# PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SUMMER 2016


## Vanishing Act:

### Recognizing and Responding to Alzheimer's in Primary Care Practice

# MUSC Children's Hospital Nationally Ranked in Six Specialties by *U.S. News & World Report*

In June, *U.S. News & World Report* released its rankings for the "Best Children' Hospitals" in the nation. Six of MUSC Children's Hospital divisions are nationally ranked. MUSC Children's Hospital heart program is ranked among the top 20 and is named a "best hospital" in that category. Here's a look at all six of the MUSC Children's Hospital divisions honored in the new rankings, based on information from about 180 pediatric centers across the country:

- Cardiology & Heart Surgery (#20)
- Nephrology (#22)
- Urology (#29)
- Cancer (#37)
- Pediatrics: Gastroenterology & GI Surgery (#39)
- Pediatrics: Diabetes & Endocrinology (#47)

The rankings take into account clinical and operational data, results from a reputational survey of board-certified pediatric specialists, and supplemental information from resources such as the National Cancer Institute.

**Mark Scheurer, M.D.**, chief medical officer of MUSC Children's Hospital, said the *U.S. News & World Report* rankings come as the hospital prepares for an important move in 2019. That's when the new MUSC Shawn Jenkins Children's Hospital is scheduled to open.

**Dr. Andrew Atz, Director of the Division of Pediatric Cardiology, checks on a patient.**

"We are working hard now to grow dedicated pediatric programs that will use this wonderful new building in the future and best serve our community now," Scheurer said. *"The U.S. News & World Report* awards are a fitting testimony to the ongoing efforts at MUSC to further develop programs to serve children and families across the state and region."

## Upcoming CME Conferences

The following conferences, sponsored by the Medical University of South Carolina, will be held in Charleston unless otherwise noted. Visit http://musc.edu/cme for a complete list of CME conferences.

| | |
|---|---|
| September 24, 2016 | 3rd Annual Update in Gastroenterology and Hepatology<br>*MUSC Drug Discovery Building—Auditorium* |
| November 4-5, 2016 | 2016 Storm Eye Institute Fall Meeting and Alumni Reunion<br>*MUSC Bioengineering Building—Auditorium* |
| November 9-11, 2016 | Neonatal Pharmacology 2016: Incorporating Evidence-Based Practice into Clinical Decision Making<br>*Francis Marion Hotel* |
| December 2-4, 2016 | 19th Annual Frontiers in Pediatrics<br>*Francis Marion Hotel* |

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On the cover: Memory loss in patients with Alzheimer's disease makes it difficult for them to reconstruct the narrative of their lives. Illustration by Timothy Banks.



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MEDICAL UNIVERSITY of SOUTH CAROLINA

# PREDICTING EARLY DELIVERIES

## An accurate, early blood test to predict preterm births

BY LINDY KEANE CARTER

**Low birth weight creates numerous health risks for babies born prematurely.**

MUSC Health was among the top-enrolling U.S. sites (800 patients) in a clinical trial that identified two serum proteins as reliable predictors of spontaneous preterm delivery. The co-investigators, including **Scott A. Sullivan**, **M.D.**, Associate Professor of Obstetrics and Gynecology and Director of the Division of Maternal Fetal Medicine at MUSC Health, reported their findings in the May 2016 *American Journal of Obstetrics and Gynecology* (doi: 10.1016/j.ajog.2016.02.001).

"Before this test, obstetricians didn't have any reliable way to know who among their asymptomatic patients was going to have a preterm birth well before the event," said Sullivan. "This blood test is 85% accurate and early. We can know at 19 to 21 weeks into the pregnancy who may have a preterm birth."

The Proteomic Assessment of Preterm Risk (PAPR) trial enrolled 5,501 pregnant women at 11 U.S. sites between 2011 and 2013. Researchers collected blood at 18 to 20 weeks gestation and then collected outcome data after the women delivered their babies. Sera Prognostics, Inc. (Salt Lake City, UT) sponsored the trial and conducted the testing using proteomics, bioinformatics, and multidimensional data analysis to test all identifiable proteins. The scientists identified and verified two serum proteins as predictors of spontaneous preterm delivery: insulin-like growth factor-binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG). These proteins were consistently overexpressed or underexpressed. A follow-up clinical study conducted in a different group of women validated that this signature based on the two proteins (identified as early as 19 weeks) was a good predictor of preterm birth before 35 to 37 weeks of pregnancy. The resulting commercial test has been on the market since March 2016.

Premature birth, defined as birth before 37 weeks gestation, is the leading cause of death in children under the age of five according to the March of Dimes, and it occurs in one out of ten pregnant women. Two-thirds of them are asymptomatic, leaving physicians with little warning that these patients will be presenting in labor too early. Sullivan thinks it's the biggest problem in obstetrics. Health officials have been fighting the prematurity rate for many years and, though it has dropped from 12.3% (2003) to 11.4% (2013), this statistic remains higher than that of most developed nations. The March of Dimes' goal is 9.6% by 2020.

South Carolina's rate is one in seven babies (13%), one of the highest in the U.S. For black Medicaid patients, one of Sullivan's largest patient populations, it is even higher: 16%.

"Prematurity prevention is a top priority for South Carolina given the sheer number of affected families and the long-term costs to the state," said Sullivan.

A follow-on clinical trial will open in late 2016 to study interventions for women with IBP4 and SHBG. The 11 PAPR sites will trial injectable progesterone, a common prophylaxis to delay preterm labor, but never studied in a group already identified with these biomarkers.

For more information on the intervention clinical trial at MUSC Health, physicians may contact Dr. Sullivan at sullivas@musc.edu.

# PRECISION MEDICINE

## Exome sequencing helps physicians target genomic variations within tumors

BY LINDY KEANE CARTER

As part of MUSC's growing translational genomics program, a genomics tumor board has been created to bring diverse specialists together to help physicians diagnose and manage cancer. The team that advises the clinicians comprises basic scientists, pathologists, bioinformaticists, and geneticists. Once a month, the team meets with oncologists, surgeons, radiologists, and others to review cases that have been chosen based not on a tumor's site but on its genetic variations and discuss existing drugs and drugs in development that target them. The genomics team's expertise, as well as the next-generation sequencing that analyzes tumor samples, is also available to all of South Carolina's oncologists and their patients. The initial priorities are melanoma, colorectal cancers, leukemias/lymphomas, and non-small cell lung cancer. The goal is to provide diagnostic, prognostic, or drug efficacy information on the somatic variants in these cancers.

The launching of the genomics tumor board was spearheaded by **Steven L. Carroll**, **M.D.**, **Ph.D.**, Professor and Chair of the Department of Pathology and Laboratory Medicine, and **Stephen Ethier, Ph.D.**, Director of the Center for Genomic Medicine, which coordinates research and treatment related to genetics and genomics at MUSC. Their aim is to facilitate the exchange of ideas and information in the nascent and rapidly expanding field of genomic medicine.

**Cynthia A. Schandl**, **M.D.**, **Ph.D.**, Associate Professor in the Department of Pathology and Laboratory Medicine, manages the genomics tumor board. "The complex nature of current genomic medicine requires increased collaboration between the Clinical Cytogenetic and Molecular Genetics Pathology Laboratory and the Center for Genomic Medicine to maximize patient benefit from available resources," she said.

Insight into DNA mutations has had immediate impact in the clinic. **John M. Wrangle**, **M.D.**, **MPH**, Assistant Professor in the Department of Medicine, was treating a lung cancer patient whose tumor was caused by a common mutation that has been treated effectively by a certain drug. But extended genomic testing revealed a second, extremely uncommon mutation. Wrangle prescribed an additional drug that is being investigated in a clinical trial. He is hopeful that it will deliver a powerful second blow.

Illustration by Alfred Pasieka. Licensed from ScienceSource.com

**Cancer cell (white) and the genetic code of a section of DNA.**

Genetic variant testing throughout the country covers a broad range of processes, from single-gene testing for medically actionable variants to whole-exome or whole-genome testing. MUSC's clinical testing will focus only on certain exome sequencing for medically actionable mutations.

Clinical application is just one part of the larger plan to build knowledge about this field. Thus, MUSC's basic scientists (specifically, pathway specialists) are encouraged to attend the tumor board meetings so they can help identify new targets. The research conducted in clinical trials is enhanced, too, when enrollment populations grow. In fact, genomic sequencing has created "basket trials" that are organized by gene mutation.

For more information on using the Clinical Genomics Laboratory, physicians may contact MUSC Health Laboratory Client Services at (843) 792-0707 or email Dr. Schandl at schandlc@musc.edu.

# PAIN ON THE BRAIN

## Electrical stimulation of neural networks may reduce pain after surgery

**BY SVER AUNE**

Photograph by Brennan Wesley

**Dr. Jeffrey Borckardt led a study of tDCS for postoperative pain**

Researchers at MUSC are developing a method to treat pain that may partly replace opiate narcotics. Transcranial direct current stimulation (tDCS) works by stimulating areas of the brain that interpret and respond to pain.

Many orthopaedic surgery patients rely on opioids for pain management after surgery, and they often already take medication for chronic pain. Their physicians are interested in reducing the risks of side effects and addiction from prolonged opioid use.

**Jeffrey J. Borckardt**, **Ph.D.**, a psychologist in the MUSC Department of Psychiatry and Behavioral Sciences, studies how pain signals travel through neural networks once they reach the brain. According to Borckardt, pain signals activate the sensory cortex—which locates the pain; the limbic system—which generates emotions about pain; and the pre-frontal cortex—which enables conscious intellectual decisions about pain's meaning. By applying low electrical current to these areas, tDCS could stimulate the parts of the brain that govern our conscious reaction to pain.

Once the pre-frontal cortex has been located, a device that looks like a wired shower cap is placed on a patient's head and fitted with electrodes. In a typical session of tDCS, very low amplitude current is applied for 20 minutes. Because the current is so low, tDCS does not actually cause neurons to fire. "We're not firing networks, we're just facilitating or inhibiting natural network activity with tDCS," Borckardt said. "It makes it easier or harder for them to fire depending upon stimulation parameters."

In a study published in the May 2016 issue of the journal *Spine* (doi: 10.1097/BRS.0000000000001525), Borckardt reported that four sessions of tDCS in the 28 hours following surgery were enough to reduce self-administration of hydromorphone by 23%. Tingling was the most common side effect. For the study, Borckardt enlisted the help of **Scott T. Reeves**, **M.D.**, Chair of the Department of Anesthesia and Perioperative Medicine**,** and MUSC Health orthopaedic surgeon **John A. Glaser**, **M.D.**

These results support the possibility that how a person thinks about his or her pain can have real consequences on the pain itself, according to Borckardt. "If you have a very realistic, non-fatalistic, optimistic view of what's going on in your body and why, all of these cognitive circuits in the pre-frontal area can really turn the volume down on how bad pain is," said Borckardt. For this reason, tDCS might be yet more effective when coupled with psychotherapy for pain.

Borckardt, who refers to several of his clinical partners as "anesthesiologist champions" for their ability to facilitate his research with surgery patients, has also teamed up with **Robert D. Warters**, **M.D.**, an anesthesiologist in the Department of Anesthesia and Perioperative Medicine and Chief of Service in the Ralph H. Johnson Veterans Affairs Medical Center. Together, they are recruiting patients for a large phase 2 clinical trial using tDCS coupled with psychotherapy in veterans with chronic lower back pain (NCT02483468), and using tDCS for postoperative pain among veterans undergoing total knee arthroplasty (NCT02241967).

Borckardt is also actively recruiting patients for clinical trials of tDCS in pain perception (NCT01860950) and pain in fibromyalgia (NCT02723175). To determine the eligibility of a patient for a tDCS clinical trial, contact Brittan Carter at (843) 792-3659.

# OUT OF TUNE

## Mismatch of vascular and neural responses at a fine scale suggests limits of fMRI

BY KIMBERLY MCGHEE

In an article published online ahead of print on May 25, 2016 in *Nature* (doi: 10.1038/nature17965), MUSC investigators report that, during sensory stimulation, increases in blood flow are not precisely "tuned" to local neural activity, challenging the long-held view that vascular and local neural responses are tightly coupled.

Many brain-imaging techniques that rely on changes in the flow and oxygenation of blood—including functional magnetic resonance imaging (fMRI)—assume that vascular changes reflect a proportional change in local neural activity.

"Because there isn't enough blood to send everywhere in the brain at the same time with the optimal levels of oxygen and glucose needed to support neural activity, it is widely accepted that the brain has a built-in auto-regulatory mechanism for increasing blood flow to regions with increased activity," said **Prakash Kara**, **Ph.D.,** Associate Professor in the Department of Neurosciences at MUSC and senior author on the *Nature* article.

But how precise is this auto-regulation? With resolution typically at about one millimeter, the fMRI signal represents the blood flow averaged across many blood vessels. Using micron-scale resolution two-photon imaging in an animal model, the MUSC team studied blood flow in single vessels simultaneously with neural activity.

In higher mammals, the neurons in the visual cortex are organized into columns, each of which specializes in responding to a specific stimulus orientation. For example, neurons responding to a "horizontal" stimulus reside in one column and those to "vertical" in another. When the specialized neurons in one of these columns respond to a horizontal stimulus, for example, it would be expected that the blood vessels in the vicinity would likewise respond by dilating and increasing blood flow locally if vascular and neural responses are indeed congruent.

Instead, Kara and colleagues showed that, while blood flow did increase with neural activity, it also increased in response to certain sensory stimuli that did not evoke local neural activity.

To account for this "surplus dilation" and the resultant increase in blood flow, Kara and colleagues have devised a hypothesis. "The blood vessel dilation triggered by local, selective neural activity does not remain entirely local," said Kara. "From a vessel deep within the brain, the dilation propagates up along the vessel walls into a surface vessel and then down into other vessels that enter neighboring columns."

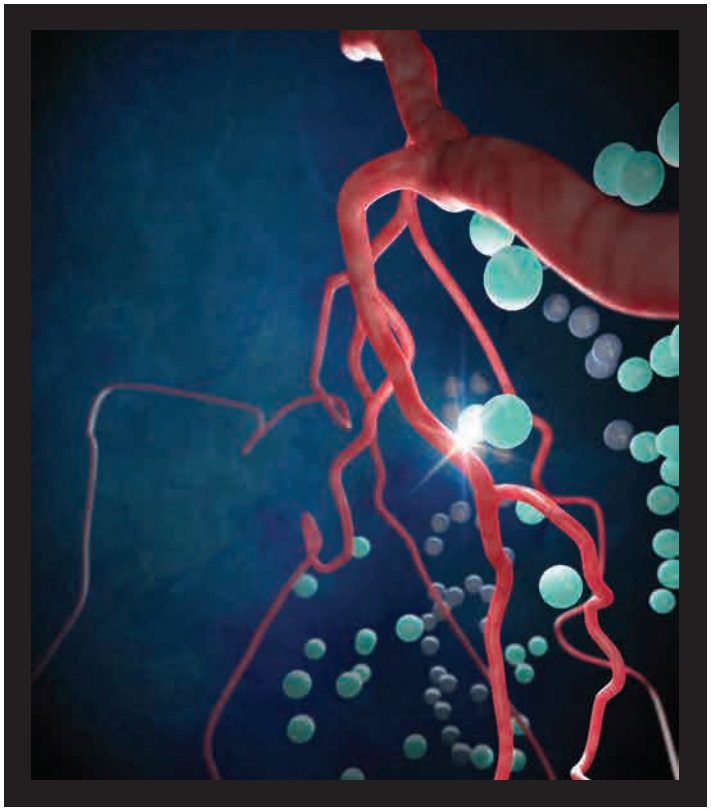


Illustration by Emma Vought

**Communication between neurons and blood vessels in the brain.**

Thus, there appears to be no tight correlation between blood flow and local neural activity, and so hemodynamic imaging techniques such as fMRI may only reveal a "blurred" representation of the underlying neural activity.

The news for fMRI could then be mixed. The good news is that the strongest vascular response matched the strongest nearby neural activity, suggesting that fMRI has much to tell us about the general function of an area of the brain. The bad news is that precisely mapping neuronal circuitry could be forever out of fMRI's reach.

But Kara cautions that much more work is needed, particularly on the generalization of this principle of "surplus dilation" and blood flow occurring in response to other forms of sensory stimuli. "Our team has just taken the first step, albeit an important one, in untangling the spatial precision of neurovascular coupling using very high-resolution imaging," said Kara.

# A GAME-CHANGER FOR LUPUS?

## Mesenchymal stem cells as targeted therapy for autoimmune disease

BY KIMBERLY MCGHEE

Illustration by Kristmar Muldrow

**A butterfly is often used to represent lupus because butterfly-shaped rashes on the face are common in those with lupus.**

The first clinical trial in the U.S. using allogeneic mesenchymal stem cells (MSCs) to treat human disease is being led by MUSC Health rheumatologists **Gary S. Gilkeson, M.D.**, and **Diane L. Kamen, M.D., MSCR**, who are studying their safety and efficacy in patients with systemic lupus erythematosus (SLE), a chronic, relapsing, multi-system autoimmune disease. The phase 2 MSCs in SLE trial (MsciSLE; NCT02633163) will randomize patients with treatment-refractory SLE to standard of care plus a single IV infusion of low-dose MSCs (1 million MSCs per kilogram), high-dose MSCs (5 million MSCs per kilogram), or placebo. It will open first at MUSC Health but will ultimately be joined by five other sites—Emory University, the University of North Carolina at Chapel Hill, the University of Rochester, Northwestern University, and Cedars Sinai. The Center for Cellular Therapy at MUSC, which houses a cGMP Class 6–compliant clean room suite, will supply the MSCs, harvested from donated umbilical cords, for infusion at all study sites.

In autoimmune diseases such as SLE, the immune system, meant to protect the body against foreign invaders, loses its ability to distinguish between self and other and begins to attack its own tissue. Mesenchymal stem cells (MSCs), which secrete immunomodulatory factors that help restore immune balance, could hold promise for treating these diseases.[1] Because MSCs do not express major histocompatibility complex 2 or costimulatory molecules, they are also "immunologically privileged" and less likely to be rejected after transplant.[1]

Most existing medications control SLE symptoms by suppressing the global immune system but at the cost of an increased risk of infection. In contrast, MSCs preferentially migrate to sites of inflammation, offering a more targeted therapy for autoimmune disease with fewer of the systemic adverse effects.

Promising results from uncontrolled trials of MSCs in autoimmune diseases in China have created excitement over this novel approach to SLE and fueled Gilkeson's interest in trying to replicate these findings in a placebo-controlled trial (MsciSLE).

Lingyun Sun, M.D., Ph.D., of the Affiliated Drum Tower Hospital of Nanjing University Medical School, a sister hospital of MUSC Health, reported four-year results of a clinical trial of MSC infusion in 87 patients with severe active SLE. Remission rates were 28% at 1 year (23/83), 31% at 2 years (12/39), 42% at 3 years (5/12) and 50% at 4 years (3/6).[2]

"These impressive data suggest MSC therapy could be a low-risk, effective treatment for refractory lupus," said Gilkeson. "However, a number of lupus therapies showed early promise only to later fail to show efficacy. That it is why a controlled trial is urgently needed."

Gilkeson is currently enrolling patients in a small phase 1 trial funded by the Lupus Foundation of America to establish the safety of MSC infusion in patients with SLE. These patients will be followed for six months to monitor for treatment-related adverse effects. If the MSC infusions prove safe, as is expected based on Chinese experience using the same dose, then the phase 2 trial will open at MUSC Health and, as funding allows, at the other approved sites. Results are expected in 2021. For more information on this or other lupus trials, contact study coordinator Carol Lambourne (lambourc@musc.edu).

**References**

[1] Cras A, et al. *Arthritis Research & Therapy* 2015;17:301.

[2] Wang D., et al. *Cell Transplantation* 2013; 22: 2267–2277.

# POWERFUL PEPTIDE

## The M10 peptide shows early promise against lung fibrosis in scleroderma

BY KIMBERLY MCGHEE

Preclinical results reported by MUSC investigators in the April 2016 issue of *Translational Research* (doi: 10.1016/j.trsl.2015.12.009) suggest that the M10 peptide protects against fibrotic damage in patients with systemic sclerosis, particularly in those who develop interstitial lung diseases (ILD), its deadliest complication.

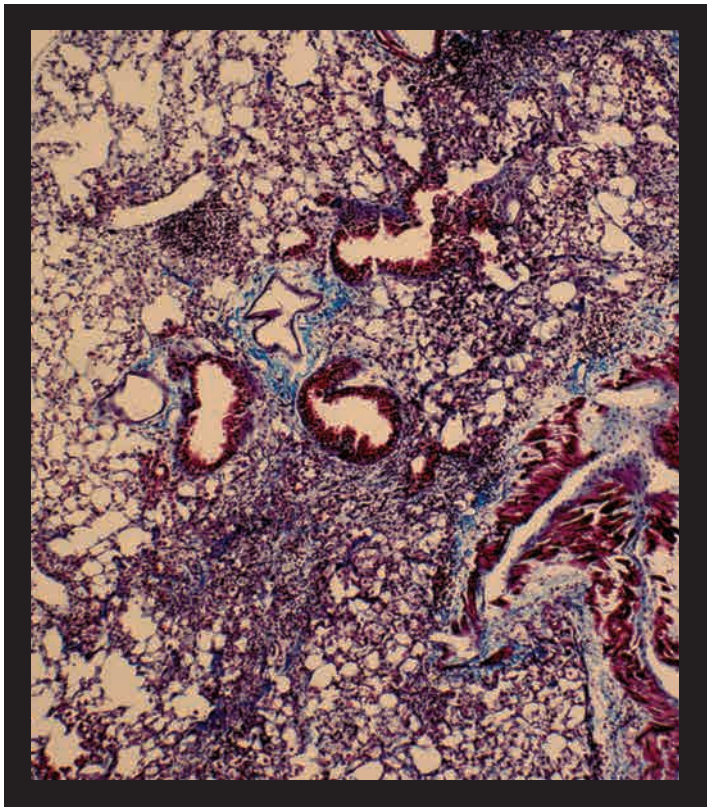
Fibrotic diseases, which are characterized by excessive scarring due to overproduction by fibroblasts of collagen and other components of extracellular matrix, account for more than 45% of U.S. deaths—more than cancer—and are estimated to cost $10 billion annually. Despite the prevalence of fibrotic diseases, only a handful of anti-fibrotic agents have been approved by the U.S. Food and Drug Administration, and none is available for systemic sclerosis.

Systemic sclerosis, or scleroderma, is the quintessential fibrotic disease, since its scarring can damage any part of the body. "Scleroderma is often more than skin deep, affecting the gastrointestinal tract, the lungs, the heart, the kidneys, and the blood vessels, so it is a model for many other more prevalent fibrotic diseases," said **Richard M. Silver**, **M.D.**, Director of the Division of Rheumatology and Immunology and a co-author on the article. "Whereas there may be 300,000 Americans with scleroderma/systemic sclerosis, millions of others suffer from fibrosis of these other organ systems."

M10 is a ten-amino acid peptide formed from the natural cleavage of the receptor tyrosine kinase MET by caspase 3. MET, also known as hepatocyte growth factor receptor, is thought to protect against injury and fibrosis, but the mechanisms by which it does so have remained unclear. The MUSC investigators showed that M10 could protect against fibrotic injury in a bleomycin-induced model of ILD and that its anti-fibrotic effects are likely due to its modulation of the transforming growth factor beta 1 (TGF-ß1) pathway. TGF-ß1 is a cytokine that has been implicated in inflammation and fibrosis.

"Intraperitoneal injection of M10 markedly improved bleomycin-induced lung fibrosis in mice, suggesting that the M10 peptide may have potential for use in the treatment of scleroderma-associated interstitial lung disease and other forms of pulmonary fibrosis," said **Galina S. Bogatkevich**, **M.D., Ph.D.**, senior author on the *Translational Research* article. Lead authors for the article are **Ilia Atanelishvili**, **M.S.**, and **Yuichiro Shirai**, **M.D.**, **Ph.D.**

When given by intratracheal injection, bleomycin causes fibrotic changes in the lungs, including peribronchial and interstitial infiltration of inflammatory cells, thickening of alveolar walls, and the development of fibrotic lesions with excess deposition of extracellular matrix protein. The MUSC investigators used this bleomycin-induced model of lung fibrosis to evaluate the anti-fibrotic effects of M10. As expected, mice receiving bleomycin plus a scrambled peptide showed greater than eight times more lung fibrosis than controls receiving saline and scrambled peptide, but that fibrosis was reversed when mice were administered both bleomycin and M10, suggesting the anti-fibrotic potential of M10.



Reprinted from *Transl Res* 2016;170: 99-111, with permission from Elsevier. doi: 10.1016/j.trsl.2015.12.009\

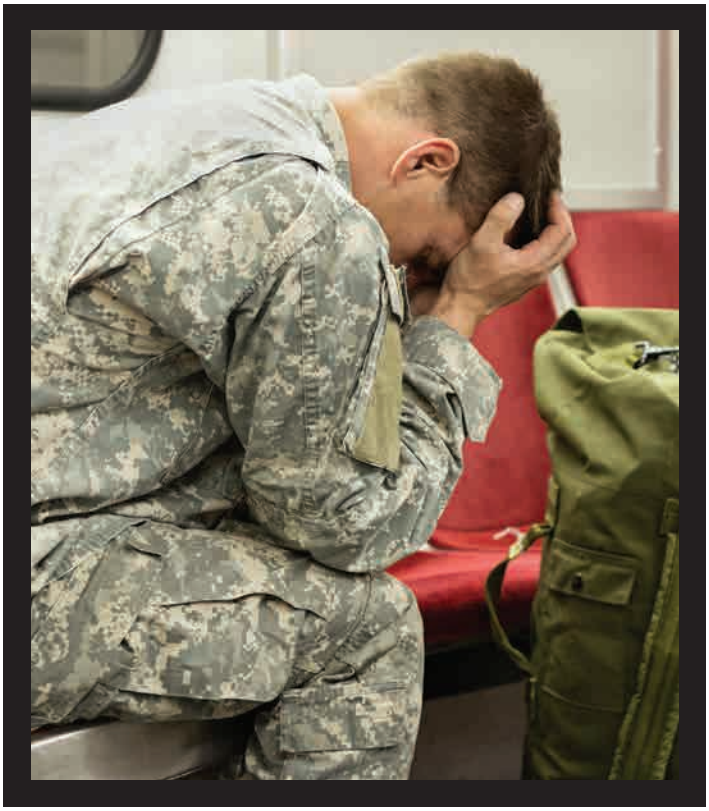
**Fibrotic lung tissue isolated from mice that received bleomycin**

Because M10 was given on the same day as bleomycin, its anti-fibrotic effects are considered preventative. To establish the therapeutic anti-fibrotic efficacy of M10, Bogatkevich and her MUSC colleagues are running experiments in which M10 is administered ten days after the instillation of bleomycin, when fibrotic damage has already occurred. The initial data have confirmed the suggested therapeutic efficacy of M10, and the study team is seeking an industry partner to help take M10 forward into clinical trials.

# CATCHING IT EARLY

## Veterans with subclinical PTSD respond better to psychotherapy

BY SVER AUNE



In the March 2016 issue of the *Journal of Anxiety Disorders*, investigators in the Department of Psychiatry and Behavioral Sciences report that veterans who fall just below the threshold for a diagnosis of post-traumatic stress disorder (PTSD) respond to psychotherapy better than those with full PTSD. The study highlights the need to recognize veterans suffering from an overlooked condition called subclinical PTSD. "The study shows not only that we can treat those experiencing subclinical presentations of PTSD, but also that those with subclinical PTSD may actually respond better to treatment than those with more severe forms of the disease," said MUSC investigator **Kristina Korte**, **Ph.D.**, who is the lead author on the article. MUSC co-authors include **Ron Acierno**, **Ph.D.**, **Daniel F. Gros**, **Ph.D.**, and **Nicholas P. Allan**, **MS**.

Like patients with full PTSD, those with subclinical PTSD have experienced a traumatic event and are regularly re-experiencing it, often in nightmares or flashbacks. Patients with full PTSD also experience hyperarousal (i.e., they are easily startled) and avoid reminders of the event, for example by withdrawing from social interaction or turning to substance abuse. In addition to re-experiencing the event, patients with subclinical PTSD may exhibit either hyperarousal or avoidance, but not both.

Psychologists began noticing this pattern more frequently in the nineties in veterans returning from the first Iraq War, and even more frequently in veterans returning from Iraq and Afghanistan in the past decade. As researchers have learned more about these patients over time, varying and sometimes conflicting symptoms have provided an incomplete picture of the disorder and how to treat it. Further confounding the issue is that those with subclinical PTSD are often excluded from clinical trials testing treatments for PTSD—patients with only some symptoms of PTSD commonly are not included in the healthy control group or in the group with full PTSD. As a result, there is still no standard psychotherapy for treating subclinical PTSD.

The researchers devised an intuitive approach—Why not treat subclinical PTSD patients with one of the standard evidence-based psychotherapy tools already being used in PTSD patients? They enrolled 200 patients with combat-related PTSD symptoms from the Ralph H. Johnson VA Medical Center located adjacent to MUSC, identifying those with either subclinical or full PTSD. For eight weeks, patients received intensive weekly sessions of behavioral activation and therapeutic exposure therapy, designed to lessen their PTSD symptoms by helping them safely re-experience and resolve elements of the original trauma. Psychologists rated the patients' PTSD symptoms and had patients rate their own symptoms before, during, and after the eight weeks.

The results were encouraging. Those with subclinical or full PTSD each experienced a real drop in PTSD symptoms after treatment. The striking result was in *how much* those symptoms dropped: 29% in those with subclinical PTSD as compared to 14% in those with full PTSD.

Symptoms of PTSD often worsen over time; as they do, treatments become less effective at reducing symptoms. In this context, subclinical PTSD could be seen as "early-stage" PTSD, in that treatment might be more effective when the disorder is caught early.

"We hope that providing treatment for subclinical PTSD will make managing this common disorder more cost effective," said Korte. "It could lead to the prevention of more intractable forms of PTSD that can occur when subclinical PTSD goes untreated."

# NO NEED TO TRY, TRY, TRY AGAIN

## Fewer ERCPs needed to treat benign biliary strictures thanks to expandable stents

BY KIMBERLY MCGHEE

Placement of a single covered, self-expanding metallic stent (cSEMS) via endoscopic retrograde cholangiopancreatography (ERCP) resolved benign obstructions of the bile ducts as well as placement of multiple plastic stents, the current standard of care, and required fewer ERCP sessions, according to the results of a randomized controlled trial reported in the March 22, 2016 issue of the *Journal of the American Medical Association*. These findings will change practice in the opinion of **Gregory A. Coté, M.D.**, an endoscopist at the MUSC Health Digestive Disease Center, lead author of the article, and the national principal investigator for the eight-center study. **B. Joseph Elmunzer, M.D.**, of the MUSC Health Digestive Disease Center is also a co-author.

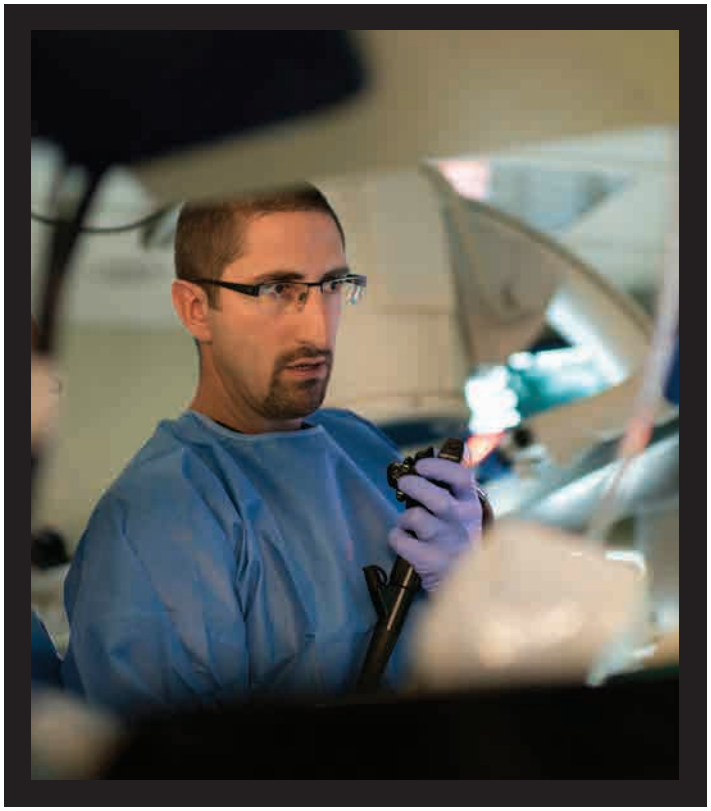
"For appropriately selected patients who are presenting for the first time with a blockage, many endoscopists will change their strategy and use these newer stents, in an effort to reduce the total procedures that are required," said Coté.

For now, the use of cSEMS in benign biliary strictures would be off-label, as they have been approved by the FDA only for the treatment of malignant biliary strictures, such as those which develop in the setting of unresectable pancreatic cancer.

Left untreated, benign biliary strictures can lead to jaundice, cholangitis (i.e., infection of the bile duct), and secondary biliary cirrhosis. Benign strictures most often occur after liver transplantation and gallbladder surgery or as a result of chronic pancreatitis. ERCP is preferred to surgery in these patients because it is less invasive.

ERCP is an endoscopic procedure in which a camera is introduced through the mouth and advanced first to the proximal duodenum and then, using endoscopy and fluoroscopy, into the pancreatic and bile ducts. Although highly effective, three to four ERCP sessions are typically required to fully stretch the blockage and minimize the chance of recurrence once the stents are removed. Because ERCP is not without its risks—complications include acute pancreatitis, infections, bowel perforation, and bleeding—minimizing the number of sessions needed to successfully treat the stricture benefits patients. Coté designed the trial to determine whether fewer ERCP sessions would be required to treat benign strictures with the use of the larger cSEMS.

The primary endpoint of the trial, which enrolled 112 patients, was the rate of benign stricture resolution after no more than 12 months of stenting. cSEMS were found to be noninferior to plastic stents for achieving stricture resolution and they did so more quickly (181 vs. 225 days) and with fewer ERCP sessions (2.14 vs. 3.24). It should be noted that the study had careful enrollment criteria; patients with small (<6 mm) bile ducts and those with intact gall bladders were excluded. "We were careful not to cross the gall bladder insertion into the bile duct in patients who still had their gall bladder because you don't want to block the gall bladder and potentially create a new problem," said Coté.



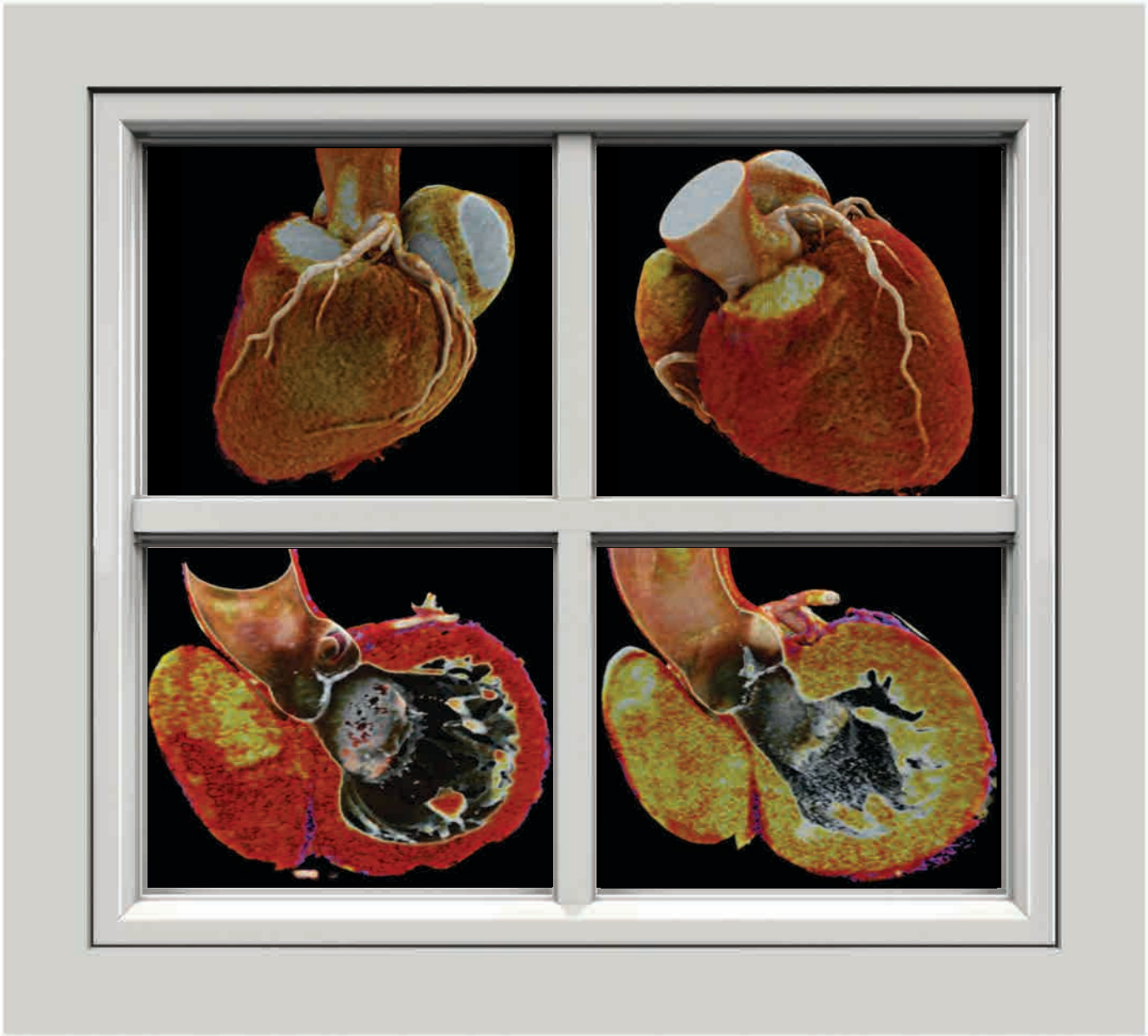
Photograph by Brennan Wesley

**MUSC Health endoscopist Dr. Gregory Coté**

Although the procedure can be performed by anyone proficient in ERCP, high-volume providers who are comfortable placing and removing cSEMS will likely achieve the best results.

"We can't universally change practice based on these findings, but, in appropriately selected patients with benign bile duct strictures, deployment of cSEMS via ERCP should be first-line treatment," said Coté.

**"We're leaders in terms of how to apply these scans, how to interpret them, and how to make acquiring the image as gentle as possible."**
**—U. Joseph Schoepf, M.D.**



Advanced computed tomography enables imaging of cardiac disease in unprecedented detail. Noninvasive computed tomography of the heart reveals diseased heart vessels (upper row) and pathologically thickened heart muscles (lower row).

# Windows to the Heart

## Safer, faster CT technology produces images that give new clinical insights into coronary artery disease

BY LINDY KEANE CARTER

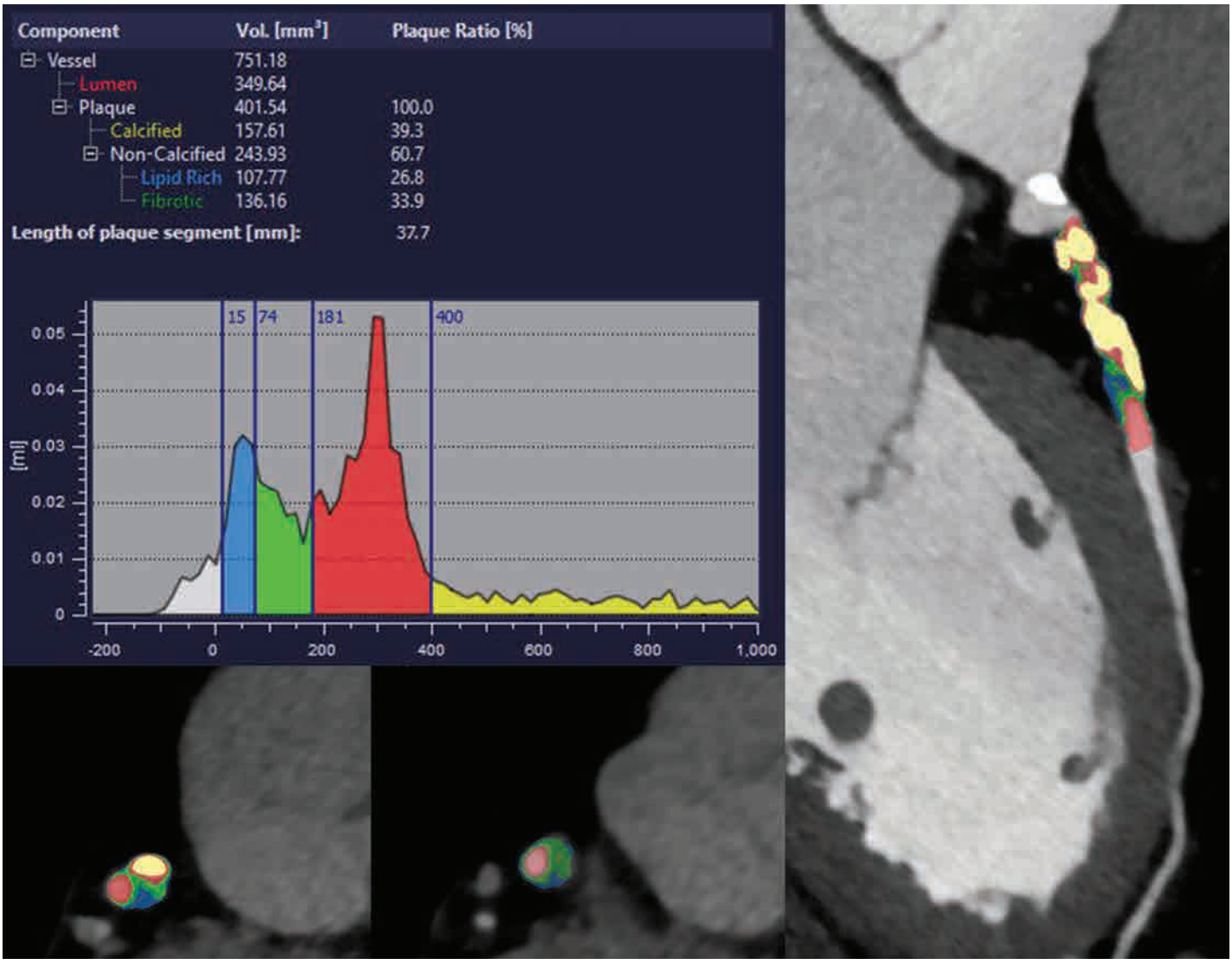
For decades, physicians making decisions about how to treat coronary artery disease (CAD) have relied on cardiac angiography, which requires cardiac catheterization. In 2011, researchers at MUSC Health's Heart and Vascular Center (HVC) reported that coronary computed tomographic angiography (CCTA), a powerful imaging test that provides detailed images of the heart and its blood vessels without the need for catheterization, provided as reliable a guide to decisions about revascularization as did conventional cardiac angiography, based on the findings of a prospective study comparing the two tests in 185 veterans with a high likelihood of CAD.[1] The CCTA scans showed that 113 patients (61%) had no significant narrowing in the vessels and so did not need to undergo revascularization. Forty two (23%) had no coronary artery calcium at all.

"This highlights the clarity of what we're seeing with CT, as opposed to tests that look at secondary markers of coronary artery disease," said **U. Joseph Schoepf, M.D.**, Professor in the Department of Radiology and Radiological Science and Director of the Division of Cardiovascular Imaging. "Only 40% of the patients had disease that required action."

Today, the HVC produces some of the most revealing coronary CT images in the U.S., having been the first in the nation to take delivery in 2014 of the industry's most advanced technology, the SOMATOM Force (Siemens Healthcare, Forchheim, Germany). This tool is producing more than 2,000 high-fidelity noninvasive imaging studies a year at the HVC, enabling dozens of research projects that are advancing understanding of CAD. For example, the Force's improved temporal resolution enables radiologists to better freeze cardiac movement, providing clearer images of the heart muscle so they can quantify its thickness as part of their evaluation. Under Schoepf's direction, the research team publishes 50 to 60 peer-reviewed journal articles a year. Its members include researchers from China, Korea, Germany, Lebanon, and Italy, among other countries, who have come to MUSC Health to gain skills in noninvasive cardiac imaging. Physicians from U.S. hospitals train with Schoepf as well. In 2008 Schoepf was named one of the most influential radiologists in the world by *RT Image* and in 2013 was selected as the Most Influential Radiology Researcher by Aunt.Minnie.com (a respected internet site for radiologists and related professionals in the medical imaging industry).

"We're leaders in terms of how to apply these scans, how to interpret them, and how to make acquiring the image as gentle as possible," said Schoepf. "We've made great leaps in reducing radiation dose, for example." Patient safety is a significant advantage with the Force. The imaging dye load can be as low as 30 to 50 cc's of contrast dye (older technology required 120 to 160 cc's) and radiation dose is much lower—in some cases as low as that of a chest X-ray.

Researchers are analyzing thousands of images and reporting significant findings. Their studies have covered, for example, myocardial




**Quantitative imaging of coronary atherosclerotic plaque. Based on noninvasive CCTA, atherosclerotic plaques in the heart vessel are quantified according to plaque components. Stable calcified plaque components are segmented in yellow; more unstable non-calcified lesions, with greater risk of causing an acute cardiac event, are in blue and green, indicating more fibrous and fatty components.**

morphology of various patient populations, differences in markers of heart disease between black and white patients, different techniques for measuring myocardial blood flow, coronary artery atherosclerotic plaque characterization, and minimizing radiation exposure.

Visualizing disease directly as it manifests moves medicine closer to quantifying it.

"We're truly seeing things in great detail, such as narrowing of the heart vessels, the makeup of atherosclerotic lesions, and whether they look stable or unstable," said Schoepf. "We're not looking at functional sequelae as we did in the past. We're looking at the disease directly. We can put a number on things."

Cardiologist **Sheldon E. Litwin, M.D.**, a coinvestigator for several cardiovascular imaging studies, said the more quantitative data cardiologists have, the more precisely they can treat patients. "Cardiology has been under fire for putting in too many stents, in part because the tests we've used to decide who gets a stent are somewhat subjective," said Litwin, Alicia Spaulding-Paolozzi Professor of Cardiac Imaging. "With CT, we can now derive quantitative estimates of blood flow and use these numbers to better decide which patients should receive stents."

## Research in racial disparities

Blacks make up a third of the population of South Carolina and have a higher rate of heart disease than that of whites. Many of the HVC's

thousands of cardiac CT images are from black patients. So HVC researchers have taken advantage of that large dataset, the robust research team, the HVC's image interpretation expertise, and the Force to elucidate heart disease in this group. They began in 2011 with a look at the offending atherosclerotic plaque in the heart vessels. Below is a summary of that study and three others that Schoepf identifies as the most significant in identifying racial disparities.

**Coronary atherosclerosis in black and white patients**. In a 2011 article in *Radiology*,[2] MUSC investigators reported that atherosclerotic plaque burden and composition as measured by CCTA differ between black and white patients, with more unstable non-calcified disease in the former and more stable calcified disease in the latter. "That helps explain why we see a higher rate of heart disease in black people," said Schoepf, "and why you don't see it with less sophisticated tests such as coronary artery calcium scoring."

**Myocardial morphology and function in black and white patients**. Analysis of CT scans of 300 patients showed larger myocardial mass in black patients, but no statistical differences in left ventricular (LV) functional parameters.[3] This suggests that LV mass might be a contributing factor to the higher rate of cardiac events in blacks.

**Comparison of epicardial fat volume by CT in black vs. white patients with acute chest pain.** Investigators found that CT-derived measurements of thoracic fat differ between symptomatic black and white patients, suggesting a differential relation between thoracic adipose tissue and CAD pathophysiology by race.[4]

**Breast arterial calcifications as a predictor of coronary atherosclerotic disease.** Researchers analyzed the digital screening mammograms and the cardiac CT (CCT) scans of 204 black women and compared them with the same type of studies done on predominantly white women. The results established a correlation between mammographic breast arterial calcifications and CAD.[5] Breast arterial calcifications were significantly associated with a coronary calcium score > 100 (odds ratio [OR], 7.66; 95% confidence interval [CI], 2.75-21.29; *P*<.001), atherosclerotic luminal narrowing (OR 9.99; CI, 3.65-27.32; *P*<.001) and stenosis ≥50% (OR, 5.48; CI, 1.97-15.23; *P* =.001) by CCT. The data suggest that mammographic breast arterial calcifications are associated with an increased probability of coronary calcification, atherosclerosis, and CAD in black women. The researchers suggest these calcifications should be routinely reported on mammograms.

## Current research

**Blood flow to the heart**. The research team is investigating two approaches to figuring out the significance of myocardial blood flow blockages: direct measurement (perfusion imaging) and the mathematical simulation of blood flow (Fractional Flow Reserve [FFR]).

**CT myocardial perfusion**. In three clinical trials, HVC researchers are actively comparing CT myocardial perfusion (a test that shows how well blood flows through the heart muscle) to traditional perfusion testing methods. For example, they are looking at patient outcomes (what does the test tell clinicians about the patient's prognosis), and the exact clinical scenario in which this test is most beneficial to the patient (a patient with acute chest pain vs. a patient with chronic chest pain who has a more intermediate risk of CAD).

**CT FFR.** Researchers are applying fluid dynamic models to the image of the coronary artery tree to determine which lesions are important and which are not and "teach" computers to recognize the difference. The computer then applies that knowledge in subsequent imaging. An article summarizing this work has been accepted for publication in the *American Journal of Cardiology*.

## Plaque characterization

Researchers are learning more every day as the HVC scans more hearts, for if a patient has a heart attack later, they are able to look back to gain clues about his or her plaques. For example, they are finding that the degree of narrowing caused by plaque is not that important, but what the plaque is made up of is. If a lesion has a high content of soft plaque, it is much more likely to be unstable and eventually rupture, impairing blood flow to the heart.

As the data grow, the computers are "learning" how to characterize thousands of plaques even in one individual, a task too laborious for the human eye. "The notion is that at some point the computer will come up with images showing all of the plaques and tell us what they're made up of, how many there are, how long they are, etc. Using this type of information, we'll come closer to being able to predict who's going to have a cardiac event," said Litwin.

## Future investigations

As CCTA evolves, the transformation of cardiovascular disease characterization will continue, delivering better ways to diagnose and treat CAD. "We believe there is benefit to visualizing coronary artery disease directly, rather than relying on an incomplete understanding of how risk factors and surrogate markers actually translate into atherosclerosis," said Litwin. "That's a superior approach."

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Photograph by Brennan Wesley

MUSC Health surgeon Dr. Virgilio George (right) offers a full spectrum of minimally invasive surgeries for colorectal cancer.

# Up From Below

## New minimally invasive surgery for patients with tumors in the lower rectum

BY KIMBERLY MCGHEE

Transanal total mesorectal excision (TaTME) has garnered a great deal of attention and created much excitement in the field of rectal surgery because it represents a reversal of perspective—literally—about how best to excise tumors and the surrounding mesorectal envelope in the lower third of the rectum. Unlike traditional TME, which involves introduction of a laparoscopic camera and specialized laparoscopic tools through small slits in the abdomen to excise these tumors from above, TaTME reverses the process and introduces these tools via a multichannel port in the anus so that the tumor can be visualized and removed from below.

For even experienced colorectal surgeons, excision of tumors in the lower third of the rectum by either open or conventional laparoscopic methods is extremely challenging, particularly in obese patients; in male patients, who have a narrow pelvis; and in patients whose anatomy has been altered by previous radiotherapy. This is due in part to the difficulty of navigating the narrow and curved pelvic space with a rigid laparoscope. By approaching from below, TaTME solves the problem of access.

"This approach enables easy visualization and better access because you are closer to the organ that you want to remove," explained MUSC Health colorectal surgeon **Virgilio V. George, M.D.**

George, who assumed leadership of the Section of Colon and Rectal Surgery in late 2015, has received specialized training in TaTME and has successfully performed 18 of these procedures, three of them at MUSC Health. A full spectrum of minimally invasive surgeries (MIS) for colorectal cancer, including laparoscopic, robotic, and transanal techniques, are now offered by MUSC Health. Indeed, more than 90% of patients opt for MIS, which require much smaller incisions than open surgery, reducing recovery time and pain for the patient.

## A Hybrid Approach

TaTME is a hybrid approach in which both traditional abdominal laparoscopy and transanal laparoscopy are used to remove a rectal tumor along with its intact mesorectal envelope.[1] Traditional laparoscopy is used to mobilize the descending and sigmoid colon and the splenic flexure, and then the transanal approach is used for the dissection and excision of the mesorectal "packet" containing the tumor. The "packet" is typically removed via the anus but, for bulky tumors, a small exit incision can be made in the abdomen. The colon and remaining anus can then be sewn or stapled together to restore continuous intestinal flow (i.e., anastomosis), enabling the patient to defecate normally instead of having to rely on a stoma (i.e., an opening from the colon to the surface of the skin).

Before TaTME, abdominoperineal resection (APR), in which the sigmoid colon, rectum, and anus are removed and a stoma is created through which the patient can void bodily waste, was considered the gold standard for excising tumors in the lower third of the rectum. In addition to preserving sphincter function, TaTME offers several other key advantages over APR performed as an open surgery, including a shorter and less painful recovery and a reduced likelihood of complications such as infections, hernias, impotence, and urinary incontinence.

The first TaTME was performed in 2009 by Antonio M. Lacy, M.D., Ph.D., at the Hospital Clinic of Barcelona in Spain. In a study of a cohort of 140 patients undergoing TaTME, published in 2015 in the *Journal of the American College of Surgeons*, Lacy and his group report shorter surgical times and very satisfactory conversion (to open procedure) and complication rates for TaTME compared with traditional TME, as well as equally good oncologic outcomes and excellent specimen quality (i.e., intact mesorectal envelope), an important prognostic factor.[2] In a separate article comparing TaTME with traditional laparoscopy, Lacy and colleagues showed that successful coloanal anastomosis was more likely and that the rate of early readmissions was reduced with TaTME.[3] Only colorectal surgeons who have received the appropriate training and who have extensive experience with laparoscopic techniques should perform TaTME.

## Local Recurrence

Richard J. Heald, CBE, MChir, one of the pioneers of traditional TME, argued that careful excision along the holy plane—a plane outside and posterior to the rectum—would allow removal of the intact mesorectal envelope, with the tumor and any spreading cancer cells confined inside. Heald reported very low rates of local recurrence using this technique, which led TME to displace APR as standard of care for rectal tumors, with the exception of those that reside in the bottom third of the rectum. Few would contest that TME has revolutionized the field of rectal surgery, achieving similarly low levels of local recurrence as APR while better preserving function. However, critics have noted that the very low rates of recurrence reported by Heald have not been replicated, drawing into question his claim that *better* control could be achieved via TME.[4]

Some would speculate that the improved visibility and access provided by TaTME should lead to better margins and superior local control than with either APR or TME. However, a definitive answer to whether TaTME can improve long-term oncologic outcomes will have to await completion of long-term clinical trials.

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**Visit MUSChealth.org/or-notes for photographs and videos of TaTME and other minimally invasive colorectal surgeries.**


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# RADICAL IDEAS

## The enduring promise of antioxidant therapy and redox balance in cancer

BY SVER AUNE
ILLUSTRATION BY EMMA VOUGHT

*Medical scientists at MUSC are uncovering new insights about how antioxidants work—details that are helping revive enthusiasm for their use in fighting cancer.*

### The oxygen paradox

Oxygen, essential for life, can be toxic. Oxygen-centered free radicals are routinely synthesized and recycled as a normal part of cellular metabolism. Oxidative stress—when these highly reactive molecules tax a cell's antioxidant systems—is a fundamental feature of many cancers.

Evolutionary theory states that, as oxygen became more abundant on primordial Earth, respiring single-celled organisms developed antioxidant systems to defend their DNA against free radicals formed from oxygen. Today, antioxidant enzymes are abundant in every cell type from bacteria to man. Conversely, cells produce low levels of oxygen-based free radicals to regulate metabolism and, when needed, to destroy invading viruses and bacteria. Maintaining the balance between oxidants and the antioxidant molecules that reduce them—redox balance—allows the body to exploit oxygen's dual nature as both a sustainer of life and a lethal weapon against pathogens.

Of great importance to cancer biologists is the oxidant milieu surrounding a cancer cell, which is vastly different from the environs of a healthy cell. Similar to healthy cells, cancer cells can secrete toxic levels of oxidants to neighboring cells. This is a feature in certain breast and lung tumors, which deploy hydrogen peroxide to surrounding epithelial cells to push them toward a cancer phenotype. The major difference in many cancer cells is that they adapt to their own oxidative stress, allowing them to resist the lower levels of oxidants that healthy cells release in efforts to destroy them.

**Kenneth D. Tew**, **Ph.D.**, **DSc**, Chair of the Department of Cell and Molecular Pharmacology at MUSC, explains the challenge of redox balance in cancer.

"When you are metabolizing more—which cancer cells do—you are essentially producing more oxidative stress, more oxygen byproducts," said Tew. "Therefore, you need to generate a different redox homeostasis in the cell to counteract that."

Understandably, the idea of using antioxidants as therapy in cancer retains promise as a means to restore redox balance. But can antioxidants help prevent cancer? And once cancer appears, can antioxidant therapies be developed to help fight it?

## Antioxidants and cancer prevention—a history of clinical trials

In the 1980s, high levels of oxidants were first observed on the molecular level in tumor cell lines. Interest in using dietary antioxidants as anti-cancer agents began to spread, spurring clinical trials.

There have been a handful of large randomized controlled trials designed to measure cancer risk when taking dietary antioxidant supplements prophylactically. Most showed that antioxidant supplements usually do not hurt, but they do not help either. In the Linxian General Population Nutrition Intervention Trial of gastric and esophageal cancer risk in the 1990s, healthy Chinese men and women took a daily combination of beta-carotene (15 mg), vitamin E (30 mg), and selenium (50 ug) for five years.[1] In the ten years following, there was no change in the risk of people developing or dying from either type of cancer.[2] In the Physicians' Health Studies I and II conducted in the U.S. throughout the 1980s, 1990s, and 2000s, neither beta-carotene supplements (50 mg every other day) nor a combination of vitamins C (500 mg daily) and E (400 IU every other day) changed overall cancer risks—this was regardless of whether the physicians smoked.[3,4] The Women's Health Study of women over 45 taking beta-carotene (50 mg every other day) or vitamin E (600 IU every other day) revealed the same.[5,6] The international HOPE-TOO trial in patients with heart disease or diabetes showed no change in cancer mortality with daily vitamin E supplementation (400 IU).[7]

**"Life developed through a process of using oxygen and sulfur as signaling molecules. It's this yin and yang effect of oxygen and sulfur that works very well for the life forms that we are."**
**—Kenneth D. Tew, Ph.D., DSc**

In the SU.VI.MAX study, another large trial out of France, the results were mixed. A daily supplement cocktail of vitamins C (120 mg) and E (30 mg), beta-carotene (6 mg), selenium (100 ug), and zinc (20 mg) taken for roughly eight years actually increased women's skin cancer risk but reduced men's overall cancer risk.[8] Five years later, both of these effects disappeared.[9]

In some people, certain antioxidant supplements should perhaps be avoided. In the Carotene and Retinol Efficacy Trial in the U.S., people with an increased risk of lung cancer due to smoking or asbestos exposure developed lung cancer more often and had overall reduced life spans when they took daily beta-carotene (15 mg) with vitamin A (25,000 IU).[10] Similarly, in the ATBC study in Finland, smokers who took beta-carotene (20 mg per day) for five years contracted lung cancer *more often* than those who did not.[11] In another U.S. study, the Selenium and Vitamin E Cancer Prevention Trial, men over 50 taking daily vitamin E (400 IU) for five years developed prostate cancer 17% more often than those on placebo.[12]

Overall, antioxidants, at least in purified supplement form, do not seem to prevent cancer. And as much as smoking is a serious health risk, certain vitamins might increase that risk.

## Antioxidants as adjuvants to cancer therapy

To date, the potential benefits of using antioxidants to prevent cancer seem equivocal. However, novel insights are enabling researchers at MUSC to target the underlying components of redox imbalance in certain cancers. New knowledge of these targets is reviving the promise of using antioxidants as adjuvant agents that could protect healthy tissue from the oxidative stresses of radiation and chemotherapy.

## Yin and yang

When considering how to treat a cancer, Tew always refers back to redox balance within normal cells. Curiously, healthy cells use sulfur, oxygen's neighbor on the periodic table, to keep oxidants in check. The ubiquitous cellular antioxidant glutathione forms sulfur-sulfur bonds with proteins, in a protein modification process called *glutathionylation*, to help them fold so they can function properly. In moments of oxidative stress—during radiation, for example—glutathionylation effectively shields proteins from being irretrievably damaged by oxidants.

"Life developed through a process of using oxygen and sulfur as signaling molecules," said Tew. "It's this yin and yang effect of oxygen and sulfur that works very well for the life forms that we are."

Tew suspects drugs that aid glutathionylation will have significant biological importance in cancer. Ezatiostat hydrochloride (Telintra®; Mabvax Therapeutics Holdings, Inc; San Diego, CA) is a drug designed as a glutathione analog and is in phase 2 clinical trials for myelodysplastic syndrome, a precursor disease of leukemia. Ezatiostat inhibits a particular enzyme complex that regulates glutathionylation and, as a consequence, affects downstream phosphorylation pathways that control cancer cell growth. Tew is working to further

determine ezatiostat's efficacy in myelodysplastic syndrome, with the goal to include it in further clinical trials at MUSC.

Tew is also performing a clinical trial with **David T. Marshall, M.D.**, a radiation oncologist at the MUSC Hollings Cancer Center, to track glutathionylation in the blood of cancer patients who have received radiation. The goal in patients is to determine how much treatment is too much and to stay on the safe side of that line.

"Radiation and drug treatment stimulate modifications of proteins because they are trying hard to achieve redox homeostasis," said Tew. "We can use these proteins as potential biomarkers of response to either drugs or radiation."

Tew and Marshall's research group has already identified several candidate biomarkers in the cheek cells of healthy volunteers who used a hydrogen peroxide mouthwash that safely mimics the oxidative stress of radiation. Initially, changes in these biomarkers will be tracked during tests of novel anti-cancer drugs. The next step will be to track those same biomarkers in patients who are receiving radiotherapy.

## Antioxidants in stealth mode

If antioxidants are to live up to their promise as anti-cancer agents, better delivery models are needed. Bioengineer **Ann-Marie Broome**, **Ph.D.**, **MBA**, believes that clinical trials with antioxidants have been disappointing thus far because the body rapidly metabolizes and clears them to maintain redox balance. To evade these natural processes, the Broome laboratory, including physical chemist **Suraj Dixit, Ph.D.**, and organic chemist **Yu-Lin Jiang, Ph.D.**, makes tiny drug delivery devices called nanoparticles that, according to Broome, "package a drug and put the entire construct in stealth mode."

Their objective is to bypass the body's powerful drug metabolism systems and deliver drugs with antioxidants directly to the tumor.

"Although we have very good drugs to treat cancer, many deleterious side effects accompany their use because we typically treat the whole body rather than a specific location," said Broome.

Chemotherapy doses are higher and more expensive than they should be, said Broome, because only a fraction of the drug reaches the target. This is especially true in glioblastoma since the chemotherapeutic agent must cross the blood-brain barrier to reach the tumor. For example, only about 0.3% of intravenous temozolomide, the current standard of care, reaches the tumor. Even after surgery and chemotherapy, glioblastoma has a 100% recurrence rate.

Broome partners with colleague **Amy Lee Bredlau**, **M.D.**, Director of the Pediatric Brain Tumor Program, to procure samples from surgically resected glioblastoma. Bredlau is working to identify vulnerabilities in glioblastoma and to understand the genetic backgrounds in which the tumors appear. They have learned that, similar to certain breast and lung cancers, these tumors thrive in a low-oxygen environment and produce cytotoxic levels of hydrogen peroxide. For the aggressive tumors, hydrogen peroxide provides the "second hit"—a chemical signal that keeps them growing and progressing.

Drug delivery devices are not just chemically synthesized, they are *built*. A typical nanoparticle will have an outer coating made to disguise it from the immune system, along with the appropriate chemotherapy drug packaged in the center, and a targeting molecule that recognizes some specific feature of the tumor. An outer cloak incorporates an antioxidant coating made of N-acetylcysteine or resveratrol (the antioxidant found in red wine) that can "mop up" the tide of hydrogen peroxide surrounding a tumor. In these cases, the antioxidant coatings are both the package and part of the therapy.

There are challenges in scaling up production of nanotherapies. The particles are tiny—small enough to cross the blood-brain barrier—and much finesse and effort are required to produce an adequate supply for experiments. But results in preclinical studies are encouraging. Broome and Bredlau have raised the temozolomide concentration in the brain from 0.3% to 3% of the original injected drug—*a ten-fold increase*. Broome hopes production will take hold on an industrial level as they augment their experimental techniques.

At MUSC, the anti-cancer promise of antioxidants is clear. Since redox balance is crucial to the survival of every cell, the field is both challenging and potentially very rewarding. The fundamental lessons learned in glioblastoma and myelodysplastic syndrome could be extended to many conditions in which redox status is disrupted—heart and lung disease, stroke, diabetes, even other types of cancer. After all, oxygen, while toxic, is also necessary for life.

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*But we are the sum of all the moments of our lives—all that is ours is in them.*—Thomas Wolfe

For physicians and caregivers, patients with Alzheimer's disease present a narrative challenge. Theirs is not an orderly linear plot but a storyline disrupted by memory gaps, repetition, and the fading of the boundaries between past and present. Learning to "read" their untraditional narratives and finding ways to reconnect them to the world are acts of compassion by physicians and caregivers that can help delay and mitigate the pain of this vanishing act.

# Vanishing Act

## Recognizing and responding to Alzheimer's disease in primary care practice

BY STEVEN L. CARROLL, M.D., PH.D.; DAVID L. BACHMAN, M.D.; DAVID G. CLARK, M.D.; ANDREANA BENITEZ, PH.D.; AND KIMBERLY MCGHEE

ILLUSTRATION BY TIMOTHY BANKS

**Upon completion of the article, readers should be able to:**

- *Describe how to perform a five-minute cognitive assessment as part of an annual wellness examination for patients 65 and older.*
- *Give examples of the community resources available to the patient and family and summarize how to access them.*
- *Recognize the importance of monitoring for behavioral problems and summarize the non-pharmacological and pharmacological options for managing them.*

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**Dr. David G. Clark is the principal investigator for the MUSC site of the Biogen-sponsored ENGAGE study of aducanumab. Dr. Steven L. Carroll, Dr. David L. Bachman, Dr. Andreana Benitez, and Kimberly McGhee have no relevant financial relationships to disclose.**

## A public health crisis

Better understanding and meeting the needs of patients with Alzheimer's disease (AD) and their caregivers is increasingly a matter of national necessity. More than five million Americans have AD, the most common cause of dementia in those 65 and older, and that number is expected to triple by 2050 due to the aging population.[1] Health, long-term, and hospice care for patients with dementia due to AD or other causes cost the nation $226 billion in 2015.[1] In addition, more than 15 million Americans provided almost 18 billion hours of informal (i.e., unpaid) care for patients with AD, at an estimated value of $218 billion.[1] It is feared that the projected increase in AD prevalence would overwhelm Medicare/Medicaid, the health care system, caregivers, and nursing homes. For these reasons, the Centers for Disease Control and Prevention have declared the rising prevalence of AD to be a public health crisis.

## Knowing the enemy

Although most AD develops late in life (i.e., late-onset AD), with risk doubling every five years after age 65, it is not a normal part of aging. Whereas some slowing of mental processes is expected with the natural aging process, AD is a neurodegenerative disease that leads to gradual but irreversible cognitive and functional decline as it disables and destroys neurons and other brain tissue. The neurons of patients with AD do not function properly due to the accumulation of amyloid plaques and the formation of neurofibrillary (tau) tangles in the axons' microtubules. Changes in the brain's white matter, the myelin sheath that covers the axons and helps them conduct messages more effectively, could also be implicated.

It is not well understood what causes these changes in brain cells and tissue, but it is thought that genetic, environmental, and lifestyle factors all have a role to play. For example, patients who carry a copy of the APOE-ϵ4 allele, which is thought to promote amyloid plaque formation, are at an increased risk of late-onset AD but not all go on to develop the disease. Lifestyle modifications such as more aerobic exercise and a healthy diet[2] as well as better sleep, less stress, and increased social interaction may decrease the risk of developing AD or improve cognitive symptoms in those with the disease.

Detrimental changes to the brain are thought to begin a decade or more before the first symptoms of AD appear, and this "preclinical" stage may represent the best opportunity for therapeutic intervention. A number of monoclonal antibodies targeting amyloid plaque formation are in clinical trials. Although phase 3 trials of a number of these agents (e.g., bapineuzumab[3] and solanezumab[4]) yielded disappointing results in mild to moderate AD in 2014 and 2015, *post hoc* analysis of the results suggested that the agents could provide benefit if administered in the preclinical or very early stages of the disease,[5] and most new trials of these and other anti-amyloid monoclonal antibodies are focused on demonstrating such a signal.

There is a great deal of optimism about the preventive promise of these amyloid-targeting monoclonal antibodies, and intensive efforts are under way to develop better cerebrospinal fluid and imaging biomarkers of preclinical AD so that these agents can be administered to the appropriate patients.

For example, amyloid scans, a form of positron emission tomography in which small molecules capable of binding to amyloid plaques are injected before imaging, hold promise for identifying patients at risk of developing the amyloid plaques that are one of the hallmarks of AD. Although these scans have a growing role in identifying appropriate participants for AD clinical trials and may be useful when there is considerable diagnostic uncertainty, they are not currently recommended for widespread clinical use and, with few exceptions, are not reimbursed by the Centers for Medicare & Medicaid Services.

While excitement is growing over the development of amyloid biomarkers and targeted anti-amyloid therapies, it should be remembered that amyloid plaques are only one piece of the Alzheimer's puzzle. As such, agents solely targeting them may be limited in their therapeutic efficacy. Ultimately, as in other chronic diseases, a combination regimen may be required to target not only amyloid but also tau as well as the white matter changes associated with the disease.

## Responding to the crisis

Primary care providers (PCPs) are likely to be the first responders to this public health crisis, as most patients with memory concerns consult with their PCP. Primary care physicians, however, are already overwhelmed trying to manage complex diseases such as hypertension, diabetes, and heart disease within the context of the typical fifteen-minute visit. As a result, 27% to 81% of patients with AD go unrecognized in primary care.[6]

Early detection of dementia due to AD in a primary care setting is vital if patients are to benefit both from current treatments that may stabilize the disease for a time and also the targeted therapies that are nearing the clinic. It also opens the door to much-needed educational and support services for patients and their caregivers and provides patients time to plan for their future care, put their affairs in order, and take any necessary legal or financial steps. It also enables a strong relationship to develop between the PCP, the patient, and the family, one that will enable them as a team to meet challenges, such as the behavioral problems that can develop in late-stage disease, while maintaining a good quality of life for patients and caregivers and delaying institutionalization.

## Early detection

Primary care physicians now have the tools they need to detect cognitive decline early. In 2011, as part of the Affordable Care Act, Medicare began paying for annual wellness examinations that include cognitive assessment for patients 65 and older.[6] The Alzheimer's Association has developed a toolkit for conducting the cognitive assessment during the annual wellness examination (http://alz.org/health-care-professionals/cognitive-tests-patient-assessment.asp#alzheimers_screening), with a detailed algorithm illustrating when these assessments should be administered and which clinical decisions need to be made based on their results (http://www.alz.org/ documents_custom/awv_algorithm_webA.pdf). It recommends three screening tools—the Memory Impairment Screen (MIS), the General Practitioner Assessment of Cognition (GPCOG), and the Mini-Cog—because, among other reasons, they require five minutes or less to administer, have been validated in a primary care setting, and can be used without copyright concerns for clinical care.[6] These tools are easy to administer and an assessment can be performed by medical staff as well as by physicians. For the three-minute Mini-Cog, for example, the patient is asked to remember three words in order, and then, as a distractor, told to draw a clock face with hands indicating a specific time, before being asked to recall the three words. For the clock drawing, "10 after 11" is often used because correctly drawing the clock hands as facing 11 and 2 requires several cognitive steps that can be challenging for people with AD. If the results from this or another screen arouse concern, the PCP can perform a full dementia evaluation or refer to a behavioral neurologist or other dementia specialist for further assessment before communicating concerns to the patient.

The Alzheimer's Association provides many resources to PCPs to help them identify and manage patients with AD (http://alz.org/hcps), including a checklist of ten warning signs for AD (http://www.alz.org/national/documents/checklist_10signs.pdf) and a new app that offers not only an interactive form of the cognitive assessment algorithm but also both physician and patient educational resources about AD, diagnostic tools, and information about the latest AD trials.

One additional resource for early detection is the patient's family or caregiver. The early symptoms of AD can be subtle, noticeable by those who know the patient well but not evident to a physician in a brief office visit. Patients themselves are often not aware of their cognitive decline. Family members may feel frustrated, and the diagnosis may be delayed, if their concerns go unheeded because patients display their best behavior for the PCP. Family members may be hesitant to mention evidence of cognitive decline in the presence of the patient, so PCPs who suspect memory or other cognitive problems due to screening or observation will likely benefit by interviewing the family member separately, perhaps using an informant screening tool that is meant to distinguish between normal aging and AD (http://www.alz.org/documents_custom/ad8.pdf).

## Diagnostic assessment

It is helpful to order laboratory tests to identify thyroid problems and $B_{12}$ or other vitamin deficiencies that could lead to cognitive problems and to obtain magnetic resonance imaging (MRI) to look for evidence of vascular disease or damage due to compromised blood flow to the brain.[7] Having these results in hand, the PCP or specialist is much better equipped to interpret information gleaned from a detailed patient history and thorough physical, cognitive, functional, and neuropsychological assessments of the patient.

For example, vascular dementia would be more likely in patients with MRI evidence of vascular damage and reflexes that are brisk on one side, suggesting damage to one of the cerebral hemispheres. A smoking history also increases risk—a 2010 study that showed that a large cohort of people who smoked heavily in middle age doubled their risk of developing vascular dementia or AD later in life.[8] Tremor or rigidity would suggest dementia due to Parkinson's.

Family and medication histories are also crucial. Having a family member with AD increases the patient's risk of developing the disease. A careful inventory of the patient's current medications could reveal a pharmacological cause of cognitive decline. For example, some first-generation over-the counter antihistamines such as diphenhydramine (oral) and other medications on the Beers list (updated in 2015) can make elderly patients more forgetful and can have especially negative effects on patients with AD.

Useful information about the patient's cognitive capacities can be gleaned by asking whether he or she is repeating questions often, misplacing items, struggling to think of words, or getting lost in familiar settings. If these answers elicit concern, a more comprehensive cognitive assessment using tools such as the Mini-Mental State Examination or the Montreal Cognitive Assessment (MoCA) should be performed. The Mini-Mental is widely used and helpful for detecting established dementia, whereas MoCA is more sensitive and better able to detect very early signs of the problem. The patient should also be screened for depression, which can be comorbid with AD, especially in its early stages.

It is equally important to ascertain a patient's functional status by asking if he or she can perform routine tasks such as paying bills, driving a car, cooking, or managing medications. A private conversation

with a caregiver can provide additional information as the patient with AD is not always insightful about his or her condition. A patient is considered to have dementia when he or she can no longer perform tasks that are required for independent living.

A neuropsychological assessment can also provide clues on the underlying causes of dementia. For example, visual hallucinations occur more frequently and earlier in patients with diffuse Lewy body disease than patients with AD, whereas the gradual onset of worsening memory and word-finding difficulty in an elderly individual is especially concerning for AD. As more targeted AD treatments become available, it will become increasingly important to exclude non-AD causes for dementia, since patients with those types of dementia are unlikely to benefit from amyloid-targeted AD therapy.

## Connecting the dots

It is estimated that only 45% of PCPs in South Carolina disclose a suspicion of AD or dementia to patients (Interview, Sam Wiley, South Carolina Chapter of the Alzheimer's Association). Studies have shown that failure to disclose an AD diagnosis stems from uncertainty over the diagnosis and fear that either the patients will not be able to understand the information or, if they do, will lose hope and motivation.[9] Although AD can be definitively diagnosed only *post mortem*, 80% of cases can be identified with the previously mentioned screening and diagnostic tools along with a detailed history and a careful physical examination. In contrast to physicians that may be hesitant to disclose a diagnosis, most patients with memory concerns and their caregivers prefer to be told about the disease so that they can plan for future care and access needed resources.[10]

When a diagnosis of AD is to be disclosed, the PCP should ask the patient to bring a family member or close friend to the visit for emotional support. The PCP should go over test results that led to a diagnosis of AD and should explain briefly to both the patient and family member what to expect as the disease progresses. Because receiving this news is highly unsettling, the PCP needs to reassure the patient and caregiver that the PCP will remain their champion and point of contact for navigating the care system and for accessing community resources. The PCP should also emphasize to the family the importance of beginning to make a long-term care plan for the patient and obtaining legal documents such as health care proxies. A follow-up visit should be scheduled within a few weeks to assess whether the patient and caregiver have absorbed the diagnosis, begun to tap into community resources, and taken the necessary financial and legal steps to ensure the best possible long-term care for the patient.

On the day of diagnosis, the PCP should provide a written list of organizations providing AD education and support to the patient and caregiver. The local chapter of the Alzheimer's Association (alz.org/sc/) offers classes to help patients and caregivers better understand the disease, including detailed information on what to expect at each stage of the disease and resources for providing appropriate care. In addition, the chapter offers a free 24/7 help line (1-800-272-3900) staffed by licensed social workers and counselors. They can provide information on AD-related legal and financial matters, point patients and caregivers toward support groups, provide information on the latest clinical trials, and help families find sitters, apply for financial aid for respite care, and locate nursing home beds. Safety programs are also available to ensure the safe return of patients who wander.

Many families also find it helpful to read accounts of how others have faced the challenges associated with caring for a patient with AD, such as Nancy Mace's *The 36-Hour Day: A Family Guide to Caring for Persons with Alzheimer Disease–Related Dementing Illnesses, and Memory Loss in Later Life*.

## Management of symptoms and behavioral problems

Although no disease-modifying therapies are currently approved for AD, a number of medications help mitigate some of its symptoms for a time. The U.S. Food and Drug Administration has approved two classes of drugs to treat the memory and other cognitive problems associated with AD. These include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine (for all patients with AD and some non-AD patients as well) and the glutamate modulator memantine (for patients with moderate to severe disease). Memantine is seldom given alone but instead combined with one of the cholinesterase inhibitors when monotherapy with cholinesterase inhibitors does not provide benefit. These medications provide patients a "cognitive boost" and can be continued long-term until patients are severely impaired. As with any neuroactive agent in the elderly, these drugs should not be terminated abruptly but tapered slowly.

In later-stage AD, behavioral problems often develop and can contribute to caregiver burnout and institutionalization. It is important to realize that these problems can be the patient's way of communicating an underlying physiological problem such as pain or an infection[6] and that it is important to perform a thorough physical examination, review medications, and run laboratory tests to rule out such a possibility. If there is evidence of comorbid depression, a selective serotonin reuptake inhibitor should be prescribed as psychotherapy does not typically provide benefit in these patients. However, physicians should be aware that certain antidepressants, such as


citalopram, can cause QT prolongation, especially at higher doses. Atypical antipsychotics are often used to control agitation in AD and are sometimes necessary when patients have psychotic symptoms, such as hallucinations or delusions. However, it is important to bear in mind that antipsychotics have a black box warning in this population. It is best to use the lowest effective dose for the shortest time possible. Physicians should try non-pharmacological options, developing a treatment plan with the family to avoid behavioral triggers and monitor results.[7] If pharmacological intervention is deemed necessary, anticholinesterase medications that have been approved to relieve the symptoms of AD should be tried before antipsychotics if possible.

## Conclusion

Early detection of AD by the PCP is integral to addressing both the private and public faces of the crisis and tools and algorithms exist to make it feasible in primary care practice. New therapies are on the horizon that will work best if administered early. Patients and caregivers alike feel less marginalized and invisible when their needs are recognized and access to community services and resources provided. Learning to read the behavior of the patient with AD may help signal underlying physiological or environmental problems that can be corrected, delaying institutionalization. Ultimately, the public health crisis posed by AD and the immense burdens it represents for the nation will be averted in one primary care practice at a time, in individual acts of empathy and compassionate care.

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**"We took our old structure, which was organization-wide councils reporting to the Nursing Executive Committee, and turned it upside down."**

—Andrea Coyle, RN, Professional Excellence and Magnet Program Director

# Clinical Connections

## Nursing leaders create a new management structure that gives nurses a stronger voice in their practice

BY LINDY KEANE CARTER

In any large medical center, a nurse's suggestion for practice improvement might be implemented in his or her unit but perhaps only in that one unit, never to see the light of day in another. A new nursing council structure at MUSC Health gives visibility to the best-practice ideas of any and all of its 2,500 nurses and empowers them to distribute them for adoption elsewhere. The MUSC Health Nursing Shared Governance (NSG) that was rolled out January 1, 2016, is a system that hears the voices of all nurses through their unit-based representatives who attend monthly NSG meetings and promotes the sharing of evidence-based practices. A second tier of the structure addresses organization-wide policy and nursing practice, which is communicated the other way, i.e., back to the unit nurses.

**Andrea Coyle, RN**, Professional Excellence and Magnet® Program Director, and **Christopher Hairfield, RN**, a medical/surgical ICU nurse, are co-chairs of the NSG and were co-chairs of the committee that designed it in 2015. "We took our old structure, which was organization-wide councils reporting to the Nursing Executive Committee, and turned it upside down," said Coyle. "We put the direct care nurses on top, then their unit-based council in support of them, and those councils supported by the organization-wide councils. This way, all nurses are represented and supported." Hairfield has heard only favorable reaction in the NSG's first three months. "Everyone's still finding their feet, but evaluations on classes for the leadership team of the unit-based councils were great," he said.

Four of the six organization-wide councils—Transformational Leadership, Structural Empowerment, Exemplary Professional Practice, and New Knowledge and Innovation—are modeled on the domains of Magnet® Recognition, which the American Nurses Credentialing Center awarded to MUSC Health in September 2015. Magnet® Recognition is a status held by only 7% of U.S. hospitals. Two other councils—Healthy Work Environment and the NSG Collaboration Council—were added to meet MUSC-specific needs.

Magnet® hospitals must outperform national benchmarks on nurse-sensitive quality indicators, such as catheter-associated urinary tract infections, central line–associated bloodstream infections, and hospital-acquired pressure ulcers. Who better than nurses to have a direct impact on these indicators? The intent of the NSG is that direct care nurses will own nursing practice and drive outcomes.

Evidence-based practice is the standard for these solutions. The medical center's Center for Evidence-Based Practice and Value Institute helps clinicians, including nurses, develop evidence-based guidelines and order sets and analyze literature for decision-making.

The NSG has been designed to evolve to meet the needs of the MUSC Health clinical enterprise. Input from the nursing staff will be considered one of its metrics of success. In Spring 2017, the annual survey of MUSC Health staff will include questions measuring nurse engagement as it relates to professional growth and development.

The NSG is also intended to produce processes and practices that can be shared with the community hospitals, health systems, and physician groups that will be part of the MUSC Health Alliance. "As we become a larger enterprise with a state presence, we should share our successes with our partners," says Coyle.

# Practice Makes Perfect Medicine

## Simulation sharpens nursing skills for optimal safety and efficiency

BY LINDY KEANE CARTER

**Mock traumas for the Pediatric Emergency Department team have improved communication and efficiency.**

Simulation activities for health care providers are on the rise at MUSC Health. In 2014, the Medical Center's nursing leadership launched an initiative to increase the use of this technology in orientation, training, and competency validation. A new position was created in the Nursing Professional Development Department to maximize the use of simulation and other resources. **Melanie Cason**, **Ph.D.**, **RN**, **CNE**, is the Clinical Simulation Program Coordinator. Her expansion of courses and her support of the hospitals' nurse educators has led to a doubling of simulation use from 1,031 hours in FY 2014 to 2,044 hours in FY 2015. Eleven new simulation courses have been created, seven of which are nurse-focused, including Continuous Renal Replacement Therapy for Critical Care Nurses, Trauma Nurse Specialty Course, Trauma Nurse Boot Camp, and CAUTI Super-user Training.

A state-of-the-art Simulation Center located on the first floor of the College of Nursing building with 14 training rooms, 32 low- and high-fidelity manikins, and other medical equipment is the home of most of this training. But increasingly, the manikins are being loaded on gurneys and moved into hospital units so that these drills can occur in real work environments, known as *in situ* (on site) simulation.

Many of the Medical Center's 34 Nursing Professional Development Facilitators (NPDF's) have seized this opportunity to use simulation, particularly the *in situ* drills. "The introduction of *in situ* or near situ has been an invaluable resource for our nurses," said **Lisa Langdale, MSN, RN**, Director, Clinical Excellence Education. "Since it occurs in or near the nurses' work environment, they have more access to training. Also, *in situ* enables them to apply the training with the actual equipment, such as Continuous Renal Replacement Therapy machines, or patient scenarios specific to their practice, such as mock codes or identification of cardiac arrhythmia."

"*In situ* is the hot topic in the industry," said Cason. "It cuts costs and identifies processes in the unit that aren't working. In an actual work setting, team members have to know where their code cart is, find supplies, and be able to identify one another's roles. Often, they identify simple interventions that improve patient care." For example, they may discover that certain medications or supplies have expired.

The *in situ* training tools include:

- Laptop computers and Surface Pro 3 tablets loaded with simulation scenarios that enable the instructor to check the staff off on manikins and actual patients.
- High-fidelity (computerized) adult and child manikins that simulate human physiology. They can breathe, moan, even talk.
- Low-fidelity manikins with basic physiological functions.

**Madeline Gehrig, RN**, an NPDF in the Pediatric Emergency Department (ED), uses low- and high-fidelity manikins for competencies and *in situ* mock codes and mock traumas. For example, she sets up a child manikin in the Pediatric ED trauma bay (sometimes unannounced) and then goes to the nurses' station to give a simulated EMS encode that alerts the trauma team of physicians, nurses, and patient care technicians. In this high-stakes exercise in a small room, the challenges (on top of giving actual patient care) are team communication, keeping the noise level down, finding the supplies, and crowd control. Gehrig doesn't interrupt the scenario for teaching, which might occur at the simulation center. The team keeps going and they debrief afterward while everyone is still there. "Debriefing is very instructive because everyone hears the perspectives of others," said Gehrig. "For example, in one scenario, one of the physicians felt he was speaking loudly enough while calling out medication orders. However, the recording nurse felt the orders and assessment were not being said clearly and concisely."

**Shawn Crowley, RN**, an NPDF in the Adult ED, helps ED nurses prepare for the Trauma Nurse Specialist (TNS) program by beginning in the simulation center to do a consistent patient assessment on all patients. Crowley has started using *in situ* training every month to help bridge the gap for newer nurses who were unable to attend the TNS training and to review how to chart during certain circumstances.

**Brenda Swant, RN,** an NPDF for the Medical/Surgical Intensive Care Unit, Post Anesthesia Care Unit, and Preoperative Unit, uses the simulation center for several classes for nurses, including Medical Emergency Team Code, Continuous Renal Replacement Therapy, Peripheral Ultrasound, and Essentials of Critical Care Orientation.

Advantages for the trainers include the ability to offer a full range of learning opportunities, customize the training, and offer detailed feedback and evaluation. Simulation training and assessment at the medical center has improved interactive learning and increased interdisciplinary collaboration, said Cason. She will be gathering patient safety statistics for comparative analyses over time.

# MUSC Health Alliance Welcomes Chief

**David S. Louder, III, M.D., MBA**, has joined MUSC Health as Chief of the MUSC Health Alliance. In this position, Louder directs the expansion of MUSC Health's regional relationships with community physicians to create an integrated model of care delivery. Previously, he served as Vice President, Physician Partnerships, at Carroll Hospital in Westminster, MD, where he also served as Executive Director of Carroll ACO, LLC (an accountable care organization) and Executive Director of Carroll PHO, LLC (a clinically integrated network). Louder, a neonatologist, has also held academic appointments in Pediatrics at the University of Texas Health Sciences Center and the University of Maryland School of Medicine. He was an officer in the U.S. Air Force Medical Corps for 20 years and retired as a Colonel in 2009. He obtained his medical degree at the University of Virginia and his Master of Business Administration at the University of Massachusetts.

"Dave brings a wealth of leadership experience following his career in the U.S. Air Force Medical Corp, which included managing Population Health within a major command structure in Washington, D.C.," said **Bruce M. Elliott, M.D.,** Chief Physician Executive, MUSC Physicians and Chief Physician Executive, MUSC Health. "His civilian experience in developing a new successful clinically integrated network, as well as developing a Medicare ACO in an academic health system and then in a private hospital system, provides MUSC Health with a very talented individual with substantial knowledge and expertise."

The MUSC Health Alliance is not a business-as-usual network, stated **Patrick J. Cawley, M.D., MHM, FACHE**, Chief Executive Officer, MUSC Health, and Vice President for Health Affairs, MUSC. "This model is about fundamentally changing and aligning behind value and quality," said Cawley. "Dave and MUSC Health see clinical integration as an inclusive program that comprises multiple health care organizations in each community."

Louder's first order of business has been setting up the MUSC Health Alliance as an ACO to enable MUSC Health and its affiliates to coordinate high-quality care for their Medicare patients. "I'm here to facilitate the collaboration of organizations and physicians to improve the quality of care and reduce cost to the system," he said. "And also, by the way, to improve the experience of providers as well." As Medicare forces health care into value-based arrangements, it's critical for MUSC Health Alliance to operate with a payment and care delivery model that aligns with Medicare's model. "So, the time is now," Louder said. He has been on the road visiting MUSC Health affiliates throughout South Carolina to discuss with their representatives the benefits of operating as a clinically integrated network in this era of accountable care.

Louder also has responsibility to provide leadership to MUSC Health's Primary Care Integrated Center for Clinical Excellence, so he will be developing a four-year strategic plan that will explore expansion possibilities and develop consistent processes across the four MUSC Health entities that deliver primary care.

Louder and his wife, Claire, are the parents of two sons.

# Division of Infectious Diseases Welcomes New Director

**Cassandra D. Salgado, M.D., MS**, Professor of Medicine and Public Health, has been named Director of the Division of Infectious Diseases, Department of Medicine. Salgado continues in her role as MUSC Health's hospital epidemiologist, serving as Medical Director of Infection Control. She came to MUSC in 2004 following her fellowship in infectious diseases at the University of Virginia Health Systems. She obtained her medical degree from West Virginia University School of Medicine and completed her internship and residency at that institution. She holds a Master of Science in Health Evaluation Sciences and Epidemiology from the University of Virginia. Salgado is the author of numerous articles about her research, the editor of two textbooks, and editorial reviewer for 20 medical journals.

"Dr. Salgado brings a combination of everything that we look for in a division director, including leadership and a commitment to our core missions of research, patient care, and education," said **Don C. Rockey, M.D.**, Professor and Chair of the Department of Medicine. "I'm absolutely delighted that we were able to recruit her to this position."

The division's work comprises MUSC hospital services, clinical care (inpatient and outpatient), research, and education. Salgado has identified several opportunities for growth to complement existing faculty expertise and guide recruitment. These include expansion of the hospital epidemiology services and outpatient HIV care; research in infection prevention and control, antimicrobial stewardship, HIV and the immunocompromised host; and offering academic fellowship training and scholarly activity for residents and medical students.

Salgado foresees opportunities to expand certain services beyond MUSC Health's current hospitals and clinics. "I'm very excited about the direction in which MUSC Health's is going. I hope that our division will be able to find ways to offer our services to more patients at our affiliated sites," Salgado said.

Salgado's research focuses on the investigation of outbreaks, prevention of hospital-acquired infections, and prevention and control of antimicrobial resistance. In 2014, she received the Lewis W. Blackman Patient Safety Champion Award: Innovation and Research Category for her work in reducing resistant bacteria in patient care areas. Her publications have been cited so frequently by her peer investigators that she was included in the 2015 Thomson Reuters "The World's Most Influential Scientific Minds," a listing of 3,000 scientists worldwide who have contributed markedly high numbers of top-cited papers from 2003 to 2013. In clinical care, her leadership was key to an 80% drop in central line–associated bloodstream infections (CLABSI) in MUSC Health's hospitals between 2005 and 2013. MUSC Health's was recognized by the Department of Health and Human Services and Critical Care Societies Collaborative in 2013 for this CLABSI reduction.

On many levels, Salgado is excited about her new position. She looks forward to the numerous opportunities to improve public health that will be provided by MUSC Health's partnering with other health care entities.

# Dr. Kathleen Brady Appointed VP for Research

**Kathleen T. Brady, M.D.**, **Ph.D.**, has been named Vice President for Research at the Medical University of South Carolina (MUSC). In this role, Brady is responsible for managing all aspects of basic, translational, and clinical research at MUSC, including all research regulatory and accreditation affairs, external research relations, and the development of the research enterprise.

In announcing Brady's appointment, **David J. Cole, M.D.**, **FACS**, President of MUSC, noted her professional stature and commitment to MUSC, the home of her 27-year career in addiction psychiatry. "Dr. Brady's passion for advancing new knowledge and scientific discoveries, combined with an enterprise-wide focus on better aligning our research and clinical efforts, will propel MUSC into new frontiers of research for decades to come," said Cole.

"I have benefited greatly from being at MUSC in my career," said Brady. "I look forward to giving back to this campus by improving infrastructure, services, and venues for communication and collaboration."

Brady received her bachelor's degree from Fordham University, her doctoral degree from the Medical College of Virginia, and her medical degree from MUSC, where she completed her residency and fellowship. She and her husband, R. B. Lydiard, M.D., Ph.D., are the parents of three daughters.

Brady is an internationally known researcher in drug and alcohol dependence. Her work has advanced scientific understanding of the biological and psycho-social gender differences in addictions and informed the development of medical and behavioral therapies best suited to women.

She was recognized in 2001 for these contributions with the Betty Ford Award and the South Carolina Woman of Achievement Award. Her mentoring of faculty and fellows has been recognized with the Marian W. Fischman Award from the College on Problems of Drug Dependence and the MUSC Women Scholars Faculty Advancement Award.

Brady has served in numerous leadership roles, including Associate Provost for Clinical and Translational Science. In 2010, Brady led the establishment of the South Carolina Clinical and Translational Research Institute (SCTR) through winning a five-year $20 million grant from the National Institutes of Health. She recently led a successful effort to obtain renewal of this grant.

Brady's new responsibilities include the creation of institutional research strategies and benchmarks as part of the strategic plan for Imagine 2020. She plans to identify areas within MUSC's colleges that are well-suited for campus-wide collaboration in research and direct resources to those projects. Ideally, these projects will involve collaborations between clinical and research programs in more than one college.

"Our strength lies in the excellence of our research and clinical communities and the fact that we work on a small campus," Brady said. "People work well together here. We wouldn't have won these prestigious NIH awards if we had not already had a critical mass of high-quality research. I am really looking forward to working with colleagues at MUSC and nationwide to advance and build the MUSC research portfolio."

Photo by Anne Thompson

# New Physicians

**Ricardo A. Arbizu Alvarez, M.D.**

Board Certification: Pediatrics // Specialty: Pediatric gastroenterology // Medical School: Universidad Francisco Marroquin // Residency: Women & Children's Hospital of South Alabama, University of South Alabama // Fellowships: Women & Children's Hospital of Buffalo, State University of New York; Boston Children's Hospital, Harvard Medical School

**Manal E. Moustafa, M.D.**

Board Certification: Neurology With Special Qualifications in Child Neurology // Specialties: Pediatric neurology, clinical neurophysiology, and epilepsy // Special interests: Medically refractory epilepsy, epilepsy surgery, and vagal nerve stimulation // Medical School: University of Tennessee // Residency: Children's Hospital of Pittsburgh of UPMC (Pediatrics and Child Neurology) // Fellowship: Children's Hospital of Pittsburgh of UPMC (Clinical Neurophysiology)

**Christina Vassileva, M.D.**

Board Certifications: General Surgery, Cardiothoracic Surgery // Specialty: Adult cardiac surgery // Special interests: Mitral valve repair // Medical School: Johns Hopkins // Residency: Johns Hopkins // Fellowship: Harvard-Brigham and Women's Hospital

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