next

The Future of Discovery at VCU Health

Summer 2022

CHAIN REACTIONS

VCU Explores Liver's Link to Greater Health

Global Leadership for Tomorrow's Greatest Challenges

Dear Friends,

We write at a special and historic time on the MCV Campus at VCU Health. In February, longtime VCU Health hepatologist R. Todd Stravitz, M.D., through his family foundation, announced a $104 million gift to establish the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health. It was the largest gift ever made to VCU, and the largest ever in the nation for liver research.

The new institute will position VCU as a global leader in researching and caring for people battling liver disease, which is a leading factor in declining life expectancy in the U.S. and afflicts 1 billion people around the globe.

At the helm of the new institute will be Dr. Stravitz's colleague of more than three decades, world-renowned researcher Arun Sanyal, M.D. We invite you to read in this issue of NEXT magazine about some of Dr. Sanyal's work with nonalcoholic fatty liver disease. It is a preview of the incredible things yet to come from the new institute.

This issue also explores some of the ways VCU's Medicines for All Institute is improving access to COVID-19 treatments, examines a little-known disease that has been found to be far more prevalent than previously thought, and looks at how research into better personalized medicine may help give a shelved cancer drug another shot.

We are more energized by every issue of NEXT magazine because it reminds us of the level at which research and national leadership exist right here in Richmond. Whether through a one-of-a-kind liver institute, through rethinking how drugs are made around the world, or through any of the amazing research highlighted in these pages, the future is bright for VCU, VCU Health, the MCV Campus and, most importantly, patients from across Central Virginia and beyond who will benefit from the advances made here for the benefit of us all.

Best wishes,

Ellen E. Spong
BOARD CHAIR, MCV FOUNDATION

Margaret Ann Bollmeier
PRESIDENT AND CEO, MCV FOUNDATION

next SUMMER 2022

COVER STORY

Engineering HOPE

VCU's Medicines for All Institute (M4ALL) has improved the world's ability to fight COVID-19 by rethinking how drugs are made and expanding access globally.

By Eric Peters

By the time 2020 arrived with a global pandemic in tow, the Medicines for All Institute, a research group at VCU's College of Engineering, was already poised to help the world fight back against COVID-19.

The M4All lab had been working since 2017 to rethink the chemistry and other processes that go into manufacturing specific drugs, which in turn had been successful in improving access and driving down global production costs of medications for HIV, malaria and tuberculosis.

So, as the pandemic began to envelop the world, Frank Gupton, Ph.D. — founder and CEO of M4ALL — put COVID-19 directly in the crosshairs of his lab's unique work.

He called his longtime partners at the Bill & Melinda Gates Foundation to ask what projects they had that he might help with. The foundation initially asked Dr. Gupton to work on a drug called remdesivir, which was the first fully approved COVID-19 drug treatment in the U.S. In fewer than six weeks, M4ALL developed a less expensive process for manufacturing the drug using more readily available materials that doubled the product yield in half as many steps to produce one of the key building blocks. By summer 2020, Gilead Sciences signed voluntary licenses with generic manufacturers to allow for distribution or manufacturing of remdesivir in 127 countries, largely thanks to M4ALL's new process.

With the fast success of remdesivir in hand, Dr. Gupton went back to the Gates Foundation in late 2020 for more work.

"They said, 'We've got this new drug that's in development called EIDD-2801,'" said Dr. Gupton, who holds the Floyd D. Gottwald Jr. Chair in Pharmaceutical Engineering, and is professor and chair of VCU's Department of Chemical and Life Science Engineering. "They gave me the structure and synthesis of it, and we really felt like we could make some huge inroads into that process as well. We started working on it right away, and within a couple of months we developed a whole new way to make that molecule."

EIDD-2801, discovered by Emory University scientists and developed by Merck & Co. in collaboration with Ridgeback Biotherapeutics, came to be known as molnupiravir. Early data suggested the broad-spectrum antiviral could cut the risk of serious disease and death due to COVID-19 by up to half. It was poised to become a pill that people infected with COVID-19 could take at home to prevent hospitalization and fill a huge gap in countries where people lack easy access to basic health care and vaccines.

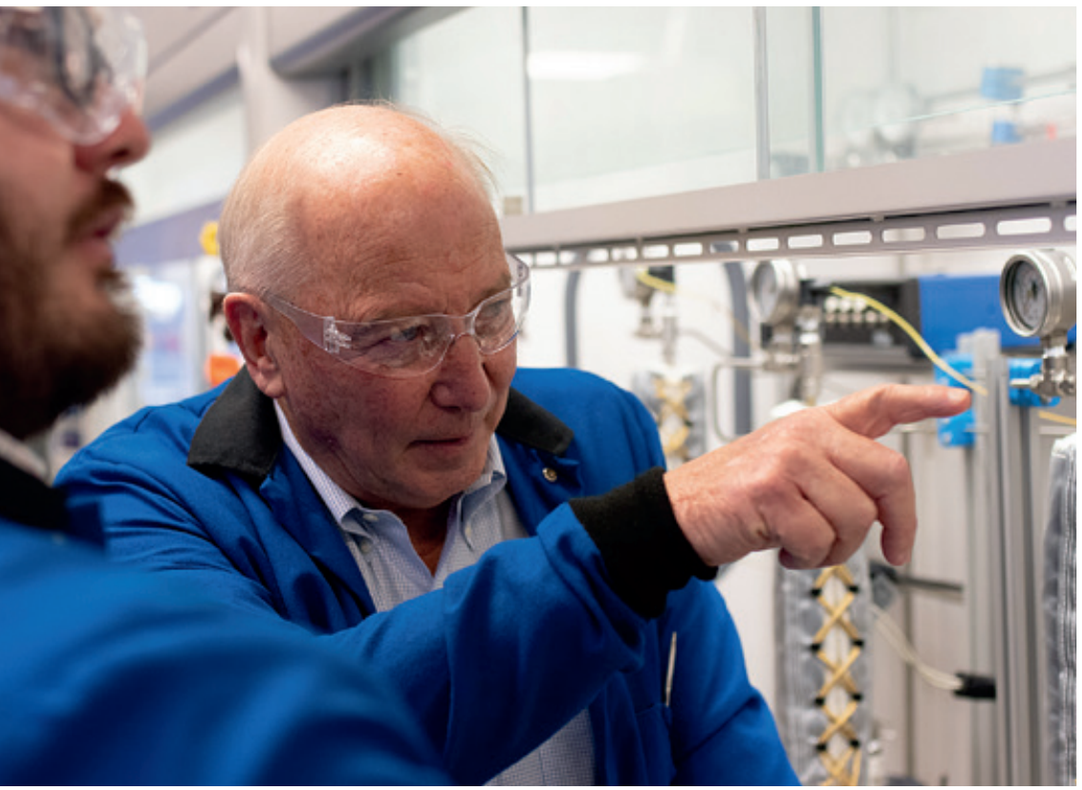
By October 2021, *The Wall Street Journal* and other news outlets had reported that the Medicines Patent Pool, a United Nations-backed nonprofit that aims to expand poor countries' access to drugs, would work with multiple drugmakers to produce molnupiravir for 105 nations, including Pakistan, Cambodia and all of Africa — and the reason it was possible was the new manufacturing process developed at M4ALL.

Dr. Gupton's M4ALL team did not slow down after its success with two COVID-19 drugs. In fact, the success was energizing, and they sought more. In 2021, the research group set its sights on a Pfizer drug called Paxlovid, which was shown to reduce hospitalization or death by 89% in high-risk groups when taken within five days of symptom onset. The M4ALL team is currently working with Pfizer and the Bill & Melinda Gates Foundation to develop a robust supply chain as well as an efficient chemical process for the production of this important treatment.

THE M4ALL APPROACH

Founded in 2017 with funding from the Gates Foundation, M4ALL examines commercial drug manufacturing processes to find ways to substitute lower-cost raw materials, simplify operations and increase yields. It then transfers its findings to manufacturers and suppliers that can reduce consumer prices and establish production closer to patients, where it previously wasn't economical to do so.

M4ALL's early work included nevirapine, a widely prescribed treatment for HIV that is on the World Health Organization List of Essential Medicines. Dr. Gupton's team pinpointed inefficient chemical conditions and production processes related to the drug, then streamlined



Frank Gupton, Ph.D., works with his team at VCU's Medicines for All Institute to develop more cost-effective and cleaner ways of manufacturing drugs. *Photo: Tyler Trumbo, MCV Foundation*

routes to the materials that come together to create its active pharmaceutical ingredient (API), ultimately reducing input materials, waste and cost.

Synthetic processes to develop new APIs, especially in times of great need such as a global pandemic, often evolve with limited regard for commercial viability and efficiency. These early processes help define the final commercial production processes because they are the fastest route to market.

When the drugs are in market but still being manufactured through their original inefficient processes, that is where Dr. Gupton's team makes an impact. "We look at drugs with a new set of eyes and some new chemistry tools, and we make them more cost-effective and more accessible to people around the world," he said.

The fresh perspective M4ALL is applying also reduces the environmental impact of drug making. Through its original production processes, for example, nevirapine produced about 60 kilograms of waste per kilogram of final product, but Dr. Gupton's team cut that waste to just 4 kilograms.

"One of the interesting things about the pharmaceutical industry is they're using 19th-century technology," Dr. Gupton said. "Active pharmaceutical ingredient manufacturing has been and still is practiced using batch manufacturing platforms." This technology is like using massive beakers to manufacture drugs in single lots. But Dr. Gupton's team is implementing continuous flow chemistry when and where it can, which is a process more akin to an assembly line.

"The pharmaceutical industry represents roughly 10% of the U.S. GDP," Dr. Gupton said. "They are essentially the only ones not using an assembly line approach to manufacture their product."

M4ALL AND MOLNUPIRAVIR

It took Dr. Gupton, who is a former pharmaceutical industry executive, and his VCU M4ALL team just a few months to completely rework the way molnupiravir can be manufactured.

"The way we typically do these projects is to begin with a benchmarking analysis, and we'll identify what the cost is of the existing process and the cost drivers associated with it," Dr. Gupton explained. "Then we'll home in on the opportunities to make improvements and potentially alternative ways of producing those molecules for the final product. And we were just fortunate in the case of molnupiravir that we came up with some really good ideas that would help quickly."

After this initial phase of brainstorming, the team went into the lab to test their ideas and the feasibility of each.

"Once we've identified which chemistry actually works, then we down select the process and do optimization work on the one or two processes that we've identified," Dr. Gupton said. "And this phase also happened really quickly."

The team's fast success had to do with a combination of things, including established protocols for these types of projects, the gravity of the historical time in medicine and human history, and the fact that all the team members were focused on one goal due to non-COVID-19 research being halted at the time.

The two processes originally developed to manufacture molnupiravir used a nucleic acid called uridine as a starting material, and one of M4ALL's major changes was to use a different nucleic acid, cytidine, which is less expensive and more readily available.

The team also developed a more efficient way to group the molecules of the drug together, and a new high-yield enzymatic process they implemented requires only two chemical transformations, cutting the number of steps in half.

All of these updates to the manufacturing process cut the cost to produce the drug from about $2,000 per kilogram to less than $200 per kilogram.

"In the end, we developed two alternative ways of making the compound," Dr. Gupton said. "We can make it by a straight chemical process, or we can take one of the steps and do it enzymatically. So, people who have experience with using enzymes in commercial operations can use that process, or people who don't have that experience can do a straight chemical synthesis. We have very strong evidence that the processes that we have developed are being taken up by commercial manufacturers around the world based on a dramatic increase of cytidine purchases, which is the key building block for our process."

As part of its agreement with the Gates Foundation, M4ALL always publishes its findings online and makes them available to any manufacturer. In this case, Dr. Gupton's team went a step further, publishing in two major journals — *Chemical Communications* and *ACS Omega*.

M4ALL AND PAXLOVID

Paxlovid is an antiviral treatment used to help speed recovery from COVID-19 in people with mild to moderate symptoms but who are at high risk of bad cases. In clinical trials, the drug reduced the risk of hospitalization or death by 89% compared with a placebo. The Medicines for All team is taking an end-to-end approach by examining two of the key starting materials that represent a major cost component of the active ingredient. In parallel, the group is evaluating alternative and potentially more efficient methods to convert the starting materials into the active ingredient. This collaboration between Pfizer, the Bill & Melinda Gates Foundation, and Medicines for All represents a unique opportunity to address this major health care issue.

IMPACT ACROSS THE GLOBE

The alternative manufacturing processes for molnupiravir and Paxlovid are expected to prevent supply chain difficulties and reduce costs around the world for drugs that have been shown to reduce risk of severe illness by 30% and 89%, respectively. Merck and Pfizer are facilitating these positive outcomes by licensing the drug to Medicines Patent Pool for production in low-and middle-income countries.

In addition, Pfizer is partnering with the United Nations Children's Fund (UNICEF). In March, *The Wall Street Journal* reported that Pfizer plans to "sell up to four million treatment courses of its COVID-19 pill Paxlovid, which will go to 95 low- and middle-income countries as part of the company's effort to expand access to the pill beyond wealthy countries." Pfizer said Afghanistan, Pakistan and Zimbabwe are among the countries where UNICEF will distribute the pill.

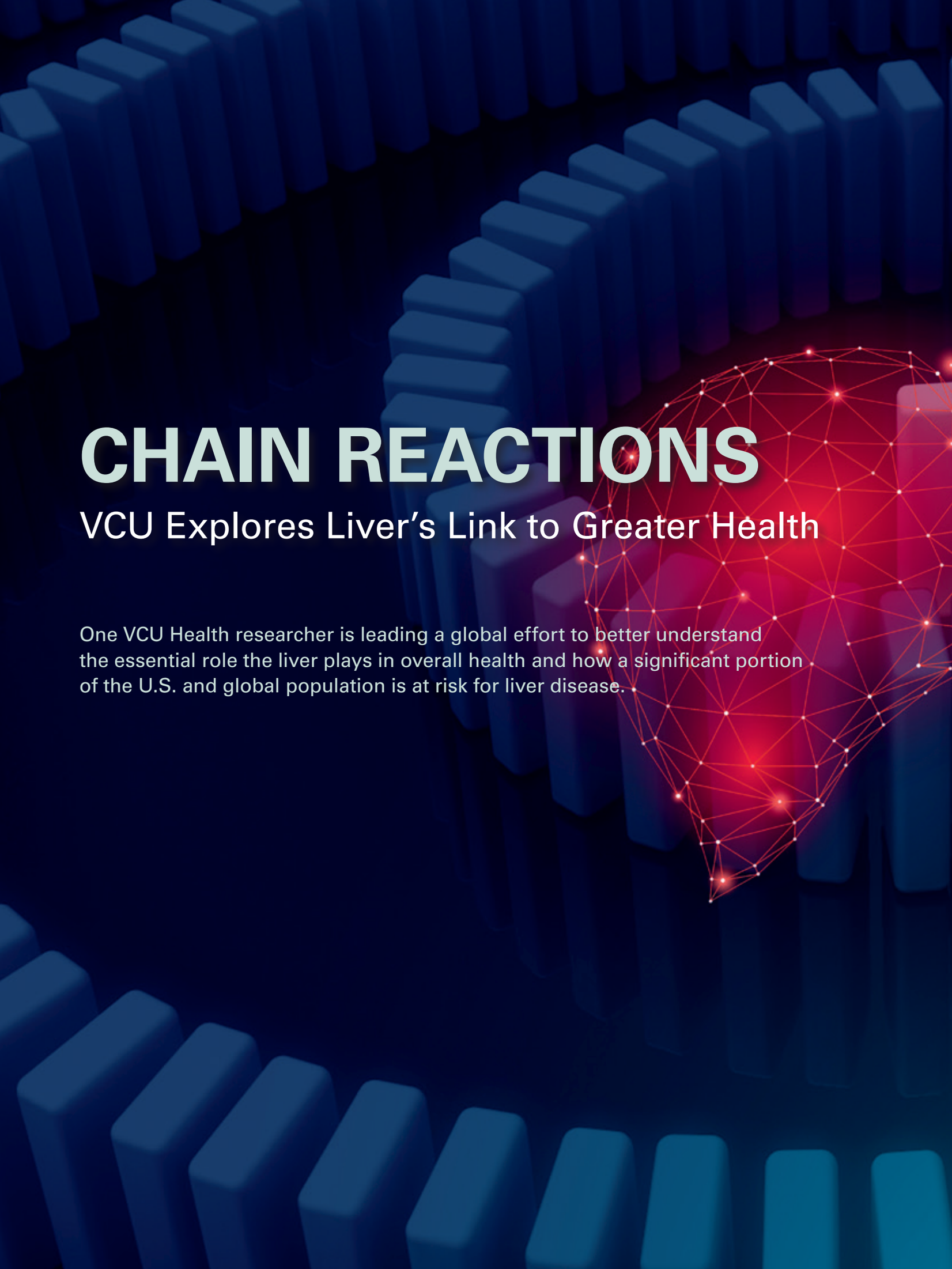
While the new processes created by M4ALL are published and available to anyone, Dr. Gupton has been working with several nations and specific manufacturers to answer questions and provide tips on best practices in manufacturing these drugs. Recent talks with facilities in South Africa could lead to M4ALL's process guiding development of one of the first APIs ever produced on the African continent.

Wealthy countries such as Australia, South Korea and the U.S. were quick to reach supply deals with Merck, but the pharmaceutical company's licensing deal with Medicines Patent Pool is an "effort designed to avoid the kind of rich-poor split in access that has marked the COVID-19 vaccine rollout," reported *The Wall Street Journal* in October.

Many of the countries covered by the molnupiravir and Paxlovid licensing deals have limited COVID-19 vaccine supplies. Supported by Gates Foundation funding, these are the countries in which M4ALL is working alongside generic drug manufacturing facilities to help implement its new cheaper, easier, higher-yield process.

"To end this pandemic, we need to ensure that everyone, no matter where they live in the world, has access to lifesaving health products. The unjust reality, however, is that low-income countries have had to wait for everything from personal protective equipment to vaccines. That is unacceptable," said Melinda French Gates, co-chair of the Gates Foundation, in a press release. "(This) commitment will ensure that more people in more countries get access."

If you are interested in helping the Medicines for All Institute improve access to critical medications in the U.S. and around the globe, contact Brian Campbell, senior campaign gift officer, at 804-828-1475 or becampbell@vcu.edu.



CHAIN REACTIONS

VCU Explores Liver's Link to Greater Health

One VCU Health researcher is leading a global effort to better understand the essential role the liver plays in overall health and how a significant portion of the U.S. and global population is at risk for liver disease.

By Paul Brockwell Jr.

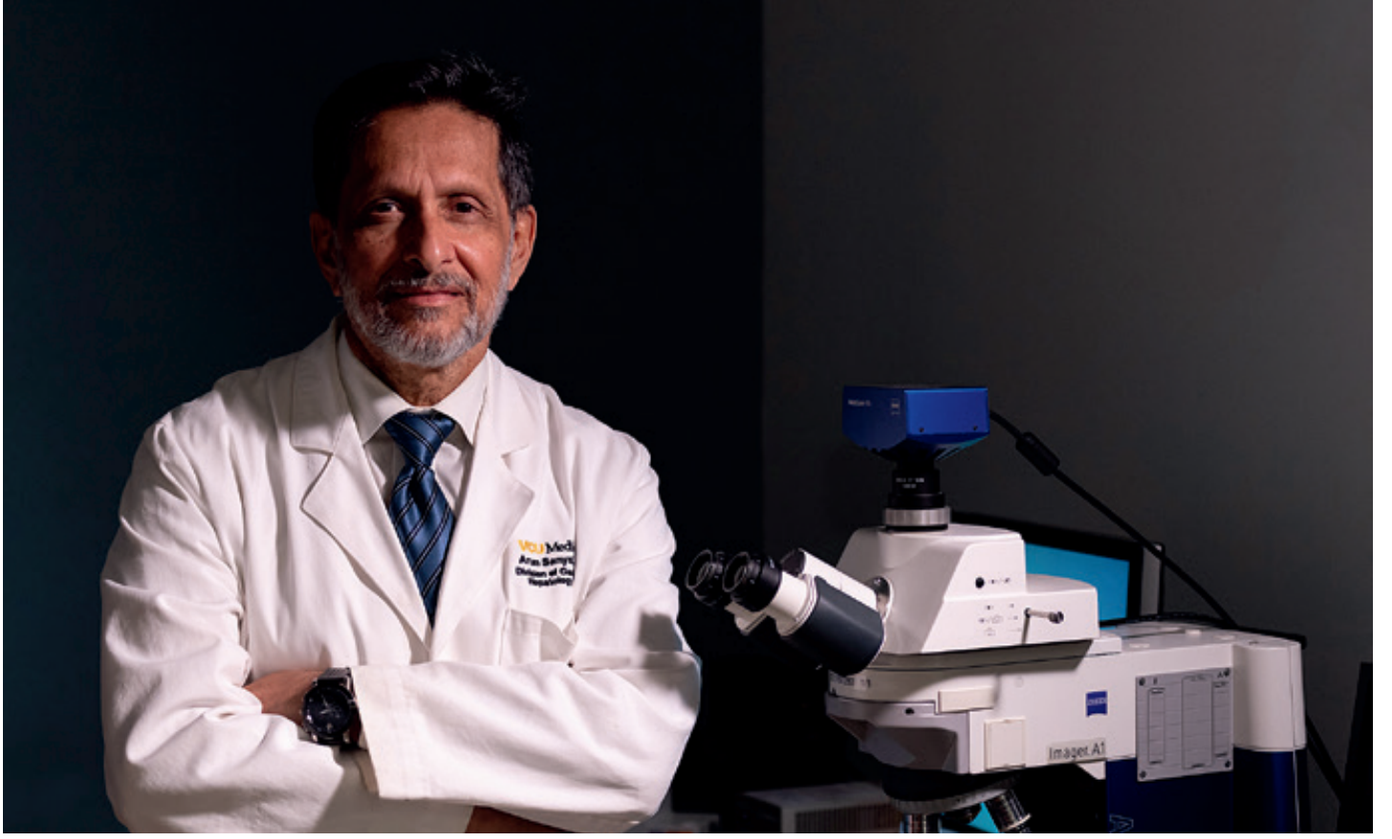
The human liver is around 15 centimeters wide and weighs a little over three pounds on average. It's the body's second-largest organ after the skin. This reddish-brown powerhouse sits beneath the diaphragm, on top of the stomach in the upper right-hand abdominal cavity. And it's probably the body's most unsung hero.

When a person nicks themselves shaving, the liver produces proteins to regulate blood clotting and ensure the bleeding stops. After a good meal, the liver works overtime to aid digestion of rich food, filtering blood as it leaves the stomach and intestines and removing harmful things like cholesterol and bacteria before they wreak havoc in other parts of the body. There are more than 500 vital functions which the liver helps the body perform, and the organ's health is linked to heart disease, cancer, diabetes, kidney failure and Alzheimer's.

"The liver is the only way you can get rid of extra cholesterol," said Arun Sanyal, M.D., professor of medicine, physiology and molecular pathology in the Department of Internal Medicine at the VCU School of Medicine. "Those who take statins are really taking a drug that works on the liver to lower cholesterol. The liver controls how the heart works, and it generates fuel and controls the supply of energy for all the body's other organs. It's complicated stuff."

Few people know more about the liver's inner workings than Dr. Sanyal, the Z. Reno Vlahcevic Professor of Gastroenterology and inaugural director of the new Stravitz-Sanyal Institute for Liver Disease and Metabolic Health. He has been researching liver health for decades after seeing patients develop liver disease and only having organ transplant as an option to survive. Dr. Sanyal knows most individuals have too little appreciation for the lobe-shaped organ he has grown to love and the critical role it plays in overall health. He chairs the National Institutes for Health's clinical research network for nonalcoholic steatohepatitis (commonly abbreviated NASH). NASH is a form of nonalcoholic fatty liver disease in which inflammation and fat deposits in the liver cause fibrosis, or scarring, which can lead to permanent damage and cirrhosis. In early stages, the damage can be alleviated, but no treatments currently exist for later-stage NASH, and transplants alone cannot solve the problem. Nationally, there are only around 9,000 liver transplants each year. Three people die on the liver transplant list each day.

Contrary to what most people assume, liver disease should not be primarily associated with alcohol and drug abuse. More than a quarter of the world's population goes about their everyday lives unaware of a potentially significant threat to their health. Many have probably never heard about nonalcoholic fatty liver disease, but new evidence suggests they should all be paying attention to Dr. Sanyal's research.



Arun Sanyal, M.D., has published several research studies in *The New England Journal of Medicine* that document his success in developing a better understanding of the prevalence of nonalcoholic fatty liver disease and the urgent need to screen and offer interventions for large portions of the U.S. adult population. *Photo: Allen Jones, Virginia Commonwealth University*

Dr. Sanyal has been studying liver dysfunction and disease for more than 25 years, and in his recent articles published in *The New England Journal of Medicine*, he paints a concerning picture for many Americans, unless the medical profession invests in the diagnostic tools and treatments needed.

Nonalcoholic fatty liver disease is a condition where fat deposits in the liver cause inflammation and scarring that can threaten the liver's function as well as instigate other issues in the body's major organs. The condition is more closely linked to obesity and diabetes than the more familiar liver diseases associated with alcohol consumption. That means many people, while running errands, enjoying time with family and working, are also gradually accumulating fatty deposits in their livers that can lead to serious organ disease and death if left undiagnosed and unaddressed.

Often, the warning signs come too late to reverse the damage. As fat builds up in the liver, inflammation and scarring affect the liver's function in more than 500 vital processes for the body. Left unaddressed, the scarring and inflammation could progress to cirrhosis of the liver, making organ transplant the only option. Demand for liver transplants has grown steadily since 2012, and the potential prevalence of severe nonalcoholic fatty liver disease will exponentially dwarf the supply of potential organs.

Since the late '90s, Dr. Sanyal has worked to develop a better understanding of the prevalence of the disease and its trajectory after recognizing troubling trends in his clinical work at VCU Health. Strangely, patients with no history of alcohol abuse were showing up with signs of liver disease. His curiosity to understand the cause has animated his research, which has changed the way physicians think about organ diseases and helped to define a still-emerging concept of metabolic health as a framework for understanding the interconnected nature of the body's functions and the diseases that affect organs. In fact, metabolic health issues create, in the view of Dr. Sanyal, competing threats to the patient's life by interfering with normal function in the major organs.

"I have always felt that we're very fortunate in an academic setting that when we walk in to see a patient in a clinic, the patient is like a road map," Dr. Sanyal said. "It's like reading a living textbook of medicine. Over the last 20 years, we have not only been able to better understand at a chemical, molecular and a cellular level how liver disease develops and progresses to cirrhosis, but also how it is linked to all these other conditions like diabetes, heart disease, kidney disease and others.

Taken together, Dr. Sanyal said, clinical understanding has evolved into the idea that doctors really should not be thinking of these various conditions as isolated issues because people who have one will frequently have the others as well. That's a way of thinking Dr. Sanyal refers to as metabolic health, and he's been a leader in elucidating the concept through his work on liver disease.

His latest findings were published in *The New England Journal of Medicine*. Through a multi-site longitudinal study of 1,773 adults followed over four years, Dr. Sanyal was

able to identify the progression patterns of the disease and the associations between advanced stages of fibrosis and liver-related complications and death. The research underscores the urgency to test for nonalcoholic fatty liver disease, particularly in patients with Type 2 diabetes, a recommendation recently added to guidelines by the American Diabetes Association.

"Historically, many primary care physicians and diabetes specialists have felt that, because the roots of the disease lie in insulin resistance, then if we treat the diabetes, we've already taken care of the problem," Dr. Sanyal said. "And what this shows is that, even within an especially obese, diabetic population, those who have advanced fibrosis are dying of liver disease. Just treating diabetes doesn't get the job done."

DIAGNOSING METABOLIC HEALTH ISSUES

In the U.S., it's estimated that there are 2 million individuals living with nonalcoholic steatohepatitis and 1.3 million living with fibrosis stages three and four. Based on mortality rates observed in Sanyal's study, around 40,000 of those people die every year.

The sheer number of adults with fatty deposits in their liver makes the traditional diagnostic tool — a biopsy — an all-but-impossible task. Given the prevalence of risk factors like obesity and Type 2 diabetes in the U.S., there are simply too many potential patients who need screening.

"The need for a biopsy becomes a barrier to access to care," Dr. Sanyal said. "We do not have 50 million people trained to do the number of biopsies we would need. We need a simple and routine way to test."

Dr. Sanyal and his team are working to develop blood-based markers that can be used with imaging-based markers to assess in a noninvasive way how active the fatty liver disease is in a patient. He hopes his work will answer whether fat deposits are present in the liver, how actively are those deposits causing damage, and whether the liver has begun to scar in ways that represent disease progressions. Through this type of diagnostic tool, Dr. Sanyal wants to eventually enable physicians to determine who has significant disease and is at risk of complications and death.

WHAT'S NEXT?

There will be a desperate need for treatments that can stop or reverse the progression of scarring in patients with

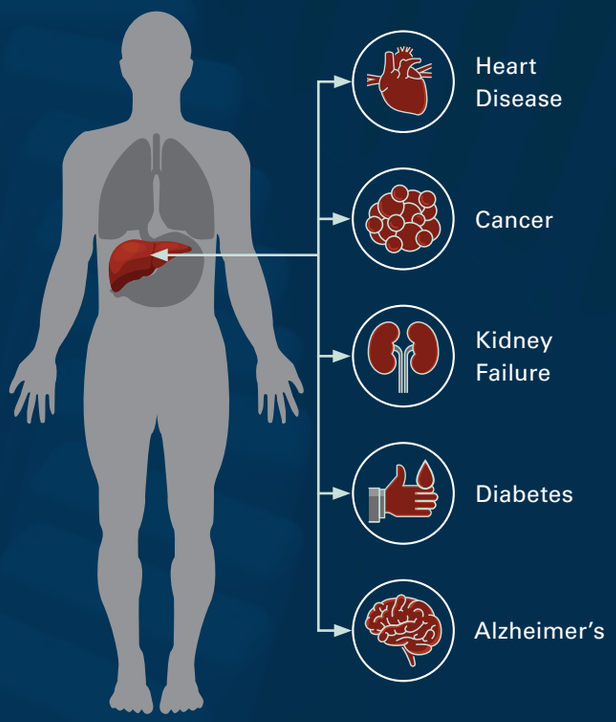
LIVER DISEASE

It's more common than you thought.

1 BILLION

People **worldwide** have some form of liver disease. It cuts across the full spectrum of society.

Liver problems are linked to



It's a leading factor for the
DECLINE IN LIFE EXPECTANCY
in the United States.

Liver transplants are lifesaving,
BUT IN SHORT SUPPLY.

3

people on the liver transplant waiting list die every day.

"I have always felt that we're very fortunate in an academic setting that when we walk in to see a patient in a clinic, the patient is like a road map... Over the last 20 years, we have not only been able to better understand at a chemical, molecular and a cellular level how liver disease develops and progresses to cirrhosis, but also how it is linked to all these other conditions."

Arun Sanyal, M.D.
Professor of Medicine,
Physiology and Molecular Pathology
Department of Internal Medicine
VCU School of Medicine

nonalcoholic fatty liver disease. While the FDA has not currently approved any drugs for the treatment of nonalcoholic fatty liver disease, Dr. Sanyal has already been thinking beyond diagnosis, interventions and disease regression toward potential therapies. His latest journal publication outlined possible treatments of nonalcoholic fatty liver disease that could reduce the need for liver transplants in patients with advanced disease and save lives.

Knowing the problems start when the body is unable to adequately regulate insulin, researchers are exploring the use of diabetes drugs to improve insulin resistance. A few months ago, Dr. Sanyal published additional research in *The New England Journal of Medicine* demonstrating his evaluation of how one drug for diabetic patients, semglutide, helped resolve fatty liver disease in almost 60% of patients. That drug is currently in phase three trials, which Dr. Sanyal hopes will replicate the successful results. But he continues to explore additional therapeutic avenues to address fatty liver disease.

"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. Lastly, we're working on very cheap, simple solutions such as vitamin E. We published a paper 10 years ago 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."

Dr. Sanyal hopes that once he and his research partners are able to identify the right dose, they will be able to conduct a more definitive study to show if vitamin E can reduce scarring of the liver and progression to cirrhosis. He's most excited about this potential treatment because it would mean that patients could have an extremely affordable first-line therapy that would be easy to access across the globe, even in countries where access to care can be challenging.

If you are interested in learning about ways to align with and support the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, contact Priscilla Cash, senior director of development at the School of Medicine, at 804-827-4933 or priscilla.wiggin@vcuhealth.org.

R. Todd Stravitz, M.D., right, and Arun Sanyal, M.D., are the namesakes of the new Stravitz-Sanyal Institute for Liver Disease and Metabolic Health. *Photo: Allen Jones, Virginia Commonwealth University*

Creating a Transformative Liver Research Institute

The MCV Campus is revolutionizing global health through liver research. Accelerated by a $104 million private gift, the new Stravitz-Sanyal Institute for Liver Disease and Metabolic Health improves all aspects of health care by connecting patients, researchers and experts across medical disciplines. The historic, transformational gift from R. Todd Stravitz, M.D., and his family's Barbara Brunckhorst Foundation will position VCU as a global leader in liver disease and metabolic health research, teaching and patient care.

Dr. Stravitz, a physician-philanthropist in the Department of Internal Medicine at VCU School of Medicine, dedicated his whole career as a liver clinician and researcher to VCU, including as medical director of liver transplantation at VCU Health's Hume-Lee Transplant Center for a decade. About 1 in 10 Americans has some type of liver disease, and it is one of the top 10 factors reducing life expectancy in the U.S. It is sometimes called a "silent killer" because it can go unnoticed until a liver transplant is the only treatment option.

"The vision for this institute is to make liver transplant the last, but not the only, option for patients," Dr. Stravitz said. "We will do this by investing in gene therapy and working hand in hand with biotech companies. In the process, VCU will train and educate the next generation of world-renowned liver experts."

The Stravitz-Sanyal Institute for Liver Disease and Metabolic Health is building on VCU's position as one of the country's top public research universities and its 50-year legacy of excellence in liver care and research. The patient-centered institute is bringing together the work of several entities already dealing with liver disease or its effects on other organs. These include the hepatology and research teams in the School of Medicine's Department of Internal Medicine, VCU Health's Hume-Lee Transplant Center, Massey Cancer Center and VCU Health's Pauley Heart Center. Over time, VCU Health will be able to serve twice the patient volume for liver-related illnesses.

Focused on translational science, the institute will grow research and health care teams for liver-related clinical specialties, such as nonalcoholic fatty liver disease, end-stage liver disease, liver transplantation, liver cancer, women's liver health issues and rare diseases in hepatology. Arun Sanyal, M.D., professor in VCU School of Medicine's Department of Internal Medicine and a researcher and liver disease specialist at VCU Health, serves as the institute's director.

"The liver impacts the health of all other organs because of its central role in metabolism and how the body uses energy. When the liver shuts down, all organs suffer," said Dr. Sanyal, interim chair of the Division of Gastroenterology, Hepatology and Nutrition at VCU School of Medicine. "Discoveries of the institute will develop new diagnostics and treatments and inform practice guidelines for liver-related diseases around the world, as well as heart disease, cancer, diabetes, Alzheimer's and kidney failure. The status quo of how we treat liver disease is no longer acceptable."

Connecting the Pieces of the Rehab Puzzle

A consortium of Central Virginia institutions rich in history and expertise has come together to establish the region as a national leader in physical rehabilitation care and research.

By Eric Peters and Jackie Kruszewski

Before 2020, physical rehabilitation beds at VCU Health were limited. If someone in Central Virginia suffered a spinal cord injury, they often had to travel hundreds of miles to Atlanta, Pittsburgh or Philadelphia to find the closest nationally recognized, comprehensive rehabilitation centers.

The distance wasn't just a nightmare logistically for recently injured people and their families — it was a barrier to the best possible physical rehabilitation care for those who did not have the means to make such a long-distance, long-term journey.

These challenges could have been very real for Jordan Smalls, who on Labor Day 2020 was in a severe car accident. Emergency medical personnel thought he had died when they first responded to the scene. Smalls' truck had flipped, and he had been ejected. Miraculously, he began breathing again and was transported to the hospital. After his acute care hospital stay, he needed to find an inpatient facility to begin regaining movement in his arms and legs.

The ingredients needed to help people like Smalls and bring a nationally renowned inpatient rehabilitation hospital to Central Virginia all existed alongside one another right here in Richmond for decades. But the region needed foresight, imagination and a partnership among major local institutions to bring it all together. When that happened, a facility emerged that was born of cooperation, prioritized patient outcomes over competition, and now serves the entire East Coast, matching or

surpassing most of its peers across the country in patient outcomes and expertise.

SHELTERING ARMS INSTITUTE, A COLLABORATION WITH VCU HEALTH

Titans of rehabilitation have always existed in Richmond — VCU and VCU Health, Sheltering Arms, and Central Virginia VA Health Care System (CVHCS, the local Veterans Affairs medical center).

With roots dating back to 1862, then formally established near the end of World War II, the VCU School of Medicine's Department of Physical Medicine and Rehabilitation (PM&R) is one of the oldest and most prestigious departments of its kind in the country. The department is strengthened by its nearly 80-year partnership with the Veterans Affairs hospital CVHCS, which fosters world-class care for military heroes and community, promotes the research that makes that care possible, and provides the education to ensure the care continues to advance and evolve.

Existing alongside these institutions has been Sheltering Arms, which began more than 130 years ago as a hospital treating families in Richmond who could not afford to pay. In January 1981, Sheltering Arms became the first private freestanding physical rehabilitation hospital in Virginia. Today, the organization offers a full continuum of rehabilitation and health and wellness services.

Jordan Smalls is rehabilitating after a severe car accident on Labor Day 2020 that left him paralyzed. *Photo courtesy Sheltering Arms Institute*

SAI brings together clinicians, scientists, innovators and technologists ... to provide exceptional care in one place for individuals who have survived strokes, spinal cord injuries, brain injuries and a variety of illnesses.

More than a decade ago, these institutions began discussing and exploring how they could fit their individual pieces of the larger regional rehabilitation puzzle together to better serve the community. VCU and Sheltering Arms signed an agreement in 2016, and by June 2020, they opened a new rehabilitation hospital in Goochland — Sheltering Arms Institute.

The 212,063-square-foot, 114-bed inpatient rehabilitation facility brings together clinicians, scientists, innovators and technologists, drawing upon the strength of its partner organizations to provide exceptional care in one place for individuals who have survived strokes, spinal cord injuries, brain injuries and a variety of illnesses. With the opening of Sheltering Arms Institute, VCU Health moved most of its rehabilitation resources to the new hospital and now sends almost all of its rehabilitation patients to the joint-venture institute.

VCU entered into this partnership having held a model system grant for traumatic brain injury (TBI) since 1987. A model system grant is awarded by the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR) to institutions that are national leaders in medical research and patient care. These institutions provide the highest level of comprehensive specialty services from the point of injury through eventual reentry into full community life. VCU was one of the first four original grantees for the program.

The VCU Model System for TBI provides comprehensive, coordinated inpatient and outpatient care through two complementary programs. The longest-running program is now centered at Sheltering Arms Institute since the organizations began their collaboration. The other program is centered at CVHCS. Both programs conduct research focused on improving care and quality of life for brain injury patients and their families. Points of emphasis include analyzing and improving the benefits of couples support and education, the effectiveness of teaching resilience for survivors, understanding caregiver resilience, and researching the long-term outcomes after brain injury.

One of the first priorities for the VCU-Sheltering Arms-CVHCS partnership was to add another area of national leadership to its repertoire of research and care. The new consortium immediately set its sights on earning an additional model system grant — one for spinal cord injury.

To reach that goal, there was a substantial 18-month planning and grant preparation effort among departments across VCU, SAI, CVHCS and community stakeholder groups. "During that time, we aligned resources and interests, mapped out potential projects, and wrote a competitive grant that we felt highlighted our research strengths and was highly congruent with local and national stakeholder priorities," said Ronald Seel, Ph.D., executive director of the Center for Rehabilitation Science and Engineering (CERSE) in VCU's PM&R department. "You're not eligible to get an SCI model system grant if you don't demonstrate a strong SCI continuum of care from acute to community, so the SAI partnership was essential. Our relationship with CVHCS was also an important component as that facility houses the largest SCI rehab unit in the U.S."

In September 2021, the regional consortium of VCU, Sheltering Arms and the CVHCS earned federal designation as one of only 14 Spinal Cord Injury Model Systems Centers in the U.S. CERSE was awarded the grant and now leads the Virginia Spinal Cord Injury Model System.

"These grants are highly competitive, so to have both the TBI and SCI grants is a recognition about this partnership, our research capabilities and our leadership in the TBI and SCI fields," Dr. Seel said. "If you're a college sports fan, it would be similar to there being very few universities who have both top 15 football and basketball programs. The grants allow us to do more innovative research and more large data research in which the associated evidence can be translated into better clinical care and outcomes."

With the marriage of the TBI and SCI model system grants, the rehabilitation and research partnership here in Central Virginia is one of only four centers in the nation to have the dual designation.

The partnerships, the collaboration and the research have all paid off for patients.

A CONSORTIUM FOR CARE

More than 3,500 patients from 18 states have received care at Sheltering Arms Institute since it opened.

"The combined clinical expertise of VCU Health and Sheltering Arms makes this institute the most complex rehabilitation hospital in Virginia," said Alan Lombardo, CEO of Sheltering Arms Institute. "We are the preferred site of rehabilitation care for spinal cord injury, brain injury and stroke patients. Additionally, we are able to care for patients who have had organ transplants, severe burn injuries, polytrauma and utilize ventilators. Our clinicians have already achieved functional outcomes for our patients that are in the top 15th percentile nationally."

There are four units in the hospital to support the variety of its patients' needs. The 9,251-square-foot main therapy gym and three satellite gyms are equipped with everything

Sheltering Arms Institute, a partnership between VCU Health and Sheltering Arms, is a 212,063-square-foot, 114-bed inpatient rehabilitation facility that has served more than 3,500 patients from 18 states. *Photo courtesy Sheltering Arms Institute*

> "Sheltering Arms Institute coming to fruition has made me proud as a Virginian, having seen two competitive entities join together to afford people with disabilities the opportunity to recover."
>
> Richard Bagby, Executive Director
> United Spinal Association of Virginia

from full-body assistive devices to fine motor skill development tools. The Motek Rysen, for example, is a 360-degree overground assistive walking device that is the first of its kind anywhere in North America. Instead of track-based linear movement, it allows free range of motion to support activities like basketball and Ping-Pong. On the other end of the movement spectrum is the Neofect Smart Glove that helps patients regain fine motor skills, as well as a robotics area, virtual reality technology and much more.

Tools are integrated throughout the entire hospital so patients can practice rehabilitation techniques outside of the gym, including the Bioness Vector Elite, a track-based, bodyweight support system located inside patients' rooms and throughout the hallways to help patients practice walking to and from most places in the facility.

All of this was designed specifically for rehabilitation care with input from former rehab patients, caregivers and, of course, health care professionals. One of the rehab patients who provided input is Richard Bagby, executive director of United Spinal Association of Virginia.

"From the outset, I was impressed with Sheltering Arms and VCU's intentionality in including a broad spectrum of stakeholders so that they could ensure that all perspectives, from clinicians to past patients to community partners, would be heard in an effort to make Sheltering Arms Institute as beneficial of a facility and community as possible for everyone," he said.

"This set the tone to achieve the best possible experience for SAI patients in both comfort and rehabilitation following a life-altering injury or illness," Bagby said.

"The product ended up being a unique approach to universal design in that each space or element of the building is accessible to all, no matter functional level, while also being part of the rehabilitative process."

All patient rooms are single-occupancy and meant to be a "home away from home," while maintaining the functionality of a traditional hospital room. They include ceiling lift systems, sliding barn doors to the bathroom, furniture that can be converted into beds for guests, roll-in showers, and flooring that is both comfortable for staff to stand on for long periods of time and suitable for a new wheelchair user.

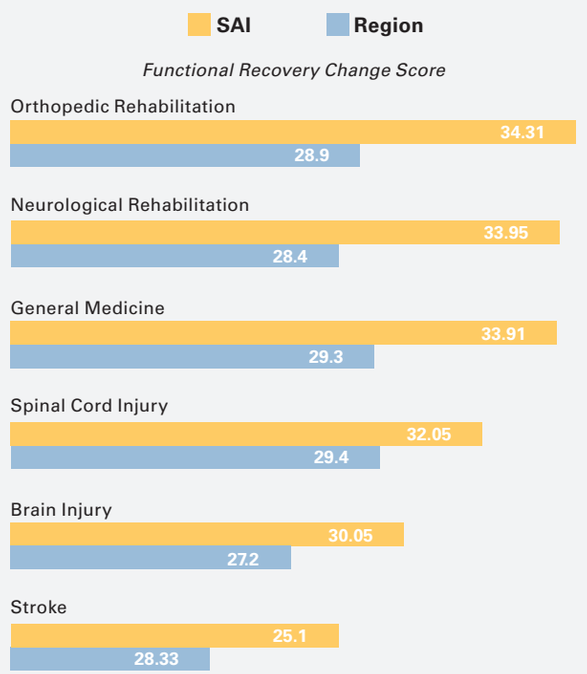
"Sheltering Arms Institute coming to fruition has made me proud as a Virginian, having seen two competitive entities join together to afford people with disabilities the opportunity to recover independence and normalcy in their lives following a devastating injury or illness," Bagby said.

Sheltering Arms Institute

3,679

Admissions Since Open

Improvement by Program (March 2021–March 2022)



After an acute care hospital stay. Jordan Smalls found Sheltering Arms Institute to help him regain movement in his arms and legs. *Photo courtesy Sheltering Arms Institute*

"Professionally, as the executive director of a nonprofit organization serving Virginians living with SCI/D, the new institute has given me hope and assurance that together we can continue building an inclusive community that benefits disabled and able-bodied."

All of the planning and all of the technology have made a difference for patients like Jordan Smalls, who fortunately found Sheltering Arms Institute after his car accident and acute care hospital stay.

"When I came in, I could not walk," Smalls said. "It is very hard to cope with this. A lot of days I just cried, and at night I couldn't sleep, but when I came to this hospital I felt way better because I was getting movement [in my legs]. I feel some sense of hope, but it's really hard. Don't ever get in your head that you want to give up. Keep on fighting, because every day you're going to get better, and this hospital really helps you get better."

A CONSORTIUM FOR RESEARCH

VCU is the anchor in the regional rehabilitation partnership, supplying some care providers and researchers at all of the locations and leading the collaborative research enterprise — CERSE — that spans all three organizations.

"From a neurotrauma perspective for inpatients and outpatients, you have here in Richmond one of the best continuums of rehabilitation care that you can get any place in the U.S.," Dr. Seel said. "Sheltering Arms Institute, the VA and VCU Health all deliver incredible clinical care. Then they all have a tight relationship with our center that brings together interdisciplinary researchers across VCU and the VA to test innovation, new technology, robotics, behavioral interventions and even analyze big data to understand what interventions might work better."

Dr. Seel gives credit for this partnership and these accomplishments to many people, dating back to VCU's Harold Young, M.D., and his pioneering leadership in acute traumatic brain injury research in the 1980s and 1990s, and continuing through David Cifu, M.D. Dr. Cifu chairs VCU's PM&R department and is associate dean for innovation and systems integration, overseeing VCU, VA and Sheltering Arms Institute clinical and research partnerships.

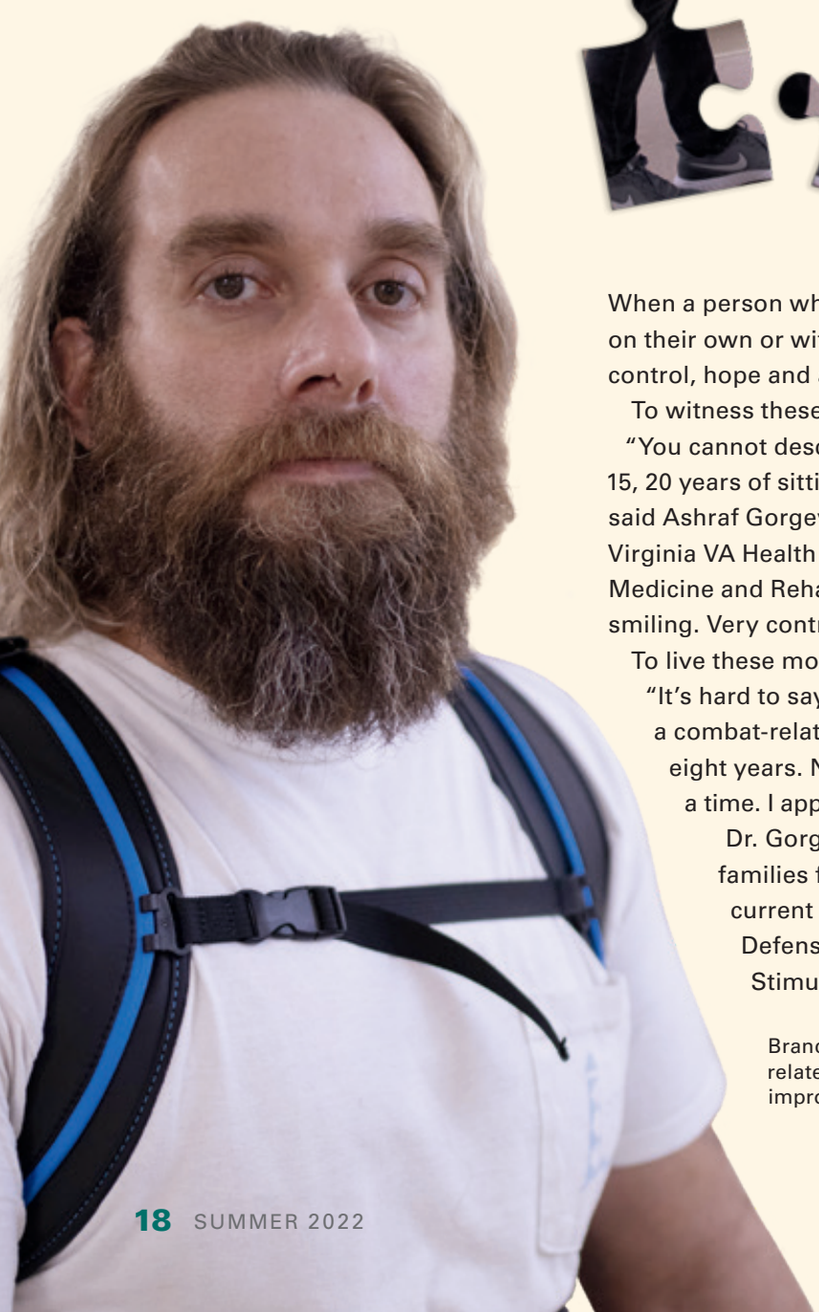
Since 2017, CERSE has expanded faculty and staff, earned $75 to $80 million in new grant funding, and been designated as a VCU-wide center, collaborating with researchers across 24 VCU departments and six institutes and centers.

Today, CERSE funding totals $115 million, advancing its mission to connect researchers across the three institutions and accelerate rehabilitation breakthroughs that empower people to overcome barriers and thrive.

"During my journey living with quadriplegia since I sustained a traumatic spinal cord injury 13 years ago," Bagby said, "as well as through my experiences administering the United Spinal Association of Virginia, I grew more and more aware that Richmond has long had all of the variables in practice which make up a premier rehabilitative experience, including knowledge, expertise and technology. Unfortunately, they were scattered across the region. What the selfless collaborative effort put forth by Sheltering Arms and VCU has done is meld the best of both systems together, while giving them an extraordinary state-of-the-sciences environment, which allows clinicians to reach their highest potential of professional practice. All of this culminates in the absolute best outcomes for Virginians and others as they now have access to the highest rehabilitative care without having to leave their community and support systems to seek out other facilities across the country."

If you are interested in supporting leading neurotrauma care and research right here in Central Virginia, contact Nathan Bick, senior major gifts officer, at 804-827-0387 or nathan.bick@vcuhealth.org.

WALKING WITH RESEARCH



When a person who has been paralyzed stands or walks again, whether on their own or with assistance, the moment can create or fortify freedom, control, hope and a new future.

To witness these moments is one thing.

"You cannot describe that emotion of the patient and family when, after 15, 20 years of sitting in a wheelchair, someone is standing for the first time," said Ashraf Gorgey, Ph.D., director of spinal cord research at the Central Virginia VA Health Care System and professor in the Department of Physical Medicine and Rehabilitation at the VCU School of Medicine. "Tears and smiling. Very contrasting emotion happening at the same time."

To live these moments is another thing.

"It's hard to say," said Brandon Kasnick, who in 2013 was paralyzed after a combat-related seizure led to a fall. "My lower body hasn't worked in eight years. Now I'm standing. I try to stay calm and take it one day at a time. I appreciate it, and I'm just trying to stay present in the moment."

Dr. Gorgey has been creating these moments for individuals and families for 17 years. Kasnick is enrolled in one of Dr. Gorgey's current projects that is supported by a 2020 Department of Defense-funded $3.7 million grant. The project — Epidural Stimulation and Resistance Training for Overground Locomotion

Brandon Kasnick (left and above) was paralyzed in 2013 after a combat-related seizure led to a fall. He is now participating in a clinical trial to improve his mobility and health. *All photos: Tyler Trumbo, MCV Foundation*

after Spinal Cord Injury — is determining whether spinal cord stimulation will help patients who are paralyzed to stand and produce step-like movement with the support of an exoskeleton device.

It is the first study anywhere to apply a new CVHCS-developed epidural stimulation process in restoring muscle control for patients with spinal cord injuries.

Dr. Gorgey has long worked with exoskeletons — robotic suits that help people with spinal cord injuries walk — but the epidural stimulation that he is using today is novel.

The two components of the study play very different, yet vital, roles. The epidural stimulation method involves a device that is implanted under the skin with wires that are placed in the spinal canal to send electrical impulses to the spinal cord. The stimulation mimics brain signals that normally would be sent to the spinal cord to initiate the process of standing and walking.

After these signals are in place, there still lies the challenge of muscle atrophy. "People who are in wheelchairs are in what we call a gravity-dependent position," Dr. Gorgey said. "Much like astronauts, their muscles weaken, and they have to learn to use them again. But unlike astronauts who are in space for 100 days or so, people who are paralyzed are in this position for years."

The exoskeleton addresses these muscle issues by providing overground step-like movement that builds muscle, restores muscle memory and allows the spinal cord circuitries to restore. The process requires enormous and extensive training and may reach three to five times weekly for up to four hours per day.

"My lower body is learning how to work again," Kasnick said. "It's a process. It's like a baby who doesn't have control of his limbs, and one day they learn to crawl, then they learn to walk."

As time passes and muscles strengthen, the exoskeleton can be set to provide as much or as little assistance as needed. Kasnick, for example, began his participation in the research in December 2020 needing 100% assistance from the exoskeleton. By October, he only needed 55% assistance from the device.

Ashraf Gorgey, Ph.D., is director of spinal cord research at the Central Virginia VA Health Care System and professor in the Department of Physical Medicine and Rehabilitation at the VCU School of Medicine.

The initial observations of improved ability to walk with assistance have been impressive, but the project is about more than helping people walk again. This therapy could ultimately lead to a standard treatment for spinal cord injury that increases cardiovascular health and bladder and bowel function.

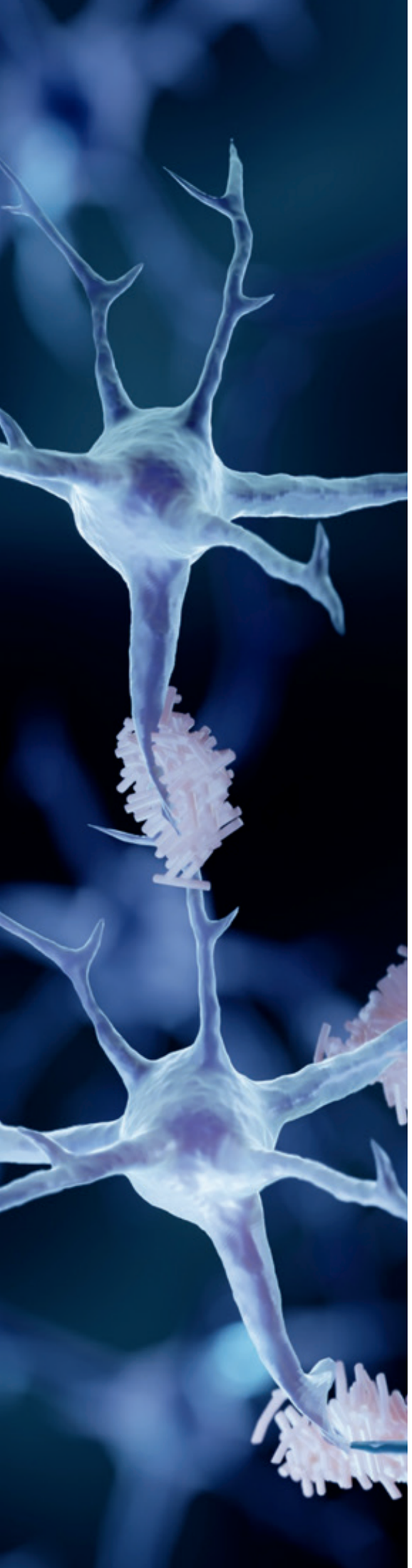
Cardiovascular disease and Type 2 diabetes are the leading killers of people who are paralyzed, so even if people who receive this therapy cannot walk independently after treatment, any level of improved mobility could add years to their lives.

"These patients experience muscle atrophy, bone loss, bedsores, obesity, kidney problems and much more," Dr. Gorgey said. "There are a lot of challenges that you just don't think about that impact their quality of life."

Thanks to the unique partnership among top-flight institutions in Central Virginia, the infrastructure now exists for those challenges and many more to be addressed, researched and reduced in people who are working hard to regain functions of everyday life — in the region and across the country.

Out of the Dark

A once rare disease is now much more prevalent, and VCU Health is a global leader in research and treatment.



By Eric Peters

Battling a rare disease means many things for those who are faced with such a challenge. Individuals and families in these situations routinely navigate delayed or completely absent diagnoses, limited treatment options, high drug prices and uncertainty about where to find the best care.

Amyloidosis, an often fatal buildup of proteins in organs that interferes with their normal function, has traditionally been one of these diseases. For one type of amyloidosis, the only approved drug therapy carries a $225,000 per year price tag, making it the most expensive cardiovascular drug ever launched in the U.S. Further, there is only one health system in Virginia where patients can find comprehensive treatment for amyloidosis. And perhaps most strikingly, there is widespread misunderstanding within the health care community about the disease.

A team of researchers and care providers at VCU Health are global leaders in changing these realities for people who live with amyloidosis now and in the future. Leading that team is Keyur Shah, M.D., the David E. Tolman Professor in Heart Failure at VCU Health. He believes the problem is bigger than anyone realizes, positing that the misunderstanding and lack of awareness have led to massive underdiagnosis, and that amyloidosis is in fact not rare at all. He says that often when the public hears of a person dying of "natural causes," "old age," or heart disease that has no apparent cause, the culprit is amyloidosis.

Thus, cultivating more treatment options and improving awareness within the medical community to improve diagnosis could save countless lives.

Dr. Shah sees a future in which diagnoses can be made earlier; patients can be directed to comprehensive treatment facilities like VCU Health; and better, less expensive drugs can be studied and made available. He and his VCU Health colleagues are on the frontlines of the movement to educate, treat and bring these new therapies to market. In 2020, their work positioned VCU Health as one of the top enrollment sites in the world for a clinical trial examining a new amyloidosis drug, and that was made possible because over the past decade, the team has built the only access point for comprehensive cardiac amyloidosis treatment in Virgina.

WHAT IS AMYLOIDOSIS?

There are more than 100 proteins in the human body that can create amyloid, which is a pink substance that builds up in organs causing amyloidosis. This amorphous material that is transported throughout the body is created when proteins unfold and then refold. Like pink cement, amyloid pours into organs, fills the space between the cells and destroys tissue.

In the heart, the muscle becomes thick and stiff. The process can occur in a matter of months, or it can take years, slowly causing heart failure, arrhythmias or valve disease. If it goes undiagnosed, patients can die suddenly because the heart is so filled with amyloid that it stops contracting.

The Formation of Amyloids

Amyloid is a substance caused by the misfolding of protein. Amyloid binds together into rigid, linear fibers (fibrils) that deposit in the tissue and organs.

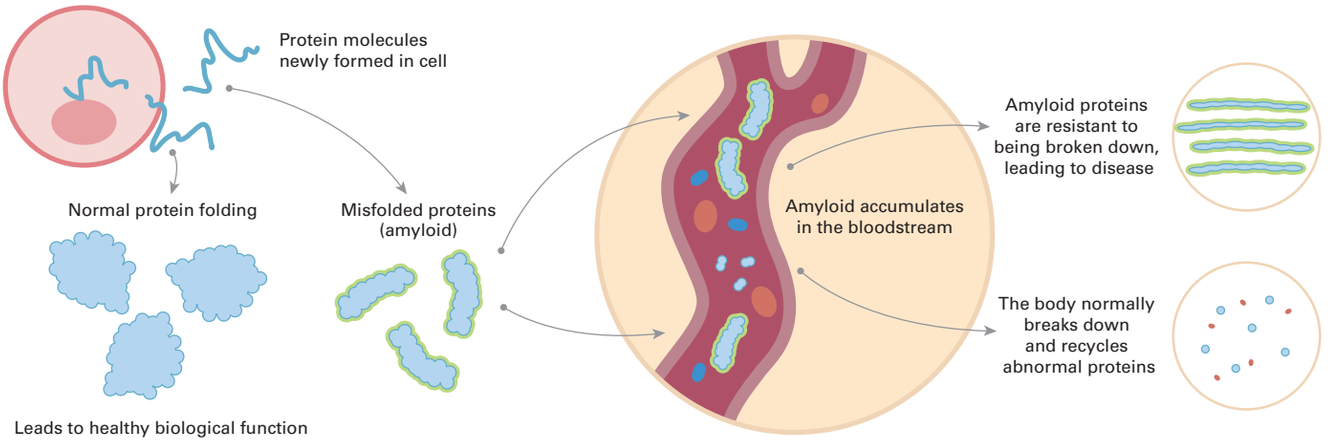


Illustration concept: Jennifer Fairman

> "For people who are 80 or 90 years old and die of supposedly 'natural causes,' one in four of them have this amyloid [acquired ATTR] in their heart."
>
> Keyur Shah, M.D.
> David E. Tolman Professor in Heart Failure
> VCU Health

There are three main types of amyloid disease that affect the heart.

Light chain amyloidosis (AL)

Also known as primary amyloidosis, light chain amyloidosis occurs when bone marrow produces too much amyloid protein. It often affects the heart, lungs, kidneys, liver, stomach, intestines and nervous system. Early detection is important, and treatment reduces symptoms and limits further amyloid buildup.

AL amyloidosis is similar to multiple myeloma and has to be treated quickly with chemotherapy. Once the heart is affected, if left untreated, survival time is six months.

Age-related amyloidosis (acquired ATTR)

This variety, which is also known as wild-type amyloidosis, is caused by a liver protein called transthyretin (TTR). During aging, TTR can accumulate in the heart, making it an underdiagnosed cause of heart disease in patients over the age of 60. In addition to heart problems, patients often have carpal tunnel syndrome, spinal stenosis and/or nerve pain. These symptoms may occur years before the disease affects the heart. With early identification, therapies can slow or halt age-related amyloidosis.

"For people who are 80 or 90 years old and die of supposedly 'natural causes,' one in four of them have this amyloid in their heart," Dr. Shah said. "So, what we're better understanding is there's a large population of patients in their late 60s and 70s that start developing heart disease for no obvious reason, and what's actually happening is they're experiencing amyloidosis amyloid deposition."

Hereditary amyloidosis (hereditary ATTR)

Hereditary ATTR is caused by a mutation in the TTR gene. The predominant variant in the U.S. is called the V1221. It came from West Africa during the slave trade, so it largely affects families who've been rooted in the southeastern U.S. and the Caribbean. One in 20 Black Americans carries this mutation, which doesn't mean all of them have amyloidosis, but it does increase the risk of any heart disease.

Acquired and hereditary ATTR are beginning to be recognized as much more prevalent than initially perceived. Until recently, the only way to diagnose the disease was a heart biopsy, which Dr. Shah says was part of the problem.

Sarah Paciulli, a nurse practitioner, and Keyur Shah, M.D., lead the only team in Virginia delivering comprehensive amyloidosis care. *Photo: Penelope Carrington, MCV Foundation*

"Amyloidosis symptoms have been blamed on high blood pressure, diabetes and other things," he said. "So, it was mistreated for a number of years until more recently when less-invasive diagnostic techniques were developed. And it might also be the reason that many patients in the past were sort of stereotyped as being difficult to treat or unresponsive to therapies — because providers were treating the wrong disease."

CLINICAL TRIALS AT VCU HEALTH

Once amyloidosis is properly diagnosed, there is no approved treatment for AL amyloidosis and only one FDA-approved drug treatment for TTR cardiac amyloidosis, and its $225,000 price tag puts it out of reach for most patients. By conducting clinical trials at VCU Health, Dr. Shah and his team are international leaders in helping bring additional therapies to market. And through these clinical trials, patients at VCU Health's Pauley Heart Center have access to new therapies earlier than most patients around the country.

ATTRibute Clinical Trial

VCU Health's international leadership is perhaps best exemplified by its effort to screen patients with ATTR cardiomyopathy (ATTR-CM) and enroll them into ATTRibute, a clinical trial testing a novel therapy called AG10. Among 51 recruitment centers in the U.S. and abroad, VCU Health ranks among the top five in recruiting patients into the trial.

AG10 simulates a mutated gene that in the past has been shown to protect against ATTR. It binds the four arms of the TTR protein and prevents it from turning into amyloid. Early data from the second phase is suggesting the medication is very effective for treating ATTR cardiac amyloidosis.

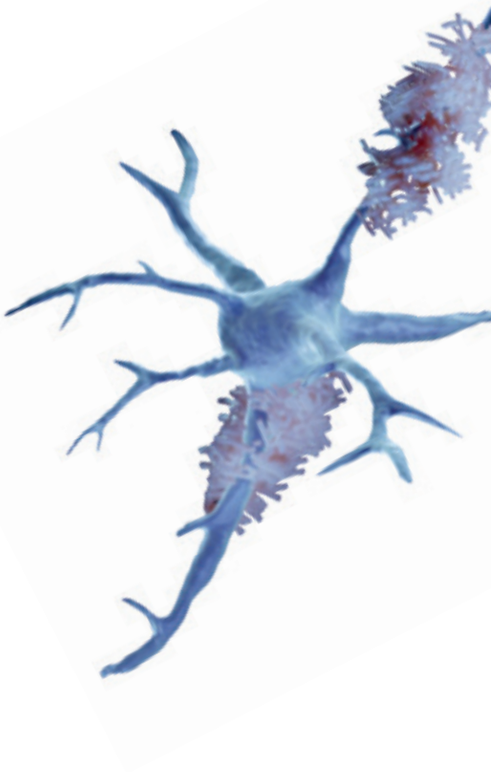
Cardio-TTRansform Clinical Trial

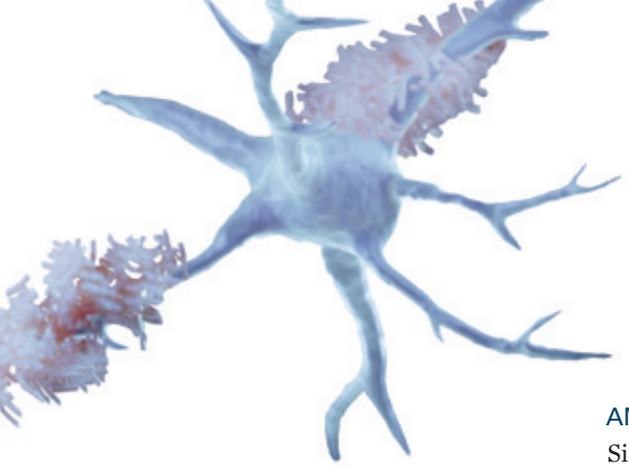
This is a multicenter, double-blind study in up to 750 participants who will be randomized to receive subcutaneous injections of either a drug known as AKCEA-TTR-LRx or a placebo once every four weeks.

"It goes to the liver like a smart bomb," Dr. Shah said. "It prevents the translation of TTR RNA, and the protein is never synthesized. It shuts down production of TTR."

Now in its third phase, this drug's phase one clinical trial showed AKCEA-TTR-LRx reduced TTR up to 94% at the highest dose.

Through both the ATTRibute and Cardio-TTRansform clinical trials, VCU Health is the only access point in Virginia for patients to receive these and other promising amyloidosis drugs.





AMYLOIDOSIS CLINIC

Since Dr. Shah arrived on the MCV Campus, VCU Health has been committed to researching, diagnosing and treating amyloidosis.

He now leads a renowned, multidisciplinary team of top providers, physicians and surgeons in a center of expertise for patients in need of amyloidosis treatment and resources. "We're one of the leading clinical trial enrollment centers in all of the U.S. because of a high population of referrals for ATTR," Dr. Shah said. "Part of that has to do with improved recognition of the disease here in the community through outreach and education."

Sarah Paciulli is a nurse practitioner who works with Dr. Shah's team to treat amyloidosis at VCU Health. She and Dr. Shah are frequently in touch with colleagues in the community to help providers understand when to consider treating someone for amyloidosis.

"Our mission is not just to get patients here in studies and treat the disease," Dr. Shah said. "It's also to make sure all providers know what they're looking for so they can make the correct diagnosis and get patients to the appropriate treatment."

At VCU Health, many state-of-the-art tools are employed to make diagnoses. These include advanced imaging procedures like cardiac magnetic resonance imaging (MRI), cardiac pyrophosphate scans, echocardiograms (heart ultrasounds), electrocardiograms (EKGs), Holter monitoring (to diagnose abnormal heartbeats), and positron emission tomography (PET) scans.

"It's really imperative to use these tools to identify and diagnose patients early on in the disease, because therapies currently available halt progression, but do not reverse the damage," Paciulli said. "And proper diagnosis is also important because people with amyloidosis don't tolerate medications traditionally used to treat congestive heart failure. If these patients are not accurately diagnosed, they are probably going to be given medications that actually make them feel worse."

The most appropriate medications and treatments are part of what the individually tailored care teams at VCU Health provide. These teams include amyloidosis doctors and researchers from several medical and surgical specialties. Depending on the type of amyloidosis the patient has, they may see specialists in cardiology, medical oncology, nephrology, neurology, organ or stem cell transplantation, or palliative care.

"The things that make VCU Health stand out most are our awareness and expertise surrounding care for these patients," Paciulli said. "I think it can be very reassuring to patients to be in a place that understands the disease and knows how to provide help. These patients are often misdiagnosed several times before learning they have amyloidosis. That sometimes wears on their trust and confidence in the medical system, but I think once they get into our clinic, it's a big relief because they now know what's going on, and they know that we know how to make them feel better."

Feeling better begins with using the latest therapies to help make it possible to manage symptoms, limit the spread of harmful amyloid proteins and live an active, productive life.

"The things that make VCU Health stand out most are our awareness and expertise surrounding care for these patients."

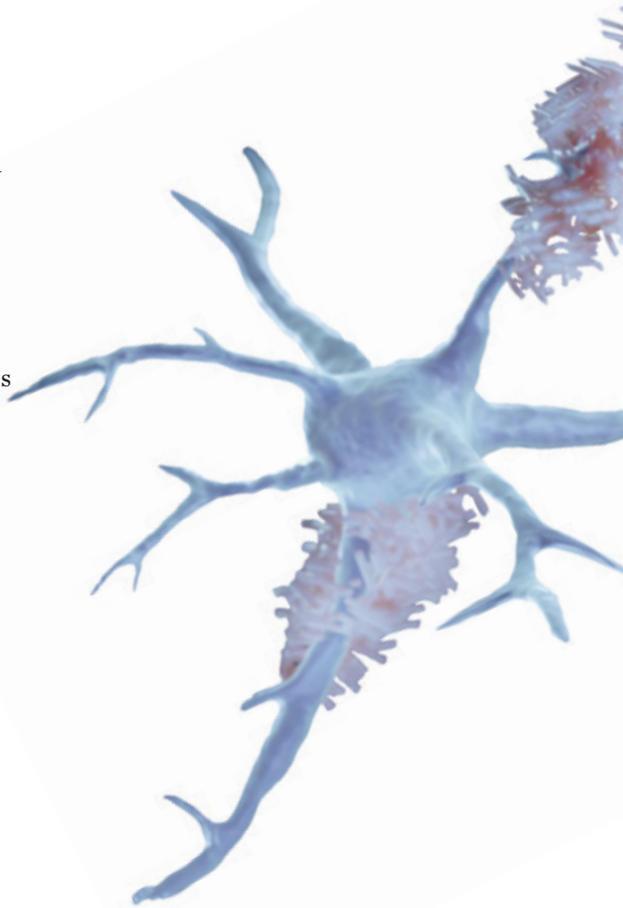
Sarah Paciulli
Nurse Practitioner
VCU Health

Sarah Paciulli, a nurse practitioner specializing in cardiac disease and amyloidosis, is part of the VCU Health team that uses a research-driven team approach to manage amyloidosis. Patients receive head-to-toe care from physicians who specialize in the different parts of the body amyloidosis impacts and who are at the forefront of the latest scientific findings and treatment options. *Photo: Penelope Carrington, MCV Foundation*

For ATTR, the acquired or hereditary forms, disease-modifying drugs like those used in the current clinical trials stabilize existing TTR proteins or prevent production of further TTR proteins in the liver. For AL, VCU Health offers bone marrow transplants or chemotherapy. And if any type of amyloidosis causes heart, kidney or liver failure, patients may be put on the wait list for a transplant at Pauley Heart Center or at the VCU Hume-Lee Transplant Center, one of the busiest transplant centers in the country.

Many liver and heart transplants for amyloidosis patients have been performed at VCU Health. In some patients with aggressive hereditary ATTR, the team has performed both heart and liver transplants for a single patient, curing the disease by replacing the source of the bad protein and replacing the damaged heart. These cases have often created the opportunity for domino transplants, which occur when the liver that is making the bad protein, but is otherwise functioning well, is given to someone who might be older with end-stage cirrhosis and doesn't have time to wait on the usual list. This unique domino procedure saves two lives at once.

"As you can see, it's a complicated disease," Dr. Shah said. "You have one group that's treated with chemotherapy and may need a bone marrow transplant. You have another group that's older and needs oral therapies. Then you get some hereditary patients, who are either older and on oral therapies or younger with a fairly aggressive mutation that may need liver or heart transplants. Then you have other patients who have neuropathy components. At VCU Health, patients can access the newest therapies and comprehensive interdisciplinary support system needed to save their lives."



If you are interested in supporting clinical care or research that will improve the lives of amyloidosis patients, contact Justin Jannuzzi, director of development for VCU Pauley Heart Center, at 804-628-8905 or justin.jannuzzi@vcuhealth.org.

Tom Cardwell

Tom Cardwell's passion is serving his community. He and his wife TJ retired to Williamsburg from the Washington, D.C., area in 2001, and since then he's enjoyed serving on various environmental, community and other nonprofit boards.

But in 2017, he found that he no longer had the energy to participate fully and effectively.

"I just felt worn out all of the time," he said. "It was like I had to drag myself to meetings and act like I was feeling good."

After many different tests over about six months, an MRI finally revealed a spot on Cardwell's heart that was indicative of amyloidosis.

"Prior to increased access to genetic testing and application of novel nuclear medicine technologies, the disease was only identified if patients agreed to undergo an invasive procedure to obtain a tissue biopsy of the heart," said amyloidosis expert Keyur Shah, M.D. "Now, patients can be diagnosed with blood samples and imaging, which has led to a marked increase in diagnosis and awareness for the disease."

Cardwell soon learned he was in the right place to battle his amyloidosis.

"My cardiologist Dr. Ellenbogen said he had the expert on his staff for amyloidosis, so they set me up for an appointment with Dr. Shah," Cardwell said.

Dr. Shah did a few more tests to confirm the diagnosis, then began treatment, which included medication for Cardwell's TTR wild-type amyloidosis.

"After so many tests, a diagnosis provides confidence," Cardwell said. "There's a fear of the unknown, but I can deal with what I know. I may not like what I know, but at least I can deal with it. And I now have a doctor who can help me through it. We can monitor it, and it gives me confidence that somebody is looking out for my wellbeing."

Cardwell's treatment at VCU Health has included tafamidis, a breakthrough treatment which is a molecule that stabilizes the TTR protein. This is the first-ever FDA-approved treatment for this disease. Although it is not a cure, it prevents further deposition of the deadly amyloid fibrils.

He will visit VCU Health for amyloidosis at least quarterly, with annual echocardiograms and monitored exercise. Providers analyze lab results and watch how the disease may or may not change over time, using their observations to determine how well Cardwell is responding to treatment.

Observations from both care providers and Cardwell's personal experience show treatment has slowed progression of the disease. Cardwell has his energy back and has returned to doing what he loves, and that's serving to make communities in central and eastern Virginia better places to live.

Cecil Hamlett

Trips to the mailbox exhausted him. Mowing the yard, usually a two-hour chore, began to take nearly six hours. His legs, ankles and feet were swelling, and he wasn't sleeping well due to extended coughing spells when lying down.

Chest X-rays showed fluid on his lungs, which physicians in Lynchburg drew off several times, but the fluid kept returning within weeks. "I said, 'We need to figure out what's causing this. Me coming in and you drawing fluid off of me and us not knowing what's causing it is not working for me,'" said Cecil Hamlett of his experiences before finding VCU Health.

His continued search for an explanation of what he was facing was not easy. Providers in Lynchburg inserted tubes and a camera into Hamlett's chest to explore further. Based on that procedure, they scraped Hamlett's lungs for fluid and glued his left lung to the inside of his chest wall (a procedure called pleurodesis), keeping him in the hospital for five days.

Seven days later, the fluid was back — and Hamlett was in the emergency room.

When his doctors turned their attention to the heart, they finally found signs of amyloidosis and sent Hamlett to VCU Health, where he met Dr. Shah in 2020.

Dr. Shah and Hamlett talked about treatment options and the lack of medication for his type of amyloidosis — the hereditary form — and possible next steps, which included a heart transplant.

"I didn't hear anything else he said after 'heart transplant,'" Hamlett said. "I thought, how did we get here so fast? I went to bed one night, and I woke up and my whole world had been turned upside down. I couldn't wrap my head around it at first."

Because Hamlett's disease was so advanced, Dr. Shah decided the transplant was the only option he had. A team from VCU Pauley Heart Center completed Hamlett's heart transplant on Sept. 19, 2020.

If Hamlett had not been diagnosed and referred to VCU Health, Dr. Shah said he could have died within the next six to 12 months. The diagnosis and heart transplant saved his life.

"You know something is going on, but you need someone to tell you what it is so you can get help," Hamlett said. "To go through something like that changes your outlook on life. I just put my faith in God."

Platinum Precision

After discovering new insights on how certain tumors respond better to treatment, two VCU researchers are breathing new life into a platinum-based drug to treat cancers resistant to available therapies.

By Paul Brockwell Jr.

Triple-negative breast cancer is one of the most aggressive cancers, and few targeted therapies exist to combat the grim diagnosis. Once the cancer recurs, the average life expectancy is about one year. That reality could be changing thanks to the work of researchers at VCU who are working across disciplines to better understand how a drug developed by Nicholas Farrell, Ph.D., could be better targeted to patients.

Dr. Farrell is now a member of Massey's Developmental Therapeutics research program and professor in the Department of Chemistry at the VCU College of Humanities and Sciences, but he was a graduate student in the late 1960s when he became fascinated by platinum chemistry. He turned his interests to the biological chemistry of metals after research in the U.S. led to the discovery of the anticancer properties of platinum-based agents. Since then, he's become an internationally recognized expert in the area of anticancer drugs, and his research improves pharmaceuticals.

New insights from research at VCU Massey Cancer Center are improving an understanding of how to personalize medicine for cancer patients, and they're also breathing new life into a once-shelved drug, Triplatin, which entered second phase clinical trials in the early 2000s.

Triplatin never made it to phase 3 clinical trials in patients as a potential treatment for ovarian, breast and lung cancer, but that could change soon after Dr. Farrell's collaborators have developed a clearer understanding of why the gold standard for treating cancer sometimes stops working in patients after initial success. Dr. Farrell hopes his novel compound could potentially avoid resistance to treatment by reengineering the platinum molecules.

The drug in development seeks to solve a problem that usually begins when patients initially do well with available therapies, but later relapse into a form of their disease resistant to treatment. The options for addressing these pernicious forms of ovarian and breast cancer are practically nonexistent, but on the MCV Campus researchers are working to better understand how to effectively target treatments to attack the cell growth gone amok. This development process is part of a larger institutional initiative aimed at drug discovery and development that brings a whole-of-university approach to health challenges that spans across disciplines and departments on campus.

"We're not talking about platinum metal, but a yellow powder that was first reported in 1845," explained Dr. Farrell, who has received awards of excellence from the university for his teaching and research. "Its anticancer activity was discovered accidentally in the mid- to late 1960s. Since the Food and Drug Administration's full approval of cisplatin in 1978, platinum-based drugs have been one of the great anticancer drug discovery stories."

Platinum-based drugs are an important tool in the arsenal against cancer, Dr. Farrell said, but despite good initial responses, some patients relapse, and resistance to available drugs is a serious clinical problem when it comes to

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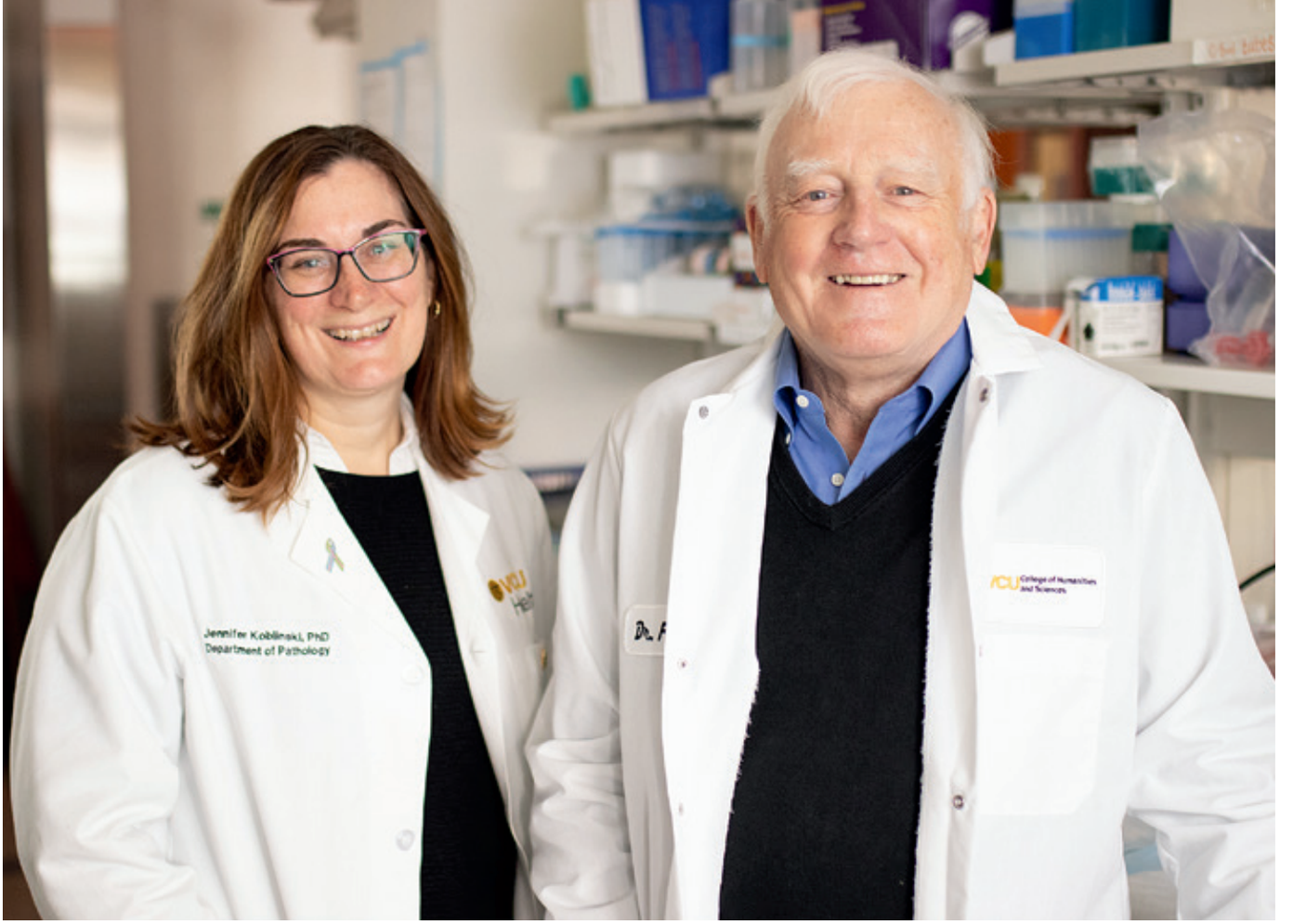
Nicholas Farrell, Ph.D.
Professor
Department of Chemistry
VCU College of
Humanities and Science



Jennifer Koblinski, Ph.D., and Nicholas Farrell, Ph.D., co-authored a study in *Molecular Cancer Therapeutics* that shares new insights on Triplatin, a drug Dr. Farrell previously developed, which could now be successful in treating triple-negative breast cancer.
Photo: Tyler Trumbo, MCV Foundation

treating ovarian and breast cancer. Today, around half of cancer patients receive platinum in combination with chemotherapy, but over time physicians observe challenges in some patients with resistance to therapy and adverse side effects. To address these challenges. Dr. Farrell and his team are engaged in what he describes as standard medicinal chemistry — the act of making new structures and designing less toxic ones. There are currently three platinum drugs fully approved by the FDA to treat cancer, and he'd like to add a fourth.

Triplatin is a platinum-based drug from a class that originated in Dr. Farrell's lab and was patented in the 1990s. Around 20 years ago, under the auspices of Novuspharma SpA, the drug made promising advancements into second phase clinical trials, but the drug fell slightly short of the efficacy thresholds needed for FDA approval. Now, Dr. Farrell may know more about why. Understanding the mechanisms that allow cancers to grow and spread through the body is a key when working to discover new therapies to stop unregulated cell growth.

That's how Dr. Farrell connected with Jennifer Koblinski, Ph.D., a professor of pathology and a researcher affiliated with VCU Massey Cancer Center. Dr. Farrell was leading a faculty seminar in Massey's developmental therapeutics group when Dr. Koblinski saw an opportunity for collaboration.

"Our interaction is a great example of two people bringing in very different backgrounds to tackle the challenges faced in medicine," Dr. Koblinski said. "Together, we can have a stronger research project that engages experts across campus. We also wouldn't have had this much success without the help of talented graduate students, postdoctoral fellows and laboratory managers like Erica Peterson in Dr. Farrell's lab."

Dr. Koblinski's research focuses on the mechanisms that facilitate breast cancer metastases to the brain. She has specifically examined how one protein, when present, often indicates an easy pathway for breast cancer to spread to the

brain. But, conversely, when the protein is neutralized or not present, the risk for metastasis lessened. Her understanding of the biology and pathology of cancer cells provided expertise that was very helpful to Dr. Farrell as he sought to identify ways to better target tumor cells with the drug and to ensure the uptake of the medicines. Developing a profile for the types of tumors that may better respond to his design of a repackaged platinum-based therapy has been one of this research group's biggest challenges and success stories.

"This meant that we had to bring the chemists, the biologists, etc., all together," Dr. Farrell said. "In testing the compounds we made, one of the thoughts was that DNA repair has a resistance to these older platinum drugs, but if we change the structure of platinum, then the new compounds could overcome resistance to the drug."

The previously developed drug — Triplatin — had some success in overcoming that resistance, and the new insight shows how to more precisely target tumor cells by exploiting the drug-sugar interactions on the surface of tumor cells. By targeting those markers, Triplatin is more effective in reducing tumor invasion, migration and growth. The team's clinical collaborators are excited about the potential.

In February, Drs. Farrell and Koblinski published a journal article in *Molecular Cancer Therapeutics*[1] that shows Triplatin can be effective against triple-negative breast cancer. Their research found that around 40% of triple-negative breast cancer cases had tumors rich in sugars called sulfated glycosaminoglycans (sGAGs). The presence of those sugars allows Triplatin to bond strongly to the surface of the tumor cells and accumulate/damage the cancerous cells more specifically.

Once inside the cell, the drug localizes to the nucleolus, decreases RNA transcription, and causes cell cycle arrest. The drug itself is a new configuration of platinum with greater effectiveness at treating drug-resistant cancers based on research work that Drs. Farrell and Koblinski have built and tested.

"We now propose to move on to clinical trials to prove Triplatin's effectiveness in human subjects," Dr. Koblinski said. "We will examine the levels of biomarkers to see if they are low or high, and the patients with high levels of biomarkers will be treated with Triplatin in a precision medicine approach."

The potential to expand effective treatment options is an exciting

> Dr. Farrell's lab has achieved what fewer than 1% of investigators typically are able to achieve, and that's getting a drug to trials with human patients.

Triplatin

Triplatin overcomes resistance by precision targeting with sugars. It works by bonding with sugars on the surface of tumor cells, eventually entering the cell and disrupting the unregulated cell growth.

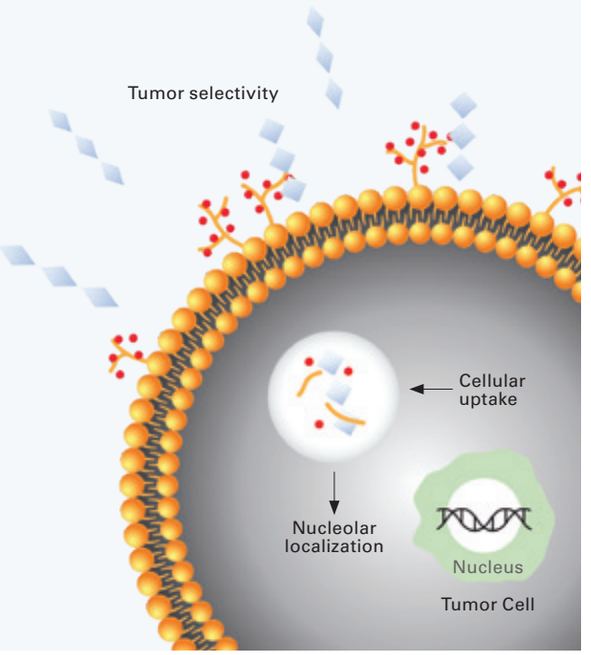


Illustration: the [Box] studio

Molecules to Medicines

VCU's approach to drug discovery is producing exciting results on multiple fronts. Part of that success is a result of the collaborative science pursued among clinicians and researchers. The institutional initiative is known as Molecules to Medicines, and it brings together basic scientists across several disciplines in partnership with clinicians to examine and develop solutions for some of medicine's most vexing issues.

"Molecules to Medicine is a platform for exchanging innovative and transformative ideas that focus on discovering novel concepts in VCU laboratories at the basic science level and based on these fundamental discoveries creating molecules (drugs and biologics) by VCU researchers that are translated to medicines by VCU clinicians to better the health in our community and beyond," said Saïd Sebti, M.D., associate director for basic research and the Lacy Family Chair in Cancer Research at VCU Massey Cancer Center.

Currently, there are around a dozen active research projects underway with the hope to expand the collaborative approach from cancer to additional disease areas in cardiology and neurology. The work of Drs. Farrell and Koblinski is one of four projects in the later stages of development. And while they are producing the platinum compounds through Dr. Farrell's lab, some projects are receiving support from VCU's Medicines for All Institute, which is helping to produce compounds needed for research and potential trials.

Massey's director, Robert Winn, M.D., is enthusiastic about the approach of Molecules for Medicine and the potential for further discoveries. "Massey's partnership in the Molecules for Medicine approach gives our researchers a new means for translating and advancing their scientific discoveries from the laboratory into clinical trials," Dr. Winn said. "Continuing to strengthen this unique collaboration will enhance and expedite our ability to develop novel therapies and bring them to cancer patients and our community."

prospect for the team involved, which has been working on this project for around five years. The approach is applicable to all cancers that have the appropriate sGAG profile, and the next important tumor targets are ovarian and pancreatic cancers. It's also a great example of how VCU's approach to scientific and medical research is inherently multidisciplinary and collaborative.

"This project is an important example of how team science moves things forward and how understandings change over time," Dr. Farrell said. "It's very important that we have some idea of how the drug works so we can only treat those who will be most likely to respond."

WHAT'S NEXT?

Dr. Farrell's lab has achieved what fewer than 1% of investigators typically are able to achieve, and that's getting a drug to trials with human patients. The results have been very promising, and he has been quick to credit the type of collaboration he's able to do at VCU and around the world with the success. He hopes to present this latest work to the FDA to show them the rationale for reinvestigating his drug Triplatin based on this new understanding of the cellular dynamics. Once they receive the clearance for investigation of a new drug, they will work to test the effectiveness of its targeting, validate the biomarkers identified and develop a new clinical protocol.

"Our compound is particularly well suited to exploiting that profile," Dr. Farrell said. "Validating the biomarker is the biggest next step — and hoping that not only will we be getting the drug into the clinic but also have a companion diagnostic to go with the new therapy."

Research like this project benefits tremendously from philanthropy in its early stages. If you would liketo support this research on effective treatments for triple-negative breast cancer, please contact the Massey Development Office at 804-828-1450.

1. J.D. Hampton, E.J. Peterson, S.J. Katner, T.H. Turner, M.A. Alzubi, J.C. Harrell, M.G. Dozmorov, P.J. Gigliotti, V. Kraskauskiene, M. Shende, M.O. Idowu, M. Puchalapalli, B. Hu, L. Litovchick, E.Katsuta, K. Takabe, N.P. Farrell, J.E. Koblinski: Exploitation of sulfated glycosaminoglycan status for precision medicine of platinums in triple-negative breast cancer. *Molecular Cancer Therapeutics*. (2022) 21, 271-281 PMID: 34815360.

follow-up

Checking in with researchers
on the latest developments

Joint Effort Aims to Reduce Cancer Disparities

VCU Massey Cancer Center and Virginia State University are part of a $1.7 million National Cancer Institute team science grant, the first of its kind in Virginia.

Robert Winn, M.D., director and Lipman Chair in Oncology at VCU Massey Cancer Center, is a principal investigator on a recent multi-year grant to help address health disparities. *Photo: Allen Jones, VCU*

The two institutions received a "team science" grant from the National Cancer Institute focused on reducing cancer disparities and providing hands-on research opportunities to students who are historically underrepresented in science. The total award amount is $1.7 million over the course of four years.

This is the first time that a Virginia-based cancer center and a historically Black college or university have joined forces to win such a grant. It will enable cross-institutional work among multiple teams of scientists, robust community engagement and in-person research training at an NCI-designated cancer center for budding scientists whose home institution is classified as an HBCU.

"This award will allow us to engage closely with both our neighboring HBCU and the community to infuse our science with new ideas," said principal investigator Robert Winn, M.D., director and Lipman Chair in Oncology at Massey, senior associate dean for cancer innovation and a professor of pulmonary disease and critical care medicine at the VCU School of Medicine. "It will also allow both universities to give back, using the resources we're blessed with here at Massey and the historical knowledge and connections of VSU — acting locally with the potential for global impact."

The principal investigator for VSU is M. Omar Faison, Ph.D., an associate vice provost of research and economic development and interim dean of the VSU College of Graduate Studies.

"We are proud to have a seat at the table to take part in this research that so heavily affects our Black American population, and to further expand the reach of Massey Cancer Center," Dr. Faison said. "Through a combination of mentorship and access to resources, this grant allows us the opportunity to provide meaningful professional development experiences to VSU faculty and students who may be interested in exploring population health for more bench-oriented science in the context of cancer."

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