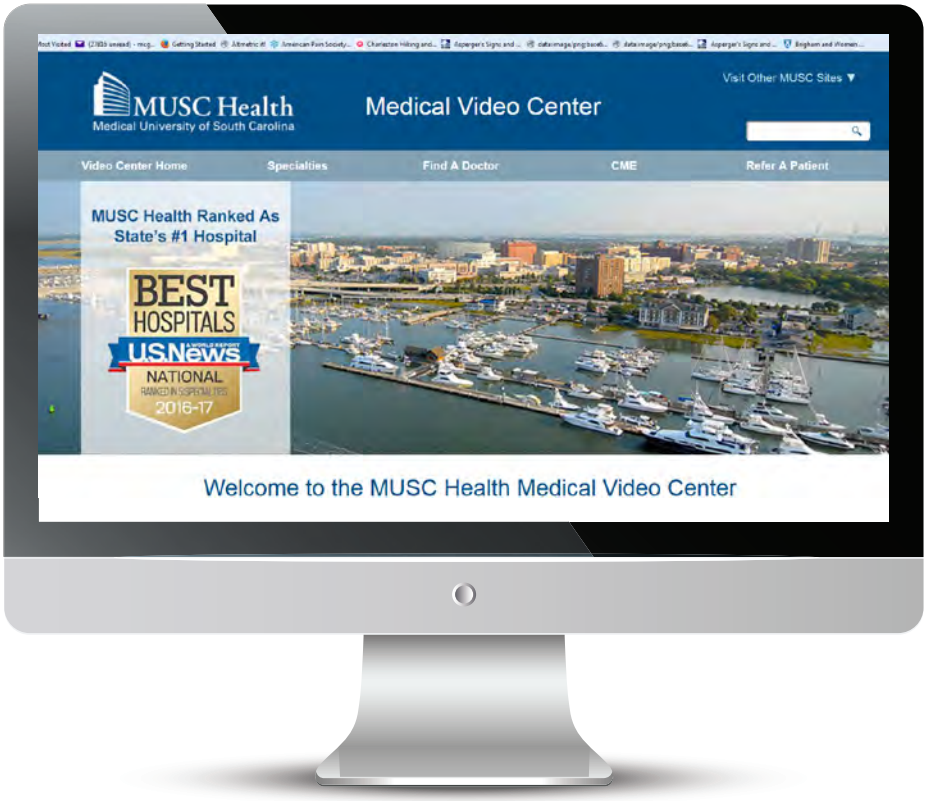
PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SPRING 2017

Take a front row seat to innovative surgeries at the new MUSC Health Medical Video Center



MUSC Health is pleased to announce the launch of the MUSC Health Medical Video Center (**http://MUSChealth.org/medical-video**), which is specifically designed for physicians who want up-to-date clinical information and wish to learn about innovative surgical techniques. Videos include interviews with MUSC Health and MUSC Children's Health physicians about innovative approaches to treatment, recent surgical videos and photography voiced over by surgeons and CME-eligible grand rounds and other presentations. The site will be updated regularly, so check back often to learn about some of the most exciting innovations in health care from experts at MUSC Health. This website takes the place of the earlier OR Notes surgical blog.

A sampling of current videos

Jeffrey R. Winterfield, M.D., director of the Ventricular Arrhythmia Service at the MUSC Health Heart and Vascular Center, discusses the latest developments in ventricular tachycardia ablation, including the latest innovations in cardiac mapping technology.

MUSC Children's Health pediatric neurosurgeon **Ramin Eskandari, M.D.**, and MUSC Health craniofacial surgeon **Jason P. Ulm, M.D.** discuss surgical approaches to correct craniosynostosis or the premature fusion of one or more of the brain's sutures.

David R. White, M.D., director of the Division of Pediatric Otolaryngology, and **Scott M. Bradley, M.D.**, director of the Division of Pediatric Cardiothoracic Surgery, discuss slide tracheoplasty, a procedure offering new hope to children with congenital tracheal stenosis.

MUSC Health ophthalmologist **George N. Magrath, M.D.**, narrates video footage showing the placement of a radioactive plaque to treat choroidal melanoma. Magrath collaborates closely with MUSC Health radiation oncologist **S. Lewis Cooper, M.D.** to make this procedure available to patients with choroidal melanoma in South Carolina and surrounding regions.

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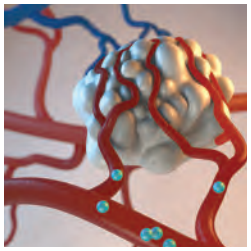


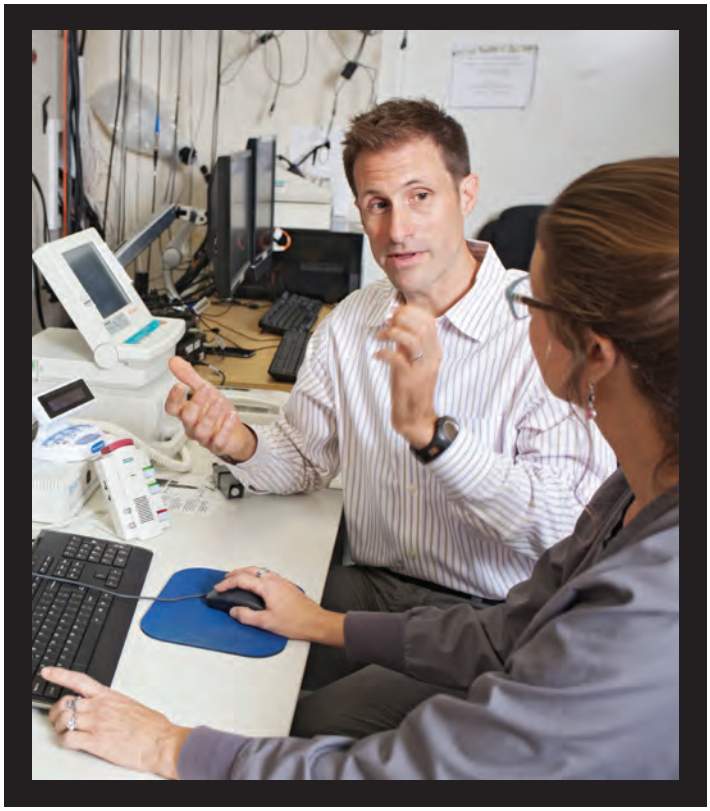
On the cover: Research by MUSC's Dr. Peter Kalivas suggests that an over-the-counter antioxidant could prevent relapse by controlling intrusive thoughts. Illustration by Emma Vought.

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

BOLD PREDICTION

Brain circuit that supports smoking cessation identified

BY SVER AUNE



Photograph by Sarah Pack

Dr. Brett E. Froeliger

Quitting smoking is hard. Yet success is more likely with strong communication between parts of the brain that inhibit automated behavior, according to a two-part study by **Brett E. Froeliger, Ph.D.**, an addiction scientist in the Department of Neuroscience and a member of the MUSC Hollings Cancer Center. Froeliger and his colleagues published their results in the March 1, 2017 issue of *JAMA Psychiatry*.

Smoking becomes an automated behavior over time. In the brain, the urge to smoke begins the same way your foot automatically moves to the gas pedal when a red stoplight turns green. "A pack-a-day smoker places a cigarette in their mouth a few hundred times a day over years," says Froeliger. "It becomes automated."

This kind of automated physical behavior is stopped by a pathway in the brain called the inhibitory control network, which includes the prefrontal cortex and the thalamus. Communication through this pathway is often disrupted in the brains of smokers.

The work began when Froeliger was a postdoctoral researcher in the laboratory of Joseph F. McClernon, Ph.D., at Duke University. Froeliger and McClernon wanted to know if this pathway was involved when smokers attempted to quit. The laboratory examined inhibitory control networks in the brains of 81 nicotine-dependent adults committed to trying a 10-week smoking cessation program.

Before the program started, the researchers used functional MRI to monitor blood oxygenation level-dependent (BOLD) responses in the inhibitory control network. The patients were instructed to strike a computer key each time a colored circle appeared on screen, except on the rare occasion when a circle of a certain color appeared. A higher BOLD response meant that the brain was using more resources to inhibit the automated response of striking the key when the rare circle appeared.

After ten weeks, about half of the smokers had quit successfully. Intriguingly, it turned out that they had lower BOLD responses in their inhibitory control networks before trying to quit. In particular, BOLD responses were lower in the right thalamus and in the right inferior frontal gyrus, which sends a signal through the prefrontal cortex to the thalamus. They also had stronger functional connections between those regions. Patients who relapsed had scored just as well on the task as those who quit successfully. It seemed that their automated behavior may have required more effort to inhibit.

Froeliger continued the work with a new twist when he became faculty at MUSC. He wondered if the same thing happened to smokers who had not committed to quitting. The group measured BOLD responses in 26 smokers performing the same task. This time, however, the smokers were then presented with an open pack of their preferred brand of cigarettes, a lighter and an ashtray. They were paid one dollar for every six minutes they did not smoke, up to an hour. The idea was to give each one a small incentive to resist the temptation to smoke.

Similar to the first finding, the lower a person's BOLD response, the longer the person resisted smoking. Those who resisted temptation longer also had stronger functional connections in their inhibitory control networks.

This study is the first to link the strength of communication in a brain circuit that inhibits automated behavior with the ability to resist smoking. Therapies that support this pathway could help certain smokers who are trying to quit. "This work helps scientists understand why some smokers have a harder time quitting," says Froeliger.

A RARE FIND

Stem cell drug screen yields potential alternative to statins

BY SVER AUNE

A novel drug screen in liver-like cells shows that cardiac glycosides, which are found in the leaves of the digitalis (foxglove) plant, could reduce low-density lipoprotein (LDL) cholesterol differently than statins and might do the same in patients. These findings were reported by **Stephen A. Duncan, D. Phil.**, SmartState™ Chair of Regenerative Medicine at MUSC, and colleagues in the April 6, 2017 issue of *Cell Stem Cell*.

Not everyone with high LDL cholesterol responds to statins. Statins increase levels of a cell surface receptor that removes LDL cholesterol from the bloodstream. However, statins do not work in patients with familial hypercholesterolemia (FH), who have a rare mutation in that receptor. FH patients have very high cholesterol and die of cardiovascular disease by their forties. The existing drugs for FH can cause fatty liver disease, and the best treatment is a liver transplant.

Duncan and his colleagues developed a drug screen to identify an alternative to statins. Apolipoprotein B (apoB) is a molecule that liver cells use to make LDL. Drugs that decreased apoB could potentially lower cholesterol independently of the LDL receptor in FH patients and also in patients with other forms of high cholesterol.

FH was a perfect model for testing alternatives to statins. Yet the rarity of FH meant these liver cells were scarce. Duncan's group made induced pluripotent stem cells out of skin fibroblasts taken from a single patient with FH. This provided a renewable source of stem cells that could be turned to liver-like cells that retained the mutation.

The group tested these liver-like cells with the SPECTRUM library, a collection of 2300 pharmaceuticals, many of which have reached clinical trials. Surprisingly, all nine cardiac glycosides in the collection, some widely prescribed for heart failure, reduced apoB in liver-like cells from the patient with FH. In further tests, they also lowered apoB in human hepatocytes and in mice engineered to grow normal human livers without the FH mutation.

Next, the team combed through more than five thousand medical records of patients prescribed cardiac glycosides for heart failure who also had LDL cholesterol records. Similar drops in LDL levels were observed in these patients as in a matching group of patients prescribed statins.

This study provides the first evidence that cardiac glycosides could potentially reduce LDL cholesterol independently of the LDL receptor, where statins act, by reducing apoB.

Image courtesy of Dr. Stephen Duncan

The cardiac glycosides are always prescribed with care, as they are known to be toxic at high doses. However, they could offer inexpensive life-saving options for patients with FH. Additionally, a cardiac glycoside in a low dose could conceivably provide an added benefit to patients already taking a statin. Duncan is exploring plans for a clinical trial that would determine the correct dose in hypercholesterolemia patients.

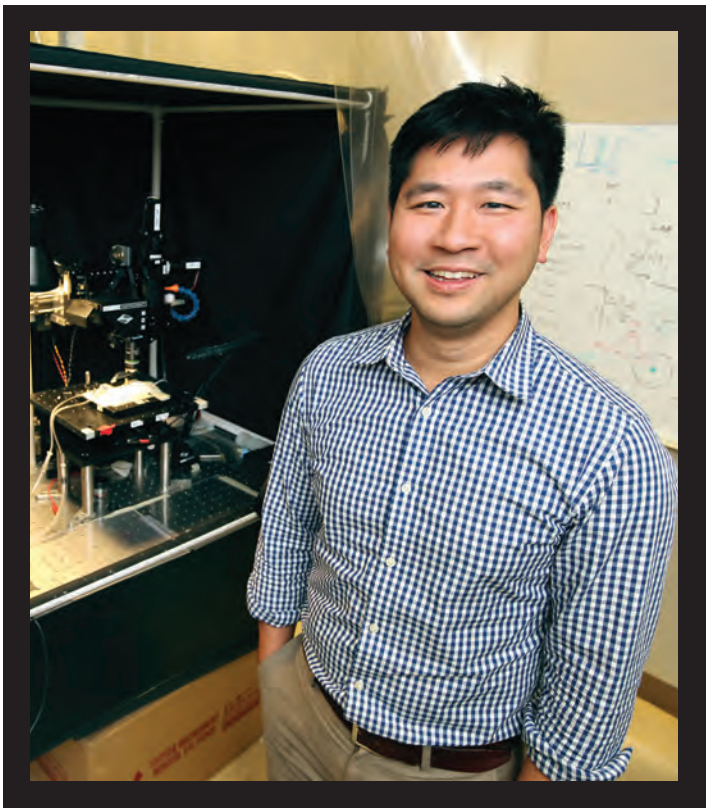
Using patient stem cells to screen drugs that are already on the market is a great way to investigate treatments for liver diseases.

"There are so few livers available for transplant," says Duncan. "Having the stem cell model where we make liver cells in the culture dish open[s] up a possibility of using this not only to investigate a disease, but also as a way to discover drugs that could fix a disease."

LITTLE EVENTS, BIG DIFFERENCE

The lasting effects of ministrokes may contribute to dementia

BY KATHARINE HENDRIX



Photograph by Sarah Pack

Dr. Andy Y. Shih

Evidence overwhelmingly supports a link between cognitive decline and cerebrovascular diseases. There is a much higher incidence of microinfarcts (mini-strokes) in people with cerebrovascular diseases and, according to post-mortem histological and *in vivo* radiological studies, a greater burden of microinfarcts among people with vascular cognitive impairment and dementia. Until now, the mechanisms by which these miniscule lesions (~0.05 to 3 millimeters in diameter) contribute to cognitive deficits including dementia have been poorly understood.

"These infarcts are so small and unpredictable, we just haven't had good tools to detect them while the person was still alive," says **Andy Y. Shih, Ph.D.**, assistant professor in the Department of Neuroscience at MUSC. "Until now, we just had post-mortem snapshots of these infarcts at the end of the dementia battle and measures of the person's cognitive decline that might have been taken years before the brain became available for study."

In an article published ahead of print on January 16, 2017 by the *Journal of Cerebral Blood Flow and Metabolism*, Shih and colleagues report preclinical findings suggesting that functional deficits caused by a single microinfarct occur across a much larger area of viable peri-lesional tissue than was previously understood and that the resulting deficits are much longer-lasting.

The team began by hypothesizing that microinfarcts might disrupt brain function beyond what was visible by histology or magnetic resonance imaging (MRI).

"Even though people may experience hundreds of thousands of microinfarcts in their lifetime, each event is extremely small and thought to resolve in a matter of days," says Shih. "It's been estimated that, overall, microinfarcts affect less than two percent of the entire human brain. But those estimates of tissue loss are based only on the 'core' of the microinfarct, the area of dead or dying tissue that we can see in routine, post-mortem, histological stains."

To investigate their theory of broader impacts, the team developed a mouse model so that they could examine the effects of individual cortical microinfarcts on surrounding tissue function *in vivo* for several weeks after the event. Post-mortem, c-Fos immunostaining revealed that an area estimated to be at least 12-times greater in volume than the microinfarct core had been affected by the event. Furthermore, *in vivo* two-photon imaging of single-vessel, sensory-evoked hemodynamics found that neuronal activity across the affected tissue area remained partially depressed for 14 to 17 days after the microinfarct.

"I knew larger strokes could have distant effects, but I was surprised that something of this scale could have such a large effect," says Shih. "Over time, after you have a lot of microinfarcts, there may be enough accumulated damage in the brain's circuitry to equal the impact of a larger event."

Could targeting these microinfarcts help protect against stroke and dementia?

"The neuroprotection idea hasn't flown very far for acute stroke, in part, because the window of time for protecting the brain from stroke damage is very narrow," says Shih. "But for microinfarcts, you don't have to know exactly when they occur. If an MRI shows a person to be at high risk for microinfarcts, maybe we could one day put them on a drug for a while to reduce the impacts of these lesions."

TREATMENT HOPE FOR SICKLE CELL DISEASE

A new drug shows clinical efficacy and safety in preventing sickle cell crises

BY VITRIA ADISETIYO

A new drug, crizanlizumab, may soon be an approved treatment option for sickle cell disease (SCD), the most common inherited blood disorder in the U.S.

Patients with this lifelong disorder experience recurrent pain episodes called *vaso-occlusive episodes* (VOE) or sickle cell crises that increase the risk of death due to tissue and organ damage. These crises are the primary cause of frequent health care visits and the source of substantial financial burden.

"Sickle cell disease is one of the most costly medical conditions next to congestive heart failure," says **Julie Kanter, M.D.**, associate professor of pediatrics and director of sickle cell disease research at MUSC.

Moreover, there are few treatments for the disorder and only one medication (hydroxyurea) has been previously approved to reduce VOE, until now. Findings from a phase 2 clinical trial published in the February 2, 2017 issue of the *New England Journal of Medicine* show that crizanlizumab (Novartis, Basel, Switzerland) significantly reduces VOE in those with SCD. Kanter, who is a co-author on the article, recruited patients into the trial and served on the publication committee.

"The goal is to prevent these episodes because this will contribute to decreased chronic pain and improved quality of life," says Kanter.

The pathology of VOE is inflammatory based. Abnormal sickle-shaped red blood cells adhere to the inner lining of blood vessels, blocking microcirculation and leading to inflammation and pain. This adhesion equires a cell adhesion molecule called P-selectin. Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin.

"Crizanlizumab prevents pain episodes by inhibiting the stickiness of the blood cells to the inside of blood vessels," explains Kanter.

In this double-blind, randomized, placebo-controlled study, 198 patients aged 16 to 65 years who were experiencing VOE were randomized to receive low-dose crizanlizumab, high-does crizanlizumab or placebo. Treatment was administered intravenously 14 times over 52 weeks, followed by a six-week evaluation phase.

The annual rate of VOE in the high-dose group was 43.3 percent lower than placebo. Additionally, the median time to the first and second crises was significantly delayed with high-dose crizanlizumab compared to placebo (4.07 vs. 1.38 months; 10.32 vs. 5.09 months, respectively), and the annual rate of uncomplicated VOE in the high-dose group was 62.9 percent lower than placebo. Low-dose outcomes did not differ from placebo.

Illustration by Emma Vought

Only minor adverse effects were associated with crizanlizumab (i.e., joint pain, diarrhea, itchy skin, vomiting, chest pain), and no group differences were noted in total adverse effects. No problems with wound healing were reported, suggesting that temporary blockage of P-selectin does not disrupt blood clotting. No antibodies against crizanlizumab were detected, suggesting that an immune response limiting long-term administration of crizanlizumab is unlikely.

Lastly, the efficacy of crizanlizumab was demonstrated in adults with all types of sickle cell disease, as findings were observed in a representative patient sample that included all common sickle cell genotypes and in patients receiving concomitant hydroxyurea therapy and/or long-term opioid therapy.

Given the comprehensive study design and robust clinical outcomes, the drug manufacturer is applying for FDA approval based on these published results. Meanwhile, plans for a pediatric clinical trial of crizanlizumab are underway. Kanter will serve on the advisory committee designing the study, and MUSC will once again serve as a leading recruitment site.

SIGHT FOR SORE EYES

Plaque brachytherapy saves vision in some patients with melanoma of the eye

BY KIMBERLY MCGHEE

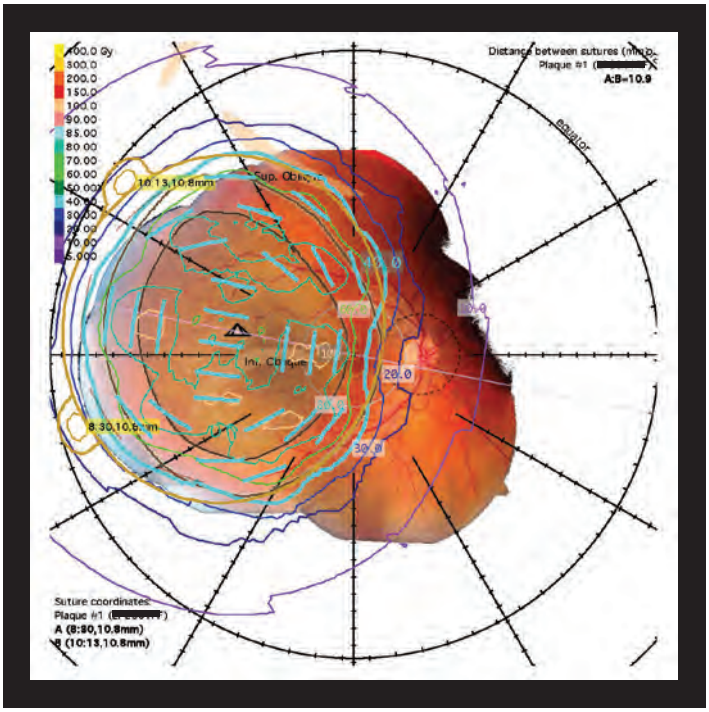


Image courtesy of Dr. George Magrath

3-D reconstructions of the eye enable radiation dose to be tailored to the tumor.

MUSC Health ophthalmologist **George N. Magrath, M.D.**, and radiation oncologist **S. Lewis Cooper, M.D.**, are collaborating to make a potentially vision-saving radiotherapy available to South Carolina patients with choroidal melanoma.

A diagnosis of choroidal melanoma once left surgeons with no choice but to remove the eye, since in 40 percent of cases the cancer spreads to the liver and lungs and is uniformly lethal. However, the Collaborative Ocular Melanoma Study showed that survival was no better in patients whose eye was removed than in those who underwent a form of radiotherapy known as *plaque brachytherapy*, which in some patients can not only spare the eye but also save some vision.

In plaque brachytherapy, a gold disk or "plaque" studded with radioactive seeds is custom fit to the tumor and seated in the back of the eye for a specified number of days, during which the patient is hospitalized. It is effective in killing the tumor in 98 percent of cases.

Although the procedure was pioneered more than three decades ago, it only became available in South Carolina last year. Patients with choroidal melanoma were once left with a harsh choice — lose an eye or travel outside the state to a center offering plaque brachytherapy. Many patients were referred to the Wills Eye Hospital in Philadelphia, a recognized center of excellence in this procedure.

When Magrath, an MUSC graduate, returned to take a faculty post last year after completing a fellowship at Wills Eye Hospital, he was determined to make this procedure available to patients closer to home, at MUSC's Storm Eye Institute.

The collaboration with Cooper and the radiation oncology team enabled him to bring to the Lowcountry new advances in the field that improve the chances of preserving vision.

Using 3D reconstructions of the eye, Cooper and the other radiation oncologists customize the radiation dose to the tumor and plan the deployment so as to minimize risk to the structures of the eye crucial for vision.

"What Lewis (Cooper) does and what they are really good at in radiation oncology is that they will tinker with the radiation and pull it away from the optic nerve and the critical structures of the eye," says Magrath. "They can customize it down to fractions of a millimeter."

The struggle to save vision continues in the two years after surgery, when radiation and the dying tumor take their toll on the macula and optic nerve. The damage done by radiation is similar to that seen in patients with diabetes, and some common diabetes medications, such as vascular epithelial growth factor (VEGF) inhibitors, are proving useful in combating radiation damage.

Radiation blocks blood flow to the retina, increases inflammation and leads to loss of different retinal cells. This causes the retina to signal for new blood vessels to grow by releasing VEGF. These new blood vessels are leaky and bleed into the eye, causing swelling and eventual scarring of the macula and the optic nerve. VEGF inhibitors help prevent the formation of these blood vessels. New postoperative laser treatments target the ischemic retina to prevent it from releasing the harmful growth factors. Corticosteroids are used to reduce the inflammation caused by the dying tumor.

"We are now able to save most of the eyes," says Magrath. "If we can catch the tumors when they are small, we can do a really good job of saving the eye and potentially some vision."

For more information or to refer a patient, contact Janet Hall at haljan@musc.edu or 843-792-4278.

UNCLOAKING CANCER

Novel cancer immunotherapy shows preclinical promise

BY SVER AUNE

Cancer immunologists at MUSC have designed an antibody-based therapy that targets the cancer cytokine TGF-beta where it could be particularly dangerous. The group reported in the December 15, 2016 issue of *Cancer Research* that the antibody binds a receptor called GARP, which stores TGF-beta on the surface of tumor cells.

The work started by considering how cancer cells use TGF-beta as a disguise from the immune system, according to **Zihai Li, M.D., Ph.D.**, chair of the Department of Microbiology and Immunology and a member of the MUSC Hollings Cancer Center. In healthy cells, TGF-beta is a secreted protein that is used by regulatory T cells (Tregs) as a signal to tell immune cells not to attack normal cells in the body. Malignant tumors mask their presence by releasing large amounts of TGF-beta to neutralize the immune cells that would attack them.

"TGF-beta is an old story. The new spin is that there is a docking receptor for TGF-beta that increases the activity of the cytokine, and this molecule is called GARP," says Li.

GARP is the only known receptor that allows TGF-beta to dock on the surface of cells. Importantly, Li knew that GARP could bind and activate TGF-beta and then float off the surface of cells that express it. Could this be a way that cancer cells store and release TGF-beta? The laboratory set about finding out.

Li and his colleagues, including first author and student **Alessandra Metelli**, first noticed that GARP expression was much higher in biopsies of human breast, lung and colon tumors than in normal tissue. To examine if GARP had a direct role in cancer development, they deleted the gene for GARP from mice with mammary tumors. The tumors grew slower and were less able to metastasize to the lungs. When the GARP gene was inserted into mouse mammary cells, they revealed increased TGF-beta signaling, tumor growth and metastasis. Mice with more GARP also had more TGF-beta-releasing Tregs. This meant that GARP enabled both cancer metastasis and immune suppression effects in breast cancer.

These were the first clues that GARP could be a diagnostic marker for cancer. It also created an opportunity to develop new treatments.

The laboratory immunized mice with human GARP in order to grow antibodies that could potentially block it. Only one antibody, 4D3, blocked human TGF-beta from binding to GARP expressed on cell surfaces. While 4D3 did not prevent growth of primary mammary tumors in mice, it did suppress the spread of these tumors to their lungs. However, 4D3 combined with cyclophosphamide chemotherapy curbed both primary tumor growth and metastasis. This means that combination immunotherapy with GARP antibody might boost the effectiveness of standard chemotherapy in breast cancer.

Alessandra Metelli (left) and Dr. Zihai Li (right)

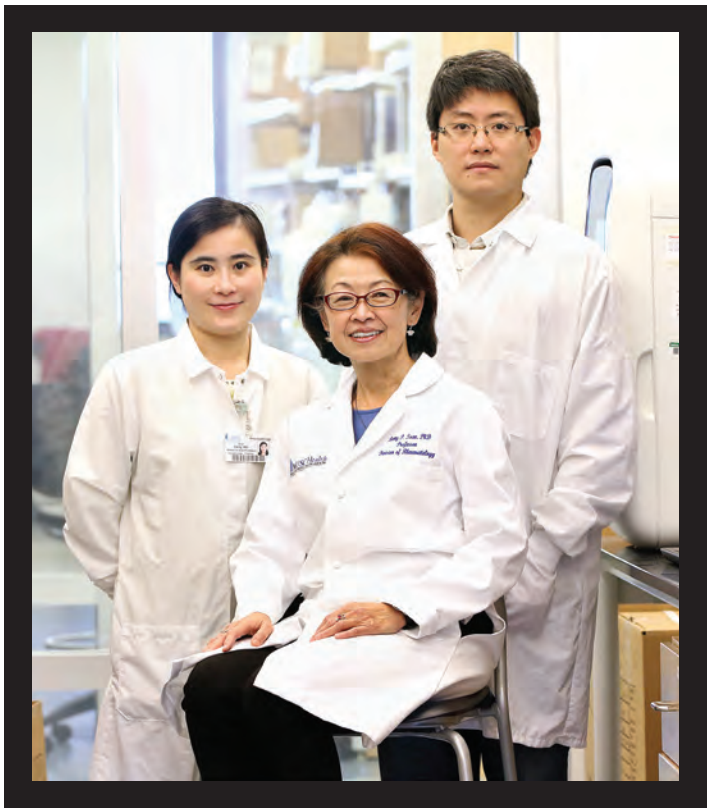
Li acknowledges that blocking GARP might also block the natural ability of Tregs to suppress the immune system, which could potentially lead to inflammatory autoimmune reactions. "Clinically some of the proven immunotherapies do induce some degree of autoimmunity," he says. "When cancer is cured and patients stop immunotherapy, the autoimmune manifestations completely disappear as well."

GARP suppression represents a novel addition to established cancer immunotherapies that also use antibodies to wake up the immune system to recognize and fight cancer. The study has drawn interest from industry partners to bring the antibody to clinical trials.

UNCOVERING HIDDEN GENETIC RISK FACTORS

Risk factor for autoimmune disease found in an underexplored genomic region

BY KATHARINE HENDRIX



Photograph by Sarah Pack

Dr. Betty Tsao (front and center) and colleagues

The March 2017 issue of *Nature Genetics* published findings by a team of MUSC researchers that a variant (p.Arg90His) in neutrophil cystolic factor 1 (NCF1, a regulatory subunit of the phagocyte NADPH oxidase) is associated with increased risk for several autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome. The amino acid substitution causes reduced reactive oxygen species (ROS), highlighting the risk of reduced ROS in developing autoimmune diseases.

Their journey started several years ago, when the team was genotyping DNA samples from Chinese, European-American and African-American SLE patients. An impressively strong signal in the Chinese sample at the rs73366469 locus (GTF2IRD1–GTF2I intergenic region at 7q11.23) caught their attention.

"This was the strongest signal I'd ever seen in autoimmune disease," says **Betty Pei-tie Tsao, Ph.D.**, MUSC professor of medicine, Richard M. Silver Endowed Chair for Inflammation Research and senior author. But the signal was only moderate in the European-American sample and nonexistent in the African-American sample. "A true risk gene should be the same in all populations," says Tsao. The team concluded that the true risk factor lay elsewhere.

But explaining this unusually strong signal wasn't going to be easy. The team had been using the Immunochip for fine-mapping — a widely used tool for conducting genome-wide association studies. However, because rs73366469 did not show linkage disequilibrium (LD) with any single-nucleotide polymorphisms (SNPs) in the Immunochip, they hypothesized that the SNP containing the true underlying risk factor was not included in it.

That's when the going got tough. "This is a very complex genomic region. The NCF1 gene has two, nearly identical twins — NCF1B and NCF1C — that are nonfunctional pseudo-genes," explains Tsao. "This makes working in this region very difficult. That's why the next-generation sequencing method that the 1000 Genomes Project uses doesn't pertain to this region."

Realizing that next-generation mapping techniques would limit their ability to find unique sequences among all the copies and duplications in this region, the team set up their own novel polymerase chain reaction (PCR) assay.

"We had to do it the old-fashioned way, which was very time consuming and labor intensive," says Tsao. "To genotype the region correctly, we used PCR to selectively amplify the NCF1 copies and conduct copy number variation tests. Then, we only used samples with no copy number variation to examine the NCF1 variant. This method ensured that what we identified as an NCF1 variant was truly a variant."

It took several years and multiple experiments in various ethnic populations before they finally identified the SNP, p.Arg90His, as the genetic variant causing SLE susceptibility. That SNP was also associated with increased risk for other autoimmune diseases, including RA and Sjögren's syndrome.

This work points out an important unmet need in genetic mapping.

"This was a labor of love. The lead author, Dr. Jian Zhao, devoted years of his life to this project," says Tsao. "But, for the future, we need to develop a more efficient platform to screen complex genome regions for variants. For many diseases, we've identified some, but not all, variants. It's likely there are more hiding in these complex regions."

GROWING UP FAST

Hospital medicine comes into its own

BY KIMBERLY MCGHEE

The rapid growth in the number of hospitalists over the past two decades — from a few hundred in 1996 to more than 50,000 in 2016 — was fueled by managed care's demands for greater efficiency and by a concern over the high rates of medical errors at hospitals. From its origins, hospital medicine has been dedicated to making hospitals more efficient and safer places. The fastest growing medical specialty, hospital medicine now has its own society, boards and fellowships.

"Hospital medicine is here to stay. We have demonstrated improvements across the nation in patient safety, throughput, increased quality at decreased cost, and it's a very good thing that is happening to the world of medicine," says **Michael M. Hawkins, M.D.**, who joined MUSC Health in May 2016 as associate chief medical officer for hospital medicine services. "But I'll say that with a caveat: It is only good if there is meticulous communication built around it."

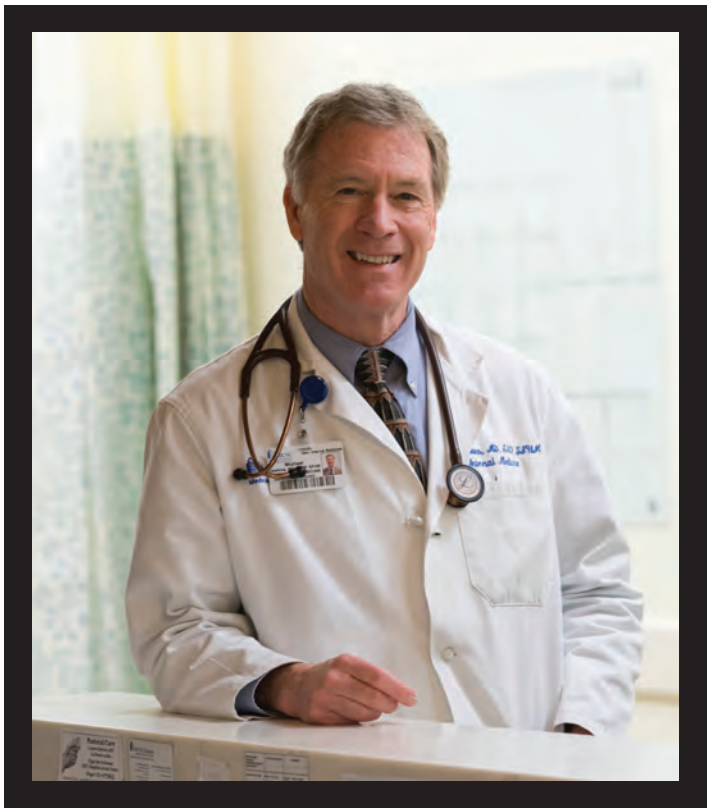
Hawkins' caveat is an important one. A hospitalist, as the name suggests, focuses exclusively on the care of hospitalized patients. Hospital medicine is a departure from the traditional model of care, in which patients' own primary care physicians traveled to the hospital to care for them. Initially, some critics feared that the new specialty could damage the bedrock of good patient care — the physician-patient relationship.

That concern can be addressed, Hawkins believes, with proper communication. "I explain to the patient that I have been on the computer and have all of their records," says Hawkins. "As long as you have that communication and you are in touch with their physician and can round on them multiple times, people really begin to appreciate the increased availability that a hospitalist provides."

Since his arrival in May, Hawkins has been very impressed with the dedication and camaraderie of his hospitalist team and how well they have aligned themselves with the institution's goals.

"I am coming into an already really, really good hospitalist team," says Hawkins. "My role is to go from good to great."

Hawkins has already made changes to improve workflow efficiency and the patient experience. For instance, he added a second private hospitalist team at the Ashley River Tower (ART) to handle referrals from the chest pain center, preventing unnecessary patient transfers from ART to another MUSC hospital.



Photograph by Brennan Wesley

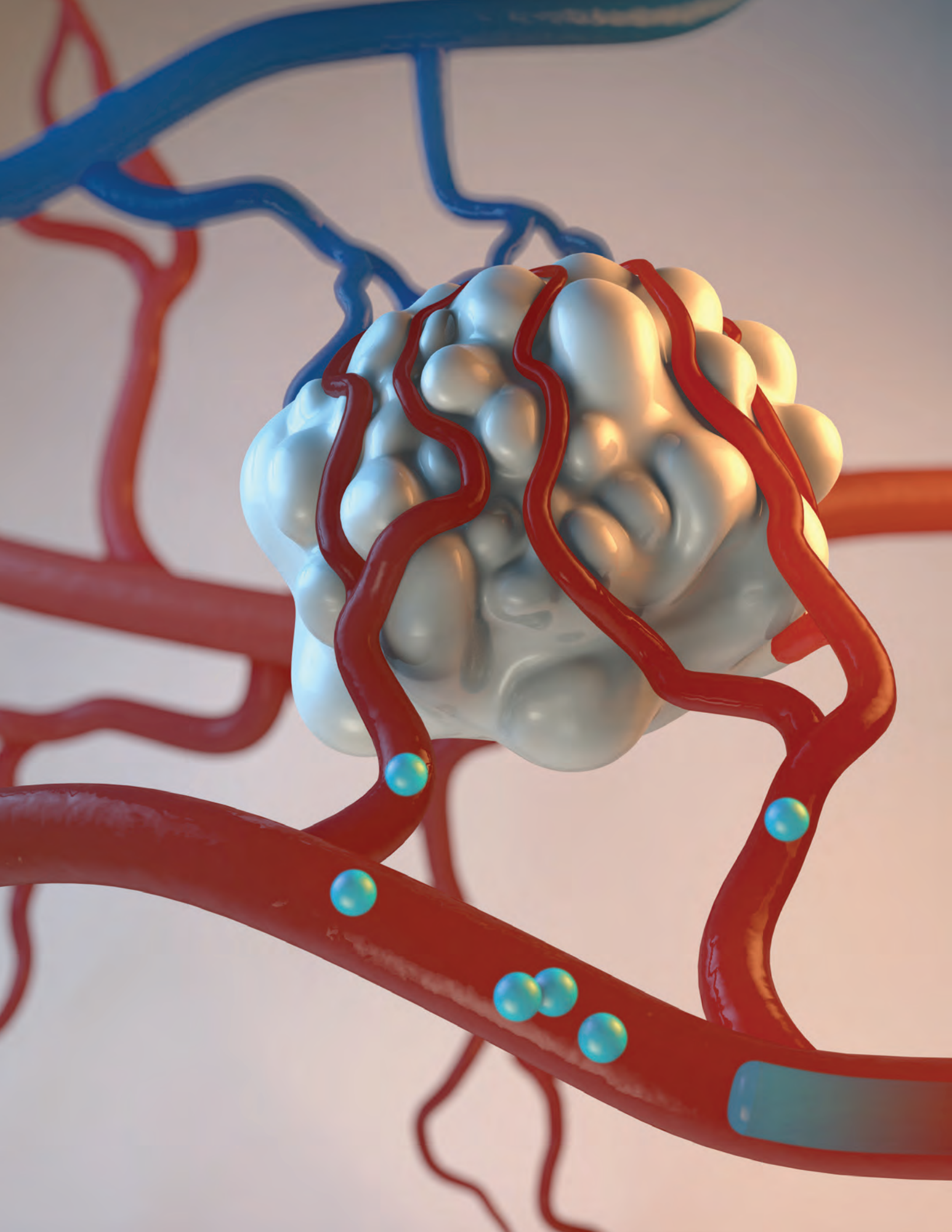
Dr. Michael M. Hawkins

He has also been hard at work building his team, a challenge given that hospitalists are in such high demand. He is particularly proud to have recruited three of MUSC's top internal medicine graduates as hospitalists for his team.

"When people who are training here and who are in the trenches day in and day out like what they are seeing enough to stay here after graduation, that's a good sign," says Hawkins. He hopes to educate more medical students and residents about the new specialty and encourage them to stay on as hospitalists at MUSC Health. He also plans to add a fellowship in hospital medicine.

Hawkins is confident that the robust team of hospitalists he is building will help the institution meet its quality metrics while also creating an even safer, more welcoming environment for patients.

Hawkins smiles at the prospect. "When you can change a system to increase efficiency and decrease costs and improve quality, that's a good place to be."



Novel Strategy Turns Liver Cancer Therapy Inside Out

BY KATHARINE HENDRIX
ILLUSTRATIONS BY EMMA VOUGHT

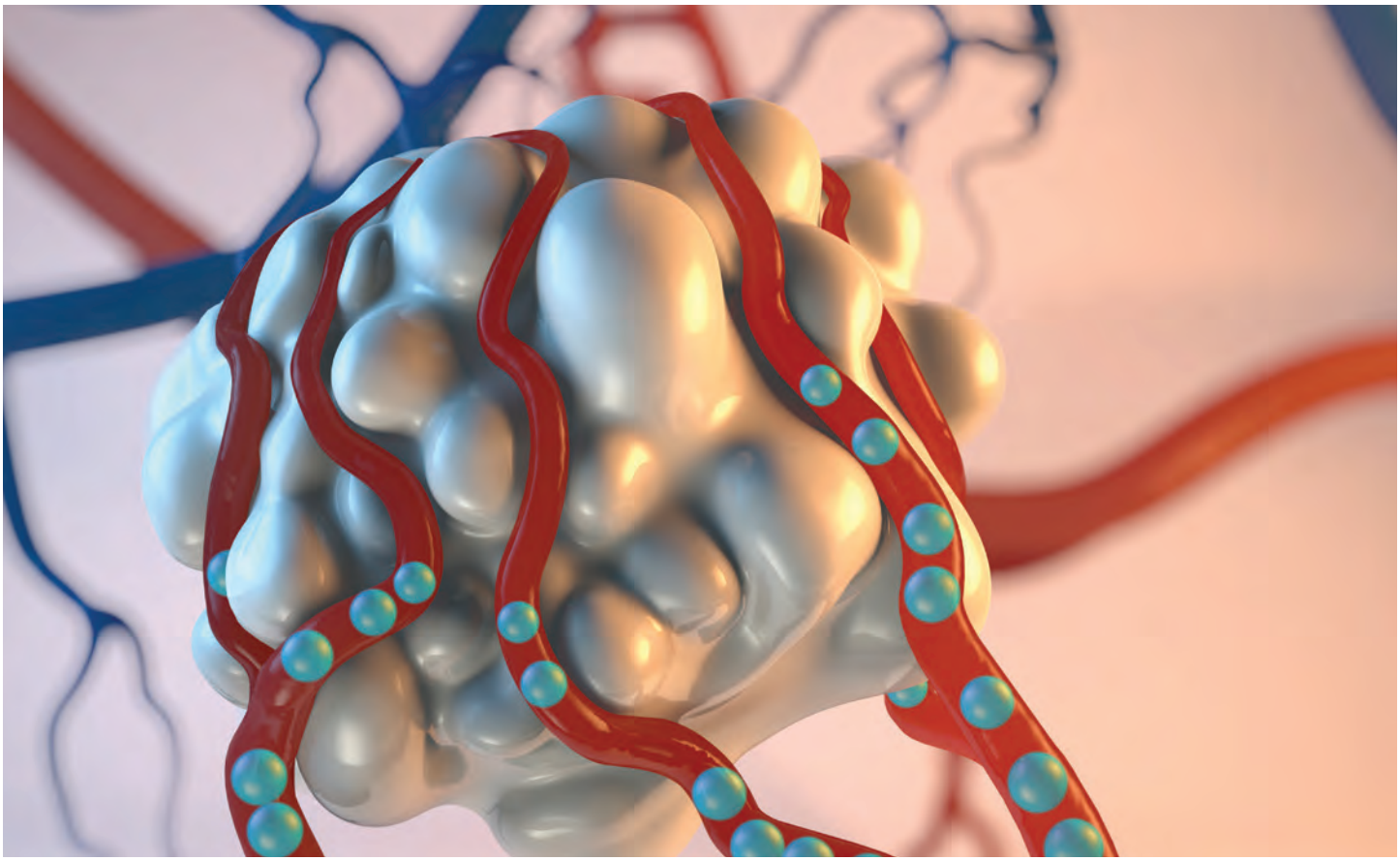
The incidence of liver cancer has more than tripled since 1980, with death rates climbing 2.7 percent annually from 2003 to 2012.[1] Intrahepatic cholangiocarcinoma (ICC), a rare but frequently fatal form of liver cancer, affects between 5,000 and 8,000 Americans a year (age-adjusted incidence 0.73 per 100,000), two-thirds of whom are older than 65.[2,3] The prognosis for ICC patients is grim: the median survival after diagnosis is about 28 months for patients who undergo surgical resection and 12 months for unresectable patients.[4,5]

Despite ICC's poor prognosis and rising incidence, there is no consensus regarding optimal treatment.[5] Complete surgical resection is the only treatment option to offer a potential cure but two-thirds of ICC patients who undergo resection will have a recurrence, most often in the remnant liver.[4] Thus, among those receiving surgical resection, reported five-year survival rates are relatively low — ranging only from 25 to 40 percent.[6]

Most patients present with locally advanced disease, and only a third are candidates for resection at the time of diagnosis.[7] The prognosis is even worse for patients with unresectable tumors, among whom just five to ten percent can expect to survive for five years after diagnosis.[8]

Therapeutic options are limited in cases of unresectable disease or a recurrence that is not amenable to further surgery, and the most effective strategies for chemotherapy and radiotherapy in both resectable and unresectable disease are poorly defined.[4] These factors converge to make choosing treatment strategies for these patients one of an oncologist's most challenging tasks.[9]

A new treatment option, currently being investigated by a collaborative team of MUSC Health Radiation Oncology and Interventional Radiology faculty, may soon provide hope for ICC patients with unresectable disease.



An artist's depiction of radioactive microspheres being delivered to a tumor through its arterial supply.

The phase 1 study evaluates a combination regimen of current first-line chemotherapy, gemcitabine/cisplatin (gem/cis), with trans-arterial embolization using Yttrium 90 (TARE Y90) microspheres. The primary goal of the trial is to determine safe doses for using these two therapies in combination.

"While TARE Y90 has been combined with chemotherapy to improve disease control in the liver for colorectal cancer liver metastases, this is the first time TARE Y90 has been combined with gemcitabine and cisplatin in the hope of prolonging survival in patients with ICC," explains MUSC Health radiation oncologist S. Lewis Cooper, M.D., the principal investigator for the study.

The trial's novelty lies not only in the combination of chemotherapy and radiotherapy, but also in the radiation delivery system that directly targets liver tumor cells from inside the liver parenchyma — in other words, radiation therapy that is delivered from the inside out.

"Our Interventional Radiology colleagues introduce a catheter into the wrist or groin and feed it to the hepatic arteries," explains MUSC Health radiation oncologist **David T. Marshall, M.D.**, a co-investigator on the project. "Then we inject radioactive microspheres that are drawn by the hepatic artery blood flow into the liver and to the tumors in the liver."

This strategy for delivering radiotherapy to unresectable liver tumors has interesting advantages over traditional, external radiation treatments. Microspheres target tumor cells more accurately than traditional radiation treatments, thereby avoiding healthy liver tissue, in two ways.

First, the liver has two blood supplies — the portal vein that brings nutrients from the gastrointestinal tract and the hepatic artery that delivers blood from the aorta in the abdomen. Tumor cells obtain 70 to 80 percent of their blood supply from the hepatic artery, whereas hepatocytes (normal liver cells) obtain 70 to 80 percent of their blood supply from the portal vein.

"So, there's a physiological advantage if we infuse the spheres through the hepatic artery," explains Marshall. "We'll get more of them around the tumor than around the normal hepatocytes."

Second, tumors typically grow their own blood supply and are more vascular than normal hepatocytes. "So the tumors get a greater proportion of the spheres because of that as well," says Marshall.

In fact, MUSC Health has deep experience using this type of microsphere technology to embolize various tumor types.

In collaboration with their Interventional Radiology colleagues **Marcelo S. Guimaraes, M.D.**, **M. Bret Anderson, M.D.**, **Ricardo T. B. Yamado, M.D.** and **Juan C. Camacho, M.D.**, Cooper and Marshall have been using microspheres to radioembolize tumors since 2007. "We were the first hospital in the state to offer this option to our patients," says Marshall. "Between 150 and 200 patients have received intra-hepatic microspheres at MUSC Health."

The (liver tumor) study uses tiny resin microsphere beads that are coated with the radioactive isotope TARE Y90, a source of beta energy, that is permanently bound to them. Each microscopic sphere is approximately the diameter of a human hair — allowing millions to be injected into the liver during a single outpatient procedure.

"The spheres lodge in the microvasculature around the tumor and attack it in two ways, via radiation and by blocking its blood supply," says Cooper.

Initially, resin microspheres were used for colorectal cancers that had metastasized to the liver, but they've been used successfully in other tumors since then, including primary liver tumors such as hepatocellular carcinoma.

"They're only FDA approved for colorectal cancer metastasized to the liver but are used off-label for many other indications," explains Marshall. "So, this is a trial of one of those uses."

The radiation's effective range is only 2.5 mm from each resin microsphere, helping to spare normal, adjacent liver tissue from damage. The half-life of TARE Y90 is 64 hours, and all of the effective radiation is delivered by 14 days after injection.

Patients go home the same day they are treated and, while most experience some side effects, these are typically mild to moderate and include right upper-quadrant pain and flu-like symptoms, such as fatigue and nausea, which usually clear up in one to two weeks. There is some risk for more serious side effects, such as formation of a gastric or peptic ulcer, and, rarely, liver toxicity.

Cooper and Marshall hope that combining gem/cis and TARE Y90 — each of which extends patient survival for about a year — will buy more time for their patients with ICC.

"This is a novel treatment for ICC that's more than just chemotherapy. It combines the standard-of-care chemotherapy with a novel radiation approach. For patients with unresectable or unablatable ICCs, this is an excellent treatment option," says Marshall. "I have some patients who are seven to eight years from treatment with Y90 who are disease free."

The requirements for patients interested in entering the study reflect the nature of this therapeutic approach that is specifically directed to the liver. Patients should have adequate liver function, be able to tolerate a little injury from the treatment, and less than 70 percent of their liver should be replaced by tumor.

"In other words, at least 30 percent of the liver needs to be normal to make sure that, once we get rid of the cancer, patients will have enough normal, functional liver left," explains Marshall.

Also required is good access to the hepatic artery and the arteries that go into the liver. "And, we make sure the arteries don't branch into the GI tract because that would deliver too many spheres to the wrong place," adds Marshall.

Potential trial participants will undergo liver function tests to ensure that they can tolerate the treatment (average bilirubin below 2, albumin 3 or higher and near-normal liver inflammatory markers). "Finally, we need patients who don't have a lot of disease that has spread elsewhere because this will only treat disease in the liver," says Marshall.

Optimism about the potential benefit of this novel therapeutic approach has already led to an expansion of the phase 1 trial.

"Sirtex, the device company that makes TARE Y90, has been excited enough about this trial to fund opening it at other academic medical centers to help speed enrollment and move this combination treatment forward," explains Cooper. "We are in the process of opening the trial at three additional sites and will run those from the MUSC Hollings Cancer Center as well."

In the bigger picture, this study takes MUSC Health another step forward as an institution offering novel treatments for rare and orphan diseases that, typically, do not attract a lot of research attention.

"Unfortunately, patients with uncommon cancers often have limited treatment options, and there are relatively few clinical trials investigating novel treatments," says Cooper. "This is an exciting trial for patients with unresectable ICC whose treatment options are limited."

References

1 American Cancer Society. What is Liver Cancer? Available at https://www.cancer.org/cancer/liver-cancer/about/what-is-liver-cancer.html Last Medical Review: 03/31/2016. Last Revised: 04/28/2016.
2 Njei B. *Hepatology* 2014;60(3):1107-1108.
3 Shaib YH, et al. *J Hepatol* 2004 Mar;40(3):472-477.
4 Mavros, MN, et al. *JAMA Surg* 2014;149(6):565-574.
5 Valle J, et al. *N Engl J Med* 2010;362(14):1273-1281.
6 Endo I, et al. *Ann Surg* 2008 Jul;248(1):84-96.
7 Maithel SK, et al. *Cancer* 2013 Nov 15;119(22):3929-3942.
8 Giglielmi A, et al. *World J Surg* 2009;33(6):1247-1254.
9 Kennedy A. *J Gastrointest Oncol* 2014;5(3):178-189.

Dr. Jeffrey R. Winterfield, director of the VT ablation program at MUSC Health

Treating the Irregular Heartbeat

Expanded program provides the most advanced care for cardiac arrhythmias

BY LINDY KEANE CARTER

Ventricular tachycardia (VT) is a rapid and potentially life-threatening rhythm originating from the bottom chamber of the heart (ventricle). In patients with heart disease, VT deteriorating into ventricular fibrillation (VF) is the most common cause of the 450,000 sudden cardiac deaths in the United States each year.[1] Ventricular fibrillation is defined as a heart rate of more than 300 beats per minute in an uncoordinated rhythm, which is fatal within a few minutes if not defibrillated (shocked) back to a normal rhythm.

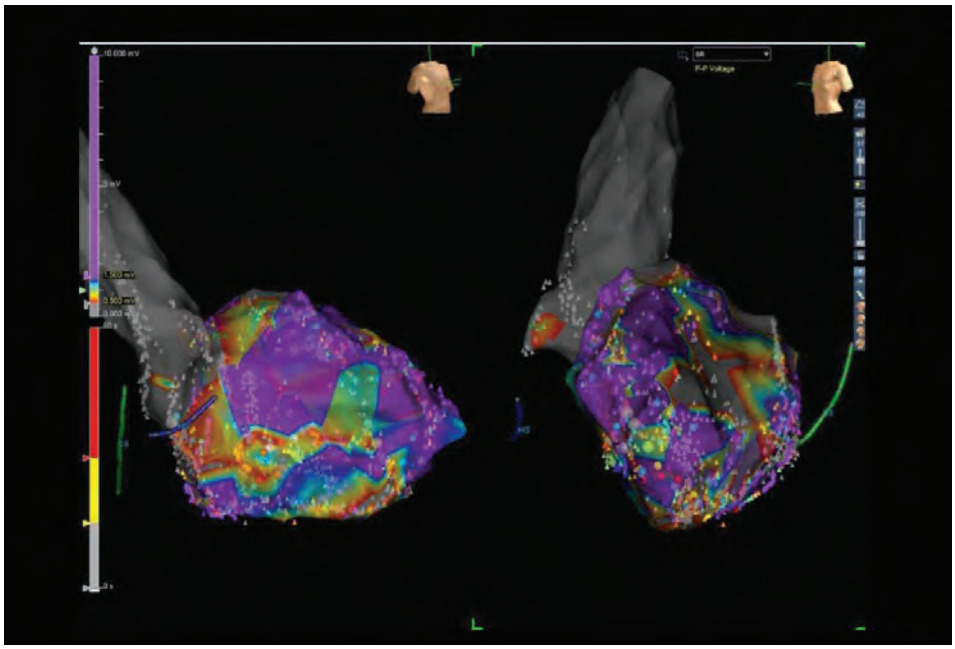
Treatment options for VT are an implantable cardioverter-defibrillator (ICD), antiarrhythmic medications, catheter ablation or some combination of these. Catheter ablation is indicated for VT patients for whom medications or ICDs have not been effective. During catheter ablation, radiofrequency energy cauterizes the "hot spots" from which the arrhythmias arise, preventing the electrical conduction that causes the irregular heartbeats.

As part of the expansion of the Heart & Vascular Center's comprehensive services in advanced heart failure, MUSC Health has named **Jeffrey R. Winterfield, M.D.**, as director of the VT ablation program. Winterfield comes to MUSC Health following five years as an assistant professor at Loyola University Medical Center in Chicago. During his fellowship training at Brigham and Women's Hospital and his faculty position at Loyola University Medical Center, Winterfield worked with William G. Stevenson, M.D., and David J. Wilber, M.D., respectively, two of the nation's leading experts in clinical cardiac electrophysiology.

In 2016, Winterfield was recruited to MUSC Health for his expertise in catheter ablation of complex arrhythmias, particularly VT, and premature ventricular contractions. He joins **Frank A. Cuoco, M.D., MBA**, associate professor of cardiology and director of cardiac electrophysiology, in performing VT ablation and other complex ablation procedures.

Patients for whom VT ablation is indicated include:

1. Those with a structurally normal heart in which the electric conduction is irregular (e.g., idiopathic ventricular arrhythmias or idiopathic premature ventricular contractions).
2. Those with a structurally abnormal or diseased heart. Advanced structural heart disease leads to weakened heart muscle and/or myocardial infarction (MI), which can cause ventricular arrhythmias. For example, following MI, the heart muscle forms scar tissue that can interfere with normal electrical impulse. In this setting, in which the scar tissue itself is interdigitated with surviving bundles of cardiac muscle cells, those bundles become the source of circuits for arrhythmias. During catheter ablation, the electrophysiologist locates those bundles and cauterizes them.
3. Those with normal, abnormal or diseased hearts who experience another kind of arrhythmia known as electrical storm, defined as recurrent episodes of VT or VF within a short period of time.



Two views of a heart affected by cardiac sarcoidosis, an autoimmune inflammatory disease, requiring ablation. Purple = normal; Red/Gray = severely scarred heart muscle.

MUSC Health has also invested in the expansion of catheterization laboratory space and the cardiac mapping technology that enables physicians to manage and treat irregular heartbeats. The Heart & Vascular Center is one of 12 heart centers in the U. S. to offer the newest generation of computerized mapping systems for treating arrhythmias with catheter ablation: the EnSite Precision™ cardiac mapping system (Abbott, Abbott Park, IL). The system enables physicians to visualize and navigate catheters in the heart while diagnosing and treating cardiac arrhythmias.

Winterfield and Cuoco are using the EnSite Precision™ system to treat atrial fibrillation, VT and supraventricular tachycardia. They are performing an average of four VT ablations a week.

"We're beginning to be able to map the cardiac chambers in three dimensions with high resolution and reduce the need for mapping in the arrhythmia to make the procedure safer," say Winterfield. "It's a very exciting time in this field. We are participating and developing trials to better address novel ablation tactics and tools for better outcomes."

This new technology uses intelligent automation tools and collects high-resolution data much faster than before, reducing patient and clinician exposure to fluoroscopic radiation. In addition, says Winterfield, "it allows us to see electrical signals in the heart to get a sense of how the heart is activating itself and how the electrical specialized conduction system of the heart is working in transmitting signals through the heart muscle."

MUSC Health has emerged as the highest volume center in the U. S. for application of this technology. Ablations have been successful in meeting prespecified endpoints in all cases, and no major procedural complications have occurred. In partnership with other academic institutions, MUSC Health will create a registry to track safety and outcomes data with this new technology and will conduct a study of a new procedural workflow to enhance ablation safety and outcomes with reduced procedure time.

Watch a video interview with Dr. Winterfield about VT ablation at the new MUSC Health Medical Video Center (http://MUSChealth.org/medical-video)

References

1 Tung R, et al. Circulation 2010;122:e389-e391.

Two decades of MUSC research suggest that an over-the-counter antioxidant could help those recovering from addiction avoid relapse by controlling intrusive thoughts

BY TONISHA KEARNEY-RAMOS, PH.D. AND NOUHOU IBRAHIM, PH.D.
ILLUSTRATION BY EMMA VOUGHT

Restoring Choice

Addiction robs its victims of free will, leaving compulsion in its place. **Peter W. Kalivas, Ph.D.**, chair of the Department of Neuroscience (Research) at the Medical University of South Carolina (MUSC), has spent two decades elucidating the biological mechanisms underlying that compulsion and identifying a means to restore choice.

The answer could come in the form an inexpensive, over-the-counter oral antioxidant called N-acetyl-cysteine (NAC), which he has shown in preclinical models to help prevent reinstatement of drug seeking by acting on a pathway whose importance in addiction he helped identify. Excitement over his findings has led to studies worldwide to test NAC's efficacy in a wide variety of addictions and compulsive disorders.

Clinical investigators at MUSC have worked closely with Kalivas to show NAC's potential for treating adolescent marijuana and alcohol abuse, smoking, cocaine addiction and for substance use that is comorbid with other compulsive disorders, such as posttraumatic stress disorder (PTSD). Collectively, their findings suggest that NAC, while not capable of causing an active user to cease taking drugs, can help those who are abstinent remain sober by reducing the intensity and frequency of intrusive, drug-seeking thoughts.

"NAC doesn't cure addiction," says Kalivas. "People still require therapy and have to relearn their life if they have been an addict for twenty years. But this drug will make it easier for them to relearn their life without drugs."

Their work could one day lead to an inexpensive and easily administered adjunct therapy to low-intensity psychosocial treatments for addiction. With its low cost and good side effect profile at therapeutic doses, NAC should translate easily to the primary care clinic, where it can benefit the most people.

But none of this would have been possible without decades of patient and tenacious basic science research to elucidate the underlying mechanisms of drug addiction and identify a drug target.

Hijacking the brain's reward system

The neurotransmitter dopamine is the primary currency of the brain's reward system. An action that elicits an increase in dopamine is experienced as pleasurable. The brain "learns" to associate that action with reward. The pleasurable experience of natural rewards such as food and sex are signaled through dopamine release in the reward system as a way to ensure continued pursuit of actions that enable survival.

Drugs of abuse, however, put the reward system into overdrive by eliciting unnaturally high increases in dopamine release. As a result, the brain "overlearns" the association between taking the drug and reward. As that association is strengthened through continued drug use, it becomes increasingly difficult for the user to think of anything other than the drug.

Yet, while dopamine drives formation of the drug-reward associations, decades of research by Kalivas have shown that another neurotransmitter, glutamate, is also implicated in drug addiction. Typically, glutamate would be released in the synapse in response to cues that signal reward but would then be cleared by a glutamate transporter (GLT-1) — a protein that regulates glutamate signaling.[1] This balanced release and clearance of glutamate facilitates the brain's ability to fine-tune and adapt learned behaviors in response to environmental stimuli.

Kalivas has shown reduced numbers of GLT-1 transporters in animals using addictive drugs. As a result, the released glutamate is not cleared from the synapse and instead "spills over" into the extrasynaptic space, activating glutamate receptors in a broader area.

This spillover and broader activation of glutamate receptors cause the brain to attribute greater weight to actions related to drug use, thereby reducing the user's willpower — the ability to choose other actions in the face of intrusive drug-related thoughts. Continued dominance of drug-related thoughts and actions precipitates the compulsive drug-seeking and use behaviors that characterize drug addiction.

Kalivas illustrates this hijacking of the brain by drug-related thoughts with an anecdote:

> I'm at work and my wife calls me and says 'Remember, I have to be out tonight, you've got to be home to cook dinner and help your daughter with homework.' So, I'm driving home, then I get a call from a buddy who's just arrived in town and everybody's meeting up at my favorite bar downtown. Now I've got two things, my wife's phone call and the phone call from my friend. So, what am I going to do? If I'm an addict, what happens is you've got these two competing plans, and pretty soon all I'm thinking about is that drinking plan, and the plan with my kids fades into the background. What we have been figuring out is how the drinking plan becomes the dominant, prepotent plan and causes the person to make the wrong choice — something that can be seen as a lack of willpower.

Target practice — Homing in on the NAC mechanism

The observation that the glutamate system was dysregulated in addiction sparked two decades of research by Kalivas. In a 1996 study published in the *Journal of Neuroscience*, Kalivas' laboratory showed that repeated cocaine administration in rodents produced sustained effects on glutamate release in the reward system, which resulted in glutamate spillover at the synapse. These findings — the first clear indication of drug-mediated glutamate dysregulation of the reward system — identified the glutamate system as a potential therapeutic target.[1]

Kalivas and colleagues next pursued the source of the glutamate spillover. In 2002, they published a study revealing the involvement of the cystine-glutamate exchanger, a protein known to play a role in regulating extracellular glutamate levels. They showed that withdrawal from repeated cocaine administration resulted in down-regulated cystine-glutamate exchangers, significantly altering extracellular glutamate levels.[2]

This led them to hypothesize that targeting the cystine-glutamate exchanger using NAC, a cystine precursor, might be a potential way to rebalance glutamate homeostasis — the balance between glutamate release and clearance — that is disrupted in addiction.

In 2003, Kalivas and colleagues published a study showing that restoration of cystine-glutamate exchange by NAC normalized the levels of glutamate in cocaine-treated rodents. On a behavioral level, reinstatement of drug seeking — the preclinical model of relapse — was prevented by stimulating cystine-glutamate exchange with NAC and restoring extracellular glutamate levels. This study demonstrated that it was possible to therapeutically alter the glutamate system and see a difference in addictive behavior.[3]

However, later work by Kalivas revealed that they may have been aiming at the wrong target. An article published in 2010 showed that repeated cocaine use reduces GLT-1, another regulator of extracellular glutamate, and that NAC inhibits cocaine seeking through restoring GLT-1 activity.[4]

The identification of an alternative pathway led Kalivas and colleagues to be less certain about their previously proposed mechanism of action for NAC in cocaine use. As a result, in 2015, Kalivas conducted a preclinical study directly aimed at disentangling whether NAC inhibits reinstatement of cocaine seeking through the restoration of GLT-1 and/or the cystine-glutamate exchanger. This was tested by determining whether blocking the ability of NAC to restore one or the other protein would prevent the ability of NAC to inhibit cocaine seeking. Kalivas discovered that restoring GLT-1, but not the cystine-glutamate exchanger, is the key mechanism by which daily NAC administration reduces cocaine reinstatement.[5]

Through many years of dedicated research and persistence in the face of misidentified scientific targets, Kalivas was able to uncover the mechanisms critical to an understanding of how NAC works in the glutamate system.

Taking NAC to rehab

Kalivas's ground-breaking work — which could only have been accomplished in preclinical models — paved the way for human clinical studies by researchers at MUSC and elsewhere that have brought NAC to the forefront as a promising new treatment for those addicted to a wide variety of substances as well as those afflicted with other complex psychiatric disorders.

Cocaine

In 2007, Kalivas and **Robert J. Malcolm, M.D.**, professor of Psychiatry, Family Medicine and Pediatrics at MUSC, published the first two human clinical studies investigating NAC for treatment in

Dr. Peter W. Kalivas has spent two decades elucidating the biological mechanisms underlying the intrusive thoughts characteristic of addiction. Photograph by Brennan Wesley

substance abuse. These small pilot studies suggested early promise for NAC use in cocaine users by demonstrating that short-term NAC treatment could stop or reduce cocaine use, as well as cocaine craving.[6,7]

However, it was not until years later in 2013 that they published the first large-scale, double-blind, placebo-controlled clinical trial that truly enabled them to investigate the efficacy of NAC treatment in substance users. Cocaine-dependent participants (n = 111) were randomized to receive daily doses of 1,200 mg of NAC, 2,400 mg of NAC or placebo. Participants were followed for 8 weeks, with urine samples collected and tested for cocaine use at periodic visits.[8]

Overall, the primary results for the clinical trial were negative — they did not find reduced cocaine use for NAC-treated vs. placebo-treated participants. However, when only the subset of participants who had achieved abstinence at trial entry was considered, results favored the 2,400 mg NAC group relative to placebo, with the 2,400 mg group showing longer times to relapse and lower craving ratings.

While the trial failed to demonstrate that NAC could reduce cocaine use in actively using cocaine-dependent individuals, this was evidence that it could prevent relapse in individuals who had already achieved abstinence from cocaine by reducing intrusive thoughts (craving) about drug use.

"If you can get someone abstinent from cocaine and then put them on NAC, that is where it seems to help them over a placebo — as a relapse preventive agent but not a curative agent," Malcolm explains.

Marijuana

Marijuana use has spiked among adolescents, and yet current cessation programs, which rely primarily on psychosocial treatments, have yielded low rates of abstinence. Currently, there is no FDA-approved pharmacotherapy for marijuana use disorder.

Evidence that NAC could play a role in treating substance abuse led **Kevin M. Gray, M.D.**, a professor in the Department of Psychiatry and Behavioral Sciences at MUSC, and colleagues to conduct the first double-blind, randomized controlled trial to assess NAC as a potential pharmacotherapy for marijuana dependence in adolescents. The results of the study were published in the August 2012 issue of the *American Journal of Psychiatry*.[9]

Led by Gray, the eight-week trial randomized marijuana-dependent adolescents (aged 15-21) to either 1200 mg of NAC or placebo twice daily, along with twice-weekly contingency management (i.e., abstinence and adherence were rewarded with small cash payments) and a weekly cessation counseling session lasting less than ten minutes.

At the trial's end, participants receiving NAC were more than twice as likely to have negative urine cannabinoid tests as those in the placebo group (adjusted odds ratio: 2.4). In the NAC group, 41 percent of participants had a negative urine screen on the last day of treatment vs. 27 percent in the placebo group.

"This is the first fully powered trial of a pharmacological agent conducted in any age group to have a positive finding as an adjunct to psychosocial treatment, and it happened to be in kids," adds Gray.

Enthusiasm over these results in adolescents led the National Institute of Drug Addiction to fund Gray to lead a randomized controlled trial in adults, the findings of which he reported in April 2016 at the American Society of Addiction Medicine's annual conference in Baltimore, MD. Unlike the adolescent trial, the six-site, 12-week trial, which enrolled 302 adults, showed that the NAC group was no more likely than the placebo group to have negative urine cannabinoid tests (unpublished data; manuscript under review).

"The effects of NAC did not seem to translate from adolescents to adults, and so I put my thinking cap on to see what the differences might be," says Gray. "A key is that quantitative urine cannabinoid levels and years of regular marijuana use at baseline were much higher in the adult than in the adolescent trial. The threshold to have a treatment effect was much higher to reach. Neurochemically, we might have been doing the same thing, but maybe it wasn't quite enough." Medication adherence was also poorer in adult patients.

Subgroup analysis of participants aged 18-21 in the multisite trial, however, suggested that those taking NAC were twice as likely to have a negative test as those in the placebo group, similar to the findings reported in the 2012 article.

"NAC-treated veterans were below diagnostic level for PTSD at the end of treatment. These are some of the best outcomes we have seen in the literature for a medication." —Dr. Sudie Back

The next step for Gray is to replicate the adolescent trial using low-intensity cessation counseling but without contingency management. The low-intensity counseling mirrors what would be widely available in primary care clinics where many adolescents seek care. If the findings are positive, NAC should be poised to translate easily into front-line care as an adjunct therapy for marijuana use disorder.

In a secondary analysis of the data obtained from the first adolescent marijuana trial, **Lindsay M. Squeglia, Ph.D.,** an assistant professor in the Department of Psychiatry and Behavioral Sciences, and Gray showed that, instead of compensating for reduced marijuana use by drinking more, the NAC-treated group actually decreased its alcohol use as well.[10] This is particularly compelling given the participants were not actively attempting to reduce their alcohol use, nor were they engaged in a combined behavioral treatment for alcohol use. These findings suggest NAC effects may generalize from marijuana to other substances and could be useful in decreasing adolescent alcohol use.

Nicotine

MUSC investigators interested in tapping NAC's potential to develop new therapies for nicotine addiction, including Gray, **Brett E. Froeliger, Ph.D.**, of the Department of Neuroscience, and **Erin A. McClure, Ph.D.**, of the Department of Psychiatry and Behavioral Sciences, noted that the design of clinical trials of NAC did not always map onto preclinical findings. Preclinical studies conducted by Kalivas and others had shown NAC to be effective at preventing reinstatement of drug-seeking behavior after a period of extinction, and yet many NAC trials were focused instead on cessation in active users. The MUSC team hypothesized that NAC would be more effective if given to smokers who had achieved at least a brief abstinence.

In 2015, they published the results of a small proof-of-concept trial that randomized 16 non-treatment-seeking smokers, who were paid to remain abstinent, to NAC or placebo for 3.5 days.[11] On day four, participants underwent functional MRI imaging. The NAC group reported less craving than the placebo group, and neuroimaging suggested that NAC positively affected the dysregulated corticostriatal connectivity characteristic of addiction.

This early evidence of NAC's potential efficacy in abstinent smokers led the group to wonder if it could prove a powerful adjunct therapy for varenicline (VAR; Chantix®, Pfizer, New York, NY), the front-line pharmacotherapy for smoking cessation.

"Compared to all smoking cessation therapies, VAR is far and away the best, but the majority of smokers that use VAR still relapse," says Froeliger. "It helps people quit (smoking) but does not do as good of job at keeping them off cigarettes."

Since VAR and NAC use different mechanisms of action, the nicotine addiction research team at MUSC hypothesized that combining VAR, which acts on the cholinergic pathway to promote cessation, and NAC, which acts on the glutamate pathway to prevent relapse, could synergistically promote long-term abstinence at higher rates in smokers than either medication alone.

In 2015, they published the results of a pilot trial in 19 adult cigarette smokers that suggested the combination regimen was safe — most side effects were mild and in line with what would be expected of the individual agents — and well tolerated and that it was feasible to take it forward into clinical trial.[12]

The group then launched a clinical trial of the combination therapy in 2015 that will eventually enroll 100 smokers. Now in year two, the trial has already enrolled a quarter of those patients.

To ensure that clinical trial design is aligned with preclinical findings of efficacy and that preclinical studies are informed by real-world results, the project's principal investigators include Kalivas, who will focus on understanding the neurobiological basis of NAC/VAR in a rodent model; Froeliger, a cognitive neuroscientist who will focus on imaging of human brains to explore whether NAC/VAR works on similar circuits in humans as in rodents; and Gray, who will lead the clinical trial. The ultimate goal is to compile the preliminary data needed to take the combination therapy forward into a much larger randomized clinical trial that would be powered to show efficacy and potentially gain FDA approval for a new smoking cessation approach.

PTSD with a comorbid substance use disorder

NAC may also have a role to play in the treatment of psychiatric disorders characterized by intrusive thoughts, such as PTSD, in which the glutamate pathway is dysregulated, as in addiction. Because NAC acts to restore balance to the glutamate system that is disrupted in both addiction and PTSD, researchers at MUSC hypothesized that it could potentially benefit patients with addiction and comorbid PTSD. Currently, there are no well-explored pharmacological treatments for patients with co-occurring addiction and PTSD, a particularly difficult-to-treat population.

Sudie E. Back, Ph.D., a professor in the Department of Psychiatry and Behavioral Sciences at MUSC and a staff psychologist at the Ralph H. Johnson VA Medical Center, randomized 35 veterans with an alcohol or drug use disorder and comorbid PTSD, all of whom were receiving group cognitive behavioral therapy (CBT) for their addiction, to either 2400 mg/day of NAC or placebo for eight weeks.[11] To be included, veterans had to have abstained from substance use for at least seven days. This was the first randomized controlled trial of NAC as a pharmacotherapy for PTSD and a broad range of comorbid addictions.

NAC plus CBT reduced symptoms of PTSD, cravings and depression significantly more than CBT alone in these veterans. Veterans in the NAC-treated group showed a 46 percent reduction in scores on the Clinical-Administered PTSD Scale (CAPS), a gold-standard measure of PTSD symptoms, vs. a 25 percent reduction in the placebo group. The threshold CAPS score for diagnosis of PTSD is 50 and "as a group, the NAC-treated veterans were below diagnostic level for PTSD at the end of treatment," says Back. "These are some of the best outcomes we have seen in the literature for a medication."

The NAC-treated group saw greater decreases than the placebo group in craving (81 vs. 32 percent) and depression (48 vs. 15 percent). "Craving is a key component of substance use and relapse," says Back. "If you have a medication that can really reduce craving, that will go a long way to helping people stay clean and sober."

It is important to note that both groups received CBT and that NAC appears to work best in those who are at least briefly abstinent. As such, NAC should not be used as a monotherapy or substitute for evidence-based behavioral treatment but instead be seen as a medication that can be added to therapy to help patients with addiction and PTSD attain positive outcomes.

The positive results seen in the pilot study of NAC among veterans with PTSD and addiction led the Department of Defense and the National Institute on Alcohol Abuse and Alcoholism to fund Back, Gray, Kalivas and colleagues at MUSC to conduct two larger-scale, randomized controlled trials in veterans and civilians with alcohol use disorders and PTSD. Both projects were initiated in 2016 and are currently enrolling participants.

Can we cure addiction?

Two decades of preclinical research with NAC is coming to clinical fruition. Collectively, these trials suggest that adding NAC to standard-of-care psychosocial therapies could help prevent relapse in those who have achieved at least short-term abstinence from a variety of addictive substances. And yet, NAC is far from a cure for addiction.

"To think that we will cure drug addiction tomorrow is to say we will get in a space shuttle and colonize the moons of Saturn. We can conceive it, we can almost taste it, we can see how we could get in orbit and maybe do it. But it's really quite a long way away — probably decades away," explains Kalivas. "And that's where we are with the brain. We have to understand how the brain works to develop the really precise interventions that will cure psychiatric disorders. For the brain, that's 20 billion cells and 100 trillion connections. That will take time, and we will just never get there without preclinical research."

References

1. Pierce RC, et al. *J Neurosci* 1996;15:1550-1560.
2. Baker DA, et al. *J Neurosci* 2002;22:9134-9141.
3. Baker DA, et al. *Nat Neurosci* 2003;6(7):743-749.
4. Knackstedt LA, et al. *Biol Psychiatry* 2010;67(1):81-84.
5. Reissner KJ, et al. *Addict Biol* 2015;20(2):316-323.
6. Mardikian PN, et al. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31(2):389-394.
7. LaRowe SD, et al. *Am J Psychiatry* 2007;164(7):1115-1117.
8. LaRowe SD, et al. *Am J Addict* 2013;22(5):443-452.
9. Gray KM, et al. *Am J Psychiatry* 2012 Aug;169(8):805-812.
10. Squeglia LM, et al. *Addict Behav* 2016 Dec;63:172-177.
11. Froeliger B, et al. *Drug Alcohol Depend* 2015;156:234-242.
12. McClure EA, et al. *Am J Drug Alcohol Abuse* 2015 Jan;41(1):52-56.
13. Back SE, et al. *J Clin Psychiatry* 2016 Nov;77(11):e1439-e1446.

Turning Point

Improving the Care of Young Adults With Sickle Cell Disease

BY JULIE KANTER, M.D., TEMEIA D. MARTIN, M.D., W. SCOTT RUSSELL, M.D., GREG A. HALL, M.D. AND KIMBERLY MCGHEE

ILLUSTRATION BY EMMA VOUGHT

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

- *Recognize that young adults with sickle cell disease are optimally co-managed by a sickle cell specialist and primary care provider*
- *Describe why a seamless transition from pediatric to adult care is crucial*
- *Discuss the importance of early aggressive opioid therapy in managing pain associated with vaso-occlusive episodes*

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Dr. Julie Kanter, Dr. Temeia D. Martin, Dr. W. Scott Russell, Dr. Greg A. Hall and Kimberly McGhee have no relevant financial relationships to disclose.

Sickle cell disease (SCD) was once considered a pediatric disease because patients rarely lived beyond childhood. Due to early diagnosis and improved medical management, many now live into adulthood. The health care system has struggled to serve this new adult SCD population, leading to an erosion of trust between patients and providers, but it is beginning to evolve to better meet their needs.

Young adults with SCD are particularly vulnerable to being lost to care as they transition from pediatric to adult providers. This is unfortunate because they are more likely to have chronic organ complications, including damage to the brain (stroke, silent infarcts), the heart (pulmonary hypertension), the lungs (fibrosis), the eyes (retinopathy), the bones (avascular necrosis) and the kidneys (renal failure).[1]

However, primary care physicians (PCPs) and hematologists willing and able to care for adult patients with SCD have been in short supply, causing affected adults to rely on emergency departments (EDs) for their care. According to an analysis of acute care utilization for patients with SCD, young adults aged 18 to 30 relied most heavily on EDs.[2] A 2013 needs assessment in South Carolina found that more than 70 percent of patients aged 18 to 35 years seen in the ED or hospital returned within 30 days.[3] Such episodic care is suboptimal and comes with a hefty price tag. In South Carolina, where the SCD burden is almost twice the national average (29.6 vs. 15.5 per 1,000 infants),[4] the cost was estimated at $43 million in fiscal year 2010[5] and $100 million in fiscal year 2014.

Bettering the lives of young adults with SCD in South Carolina while controlling costs will require a multi-pronged approach that includes informed and compassionate care by ED staff, robust transition counseling by pediatricians, enhanced training of adult providers in evidence-based best practices for SCD and innovative health care delivery models that will enable access to sickle cell specialists and closer collaboration between specialists and PCPs in the provision of coordinated care.

Mistaken identity

Most adolescents and young adults with SCD arrive at the ED in search of pain relief from vaso-occlusive episodes (VOE), which are the hallmark of SCD. VOE occur when the sickled red blood cells, along with white blood cells and platelets, block the microcapillaries and prevent blood flow and oxygen from reaching tissues. These blockages cause intense pain but also injure the affected tissue and, over time, can cause organ damage and premature death.

Aggressive opioid management, ideally administered in accordance with an individualized pain plan, is strongly recommended for treatment of VOE-associated pain by the 2014 National Heart, Lung and Blood Institute (NHLBI)–sponsored guidelines for the management of SCD.[6] However, the growing opioid epidemic has left ED staff wary of requests for narcotics, leading in some cases to those with SCD being mistaken for drug seekers.

"A review of the literature makes it very clear that those with sickle cell disease have a baseline level of pain that they live with that none of us can fully understand," says **W. Scott Russell, M.D.,** medical director of pediatric emergency medicine at MUSC Children's Health.

The pediatric and adult emergency medicine teams have worked closely with hematologist **Julie Kanter, M.D**., who also serves as the director of sickle cell research, and her team to develop specific order sets and treatment protocols for these patients. "We train our staff to trust those protocols to ensure these patients receive timely pain relief," adds Russell.

Communication between the ED and the patient's PCP and SCD specialist will also be crucial to ensuring continuity of care for these patients. "The electronic mecial record offers all providers the opportunity to communicate quickly so that young adults can continue the care they have been receiving up until age 18," says **Greg A. Hall, M.D.**, medical director of the adult ED.

Improving the transition from pediatric to adult care

For adolescents with SCD, the transition from pediatric to adult care can be both terrifying and confusing. They must leave behind a long relationship with a trusted physician to venture forward into what can seem the confusing maze of adult health care. To help allay their fears and prepare them for the change, pediatricians should begin discussing transition early with patients and their families, certainly by the time the child is 12 or 13, and continue throughout the adolescent years. Topics should include differences between pediatric and adult care systems, strategies for navigating and paying for adult care, self-management skills and the importance of self-advocacy. Tours of adult care facilities can remove fear of the unknown. Ideally, the pediatric hematologist should assist in locating an adult provider and should "co-manage" the affected adolescent initially to enable him or her to become more familiar and comfortable with adult care.

Adult primary care practices can act as a patient-centered medical home (PCMH) for young adults with SCD, providing them a personal and ongoing relationship with an adult PCP that can ease the anxiety accompanying the transition from pediatric care. A PCMH can closely monitor young adults and offer them primary and secondary preventive strategies to improve their overall outcomes, reduce their risk of complications and decrease their reliance on the ED. A PCMH can help coordinate care with subspecialists (including a hematologist), ED physicians and in-patient physicians to provide seamless care. For example, the PCMH for SCD at MUSC Health, directed by **Temeia D. Martin, M.D.**, prescribes and monitors specialized disease therapy, including hydroxyurea (HU) and iron chelation therapy, and supervises long-term transfusion and anticoagulation programs in collaboration with pharmacy specialists. Additionally, it provides management for acute pain and other complications of disease, including access to intravenous narcotics, hydration and other treatments at a fraction of the cost of ED visits.

SCD-specific specialty clinics that treat all ages are another approach to ensuring seamless care for young adults with SCD. This type of clinic allows affected patients to remain in the same outpatient setting with continuity of care provided by nurses, social workers and case managers. One example is MUSC Health's Lifespan Comprehensive Sickle Cell Center, which provides access to long-term transfusion therapy, intravenous pain management, hydration and disease-modifying therapy in a specialty environment. "This is one of the only clinics that treats patients with SCD from cradle to grave in one place in an effort to decrease loss to follow-up and care," explains Kanter, who serves as its director.

Whether accomplished via improved transitional counseling, establishment of PCMHs or access to an SCD-specific clinic that accepts all ages, successful transition to adult care is key to better outcomes for young adults with SCD and for reducing their ED use.

Better educating adult providers

Transition programs can only be successful if there are adult providers willing and able to provide SCD care. Young adults with SCD who receive preventive care by a knowledgeable PCP in close collaboration with a sickle cell specialist are less likely to rely on the ED for their care. Indeed, a recent study showed that those who received such comprehensive care had half the number of ED visits and hospitalizations as those without it.[8]

Preventive care comprises immunizations, regular screening and HU treatment for eligible patients.[6] Adult patients with SCD should receive a single dose of *Haemophilus influenzae* type b vaccine, two doses of the meningococcal ACWY vaccine 8 to 12 weeks apart, the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine (with revaccination five years later). They should also undergo an annual dilated eye examination to screen for retinopathy, an annual echocardiogram to screen for pulmonary hypertension, regular monitoring of bones for evidence of avascular necrosis and regular screening for iron overload.

The 2014 NHLBI guidelines recommend HU therapy in all adults with sickle cell anemia (hbSS or hbSB0).[6] The only FDA-approved therapy that changes the clinical course of SCD, HU is a daily oral medication that has been shown to increase levels of fetal hemoglobin, reduce the frequency of VOE and improve survival.[9,10] Currently, HU remains underutilized,[5] in part because of concern for side effects and because some PCPs may be uncomfortable with their ability to prescribe and monitor it appropriately.

With proper monitoring and in collaboration with a sickle cell specialist, HU therapy can be safely implemented in primary care. Because HU can harm the developing fetus and can be passed through breast milk, it should not be prescribed in pregnant or lactating women, and both male and female patients receiving HU should practice contraception. HU should be discontinued at least 90 days prior to attempts to start a family. HU can cause a decrease in the number of blood cells in the bone marrow and so requires monitoring of blood cell counts, but no HU-related infections have been reported. Patients should be screened with full blood panels and renal and liver function tests before beginning therapy and monitored monthly for the first year for dosage titration. If absolute neutrophil counts drop below 2000/ L and platelet counts below 80,000/ L, HU therapy should be temporarily discontinued until levels return to normal and then resumed at a dose reduction of 5 mg/kg/d.[6]

New models of health care delivery

Co-management by an adult PCP and a sickle cell specialist is optimal for those with SCD, but specialists tend to be located in urban centers while many patients and their providers, especially in South Carolina, are located in rural regions. Project ECHO, developed at the University of New Mexico for hepatitis C, adopts a telementoring model for training more front-line providers in specialty care. Following the ECHO model, Kanter's Lifespan clinic serves as the hub of the (SC)^2 network (sc2.org), which extends across the state. Each of the spokes is initiating a sickle cell center with a PCP trained in SCD care as well as an infusion center to work with Kanter via telemedicine to provide disease-specific management for affected adults. This innovative health delivery system promises to make evidence-based, coordinated care for SCD a reality in the state by overcoming issues of access and training a new generation of providers.

References

1. Kanter J, Kruse-Jarres R. *Blood Rev.* 2013 Nov;27(6):279-87.
2. Brousseau DC, et al. *JAMA* 2010 Apr 7; 303(13):1288-1294.
3. Schlenz AM, et al. *Public Health Rep.*2016 Jan-Feb;131(1):108-116.
4. Ojodu J, et al. *MMWR* December 12, 2014: 63(49):1155-1158.
5. Lòpez-De Fede A., et al. Sickle cell disease and SC Medicaid recipients: SFY 2010 factsheet. Columbia, SC: University of South Carolina. 2012.
6. Yawn BP, et al. *JAMA*. 2014;312(10):1033-1048.
7. DeBaun MR and Telfair J. *Pediatrics* 2012;130:926-935.
8. Wolfson JA, et al. *Pediatr Blood Cancer*. 2012;58:66-73.
9. Charache S, et al, *N Engl J Med*. 1995 May 18;332(20):1317-1322.
10. Le PQ, et al. *Pediatr Blood Cancer* 2015; 62: 1956-1961.

Interview

An Interview with MUSC Hollings Cancer Center's New Director

Gustavo W. Leone, Ph.D.

Gustavo W. Leone, Ph.D., began his appointment as the new director of the MUSC Hollings Cancer Center on March 1. As director of the state's only National Cancer Institute (NCI)-designated cancer center, Leone will oversee patient care and lead cancer-related research efforts.

Leone earned his doctoral degree from the University of Calgary and completed a postdoctoral fellowship at Duke University in 1998 before joining the NCI-designated James Comprehensive Cancer Center at The Ohio State University. In his leadership positions as director of the Solid Tumor Biology Program and associate director for basic research, he was instrumental in the rise of the James Comprehensive Cancer Center to the top tier of all cancer centers.

Progressnotes (PN) spoke with Leone.

PN: What attracted you to MUSC?

First, the basic sciences here are really quite strong and that gives you a platform to spring from. Second, the leadership, right from the president, provost and MUSC Health CEO down to the deans and Hollings Cancer Center, are aligned, and I thought that was a real strength and a sign that this is a place where change and growth can be implemented. I thought, "they are ready for this."

PN: What are some of your immediate goals for Hollings?

We are going to place a large investment in the recruitment and retention of physician-scientists — physicians who are doing research that can be translated into the clinic. Increasing investigator-initiated clinical trials is another area we need to focus on because, in the end, much of the basic research has to end with fruitful clinical trials that inform patient care. We should be leading the way towards new therapies, and we can only do

that if we have strong basic sciences and an innovative clinical trials portfolio here.

PN: What are your long-term goals for Hollings?

Charleston is a beautiful city with a rich history, great food and a vibrant arts scene, and it's becoming a center for advanced technologies and businesses. We need a health care system and research institute here that shine as brightly as any of that, if not brighter, to complete the package.

To do that, we first need to become world leaders in key areas of basic and clinical research. People are very savvy about their health care and are becoming savvier. They demand the latest, most innovative therapies from their local health care providers. Thus, our second goal is to develop state-of-the-art clinical care that can only be delivered by, or in partnership with, NCI-designated cancer centers such as Hollings, where expertise in advanced clinical trials is homegrown. If we succeed in attaining scientific eminence and developing advanced clinical trials, the third goal would be to take advanced clinical care to the rest of South Carolina. If we can accomplish all of this, then Hollings and South Carolina would serve as a model for how cancer centers and communities can work together to elevate cancer care across underserved populations in states with relatively modest resources.

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

Molecular epidemiology, for one. For the most part, we don't yet know which of us is more or less susceptible to cancer and what the underlying reasons for these predispositions might be. If we knew, that would be an empowering, life-saving advantage. We could provide patients who are more susceptible to colon cancer with the necessary preventive measures, such as annual colonoscopies. But right now, for the most part, we don't know. It's a wait and see situation — I would rather know instead of waiting to see. Another strong area at Hollings is immunology and immunotherapy and I'd like to build on that. I would also like to strengthen our efforts in chemical and structural biology. These are fundamental sciences that tell us about the structure and chemistry of molecules to a degree of precision that enables successful drug design.

PN: What motivates you as a cancer researcher?

That moment of exhilaration when you first discover something new — it provides an elation I cannot describe. For a brief moment, you know something that no one else in the world knows. It's an addiction that is probably like any other chemical addiction. You don't know you have it until you experience it and then you can't get enough.

What we accomplish scientifically today will provide stepping stones to what might be known 50 to 100 years from now. If we accomplish the goals that we are setting here at MUSC Hollings Cancer Center in the next five to ten years, the people of South Carolina will experience the positive health outcomes for generations to come and will know that Hollings is supporting every family's well-being. It's not an opportunity that most people get a chance to experience. We have the opportunity to do it here and I am privileged to be a part of it.

PN: Tell us about your own research.

There are two broad areas. One is understanding the regulatory mechanisms that control cell division. A cell that divides has to replicate its genome, the blueprint of what and who we are. After the genome duplicates, the cell divides and separates the two genomes equally into two daughter cells. This is incredibly complex and highly regulated because it has to be 'perfectly' executed. It has to be precise because, in the duplication and separation steps, any mistake could lead to a platform for genetic mutations. We know many of the critical molecules that are involved in that division but we don't know how they work exactly. So we are developing tools to understand how these proteins turn genes on and off, how they work individually and how they work together as a group. As it turns out, these "control" proteins are deregulated in almost all cancers. After all, unregulated cell division is one of the hallmarks of cancer.

Another side of cancer that we don't talk about much is that these tumor cells grow in the context of our body's other tissues and cells, such as blood vessels and immune cells that play normal roles in our general well-being. These microenvironments are typically inhibitory, so that every cell that has a mutation and goes wrong does not result in a cancer. But there are times when that environment is no longer suppressive but is either neutral or actually helps the tumor cells take off. That is why sometimes you can have a cancer for a long time and be okay and then there's a switch and that switch coincides with changes in the microenvironment. I find that fascinating. How do cancer cells talk with neighboring cells? We know some of the language that cells use to communicate with each other but relatively very little. Cell-to-cell communication is the second focus of my laboratory's research.

PN: Would you like to tell us something about your family?

I have two wonderful children, Anna-Maria and Marcelo Leone. One is going to medical school this year and the other has a master's in computer engineering. They are my soul.

MUSC Health Welcomes New Executive Chief Nursing Officer

Jerry A. Mansfield, Ph.D., RN, NEA-BC, joined MUSC Health in August 2016 as the executive chief nursing officer (ECNO) and the chief patient experience officer.

As ECNO, he will set the strategic vision for nursing and lead the effort for Magnet® redesignation. MUSC received Magnet® designation in 2015 and will apply for redesignation in September 2018. Only 7.7% of hospitals nationwide achieve Magnet® and only 3.3% earn redesignation.

As chief patient experience officer, he will ensure that patients receive quality, coordinated care across the enterprise. Mansfield thinks MUSC Health CEO Patrick J. Cawley, M.D., MHM, FACHE, described the role best at his interview as "somebody who gets up every morning and is thinking about patient experience as a significant part of his or her role."

Mansfield brings to the new position more than 30 years of health care experience, 11 years at OhioHealth and 20 years at The Ohio State University (OSU) Wexner Medical Center. He began as a bedside staff nurse, but his interest in having a broader impact on the quality of patient care led him into administration. "I wanted to improve the work environment where we practiced," says Mansfield. "My idea was if we improved that, we would help our patients and their families even more."

Before joining MUSC Health, Mansfield served as chief nursing officer (CNO) for two hospitals at The Ohio State University (OSU) Wexner Medical Center. His 20-year record at OSU is testimony both to his versatility and his willingness to embrace innovation. There, he served as the first CNO in a community-based hospital purchased by OSU, the first corporate administrator for quality, research, evidence-based practice and staff development for nursing and the first CNO for ambulatory services.

Photograph by Brennan Wesley

Dr. Jerry A. Mansfield

That taste for innovation will serve him well in his new combined role at MUSC Health. For Mansfield, combining the roles of ECNO and chief patient experience officer makes perfect sense because nursing care lies at the heart of the patient experience. He was attracted to MUSC Health in part because its leadership wholeheartedly agreed with that assessment. "To hear Chief Operating Officer Matt Wain say that 'Nursing is the group that spends the most time with patients in the most settings and thus has the greatest potential to impact the patient experience' edified my choice," says Mansfield.

Another personal goal of Mansfield is to align performance improvement initiatives underway at MUSC Health to improve population health. "I'd like to work with interprofessional teams and use our data analytics to help us understand our patient population better and increase our focus and strategy about those initiatives," says Mansfield. His experience in administration in inpatient, outpatient, for-profit and non-profit settings, along with a doctorate in public health, underpins that commitment.

Mansfield's ultimate aim is simple. "In the end, I want our employees and patients not to hesitate to recommend MUSC Health to family, friends and community members; there should be confidence that they will have a good experience here," says Mansfield. "They should feel absolutely certain regarding their choice of MUSC Health to meet or exceed their expectations of health care. Period. End of Story."

New Physicians

Mileka R.Gilbert, M.D., Ph.D.

Board Certification: Pediatrics // Specialty: Pediatric rheumatology // Medical School: University of North Carolina School of Medicine // Residency: Virginia Commonwealth University Health System // Fellowship: University of Texas Southwestern Medical Center

Marc R. Katz, M.D., MPH

Board Certification: Thoracic Surgery // Specialty: Cardiothoracic surgery // Special Interests: Mitral valve prolapse, mitral valve regurgitation, aortic stenosis, aortic regurgitation, cardiac valve surgery, left ventricular assist device (LVAD) care, cardiothoracic surgery, heart failure, heart transplant, tricuspid regurgitation // Medical School: Tulane University School of Medicine // Residency: Medical College of Virginia // Fellowships: Medical College of Virginia, Boston Children's Hospital

Emil A. Say, M.D.

Specialty: Ophthalmology // Medical School: University of Santo Tomas Faculty of Medicine and Surgery // Residency: University of Philippines - Philippine General Hospital // Fellowships: Wills Eye Hospital (ocular oncology), University of North Carolina (vitreoretinal surgery), Children's Hospital Los Angeles (pediatric vitreoretinal disease)

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