

PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SPRING 2019



MUSC buys four new hospitals

Facilities in Chester, Florence, Lancaster and Mullins, SC join MUSC Health network

The Medical University of South Carolina (MUSC) closed the purchase of four community hospitals from subsidiaries of Community Health Systems, one of the largest publicly traded hospital companies in the United States. The following hospitals were officially acquired March 1:

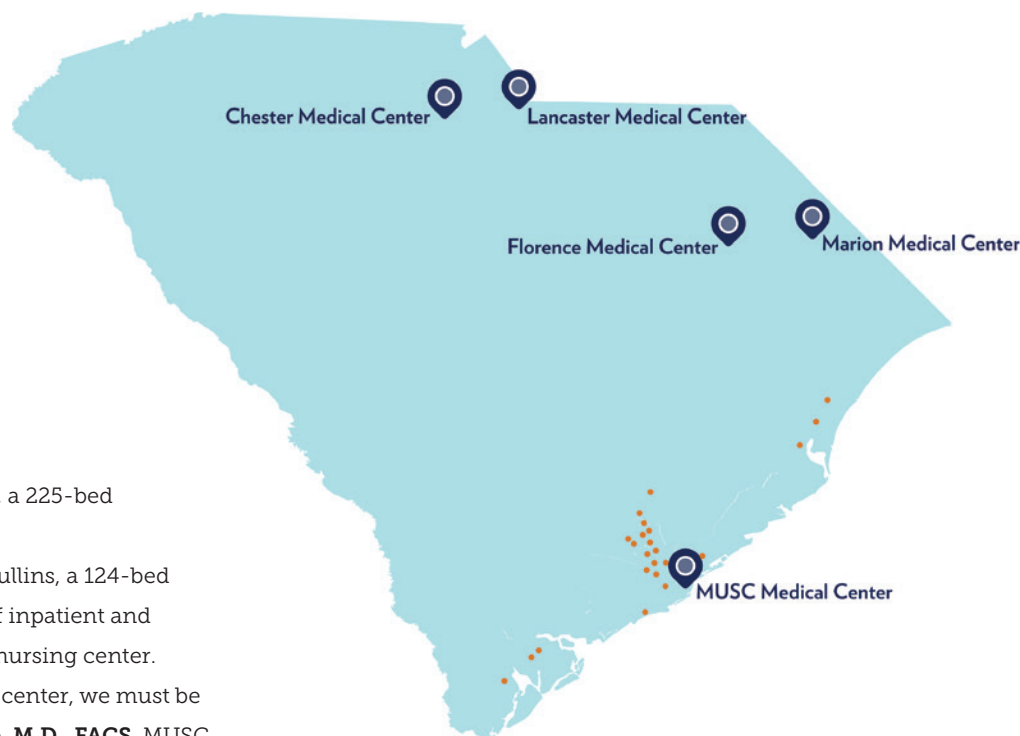
- Chester Regional Medical Center, an 82-bed licensed facility
- Carolinas Hospital System in Florence, a 396-bed regional acute-care facility
- Springs Memorial Hospital in Lancaster, a 225-bed all-private-room facility
- Carolinas Hospital System-Marion in Mullins, a 124-bed acute-care facility providing a variety of inpatient and outpatient services, as well as a 92-bed nursing center.

"As the state's leading academic health center, we must be prepared for the future," said **David J. Cole, M.D., FACS**, MUSC president. "MUSC is committed to providing the best health care possible for our communities and state through strategic partnerships and our emerging MUSC Health network."

In 2017, the four hospitals combined delivered care through more than 129,000 emergency department (ED) visits, 159,000 outpatient visits (excluding ED visits), 18,800 hospital admissions and 339,000 clinic visits with physicians. With the addition of these four hospitals, MUSC now employs more than 16,400 team members throughout the state.

"This transaction is the first time MUSC has acquired other hospitals," said **Charles W. Schulze, CPA**, chairman of the MUSC board. "The additions will increase the size and scale of the MUSC Health network, and in today's environment, larger, more efficient health care systems can deliver greater value to patients and have a positive impact on population health."

"We look forward to welcoming the patients, families and employees of these hospitals into the MUSC Health network," said **Patrick J. Cawley, M.D.**, MUSC Health CEO and vice president for

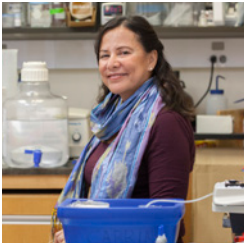


Health Affairs, University. "Through affiliations with other hospitals and health systems across South Carolina, and through our robust telehealth network, MUSC's clinical outreach allows us to serve the citizens of our state no matter where they are. The purchase of these four hospitals is the natural extension of our mission to preserve and optimize human health in South Carolina."

Although MUSC is a state-assisted organization, state appropriations for the university and hospital authority are less than three percent of their combined annual budget. As a result, MUSC works diligently to fulfill its mission through prudent financial management, dedicated philanthropic support and strategic business growth. Roughly 60 percent of all MUSC Health patient care revenues are generated from statewide communities outside the tri-county area, while the remaining 40 percent of patient care revenues are driven by services delivered within the tri-county market (Charleston, Berkeley, and Dorchester counties).

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3D technology gives head and neck cancer patients a chance for the quality of life they had before diagnosis



On the cover: MUSC physicians use scans to create a 3D-printed version of a patient's skull prior to surgery.

PHOTO: BRENNAN WESLEY



Dr. Antonieta Lavin (above) studies estrogen and its effect on methamphetamine addiction with Dr. Carmella Reichel.

DISCOVERY

Estrogen may influence methamphetamine addiction

New research identifies one possible explanation for why male and female rats react differently to methamphetamine

BY CELIA SPELL

Male rats have held steady as the focus of most addiction studies in the past. But as the field begins to take female rats into account, scientists see that drugs like methamphetamine affect the sexes differently, suggesting the basis for a change in addiction treatment.

“The brain changes when you’ve been addicted to methamphetamine,” said

Antionieta Lavin, Ph.D., an associate professor in the neuroscience department at the Medical University of South Carolina who worked on the study with fellow researcher **Carmela Reichel, Ph.D.** “But we have limited information on how our sex hormones affect that addiction.”

In a paper published January 10, 2019 in

eNeuro, MUSC researchers suggest that the brain of a female rat responds differently to drugs like methamphetamine and that these differences may be due to the presence of estrogen and its effect on addiction.

According to the Centers for Disease Control and Prevention, methamphetamine alone is responsible for 11,000 deaths in the United States each year, and with more than 70,000 total drug-related deaths in 2017, researchers like Lavin and Reichel are working to improve treatment for those with substance use disorder.

As a stimulant, methamphetamine increases activity in certain areas of the brain, such as the prefrontal cortex. And according to the American Addiction Centers, the drug releases dopamine in the brain, which gives the user a sense of pleasure. In addition to this rewarding feeling, dopamine also controls a person’s motivation, movement, memory and learning.

By consistently releasing excess dopamine, methamphetamine users train the brain to expect and crave heightened levels of this neurotransmitter, and the same happened with the male and female rats in this study.

Researchers gave their test subjects the ability to self-administer methamphetamine, meaning that the rats were able to control how much of the drug they consumed and how often they took it. Female rats consistently took more methamphetamine more often during the first six hours of their addiction, and the researchers involved suggest that this window may be crucial in explaining why female addiction is so powerful.

Over time, methamphetamine addiction alters the way in which signals are carried throughout the brain, specifically targeting the synapses in the prefrontal cortex, where the brain controls decision-making and learning.

When MUSC researchers examined the prefrontal cortices of both male and female rats addicted and not addicted to methamphetamine, they found that the synaptic response in this area was different between males and females as well as between the addicted and non-addicted animals. For example, Lavin and Reichel found that female rats showed lower resting activity than male rats but then experienced a faster rise in their brain's synaptic activity after taking the drug. This stronger response was then followed by a faster fall once the drug wore off.

This synaptic difference between males and females suggests that sex hormones play a larger role than previously thought in how rats, and potentially humans, process drugs and could lead to more male- and female-specific substance use disorder treatment in the future.

"Next, I would like to study how meth addiction changes throughout the different phases of the female cycle," said Lavin. "This insight would help us improve treatment for women suffering from substance use disorder."

DISCOVERY

Breaking down AGEs

Insight into how lifestyle drives ER-positive breast cancer

BY CAROLINE WALLACE

The underlying biological connection of poor diet and lack of exercise to cancer development is not well understood. Insight into advanced glycation end products (AGEs) offers a biological link between certain lifestyle behaviors and cancer risk. AGE accumulation is the natural and unavoidable result of the breakdown of sugars and fats. AGE levels, however, are increased by the over-consumption of foods high in sugar and fat.

High AGE levels could prevent patients with estrogen receptor (ER)-positive breast cancer from responding to tamoxifen therapy, suggest preclinical findings reported by MUSC researchers in a recent issue of *Breast Cancer Research and Treatment*. The research team was led by College of Medicine Assistant Professor **David P. Turner, Ph.D.**, Professor **Marvella E. Ford, Ph.D.**, and **Gayenell Magwood, R.N., Ph.D., F.A.A.N.** Ford is also the associate director of population sciences and cancer disparities at Hollings Cancer Center.

"By showing that AGEs in the diet may impact how well breast cancer patients respond to therapy, we can make breast cancer patients aware of their existence," says Turner. "And we can design lifestyle interventions aimed at reducing AGE intake."

AGEs cause an imbalance between molecules called free radicals and antioxidants. This imbalance leads to



IMAGE: SON NGUYEN

chronic inflammation that can promote the development of a variety of chronic diseases such as diabetes, Alzheimer's Disease, cardiovascular disease, arthritis and cancer. However, AGEs have not been studied in-depth in the context of cancer.

High AGE levels lead to continual activation of pro-cancer pathways. A central molecule turned on by the pro-cancer pathways is important in the context of ER-positive and -negative breast cancers. The MUSC team found that AGEs actually increase the function (through phosphorylation) of estrogen receptor alpha in breast cancer cell lines. Adding tamoxifen to the cancer cells prevented their growth. However, adding AGEs caused them to grow once again. This indicates that patients with high AGEs may be less likely to respond to tamoxifen treatment.

In fact, a defined lifestyle intervention of exercise and dietary counseling lowered systemic levels of AGEs in overweight women with non-metastatic, ER-positive breast cancer.

Expanding the published study to determine the effects of the intervention on a larger scale will shed light on how lifestyle interventions can beneficially affect cancer treatments by reducing AGE levels.

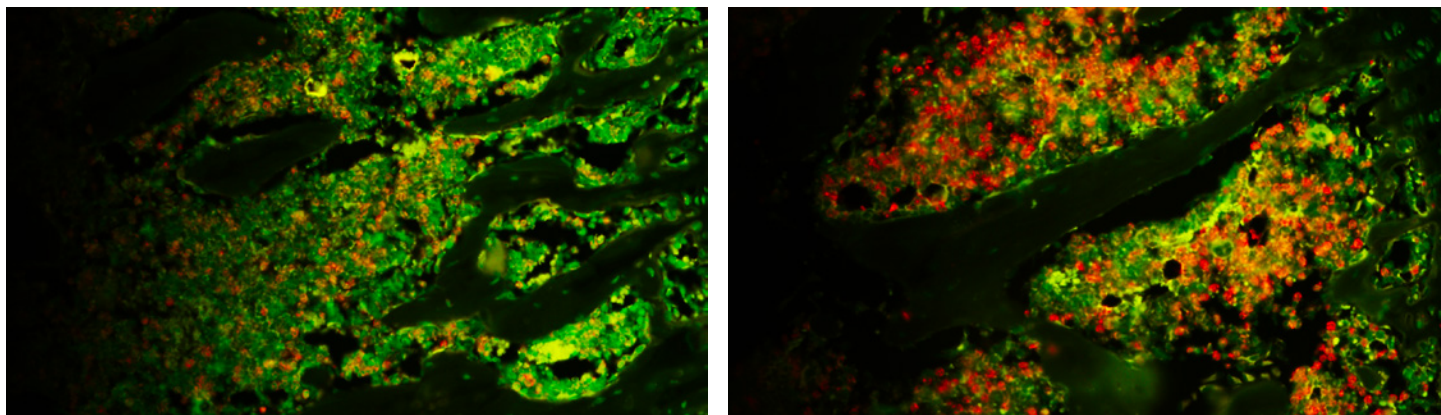


IMAGE: DR. CHAD NOVINC

MDSCs, shown in red, are increased in the bone marrow of mice treated with antibiotics (ABX, right) compared to control treated animals (left).

DISCOVERY

Unintended side effects

Antibiotic disruption of the gut microbiome dysregulates skeletal health

BY MATTHEW GRESETH

Researchers at MUSC have examined the impact of disrupting the healthy gut microbiome with antibiotics on post-pubertal skeletal development. Their results, published in the February 2019 issue of *American Journal of Pathology*, showed that antibiotic disruption of the gut microbiota dysregulates communication between immune cells and bone cells.

“This report introduces antibiotics as a critical exogenous modulator of gut microbiota osteoimmune responses during post-pubertal skeletal development,” says **Chad M. Novince, D.D.S., Ph.D.**, an assistant professor in both the Colleges of Medicine and Dental Medicine who studies the impact of the microbiome on osteoimmunology and skeletal development. “Antibiotics are known to perturb the microbiota, but this is the first known study evaluating how that has downstream effects on immune cells that regulate bone cells and the overall skeletal phenotype.”

Working with team members at MUSC, Novince’s lab treated mice with a cocktail of three antibiotics. In collaboration with microbiome scientist **Alexander V. Alekseyenko, Ph.D.**, associate professor in the Biomedical Informatics Center and founding director of the MUSC Program for Human Microbiome Research, they were able to show that antibiotic treatment altered the gut microbiota by inducing specific changes to large groups of bacteria.

Following antibiotic disruption of the microbiota, the Novince lab examined the integrity of the skeletal system. Antibiotic-induced changes in the microbiota significantly impacted trabecular bone, the type of bone that undergoes high rates of metabolism, which is controlled through actions of bone-resorbing (osteoclast) and bone-building (osteoblast) cells. Focusing on the cellular details, they saw no changes to osteoblasts, while osteoclast cell number, size and activity were increased.

To determine what enhanced osteoclast outcomes, the Novince lab assessed the levels of osteoclast signaling molecules. They found that pro-osteoclastic signaling molecules were increased in the circulation of antibiotic-treated animals, suggesting that increased osteoclast activity is the result of a specific immune response to a change in the microbiota.

“Our study is able to dive into specific adaptive and innate immune cell mechanisms within the bone marrow to show that there is an effect on the bone cells,” says **Jessica D. Hathaway-Schrader, Ph.D.**, post-doctoral scholar and first author on this study.

Examination of immune cell populations in the bone marrow surprisingly revealed a significant increase in myeloid-derived suppressor cells (MDSCs) of antibiotic-treated animals. MDSCs are known to regulate the immune response during various diseases but have not been extensively studied in health.

Future studies are focused on incorporating an antibiotic regimen that better translates to human treatments. These studies could lead to clinical trials aimed at defining the impact of specific antibiotics on the gut microbiome. This research would support developing non-invasive interventions in the microbiome intended to prevent and treat skeletal deterioration.

CLINICAL RESEARCH

New therapeutic target for graft-vs-host disease

Targeting Sirt-1 shows preclinical promise in controlling GVHD

BY MARIA CUITINO

Bone marrow transplant (BMT) offers patients with leukemia and lymphoma a potentially curative treatment. Bone marrow from the donor contains healthy immune cells (T cells and B cells) that can target the recipient's cancer cells, helping to protect against tumor relapse.

This procedure, however, is not without risk. Donor T cells can also see the recipient's tissues as foreign and attack them. This phenomenon, known as graft-vs-host disease (GVHD), can cause serious complications and reduce the quality of life in transplant recipients.

The standard procedure for preventing GVHD is to treat patients with immunosuppressive drugs. However, this makes patients susceptible to infections and increases the risk of tumor relapse. Even with this therapy, 30 to 50 percent of patients develop acute GVHD, and 70 percent develop some degree of chronic GVHD.

"GVHD can be expected to occur in the majority of transplanted patients," says **Xue-Zhong Yu, M.D.**, professor of Microbiology and Immunology in the College of Medicine at the Medical University of South Carolina (MUSC) and SmartState Endowed Chair in Cancer Stem Cell Biology and Therapy at Hollings Cancer Center. "More treatment options are desperately needed."

Yu led a team of MUSC researchers who showed that targeting the enzyme Sirt-1 helped control GVHD in mice, without

increasing the incidence of tumor relapse. They recently reported their findings in *Blood* (published online December 4, 2018). In BMT models, mice that received a Sirt-1 inhibitor lived longer and had better clinical scores than those that did not.

"What's exciting about our study is that Sirt-1 regulates different subsets of T cells differently," says Yu. "So by inhibiting it, we can suppress T cells that lead to GVHD without affecting those that protect against tumor relapse."

Acute and chronic GVHD are different diseases. Acute GVHD occurs during the first months after transplant, while chronic GVHD reduces the long-term quality of life

of patients. Although treatment options have improved for acute GVHD, chronic GVHD remains a therapeutic dilemma.

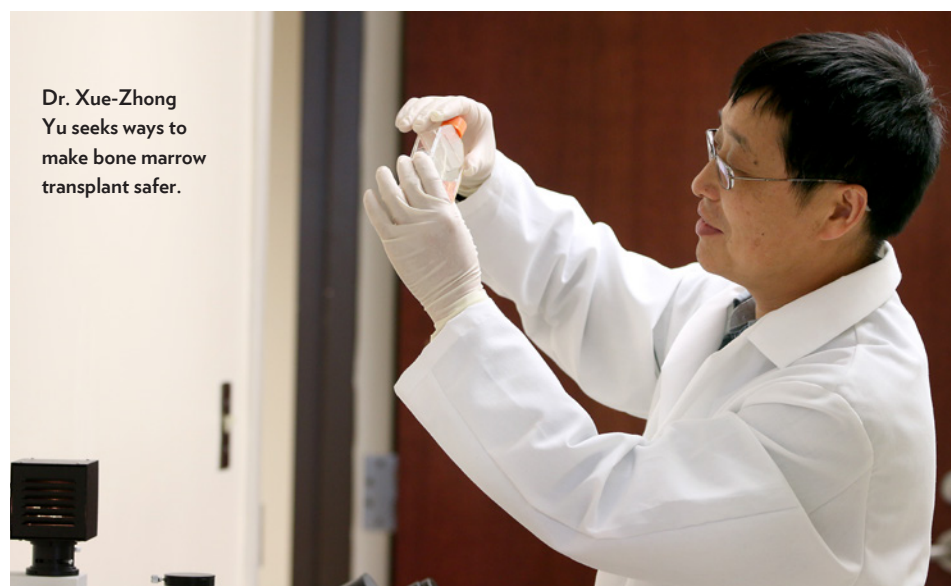
In this study, Sirt-1 blockage improved chronic GVHD. The study showed that Sirt-1-deficient T cells reduced B-cell activity in mice with the disease.

"This indicates that Sirt-1 plays a role in T- and B-cell interaction in GVHD development," says **Anusara Daenthanasanmak, Ph.D.**, who was a postdoctoral fellow in the Yu lab while doing this work and is now at the National Institutes of Health. "By blocking Sirt-1, we could have a treatment for both acute and chronic GVHD."

Yu's lab is interested in further exploring the role of Sirt-1 in the regulation of B cells. "B cells are critical in the pathogenesis of chronic GVHD," says Yu. "That is still a gap we need to fill."

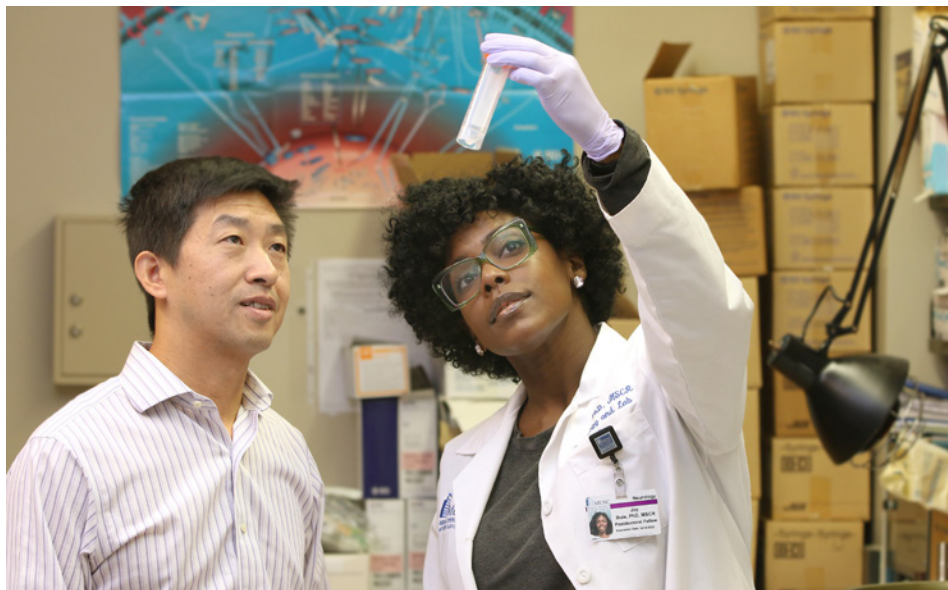
Although the preclinical results are strong, much needs to be done before they can affect patient care.

"I hope to be able to translate the findings in my lab to the clinic," says Yu. "But, first, further studies are needed to examine the role of Sirt-1 in human T cells and in a human setting."



Dr. Xue-Zhong Yu seeks ways to make bone marrow transplant safer.

PHOTO: SARAH PACK



Dr. Hongkuan Fan is an assistant professor in the Department of Pathology and Laboratory Medicine at MUSC who studies vascular dysfunction in sepsis and is pictured with Dr. Joy Jones Buie, a postdoctoral fellow at MUSC.

TECHNOLOGY

Targeting sepsis

Nanocarrier delivery of microRNA 126 improves survival in a mouse model of sepsis

BY KIMBERLY MCGHEE

One in three patients who die in the U.S. dies of sepsis, according to the Centers for Disease Control and Prevention. It is one of the leading causes of death in intensive care units and, with an estimated price tag of \$20 billion in 2011, the most expensive condition that hospitals treat.

Researchers at MUSC found that nanocarrier delivery of microRNA (miRNA) 126, an miRNA known to protect against sepsis, doubled survival in a preclinical model. Their findings were reported in an article published online on September 23, 2018 in *Inflammation*.

“The exciting part is that we can use nanoparticles as a delivery system to carry

microRNAs. It’s feasible—we can do this,” says **Hongkuan Fan, Ph.D.**, senior author of the article and an assistant professor in the Department of Pathology and Laboratory Medicine at MUSC who studies vascular dysfunction in sepsis.

Sepsis is an overreaction of the body’s immune system to an infection. Cytokines flood the bloodstream in an attempt to fight the infection but also cause blood vessels to become leaky. White blood cells escape from the vessels, causing inflammation and damage to surrounding tissue, ultimately leading to multiorgan failure and death.

MicroRNAs are noncoding RNAs that are being assessed for therapeutic use in

cancer and other diseases because they can prevent messenger RNA from creating proteins that can harm the body. Previous research by Fan’s group has shown that an miRNA — miR-126 — is protective against sepsis. It is a major component of the fluid-filled sacs produced by endothelial progenitor cells. Fan’s group has also shown that these cells, which regenerate the lining of blood vessels, help protect against the vascular damage caused by sepsis.

One obstacle to the clinical use of miRNAs, however, are ribonucleases (RNases), whose job it is to seek out and destroy them. Naturally occurring miRNAs are protected from RNases by a fluid-filled sac that covers them or a protein to which they are attached, but those introduced therapeutically have no such protection.

“If we were to just put an unprotected microRNA into the body, then it would immediately get chewed up by RNases,” explains **Joy N. Jones Buie, Ph.D., MSCR**, a postdoctoral fellow at MUSC and the first author on the article. “So that’s why you have to have some type of vehicle system to deliver the microRNA.”

The MUSC team showed that a proprietary nanocarrier (DEAC-pGlcNAc; Marine Polymer Technologies [Burlington, MA]) could deliver miR-126 effectively in a mouse model of sepsis, protecting it against damage by RNases. Its small size prevented its elimination by the liver, and its electrical charge was such that it was easily taken up by cells. The miR-126/nanocarrier complex more than doubled the proportion of mice alive at seven days vs. untreated mice in a preclinical model of sepsis (almost 67 percent vs. 25 percent).

“Based on this and our previous studies, we know that targeted delivery of miR-126 has some therapeutic effect in a preclinical model of sepsis,” says Fan. “Something is working, and that is exciting in a condition as severe and complicated as sepsis.”

TRANSLATIONAL RESEARCH

Triple Threat

A triple combination immunotherapy quadrupled survival in a preclinical melanoma model

BY JULIA LEFLER

Adoptive cell transfer (ACT) is a promising cancer immunotherapy that involves isolating tumor-targeting T cells from cancer patients, selecting the more active T cells, expanding those in the lab, and then transfusing them back into patients. ACT is already available in the clinic for some diseases, like CAR-T therapy, and many clinical trials of another form of ACT are under way for melanoma treatment.

Although ACT has produced dramatic results in some of these patients, not all respond, and the therapy has thus far proven less effective against solid tumors.

Combining ACT with a pan-PIM kinase inhibitor and a PD1 inhibitor improves outcomes in a preclinical model, report a team of MUSC investigators in the February issue of *Clinical Cancer Research*. They showed that this triple combination treatment (PPiT) doubled the migration of anti-tumor T cells to the tumor site and quadrupled survival in mice compared to ACT alone. The team was led by **Shikhar Mehrotra, Ph.D.**, co-scientific director of the oncology and immunotherapy programs in the Department of Surgery and a Hollings Cancer Center researcher.

"With this triple combination therapy, many more T cells persisted. The longer the transfused T cells stay inside the host to fight tumor cells, the better," explains Mehrotra.

Of the two agents administered along with ACT as part of this triple combination therapy, PD1 inhibitors are far better understood. PD1 and PDL1 inhibitors, also called checkpoint inhibitors, take the breaks off the immune system, enabling its T cells to "see" tumors that had been hiding in plain sight.

In contrast, PIM kinase inhibitors are relatively new kids on the block. PIM kinases are proteins that can control many cellular processes, including energy. A clinical roadblock for ACT has been the lack of energy shown by readministered T cells.

"A T cell that starts proliferating is like any person who starts out fresh in the morning with a lot of energy," explains Mehrotra. "Just as the person may have less energy as the day goes on, the T cell can become 'tired' and less effective. We wondered whether the PIM kinase inhibitors could help prevent that from happening."

Mehrotra and his team targeted PIM kinases in T cells to make them act like central memory T cells, which produce more lasting responses against tumors. Most ACT trials use rapidly expanding effector T cells (T cells that are ready to

Adoptive cell transfer (ACT) involves isolating tumor-targeting T cells from cancer patients, selecting the more active T cells, expanding those in the lab, and then transfusing them back into patients.

attack the tumor), but these T cells often become exhausted when put back into patients. When Mehrotra and his team blocked PIM kinases in T cells, the cells started acting like memory T cells.

The triple combination therapy controlled the growth of established melanoma better than ACT, checkpoint therapy, or PIM kinase inhibitors alone or dual combinations of ACT and a PIM kinase inhibitor or ACT and checkpoint therapy. In addition, more T cells infiltrated the tumor and had decreased expression of PD1, making it harder for tumors to turn them off.

"We ultimately want to be able to implement this therapeutic approach in the clinic," says Mehrotra. "However, we must first explore any potential side effects of the pan-PIM kinase inhibitors and determine whether a more selective inhibitor targeting just one type of PIM kinase might be as effective while posing fewer potential side effects."



IMAGE: ISTOCK

Around the Bend



New clinical trial at MUSC treats complex aortic aneurysms

BY CARIN MOONIN

The aorta is as thick as a garden hose. Over time or with pathologies such as atherosclerosis, parts of the aorta can deteriorate, creating an aneurysm—a bubble or weak spot in the hose.

When the aorta is straight, it maintains steady, even blood flow. But, it can develop bends or kinks, which makes treating aortic aneurysms difficult.

Many aortic aneurysms, especially in the abdominal area, are repaired through endovascular aneurysm repair (EVAR) instead of

traditional surgery. During the procedure, a stent graft is inserted into the aneurysm through the groin to the femoral artery. This helps prevent the aneurysm from rupturing by providing an alternate channel for blood flow.

“When we use aortic stents to treat aneurysms, it has to be a nice, long, straight segment of aorta for the stent to work best,” explained **Ravikumar Veeraswamy, M.D.**, vascular surgeon at MUSC. “The blood goes through the stent and doesn’t hit the aneurysm below it.”

But some patients don’t have a straight enough stretch of aorta for this treatment. When a typical stent is placed into a bent aorta, it can’t push up against the walls of the aorta to form a seal, so it leaks. Vascular surgeons can fix this by stapling the area to secure or change the stent’s location, but then they have to ensure it isn’t adversely affecting other areas, such as the kidneys.

“There needs to be a balance,” explained Veeraswamy. “The stent has to be strong enough to stay sealed and stay in place but flexible enough to bend.”

Bending over backwards

As part of the GORE® EXCLUDER® Conformable AAA Endo-prosthesis study, MUSC will assess the safety and effectiveness of this particular stent in treating abdominal aortic aneurysms below the kidney in patients with challenging anatomy. MUSC is one of 56 centers involved in this clinical trial.

This study evaluates two types of patients who have angled aortic anatomies: those whose aorta is angled at 0 to 60 degrees and those with an aortic angle of 61 to 90 degrees. The stent is made of a combination of Gore’s proprietary ePTFE graft material as well as nickel titanium, also known as Nitino. It includes angulation control, which gives the vascular surgeon the ability to bend the device to a patient’s unique anatomy.

The procedure is performed similarly to EVAR, with a stent graft through the groin and femoral artery, and typically takes about two hours even though patients remain in the hospital overnight for observation. Veeraswamy says preliminary results show quick procedure and recovery times in participants.

“It simplifies a complex anatomy, which is a great advantage to patients,” he added. “They appreciate a fairly straightforward procedure versus having a complex and longer stay.”

World-class care

Because MUSC provides tertiary care for all of South Carolina, many patients come to the Heart & Vascular Center for exceptionally



MUSC is one of only 56 centers involved with the GORE EXCLUDER clinical trial, which is designed to treat patients with complex aortic anatomies.

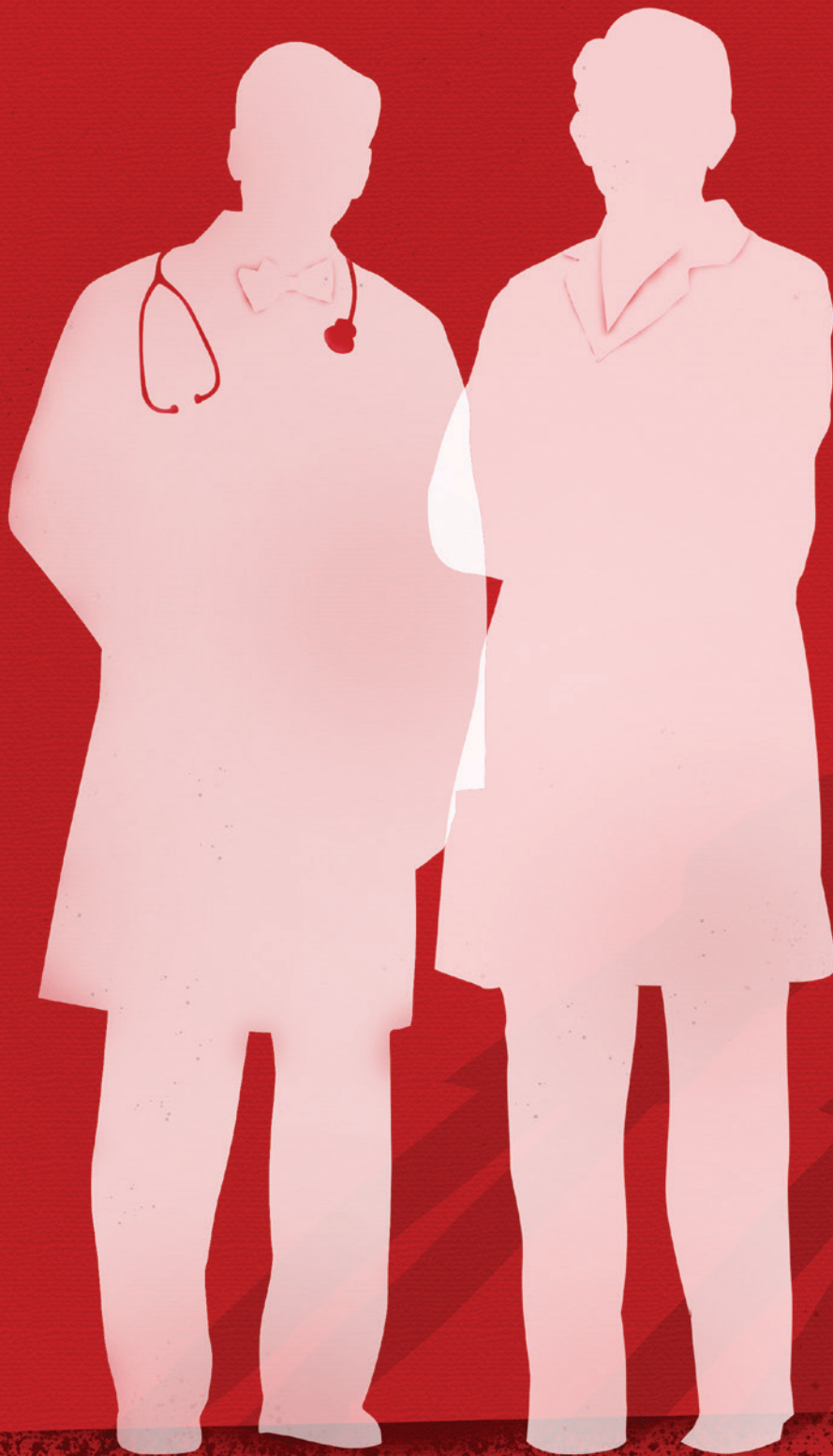
Dr. Ravikumar Veeraswamy pictured above. PHOTO: BRENNAN WESLEY

challenging aortic concerns. The division as a whole cares for a wide range of vascular conditions, including diseases of the carotid and peripheral arteries as well as vascular surgery. And according to Veeraswamy, patient volumes have increased with double-digit rates of growth over the past few years.

“We are seeing more and more patients with complex problems,” he said. “And we work internally and externally with industry partners to help us meet those needs. It’s important to have clinical trials like these, because they allow us to treat complicated problems in a more effective manner.”

The division is currently carrying out additional clinical trials. They include trials for a drug-eluting stent, which would slowly release medication and treat peripheral artery disease; a stem cell trial to help grow new arteries and help with blood flow to legs; and a carotid artery disease clinical trial to understand which patients can be managed medically versus surgically.

“We are always trying to stay at the cutting edge of new technology and leveraging existing technology in very creative ways,” he said. “We’re trying to give the people of South Carolina the best care available anywhere in the country; they don’t need to travel out of the state to get state-of-the-art care.”



Under New Leadership

New director of Division of Rheumatology and Immunology continues
a strong research and clinical care legacy

BY MATTHEW GRESETH

“The whole body becomes painful, the face in some becomes red, the pain rages especially about the joints, so that indeed neither the foot nor the hand, nor the finger can be moved without pain & outcry. Although the arthritis is in a certain part, this rheumatism itself is in the entire body.” —*Guillaume de Baillou*

Leading for more than 20 years

The Division of Rheumatology and Immunology was founded by **E. Carwile LeRoy, M.D.**, in 1974. In 1981, he recruited **Richard M. Silver, M.D.**, now Distinguished University Professor in the College of Medicine, following Silver’s fellowship at the University of California, San Diego. In 1995, when LeRoy stepped down, Silver became division chief and proceeded to lead the division for the next 23 years.

When Silver joined the division, there was a strong need to care for pediatric patients suffering from rheumatic diseases; however, South Carolina did not have any expertise in this field. Silver began seeing these individuals because of his experience caring for juvenile arthritis patients while studying in London with Barbara Ansell, CBE, FRCP, FRCS, the founder of pediatric rheumatology. He developed a program to care for these patients and eventually recruited the state’s first board-certified pediatric rheumatologist. One of his proudest achievements was helping the Department of Pediatrics develop its own Pediatric Rheumatology Division.

According to Silver, being a division director has its headaches but also can be very rewarding.

“I think one of the ideal attributes of being a division director is the ability to recruit people and build programs and I think we did that very successfully,” says Silver. “I’m also proud of the fact that

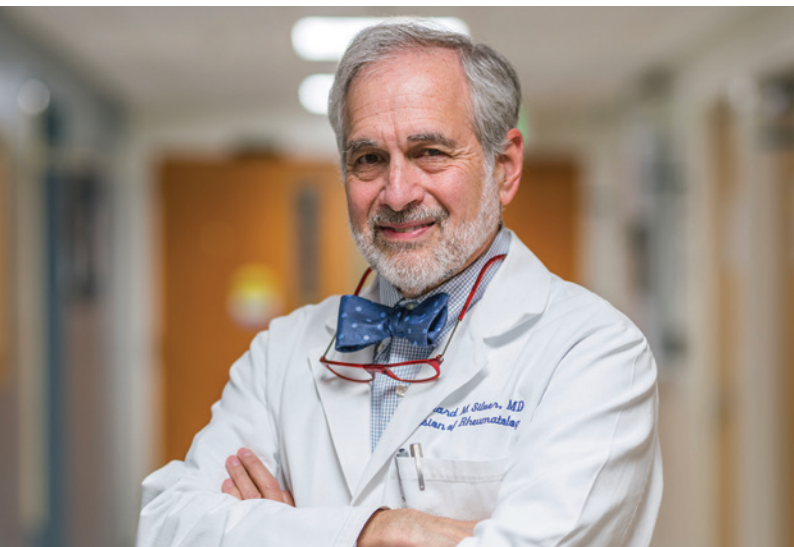
we have trained so many rheumatology fellows who now practice throughout the U.S.”

Silver recruited many outstanding researchers to maintain the division’s strong national and international reputation in lupus and scleroderma research. He also developed a SmartState program—the South Carolina Inflammation and Fibrosis Center for Excellence. To create this program, he raised \$5 million in large and small philanthropic donations that were matched by the state to fund critical research into lupus and scleroderma and to fund two endowed professorships.

Changing of the guard

In 2018, the Department of Medicine led a nationwide search for a new director after Silver decided to step down. At the end of the search, **James C. Oates, M.D.**, now professor and director of the Division of Rheumatology and Immunology, was hired to head the division. Oates moved to MUSC in 1996 for a year-long research fellowship with **Gary S. Gilkeson, M.D.**, and he joined the rheumatology faculty in 1997.

“I feel very good that Jim was selected,” says Silver. “I think he was clearly the best candidate, and he provides some continuity to the division as we move forward.”



Dr. Richard Silver helped MUSC develop its own Pediatric Rheumatology Division during his time as director of the Division of Rheumatology and Immunology.

Oates sees a lot of potential to advance the research and clinical care arms of the division.

“Key strengths of the division are the faculty, the culture and the national and international reputation in research and clinical care that Dr. Silver has built,” says Oates. “I’d like to maintain our strength in scleroderma and lupus clinical care and research.”

One way to maintain continuity with Silver’s tenure as director is to recruit new research faculty. Oates envisions recruiting a mid-level scleroderma physician scientist to maintain strong scleroderma research under the mentorship of excellent faculty such as Silver. Additionally, Oates would like to recruit a mid-level physician scientist to help develop an area of excellence for vasculitis, a related autoimmune disease.

Some new developments to the division include the formation of more formal centers that coordinate clinical care, research and education. For example, incorporating a care coordinator into the clinic to focus care on those at highest risk may reduce health disparities. Resources for that position are sometimes difficult to obtain, but Oates will work hard to bring such centers to fruition.

“With optimal patient care and reduction of health disparities as outcomes, I am hopeful that people will be on board for that type of initiative,” says Oates.

MUSC leads research into treatments for lupus and scleroderma

Autoimmune diseases are a result of the body’s immune system attacking and damaging its own tissues. There are more than 80

different types of autoimmune disease, and this group of researchers at MUSC are focused on better understanding two of them: lupus and scleroderma. While not very prevalent, they are very important diseases and serve as models for other, more prevalent diseases.

Systemic lupus erythematosus (the most common type of lupus and the one studied here at MUSC) is a systemic disease resulting in inflammation of vital organs. The Lupus Foundation estimates that 1.5 million Americans have lupus; 90 percent of diagnosed individuals are women, and women of color are two to three times more likely to be diagnosed. Scleroderma, or systemic sclerosis, is a chronic connective tissue disease that involves the hardening and tightening of skin and connective tissue. According to the American College of Rheumatology, 75,000 to 100,000 people in the U.S. are affected by scleroderma, with the highest incidence among women between the ages of 30 and 50.

Lupus

In addition to running the Division of Rheumatology and Immunology, Oates also leads a strong research lab focused on lupus nephritis and lupus atherosclerosis. In work funded through a VA Merit Award, the Oates lab is studying how endothelial dysfunction may link the accelerated atherosclerosis seen in lupus patients with the process of immune cells becoming attracted to and migrating into kidney tissues to cause local inflammation. Nitric oxide, a potent vasodilator, is highly expressed in the kidney and may be a key mediator and modulator of disease.

To help guide therapy, the Oates lab is also looking at biomarkers at baseline that predict one-year outcomes. Furthermore, they are using a type of machine learning, random forest analysis, to assess variables that are already in the electronic health record in an attempt to model patients who are at risk for poor outcomes.

Another lab is taking a genetic approach to identify novel lupus biomarkers. **Betty P. Tsao, Ph.D.**, professor and inaugural holder of the Richard M. Silver Endowed Chair for Inflammation Research in the Division of Rheumatology and Immunology, is analyzing patient genomes from different ethnic backgrounds to understand lupus risk variants, in both the coding and noncoding regions of the genome, which might reveal novel mechanisms underlying disease. Variants that appear in multiple major ethnic groups are more likely to be causal and may serve as novel drug targets.

“It seems so unfair that lupus affects young women,” says Tsao. “You want to be able to figure out something to help them.”

Indeed, her work has identified several interesting targets, including proteins involved in autophagy and the generation of

reactive oxygen species. A better understanding of the pathways these proteins are involved in could aid in the development of more targeted therapies or personalized medications.

There is a large, multicenter clinical trial centered at MUSC that is using mesenchymal stem cells (MSCs) to treat patients with treatment-refractory lupus. The trial is headed by **Gary S. Gilkeson, M.D.**, Distinguished University Professor in the College of Medicine and associate dean for faculty affairs and faculty development.

“The appeal of MSCs is their relative safety,” says Gilkeson. “They have been tried in other diseases, and there haven’t been reports of any major side effects. If they work, and if they work for a long period of time, that would be advantageous.”

Six patients were treated in the phase I trial. They were given a single infusion of MSCs and allowed to remain on their other medications. Five of the six patients met the response criteria, and some had remarkable responses to the treatment.

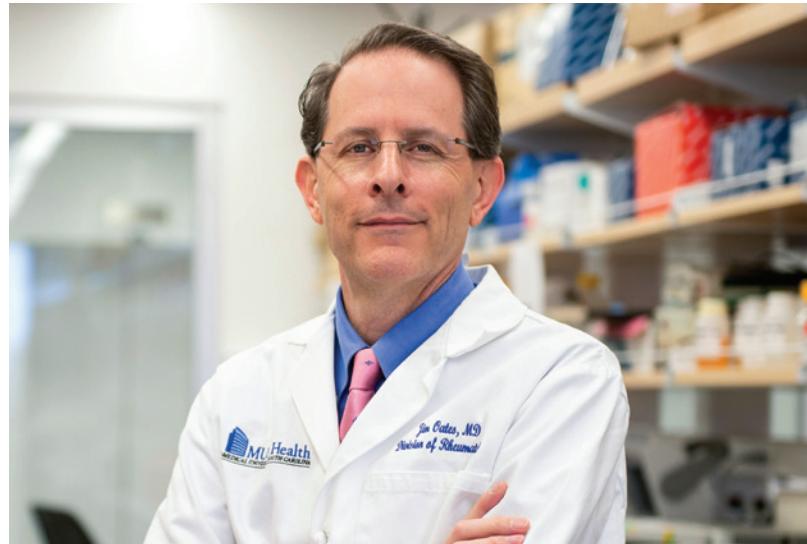
Trying to better understand the impact of MSCs on the immune system, Gilkeson and colleagues made a shocking observation. Infusion of the MSCs resulted in significant differences in the B cell compartment—the B cells that make autoantibodies and are increased in lupus patients returned to normal levels. Currently, they are unsure of the reason for these changes, but they hypothesize that transforming growth factor beta expressed from MSCs affects the B cell population.

Scleroderma

Having retired from directing the division, Silver can now see more patients and focus on teaching and conducting cutting-edge scleroderma research. By examining data from scleroderma patients, he found that the level of thrombin, a coagulation factor, was elevated in the lung. In tissue culture models, addition of thrombin converted normal lung fibroblasts into myofibroblasts that exhibited all the hallmarks of fibrotic tissue.

Silver and his colleague, **Galina S. Bogatkevitch, M.D., Ph.D.**, went on to show that an FDA-approved thrombin inhibitor was capable of transforming a scleroderma fibroblast back into a normal fibroblast. They then used an animal model of lung fibrosis to show that they could attenuate disease in animals that were given the thrombin inhibitor. Now they have found a natural antifibrotic peptide that is effective at blocking fibrosis *in vitro* and in animal models through a pathway distinct from the thrombin path.

Down the hall, **Carol Feghali-Bostwick, Ph.D.**, professor and SmartState and Kitty Trask Holt Endowed Chair for Scleroderma Research in the Division of Rheumatology and Immunology, and members of her lab study the molecular differences that



Dr. James Oates, now head of the Division of Rheumatology and Immunology, leads a strong research lab focused on lupus nephritis and lupus atherosclerosis.

differentiate twins discordant for scleroderma. While trying to identify profibrotic factors, they realized that a fragment of collagen 18, endostatin, was induced.

Surprisingly, endostatin exhibited an antifibrotic effect. Subsequently, they chopped endostatin into smaller peptides to determine which region was antifibrotic. They identified a peptide that inhibits multiple pathways that have been implicated in fibrosis. This may be why it is more effective than other treatments and is likely to stop, even possibly reverse, fibrosis. The peptide has been licensed for cost-effective production in plants. Upon passing an investigative new drug approval by the FDA, this new peptide could be seen in the clinic in the near future.

“It looks promising so far,” says Feghali-Bostwick. “The encouraging part is that the parent molecule, endostatin, has been used in advanced clinical trials for its antiangiogenic activity in cancer and has shown no toxicity or drug resistance.”

Positive signs ahead for treating lupus and scleroderma

Currently, there is no cure for lupus or scleroderma. Treatments for this class of ailments can be toxic and focus on inhibiting immune system activity and reducing inflammation. Researchers at MUSC are pursuing several exciting research projects that aim to provide better alternatives.

“I think we are nicely integrating the clinical and research missions of the division, where both our clinicians and researchers are all focused on how to improve people’s lives,” says Oates.



MORE THAN JUST A Cure

3D technology gives head and neck cancer patients a chance
for the quality of life they had before their diagnosis

BY CELIA SPELL

“The first thing he wanted to do with his new smile was eat pizza.”

Betsy Davis, DMD, a maxillofacial prosthodontist at the Medical University of South Carolina (MUSC), works with head and neck cancer patients to use 3D printing to build exact replicas of their teeth, nose or ear, offering the best chance to return to the quality of life they had before their diagnosis. By taking precise measurements and scans of unaffected areas, maxillofacial prosthodontists like Davis can build accurate prosthetic replacements that fit together like puzzle pieces.

One of her patients had been diagnosed with a form of head and neck cancer that required surgeons to remove his teeth and part of his jaw. But after treatment with the physician team at the Wellin Head and Neck Tumor Center at MUSC, he received new teeth and part of a jaw, which was planned virtually using 3D-printed parts. This level of attention and precision can give a patient like hers the ability to do the small things they’ve missed—like eating pizza.

A Rising Epidemic

Head and neck cancer starts in the nose, mouth, throat, voice box and

sinuses, and treatment may call for partial or complete removal of the affected area, which means that patients are not able to do everyday tasks. And while head and neck cancer comprises only four percent of all cancers, it has a high mortality rate. It is estimated that 64,500 people will be diagnosed with some form of head and neck cancer in 2019, and almost 14,000 people will die from it.¹

“Many of us take for granted that we can talk, eat, drink, smile and chew, and even swallow and breathe, without any problems,” explains **Terry Day, M.D.**, endowed chair for the Wendy and Keith Wellin Head and Neck Tumor Center at MUSC. “But if you have an abnormality in those areas, it affects those things we use all the time.”

Most head and neck cancers are classified as squamous cell carcinomas, meaning the disease begins in the flat, scale-like cells that make up the thin layer of skin around the head and neck, as well as the linings of the respiratory and digestive tracts and hollow organs throughout the body. There are five main types of head and neck cancer, named for the areas they affect: laryngeal and hypopharyngeal cancer, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, oral and oropharyngeal cancer and salivary gland cancer.¹



By taking scans of unaffected areas, physicians can build precise prosthetic replacements that fit together like puzzle pieces.

The two biggest risk factors for head and neck cancer in the past have been alcohol and tobacco use, and using these products in conjunction, whether through drinking, cigarettes or smokeless tobacco, also known as “chewing tobacco,” creates an even higher risk.² But as cigarette use has declined over the last 30 years, so has the prevalence of related oral and oropharyngeal cancers, leaving room for a new risk factor: human papillomavirus (HPV).

HPV is best known for its association with cervical cancer, but HPV-associated head and neck cancers have been cropping up in new cases across the country, with the most common being HPV-associated oropharyngeal cancer. It is estimated that between 70 and 90% of new cases can be linked back to the virus.³

This risk factor change brings a patient demographic change as well as a treatment and prognosis change. Patients with HPV-associated head and neck cancer are more likely to be white males in their 40s and 50s who do not smoke or drink excessive amounts of alcohol. They are almost three times more likely than women to be diagnosed with certain forms of head and neck cancer, like that of the back of the throat.¹

While HPV-associated cancers are becoming more common, they are also more responsive to treatment.⁴ For instance, the overall survival rate for HPV-associated oropharyngeal cancer is 95% after two years, while oropharyngeal cancer not linked to HPV has a survival rate of only 62% after two years.

A team effort

Treatment for head and neck cancer is complicated. The areas it affects are both highly visible and critical to quality of life, so the team of doctors needed covers many specialties. At MUSC, these specialists reside under the same roof, the Wellin Head and Neck Tumor Center, which is critical for ease of travel, treatment and treatment adherence.

From a treatment standpoint, the team consists of a head and neck surgeon, a radiation oncologist, and a medical oncologist, but additional team members are needed to address the quality-of-life perspective, such as a dental expert trained in maxillofacial prosthodontics, speech and swallowing therapists, and a physical therapist. Truly complex cases also require a highly specialized head and neck reconstructive surgeon.

At the Wellin Center, all of these physicians are in one place. They meet weekly at a tumor board meeting to review the CAT scans, PET scans, MRIs and pathology results for each individual patient before any kind of surgery. Then they come to a consensus on the best plan for treatment and work in tandem, both in and out of the operating room, to bring the best results, investing not only in their patient's cure but also in their life after cure.

“We focus on function, quality of life and cure,” said Davis. “I think those three things are equally weighted in a patient's mind. And the MUSC head and neck team works together to give them at least a chance at all three.”

Modern treatment strategies

Each case is unique when it comes to treatment, which is one reason that the tumor boards are so effective. Patients will likely need some combination of radiation therapy, surgery, maxillofacial prosthodontics and physical therapy with voice, speech and swallowing specialists.

For instance, surgeons might need to remove the jawbone along with some teeth and the tongue of a patient with advanced oropharyngeal cancer. In that case, the team may decide to either bring in bone from the fibula to rebuild the jaw or place dental implants to serve as anchors for prosthetic teeth.

If the team decides to use existing bones, they will use the scans and the 3D printer to plan exactly where to cut the bone and how to shape it before the operation. They will then slice the bone into pieces and attach the parts in the proper configuration by use of titanium plates. **Joshua Hornig, M.D.**, a head and neck surgical oncologist at MUSC, said he is always surprised to see how well a patient's leg recovers after removal of part of the leg bone.

A more cutting-edge method for rebuilding the jaw is to print it out of a plastic called methyl acrylate. Using MUSC's specially adapted CAT scan machine, physicians can take a scan and convert it into a 3D model that can then be printed.

"We can hold it out to the patient," said Day. "And we can walk them through their upcoming procedure using a model of their very own jaw."

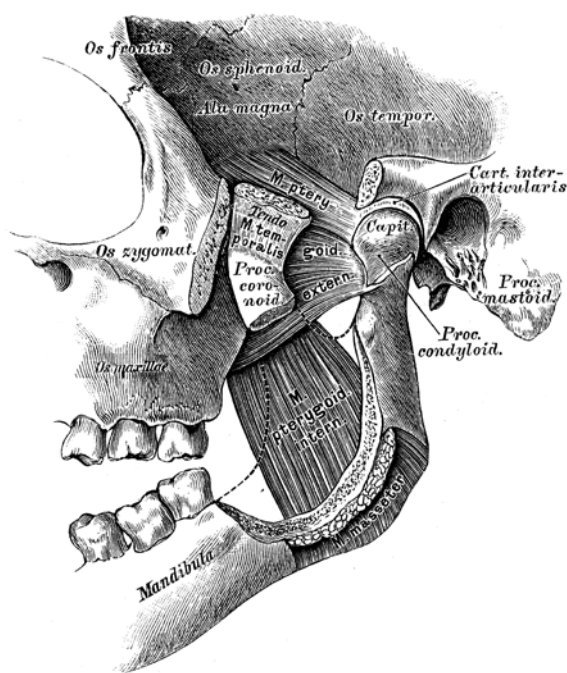
In addition to rebuilding the jaw, the team also uses free tissue transfers from muscles of the body to replace the teeth, tongue and lips that were removed, leaving the patient with a quality of life that extends beyond just a cure.

The tumor removal procedure, the surgical reconstruction and the placement of dental implants take place on the same day. With a potential total surgery time of 15 hours or more, Day starts by removing the tumor and any affected area, and Hornig follows with the surgical reconstruction of the fibula while oral surgeons follow with dental implant placement.

Hornig looks at the surgery as more than just a technical feat. "You have to be a great surgeon," he said. "But you also have to be a fellow human being and listen to them. You have to find out how this is going to impact their life and guide them through these changes."

Life after plastic

The goal of the team at the Wellin Center is to one day create a living piece of the patient's bone to implant. Physicians have successfully implanted 3D-printed bladders and kidneys into patients, but they have yet to regrow a mandible or skull from the patient's own



cells.⁵ That's where Hornig thinks this field is headed next.

3D printing first made its debut 50 years ago as stereolithography, which allows construction of a 3D model by use of a laser to etch a design into a specific photopolymer.⁵ Initially used to create industrial prototypes, the technology quickly moved on to large-scale manufacturing and engineering. Next, 3D printing advanced into health care, and its uses have expanded ever since.

MUSC started using 3D printing to assist physicians in reconstructive surgeries 20 years ago, and it continues to advance this practice today. Initially met with skepticism from the medical field, 3D printing is now widely used for this method. Between 2016 and 2019, MUSC produced a total of 57 3D-printed models and prosthetics for patients.

Davis once had a patient who wore his best suit to the hospital on the day he received his prosthesis. He walked in and said, "Today I get my face back." And Davis thought: a feeling like that is priceless.

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Room for Growth



Kardia (AliveCor, Inc.) is a sensor device that pairs with a smartphone application to run a one-lead ECG.

PHOTO: BRENNAN WESLEY

Adopting Mobile Health Technology in Pediatric Telehealth

BY SVER AUNE

Smartphones paired to mobile devices can send health data directly from patients to their doctors. For example, mobile health (mHealth) technologies can take an electrocardiogram (ECG), track blood sugar or monitor medication adherence. Collected data can then be sent to a patient's health care team.

Yet mHealth offers more than just data collection. It can be a valuable tool in the delivery of long-distance health care to patients. New technologies may incorporate remote monitoring of health data, videoconferencing with patients or syncing with electronic health records.

Home-based telehealth is promising for management of pediatric patients with complex or chronic medical conditions that require frequent follow-up with specialty care. By combining telehealth with

the concept of the "patient-centered medical home," physicians can work with patients and their families to improve the delivery of care.¹

As stated by **S. David McSwain, M.D.**, interim chief medical information officer and medical director for telehealth optimization at the Medical University of South Carolina (MUSC), "One of the most promising areas in telehealth development is the ability to connect patients in their homes with a coordinated care team that also incorporates their primary care physician."

Community investment

Abnormal heart rhythms in children are fleeting and often occur outside the hospital, making them difficult to detect and diagnose. Children with supraventricular tachycardia, the common rhythm

disturbance in the pediatric population, may need medical or surgical treatment for the condition.² But not everyone can afford a smart-watch with ECG capability.

A grant to MUSC from the South Carolina Telehealth Alliance covers the device and subscription costs of Kardia (AliveCor, Inc.), a sensor device that pairs with a smartphone application to run a one-lead ECG. The device is FDA approved but usually is not covered by insurance. Families with children who report symptoms are loaned the tool for 30 days. A patient experiencing physical symptoms can use the tool to automatically record an ECG; the application then sends the ECG to the patient's cardiologist for reading.

During the first six months of the loan program, 33 patients received the Kardia device. Eight were diagnosed with an abnormal finding which required further treatment—seven with premature ventricular contractions and one with supraventricular tachycardia.

MUSC pediatric cardiologists **Nicole Brooks Cain, M.D.**, and **Hamilton Baker, M.D.**, hope to demonstrate that the technology can be integrated into pediatric cardiology practice. According to Baker, it is scalable for larger programs as well.

"This type of a program could be used for numerous devices as this market grows to prevent those higher-priced telehealth products from only being available to those with means to purchase them," said Baker.

In the second phase of the project, the Kardia device will become available to school nurses. Although they will not use the device in emergent or urgent situations, nurses can capture rhythm readings if a child is experiencing any symptoms.

Virtual visits

Pediatricians at MUSC are testing a mobile health platform designed to help children with severe asthma and their families stay connected to care.

According to the National Heart, Lung, and Blood Institute, regular assessment of asthma patients is key to controlling their disease. Children with severe asthma often take daily maintenance medication and use rescue inhalers to manage flare-ups, but they may need more frequent contact with an asthma specialist to manage their symptoms, which can be difficult if the specialist is far away.³

The preservation of face-to-face contact is the central idea behind the Smartphone Asthma Monitoring System (SAMS). SAMS includes two major components: medication tracking and video chatting for virtual visits with a nurse educator. Pediatric patients are given Bluetooth inhalers to track their maintenance and rescue inhaler use, and they are encouraged to fill out daily symptom surveys.

Symptom and medication use data are downloaded from inhalers to a smartphone and then sent by SAMS to a secure internet portal, where a health care team can view the data in real time.⁴

When MUSC clinicians first started collecting this data, they learned that patients wanted more connection with their care team, according to **Ronald J. Teufel, M.D.**, MUSC Children's Hospital Director of Pediatric Hospital Medicine and the clinician leader of the SAMS project. They thus added video chat capability in an effort led by Sachin K. Patel, Chief Technology Officer for MUSC Digital Health Solutions.

Anita Shuler, lead nurse educator for SAMS and a respiratory therapist at MUSC Children's Hospital, conducts regular video chats with pediatric patients and their families. Shuler assesses patient symptoms, encourages regular inhaler use, provides inhaler technique instruction and outlines which asthma symptoms may require medication adjustment.

"SAMS is designed to follow national guidelines for assessing asthma patients, and then we use that data to either work on adherence with the patient or change their inhaled corticosteroid dose," said Teufel.

Virtual visits with pediatric patients are not designed to replace in-person visits with the pediatrician. Rather, SAMS allows the asthma specialist to provide added care as needed. At present, virtual visits are scheduled in advance, but Teufel and his team will begin collecting data to help determine the best time to intervene with a virtual visit.

mHealth integration

As mHealth technology is refined, efforts to adopt it on a wider scale are ongoing. For example, the telehealth approach to pediatric asthma care is being deployed through the MUSC Center for Telehealth's school-based program. Such approaches are still in early phases, but they provide a model for how pediatric telehealth can grow into the future.

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Dr. Minoo Kavarana
places a reversible
pulmonary artery band
into a pediatric patient.

BRIDGING THE G A P

MUSC's heart failure team uses novel approach to help pediatric patients

BY CELIA SPELL

As the organ responsible for taking blood from the body and enriching it with oxygen before recirculating it, the heart provides a vital function for human existence. Any problem with the muscles involved could deprive the body of the circulating blood, and therefore oxygen, that it needs to carry on.

Both ventricles keep the heart functioning and circulating blood, but the left ventricle is the one responsible for supplying blood to the rest of the body while the right ventricle sends blood to the lungs. In left sided heart failure, or left ventricular dysfunction (LVD), the left pump cannot keep up with the body's demands.

Heart failure in general, and especially LVD, has been widely studied and treated in adults but not in children, so physicians take the data that is available and combine it with their clinical experience to treat infants, young children and even teenagers with LVD.¹

Children can be born with heart defects that then lead to heart failure when attempts at surgical repair and medical intervention do not work. They can also develop heart failure from a viral infection, but it is rare, and children are more likely to recover with temporary help.

"Most young patients with congestive heart failure will likely need a heart transplant," said **Minoo Kavarana, M.D.**, a pediatric cardiothoracic surgeon at MUSC Children's Health. But after hearing about a new procedure in Germany, Kavarana talked with the rest of the team about bringing it to the Southeast.

It takes an average of 2 to 6 months for a child on the transplant list to find a heart, and many are too sick to wait that long. Historically, surgeons have implanted assist devices into the chamber that needs help pumping blood. While these devices do not remove the need for a transplant, they give the child more time to wait for a heart to become available. They also provide the chance to recover function in their other organs as well as improve their nutrition and overall condition, which makes them a better candidate for a transplant.

Many assist devices are initially designed for adults and then modified to treat children; however, this can lead to infants with assist devices (such as the Berlin heart) having a high risk of complications that may lead to stroke.² Studies that indicated a high incidence of embolic stroke, bleeding and infection with assist devices led the heart failure team at MUSC to look into a new procedure: reversible pulmonary artery banding (PAB).

As one of the first centers in the country to offer the procedure, MUSC brings a new treatment option to parents. The procedure involves placing a band around the main pulmonary artery, the vessel which carries blood from the right ventricle to the lungs for oxygenation. By increasing the pressure in the artery, the band causes the

partition between the right and left sides of the heart, the ventricular septum, to alter its orientation toward the left. This slight change provides more support to the valves and pumping chambers on the left side of the heart.

Abnormally high pressure on the left side of the heart can shoot from the normal range of 5-10 millimeters of mercury (mm) to 20-30 mm, but with PAB this pressure can drop to 10-20 mm.

This decrease in pressure may allow the physician to wean these pediatric patients off both the ventilator and medications required to support their blood pressure and then sometimes even send them home. The key to the procedure's success is the patient's type of heart failure. If the patient's condition also affects the right ventricle, the pulmonary artery band would put too much pressure on the right side of the heart, so physicians don't consider the reversible PAB an option in this case.

While the procedure has been performed only a few times at MUSC for children with LVD, some have recovered and are no longer on the transplant list, and others have used the pulmonary artery band in place of assist devices while waiting for a transplant to become available.

"We like to think of this procedure as either a bridge to transplantation or even a bridge to recovery," said Kavarana.

MUSC, Loma Linda University and Texas Children's Hospital are among the first institutions in the United States to use this heart failure treatment technique for LVD in infants. The heart failure team at MUSC explored the technique due to its minimally invasive nature when compared to assist devices, its reversibility and the fact that the child's heart does not need to be stopped during surgery.

"The next step is to look into an adjustable band known as a Flo Watch," said Kavarana. "It could be adjusted as the child's blood pressure and condition change." The heart failure team at MUSC is currently working with Clemson University to assess the band in a computational flow model and then in animal models before its use in the clinic.

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Maternal Safety Comes in Threes

Keeping moms healthy with
new safety bundles





SUBJECT MATTER EXPERTS:
DR. SCOTT SULLIVAN AND DR. JUDITH BURGIS

BY KATHARINE HENDRIX

On completion of this article, readers should be able to:

- Describe current maternal mortality and morbidity trends in the U.S. and SC.
- Describe populations that are most likely to experience pregnancy-related death or morbidity.
- List the most common complications that lead to pregnancy-related deaths, many of which are preventable.
- Identify proven-effective treatment protocols that can be adopted in SC to reduce the upward trend in maternal mortality and morbidity.
- Describe why improved maternal morbidity data reporting is needed in SC.

Maternal mortality

Approximately 700 women across the United States die each year as a result of pregnancy or pregnancy-related complications.¹ The U.S. maternal mortality rate is 14 deaths per 100,000 live births and is substantially higher than in peer nations like Canada which has 7 maternal deaths per 100,000 live births and the United Kingdom which has 9 maternal deaths per 100,000 live births.² High income countries typically have low annual maternal death rates (3–12 deaths per 100,000), and rates have consistently declined over the last 25 years. Unfortunately, the U.S. has seen an opposite trend with a 16.7 percent increase in the maternal mortality rate from 1990 to 2015.

The South Carolina maternal mortality rate is approximately 24 per 100,000 live births and is significantly higher among black women than white women (41.9 vs. 14.9 per 100,000).³ This disparity is also observed nationally, with U.S. in-hospital maternal mortality being three times higher for black women than for white women in 2015 (11 vs. 4 per 100,000 deliveries).⁴

Maternal morbidity

For each woman who dies as the direct or indirect result of pregnancy, exponentially more women experience life-threatening complications. Severe maternal morbidity (SMM) refers to unexpected outcomes of labor and delivery that have significant short- or long-term consequences for a woman's health. Nationwide, SMM is about 100 times more common than pregnancy-related death,

Date of Release:
April 9, 2018
Date of Expiration:
April 9, 2020

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Dr. Burgis works as a Nexplanon trainer with Merck & Company, Inc., and Dr. Sullivan works as a consultant with Hologic testing for HPV. Katharine Hendrix has no relevant financial relationships to disclose.

affecting approximately 52,000 American women annually.⁵ In other words, for each maternal death in the U.S., an estimated 50–100 women experience SMM. Sometimes referred to as “near-misses,” instances of SMM include potentially fatal events such as acute myocardial infarction, pulmonary embolism and sepsis.

Like maternal mortality, the U.S. SMM rate (as defined by 21 conditions and procedures) has also increased sharply – rising 45%, from 101.3 to 146.6 per 10,000 delivery hospitalizations between 2006 and 2015.⁴ In addition, SMM also disproportionately affects minority and low-income women, especially non-Hispanic black women and those with Medicaid coverage. The U.S. SMM rate is 112–115 percent higher for black women than for white women, and this inequity

has not changed in over a decade – with black vs. white SMM rates of 164 vs. 76 in 2006 and 241 vs. 114 in 2015 (per 10,000 delivery hospitalizations).⁴

Contributing factors

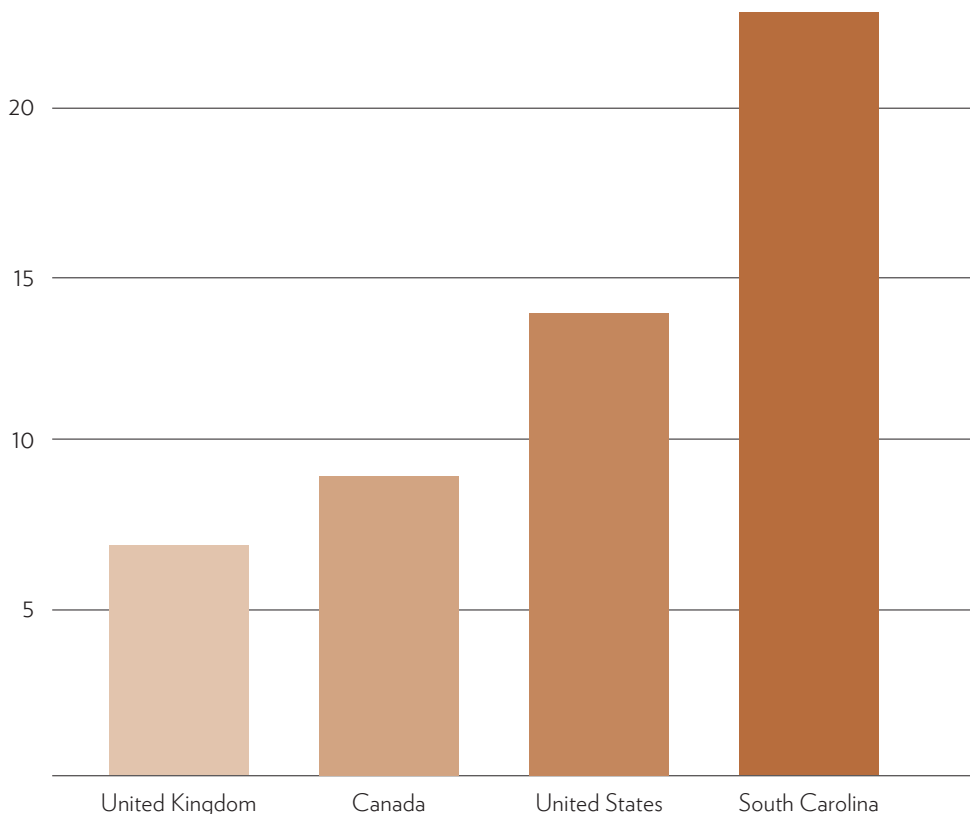
Delay and a lack of urgency in addressing our rising rates of maternal mortality and morbidity can be largely attributed to two environmental factors. First, many physicians do not personally experience a maternal death at their own facilities in any given year. Second, SMM events may occur before or after the actual delivery and may be treated by another physician or facility. Thus, documentation and medical records may not correctly associate an SMM event with a woman's pregnancy or delivery.

While maternal mortality is regularly and consistently reported,

SMM is inconsistently defined and reported, making the task of assessing these data and identifying priorities difficult at both state and national levels. Nonetheless, it is clear that meeting the Healthy People 2020 target of reducing the U.S. maternal death rate to 11.4 per 100,000 live births and complications during hospitalized labor and delivery to 28 percent (from 31.1 percent) will require a concerted, state-level effort.

From 2011–2013, 15.1 percent of U.S. pregnancy-related deaths were caused by cardiovascular disease, 14.5 percent by non-cardiovascular diseases, 12.7 percent by infection and sepsis and 11.4 percent by hemorrhage.⁶ A legislative brief from the SC Maternal Mortality and Morbidity Review Committee finds that the most common causes of maternal death in SC are cardiovascular and coronary conditions, hemorrhage, infection and embolism.⁷

Maternal Deaths per 100,000 Live Births



The U.S. maternal mortality is significantly higher than that of other developed countries like Canada and the UK, and the rate in South Carolina is even higher.

700 women

across the U.S. die each year as a result of pregnancy or pregnancy-related complications.

IMAGE: CELIA SPELL

The SC Maternal Mortality and Morbidity Review Committee also recently collaborated with the Centers for Disease Control and Prevention on a report combining data from nine states.¹ Nearly half of all pregnancy-related deaths in participating states were caused by hemorrhage, cardiovascular and coronary conditions, cardiomyopathy or infection. Importantly, the authors estimated that over 60 percent of pregnancy-related deaths reviewed were preventable.

Nationwide, severe maternal morbidity is about 100 times more common than pregnancy-related death.

The report cited three common contributing factors to maternal death: patient/family factors (e.g., not recognizing warning signs and the need to seek care); provider factors (e.g., misdiagnoses and ineffective treatments) and care systems factors (e.g., lack of coordination between providers). It concluded by recommending broad steps that birthing facilities can take to reduce maternal mortality and morbidity, which included: adopting levels of maternal care, improving prevention policies and initiatives, enforcing policies and procedures related to hemorrhage and improving patient management policies.

Effective tools for prevention

A set of proven-effective safety protocols called *Maternal Safety Bundles* have been developed by the Alliance for Innovation on Maternal Health (AIM) in association with the American College of Obstetricians and Gynecologists (ACOG) to help birthing centers reduce maternal mortality and morbidity.

These condition-specific treatment protocols are readily available and represent best practices in maternity care.⁸ The three core *Safety Bundles* focus on: *OB Hemorrhage*, *Severe Hypertension in Pregnancy* and *Venous Thromboembolism Prevention in Pregnancy*. Three supplemental *Safety Bundles* address: *Maternal Early Warning Criteria*, *Facility Review* and *Family and Staff Support*.⁹ After implementing these protocols, maternal death rates in California fell from 16.9 per 100,000 live births to 7.3.¹⁰

A 2015 ACOG opinion further supports statewide implementation of *Maternal Safety Bundles*, stating: “Protocols and checklists are shown to reduce patient harm through improved standardization and communication. The use of checklists and protocols has been clearly

demonstrated to improve outcomes...Variation in processes of care is problematic because it may lead to increased errors... Performing critical tasks the same way every time can reduce human error, especially when fatigue is a factor, and the environment is stressful.”¹¹

Finally, it is essential to improve statewide data collection and reporting of SMM cases in order to determine how to best focus efforts and resources for reducing maternal morbidity in SC. It is recommended that birthing facilities across the state put screening processes in place to detect and review SMM cases. ACOG and the Society for Maternal-Fetal Medicine recommend two SMM screening criteria: (1) transfusion of four or more units of blood, and (2) admission of a pregnant or postpartum woman to an ICU. Individual institutions may also incorporate additional screening criteria to identify SMM cases.⁹

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Interview

MUSC Health is Excited to Have Dr. Robert Harrington Join the MUSC Family



Robert Harrington, M.D., joined the MUSC family in October and serves as Chief Medical Officer of the Affiliate Network. He will serve as the liaison between the medical staff here at MUSC and the medical staff of our partner hospitals. He will also serve a critical role in developing further strategic partnerships. Harrington received his degree from Temple University – Lewis Katz School of Medicine and performed his residency in family medicine at the Medical Center of Delaware – Christiana Hospital. *Progressnotes* spoke with Harrington in January.

PN: What attracted you to MUSC?

I've known Pat Cawley, M.D., Michael Hawkins, M.D., and Danielle Scheurer, M.D., MSCR, for a number of years. One of the reasons I was attracted to MUSC was the quality of those three people and the opportunity to work with them. In addition to that, I was very intrigued by the position. Getting involved in a program such as this at the grassroots level and building the future of affiliations here at MUSC was exciting to me. Things changed dramatically in December when MUSC announced we were buying four hospitals. This has certainly increased the speed at which I'm getting engrained into the MUSC family. I've been in this position for four months now, and I am impressed by the quality of the people I run into every single day. It's been a tremendous experience to be a part of this.

PN: What will you be doing in your new role at MUSC?

There are really two aspects to my role at MUSC. One role is to interface with the affiliate partners' medical staff, and the other is to help design how a strategic affiliate relationship looks. For example, if a community has an interest in developing a neuroscience

PHOTO: SON NGUYEN

program but does not know how to achieve it on their own, they may ask us to partner with them on various levels to help develop that program. First, we would identify what services the program would include, such as neurosurgery, general neurology or physical medicine and rehab. Then we can figure out the best way we can partner on those particular services and determine who will staff it, who will run it, who will do billing and collection and other facets of running a program. We will be offering that type of program in four service lines: oncology, heart and vascular, neuroscience and children's and women's health.

PN: What are the greatest strengths of the MUSC Affiliate Network?

Our mission as an enterprise and as a health system is to promote the health and welfare of South Carolinians across the state. For years, we have been focused on the peninsula and have achieved some incredible things locally. We now have a vision that we can be a statewide leader, not just a local or regional player. I think our Affiliate Network gets to the core of that mission by delivering the expertise and specialty services we have here at MUSC across South Carolina.

PN: How has your previous experience helped shape your vision for MUSC Health?

I've spent my entire career in the community hospital setting, and I think that lends itself well to what we're trying to do here. Community hospitals operate differently than academic medical centers, and having expertise from a community hospital perspective on the team is important as we go out and begin to have conversations with potential partners. We can sit at the table with them and understand how they operate and know that their priorities may be different than

those things that are important to us at an academic medical center.

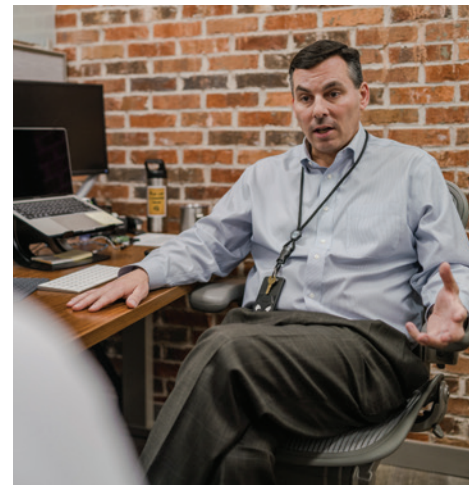
Another critical piece, especially as we go through the acquisition of the four hospitals, is integrating those new physicians into the MUSC system. I've spent the better part of my career managing multi-site, multi-state physician practices. Being able to understand the challenges associated with integration and with remote operation of those physician practices is another strength I bring to the table.

PN: How can MUSC Health continue to grow as a health care system?

Our philosophy is that health care should be delivered locally whenever possible. Community hospitals who are not affiliated with larger health systems are struggling right now because they don't have a lot of buying power, they don't have a lot of leverage with the payers and they don't have a lot of expertise in some of the new technologies. We need to develop a set of community-focused specialty services that complement the primary care base and allow people access to the specialty services here at MUSC through a community network. One of the ways we will deliver our expertise throughout the state is through continued growth of our Telehealth programs. We are already giving communities that traditionally had no access to some of these services ready access to the experts here at MUSC. This keeps care local. I also think the affiliate program is core to our ability to continue to grow through partnering with community hospitals across South Carolina.

PN: What are some of your immediate and long-term goals for the Affiliate Network?

My immediate goal is to build strong relationships with all of the key stakeholders.



I think that will serve me well as we get up and running. I want to build a strong level of trust internally at MUSC such that the Integrated Centers of Clinical Excellence chiefs and department chairs don't feel like we're selling something we can't deliver. I want to help them through the process of developing and articulating what it is that we can deliver so that we can truly underpromise and overdeliver as it relates to our partners. The secondary goals for me are to develop our four service line offerings, and potentially more after that. Ultimately, to have a menu of services that we think are valuable to community hospitals and that we know we can deliver.

PN: In which areas would you like for us to be world leaders?

I think Telehealth is certainly one where we are already ahead of the crowd, and I think that we should continue to grow this program and leverage our expertise here as much as we can. I'd like to see us be a leader in the way we partner with community hospitals. To me, our development of these affiliate relationships and the strength of those relationships is something that we can excel in.

New Physicians

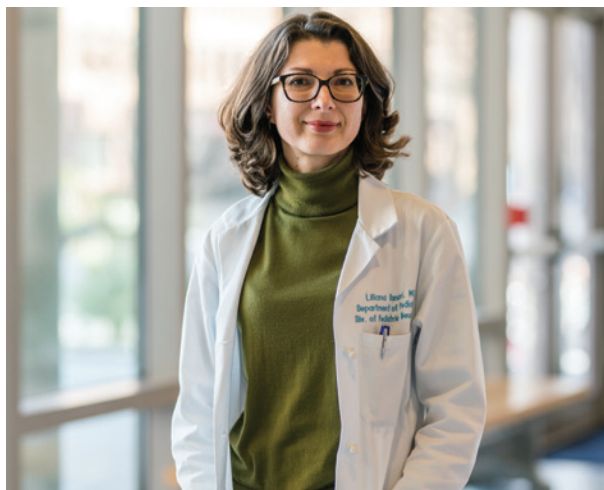
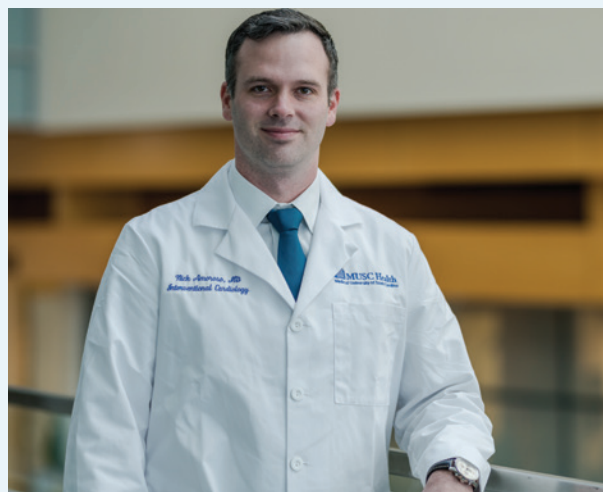


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