Fighting Fibrosis
MUSC Receives National Quality Improvement Award

MUSC Medical Center is one of five hospitals in the nation that have been recognized by the American Hospital Association (AHA) for leadership and innovation in quality improvement and safety.

Patrick J. Cawley, M.D., Executive Director and CEO of the MUSC Medical Center, accepted the AHA’s Citation of Merit on July 20, 2014 at the Health Forum-American Hospital Association Leadership Summit in San Diego. This award honors hospitals that are making progress in quality improvement and offer models that can be replicated by others in the hospital field.

Specifically, MUSC was recognized for hard-wiring clinical decision support tools and harnessing academic resources and talent, as well as engaging families and patients in committees and projects, to achieve its goal of improving quality. Since 2007, central-line infections at the medical center have dropped by 84% and ventilator-associated pneumonia by 52%.

“We are dedicated to the science of quality improvement,” states Cawley. “We focus on building a culture of safety, empowering leadership at all levels, and supporting robust process improvement. Above all, we involve our patients in creating the processes that promote wellness and the best possible outcomes.”

Other hospitals named as Citation of Merit honorees for the American Hospital Association-McKesson Quest for Quality Prize were the Richard L. Roudebush VA Medical Center in Indianapolis, IN and the University of Wisconsin Hospital and Clinics in Madison, WI. The Quality Prize Winner was Virginia Commonwealth University Medical Center in Richmond, VA. Finalist for the Quality Prize was Carolinas Medical Center-NorthEast in Concord, NC.

Criteria for the 2014 award included the demonstration of an organizational commitment to and progress in achieving the Institute of Medicine’s six quality aims for safe, effective, efficient, timely, patient-centered and equitable health care.
On the cover: Fluorescent micrograph of fibroblasts, which give rise to connective tissue (e.g., collagen). Overproduction of collagen is a hallmark of pathological fibrosis. Image by Dr. Torsten Wittmann; licensed from sciencesource.com.
AN ON-OFF SWITCH FOR CONSCIOUSNESS?

Targeting neurons in the locus coeruleus to trigger arousal from anesthesia

BY KIMBERLY MCGHEE

Although certain regions of the brain are thought to be associated with waking, little is known about the precise mechanisms underlying arousal from general anesthesia. “It’s been a big black box,” says Elena M. Vazey, PhD, a senior postdoctoral fellow in the Department of Neurosciences.

In the March 11, 2014 issue of the Proceedings of the National Academy of Sciences, Vazey and Gary S. Aston-Jones, PhD, the Willam B. Murray SmartState™ Endowed Chair in Neuroscience, showed for the first time that a specific subset of norepinephrine neurons (Figure, green stain) in the locus coeruleus (LC) are a potent trigger for inducing arousal from isoflurane general anesthesia. The LC, the main site in the brain for the production of norepinephrine, governs responses to stress and panic and has been linked to the sleep-wake cycle.

Vazey and Aston-Jones were able to activate precisely the targeted norepinephrine neurons using DREADDs (Designer Receptors Exclusively Activated by a Designer Drug), a novel targeted genetic approach. The designer receptors (Figure, magenta stain) were delivered via an adeno-associated virus fitted with a promoter to target the norepinephrine neurons of the LC. The DREADDs and the designer drug clozapine-N-oxide (CNO) act together, the latter serving as a key to unlock the former. “You can essentially pop a pill to turn these designer receptors on or off,” explains Vazey.

By administering CNO to “turn on” the designer receptors and activate the targeted norepinephrine neurons, Vazey and Aston-Jones were able to awaken rats that had been anesthetized with isoflurane or to slow the induction of anesthesia. Administration of β or α-1 noradrenergic antagonists prevented arousal and increased the duration of anesthesia.

These findings challenge a prominent theory about how general anesthesia works. Proponents of the “membrane fluidity” theory speculate that the anesthetic agent acts broadly on the brain’s neurons by permeating their membranes. In contrast, Vazey and Aston-Jones showed that activating only a small fraction of neurons could have a very profound effect on anesthesia.

This study in an animal model could have implications for clinical practice. Patients with high levels of stress, such as those with anxiety disorders, have elevated levels of norepinephrine and so may be harder to anesthetize and more prone to remaining “lightly” sedated. In contrast, patients taking β-blockers for cardiovascular disease, which lower norepinephrine levels, may be very sensitive to anesthesia and slower to awaken. Providing a β-blocker before administering anesthesia in the former and selecting β-blockers that do not cross the blood-brain barrier in the latter could help offset these effects. Studies in humans will be needed to confirm the potential benefits of these clinical strategies.

Currently used primarily for research, DREADDs also have broad therapeutic potential because they make possible a manipulation of the brain that is much more focused and transient than that achieved by deep brain stimulation or transcranial magnetic stimulation. They could also provide a less invasive method than the currently used surgical resection for disabling the region of the brain in which an epileptic seizure originates.

Reference

The buildup of amyloid plaques in the brain is one of the causes of the neuronal loss and memory deficits of Alzheimer’s disease (AD). For years, researchers have focused on one kind of enzyme that produces the plaques—the β-secretase (BACE-1). But now an MUSC scientist and his collaborators have established in mouse models that a different enzyme is actually the primary plaque producer. Furthermore, they have identified a drug compound that shows promise for being developed into an inhibitor of that enzyme.

Mark S. Kindy, PhD, Associate Chair in Regenerative Medicine and Cell Biology at MUSC, was one of the five researchers who reported their findings in several journals, including the Journal of Alzheimer’s Disease. “We have identified cathepsin B as the primary β-secretase, not BACE-1,” says Kindy. “This explains why BACE-1 inhibitors have not been successful in the past.”

This finding advances scientific understanding of how to better disable the main culprit in one of the causes of AD.

The promising drug compound is E64d, a cysteine protease inhibitor of cathepsin B that has already been shown in clinical trials to be safe in humans. No other AD therapeutic research program is known to be investigating this kind of inhibitor.

“If we can inhibit the cathepsin B activity, we may be able to slow the progression of Alzheimer’s disease and extend years of healthier life for many people,” Kindy explains. Currently, AD drugs only treat symptoms. There are no drugs that slow, prevent, or cure the disease.

Another distinction of this group’s research was the use of oral administration of the drug, as opposed to the brain injections done in earlier mouse studies. This finding is important for potential future human use of the drug because oral administration is simpler.

β-amyloid plaques are the hallmark of AD. Their creation begins when amyloid-β (Aβ) peptides are released by the “cutting” of a larger protein called amyloid precursor protein (APP). The enzyme “scissors” is β-secretase, of which there are several kinds. BACE-1 was thought to be the primary β-secretase and cathepsin B a secondary. As Aβ peptides collect in the brain, they form plaques in the regions responsible for memory. In addition, cathepsin B is responsible for the generation of a pyroglutamate form of Aβ that is important in the development of the disease process. The drug E64d inhibits the “scissors” from cutting APP into smaller toxic peptides and prevents the production of Aβ pyroglutamate. Researchers also confirmed cathepsin B as the right target when they tested mice with a gene knockout of BACE-1 vs mice with a gene knockout of cathepsin B. They found that the mice with the latter had reduced AD-like pathology. Moreover, cathepsin B knockout as well as E64d treatment were shown to improve memory deficit in mice.

The research team will now seek to modify E64d so that it, or other iterations of it, will more effectively inhibit cathepsin B and produce fewer side effects, with their goal being to eventually move into clinical trials. Funding for the initial research was provided in part by the Veterans Health Administration, the National Institutes of Health, and the Alzheimer’s Association.

Reference
Transplant medicine has made significant strides over the last 30 years in developing immunosuppressive drugs that decrease organ rejection within the first three months, but the Holy Grail—drugs that will improve long-term graft outcome without systemic effects—remains elusive. Graft rejection occurs in 15% to 20% of kidney transplants and up to 50% of heart and lung transplants. Although drugs such as rapamycin can improve these odds, they are seldom used during transplant because of their negative effects throughout the body.

Three MUSC scientists have successfully demonstrated in mouse models a way to deliver rapamycin via a nanocarrier to a transplanted kidney and its local environment only, leaving the rest of the body’s immune system unaffected. Their initial findings were presented at the State of the Art Winter Symposium of the American Society of Transplant Surgeons in January 2014.¹

The novelty in their approach is that they have combined therapeutic tools that are already in use in medicine—nanocarriers, targeted therapy, and rapamycin—and introduced them to transplant surgery. “This has never been done before in transplant medicine,” says Nadig. “It’s the opposite of the approach used currently in cancer. While many oncologists are trying to enhance the immune system surrounding a tumor to fight it, we are facilitating the proliferation of the T-cells that induce tolerance to the organ while suppressing the effector cells that attack the new graft.”

Nadig’s experience as a transplant surgeon led him to choose laboratory models that would translate to the clinic. For example, the team added the rapamycin nanocarrier, referred to as TRaM, to the perfusion solution in which the organ was stored. “So before it experienced the insult of transplant, the organ was immunologically protected,” says Nadig.

Broome’s TRaMs are “decorated” with tracking fluorophores and various other molecules that target the endothelial cells lining the kidney’s blood vessels and the transplanted kidney itself. The nanoparticles are taken up into the cells, where a change in pH triggers their rupture and the release of the drug. In this way, the immunosuppressant is delivered only to cells in the region involved in the surgery. The nanoparticles not internalized by the target cells remain intact, their payload of immunosuppressant safe inside, and circulate harmlessly until excreted.

Broome anticipates that she will be able to tailor these nanoparticles to other organs and applications. “We can personalize the nanoparticle to any transplanted organ,” says Broome. “This is a novel platform technology with endless possibilities, not just a one-trick pony.”

The collaborators are planning to develop these approaches through their new company, ToleRam Nanotech, LLC.

Reference
Bacteria resist β-lactam antibiotics by attacking them with an enzyme, by blocking their entry via reduction in the size of channels in the outer membrane, by expelling them with pumps, or by altering the active site of the PBP to make it a less attractive target.

The story of our efforts to control Neisseria gonorrhoeae illustrates just how effective such bacterial resistance can be. After seemingly being dealt a death blow by the introduction of β-lactam antibiotics in the 1940s, N. gonorrhoeae began to strike back, developing resistance first to penicillin and then to a long line of other antibiotics, including narrow-spectrum cephalosporins, tetracyclines, macrolides, and fluoroquinolones. In recent years, only two extended-spectrum cephalosporins—ceftriaxone and cefixime—have remained effective. In 2011, a cephalosporin-resistant strain of N. gonorrhoeae was reported in Japan. Subsequently, the Centers for Disease Control and Prevention withdrew its recommendation of cefixime as a first-line treatment for gonorrhea in the U.S. due to this growing resistance. This has left treatment options very limited and may portend a new era of untreatable gonorrhea.

In an effort to identify critically needed compounds with efficacy against resistant strains of N. gonorrhoeae, Davies and his team developed a high-throughput assay with which they screened a 50,000-compound library in MUSC’s Drug Discovery Center. To develop the assay, they focused on a tried-and-true target—a PBP, specifically PBP2. At the heart of their assay is Bocillin-FL™, a fluorescent penicillin that competes with the tested compound to bind to PBP2 and emits different intensities of fluorescence in its bound and free forms. If the tested compound is a potent PBP2 inhibitor, it will successfully bind with PBP2, and Bocillin will remain in solution in its free form. In contrast, if the compound is a poor inhibitor, Bocillin binds to PBP2. Using this assay, the team identified several compounds with antimicrobial activity against N. gonorrhoeae—some effective even against resistant strains.

Because PBPs occur in most bacteria, the assay can be used to identify novel compounds against virtually any bacterial pathogen. The golden age of β-lactam antibiotics may be almost over, but Davies is restoring some of their luster by using PBPs, their primary target, to identify compounds that could one day protect us against increasingly resistant pathogens.

Reference

REACHING FOR
New Lows
Since the introduction of computed tomography (CT) four decades ago, physicians have sought to balance the benefit of this unequaled diagnostic tool with its downside of radiation exposure. Now, that risk has dropped with FDA approval in May of a next-generation CT scanner that delivers the lowest radiation dose in the industry. The Somatom Force (Siemens Healthcare USA, Malvern, PA), located in MUSC’s Heart and Vascular Center, is so new it is one of only three in the United States.

U. Joseph Schoepf, M.D., Professor in the Department of Radiology and Radiological Science and Director of the Division of Cardiovascular Imaging at MUSC, led the clinical evaluation of the new technology. “This scanner, because of its massively increased tube power, enables us to use very low-energy X-rays and photons, the lowest possible to date,” Schoepf says. “There is no other system on the market that can image with an X-ray energy of 70kV. Compared to what was required previously in terms of radiation exposure and contrast media, this is a warm breeze of a test.”

Diagnostics can now embrace the benefits of 4-D imaging of organs and the tiniest anatomical structures with less worry about radiation exposure because the Force delivers a dose that is, for certain examinations, considerably lower than that delivered by previous CT systems.

The advances of this technology over earlier technology include:

• More powerful Vectron X-ray tubes that produce higher currents at lower voltages (70 – 150 kV in increments of 10 kV). The lower kV settings produce clearer images with less “noise.”
• Two detectors that are bigger than those in Siemens’ previous high-end scanner (the Somatom Definition Flash), increasing coverage to 2 x 96 rows (2 x 192 slices) and allowing for a perfusion range of up to 22 cm, thus enabling the imaging of blood flow through entire organs—for example, the brain or the heart.
• A faster table. The Force table has a speed of 737 mL per second and can provide a field of view of up to 50 cm at Flash speed coverage. A body scan can be completed in two to three seconds.
• Higher rotation speed of the scanner gantry, which produces a faster “shutter speed.” Thus, the Force is particularly well-suited for capturing crisp and clear images of the beating heart and coronary arteries. It can complete an entire study of the heart within a quarter of a heartbeat.
• Two dedicated spectral filters that optimize the X-ray spectrum as it relates to air-to-soft tissue contrast, which is helpful when imaging the lung or colon.

Schoepf, an internationally renowned expert in cardiovascular imaging, supervised the Force’s clinical testing in early 2013 at MUSC. He and his colleagues continue to conduct numerous studies of the efficacy of this third-generation technology and have published widely on the topic.

In one article that reported on a study of contrast medium volume, the researchers validated that CT of heart vessels at 70 kV results in robust image quality for studying the narrowing and blockage of arteries at significantly reduced radiation dose (0.44 mSv) and contrast medium volume (45 ml). In another study, they found that the Force’s enhanced ability to analyze the X-ray spectrum enables better tissue characterization of the liver, resulting in improved early detection of liver cancer and metastasis.
Schoepf’s relationship with Siemens goes back to 1998 when he worked with that company to develop the first mechanical CT scanner for heart imaging. In 2004, he and Philip Costello, M.D., FACR, Chair of the Department of Radiology and Radiological Science, who also worked with Siemens in Boston, arrived at MUSC. They continued to develop every major iteration of CT scanners: the first 16-slice scanner, the first 64-slice scanner, and the first dual-source CT scanner, which advanced through the three iterations. The Somatom Force is the last of these.

Advantages for Patients
For decades, Americans have been receiving increasing doses of ionizing radiation. Between 1980 and 2006, the annual per-capita radiation dose in the U.S. from medical procedures increased 600%. Previously, the sources were natural background, nuclear, occupational, and consumer products.

Lower-radiation, faster CT technology benefits all patients, but in particular the following:

Young patients and children. Because the tissues of their bodies are still developing or turning over faster, younger individuals are more vulnerable to radiation. A 2012 article in The Lancet reported that multiple use of CT scans in children can nearly triple the risk of leukemia and brain cancer.

Patients who require frequent surveillance with CT scans. At MUSC’s Heart and Vascular Clinic, many patients are monitored periodically via CT scans for progression or resolution of various disorders, for example Marfan’s Syndrome (scanned annually) or other aortic pathologies. The Force drastically reduces their cumulative dose.

Obese patients. There is an overwhelming need for adequate diagnostic and treatment tools that are scaled for the obese. In the past, these patients were a challenge during CT scans because either an excessive radiation dose was necessary to generate sufficient penetration power, or the images were poor and of little diagnostic value because of insufficient photons. The Force has sufficient power to bestow the benefits of low tube voltage and low-radiation-dose techniques even upon obese patients.

Patients who are unable to hold their breath. The capability to scan a trauma victim, a critically ill patient, or an intubated person in less than one second produces images with fewer respiratory motion artifacts that make accurate diagnosis difficult.

Patients with impaired kidney function. By producing low-energy X-rays and the resulting weaker photons that are more readily absorbed by iodine contrast medium, the Force provides scans of higher attenuation and higher iodine contrast. Therefore, radiologists can use less contrast dye. “The weaker the photons we use,” says Schoepf, “the higher the signal we get from the dye that we inject for studies. That means we can reduce the volume from the usual 100-150 ml to between 30 and 50 ml.”

Patients on the brink of congestive heart failure. Any reduction of contrast medium used during vascular studies on these patients is beneficial, as the injection of dye can trigger volume overload.

MUSC as a Productive Proving Ground
Why was MUSC chosen as one of only three U.S. locations for installing this ground-breaking technology, the others being the Mayo Clinic in Rochester, MN and the National Institutes of Health in Bethesda, MD?

“We lead the country in imaging innovation,” explains Costello. MUSC’s radiology department benefits from strong collaborative relationships with other departments, says Costello, particularly with cardiology, pediatric cardiology, vascular medicine, vascular surgery, emergency medicine, and cardiothoracic surgery. Because of this, the clinicians are able to develop innovations more rapidly. The department is highly productive in producing publications and presentations that demonstrate the clinical utility of these innovations, resulting in high visibility. Furthermore, Costello feels that the department’s support staff is engaged and supportive. “We have a well-trained and interested group of technologists who help us with these innovations,” he says. “They are willing to learn the technology and software that makes it happen. So, the whole environment is positive.”

“Overall, this is a safer, gentler way of imaging our patients from a radiation perspective as well as a contrast media dye perspective.” — Dr. U. Joseph Schoepf
The innovative spirit of MUSC’s imaging programs is internationally recognized as well, says Schoepf. “Physicians from all over the globe come here to get trained in advanced imaging methods and perform research in cutting-edge non-invasive, diagnostic applications,” he notes. In addition, MUSC has become an important training ground for many U. S. physicians who seek to update their qualifications and obtain credentials in some of the more advanced imaging techniques.

“Our biggest goal with an industry relationship,” says Costello, “is to introduce new technology that advances patient care by providing accurate diagnostic tests that decrease invasive procedures and shorten hospitalization times. We have the opportunity to bring into our institution devices or equipment that eventually will be introduced in a broader market, but the central benefit is to prove feasibility and enhance clinical utility at the same time.”

One of the markers of medicine’s vigilance about radiation exposure is the Joint Commission’s mandate that CT radiation doses must be documented in a patient’s medical record. With the increasing scrutiny of cumulative dosage, it is clear that industry and academic medicine must continue to work together to refine technology to achieve the safest possible patient outcomes.

References
1 Meyer M, Haubenreisser H, Schoepf UJ, et al. Closing in on the K edge: Coronary CT angiography at 100, 80, and 70 kV—initial comparison of a second- versus a third-generation dual-source CT system. Radiology 2014; 140244.
It has been estimated that some 45% of all deaths in developed countries are due to organ dysfunction resulting from fibrosis. It is implicated in diseases that take a heavy toll on our society, including cardiovascular disease, pulmonary fibrosis, liver cirrhosis, and chronic kidney failure. Virtually every organ in the body is vulnerable; the affected organ shrinks, hardens, and ceases to function properly, leaving little treatment recourse for patients other than transplant.

“Fibrosis is the final common denominator in all those who require a transplant,” explains Kenneth D. Chavin, M.D., PhD, Surgical Director of Liver Transplant at MUSC, “and it rears its head as part of the process of chronic rejection as well.” (See “Special Delivery” on page 4 for a novel technique for combating rejection.)

Although the specific factors leading to fibrosis may vary slightly by body compartment, all organ systems are thought to share a common final pathway to fibrosis (i.e., the excessive production of collagen). Thus, an anti-fibrotic agent shown to have efficacy in one fibrotic disease could hold promise for others. Despite the overwhelming need, few agents with anti-fibrotic effects have made it to the market in the U.S., leaving millions of patients with very limited treatment options.

That could be changing, as 2014 is proving to be a watershed year for advancing anti-fibrotic therapies. Positive findings were reported from important clinical trials of anti-fibrotic agents for idiopathic pulmonary fibrosis and heart failure. Trials are also under way in fibrotic diseases of the liver and kidneys.

Overcoming Obstacles
What have been the obstacles to advancing anti-fibrotic agents through clinical trials and into the clinic? For many years, pharmaceutical industry interest has been faint for a number of reasons. The underlying mechanisms of fibrosis were poorly understood. There were few biomarkers for fibrotic disease, and so invasive
Organ-specific diseases leading to fibrosis

Eye
- Advanced macular degeneration

Heart
- Diastolic dysfunction
- Heart failure with reduced ejection fraction
- Heart failure with preserved ejection fraction

Lungs
- Idiopathic pulmonary fibrosis
- Scleroderma-associated interstitial lung disease

Liver
- Chronic viral hepatitis
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis

Kidneys
- Diabetic nephropathy
- Polycystic kidney disease

Pancreas
- Acute pancreatitis

Skin
- Scleroderma
- Keloids

Systemic
- Systemic sclerosis
- Cystic fibrosis

Injury-Related Fibrosis
- Surgery-induced
- Radiation-induced
- Burn-induced
biopsies were necessary to assess outcomes. Fibrosis and the chronic diseases with which it is associated take years to do their damage, making them poor fits for typical clinical trials that follow patients for restricted periods of time.

As the mechanisms underlying fibrosis are becoming better elucidated and as more and more biomarkers of disease are being identified, pharmaceutical interest in developing anti-fibrotic agents has been growing. According to Karen Lackey, the new Director of the South Carolina Center for Therapeutic Discovery and Development, “Within the last few years, there have been significant breakthroughs in our understanding of the pathophysiology of these diseases and the role of relevant biochemical pathways, and perhaps most importantly, there are now examples of drugs that seem to work (i.e., pirfenidone). These advances make it highly likely that effective therapeutic agents to treat diseases like idiopathic pulmonary fibrosis, scleroderma, diabetic kidney disease, and even liver fibrosis can be created.” A number of leading pharmaceutical companies (e.g., Bristol Myers Squibb, Biogen Idec, Gilead Sciences, Pfizer, Sanofi, GlaxoSmithKline) have anti-fibrotic agents in their drug pipelines or are working to develop them.

Challenges, of course, remain. Perhaps one of the most serious is preventing off-target effects of anti-fibrotic agents. The flip side of the good news that an anti-fibrotic agent might be effective across a number of organ systems is that it could target not only pathological, but also normal, fibrosis. Impairing normal fibrosis could limit the ability of the body to heal itself and make healthy connective tissue. As with anti-cancer therapies, efforts are being made to better target anti-fibrotic therapies. Taking a page from the playbook for personalized cancer treatment, researchers are working to develop better biomarkers that will predict which patients might benefit from a particular therapy. Pharmaceutical companies are taking care to develop diagnostic tools to accompany each targeted therapeutic agent to ensure proper patient selection.

**Cellular and Molecular Mechanisms Underlying Fibrosis**

After injury, organs in the body undergo a wound-healing response, intended to create new connective tissue that provides structure to the organ. This process is extremely complicated and involves a wide variety of cells, molecules, and signaling pathways. A critical cell in the process is the fibroblast, which both produces extracellular matrix (ECM) and governs its resorption.

In pathological fibrosis, the balance is lost between normal production of ECM (scar tissue) and its resorption. With progressive fibrosis, the tissue becomes less elastic and pliable and more fibrous, stringy, and tough. These changes in tissue architecture alter organ function and can ultimately lead to organ failure.

Effective anti-fibrotic therapeutics will require an understanding of all of the cells involved in fibrosis. According to Lynn M. Schnapp, M.D., Director of the Division of Pulmonary and Critical Care, who is seeking to identify myofibroblast precursors implicated in pathological fibrosis: “If you are going to develop additional therapies to target collagen synthesis, you need to identify each of those cells that are potential collagen producers. Each could have its own distinctive cell markers, its own cell surface profile, that could be targeted by a therapeutic.”

Fibroblasts and the smooth muscle–like myofibroblasts into which they differentiate are prolific producers of ECM. However, it is still debated whether fibroblasts residing in an organ compartment are activated by injury to produce excess ECM or whether fibrocytes in the bone marrow are recruited to the area of injury, where they then differentiate into fibroblasts/myofibroblasts. Pericytes, which typically form a sheath around blood vessels and regulate vascular stability, are another group of fibrogenic cells in which there is growing research interest. Schnapp has shown that pericytes are major contributors to the myofibroblast population in a mouse model of pulmonary fibrosis. Finally, epithelial-mesenchymal transition (EMT), in which epithelial cells differentiate into mesenchymal cells, is thought to create an environment conducive to fibrosis. The contribution of EMT to collagen synthesis remains hotly debated.

Pathological fibrosis in any given organ system likely involves more than one of these myofibroblast precursors, suggesting that combination regimens of anti-fibrotic agents, each targeting a different precursor, might be necessary for successful therapy, as is often the case with cancer and chronic conditions such as hypertension. Such combination regimens would use lower doses of more than one anti-fibrotic agent to improve efficacy and mitigate side effects.

The role of inflammation in the development of fibrosis is another hotly debated topic. In many organ systems, acute or chronic inflammation precedes fibrosis; however, inflammation has not been found to play a role in idiopathic pulmonary fibrosis. Proponents of inflammation as the driver of fibrosis argue that damaged epithelial or endothelial cells secrete inflammatory mediators such as cytokines and chemokines that recruit lymphocytes, macrophages, and other inflammatory cells to the site of injury. These cells and their secretions then activate effector cells—typically fibroblasts and myofibroblasts—to make ECM and lead to fibrosis and scarring.

Collectively, MUSC researchers are investigating almost all of the molecular pathways associated with fibrosis, including peptides,
cytokines, and growth factors (Don C. Rockey, M.D.; Galina S. Bogatkevich, M.D., PhD), TGF-β (Lynn M. Schnapp, M.D.), the caveolin-1 signaling pathway (Stanley R. Hoffman, PhD; Elena V. Tourkina, PhD); and integrin and matrix pathways (Amy D. Bradshaw, PhD).

**Systemic Sclerosis**

In many ways, systemic sclerosis, the systemic form of scleroderma, is the fibrotic disease. Scleroderma, which translates literally as “hard skin,” is characterized by deposition of excessive collagen in the skin of the face, extremities, and trunk as well as injury to the capillaries. However, according to Richard M. Silver, M.D., FACP, FACR, Director of the Division of Rheumatology and Immunology: “In many cases, it’s more than skin deep and affects the gastrointestinal tract, the lungs, the heart, the kidneys, and the blood vessels, so it is a model for many other more prevalent diseases. Whereas there may be 300,000 Americans with scleroderma, millions of others suffer from fibrosis of the kidneys, the liver, the lungs, the heart, and the blood vessels.” If an anti-fibrotic agent is demonstrated to be efficacious in systemic sclerosis, that could mean that it holds promise for treating fibrotic diseases that are more confined to particular organ compartments.

**Translational Anti-Fibrotic Research at MUSC**

In addition to leading and participating in clinical trials of breakthrough anti-fibrotic therapies (for more detail on these trials, see the organ-specific articles that follow), MUSC’s impressive cadre of fibrosis researchers engage in translational research that is laying the foundation for the breakthrough therapies of tomorrow. A number of researchers have identified and patented promising anti-fibrotic agents and hope to partner with industry to carry them forward toward clinical trials.

**Stanley R. Hoffman, PhD.** Professor in the Division of Rheumatology and Immunology, and Elena V. Tourkina, PhD, Associate Professor in the Division of Rheumatology and Immunology, have characterized a mouse model of systemic sclerosis, in which mini-osmotic pumps emitting bleomycin, known to cause fibrosis, are inserted under the skin. These mice, like humans with scleroderma, have been shown to be deficient in the protein caveolin-1. Underexpression of caveolin-1 promotes the differentiation of monocytes in the bone marrow into fibrocytes and their migration via the circulatory system to sites of injury, where they further differentiate into fibroblasts and make collagen. Administered caveolin-1 scaffolding domain (CSD) peptide substitutes for the lost caveolin-1 and prevents fibrosis. Mice implanted with the bleomycin pump showed a significant thickening of the skin (along with other systemic symptoms), whereas those receiving both bleomycin and CSD did not. Hoffman and Tourkina are inventors on an issued U.S. patent for the use of CSD as an anti-fibrotic treatment and, on the basis of promising results in small animal studies, are now working to optimize the peptide for drug development and planning other studies that must be performed before the initiation of clinical trials. They are also assessing whether CSD, currently delivered as an injection or via a mini-pump, could be administered orally, as oral agents are generally better tolerated by patients.

**Silver, Galina S. Bogatkevich, M.D., PhD.** Associate Professor in the Division of Rheumatology and Immunology, and Yuichiro Shirai, PhD, a postdoctoral research fellow in the Division of Rheumatology and Immunology, have also identified a potentially anti-fibrotic peptide that could help protect against scleroderma-associated interstitial lung disease, and the MUSC Foundation for Research Development has filed a provisional patent application for it. When purified, the peptide has been shown in preliminary studies to reduce collagen and other ECM proteins in scleroderma lung fibroblasts (unpublished data).
Silver is also investigating the role of thrombin, which is important for blood coagulation and clotting, in fibrosis. The lung fluid of patients with systemic sclerosis has very high levels of thrombin. Using dabigatran to block thrombin in bleomycin mouse models of scleroderma reduces the severity of fibrosis compared with controls. Silver and colleagues at MUSC have applied for NIH funding and are planning a pilot study of dabigatran in patients with scleroderma to establish the safety of proposed doses. Once the doses have been shown to be safe, Silver would like to conduct a much larger trial to assess efficacy.

In October 2013, MUSC recruited Carol A. Feghali-Bostwick, PhD, a noted fibrosis researcher, as the Kitty Trask Holt Endowed SmartState Chair in Scleroderma Research. She joined MUSC from the University of Pittsburgh, where she was instrumental in developing a promising anti-fibrotic peptide, E4, that is derived from endostatin. The peptide showed efficacy in bleomycin animal models, but results of animal trials are not always predictive of clinical success. Feghali-Bostwick and her colleagues went a step further and showed that the peptide was effective in a human skin organ model of fibrosis, a novel methodology that she developed. Fibrosis was induced in cultured human skin cells by administration of TGF-β and, two days later after fibrosis had become established, E4 was added. These studies showed that addition of E4 significantly reduced the thickness of the cultured skin, suggesting that it could reverse ongoing fibrosis. On the basis of these promising results, the peptide was licensed by iBio, Inc, a small biotechnology company, which is planning on taking the plant-manufactured peptide into clinical trials in early 2015. Because of Feghali-Bostwick’s involvement in the development of the peptide, MUSC will be one of the first sites in the nation to enroll patients in these trials.

The pages that follow highlight the damage done by fibrosis to several key organ compartments—the lungs, the heart, the liver, and the kidneys—and summarize recently reported clinical trial results that presage likely FDA approval of novel anti-fibrotic agents for pulmonary and cardiac fibrosis. Ongoing clinical trials of anti-fibrotic agents in other organ systems are also briefly discussed.
For eligible patients, lung transplant is the last recourse and has been shown to confer a clear survival benefit. However, most IPF patients do not qualify for lung transplant and have few treatment options available other than supportive care. With the publication of the results of the ASCEND and INPULSIS clinical trials in the New England Journal of Medicine in May 2014, that will be changing.

Previous clinical trials in IPF have yielded disappointing results. Both anti-inflammatory agents and IFN-γ were eventually shown to be of little efficacy, and the former were actually found to do harm to clinical trial participants, leading the National Heart, Lung, and Blood Institute to recommend against their use in patients with IPF.

Such past disappointments made the news of the positive results of the ASCEND (NCT01366209) and INPULSIS trials (INPULSIS-1: NCT01335464 and INPULSIS 2: NCT01335477) even more welcome. “There is a lot of excitement in the pulmonary fibrosis community. These are the first drugs that have shown promise in clinical trials and so everyone is almost giddy,” says Lynn M. Schnapp, M.D., Director of the Division of Pulmonary and Critical Care at MUSC. These trials showed that the characteristic decline in forced vital capacity (FVC) seen in patients with IPF was slowed by both pirfenidone (ASCEND), an anti-fibrotic agent already approved in Europe on the basis of the results of the earlier CAPACITY trials, and nintedanib, a tyrosine kinase inhibitor (INPULSIS). Side effects (rash and gastrointestinal upset for pirfenidone and diarrhea for nintedanib) were mild and were tolerated by most patients at a full or a slightly reduced dose.

“These trials mark an important turning point for the treatment of IPF,” says J. Terrill Huggins, M.D., Associate Professor in the Division of Pulmonary and Critical Care, who served as the principal investigator for the MUSC site in both studies. “We have clearly reached a point where we can slow progression. This was a black box ten years ago, and now we have two drugs that will likely be approved by the FDA.”

“Idiopathic pulmonary fibrosis was a black box ten years ago, and now we have two drugs that will likely be approved by the FDA.” —J. Terrill Huggins, M.D.

Where do we go from here?
As good as this news is, there is still much more work to be done. The drugs slowed decline in FVC but did not reverse disease, and the patients were carefully selected, meaning that results may not be generalizable to patients with other types of pulmonary fibrosis. “People are excited because these are the only drugs we have, but by no means are they the cure. We still need much more research on pulmonary fibrosis,” cautions Schnapp.

Because most novel therapies are likely to have maximal effect in patients with early-stage IPF, clinical biomarkers that could help to identify those patients even before symptom onset are an area of active research at MUSC and nationwide. The Division of Pulmonary and Critical Care is participating in a prospective outcomes registry with Boehringer Ingelheim to help track how IPF is diagnosed and managed in these patients and with what results and to analyze blood samples from these patients to identify possible biomarkers for IPF. It is also applying through the Pulmonary Fibrosis Foundation to participate in its Patient Care Network and Patient Registry, which seek to track outcomes and identify biomarkers in patients with IPF as well as to standardize the treatment for IPF by establishing regional centers following best practices where these patients can be referred.

How do these trials change practice?
With two pharmacological therapies for IPF likely to be approved by the FDA in the next few months, correctly identifying patients with IPF is crucial. Too often, patients with IPF go years after onset of symptoms (shortness of breath, dry cough, fatigue, sometimes finger or toenail clubbing) without an accurate diagnosis, are mistakenly believed to have chronic obstructive pulmonary disease (COPD) or another lung disease, and receive inappropriate treatment.

Patients with suspected ILD or with COPD or other lung disease that does not improve with treatment should be seen in a tertiary care center such as MUSC with a high volume of patients with IPF and access to the latest clinical trials. “At MUSC, we see on average...
eight to ten patients with IPF per week who are on active clinical trials,” says Huggins. Because of its participation in the ASCEND and INPULSIS trials, MUSC is the only institution in the state to be approved to participate in the expanded-access trial for the former and expects to receive approval for the latter shortly. These expanded-access trials provide appropriate patients with continued access to the drugs while the final FDA ruling is awaited. Patients with more serious disease can be screened for a lung transplant. Patients who are diagnosed with an ILD other than IPF can benefit from MUSC’s expertise in scleroderma and sarcoidosis and in treating all of the affected organ compartments.

“There are a lot of things we can offer proactively for patients with IPF. Even though we may not have a potential cure for IPF, we have made significant progress. Having patients active in clinical trials may allow us to get to the summit of cure down the road,” says Huggins.

Patient participation in clinical trials is the best way to ensure that a cure for IPF will one day be found. To refer a patient for a pulmonary clinical trial, including several for IPF, and to find contact information for study coordinators, visit clinicaldepartments.musc.edu/pulmonary-trials.

Currently Recruiting Clinical Trials of Anti-Fibrotic Agents at MUSC

<table>
<thead>
<tr>
<th>Trial Name</th>
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<th>Sponsor</th>
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<td>Expanded Access Program</td>
<td>Pirfenidone/IPF*</td>
<td>InterMune</td>
<td>NCT02141087</td>
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<td>PARAGON-HF</td>
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<td>Novartis</td>
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<td>Michael R. Zile, M.D (<a href="mailto:zilem@musc.edu">zilem@musc.edu</a>)</td>
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<td>SONAR</td>
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<td>NCT01858532</td>
<td>Ruth C. Campbell, M.D./Vickie Hunt, RN (843-792-7852 or <a href="mailto:huntv@musc.edu">huntv@musc.edu</a>)</td>
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IPF = idiopathic pulmonary fibrosis; HFpEF = heart failure with preserved ejection fraction.
*All open pulmonary trials are available at musc.edu/medicine/divisions/pulmonary/research/Clinical Trials

A New Paradigm for the Treatment of Heart Failure?

More than 20 million people in the U.S. and Europe are thought to have heart failure. Approximately half of those patients have chronic heart failure with reduced ejection fraction (HFrEF), meaning that the heart’s forward pumping capacity is compromised and it cannot send adequate blood and oxygen to the organs. In the other half of patients with chronic heart failure, the ejection fraction is preserved, meaning the heart is able to pump effectively but cannot relax and fill rapidly and completely due a ventricle that is stiffened by fibrosis.
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are the mainstay of treatment for patients with HFrEF and have helped prolong the lives of these patients, though many are still frequently hospitalized. In contrast, no pharmacological option has been available for patients with HFpEF. According to Michael R. Zile, M.D., the Charles Ezra Daniel Chair in Cardiology and Director of the SmartState Center for Molecular Proteomics in Cardiovascular Disease and Prevention at MUSC, “The most important unmet need in cardiology today is a treatment for heart failure with preserved ejection fraction.”

According to Zile, 60% of patients with heart failure with preserved ejection fraction (HFpEF) will not survive beyond five years, and 50% of those hospitalized are likely to be readmitted within six months. Like HFrEF, HFpEF has a devastating effect on quality of life. “HFpEF is very common, very lethal, and it causes an unbelievable burden on our patients. To date, zero clinical trials have demonstrated that you can improve morbidity and mortality in HFpEF,” says Zile.

Recent results from the PARADIGM-HF trial (NCT01035255), the largest heart failure clinical trial ever conducted (8,436 patients), has important implications for both populations of patients, according to Zile, who served on the steering committee of the trial.

For patients with HFrEF, it could mean improved outcomes and a new standard of care. The PARADIGM-HF trial was stopped early because it compellingly showed that 200 mg of a twice-a-day investigational, first-in-class agent with anti-fibrotic effects (LCZ696, Novartis Pharmaceuticals) reduced cardiovascular death more than did 10 mg twice daily of the ACE inhibitor enalapril. If the FDA approves LCZ696 (an angiotensin receptor neprilysin inhibitor), as it is expected to do based on the results of the PARADIGM study, it “will replace ACEs and ARBs as the cornerstone of therapy for patients with HFrEF,” says Zile.

For patients with HFpEF, the PARADIGM-HF trial could help clear the way for an important future therapy. On the basis of its compelling results, Novartis is opening a second five-year study of the same investigational agent in patients with HFpEF—the PARAGON-HF trial (NCT01920711). Zile plans on MUSC being among the first institutions in the world to enroll a patient in this trial.

The trials also herald the coming of age for anti-fibrotic therapy for heart failure. Fibrotic pathways play a role in both types of heart failure. The stiffness of the ventricular wall depends largely on the total quantity of collagen, the relative proportion of collagen type I, and the degree of cross-linking between collagen fibers. Continual turnover of collagen is necessary in highly stressful environments such as the heart and lungs to ensure that the extracellular matrix (ECM) stays pliable and new and does not become cross-linked and thus more resistant to turnover. The two types of heart failure represent two ways in which such a healthy homeostasis can be lost. In HFrEF, the degradation of the ECM occurs too quickly, leading to thinner walls in and dilation of the ventricles. Such dilated cardiomyopathy impairs the heart’s ability to contract. In contrast, in HFpEF, the degradation of the ECM occurs too slowly, allowing cross-linking to occur and resulting in the thickening and stiffening of ventricular and blood vessel walls. The stiffer left ventricle is unable to relax, so it cannot adequately and rapidly fill with fluid. In addition to a lethargic turnover rate for the ECM, HFpEF is also typically characterized by increased collagen deposition. The resulting stiffness and inelasticity can wreak havoc in a dynamic environment like the heart.

Amy Bradshaw, PhD, Associate Professor in the Division of Cardiology, who works with Zile to elucidate the anti-fibrotic pathways underlying HFpEF, sums it up as follows: “It is not only important to break down but to make new stuff—you want to keep ECM young—particularly in tissues, such as cardiac tissues, that require high rates of turnover.”

Although fibrotic pathways are implicated in both types of heart failure, many, such as Zile, think that they are more profoundly involved in HFpEF, and thus hypothesize that the new anti-fibrotic drug found efficacious in HFrEF could hold even greater promise among patients with HFpEF.

Zile and Bradshaw have studied the fibrotic pathways that underlie HFpEF. Zile’s laboratory recently completed a study of biopsy samples from healthy patients, those with high blood pressure, and those with HFpEF (unpublished data). Zile and his colleagues demonstrated greater left ventricular stiffness in patients with HFpEF by using a special device to stretch biopsy samples, measure stiffness, and monitor the effects on the individual sarcomeres. They also helped identify biomarkers that could be useful in assessing the severity or aggressiveness of a patient’s disease by analyzing blood samples taken from the same patients from which biopsy samples were obtained (unpublished data).

“At MUSC, we are involved in the discovery of the basic mechanisms of HFpEF, in proving that the basic mechanisms we identify in animal models are relevant to human models, and in developing novel therapeutic strategies to treat these patients,” notes Zile.
A Final Common Pathway to Fibrosis in the Liver

“If injured, the liver, like any other organ, will become fibrotic,” says Don C. Rockey, M.D., a noted investigator of fibrosis in the liver and Chair of the Department of Medicine at MUSC. The liver responds to any injury—whether caused by fatty liver disease, a viral infection, alcohol, or any of a variety of chronic hepatic diseases—with a wound-healing response. In some patients, that healthy response can become exaggerated, leading to fibrosis and eventually to cirrhosis. The fact that such a wide variety of inciting factors culminate in the same outcome—cirrhosis—has fueled speculation that there is a final common pathway to fibrosis in the liver. An anti-fibrotic agent targeting that final pathway could help prevent or delay cirrhosis and the catastrophic complications with which it is associated, including portal hypertension, ascites, variceal bleeding, and liver failure.

Fibrosis in the liver, more so than in perhaps any other organ, is associated with inflammation. When the infection is treated, the fibrosis begins to resolve, providing the best evidence to date that fibrosis can be reversed.

The cellular and molecular mechanisms underlying fibrosis are perhaps better delineated in the liver than in any other organ. Injury and inflammation activate resident hepatic stellate cells, the principal effector cells in the liver, causing them to transform into myofibroblast-producing extracellular matrix and deposit the scar and fibrous tissue typical of cirrhosis. Fibrocytes recruited from the bone marrow and other cells also contribute to matrix synthesis in the liver. A variety of growth factors, integrins, and other factors such as chemokines and vasoactive peptides are produced by stellate cells, and these help create an environment conducive to fibrosis. As the liver becomes more fibrotic, it loses functionality and shrinks from an average of three pounds to one and a half.

Clinical trials in fibrotic liver disease have been hampered by the lack of biomarkers to measure liver fibrosis. Although more such biomarkers have been identified for the liver than for most other organ compartments, too often invasive liver biopsies are necessary to assess disease severity during a clinical trial. Rockey’s laboratory is working to elucidate the basic molecular and cellular mechanisms underlying liver fibrosis in order to establish more serum markers of fibrosis.

The Rockey laboratory is also elucidating how fibrosis affects the vasculature of the liver. Fibrosis damages the endothelial cells lining the blood vessels that supply the liver. Portal hypertension can develop when blood flow is blocked by scar tissue or by stellate cells that have become contractile. Serhan Karvar, M.D., Songling Liu, M.D., and Zengdun Shi, M.D., members of the Rockey laboratory, have developed a robust technique for isolating hepatic stellate cells and endothelial cells and are examining interactions and cross-talk among the epithelial, endothelial, and mesenchymal cells of the liver.

Rockey’s group also collaborates with industry partners to examine the effect of the latest and most promising anti-fibrotic drugs. MUSC is among the nation’s top enrollers for a Gilead trial of GS-6624, a novel anti-fibrotic agent. This monoclonal antibody targeting lysyl oxidase-like 2 (LOXL2) is being tested in patients with liver fibrosis secondary to non-alcoholic steatohepatitis (NASH or fatty liver disease) to determine whether it can delay or prevent disease progression. The same compound is also being trialed in patients with IPF (Principal Investigator: Timothy Whelan, M.D.) and has been studied in patients with a variety of adenocarcinomas.

Delaying Hypertension- and Diabetes-Induced Fibrosis in the Kidneys

In the kidneys, as in other organ systems, fibrosis represents a final common pathway for a variety of diseases. That pathway can lead to organ failure (e.g., end-stage renal disease [ESRD]) and leaves patients little recourse beyond dialysis or transplant.

As with fibrosis of the heart, fibrosis of the kidneys is closely associated with hypertension and diabetes. Each kidney is composed of a filtering unit known as the glomerulus and a series of tubules that perform the final processing of urine. The glomerulus, which has a rich supply of blood vessels by which it receives oxygen and delivers it to the tubules, is very susceptible to high blood pressure and is destroyed by long-term exposure to such stresses. The clinical manifestation of this damage is a reduced glomerular filtration rate. As the glomerulus becomes fibrotic and shuts down, it blocks blood flow, resulting in a hypoxic state in all surrounding tissues that further
promotes fibrosis. Thus, even primary glomerular disease often has marked tubular manifestations due to restrictions in blood flow. In addition, multiple other stressors associated with chronic disease such as production of reactive oxygen species and immune system dysregulation can lead to fibrosis. The mechanisms by which diabetes damages the kidneys is less well understood, but high blood glucose levels are thought to directly damage the glomerular filtration unit and the tubular structures.

As opposed to fibrosis in organs such as the liver, fibrosis in the kidneys is not thought to be reversible. This is especially true of the glomerulus, which is very susceptible to scarring and permanent damage. There is some evidence that fibrosis in the tubules can be reversed, but to a lesser degree than is seen in the liver.

Fibrosis does not result solely from chronic diseases such as hypertension and diabetes. Fibrosis of the kidneys can also be caused by certain genetic diseases, such as polycystic kidney disease. The laboratory of P. Darwin Bell, PhD, Professor in the Division of Nephrology, is seeking to understand the pathways underlying cyst formation and fibrosis in these patients, particularly the mTOR (mammalian target of rapamycin) pathway.

Researchers are also investigating biomarkers of fibrosis in the kidneys. John M. Arthur, M.D., PhD, Professor in the Division of Nephrology and Director of the Renal Disease Biomarkers Smart-State Program, is seeking to identify biomarkers for a number of kidney diseases. He notes that, so far, the biomarkers for fibrosis have been indirect, indicating the presence of an underlying injury process that causes fibrosis rather than the fibrosis itself. The Bell laboratory is working to identify serum biomarkers of polycystic kidney disease.

Bell’s laboratory has also explored the renin-angiotensin system (RAS) in relation to fibrosis. For instance, although angiotensin-2 is a necessary hormone, an excess of it can promote fibrosis through the renin-angiotensin system (RAS). For example, angiotensin-II overactivity through the angiotensin-1 receptor antagonist or angiotensin receptor blockers (ARBs) can be effective in reversing the fibrotic effects in diabetic nephropathy. However, adjunctive therapies may be necessary for further slow or reverse disease progression. One agent being investigated as possible adjunctive therapy for patients with diabetic nephropathy is atrasentan, an endothelin A receptor antagonist.

Ruth C. Campbell, M.D., Associate Professor in the Division of Nephrology, is the principal investigator for the MUSC site of the Study Of Diabetic Nephropathy With Atrasentan (SONAR; NCT01858532), a double-blind, parallel, placebo-controlled trial of the effects of atrasentan on renal outcomes in patients with type 2 diabetes and nephropathy. The study seeks to evaluate whether atrasentan can delay the time to the doubling of serum creatinine levels or the onset of ESRD compared with placebo in patients who are receiving the maximum dose of a RAS inhibitor. The study is currently recruiting patients. For more information on enrolling a patient in the SONAR trial, contact Vickie Hunt at 843-792-7852 or huntv@musc.edu.

References
New Directions
in the Endoscopic and Surgical Management of Chronic Pancreatitis
On completion of this article, the reader will be able:

• To recognize that alcohol and smoking, alone or in combination, are important risk factors for chronic pancreatitis (CP).
• To recognize that debilitating pain of variable nature is often a presenting symptom of CP and to provide proper pain management to these patients.
• To recognize the diagnostic value of endoscopic ultrasound and magnetic resonance cholangiopancreatography for CP.
• To summarize the challenges and best practices for treating exocrine and endocrine disorders in patients with CP.
• To describe the advantages and disadvantages of the principal endoscopic and surgical treatment options for CP.

Chronic pancreatitis (CP) confronts clinicians and patients alike with a tragic Catch 22. Treatments are most likely to be effective when delivered early in the disease, but the morphological and functional changes that are required for diagnosis typically occur late, when damage is already irreversible.

To enhance our current understanding of CP and to identify novel therapies, David B. Adams, M.D., Interim Chair of the Department of Surgery and Co-Medical Director of MUSC’s Digestive Disease Service Line, Katherine A. Morgan, M.D., Interim Head of the Division of Gastrointestinal and Laparoscopic Surgery and Clinical Director of the Islet Transplant Program, and their colleagues organized a multidisciplinary symposium on CP—inviting gastroenterologists, endoscopists, and surgeons, typically siloed at different conferences, to the same forum for a comprehensive and collaborative discussion of CP. Some of the recent findings about the pathophysiology of and risk factors for CP and new directions in diagnosis and management are summarized here.
What is chronic pancreatitis?
Chronic pancreatitis is defined as a chronic inflammatory state resulting in scarring that damages the architecture and the function of the pancreas. It leads to exocrine and endocrine deficiencies, malnutrition, and, in most patients, debilitating pain.

Risk Factors and Etiology
Mutations in a number of genes (e.g., PRSS1, CFTR, SPINK1) have been linked to CP. In healthy people, PRSS1 governs the production of trypsinogen, a pancreatic enzyme that, in its active form trypsin, aids in the digestion of food and then breaks down when no longer needed. In patients with hereditary pancreatitis and a PRSS1 mutation, trypsin is either activated too early or not broken down properly, leading to excessive levels that can damage pancreatic tissue and cause inflammation, increasing the risk for CP and pancreatic cancer.

Alcoholism was once thought to be the primary cause of CP, leading to negative stereotyping of these patients. Although alcohol abuse is the single most common explanation, it accounts for only 30% to 40% of all cases seen at referral centers. Smoking has also emerged as an important risk factor, increasing the rate of virtually every complication of CP, and the risk is increased in patients with a history of both smoking and alcohol abuse. Smoking cessation may be a critical intervention in slowing the progression from acute to chronic pancreatitis and yet few clinicians ask patients about their smoking histories or encourage smoking cessation.

Although genetic mutations play an important role in the etiology of CP, an inciting event, such as an episode of acute pancreatitis, is typically necessary to trigger the fibrotic cascade that will, over time, destroy the pancreas. Patients with a history of acute pancreatitis should be closely monitored for the development of CP and every attempt made to prevent recurrent episodes of acute pancreatitis.

Diagnosis
Moderate to severe CP is now diagnosed with imaging tools such as magnetic resonance cholangiopancreatography (MRCP), which allows noninvasive visualization of pancreatic ducts, and endoscopic ultrasound (EUS), which allows visualization of both ducts and pancreatic tissue. In one study, availability of MRCP studies led to a substantial change in clinical management for 67 of 171 patients. However, detecting CP before the onset of overt scarring, when intervention has the best chance of success, remains a challenge.

Endoscopic ultrasound, in which a small ultrasound transducer fitted on the tip of an endoscope is inserted into the mouth and advanced to the stomach and upper intestine, can provide precise and detailed imaging of the pancreas that correlates well with histological findings. Precision imaging of tissue coupled with a low-risk profile has led to EUS largely replacing endoscopic retrograde cholangiopancreatography (ERCP) as a diagnostic modality for CP.

Endoscopic ultrasound is superior to magnetic resonance imaging (MRI) or computed tomography (CT) for detecting early-stage disease because it can identify more subtle changes (e.g., very small pancreatic cysts or dilated side branch ducts). More timely diagnosis may encourage patients to adopt lifestyle changes that could slow progression of the disease. According to Gregory A. Coté, M.D., an endoscopist specializing in CP who recently joined MUSC as an Associate Professor in the Division of Gastroenterology and Hepatology, “Having objective evidence of damage in the pancreas helps us drive the message home and helps us convince patients to quit smoking and drinking, where relevant.” Finding an etiology for a patient’s pain also lessens the need for further downstream diagnostic testing.

Management
Physicians can find these patients—who can have debilitating, chronic pain, often without a firm diagnosis—difficult to manage. Too often, they assume that little can be done for them. To the contrary, interventions, whether medical, endoscopic, or surgical, are available to provide relief for pain and/or improve quality of life.

Medical Therapy
Medical therapy is the first-line treatment for most patients and focuses on treating symptoms, the most important of which is pain, and addressing exocrine (i.e., inadequate levels of pancreatic enzymes) and
endocrine (i.e., diabetes) insufficiencies associated with CP. Patients with hereditary CP are an exception because of the more aggressive disease course. For these patients, surgical options may be considered sooner.

**Pain Management**

Patients often experience excruciating pain long before the morphological and functional changes needed to establish a definitive diagnosis of CP can be detected, and their pleas for pain relief can be mistaken for aberrant drug-seeking behavior.

The etiology of pain in CP is not fully understood, but the build-up of fluid and increased pressure caused by obstruction of the pancreatic and bile ducts and inflammation of nerves responsible for pain signaling from the pancreas are thought to play important roles. The severity of the pain does not correlate well with the extent of disease. Patients with early CP sometimes feel more pain than patients with irreversible fibrotic damage, whereas some patients with even severe CP feel no pain at all.

Although the “textbook” description of CP pain is an upper abdominal pain radiating to the back, the pain can in fact be variable in severity and duration. Relentless pain, even of lesser severity, takes the greatest toll on patient quality of life.

Failure by the physician to acknowledge that a patient’s life has been dramatically altered by pain can alienate the patient and make treatment adherence less likely. According to Jayne Quinn, BSN, RN-BC, CHPN, a pain resource coordinator at MUSC, “Not believing the patient is very damaging. You can’t have a satisfactory therapeutic relationship with a patient if they don’t feel listened to.”

It is important to begin pain management soon after the symptom arises and before a chronic pain syndrome, which involves changes in neurological pathways, can become established. Once such syndromes are entrenched, pain will continue despite resolution of the problem in the pancreas, just as an amputated limb continues to hurt. Although the brain can be reprogrammed over time to give patients relief from such chronic pain syndromes, it is far easier to treat pain early. Nonsteroidal antiinflammatory drugs, nonopioid analgesics, long-acting opioids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and other centrally acting neuromodulators are among the agents that can effectively relieve pain. Nonopioid therapies should be considered first, but opioids will be required in some patients. It is advised to begin with less potent opioids, progressing to more potent ones only as needed. Online training opportunities in proper opioid management are available to physicians, such as those offered by The American Psychiatric Association (http://nmbon.skns.com/uploads/files/PCSS-O20 Training%20Database.pdf).

Nonpharmacological therapies, including yoga, meditation, mind-body exercises, and biofeedback, can also be important tools for patients in managing their pain. Patients can begin to take back control over their lives by recognizing triggers for their pain and understanding strategies they can use to minimize it (for more information, visit www.painaction.com).

**Diet and Pancreatic Enzyme Replacement Therapy**

Many patients with CP secrete insufficient quantities of pancreatic enzymes, leading to malabsorption.

Often, they are malnourished or have fat-soluble vitamin, B12, or trace element insufficiencies, leading to metabolic bone disease (i.e., osteoporosis, osteopenia) in some. Pain can deter patients from eating, further exacerbating the problem.

Patients with CP often experience exocrine pancreatic insufficiency, leading to oily stools. Some cases of steatorrhea are obvious, while others may be subtle and require blood and stool studies to establish exocrine insufficiency. Low-fat diets are sometimes recommended in these patients. However, MUSC clinical dietitian Maria Nestleroad, MS, RD, LD, CNSC, who often works with patients with CP, worries that recommending a low-fat diet could be harmful in an already malnourished patient. “Instead, I work on diet plans tailored to the needs of each patient, so they can eat what they can tolerate,” says Nestleroad. Patients with CP will tolerate frequent small meals better than less frequent heavier ones.

Proper nutrition is especially important in patients with CP who are considering surgery, because outcomes can be worse in malnourished patients. Vitamin deficiencies should be addressed, and temporary jejunal feeding tubes are recommended for patients who cannot obtain adequate nutrition orally.

Pancreatic enzyme replacement therapy is often necessary to improve digestion and nutrient absorption in patients with CP. Compliance can be an issue, as a number of pills must be taken with every meal. Pills should be taken during and after the meal, not before, to better mimic how the healthy pancreas works.

**Management of Pancreatogenic Diabetes**

Many patients with CP will develop diabetes. Though type 1 and type 2 diabetes mellitus can occur in these patients, type 3c diabetes, is specific to them. Type 3c diabetes develops when entire islet cells (not just β-cells) are lost and has a higher rate of treatment-induced hypoglycemia than other types of diabetes.

Strong consensus exists that fasting glucose and HbA1c should be measured each year in patients with CP; that abnormal findings should
Nutrition goals should be preventing malnutrition, controlling symptoms of steatorrhea, and minimizing meal-induced hyperglycemia. Most patients with type 3c diabetes will need insulin, some requiring an insulin pump, and the insulin sensitizer metformin may prove an effective adjunctive therapy.

Endoscopic Management

Endoscopic treatments for CP-associated pain include celiac plexus block, in which EUS is used to direct a small needle into the celiac plexus and inject a local anesthetic with or without a steroid. The celiac plexus is a bundle of nerves in the upper abdomen that transmits pain signals from the pancreas to the spinal cord. Endoscopic retrograde cholangiopancreatography (ERCP), which involves the placement of a catheter through the endoscope and into the pancreatic and bile ducts, can be used to improve drainage (blockage of the duct may cause pain) by removing stones, expanding the opening of the duct by cutting away fibrotic tissue, deploying a balloon to stretch the tube draining the pancreas, or placing stents. Often, endoscopic procedures must be repeated several times for efficacy. However, some patients prefer endoscopy, according to B. Joseph Elmunzer, M.D., who joined MUSC in July 2014 as the Peter B. Cotton Endowed Chair in Endoscopic Innovation and Associate Professor in the Division of Gastroenterology: “They don’t have any recovery time in terms of time off of work or time away from family. They prefer three or four ERCPs over the course of six months to one operation.”

Both Coté and Elmunzer are working to optimize endoscopic interventions. Coté is leading a multisite clinical trial (NCT01221311) testing whether a single expandable silicone-coated metallic stent can be used instead of the many small plastic stents currently used to fully treat a blocked bile duct caused by CP or other noncancerous conditions. If the metallic stent is shown to be effective, it would mean patients would undergo fewer procedures than are currently required to implant the numerous plastic stents. Elmunzer recently reported the results of a clinical trial showing that, compared with placebo, rectal indomethacin significantly reduced the incidence of the most common post-ERCP complication—acute pancreatitis. Elmunzer and Coté plan to develop a robust clinical trials platform at MUSC to encourage endoscopic innovation, improving diagnosis and treatment for patients with CP and other pancreatobiliary diseases.

Surgical Management

Surgical options (a Frey or Puestow procedure) are also available for draining a dilated pancreatic duct. The procedures show little benefit in patients whose duct is not dilated or whose tissue is fibrotic. If damage is localized to a particular region, then either the head (Whipple procedure) or the tail (distal pancreatectomy) of the pancreas can be removed in an effort to control pain.

For patients without benefit from prior surgeries or for those with diffuse small duct disease, where damage is not regionalized, total pancreatectomy and islet autotransplantation (TP-IAT), pioneered at the University of Minnesota, is a novel treatment option. Patients with hereditary pancreatitis are also good candidates. “In these patients, there is more of a push for islet cell transplant. Once they start to have problems, they will continue to have problems,” says Morgan.

In TP-IAT, islet cells isolated from the excised pancreas are reinfused into the patient via the portal vein of the liver in hopes of preventing brittle diabetes. In the year after TP-IAT, patients report better quality of life and decreased reliance on narcotic analgesics. After TP-IAT, some patients are free of diabetes, while in others it becomes much more manageable. Although some patients may require higher insulin doses after TP-IAT, a recent study by Adams, Morgan, and colleagues showed that the necessity of these higher doses does not negatively affect quality of life. All patients undergoing TP-IAT will need pancreatic replacement therapy for life, and patients should realize that, though the goal of the procedure is pain relief, there will be postoperative pain that will resolve over time.

Endoscopic vs Surgical Approaches to CP

The decision whether an endoscopic or surgical approach would be better in a particular patient is best made with the input of a multidisciplinary team that includes endoscopists, surgeons, and
gastroenterologists. Peter B. Cotton, M.D., Professor in the Division of Gastroenterology and Hepatology and a pioneer in endoscopic innovation, champions the importance of such collaboration and made it a founding principle of MUSC’s Digestive Disease Center: “It’s been said that if you have only a hammer, everything looks like a nail. If you are an endoscopist, you might jump on the ERCP wagon too quickly; and if you are a surgeon, you might consider only surgical solutions. A multidisciplinary approach is essential.”

Endoscopy-based approaches are important treatment options for patients who are not candidates for surgery or who refuse it. However, recent studies have shown that surgery offers more durable and cost-effective benefits in select patients.\(^1\)\(^-\)\(^6\)

The Way Forward

The February 2014 symposium organized by MUSC focused attention on the plight of CP patients and the need to advance their therapeutic options, leading The National Institute of Diabetes and Digestive and Kidney Diseases to hold a workshop on CP in July 2014. The workshop was intended to identify best practices for the treatment of CP and to clear the way for clinical trials of novel therapies by establishing a patient registry and identifying consistent outcome measures. This renewed, multidisciplinary focus on CP and the resolve of clinicians and governmental agencies to identify promising therapies and assess them in clinical trials offer hope for a brighter future for this sometimes neglected patient population.

References


\(^12\) Sutherland BE, et al; Islet autotransplant outcomes after total pancreatectomy: a contrast to islet allograft outcomes. Transplantation. 2006 Dec 27;82(12):1799-1802.


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MUSC nurses are integrating research into service throughout the medical center.

Barbara Cobb (top left), Deidra Huckabee (bottom left), Merrissa Searcy (bottom right)
When Brian T. Conner, PhD, RN, CNE, an Assistant Professor at MUSC’s College of Nursing (CON), was pursuing his doctoral degree several years ago, he researched the pervasive problem of catheter-associated urinary tract infections (CAUTIs). He found in the scientific literature that duration of the indwelling catheter is the most important factor in UTI rates, so he launched his own research project at the MUSC medical center. During this study, nurses were able to determine whether a patient still needed a catheter and, if not, to remove it without a physician’s order. He studied the adoption of the protocol by staff nurses and its effectiveness in reducing CAUTI. His findings eventually led to MUSC’s adoption of a nurse-driven Foley catheter discontinuation policy that has been one of the contributing factors to a decline in CAUTI at the medical center.

Conner, now a mentor to other MUSC nurse investigators, points to research as the foundation for developing the kind of evidence-based practice (EBP) that drives better patient outcomes. With health care reform’s emphasis on quality and value, hospital administrators are encouraging clinical staff to investigate whether there is a better or faster or safer way to care for their patients. The Institute of Medicine has set a goal for 2020 that “90 percent of clinical decisions will be supported by accurate, timely, and up-to-date clinical information and will reflect the best available evidence.”

Throughout the three MUSC hospitals, nurses and physicians are conducting research projects and developing new policies based on their findings. Nurses have been guided and educated primarily by the Nurse Alliance Research Council (NARC) and the Evidence-Based Practice Nurse Scholars Program.

**Research at the Bedside**

The NARC is one of five councils that make up the Nurse Alliance, the hospitals’ nursing collaborative governance structure that was created in 2006. (The other councils are Practice, Education, Leadership, and Quality.) Conner and Andrea Urbanski, RN, BSN are the co-chairs of the NARC. Its goal is to educate the nursing staff about research and encourage the use of EBP and nursing inquiry.

“We want nurses to ask, ‘Why are we doing it this way? Is there a better way?’ That’s what the Research Council is trying to promote,” says Conner.

In 2011, the NARC surveyed the medical center’s 2,500 nurses to assess their understanding of the difference between research, EBP, and quality improvement. Heather Craven, MS, RN, CMSRN is a member of the NARC who helped implement the survey and follow-up. “We found that a good proportion of experienced nurses didn’t understand the distinctions between these three, but nursing schools did not teach how to implement evidence-based practice until the last decade or so,” says Craven. So the NARC set out to do just that. NARC created educational resources and launched the Clinical Nurse Scholar Fellowship program in 2013 that mentors nurses in their research. Currently, three MUSC nurses are conducting studies in their units with Conner’s guidance.
**Current Clinical Nurse Scholars**

**Barbara Cobb, MS, MHA, RN:**
Evaluating sedation methods after cardiac catheterization

Cobb is a nurse in the pediatric cardiology catheterization laboratory preparation and recovery area where 14 to 16 patients per week, aged six-months to teens, are managed. Post-catheterization patients must lie still and flat for at least an hour after the bleeding from the catheter site has stopped, but this can be difficult to ensure in youngsters. MUSC Hospital practice for these patients recommends using the sedative Precedex intraoperatively to reduce agitation and postoperatively as a bolus, but there is no consistent practice recommendation to use it for continued sedation for one hour post procedure. Cobb plans to compare the effectiveness of administering Precedex as a one-hour infusion vs administering it only as a loading bolus after extubation (which wears off in about 15 minutes).

With colleagues from the Cardiothoracic Anesthesia team, Cobb is currently preparing an application to the Institutional Review Board to lay the groundwork for actual clinical research: comparing a non-Precedex control group with a Precedex group. Her eventual goal is to establish a practice recommendation for using Precedex as a one-hour infusion. “I’m excited because I feel passionate that the recovery area should be a good experience for patients and their parents,” says Cobb. “If you take away the agitation time during which we have to hold children down, recovery will be better for all.”

**Deidra Huckabee, MSN, RN, CCRN:**
Improving patient and family communication

Huckabee is a staff nurse in the Medical ICU. Because her patients are often intubated and sedated, she feels that it is important to ensure good communication between the medical team and the family members. Huckabee’s research project seeks to determine whether changes in communication methods and the creation of structured meetings with families will improve the overall patient and family experience. She implemented three changes from earlier practice: the interdisciplinary team of medical professionals who round on the patient increased their meetings from once a week to twice; they hold their initial meeting at the bedside (no longer in a conference room); and meetings are now scheduled for family members and the attending physician and nurse for question-and-answer sessions. Huckabee has seen initial results of improved patient satisfaction scores compared with scores from a control ICU in which these specific methods are not used. When she concludes her study in 2015, she plans to share her results with the other ICUs in the MUSC medical center and publish in a professional journal.

**Merrissa Searcy, BSN, RN, RNC-NIC:**
Reducing risk of a devastating disease in neonates

Searcy cares for some of the hospital’s most vulnerable patients, the infants in the Neonatal ICU (NICU). The most common life-threatening emergency experienced by premature infants is necrotizing enterocolitis (NEC), a gastrointestinal disease that is associated with severe sepsis, intestinal perforation, and significant morbidity and mortality. Of the NICU’s 36 beds, there are generally two or three babies with NEC, says Searcy. The introduction of enteral feedings in neonates plays a key role in the development of NEC, but hospital policies on when to feed, what to feed, and how quickly to advance enteral feedings in this population vary from institution to institution.

Studies have shown that giving low birth-weight, premature neonates blood transfusions while feeding them increases their risk of developing NEC. Searcy plans to compare two groups of babies: those who are fed during transfusions and those who receive only IV fluids during transfusions (with food given hours later). “I’ve been interested in this for a long time, ever since I wrote a paper on this subject during nursing school,” says Searcy. “It’s hard to do the blood transfusion and not stop feeds when you believe there is an association.”

Searcy is now gathering data from the medical records of every low-birth weight neonate who received a blood transfusion in the NICU during the last five years and will examine how many of these were being fed at the same time vs those who were not. Ultimately, Searcy will compile a report for the appropriate physicians that covers her findings and the findings from other institutions on this subject.
**Putting Research Into Practice**

The Evidence-Based Practice Nurse Scholars Program was created in 2012 by Elizabeth A. Crabtree, MPH, PhD, Assistant Professor of Library Science and Informatics, and Andrea Coyle, MSN, MHA, RN, Nursing Excellence Manager. The program was designed to teach clinical nurses how to evaluate existing literature and integrate evidence into practice.

Together with Emily Brennan, MLIS, Research Informationist at the MUSC Library, Crabtree has conducted two twelve-week courses for MUSC staff nurses in which they learned how to frame answerable clinical questions, conduct systematic searches of the literature, and critically appraise and evaluate the evidence. Crabtree and Brennan also offered an EBP course to multidisciplinary teams at the Children’s Hospital. This kind of education reduces what Crabtree sees as the biggest barrier to EBP implementation: lack of skills in literature search, statistics, and data interpretation. The goal of her program is not only to generate new best practices for MUSC, but also to disseminate the findings in scholarly journals to encourage adoption.

“I think what we’re doing at MUSC is somewhat innovative,” says Crabtree. “There are other programs in the country that have developed EBP nurse mentoring programs, but ours is still unique, as is our drive to communicate the need for and value of doing it.”

Examples of nurse-led studies include:

- a Heart and Vascular Center nurse’s evidence review of the recommended bed-rest time following certain procedures. Her finding led to a new policy that standardized and shortened the postoperative bed-rest times in her unit, enabling nurses to get patients up and moving sooner.
- a pediatric nurse’s examination of topical analgesics that were most effective in minimizing discomfort for children receiving medications by IV. MUSC Children’s Hospital now has a standing order that all children who have an order for an IV will receive this analgesic prior to drug administration.

**Prevention Pays**

As the clinicians who are on the front lines of moment-to-moment patient care, nurses are key to preventing the kinds of outcomes that the Centers for Medicare and Medicaid Services will no longer pay for (e.g., hospital-acquired pressure ulcers and hospital-acquired infections). Their science-driven care will ensure high quality and value for patients, hospital administrators, and payors alike in the coming years.

**References**

Interview

MUSC Welcomes One of Its Own as New President

On July 1, 2014, David J. Cole, M.D., assumed the presidency of the Medical University of South Carolina. Dr. Cole established his national reputation as a skilled surgeon, noted researcher, and medical education leader for the most part at MUSC, having served in numerous executive positions at this institution over the past 20 years. He is the former Chair of the Department of Surgery and immediate Past President of MUSC Physicians. Progressnotes invited him to share his vision for MUSC.

PN: Congratulations on being selected as our new president. How did it feel when you received that phone call?

DC: I think it was somewhere between disbelief, excitement, and relief. It took a while for it to sink in. I remain very honored and humbled to have been given this opportunity.

PN: Why do you think it’s important that MUSC has a practicing clinician as president?

DC: As a nation we’re going to have to change how we provide health care. We’ve been focused on the “what” of health care—what we have, what scans we could do, what procedures we could do—and there’s clear need and opportunity for us to transform “how” we provide health care. We have to become more multidisciplinary, more team-based, and ultimately more patient-focused. That’s a cultural shift. Unless you’ve been in the middle of it, you don’t truly understand what the problem is and how to lead forward out of that. Honestly, I believe one of the reasons I was considered for this position is that there are inherent strengths in having a leader who has 20 years of clinical experience and knowledge plus enough presence
at this institution to have established a solid level of trust.

**PN:** What is your vision for MUSC and its role in the transformation of health care?

**DC:** As I was noting previously, in the next five years we’re going to have to drive a fundamental transformation in how we provide health care. We’re being held more accountable, asked not to be wasteful. In the past, that sort of accountability was assumed but not really defined. Now, quality measures are a click away on the internet. We have to become a patient-focused, high-quality, value-based care provider. That’s what is expected by our patients.

**PN:** How important will affiliations with community hospitals and physicians be?

**DC:** Underlying my vision for providing patient-focused, high-quality care is an emphasis on efficiency of care. We have to be able to provide the right care for a patient at the right place at the right time. By definition, that means we need to start forming partnerships because not every patient needs to be at MUSC. We need to be a little more diverse and less siloed when we’re talking about achieving population health. We’re talking about maintaining health first, and that’s possible only through an alliance with community physicians.

Historically, a hospital CEO says a full hospital is a good hospital. That’s generally true, but now we need to start asking questions about whom we can best serve at the MUSC Medical Center. Do patients require the type of care that only we can provide? If the answer is yes, then they need to be here. If the answer is no, then maybe they need to be supported with our partnership with a local community hospital and physicians.

**PN:** How will you ensure that MUSC continues to attract the best future clinicians to its training programs?

**DC:** MUSC is emerging in the national academic medical center arena as a rising star. With our six colleges, we have our finger on the pulse of every dimension of health care. We have the ability to lead the way nationally in terms of multidisciplinary care and multidisciplinary education. We need to change the culture so that’s the expectation. To me, the exciting opportunity is that we can not only change the way health care providers interact with one another but also teach those new modes of interaction to our students. That’s how we will achieve the profound cultural shift that is needed.

We are already attracting high-quality students and residents to our programs. Why is that? Well, it’s the quality of our educators and clinicians. It’s our culture. I think MUSC provides a very dynamic, forward-thinking environment. We would rather do something, build something, than wait it out. That’s always been our strength. Part of the magic formula, if you will, behind our growth over the past 20 years has been that we’ve been able to share common purpose and figure out how to work together in a manner that’s productive rather than destructive. Students and faculty alike see something they want to be part of and choose to be here.

**PN:** How can MUSC continue to enhance its strong national profile in basic and clinical research at a time when research dollars are very scarce?

**DC:** Another challenge. You don’t have to read too many newspapers to hear about NIH and clinical funding being strained. As an institution, we need to acknowledge, align, and build on our clinical and basic research strengths. If we focus on our strengths and build into those domains, we will continue to receive national recognition. To do that, we’re going to have to intentionally diversify the financial base that provides support. That’s not to say that we shouldn’t be as competitive as possible for NIH funding, but there are many ways that we can get resources. One way is continuing to develop key industry partnerships based on our academic strengths. We need to identify the major programs that have enough of a name to attract industry partners that can provide resources for what we collaboratively need to do. Also, we need to be prepared to leverage new domains for funding, such as the Centers for Medicare and Medicaid Services and the Patient-Centered Outcomes Research Institute. Furthermore, we need to leverage more effectively our intellectual property. I think MUSC has an opportunity to continue to develop a more robust technology transfer platform that will add value to the institution.

Finally, strong development efforts provide critical resources for our programs. Obviously, as president, I am going to spend a significant portion of my time working on fundraising.

**PN:** Is there anything you’d like to add?

**DC:** Part of this position requires not only my presence, but also my wife’s as we are the external face of the institution. In the Department of Surgery we always tried to build a positive, forward-thinking culture that sent the message that we are family. It’s not “them” and “us.” We are “us.” I’d love to bring that feeling of engagement to the entire institution.
New Physicians

Richard R. Bayer II, M.D.
Board Certification: Internal Medicine; Board Eligible: Cardiovascular Disease // Special Interests: Cardiovascular Imaging // Medical School: The Ohio State University School of Medicine and Public Health // Residency: Medical University of South Carolina // Fellowship: Medical University of South Carolina

B. Joseph Elmunzer, M.D., MSc
Peter B. Cotton Endowed Chair in Endoscopic Innovation
Board Certification: Internal Medicine: Gastroenterology // Special Interests: Advanced diagnostic and therapeutic endoscopy including ERCP, endoscopic ultrasound (EUS), endoscopic mucosal resection, and quaternary-level endoscopic interventions, such as pancreatic necrosectomy, EUS-guided biliary and pancreatic drainage, luminal stenting and suturing, and per oral endoscopic myotomy (POEM) // Medical School: University of Miami // Residency: University of Texas-Southwestern Medical Center // Fellowship: University of Michigan

Jean Marie Ruddy, M.D.
Board Certification: Surgery // Special Interests: Abdominal aortic aneurysms, critical limb ischemia, carotid stenosis, venous insufficiency // Medical School: Jefferson Medical College // Residency: Medical University of South Carolina // Fellowship: Medical University of South Carolina
**Jacob Klapper, M.D.**  
Director, Division of Nephrology  
Board Certification: Internal Medicine: Nephrology // Medical School: Indiana University School of Medicine // Residency: Indiana University School of Medicine // Fellowship: University of California, San Francisco

**Rochelle L. Ringer, M.D.**  
Board Certification: Surgery // Special Interests: Breast disease, breast surgery // Medical School: Indiana University School of Medicine // Residency: Good Samaritan Hospital // Fellowship: University of Pittsburgh Medical Center

**Joshua H. Lipschutz, M.D.**  
Director, Division of Nephrology  
Board Certification: Internal Medicine: Nephrology // Medical School: Indiana University School of Medicine // Residency: Indiana University School of Medicine // Fellowship: University of California, San Francisco

**Jacob Klapper, M.D.**  
Board Certification: Surgery // Special Interests: Benign and malignant diseases of the lung and esophagus, lung transplantation // Medical School: Indiana University School of Medicine // Residency: Indiana University School of Medicine // Fellowships: National Cancer Institute – Surgery Branch; Duke University School of Medicine
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