

PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SUMMER 2018



**First-in-Human Trial of
Novel Immunotherapy
Shows Promise**

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.

July 13-14, 2018	The Charleston Course: 8th Annual Otolaryngology Literature Update <i>Osprey Point, Kiawah Island, SC</i>
September 7-8, 2018	2018 Storm Eye Institute Fall Meeting and Alumni Reunion <i>MUSC Bioengineering Auditorium</i>
September 22, 2018	5th Annual Update in GI/Hepatology <i>MUSC Bioengineering Auditorium</i>
October 5-7, 2018	Rock the MOC 2018 <i>MUSC Bioengineering Auditorium</i>
October 16-19, 2018	Charleston Child Trauma Conference <i>Francis Marion Hotel</i>
November 2-3, 2018	The Charleston Vestibular Conference 2018 Update <i>MUSC Bioengineering Auditorium</i>
November 5-7, 2018	Neonatal Pharmacology 2018 <i>Hyatt Place Hotel</i>
November 30 - December 2, 2018	21st Annual Frontiers in Pediatrics <i>Francis Marion Hotel</i>

MUSC Health Medical Video Center

MUSChealth.org/medical-video

A sampling of current videos:

Evolving Therapies for Advanced Heart Failure

MUSC Health Heart Transplant Program Medical Director **Ryan J. Tedford, M.D.**, and Surgical Director **Lucian Lozonschi, M.D.**, discuss the profound effects ventricular assist devices have had on the care of patients with advanced heart failure, both as a bridge to transplant and as destination therapy.

Reanimating the Paralyzed Face

Samuel L. Oyer, M.D., assistant professor of Facial Plastic & Reconstructive Surgery in the Department of Otolaryngology, discusses a technique used in facial reanimation surgery — masseter-to-facial nerve transfer — that can restore a patient's ability to smile. The technique is demonstrated with surgical footage from a pediatric case.

Elbow Arthroscopy

Adolescent athletes, such as baseball players and gymnasts, with pain and swelling of the elbow should be closely evaluated for potential osteochondral injuries. Simpler cartilage injuries in younger athletes can be resolved with arthroscopic removal of the lesion and time off from sport. MUSC Health orthopaedic surgeon **Josef K. Eichinger, M.D.**, discusses the case of a 13-year-old baseball player with left elbow pain who was successfully treated with elbow arthroscopy.

A New Rule-Out Test for Lung Cancer

Findings of the multicenter PANOPTIC study show that a new biomarker is 98 percent effective at distinguishing benign from malignant lung nodules. **Gerard A. Silvestri, M.D.**, who led the trial, discusses the biomarker as a promising rule-out test for lung cancer in patients with low-to-moderate-risk nodules.

PROGRESS NOTES

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- A rule-out test for lung cancer
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- Treating glioblastomas with electrical currents
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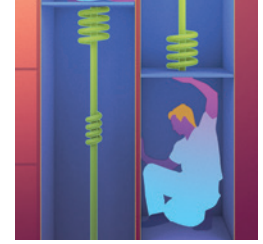
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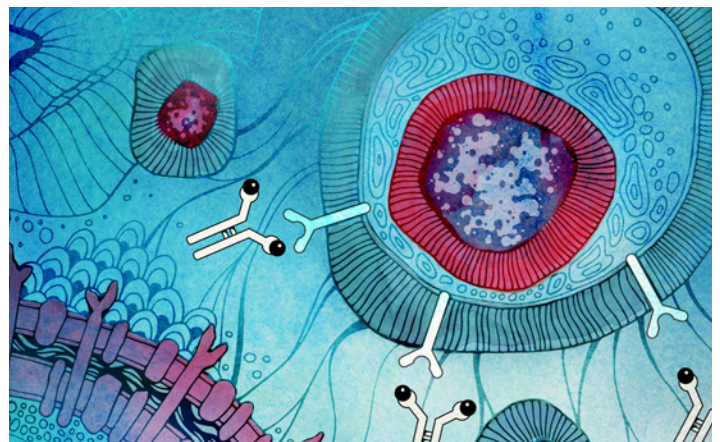
Welcome

New Physicians

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Dynamic Duo

Novel immunotherapy combination for lung cancer shows promise of success



On the cover: Stylized depiction of a molecular environment, featuring ALT-803, a novel anti-cancer IL-15 superagonist complex. Illustration by Emma Vought.



The VIPS device, worn like a visor, can detect emergent large-vessel clots in patients with suspected stroke.

CLINICAL RESEARCH

Machine Learning

Wireless visor detects severe stroke in seconds

BY SVER AUNE

Clinical researchers at the Medical University of South Carolina (MUSC), Mount Sinai, the University of Tennessee Health Sciences Center and elsewhere tested a new device worn like a visor that can detect emergent large-vessel occlusion in patients with suspected stroke. In a study appearing online on March 6, 2018, in the *Journal of Neurointerventional Surgery*, the volumetric impedance phase shift spectroscopy (VIPS) device (Cerebroteck Visor™, Cerebroteck Medical Systems, Pleasanton, CA) displayed

92 percent accuracy when detecting large-vessel stroke, compared to 40 to 89 percent accuracy using standard physical examinations.¹

Endovascular therapy at a comprehensive stroke center within 24 hours is the standard of care for emergent large-vessel occlusion, but the chance of achieving a good outcome decreases by approximately 20 percent for each hour that passes before treatment.² The accuracy of the device simplifies the decisions made by emergency

personnel about where to take patients first, according to **Raymond D. Turner, M.D.**, professor of neurosurgery and chief of the Neuroscience Integrated Center of Clinical Excellence at MUSC Health. Turner served as principal investigator for MUSC in the VIPS for the Non-Invasive Detection of Hemispheric Bioimpedance Asymmetry in Severe Brain Pathology (VITAL, NCT03148340) study reported in the article.

“Transfer between hospitals takes a lot of time,” says Turner. “If we can give the information to emergency personnel out in the field that this is a large-vessel occlusion, that should change their thought process in triage as to which hospital they go to.”

The noninvasive wireless VIPS device works by sending low-energy radio waves through the brain. When a patient has a severe stroke, the brain’s fluids change,

producing an *asymmetry* in the radio waves detected by the device. The greater the asymmetry, the more severe the stroke.

In the study, the VIPS device was deployed with emergency medical personnel in regions served by five comprehensive stroke centers. Both healthy participants and those with suspected stroke were evaluated by three readings taken and averaged using the VIPS device — a process that takes about 30 seconds. Patients were later evaluated by neurologists who provided definitive diagnoses using neuroimaging.

Compared with the neurologists' diagnoses, the device displayed 92 percent specificity — the ability to detect the difference between severe stroke and mild stroke or no brain pathology. This places the VIPS device above standard physical examination tools used by emergency personnel such as the Prehospital Acute Stroke Severity Scale that display specificity scores between 40 and 89 percent.

In their next steps, the researchers are undertaking the VITAL 2.0 study to determine if the VIPS device can use complex machine learning algorithms to teach itself how to discriminate between minor and severe stroke without the help of neurologists. This could lead to widespread clinical implications. "This could potentially be something like an electrocardiogram," says Turner. "You can find out if a patient is having a stroke, just like you can use an electrocardiogram to see if a patient is having a heart attack."

References

1. Kellner CP, et al. *J Neurointerv Surg*. Published Online First: 06 March 2018. doi: 10.1136/neurintsurg-2017-013690.
2. Saver JL, et al. *JAMA*. 2016;316:1279-1288.

CLINICAL RESEARCH

A Rule-Out Blood Test for Cancer?

New classifier differentiates benign from malignant tumors

Every year, U.S. health care providers discover more than 1.6 million lung nodules. Although most turn out to be benign, they can still pose a diagnostic dilemma.

Patients with a high-risk nodule may require invasive testing such as biopsy or even surgery to remove it. However, when there's a low-to-moderate probability of cancer—anywhere from 5 to 65 percent—providers may debate whether patients should be monitored with serial PET or CT scans or undergo complex diagnostic tests.

Recently, researchers at MUSC participated in a multicenter clinical trial to evaluate the accuracy of a blood test that measures the levels of two proteins in a patient's plasma, LG3BP and C163A. When integrated with clinical predictors of cancer, such as age, size of the nodule and other nodule characteristics, the blood test was 98 percent effective at distinguishing benign from malignant nodules.

Gerard A. Silvestri, M.D., a lung cancer pulmonologist at the MUSC Hollings Cancer Center, led the study. Results were reported in an article published online in the journal *Chest* on March 1, 2018 (doi: 10.1016/j.chest.2018.02.012).

If a patient has less than a 50 percent chance of having cancer and the test result is negative, it's likely not cancer. The provider can be confident in a diagnosis and treatment plan.

"It serves as a 'rule out' test for those with low-to-moderate risk," says Silvestri. "The biomarker is a tool to help calculate the general risk of cancer and present a patient with recommendations and



IMAGE: ISTOCK

options. It can push people out of indeterminate risk and into low-risk — without having to undergo invasive and potentially risky procedures."

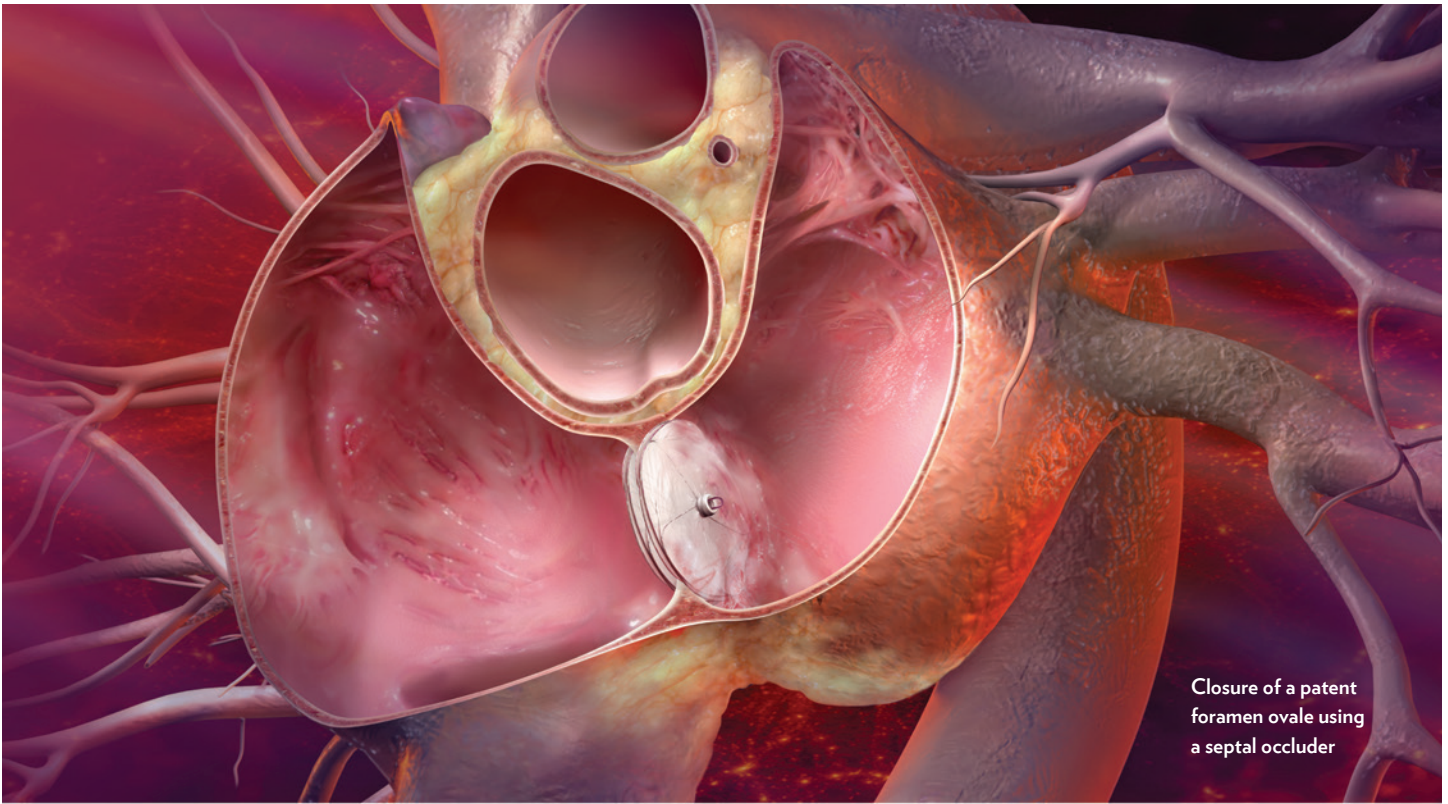
Biopsies and surgeries can be complicated in an organ as delicate as the lung.

"Think of your lung as a two-liter bottle of soda, and the nodule as a pea in the center of it," explains Silvestri. "During a biopsy, for example, the lung could collapse and need a tube to expand it. Our goals for this biomarker are to help calculate the risk of cancer, present the patient with options and recommendations and avoid subjecting patients with benign disease to expensive, unnecessary and intrusive procedures."

Even if biomarker results are negative, patients will need ongoing CT scans to monitor a lung nodule. "A low-risk nodule will be followed with serial imaging. After two years of CT scans being performed periodically and without evidence of growth, we can say it's benign," Silvestri says.

This research is part of the Pulmonary Nodule Plasma Proteomic Classifier (PANOPTIC) study, a clinical trial of 685 patients 40 years old or older, with newly discovered lung nodules 8 to 30 millimeters in diameter as shown on a recent CT scan. —CARIN MOONIN

Disclosure: The study was funded by Integrated Diagnostics, Inc. but the sponsor had no role in the design of the study or the collection and analysis of the data.



Closure of a patent foramen ovale using a septal occluder

CLINICAL RESEARCH

Healing a hole in the heart

BY CARIN MOONIN

One in four people is born with a small hole in the heart, such as a patent foramen ovale (PFO). For many, a PFO does not cause symptoms or disease; few people are even aware they have the condition. However, when a patient has a stroke for an unknown reason (i.e., cryptogenic), PFO is a likely contributor. It's twice as prevalent in patients who experience a cryptogenic stroke.

Closing PFOs using a septal occluder reduced the risk of recurrent stroke in patients who had experienced a cryptogenic stroke, according to study findings reported in the September 14, 2017 issue of the *New*

England Journal of Medicine (doi: 10.1056/NEJMoa1707404).

John F. Rhodes, M.D., a pediatric and adult congenital interventional cardiologist at MUSC Children's Health, was one of the national principal investigators for the REDUCE study (NCT00738894), a multinational, multicenter study to lower the risk of recurrent stroke for patients who have previously experienced cryptogenic stroke. Participants in the study had no other probable reason for their stroke, aside from PFO.

The controlled, open-label REDUCE study compared antiplatelet therapy on

its own with transcatheter closure of a PFO using a septal occluder (the GORE® CARDIOFORM Septal Occluder or its predecessor, the GORE® HELEX® Septal Occluder; W.L. Gore & Associates; Newark, DE), along with antiplatelet therapy. The research involved 644 patients ages 18 to 59; they will be followed for five years. Locations included 63 sites in the U.S., Denmark, Sweden, Norway, United Kingdom, Finland and Canada.

In the initial analysis published in the *New England Journal of Medicine*, the average risk of cryptogenic stroke decreased by 77 percent with use of a septal occluder compared to medical therapy alone.

"This is pretty compelling evidence that closure is the better treatment, especially in someone under 60 who has no indication for stroke, aside from a PFO," says Rhodes.

Disclosure: The study was funded by W.L. Gore & Associates. As a national principal investigator, Rhodes was compensated for his time by the sponsor and serves as a paid consultant.

CLINICAL RESEARCH

Wireless Wonder

As many as 5.7 million Americans suffer from heart failure. In some cases, heart failure is due to an electrical problem that causes the ventricles of the heart not to contract.

"We can correct that in part by pacing both sides of the heart, which is called cardiac resynchronization therapy or CRT," says MUSC Health cardiologist **Michael R. Gold, M.D., Ph.D.**, a pioneer in the field of CRT. In traditional CRT, a pacing device about the size of a half dollar is implanted under the skin near the collar bone; it is attached to three leads that are usually placed in the top part or atrium of the heart, the right ventricle and the coronary sinus vein (to access the left ventricle of the heart).

Studies show that this therapy improves heart function, reduces hospitalizations and even prolongs life. But up to 30 percent of people do not respond to conventional CRT, in part due to failure to pace the best location on the left ventricle. Pacing from inside the left ventricle is thought to be better but has not been feasible because large leads increase the risk of blood clots that can cause stroke or heart attack.

A pivotal trial, SOLVE-CRT (NCT02922036), is testing the safety and efficacy of a new wireless implant (WiSE CRT System; EBR



PHOTO: BRENNAN WESLEY

Systems, Sunnyvale, CA) that is no bigger than a grain of rice. Because the implant is so small—it has no batteries or computer—and because no leads are required, pacing from within the left ventricle of the heart is possible. Gold serves on the trial's international steering committee. "It's a very novel, creative approach, using ultrasound to avoid putting leads in a heart," says Gold. Cardiologist **John Lacy Sturdivant, M.D.**, who is leading the trial at MUSC, was the second surgeon in the U.S. to implant the device.

Dr. John Lacy Sturdivant was the second surgeon in the nation to implant the WiSE CRT System, a wireless pacing device that can be placed inside the heart.

Getting into the Rhythm

MUSC Health has become the first hospital in South Carolina and the second in the U.S. to use a new, high-tech catheter called the HD Grid (Abbott; Chicago, IL) to give physicians more insight into the mechanisms of heart rhythm problems, such as ventricular tachycardia (VT).

In a person with VT, abnormal electrical signals cause the heart to beat more quickly than normal. It can run the gamut from mild, with no symptoms, to dangerous, causing the heart to stop.

"Previously understood mechanisms of arrhythmias may have oversimplified circuits of these fast heart beats," explains **Jeffrey R. Winterfield, M.D.**, director of the Ventricular Arrhythmia Service at MUSC Health. "Using this technology, we have

gained a much richer and more detailed sense of how to localize circuits, which may result in shorter and safer procedures."

So far, the MUSC Health team has used the technology on five patients. "The outcomes exceeded our expectations," says Winterfield. "We shaved off two hours from procedure times for complex VT cases."

The new catheter is similar to other high-density catheters but has an important difference. "It has multiple spines, each with four small electrodes evenly spaced from each other," explains Winterfield. "These small and tightly spaced electrodes create a very small and sensitive antenna to detect abnormal electrical activity in scarred or diseased areas of the heart."

Older catheters would be limited to just two electrodes that are larger and more widely spaced. "The result of the old arrangement would be that we would see only the larger signals and miss the rich and detailed circuits in the very diseased areas of the heart," says Winterfield.

Winterfield is collaborating with Roderick Tung, M.D., at the University of Chicago to open a clinical trial assessing whether using ultra-high-density mapping methods with the HD Grid catheter can reduce procedure times and improve outcomes for VT ablation. VT ablation involves using radiofrequency to destroy small areas of scarred heart tissue responsible for causing VT.

TECHNOLOGY



PHOTO: BRENNAN WESLEY

A patient being treated with tumor-treating fields

Tasing brain tumors

Treating glioblastomas with electrical currents to prolong survival

BY MATTHEW GRESETH

Of all brain tumors, glioblastoma has one of the worst prognoses. After surgery and chemotherapy, patients survive on average around 15 months; approximately 30 percent are still alive at two years. “Glioblastoma is still thought of as an incurable disease and, for that reason, additions to the standard of care regimen are necessary and beneficial,” says **Scott M. Lindhorst, M.D.**, a neuro-oncologist at MUSC Hollings Cancer Center.

News that a novel noninvasive therapy—tumor-treating fields (TTFields)—extended survival by five months in recurrent glioblastoma generated considerable interest in 2011, and it soon became part of the standard of care for that disease. Last year, TTFields were approved by the FDA for use in patients with newly diagnosed glioblastoma as well.

TTFields are low-intensity, alternating electric fields that prevent proliferation of cancer cells by disrupting mitosis. Patients wear a battery-operated cap containing an array of ceramic discs, which deliver the

fields to targeted regions of the brain. The cap and its placement are customized to the patient’s tumor, based on their MRI brain imaging. The longer the patient is able to wear the cap throughout the day, the better the outcomes seen. Although the therapy requires a lifestyle adjustment, it is well tolerated by most motivated patients.

“The next step is now to determine whether we can expand the use of this device to other tumor types, and that’s where the research we’re doing is heading,” says neuro-oncologist **David M. Cachia, M.D.** Cachia and Lindhorst are beginning clinical trials in patients who have lung cancer that has metastasized to the brain and are collaborating with investigators at other institutions to monitor outcomes with TTFields in patients with lower-grade gliomas. While TTFields do not currently cure brain tumors, they do significantly prolong survival of patients with these notoriously difficult-to-treat tumors.

A Perfect Fit

Image-guided shoulder arthroplasty enables surgeons to plan their surgeries virtually and then be guided by real-time feedback during the operation, resulting in more precise placement of components and improving both range of motion and longevity of the shoulder replacement.

“The beauty of this is we can now be a lot more precise with the placement of the component parts,” says MUSC Health orthopaedic surgeon **Josef K. Eichinger, M.D.**, who was among the first surgeons in the Southeast to perform shoulder replacements using the new technology (ExactechGPS shoulder application, Exactech; Gainesville, FL). MUSC Health orthopaedic surgeons **Richard J. Friedman, M.D.**, and **Shane K. Wolf, M.D.**, also use the technology for shoulder replacement surgeries.

Shoulder replacement components include a metal ball that takes the place of the humeral head, a rod that is inserted into the humeral shaft to hold the ball in place and a smooth plastic apparatus fitted onto the surface of the glenoid cavity or “socket” that ensures a smooth fit for the metal ball. Inaccurate fits can decrease the longevity of the replacement and limit the joint’s range of motion. Unfortunately, visualization of the scapula is difficult through the socket. The lack of visualization is particularly challenging in patients who require bone grafts or augmentation before placement of the components, such as those with arthritis who have unusual wear patterns or those with congenital abnormalities that affect the socket.

The new technology uses a patient’s CT scan to create a 3D reconstruction of his or her shoulder anatomy. The

surgeon can then preplan the operation in virtual reality with perfect visualization. On the day of surgery, trackers are placed on designated areas of the shoulder anatomy and on the surgeon's instruments and registered in the system. A specially designed tablet that can "see" both sets of trackers enables triangulation so that the system knows exactly where the surgeon is cutting. The virtual surgery provides a map for the surgeon to follow, and the system provides real-time visual feedback to guide the surgeon's decisions.

"With this technology, we can assure more complex patients that we are doing everything we can to ensure accuracy, avoid complications and provide maximum longevity of their shoulder replacement," says Eichinger. —KIMBERLY MCGHEE



MUSC Health orthopaedic surgeon Dr. Josef Eichinger performing image-guided shoulder arthroplasty

PHOTO: COURTESY OF DR. JOSEF EICHINGER

TECHNOLOGY

No Longer a Waiting Game

Treatment for patients with complex rib fractures used to be a waiting game. MUSC Health trauma surgeon **Evert A. Eriksson M.D.**, remembers being taught in medical school to provide only supportive care, often including mechanical ventilation, to the most severely injured patients, those with "flail chest," and wait for the ribs to mend well enough for normal breathing to resume. In flail chest, at least two ribs are broken in two places, compromising the chest wall's rigidity and leading to difficulties breathing and severe pain. Unfortunately, due to prolonged periods on the respirator, these patients had a higher risk of pneumonia and often required narcotics for pain control.

The wait is over. New rib fixation technology and minimally invasive techniques for its implantation enable rib stabilization in patients with flail chest, leading to better respiration and lower rates of ventilator usage.¹ These encouraging findings led surgeons to extend the use of surgical rib fixation to patients who begin to fail ventilation and to those with major chest wall injuries who do not require ventilation. "We're changing how we manage rib fractures," says Eriksson. "We can now put in specially designed

plates to fix the ribs and get these patients out of the hospital faster, decrease their pain and get them back to their lives sooner. Their ICU length of stay and their risk of pneumonia go down."

The Chest Wall Injury Society (CWIS; <https://cwisociety.org/>) recently conducted a survey of trauma surgeons to learn when they opted for surgical rib fixation. For patients with three or more rib fractures with at least 50 percent displacement, there was a split decision, with roughly half of respondents opting for surgical fixation and half opting for a "wait and see" approach. The CWIS is sponsoring a multicenter trial to test whether surgical fixation improves pain control, breathing function and quality of life in these patients. Eriksson is the principal site investigator for MUSC Health, which is the second center in the nation to open the trial and currently the second highest-enrolling site. Eriksson also serves on the national research committee and guidelines committee for the CWIS. —KIMBERLY MCGHEE

1. Pieracci FM, et al. *J Trauma Acute Care Surg.* 2016 Feb;80(2):187-194.

NEWS

MUSC hearing researcher wins Governor's Award for Excellence in Science



On April 11, Gov. Henry D. McMaster presented **Judy R. Dubno, Ph.D.**, the Governor's Award for Excellence in Science.

Dubno is considered one of the premier

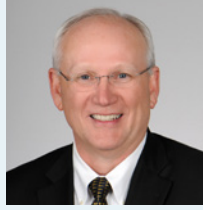
age-related hearing loss scientists in the country. She is a professor in the MUSC Department of Otolaryngology-Head and Neck Surgery and serves as the director of the hearing research program.

This prestigious award is presented to a scientist whose contributions to scientific discovery merit special recognition and have affected the respective discipline on a national and international basis.

The quality of Dubno's work is demonstrated by the continuous funding she has received for more than 30 years. She is the primary investigator on a coveted National Institutes of Health Research Project Grant, which has had more than three decades of continuous support. Hers is the longest-funded grant in the United States related to age-related hearing loss. During her tenure at MUSC, she has brought more than \$70 million to the institution.

Widely acknowledged as an auditory scientist for her expertise in hearing loss and aging, Dubno has served as a leader in scientific societies and worked extensively in public policy related to hearing loss to improve access and affordability of hearing-loss treatments.

MUSC cancer researcher appointed to national leadership positions



Cancer researcher **Raymond N. DuBois, M.D., Ph.D.**, dean of the College of Medicine, was recently named to two positions in the cancer community. DuBois was elected vice chair for the Stand Up 2 Cancer (SU2C) Scientific Advisory Board, and he was named to the newly formed six-member Steering Committee for the AACR (American Association for Cancer Research) Academy.

The AACR Academy was established to honor distinguished scientists whose major scientific contributions have propelled significant innovation and progress against cancer. The AACR Academy Steering Committee will provide ongoing advice and counsel to the AACR leadership on scientific and policy topics as well as other matters of importance to the cancer field.

DuBois served as AACR president from 2008 to 2009 and was elected an AACR Fellow in the inaugural class in 2013. He is a former member of the SU2C Management Committee and is currently chair of the SU2C Catalyst Industry Steering Subcommittees and serves on the Scientific Advisory Board as a reviewer.

DuBois was also named editor in chief for *Cancer Prevention Research*, a journal published by the AACR, effective July 1, 2018.

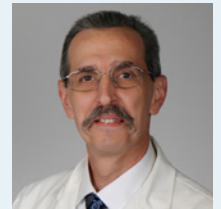
Two MUSC Physician-Scientists Join the Association of American Physicians

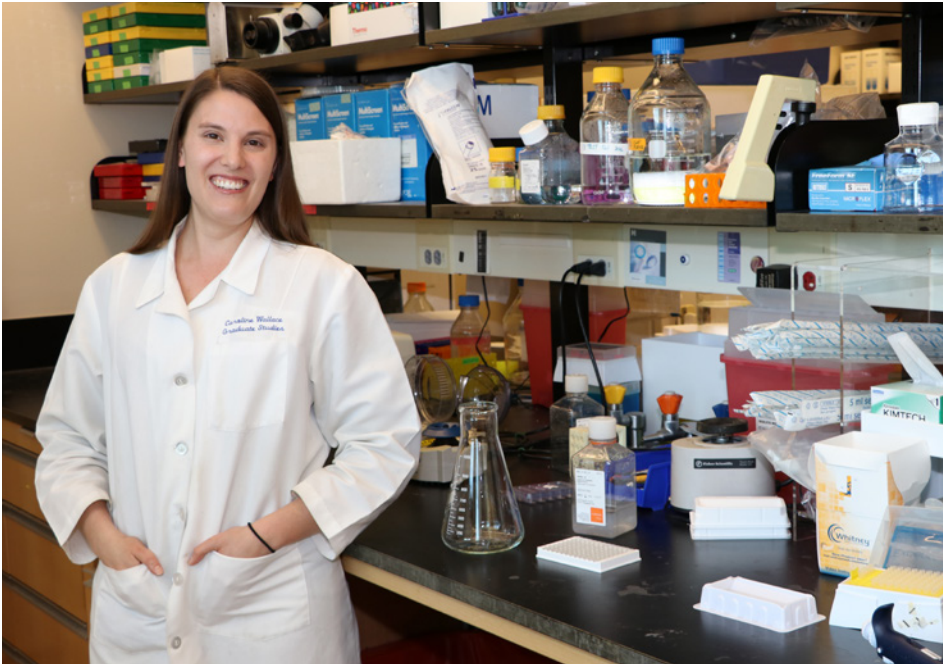
MUSC Hollings Cancer Center immunologist **Zihai Li, M.D., Ph.D.** (pictured at top), and MUSC Health endocrinologist **Louis M. Luttrell, M.D., Ph.D.** (pictured at bottom), were inducted into the Association of American Physicians (AAP) in April.

The AAP, established in 1885, is an honorific, elected society of America's leading physician-scientists who have made enduring contributions to improve health. Nominations for membership are accepted only from current AAP members.

Li, who was nominated by MUSC College of Medicine Dean **Raymond N. DuBois, M.D., Ph.D.**, was recognized by AAP for his work in chaperone biology and cancer immunology. He and his team have elucidated the immunological properties of heat shock proteins in cancer immunotherapy and immune tolerance. Li is chair of the Department of Microbiology and Immunology at MUSC and co-leader of the Cancer Immunology Research Program at Hollings Cancer Center.

Luttrell, who was nominated by 2012 Nobel Laureate in Chemistry Robert J. Lefkowitz M.D. of Duke University, was recognized for his efforts to understand G protein-coupled receptor (GPCR) signal transduction and pharmacology. His recent work has paved the way for development of novel GPCR-targeted therapeutics for multiple indications. Luttrell holds the James A. Keating Endowed Chair for Diabetes in the Department of Medicine.





Left: Caroline Wallace

DISCOVERY

Tolerating yourself

A novel pathway to regulate B cell activity and prevent autoimmunity

BY MATTHEW GRESETH

Autoimmune diseases result from an abnormal immune response against a normal self-tissue. There are over 80 types of autoimmune disease involving all parts of the body, and an estimated 24 million Americans are affected.

The immune system has several strategies to prevent autoimmune disease, known as tolerance, and MUSC researchers have identified a novel checkpoint of peripheral tolerance, specifically in B cells. In an article published online April 5, 2018 by *JCI Insight* (doi: 10.1172/jci.insight.99863), the researchers showed that a specific form of transforming growth factor (TGF)-beta binds the membrane receptor glycoprotein-A repetitions predominant (GARP) to regulate B cell activity.

“This pathway is very important in balancing immunity against pathogens and tolerance against self,” says **Zihai Li, M.D., Ph.D.**, professor and chair of the Department of Microbiology and Immunology at MUSC, co-leader of the Cancer Immunology Research Program at the MUSC Hollings Cancer Center, and senior author on the article. **Caroline Wallace**, a graduate student in Li’s laboratory when the study was conducted, is first author on the article.

TGF-beta has been studied for more than 40 years and is a master cytokine that regulates inflammation and tolerance. More recently, the membrane receptor GARP was shown to bind to TGF-beta on regulatory T cells and platelets to modulate their activity. Although it was known that GARP is

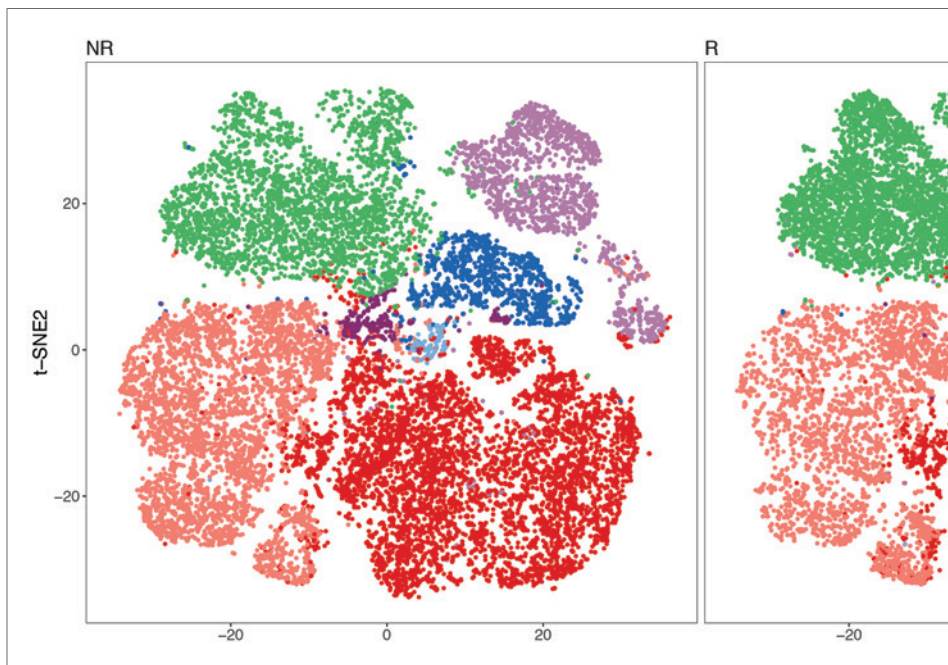
expressed on B cells, it was unknown whether and how the GARP:TGF-beta axis contributes to peripheral B cell tolerance.

The study by Li’s laboratory showed that GARP was expressed upon activation of B cells and may therefore act as an important checkpoint for B cell tolerance. To address the contribution of the GARP:TGF-beta axis to B cell biology, the Li lab generated two preclinical models: one in which GARP was overexpressed and one in which GARP expression was reduced. Overexpression of GARP reduced the proliferation and activation of B cells. Interestingly, loss of GARP led to the development of spontaneous lupus-like disease. Furthermore, in a lupus-prone model, loss of GARP exacerbated the lupus symptoms.

The findings by Li’s laboratory demonstrated the importance of this pathway in lupus, but the GARP:TGF-beta axis is likely a key regulator of peripheral B cell tolerance in preventing all autoimmune disease. Follow-up studies will closely examine how the GARP:TGF-beta axis functions in patients with autoimmune diseases, such as systemic lupus erythematosus (SLE), scleroderma and rheumatoid arthritis, to see whether this pathway is indeed as important as they found it to be in their lupus model system. Over the long term, the Li laboratory will pursue the GARP:TGF-beta pathway as a potential therapeutic target for autoimmune diseases.

There is no cure for autoimmune diseases and treatment generally focuses on reducing the activity of the immune system. The current study lays the groundwork for improving the outcomes of patients with these diseases. Monitoring the levels of GARP on B cells may provide a very useful diagnostic marker for autoimmune disease. Moreover, this pathway, specifically GARP, may be a potential future therapeutic target for treatment.

IMAGE: COURTESY OF DR. CARSTEN KRIEG



DISCOVERY

Cancer Instagram

Snapshot of immune system proteins predicts patients' response to immunotherapy

BY MATTHEW GRESETH

Checkpoint therapy blocking PD-1, a cellular surface marker that dampens the immune response, has revolutionized cancer care, enhancing overall survival in 33 to 40 percent of melanoma patients. However, it does not work in most patients and can have adverse effects and considerable costs to the health care system. Thus, it is crucial to identify patients likely to benefit from blocking PD-1 before administering therapy. MUSC Hollings Cancer Center researcher **Carsten Krieg, Ph.D.**, an assistant professor in the MUSC Department of Microbiology and Immunology and the Department of Dermatology, and colleagues are using a novel technology to answer that question.

The technology, single-cell mass cytometry (called “Helios”), allows Krieg to generate an ‘Instagram’ of a patient’s immune system to identify the molecular details of the immune cells. An article reporting these results was featured on the cover of the February 2018 *Nature Medicine* (doi: 10.1038/nm.4466).


To date, researchers have tried to use patient-derived killer T-cells to identify biomarkers; however, this approach is limited by the small sample sizes that can be attained. Krieg and others in the field are starting to widen their approach by collecting peripheral blood mononuclear cells from a simple blood draw, so-called liquid biopsies.

The cells are stained with metal-conjugated antibodies that target surface and intracellular proteins. This allows for sensitive detection of more than 30 proteins on a single cell over millions of blood cells. The stained cells are placed in Helios and are ionized. Because the metals placed on each antibody weigh differently, the resulting ions can be separated into different pools. Using artificial intelligence-guided bioinformatics and expert-guided analysis, researchers can create “immune Instagrams,” or simplified visualizations of the blood immune response in a tumor patient.

Using this technology, Krieg and his colleagues confirmed that, as intended, T cells respond to anti-PD-1 immunotherapy. They showed that the frequency of classical monocytes, a type of immune cell, in the peripheral blood correlated with a patient’s response rate: the more monocytes in the blood, the better the response to anti-PD-1 therapy.

Generating immune profiles enables clinicians to sort patients towards immunotherapeutic regimens to which they are most likely to respond, thus supporting precision medicine. Not only will this technology allow clinicians to identify the subset of advanced melanoma patients who will respond positively to anti-PD-1 therapy, it may also identify alternative targets for patients who would not respond. Additionally, since this approach uses a simple blood test, samples could be taken throughout the treatment regimen. This would allow clinicians to monitor any changes to patients’ profiles that might require changes to their treatment.

“Here at MUSC, we hope to use the technology to help clinicians monitor success in their clinical trials or tell them to switch the immunotherapy,” says Krieg.

 **Watch an interview with Dr. Krieg on the oncology page of the MUSC Health Medical Video Center (MUSChealth.org/medical-video).**

DISCOVERY

Safeguarding Neurons After Stroke

Novel drug therapy prevents destruction of salvageable neurons

BY KAT HENDRIX

Currently, tissue plasminogen activator (tPA), a so-called clot buster drug, is the only pharmacological stroke intervention available. It must be administered within 4.5 hours after the stroke and cannot be given to patients who take blood-thinning drugs due to their elevated bleeding risk. However, recent discoveries by a team of MUSC investigators led by **Stephen Tomlinson, Ph.D.**, professor and vice chair for research and faculty development in MUSC's Department of Microbiology and Immunology, may soon expand post-stroke treatment options.

The team's findings, published online May 16 by *Science Translational Medicine* (doi: 10.1126/scitranslmed.aaa6459), describe a novel pharmacological agent that links an antibody fragment, which is capable of recognizing specific cell damage markers appearing after an ischemic stroke, to a complement inhibitor. The therapy, called B4Crry, masks damaged but living neurons—preventing their removal and allowing them time to regain functionality.

“There’s an ischemic core where the greatest oxygen deprivation occurs. Neurons in that area are irreparably damaged and die,” Tomlinson explains. “But damaged neurons outside the stroke core can be salvaged. Unfortunately, complement becomes activated and signals that these damaged neurons should be cleared from the brain before they get a chance to recover.”

The complement system is a component of both the innate and adaptive immune

responses, but its dual roles in injury and recovery (neurodegenerative and neuroregenerative processes) make it a challenging target for potential stroke therapies. Tomlinson's team found that live but stressed neurons display danger-associated molecular patterns that trigger complement C3d deposition on the outer cell membrane, tagging the neuron for rapid clearance by inflammatory microglia. “B4Crry also breaks the inflammatory response cycle and prevents chronic inflammation, which we know can continue for many years after a stroke,” adds **Ali Alawieh**, an M.D./Ph.D. candidate in the Department of Microbiology and Immunology and first author on the article.

In a murine model of ischemic stroke, animals treated post-stroke with B4Crry showed reduced C3d deposition in the brain, fewer neurological deficits and reduced infarct volume compared to control animals. Over the course of a 15-day recovery period, B4Crry-treated animals also had greater recovery of initial deficits than controls. Overall, the B4Crry-treated group had faster learning curves, better learned memory retention and a four-fold increase in cortical and hippocampal neuroblasts than untreated animals. Importantly, these benefits were evident in animals treated up to 24 hours post-stroke—a markedly longer treatment window than for tPA. Also, unlike tPA, B4Crry in theory could be administered to patients who are at risk for bleeding, once its safety and efficacy have been verified in

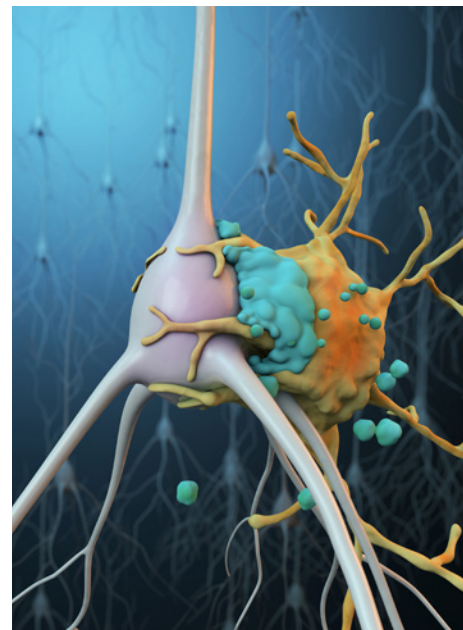



ILLUSTRATION: EMMA VOUGHT

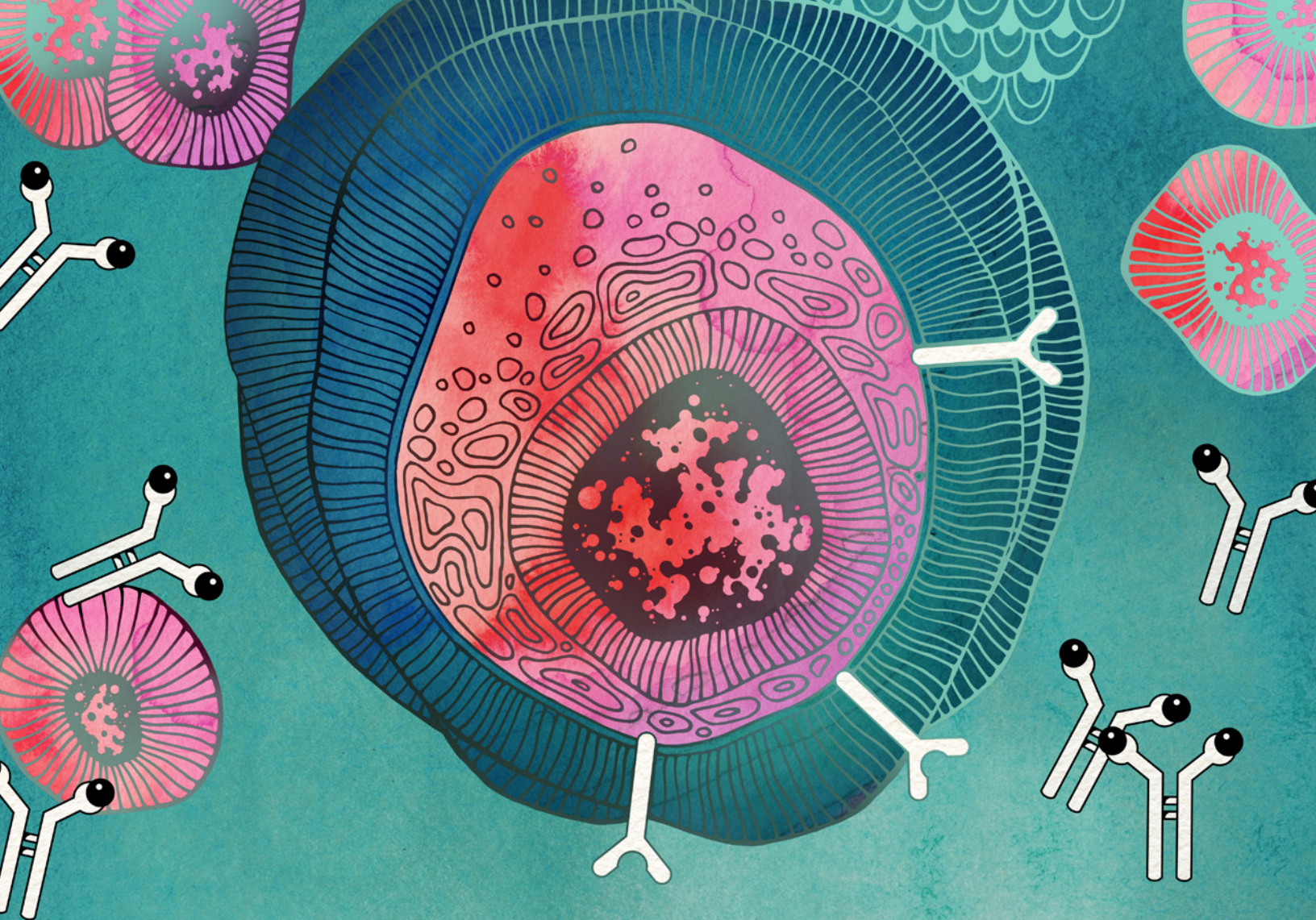
A microglial cell (yellow) attached to an ischemic neuron (gray) that has been tagged by complement proteins (blue)

human clinical trials. Another critical advantage of B4Crry treatment is that, because it is targeted to the site of injury in the brain, it does not increase risk for infections such as pneumonia.

The team has shown that the B4 epitope is expressed on other injured human tissues and has begun to apply the approach to cardiovascular disease research. Future plans include studying how complement-dependent mechanisms affect outcomes in traumatic brain injury and taking B4Crry therapy into human clinical trials.

Disclosure: Tomlinson is an inventor on a patent application for natural antibody targeted complement inhibitors filed by the University of Colorado and is a consultant for and holds stock from AdMIRx, Inc., a company developing complement inhibitors.

 **Watch a video interview with Ali Alawieh about this research on the Neurosciences page of the MUSC Health Medical Video Center (MUSChealth.org/medical-video).**



Dynamic Duo

Novel immunotherapy combination for lung cancer shows promise of success

BY S. CORRIN GARR

ILLUSTRATION BY EMMA VOUGHT

Recent results from a clinical trial to treat lung cancer show that a novel immunotherapy combination is surprisingly effective at controlling the disease's progression. The study, published in the May issue of *The Lancet Oncology*, focused on non-small cell lung cancer, which is the most common form of lung cancer.

John M. Wrangle, M.D., a medical oncologist at the MUSC Hollings Cancer Center, says it's a promising therapy that can be delivered in an outpatient setting. "People don't talk about curing patients with metastatic lung cancer. We now get to flirt with the idea for certain patients using immunotherapy," says Wrangle. "And at the very least we have a significant proportion of patients enjoying prolonged survival, even if we can't call them cured."

Along with immunologist **Mark P. Rubinstein, Ph.D.**, also of the Hollings Cancer Center, Wrangle designed a clinical trial that started in 2016.

Patients with metastatic non-small cell lung cancer will always progress after chemotherapy, so most patients go on to be treated with checkpoint immunotherapy. Checkpoint therapies work by cutting the brake cables on the white blood cells that are inherently able to kill tumor cells. "Tumor cells often produce suppressive factors that essentially put the brakes on tumor-killing white blood cells," explains Rubinstein. "What's unique about the therapy that we're testing is that, in addition to cutting the brake cables on white blood cells, we're providing fuel to them so that they can more effectively kill cancer cells."

Wrangle and Rubinstein's therapy is a combination of a checkpoint drug, nivolumab, with a new and powerful immune stimulation drug, ALT-803 (Altor Bioscience, Miramar, FL). "What's unique about our trial is that it's two completely different types of drugs that have never been combined in humans before, and the trial demonstrated that these drugs can be safely administered, and also, there's evidence that it may help patients where checkpoint therapy is not good enough alone," says Rubinstein.

Of the 21 patients treated, nine previously either had stable disease or responded to single-agent immunotherapy before becoming resistant to this treatment. Of these nine patients, 100 percent either had stable disease or had a partial response to the treatment used in this study.

"We can reassert control, at least in terms of stable disease, in essentially everybody we've treated so far," Wrangle says.

In the past decade, immunotherapy has joined surgery, radiation and chemotherapy as the fourth pillar of cancer treatment. "Immunotherapy fundamentally alters the balance of power between your body and your cancer," says Wrangle. "If ten years ago you were

talking about defining a five-year survival rate for metastatic non-small cell lung cancer patients, someone would have laughed in your face. It's just a very different time now."

He credits Rubinstein's work, instrumental in the development of a precursor to ALT-803, in helping to make this advance. Research into ALT-803 started years ago while Rubinstein was doing his postdoctoral training at the Scripps Research Institute. It was there that he co-discovered the powerful immune system stimulator used in this trial. The stimulator, known as IL-15 complexes, is actually a combination of an immune system growth factor and its soluble receptor. IL-15 is a growth factor for certain kinds of white blood cells,

"We can reassert control, at least in terms of stable disease, in essentially everybody we've treated so far."

— John M. Wrangle, M.D.

including natural killer cells and T cells. Natural killer cells are the chief arm of the innate immune response. "They are an important part of the anti-cancer response that haven't been really talked about for a long time," explains Wrangle.

In contrast to other immunotherapies that require admission to a hospital, this new therapeutic combination can be administered in an outpatient setting. "The plan was to do it all as an outpatient therapy because inpatient therapy is just infeasible. My patients feel like they have the flu, but they go about their day, and it's totally manageable. That's kind of the revolutionary part with regard to this class of agent," Wrangle says.

Much remains to be done before the new combination of drugs can be used outside of a clinical trial. "We need to treat a few hundred patients in order to get a better sense of how to refine the synergy of these two classes of drugs. That's just going to take time," says Wrangle.

Successful trials for the treatment of cancer are incredibly rare. "There are very few people who get the privilege of developing a new therapy for any human disease, much less cancer. Mark and I are now in this weird micro-club of folks who have developed the promise of a new therapy for cancer. That's such an amazing privilege to be able to do that," Wrangle says.



Pediatric and adult congenital interventional cardiologist Dr. John Rhodes. Photograph by Brennan Wesley.

A Release Valve

Nonsurgical options for patients with pulmonary valve conditions

BY CARIN MOONIN

Patients with congenital heart disease—such as tetralogy of Fallot, pulmonary atresia or pulmonary valve stenosis—often undergo several surgeries over the course of their lives to implant and/or replace a conduit or heart valve. Yet transcatheter pulmonary valve replacement (TPVR) is minimally invasive, safe and has been shown to be a viable, longer-lasting alternative to open surgery—and possibly even multiple procedures.

After TPVR, most patients are able to resume their normal daily activities within the week. This is quite a difference from the four to six weeks of aftercare and activity restrictions generally required to recover from open heart surgery.

Since December 2017, **John F. Rhodes, M.D.**, a pediatric and adult congenital interventional cardiologist, has been performing TPVR—along with other interventional cardiology measures—to revise right ventricular outflow tracts. Rhodes has recently returned to MUSC as the operations director for the MUSC Children’s Health Congenital Heart Center and as an interventional specialist for children and adults with congenital heart disease.

A brief overview of TPVR

Although transcatheter aortic valve replacement (TAVR) has been performed since the early 1990s, it has only been since about 2000 that transcatheter procedures have been used for pulmonary valve concerns. The lag is largely a numbers issue: aortic valve disease (often age-related) is simply more common than pulmonary valve disease (often congenital).

In 2000, Philipp Bonhoeffer applied the TAVR model toward treating congenital heart disease. This led to what became Medtronic’s Melody transcatheter pulmonary valve, which treats narrowed or leaking pulmonary valve conduits between the heart’s right chamber and the lungs. It consists of a bovine jugular vein valve sutured within a platinum iridium frame. Currently, the Melody Valve (Medtronic; Minneapolis, MN), along with the Edwards SAPIEN XT transcatheter heart valve (Edwards Lifesciences; Irvine, CA), made from cobalt-chromium and bovine pericardial tissue, are both used for TPVR. In both devices, the valve is sewn onto the stent apparatus and crimped onto a balloon.

The minimally invasive procedure can be performed on adults and pediatric patients. Contraindications are rare and include inadequate vascular access, pulmonary tract outflow not large enough to sustain a strong cardiac output, metal allergies or vascular structures that may interfere with placement.

The TPVR process

TPVR is a nonsurgical, endovascular procedure, typically done in MUSC’s cardiac catheterization laboratory. Usually the catheter is started through the patient’s femoral vein, but occasionally the jugular vein is used if there are concerns with venous access or the size and shape of the femoral vein. The catheter goes through the right ventricle and into the lungs; a support wire is used to move the valve over the wire into the right ventricular outflow tract and deploy the valve using the balloon.

After the procedure, patients are typically kept overnight for evaluation and an echocardiogram to assess placement. Healing time is approximately two to three days; as it is not a surgical procedure, there is little that needs to heal aside from the small access point of the femoral vein.

“The rate of any complications is very low—less than three percent,” says Rhodes. “The main risk is bleeding, infection or calcification to the existing graft.”

Outcomes appear positive

Follow-up data for patients who have had TPVR compare favorably with those for patients who have undergone surgical valve replacement. Rhodes believes much of that is due to less of the body’s inflammatory response with transcatheter procedures versus open surgery.

He also feels encouraged that the data suggest TPVR will further improve on outcomes. “Surgical valve replacement [in patients who have had prior valve replacement surgeries] has been shown to last about seven to ten years at most,” says Rhodes. “We’re hoping TPVR will be more like ten to twenty years.” Rhodes would like to see TPVR used for patients who have not had previous surgeries—the “native outflow” tract; he believes response will be even better for that patient subset.

Going forward

“This is profound for the patient,” adds Rhodes. “When you do an operation and fix the pulmonary valve, it usually doesn’t last a lifetime. Many patients have about two or three operations before they even turn 18. But what if we could prevent major surgeries, and the patient could improve both physical and psychological recovery? This is revolutionizing medicine. It’s amazing technology, and I can’t wait to see where we go next.”



To watch a video interview with Dr. Rhodes, visit the Pediatrics page of the MUSC Health Medical Video Center ([MUSChealth.org/medical-video](https://www.muschealth.org/medical-video)).



da Vinci ^{Si}
SURGICAL SYSTEM

Not Missing a Beat

A hybrid approach to coronary revascularization relieves multi-vessel blockages
without spreading the ribs or stopping the heart

BY KIMBERLY MCGHEE

The most feared myocardial infarction, known colloquially as the “widow maker,” occurs when the left anterior descending artery (LAD), which runs down the front of the heart and supplies the front and main wall, is critically blocked by plaque buildup. Coronary artery bypass grafting (CABG) has long been the gold standard for treating blockage of the LAD due to coronary artery disease (CAD), especially in patients with multivessel disease¹ or diabetes.² The CABG procedure with the best survival rates involves harvesting the left interior mammary artery (LIMA), which runs behind the sternum, and grafting it to the blocked LAD in order to restore blood flow.³ LIMA to LAD bypass provides very durable results, with ten-year patency rates of 95 to 98 percent.⁴

However, traditional CABG requires that the chest be fully open to reach the heart, and then that the heart be stopped during the operation, necessitating use of cardiopulmonary bypass. Several weeks of recovery are required after open surgery. When percutaneous coronary intervention (PCI) with drug-eluting stents began to show similar short-term outcomes as open CABG, many patients opted for the less invasive approach because it could be performed without cardiopulmonary bypass and without opening the chest. For PCI, a catheter is used to unblock the artery and a stent is implanted via the catheter to hold the artery open. Recovery time is shortened from a few weeks to a few days. This approach can also be used in patients who are not good candidates for open CABG. Results are not as durable as with LIMA to LAD CABG, however, and repeated revascularization is often necessary.² In contrast, PCI has achieved better long-term results than CABG for non-LAD blockages.⁵

Hybrid coronary revascularization (HCR) maximizes the strengths of both approaches while minimizing their drawbacks. The LIMA to LAD bypass is performed with the help of a surgical robotic system, and then PCI is used to open up any non-LAD blockages. The patient benefits from the durability of the CABG procedure and the superior outcomes of PCI for non-LAD blockages without having to experience the prolonged recovery and surgical morbidity associated with traditional open CABG. A follow-up study of the POLMIDES (NCT01035567) trial, which compared HCR to traditional CABG in 200 patients, found similar rates of survival at five years for the two approaches.⁵

“Hybrid coronary revascularization is using the best of both worlds to treat coronary artery disease,” says **Lucian Lozonschi, M.D.**, director of surgical heart failure and cardiac transplantation at the MUSC Health Heart and Vascular Center.

Seated at a monitor displaying endoscopic images of the surgical field, Dr. Lucian Lozonschi performs robotic CABG.

Lozonschi is one of the site principal investigators, along with interventional cardiologist **Daniel H. Steinberg, M.D.**, of the Hybrid Coronary Revascularization Trial (NCT03089398), which is randomizing patients with multivessel CAD to either minimally invasive CABG plus PCI or PCI alone. This trial should provide definitive evidence as to which of these modalities is most effective in these patients. The MUSC Health Heart and Vascular Center was chosen as a site for this trial because it has expertise in both minimally invasive (robotic) CABG and PCI. It also offers a hybrid OR that is ideal for such hybrid procedures.

Unlike open CABG, robotic CABG does not require a large incision or opening of the breastbone, and it is performed without cardiopulmonary bypass. For robotic CABG, Lozonschi makes three very small thoracic incisions to enable docking of the robot’s arms and placement of an endoscopic camera. Then, seated at a monitor displaying endoscopic imaging of the surgical field, Lozonschi uses the robot in the harvest of the LIMA. Lozonschi then hand sews the LIMA to the LAD through a mini-thoracotomy (roughly 6 cm) to complete the CABG. Once Lozonschi completes the robotic CABG, Steinberg opens non-LAD blockages using PCI with drug-eluting stents.

Robotic surgery is best performed at high-volume tertiary care institutions by surgeons with specialized training, such as Lozonschi for robotic CABG and **Marc R. Katz, M.D., MPH** for robotic mitral valve repair (see “A Robotic Revolution” in the summer 2017 issue). The MUSC Health Heart and Vascular Center is one of a handful of heart centers offering both robotic CABG and robotic mitral valve repair.



To watch video interviews with Heart & Vascular Center specialists, including a video with Katz about robotic mitral valve surgery and a video with Lozonschi and Ryan J. Tedford, M.D., about heart transplant, visit the Cardiology page of the MUSC Health Medical Video Center (MUSChealth.org/medical-video).

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A watercolor-style illustration of a woman's face. She has light skin, green eyes, and red lips. Her mouth is covered by a blue-gloved hand, with the index finger pointing upwards. The background is a mix of light blue and grey washes.

~~Nothing by Mouth~~

Enhanced recovery after surgery protocols challenge the traditional tenets of surgical care, using evidence-based recommendations to reduce complications and speed recovery

BY KIMBERLY MCGHEE

ILLUSTRATION BY EMMA VOUGHT

Nothing by mouth. Administration of generous IV fluids. Opioids for pain. Bed rest.

These age-old guides for the care of surgical patients were based on the best intentions for the patients' well-being but not, as it turns out, on good evidence. Instead, they put patients at greater jeopardy, making complications more likely and delaying recovery. Enhanced recovery after surgery (ERAS) initiatives strive to improve outcomes by replacing time-worn but ill-supported practices in the care of patients before, during and after surgery with ones grounded in evidence. Their ultimate goal is to reduce patients' stress response to surgery, which can cause biological changes, such as catabolism and insulin resistance, that delay and complicate recovery. Minimizing surgical trauma and maintaining good physiological functioning in the patient can help guard against such stress. Studies have shown that ERAS initiatives can reduce hospital length of stay by 30 percent and general complications by 40 percent or more.¹

"Patients who are kept without food or even water are stressed and almost in a starvation mode when they come into surgery. Because of that, they would get a lot of extra fluid when they arrived at the OR," explains ERAS nurse navigator, **Geri Johnston, M.S.N.** "We were keeping people without anything and then giving them too much all at once—that can cause fluid imbalance and slow down recovery."

In addition to ensuring that patients are properly nourished and hydrated before surgery by avoidance of fasting and use of liquid carbohydrate supplements, common ERAS elements are a preference for minimally invasive surgery and regional anesthesia and early resumption of food, drink and activity, as early as the day of surgery. Use of nasogastric tubes, drains and catheters is minimized to promote the return to normal eating and greater mobility. Pain is carefully controlled, but opioid use is discouraged because it can compromise bowel function and prolong recovery and because of its potential for addiction.

Johnston was hired as the ERAS nurse navigator in April 2016 after promising results were achieved by an ERAS initiative for pancreatic surgery, one of the first in the country, led by MUSC Health gastrointestinal surgeon **Katherine A. Morgan, M.D.** Length of stay was cut by two days and the cost of surgery by more than \$4,000 in the first year of the initiative.² Johnston's mission was to facilitate the rollout of initiatives in other surgical specialties, including colorectal surgery, orthopaedic surgery (joint replacement), gynecologic surgery and cardiac surgery. In its first year of implementation, the colorectal surgery protocol, under the leadership of surgeon **Virgilio George, M.D.**, and anesthesiologist **Laura L. Roberts, M.D.**, shaved three

days off patients' length of stay and dramatically reduced the percentage of patients receiving opioid medications for pain control (from 75 to 10 percent; unpublished results). Protocols and order sets are also in place for gynecologic oncology and are expected by the end of the year in all of gynecology, orthopaedic surgery and cardiac surgery.

The care provided by any team is constrained by the decisions made earlier in the care pathway and in turn has consequences for the later care of the patient. ERAS initiatives work in part because they strive to implement evidence-based recommendations across the continuum of care. Specialty-specific protocols help to guide treatment, education materials are developed for patients, and order sets are programmed into the electronic health record to standardize care.

Although these initiatives are typically championed by the surgeon and anesthesiologist, they are crafted and implemented by multidisciplinary teams representing all of the units providing the patient's care. Participation of bedside caregivers is particularly important for the success of ERAS, because they implement the initiatives and can help patients understand how the changes help speed recovery.

"Everyone has to work as a team and understand the protocol and how patients are going to get better sooner, or it's not going to work," says Johnston.

Another key ingredient to a successful ERAS initiative is sustainability. Frequent audits of outcomes can reveal lack of adherence to ERAS protocols and motivate continuous process improvement. Protocols too will evolve as the evidence changes, meaning that the team must be prepared to adapt.

But the payoff for patients is undeniable.

"There is a lot of evidence showing that this is an improved way to take care of patients. This is how we are going to go forward with patients having surgery," says Johnston.

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MISCONNECTIONS

IN

Developmental Disorders

AND

Addiction

Revealing possible links through genes that control brain wiring

BY VITRIA ADISETIYO

Sparks to discoveries

How do humans have different personalities, different strengths or weaknesses, different ways of perceiving and adapting to the world? These are the fundamental questions that continue to fascinate **Christopher W. Cowan, Ph.D.**, a professor and vice chair in the Department of Neuroscience and the William E. Murray Smart-State™ Endowed Chair of Excellence in Neuroscience at MUSC—a career progression that stems from his early curiosities as a fourth-grader dissecting frog brains in his garage.

In his laboratory, Cowan and his team unravel the brain's mysteries by exploring the genes and molecular mechanisms that control proper brain wiring during development. His goal is to understand their roles in developmental disorders and addiction which, according to Cowan, are both disorders of brain connectivity and function.

"It comes down to brain plasticity, how the brain changes in response to an experience," explains Cowan. "The genetics of brain development represents the crude blueprint. Our cells have all the basic information but have evolved to respond to changes, especially as there are important gene-environment interactions that occur throughout life. During development, you're experiencing the world for the first time and the brain is shaping neural circuits in response. In individuals suffering from substance use disorders, these same systems are being hijacked in parts of the brain that process reward experiences."

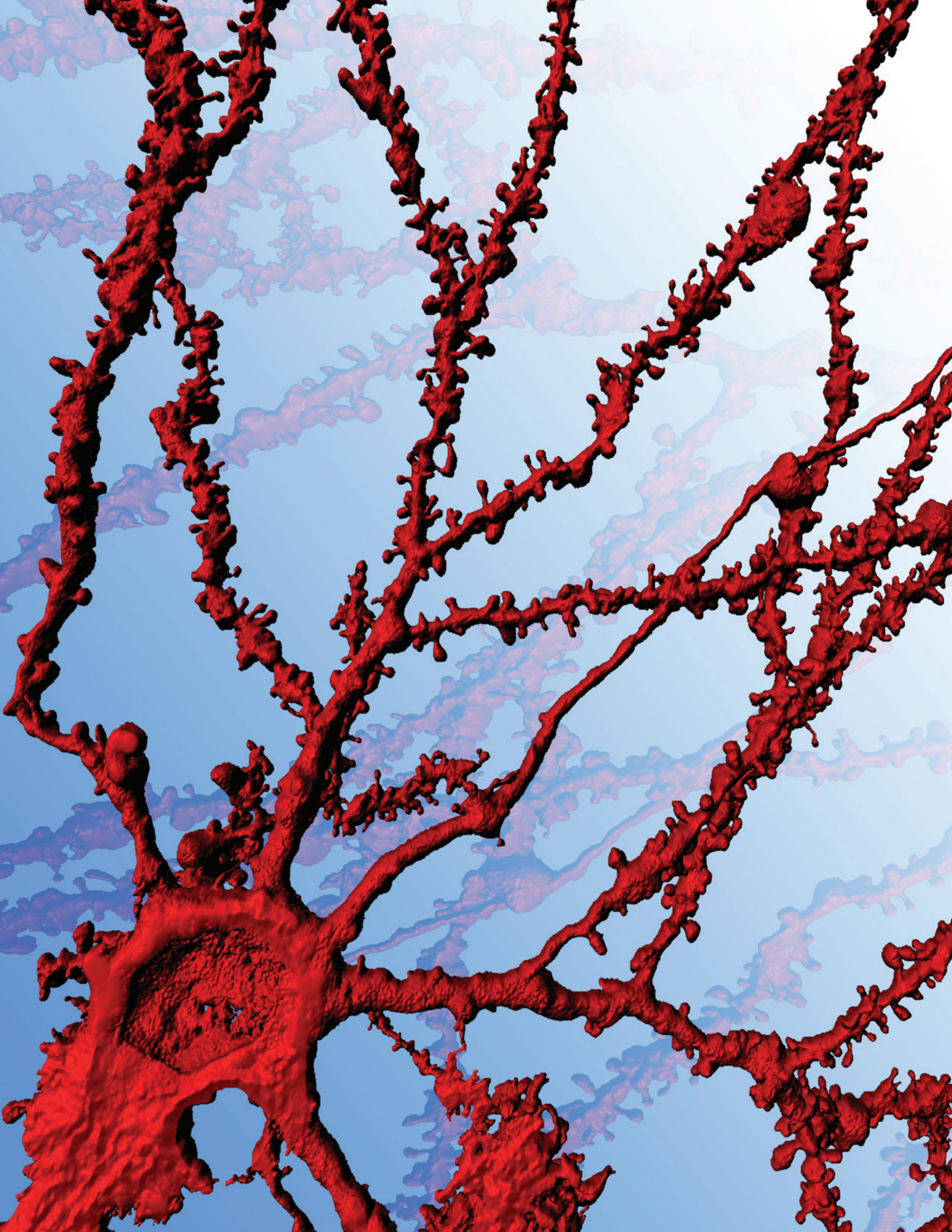
Groundbreaking work from Cowan's laboratory reveals that abnormal brain wiring may be the culprit in many developmental disorders and addictions. His team has pinpointed several important genes that influence brain connectivity that may hold promise for generating desperately needed therapies.

"I think that most brain disorders are influenced strongly by our genetics," says Cowan. "My principal interest is to understand the genes that are orchestrating typical brain development, particularly the signaling pathways that translate individualized experiences to the nucleus and tell the cell to adapt."

Developmental disorders: master regulators gone awry

According to the National Center for Health Statistics, seven percent of children ages three to seventeen have been diagnosed with a developmental disorder; this includes autism spectrum disorder, intellectual disability and developmental delay.¹ Although there is no cure, early intensive cognitive behavioral therapy has been shown to improve outcomes. Motivated by the urgency for earlier screening and intervention, Cowan has centered one part of his research on understanding the genetic risk factors for developmental disorders.

Image of neuron courtesy of Jennifer Cho, an M.D./Ph.D. student in Cowan's laboratory. Image acquired from a confocal microscope that was funded through an S10 Shared Instrumentation Grant Program (OD021532).



Dr. Christopher Cowan

Photograph by
Sarah Pack.

brain connectivity. They found a decrease in the neural connections that excite brain activity and an increase in connections that inhibit brain activity. Remarkably, these

effects were reversed when MEF2C was put back into the cells from which it had been deleted.²

The therapeutic implications of these findings are significant, particularly as prenatal screening for MEF2C mutations is not a standard clinical practice. Genetic profiling is typically conducted when a child presents with developmental delay around one to two years of age. Given this reality, a pressing question Cowan hopes to address is whether interventions are possible during this clinical window.

“We know what the problem is, these kids don’t have enough MEF2C,” says Cowan. “What we want to know is, ‘Can we reverse these changes with drugs that increase MEF2C function, and when can we act? Is MEF2C playing a more important role prenatally or postnatally? And since every cell in the body has lost a copy of MEF2C, which cells are mediating the greatest effect?’”

Understanding the holistic effects of MEF2C would significantly inform therapeutic strategies. Cowan’s team has already shown how MEF2C is important for shaping brain connections during development, but more work is being done to elucidate MEF2C’s role in other systems in the body. More recently, Cowan’s group is working with South Carolina’s Greenwood Genetics Center to help move their animal studies into future treatments for this genetic disorder.

Addiction: hijacking brain plasticity

The profound effects that an imbalance of brain connections has on behavior during development also extends to addiction, a still incurable disorder that affects over 20 million Americans.³

“During development, brain plasticity is happening dynamically. Anytime we have an experience that is very impactful to us, those events can become fairly hardwired in the brain,” explains Cowan. “This occurs with drugs of abuse, but at a level beyond what our brain is adapted to handle. Drugs appear to hijack healthy brain plasticity by triggering strong, enduring changes in the way the brain reward circuit is responding.”

Although environmental risk factors play an important role in addiction, identical twin studies indicate that at least half of addiction risk is genetic. Cowan’s other main area of research is on understanding this genetic vulnerability for addiction.

One family of genes that his team is focused on is epigenetic enzymes. These are unique enzymes that modify gene expression by changing the structure of DNA rather than the genetic code itself.



“Many of the genes that are important for development turn out to be master regulators, in that they affect the expression of hundreds or thousands of other genes,” says Cowan. “My lab is focused on transcription factors that are developmentally regulated, because a transcription factor is a protein that sits on your DNA in the cell nucleus, and it reads off the genes that ultimately make the protein products.”

Work from Cowan’s laboratory has shown that MEF2C is one such “hub gene” that may play a central role in developmental disorders. The MEF2C gene is highly expressed in the brain, immune system and muscle. It encodes for a transcription factor that acts as a temporary “on and off switch” for many other genes, including hundreds of autism risk genes and genes controlling brain connectivity. Children with MEF2C haploinsufficiency (deletion or mutation in one of two copies of MEF2C) have intellectual disabilities and symptoms resembling autism and attention-deficit/hyperactivity disorder. However, it is unclear how or why MEF2C gene mutations disrupt typical development.

Cowan and his team have begun to unearth some clues, first by examining MEF2C’s role in the brain. They demonstrated that when the MEF2C gene is selectively deleted in the developing mouse brain, the animal displayed reduced social behaviors and vocalizations, increased repetitive movements and deficits in learning and memory—all common autism-associated symptoms.²

Cowan’s group discovered that these MEF2C mutant mice had dramatically decreased brain activity stemming from an imbalance in

Unlike the temporary control that transcription factors often have on genes, these enzymes can semi-permanently change the way DNA is folded, making genes accessible or inaccessible.

“Epigenetic enzymes are powerful molecular mechanisms to control change within neurons and brain circuits, because changes at the level of the DNA structure can be very long-lasting,” explains Cowan. “Once inside the nucleus, these enzymes are able to turn genes on or off, often in a very stable way.”

“We may have stumbled onto a potential mechanism by which we can suppress relapse—possibly across multiple classes of abused substances.”
—Christopher W. Cowan, Ph.D.

Cowan’s team discovered that a class of epigenetic enzymes called histone deacetylases (HDACs) respond to cocaine by acting as a “brake” to stop the drug’s hijacking of brain plasticity. As Cowan explains, cocaine acts as “supernatural gas” for the dopaminergic system, triggering epigenetic changes within the reward circuit. One particular HDAC the group has studied appears to respond to cocaine by temporarily entering the nucleus and turning genes off, but its efforts may have come too late as changes in brain connectivity have already been made.

In recent breakthrough studies, Cowan and his team devised a way to engineer more “powerful brakes” into the system in rats.^{4,5} They inserted HDACs that permanently stayed inside the nucleus of brain cells in an important reward center called the *nucleus accumbens*. Rats with and without these modified HDACs were trained to press a lever to receive cocaine; a light or sound was presented with the cocaine to serve as an environmental cue. All rats acquired cocaine dependence to the same degree. However, after a period of abstinence, when the rats were exposed to the same light or sound and given the option to press the cocaine lever, rats with the modified HDACs pressed the lever far less than controls.

“We got really excited because we’ve tapped into brain mechanisms that strongly connect the rewarding drug experience with environmental cues that trigger later drug seeking,” says Cowan. “We may have stumbled onto a potential mechanism by which we can suppress relapse—possibly even across multiple classes of abused substances. One of our goals now is figuring out how we could use

this mechanism to develop a therapeutic for recovering addicts to reduce their drug cue reactivity.”

Future directions: discoveries to therapies

For Cowan, understanding the genetic predisposition for addiction and developmental disorders provides the best foothold for developing effective therapies, but he stressed that many basic questions must be addressed before medications can be intelligently generated.

In the case of developmental disorders, although there are several FDA-approved drugs that might enhance MEF2C function, testing them in children with MEF2C Haploinsufficiency Syndrome without understanding their downstream effects could be harmful. For example, children with MEF2C gene duplications also present with developmental disorder symptoms. Similarly, very little is known about how inserting HDACs

permanently into the cell nucleus is preventing addiction relapse.

Ongoing work in Cowan’s laboratory is directed toward dissecting the nuances of these signaling pathways in animal models that more closely replicate the disease state in humans. Cowan underscores the importance of this latter aspect of translational research. “The better our animal models are, the more likely it is that a candidate compound with a promising therapeutic effect can move quickly into the clinic and help humans,” he says.

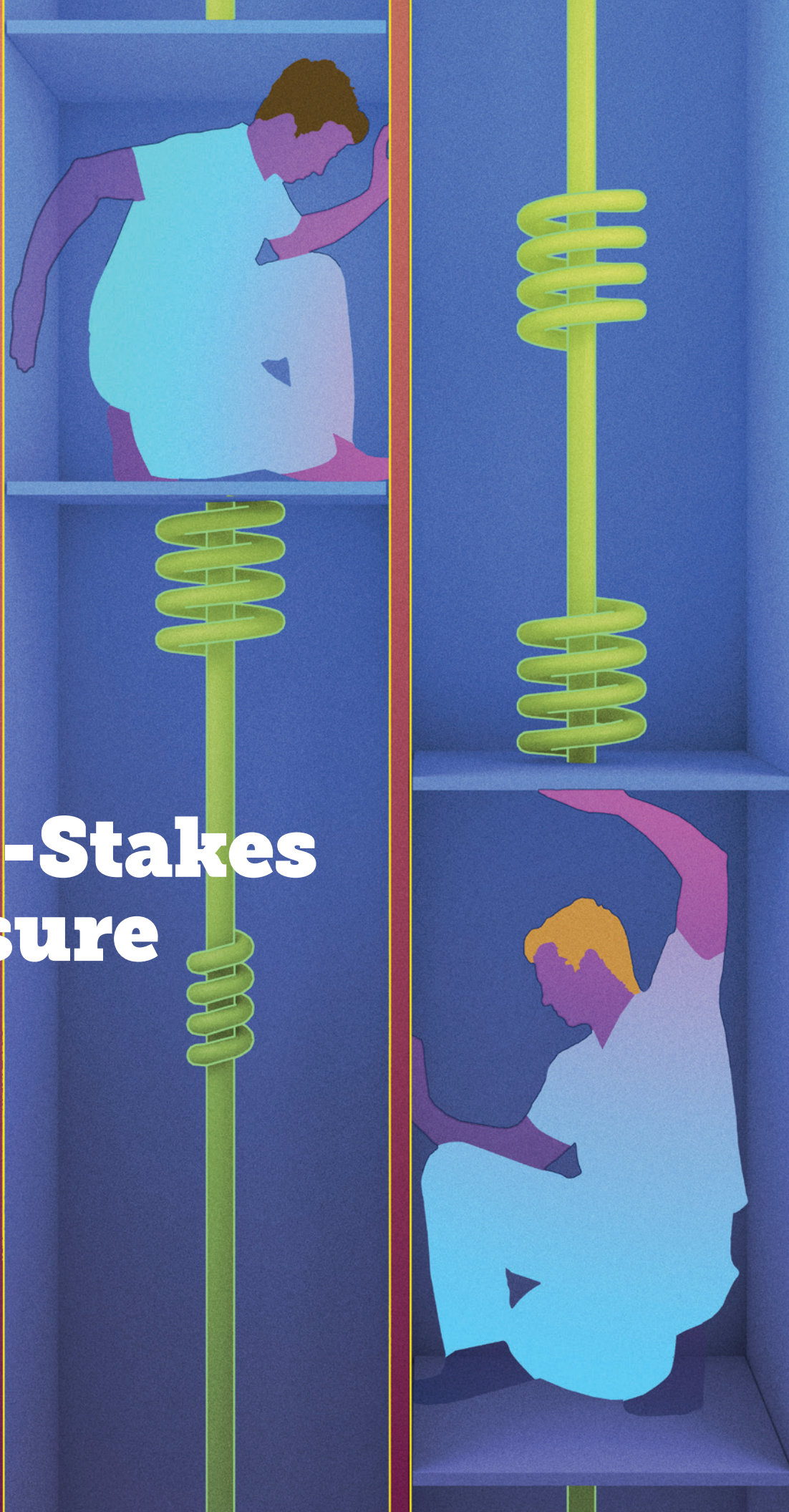
Preliminary findings in both areas of Cowan’s research suggest that his team has tapped into intersectional mechanisms involved in many developmental disorders and classes of abuse substances. This overlap may represent promising leads for generating therapies with widespread impact.

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High-Stakes Pressure

New guidelines take aim at hypertension to lower risk of cardiovascular disease





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ILLUSTRATION BY EMMA VOUGHT

Date of Release:

July 11, 2018

Date of Expiration:

July 11, 2020

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Dr. Lackland and Kimberly McGhee have no relevant financial relationships to disclose.

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

- Describe the new cutoffs for stage 1 hypertension in the 2017 updated AHA/ASA guidelines and the role of cardiovascular risk in guiding therapy
- Recognize the importance of home monitoring to the accurate measurement of blood pressure
- Discuss how fixed-dose regimens can encourage patient adherence to therapy

Cardiovascular disease (CVD) is the leading cause of death in the U.S.: one in four deaths can be attributed to it.¹ Of all the modifiable CVD risk factors, hypertension accounts for the most CVD-related deaths,² including those caused by coronary artery disease and stroke. Thomas Frieden, M.D., former director of the Centers for Disease Control and Prevention, has said that improving blood pressure (BP) control could save more lives than any other single clinical intervention.

Healthy People 2020 has set a target to increase the number of hypertensive patients whose blood pressure is under control to 61.2 percent. According to most recent estimates, only about half (48.9 percent) of Americans with hypertension have their blood pressure under control.³ In an effort to improve those numbers and to target interventions at the highest-risk patients, the American Heart Association and the American Stroke Association published an updated set of hypertension guidelines in 2017,⁴ the first since 2003.

A new definition of hypertension

The guidelines modified the definition of hypertension for the first time since the late 1990s. Individuals with a systolic blood pressure between 130 and 139 mm Hg or a diastolic pressure of 80 to 89 mm Hg are no longer classified as “prehypertensive,” a category that has been discontinued, but instead as having stage 1 hypertension. The former stage 1 hypertension ($\geq 140/90$ mm Hg) was reclassified as stage 2. Due to this change in classification, the number of Americans with high blood pressure increased from 32 to 46 percent, meaning that almost half of all Americans are affected.

Treatment recommendations and goals

The modified classification is meant to encourage treatment of individuals with a blood pressure of 130/80 mm Hg or higher, who already have twice the risk of developing CVD. Most of these patients can be treated with nonpharmacological therapies and followed up in three to six months to gauge progress. However, patients with stage 1 hypertension at high risk for CVD, i.e., those with a history of CVD or a calculated risk of ten percent or greater of developing CVD in the next ten years, require pharmacological therapy and should be followed up within a month. To assess ten-year CVD risk, the guidelines advise use of the ACC/AHA Pooled Cohort Equations (<http://tools.acc.org/ASCVD-Risk-Estimator/>).⁵ Recommended first-line antihypertensive agents include thiazide

diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs).⁶

For patients with stage 2 hypertension ($\geq 140/90$ mm Hg) or for those older than 65, who almost always have at least a ten percent risk of developing CVD in ten years, a combination pharmacological therapy with two or more antihypertensive agents and a follow-up at one month is recommended. Using two classes of antihypertensive agents, such as a thiazide diuretic and an ACE or ARB, can more

Individuals with a systolic blood pressure between 130 and 139 mm Hg or a diastolic pressure of 80 to 89 mm Hg are no longer classified as “prehypertensive,” a category that has been discontinued, but instead as having stage 1 hypertension.

effectively lower blood pressure. As a general rule, however, physicians should avoid using two agents from the same class (i.e., beta blockers) or two drugs that act on the same mechanism (i.e., ACE inhibitors and ARBs), because such combinations may be less effective and even harmful.

Patients with a systolic blood pressure of 180 mm Hg or higher or a diastolic blood pressure of 110 mm Hg or higher require immediate evaluation and prompt initiation of antihypertensive treatment.

In part because of the findings of the SPRINT trial that tighter control of blood pressure led to a 33 percent reduction in cardiovascular events and a 25 percent reduction in deaths,⁷ the new guidelines recommend that almost all patients, including those with comorbidities and previous CVD, be treated to a goal of less than 130/80 mm Hg (previously less than 140/90 mm Hg).

Side effects from medications and the need to take multiple medications several times daily can deter patient adherence to treatment. To address these issues, the guidelines recommend prescribing, when possible, medications that can be taken only once daily and combination therapies that, because they require smaller doses of individual medications, are less likely to lead to side effects. Ideally, combination therapies would be prescribed in a fixed-dose formulation (one pill that contains the correct dose of two or three medications) to lessen the burden on patients and encourage adherence. Adherence can also be improved with better communication between care members and patients between visits, for example via telehealth, to identify and solve problems.

For good measure

If blood pressure measurements, in tandem with risk assessment, are to guide treatment, they must be accurate. The blood pressure that drives treatment should be the average of at least two measurements taken at different sessions. Improper technique can result in inaccurate measurements that can trigger inappropriate therapies.

Accurate blood pressures can be attained using the traditional auscultatory method provided proper steps are taken. However,

evidence is accruing that the use of automated oscillometric devices can improve the accuracy of blood pressure measurement, provided that they are accurately calibrated.⁸ These devices often take multiple measurements of blood pressure while the patient is seated alone in a room, achieving effortlessly some of the goals of the staff training required for proper auscultatory determinations.

Other barriers to accurate measurement include “white coat” syndrome, in which patients’ blood pressures are higher in the office than at home, and “masked hypertension,” in which patients’ blood pressures are higher at home than in the office. The former can result in unnecessary treatment, and the latter can mean that patients at high risk for CVD remain untreated or undertreated. At-home blood pressure monitoring using automated, well-calibrated devices can help clarify which of these patients require or are responding appropriately to treatment.⁹

Race and ethnicity

Blacks

In the U.S., blacks, particularly black men, have the highest burden of hypertension, and their hypertension, like that of Hispanic and Asian Americans, is less likely to be controlled than for whites. In non-Hispanic blacks, only 43.8 percent of men and 52.3 percent of women achieve control, compared with 53.8 and 59.1 percent of white men and women. Although rates of awareness and treatment in blacks are similar to those in whites, black men are far more likely to die as a result of their hypertension: 1 in 20 black men die from hypertension-related causes compared with 1 in about 52 white men. Blacks also have a higher incidence of nonfatal strokes, fatal strokes and heart failure than other populations, and those with an APOL-1 gene mutation are 4.2 times more likely to develop end-stage renal disease.¹⁰

Achieving a target blood pressure of less than 130/80 mm Hg in black adults, as in other populations, is likely to require two or more

medications. In black adults, one of those agents should be a thiazide diuretic or a calcium channel blocker. Thiazide diuretics have been shown to better prevent hypertension than drugs that act on the renin-angiotensin system, such as ACEs, ARBs and beta blockers, in these patients.¹¹ A single-tablet combination that includes either a diuretic or calcium channel blocker is recommended, as it lessens the burden on patients and is likely to improve adherence.

Other ethnic groups

Hispanics have very similar rates of hypertension control as non-Hispanic blacks (43.5 vs. 43.8 percent, respectively). Compared with blacks, Hispanics are much less likely to be aware of their condition and seek treatment. Although control rates are similar between Hispanics and non-Hispanic blacks, mortality rates are considerably lower in the Hispanic population (about 1 in 52 men and 1 in 69 women), slightly lower than mortality rates in whites. However, this is a highly diverse population and it is difficult to generalize risk. For example, Hispanics from Mexico and Central America have lower CVD rates than white Americans, while Hispanics of Caribbean origin have higher rates.¹² Hispanic Americans have a high rate of comorbid CVD risk factors, such as obesity and diabetes.

Non-Hispanic Asians have some of the lowest rates of blood pressure control (39.9 percent for men, 46.9 percent for women). They have a higher incidence of ACE inhibitor–induced cough than other subgroups.

Treatment goals and recommendations for these groups follow those in the general population.

Older adults

There is a very high prevalence of hypertension in older adults: 77 percent for men and 75 percent for women aged 65 to 74 and 79 percent for men and 85 percent for women older than 75. Blood pressure is lower in women until their fifties but begins to rise thereafter. Randomized trials have shown that reducing blood pressure in those older than 65 decreases CVD and mortality without increasing the risk for falls or orthostatic hypotension.¹³ For this reason, the guidelines recommend that ambulatory, non-institutionalized older adults be treated to a goal of less than 130 mm/Hg, as in younger adults, but physicians should be cautious in prescribing combination regimens that could trigger orthostatic hypotension. For institutionalized seniors or those with serious comorbidities or limited life expectancies, the guidelines leave it to the judgment of the clinician, the patient, and the care team as to how aggressively to manage blood pressure.

Further reading

A full version of the new guidelines and further physician resources are available at http://professional.heart.org/professional/ScienceNews/UCM_496965_2017-Hypertension-Clinical-Guidelines.jsp. Learn more about the evidence-based M.A.P. framework for improving hypertension control through the AMA's Steps Forward module at <https://www.stepsforward.org/modules/hypertension-blood-pressure-control>.



To watch a video interview with Dr. Lackland about the new hypertension guidelines, visit the Cardiology page at the MUSC Health Medical Video Center (MUSChealth.org/medical-video).

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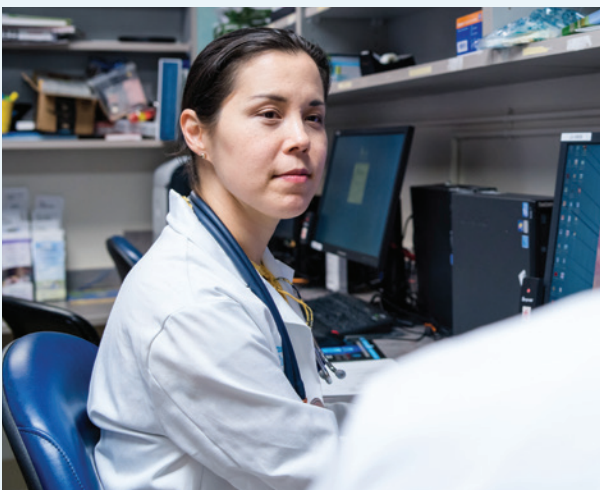
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