

# PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // FALL 2017



## **Neoantigens: Cancer's Achilles Heel?**

**A neoantigen -  
targeted TIL therapy  
for lung cancer**

# MUSC ranked state's No. 1 hospital third year in a row

MUSC Health only hospital in state to achieve national ranking by *U.S. News & World Report*

MUSC Health was named by *U.S. News & World Report* for the third year in a row as the No. 1 hospital in South Carolina, and one of the country's top 50 hospitals in the treatment of ear, nose and throat disorders, gynecology, urology and cancer. MUSC was also high-performing in gastroenterology & GI surgery, geriatrics, nephrology, neurology & neurosurgery, orthopedics, pulmonology and rheumatology.

**Patrick J. Cawley, M.D.**, MUSC Health CEO and MUSC Vice President of Health Affairs, said the ranking is a reflection of the team's commitment to putting patients and families first, advancing innovation in the delivery of care and striving to make our communities healthier in ways that go beyond the hospital setting. "There are lots of ranking systems out there, but this particular designation means more than reputation," Cawley said. "These rankings reflect strong patient outcomes, excellence in teaching the next generation of care providers, new innovations that improve health and strong health care leadership."



## MUSC Health Medical Video Center

MUSChealth.org/medical-video

### A sampling of current videos:

#### Coronary CTO-PCI

Interventional cardiologist **Anbukarasi (Arasi) Maran, M.D.**, who leads the chronic total occlusion team at MUSC Health's Heart & Vascular Center, discusses an advanced hybrid approach to revascularize CTOs in this video.

#### Balloon-Assisted Enteroscopy in Children

**J. Antonio Quiros, M.D.**, chief of the division of gastroenterology, hepatology and nutrition at MUSC Children's Health, discusses the advantages of balloon-assisted enteroscopy, a form of deep enteroscopy that enables the physician to explore much further into the small intestine than would be possible with traditional endoscopy.

#### A Shuntless Technique for Treating Hydrocephalus

MUSC Children's Health pediatric neurosurgeon **Ramin Eskandari, M.D.**, discusses a new shuntless procedure for treating hydrocephalus — endoscopic third ventriculostomy and choroid plexus cauterization (ETV/CPC).

#### Nipple-Sparing Mastectomy Followed by Prepectoral Implant

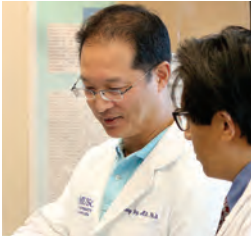
Surgical oncologist **Andrea M. Abbott, M.D.**, narrates photos from a nipple-sparing mastectomy, and plastic surgeon **Jason P. Ulm, M.D.**, walks viewers through a prepectoral breast reconstruction.

#### Robotic Mitral Valve Surgery

MUSC Health cardiothoracic surgeon **Marc R. Katz, M.D., MPH**, discusses the advantages of robotic mitral valve surgery, the least invasive of all mitral valve repair techniques. Katz has more than 15 years of experience with the da Vinci robotic system.

# PROGRESS NOTES

MUSC'S MEDICAL MAGAZINE // FALL 2017



## 24

### The RNA Family

A group of experts has formed at MUSC to study the roles of different RNAs in cancer

## 2

### In Short

New trigger identified for metabolic disorders

Controlling cancer-linked AGEs pharmacologically?

Testing an SK2 inhibitor in hepatocellular carcinoma

Peptide to treat HPV-negative cancer

## 8

### First ACT

FDA approves the first-ever genetically modified adoptive cell transfer therapy for pediatric acute lymphoblastic leukemia

## 18



### A Question of Timing

Rethinking treatment sequencing in metastatic prostate cancer

## 26

### Welcome

MUSC Appoints New Chair of Pediatrics

New Physicians

## 6

### Frontiers In Neuroblastoma Treatment

MUSC Children's Health is conducting pioneering clinical trials on upfront precision medicine therapy and relapse prevention for neuroblastoma

## 12

### Neoantigens: Cancer's Achilles Heel?

Team seeks expanded lung cancer treatment options at the interface of genetics and immunotherapy

## 22

### Interview

A Conversation About Palliative Care

## 16

### Same Gain, Less Pain

Video-assisted thoracoscopic surgery is standard of care for most patients with stage 1 nonsmall cell lung cancer



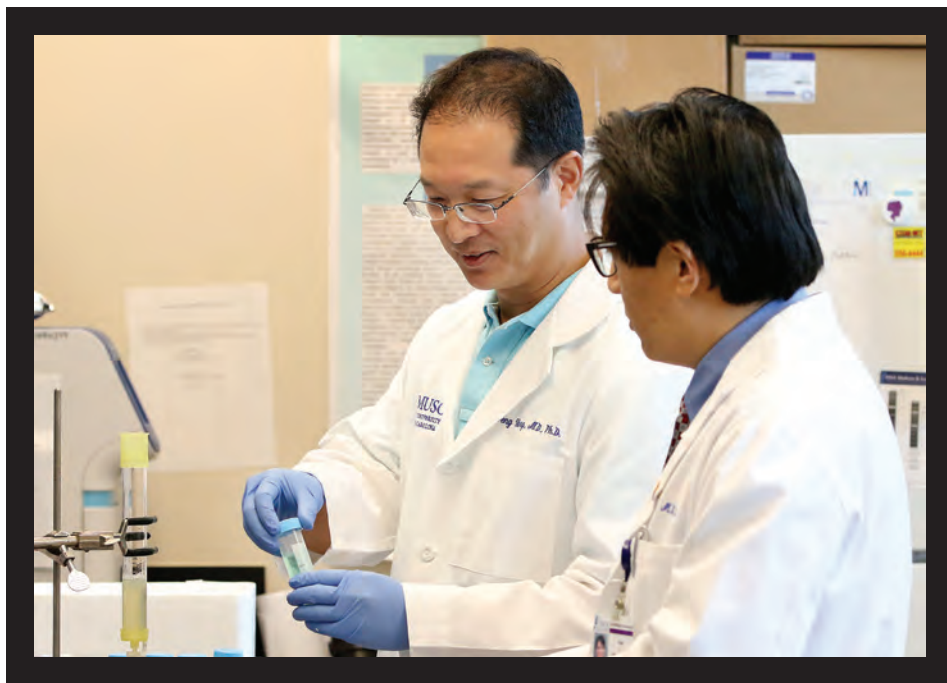
On the cover: Neoantigens could be cancer's Achilles heel. Illustration by Emma Vought.

## A NEW WRINKLE

### Mysterious protein-folding molecule could trigger metabolic disorders

BY SVER AUNE

Photograph by Sarah Pack



Dr. Zihai Li (right) and Dr. Feng Hong (left)

The cell's response to unfolded or misfolded proteins could be a cause, rather than a consequence, of metabolic disorders, report MUSC researchers in an article published online ahead of print on September 4, 2017 by *Nature Structural & Molecular Biology*. The researchers identified a little-known molecule as the trigger for this response.

There are links between protein-folding problems at the cellular level and a range of metabolic disorders, though it is unclear if those problems are causes or manifestations of such disorders. This study provides evidence that problems with protein folding contribute to certain metabolic disorders, according to senior author **Zihai Li, M.D., Ph.D.**, chair of the Department of Microbiology and Immunology in the MUSC College of Medicine, who also leads the cancer immunology program at MUSC Hollings Cancer Center. **Feng Hong, M.D., Ph.D.**, is lead author on the article.

"The unfolded protein response in the cell plays important roles in aging and in many diseases, such as cancer, diabetes and neurodegenerative disease," says Li. "Our study has uncovered a novel mechanism that triggers this response."

When improperly folded molecules are encountered in cells, the unfolded protein response (UPR) is activated within the endoplasmic

reticulum (ER). The ER is in charge of molecular quality control, making sure proteins, lipids and other molecules are folded properly before the cell attempts to use them for metabolic processes. Here, a master protein called grp78 is in contact with three main signaling hubs that make up the control center of the UPR. When an unfolded or misfolded protein is encountered by grp78, it breaks contact with those sensors and activates the UPR. The UPR then refolds or disposes of such molecules before they are shipped to the parts of the cell that need them.

There is a wrinkle in the UPR, however. When too many unfolded proteins build up, the UPR senses that the cell has become overstressed and activates programs to recycle the cell. Yet if a number of cells

experience such stress and are similarly retired, whole organs can suffer. This appears to be where the CNPY2 molecule exerts influence during the development of metabolic problems, according to experiments performed by Li and his group.

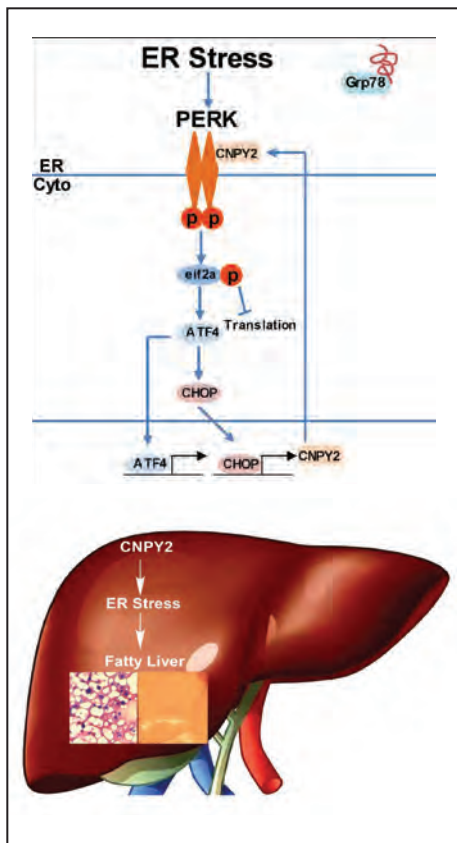
CNPY2 has been known for some time to reside within the ER, but its function there has remained a mystery. To help clarify its role, the researchers began by generating mice without CNPY2 to see how they would grow. Although the rodents were slightly smaller, they were otherwise normal. Important differences appeared, however, when they were fed small amounts of tunicamycin, a known inducer of the UPR. Control mice exhibited signs of liver stress and activation of PERK, one of the three main UPR sensors, while the livers of knockout mice remained stress-free. This was the first sign that CNPY2 could be involved in metabolic stress in the liver.

The investigators then examined mouse cells with and without CNPY2 and isolated the PERK protein and its downstream signaling molecule, CHOP, within them. This interestingly named PERK-CHOP pathway, which is a major enabler of liver stress when the UPR is induced, was not activated in cells without CNPY2. When they added CNPY2 back to those cells, suddenly the pathway was restored.

The researchers also found that the PERK-CHOP pathway, when activated by free CNPY2, further increased levels of CNPY2 in the liver. In other words, CNPY2 was able to further reinforce itself once activated.

Taken together, the team's experiments showed that CNPY2 powerfully sustains cellular stress when the unfolded protein response becomes active, providing a link between the UPR and the development of metabolic problems in the liver.

This opens an opportunity, according to Hong. "This novel finding has raised the possibility of developing new treatments for metabolic diseases by targeting CNPY2," says Hong.



CNPY2 is required for endoplasmic reticulum (ER) stress-induced non-alcoholic fatty liver disease.

## stAGEs of Cancer

Grape compound could reduce cancer-linked molecule in the diet

BY SVER AUNE

Could a common byproduct of the Western diet thought to promote cancer be reduced pharmacologically? Researchers at MUSC Hollings Cancer Center are testing compounds designed to block advanced glycation end products (AGEs) in patients with metastatic breast cancer who are receiving endocrine therapy. The pilot trial is led by **Carolyn D. Britten, M.D.**, associate director for clinical investigations at Hollings, and inspired by the preclinical work of MUSC cancer biologist **David P. Turner, Ph.D.**

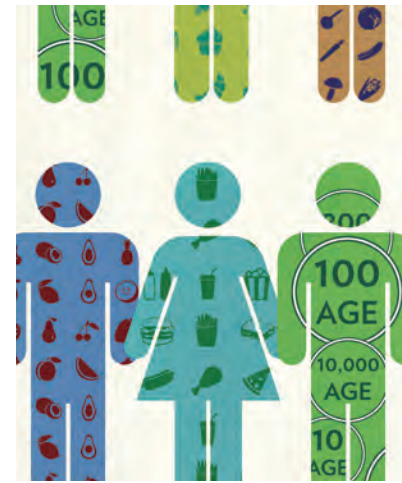


Illustration by Emma Vought

Scientists have known that patients with

diabetes have high concentrations of AGEs in their blood. Yet Turner is among the first researchers to study how AGEs set the stage for cancer. AGEs accumulate in the body as a byproduct of breaking down sugar but are also found in red meats and fried and processed foods. Once in the body, they cause the formation of reactive oxygen species that can encourage the development and spread of cancer.

"AGEs are highly volatile and promote inflammatory and immune responses in the body," says Turner. "We want to try to reduce AGEs in cancer patients because those responses may contribute to the return of cancer."

Britten's trial will test whether AGEs can be reduced pharmacologically with a compound isolated from grapes called oligomeric proanthocyanidin complex (OPC) in women with estrogen receptor-positive metastatic breast cancer. Patients must be receiving endocrine therapy to block the production of estrogen that is likely driving metastasis. Patients will take the oral hypoglycemic metformin along with OPC for 12 weeks. AGE concentration in the blood will be tracked before and after treatment to see if AGEs drop as a result of receiving OPC and metformin.

This follows preclinical studies by Turner that found that AGE levels were the highest in tumors of men with the worst prognosis for prostate cancer. A trial already underway in patients with prostate cancer, led by **Michael B. Lilly, M.D.**, associate director of translational research at Hollings, is also tracking the reduction of AGEs in men taking OPC. In a recently completed trial, Turner worked with **Marvella E. Ford, Ph.D.**, associate director of population sciences and cancer disparities, and **Gaynell Magwood, Ph.D.**, professor in the College of Nursing, and showed that exercise and a healthy diet can reduce AGE levels in breast cancer survivors. Turner was recently funded to conduct a dietary and physical intervention trial in prostate cancer survivors and to measure the effects of those interventions on AGE concentration.

## FIRST OF ITS KIND

### Novel inhibitor shown safe in first-in-kind phase 1 trial at Hollings Cancer Center

BY NOUHOU IBRAHIM

Illustration by Emma Vought



A phase 1 trial at MUSC Hollings Cancer Center of a first-in-kind sphingosine kinase (SK) 2 inhibitor (YELIVA™, RedHill Biopharma Ltd, Israel) showed it to be safe and well-tolerated by patients with solid tumors, report MUSC investigators in the August 2017 issue of *Clinical Cancer Research*.

Led by **Carolyn D. Britten, M.D.**, associate director for clinical investigations at the MUSC Hollings Cancer Center, the trial also established a recommended dose for the SK2 inhibitor and showed that it lowers plasma levels of sphingosine 1 phosphate (S1P) in patients with solid organ tumors.

“Sphingolipid metabolism has been widely studied in cancer models, but translation of these basic science results to the clinic is limited,” says Britten. “The phase 1 trial was unique because it provided the first data on sphingolipid profiles in patients treated with an SK inhibitor.”

Sphingolipids are a class of lipids known to be involved in the growth of solid tumor cancers. S1P, formed when sphingosine picks up a phosphate group from SK1 or SK2 enzymes, has been shown

to promote the proliferation of cancer cells and the development of treatment resistance.

By blocking the activity of SK2, the inhibitor helps prevent the formation of S1P. The SK2 inhibitor was developed by Charles D. Smith, Ph.D., formerly a professor at MUSC, and was later licensed to RedHill Biopharma. Smith is currently on faculty at Penn State University and is a co-author of the *Clinical Cancer Research* article.

Britten is also the principal investigator of a phase 2 trial of the SK2 inhibitor as a second-line monotherapy in patients with advanced hepatocellular carcinoma (HCC) who have experienced tumor progression despite treatment with currently available FDA-approved therapies. The most common primary malignant cancer of the liver, HCC also has one of the highest mortality rates among cancers. The phase 2 trial is now open and recruiting patients at Hollings, with an initial goal of enrolling 12 patients. If a response is seen in these patients, additional patients will be recruited, with a target enrollment of 39.

The study is being funded by a grant from the National Cancer Institute (NCI) awarded in 2016 to Hollings, an NCI-designated cancer center, with additional support from RedHill. **Besim Ogretmen, Ph.D.**, Endowed Chair in Lipidomics & Drug Discovery in the SmartState® Center for Lipidomics, Pathobiology and Therapy and professor of Biochemistry & Molecular Biology at MUSC, is the principal investigator for the \$8.9 million NCI Program Project Grant (PPG), which funds a total of three projects and four shared resources. The collective aim of this PPG is to foster collaboration across clinical and laboratory research for the study of signaling in sphingolipids for cancer therapeutics.

“It is gratifying to see that Hollings is becoming a center for clinical trials of sphingolipid-related therapeutics,” says Ogretmen.

Other trials with the selective SK2 inhibitor are underway to assess its efficacy in a wide range of advanced tumors that are not responsive to standard treatments.

## FROM BED TO BENCH AND BACK TO BED

### A synthetic peptide designed to treat HPV-negative cancer

BY MATTHEW GRESETH

Patients with head and neck cancer, specifically oropharyngeal cancer, who are also positive for human papilloma virus (HPV) have been observed to respond significantly better to chemo-radiotherapy than patients who are HPV-negative. This observation is surprising because HPV infection leads to an increased risk of developing oropharyngeal cancer. To date, the reason for this dichotomy has not been well understood.

In an article in the August 2017 issue of *EMBO: Molecular Medicine*, MUSC researchers and clinicians report having identified one of the underlying mechanisms — expression of a specific viral protein leads to cell death through ceramide-induced mitophagy, a process that destroys the mitochondria.

“This study looked at both the clinical aspects as well as the mechanistic and therapeutic aspects of oral cancer. We are very excited about these findings because they represent what is happening in the clinic,” says **Besim Ogretmen, Ph.D.**, Endowed Chair in Lipidomics & Drug Discovery in the SmartState® Center for Lipidomics, Pathobiology and Therapy and senior author for this study.

Ogretmen’s laboratory, which studies mitochondria and the signaling lipid ceramide, built upon the clinical observation that patients with HPV-positive cancer respond significantly better to treatment with cisplatin, a chemotherapeutic agent that resembles ceramide. The findings described in their recent work detail the molecular signaling cascade that induces cell death through a process termed *ceramide-induced mitophagy* in HPV-positive cancers.

Having described the mechanism by which HPV-positive cancer cells succumb to chemotherapy, the Ogretmen laboratory next wanted to determine if they could apply these findings to HPV-negative cancers, since patients with these cancers are much more likely to succumb to their disease.

In order to accomplish this, they developed a peptide that turns on the molecular signaling cascade, even in the absence of HPV. Treatment of HPV-negative oral cancer cells with cisplatin and this novel peptide led to increased cell death in a manner that was similar to treatment of HPV-positive cancer cells with cisplatin. Further experiments showed that this peptide was effective at killing HPV-negative cancer cells in a mouse model.

Overall, these results define the mechanism that underlies the increased efficacy in treating HPV-positive cancer with cisplatin and



Photograph by Brennan Wesley

**Dr. Besim Ogretmen**

show that this improved efficacy can be achieved in HPV-negative cancer cells through co-treatment with this novel peptide.

This work required the coordinated collaboration of clinicians and basic science researchers and exemplifies the “bed – to bench – to bed” ideal that scientific research strives to achieve. Patients who were seen in *the clinic* were asked to donate the leftover cancer tissue from their surgery. Then the tissues were tested *in the laboratory* and in animal models. The results of these tests are now being taken back into *the clinic* (bedside) in an attempt to treat patients with HPV-negative head and neck cancers.

“Given the profound impact of HPV status on survival, it has become clear that understanding the mechanisms driving the sensitivity of HPV-positive disease to cytotoxic therapies could provide the foundation for novel therapies in HPV-negative head and neck cancer,” says **David M. Neskey, M.D.**, a surgeon at MUSC Hollings Cancer Center specializing in treatment of head and neck cancers.



Dr. Jacqueline Kraveka with patient Victoria Thompson, who is enrolled in the first upfront pediatric precision medicine trial. Photograph by Sarah Pack

# Frontiers in **NEUROBLASTOMA** Treatment

MUSC Children's Health is conducting pioneering clinical trials on upfront precision medicine therapy and relapse prevention for neuroblastoma

BY VITRIA ADISETIYO



Beat Childhood Cancer (BCC), a national clinical trials consortium,<sup>1</sup> is sponsoring two multicenter phase 2 trials on advanced treatments for high-risk neuroblastoma. As part of BCC, MUSC Hollings Cancer Center will serve as a site for both trials, each led by **Jacqueline M. Kravaka, D.O.**, a pediatric hematologist-oncologist at MUSC Children's Health.

Neuroblastoma is a solid extracranial cancerous tumor that develops from improperly matured nerve cells. With 700 cases diagnosed annually in the U.S., neuroblastoma is the most common cancer in infants and the third cause of childhood death from cancer.<sup>2</sup> Neuroblastoma has diverse clinical presentations and outcomes. Patients are stratified into low, intermediate or high risk for recurrence. While non-high-risk patients have a survival rate of more than 90 percent, the survival rate for the 40 percent of patients who are high-risk is less than 50 percent.

Standard upfront (initial) therapy for high-risk neuroblastoma typically consists of induction (six cycles of chemotherapy, with stem cell collection after cycle two), surgical resection of tumors, consolidation (stem cell transplant to restore bone marrow), radiation of residual tumors and maintenance (retinoic acid therapy to help cells mature and anti-Ganglioside GD2 immunotherapy to eradicate minimal residual disease by targeting the GD-2 positive neuroblastoma cells). Unfortunately, up to 20 percent of patients do not respond to induction and at least half of all high-risk patients will relapse during or after maintenance.<sup>2</sup>

"The issue is how to improve these outcomes," says Kravaka. "One way would be to add a targeted agent during induction to improve response rate — this is the front-end approach of the Pediatric Precision Laboratory Advanced Neuroblastoma (PEDS-PLAN) trial (NCT02559778). Another way would be to prevent relapse — this is the back-end approach of the PEDS-PLAN and Neuroblastoma Maintenance Therapy (NMTT; NCT02679144) trials."

The PEDS-PLAN trial is the first to incorporate precision medicine into upfront therapy for newly diagnosed high-risk neuroblastoma. This study uses a novel, molecular-guided therapy protocol established in a previous BCC clinical trial in relapsed patients that demonstrated safety and feasibility. For each patient, tumor and blood samples are collected to generate a genomic report that identifies genetic mutations (via DNA exomes) and altered molecular pathways (via RNA sequencing) in the cancer. An algorithm identifies known drugs that target these features and predicts the best drug to add to upfront therapy (during cycles three through six of induction). An interdisciplinary molecular tumor board then reviews the report and the scientific literature and decides on the patient's treatment.

"Most personalized medicine studies only look for one specific genetic mutation and offer one targeted agent. Consequently, these studies find a match for only 25 percent of cases," explains Kravaka. "By including RNA sequencing and bioinformatics, we've come up with a precision medicine plan that includes six possible drugs for all patients."

Another novel arm of the PEDS-PLAN trial is the addition of difluromethylornithine (DFMO) to maintenance as a strategy to prevent recurrence. DFMO is a low-cost and readily available oral drug developed to treat African sleeping sickness but is also being studied for high-risk neuroblastoma. As an inhibitor of a cell growth enzyme associated with the MYCN oncogene (overexpressed in high-risk tumors), DFMO has been used to prevent recurrence in relapsed patients.<sup>3</sup> In the PEDS-PLAN trial, patients are given DFMO for two years in the remission setting. Administration of DFMO is randomized to start at the beginning or end of immunotherapy. Twenty patients have been enrolled, and early findings show no reports of toxicity.

"Preventing relapse is key. After immunotherapy, there's nothing we can do for prevention in standard care," says Kravaka. "Once someone relapses, neuroblastoma is very difficult to cure, but there are a lot of things we can still do."

For patients who received upfront therapy outside of the PEDS-PLAN trial, the NMTT trial is another way they can receive DFMO during remission. In a recently completed component of this trial (enrolling 139 patients), the two-year event-free survival rate was 84 percent for those receiving DFMO after standard upfront therapy and 52 percent for those receiving DFMO during remission after relapse. Mild elevation of liver function enzymes was the only side effect. The NMTT trial will next expand enrollment to patients who completed non-standard upfront therapy and refractory patients who are in remission after additional therapy.

Kravaka is taking patient referrals for both trials until 2025, and there are no additional costs to patients. The studies cover genomic screening and DFMO, while insurance covers standard treatments.

"There hasn't been any treatment in the past that achieved this level of survival," says Kravaka. "Kids are able to go to school and DFMO is well tolerated. It's been really exciting to be able to offer these treatments to our patients."

#### References

- 1 Beat Childhood Cancer. 2017. <https://beatcc.org>
- 2 Whittle SB, et al. *Expert Rev Anticancer Ther*. 2017 Apr;17(4):369-386.
- 3 Saulnier Sholler GL, et al. *PLoS One*. 2015 May 27;10(5):e0127246.



# First ACT

FDA approves the first-ever genetically modified adoptive cell transfer therapy for pediatric acute lymphoblastic leukemia

BY SVER AUNE

ILLUSTRATION BY EMMA VOUGHT

The first adoptive cell transfer (ACT) therapy for the most common childhood cancer was approved by the Food and Drug Administration (FDA) on August 30, 2017, less than two months after a subpanel reviewing the dramatic results from clinical trials unanimously recommended its approval. Prior to FDA approval, there were no clinical treatments other than palliative care for patients with treatment-resistant acute lymphoblastic leukemia (ALL).<sup>1</sup>

Tisagenlecleucel, a chimeric antigen receptor (CAR) T cell therapy marketed by Novartis as Kymriah™, is the first-ever FDA-approved ACT therapy that incorporates genetic engineering of patients' own T cells to fight their cancer.<sup>1</sup> Kymriah™, also called CTL019 after the cancer antigen it targets, was officially approved for patients up to 25 years of age who have refractory B-cell ALL that has relapsed at least twice. Approval came after dramatic remission rates of 69 and 95 percent were observed in the two main trials reviewed by the FDA. With approval, CTL019 joins checkpoint modulators in the family of immunotherapies that are now considered the fourth pillar of cancer treatment after the historical triad of surgery, chemotherapy and radiation.

FDA approval opens the way for more equipped hospitals to provide CTL019 and other CAR T cell therapies. Medical centers that have the necessary clinical expertise and infrastructure in place to treat ALL and, importantly, to handle the challenging side effects of adoptive cell treatment, are now working with Novartis to be certified as CTL019 centers so that they can begin to offer the new therapy to their patients.

MUSC Children's Health is ready, according to **Michelle P. Hudspeth, M.D.**, director of the Division of Pediatric Hematology/Oncology at MUSC Children's Health. "CAR T cell therapy depends on the very infrastructure that we use every day," says Hudspeth. "This includes bone marrow transplant coordinators, hemapheresis nurses, cryopreservation technologists, oncology physicians, critical care physicians and oncology and critical care nurses."

## Therapy for ALL

According to the American Cancer Society, ALL is the most common pediatric cancer in children under the age of 14, making up an estimated 26 percent of all cancers in that age group.<sup>3</sup>



Stylized illustration of the CART "Supercell."

Roughly 3,100 patients in the U.S. are diagnosed with B-cell ALL every year, but only about 600 or so fall under Kymriah's™ label.<sup>1</sup> ALL is a blood and bone marrow malignancy that develops when blood stem cells make precursor B-cell lymphocytes that do not mature properly and instead proliferate throughout the blood. It is diagnosed with a biopsy of the bone marrow, where normal B-cell lymphocytes mature.

Not surprisingly, ALL is one of the most frequently treated pediatric cancers at MUSC Children's Health, according to Hudspeth. About 85 percent of children with ALL achieve long-term survival lasting five years following chemotherapy or stem cell transplants, but the remaining patients are unable to achieve remission, leaving them with few treatment options and a median life expectancy of three months.<sup>3</sup> CTL019 gives those patients a new option. "Some patients can't get a stem cell transplant because they have to be in remission to have it work," says Hudspeth. "Those 10 to 15 percent of patients are incredibly difficult to treat. It's tremendous that we could have a treatment for those patients."

### Supercells

CTL019 ingeniously supercharges a patient's own killer T cells to destroy cancerous B cells, according to **Chrystal M. Paulos, Ph.D.**, associate professor of Microbiology and Immunology and Endowed Peng Chair of Melanoma and Cutaneous T Cell Lymphoma. "Cancer cells downregulate ways in which they can be recognized by natural T cells," says Paulos. "We can engineer a T cell to recognize a cancer again through a manmade chimeric antigen receptor."

The immature lymphoid B cells overwhelm T cells in number and are disguised from patients' immune systems through secretion of anti-inflammatory mediators that subvert the attack from T cells.<sup>4</sup>

During treatment, some of a patient's T cells are separated from a blood sample. Then a gene that encodes a chimeric antigen receptor to recognize a molecule called CD19 on the surface of B cells is delivered to the T cells by a retrovirus. Those supercharged T cells are stimulated to multiply and are finally infused back into the patient in much greater number. CARs earn their characterization as chimeras because they are composed of synthetic pieces and different molecular parts, the whole of which does not exist in nature.<sup>5</sup>

Paulos worked on T cell immunology with Carl H. June, M.D., director of translational research at the University of Pennsylvania, who shepherded the current therapy through the clinical trials that most recently informed FDA approval.<sup>6</sup> After Steven A. Rosenberg, M.D., Ph.D., chief of the surgery branch at the National Cancer Institute, first reported the use of CAR T cell therapy in treating cancer in 2012, June reported that the retrovirus used to deliver the gene for the CD19 receptor to T cells was safe and effective, as evidenced by a decade of research encompassing five hundred total patient years.<sup>7,8</sup>

**Juan Carlos Varela M.D., Ph.D.**, professor of Hematology/Oncology, partners with Paulos to develop strategies using T cells to fight cancer. Together, the two focus on T cell therapies with clinical potential. “All the immunotherapy before was developed for solid

**“MUSC is working with Novartis to become a certified site to provide this therapy.”**

**—Dr. Juan C. Varela**

tumors, but there wasn’t anything for leukemias and lymphomas until CARs came along,” says Varela.

Varela and Paulos are studying the potential of other CAR T cell therapies in adult ALL and other malignancies. Although CARs can be designed to recognize several different molecules on cancer cells, CTL019 works so well because it targets CD19, a molecule expressed on both normal and cancerous B cells but not on other blood cells. As a result, CAR T cells are very effective at destroying cancerous and healthy B cells in the blood while sparing others. This makes CTL019 attractive for use in other B-cell cancers such as chronic lymphocytic leukemia, the most common leukemia among adults in the U.S.<sup>9</sup>

“We’re still at the beginning, but to harness this [tumor] response so we can do it in elegant, clean and affordable ways is going to be an exciting new step,” says Paulos.

## ALL In

Novartis is currently choosing which sites outside of those used in CTL019 clinical trials will be the first to treat patients. The adult and pediatric blood and marrow transplantation teams are working to bring Novartis’ CAR-T cell therapy to MUSC to treat pediatric patients. “MUSC is working with Novartis to become a certified site to provide this therapy, and we’re also on our way to being a site for clinical trials for the future of CAR T therapies,” says Varela.

Along with approval for the new therapy, the FDA mandates that facilities providing CTL019 must have a specific “risk evaluation and mitigation strategy” in place to handle cytokine release syndrome, the side effect that occurs in nearly 80 percent of patients.<sup>6</sup> Required as part of the strategy is immediate access to tocilizumab, which reduces IL-6, the inflammatory cytokine that is released in the greatest amounts in clinical trials and is believed to be causing the syndrome.<sup>8</sup> Fever and life-threatening neurotoxicity can also occur. Also, as of now, patients who receive CTL019 experience a loss of B cells with treatment and must take immunoglobulin infusions monthly for life.

It is still unclear whether insurance payers will cover the treatment, which may cost up to \$700,000.<sup>10</sup> Still, conducting clinical trials with Novartis and other companies making CAR T cell therapy is a way for the industry to subsidize investment in patients with ALL, according to Varela.

Finally, bringing CAR T therapy to MUSC will hold an additional benefit for pediatric patients with ALL: the nearest centers to provide the therapy — in clinical trials — are Emory University in Atlanta and Duke in North Carolina. “We are here to make sure patients get whatever therapy they need in South Carolina,” says Hudspeth. “It has a major impact for the child and their family to get treatment close to home.”

*\*\*\*Update: On October 18, the FDA approved a second CAR T therapy — axicabtagene ciloleucel (Yescarta; Kyte Pharma, a Gilead Company) — to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.*

## References

- 1 FDA News Release. [fda.gov](http://fda.gov). 2017. *website*. Retrieved from [fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm](http://fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm).
- 2 FDA Advisory Committee. [fda.gov](http://fda.gov). 2017. Tisagenlecleucel (CTL019). Retrieved from <https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm566168.pdf>.
- 3 Ward E. 2014. American Cancer Society. Childhood and adolescent cancer statistics [PowerPoint slides]. Retrieved from [cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2014.html](http://cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2014.html).
- 4 Rachidi S, et al. *Sci Immunol*. 2017;2(11):eaai7911.
- 5 Dai H, et al. *J Natl Cancer Inst*. 2016;108(7):djv439.
- 6 Tisagenlecleucel. [fda.gov](http://fda.gov). 2017. Retrieved from <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf>.
- 7 Scholler J, et al. *Sci Transl Med*. 2012;4(132):132ra53.
- 8 Kochenderfer JN, et al. *Blood*. 2012;119(12):2709-2720.
- 9 Siegel R, et al. *CA Cancer J Clin*. 2012;62(4):220-241.
- 10 Onclive.com. Hagen T. 2017. *website*. Retrieved from <http://www.onclive.com/web-exclusives/novartis-sets-a-price-of-475000-for-car-tcell-therapy>.



# Neoantigens: Cancer's Achilles Heel?

A multidisciplinary team of MUSC investigators is working at the interface of immunotherapy and genetics to expand treatment options for patients with lung cancer

BY KIMBERLY MCGHEE

ILLUSTRATION BY EMMA VOUGHT

Checkpoint modulators such as PD-1 and PDL-1 inhibitors have changed the face of cancer care, eliciting long-lasting responses in select patients with solid tumors that have metastasized. Although a few patients receive great benefit, there is some frustration in the field that these new immunotherapies do not as yet help more patients.

“Checkpoint modulators in lung cancer have had spectacular results in a few cases and responses in about 20 percent of patients but have done little in the other 80 percent,” says **John M. Wrangle, M.D.**, an MUSC Health medical oncologist who specializes in immunotherapeutic approaches to cancer, especially lung cancer. “That is disappointing clinically. We want immunotherapy to work for more people.”

Combining checkpoint modulators with other immunotherapeutic strategies will likely be necessary if more lung cancer patients are to benefit. Wrangle and his collaborators, which include cancer immunologists **Mark P. Rubinstein, Ph.D.**, and **Chrystal M. Paulos, Ph.D.**, thoracic surgeon **Chadrick E. Denlinger, M.D.**, and bioinformatician **Jeff Hammerbacher**, are currently working on two related strategies that lie at the interface of immunotherapy and genetics.

The first and most immediate goal of the team is to create a tumor-infiltrating T lymphocyte (TIL) product for lung cancer that they hope to bring to clinical trial at MUSC Hollings Cancer Center. In TIL therapy, a type of adoptive cell transfer (ACT) therapy, T cells

are harvested from a patient's tumor, expanded outside the body and reinfused into the patient to enhance the immune response against cancer. The availability of an FDA-registered clean room suite in the MUSC Center for Cellular Therapy, where cells harvested from the patient can be expanded and manipulated safely before reinfusion, makes a trial of TIL therapy feasible at Hollings.

“The Center for Cellular Therapy is one of the few GMP- and FACT-accredited facilities in the country that is able to move a trial such as that for TILs to clinic with efficiency and safety,” says MUSC Health transplant surgeon **Satish N. Nadig, M.D., Ph.D.**, medical director of the center. **Shikhar Mehrotra, Ph.D.**, is the center's co-scientific director for oncology and immunotherapy programs.

The second goal of the team is to identify neoantigens that are relevant to lung cancer and can be used to fine tune their TIL product and, in the longer term, to create custom personalized vaccines that can be given in combination with other immunotherapies to improve outcomes for patients with lung cancer.

## Developing TIL therapy for lung cancer

Approval of chimeric antigen receptor (CAR) therapy, a type of ACT, by the FDA in August 2017 for pediatric acute lymphoblastic leukemia (see story on page 8) has helped ignite enthusiasm about ACT's clinical potential. While the FDA-approved CARs are

genetically engineered to target CD19, which is expressed on both healthy and cancerous B cells, TILs are naturally occurring and target the tumor only. “TILs are already within you, and that is one reason they are so good,” says Paulos, whose laboratory is growing TILs from patients with lung cancer and other solid tumors, including melanoma and breast cancer. “They are natural and fine-tuned to elicit a specific immune response against a mutated tumor.”

Steven A. Rosenberg, M.D., Ph.D., at the National Cancer Institute and others have achieved impressive clinical responses in a substantial subset of patients with metastatic melanoma. A few patients have had such long-lasting responses that they are likely cured. In a pooled analysis of recent clinical trial protocols, the overall response rates and complete response rates for metastatic melanoma were around 50 percent and 20 percent, respectively, with 95 percent of those with complete responses remaining disease free for at least five years.<sup>1</sup>

In 2017, Wrangle, Rubinstein and Paulos traveled to M.D. Anderson, a leader in TIL therapy, to learn its protocols for expansion and reinfusion of TILs. They then sought out Denlinger, who has been providing them with lung tumor tissue removed during surgery. “We are taking lung cancer specimens and preserving them fresh and sending them straight to the laboratory with the intent of growing out the T cells,” says Denlinger. They have now isolated TILs from about two dozen tumors and have successfully navigated the methodological and logistical challenges of expanding them in the laboratory. Although their initial focus has been on lung tumors, they are also working on isolating and expanding TILs from metastatic tumors in the liver, provided by Nadig, and in the brain, provided by resident neurosurgeon **Fraser C. Henderson Jr., M.D.**, via the Hollings Cancer Center Tissue Biorepository.

The next steps are to implement the protocols optimized in the laboratory at the Center for Cellular Therapy, to complete an investigational new drug application and to find funding for the trial.

### The role of neoantigens

Realizing that alternative approaches are likely to be necessary, the MUSC team is also working at the interface of immunotherapy and genetics to help fine tune TIL therapy and to develop custom, personalized vaccines that could one day be administered in combination regimens to expand the number of people with lung cancer who benefit. Next-generation genomic sequencing of both healthy and cancerous tissues has enabled identification of cancer-associated mutations known as *neoantigens*. Because these neoantigens result from mutations that are unique to cancer cells, immunotherapies

targeting them should not in principle damage normal tissue. Cancer, which develops due to mutations, could in fact be made recognizable — and precisely targetable — by the immune system as a result of some of those very mutations. Ironically, the mutations that define cancer and make it such a fearsome foe could become its Achilles heel.

### Fine-tuning TIL therapy

TILs have historically shown efficacy in metastatic melanoma, a cancer with a high mutational load and one that has responded well to a variety of immune-based therapies. Because lung cancer has almost as high a mutational load as melanoma and has recently been shown to respond to checkpoint therapy, the MUSC team thinks that TIL therapy could also offer benefit to patients with lung cancer.

Relying on the Center for Genomic Medicine directed by **Stephen P. Ethier, Ph.D.**, the MUSC team is having each of the tumor samples sequenced so that neoantigens can be identified. Sophisticated machine learning and other advances in bioinformatics have enabled predictive algorithms to be developed to identify which of these neoantigens are most likely to trigger an immune response. The MUSC team is using a predictive algorithm that is being optimized by Hammerbacher, who holds faculty positions at both MUSC and Mount Sinai and was formerly a data manager for Facebook, to identify the neoantigens most likely to provoke an anti-cancer immune response.

“Out of the tens of thousands of mutations a tumor may harbor, maybe only a handful interact with the immune system,” says Wrangle. “The purpose of the algorithm is to separate the wheat from the chaff.”

It is hoped that one day the team could use that information to identify TILs that target the most immunoreactive neoantigens. “When we identify a neoantigen, we can match a certain T cell with a certain antigen and that becomes the finely tuned TIL product that we give back to the patient,” says Denlinger.

However, it is also possible that the appropriate T cells could be found in the blood, pointing the way forward for a much less logistically challenging form of ACT — one which requires a simple blood draw instead of surgery to obtain tumor tissue.

### Customizing vaccines

An alternative strategy would be to develop customized vaccines tailored to the neoantigenic profile of a patient’s cancer. Such a vaccine could consist of a mutated protein or peptide (i.e., the neoantigen) administered with an adjuvant to optimize the immune





response. “If less than one percent of T cells in the blood of a patient are tumor-reactive, and we can use a vaccine to activate and expand these cells to over 20 to 30 percent in circulation, that might have dramatic therapeutic value, particularly when such a vaccine is combined with other newer therapies,” says Rubinstein.

Many pharmaceutical companies — both long-established ones and startups — are conducting clinical trials of these customized vaccines, both as monotherapies and in combination with other treatment approaches such as checkpoint modulators, radiotherapy and chemotherapy. These trials are in their infancy, with very little actual clinical data reported. The very nature of these vaccines challenges the usual pathway to regulatory approval. Because they are customized to the patient, there is no “one” product that can be tested in clinical trial. The efficacy of the treatment may need to be judged in part on the sensitivity and accuracy of the predictive algorithm itself.

“If you’ve got a typical FDA-approved drug, it’s been tested in a thousand people and has been given in exactly the same manner to everyone,” says Wrangle. “With a custom vaccine, if it is based on a predictive algorithm, that algorithm is the thing that is critical for the ultimate efficacy of the therapy.”

Wrangle is confident in the predictive algorithm being optimized by Hammerbacher and in the ability of his team to compete in this new pharmaceutical space.

“How will we compete with companies worth hundreds of millions of dollars?” asks Wrangle. “It’s through innovation in terms of the vaccination strategy. That’s where basic science is indispensable. If existing groups had it right already, we would have heard about it.”

The MUSC team is working hard to get it right. They are seeking answers to fundamental questions, such as the number of neoantigens needed for an effective vaccine and the proper adjuvants to use with it to increase immune response, and are refining the manufacturing process for proteins and the software they will need to interpret their results.

“We don’t think custom vaccines will do it by themselves,” says Wrangle. “So it is important to do preclinical work to understand how you fully engender or accomplish an effective immune response and how we can best optimize our vaccine strategies.”

#### References

- 1 Rosenberg SA, et al. *Clin Cancer Res*. 2011;17:4550–4557.
- 2 Hinrichs CS and Rosenberg SA. *Immunol Rev*. 2014 Jan;257(1): 56-71.



Thoracic surgeon Dr. Chadrick E. Denlinger. Photograph by Emma Vought

# Same Gain, Less Pain

Video-assisted thoracoscopic surgery achieves similar outcomes to thoracotomy in stage 1 non-small cell lung cancer with less pain, fewer complications and quicker recovery

BY KIMBERLY MCGHEE

For stage 1 nonsmall cell lung cancer (NSCLC), lobectomy is the preferred treatment with optimal oncologic outcomes for most patients.<sup>1,2</sup> Five-year survival rates range from 45 to 65 percent in those undergoing a lobectomy,<sup>2</sup> but only about six percent in those who go untreated.<sup>3</sup>

Traditionally, lobectomy has been performed with a thoracotomy, which requires a large incision in the chest and the use of a rib spreader to gain visual and physical access to the chest cavity. The use of a rib spreader can result in rib fractures, which are very painful and require several weeks to heal, delaying recovery.

When performed by an appropriately trained surgeon in a high-volume center, video-assisted thoracoscopic surgery (VATS) achieves oncologic outcomes as good as those obtained with thoracotomy in patients with stage 1 NSCLC,<sup>4</sup> with decreased pain, reduced hospital length of stay, more rapid return to function and fewer complications.<sup>5</sup> For patients with stage 1 NSCLC who have no anatomic or surgical contraindications, the National Comprehensive Cancer Network guidelines recommend VATS as standard of care.<sup>5</sup>

“More than 95 percent of our surgical cases for stage 1 lung cancers are performed with VATS,” says MUSC Health thoracic surgeon **Chadrick E. Denlinger, M.D.** “That is far higher than at most U.S. centers that treat lung cancer and on par with most major medical centers across the country.”

VATS uses an endoscopic camera inserted through a 2-cm “port” to visualize the surgical field and special instruments to perform the lobectomy through one or two additional 5-8-cm ports. Surgeons watch a monitor displaying the endoscopic images to guide them as they perform surgery through the small ports. Because a rib spreader is not required and incision sizes are much smaller, patients experience less pain and can resume normal activities much sooner than after a thoracotomy.

“Patients recognize that the incisions are much smaller and the postoperative pain is significantly less,” says Denlinger. “A fair amount of the pain from thoracic surgery comes from spreading the ribs, which we don’t do with VATS.”

The ideal patient for VATS has a smaller, more peripheral tumor. Because VATS causes less surgical trauma, it can be used in patients with NSCLC older than 65 who might not otherwise qualify for surgery, with improved overall and lung cancer-specific survival, decreased intensive care admissions and shorter hospital stays.<sup>6</sup> However, patients with more central tumors and those who require reconstruction of the bronchus or pulmonary artery are better served by a thoracotomy.

Whether performed by thoracotomy or VATS, it is crucial that the surgeon harvest sufficient lymph nodes from the affected lung and from the area between the lungs for pathology. Failure to obtain sufficient lymph nodes for analysis can mean missed opportunities for upstaging (e.g., from clinical stage 1 to pathological stage 2 or 3) that could affect treatment, leading to poorer outcomes. Questions about whether VATS could obtain sufficient lymph nodes for proper pathological staging were put to rest by a retrospective study of 4,215 patients with NSCLC from the NCCN database, which showed that most patients undergoing either procedure had sufficient (three or more) lymph node stations harvested for pathology.<sup>7</sup>

Because they experience less surgical trauma, patients who undergo VATS may be able to better tolerate adjuvant chemotherapy. A recent study reconfirmed that VATS patients experienced significantly less morbidity after surgery than those undergoing thoracotomy and showed that they were more likely to be able to complete a full regimen of chemotherapy without the need for dose adjustments, though differences did not meet statistical significance.<sup>8</sup>

The bottom line, according to Denlinger, is that VATS resection is the standard of care for stage 1 NSCLC. “If patients are receiving something other than that for routine cancers, it is probably suboptimal,” says Denlinger. “The recovery is slower and return to work is delayed.”



**To watch a video interview with Dr. Chadrick E. Denlinger about VATS, visit the MUSC Health Medical Video Center ([MUSChealth.org/medical-video](https://www.musc.edu/health/medical-video)) and choose “Oncology” from the dropdown list of specialties.**

#### References

- 1 Ginsberg RJ, Rubinstein LV. Lung Cancer Study Group. *Ann Thorac Surg*. 1995; 60:615-622.
- 2 Ettinger DS, et al. *J Natl Compr Canc Netw*. 2010; 8:740-801.
- 3 Raz DJ, et al. *Chest* 2007;132:193-199.
- 4 Berry MF, et al. *Ann Thorac Surg*. 2014 Jul;98(1):197-202.
- 5 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 7.2015. Available at [NCCN.org](https://www.nccn.org).
- 6 Smith CB. *Seminars in Thoracic and Cardiovascular Surgery Summer 2017*; 29(2):223-230.
- 7 D’Amico TA, et al. *Ann Thorac Surg*. 2011 Jul;92(1):226-31; discussion 231-232.
- 8 Tane S, et al. *Asian Cardiovascular & Thoracic Annals* 2015; 23(8):950-957.

# A Question of Timing

Rethinking treatment sequencing in metastatic prostate cancer





SUBJECT MATTER EXPERTS: THOMAS E. KEANE, M.D.;  
MICHAEL B. LILLY, M.D.; AND THEODORE S. GOURDIN, M.D.

BY KIMBERLY MCGHEE AND RACHEL WEBER

ILLUSTRATION BY EMMA VOUGHT

Date of Release:  
November 5, 2017  
Date of Expiration:  
November 5, 2019

You can complete the steps necessary to receive your *AMA PRA Category 1 Credit(s)*<sup>™</sup> by visiting [MUSChealth.org/progressnotescme](http://MUSChealth.org/progressnotescme).

#### CREDIT DESIGNATION:

**Physicians:** The Medical University of South Carolina designates this enduring material for a maximum of .50 *AMA PRA Category 1 Credits*<sup>™</sup>. Physicians should claim only credit commensurate with the extent of their participation in the activity.

**Nursing Credit:** Most states accept CMEs that apply to a specific nursing specialty as nursing continuing education. Please check with your respective State Board of Nursing to ascertain the equivalent number of contact hours offered for .50 *AMA PRA Category 1 Credits*<sup>™</sup>.

**All Participants:** The Medical University of South Carolina will award .05 CEU (.50 contact hour) for reading the article and passing the post-test. (1 contact hour equals .1 CEU)

The Medical University of South Carolina is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

**Disclosure Statement:** In accordance with the ACCME Essentials and Standards, anyone involved in planning or presenting this educational activity is required to disclose any relevant financial relationships with commercial interests in the healthcare industry. Authors who incorporate information about off-label or investigational use of drugs or devices will be asked to disclose that information at the beginning of the article.

Dr. Keane serves on advisory committees for Astellas, Janssen, Ferring, Churchill and Bayer. Dr. Gourdin has an immediate family member with a research grant from Ferring. Dr. Lilly, Kimberly McGhee and Rachel Weber have no relevant financial relationships to disclose.

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

- Summarize recent findings of the LATITUDE and STAMPEDE arm G trials and discuss their implications for the sequencing of treatment
- Recognize that genomic profiling will likely have a growing role to play in the selection and sequencing of treatment in prostate cancer
- Explain why closer collaboration between urologists and medical oncologists is needed to ensure that care can nimbly adapt to evolving therapies

The American Cancer Society estimates that one in seven men will be diagnosed with prostate cancer, the most common noncutaneous cancer in men. For men with metastatic disease, the five-year survival rate is just 29 percent. The treatment for metastatic prostate cancer remained unchanged for almost six decades, but over the past 15 years new therapies have been approved that, when used together, can extend the life of men with the disease, though they do not provide a cure.

#### Overview of current treatments

Since 1941, androgen deprivation therapy (ADT) has been the mainstay of treatment for metastatic prostate cancer. Androgens such as testosterone stimulate prostate cancer cells to grow and metastasize. Reducing testosterone levels to 20 ng/dL has been associated with improved outcomes.<sup>1-4</sup>

Most clinicians rely on gonadotropin-releasing hormone (GnRH) agonists to achieve castrate levels of testosterone, the goal of ADT, but these have the serious drawback of initially causing a surge in testosterone levels and typically take four weeks to achieve castration. GnRH antagonists achieve castrate levels of testosterone in 72 hours without such a surge and were shown to be noninferior to agonists in the CS21 trial, with superior results in patients with higher prostate-specific antigens (PSAs) and more metastatic disease.<sup>5</sup> Some evidence suggests they may also be associated with less cardiovascular morbidity than agonists.<sup>6</sup> A head-to-head clinical trial of these agents is needed to determine which provides superior androgen deprivation in which patients.

Unfortunately, most patients with metastatic prostate cancer who initially respond to ADT will develop resistance on average 18 to 24 months after beginning treatment and then are considered to have metastatic castration-resistant prostate cancer (mCRPC). Treatment options for these patients were very limited until 2004, when the chemotherapy agent docetaxel was shown to provide an increase in quality of life and overall survival.<sup>7,8</sup> In 2010, the first immunotherapeutic agent, sipuleucel-T (Provenge, Dendreon, Seattle, WA), an individualized treatment that leads white blood cells to attack prostate cancer cells, was approved by the FDA. Approval for abiraterone, a steroid that inhibits androgen synthesis, and enzalutamide, a nonsteroidal antiandrogen, followed in 2011 and 2012, respectively. Both abiraterone and enzalutamide are considered second-line ADT,

targeting the production of testosterone not only by the testes (the goal of first-line ADT) but also by the adrenal gland and the tumor itself. Thus, they still have a role to play after the development of resistance to first-line ADT. Lastly, radium-223, approved in 2013, emits low levels of radiation in areas of bone metastasis and can be used for palliation.

The standard practice has been for urologists to treat early-stage disease with ADT and to refer patients once they develop mCRPC to medical oncologists for chemotherapy.

### Efficacy of docetaxel and abiraterone in castration-sensitive disease

Therapies currently used to prolong survival in patients with mCRPC were recently shown to do so as well in patients with metastatic castration-sensitive prostate cancer (mCSPC). In 2014, two of three large randomized phase 3 trials (CHAARTED, STAMPEDE, GETUG-AFU15) showed marked improvement in four-year survival in men with mCSPC who received both docetaxel and ADT.<sup>9-11</sup> In 2017, the LATITUDE<sup>12</sup> and STAMPEDE Arm G<sup>13</sup> trials established a survival benefit for abiraterone plus ADT vs. ADT alone in the same patient population.

The docetaxel findings have already changed care, and the abiraterone findings are poised to do so. Because docetaxel is now standard of care in patients with high-volume mCSPC (four or more bone metastases or metastases in the lung or liver), urologists and medical oncologists are collaborating more closely to ensure comprehensive care for these patients. Large urology practices have begun to incorporate medical oncologists, and urologists have begun participating in multidisciplinary clinics. The recent abiraterone findings have raised further questions about optimal sequencing and the benefits, as well as possible drawbacks, of using second-line androgen therapy in castration-sensitive disease.

### Optimizing treatment sequence

Although docetaxel and abiraterone provide a clear survival benefit in both mCSPC and mCRPC patients, it is not known how best to sequence these treatments. Patient preference, finances, and fitness will certainly affect choice of therapy. Docetaxel is given intravenously for six doses, whereas abiraterone is taken orally and has fewer side effects but must be taken long-term. There may also be cost differences. A recent article estimated the cost for each life year gained was \$26,330 for generic docetaxel and \$194,087 for abiraterone.<sup>14</sup>

“Medical oncologists and urologists are faced with a question — Are you going to give therapy in addition to medical castration to

newly diagnosed patients with high-volume disease and, if so, in what order?” explains MUSC Health medical oncologist **Theodore S. Gourdin, M.D.**

To help answer those questions, Gourdin is conducting a phase 2 trial in men with newly diagnosed untreated metastatic prostate cancer (NCT03069937) to examine whether giving docetaxel before medical castration might enhance outcomes. Preclinical data in breast cancer, another hormonally driven cancer, show improved outcomes when chemotherapy is separated from manipulation of the hormonal axis. Patients enrolled in the trial will be given six cycles of docetaxel, the first four as monotherapy and the final two in combination with degarelix, an ADT agent, which will then be continued. The study examines whether an undetectable PSA (<.02 ng/dL), which has been correlated with better overall survival, can be obtained within ten months of treatment initiation. Seven patients have already been enrolled at MUSC Hollings Cancer Center, the lead site for the study that will eventually enroll 50 patients. Other sites include the Ralph H. Johnson VA Medical Center and the University of Maryland.

If the findings of the trial suggest that providing docetaxel before ADT improves outcomes, Gourdin would like to organize a phase 3 trial that would likely also be designed to answer questions about sequencing with abiraterone. “We would like to ask whether, in the right patient, we would be able to improve outcomes by giving chemotherapy before medical castration. What about abiraterone and chemotherapy? Do we give them all early on?” asks Gourdin. “We don’t know yet and the trial would help to shed light on these questions.”

### Is there a downside to changing the sequence of treatments?

Providing treatment once reserved for mCRPC to patients with mCSPC also raises questions about whether these treatments will still work — or work as well — when the patient eventually develops castration-resistant disease.

If second-line ADT with abiraterone or enzalutamide, once reserved for mCRPC, is used earlier in mCSPC, what options remain for patients when they become resistant, wonders **Thomas E. Keane, M.D.**, chair of the Department of Urology at MUSC and co-investigator on this trial.

“Docetaxel, which can provide a 17-month survival advantage in non-castration-resistant prostate cancer patients, offers only a three-month benefit in those with mCSPC whose cancer progresses despite second-line ADT,” explains Keane. “Could it be that multiple-agent treatment should be reserved for patients with high-volume disease?”

Answering such questions will be critical in determining the proper sequencing of newly available treatments for metastatic prostate cancer. Ongoing trials, including STAMPEDE Arm J, PEACE-1, ARCHES and ENZA-MET, are currently assessing the efficacy of ADT, docetaxel, and a second-line ADT agent vs. either ADT and docetaxel or a second-line ADT agent alone.

### Using genomics to inform treatment selection

Genomic profiling will likely play a role in deciding which patients will benefit from approved and investigational therapies. Circulating tumor DNA (liquid biopsy) is an investigational technology that promises to facilitate genomic profiling in prostate cancer.<sup>15</sup> Since the genetic landscape in prostate cancer patients varies greatly from patient to patient, and across time, data gleaned from an old tumor biopsy may have only limited relevance to metastatic disease. “Prostatectomy or the original biopsy tissue could have been obtained 20 years ago, and the genomic landscape may have changed markedly in the following years,” says **Michael B. Lilly, M.D.**, associate director of translational research at MUSC Hollings Cancer Center. “It’s a very dynamic system. What you would find from the original sample may no longer be relevant.” Furthermore, there can be a great deal of genetic heterogeneity in a single tumor or among several tumors. For these reasons, liquid biopsies based on circulating tumor DNA in the bloodstream could provide relevant, real-time data about the genetic makeup of metastatic prostate cancer and do so in a cheaper, less invasive manner.

One example of the importance of genomic profiling to treatment selection is the recent finding that some patients with mCRPC have mutations associated with faulty DNA repair (e.g., BRCA1, BRCA2, ATM).<sup>16</sup> Studies show that patients with such mutations could respond better to platinum chemotherapy<sup>17</sup> or PARP inhibitors such as olaparib.<sup>18</sup> Other patients, who have a hypermutator phenotype, may respond to checkpoint antibodies.<sup>19</sup>

“Circulating tumor DNA analysis might tell us ‘Give this’ or ‘Don’t give that’ or ‘Is the patient responding?’” says Lilly. “This technology could be a great help in clinical decision making.”

### Rethinking prostate cancer vaccines

On September 15, 2017, the Data Monitoring Committee for the multinational phase 3 PROSPECT trial of the PROSTVAC V/F vaccine announced that the trial was being closed because the vaccine had failed to show efficacy in men with mCRPC. PROSTVAC, the brand name for rilimogene, is a PSA-targeted immunotherapy designed to stimulate the body’s immune response. James L. Gulley,

M.D., Ph.D., chief of the genitourinary malignancies branch of the National Cancer Institute, who has been involved in the clinical development of the vaccine, expressed his disappointment at this failure but also his determination to try combination strategies, such as the PROSTVAC vaccine plus checkpoint inhibitors. A number of phase 2 trials using that strategy are underway.

Timing of therapy could again play a role. Men in the PROSPECT trial had advanced, metastatic disease and had received years of ADT that could have impaired their immune systems. Could better results be obtained if the vaccine were given in earlier-stage disease? Lilly is the principal investigator of a phase 2 trial of PROSTVAC (NCT02772562) in men at high risk for recurrence after radical prostatectomy. The trial has already enrolled 11 of the targeted 40 patients.

“It makes sense to use a vaccine as early as possible,” says Lilly. “The patients in the PROSPECT trial had very advanced cancer. This will be a more optimal trial in people who have minimal disease right after surgery and are not weakened by years of hormone suppression.”

Treatment for metastatic prostate cancer, which had been stagnant for 60 years, has quickly evolved in the past decade and a half. New agents have been introduced, some of which have shown efficacy in both castration-sensitive and castration-resistant metastatic disease. As clinicians learn how best to sequence these treatments and as more genetic biomarkers are discovered to aid in treatment selection, patients with metastatic prostate cancer may begin to see ever more meaningful survival benefit.

### References

- 1 Klotz L, et al. *J Clin Urol*. 2015;33(10):1151-1156.
- 2 Morote J, et al. *J Urol*. 2007;178:1290-1295.
- 3 Perachino M, et al. *BJU Int*. 2010;105:648-645.
- 4 Bertaglia V, et al. *Clin Genitourin Cancer*. 2013;11:325-330.
- 5 Crawford ED, et al. *J Urol*. 2011 Sep;186(3):889-897.
- 6 Greiman AK, Keane TE. *Curr Urol Rep*. 2017 Jun;18(6):41.
- 7 Tannock IF, et al. *N Engl J Med*. 2004 Oct 7;351(15):1502-1512.
- 8 Petrylak DP, et al. *N Engl J Med*. 2004 Oct 7;351(15):1513-1520.
- 9 Sweeney CJ, et al. *N Engl J Med* 2015;373:737-746.
- 10 James ND, et al. *Lancet* 2016;387:1163-1177.
- 11 Gravis G, et al. *Lancet Oncol* 2013;14:149-158.
- 12 Fizazi K, et al. *N Engl J Med* 2017;377:352-360.
- 13 James ND, et al. *N Engl J Med* 2017;377:338-351.
- 14 Guirgis HM. *J Community Support Oncol*. 2015 Oct;13(10):362-366.
- 15 Maas M, et al. *Asian J Androl*. 2017 Aug 22. doi: 10.4103/aja.aja\_29\_17. [Epub]
- 16 Pritchard CC, et al. *N Engl J Med*. 2016 Nov 3;375(18):1804-1805.
- 17 Cheng HH, et al. *Eur Urol*. 2016 Jun;69(6):992-995.
- 18 Mateo J, et al. *N Engl J Med*. 2015 Oct 29;373(18):1697-1708.
- 19 Topley BA, et al. *Expert Rev Clin Pharmacol*. 2017 Aug;10(8):889-898.

# A Conversation About Palliative Care



Dr. John H. Gibson

The palliative care program at MUSC Health has expanded rapidly since **Patrick J. Coyne, MSN**, began as director in July 2015, growing from two physicians and a nurse practitioner to a 16-person interdisciplinary team. Coyne joined MUSC Health from Virginia Commonwealth University, where he ran one of the first palliative care programs in the country for 24 years.

MUSC Health's program now offers palliative care services to both adults and children. Adult services are provided through both an inpatient consult service and an outpatient clinic at MUSC Hollings Cancer Center.

A palliative care fellowship program has been developed to help meet the rapidly growing demand for palliative care providers. In addition, Coyne is training care givers throughout rural South Carolina in palliative

care, leading two-day CME-eligible courses at South Carolina Area Health Education Consortium sites.

*Progressnotes* sat down with three members of the expanded palliative care team — physicians **John H. Gibson, M.D.**, and **Jennifer D. Dulin, M.D.**, and social worker **Kate Rogers, MSW**.

**PN: What do you find most satisfying about working in palliative care?**

**JD:** That it is about the patient, the person. Palliative care does not isolate disease but focuses on the person. Too often in medicine we get fixated on labs, tests, medicines — what can be done — and we forget the patient who is sitting right in front of us. Palliative care brings the individual back into focus. Being a physician is incredibly humbling; being a palliative care physician is

even more so. It's amazing that people invite me in and let me take care of them at such a vulnerable time. There is no higher honor.

**KR:** I think what I find most satisfying is the way that patients open up to our providers and team. It's satisfying — and integral to the work we do — to be given the time to sit down and talk with patients and to meet with families.

**JG:** I value most the integrated nature of the care. This system provides the resources the patients and families need.

**JD:** Every morning we round as a team. This includes clinicians — physicians, fellows and nurse practitioners — as well as social workers, chaplains, volunteers and our volunteer coordinator. Dietary joins us on Mondays and Thursdays, an occupational therapist is available in clinic on Tuesdays and speech therapy is very supportive. Not only do we round with the team, but the whole team works with the patient and family. Our interdisciplinary team allows us to focus on the whole person — extending beyond the individual patient and including the family. Palliative care takes into consideration everything that's going on with the patient and family and strives to provide them with the care and resources they need.

**PN: What are the goals of palliative care?**

**JG:** The outpatient clinic is designed for people who are still pursuing active treatment. It's symptom managing and counseling as they go through the stresses of treatment. We also help them plan for what happens if things don't go the way we hoped.



**KR:** If a patient is hospitalized in a pain crisis, it can be difficult for him or her to get back to therapy. Palliative care allows the patient to get back to therapy and to have better outcomes than he or she would have had otherwise.

**JD:** We help manage symptoms as well as help the patients identify goals of care. We "hope for the best, but plan for the rest." Sometimes we alleviate burdens by building relationships with patients, by showing them that they can be less symptomatic, tolerate things and enjoy life. When they are ready, we talk about what they want. Patients sometimes tell us when things have become too burdensome. It's hard to have those conversations with family members or their treating physicians. They don't want to look like they are giving up.

**PN: How does palliative care benefit families as well as patients?**

**KR:** We focus not just on the patient but also on the family, whatever the patient defines it to be, as our unit of care. Bringing in the additional disciplines is how we provide that support and we try to gauge the family at every stage of the process.

**JD:** We provide support and educational resources to the family. Some patients are not able to engage with us because of the advanced nature of their illness or medical status. The family looks to us as a source of information, and we in turn rely on the family as the expert on the patient and his/her desires. We recognize that what the patient is going through is affecting the family, and that what the family is going through is in turn affecting the patient. Including the family helps us provide optimal care.

*For more information about MUSC's Palliative Care Program, call 792-6062.*

## Pain Control Almost Too Good to Believe

Scrambler therapy (Calmare™ Therapeutics, Fairfield, CT), now available at MUSC Hollings Cancer Center, successfully relieves pain in four of five patients with chemotherapy-induced or diabetic neuropathic pain. Success is defined as a reduction of 30 to 50 percent in pain levels, but Hollings has seen pain reduction rates well above 50 percent in many patients. The therapy is also effective for pain due to failed back surgery or postherpetic neuralgia.

"The device is thought to work by perceiving a nerve firing and then firing against it to block the nerve," says **Patrick J. Coyne, MSN**, director of palliative care at MUSC Health and one of the first to conduct a pilot trial of the new therapy.

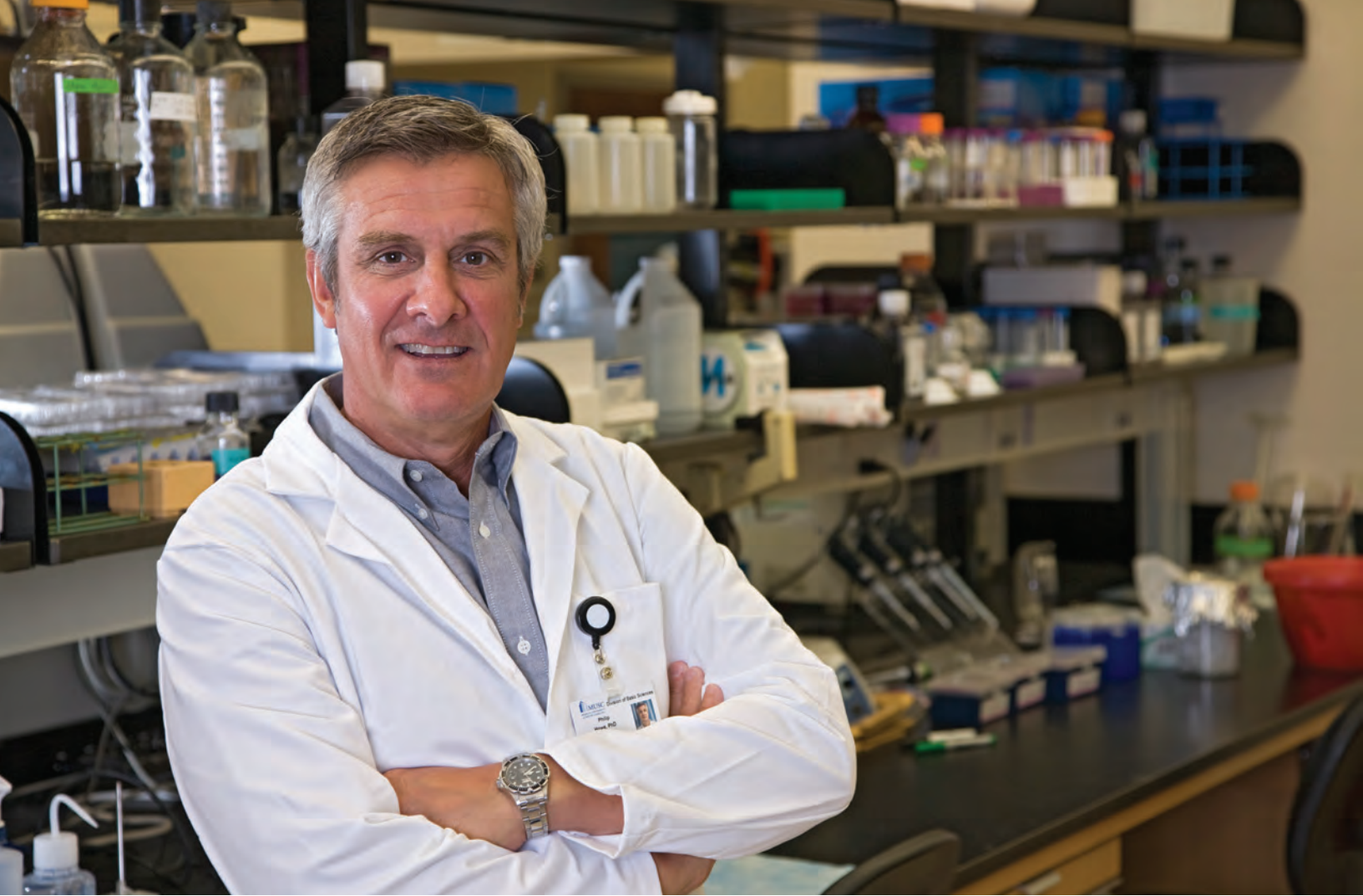
When first approached about the device, Coyne was skeptical of the pain reduction claims made by the manufacturer. He and a colleague set out to test, and likely disprove, those claims in a pilot study. "But damned if the device didn't work," says Coyne. Skeptical of the results of that trial, physicians at Mayo Clinic ran their own study, confirming the device's efficacy. Mayo Clinic now has its own Scrambler clinic. The Hollings Scrambler clinic is the only one in South Carolina or surrounding states.

For Scrambler therapy, electrodes deliver electric currents to affected areas for 30 to 45 minutes per day for ten days straight, excluding weekends. Patients can return for a three-day booster treatment if pain recurs. Scrambler therapy is approved by both Medicare and Medicaid.

"It has turned so many lives around," says **Julie Watson**, the palliative care RN coordinator who runs the Scrambler clinic at Hollings. "Some patients have such severe pain they can't even be touched or do certain activities. Changes after treatment may include being able to smile without pain, play on the floor with their grandkids, walk the mall, drive their car, take a hike or even go dancing without burning pain in their feet." To meet the high demand for the new therapy in the region, Hollings plans to acquire a second machine and to hire additional clinic staff in coming months.



The Calmare® device (Calmare™ Therapeutics, Fairfield, CT) is used for Scrambler therapy.



Dr. Philip Howe. Photograph by Julia Lynn

# The RNA Family

A group of experts has formed at MUSC to study the roles of different RNAs in cancer

BY SVER AUNE

New research is finding that different types of ribonucleic acids (RNAs) that do not encode protein are key players in cancer.<sup>1</sup> One specialized RNA research group has coalesced at MUSC and is finding that these so-called regulatory RNAs can keep cancer in check or promote its development, depending on the presence of other pro-tumor molecules.

Before the human genome project, geneticists predicted that humans would have at least 100,000 different messenger RNAs, the type that encode proteins, within their DNA. There would have to be this many, they reasoned, to account for all the genetic variability observed in humans. But in 2012, the human genome project revealed that the number of protein-coding RNAs are less than a third of that predicted. What then could account for all the differences in human health and disease? The genome project revealed that non-coding RNAs, previously thought to be mere cellular junk, provide extra layers of regulation in our genes.

**Philip H. Howe, Ph.D.**, the Hans & Helen Koebig Endowed Chair in Oncology and chair of the MUSC Department of Biochemistry & Molecular Biology, is an expert on RNA and the inflammatory molecule TGF-beta. Howe studies the functions of long non-coding RNAs (lncRNA) in cancer development. He and cell cycle and microRNA expert **J. Alan Diehl, Ph.D.**, SmartState® Endowed Chair in Lipidomics & Pathobiology and associate director of basic sciences at the MUSC Hollings Cancer Center, recently embarked on a project involving both of their RNA types of interest. In their work, published in *Nature Cell Biology* in September 2017, they deciphered an interaction between different types of RNA that enables cancer cells to encourage their own growth.<sup>2</sup>

Howe and Diehl pondered a natural phenomenon during which DNA is converted to lncRNA instead of its normal protein-coding form. They found that TGF-beta released by cancer cells causes normal cells to make more lncRNA instead of the protein-coding form. When this happens, the lncRNA becomes a pro-tumor molecule. It soaks up a microRNA that usually discourages cancer growth, allowing normal epithelial cells to take on the features of cancer cells. The researchers confirmed that this process contributes to breast and lung cancer, thereby providing a new understanding of how cancer cells rid normal cells of healthy RNA to make way for RNA that encourages tumor growth.

There are dozens of different types of RNAs, each with distinct regulatory functions, that tweak the concentration of messenger RNAs through degradation, gene silencing or interfering with transcription.<sup>3</sup> Howe recently recruited other young RNA experts to the department to reach the larger goal of building a team to understand the roles of

these diverse RNAs in cancer. Among them are **Vamsi Gangaraju, Ph.D.**, assistant professor, trained at Yale University, who studies how heat shock proteins and piwi-piRNA relate, and **Viswamathan Palanisamy, Ph.D.**, associate professor, trained at the National Institutes of Dental and Craniofacial Research, who studies the roles of various RNA-binding proteins in oral cancer progression. Howe also recently brought in **Je-Hyun Yoon, Ph.D.**, assistant professor, trained at the National Institute on Aging, to study the function of RNA-binding proteins. The group also started a collaboration with oral cancer researcher **Andrew Jakymiw, Ph.D.**, assistant professor in the MUSC College of Dental Medicine, who has R21 funding to build delivery systems for silencer RNAs targeted to head and neck tumors.

**“Metastasis accounts for over 90 percent of cancer-related mortalities, yet it is probably the least understood process of cancer progression. To better understand it, we need to find each RNA’s functional significance and mechanism of action.”**  
—**Dr. Philip Howe**

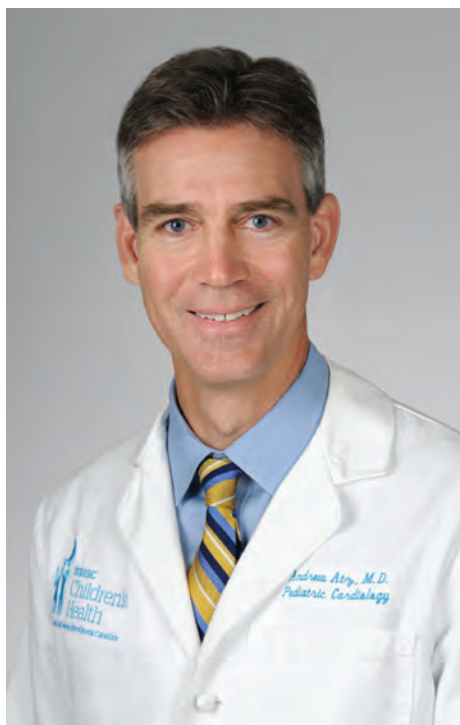
This group of investigators has been working collaboratively for over two years to acquire the technology to discover and characterize these RNA species and their binding partners. This research effort has been supported by a pilot award from Hollings to foster team science, and in the upcoming year the group plans to submit a program project grant (PPG) to the National Cancer Institute. Their focus is to determine how these RNAs and their binding partners regulate the late stages of tumor progression, namely metastasis. “Metastasis, or the spread of cancer from a primary site to other tissues and organs, accounts for over 90 percent of cancer-related mortalities, yet it is probably the least understood process of cancer progression,” says Howe. “To better understand it, we need to find each RNA’s functional significance and mechanism of action. Then, long term, we need to consider whether these could be therapeutic targets.”

#### References

- 1 Batista, PJ, et al. *Cell*. 2013;152:1298–1307.
- 2 Grelet S, et al. *Nat Cell Biol*. 2017;19(9):1105-15. doi: 10.1038/ncb3595.
- 3 Morris KV & Mattick JS. *Nat Rev Genetics*. 2014;15:423-37. doi: 10.1038/nrg3722.

# MUSC Appoints New Chair of Pediatrics

Photograph by Anne Thompson



**Dr. Andrew M. Atz**

“I say the word team a lot because I really do believe in it,” says **Andrew M. Atz, M.D.**, who was appointed chair of the Department of Pediatrics in May 2017, having served for a year as interim chair.

Atz joined the department in 1998 after completing residency and fellowship training at Johns Hopkins University, Harvard Medical School and the Children’s Hospital Boston. He has served as director of pediatric intensive care, vice chair for clinical research and, most recently, as chief of pediatric cardiology.

During his tenure as chief, pediatric cardiology rose in the *U.S. News & Reports World Report* rankings, a success that Atz attributes to teamwork. “In the most recent rankings,

we were number 11 in the country, the highest we have ever achieved, which I attribute to collaborative teamwork,” says Atz. Five other pediatric specialties — nephrology, cancer, urology, gastroenterology & GI surgery and neurology & neurosurgery— also ranked in the top 50.

Atz believes that focus on teamwork will serve him well as chair of a department as diverse as pediatrics, with at least 17 different divisions and 25 specific programs. “It is important that all members of the team realize that they can perform their clinical and research missions and that each of those missions is just as important a piece in the overall puzzle,” says Atz. He credits the collaborative atmosphere at MUSC Children’s Health for the high number of residents who decide to remain after they complete their training.

Atz is assuming the helm as two new children’s health facilities approach completion. The MUSC Shawn Jenkins Children’s Hospital, an inpatient facility that will offer sub-specialty care, such as transplant and cardiac surgery, to the state’s sickest children, will open in 2019. An outpatient facility will open in North Charleston in early 2019 to better serve Lowcountry families. In addition to providing convenient and accessible care, the dual campus will offer an opportunity for residents. “It will give us an exciting new diversity in our training mission,” says Atz.

Teamwork was also integral to the design of the MUSC Shawn Jenkins Children’s Hospital. Nurses, physicians and family members all helped create a truly healing space. That sometimes meant rethinking the

way care was delivered. For example, Atz was persuaded to a new ICU design by a mother’s plea for greater privacy.

“As an old ICU doc, my greatest comfort is being able to stand in the middle of an ICU and look 360 degrees and see patients in every direction. That is, however, not the best for families or the best for healing because it leaves them out in the open with a lot of noise and distraction,” says Atz. “A heartfelt letter came from a parent about how important it was to have walls to provide privacy, and so we decided to go with glass walls. It’s a classic example why we should continue to listen to all the stakeholders, including the people we treat.”

Most of all, Atz believes in teamwork when it comes to the state’s children’s hospitals. “Where children’s health is concerned, it is not about competition. It’s about collaboration,” says Atz. “Formed in 1994, the South Carolina Children’s Hospital Collaborative is a nonprofit association of the state’s four children’s hospitals. Through a variety of initiatives, we are elevating the quality of care provided to all of the children of South Carolina.”

# New Physicians

## **Avery L. Buchholz, M.D., MPH**

Board Certification: Neurological Surgery // Specialty: Neurosurgery  
// Medical School: University of Wisconsin School of Medicine and  
Public Health // Residency: Medical University of South Carolina //  
Fellowship: University of Virginia Department of Neurosurgery

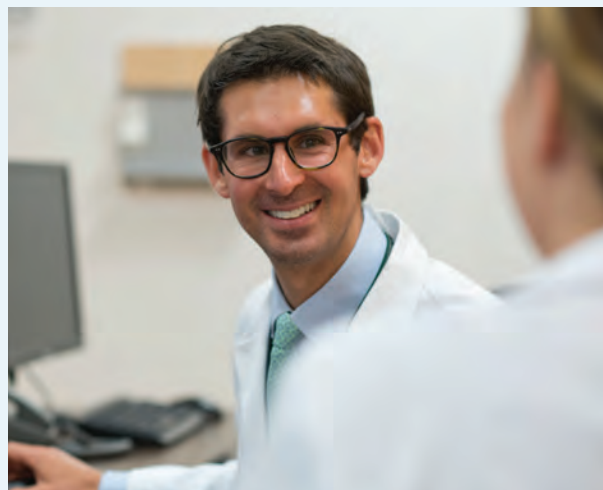


## **Barry C. Gibney, D.O.**

Board Certification: American Board of Surgery // Specialty:  
Cardiothoracic Surgery, Cancer - Lung and Thoracic // Medical  
School: Nova Southeastern University // Residency: Pennsylvania  
State University/ Hershey Medical Center // Fellowship: Brigham  
and Women's Hospital/ Harvard Medical School (thoracic surgery)

## **Evan M. Graboyes, M.D.**

Board Certification: American Board of Otolaryngology //  
Specialties: ENT - Head & Neck Oncology, Cancer - Head &  
Neck Tumors // Clinical Interests: Microvascular reconstruction  
// Medical School: Washington University in St. Louis School of  
Medicine // Residency: Washington University in St. Louis School of  
Medicine // Fellowship: Medical University of South Carolina



# New Physicians



## **Barbara B. Head, M.D.**

Board Certification: Obstetrics and Gynecology: Maternal-Fetal Medicine // Specialty: OB-GYN – Maternal-fetal medicine // Medical School: Virginia Commonwealth University Medical College of Virginia // Residency: Medical University of South Carolina // Fellowship: University of Alabama at Birmingham

## **Heather T. Henderson, M.D.**

Board Certification: Pediatrics: Pediatric Cardiology // Specialty: Pediatric Cardiology // Clinical Interests: Congenital heart disease, pediatric cardiomyopathy, pediatric heart failure, pediatric heart transplant, immunosuppression, advanced heart failure, mechanical circulatory support, ventricular assist devices, left ventricular assist device care // Medical School: Medical University of South Carolina College of Medicine // Residency: University of Alabama at Birmingham // Fellowship: Emory University/Children's Healthcare of Atlanta



## **Ling-Lun Bob Hsia, M.D.**

Board Certification: Dermatology // Specialties: Mohs and Dermatologic Surgery, Cutaneous Oncology // Medical School: University of Virginia School of Medicine // Residency: East Carolina University // Fellowship: University of North Carolina, Chapel Hill



**Amarendra K. Neppalli, M.D.**

Board Certification: Internal Medicine: Hematology // Specialties: Hematology/Oncology, Cancer – Blood and Lymphatic // Medical School: Osmania Medical College // Residency: Louisiana State University Health Science Center // Fellowship: Stanford University, Louisiana State University Health Science Center

**Marc J. Rogers, M.D.**

**Director of Men's Health**

Specialties: Urology, Male Infertility and Sexual Medicine // Medical School: University of Pittsburgh School of Medicine // Residency: University of Pittsburgh Medical Center // Fellowship: University of Washington Medical Center



**Ryan J. Tedford, M.D.**

Board Certification: Advanced Heart Failure and Transplant Cardiology, Internal Medicine: Cardiovascular Disease // Specialty: Cardiology - Heart Failure & Transplant // Clinical Interests: Advanced heart failure, congestive heart failure, diastolic heart failure, right-sided heart disease, pulmonary hypertension, heart transplant, left ventricular assist device care, endomyocardial biopsy // Medical School: University of Texas Southwestern Medical School // Residency: Johns Hopkins Hospital // Fellowship: Johns Hopkins Hospital



Changing What's Possible®

Nonprofit Org.  
US Postage  
**PAID**  
Permit No. 254  
Charleston, SC

171 Ashley Avenue  
Charleston SC 29425

## Progressnotes Credits

### Co-Executive Editors

Patrick J. Cawley, M.D., MHM, FACHE  
Chief Executive Officer, MUSC Health  
Vice President for Health Affairs

Raymond N. DuBois, M.D., Ph.D.  
Dean, College of Medicine

Scott T. Reeves, M.D.  
Chief Physician Executive  
MUSC Physicians and MUSC Health

### Medical Editor

Daniel A. Handel, M.D., MPH, MAS  
Chief Medical Officer/  
Executive Medical Director,  
MUSC Medical Center

### Managing Editor

Kimberly McGhee, Ph.D.  
mcgheek@musc.edu

### Medical Science Writers

Vitria Adisetiyo, Ph.D.  
Sver Aune, Ph.D.  
Matthew Greseth, Ph.D.  
Nouhou Ibrahim, Ph.D.  
Kimberly McGhee, Ph.D.  
Rachel Weber, Ph.D.

### Art Director

Brennan Wesley

### Photographers

Sarah Pack  
Brennan Wesley

### Illustrator

Emma Vought

### Digital Communications

Ethan Fugate

### Design services provided by

Network Media Partners

Visit [MUSChealth.org/pn](http://MUSChealth.org/pn) for  
additional online content.

Visit [MUSChealth.org/pn/Subscribe](http://MUSChealth.org/pn/Subscribe)

# PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // FALL 2017

## MUSC Health CareLink | Enhanced Communication Between Caregivers

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

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

### Eligibility for access:

- Physicians or advanced practice practitioners who refer their patients to MUSC for care
- Medical support staff (nurses, medical assistants, office managers, and referral coordinators) sponsored by their physician or advanced practice practitioner
- **It's free:** There are no costs associated with this service.

### Ready to sign up?

**Go to:** [www.muschealthcarelink.com](http://www.muschealthcarelink.com), click the *Request New Account* link, and follow the steps to create and submit a practice agreement and all necessary user requests.

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

**Email:** [carelink@musc.edu](mailto:carelink@musc.edu)