PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SUMMER 2017

Six pediatric programs at MUSC rank in *U.S. News & World Report*

MUSC Children's Hospital is once again the only such institution in South Carolina to be ranked among *U.S. News & World Report's* 2017-18 edition of "America's Best Children's Hospitals." The latest rankings are published online at http://health.usnews.com/best-hospitals/pediatric-rankings.

The leading specialties for MUSC Children's Hospital are: No. 11 for cardiology & heart surgery, No. 28 for nephrology, No. 36 for cancer, No. 37 for urology, No. 47 for gastroenterology & GI surgery and No. 45 for neurology & neurosurgery.

"These rankings represent a steadfast commitment by the entire children's hospital staff to delivering the highest-quality pediatric care in the region," says **Mark A. Scheurer, M.D.**, chief of clinical services at MUSC Children's Health.

Photograph by Brennan Wesley

MUSC Children's Health Chief of Clinical Services Dr. Mark A. Scheurer in conversation with a colleague

MUSC Health
Medical Video Center
MUSChealth.org/medical-video

A sampling of current videos:

The first robotic DIEP flap harvest for breast reconstruction was performed in February 2017 at MUSC Health by plastic surgeon **Kevin O. Delaney, M.D.**,and robotic surgeon **Rana C. Pullatt, M.D.**, who directs the robotic surgery program for the Department of Surgery. Dr. Pullatt narrates surgical video from the case.

Virgilio V. George, M.D., head of the section of colon and rectal surgery at MUSC Health, narrates footage from a **transanal total mesorectal excision** (TaTME), a new minimally invasive procedure for removing tumors of the lower rectum.

Jonathan R. Lena, M.D., a neuroendovascular surgeon at the MUSC Health Comprehensive Stroke & Cerebrovascular Center, narrates footage from a **thrombectomy performed in record time** — five minutes instead of the 40 to 45 minutes that is often required — using the new ACE68 catheter (Penumbra) and the ADAPT technique that was pioneered at MUSC Health.

Chief of Neurosurgery **Sunil Patel, M.D.**, discusses a rare case of **Bobblehead Doll Syndrome**. Characterized by a "yes-yes" head bob, the syndrome is often associated with cystic abnormalities in the third ventricle. Patel drained the cyst endoscopically.

PROGRESSNOTES

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On the cover: "Our DNA Landscape," an artistic play on a DNA-sequencing gel. Illustration by Emma Vought.

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

A NOSE FOR RESEARCH

MUSC's otolaryngology clinical trials program draws large industry investment

BY SVER AUNE

Photograph by Alison Padlan Gillette

Dr. Shaun A. Nguyen leads the ENT clinical trials program.

The clinical trials program for common ear, nose and throat (ENT) disorders in the MUSC Department of Otolaryngology-Head and Neck Surgery is among the top three academic ENT programs in the country for industry-sponsored research. Current investment in the program is at nearly five million dollars due to an emphasis on new devices and pharmaceuticals in addition to traditional surgical interventions.

During any given year, there are 15 to 20 clinical trials of all phases running in the department. Industry sponsors are always eager to gain new treatment indications for devices and drugs already approved by the FDA for other disorders, allowing several current trials to start in phase 3.

Partnering with industry in this way gives MUSC Health otolaryngologists an edge in clinical trials, according to **Shaun A. Nguyen, M.D.**, professor of otolaryngology, who leads the ENT clinical trials program. Nguyen was the first physician at MUSC Health to become a Certified Principal Investigator and was one of the first physicians in the country to be inducted as a fellow by the Academy of Physicians in Clinical Research.

"We have world-renowned surgeons, including **Paul R. Lambert, M.D.**, **Terrence A. Day, M.D.**, and **Rodney J. Schlosser, M.D.**, and the latest clinical trials in chronic sinusitis, head and neck cancer, hearing loss, Meniere's disease, obstructive sleep apnea and snoring," says Nguyen. "This gives our patients access to the best expertise and latest treatments."

Four clinical trials now in phase 3 at MUSC are helping patients with disorders that affect breathing while asleep or awake.

The THN3 trial (NCT02263859), sponsored by ImThera Medical, Inc., is recruiting patients with moderate to severe obstructive sleep apnea (OSA) for treatment with the aura6000 device. During sleep, the device stimulates four tongue muscles controlled by the hypoglossal nerve to more efficiently control the symptoms of OSA. The new device promises to provide an alternative to cumbersome continuous positive airway pressure masks.

A minority of patients who snore have OSA. For the rest, Zelegent, Inc.'s SILENCE study, which began recruiting patients in 2017 at MUSC and other institutions, is testing a new minimally invasive medical device to treat snoring by shortening, suspending and stiffening the patient's soft palate.

MUSC is also a trial site for a drug that may help people who have chronic sinusitis with polyps. Sponsored by Sanofi, the SINUS-52 (NCT02898454) trial is testing a new monoclonal antibody that blocks the type of inflammation from chronic sinusitis that leads to nasal polyps. The drug may prevent polyps from returning in patients who have already had surgery to remove them.

In addition to a large investment from industry, this flurry of clinical research is helping Nguyen and his colleagues train the next generation of clinical investigators. The department's three-month research rotation and yearlong clinical research fellowship program — one of the nation's first research training programs in otolaryngology — have attracted medical students and physicians from around the world.

"Our fellows gain a background in outcomes research and clinical trials," says Nguyen. "That combination is what makes our program so unique."

ADVANCING ADDICTION TREATMENT

MUSC Health offers a new implantable treatment for opioid use disorder

BY RACHEL WEBER

Thanks to the efforts of a multidisciplinary team of clinicians, MUSC Health is the first hospital in the state to offer patients with opioid use disorder maintenance treatment with Probuphine (Braeburn Pharmaceuticals, Princeton, NJ), a recently FDA-approved implant providing a constant dose of buprenorphine. This new line of treatment ensures good adherence and offers added convenience to the patient while decreasing the potential for abuse and diversion.

Psychiatrist **Sarah W. Book, M.D.**, prescribes the buprenorphine implants to eligible patients with opioid use disorder, and obstetrician/gynecologist **Angela R. Dempsey, M.D., M.P.H.**, who has expertise in contraceptive implants in women, performs the implantations. Dempsey performed the first implantation on May 1. Book and Dempsey, along with eight other MUSC Health physicians, went through the risk evaluation mitigation strategy training mandated by the FDA and provided by Braeburn Pharmaceuticals. Both have been working with pharmacy coordinator, **Amy Hebbard, PharmD**, to successfully navigate the logistical challenges of bringing this new therapy to patients.

Fifteen years ago, buprenorphine, a partial mu-opioid receptor agonist, was approved by the FDA for the treatment of opioid use disorders. Partial mu-opioid agonists do not activate the mu receptors to the same extent as full agonists, such as methadone, allowing for a ceiling effect that decreases the likelihood of overdose.

The buprenorphine implant can remain in the patient's arm for six months, providing a consistent, low dose of medication without requiring the patient to take a pill. To qualify for the new implantable treatment, patients must be stable on a relatively low dose (8 mg or less) of buprenorphine for 90 days and be enrolled in an ongoing psychosocial intervention program. Initial studies showed similar plasma levels of buprenorphine and a significantly higher percentage of opioid-free urines for the entire six months in patients receiving the implant than in those receiving 8 mg/day of buprenorphine (86 vs. 72 percent).[1]

"Put the implant in and patients go interface with the world for six months without taking anything. I think there is a huge benefit to that," says Book. Additionally, there is an added convenience for patients, who do not have to refill a prescription for a controlled substance every month. In South Carolina, controlled substances can only be filled every 30 days, and written prescriptions must be given to the pharmacy. These regulations can create barriers to adherence, such as travel, lost medications and difficulties refilling prescriptions; they can also cause patients to feel stigmatized. Buprenorphine implants bypass these problems. Because no pills are involved, these implants also decrease the risk of abuse and diversion.

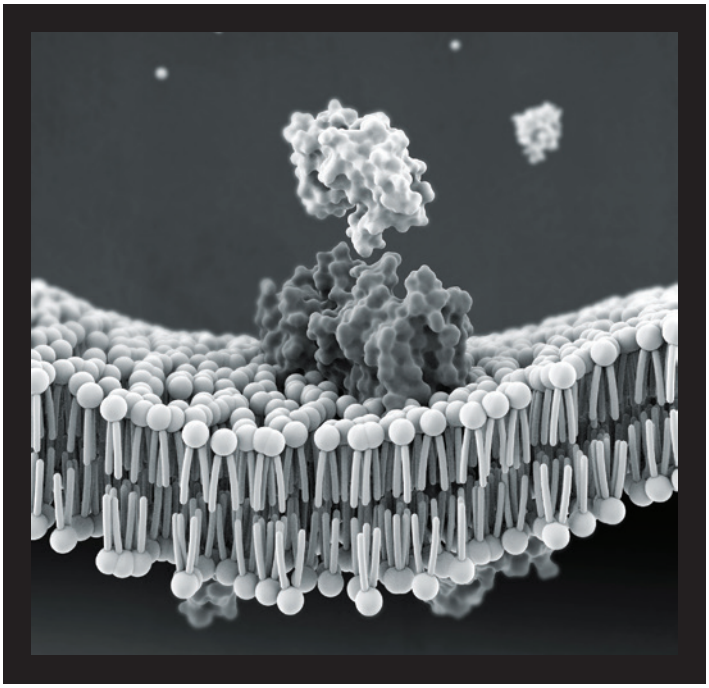


Illustration by Emma Vought

A rendering of buprenorphine being released from the implantable rod and binding to receptors

Patients continue regular follow-up in a psychosocial intervention for six months after implantation. Afterward, if it is deemed necessary, the patient can receive a second implant in the other arm.

Book wants patients and physicians to remember that there is hope in the treatment of opioid use disorder. "Medication-assisted therapy with buprenorphine is truly life changing," she says. "We have seen people in our treatment program regain the trust of their friends and family and regain their faith in themselves."

References

1 Buprenorphine Implants (probuphine) for opioid dependence. *JAMA*. 2016 Nov 1;316(17):1820-1821.

TO A "T"

Aspirin could augment adoptive T cell therapy for cancer

BY SVER AUNE

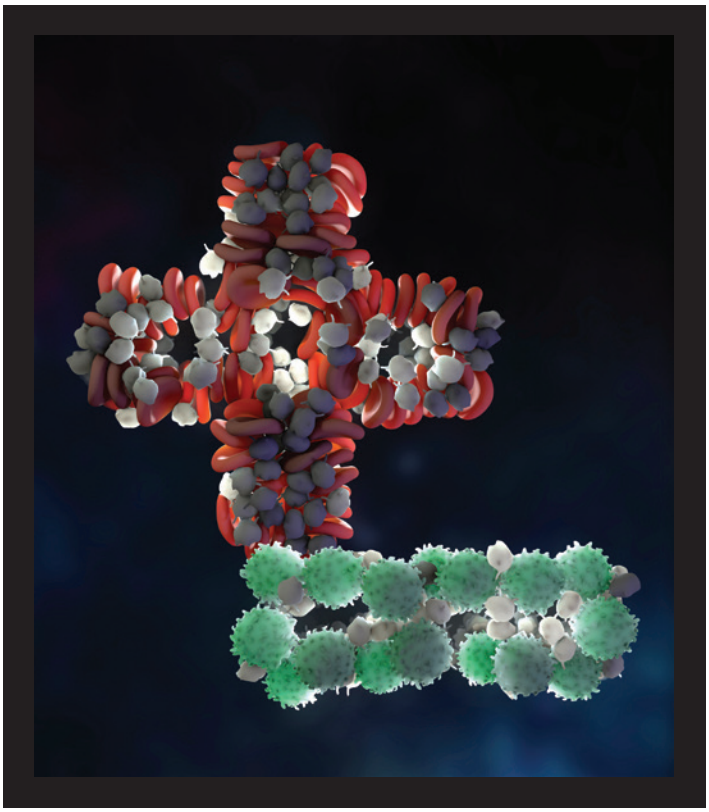


Illustration by Emma Vought

Stylized illustration of a T cell and platelet.

Blood platelets help disguise cancer from the immune system by suppressing T cells, according to a new study by MUSC scientists featured on the cover of the May 5, 2017 issue of *Science Immunology*. Adoptive T cell therapy more successfully boosted immunity against melanoma when common antiplatelet drugs such as aspirin were added.

Zihai Li, M.D., Ph.D., chair of the MUSC Department of Microbiology and Immunology, is senior author on the paper. Li studies how tumors hide themselves from the immune system. His team found that platelets release a molecule that suppresses the activity of cancer-fighting T cells. That molecule, unsurprisingly, was TGF-beta, which has been recognized for decades for its role in cancer growth.

Yet this study is the first of its kind. Li and his group found that the surface of platelets has a protein called GARP, a molecular hook that is uniquely able to trap and activate TGF-beta. With GARP, platelets are the major source of activated TGF-beta that invading tumor cells use as an invisibility cloak from the immune system.

There was some prior evidence that platelets might make cancer worse. For example, patients who have excessive clotting related to their cancer almost always have a worse prognosis, according to Li.

The first clue arose when the team gave melanoma to mice with genetically defective platelets. Tumors grew much more slowly and primed T cells were much more active than in mice with normal platelets. Next, they found that human and mouse platelets with activated clotting suppressed T cell activity. Mass spectrometry revealed that the molecule with the most T cell suppression was TGF-beta.

The investigators zoomed in closer to see how platelets actually activated TGF-beta. In genetically modified mice without GARP, platelets were not able to suppress cancer-fighting T cells. This finding was confirmed in similar experiments in mice with colon carcinoma. Finally, mice with normal platelets that were given melanoma and then adoptive T cell therapy survived longer and relapsed less when aspirin and clopidogrel, two antiplatelet drugs, were added.

The study could inform future treatment of melanoma and other cancers and offers a sound reason to test antiplatelet drugs in clinical trials of adoptive T cell therapy. Li and his group also want to know if combining antiplatelet drugs with checkpoint inhibitors can improve existing treatments for melanoma. They are waiting for approval for a clinical trial to test certain checkpoint inhibitors in combination with aspirin and clopidogrel in patients with advanced cancers. Li's trial will complement clinical trials that are already testing adoptive T cell therapy as a single treatment for cancer.

"I'm very excited about this," says Li. "We can test simple, over-the-counter antiplatelet agents to really improve immunity and make a difference in how to treat people with cancer."

TH17 T CELLS PROVIDE ROBUST CANCER THERAPY

Th17 cells generate long-lasting T cells for adoptive cell immunotherapy

BY KATHARINE HENDRIX

The March 2017 issue of *JCI Insight* published ground-breaking findings by a team of MUSC researchers showing that Th17 T cells are superior to the commonly used $CD8^+$ T cells for adoptive cell therapy (ACT). The Th17 T cells not only provided highly potent antitumor activity but also circumvented long-standing problems associated with rapid expansion.

ACT is highly effective in activating the body's immune defenses to fight cancer. This immunotherapy involves extracting, expanding and enhancing autologous T cells before reinfusing them into the patient where they can induce a complete and durable antitumor response. For example, approximately 54 percent of metastatic melanoma patients achieve an objective response with ACT, and 24 percent achieve complete remission.

The patient's cells are extracted and treated with a rapid expansion protocol (REP) to generate the very large number of T cells needed for a successful antitumor response. Even when state-of-the-art REPs are used, patients wait up to three months before enough tumor-reactive T cells are produced. Furthermore, $CD8^+$ T cells — which are commonly used for immunotherapy — quickly lose their cancer-fighting potency when they are extensively expanded outside the body.

Because Th17 cells have stem-cell-like properties (i.e., stem memory) and durable efficacy *in vivo*, MUSC investigators, under the direction of **Chrystal Paulos, Ph.D.**, associate professor of microbiology and immunology and Peng Endowed Chair of Dermatology, hypothesized that they would retain their potent antitumor effectiveness after long-term expansion. Using murine and human $CD4^+$ T cells polarized to a Th17 phenotype, they demonstrated for the first time that this T cell subset multiplies faster and resists degradation better during expansion than other commonly used cells. They found that, even without being restimulated, Th17 cells robustly expanded for 21 days *in vitro* — producing approximately 5,000 times the original number of $CD4^+$ cells. Furthermore, their stem memory signaling remained intact.

"In contrast to $CD8^+$ T cells, we found Th17 cells can be expanded to large numbers without compromising their therapeutic quality," Paulos explains. "Th17 cells have a natural propensity to logarithmically expand without restimulation. And restimulation didn't dramatically impair the antitumor response as with $CD8^+$ T cells. Our findings have major implications for the field of cancer immunotherapy."

Photograph by Sarah Pack

Cancer immunologist Dr. Chrystal Paulos

The Th17 cells resisted degradation (senescence) and remained capable of eliminating melanoma in mice after two weeks of *in vitro* expansion — something that Th1 and $CD8^+$ T cells could not accomplish. In addition, Th17 cells expanded for 14 days showed the same ability as those expanded for only seven days to persist in the tumor-bearing host after reinfusion. "Cytotoxic $CD8^+$ or Th1 cells were less effective at clearing tumor, whereas the Th17 cells persisted much longer. The durability of Th17 cells is due, in part, to their resistance to apoptosis and senescence," says Paulos.

Treatment with Th17 cells that were expanded for only two or three weeks rapidly and completely eradicated aggressive tumors in mice. "In just two weeks, we expanded enough Th17 cells to eradicate very large tumors, and they mediated durable responses," explains Paulos. "When we came back again 100 days later and gave the same mice lung tumors, they were all still protected." In all experiments, Th17 cells produced antitumor immunity superior to that provided by classic $CD8^+$ cells or $CD4^+$ subsets such as Th1 cells.

These findings are important for immunotherapy product development because Th17 cell durability provides a larger window for obtaining potent T cells through *in vitro* expansion. Th17 cell resilience could also simplify clinical trial protocols — making ACT T cell preparation easier for cancer centers around the world and, thus, extending the benefits of ACT to more patients.

PREMETASTATIC NICHE FORMATION

Primary colorectal tumors affect distant organs before cancer cells arrive on site

BY KATHARINE HENDRIX

Photograph courtesy of Dr. DuBois

Dr. Raymond N. DuBois

It is critical to better understand the mechanics of colorectal cancer (CRC) metastasis, as it is the second leading cause of cancer deaths in the nation. Patients with advanced cases often die because current treatments for widely metastasized disease are not effective.

Recent cancer research shows that premetastatic niches form at sites far from the original tumor before new tumors occur. In CRC, these supportive microenvironments form in preferred secondary organs, such as the liver and lung, and facilitate the colonization, survival and growth of metastasizing tumor cells. However, the mechanisms responsible for the formation of these premetastatic niches, including what role(s) the primary tumor may play, are not well understood.

MUSC investigators led by **Raymond N. DuBois, M.D., Ph.D.**, dean of the MUSC College of Medicine and professor of biochemistry and molecular biology, have now illuminated how primary CRC tumors contribute to premetastatic niche formation.

In an April 28, 2017 *Cancer Research* article (doi: 10.1158/0008-5472.CAN-16-3199), they report that primary colorectal tumors secrete vascular endothelial growth factor (VEGF)-A, inducing CXCL1- and CXCR2-positive myeloid-derived suppressor cell (MDSC) recruitment at distant sites and establishing niches for future metastases. Liver-infiltrating MDSCs help bypass immune responses and facilitate tumor cell survival in the new location. This research suggests CXCR2 antagonists may reduce metastasis.

"The idea that some sort of 'priming' needs to take place for metastasis to occur in distant organs — that there is some sort of activity in the future tumor location — is not new. But most research has focused on growth factors, chemokines and proinflammatory cytokines. There hasn't been much work looking at immune cell activity in distant organs prior to metastasis," explains DuBois. "We knew that the type and density of immune cells in the primary tumor play a role in progression. For example, when more immature myeloid cells are present in the tumor, it becomes resistant to immune attack. But we didn't know what to expect in a metastatic model."

To explore this area, the team first evaluated whether the presence of a primary tumor affected immune cell profiles in premetastatic liver and lung tissues of mice. They found that the presence of a primary cecal tumor caused MDSCs to begin infiltrating the liver before metastasis began. Working backward from this finding, they used a series of experiments to reveal the chain of events that led up to MDSC infiltration.

Because CXCR2 is essential for drawing MDSCs out of the bloodstream and toward CRC tumors and colonic mucosa, the team began looking for CXCR2 and its ligands in mouse liver tissue. The team not only found that the ligand CXCL1 attracted MDSCs from the bloodstream into premetastatic liver tissue, but also that administering a CXCR2 antagonist inhibited CXCL1 chemotaxis. This demonstrated that CXCR2 is required for CXCL1 to induce MDSC liver infiltration. Of importance, they also found that liver-infiltrating MDSCs secrete factors that promote cancer cell survival and

metastatic tumor formation without invoking the innate and adaptive immune responses.

Next, because VEGF is known to induce CXCL1 expression in lung cancer, the research team examined whether VEGF secreted by CRC tumors also regulated CXCL1 expression. Their results demonstrated that VEGF-A secretion by primary CRC tumor cells stimulates macrophages to produce CXCL1. Interestingly, although VEGF-A knockdown inhibited liver metastasis, it did not affect the growth of the primary tumor.

"We did not expect to find that a primary tumor could affect a distant organ before any of the cancer cells arrived on site," says DuBois. "We were surprised to see these changes before a single metastatic cell took up residence."

Together, these studies reveal that VEGF-A secreted by the primary CRC tumor stimulates macrophages to produce CXCR1, which recruits CXCR2-expressing MDSCs from the bloodstream into healthy liver tissue. The MDSCs then create a pre-metastatic niche or microenvironment where cancer cells can grow to form new tumors. These results demonstrate for the first time that cells in the primary tumor contribute to forming distant premetastatic niches, which facilitate the spread of disease.

"Now that we know the primary tumor puts things in motion remotely prior to metastasis, we should be able to inhibit this process and have a positive impact on survival," explains DuBois. "We now know which molecules and immune cells are involved and that, if we disrupt the CXCL1-CXCR2 axis, we can possibly reduce the spread of disease. Both antibodies and small molecules can inhibit this pathway, but they have not yet been optimized. I hope these findings will speed up the development of inhibitors of the CXCR2 pathway."

Innovations in the Management of Chronic Pancreatitis

A new textbook and an international conference share the latest advancements in diagnosing and treating chronic pancreatitis

BY LINDY KEANE CARTER

Chronic pancreatitis (CP), or long-standing inflammation of the pancreas, is a challenging disease for health care practitioners because it is difficult to diagnose and treat. CP is characterized by severe abdominal pain and irreversible damage to the pancreas.

Photograph by Brennan Wesley

Dr. Peter B. Cotton and Dr. David B. Adams

In the past decade, new medical and surgical treatments have emerged that enable multidisciplinary teams to better recognize and manage this disease. In 2014, MUSC Health gastrointestinal specialists led by **David B. Adams, M.D.**, professor of surgery and an expert in CP, organized the first international exchange of information on these advancements.

The 2014 International Symposium on the Medical and Surgical Treatment of Chronic Pancreatitis brought together experts from the fields of medicine, surgery, psychology, physiology, pharmacology and genetics. Conference presentations provided new research findings about the causes of CP and its pain pathways, updates on the endoscopic management of CP and updates on total pancreatectomy combined with auto islet cell transplantation.

In April, a textbook covering the information from that meeting was published. "Pancreatitis: Medical and Surgical Management" (Wiley-Blackwell) covers acute pancreatitis as well as CP. Adams is the chief editor and **Peter B. Cotton, M.D.**, professor of medicine at MUSC, is one of the co-editors. The book provides gastroenterologists and gastrointestinal surgeons with an evidence-based approach to the most recent developments in the diagnosis and clinical management of pancreatitis. In addition to new surgical procedures such as endoscopic biliary intervention and minimally invasive necrosectomy, these advances include medical therapies, such as antiprotease, lexipafant, probiotics and enzyme treatment.

"This book is the latest information from international experts in all of the relevant disciplines of medicine," says Adams. "This represents the first time all of these experts have come together to share their knowledge and experience."

MUSC will host a second international CP symposium in 2018 in Charleston, SC. International experts will exchange ideas and identify developments in the diagnosis and management of CP needed to enhance clinical effectiveness, encourage adoption by healthcare providers and engage patients in care. For more information, visit www.pancreatitissymposium.org.

3D ICAD PHANTOM

3D-printed model of stenotic intracranial artery enables MRI standardization

BY RACHEL WEBER

Photograph by Sarah Pack

Dr. Tanya N. Turan

A collaboration between stroke neurologists at MUSC Health and bioengineers at the University of Massachusetts has led to the creation of a realistic, 3D-printed phantom of a stenotic intracranial artery. It is being used to standardize protocols for high-resolution MRI, also known as vessel-wall MRI, at a network of U.S. and Chinese institutions, according to an article published online on March 9, 2017 by the *Journal of NeuroInterventional Surgery* (doi: 10.1136/neurintsurg-2016-012974). High-resolution or vessel-wall MRI has been used to study the plaque components in vessels in the brain for more than ten years and has the potential to elucidate the underlying pathology of intracranial atherosclerotic disease (ICAD), the leading cause of stroke worldwide, as well as to gauge patient risk and inform clinical trials of new therapies. However, progress has been stymied by the lack of standardization in high-resolution MRI protocols, which poses an obstacle to multicenter trials.

"There is a lot of exciting research that is possible with high-resolution MRI techniques, but it has much less opportunity to affect patient care if it can't be systematically distributed to multiple sites and multiple populations," says **Tanya N. Turan, M.D.**, director of the MUSC Stroke Division and senior author of the article.

To overcome this obstacle, Turan worked with bioengineers at the University of Massachusetts to produce a phantom of a stenotic intracranial vessel using imaging sequences obtained from a single patient with ICAD at MUSC Health. The 3-D-printed ICAD phantom mimics both the stenotic vessel and its plaque components, including the fibrous cap and the lipid core. The phantom is being shared with collaborating institutions so that it can be used to standardize high-resolution MRI protocols. The imaging data presented in the *Journal of NeuroInterventional Surgery* article were obtained from six participating U.S. sites and demonstrate the feasibility of using the phantom for standardization.

Producing the phantom was a major step in the right direction for standardizing high-resolution MRI ICAD protocols. However, several more years may be necessary to complete the process. The next major challenge for these investigators will be establishing parameters for MRI machines from a variety of manufacturers. So far, MRI parameters have been established for Siemens and General Electric systems but work is still under way on Philips systems.

The phantom is also being shared with sites in China, where the burden of intracranial stenosis is especially high. Turan and Weihai Xu, M.D., of Peking Union Medical College, the lead Chinese site, have received funding from the Fogarty International Center at the U.S. National Institutes of Health. Additional data from the U.S. and Chinese sites are being collected to assess interrater reliability among the participating institutions. Once high-resolution MRI protocols have been standardized and good interrater reliability demonstrated, the international team plans to conduct a prospective observational trial to examine risk prediction at participating centers in the U.S. and China, which would more quickly meet the required patient enrollment than would a trial conducted in the U.S. alone.

"We're only going to advance the field more quickly if we work together," says Turan. "The phantom gives us the tool to do so."

STEMMING BRAIN INJURY

Two clinical trials test stereotactic implantation of stem cells

BY SVER AUNE

MUSC Health is a surgical site for two nationwide phase 2 clinical trials to treat salvageable brain regions with modified stem cells following stroke or traumatic brain injury (TBI). The treatment could rehabilitate movement in patients with chronic motor deficits persisting years after injury.

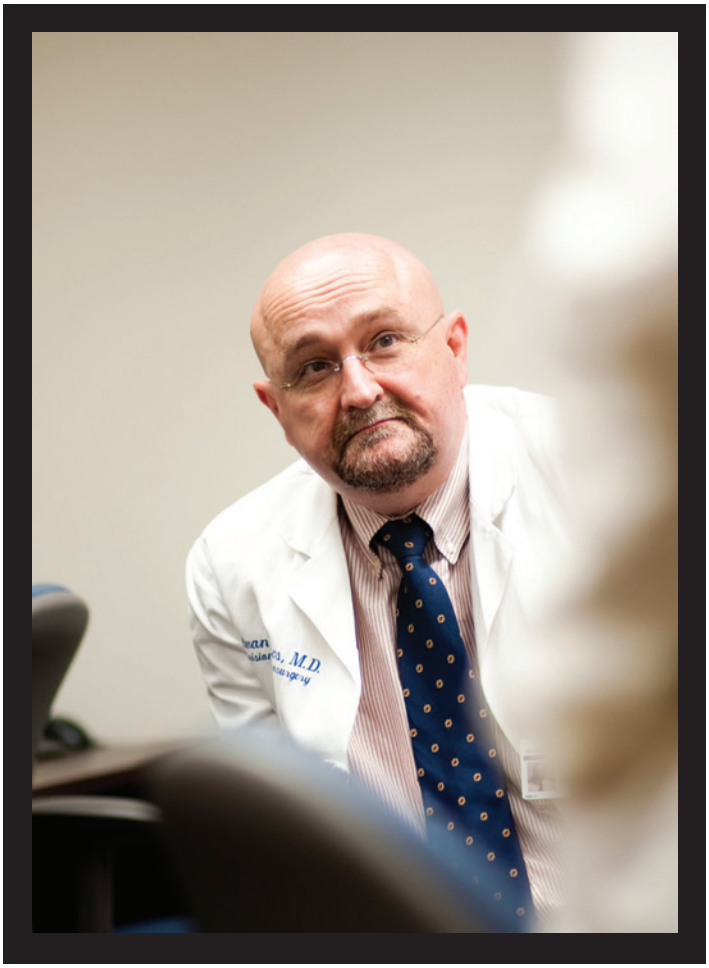
After stroke or TBI, brain cells in the vulnerable region next to dead cells — the ischemic penumbra — are vulnerable to inflammation and edema. When there is injury in regions that control motor function, the chances of recovering movement through rehabilitation drop as months pass.[1]

Researchers in the trials believe that recovery can be accelerated or extended within the ischemic penumbra. When injected in such a vulnerable region, the modified stem cells work by secreting factors that stimulate the brain's natural ability to repair itself, according to preclinical studies. They do not turn into brain cells, but rather help the stressed cells build strong connections with each other and with healthy cells.[2]

Not every site in the trials — the ACTIsSIMA trial for chronic ischemic stroke and the STEMTRA trial for TBI — has both the neurologists needed to comprehensively evaluate patients and the neurosurgical expertise to implant the modified stem cells in the correct brain regions. To address this, the trials include stereotactic surgeons at implant sites and neurologists at assessment sites who collaborate to evaluate and treat patients.

In those cases, MUSC Health neurosurgeon **Istvan Takacs, M.D.**, volunteers his stereotactic skills. In designing a treatment plan, Takacs works with neurologists to construct a computerized atlas of a patient's ischemic penumbra from MRI. Using the atlas as a guide, stereotactic surgeons such as Takacs use minimally invasive techniques to inject millions of modified stem cells into precise areas within the ischemic penumbra. Patients are followed closely thereafter with MRI and motor function tests.

Researchers in the trials do not expect the treatment to help patients recover all the movement that was lost after their stroke or TBI. Yet, in addition to speeding recovery after injury, the treatment might extend the time window during which recovery can be achieved through neurological and physical rehabilitation. In fact, patients who have had motor deficits for as long as five years are being accepted into the trials. Such deficits are usually considered permanent a year or two after injury, according to Takacs.



Photograph by Brennan Wesley

Dr. Istvan Takacs

"I don't think this particular stem cell therapy will cure brain injury, but it will perhaps take recovery a little farther than it would otherwise have gone, and it will reach that endpoint hopefully sooner," says Takacs.

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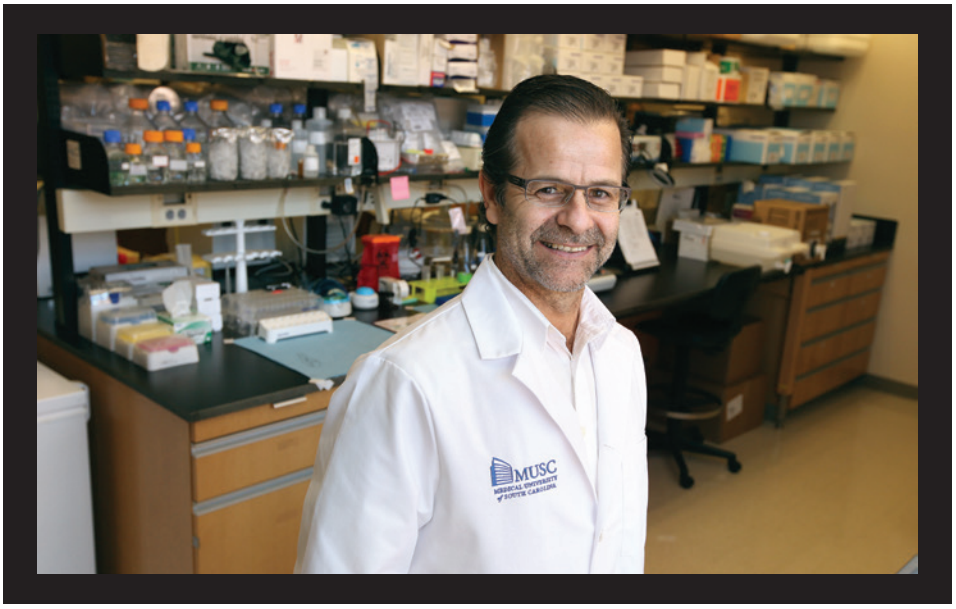
2 Steinberg GK, et al. *Stroke* 2016;47:1817-1824.

AN ELEGANS SOLUTION

Worm genetic screen maps cell-to-cell communication in human cancer

BY SVER AUNE



Photograph by Sarah Pack

Dr. Gustavo W. Leone

Some major cell-to-cell communication networks were first studied in worms. Now those worms, *Caenorhabditis elegans*, are being used to understand the influence of cancer mutations on those networks, report a team of investigators led by **Gustavo W. Leone, Ph.D.**, director of MUSC Hollings Cancer Center and the Grace E. DeWolff Endowed Chair in Medical Oncology, in an article in the May 22, 2017 issue of *Developmental Cell* (doi: 10.1016/j.devcel.2017.04.024).

Because many genes involved in cell communication are often conserved across species, *C. elegans* is an ideal organism to study the genes that influence them. This makes the worm a very useful genetic tool for exploring the basis of human cancer, according to Leone.

"If the genetic network within tumor cells or epithelial cells is similar among *C. elegans*, mice and humans, the communication of neighboring cells with epithelial cells in tumors at some level might also be similar," explains Leone.

Leone is corresponding author on the study along with his collaborator Helen Chamberlin, Ph.D., a *C. elegans* expert in The Ohio State University Department of Molecular Genetics. The two laboratories collaborated to approach a big-picture question about cancer. A number of important individual cancer genes have been discovered by Leone and many others, but is there a way to identify all of the genes — a genetic signature — involved in cell-to-cell communication in cancer? In particular, Leone sought to identify which genes within the neighboring cells that make up the tumor microenvironment could control tumor and epithelial cell proliferation.

Yet determining networks of cell-to-cell communication requires a genome-wide screen that tests genes individually, an approach that is impractical in mice.

This was where *C. elegans* became so essential to answering the group's question. Part of the tumor microenvironment is supported by mesodermal cells, which send molecular signals to epithelial cells that tightly control their proliferation. This mesodermal-epithelial communication is needed in normal conditions, such as during pregnancy and wound healing, but is disrupted in cancer. Similar communication exists between those cells in the egg-laying organ of *C. elegans* called the vulva. When similarly disrupted during worm development, this network can unleash epithelial cell proliferation that causes a multivulva, or Muv, feature. This feature, which becomes prominent when adult worms reach one millimeter in length, is easily visible under a microscope.

First author Huayang Liu, Ph.D., was a student in Leone's laboratory who helped design and build the genome-wide screen to identify which mesoderm genes worms need to prevent such Muv defects. Very importantly, the worms were also given a human cancer mutation in the *gap-1* gene to sensitize their epithelial cells to communication signals that encourage proliferation. In this way, the screen was designed to test the influence of each of the nearly 20,000 *C. elegans* genes on the proliferation of epithelial cells carrying a common cancer-sensitizing mutation.

From the entire *C. elegans* genome, the screen uncovered 39 worm mesoderm genes that, when reduced in expression, encouraged microscopic Muv defects suggestive of epithelial cell proliferation. Thirty-three of those genes are conserved in humans. Their identities were unexpected, according to the authors. They are

not involved in 33 random processes that control cell behavior. Rather, many of them converge on hubs of regulation that control major gene expression signatures.

It appeared that the mesodermal-epithelial communication network containing this 33-gene signature could be fundamental to cell behavior in worms. Yet was it relevant in higher animals? In fact, the group tested three of these 33 genes in female mice and found that reducing their expression within fibroblasts (another mesodermal-type cell) encouraged proliferation in mammary epithelial cells.

There was a final need to prove the relevance of this work to human cancer. Tests were performed in the stromal-part of the microenvironment of tumor samples taken from human breast cancer patients. As suspected, the expression of those 33 genes was very different between normal and tumor stroma. In further experiments, depletion of 22 of these genes in human fibroblasts encouraged proliferation of breast tumor epithelial cells.

The group had confirmed a genetic signature of mesodermal-epithelial communication unique to cell proliferation in cancer.

This study uncovered a small sector of the network that allows mesodermal and epithelial cells to communicate. Yet the screen is designed to work with many cancer-sensitizing genes other than *gap-1*, which can reveal more of the network. Leone's group has repeated the screen using another genetic mutation that seems to influence completely different cellular processes involved in cell-to-cell communication. A complete roadmap will guide new cancer therapies, according to Leone.

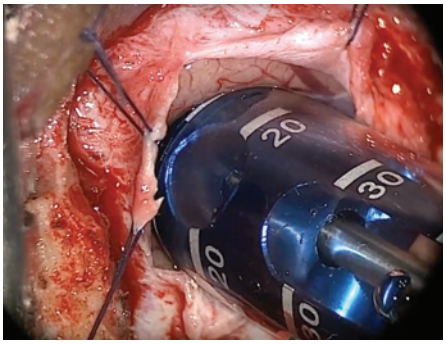
"This provides an avenue to understand why drugs work or don't work, and it provides new targets that we can now begin to drug," says Leone.

Triple Threat

All three minimally invasive techniques to evacuate hematoma after intracerebral hemorrhage are available at MUSC Health

BY KIMBERLY MCGHEE

MUSC Health neurosurgeons **Alejandro M. Spiotta, M.D.**, **Jonathan R. Lena, M.D.**, and **Raymond D. Turner, M.D.**, now offer all three minimally invasive surgical (MIS) options for evacuation of hematoma after intracerebral hemorrhage (ICH), the most deadly and debilitating form of stroke. Reducing hematoma volume after ICH could help improve survival and reduce disability. However, trauma to brain tissue caused by open surgical approaches outweigh any of the benefit over medical management gained by hematoma reduction. As a result, most patients with ICH are medically managed, but as many as half die from the disease and most become too disabled to live independently. MIS techniques for hematoma evacuation were developed to improve the odds for these patients and, if proven effective, could swing the balance from medical management toward surgical intervention.



Creating the surgical corridor with Brain Path

In contrast to open surgical approaches that require the neurosurgeon to make a large window in the skull and to dissect through healthy brain tissue to reach the hematoma, the newest technique — minimally invasive parafascicular surgery — necessitates only a tiny hole in the skull large enough to fit a 15-mm surgical tool called an obturator that gently parts brain tissue and makes way for the placement of the NICO Brain Path sheath. The obturator is then removed and the sheath acts as a corridor through which the hematoma can be accessed and evacuated.

Brain Path is the third-generation MIS technique offered by the neurosurgical team for this purpose. MUSC Health served as a site for the trials of two earlier MIS techniques for hematoma evacuation. The first involved a combination of MIS and clot lysis using tissue plasminogen activator (MISTIE II trial), and the second used a suction device (Apollo; Penumbra; INVEST trial) to evacuate the hematoma under endoscopic guidance. A definitive answer as to which of these three techniques achieves the best outcomes in these patients awaits the results of the MISTIE III, INVEST and ENRICH trials, but optimism is growing that hematoma reduction using MIS techniques could begin to reduce ICH-related mortality and disability.

"It is very rare for a center to have experience with all three of these techniques," says Spiotta. "We provide patients a lot of options."

Not Your Dad's Emergency Medicine

Emergency Medicine Interim Chair Dr. Edward C. Jauch

Photograph by Brennan Wesley

On July 1, Emergency Medicine at MUSC Health came of age, transitioning from a division to a full-fledged department. Interim Chair **Edward C. Jauch, M.D., MS**, sat down with *Progressnotes* to discuss how the specialty has evolved. Jauch, who has a more than 20-year career in Emergency Medicine and a research interest in neurosciences, is the lead author on the 2013 stroke guidelines from the American Stroke Association (ASA), a past chair of the ASA Stroke Council and the chair of the Stroke Advisory Committee for the South Carolina Department of Health.

PN: How has the definition of Emergency Medicine changed over the years?

The need for acute stabilization and resuscitation was first appreciated on the battlefields of the Korean and Vietnam Wars. Until the 1960s, emergency departments (EDs) in the U.S. were staffed solely by trainees, most of them interns. They weren't necessarily staffed 24/7 and there wasn't an established standard of ED care. But the military experience showed that specialized training and very early and aggressive therapies could actually save lives and reduce mortality and morbidity. Interest grew in creating a unique training experience, and the first programs were launched in the 1970s. Since 1979, the American Board of Medical Specialties has recognized Emergency Medicine and offers a specialty board certification. And so Emergency Medicine has evolved from care being provided by those without specialized training to care being provided by those with three of four years of formalized, dedicated training in Emergency Medicine.

PN: How has Emergency Medicine evolved at MUSC Health?

We have come a long way since the 1980s and 1990s when most of the emergency

care in the area was provided by Charleston Memorial Hospital. It wasn't until the 1990s that MUSC dedicated areas to provide emergency care.

Over the past 20 years, Emergency Medicine has evolved into a dynamic academic program. We now have fellowship-trained content experts in many domains, including ultrasound, emergency medical services, global health, event medicine, critical care and cardiology. We have **Nicholas J. Connors, M.D.**, one of only three toxicologists in the state. These content experts share their knowledge with the community and their colleagues on campus. Each faculty member has a liaison role with another division or department because this is critically important for establishing good transitions in care. A good example is that many pediatric patients will eventually need emergency services in the adult world. Building strong ties with our pediatric colleagues helps ensure that children with life-long conditions, such as autism, cystic fibrosis, congenital cardiac conditions or sickle cell disease, transition seamlessly from pediatric to adult emergency care.

Since 2007, we have been educating the next generation of Emergency Medicine physicians in our residency training program. Although the program has existed for only ten years, it attracts 1,200 residency applicants a year for just six positions. That reflects how well MUSC Health is viewed in the Emergency Medicine community. We have fellowships in ultrasound and global health, and we anticipate a fellowship in emergency medical services (EMS)/ prehospital emergency care in the near future.

PN: How do prehospital management experts interface with the community?
Every EMS or prehospital service that provides acute assessment, care and transport of a patient requires a physician medical director. Up until about five years ago, none of the medical directors for fire departments or emergency services in the Lowcountry had any formal relationship with MUSC Health. This is quite alarming as we offer tertiary and quaternary care and have the only level-1 adult and pediatric trauma centers, pediatric burn center and comprehensive stroke center in the region. Over the past four years, we have very deliberately recruited leading faculty such as **David M. French, M.D.**, who has formal EMS training, was the EMS director at Baylor University and is now the medical director for Charleston County EMS and the consolidated 911 center. **Christine M. Carr, M.D.**, **W. Brett McGary, M.D.**, **L. Wade Manaker, M.D.**, and I also provide medical direction for numerous agencies in the Lowcountry, including the fire departments for Charleston, North Charleston, Mount Pleasant, Sullivan's Island, Isle of Palms and St. Johns; the Berkley County EMS; several paramedic training programs, and Meducare Air and Ground. Because we are now working with every agency that is engaged in responding to an emergency, we can ensure consistent quality of care for everyone in the Lowcountry. Our new department has recruited another EMS fellowship–trained expert in event medicine, **Dustin LeBlanc, M.D.**, who will help lead our event medicine outreach efforts, including the Cooper River Bridge Run. Many of our physicians also serve at the state level to help drive policies that elevate emergency care across the state and ensure that it is adherent to national guidelines. Since several of us are involved at the national level in establishing best practice, it is easier for us to bring what we know is best science and clinical practice at the national level home to South Carolina.

PN: What do you find fulfilling about a career in Emergency Medicine?
It is a privilege to be part of a patient's moment of need. The opportunity to make the experience for the patients and families as tolerable as possible and to show compassion during a time of crisis is a privilege.

It's also a privilege to be the first point of contact for people who do not normally engage the health care system. Showing empathy and compassion encourages the person to continue to engage health care, and not just in the emergency setting. We have an obligation to make sure that the first contact or the rare contact is a good one. A crisis precipitated by some behavior is an inflection point, a teachable moment. Working with someone addicted to heroin is very difficult, but if you revive that person after an overdose, that is a moment when a physician interaction may resonate more than seeing a billboard that says drugs are bad. We initiate a lot of public health projects here — we screen for HIV and hepatitis C, participate in smoking cessation interventions and screen for domestic violence. Will I solve these challenges in the ED? No, but I can make a dramatic difference by getting those patients engaged in the health care system long term. And if I don't do that, and that patient doesn't see a physician again, then we have lost an opportunity. It's these human interactions and contacts that are a privilege. They offer a great opportunity to make the quality of someone's life better in the long term.

"The opportunity to show compassion during a time of crisis is a privilege." — Dr. Edward C. Jauch

Dr. Marc R. Katz (left, seated at console) performs robotic mitral valve repair. Photograph by Brennan Wesley

A Robotic Revolution

Robotic mitral valve repair, now available at MUSC Health, achieves similar outcomes to open surgery with less pain and a quicker recovery for select patients

BY KIMBERLY MCGHEE

MUSC Health cardiothoracic surgeon **Marc R. Katz, M.D., MPH**, is the first to offer robotic mitral valve surgery, the least invasive of all mitral valve repair techniques, to patients in South Carolina. Katz has more than 15 years of experience with the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA) — he had the third robot in the U.S., was an investigator on the clinical trials that led to its approval and has been engaged in each of its developmental iterations.

In appropriately selected patients, and when performed at high-volume centers such as the MUSC Health Heart and Vascular Center by surgeons experienced in the technique, robotic mitral valve repairs achieve results at least as good as those attained by other minimally invasive techniques[1] or via open surgery but with less pain, a shorter hospital stay, a quicker recovery and a more rapid resumption of normal activities.

"[The robot] translates the normal motions of the surgeon's hands in through tiny incisions in the chest."
—Dr. Marc R. Katz

"Patients return to work when they feel like it after robotic repair," explains Katz. "For most, that's within a week or two instead of the eight to 12 weeks required after open heart surgery."

Open surgeries require that the breast bone be split to gain access to the heart and then be rewired back together. In contrast, for robotic mitral valve surgery, the surgeon makes several small portholes — approximately half an inch long — into which the robot's arms are docked and a small camera is inserted.

The da Vinci SI System available at MUSC Health provides high-definition 3D visualization of the valve and has wristed robotic arms that are capable of greater dexterity than human hands.

Because the endoscopic camera can be positioned near the valve, it provides excellent visualization. "The scope is sitting right next to the valve and so the valve looks like it is ten feet tall," says Katz. "Due to that better visualization of the valve, we can achieve excellent mitral valve results."

Guided by those images, Katz, seated at a console, directs the robot's arms, which have seven degrees of freedom of movement, to replace any ruptured cords (i.e., the fibrous strings that control the opening and closing of the valve) and to place an annuloplasty ring around the valve to help give it shape and support.

"The robot does what the surgeon's hands do," says Katz. "It translates the normal motions of the surgeon's hands in through tiny incisions in the chest."

The mitral valve's job is to keep blood flowing in the right direction through the heart. Connecting the left atrium and left ventricle, the valve opens as the atrium fills with blood to enable the blood to pass into the left ventricle and then clamps shut to prevent backflow. As the mitral valve degenerates, this seal becomes leaky, leading to backflow of blood into the atrium. When the leak is severe, backflow may reduce both the supply of oxygenated blood to the body's organs, causing shortness of breath and other symptoms, and result in a backup of fluid in the pulmonary vessels, which can lead to pulmonary hypertension. The resulting stresses on the heart can cause congestive heart failure.

In the past, the mitral valve was replaced with a prosthetic and surgery was reserved largely for those who had already developed congestive heart failure. Due to improvements in mitral valve repair techniques, current guidelines recommend surgical mitral valve repair in those with severe regurgitation, even if they have not yet developed symptoms. Indeed, more than 90 percent of degenerative mitral valves are suitable for repair, and better short- and long-term results are achieved with repair than with replacement.[2] Although not appropriate for patients who require additional procedures, such as multiple valve repairs or bypasses, robotic mitral valve surgery can offer a new lease on life to patients with isolated mitral valve leaks. The surgery restores mitral valve function and, unlike replacement, does not require long-term anti-coagulation.

"Following surgery, many patients feel physically much better because they are no longer affected by the symptoms of their valve disease," says Katz. To learn more or to refer a patient, contact Betsy Hyland at 843.876.4842.

To watch an interview with Dr. Katz about robotic mitral valve surgery, visit the MUSC Health Medical Video Center at MUSChealth.org/medical-video and select cardiology from the dropdown menu of specialties.

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Dr. Ramin Eskandari (right) discusses a case with a colleague. Photograph by Brennan Wesley

Necessity Spurs Invention

MUSC Children's Health offers a new shuntless technique, developed in Africa, to address hydrocephalus

BY VITRIA ADISETIYO

Since arriving at MUSC Children's Health in 2014, pediatric neurosurgeon **Ramin Eskandari, M.D.**, has been offering a new shuntless procedure for treating hydrocephalus — endoscopic third ventriculostomy and choroid plexus cauterization (ETV/CPC) — and training residents and neurosurgery colleagues on the technique.

As chief resident at the University of Utah, Eskandari was one of the first residents in the U.S. to travel to Uganda, where the technique was developed, for training. While a fellow at Stanford University, he trained his colleagues and mentors to perform the procedure.

Traveling to a developing country for advanced medical training might seem counterintuitive, but necessity spurs innovation, and the urgent need to address the high shunt infection rates in Africa led to the development of the novel ETV/CPC technique that is now being adopted in more developed countries.

Hydrocephalus is a common disorder in which build-up of cerebrospinal fluid (CSF) in brain ventricles creates harmful pressure on neural tissue. If untreated, hydrocephalus leads to abnormal brain, cognitive and physical development and eventually death. Traditionally, a ventriculoperitoneal shunt is implanted to drain excess CSF from the brain to a peripheral part of the body, where it can be readily absorbed. Since the 1960s, this approach has proven to be an effective treatment, albeit an imperfect one that requires life-long maintenance. Patients face high infection rates from the hardware implant along with a high likelihood of reoperation due to shunt malfunction.

In Uganda, as in other sub-Saharan countries, hydrocephalus is widespread due to high rates of post-meningitis and post-ventriculitis infections. Despite shunt treatment, the survival rate for hydrocephalus has been abysmal because of high infection rates and limited access to medical care.

In 2000, Benjamin C. Warf, M.D., an American neurosurgeon working in Uganda, began to look for a solution. The advent of the flexible endoscope led Warf to revisit an old surgical technique wherein a hole is created in the floor of the third ventricle to reroute excess CSF followed by shrinkage of the choroid plexus to temporarily reduce CSF production. This approach allows the brain to gradually reabsorb the extra CSF and establish a new equilibrium. While historically the technique was performed as an open brain surgery, Warf advanced the method into a minimally invasive procedure by conducting the surgery with a flexible endoscope through a small hole in the skull.

Warf published outcomes for hundreds of patients treated with ETV, demonstrating that the procedure was effective and that, when combined with CPC, it could be used successfully even in children younger than one year.[1] Moreover, he showed that, even if the ETV/CPC procedure fails, the shunt option remains available,[2] whereas ETV/CPC care can rarely be done after a shunt is placed. Today, the ETV/CPC method is the mainstay for hydrocephalus treatment in sub-Saharan Africa.

As word spread, more neurosurgeons in developed countries sought training for the ETV/CPC procedure. Capitalizing on sophisticated neuroimaging, neuropsychological and big-data technology available in developed countries, a multi-center Hydrocephalus Clinical Research Network (HCRN; http://hcrn.org/) has been established to rigorously study ETV/CPC treatment outcomes.

"In the developed world, we are well beyond mere survival as a benchmark of success," says Eskandari. "Families are rightly demanding that medicine and science strive to produce durable treatments for their children that allow them not just to survive but also to thrive in terms of their physical and cognitive abilities."

Collective data thus far suggest the ideal patients for the procedure are those with an anatomical obstruction that prevents correct CSF flow and those without a history of infection or post-hemorrhagic hydrocephalus. However, in infants aged three to nine months, even those with post-hemorrhagic hydrocephalus have a 25 to 45 percent chance of success. Patients who lack CSF absorption capacity, such as premature babies, do better with shunt treatment. [3]

As for the future of hydrocephalus treatment at MUSC Children's Health, Eskandari's goal is to establish a large pediatric center for hydrocephalus and to propose a study to the HCRN, for which the center would serve as a site.

"Long-term data are needed to truly establish the value of the technique. If we can show that the outcome of the ETV/CPC surgery is the same as shunting at age five, age ten, and during the college years, then that really supports continuing to perform this procedure in this patient population," says Eskandari. "I would love to see us continue down this evidence-based path because it really is the best care we can offer our patients."

To watch a video of Dr. Eskandari discussing the technique and narrating surgical footage from a case, visit the MUSC Health Medical Video Center at MUSChealth.org/medical-video and select pediatrics from the dropdown menu of specialties.

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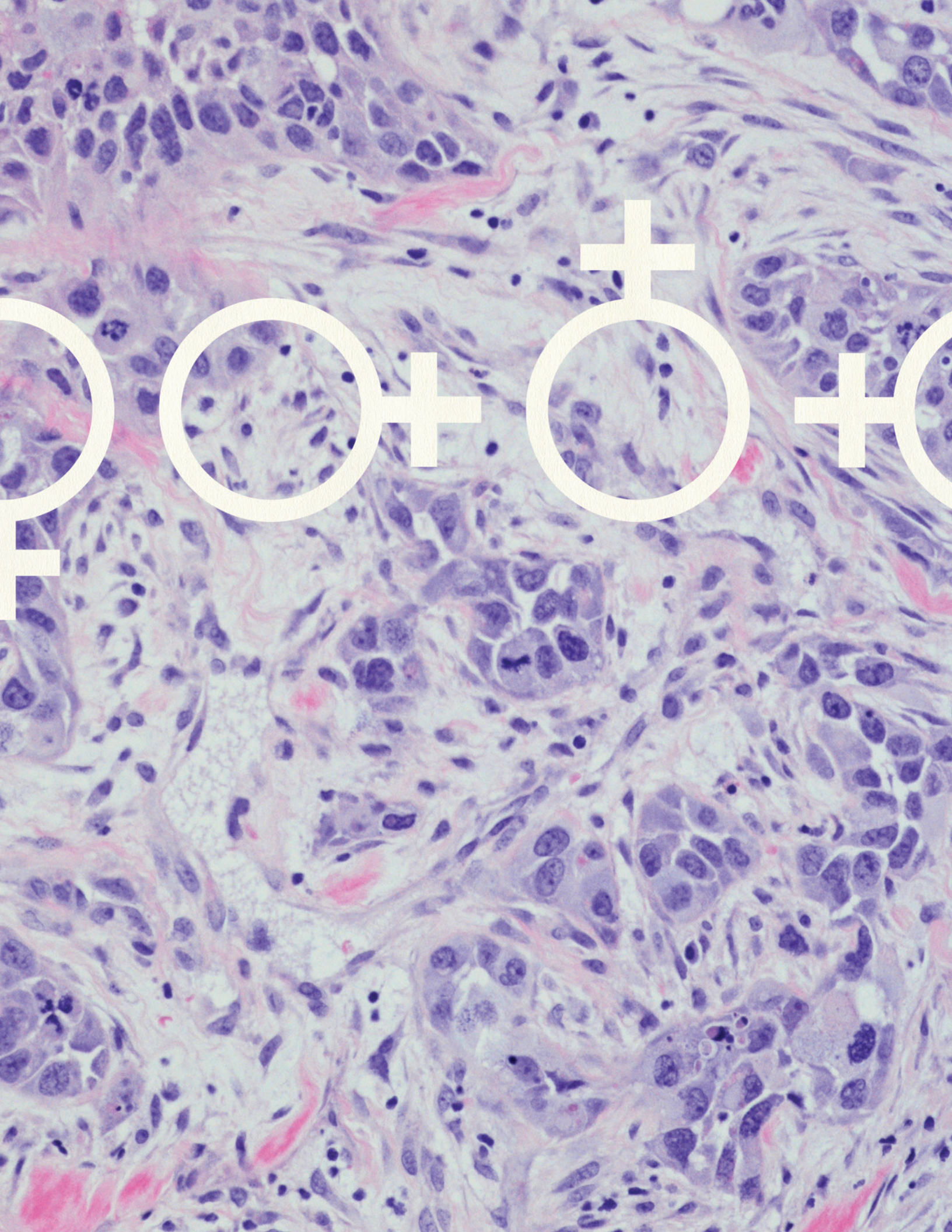

Agents of Change

Specialists at the MUSC Breast Center innovate to advance care for women with breast cancer

BY KIMBERLY MCGHEE AND TONISHA KEARNEY-RAMOS

The Breast Center at MUSC Hollings Cancer Center, led by renowned breast surgeon and translational cancer researcher **Nancy K. DeMore, M.D.**, offers women with breast cancer multidisciplinary and comprehensive care delivered by specialists who have devoted their careers to combatting the disease. Care teams comprise breast cancer surgeons, medical oncologists, radiation oncologists, genetic counselors, pathologists and nurse navigators who have completed fellowships or received other specialized training in the management of breast cancer. The team meets weekly at a breast cancer tumor board to discuss cases, so that patients can be assured that all of their care providers are operating from the same game plan and that all treatment decisions draw upon the collective wisdom of the team. That spirit of collaboration and the desire by team members to continually optimize the screening, diagnosis and surgical management of breast cancer fosters an environment where innovative solutions to address limitations in current standard-of-care techniques are encouraged. Providers act as agents of change, working to continually improve patient experience and outcomes.

Screening and Diagnosis

LIMITATION: Although traditional 2-D digital mammography has saved many lives, it does not always accurately identify abnormalities in dense breast tissue.

INNOVATION: Digital breast tomography

Digital breast tomography (DBT) , also known as breast tomosynthesis or 3-D mammography, is a procedure in which several low-dose x-rays are taken at different angles; these source images are then reconstructed into multiple thin slices that can be scrolled through one by one. This helps to reduce diagnostic uncertainties caused by the overlap of normal fibroglandular breast tissue. It is performed in addition to traditional 2D-mammography, takes only a few seconds longer but requires additional radiation (still within FDA-prescribed limits). Studies have shown that DBT can increase breast cancer detection and lessen the likelihood that patients will need to return for additional imaging. Although DBT is now available at Hollings and MUSC East, as well as many other sites in the country, randomized clinical trial (RCT) data are needed to assess its diagnostic value.

Radiologists **Susan J. Ackerman, M.D.**, and **Dag Pavic, M.D.**, will be the principal investigators for the Holllings and MUSC East sites, respectively, of TMIST, an RCT that will begin recruiting in mid-2017 and aims to enroll 165,000 asymptomatic U.S. and Canadian women between 45 and 74. Participants will be randomized to either 2D mammography or DBT and followed up for four years so that the incidence of advanced cancer can be compared in the two groups. Results from this trial should provide a definitive answer as to whether DBT should be more widely adopted in the clinic.

LIMITATION: Breast biopsies have a high rate of false positives, i.e., a number of tissues thought to be abnormal on imaging turn out to be normal when biopsied.

INNOVATION: SFRP2-targeted molecular ultrasound (investigational)

DeMore is collaborating with bioengineering colleagues at The University of North Carolina – Chapel Hill (UNC) to optimize

SFRP2-targeted molecular ultrasound. DeMore's laboratory identified a novel stimulator of tumor angiogenesis (secreted frizzle-related protein 2 [SFRP2]), showed that it was overexpressed in breast cancer and created an antibody to target it. Her UNC colleagues have conjugated that antibody to a microbubble containing contrast agent. By targeting SFRP2, the antibody selectively steers the microbubble to cancerous cells, which then bind with the contrast agent. Areas of high contrast suggest cancerous tissue in need of biopsy. In an article published online on March 23, 2017 by *PLOS One* (doi: 10.1371/journal.pone. 0174281), DeMore and her UNC collaborators demonstrated the feasibility of this approach in a preclinical tumor model. DeMore has a large grant from the National Institutes of Health to test the new approach in preclinical models of various types of breast cancer. Although still years out of the clinic, the technique could one day help prevent unnecessary biopsies.

"The hypothesis is that if you had a lesion that did not enhance with contrast agent, that would be predictive of it not being a malignancy, and then you wouldn't need to have a biopsy," explains DeMore.

Surgical Management

LIMITATION: Wire localization of nonpalpable breast lesions, which is typically performed on the same day as surgery, causes logistical challenges that reduce operating room efficiency.

INNOVATION: Savi Scout®, a new FDA-approved localization technique

Because most biopsies today are of nonpalpable lesions identified by mammography, localizing the lesion to be surgically excised typically involves the insertion of a wire into the abnormal tissue by a radiologist under mammographic guidance. Wire localization requires the patient to undergo a second invasive procedure and, because it is typically performed the day of surgery, can lead to logistical difficulties for the operating room (OR).

The MUSC Health breast surgical oncology team, which includes DeMore, **Andrea M. Abbott, M.D.**, **David J. Cole, M.D.**, and **Mark A. Lockett, M.D.**, is now offering Savi Scout®, a novel localization technique in which the radiologist places a reflective chip next to the titanium clip that was inserted at the time of biopsy (to guide the surgeon in case a malignancy was found). The reflector chip can be implanted from one to 30 days before surgery. On the day of surgery, the surgeon uses a probe that bounces radiofrequency off the reflective chip to localize the clip and the tissue requiring excision. Because this technique uncouples the localization and surgical excision procedure, enabling them to be performed days apart, OR efficiency is improved and delays in surgery are less likely.

INNOVATION: Direct localization of the titanium clip with a metal detector (investigational)

Like SaviScout, other novel localization techniques, including magnetic seed localization and radioactive seed localization, promise improved OR efficiency because the tiny magnetic or radioactive seed can be implanted well in advance of surgery, avoiding last-minute logistical delays. The surgeon then uses the appropriate probe to locate the seed and the abnormal tissue for excision. However, all three localization procedures share the same disadvantage: patients are required to undergo a second invasive procedure and must take a second day off work. In addition, radioactive seed localization could pose a radiation hazard should the seed break.

DeMore wondered whether a metal detector could be developed to detect the titanium clip directly, avoiding the need for an invasive localization procedure before surgery. Titanium is the metal of choice for the marker clip, which will remain in the patient indefinitely if the tissue is noncancerous and no surgery is required, because it is very weakly electromagnetic and will not be detectable on airport scanners or interfere with MRI.

DeMore consulted with Clemson bioelectrical engineer Delphine Dean, Ph.D., to see if developing such a detector was possible. Dean challenged her design class to draw up plans for the detector, which they did, and, within a matter of months of having the idea, DeMore had a prototype she could test in specimens of breast tissue. The next step is to produce a prototype that is compliant with Good Manufacturing Practice that can be taken forward into clinical trial.

In 2017, the titanium detector won the new technologies award at the Innovations in the Operating Room conference hosted by the Society of Surgical Oncology. DeMore also won a local "shark tank" contest — the Southeastern Medical Device Charleston Road Pitch Competition — and competed in the regional contest in Atlanta.

LIMITATION: In traditional mastectomy, the nipple is removed along with the rest of the breast, requiring nipple reconstruction or tattooing as the last phase of breast reconstruction.

INNOVATION: Nipple-sparing mastectomy followed by prepectoral implant

The loss of a breast can mar a woman's self-image and shake her sexual confidence. Nipple-sparing mastectomy, in which breast glandular tissue is extracted through a small incision while the skin and nipple of the breast remain intact, minimizes scarring and sets the stage for a more natural, cosmetically pleasing breast reconstruction.

The MUSC Health breast surgical oncology team collaborates with plastic surgeons **Jason P. Ulm, M.D.**, and **Kevin O. Delaney, M.D.**, who offer a novel reconstruction technique called prepectoral implant that can be performed either immediately after nipple-sparing mastectomy or some time thereafter. Unlike traditional implants, which are placed under the chest muscle and require cutting of the pectoralis major, prepectoral implants are placed above the muscle just under the skin, considerably reducing patient pain and morbidity. The appearance of "rippling" under the skin that was an early drawback of the technique has been overcome by the availability of lipofilling, in which fatty tissue harvested from the abdomen is layered over the prepectoral implant, improving its appearance. The reconstructed breast looks very natural, boosting patients' self-image and sexual confidence. Patients should be aware, however, that the implants do not feel like natural breasts.

To view voiced-over surgical photographs from a nipple-sparing mastectomy by Dr. Abbott followed by a prepectoral implant by Dr. Ulm, visit MUSChealth.org/medical-video and select oncology from the dropdown menu of specialties.

LIMITATION: The long incision required for traditional deep inferior epigastric perforator (DIEP) flap harvest for breast reconstruction causes considerable pain, extends recovery, is vulnerable to hernia and can weaken abdominal muscles.

INNOVATION: Robotic DIEP flap harvest

For more than 20 years, DIEP flaps have been used to provide living tissue for breast reconstruction. A flap of tissue and fat, along with the associated vasculature, is harvested from a patient's abdomen or flank and used to reconstruct a breast. The vessels attached to the excised flap are connected to the internal mammary artery and vein to ensure a blood supply for the new breast. Traditionally, DIEP flap harvest has required an incision along the entire abdominal wall to provide the surgeon with access to and visualization of the deep inferior epigastric artery and veins so that the blood vessels could be safely dissected from surrounding tissue. This necessitates the cutting of the abdominal fascia from just underneath the belly button to the groin crease.

Dr. Rana C. Pullatt (right) during the robotic DIEP flap harvest

Wondering if a robotic approach would enable a smaller incision and less morbidity, Delaney contacted **Rana C. Pullatt, M.D.**, a highly skilled and experienced robotic surgeon who directs the robotics program for the Department of Surgery at MUSC Health, to discuss the possibility. The two agreed the approach had merit and, in February 2017, they together performed the first-ever robot-assisted DIEP flap harvest.

Instead of the 15-cm incision that would have been required for traditional DIEP flap, Delaney was able to make only a 2.5-3.0-cm incision to free the tissue and fat and dissect the portion of the vessels that was accessible from outside the abdominal wall. Pullatt then made a few very small portholes where he was able to insert an endoscopic camera and dock the robot. Then, seated at a console, and with access to endoscopic images, he guided the hands of the robot to dissect the vessels underneath the abdominal fascia from the surrounding tissue until he reached the point where Delaney had stopped. Delaney was then able to lift the flap out with the vessels attached. Although the procedure took a little longer than the traditional surgery, it was much less invasive and resulted in less pain and morbidity for the patient.

More research is needed to identify the patients most likely to benefit from the new approach, but Delaney and Pullatt suspect it will be best-suited to those in which traditional DIEP flap harvest is difficult, such as obese patients or those with a great deal of intramuscular mass.

To watch footage of the robotic DIEP flap harvest narrated by Dr. Pullatt, visit MUSChealth.org/medical-video and choose oncology from the dropdown menu of specialties.

Rewriting Fate

Gene editing as tool and treatment

BY SVER AUNE

For some patients, genetic disorders can seem written into DNA as permanently as eye color. Yet defective genes and their attendant symptoms could be quelled with gene therapy.

Laboratory techniques to write over faulty genes typically use pieces of viruses called vectors. Viral vectors infect diseased cells with the functional human gene, which is then replicated alongside the defective one. In order to avoid immune reactions, the ability of the virus to replicate itself is first neutralized. But past success in experiments did not guarantee success in clinical trials. Gene therapy research was shaken in 1999 when an 18-year-old man in a clinical trial died from an overreaction to the virus carrying the therapeutic gene for his condition.[1]

That experience transformed the field. Since 1999, gene therapies have improved greatly due to intensive preclinical research. Viral vectors have been modified to more accurately target only diseased cells. Novel methods such as CRISPR enable researchers to remove a defective gene entirely through genome editing. At MUSC, researchers are conducting new clinical trials and original research that give hope to patients with genetic disorders.

Our cells, ourselves

A genetic mutation affects the cells or organs that need the protein encoded by that gene. A pair of high-profile clinical trials now underway at MUSC are testing therapies for mutations in genes that encode blood proteins. The goals are to determine how to guide the functional gene to the cells that need it and how much encoded protein is needed to offset the mutation.

Alpha-1

MUSC is a site for a new phase 1/2 clinical trial of safety and efficacy for a first-in-man gene therapy to treat the lung and liver disease alpha-1 antitrypsin deficiency (Alpha-1). **Charlie B. Strange, M.D.**, professor of medicine in the Division of Pulmonary, Critical Care and Sleep Medicine, is principal investigator on the trial and director of the national Alpha-1 Foundation Research Registry.

The new therapy is administered to combat the development of emphysema in patients as young as thirty by more efficiently boosting alpha-1 antitrypsin protein (A1AT) levels in the lungs. A1AT is the second-most abundant protein in the blood and protects lung epithelial cells from environmental toxins such as cigarette smoke, according to Strange. Alpha-1 patients have about 15 percent of the normal level of A1AT due to a rare genetic mutation that prevents A1AT from folding correctly in the liver. To prevent early-onset lung disease, patients require weekly intravenous infusions of A1AT for life.[2]

In the trial, an adeno-associated viral vector (AAV) carrying the normal gene for A1AT is infused into the pleural space that wraps around the lungs. If enough A1AT protein persists in the pleural space, it could halt emphysema progression and improve symptoms.

AAV is not known to cause disease in humans and can sustain replication of the functional DNA it carries into human cells, thereby

allaying the symptoms caused by the mutated gene. However, AAV works in only a minority of the human cells it contacts.[3] For example, in the first clinical studies using AAV to deliver the gene for A1AT to the leg muscles of patients, only a fraction of muscle cells produced A1AT protein. As a result, protein levels in the bloodstream rose, but not nearly enough to change the course of the disease.[2]

The trial is testing pleural infusion versus intravenous infusion of a viral vector (Adverum Biotechnologies). In preclinical studies, more A1AT was made in the lungs when the vector was infused into the pleural space than when it was injected through the bloodstream. The trial is being conducted at MUSC and Temple University.

The ultimate goal is to achieve complete remission of symptoms while freeing Alpha-1 patients from weekly infusions.

"We want to get gene therapy that will be given once and cure your symptoms for the rest of your life," says Strange.

Pushing the envelope to treat sickle cell disease

Julie Kanter, M.D., a hematologist and director of sickle cell research, is an investigator on an international phase 1/2 clinical safety trial — the HGB206 trial — for a new gene therapy for sickle cell disease (SCD). As with Alpha-1 gene therapy, there is hope that the therapy will repair enough red blood cells to compensate for those with the sickle defect. In fact, a 13-year-old patient in a clinical trial in France has experienced complete resolution of symptoms with the therapy.[4]

Patients with SCD have inherited from both parents a mutation in the gene for hemoglobin that gives red blood cells a sickle-like shape and reduces oxygen delivery throughout the body. SCD can cause episodes of severe pain and complications including stroke. Currently, a stem cell transplant is the only cure.[4]

The gene therapy in the trial, sponsored by Bluebird Bio, uses a lentiviral vector designed to carry a globin gene that is very similar to normal hemoglobin A with an alteration that makes it even more anti-sickling like hemoglobin F.

"Lentiglobin is the lentiviral vector, which I always think of as the envelope," says Kanter. "They put a new globin gene in as the letter, and that's called T87Q."

Lentiviral vectors are more efficient than AAV at incorporating the DNA they carry into host cells. However, lentiviruses can cause severe disease in humans, limiting their potential use in gene therapy.[5]

The use of stem cells may solve this problem. Stem cells are removed from a patient's bone marrow and infected with lentiglobin. The virus is then removed to mitigate an immune response, and the stem cells containing T87Q DNA are transplanted back into the patient's bone marrow. Those stem cells can then develop into normal red blood cells that make T87Q that counteracts the SCD defect.

There is considerable excitement building around gene therapy for SCD. Yet while 50 percent of the French teen's red blood cells are making T87Q, the rest are sickled cells.

"While we're excited about some of the early successes, we have a long way to go," says Kanter.

Brainstorming new gene therapies

These are just two examples of gene therapies that are moving from time-tested research tool to treatment at MUSC Health. Preclinical work on new gene-editing tools can give us a glimpse at the future of gene therapy in common brain disorders and beyond.

Mapping addiction

At the MUSC Charleston Alcohol Research Center (ARC), scientists are charting addiction in the brain with a unique tool: designer receptors exclusively activated by designer drugs (DREADDs).[6] In preclinical models, a given DREADD delivered to specific brain regions can render neurons active or inactive in response to systemic administration of a specially designed drug that is otherwise innocuous. The genes that encode these receptors are delivered to neurons by AAV. Several different types of DREADDs can be used at once, providing a sophisticated level of control called *multiplexing*. In this way, researchers in the ARC can determine which circuits in the brain are involved in addiction, relapse and automated behavior.

In the future, patients might pop a pill to calm the addiction circuit of their brain each time a craving arises. Yet there are puzzles to solve before that can happen, according to **Howard C. Becker, Ph.D.**, director of the ARC. For example, it may be difficult to target the many areas of the brain and many genes affected by addiction. Also, the viruses must be injected directly into the brain during neurosurgery.

"Because we don't have easy access to the brain, that's a barrier," says Becker. "But in time and with more research, eventually this could very well be the wave of the future, especially for neuropsychiatric-related illnesses."

Shining a light on narcolepsy

Another brain research group is modifying the gene suspected in narcolepsy in preclinical tests. **Meng Liu, M.D., Ph.D.**, of the Department of Psychiatry and Behavioral Sciences received R01 funding in 2016 to develop a gene therapy for narcoleptic cataplexy, a condition affecting two-thirds of narcolepsy patients, in which irresistible sleep

is triggered by strong emotion. Although the exact cause is unknown, many patients have very low levels of the neuropeptide orexin, which regulates sleep.[7] Liu's research team is following this promising clue in preclinical studies. The group is testing an AAV carrying the gene for orexin. They are combining delivery of the orexin gene and optogenetics, a technique that renders neurons sensitive to tiny lights inserted in the brain. The plan is to map the exact neural pathways that control narcolepsy and, eventually, develop therapies such as orexin gene delivery to treat the disorder.

Latest gene-editing tools

Many researchers at MUSC are embracing innovations in gene-editing tools. One such tool — CRISPR — is considered the future of gene therapy for patients with genetic conditions ranging from Down Syndrome to Alzheimer's disease to cancer.[8] This enthusiasm stems from CRISPR's power to target any DNA sequence with unparalleled precision. In contrast to viral vectors that compensate for a mutation, the CRISPR system retools an antiviral defense mechanism found in bacteria to remove a faulty gene completely and permanently replace it with the correct one.

CRISPR has become the method of choice for rewriting genes in preclinical models, according to **Alexander Awgulewitsch, Ph.D.**, scientific director of the new transgenic and genome editing core at MUSC. The core opened in May 2017 to meet the growing demand for gene editing among preclinical researchers across the state of South Carolina. The new core uses CRISPR and other tools to help researchers add, subtract or silence genes to better understand disease and look for cures.

Gene therapies are maturing, driven by new research and enthusiasm for their potential to help patients. With new clinical trials and gene-editing tools in the pipeline, there is hope in the medical community that gene therapy will help patients with a genetic disorder rewrite their fate.

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Loosening the Grip of Physician Burnout

Loss of autonomy fuels burnout. Involving physicians and other clinicians in designing burnout interventions could be an important step toward a solution.

SUBJECT MATTER EXPERTS: JENI BOWERS-PALMER; EDWARD W. CHEESEMAN, M.D.; BENJAMIN CLYBURN, M.D.; CONSTANCE GUILLE, M.D.; ROBERT J. MALCOLM, M.D. AND ALEJANDRO M. SPIOTTA, M.D.

BY KIMBERLY MCGHEE

ILLUSTRATIONS BY EMMA VOUGHT

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

- *Recognize the warning signs of physician burnout.*
- *Explain why physician burnout is a patient safety issue and recognize that obtaining help to address it is the best way to ensure that patient care is not impaired.*
- *Discuss institutional and physician-directed strategies to address physician burnout.*

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Jeni Bowers-Palmer, Dr. Edward W. Cheeseman, Dr. Benjamin Clyburn, Dr. Constance Guille, Dr. Robert J. Malcolm, Dr. Alejandro M. Spiotta and Kimberly McGhee have no relevant financial relationships to disclose.

Physician burnout is a syndrome characterized by emotional exhaustion, depersonalization and a loss of meaning in work and is driven principally by stressors in the workplace.[1] Although physician burnout is not new, recent years have seen a spike in its prevalence. According to one much-cited Mayo Clinic–led study, the proportion of physicians reporting at least one symptom of burnout on the Maslach Burnout Inventory increased almost ten percent in just three years, from 45.5 percent in 2011 to 54.4 percent in 2014.[2] The 2016 Medscape Lifestyle Report showed that, though burnout is rising rapidly among all physicians, women have higher rates of burnout than men (55 vs. 46 percent).[3] Clinical leaders and administrators as well as physicians have begun to recognize the problem: 96 percent of those responding to a recent survey by *NEJM Catalyst* identified burnout as a moderate or serious threat to the health care system.[4]

What fuels burnout?

Most physicians go into health care to provide quality care to patients, and obstacles that prevent them from doing so are, in the opinion of **Danielle B. Scheurer, M.D.**, MUSC Health chief quality officer, leading causes of burnout.

"Anything that makes it difficult for clinicians to take good care of a patient burns them out," explains Scheurer.

In recent years, the health care industry has undergone unprecedented changes that have affected the ways physicians deliver care. At one time, most physicians were small business owners who could control the parameters of care. Now, in part because of need to pay back large student debts, most physicians are employees of health care systems and some feel a loss of autonomy that is a risk factor for burnout.

"What makes work really stressful for physicians is that we have a really high degree of responsibility but increasingly a lower degree of autonomy and control," says **Constance Guille, M.D.**, an associate professor in the Department of Psychiatry and Behavioral Medicine, who has studied the effects of stress on medical students and interns and is a member of the physician burnout workgroup created by the American Psychiatric Association. "So when we are unable to make decisions that are going to affect patient outcomes but are completely responsible for those outcomes, it is incredibly stressful and those are the things that are leading to burnout," explains Guille.

Increases in regulatory and payer demands, pressures to increase productivity and the institution of the electronic health record (EHR) have dramatically affected clinicians' workflows, leaving many physicians feeling overwhelmed and unable to control the quality of care they provide. Some worry that the physician-patient relationship could be one unintended casualty of the requirements for increased documentation. A recent study of physicians working in ambulatory care revealed that they spend almost twice the time on the EHR and clerical and administrative tasks (49.2 percent) as on direct clinical face time with the patient (27 percent).[5] Many of the physicians report spending another one to two hours each evening finishing

documentation and administrative tasks at home, which physicians have dubbed "pajama time."[5] Feeling overwhelmed by clerical responsibilities, physicians lose sight of what brought them into medicine — the desire to interact with and heal patients.

Feeling the fallout

Burned out physicians are also more likely to leave the profession or to recommend against others pursuing it, exacerbating already severe physician shortages in some areas. A recent survey by the Physicians Foundation revealed that 63 percent of respondents said they have negative feelings about the future of the medical profession, 49 percent said they often or always experience feelings of burnout and 49 percent said that they would not recommend a career in medicine to their children.[6]

Burnout is a risk factor for depression, and studies have shown an association between burnout and substance abuse, particularly alcohol abuse.[7] Both depression and substance abuse are in turn risk factors for suicide. Male physicians are 1.5 times more likely and female physicians 2.2 times more likely to commit suicide than their counterparts in the general population.

Positioned at the apex of medical care, a burned out physician can demoralize his or her staff and colleagues. Burnout is not solely a physician problem and can affect all members of the clinical care team.

Most important of all, burnout can affect patient care. A well physician is better able to "heal" patients and to earn his or her patients' trust, whereas burned out physicians are more prone to experience compassion fatigue and to make medical errors. Each one point increase in depersonalization (on a scale from 1-33) or emotional exhaustion (on a scale of 1-54), both measures of burnout, led to an increase of 11 percent and five percent, respectively, in the likelihood of a surgeon reporting a medical error.[8]

"It's overdue to have a local, state and national conversation around clinician burnout and its impact on patient care," says Scheurer.

Joining the national conversation

In late March 2017, the CEOs of the American Medical Association and ten leading health care systems declared physician burnout a public health crisis, committed themselves to addressing it and issued a call to arms for other health care administrators to join them in their efforts.[9] A number of MUSC Health physicians heard that call and have begun to work to raise awareness about the issue among both resident and attending physicians.

With the help of Jeni Bowers-Palmer of the MUSC Employee Assistance Program (EAP), **Benjamin Clyburn, M.D.**, senior associate dean for graduate medical education at the Medical University of South Carolina, has begun discussing the topic at new resident orientations and chief resident conferences to ensure residents can recognize the warning signs of burnout (Table) and know how to find help on campus. Clyburn and Bowers-Palmer are working to ensure that residents have 24/7 access to EAP services, a new requirement for graduate medical education.

Pediatric ophthalmologist **Edward W. Cheeseman, M.D.**, became concerned about burnout as more and more of his colleagues confessed to feeling overwhelmed, and his concern only grew as he versed himself in the literature surrounding burnout, including an influential series of articles[10,11] in *Mayo Clinic Proceedings* by Tait Shanafelt, M.D., who runs the physician wellness program at Mayo. Feeling compelled to raise awareness about the scope of the problem, he delivered a grand rounds presentation on the topic to his fellow ophthalmologists, prompting the department to decide to survey its physicians about burnout.

"The Maslach Burnout Inventory is the best in class in the industry for measuring burnout," explains Scheurer, who attended Cheeseman's grand rounds at his request. Scheurer, Cheeseman and **Andrew S. Eiseman, M.D.**, chair of the Department of Ophthalmology, are working together to purchase a license for the inventory as well as an extra set of questions that more deeply probes the drivers of burnout. They will use the inventory to gauge burnout among

Some Warning Signs of Clinician Burnout

- Feeling empty or numb
- Being emotionally exhausted
- Lacking motivation
- Feeling hopeless
- Believing that nothing you do at work will make a difference
- Feeling constantly frustrated
- Feeling trapped in your job
- Feeling like a failure
- Being cynical or sarcastic
- Avoiding others or lacking patience with co-workers, customers or patients
- Procrastinating
- Difficulty sleeping

residents and faculty in the ophthalmology department and to inform the development of interventions to address it. The inventory and the interventions that prove useful will be made available to other interested departments, which are encouraged as well to develop new interventions tailored to their specialty.

"We started with ophthalmology because they were the first to raise their hand," says Scheurer. "To roll the effort out further, we will need more departmental champions and physician partners to help develop meaningful interventions."

Interventions to address physician burnout

Most interventions to target burnout focus either on developing physician resiliency or on making institutional changes that reduce the triggers of burnout. Although both types of initiatives are effective,[12] a recent meta-analysis[1] of 19 randomized controlled trials (RCTs) of burnout interventions suggests that institutional efforts are more effective, not surprising since workplace stressors are the primary triggers of burnout. Subgroup analyses showed that organization-directed interventions reduced burnout measures of emotional exhaustion significantly more than physician-directed ones (standardized mean difference [SMD], -.045 [95% confidence interval ,–0.62 to –.28] vs. SMD, –0.18 [95% CI, –0.32 to –0.03).[1]

In May 2017, the Physician Burnout Workgroup of the American Psychiatric Association began work on its own meta-analysis of 26 RCTs of burnout interventions, three quarters of which were physician-directed interventions and a quarter of which were institution-directed efforts. Early findings show that 71 percent of institution-targeted interventions successfully reduced burnout, while only 42 percent of physician-directed efforts did so. "If you are burned out, you should by all means go get help for that," says Guille, who is a member of the APA workgroup. "But if there are going to be real changes in burnout, that has to come at the organizational level because burnout is the function of an organization, not an individual."

Physician-directed interventions

Most physician-directed interventions attempt to improve physicians' resiliency — their ability to withstand stress with their self-esteem, love of their profession and ability to relate to others intact — by teaching them communication and coping skills through cognitive behavioral therapy (CBT) and stress reduction techniques such as mindful meditation. They also encourage small group discussions that build camaraderie and physician wellness programs.

Most EAPs offer, or can make confidential referrals for, CBT and mindfulness-based interventions. Online resources are also available,

including a free CBT training program intended to help identify and address depression and anxiety (https://moodgym.anu.edu.au / welcome), mindfulness-based and other wellness tools at Stanford Medicine's Well MD (https://wellmd.stanford.edu) and four modules on physician wellness developed by the AMA Steps Forward program (https://www.stepsforward.org/).

Small group discussions have shown promise in helping physicians feel less isolated, one of the symptoms of burnout, and provide a necessary release valve for stress. Balint groups, for example, which dedicate weekly sessions to exploring a case that has proven emotionally difficult for one of the participants, enable physicians to express their feelings in a safe, controlled environment and to reconnect with and draw support from colleagues. (Learn more at http://americanbalintsociety.org.)

In light of evidence that physicians-in-training often experience a deterioration in both physical and mental health, a number of training programs have instituted physician wellness programs. Long hours, a stressful work environment, heavy workloads, disturbed sleep cycles, poor diet and lack of physical activity all take their toll, leading to burnout, which in turn increases the risk of depression and anxiety. A 2010 study showed that the percentage of students meeting criteria for depression increased from 3.9 percent the year before internship to a mean of 25.7 percent during internship.[13] Indeed, suicide is the second leading cause of death among residents.

At MUSC Health, a number of training programs have begun wellness programs for their residents. For example, in the two years since the creation of Operation La Sierra, a wellness program for both resident and attending physicians in the Department of Neurosurgery, the physical and mental health of its participants has markedly improved, drawing the notice of leading institutions across the country. Two keys to the success of the program have been the involvement of resident and other physicians in the design of the assessments and interventions and the decision to make the program voluntary, leaving it to physicians to decide, without consequence, whether they wanted to participate.

Participants in the program underwent a battery of health screenings, military style drills and psychological tests to establish baseline values for physical and emotional health. The results were shocking: 80 percent of participants had abnormal findings on screening, 67 percent had a higher-than-ideal body weight and 79 percent reported a quality of life that was below that of an average healthy adult.[14]

"Many of our residents had been college athletes," says **Alejandro M. Spiotta, M.D.** "But within a couple of years of residency, we had high rates of anxiety, depression, poor sleep, high cholesterol and high blood pressure, and this was in physicians in their late twenties and early thirties. It was really alarming. This was having a drastic, negative and almost toxic effect on both the physical and mental health of our trainees. This was not really the physician that patients wanted coming out the other end of training."

The Department of Neurosurgery set out to change that by integrating presentations on wellness topics such as sleep hygiene, stress management, substance abuse and mental health disorders into their weekly departmental meetings. It also instituted a weekly one-hour trainer-supervised group exercise section for all departmental members. These department-level efforts inspired independent efforts by faculty members: one invites resident and attending physicians to a weekly game of squash and another runs a cycling group from his home on weekends. Overall, the efforts have increased camaraderie and made it less likely that residents feel isolated. When the participants were retested after these interventions, it was clear that they were getting healthier both physically and mentally — blood pressure and cholesterol levels were down, quality of life and sleep quality had improved and anxiety levels had fallen to levels below those seen in the general population (unpublished results; accepted for publication in *Neurosurgery*).

"You can work hard and sacrifice for patient care and still find time for yourself," says Spiotta. "They are not mutually exclusive. It's a philosophical change. You will live longer, have a longer career, be more productive academically and it will help everybody, including the patients you are taking care of."

Institution-directed interventions

More and more institutions have begun showing their commitment to addressing burnout by making physician wellness and satisfaction one of their quality indicators. Many create an institution-wide physician wellness committee to assess the degree of burnout, identify drivers and create and trial interventions with input from front-line physicians, resurveying periodically to measure success. That same committee can also identify inefficient processes that frustrate physicians and develop performance improvement initiatives to resolve them.

Since burnout develops when job demands and performance expectations are high while the ability to control work is limited, institutional interventions that seek to mitigate workplace stressors by adjusting workloads or schedules and decreasing clerical burden, all with an eye to restoring physician autonomy, are among the most successful.

Physicians who are allowed to spend at least 20 percent of their work life doing something that they care deeply about are less likely to develop burnout. Flexible scheduling can increase physician satisfaction and decrease stress. An ICU study found lower degrees of burnout, better work-life balance and lower levels of physician distress with cross-coverage on the weekends than with continuous scheduling.[15] At Hennepin County Medical Center in Minneapolis, MN, stress levels of female physicians came down when an effort was made not to schedule complicated cases as the last case of the day so that they could more reliably leave to pick up their children from daycare by 5:30 pm (https://www.stepsforward.org/modules/physician-burnout).

A number of measures have been developed to reduce the clerical burden on physicians. Tap and go devices enable physicians to instantaneously log into the EHR with the swipe of a badge, saving the physician the frustration of logging in dozens of times each day and as much as an hour a day of work time. Medical scribes, who sit in

on the visit and document its details in the EHR, can also help relieve physicians of administrative burden and are allowed per MUSC Health policy. However, some authorizations in the EHR must be completed by providers and many of the EHR-provided clinical decision aides are intended for them as well. Adding advanced care providers to the care team, who could complete the necessary authorizations and documentation and discuss salient features with the physician before the patient visit, could be one answer. Other ideas for optimizing workflow to reduce physician burnout are available through the AMA Steps Forward program (https://www.stepsforward.org/modules?category=workflow).

To date, small reductions in burnout have been achieved with a variety of interventions, but institutional efforts are showing the most promise. To make real headway with burnout, however, more research is needed to determine which of the institution-directed interventions are most effective, whether a combination of institution-directed and physician-directed interventions works better than either alone and whether involving physicians in designing the intervention improves its efficacy. If loss of autonomy fuels burnout, restoring it by calling on frontline physicians to help craft solutions could well be an important step in loosening its grip.

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MUSC Welcomes New Chief of Endocrinology

Noted diabetes researcher **Timothy J. Lyons, M.D.**, who joined MUSC in early 2017 as division chief of endocrinology**,** is a man with a mission. Thirty years ago, when he was a fellow at MUSC, he worked with John Colwell, M.D., then the division chief, to help launch a landmark trial of patients with type 1 diabetes — the Diabetes Control and Complications Trial (DCCT). As an MUSC faculty member in the 1990s, he began to collect samples from trial participants for study in the laboratory. In the early 2000s, he left MUSC to take a position as division chief of endocrinology at the University of Oklahoma, where he built a multispecialty diabetes center, supported by millions in funding from governmental and philanthropic sources, and worked with local Native American tribes to improve their diabetes care. Now back at MUSC, Lyons will be the first to hold the John Colwell Endowed Chair in Endocrinology and will continue the work that his mentor started, realizing the potential of DCCT long-term data to yield invaluable insights into the vascular complications of diabetes.

The DCCT trial randomized 1400 patients with type 1 diabetes at 28 sites to aggressive glucose management or much less intensive standard management to evaluate whether tight glucose control would reduce complications, which include eye and kidney damage, heart attack and stroke. Although the trial was supposed to continue for ten years, it was stopped in its ninth year by its safety oversight committee because eye damage in patients who received aggressive management of their glucose was reduced by 70 percent. Aggressive management of glucose levels became the new standard of care for reducing the shorter-term complications of type 1 diabetes. "Those findings changed the management of type 1 diabetes worldwide," says Lyons.

Although the trial ended decades ago, 95 percent of the patients continue to be followed up yearly as part of an observational study. The goal of the study is to understand whether the aggressive management provided during the years of the trial helped protect patients against the longer-term complications of diabetes, such as cardiovascular disease. Results thus far point to highly significant reductions in cardiovascular disease and early mortality in those whose glucose level was aggressively managed during the trial.

As more data about long-term outcomes in the DCCT participants become available, the specimens that Lyons obtained in the 1990s become ever more valuable because basic science findings can now be correlated with the clinical course of the patients from which they were obtained. With access to both the clinical and basic science data, MUSC diabetes researchers are uniquely positioned to begin to understand the vascular complications of diabetes. "In the DCCT samples, in particular, MUSC has something that is absolutely unique here," explains Lyons. "No one else has gotten anything like that."

It was a desire to safeguard the legacy of that trial that brought Lyons back to MUSC. "The patients are starting to get old in DCCT, but so are the investigators — I came back to make sure we keep it alive and recruit in the next generation of investigators. We collected all of these samples and clinical data and they are in our hands, and it is up to us to make sure it comes to fruition or we could lose the whole thing." Lyons is not about to let that happen. He is already busy recruiting young investigators to work on the study, which he estimates will continue to yield insights for at least another 20 years.

Dr. Timothy J. Lyons

Photograph by Brennan Wesley

New Physicians

Michael G. Hillegass, M.D.

Board Certification: Anesthesiology: Pain Medicine // Clinical Interests: Back pain, epidural steroid injections, facet injections, radiofrequency ablation, ultrasound-guided interventional pain procedures, central and peripheral neuromodulation and neuroablation, postoperative pain syndromes // Medical School: Wake Forest School of Medicine of Wake Forest Baptist Medical Center // Residency: Medical University of South Carolina // Fellowship: Brigham & Women's Hospital, Harvard Medical School

John M. Kaczmar, M.D.

Specialties: Hematology/oncology, cancer - head & neck tumors // Clinical Interests: Head and neck cancer, immunotherapy, cancer survivorship // Medical School: Columbia University College of Physicians and Surgeons // Residency: University of Pennsylvania // Fellowship: Temple Fox Chase Cancer Center

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Board Certification: Obstetrics and Gynecology // Clinical Interests: Contraception and family planning, gynecologic surgery, menstrual disorders, vaginal birth after cesarean (VBAC) // Medical School: University of Connecticut School of Medicine // Residency: Brown University – Women & Infants Hospital of Rhode Island

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