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

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Taking Center Stage
Immunotherapy joins the ranks of mainstream cancer treatments

Digital Exclusive
Science Fare: Nurses improve clinical practice with their research
Physicians treating patients with cancer now have a resource at MUSC Health that can help them predict which patients may have a therapeutic response to a specific drug. The 2014 acquisition of the MiSeq™ desktop sequencer (Illumina; San Diego, CA) enabled the Clinical Genomics Laboratory at MUSC Health to offer state-of-the-art next-generation sequencing to its cancer patients. This screening service was described in a feature article in the Summer 2014 Progressnotes (available at MUSChealth.org/pn/summer-2014/index.html). Now, the laboratory is extending that service to cancer patients with certain solid tumors throughout South Carolina. The MiSeq™ analyzes tumor samples against a panel of 26 cancer-related genes to identify variants for which targeted therapies have been developed or are being evaluated in clinical trials. Molecular information will play an increasingly important role in clinical diagnosis and management of patients with cancer. For example, an international working group of neuropathologists recently recommended guidelines on how this information will be incorporated into the next World Health Organization classification of central nervous system tumors.

“We are pleased to offer this important testing to patients beyond our clinics so that all patients in South Carolina can benefit from precision medicine initiatives,” says Dayna J. Wolff, Ph.D., Professor in the Department of Pathology and Laboratory Medicine and Director of Cytogenetics and Molecular Genetics and Genomics.

Targeted cancer therapy blocks the growth and spread of cancer by disrupting the signaling pathways that promote tumor growth. In contrast, most standard chemotherapies act on all rapidly dividing cells, normal and cancerous. Because targeted therapy is directed at the tumor growth process, it does not affect the healthy surrounding cells. Thus, the new approach to fighting cancer is to focus on the gene mutation that gives rise to the tumor, not the type or location of the tumor. As an example, 40% to 60% of melanoma patients with a certain mutation will respond to a known therapeutic drug.

The cancers that can be screened are colorectal cancer, non-small cell lung cancer, melanoma, and any metastatic tumor, regardless of origin. The 26 genes in the cancer panel are: AKT, ALK, APC, BRAF, CDH1, CTNNB1, EGFR, ERBB2, FBXW7, FGFR2, FOXL2, GNAQ, GNAS, KIT, KRAS, MAP2K1, MET, MSH6, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SRC, STK11, TP53.

The laboratory is currently revising this panel to include the IDH1 and IDH2 genes so that the test can also help to guide therapy for glioblastoma brain tumors. Additional genes will be added as new therapies are introduced. Julie Woolworth Hirschhorn, Ph.D., Associate Director of the Genomics Laboratory, reviews current literature and communicates frequently with MUSC Health’s clinicians to stay up to date on new gene targets or therapies. The laboratory staff then integrates this information into the gene-sequencing panel.

The ordering physician will receive a report that indicates the gene variants that are present, the mutations known to respond favorably to targeted therapy, and resistant mutations known to negate the therapeutic response to targeted therapies. Potential clinical trials also can be shared with the physician upon request.

“We tend to see a dramatic effect with these targeted therapies because you’re targeting more of the drug to the tumor and because, when the pathways are inhibited, the tumor growth slows or stops,” says Wolff.

For more information or specific instructions on using the services of the Clinical Genomics Laboratory, physicians may contact MUSC Health Laboratory Client Services at (843) 792-0707. The ordering physician will receive a report within 7 to 12 business days.
n the summer of 2015, the MUSC Health Tele-ICU operations center in Charleston, SC will go live. In partnership with Advanced ICU Care, the center will help to deliver comprehensive, around-the-clock ICU patient monitoring provided by board-certified intensivists, nurse practitioners, and critical care registered nurses. Through real-time, two-way videoconferencing and streaming of the patients’ health metrics from the bedside, these medical professionals will provide specialized care and consultation to clinicians, patients, and families in ICUs across the state. Two community hospitals will be the first to receive these services.

Critical care administrators at MUSC Health have had a long-standing interest in supporting ICU needs across the state, even prior to the 2013 telehealth funding from the South Carolina legislature, explains Dee Ford, M.D., MUSC Health Tele-ICU director. “With this operations center and our interprofessional team education program, hospitals can be certain that patients’ needs are being matched to the level of care they need,” she says. “We believe that this will benefit community hospitals because ICU care is complex and costly.”

The operations center will assist with the care of critically ill patients in partner hospitals’ ICUs by providing:
- 24/7/365 access to board-certified intensivists;
- Two-way audiovisual communication;
- Continuous, sophisticated vital sign monitoring technology that alerts intensivists and nursing staff to adverse patient changes; and
- In-room cameras with superior zoom capability that not only allow for inpatient assessment, but give precise visualization of IV pump or ventilator settings.

MUSC Health will also offer an outreach program for the partner hospitals. “ICU Innovations,” supported in part by a Duke Endowment Foundation award, provides quarterly on-site case-based interprofessional team education, collaborative protocol development and implementation, recurring clinical case conferences, and ad hoc discussions with MUSC Health’s interprofessional team for unique dilemmas. “Our goal is to ensure teamwork in these ICUs and provide quality and process improvement guidelines that are applicable to each hospital,” says Ford.

The MUSC Health-Advanced ICU Care partnership was launched in August 2013 and created a new model of providing ICU care to South Carolina patients. Advanced ICU Care, based in St. Louis, MO, is the nation’s largest tele-ICU provider. This collaboration was made possible in part by the South Carolina legislature, which provided financial support to MUSC Health to expand telehealth services throughout the state. In April 2015, the legislature proposed additional funding for telehealth.

“Since our ICUs are often at full occupancy, we can’t always provide timely transfers from community hospitals,” says Ford. “With the tele-ICU, we can provide the right care for South Carolina’s most severely ill patients by providing 24/7 support to community physicians and nurses. Patients and their families will know they are receiving top-quality care from their local clinical team supported by MUSC Health’s tertiary care expertise.”

For more information about tele-ICU or ICU Innovations, visit www.muschealth.org/telehealth/locations/icu-innovations.html.
Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors dramatically reduce LDL-C levels

BY KIMBERLY MCGHEE

PCSK9 inhibitors can lower low-density lipoprotein cholesterol (LDL-C) levels by 25% to 50%, but for many patients that is not enough to reach target levels, leaving them at residual risk for cardiovascular events. Some patients experience muscle aches when taking statins and must discontinue therapy or take a suboptimal dose. The search has been on for agents that can provide additional benefit in patients already taking statins or that can provide an alternative therapeutic option for those who do not tolerate them.

That is why the dramatic reduction in LDL-C levels achieved by PCSK9 inhibitors is being met with such excitement. The interim results of the OSLER-1 and -2 trials (NCT01439880 and NCT01854918) and the ODYSSEY Long Term trial (NCT01507831) were published in the April 16 issue of the *New England Journal of Medicine* (OSLER: doi: 10.1056/NEJMoa1500858; ODYSSEY: doi: 10.1056/NEJMoa1501031). The results showed a more than 60% decrease in LDL-C levels in patients taking the PCSK9 inhibitor evolocumab (Amgen; OSLER) or alirocumab (Sanofi/Regeneron; ODYSSEY) in addition to standard therapy vs those receiving standard therapy alone. Median LDL-C levels decreased from 120 mg/dL to 48 mg/dL in the OSLER trials and from 122 mg/dL to 48 mg/dL in the ODYSSEY trial (*P* <.001), and these decreases were maintained over time. Although these trials were not designed to assess cardiovascular outcomes, interim safety and efficacy data show that both agents are well tolerated and that there appears to be a signal for reduction in cardiovascular events in patients receiving PCSK9 inhibitors. The FDA has scheduled a target action date for evolocumab and alirocumab for August and July, respectively, and could approve both for certain indications as early as September 2015.

“PCSK9 inhibitors are the most exciting thing going on right now in the field of lipids. They are rocking the lipid world,” says MUSC Health cardiologist Pamela B. Morris, M.D., who is the principal investigator for the MUSC Health site of two trials of these inhibitors: GAUSS III, which is testing the efficacy of evolocumab in patients who have been verified as being statin intolerant, and FOURIER (NCT01764633), which is seeking to definitively establish whether the dramatic decreases in LDL-C seen with evolocumab indeed reduce the risk for cardiovascular events long term in patients already receiving statin therapy.

Side effects of PCSK9 inhibitors include minor injection-site reactions and, in a few cases, memory deficit. OSLER showed that these deficits are not attributable to excessively low LDL-C levels.

PCSK9 inhibitors are monoclonal antibodies that must be subcutaneously injected, and it is still being assessed whether better efficacy and patient adherence can be achieved with a smaller dose every two weeks or a larger dose once a month.

If approved, PCSK9 inhibitors will offer a promising new therapy for statin-intolerant patients and for patients who do not reach target LDL-C levels despite taking the highest-tolerated dose of statins.

**How They Work:** LDL receptors on the surface of liver cells bind to LDL-C and target it for degradation. Depending on the body’s needs, LDL receptors are then either degraded or recycled to clear more LDL-C. PCSK9 binds to the LDL-C/LDL receptor complex and targets the receptors for degradation rather than recycling. Inhibiting PCSK9 ensures that more of the receptors are recycled to the cell surface to clear LDL-C. Indeed, patients with a loss-of-function PCSK9 mutation tend to have very low levels of LDL-C and very low rates of cardiovascular disease, an observation that helped spark interest in PCSK9 inhibitors.

How the PCSK9 Inhibitor Worked

OSLER and ODYSSEY trialists published their data in the *New England Journal of Medicine*. OSLER showed that the PCSK9 inhibitors evolocumab and alirocumab reduced LDL-C levels by more than 60% compared to standard therapy alone. ODYSSEY showed similar results.

**Inhibiting PCSK9 ensures that more of the receptors are recycled to the cell surface to clear LDL-C.** Indeed, patients with a loss-of-function PCSK9 mutation tend to have very low levels of LDL-C and very low rates of cardiovascular disease, an observation that helped spark interest in PCSK9 inhibitors.
The American Heart Association is expected to issue a scientific statement this summer that recommends rapid endovascular clot retrieval in addition to standard of care in patients experiencing stroke secondary to large-artery occlusions. This is in response to the positive results of several recent landmark stroke thrombectomy trials, including the ESCAPE trial* (NCT01778335), for which MUSC Health served as a site.

ESCAPE is a multicenter, prospective, randomized controlled trial with blind outcome evaluation designed to test whether patients with acute ischemic stroke secondary to large-vessel occlusion would benefit from rapid endovascular treatment using retrievable stents (stentreivers) for clot removal in addition to standard of care (including intravenous thrombolysis).

Patients were selected based on computed tomography (CT) and CT angiography (CTA). Inclusion criteria included large proximal intracranial vessel occlusion with small-core ischemic infarct in the anterior brain (i.e., patients with blockages in the large vessels of the head and neck who had a small amount of dead brain but a large area of at-risk brain). The procedure consisted of obtaining a cerebral angiogram, delivering a stentreiver to the blockage in the brain’s artery through the endovascular system, and suctioning out the thrombus (blood clot).

Christine A. Holmstedt, D.O., Co-Director of MUSC Health’s Comprehensive Stroke & Cerebrovascular Center, was a co-investigator and co-author of the resulting report published in the New England Journal of Medicine (March 12, 2015; Epub ahead of print, February 11, 2015). “We found that patients who had this procedure—with or without tissue plasminogen activator—had significantly improved clinical outcomes and reduced mortality,” says Holmstedt. The stroke team’s goal was door to retrieval of the blood clot (and revascularization of the brain) in 90 minutes or less. The researchers found that the patients who had this procedure had a 50% better outcome at 90 days.

The ESCAPE trial, which comprised 316 participants in 22 centers around the world, measured outcomes with the modified Rankin scale, which ranges from zero (no symptoms) to six (death). Functional independence (defined as a modified Rankin score of zero to two 90 days out) improved in 53% of study patients undergoing thrombectomy vs 29.3% of control patients.

* ESCAPE = Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times

“Although a very small number of patients will qualify for this procedure,” says Holmstedt, “it will have a tremendous impact because the patients who are candidates for endovascular thrombectomy are those patients who are having the most neurologically disabling strokes.”

Holmstedt recommends that these procedures be done at high-volume, comprehensive stroke centers, such as MUSC Health, where the stroke-dedicated teams have been trained to work together quickly, highly experienced endovascular interventional surgeons are readily available, and the brain imaging technology is accessible. This therapy will have ramifications for stroke system organization and Emergency Medical Services triaging to facilitate stroke patient transfers to appropriate levels of stroke care.

CT image of an occlusion of the first part of the left middle cerebral artery (white arrow), which was successfully treated with thrombectomy.
Current, more than 28 million Americans have impaired hearing, and approximately 75% of these persons are over the age of 55. Nearly 30 years ago, hearing scientist John H. Mills, Ph.D., brought together a multidisciplinary team of MUSC researchers including audiologists, histopathologists, biochemists, and electrophysiologists to study the causes of age-related hearing loss. Since its inception, this National Institutes of Health–funded program, currently directed by Judy R. Dubno, Ph.D., Professor and Director of the Hearing Research Program in the Department of Otolaryngology-Head and Neck Surgery, has included projects headed by investigators from both Dr. Dubno’s department and the Department of Pathology and Laboratory Medicine.

Hearing losses can occur from a variety of causes, including environmental factors such as exposure to noise and ototoxic drugs, making it difficult to distinguish these factors from the effects of age. However, early studies with laboratory animals conducted at MUSC under carefully controlled conditions identified a metabolic component to age-related hearing loss that is associated with a decline in the endocochlear potential. The endocochlear potential is an electrical potential of 80-100mV in the cochlea that acts like a battery to drive auditory transduction. These early studies with laboratory animals also pointed to a genetic component for age-related hearing loss and, along with more recent laboratory animal and human studies, have shown that hearing loss in older adults is a consequence of accumulated environmental stresses to the cochlea and an intrinsic genetically controlled aging process. As much as 60% of hearing loss in older adults can be attributed to heritability.

In parallel with laboratory animal studies, the research team has collected audiometric data and DNA samples from more than 800 research participants aged 55 years and older and has been able to stratify their hearing loss into metabolic and non-metabolic phenotypes. Taking advantage of this large human database, Bradley A. Schulte, Ph.D., Vice Chair for Research in the Department of Pathology and Laboratory Medicine, is now conducting a whole-exome sequencing (WES) study to identify genetic variants associated with metabolic hearing loss. The recent acquisition of a high-throughput sequencing platform (Illumina HiSeq™2500) has enabled this next-generation sequencing to be performed at MUSC.

Approximately 100 genes implicated in metabolic hearing loss have been identified through a combination of studies in laboratory animals and in adults with normal and impaired hearing. These candidate genes will be the initial focus of the WES. Once relevant mutations are identified, the team will attempt to localize the proteins involved to specific tissues and cell types in the mouse and human inner ear using histochemical and biochemical techniques. Ultimately, gene knockout animal models will be developed to better determine how the mutations affect hearing.

Schulte plans to sequence genes from 400 research participants by the end of the year and hopes to identify some relevant gene mutations over the next two years. “If we see a good correlation between the results from laboratory animal and human studies, we will know we have a promising gene candidate and we will go after that variant,” says Schulte. Once mutations have been identified, it may be possible to develop therapies to target them—either by correcting the defect through genetic engineering or by modulating protein expression with a novel or existing drug. 
During many complex surgical procedures, a patient’s blood-clotting ability continually changes for a variety of reasons. To effectively manage the patient and minimize unnecessary transfusions, the anesthesiologist must constantly monitor these changes. Unfortunately, conventional coagulation assays can take 30 to 45 minutes to assess clotting factor levels. When surgeons cannot wait, the traditional perioperative blood management practice has been to make a clinical assessment of the patient’s bleeding and administer the blood component that they judge appropriate to minimize the bleeding. This practice has downsides for the patient as well as the hospital. In February 2015, the American Society of Anesthesiologists recommended in its perioperative blood management practice guidelines the use of goal-directed algorithms guided by viscoelastic testing that deliver the critical coagulation information within 10 to 15 minutes.

Since 2013, MUSC Health has used one of the first such testing devices. The ROTEM® Hemostasis Management System (ROTEM®; Tem International GmbH, Munich, Germany) uses a transfusion algorithm that enables anesthesiologists to deliver the right blood component quickly. This technology is not only faster, it is more informative, according to Jerry Squires, M.D., Ph.D., Associate Professor of Pathology and Laboratory Medicine and Director of Transfusion Medicine at MUSC Health. “The traditional assays measure only clotting factor levels. With ROTEM®, we get a more global picture of hemostasis, which, in turn, helps the clinician choose the appropriate blood product to control bleeding,” he says. This technology is also useful when treating other patients with active bleeding, e.g., complex patients and patients with acute liver failure or trauma. “We are a hospital that treats complex medical problems,” says Squires. “We need to be able to manage our patients effectively and preserve the availability of blood.”

ROTEM® was evaluated at the University of Toronto and Université Paris-Diderot in patients who underwent cardiac bypass surgery before (n=1,311) and after (n=1,170) the hospital instituted ROTEM®. The study’s conclusions, published in the March 2015 issue of Anesthesiology, state that transfusion rates for all blood products (except cryoprecipitate, which did not change) were decreased after the institution of the algorithm. The posttransfusion odds ratios (95% confidence intervals) for erythrocytes, platelets, and plasma were 0.50 (0.32-0.77), 0.22 (0.13-0.37), and 0.20 (0.12-0.34), respectively.

This coagulation testing device is just one component of MUSC Health’s Patient Blood Management Program that is being developed. For trauma and surgical bleeding, the program recommends preoperative and postoperative anemia management and the ROTEM-guided algorithms. For inherited bleeding disorders, the program provides the Anticoagulation and Bleeding Management Consult Service, which ensures the safe replacement of coagulation factors. The service includes, for example, the program nurse coordinator’s daily review of orders for anti-coagulants or blood-clotting factors. Charles S. Greenberg, M.D., Professor in the Division of Hematology-Oncology and Director of the Consult Service, explains, “Our goal is to avoid unnecessary use of blood and blood products because, if you don’t choose wisely, you can cause additional bleeding and other complications. It is well-established that unnecessary transfusions may lead to poor outcomes.” For more information on the Patient Blood Management Program at MUSC Health, see the article “Honoring the Blood Covenant,” in the March-April 2013 issue of Progressnotes.
Despite decades of a war on cancer, progress has been incremental, with new drugs offering patients only an extra few months of life. News that novel T cell–based immunotherapeutic approaches such as immune checkpoint blockade and adoptive cell transfer are achieving durable responses in patients with aggressive cancers has created excitement in the world of cancer research. It has raised hopes that the body’s immune system may be nimble, potent, and dynamic enough to eradicate tumors despite their ability to mutate and develop resistance, setting the stage for durable responses and cures. After years in the wings of cancer treatment, immunotherapeutics—previously used only as a last resort in patients who failed other therapies—is now taking center stage. Part I of this article will focus on immune checkpoint blockade and Part II, which will appear in the Fall 2015 issue of Progressnotes, on adoptive cell transfer.

**Part I: No Longer Hiding in Plain Sight**  
**Immune Checkpoint Inhibitors Uncloak Cancer**

Immune checkpoint inhibitors are a novel class of immunotherapeutic agents that take the blinders off the immune system and enable T cells to “see” and target tumors that had previously been hiding in plain sight. In clinical trials of these new agents, durable responses and impressive gains in survival have been achieved, demonstrating that T cells are capable of mounting a successful defense against cancer—a point about which many had been skeptical until recently. Much of that skepticism was erased when promising gains in survival were seen with ipilimumab (Bristol-Myers Squibb), an immune checkpoint inhibitor (specifically, a CTLA-4 inhibitor), in pretreated and untreated patients with advanced melanoma that had metastasized to the brain (NCT00094653 and NCT00324155, respectively).

According to MUSC Health hematologist/oncologist Keisuke Shirai, M.D., MSCR, who participated in an expanded-access trial of ipilimumab for advanced, metastatic melanoma before its approval by the FDA in 2011, ipilimumab is the “first agent [in] the last 30 years to provide survival benefit in stage 4 melanoma. The beauty of this drug is that, if patients respond, the response can be sustainable.” He is following up study patients three, four, and five years out who were once assumed to be terminal but who have now returned to work and lead relatively normal lives.

Of the pretreated patients receiving ipilimumab—patients who would otherwise only have had a few months to live—one fifth were alive at two-year follow-up, and twice as many patients who received ipilimumab in addition to standard of care (i.e., dacarbazine) were alive at five years compared with those given standard of care alone. A pooled analysis of data from ten prospective and two retrospective studies of ipilimumab, including two phase 3 trials, showed a median overall survival of 11.4 months, and a three-year survival rate of 22% in patients overall, 26% in untreated patients, and 20% in pretreated patients.
Even more exciting is that immune checkpoint inhibitors are proving relevant not only to cancers that have historically shown some susceptibility to immunological approaches, such as melanoma and hematological cancers, but also to solid tumors. “With immune checkpoint inhibitors, we are harnessing the immune system to fight cancers that were previously thought to be resistant to immunotherapy,” explains Carolyn D. Britten, M.D., Director of the Phase 1 Clinical Trials Research Program at MUSC Hollings Cancer Center.

A number of recent high-profile articles have reported their efficacy in a broad range of tumor types. For instance, five letters published in the November 27, 2014 issue of *Nature* document “profound clinical response” in 175 efficacy-evaluable patients with a variety of cancers: confirmed objective response was observed in 18% of all study patients, 21% of patients with non-small cell lung cancer, 26% of patients with melanoma, 13% of those with renal cell carcinomas, and 13% of other tumors (e.g., colorectal cancer, gastric cancer, and head and neck squamous cell carcinoma). Preliminary data suggest that immune checkpoint blockade could be a promising approach for breast and ovarian cancer, and research is underway in a host of other cancers.

“Cancer immunotherapy reflects a paradigm shift in oncology. Instead of targeting cancers, immunotherapy focuses on rejuvenating the cancer-fighting immune system.”
—Dr. Zihai Li

MUSC has had a long interest in T cell immunity. In the 1990s, surgeon and current MUSC President David J. Cole, M.D., opened one of the first immunology laboratories at MUSC focused on the role of T cells in tumor immunity. In the two decades since, a talented cadre of basic and translational immunologists, currently under the direction of Zihai Li, M.D., Ph.D., Chair of the Department of Microbiology and Immunology, has continued to work in close collaboration with hematologists/oncologists at MUSC Hollings Cancer Center to study the mechanisms underlying T cell immunity and further optimize T cell–based immunotherapies. Currently, trials of immune checkpoint inhibitors are underway at MUSC in patients with advanced melanoma, lung cancer, head and neck cancer, and glioblastoma. Phase 1 trials offer patients with many more types of cancers access to these exciting new immunotherapeutic agents.

How Immune Checkpoint Inhibitors Work

The job of the immune system is to distinguish between self and other and to mount a defense against invaders without harming the body’s own tissue. T cells are the body’s defenders, charged with eliminating threats from the outside. However, T cells in the vicinity of tumors may show little interest in cancer cells, which develop as a result of mutations to the body’s own cells and so are not perceived as a threat. Cancer cells often “hide” from neighboring T cells by hijacking a regulatory mechanism meant to prevent an attack on the body’s healthy cells (i.e., autoimmunity).

To prevent autoimmunity, the immune system has evolved a number of important safeguards. For example, the T cell, which is switched on when a receptor on the T cell surface binds to an antigen presented on the surface of antigen-presenting or tumor cells, can be switched back off when immune checkpoint proteins on T cells bind to their cognate proteins on tumors.

Immune checkpoint inhibitors block the binding of key immunosuppressive proteins such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1, a cognate protein for PD-1), enabling a robust T cell response. In contrast to chemotherapeutic agents, which directly kill cancer cells at the expense of harming healthy cells, immune checkpoint inhibitors license the immune system to attack the malignancy. As a result, patients do not experience the side effects often associated with chemotherapy (e.g., nausea and vomiting, blood disorders, hair loss).

However, because these agents override a safeguard against autoimmunity, the T cells that have been licensed to attack cancer by immune checkpoint inhibitors could also target healthy tissues, causing inflammation. For example, patients receiving the CTLA-4 inhibitor ipilimumab may experience vitiligo (i.e., a loss of pigment or white patches in otherwise normally pigmented skin) and colitis, whereas those receiving anti-PD1 are more vulnerable to pneumonitis. These side effects are usually quite manageable with high-dose corticosteroid therapy and, in rare, intractable cases, with tumor necrosis factor (TNF)-blockers. However, these side effects can be life-threatening if they are not treated, and so physicians should be vigilant in monitoring for them as immune checkpoint inhibitors enter more broadly into the clinic.

Immune checkpoint blockade enables manipulation of a patient’s T cells, favoring effector T cells (that could promote a robust immune
response against cancer) over regulatory T cells (that promote tolerance and help prevent autoimmunity). However, it may teach us how to more effectively approach autoimmune disease as well. In such diseases, it might be desirable to instead increase the number of regulatory T cells. A recent article by MUSC immunologist Shikhar Mehrotra, Ph.D., and colleagues reported a significant reversal of the depigmentation caused by vitiligo when the chemokine CCL22 was administered to mice to increase regulatory T cell numbers.7

**Rapid Entry into the Clinic**

Very recently, two PD-1 inhibitors received FDA approval—pembroluzimab (Merck) for ipilimumab-refractory advanced melanoma (September 2014) and nivolumab (Bristol-Myers Squibb) for medication-refractory unresectable or metastatic melanoma (December 2014). The latter approval came after impressive clinical trial results were reported for patients with untreated advanced BRAF wild-type melanoma: one-year overall survival was 72.9% in those treated with nivolumab vs 42.1% in those treated with standard-of-care dacarbazine.8

Melanoma was known to be amenable to immunotherapy, but few thought that this approach would be effective against other solid tumors, making the approval of nivolumab for the treatment of metastatic squamous non-small cell lung cancer (March 2015) an important milestone in the development of anticancer immunotherapy. Nivolumab’s approval for this indication also offered the benefit of this new class of immunotherapeutic agent to a much larger population of patients—about ten times as many people have lung cancer as have melanoma. Other immune checkpoint inhibitors are in the pipeline,
including the PDL-1 inhibitors MPDL3280A (Roche/Genentech) and MEDI4736 (AstraZeneca).

“There are medications entering the clinic at a historically high rate—a remarkably high rate—that are really bending the curve in terms of survival,” explains MUSC hematologist/oncologist John M. Wrangle, M.D.

Researchers worldwide are making a concerted effort to bend that curve further. The most durable responses are seen only in a small cohort of patients, and so the search is on to identify biomarkers that could predict response. At MUSC, Shirai and Jennifer D. Wu, Ph.D., Associate Professor in the Department of Microbiology and Immunology, recently received Institutional Review Board approval to study biomarkers that could predict response and, once promising biomarkers have been identified, plan to open a trial to determine whether better responses are seen in patients identified as having those biomarkers.

Extending the Reach of Immune Checkpoint Therapy
Investigators at MUSC Hollings Cancer Center are developing novel concepts for clinical trials with these new immunotherapeutic agents in an effort to increase the number of patients with melanoma and lung cancer who achieve durable responses and to extend the benefits of immune checkpoint inhibitors to new populations of cancer patients.

Shirai and Wrangle are intent on bringing South Carolina’s large lung cancer population more clinical trials of next-generation immunotherapy. Shirai has already completed a trial randomizing patients with stage IV or recurrent PD-L1+ non-small cell lung cancer to nivolumab or the investigator’s choice of chemotherapy as first-line therapy (CheckMate 026, NCT02041533); data are under analysis by Bristol-Myers Squibb, the study’s sponsor. (Immune checkpoint inhibitors mediate better response in cancers with greater PD-L1 expression on their tumors.) That an immunotherapeutic agent is being assessed as a first-line therapy for lung cancer would have been unthinkable a decade ago and is testimony to immunotherapy’s entrance into the mainstream of cancer treatment.

Scott M. Lindhorst, M.D., who holds a dual appointment in the Division of Hematology/Oncology and the Department of Neurosurgery, is the principal investigator of a clinical trial evaluating the efficacy and safety of nivolumab vs the angiogenesis inhibitor bevacizumab, which is standard of care (CheckMate 143, NCT02017717), in patients with recurrent glioblastoma. Anecdotal accounts of prolonged survival after surgery in glioblastoma patients who develop an infection near the tumor bed suggest that immunotherapeutic approaches could play a role in treating this disease.

Other trials explore whether the potency of immune checkpoint inhibitors could be increased when administered with traditional anticancer treatments. The rationale behind combination regimens pairing a traditional therapy with an immune checkpoint inhibitor or other novel immunotherapeutic agent is that lower-dose chemotherapy may kill enough tumor cells to “prime” the immune system by freeing more antigen for T cell presentation. Surgery could also elicit a robust T cell response. Immune checkpoint inhibitors would prevent the activated T cells from being turned back off. Shirai is in the process of opening a trial at MUSC that will explore whether ipilimumab or nivolumab is more effective at preventing recurrence after complete resection of Stage IIIb or Stage IV melanoma (CheckMate 238, NCT02388906).

Regimens combining more than one immune checkpoint inhibitor are also being studied to determine whether the impressive results seen with such combination therapies in melanoma can be replicated in other cancers. The combination of a CTLA-4 inhibitor and a PD-1 inhibitor looks especially promising. A recent phase 1 dose-escalation study of patients with melanoma and a known BRAF mutation (NCT01927419) showed that 22% of patients receiving combination therapy with ipilimumab (a CTLA-4 inhibitor) plus nivolumab (a PD-1 inhibitor) but none of those receiving ipilimumab alone achieved a complete response. A phase 2 trial at MUSC Hollings Cancer Center led by Shirai is testing the efficacy of the PD-L1 inhibitor MEDI4736, the CTLA-4 inhibitor tremelimumab (Pfizer), and a combination of the two in patients with PD-L1+ squamous cell carcinoma of the head and neck (NCT02319044). By late 2015, Shirai and Wrangle plan to open a trial of a combination regimen of nivolumab and ipilimumab in lung cancer.
Under Britten’s leadership, MUSC Hollings Cancer Center has recently opened and is recruiting patients for two phase 1 trials of PD-L1 inhibitors. Some speculate that PD-L1 inhibitors may be associated with fewer autoimmune side effects because they block the binding of PD-1 and PDL-1, known to be immunosuppressive, but do not interfere with the binding of PD-1 to PD-L2.

One trial is an open-label dose-escalation trial of the PD-L1 inhibitor avelumab (MSB0010718C; EMD Serono/Merck) with consecutive parallel group expansion in patients with metastatic and locally advanced solid tumors (NCT01772004). Now that the safe and tolerated dose has been determined, avelumab is being administered to patients with diverse tumor types, including non-small cell lung cancer, head and neck cancer, and urothelial cancer. The design of this trial will enable patients in South Carolina with a wide variety of cancers to have access to an exciting new class of anticancer agents.

The second phase 1 trial (NCT02118357) is an open-label study intended to evaluate the safety and tolerability of a combination regimen of the PD-1 inhibitor MEDI0680 (MedImmune/AstraZeneca) and the PD-L1 inhibitor MEDI4736 (MedImmune/AstraZeneca) in patients with advanced malignancies. The PD-1 inhibitor prevents the binding of PD-1 to PD-L1 but does not prevent PD-L1 from binding to other proteins. The rationale for a combined PD-1/PD-L1 regimen is that the PD-1 inhibitor would block PD-1/PD-L1 binding and the PD-L1 inhibitor would prevent all other PD-L1 binding. MUSC Hollings Cancer Center is one of only a handful of cancer centers in the country offering this novel combination of therapies in a phase 1 trial.

Immunologists at MUSC are focused on working with their clinical colleagues to improve immune checkpoint blockade. Mark P. Rubinstein, Ph.D., is studying the mechanism by which immune checkpoint inhibitors revive T cell function in the tumor. Chrystal Paulos, Ph.D., has partnered with Shirai to study the immunological mechanisms underlying the effectiveness of CLTA-4 and PD-1 therapies in patients with melanoma and lung cancer. Wu, who has developed a unique humanized bi-transgenic mouse model of prostate cancer, was awarded a Department of Defense grant this year to use the mouse model to study how CTLA-4 therapy could be enhanced for patients with prostate cancer. Wu plans to use her unique mouse model to explore how PD-1 checkpoint therapy could be improved across a variety of cancer types. Li has just received a five-year grant from the National Cancer Institute to further improve T cell checkpoint inhibitors by combining the strategy with inhibitors of thrombocytes or platelets.

The arrival of immune checkpoint inhibitors in the clinic—and the growing number of cancers in which they are showing promising signs of efficacy—has ushered in a new era of cancer treatment. Once a casualty of more traditional approaches such as chemotherapy and radiation, the immune system is now assuming a leading role in the fight against cancer.

Part II of this article will appear in the Fall issue of ProgressNotes and will explore other immunotherapeutic approaches with strong clinical promise, including adoptive cell transfer, and how they could potentially be combined with immune checkpoint blockade to achieve even better responses.

For more information on enrolling a patient in one of the immune checkpoint inhibitor trials, contact the main MUSC clinical trials office at 843-792-9321.

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“There is no discovery without risk and what you risk reveals what you value.” —Jeanette Winterson, Written on the Body

When resources are tight, some prefer to play it safe. Karen Lackey, Director of the South Carolina Center for Therapeutic Discovery and Development (SCCTD), is not one of those people. “I can’t even watch the same movie twice,” she jokes.

Lackey, who led successful drug discovery efforts in the pharmaceutical industry for more than 25 years before joining MUSC, is on a mission. “The reason I am here is that I believe there is a better way to do drug discovery,” says Lackey.

She has seen hard times hit. She has watched as pharmaceutical companies laid off their research and development (R&D) staff—unable to support them when nine in ten compounds failed to show efficacy. She has seen the anxiety of academic researchers in the wake of restricted NIH funding. She turned a skeptical eye toward efforts by academic drug discovery centers to make themselves into “mini-pharmas” to meet industry’s R&D needs—only, like industry before them, to find the model unsustainable.

“We’ve done drug discovery the same way for 50 to 60 years and we’re stuck. It’s time to try something new,” says Lackey. “Separately, I don’t think either the pharmaceutical industry or the academic world has the answer. But if we could integrate the best of both those worlds and could change the 90% failure rate to 80% or 70%, that would be huge.”

The announcement in 2015 of two new MUSC/industry collaborations shows that Lackey’s innovative model is working. In late March, MUSC partnered with Aeterna Zentaris, receiving a 100,000-compound library valued at $5 to $15 million in return for using that library to identify new drug candidates in the company’s fields of specialty: oncology, women’s care, endocrinology, and neurology. In early May, MUSC partnered with Bristol-Myers Squibb (BMS) and will receive a multimillion dollar investment over three years to identify biomarkers and targets for fibrotic disease. “Our model is unproven, untested, and innovative, but now we have two deals and so clearly something we are doing is working,” says Lackey.
Why a new model is needed
Simply put, the current models of drug discovery are not working.

“The industry model is extremely efficient,” says Lackey. “They have a lot of projects they can push through the system, but many go step by step through the efficient process and then fail.” A better success rate will require a more careful selection of targets and compounds. A deeper understanding of clinical pathology and biological mechanisms—something academic researchers can provide—will help identify promising candidates to take forward into development.

Academic drug discovery has been focused traditionally on the work of individual researchers who seek grants to fund their work in a particular field. If an investigator identifies a promising candidate, the institution files for a patent. In Lackey’s opinion, too much is staked on a single compound in this model, and creativity is prematurely shut down by the need to protect intellectual property. “After this initial disclosure, very little additional work gets done on the therapeutic agent. That’s why it keeps failing—it is almost like you are sending your baby out before it has been completely worked on.”

A team sport
Why not let people do what they do best, and then form teams that capitalize upon their expertise? Physician team members could tap into their wealth of clinical experience and intimate knowledge of the pathology of a disease. Basic scientists could bring their deep understanding of a disease’s biology and the models they have developed to study it. “I wouldn’t run a drug discovery project without a basic scientist, a translational scientist, and a clinician,” says Lackey.

We’ve done drug discovery the same way for 50-60 years and we’re stuck. It’s time to try something new.
—Karen Lackey

To encourage the creation of these teams, Lackey is developing a “virtual huddle” with support from a MUSC Strategic Planning Award. Intended to break down silos, the virtual huddle will enable clinical and basic science researchers across campus to access proposed drug discovery initiatives and, if they see a fit, to offer their own technologies to move the project forward. The projects that find the most support and collaboration and that form the strongest teams would then become part of MUSC’s portfolio of opportunities that can be offered to industry.

“This makes us look like teamwork people when we present to industry,” says Lackey, showcasing the close connection at MUSC between basic science research and clinical care that industry lacks and finds appealing.

A pharmaceutical partner brings a new piece to the puzzle—its expertise in taking a compound through all the testing that must be done to bring a compound to market. “Think about it. You take a pill, you swallow it, and you expect that pill to ignore everything else and go exactly where it needs to go and work its business and then get out cleanly without touching anything on its way out,” explains Lackey. “A lot of testing is involved to prove that, and that’s what industry can offer. But you really need that deep understanding of the pathology at each and every point and that’s what we bring.”

Partnering with Aeterna Zentaris to develop novel drug candidates
The agreement with Aeterna Zentaris offers MUSC investigators an invaluable asset—a large library of novel compounds that they can test for efficacy against identified targets. Most academic medical centers rely on the same commercial compound libraries, hampering drug discovery. “It’s like casting a net in the same pond for ten years and then expecting to find a new fish,” says SCCTD computational biologist Yuri Peterson, Ph.D.

Even more notable is the provenance of the compound library. In 2002, Aeterna acquired Germany-based Zentaris, itself a conglomerate of biotech startups, to do its R&D. “Medicinal chemists at those start-ups were synthesizing compounds directed at very important biologically active targets, and those are now part of the compound library,” says Lackey.

Lackey and Peterson are convinced that this novel and diverse compound collection will add momentum to drug discovery efforts at MUSC. “The Aeterna Zentaris discovery set is proprietary information built by their expert chemists, and now MUSC has exclusive access. This gives us a huge advantage in creating new drugs,” says Peterson.

In return, MUSC has agreed to provide the company at least one drug candidate per year beginning in 2018 in one of its specialty areas (i.e., oncology, women’s care, endocrinology, and neurology). The company can then decide whether to develop the candidate further; if not, MUSC can take the compound forward if it pays royalties. If an MUSC researcher identifies a drug candidate that is not in one of those four areas, MUSC can patent that compound and owe no royalties.

Planning a long-term partnership with MUSC, Aeterna Zentaris recently relocated its home office to Charleston, raising hopes that
the city is on its way to becoming a biotech hub, like the Research Triangle in North Carolina. “This is something that Charleston as a community should be paying attention to, because MUSC has amazing opportunities in making an impact in patient care, whether in devices or in therapeutic agents,” says Lackey.

**Partnering with Bristol-Myers Squibb to fight fibrotic disease**

The goal of MUSC’s collaboration with BMS is to identify biomarkers and possible drug targets for fibrotic disease. Instead of betting its entire investment on a single target or even a single disease, BMS is funding basic and translational scientists and clinicians at MUSC studying three fibrotic diseases: scleroderma, idiopathic pulmonary fibrosis (IPF), and diabetic kidney disease (DKD), thus improving the odds that a druggable target will be identified.

Not only does the industry funding encourage a deeper exploration of fibrosis in each of the three chosen diseases, but it will help identify commonalities that characterize fibrosis across organ compartments and encourage the free flow of ideas among fibrosis researchers in different disciplines. “This collaboration among different fibrosis groups at MUSC and the infrastructure provided by the BMS partnership can be the basis for spin-off projects, such as program project grants,” explains pulmonologist Lynn M. Schnapp, M.D. MUSC investigators will also benefit from a close collaboration with BMS teams specializing in fibrosis, biomarkers, and immunology. The initiative will be governed by a joint steering committee that will help drive results by allocating more funds to the groups with the most promising findings. By casting a wider net, this drug discovery initiative will increase its chances of finding a promising target or compound.

The agreement offers Bristol-Myers Squibb something that Lackey thinks industry has been lacking—access to patients early in the drug development process. As a major referral site for scleroderma, IPF, and DKD, and as the highest-enrolling site of the trials that led to FDA approval of pirfenidone and nintedanib, the first drugs ever approved to treat IPF, MUSC can provide the company access to a large clinical population of fibrosis patients. Rheumatologists Richard M. Silver, M.D. and James C. Oates, M.D., pulmonologist Lynn M. Schnapp, M.D., and endocrinologist Maria F. Lopes-Virella, M.D., Ph.D., will collect samples from patients with scleroderma, IPF, and DKD, respectively. According to Silver, “These biological samples from well-defined patient populations will be used in novel explorative studies designed to identify and verify new targets to treat fibrosis.” In return, BMS will offer MUSC its platform technologies—for example, it can efficiently and inexpensively run the microarray analyses of the collected samples.

MUSC researchers also offer innovative models of fibrotic disease that can be used to test promising compounds—both animal models, such as the bleomycin mouse model of systemic sclerosis adapted by Stanley R. Hoffman, Ph.D., and humanized ones, such as the human skin organ model of fibrosis developed by Carol Feghali-Bostwick, Ph.D., that could be a better predictor of patient response. In addition, compounds can be tested in primary human fibroblasts collected and grown from patient specimens. These models enable BMS to select the best compounds to take forward into development—a compound showing efficacy across these models would be considered particularly promising. (For more on these models and on fibrosis research at MUSC, see “Fighting Fibrosis” in the Fall 2014 issue of Progressnotes.)

**A risk worth taking**

Adhering to the status quo of drug discovery would almost surely deliver the same results—a 90% failure rate. Asking both academia and industry to adjust their mind sets, acknowledge their weaknesses, and combine their talents is risky, but it could improve the success rate of drug discovery and bring novel therapies to patients who desperately need them. That is a risk Lackey, MUSC, and an increasing number of pharmaceutical companies are willing to take.
Neuroimaging is on the verge of revealing some of the brain’s long-kept secrets and in so doing could revolutionize our understanding of neurodegenerative and other neurological diseases.

Novel imaging modalities are exposing tiny cracks in the brain’s microarchitecture that could herald the onset of disease long before the first clinical symptoms appear. They are also being used to map the white matter fiber tracts or “networks” that carry messages from one part of the brain to the other, a process known as fiber tractography.

Mapping all those connections in the healthy brain is the goal of a nationwide initiative known as the Human Connectome Project (humanconnectomeproject.org). Once the connectome of the healthy human brain—a blueprint of its wiring—has been completed, work will begin on the connectomes of a variety of neurological disorders. Comparing the connectome of a diseased brain to that of the healthy brain should help identify areas of faulty wiring that can become the focus of therapy.

The imaging tool of choice for gaining deeper insight into both the brain’s microarchitecture and its wiring has been diffusion magnetic resonance imaging (dMRI), and in particular diffusion tensor imaging (DTI). DTI, which maps the diffusion of water through brain tissue, can be used to determine both the rate and directionality of diffusion. The dMRI image is composed of thousands of voxels (a portmanteau word combining “volume” and “pixel”), each containing a shape that represents the diffusion of water in that area of tissue. These range from spheroids that represent isotropic (i.e., direction-independent) diffusion to ellipsoids that represent anisotropic (i.e., direction-dependent) diffusion.

Although diffusion spectrum imaging (DSI) is by far the most sensitive dMRI imaging technique, DTI has been widely adopted in the clinic because of its simplicity and because images can be obtained in just a few minutes (vs 40 minutes with DSI) using widely available scanners and processed using standardized methodologies.

But is DTI the best tool for moving neuroimaging forward, or has it simply been the most convenient?

**Diffusional Kurtosis Imaging**

Joseph A. Helpern, Ph.D., SmartState™ Endowed Chair in Brain Imaging and Director of MUSC’s Center for Biomedical Imaging, and long-time collaborator Jens H. Jensen, Ph.D., noted a fundamental limitation of DTI—it assumes a normal or Gaussian
White matter fiber architecture of the brain. Image courtesy of G. Russell Glenn. Diffusional kurtosis imaging can be used for fiber tractography.
distribution of water diffusion throughout the tissue. When a barrier impedes diffusion—as is common in complex physiologic milieus—the diffusion deviates from the Gaussian model; the degree to which it does so is known as the kurtosis. In a seminal 2005 article, Helpern and Jensen described diffusional kurtosis imaging (DKI), a dMRI technique that uses kurtosis metrics to arrive at more precise and detailed measures of tissue microstructure.1

Credited with building the first 3-Tesla human MRI machine, Helpern knows what it takes to create a new imaging technology and translate it effectively into the clinic. “There is a high bar for change,” says Helpern. “You have to show that it is at least as good as what you are trying to change, doesn’t cost more, and doesn’t create longer imaging times for the patient.”

Helpern believes that DKI provides much more data on microstructural changes than DTI but is more clinically translatable than DSI, the gold standard of dMRI imaging. Data for DKI can be acquired on the same scanners used for DTI and almost as quickly. “DTI takes three to four minutes, and DKI could take six to seven—a little longer, but only by a few minutes,” explains Helpern. Several major medical centers, including New York University and the Medical University of South Carolina, have already incorporated DKI into their standard clinical protocols. Because DKI builds upon the DTI dataset, a DKI-based protocol provides supplemental information to physicians without sacrificing any of the DTI data.

In stroke patients, for example, supplemental DKI information continues to suggest microstructural abnormalities in the region of the stroke long after the DTI image has returned to normal. “The contrast that you see in the stroke area with DKI is not the same as the contrast in DTI images. Something is going on there,” explains Helpern. “Maybe the additional information could help differentiate which tissue is salvageable and which is not. We don’t know, but that’s the kind of question we are exploring.”

Helpern and his colleagues are busy mining the additional data provided by DKI to see whether it enhances our understanding of neurological or neurodegenerative diseases such as Alzheimer’s disease (AD),2,3 stroke,4 Parkinson’s disease, and attention deficit hyperactivity disorder5 or enables an earlier or more definitive diagnosis. For example, it was long presumed in AD that neurons died first, leading axons to wither. Recently, however, some have wondered whether structural damage to axons could precipitate the death of neurons. With its sensitivity to microstructural changes, DKI could help answer that question, and if it does so affirmatively, could be used to detect the early changes in axonal structure that presage the onset of AD.

In the ten years since Helpern and Jensen first described DKI, more than 380 laboratories worldwide have begun to explore its usefulness in a wide variety of diseases, particularly in the early diagnosis or staging of neurodegenerative diseases, such as Parkinson’s and Huntington’s; traumatic brain injury; stroke; and a variety of tumors.6

To help speed research with DKI and the recruitment of patients for clinical trials, Helpern’s laboratory has invited other laboratories conducting DKI research worldwide to work cooperatively through the Kurtosis Imaging Network (KIN), which serves as a clearinghouse for DKI data. “I wanted to provide a playground for these labs to deposit data, so that instead of having to get DKI images of 500 AD patients, 50 sites could get ten AD patients each, thereby pooling their resources,” explains Helpern.
Helpern knows that critics will likely question whether data obtained with scanners at different sites can be usefully compared, but he has confidence in DKI. “A technique that will survive has to survive in the real world and not just in one medical center,” says Helpern. “Using data from multiple scanners will add noise to your data, but if your technique is strong enough, it will survive that additional noise.”

Fiber Tractography
Not all of the clinical applications of DKI—most notably its ability to distinguish when fiber tracts cross each other in tractography—were foreseen by Helpern and Jensen. “When we started doing kurtosis, we weren’t even thinking about tractography,” admits Helpern.

White matter fiber tracts are the insulated wires that connect the brain to the spinal cord and one area of the brain to others. White matter is named for the whitish myelin sheaths (insulation) that cover the many axons (wires) that make up these fiber tracts.

Water flows more freely in parallel with fiber tracts than perpendicular to them. “If water is diffusing inside axons, which are the wires of the brain, it can diffuse down axons more easily than through their insulation (the myelin sheath),” explains Helpern. “It goes down the pipe, if you will.”

Because water has the propensity to travel “down the axon” and because DTI can be used to determine the directionality of its diffusion, DTI can be used to track the fiber as it passes from voxel to voxel. The Human Connectome Project is following the trajectories of many such fiber tracts, essentially creating a blueprint of the brain’s connections.

However, in almost 30% of voxels in an MRI image, two or more fiber tracts cross, causing the typical algorithms used with DTI to fail. As a result, DTI cannot determine the direction of both fibers and can mistakenly interpret the crossing as an abnormality or lesion. Such fiber crossings can be resolved effectively with the far more sensitive DSI method but at the cost of longer imaging times and more complicated post-processing.

DKI, which collects more information than DTI but less than DSI, offers a useful compromise. Like DSI, it can resolve fiber crossings and so accurately map the trajectories of white matter fiber tracts. Like DTI, it can do so in a clinically relevant time frame. The connectomes of disease that will be developed by the Human Connectome Project could offer useful reference maps against which to compare tractography obtained from at-risk patients, leading to earlier and more definitive diagnoses of neurological diseases. However, that promise will only be realized if there is a reliable clinical tool for performing fiber tractography. Both sensitive and clinically translatable, DKI is certainly a strong contender to be that tool.

References
Putting the Pieces Together

A primary care provider’s guide to autism spectrum disorder

BY JANE M. CHARLES, M.D., LAURA A. CARPENTER, PH.D.,
MCLEOD F. GWYNETTE, M.D., AND KIMBERLY MCGHEE

Above: An autistic child receiving speech therapy. Many autistic children respond well to autism-specific apps for tablets and devices.
Part II: Management

On completion of this article, the reader should be able to:

• List the principal therapies that have been proven useful as early interventions for autism spectrum disorder (ASD) and summarize their benefits.

• Manage behavioral problems in children with ASD by treating underlying physiological issues, ensuring adequate behavioral and other therapy, and prescribing medications when appropriate.

South Carolina is at a crossroads when it comes to providing care to its children with autism spectrum disorder (ASD). It is universally agreed that early intervention leads to improved outcomes, but ASD services are expensive and out of reach for many families. As the Affordable Health Care Act continues to roll out, many more of South Carolina’s children with ASD will become eligible for such services. To help their patients with ASD benefit from this expanded access to treatment, primary care providers will need to be familiar with recommended therapies and interventions and with the governmental and community resources that can provide or pay for them.

Providing a medical home

The primary pediatric provider offers a medical home for the child with ASD, partnering with parents to ensure that the child receives the services needed at each developmental stage. For toddlers, the emphasis of care will be proper assessment and the provision of early, intensive therapy. For the school-aged child, behavioral issues may come to the fore. For the adolescent, the pediatrician will need to help the family with vocational and housing needs and the transition of care to an adult provider.

Early intervention

As soon as a child screens positive for ASD, and without waiting for a confirmed diagnosis, the physician should refer him or her to the South Carolina Department of Disabilities and Special Needs (DDSN) for early intervention. This could include applied behavioral analysis (ABA), speech, occupational, and other therapies.

For children three years and younger, Baby Net will pay for these services. For children older than three, parents have in recent years
been able to apply for a Medicaid waiver program for their child. Up to $50,000 is available for services over three years for those receiving a waiver. Demand for these waivers far exceeds supply—for every child who receives a waiver, two more are wait-listed.

In 2014, the federal government clarified that, under the Affordable Health Care Act, Medicaid is expected to pay for services for children with ASD. To facilitate applications for medically necessary ASD services, South Carolina has established an interim program that is open to Medicaid patients with ASD who are 21 years or younger. Children who are currently wait-listed for a waiver or those whose waiver has expired are eligible. As children with ASD transition to the new program, the waiver program will be discontinued.

Applications for the interim program should be submitted to Pete Liggett, Ph.D., at the South Carolina Department of Health and Human Services, P.O. Box 8206, Columbia, SC 29202-4500 or autism@scdhhs.gov along with required documentation. (For more information, visit https://www.scdhhs.gov/press-release/autism-spectrum-disorder-services-interim-process.)

Applied behavioral analysis
Applied behavioral analysis is the gold standard for ASD therapy. When administered early and intensively, it has been shown to improve social and communication skills in about 50% of children with ASD, enabling them to be “mainstreamed” at school. One of the child’s behaviors—either one that needs to change or one that is desired—is analyzed to determine what triggers and reinforces it, and then an intervention is designed to help bring about the desired change. Checklists are used to measure the success of an intervention and to guide future therapy.

Best results are seen when children receive 25 to 40 hours of ABA weekly, ideally delivered in the home. Unfortunately, there is a shortage of adequately trained therapists and not all parents can afford to pay for the recommended hours of therapy. According to Carpenter, “We have had kids who have had amazing outcomes, but my personal observation is that the outcomes are not as good when you are diluting the service.” Expanded Medicaid funding should help more children fully benefit from ABA by offering additional hours of therapy.

Social skills training
Social deficits and challenges making friends are hallmarks of ASD. Social skills training is effective across a wide age range of patients with ASD, especially for adolescents with cognitive abilities in the normal range. One social skills intervention that has a particularly strong evidence base is the UCLA Program for the Education and Enrichment of Relational Skills (PEERS), a parent-assisted model that has been shown to improve core social deficits for as long as five years after treatment and to significantly reduce both the child’s social anxiety and his or her parents’ feelings of family chaos.

MUSC Health’s Project Rex (ProjectRex.org) at the Institute of Psychiatry provides social skills training for high-functioning patients with ASD from age six years through adulthood, along with support and educational programming for their families. The Project Rex clinical team was certified by the UCLA PEERS program in 2014 and is now providing this evidence-based intervention for patients at MUSC Health. Other Project Rex clinical offerings include a yoga group designed for children with ASD, social skills groups for school-aged children, and adult social skills training.

Speech therapy
All children with ASD will have difficulties communicating, though the nature of those difficulties can vary widely. Some children will need help with articulation and vocabulary building, whereas high-functioning children, who once would have been diagnosed
as having Asperger’s Syndrome, may need help only with the social aspects of communication.

Speech therapy, whether provided in the home, the school, or a center, should begin as early as possible. For very young children (18 months), who are typically nonverbal, speech therapy focuses on augmentative communicating, i.e., teaching the child to use a gesture or a symbol to ask for what he or she wants. Common techniques are baby sign language and picture exchange communication, in which the child expresses a want to a communication partner by handing that person the appropriate picture card (e.g., a card picturing a cookie). For children who have begun to speak, therapy would prioritize articulation and clarity.

Communication devices and apps, such as the many autism apps available for tablets and smart phones, can be very helpful tools for these children, but they should be considered an enhancement of and not a substitution for therapy. Apps such as Proloquo2Go enable children with ASD to communicate their needs by pressing a series of icons to form sentences that are then enunciated by the device.

Occupational therapy
The occupational therapist assesses the individual child’s strengths and weaknesses and draws up an individualized treatment plan. Because parents know their child and their family best, the therapist works with them to set the priorities for treatment. The therapist can help the child gain better motor control, better manage sensory processing issues, and improve self-care and social skills as well as emotional regulation. New situations can be stressful to children with ASD, who do not like disruptions to their routine. Their stress can be greatly alleviated by visual schedules, which break down an event or task into a sequence of icons and model appropriate behavior in each scenario.

Support for the school-aged child
The individualized education plan
The Individuals with Disabilities Education Act requires that an individualized education program (IEP) be tailored for each student with a disability and that education be provided in the least restrictive environment possible. This document helps all of the child’s teachers understand the nature of the child’s disabilities and how to best help him or her learn. The IEP is meant to ensure the child with ASD has access to needed special education classes (e.g., speech and occupational therapy) while also having as much exposure as possible to the mainstream classroom. Even children with high-functioning autism benefit from an IEP, but schools often resist providing one to these children because they are progressing well academically. Physicians should act as advocates for children with ASD and their families by helping ensure that an appropriate IEP is in place.

Addressing behavioral problems
Behavioral issues may come to the forefront of parental concerns as children start school and spend increasing amounts of time in public away from the family. Physicians should be prepared to manage a new disruptive behavior in a child with ASD. Before immediately assuming that a new bad behavior is autism-related, the physician should investigate whether it stems from the child’s frustration at not being able to communicate a health concern. A thorough review of systems will identify any underlying physiological problem. Physicians can help prevent discomfort-triggered disruptive behavior by ensuring that children with ASD are adequately treated for any chronic illness (e.g., allergies, gastrointestinal problems) and that they are receiving routine dental care.

If the behavior manifests at school, the environment should be modified to minimize sensory distress and provide adequate visual supports to orient the child. Providing the child with communication devices could help facilitate expression and relieve frustration at not being understood. The physician may need to ensure that an appropriate IEP is in place or suggest needed modifications. If the child is on medications, possible side effects should be considered and dosage should be checked.

It is also important to ensure that the child is getting enough sleep. Asking children to keep sleep diaries and to improve their sleep hygiene is often all that is required to restore healthy sleep patterns. If problems continue, melatonin or another sleeping medication can be prescribed.

Pharmacological management of comorbid psychiatric conditions
While there are no FDA-approved medications for the treatment of core ASD symptoms, medications for comorbid psychiatric conditions such as attention deficit hyperactivity disorder (ADHD), anxiety, or aggression can be considered. When present together, ADHD and autism are more difficult to diagnose. Stimulants have proven effective in treating symptoms of hyperactivity and inattention for children who have both ASD and ADHD, but at lower response rates compared to children without ASD. Clinicians should be aware that the stimulants as a class can cause decreased appetite, disrupted sleep, irritability, tics, and psychotic symptoms, which are present in a significant number of patients with ASD at
baseline. Alpha-agonists such as guanfacine and clonidine can also help reduce the symptoms associated with ADHD and have been shown to have some positive effect on irritability and aggression in several small trials.\textsuperscript{10-12} The serotonin–norepinephrine reuptake inhibitor atomoxetine can effectively control ADHD symptoms in patients with ASD and is generally well tolerated.\textsuperscript{13}

Although few studies support the use of selective serotonin reuptake inhibitors (SSRIs) in children with ASD for treatment of comorbid symptoms of anxiety, SSRIs may have some positive effect on repetitive behaviors.\textsuperscript{14} To avoid hyperactivity and mood lability, both potential side effects of SSRIs, it is advised to begin with a low dosage and titrate up slowly. All antidepressants, along with atomoxetine, carry black box warnings from the FDA regarding suicidal thoughts in patients aged twenty-five years and younger. When starting patients with ASD on antidepressant therapy, physicians should follow them very closely, seeing them at least every two weeks for the first month. As noted above, alpha agonists are the first choice for violent behaviors, with neuroleptics and anticonvulsants also showing some efficacy in controlling disruptive behavior.

The neuroleptics aripiprazole and risperidone have both been approved by the FDA to treat agitation and aggression in children with ASD. Because weight gain and diabetes can be a side effect of these medications, lipid and HGbA1\textsubscript{c} levels should be monitored. Other side effects include daytime drowsiness, rigidity in the jaw or extremities, abnormal involuntary movements, and sialorrhea (i.e., drooling). Because risperidone can cause gynecomastia, prolactin levels should be monitored in patients taking this medication. Anticonvulsants, indicated in children with ASD who experience seizures, can also be used as an adjuvant to neuroleptic therapy to help stabilize mood.

If a medication does not work, confirm that the child is receiving an adequate dosage and that the medication is being taken as directed (e.g., extended-release medications must be taken whole). If no benefit has been achieved with the medication after an adequate trial (3-8 weeks for an antipsychotic or 6-8 weeks for an SSRI) or if the side effect profile is unacceptable, taper the medication and try another family of medications. However, if some improvement has been seen in the targeted symptom, continue the drug and add an agent from another family of medications with proven efficacy for that symptom. For example, prescribe a mood stabilizer to a patient taking an antipsychotic agent for agitation and aggression or an antipsychotic agent to a patient taking an SSRI for anxiety and agitation.

If good control of symptoms is not achieved with these measures, refer the child to a psychiatrist for a psychopharmacological consultation. In South Carolina, these referrals should be made to DDSN psychiatrist Jesse Raley, M.D., through the county Disability Board service coordinator.

**Transitions in care**

The transition from pediatric to adult care can be difficult for patients with ASD as very few adult providers specialize in autism. Until urgently needed training programs in adult developmental disorders are developed, the adult patient with ASD is left with three options: continue seeing his or her pediatrician, seek out a psychiatrist specializing in ASD, or rely on emergency departments (EDs) for care.

Many EDs are not equipped to meet the needs of patients with ASD. The Autism Friendly Healthcare Initiative, led by MUSC Health developmental pediatrician Jane M. Charles, M.D., and Division Chief of Emergency Medicine Edward D. Jauch, M.D.,
will offer training about how to provide developmentally sensitive and appropriate health care for patients with ASD. This training will first be provided to MUSC Health staff and then offered to the staff of other EDs. To receive certification as “autism friendly,” EDs must ensure that all staff complete the required training, establish “desensitized rooms” where ASD patients can find relief from the sensory overload of the ED, and demonstrate their readiness to treat patients with ASD through an onsite visit.

In addition to facilitating the transition to adult care, pediatricians should inform patients with ASD and their parents about vocational and housing opportunities. The South Carolina Vocational Rehabilitation Department (http://scvrd.net/common/index.php) provides autistic teens and young adults vocational training tailored to their skills and employment goals. Autism Speaks offers an Autism Employment Network and a toolbox for securing housing for people on the autism spectrum (http://www.autismspeaks.org/family-services/housing-and-community-living). Some will be able to live independently, but others will require additional support in group homes or other residential settings. Community-based autism organizations, such as the Lowcountry Autism Consortium (lowcountryautismconsortium.org) and the Lowcountry Autism Foundation (lafinc.org), help families access ASD services and provide them a much-needed social support.

A strong partnership between the pediatrician and parents ensures the best possible transition into adulthood for the child with ASD.

### Additional Resources

Overcoming Autism, coauthored by Lynn Koegel, a leading autism expert, and Claire LaZebnik, the mother of a child with ASD, was updated and reissued in 2014 and serves as a useful introduction to physician and parent alike on the best available interventions for ASD.

Mark Durand’s Sleep Better offers useful guidance for the physician or parent managing an ASD child with a sleep disorder.

### References

When surgeons are operating, the fewer the OR door openings (which increase surgical site infections), the better. Nurses are evaluating a door-mounted device that may help reduce occurrences of door openings.
Tradition and opinion still drive many practices in medicine, sometimes because of a lack of evidence, sometimes despite the evidence. In today’s health care environment, in which all members of the medical team are expected to accept responsibility for outcomes, registered nurses have an increasingly important role in questioning the methods and processes they encounter. To empower MUSC Health nurses to develop best practices, nursing administrators are enhancing resources and support for the bedside nurse.

The Nurse Alliance (NA) at MUSC Health, co-chaired by Katie Steidle, MSN, RN-BC and Heather Sodee, MSN, MHA, RN, is the hospitals’ nursing governance structure. The NA committee charged with implementing research activities (the Evidence-Based Practice and Research Council) is co-chaired by Heather Craven, RN, Nursing Quality Data Lead, and Teresa Atz, Ph.D., RN, Assistant Professor in the College of Nursing. Together with Andrea Coyle, MSN, MHA, RN, Professional Excellence Manager, and other colleagues, these leaders are strengthening the research culture at MUSC Health. Such efforts have been a major part of the hospitals’ application to the American Nurses Credentialing Center’s (ANCC) Magnet Recognition Program. A site visit is scheduled for July 2015.

“For the Magnet Recognition Program, we have to outperform in quality measures, nurse engagement, and patient satisfaction. Of course, these are MUSC Health’s goals as well, so we want to put all the things in place that will enable us to meet those goals,” says Coyle.

To support registered nurses in their investigations and build a strong research culture, NA leaders have launched several initiatives. In 2013, Coyle established a partnership with MUSC Health’s Center for Evidence-Based Practice, resulting in a workshop for nurses in research methodology. An advanced course is now being planned. Their collaboration continued with the first offering of the MUSC Health Evidence-Based Practice and Nursing Research Conference in May 2015.

The NA has also launched a “research challenge,” which is an invitation to hospital units to create a team that identifies an area of inquiry, attends a research workshop, and presents a proposal that...
The importance of nurses as scientist-researchers who generate new knowledge about health, wellness, and disease has been recognized for nearly 60 years. The federal government first supported nursing research in 1946 with the establishment of the Division of Nursing within the Office of the Surgeon General, Public Health Service. In 1955, the National Institutes of Health (NIH) established a section within the Division of Research Grants to review the growing number of applications. Thirty years later, the National Center for Nursing Research at NIH (now the National Institute of Nursing Research) was created in response to a 1983 federal study that recommended that nursing research be included in the mainstream of biomedical and behavioral science and included in a 1984 NIH Task Force study.

Today, professionals and students must understand the fundamentals of research. Health care trends are driving health systems to focus not only on patient safety, quality, and cost-effectiveness, but also encouraging ownership on the part of the whole care team.

**Bedside nursing research**

Coyle and Jessica Koenig, MSN, RN, Meduflex Assistant Nurse Manager, recently concluded a study funded by the Beryl Institute Patient Experience Grant Program on whether the availability of seating for health care providers improves the patient’s perception of effective listening and creates an environment for patient-centered care. For three months, folding chairs were put in patient rooms in two units to enable nurses and physicians to sit when speaking to the patient in the bed. The goal was to measure change in the patient experience (i.e., how often physicians and nurses listened carefully to him or her) by comparing Hospital Consumer Assessment of Health-care Providers and Systems scores before and after chair placement. In addition, the staff in those two units were surveyed regarding the use of the chairs. “Current literature shows that there is a link between physicians sitting at the bedside to talk and a decrease in health care costs and litigations. We’re still compiling our results, but hope to see that these chairs have made it easier for staff to sit down and build a relationship. It’s a simple, inexpensive tool, but could have a big impact on patient satisfaction scores,” says Coyle.

**Academic research**

One of the pillars of MUSC’s College of Nursing’s mission is advancing knowledge about improving patient care. Thirteen faculty members are currently conducting 28 research projects (listed on the following pages). One example, funded by the National Institutes of Health/National Institute of Nursing Research, is led by Teresa Kel-echi, PhD, RN, FAAN, Professor and David and Margaret Clare Endowed Chair. Kel-echi is conducting a two-year study to examine the use of a natural homeopathic powder to provide a non-invasive treatment for chronic wounds in patients receiving palliative care (clinicaltrials.gov identifier NCT02008487).

**The Magnet journey**

The ANCC Magnet Recognition Program expects to see evidence-based practice (EBP) embedded in the culture of the organization, as well as visionary leadership, nursing structure, professional practice, quality improvement, and outcomes.

“The ANCC looks for structures and processes that support nursing clinical inquiry,” says Craven. “We are working on several initiatives that will support that.”

To that end, the NA is reorganizing the nursing governance structure, developing an RN IV level that incorporates EBP, revising the review process for nursing proposed studies to include the NA as part of the IRB review, and other activities.

“At Magnet-designated hospitals, nurses need to feel empowered, to be able to say they need to do what’s best for their patients,” says Craven. “We are building a culture that empowers nurses to control their own practice.”

**Dee San, MBA, BSN, CSSBB, CPBN**

Perioperative Services Program Manager at MUSC Health, is the Principal Investigator of a study titled, “Effect of Human Factors on Operating Room Traffic Control and Associated Hospital Acquired Infections.” Operating room (OR) traffic, particularly OR door openings, increases ambient bacteria counts, which have been correlated with increased surgical site infection (SSI) rates. Current efforts to reduce door openings are not highly effective. This study will introduce a real-time visual cueing device to monitor door openings during procedures. During case debriefings, surgical teams will review door opening occurrences, controllable factors, and opportunities to reduce frequency in subsequent cases. Research outcomes will determine whether the use of such human factor techniques affect OR physician and staff behavior and ultimately reduce SSI rates.
Current methods to discourage OR door openings (e.g., yellow tape) are not optimally effective.
## Currently Funded Research Projects at the College of Nursing

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<td>Preventing Venous Leg Ulcers with Cryotherapy: A Randomized Clinical Trial</td>
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Interview

MUSC welcomes two new leaders in research and executive administration

Paula Traktman, Ph.D. (left) and Stephen A. Duncan, D.Phil. (right), are new scientist-leaders at MUSC.

On July 1, MUSC welcomed two senior administrators from the Medical College of Wisconsin (MCW) who shared the moving van that brought their belongings south in June. **Stephen A. Duncan, D.Phil.**, the new Chair of the Department of Regenerative Medicine and Cell Biology, is married to **Paula Traktman, Ph.D.**, the new Dean of the College of Graduate Studies. Duncan was the Director of the Regenerative Medicine Program and Vice Chair of the Department of Cell Biology, Neurobiology, and Anatomy at MCW. Traktman was the Chair of the Department of Microbiology and Molecular Genetics, as well as the Associate Director for Basic Sciences in the MCW Cancer Center. In her new position at MUSC, she also will hold faculty appointments in the Department of Microbiology and Immunology, the Department of Biochemistry and Molecular Biology, and the Hollings Cancer Center. Duncan and Traktman bring an impressive combination of research, teaching, and administrative skills to MUSC. Progressnotes spoke with them about their plans for their units and their basic science research interests.

**PN: What attracted you to MUSC?**

**SD:** We knew a lot about MUSC from Dr. John R. Raymond Sr., MUSC’s former Vice President for Academic Affairs and Provost, who is now the President and CEO at MCW. He brought a lot of what he admires about MUSC to MCW.

**PT:** Life has chapters, and for many professional and personal reasons, I think for both of us it was time for another chapter. Miraculously, two excellent jobs became available at MUSC. I had been Chair of the Department of Microbiology and Molecular
Genetics at MCW for 17 years and loved it and thought Stephen would love being a department chair. I’ve also been active in graduate education, so for me being the Dean of the College of Graduate Studies would be the next step that I’d want to take.

**PN:** What are your plans for your respective units?

**SD:** Dr. Roger Markwald has done a fabulous job during his tenure as Chair. The department is focused on cardiovascular disease and that has given rise to the collaboration with Clemson University in the Center for Biomaterials for Tissue Regeneration.

I have a background in stem cell biology, so I’d like to keep the existing areas strong, but also bring in new faculty and researchers who use stem cells in their research and can integrate the strengths of the department with other MUSC missions. I’m particularly keen on researchers who see a connection between their basic work and work that’s being done in clinical departments, so that it’s more . . . well, translational is maybe too strong a word but maybe more applied. For example, I’d like to expand the number of researchers on campus who use stem cell technologies to look at a broad range of diseases, everything from neural disease, such as Lou Gehrig’s Disease, through inborn errors in metabolism to diabetes.

**PT:** Perry Halushka deserves tremendous credit for his hard work and success in building the graduate school. There are a lot of training grants to support diversity, program development, and student development. The school has a nationally funded Medical Scientist Training Program (MSTP) that is well regarded, and it has strong associate deans and a dedicated administrative staff. It’s by no means a fixer-upper—quite the opposite—but all programs can benefit from an outside look and fresh leadership.

Clearly, diversity is a strong national issue and I’d like to build upon and expand the diversity initiatives that the school already has in place. I also think that we’re going to put together some master’s programs that are interdisciplinary among several health professions. It’s the wave of the future. The final thing I’ll say is that I’m committed to exploring the possibility of building a master’s program in science communication.

**PN:** Tell us about your research, Dr. Duncan. You’re a principal investigator on three grants with direct costs of around $2.5 million and a co-investigator on two grants.

**SD:** My lab is examining the role of specific factors that have been linked to diabetes, heart disease, and the control of cholesterol levels. The disease we’ve made the most progress on is familial hypercholesterolemia, a liver disease that results in cardiovascular disease. We’ve made liver cells from patients’ stem cells, recreated the disease in the culture dish, and then screened for drugs already on the market that can be used to treat the disease. We’ve found that certain heart failure drugs lowered cholesterol levels in avatar mice with human livers as well as in human patients, and we have a paper about our findings under review at *Science Translational Medicine.*

We’re also using this same technology with induced pluripotent stem cells to investigate the liver’s role in rare forms of metabolic disease in children as part of a large, multi-center collaboration to introduce the use of stem cells into personalized medicine.

**PN:** Dr. Traktman, are you planning to continue your research at MUSC?

**PT:** Absolutely. Fifty percent of my time will be my research and I am bringing three NIH grants to MUSC. A major focus of my lab is the analysis of the life cycle of vaccinia virus, which was the vaccine used to eradicate smallpox. Vaccinia is a complicated virus that’s an excellent model system for many of the processes that are essential for the replication of human cells. We are seeking to understand all of the steps from when the virus comes in to the birth of a thousand viruses 12 hours later. These processes are illustrative of all the things that human cells do every day. At the heart of that is DNA replication. Our work also has implications for the development of antiviral therapeutics. Poxviruses are emerging as important for oncolytic therapy. So, if you are going to put these viruses in people to eradicate tumors, you had better be buttoned up about knowing every aspect of this virus so that if something goes wrong you are able to combat the virus.

A second area of work in our lab concerns a cellular enzyme that when overexpressed is associated with cancer and when deficient can impair fertility. I’m looking forward to expanding this project here. MUSC is a great institution for taking basic research to the clinics. With a Clinical and Translational Science Award that has created your South Carolina Clinical and Translational Research Institute, Hollings Cancer Center, a strong drug discovery initiative, and the MSTP programs, MUSC will be a prime location for taking the lessons from research and translating them into the care of patients tomorrow.
Department of Surgery Welcomes New Chair

Prabhakar K. Baliga, M.D., Chief of the Division of Transplant Surgery at the Medical University of South Carolina (MUSC), has been named the 20th Chair of the Department of Surgery. Baliga is also the Director of the Kidney Transplant Program and Medical Director of the Transplant Service Line. He came to MUSC in 1992 following a fellowship in transplant surgery at the University of Michigan. Baliga obtained his medical degree at the Madras Medical College in 1984 and completed his internship and residency in surgery in 1990 at Tulane University Hospital Systems.

Baliga fills the position previously held by David J. Cole, M.D., President of MUSC, and most recently held by Interim Chair David B. Adams, M.D.

Bruce Elliott, M.D., Interim Vice President of Medical Affairs, states, “After interviewing some extraordinarily well-qualified candidates, we were impressed that the most qualified candidate was right here among our own, which attests to the quality of the faculty in the Department of Surgery.”

Cole and Baliga have worked together for 20 years. “Dave Cole has created such a great legacy for this department. It’s recognized at a national level for excellence in several domains,” says Baliga. “He’s a man with tremendous vision who broadened the horizons of the department and established an organizational structure and foundation that allows a newcomer to build to the next level. I’m sure there will be many times I’ll seek his wise counsel.”

The Department of Surgery, which comprises the divisions of Cardiothoracic Surgery, General and Trauma/Acute Care Surgery, GI/Laparoscopic Surgery, Pediatric Surgery, Plastic Surgery, Surgical Oncology, Transplant Surgery, and Vascular Surgery, has 66 faculty members. The graduate medical education program comprises 73 interns, residents, and fellows.

Baliga cites several challenges to the field of surgery in today’s health care setting. “The environment we’re working in is collaborative. We’re no longer individual practitioners. We’re dependent on others for best outcomes, which in turn affects how we’re paid, another change, plus we must balance our academic mission of education and research with declining clinical revenue,” he says. As for training the next generation of surgeons, Baliga says his goal will be to ensure that MUSC graduates are outstanding citizens and safe surgeons. “A safe surgeon in the sense that he or she not only pays attention to the outcomes, but also delivers care efficiently and has a strong sense of the cost of everything that is associated with the surgery, because that’s the new era in which these surgeons will be practicing.”

Best-practice preparation for all of South Carolina’s surgery residents will soon be enhanced with the 2015 rollout of the South Carolina Surgical Quality Collaboration, made possible by a $3.8 million grant from the BlueCross BlueShield of South Carolina Foundation. Cole and Baliga were among the state’s health care and surgical leaders who initiated the three-year program that will benchmark surgical outcomes and create approaches that will improve quality and safety for South Carolina citizens.

The MUSC Department of Surgery will continue to be a resource to all South Carolina physicians, says Baliga, particularly for complex cases and continuing medical education, and he invites the medical community to invest as well. “It’s becoming more challenging to support our academic mission and use innovative techniques,” he says. “It’s important for the community to take pride and be involved and join us in developing the next generation of health care providers.”

Baliga and his wife, Kamashi, have two sons. One is a graduate of Georgia Tech University and the other is a graduate of Colorado State University.
New Chair for the Department of Dermatology and Dermatologic Surgery

MUSC’s College of Medicine has announced the appointment of Dirk M. Elston, M.D., FAAD, FCAP as Chair of the Department of Dermatology and Dermatologic Surgery, effective July 1, 2015. Elston comes to MUSC from the Ackerman Academy of Dermatopathology in New York, NY, where he served as Director. Previously, he was Director of the Department of Dermatology at Geisinger Medical Center from 2002 to 2011. He is President-Elect of the American Society of Dermatopathology, Deputy Editor of the Journal of the American Academy of Dermatology, and a past president of the American Academy of Dermatology. Elston is one of three authors of Andrews’ Diseases of the Skin and has edited seven textbooks. He is also co-author of a textbook on dermatopathology that received an international award for innovation in education. Elston received the 2008 Walter Nickel Award for Excellence in Dermatopathology Education, as well as the Founder’s Award of the American Society of Dermatopathology, the society’s highest honor.

“Dr. Elston brings an impressive combination of clinical, teaching, research, and administrative skills to lead the continued growth and development of the department,” says Deborah Deas, M.D., MPH, Interim Dean of the College of Medicine.

“Dirk Elston is not only a leader in medical education and program management, but also a nationally recognized researcher and prolific author. MUSC welcomes his breadth of experience and his vision for the department,” says Bruce Elliott, M.D., Interim Vice President for Medical Affairs.

Top priorities for Elston are collaborating with other MUSC departments and building a strong foundation of basic and translational research. The department is actively recruiting for an endowed chair in melanoma research. Elston’s own research has focused on skin cancer and scarring alopecia. “Cutaneous oncology has long been a strength in the department,” he says. “We plan to partner with the Hollings Cancer Center, the Department of Pathology, and other clinical departments to build a research base to improve the outlook for patients with melanoma, cutaneous lymphoma, and other forms of skin cancer.”

Another priority is increasing the number of postdoctoral fellows. Elston is working with MUSC’s Office of International Programs to set up cooperative agreements with Central South University in China, China Medical University, and Peking University. The first postdoctoral fellow from Peking University will arrive in July.

Elston recognizes Bruce H. Thiers, M.D., former chair, for leading the department into its international reputation for excellence in clinical services and education. Thiers will remain as a member of the faculty. Elston looks forward to partnering with him, former chairs Richard Dobson, M.D. and John Maize, M.D., Director of the Division of Dermatologic Surgery Joel Cook, M.D., and all of the talented members of the department to continue to advance its reputation. “We are lucky to have a seasoned group of superb clinicians within the department. This really will be a team effort, with these leaders continuing to help the department grow and achieve what it should,” he says.

Elston and his wife, Kathy, are the parents of a high-school-aged son and a daughter who is a resident in dermatology.
New Physicians

James F. Bethea, M.D.
Board Certification: Orthopaedic Surgery // Special Interests: Foot and ankle treatment, general orthopaedics, non-operative procedures // Medical School: Medical University of South Carolina // Residency: Medical University of South Carolina

I-Hweii Amy Chen, M.D., Ph.D.
Board Certifications: Neuromuscular Medicine, American Board of Electrodiagnostic Medicine, Neurology // Special Interests: Diagnosis and management of amyotrophic lateral sclerosis, muscular dystrophy, myopathy, myasthenia gravis, and neuropathy // Medical School: Columbia University // Residency: Albert Einstein College of Medicine // Fellowships: Columbia University (neuromuscular and clinical neurophysiology)

Barbara S. McManus, M.D.
Board Certification: Neurology // Special Interests: General neurology, clinical epilepsy // Medical School: University of North Dakota School of Medicine and Health Sciences // Residency: University of Minnesota // Fellowship: University of Minnesota (clinical neurophysiology with a focus on epilepsy)
**Katherine Ruzhansky, M.D.**
Board Certification: Neurology; Clinical Neurophysiology // Special Interests: Dysautonomia, familial amyloidotic polyneuropathy, myasthenia gravis, neuromuscular disorders, peripheral neuropathy // Medical School: Albany Medical College // Residency: Yale-New Haven Hospital // Fellowship: Columbia University-NY Presbyterian Hospital (clinical neurophysiology, peripheral neuropathy)

**Charles Reitman, M.D.**
Vice Chair, Department of Orthopaedics Co-Director, MUSC Health Spine Center
Board Certification: Orthopaedic Surgery, Spine Surgery // Special Interests: General orthopedic surgery, orthopedic spine surgery, spine deformity (kyphosis), spinal cord injury, cervical spine disorders // Medical School: Baylor College of Medicine // Residency: Baylor College of Medicine // Fellowship: Baylor College of Medicine (spine)

**Zeke J. Walton, M.D.**
Board Certification: Orthopaedic Surgery // Special Interests: Orthopaedic oncology // Medical School: Medical University of South Carolina // Residency: Medical University of South Carolina // Fellowship: Emory University (orthopaedic oncology)
MUSC Health CareLink | Enhanced Communication Between Caregivers

Up-to-Date, Real-Time Information Regarding Patients You Have Referred

- Patient documentation (operative notes, discharge summaries, progress notes)
- Outpatient visits (including future scheduled appointments for your patients)
- MUSC Health ED visits
- Reports (e.g., radiology, pathology, laboratory)

Eligibility for access:
- Physicians or advanced practice practitioners who refer their patients to MUSC Health for care
- Medical support staff (nurses, medical assistants, office managers, and referral coordinators) sponsored by their physician or advanced practice provider
- It’s free.

Ready to sign up?

Go to: www.muschealthcarelink.com, click the Request New Account link, and follow the steps to create and submit a practice agreement and all necessary user requests.

Call: The MUSC Health CareLink liaison for assistance or questions at 843-792-5348.

Email: carelink@musc.edu

To refer a patient, call MEDULINE at 800-922-5250 or 843-792-2200.