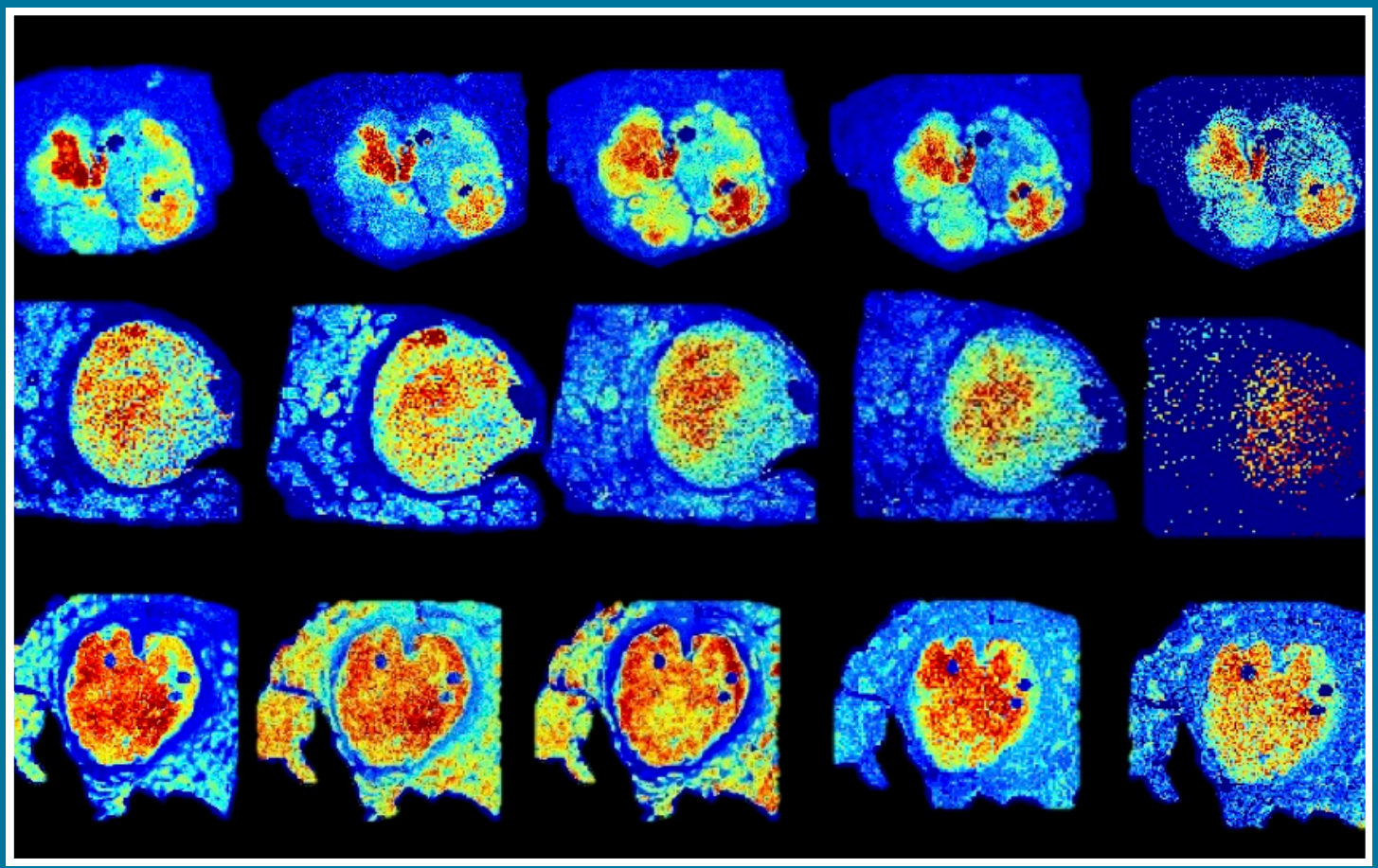
Scientia

MUSC's Research Magazine

The Future of Stroke Rehabiliation

Developments in Cancer Research

Investigating Mechanisms to Prevent Relapse



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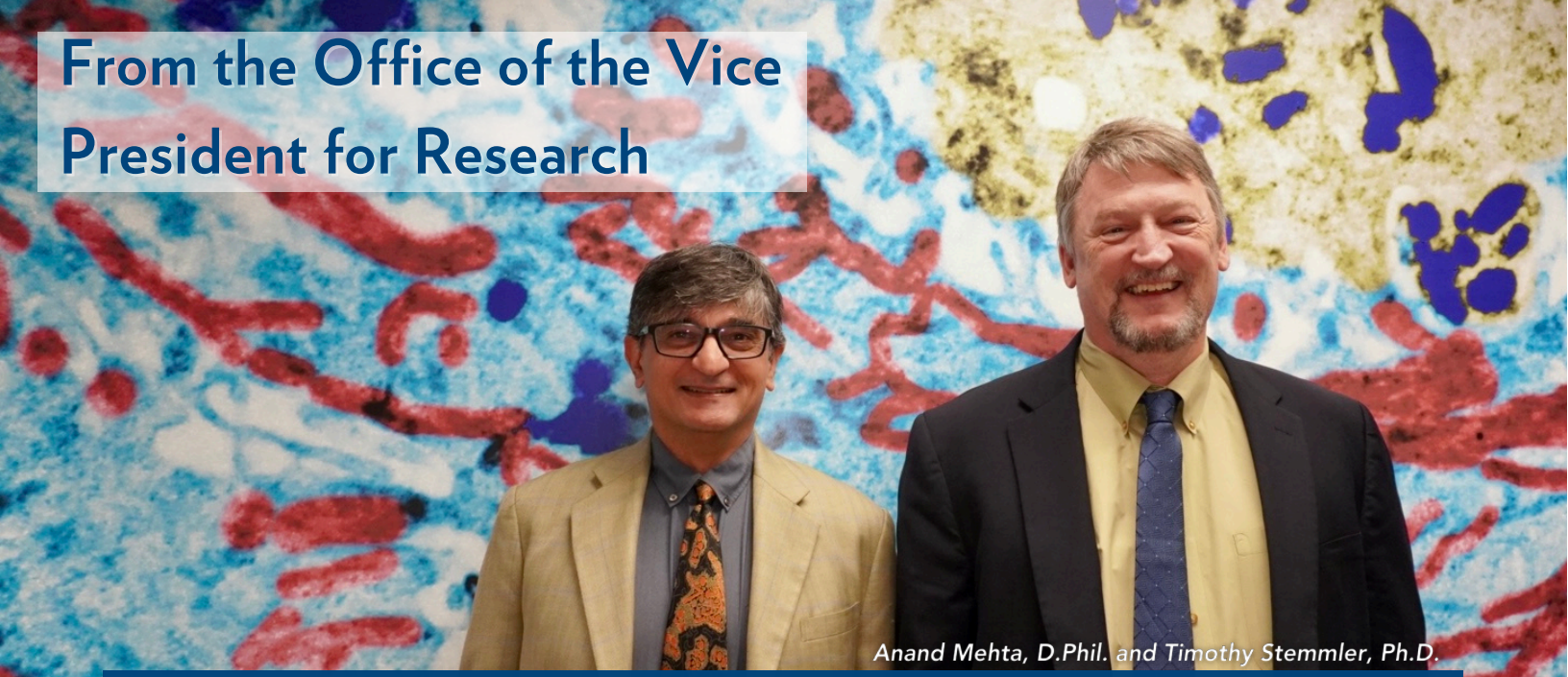
From the Office of the Vice President for Research



Anand Mehta, D.Phil. and Timothy Stemmler, Ph.D.

We are thrilled to present the first issue of Scientia, a new publication dedicated to celebrating the groundbreaking scientific research at the Medical University of South Carolina (MUSC). As we move forward from MUSC's momentous 200th anniversary, we are excited to share a selection of incredible research stories from our Bicentennial year – stories that highlight the biomedical discoveries shaping the health and well-being of the communities we serve.

In this special issue, we reflect on MUSC's ambitious vision for the future as outlined in the OneMUSC strategic plan. This plan sets the goal of making MUSC one of the nation's top 20 academic health centers in the next two decades, with research excellence at its core. We are well on our way, as we continue to foster a culture of innovation, discovery and collaboration, all with the ultimate goal of improving lives through transformative health care.

At MUSC, we are committed not only to advancing scientific research but also to ensuring that this research translates into tangible benefits for many communities. As we continue to work alongside health care professionals, policymakers and community leaders across the state, we remain focused on addressing the unique health challenges of South Carolinians and creating solutions that are both innovative and accessible.

MUSC closed the 2024 fiscal year with a record $350 million in sponsored research, reflecting our commitment to advancing science and improving health care outcomes for the people of South Carolina. Nearly 50% of our professor-level faculty are among the highest-rated recipients of grants from the National Institutes of Health (NIH), further demonstrating the caliber of research at MUSC. In recognition of these outstanding achievements, MUSC was designated a Carnegie R1 research institution in 2024, one of only 187 universities and colleges out of over 4,000 nationwide to receive this prestigious classification. As our research enterprise continues to grow across all colleges and within our Regional Health Network, we are confident that our trajectory of excellence will only strengthen in the years to come, with South Carolina's residents at the heart of our efforts.

MUSC is home to several prestigious research centers that drive our mission forward, including the Silvio O. Conte Digestive Diseases Research Core Center, one of only 17 national centers supporting infrastructure for digestive disease research; Hollings Cancer Center, a National Cancer Institute (NCI)-designated comprehensive cancer center that offers cutting-edge clinical care and research for the state of South Carolina; and the South Carolina Clinical & Translational Research (SCTR) Institute, one of 60 nationally recognized Clinical and Translational Science Award (CTSA) programs dedicated to advancing clinical and translational research. These centers are supported by highly competitive funding from the NIH and serve as a testament to the quality and impact of research at MUSC – research that is transforming health care for South Carolinians and beyond.

As we continue to grow and improve, we invite your feedback and suggestions. Please don't hesitate to reach out with ideas or comments to help us enhance future issues of Scientia and stimulate meaningful conversations. The contact information for the Office of the Vice President for Research is located on the back cover of this issue. Thank you for being part of this journey as we continue to push the boundaries of science, health care, and innovation.

Timothy Stemmler, Ph.D.
Vice President for Research

Anand Mehta, D.Phil.
Senior Associate Dean for Research, College of Medicine

Drug developed for pancreatic cancer shows promise against most aggressive form of medulloblastoma

Dr. Jezabel Rodriguez Blanco primarily focuses on the Sonic Hedgehog subtype of medulloblastoma, but a project she's nurtured since her post-doc days on the Group 3 subtype is pointing to a promising potential treatment.

By Leslie Cantu
Photo by Clif Rhodes

A drug that was developed to treat pancreatic cancer has now been shown to increase symptom-free survival in preclinical medulloblastoma models – all without showing signs of toxicity. Medulloblastoma is the most common malignant brain tumor in children. Survival rates vary according to which one of the four subtypes a patient has, but the worst survival rates, historically at about 40%, are for Group 3, which this research focused on.

Jezabel Rodriguez Blanco, Ph.D., an assistant professor who holds dual appointments at MUSC Hollings Cancer Center and the Darby Children's Research Institute at MUSC, led the research, published in the Journal of Clinical Investigation.
Her research focused on the drug triptolide, which is extracted from a vine used in traditional Chinese medicine, and its water-soluble prodrug version, Minnelide. A prodrug is an inactive medication that the body converts into an active drug through enzymatic or chemical reactions.

MYC is an oncogene, or gene that has the potential to cause cancer. MYC is dysregulated, or out of control, in about 70% of human cancers, and it shows up in much higher levels in Group 3 medulloblastoma than in the other medulloblastoma subgroups. Despite its well-known role in cancer, this oncogene historically has been considered impossible to target with drugs. Despite its poor druggability, previous research in other cancers had shown that triptolide and its derivatives had the ability to target MYC. When Blanco was still a postdoctoral fellow at the University of Miami, her mentor, David Robbins, Ph.D., attended a presentation by the research team that showed that the more copies of MYC that a tumor has, the better that triptolide works.

"He came to me, and he told me, 'You know, as Group 3 medulloblastoma has many MYC copies, you should get some research models and try the drug," Blanco recalled. She started the project from scratch. "I started talking to people, getting cell lines and animal models, learning how to propagate them, getting the drug, using it."

> **"The fact that it's working through two different mechanisms on this oncogene may explain why it's so effective in tumors that have extra copies of MYC."**
>
> **– Jezabel Rodriguez Blanco, Ph.D.**

Blanco received a three-month grant intended for cancer center trainees to develop ideas. Then her lab at the time was awarded a one-year grant from the Southeastern Brain Tumor Foundation in 2018. Since then, she's received no additional funding specific to this project.

Even as she started her faculty position at MUSC and began to focus most of her research on the Sonic Hedgehog subgroup of medulloblastoma, she continued to work on the Group 3 research as a side project. She knew how well triptolide was working in these hard-to-treat tumors, and she did not want her initial results to fall through the cracks.

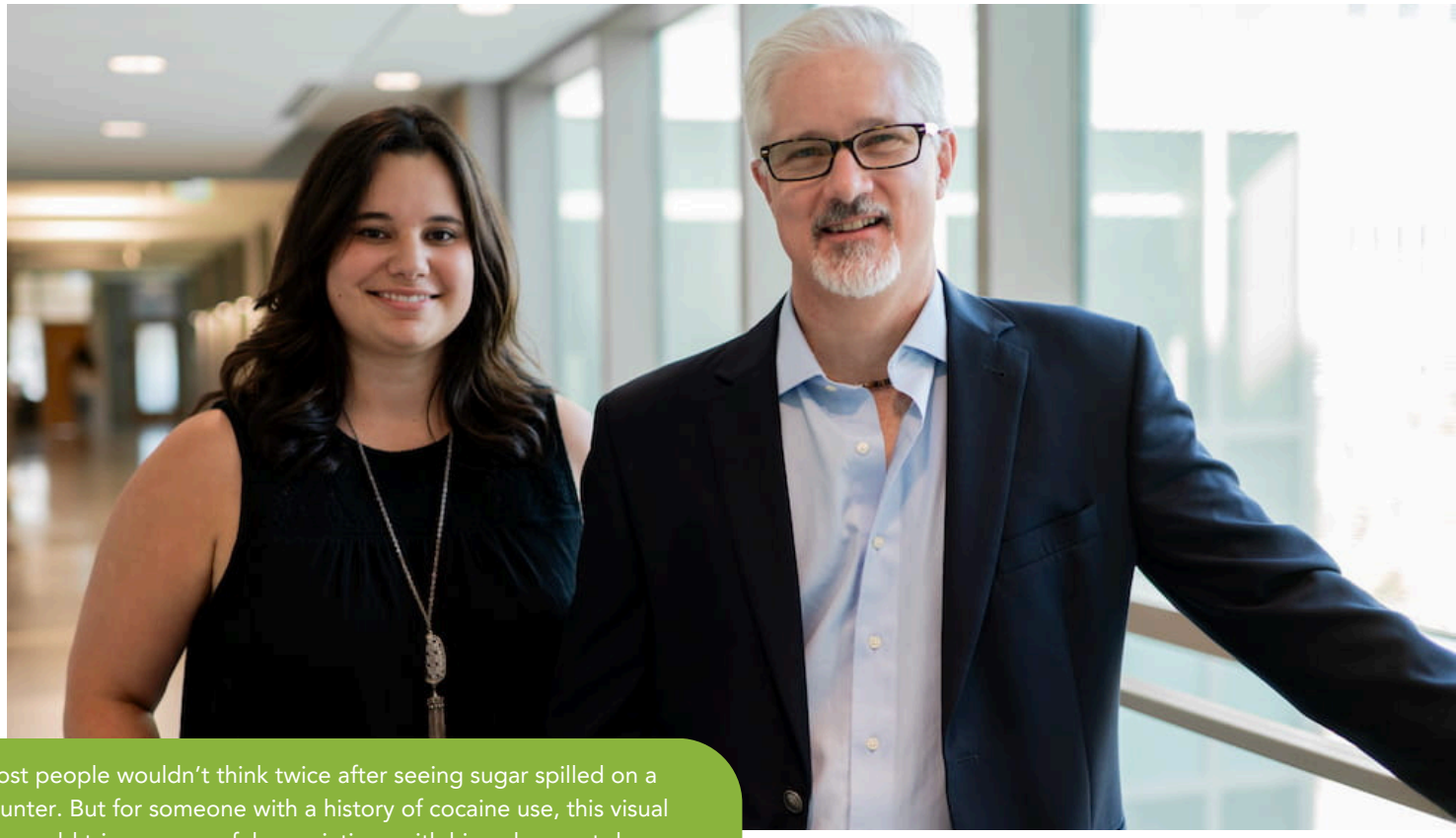
Determining the mechanism of action has been the most challenging part of the project, she noted, due to the drug's multiple effects, and there could still be additional mechanisms beyond those that Blanco identified. "It was affecting MYC gene expression by affecting the RNA pol II activity, and then it was affecting how long the protein lasts. So, the fact that it's working through two different mechanisms on this oncogene may explain why it's so effective in tumors that have extra copies of MYC," she said, explaining that RNA polymerase II is a protein that helps to make copies of DNA instructions, which are used to produce proteins in the cell.

Despite the challenges of narrowing down the mechanism of action specific to the cancer, it was quite clear that however it worked, it did work, she said. The efficacy was 100 times higher in the Group 3 tumors with extra MYC copies than in the Sonic Hedgehog tumors with normal levels of MYC, she said. She found that Minnelide reduced tumor growth and the spread of cancer cells to the thin tissues that cover the brain and spinal cord, called leptomeninges. It also increased the efficacy of the chemotherapy drug cyclophosphamide, which is currently used in treatment. Blanco decided to move forward with publication rather than waiting to write a manuscript that answered all possible questions. Knowing that most parents whose children receive a Group 3 medulloblastoma diagnosis will lose their child in less than two years was the incentive she needed to push this work out.

"There was a point at which I could not hold these data anymore because it was working so well that it needed to go out," she said. "The preclinical models were showing such a nice efficacy that it was like, 'OK, I cannot keep on holding this work, digging deeper into the mechanism of action because the kids that have Group 3 medulloblastoma are dying while we are doing those experiments." Minnelide has been tested or is currently in testing in phase I and phase II clinical trials of adults with different types of cancer, including pancreatic cancer, where it showed some efficacy. Blanco is hopeful that, with this new research on Group 3 medulloblastoma, a clinical trial for children with this disease can be launched.

Her paper is dedicated to the memory of Insley Horn, a 9-year-old Charleston girl who succumbed to one of these aggressive brain tumors. Research, Blanco said, is the only tool we have to prevent the loss of lives like Insley's.

Investigating a critical factor for promoting drug-context associations and relapse



Drs. Jessica Huebschman, left, and Christopher Cowan, right.

Most people wouldn't think twice after seeing sugar spilled on a counter. But for someone with a history of cocaine use, this visual cue could trigger powerful associations with his or her past drug use and a compulsive urge to seek the drug.

Certain circuits within the brain help to form natural associations between one's experiences and the context in which those experiences occur. These associations play a critical role in the orchestration of adaptive learning. When addictive substances are introduced, this coupling mechanism can be hijacked so that the drug-taking behavior becomes associated with cues, such as people, places or situations, linked to the drug experience. These drug-context associations become critical factors that contribute to one's relapse vulnerability.

In a recent publication in Nature Communications, a research team at the Medical University of South Carolina (MUSC) led by Department of Neuroscience Chairman Christopher Cowan, Ph.D., identified a mechanism by which these drug-context associations are regulated by a small population of cells in the nucleus accumbens.

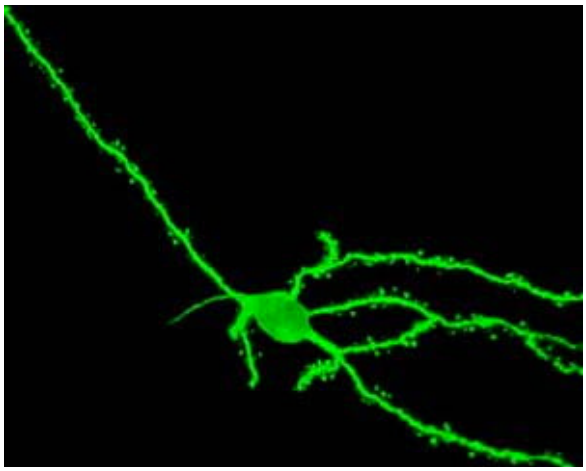
By Anna Tsyrulnikov

These drug-context associations become future triggers for drug-seeking," explained Cowan, highlighting why it's important that scientists understand how these associations are formed. The MUSC team included former graduate student Brandon Hughes, Ph.D.; current postdoctoral fellow Jessica Huebschman, Ph.D.; and Makoto Taniguchi, Ph.D., an assistant professor in the Department of Neuroscience. For individuals with a substance use disorder, experiencing a context or certain cues that remind them of drug use can hinder abstinence and promote a return to active drug use.

The MUSC researchers identified a small group of cells within the nucleus accumbens that appear essential for drug-context associations. They found that the percentage of these of these NPAS4-expressing neurons increased when exposed to cocaine. NPAS4 is a transcription factor that helps to regulate how a cell responds to neuronal activity induced by various stimuli, including drugs. The MUSC team looked specifically for NPAS4 in the nucleus accumbens because this region is known to regulate motivation and reward-associated learning.

After identifying this small population of neurons that expressed NPAS4 in response to cocaine, the researchers investigated the behavioral effects of inhibiting these neurons. Without the activity of these cells, mice no longer displayed drug-seeking behavior when put in the context they associated with cocaine. "NPAS4 is a molecule in the brain that is trying very hard to keep systems functioning as normally as possible," said Cowan. "But drugs are tapping into this and using it to their advantage."

The nucleus accumbens is where drug-dependent dopamine increases are associated with their rewarding effects. The MUSC team sought to understand how a regulatory factor, neuronal PAS domain protein 4, or NPAS4, controls the formation and maintenance of drug-context associations. This study also revealed how NPAS4 affects future drug-taking using a mouse model.



Medium spiny neuron fluorescently labeled via a spaghetti monster tag in the nucleus accumbens. Image by Dr. Cowan.

Next, the team wanted to understand how NPAS4 helps to form drug-context associations. To do so, they looked at NPAS4 within the two major types of cells in the nucleus accumbens – D1 and D2 dopamine receptor-expressing neurons. Dopamine, a major neurotransmitter in the brain, plays a crucial role in reward-associated learning.

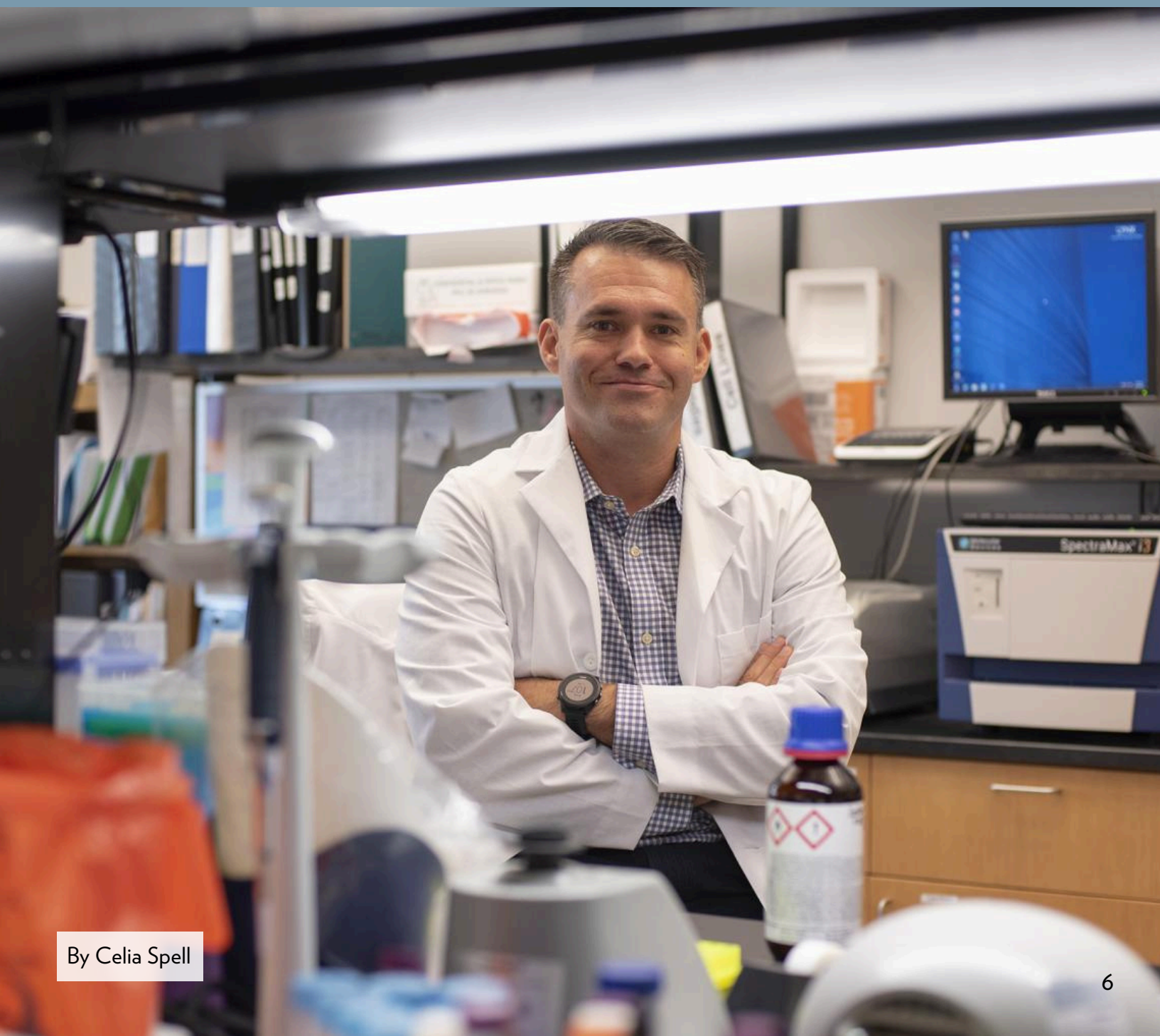
"Classically, D1 neurons tend to promote drug-seeking behavior, while D2 neurons tend to oppose it," explained Cowan. "So, it's a bit of a Yin and Yang, a push and the pull, of this motivational circuit. When an animal encounters a drug-associated context, it's going to activate D1 and D2, but D1 typically wins. Surprisingly, the study showed that NPAS4 in D2 neurons, but not D1, is necessary for context-associated drug seeking. At first, this finding appeared somewhat counterintuitive, said Cowan. How can this protein promote drug-seeking behavior by acting in the cells that typically oppose it?

"Drugs are presumably doing multiple things," said Cowan. "Obviously, they're strengthening and forming the context memory, but they're also suppressing the ability of the brain to oppose this association."

If researchers can better understand the factors contributing to drug-context associations, they will be able to identify new therapeutic targets to reduce a return to drug use. "Ultimately, the long-range goal is to understand how NPAS4 mediates these effects to aid in the design of potential therapeutics," explained Cowan.

Cancer vaccine ready for commercialization as part of growing MUSC startup community

Nathan Dolloff, Ph.D., is founder and chief scientific officer of Leukogene as well as a researcher for the MUSC Hollings Cancer Center.



By Celia Spell

In the 12 years since its inception, Leukogene Therapeutics Inc. has had one goal: to take an idea from the academic lab into the real world where it can benefit patients.

With a new cancer vaccine platform designed to stimulate the immune system and attack cancer, Leukogene offers a therapeutic solution for acute myelogenous leukemia, or AML, and pancreatic cancer.

And while it is currently in the preclinical phase, Nathan Dolloff, Ph.D., founder and chief scientific officer of the company, as well as a researcher for the MUSC Hollings Cancer Center, said that with the right strategic partner, they could be ready for clinical trials in 18 months.

Current treatment for AML and pancreatic cancer relies on chemotherapy drugs, which can have bad side effects and often don't extend a patient's life significantly in these cancers. Newer immunotherapy drugs have revolutionized the treatment of some cancer types but are largely ineffective in others like AML and pancreatic cancer.

"I've always believed in the importance of entrepreneurship in academia. It's essential if we are serious about taking ideas from the lab and getting them out into the world, so to speak."

– Nathan Dolloff, Ph.D.

Leukogene aims to fill the gap in treatment options with its cancer vaccine. By directing immune cells to attack specific proteins on malignant cancer cells as if they were foreign antigens, the vaccine harnesses the natural power of the body's immune system and redirects it. Results from preclinical studies in mice have Dolloff excited for the vaccine's clinical future. "We've seen some remarkable antitumor effects in the lab," he said. "And in some cases, we're even curing mice in certain tumor models where that's really difficult to do." Dolloff and his team hope to get this therapy into the hands of clinicians and patients as soon as possible. "Our product is safe and works incredibly well," he said. "We have the pathway to get it to patients, but our greatest challenge right now is funding."

MUSC startup companies like Leukogene will soon be housed in the new Blue Sky Labs on the hospital's Charleston campus. In addition to its own company growth, Leukogene is a good example of MUSC's expanding innovation and entrepreneurship ecosystem. It's that opportunity for growth that first brought Dolloff from Pennsylvania to Charleston in 2014.

"One of the reasons I came down here was because I wanted to have an impact on the startup community at MUSC," he said. "I've always believed in the importance of entrepreneurship in academia. It's essential if we are serious about taking ideas from the lab and getting them out into the world, so to speak."

Dolloff said MUSC inspires and encourages innovation by creating an environment with programs that promote collaboration between researchers. Through a partnership with the College of Charleston, Carol Feghali-Bostwick, Ph.D., a professor and researcher at MUSC with a passion for mentoring, encourages women to pursue entrepreneurship skills. She recruits researchers and clinicians for her Coaching and Resources for Entrepreneurial Women program, or CREW, to be mentored and advised by seasoned entrepreneurs like Dolloff.

Jesse Goodwin, Ph.D., MUSC's chief innovation officer, was part of the founding of CREW with Feghali-Bostwick, and she points to MUSC's unique position as an academic medical center, which provides both a hospital and education opportunities to its community with research and innovation at the heart of its mission. "One of our primary jobs in our innovation ecosystem," she said, "is helping entrepreneurs grow their companies to the point where they can be attractive to venture capital, established industry partners or customers, depending on the technology. Blue Sky Labs and our Innovation District will provide a physical home for our companies and also offer opportunities to network with such partners."

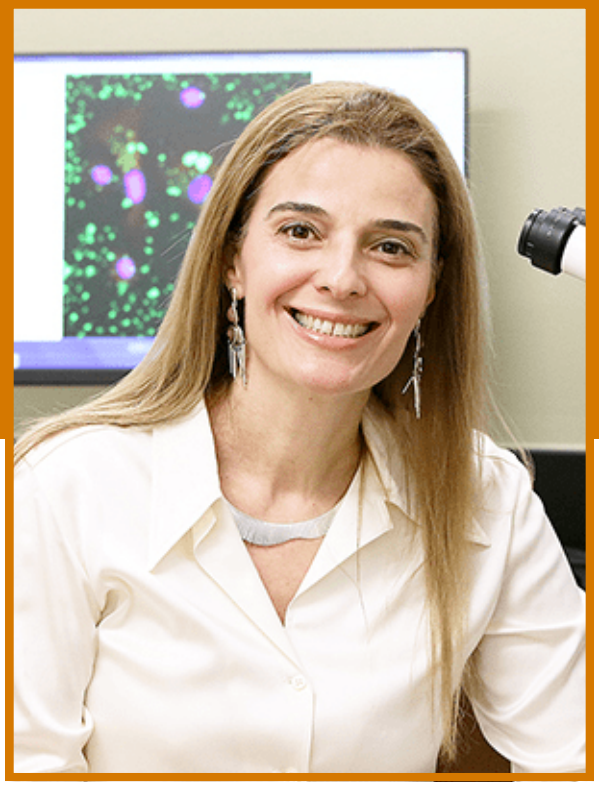
Leukogene Therapeutics Inc. received a small business grant from the National Cancer Institute in 2022, and since then, Dolloff said the team has generated more data and even more confidence in their platform. "We've gone from an interesting concept with a little bit of data to something that is potentially paradigm-shifting with a lot of data to support it," he said.

Dolloff is looking forward to moving ahead and seeing their drug platform reach patients in the clinic. "That's the reason we do this. Getting to the clinic and having an impact would be a major milestone for us," he said. He also said none of this would be possible without basic science. He noted that decades of great basic science enabled their research and paved the way for new drugs and medical products.

He's seeing basic science and its commercialization intersect at MUSC, which, for Dolloff, makes the opening of Blue Sky Labs pivotal to that process and to companies like Leukogene.

Interdisciplinary team maps role of P. gingivalis in drug resistance

By Leslie Cantu



Özlem Yilmaz, D.D.S, Ph.D.

Besim Ogretmen, Ph.D.

A new paper from an interdisciplinary team at MUSC Hollings Cancer Center describes how the bacteria Porphyromonas gingivalis interferes with chemotherapy-induced mitophagy, allowing oral cancer tumors to become resistant to the drug's effects.

Besim Ogretmen, Ph.D., SmartState Endowed Chair in Lipidomics and Drug Discovery in the College of Medicine, and Özlem Yilmaz, D.D.S., Ph.D., a professor, clinician-scientist and microbiologist in the James B. Edwards College of Dental Medicine, worked with graduate student Megan Sheridan and other Hollings researchers to uncover how P. gingivalis promotes chemotherapy resistance. Their paper was published in iScience.

P. gingivalis is a bacterium found in the mouth. In a healthy mouth, P. gingivalis and other disease-causing bacteria are kept in check by beneficial bacteria. But when that balance is disrupted, P. gingivalis is a major contributor to periodontitis – severe gum disease that can destroy gums and the bones holding the teeth in place.

P. gingivalis can enter and survive inside the first lining cells of mucosa in the mouth, and then the microorganism can invade deeper tissue and spread systemically. Increasingly, it is being implicated in other diseases like Alzheimer's, diabetes and gastrointestinal cancers.

It's also been observed that oral cancer patients infected with P. gingivalis have worse outcomes. This paper maps out how that could be occurring, focusing on how intracellular P. gingivalis prevents ceramide-dependent mitophagy in oral squamous cell carcinomas.

Mitophagy, a specific form of autophagy, is the removal of damaged mitochondria. Ceramide is a sphingolipid that plays a key role in starting the process of lethal mitophagy.

"We understood that P. gingivalis is interfering with the lethal autophagy, making the cells not go to cell death – which is something you do not want," Yilmaz said. "We needed to understand which part of the bacterium is interacting with those host molecules to create this resistance, or this protection against lethal mitophagy."

After a few dead ends, the team homed in on the fimbriae – protruding pili-like protein structures on the outside of the bacteria. Whereas pili's function is sensing or synchronized movement to move fluids or objects, the fimbriae's major role is to attach.

"This molecule has been studied in this bacterium in a variety of contexts, like attaching to other bacteria, attaching to the collagen, attaching to fibrinogen. But it's not like it's just attaching to anything. It's a very specific event," Yilmaz said.

Ogretmen, whose lab focuses on the regulation and function of bioactive sphingolipids, figured out where the interaction was occurring, while Yuri Peterson, Ph.D., a Hollings researcher in the College of Pharmacy, used prediction analysis to identify the strong interactions between the bundles of peptides and the ceramide drug, Yilmaz said. But it was Yilmaz who first suggested they look at the fimbriae.

It was your insight," Ogretmen pointed out to Yilmaz. "Because we didn't know how this microorganism inhibited this chemotherapy effect. We tried many different things. Then Özlem said, 'Maybe you should try this protein.' We looked, and that was it."

The team's work suggests that the fimbriae attach themselves to specific proteins on the mitophagic membrane, blocking the ceramide drug from its attachment point and therefore stopping the lethal mitophagy in its tracks.

"So then the next goal is, 'Can we use antibiotics to inhibit the protrusion protein so that it cannot interfere?'" Ogretmen said.

A visiting summer student will start work on this question, he said.

Yilmaz noted that another question is how the variations in fimbriae affect their interference with mitophagy. There are many strains of P. gingivalis, and different strains may have modifications in the fimbriae structure that can affect its interactions with host target molecules.

Yilmaz said this research was possible only because of the individual expertise of each of the investigators in vastly different fields.

"It was a true collaboration," Ogretmen agreed. "And we complement each other's expertise."

Pictured: Hollings Cancer Center

A genetic difference in THC metabolism may explain why some young adults have negative experiences with cannabis

In a new study, Rachel Tomko, Ph.D., explored how genetic differences in THC metabolism impact young adults' experiences with cannabis and their potential risk for developing cannabis use disorder.

By Anna Tsyrulnikov

Differences in how young adults metabolize THC, the main part of cannabis that makes people feel "high," can influence how they feel after taking the drug as well as their potential risk for developing cannabis use disorder, or CUD. These findings were recently published in Addictive Behaviors by MUSC researcher Rachel Tomko, Ph.D., and former psychology intern Christal Davis, Ph.D., who is now a postdoctoral fellow at the University of Pennsylvania, as well as other MUSC colleagues and collaborators at the University of Florida and University of Colorado. Tomko and Davis also explored whether the effects of a genetic difference in THC metabolism on future outcomes of cannabis use depend on a person's sex.

CUD, which affects one in five people who use cannabis, leads to problems such as withdrawal symptoms and cravings when not using cannabis, difficulty reducing cannabis use and a need to consume more of the drug to experience the same effects. THC metabolism, the process by which this active component gets broken down in your body into psychoactive and inactive components, can be influenced by genetic differences in enzymes.

About one in four people have a gene that causes these enzymes to break down THC less effectively than others, which can increase the strength and duration of the effects of cannabis. Differences in metabolism have been linked to an increased risk for substance use disorder for other drugs but not yet cannabis. "Unfortunately, we're just beginning to understand some of the effects of how people metabolize and process cannabis," explained Davis.

For their study, the researchers recruited 38 young adults ages 18 to 25 with CUD and 16 with a non-CUD substance use disorder. This age group was chosen as they are three times more likely to have CUD than teens or adults over 26 who use cannabis. "This age group is super important to study because the brain is still developing up through young adulthood," said Tomko. "So, this is a key time for intervention." Blood samples were collected from study participants, and gene variants for THC-metabolizing enzymes were tested. Participants also completed a questionnaire designed to measure their reported positive and negative effects from cannabis use.

Based on their gene variant, participants were categorized as either normal or slow THC metabolizers. The researchers then correlated metabolism with the subjective effects reported by the participants. Davis was surprised by the sex difference evident in the data. "Looking at our data, we realized very quickly that there were sex-specific effects going on that we couldn't ignore."

Notably, the study showed that young females with CUD were more likely to be slow metabolizers of THC compared with young females with other (non-CUD) substance use disorders. This suggests that young females who metabolize cannabis more slowly may be at higher risk for developing CUD. When looking at young adult males, the researchers found that those who had a gene variant contributing to slower THC metabolism reported more negative effects during initial cannabis use, like drowsiness, laziness and difficulty concentrating. Overall, participants of both sexes who were categorized as slow metabolizers of THC experienced more negative effects during cannabis use.

Although the study recruited young adults, the most important implications of its findings may be for teens. Many young adults who develop CUD start using cannabis in their teens. As the social acceptance of cannabis grows and its perceived risk diminishes, teens may use cannabis more if they are not aware of potential harms.

The study highlights that not all young people who use cannabis experience the drug the same way, and that how people metabolize THC may be one factor that could contribute to risk for CUD. Although slower THC metabolizers experience more negative effects, the experience of simultaneous positive effects may lead them to continue cannabis use regardless of bad outcomes. "We might think that if you're experiencing negative effects, you don't continue to use, but in the face of positive, rewarding effects, maybe you do," said Tomko.

Tomko and Davis believe it is important to educate teens about the differences in how people experience cannabis. For example, educational programs targeted to adolescents can improve their understanding of risk factors for CUD. The Just Say "Know" program, led by Lindsay Squeglia, Ph.D., at MUSC, offers presentations and hands-on training to teach middle and high school students about the neuroscience of drug addiction. Since most people don't get genetic testing for these potential risk factors, it's important to understand how these findings can better inform treatment options for people struggling with CUD.

"Our study opens up new hypotheses and options to explore medications that might modify THC metabolism as a potential treatment for cannabis use disorder," suggested Tomko. The initial findings from this research may be particularly important in the context of the continual rise in cannabis potency that has been observed over the past couple of decades as well as the availability of high-potency cannabis products in legal markets. "The increases in THC levels found in cannabis could mimic some of the more pronounced effects that we see for people who are slower metabolizers," said Davis. "The effects of cannabis are lasting longer because it's stronger THC."

With a lack of regulation of cannabis products, combined with an increase in acceptance of cannabis use, additional research to identify risk factors for CUD will be necessary to advise vulnerable groups, like adolescents.

First US trial of varenicline for e-cigarette cessation shows positive results

Drs. Benjamin Toll, left, and Lisa Fucito developed a clinical trial for e-cigarette cessation that was meant to mimic real-world conditions.

The first U.S. trial of varenicline for e-cigarette cessation shows promising results and warrants larger-scale trials, the researchers said. Researchers from Yale Cancer Center and MUSC Hollings Cancer Center published the results of their clinical trial of varenicline to help adults to stop using e-cigarettes in the American Journal of Preventive Medicine in May 2024.

The results showed a significant disparity between the placebo group and the group receiving the medication. "We had a 15% difference in quit rates, with those in the medication group having a quit rate of 45%," said Lisa Fucito, Ph.D., lead author and director of the Tobacco Treatment Service at the Yale Cancer Center and Smilow Cancer Hospital.

Benjamin Toll, Ph.D., director of the Tobacco Treatment Program at MUSC Health and senior author on the study, said that the researchers designed the trial to mimic real-world conditions as much as possible – from the people who enrolled in the trial to the type of support they would likely receive from primary care providers.

The publication of their results closely followed publication of a trial of cytisinicline for e-cigarette cessation. The two drugs work similarly. However, varenicline is already on the market in the U.S. in generic versions while cytisinicline has not yet received Food and Drug Administration (FDA) approval and is not currently available for use by patients.

By Leslie Cantu

Varenicline, perhaps better known by the brand name Chantix, is FDA-approved to help adults to stop smoking traditional cigarettes. But, despite the growing numbers of people who use e-cigarettes, there are no approved medication options to help them to stop using e-cigarettes. "People can get to very high levels of nicotine exposure with these e-cigarette products, and they can use them near constantly throughout the day. So, the question we all have is, 'Can any pharmacotherapy stand up to this challenge?'" Fucito said.

It's a question of logistics. People who smoke cigarettes have to get a cigarette from the pack and light it. It's easy to track use. There are also natural stopping points – when the cigarette is finished, it must be snuffed out, and when the pack is used up, it must be thrown away and a new one purchased and opened before the person can smoke again. E-cigarettes, however, can last for 5,000 or more puffs, making them harder to track intake but easier to use. Toll said he has patients who describe keeping their e-cigarettes under their pillows so they can vape right before going to sleep and then again immediately upon waking in the morning.

Previous studies have shown that a majority of people using e-cigarettes want to quit. But it's been unclear whether products used to stop smoking traditional combustible cigarettes would also work for e-cigarettes.

"We need more pharmacotherapy treatments to help address the really strong physical dependence that can develop from e-cigarette use. People undergo significant withdrawal when they try to stop, and that withdrawal is so unpleasant and hard to manage with just behavioral support alone," Fucito said.

> **"If you have a former smoking history, one of the worries in the field is that you're going to go back to smoking when you quit vaping. And we did not find that."**
>
> **– Benjamin Toll, Ph.D.**

A recent Italian study married pharmacotherapy with intense weekly behavioral counseling sessions, and the trial of cytisinicline also included weekly 10-minute sessions with trained counselors.

In this study, however, the researchers wanted to see how well the pharmacotherapy could work given typical health care conditions – meaning, the patient would likely get a brief discussion with a primary care provider along with a prescription and information about resources for quitting but no follow-up counseling sessions.

To recreate this, they developed a self-guided cessation booklet for patients, with practical tools and tips for quitting.

A licensed health care provider also met with each patient to inform them of how to use the medication, offer brief advice and instruct them to set a quit date for one to two weeks after starting the medication.

"We took a much lighter touch to reflect the behavioral support that you'd likely experience if you went to your doctor and asked for help with quitting e-cigarettes," Fucito said.

The study also included some patients with histories of depression. This was significant because Chantix, at one point, had a "black box warning" after reports linking the drug to psychiatric side effects. That warning was dropped in 2016 after a very large study showed the drug to be safe, but Toll and Fucito said the stigma of the warning remains in the minds of both health care providers and the general public. "There's still some hesitancy to prescribe this very safe – now generic – drug, and it really shouldn't be that way," Toll said.

None of the participants in this study experienced serious side effects, although a larger study would be needed to verify this finding. Most of the side effects were along the lines of nausea, insomnia or vivid dreams. Another piece of good news – those who stopped vaping didn't boomerang back to cigarettes.

"If you have a former smoking history, one of the worries in the field is that you're going to go back to smoking when you quit vaping," Toll said. "And we did not find that."

On the other hand, one potential challenge that the researchers uncovered in the results indicated that people without a cigarette smoking history – in other words, those who have only ever used e-cigarettes – might have a harder time quitting. That could be because that group is more likely to use e-cigarettes continuously throughout the day, therefore getting more nicotine into their systems. Larger trials are needed to delve into these questions. But this trial, at least, should give health care providers some confidence in prescribing varenicline for patients trying to stop using e-cigarettes.

"We want people to come back to this medication," Fucito explained. "There are people who need help now and are likely to struggle to quit e-cigarettes on their own because the technology facilitates nicotine use on a level that we've never seen before."

Revolutionary bioengineering research may transform Type 1 diabetes care, pave way for tackling cancer and autoimmune disease

Leonardo Ferreira, Ph.D., a researcher at MUSC Hollings Cancer Center, focuses on regulatory T-calls, or Tregs.

By Shawn Oberrath

Regenerative medicine holds the extraordinary promise that future patients in need of new cells, tissues or organs will no longer have to rely on donors. Organ shortages and cell-type mismatches will become past problems, replaced by safe, on-demand options for anyone who needs a transplant. This revolutionary field still faces many challenges, including the nontrivial task of convincing stem cells to differentiate into desired cell types for treatment. And even if the correct cells or tissues are created and can function successfully in the body, immune rejection presents a formidable barrier to their use. To overcome this obstacle, regenerative medicine treatments in use today require systemic immunosuppression, leaving patients vulnerable to environmental hazards like viruses, bacteria and cancer cells.

In a novel approach to tackling these obstacles, researchers at the Medical University of South Carolina and the University of Florida recently collaborated on a novel, highly specific strategy to treat Type 1 diabetes (T1D) using a tagged beta cell transplant in tandem with localized immune protection provided by specialized immune cells also tagged with a complementary but inert targeting molecule.

According to Leonardo Ferreira, Ph.D., a researcher at MUSC Hollings Cancer Center and one of the principal investigators on the study, marrying stem cell engineering and regulatory T-cell (Treg) engineering allowed the first step toward a readily available, off-the-shelf solution to treating T1D.

In their recent study published in the journal Cell Reports, the researchers described a unique collaboration that leveraged the beta cell engineering expertise of the lab of Holger Russ, Ph.D., associate professor of pharmacology and therapeutics at the University of Florida, combined with the delicate surgical expertise and chimeric antigen receptor (CAR) T-cell expertise available at Hollings. For T1D patients, the trouble begins with an immune system self-attack on pancreatic beta cells, the cells that produce the hormone insulin to regulate blood sugar levels. Without a reliable way to self-regulate blood glucose levels, patients are forced to live with a high-maintenance regimen of glucose monitoring and insulin management to maintain health and avoid dangerous complications like neuropathy, amputation and blindness.

For now, some patients with poorly controlled T1D may consider islet cell transplantation using beta cells from a donor. Beta cells are isolated from a donor pancreas, purified and delivered to the patient's liver, where they can take up residence and begin secreting insulin. However, this option requires patients to undergo immunosuppression for the rest of their lives to keep the body from rejecting the foreign beta cells. It also requires the availability of donor cells, which might require long waits or may not happen at all.

To focus on an alternative solution, the researchers used an engineering strategy with tagged beta cells generated from stem cells. And to induce localized immune protection, the researchers chose to use Tregs, a type of immune cell that monitors and controls the immune response. "Most of the cells of the immune system are focused on killing invasive elements," Ferreira said. "But Tregs are the generals of the immune system. They make sure that nothing goes overboard, and they train the immune system on how to respond in the future."

The researchers used a mouse model to test their strategy. By transplanting beta cells that were engineered from stem cells and included a nonreactive tag – an inactivated version of epidermal growth factor receptor – into the kidney capsules of immunodeficient mice, they showed that the cells were incorporated and began to manufacture functional insulin. In the next phase of testing, the mice were exposed to an aggressive type of immune cell to check on the viability of the transplanted beta cells in the face of a simulated immune response.

As expected, all of the beta cells were killed by the immune response, the same thing that happens in people with T1D. To avoid the killing response in the next phase, the researchers added specialized Tregs along with the immune challenge. These cells were tagged with CAR technology using a receptor that specifically recognized the inert EGFR tag present on the transplanted beta cells. With this added step, the researchers observed the immune protection they hoped for, as they observed the transplanted beta cells remaining safe, sound and functional in their new home.

Ferreira was delighted with the results and energized to take the next steps. "With this approach," he said, "we made both the lock and the key for creating immune tolerance." Now that Ferreira and colleagues have shown the feasibility of their approach to T1D treatment, they plan to continue their research efforts, including building a whole library of locks and keys – differentiated stem cells and tagged protective Tregs – for multiple purposes, such as targeting certain cancers, lupus and other autoimmune diseases.

A few questions remain, such as the specific ligand that should be used for human transplantation and the longevity of Treg-mediated immune protection. The ligand or tag must be inert and have no negative impact on the function of the cells or create any reaction that could cause side effects. And it is still unknown if one Treg treatment will be effective or might need to be repeated at intervals that have yet to be established. Because Tregs can educate immune cells to maintain immune tolerance, it is possible that one treatment will be adequate, but further research is needed to understand the long-term effects.

Answering these questions and confirming the validity of the approach in humans may soon transform T1D from a chronic, high-maintenance disease with many complications to one that can be managed much more easily.

Finding the right path(way) to reduce fat accumulation in the liver

By Emma Funk

Stephen Duncan, Ph.D.

Caren Doueiry

Using a novel stem cell platform, a team of MUSC researchers has identified a pathway that could be targeted by drugs to reduce fat accumulation in patients with a common form of fatty liver disease known as metabolic dysfunction-associated steatotic liver disease, or MASLD.

The MUSC team was led by Stephen Duncan, Ph.D., SmartState Endowed Chair in Regenerative Medicine, and Caren Doueiry, an M.D.-Ph.D. candidate in Duncan's laboratory. The team reports its findings in the International Journal of Molecular Sciences.

Almost a quarter of Americans have MASLD, formerly known as non-alcoholic fatty liver disease. It is estimated that three in four people who are overweight and as many as two in three patients with Type 2 diabetes have the disease. In MASLD, fat accumulates over time in the liver, leading to fibrosis, or scarring of the liver, as well as cancer. In fact, MASLD is the leading cause of hepatocellular carcinoma, the most common primary liver cancer in adults.

Understanding MASLD using stem cells

Stem cells are a group of cells that have not yet determined what types of cells they will become. During early development, they respond to signals in their environment that guide them to differentiate into specific cell types, such as liver, nerve or muscle cells. Scientists have developed technologies that enable them to take blood samples from patients and erase the specialized markers that make them blood cells.

These reprogrammed cells are called induced pluripotent stem cells (iPSCs), and they serve as a blank canvas for scientists, who can instruct them to become any type of cell they wish to study. This technology allows these cells to organize into complex tissues and organs, providing a deeper understanding of the human body.

Doueiry used CRISPR, a gene-editing tool, to engineer a line of iPSCs with a mutation in the PNPLA3 gene that is common in patients with MASLD. CRISPR stands for clustered regularly interspaced short palindromic repeats. "A lot of patients with fatty liver have this mutation, and we don't know what it's doing or why it's increasing susceptibility to fatty liver," said Doueiry, lead author of the article.

To learn more about the mutation's role in MASLD, Doueiry induced the iPSCs carrying the mutation to become liver cells. She observed that the mutated liver cells had higher levels of fat accumulation. This finding links this common genetic mutation to a key characteristic of MASLD, showing that it plays an important role in regulating fat accumulation in the liver.

Doueiry is most excited that she now has a model that mirrors the human disease right in a cell culture plate. "I knew that the mutation in humans was causing the fat accumulation, but I had no idea what I was going to see in the plate," she said. "Looking at the liver cells carrying the genetic mutation for the first time was so exciting because I knew we had a model that we can use to find some answers."

No current pharmaceutical treatments target the excess fat accumulation that leads to MASLD. To look for potential contenders, Doueiry screened 1,100 small molecules from a library of compounds to see which ones reduced fat accumulation in her genetically modified liver cells. After a series of screens, Doueiry was able to identify five compounds that more than halved the number of fat droplets on the treated liver cells.

Surprisingly, these compounds all interacted with proteins in the same cellular pathway. Even more remarkably, this cellular pathway is known to regulate cell growth and is commonly targeted by cancer therapeutics to stop tumor development. Several approved cancer drugs that inhibit proteins in this pathway are already being administered to patients. When Doueiry used cancer drugs to treat her genetically modified liver cells, fat accumulation dramatically decreased, just as it had with the five compounds she initially discovered.

"Looking at the liver cells carrying the genetic mutation for the first time was so exciting because I knew we had a model that we can use to find some answers."

– Caren Doueiry

"With these results, we knew we weren't just looking at random molecules doing something. The fact that they all connected through a pathway showed us that we were onto something," she explained.

Doueiry was even able to use her model to determine the appropriate drug dosage needed to achieve this therapeutic effect with minimal unwanted effects. She discovered that a low dose of the inhibitor was sufficient to lower fat accumulation in liver cells lacking the mutation, with little effect on cell viability, promising findings for future clinical studies.

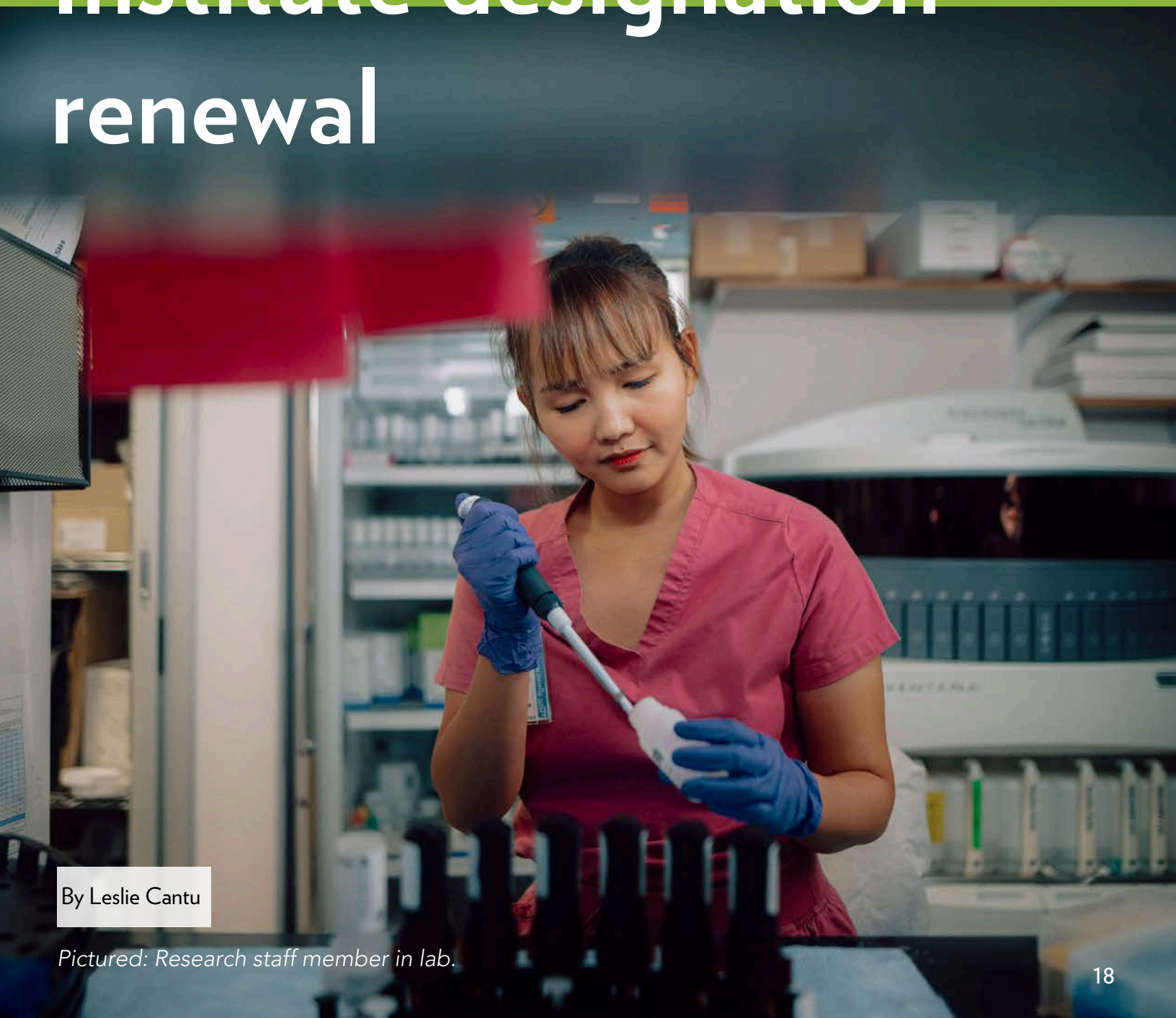
In short, Doueiry's iPSC disease model not only mimicked the disease in the laboratory but also provided a better sense of how human cells would respond to treatment. It showed that low dosages of selected pathway inhibitors achieved a good response, with few unwanted effects.

Duncan is excited about the potential of this new model. "Caren's study has shown that human stem cell-derived liver cells with MASLD mutations can be used effectively to identify pathways that can be targeted by drugs to reduce fat levels in the liver," said Duncan.

This study's finding suggests that MASLD, particularly when caused by this common genetic mutation, could one day be a treatable condition, possibly using repurposed already-approved drugs.

Though much work remains before a pharmaceutical treatment reaches the clinic, Duncan and Doueiry's work inspires hope – not just for patients with MASLD but also for the potential of iPSCs to serve as models for screening therapeutics for other genetically linked diseases.

MUSC Hollings Cancer Center celebrates National Cancer Institute designation renewal



By Leslie Cantu

Pictured: Research staff member in lab.

"Outstanding."

That was the score that MUSC Hollings Cancer Center received on its National Cancer Institute designation review in April 2024, the highest that the center has scored since first earning NCI designation in 2009. The rating underscores Hollings' deep commitment to research into cancer diagnosis, development, progression, treatment and treatment resistance. "We've assembled a top-notch team of scientists who are motivated to see their work in the lab make a difference to patients in the clinic," said Raymond N. DuBois, M.D., Ph.D., Hollings director.

He pointed to a CAR-T clinical trial that is showing positive results so far. The seeds of this clinical trial, which received a $3.2 million grant from the National Cancer Institute in spring 2024, were planted several years ago when Hollings invested pilot funding in the CAR-T research of Shikhar Mehrotra, Ph.D., who now serves as a co-leader of the Cancer Biology and Immunology (CBI) Research Program at Hollings. CAR-T cell therapy is approved for several forms of blood cancer but can generate serious side effects. Mehrotra and his team developed and patented a cytokine "cocktail" that can be used to reduce CD38 expression on T-cells, which then forestalls T-cell exhaustion in the tumor microenvironment. The expectation is to reduce side effects and increase the amount of time that the CAR-T cells are effective.

A clinical trial using Mehrotra's recipe is now underway. It has been able to take patients with blood cancers who do not have an approved CAR-T cell therapy treatment, and the results of this multi-year study look good so far. By the end of 2024, eight patients had been infused and, of the seven who were at least 30 days out and had a follow-up scan, five were in remission. Immunotherapy, as in this CAR-T project, is a focus for Hollings.

"Channeling the body's own immune system to fight off cancer – this is some of the most exciting science in cancer right now," DuBois said.

In the lab of Besim Ogretmen, Ph.D., researchers uncovered a mechanism by which triple-negative breast cancer becomes resistant to immunotherapy. This insight will allow researchers to manipulate that mechanism to restore sensitivity to treatment.

And in DuBois' lab, researchers found that a receptor called PPAR δ is an important player in a pathway that disables the immune system so that T-cells can't kill cancer cells.

In addition to Cancer Biology and Immunology, Hollings also has research programs in Developmental Cancer Therapeutics and Cancer Prevention & Control.

In all of these programs, Hollings leaders make a special effort to promote good ideas by offering pilot funding mechanisms to help novel research to gain traction, with an emphasis on high-risk, high-reward objectives. Mehortra's CAR-T research is one example of work that started with internal funding.

Gynecologic oncology researcher Joe Delaney, Ph.D., published work in Cell Cycle in 2024 that grew out of an internal Hollings grant. His research showed why hydroxychloroquine, an anti-malarial that showed promise against cancer because it blocks autophagy, has failed in clinical trials. The drug does not actually work against cancer in the way that everyone assumed. By uncovering its actual mechanism of action, Delaney and his team can now work to identify the best drug to pair with hydroxychloroquine to overcome resistance.

John Wrangle, M.D., was awarded a $792,000 grant from the Department of Defense in 2024 to continue lung cancer research that started with a pilot grant from Hollings. He and his team are developing a gene therapy to deliver to cancer cells the instructions to build the very therapy that will kill them. He hopes to be able to move into clinical trials in three to five years.

And Evan Graboyes, M.D., and Jennifer Dahne, Ph.D., together received a $3.1 million grant from the National Cancer Institute to build upon a pilot project funded by Hollings to develop a new model for getting timely and appropriate depression treatment to people living with likely incurable cancer. Their clinical trial is underway now.

"These projects showcase the range of inventive, creative work happening here at Hollings. Our researchers and clinicians are continually seeking ways to understand cancer, to improve treatments for people with cancer and, ultimately, to prevent cancer," DuBois said.

The transformative tenure of Paula Traktman, former Dean of the College of Graduate Studies

By Allison Olawsky

When Paula Traktman, Ph.D., stepped into the role of dean of the College of Graduate Studies (CGS) in 2015, she brought with her a vision to redefine graduate education at MUSC. Over the next nine years, her tenure became a period of profound transformation, leaving a legacy that resonates throughout the University and beyond.

From the outset, Traktman identified curriculum innovation as a cornerstone of her mission. She spearheaded a complete overhaul of the Biomedical Sciences core curriculum for first-year students, ensuring it reflected the ever-evolving demands of modern science. Recognizing the growing importance of data in research, she introduced new courses focused on "big data" and coding, equipping students with tools to navigate the complexities of contemporary biomedical research.

Her leadership extended beyond academics into fostering a supportive environment for graduate students. By establishing the Graduate Student Advisory Council (GSAC), she created a platform where students' voices could be heard, enabling honest feedback and proactive solutions. This initiative, coupled with the innovative "Ready, Willing, and Able List," streamlined the mentorship process, ensuring meaningful faculty-student connections.

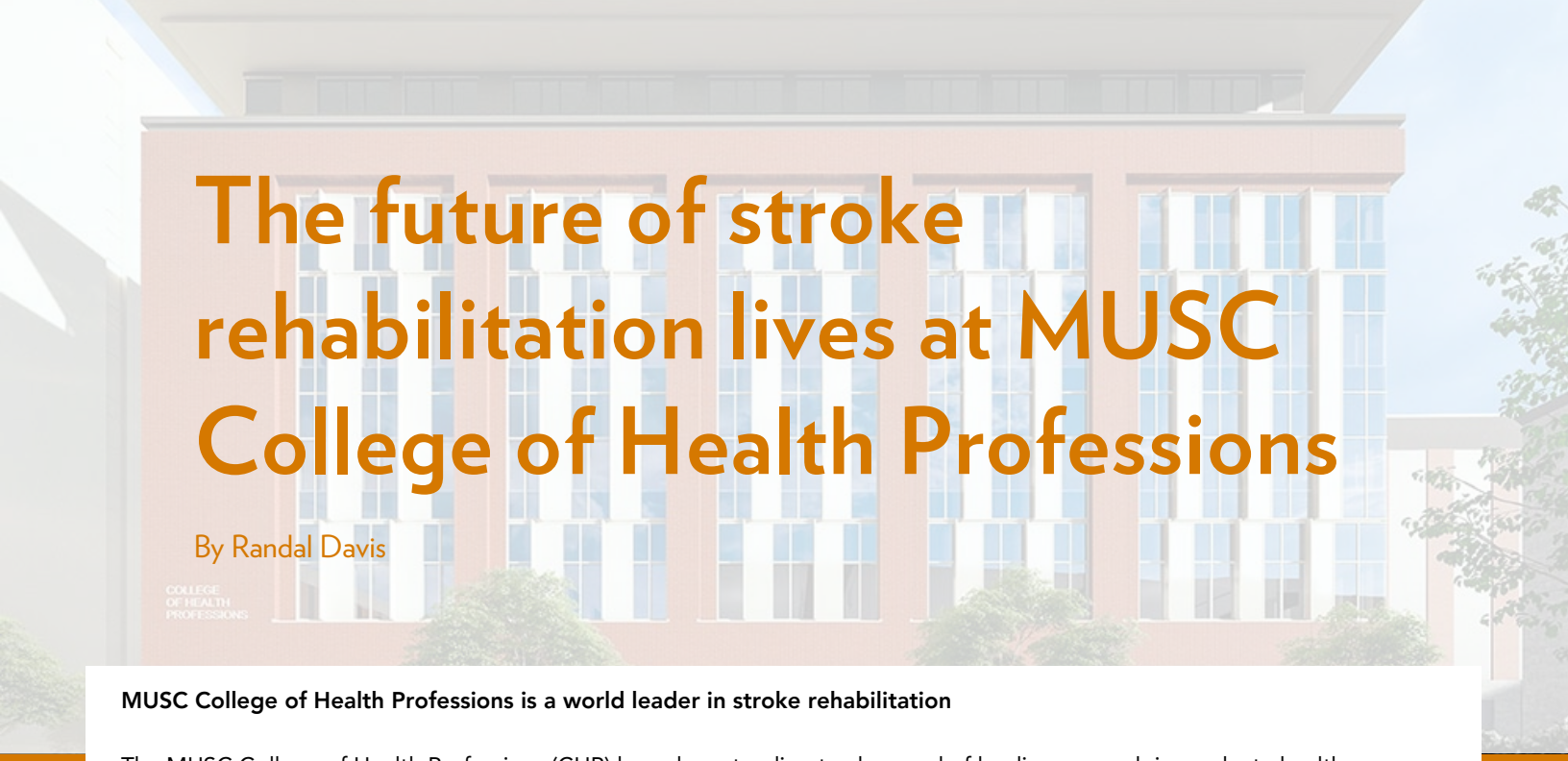
One of Traktman's crowning achievements was the launch of the Graduate Faculty Research Database. This publicly accessible resource not only served as a recruitment tool for students and faculty but also became a catalyst for fostering interdisciplinary collaboration within MUSC's research community.

Under her guidance, CGS expanded its horizons through robust recruitment strategies. Hiring the college's first director of Recruitment and Admissions and upgrading the admissions process resulted in a significant increase in Ph.D. program enrollment. Meanwhile, the introduction of a Marketing and Communications director brought CGS into the digital age, with a vibrant social media presence and a weekly newsletter that kept students, postdocs and faculty informed and connected.

Traktman was also a champion of career development. The annual Career Day she established highlighted the diverse opportunities available to graduates, while initiatives like the "Accelerate to Industry" (A2i) and "Accelerate to Academia" (A2A) workshops prepared students for futures in both corporate and academic settings. Her emphasis on communication led to the creation of the SWIFT Science Writing Internship, offering students practical experience in science communication and digital badges to showcase their expertise.

Always a strong advocate for mentorship, Traktman worked to elevate the standard of training for faculty and students alike. Through workshops developed in collaboration with the Center for the Improvement of Mentored Experiences in Research (CIMER), she set the stage for a culture of effective communication, aligned expectations and cultural awareness. The impact of her tenure is perhaps best exemplified by the grants and programs she developed or managed. From successfully renewing NIH-funded initiatives like PREP and IMSD to securing and renewing the CBAMS T32 grant, Traktman ensured that CGS had the resources to support its students and faculty. The CBAMS program, in particular, became a hallmark of her leadership, fostering a vibrant community of students prepared for the multifaceted challenges of biomedical science.

Paula Traktman leaves behind a college that is not only stronger and more dynamic but also firmly positioned as a leader in graduate education. Her legacy is one of innovation, inclusivity and excellence – a legacy that will inspire future generations of students and faculty at MUSC.



The future of stroke rehabilitation lives at MUSC College of Health Professions

By Randal Davis

MUSC College of Health Professions is a world leader in stroke rehabilitation

The MUSC College of Health Professions (CHP) has a longstanding track record of leading research in graduate health professions across a variety of areas ranging from stroke rehabilitation and spinal cord injury to health services research and veterans' health. New rankings from Expertscape reflect the college's substantial and enduring impact on the field of stroke rehabilitation, which ranks MUSC as fifth among universities in the United States and 17th in the world.

Steven Kautz, Ph.D., chair of the Department of Health Sciences and Research, has been the driving force of CHP's research engine in this area since his recruitment in 2010. In recognition of his strong advocacy for translating laboratory findings into clinical practice, passion for mentoring the next generation of early career faculty and $395 million economic impact over the last 15 years, Kautz received the 2025 South Carolina Governor's Award for Excellence in Scientific Research.

Kautz was recently awarded a $7.9 million federal construction grant from the NIH to build the Clinical Research Center for Restoration of Neural-Based Function in the Real World (RENEW). "The one-of-a-kind center will create a state-of-the-art research facility dedicated to restoring nervous system function to rehabilitate how people move, sense, understand and interact with the world around them, leading to lasting improvements in their home environments," Kautz explained.

Zoher Kapasi, Ph.D., PT, dean of the College of Health Professions, said, "There's nothing like RENEW in the state of South Carolina, and it is possibly one of only a handful in the country." He added, "What's extraordinary about the new facility and MUSC is that stroke rehabilitation and restoring brain function are priorities at MUSC, and we're fortunate enough to have some of the top investigators in those fields here."

New telerehabilitation study focuses on the mental health aspect of stroke recovery

Every year, more than 795,000 strokes occur in the United States. In addition to the physical impacts caused by a stroke, the emotional effects can be devastating. Michelle Woodbury, Ph.D., OTR/L, a longtime neurorehabilitation occupational therapist and professor in the College of Health Professions, explained, "Stroke often causes an overwhelming emotional burden on stroke survivors and their care partners. More than half of stroke survivors experience emotional symptoms such as anxiety, dread, fear and hopelessness. Shockingly, those with these symptoms are five times more likely to die within the first year post-stroke and are twice as likely to experience suicidal ideation."

To study this issue and explore a new therapeutic intervention model, Woodbury was awarded a $1 million grant from The Duke Endowment titled "Centering Emotional Recovery Post-Stroke." The grant will bring together an interprofessional team of psychologists, occupational therapists and speech-language pathologists to design and implement an emotional support-centered intervention – Cognitive Behavioral Therapy – to address the emotional support needs of stroke survivors. Further, working with the MUSC Telehealth Center, the intervention study will be made available across South Carolina, including in rural and medically underserved communities. "We are thrilled to partner with The Duke Endowment to make this first-of-its-kind emotional health telerehabilitation intervention available to South Carolinians to address this critically important unmet need," said Woodbury.

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Front Cover Image: Glycan imaging of hepatocellular carcinoma tissue using matrix-assisted laser desorption/ionization. Images from the Mehta, Angel and Drake laboratories.

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