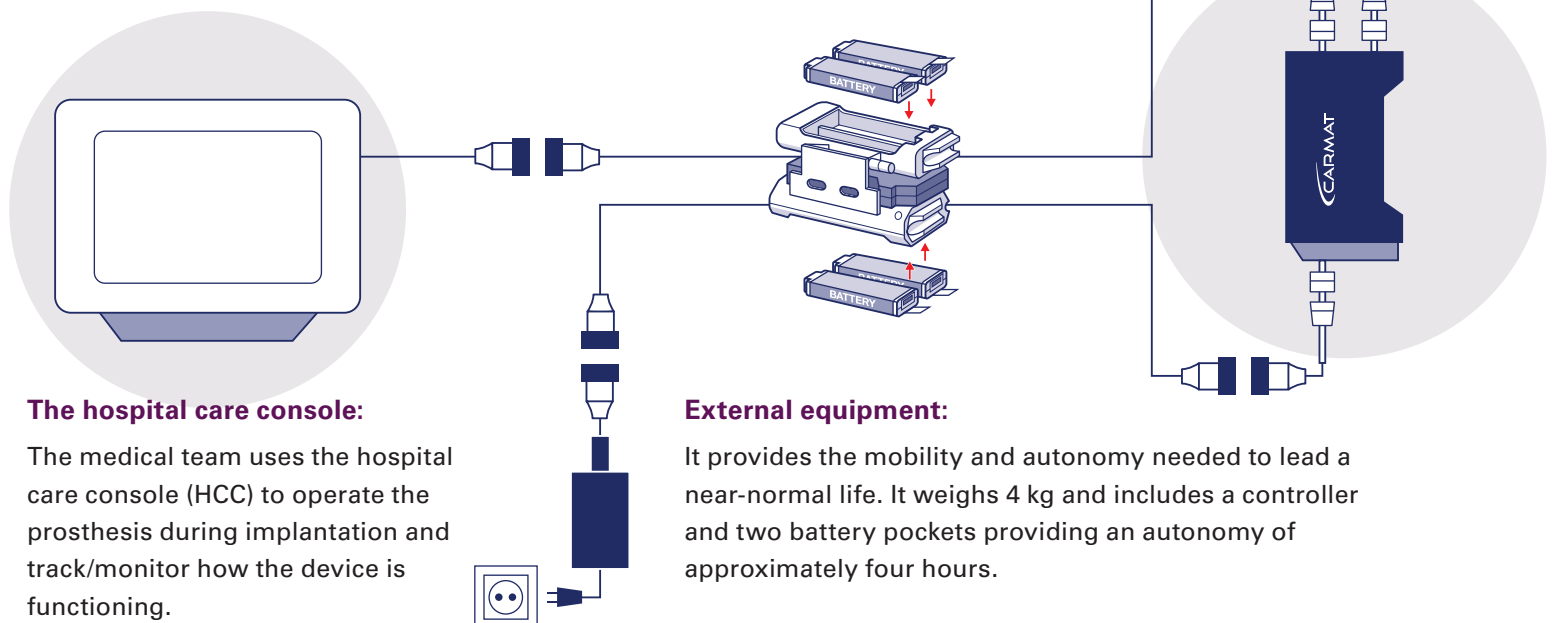
The current artificial heart also uses mechanical valves and requires the patient to take blood thinners, which increase the risk of bleeding. The new total artificial heart is made of biological materials, which Dr. Kasirajan believes will reduce the need for blood thinners.

In addition, the CARMAT has internal sensors that recognize changes in blood pressure, allowing physicians to customize the patient’s response to exercise. This is important because previous versions of the total artificial heart produced fixed heart rates and blood pressures, limiting capacity for exercise. Hopefully, research will show the CARMAT can successfully increase cardiac output to improve capacity for movement and exercise.

The first step in the research begins this year under Dr. Kasirajan’s leadership. His trial aims to prove that

How It Works

The CARMAT total artificial heart is composed of three parts:



The hospital care console:

The medical team uses the hospital care console (HCC) to operate the prosthesis during implantation and track/monitor how the device is functioning.

External equipment:

It provides the mobility and autonomy needed to lead a near-normal life. It weighs 4 kg and includes a controller and two battery pockets providing an autonomy of approximately four hours.

the CARMAT can meet FDA standards for performance and safety. Ten patients will be enrolled at the seven sites across the country. “There are many patients who could benefit from the total artificial heart,” Dr. Kasirajan said. “But because this is new technology, we are restricting the trial to a small group to allow us to study their outcomes carefully before we expand its use.”

The trial will take two to three years because enrollment criteria are quite strict. The teams are looking for patients who are ill, but not so ill that they might die on the device. The team is also looking for people who are the right size because, for now, the device is only one size, which is quite large. Patients also need financial and social support, among other criteria.

“VCU Health is focused on innovation to benefit patients. We’re constantly looking at new ways to make life better for them,” Dr. Kasirajan said. “That can be done only by working together in large teams, in a complex system where we can partner with others to create new knowledge and new technology. There are lots of things we need to learn as we go forward, but as an institution and as a heart center, to be able to be a part of a large trial like this, to help patients in the future — this trial is a very exciting step for us.”

WHAT’S NEXT

“No matter how hard we work to increase the number of donors available for heart transplantation, that gap is too broad,” Dr. Kasirajan said. “We need an off-the-shelf device that could be used for the variety of patients, such as

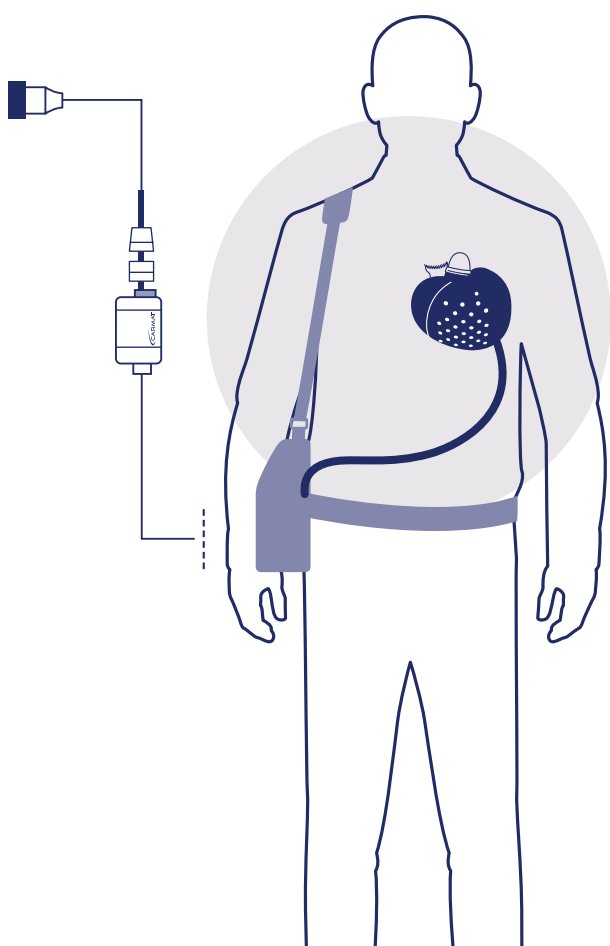
different sizes and different ages, and would produce good outcomes similar to a heart transplantation.”

He thinks that in another five to 10 years, research will lead to multiple modifications of the CARMAT to benefit patients with advanced heart disease who could have a pump put in and maintain a good quality of life for long periods of time. This will be important for patients who might not be able to survive a heart transplant, or those who might want to avoid a transplant for any number of reasons.

“Ultimately, when you have a smaller pump, it allows you to exercise more, it’s quieter and it can be implanted with low risk in selected patients. I think we’re going to have a population who will choose to live with the pump rather than go with a transplant and the consequences of a transplant, which include immunosuppressive therapy and other long-term realities,” Dr. Kasirajan said. “That’s a future state and the goal. We’re not there yet, but someday my hope is that we get there.”

If you are interested in supporting clinical trials and other research that advances lifesaving and life-changing research for people who need heart transplants, contact Carrie Mills, senior major gift officer at VCU Health, at 804-828-0423 or carrie.r.mills@vcuhealth.org.

1. Centers for Disease Control and Prevention. “Heart Failure.” www.cdc.gov/heartdisease/heart_failure.htm. Accessed March 2021



The implanted prosthesis consisting of the following components:

- One motor pump group composed of two micro pumps that push the actuator fluid to the membranes and generate the systole and diastole.
- Two ventricular chambers, separated into two parts by a membrane, one for the blood and one for the actuator fluid. The blood-contacting layer of this membrane is made of biocompatible materials.
- Embedded electronics, microprocessors and integrated sensors allowing autoregulated responses to the patient’s physiological needs.
- One flexible external bag containing the actuator fluid.
- Four biological valves at the inlet and outlet providing unidirectional pulsatile blood flow.
- Two outlet conduits allowing connection of the prosthesis to the pulmonary artery and aorta.
- One percutaneous driveline connecting the prosthesis to external components.

Hearts Full of Gratitude

2009

JOSEPH COX

The patient who received the 25th artificial heart implant at VCU, Joseph Cox, a 29-year-old carpenter from eastern Virginia, is well aware of how close he came to dying.

“I had 50 clots and two strokes” prior to receiving the implant in October 2008, Cox said. He received a donor heart November 14 and went home December 2. Vigneshwar Kasirajan, M.D., explained that Cox arrived at the hospital very ill and progressed rapidly to heart failure.

“His heart was irreversibly damaged. He had clots going to his lung and brain and we really had to take the heart out,” he said. “A suitable transplant could not be found in a timely



Artificial heart patient Joe Cox with girlfriend Karen Cottrell.
Photo: VCU University Marketing

“A suitable heart transplant could not be found in a timely fashion because his risk of death or complications was just days.”

— Vigneshwar Kasirajan, M.D.

fashion because his risk of death or complications was just days.

“So after careful consideration and discussion with him, we elected to put the total artificial heart in,” Dr. Kasirajan said. “He was extubated off the respirator the next day and walking within 24 hours and did remarkably well.”

2011

JARROD RUSSELL

At 32 years old, Jarrod Russell received an echocardiogram that revealed an enlarged, poorly functioning heart. Despite the premature deaths of his father and grandfather from heart complications, Russell admitted he was a little surprised he was having heart issues so soon.

“Knowing my history, I’ve made a conscious effort to live a healthy life — no smoking, staying in shape — but you never know,” he said.

Several procedures to save his ailing heart failed. He needed a new one soon. So, in December 2010, Russell received a total artificial heart that kept him alive until a donor heart became available. As he waited, he was an early recipient of a portable driver, which allows artificial heart recipients to have more freedom.

Following surgery to implant a total artificial heart, all patients awake tethered to a large, 400-pound console — nicknamed Big Blue — that powers the heart. The Pauley Heart Center team wastes no time getting patients moving and, with assistance, Big Blue often rolls with the patient on walks and to physical therapy.

After several weeks of recovery, patients who meet a variety of criteria have the option of being transferred to the portable driver and ultimately a chance to recover at home until a donor heart becomes available. A new clinical trial at the health system is testing a device that is more portable and quieter than the one Russell received.



As he waited for a new heart, Jarrod Russell was an early recipient of a portable driver for his total artificial heart. The driver, on which VCU Health led clinical trials, gives patients the chance to recover at home until a donor heart becomes available.

Photo: VCU University Marketing



Mother and son, Diane and Albert Kurtyka received their artificial hearts two years apart. *Photo: VCU University Marketing*

Diane and Albert were the 59th and 75th patients, respectively, to be implanted with the SynCardia Total Artificial Heart at VCU.

2012 / 2014

DIANE AND ALBERT KURTYKA

In 2014, Albert Kurtyka was ready to leave the hospital for the first time in 50 days.

As the automatic doors at VCU Medical Center slid open, the 34-year-old breathed in the crisp February afternoon. The donated heart pumping blood to his lungs had only been in his body for 10 days, and fresh air was one of the little things Albert knew he would never again take for granted.

“He’s going to have some bad days and some good days,” said Diane Kurtyka, Albert’s mother. “There will be emotional days and you just have to try to not get too overwhelmed with it, and you have to learn to truly live life every day.”

Diane spoke from experience. Two years earlier, she had walked through the same hospital doors with a donated heart of her own.

Diane and Albert were the 59th and 75th patients, respectively, to be implanted with the SynCardia Total Artificial Heart at VCU.

Diane and Albert’s shared experiences connected them to each other in a way few mothers and sons ever will be, and it left them both ready for that first step from the hospital, that first breath of fresh air and all that will follow.

2018

CHERRON GILMORE

Cherron Gilmore called her husband as she sat anxiously in a North Carolina hospital room in September 2018. They both were listening intently when — at age 37 — Gilmore learned she was going to die.

“You’re too risky, and we don’t think you’ll make it through surgery,” Gilmore said the doctor told her. “Even if we put it in, we don’t think you’ll make it through transplant.”

It was the fourth time she was turned down for a heart transplant from three hospitals in her home state.

Without knowing how much time she had left, Gilmore began preparing for her death by writing goodbye letters to her three children, ages 17, 13 and 8. She drafted notes filled with the wisdom she’d like her young daughter to know when she went to prom and on her future wedding day.

It was not until Gilmore was medevacked to VCU Health’s Pauley Heart Center — defeated and on her deathbed — that she realized her story did not yet have an ending.

Gilmore was admitted to the Pauley Heart Center on September 6 and within four days was in the operating

It was not until Cherron Gilmore was medevacked to VCU Health’s Pauley Heart Center — defeated and on her deathbed — that she realized her story did not yet have an ending.

room, where a skilled team removed her heart and replaced it with an artificial heart. After the surgery, Gilmore was able to go home to be with her family. Three weeks later, she got the call she had been praying for: She was getting a new heart.

Cheyne Gray, Cherron Gilmore, Gian Gilmore and Khori Gilmore, in front, participated in the 2017 American Heart Association Heart and Stroke Walk in Winston-Salem, North Carolina. *Photo courtesy of the Gilmore family*



Remaining *Active* with AFib

By Carla Davis and Eric Peters



VCU Health leads a clinical trial that could mean the end of blood thinners for AFib patients.

Atrial fibrillation, or AFib, is the most common type of heart arrhythmia in the U.S., and is expected to affect 12.1 million people across the country by 2030.¹⁻²

With symptoms that include lightheadedness, shortness of breath or fatigue, this abnormal heart rhythm occurs when the upper part of the heart — the atria — beats irregularly and too fast, causing the heart to quiver, or fibrillate.

While the symptoms usually are not painful, AFib increases the risk of stroke five to seven times, and it is responsible for one in every four strokes that occur.

The Centers for Disease Control and Prevention reports that AFib was mentioned on 175,326 death certificates in 2018, and that AFib was the underlying cause of death in 25,845 of those cases.³

For years, blood thinners have been used to prevent blood clots that lead to AFib-related strokes, while cardiac assist devices, catheter ablation procedures and a variety of minimally invasive approaches have been used to reset the rhythm or control the rate of the heart. And as a last resort, VCU Health and other institutions have offered surgical

implantation of a device known as the WATCHMAN, which is permanently placed at the opening of the left atrial appendage.

Today, however, it looks as though the latest version of the WATCHMAN might actually be the best *first* solution and could free patients from having to take anticoagulants that thin blood and can cause serious bleeding problems — an especially concerning issue for those who would like to stay active as they advance in age.

“If you’re on a blood thinner and you start bleeding on an airplane, or on a boat, or when you’re hiking in the woods, that could be disastrous,” said Kenneth Ellenbogen, M.D., the Martha M. and Harold W. Kimmerling, M.D., Chair of Cardiology at the VCU School of Medicine. “Furthermore, if you like playing basketball or going mountain biking, and you’re on a blood thinner, you’d better think twice before doing those things.”

In addition, being on blood thinners means increased risk for internal bleeding in the brain, the gut and elsewhere. Some people even experience chronic bleeding and become very sick over time.

These risks are why Dr. Ellenbogen is studying whether freedom from blood thinners could become a reality for patients with non-vascular AFib who are at high risk of stroke. He is a co-chair of CHAMPION-AF, a global, head-to-head clinical trial of the WATCHMAN FLX device versus non-vitamin K antagonist oral anticoagulants (NOACs) such as Eliquis.

“This is a groundbreaking study that looks at a device that the doctors here have been implanting for a number of years successfully, and looks at it as first-line therapy for preventing stroke in patients with atrial fibrillation,” Dr. Ellenbogen said. “That’s huge.”

WATCHMAN VS. NOAC

The CHAMPION-AF clinical trial compares NOACs like Eliquis with the WATCHMAN FLX, putting the best available drugs up against the best available left atrial appendage closure device.

“We’re studying different strategies for preventing stroke in patients with atrial fibrillation. And of course, the strategy most commonly used has been drug strategy,” Dr. Ellenbogen explained. “Blood thinners are great, but they make it harder for you to stop bleeding when you start bleeding. So, in patients who have atrial fibrillation, most of their strokes come from what we call the left atrial appendage, which some surgeons call the appendix of the heart. Somebody came up with the idea of if we could close off the left atrial appendage, we might be able to prevent strokes for patients with atrial fibrillation. And they wouldn’t have to take blood thinners.”

In a number of pivotal studies, Ellenbogen said, it was found that patients who can’t take blood thinners but who received the WATCHMAN did well with an aspirin a day, or nothing.

The WATCHMAN device has now gone through several iterations, and the implantation procedure has been improved. “Maybe this type of device might be better than drugs for most people,” Dr. Ellenbogen said. “That’s the question our study is attempting to answer.”

The CHAMPION-AF trial will use the next-generation FDA-approved WATCHMAN FLX device. Manufactured by Boston Scientific, WATCHMAN FLX is built on the WATCHMAN, the most studied and most implanted left atrial appendage closure device. More than 100,000 have been implanted worldwide, Dr. Ellenbogen said.

The WATCHMAN is permanently placed at the opening of the left atrial appendage, which is the part of the heart that is targeted because more than 90% of stroke-causing clots related to AFib begin there. “Most of the atria walls



“Maybe this type of device might be better than drugs for most people. That’s the question our study is attempting to answer.”

Kenneth Ellenbogen, M.D.
the Martha M. and Harold W. Kimmerling, M.D.,
Chair of Cardiology
VCU School of Medicine

Through an incision in a patient’s upper leg, Kenneth Ellenbogen, M.D., (at left with a WATCHMAN device) implants a WATCHMAN device at the opening of the left atrial appendage. *Photos: Allen Jones, VCU University Marketing*



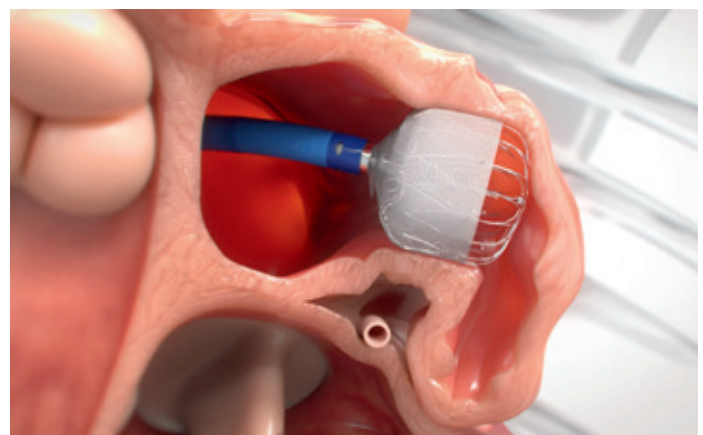
are smooth, and blood clots don’t form on smooth walls,” Dr. Ellenbogen said. “But the left atrial appendage has ridges, nooks and crannies. If you get a blood clot there — and let me remind you I’m talking about something the size of the tip of a ballpoint pen — it usually goes through the carotid artery and to the brain.”

Implanting the device requires an overnight stay in the hospital, and recovery takes about 24 hours. The trial includes about 150 sites globally and will enroll approximately 3,000 patients. Marty Leon, M.D., director of the Center for Interventional Vascular Therapy at New York Presbyterian/Columbia University Irving Medical Center, is a co-chair. Principal co-investigators are Shephal Doshi, M.D., cardiac electrophysiologist at Pacific Heart Institute, and Saibal Kar, M.D., interventional cardiologist at Los Robles Health System.

To be enrolled in the study, patients must have at least a moderate risk of stroke from AFib.

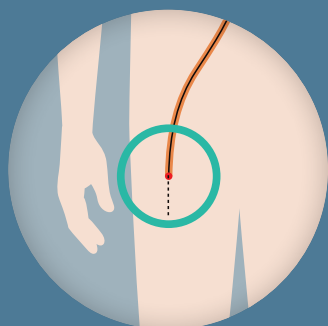
“We have a lot of patients who come to see us who don’t want to take blood thinners because they’re active, or they’ve had some bleeding,” Dr. Ellenbogen said. “This study gives them the opportunity to get a device implanted without having to have had a bleeding episode to get the

The WATCHMAN is permanently placed at the opening of the left atrial appendage, which is where 90% of AFib-related strokes begin.

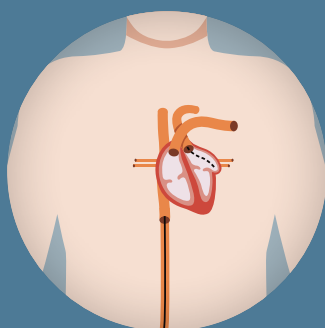


The WATCHMAN Procedure

The WATCHMAN is permanently placed at the opening of the left atrial appendage, which is where 90% of AFib-related strokes begin.



1. An incision is made in the upper leg.



2. Device is guided to the heart.



3. The patient stays overnight.



4. Blood thinners are used for 45 days.



5. Tissue grows over the WATCHMAN.

device implanted. So, if you're 70 years old and you have high blood pressure, you're going to be on blood thinners the next 20 years of your life. But if you participate in this study, you have a 50% chance of having a device implanted. So, we can see which is better, the medicine or the drugs."

After receiving the device, patients will be evaluated in three years. "We'll be looking to see if this device is safe and effective compared to the drug," Dr. Ellenbogen said. "If this study proves that the WATCHMAN is as good as or better than blood thinners, then why ever put someone on a blood thinner? We could allow people to live the type of life they want."

WHAT'S NEXT?

"This is probably one of the most important studies being done in the next five years in clinical cardiology," Dr. Ellenbogen said. "I'm going to be involved as one of the two people who is going to steer the study to its conclusion. Whether it's positive or negative, it's going to possibly change the way we practice."

That change could mean that any patient with AFib gets a WATCHMAN device implanted to prevent a stroke. The implant would be in place of drug therapy, which is perfect for active people who have years of full life ahead of them — trips to take, grandkids to raise and races yet to win.

If you are interested in supporting clinical trials and other research that advances lifesaving and life-changing research for people facing atrial fibrillation or other heart arrhythmias, contact Carrie Mills, senior major gift officer at VCU Health, at 804-828-0423 or carrie.r.mills@vcuhealth.org.

1. Miyasaka, Y, Barnes ME, Gersh BJ, et al. "Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence external icon." *Circulation*, July 2006; PMID: 16818816
2. Colilla, S.; Crow, A.; Petkun, W.; Singer, D.E.; Simon, T. and Liu, X. "Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population." *American Journal of Cardiology*, Oct. 2013; PMID: 23831166
3. Centers for Disease Control and Prevention. "Atrial Fibrillation." www.cdc.gov/heartdisease/atrial_fibrillation.htm. Accessed March 2021

Skiing Easy



Retired dentist and internationally ranked water skier John Howell elected to receive the WATCHMAN so he could continue to do the things he loves without fear of bleeding complications. *Photo: Eric Peters*

Freedom from blood thinners means peace of mind when doing what you love.

When competitive water skier John Howell developed chronic atrial fibrillation in his 70s, he started a blood thinner regimen to treat and prevent blood clots and reduce the risk of stroke. But participating in sports can be dangerous for someone taking anticoagulants, which can cause excessive bleeding. One spill from his skis and Howell could bleed uncontrollably.

"You want a nice, efficient heart when you're exercising," he said. "Unfortunately, when you ski, you can take some dramatic crashes that can be life-threatening."

After four or five years on the drug Eliquis, Howell, 80, wanted his AFib cured. Twice he tried cardioversion, a procedure that can restore normal heart rhythm by applying a controlled electric shock to the heart to break the pattern of abnormal electrical signals. After each time, however, his AFib returned.

Out of options, Howell's cardiologist in Fredericksburg, Virginia, referred him to VCU Health Department of Cardiology chair Dr. Kenneth Ellenbogen, whom they were confident could help the retired dentist. Pauley Heart Center's Atrial Fibrillation Program offers a full spectrum of innovative therapies and treatments and is focused on meeting the individual needs of each patient. Because Howell had a high risk of stroke, Dr. Ellenbogen

recommended he receive a WATCHMAN implant. The parachute-shaped device is designed to keep harmful blood clots that form in the left atrial appendage from entering the blood stream and potentially causing a stroke.

The WATCHMAN is permanently placed at the opening of the left atrial appendage. The procedure requires an overnight stay in the hospital, and recovery takes about 24 hours.

"I was all for having it done," Howell said. "I have the highest regard for Dr. Ellenbogen and felt like I was in really good hands."

He had the procedure done without incident. "Then, I went about my life playing tennis and water skiing," said Howell, a multi-time Eastern regional timed slalom champion.

"It was a relief being on blood thinners because it cut back on my chance to have a blood clot that could go to my brain and have a tragic ending, but because I'm so active, the blood thinners could have created their own tragic ending," he said. "The WATCHMAN allows me to get off the blood thinners and peel away that layer of concern."

SIGNAL

DISRUPTIONS

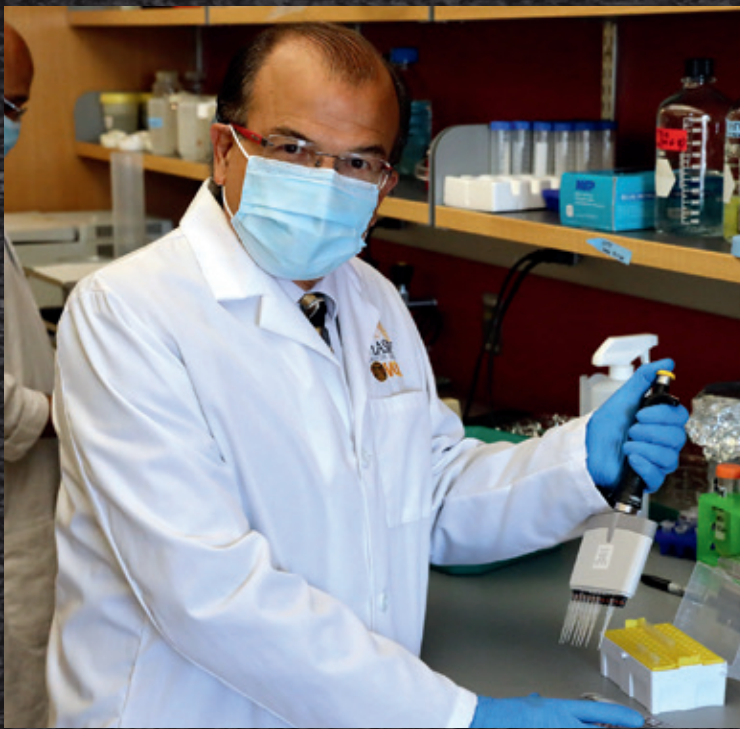
A promising approach to discovering new cancer treatments is at the heart of MCV Campus research to interfere with the cell signals that instigate cancerous growth.

By Paul Brockwell Jr.

Saïd Sebti can trace his interest in combatting some of the most vicious cancers to a sleepless summer night in his teens. He vividly remembers visiting a friend in Rabat, Morocco, and being kept awake most of the night by the agonizing sounds and screams of pain he could hear from his friend's next-door neighbor, a woman he would learn the next morning was suffering from cancer. As a teen, he wondered why this woman could not simply go to a doctor to receive medication and relief from her torment. That moment stuck with a 14-year-old Sebti and has been a strong undercurrent in his drive to discover potential solutions to cancer. He earned his doctorate in the U.S. and has steadily worked to shine new light on what causes various cancers and to develop treatments that might work against those causes.

Today, Saïd Sebti, Ph.D., is the associate director for basic research at VCU Massey Cancer Center, the Lacy Family Chair in Cancer Research, and a professor of pharmacology and toxicology in the VCU School of Medicine. His lab focuses on understanding the mechanisms by which normal body cells turn cancerous. Cancer develops when mutations occur in some of our genes, which cause aberrant signals that trigger uncontrolled cellular division, growth and metastasis, all hallmarks of cancer. Dr. Sebti hopes to better understand the aberrant signals that cause cancer and, armed with that knowledge, his team seeks to find novel anti-cancer drugs to disrupt the signals that cause some cells to run amok and wreak havoc on the body.

Dr. Sebti came to the MCV Campus from the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida, where he led programs in drug discovery, chemical biology and molecular oncology research. Dr. Sebti's research has received more than \$60 million in funding from the National Cancer Institute (NCI), National Institutes of Health, American Cancer Society and others. In 2016, Dr. Sebti received a prestigious NCI R35 Outstanding Investigator Award, which provides \$6.4 million over seven years.



An expert in drug discovery, design and development, Saïd Sebti, Ph.D., holds 80 patents and several technology licenses for his scientific inventions. He has co-developed two drugs that have reached clinical trials, published more than 300 manuscripts in peer-reviewed academic journals, and has been continuously grant funded by the National Cancer Institute since 1989.
Photo: John Wallace, VCU Massey Cancer Center

Dr. Sebti's lab has a special interest in a cancer-causing protein called KRAS that is found mutated in about 20% of all human cancers and which activates many of the aberrant signals of cancer. The mutated KRAS protein is frequently involved in the development of some of the deadliest cancers such as lung, colon and pancreatic. Understanding how mutant KRAS functions is the first step, Dr. Sebti said, to discovering potential ways to interfere with cell processes and signals and hopefully stopping the unfettered growth of cancers.

Prior to his arrival on the MCV Campus, he made major contributions to the understanding of mechanisms by which KRAS proteins cause cancer and identified several drugs that interfere with these processes, particularly in pancreatic cancers, including inhibitors of farnesyltransferase, geranylgeranyl-transferase, Akt, GSK3, and CDKs, proteins required for KRAS-causing activity. Slightly more than half of pancreatic cancers go undetected until the mutated cells have spread to other parts of the body, where the uncontrolled growth begins to cause more pronounced symptoms. The five-year survival rate for patients is around 10% according to the Centers for Disease Control and Prevention. Cancers of the pancreas are the fourth leading cause of cancer-related deaths in the U.S., and around 90% of pancreatic cancers have a KRAS mutation, which causes more aggressive tumor growth and resistance to chemotherapy and other targeted therapies. The NCI has placed a priority on solutions that target this cancer-causing protein and the development of therapies specific to inhibiting it.

"At present, there are no FDA-approved drugs to directly target mutant KRAS-driven human cancers, and novel drugs are urgently needed for the large number of afflicted patients," said Dr. Sebti, a member of the Developmental Therapeutics research program at Massey. "We developed several small molecules that overcome the major hurdle of mutant KRAS-dependent resistance that can help with thwarting growth in primary and metastatic tumor samples."

20%

The protein KRAS is found mutated in around 20 percent of all human cancers.

90%

Around 90 percent of pancreatic cancers have a KRAS mutation.

4th

Pancreatic cancers are the fourth leading cause of cancer-related deaths in the U.S.

“What is exciting about this is that we’ve identified a genomic signature that could tell us which tumors are, and which are not, KRAS-addicted. If validated in patients, the consequences could be huge.”

Saïd Sebti, Ph.D.
Associate Director for Basic Research, VCU Massey Cancer Center
Lacy Family Chair in Cancer Research
Professor of Pharmacology and Toxicology
VCU School of Medicine

Dr. Sebti’s lab and collaborators at Moffit and other institutions developed drugs that inhibit the cancer-causing activity of KRAS.¹⁻³ The drugs proved effective when applied to human pancreatic, lung and colon tumors in early research.¹⁻³ They also prevented tumor growth in mutant KRAS tumor samples from pancreatic cancer patients, some of which were resistant to chemotherapy and radiation therapy.

Since arriving at Massey, in addition to molecular and cellular biologists, Sebti is expanding his research team to include structural biologists and computational biologists, taking a multidisciplinary approach to understanding why some tumors are addicted to mutant KRAS, when others are not. Recently, the Sebti lab discovered a genomic signature that may enable scientists and physicians to predict which patient tumors may be KRAS-addicted and which drugs these tumors may respond to. The MCV Campus work using computational biology has enabled his lab to analyze hundreds of individual cancers in an attempt to understand why some tumors are KRAS-addicted and others are not. These extensive efforts paid off, and what his lab discovered here in Richmond is a set of genes that contribute to the hallmark of KRAS addiction in tumors.

“What is exciting about this is that we’ve identified a genomic signature that could tell us which tumors are, and which are not, KRAS-addicted,” Dr. Sebti said. “If validated in patients, the consequences could be huge — we would have a more refined understanding of what factors to potentially attack and how to pursue therapy development for these cancers.”

Establishing a genomic signature for KRAS addiction in tumors allows clinicians to better understand which patients will respond better to certain treatments, depending on whether their tumor is addicted to KRAS. This gene signature can predict whether patients may have more aggressive forms and poorer outcomes, but this signature also provides the next building block for hope, making it easier to develop drugs that may work best for certain types of cancers.

If you would like to help strengthen the work of Dr. Sebti and Massey researchers working to develop novel therapies to treat cancer, please consider reaching out to Martha Quinn, executive director of development for VCU Massey Cancer Center, at 804-827-0652 or mquinn3@vcu.edu.

1. Kazi, Aslamuzzaman; Xiang, Shengyan; Yang, Hua; Delitto, Andrea; Underwood, Patrick W.; Fleming, Jason B.; Trevino, J.; Hamilton, Andrew D. and Sebti, S.M., et al. “Dual Farnesyl and Geranylgeranyl Transferase Inhibitor Thwarts Mutant KRAS-Driven Patient-Derived Pancreatic Tumors.” *Clinical Cancer Research*, Oct. 2019; PMID: 31227505
2. Kazi, A.; Xiang, S.; Yang, H.; Delitto, D.; Trevino, J.; Jiang, H.; Ayaz, M.; Lawrence, H.; Kennedy, P. and Sebti, S.M. “GSK3 Suppression Upregulates β -Catenin and c-Myc to Abrogate KRAS-Dependent Tumors.” *Nature Communications*, Dec. 2018; PMID: 30514931
3. Kazi, A.; Chen, Liwei; Xiang, S.; Vangipurapu, Rajanikanth; Yang, Hua; Beato, Francisca; Fang, Bin; Williams, Terence M.; Husain, Kazim, Underwood, P.; Fleming, J.; Malafa, Mokenge; Welsh, Eric; Koomen, John; Trevino, J. and Sebti, S.M. “Global Phosphoproteomics reveal CDK suppression as a vulnerability to KRAS addiction in Pancreatic Cancer.” *Clinical Cancer Research*, April 2021; PMID: 33879459

follow-up

Checking in with researchers
on the latest developments

NIH Grant Expands Parkinson's Research

Researchers on the MCV Campus received grant funding from the National Institutes for Health to expand important inquiry efforts related to Parkinson's disease.

A team of five researchers — jointly led by Ingrid Pretzer-Aboff, Ph.D., senior nurse researcher in the VCU School of Nursing, and Leslie Cloud, M.D., the Rogliano Family Endowed Chair and director of the Parkinson's Disease Program at the VCU Parkinson's and Movement Disorders Center — have been testing a vibrating device worn just above the shoe that could reduce or put an end to freezing of gait.

Freezing of gait is a symptom commonly experienced by 60% of Parkinson's patients. It manifests in a complete stop or prolonged shuffle in the feet or legs despite an individual's best intentions to move forward. No medications or surgeries currently are available to treat it.



A wearable vibrating device helps with freezing of gait, a common symptom of Parkinson's disease.
Photo: Ingrid Pretzer-Aboff, Ph.D.

Our Spring 2020 Q&A with Dr. Pretzer-Aboff mentioned the generous early-stage research support from the Michael J. Fox Foundation and the promising results of the effort. The research on vibration technology is now able to expand from the lab to real-world applications, thanks to an \$800,000 grant from the National Institutes of Health. The project's expansion with NIH funding will allow the research team to pair the ankle device with a second Bluetooth-enabled device from researchers at William & Mary. Together, the gadgets can sense the slightest hint of freezing of gait in a patient's walk and trigger the ankle device to vibrate — within

a second — to help the wearer stay in motion as usual.

"The population of people that suffers from freezing of gait with Parkinson's is a really vulnerable population. If you can't walk, your quality of life is awful," Dr. Cloud said. "There are many treatments for Parkinson's, but walking problems tend to be resistant to medications and surgery. This therapy could be a safe and affordable option for a population that currently has no options."

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