BreakThroughs

Duke Cancer Institute

FALL 2019

ACCELERATING IMMUNOTHERAPY

AT THE HEART OF IT

Using tech to track cardiovascular health while beating cancer.

Page 04

HOPE FOR OSTEOSARCOMA

Man's best friends are helping out.

Page 07

A LIVING DRUG

The promise of CAR-T Therapy.

Page 16

Shaping the Future of Cancer Care

LES TODD

MICHAEL B. KASTAN

ON THE COVER:
Metastatic melanoma survivor Stephen Totty with sons Harrison and Craig and wife, Heather. Totty currently shows no evidence of cancer thanks to treatment with immunotherapy. Read the story on page 13. Cover photo by Alex Boerner.

I HAVE EXCITING NEWS TO SHARE FROM DUKE CANCER INSTITUTE (DCI). After many months of preparation and an extensive review process, DCI was renewed as a National Cancer Institute-designated Comprehensive Cancer Center for another five-year period.

This award means that we retain the elite designation of a "comprehensive" cancer center, an honor held by only 51 institutions in the United States. The accompanying five-year grant of approximately $30 million supports our broad range of clinical, research, and educational programs, which aim to reduce the impact of cancer on the lives of people in North Carolina and beyond.

As one of the original eight comprehensive cancer centers designated by the National Cancer Institute (NCI), our cancer center has been continuously funded by NCI since 1973. So, while this grant renewal is not a new infusion of funding, it does mean that NCI recognizes DCI's continuing leadership in shaping cancer research and care.

I am also happy to share with you some of our recent investments in one of our priority focus areas—cancer immunotherapies (treatments that boost the immune system's own ability to fight cancer).

In addition to running industry-sponsored clinical trials of these treatments, DCI has untapped potential to develop and test truly novel immunotherapies based on discoveries made right here at Duke.

To build on that opportunity, we have launched the new DCI Center for Cancer Immunotherapy. Leaders of this center (see "Accelerating Immunotherapy," page 10) are partnering with the outstanding talent across Duke to accomplish the many steps required to move new immunotherapy discoveries from the research lab into a human clinical study.

Friends and donors like you are vital partners in this work. Without you, many promising therapies would never get beyond a culture dish or a mouse study. Donations can provide support to gather early data to prove that a new discovery is worth investment from a large funding agency.

With your help, we will build upon our strengths and advance new priorities like immunotherapy to achieve our mission of delivering tomorrow's cancer care…today.

Will you please join us?

Michael B. Kastan, MD, PhD
Executive Director, Duke Cancer Institute
William and Jane Shingleton Professor,
Pharmacology and Cancer Biology
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Breast Cancer: Cost Matters

Even among well-educated women with health insurance, a significant proportion said the costs of cancer treatment influenced the type of surgery they chose for breast cancer treatment, a study led by Duke Cancer Institute and published online in the *Journal of Oncology Practice* found.

"Eligible women with early-stage breast cancer often have choices for surgical treatments that are equally effective and result in excellent cancer outcomes," says lead author Rachel Greenup, MD, assistant professor of surgery. "Surgeons often discuss the emotional and physical side effects of treatment, yet we rarely discuss the costs."

Greenup and colleagues conducted an electronic survey of women with stage 0-III breast cancer. They were recruited from members of the Army of Women, a national coalition of breast cancer survivors and activists, and the Sisters Network of North Carolina, an African American breast cancer survivors' group.

A substantial proportion of the women (43 percent) reported that they considered costs when making breast cancer treatment decisions, and nearly a third said cost played a role in their surgical choice. For women whose household incomes were under $45,000 a year, costs were more important than keeping their breast or its appearance.

Overall, 35 percent of respondents reported that their cancer treatment created a financial burden, and 78 percent never discussed costs with their cancer team. Even among participants with the highest incomes, 65 percent said they were fiscally unprepared for the cost of breast cancer treatment.

Among the procedures available for breast cancer—including breast-conserving surgery (lumpectomy with radiation), mastectomy, and double mastectomy with or without breast reconstruction—double mastectomy was associated with higher patient-reported debt and financial hardship.

KEN HUTH

RACHEL GREENUP

Uncloaking Cancer

LES TODD

DONALD MCDONNELL

Breast tumors are good at sending out signals to tell the immune system, "Don't attack me," says Donald McDonnell, PhD, chair of Duke's Department of Pharmacology and Cancer Biology.

Now he and other Duke researchers think they have found a way to stop those signals.

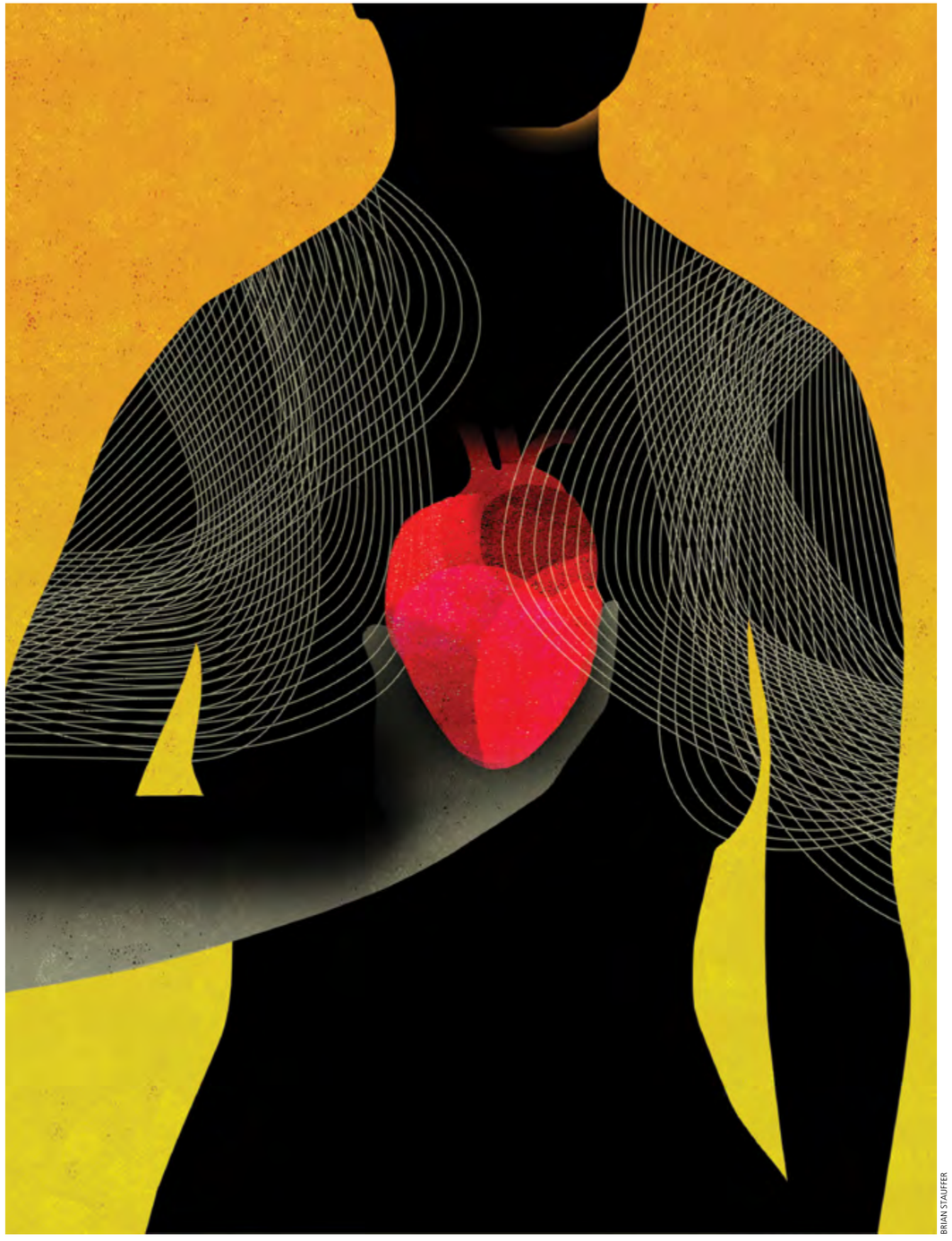
McDonnell and colleagues, including lead author Luigi Racioppi, MD, PhD, assistant professor in medicine, reported in the journal Nature Communications that an enzyme called CaMKK2 is highly expressed in immune system cells within human breast tumors.

"We found that inhibition of the activity of this enzyme decreased the ability of macrophages in tumors to suppress an immune attack on cancer cells and indeed encouraged them to start producing chemicals that attract more cancer-killing T cells into the tumor," says. "We can basically uncloak the tumor to the immune system."

Working with colleagues at the University of North Carolina at Chapel Hill, they developed a new class of drugs that inhibit CaMKK2 and showed that they could reduce the growth of human breast tumors grown in mice.

"The use of this molecule suppressed tumor growth not only by increasing the accumulation of tumor-killing T cells, but also by reducing the tumor's capability to suppress T cell activity," McDonnell says. "It's solving two problems, like we couldn't get into the bar, and if we did, we couldn't get a drink. Now we can do both."

The team is conducting studies to gather additional data and aim to launch a clinical trial in breast cancer patients in the next 18 months. McDonnell thinks that this approach could work for other types of cancer. Philanthropy could help him develop a small team to expand animal studies into other cancers, including ovarian cancer.



BRIAN STAUFFER

KEEPING THE HEART HEALTHY WHILE BEATING BREAST CANCER

BY **WHITNEY J. PALMER**

Today, thanks to treatment advancements, the majority of women diagnosed with breast cancer can expect to be cured. But what if focusing on beating the cancer means weakening what beats in her chest? Two Duke researchers are now looking beyond cancer therapy to potentially save more lives by focusing on heart health.

By bringing together oncologists and primary care providers, Kevin Oeffinger, MD, director of the Duke Cancer Institute (DCI) Center for Onco-Primary Care, and Susan Dent, MD, co-director of the Duke Cardio-Oncology program, are examining the long-term impact that cancer therapies can have on a woman's heart health. With a roughly 88 percent cure rate for breast cancer, Oeffinger says, it's more important than ever to concentrate on the detrimental side effects that can accompany life-saving treatments.

"We focus so much on the cancer that sometimes we forget to pay closer attention to blood pressure, cholesterol, and diabetes, allowing those conditions to be less than optimally managed," he says. "Over time, we've learned that women who've undergone oncology treatments are more likely to die of a heart attack or stroke than they are breast cancer. And, it's not because of the things we do. It's because of the things we don't do."

Oeffinger and Dent are involved in two clinical trials—one examining blood pressure during cancer treatments and the other investigating whether breast cancer treatments (including chemotherapy and/or radiation) can induce other health problems after cancer therapy ends. Both studies aim to forge and strengthen collaborations between oncologists, cardiologists, and primary care providers.

LES TODD

KEVIN OEFFINGER is leading a study in which cancer patients will use a Bluetooth blood pressure monitor to measure their levels at home. The system reminds patients to take three measurements weekly and connects to a smartphone app that records and transmits readings to the patient's electronic health record.

HIGH-TECH, AT-HOME HYPERTENSION MONITORING

During cancer treatments, hypertension is often overlooked, Dent says, and left uncontrolled, it remains the biggest predictor of long-term

KEN HUTH

SUSAN DENT is leading the Duke site of a clinical trial that will define which women are at increased risk of developing cardiac problems related to their breast cancer treatment.

cardiovascular morbidity and mortality. Consequently, health-care providers need a better way to track and share information about this crucial indicator.

In a Duke Institute for Health Innovation-supported, first-of-its-kind pilot study, Oeffinger plans to enroll 10 women actively receiving breast cancer treatment, as well as 10 prostate cancer, lymphoma, and post-bone marrow transplant patients each. Patients will use a Bluetooth blood pressure monitor to measure their levels at home. Not only does the system remind patients to take three measurements weekly, but it also connects to a smartphone app, immediately recording and transmitting readings to the patient's electronic health record, as well as sending providers messages if readings are too high.

"This system does what primary care providers and oncologists say they need," Oeffinger says. "The primary provider needs to know when to intervene and what strategies to pursue that don't conflict with the patient's chemotherapy. And, the oncologist needs a simple way to partner directly and routinely with the primary provider."

The goal, he says, is to identify when cancer therapies increase blood pressure, potentially pinpointing any increased risk of heart attack or stroke within the subsequent 10 years. Additional financial support for the study could open enrollment to more patients.

ANALYZING ONCOLOGY'S IMPACT

Dent is leading the Duke site of a National Cancer Institute-funded, multi-center study, called UPBEAT, that is intended to examine the long-term impacts of chemotherapy and radiation on the cardiovascular health of women treated for early-stage breast cancer. Similar work has studied the impact of cancer treatments on cardiovascular health in pediatric cancer survivors, but little adult-focused research exists, she says. The study will recruit 1,000 women nationally, including 160 women without breast cancer, but additional funding is needed to cover the cost of recruiting patients at Duke.

"This study is very important because it will help define which women are at increased risk of developing cardiac problems related to their breast cancer treatment," Dent says. "And, if we know, we can think of preventive strategies to attenuate or diminish the risk of long-term cardiovascular effects."

By following the participants for several years and collecting data on their medications, cardiovascular risk factors, other health conditions, physical activity, and neurocognitive health, researchers hope to determine the long-term consequences of standard therapies on heart function, exercise ability, neurocognitive function, and fatigue. For example, some cancer treatments increase the risk of developing heart failure, and radiation treatment can increase the risk of developing coronary artery disease years after cancer therapy. Additionally, previous research conducted at Duke revealed that cancer treatments can have a negative impact on an individual's exercise capacity: after receiving breast cancer treatment, a 50-year-old woman can have a fitness level equivalent to a sedentary 70-year-old woman. Being able to decrease the impact of cancer therapy on an individual's fitness level will greatly improve patients' overall health.

> "Over time, we've learned that women who've undergone oncology treatments are more likely to die of a heart attack or stroke than they are breast cancer. And, it's not because of the things we do. It's because of the things we don't do."
>
> —Kevin Oeffinger

To date, it's been difficult for oncologists to know how their prescribed treatments affect patients years after completion of their cancer therapy, Dent says, because oncologists rarely stay in contact once patients are discharged back to their primary care providers.

"Ten to 15 years after surviving cancer, a patient can end up on the cardiology ward in heart failure potentially related to our treatments," she says. "That's why it's important for us to collaborate and look holistically at our patients to determine the best cancer-care strategies that won't potentially compromise their cardiovascular health."

A Tale of Two Drugs

Research in mice suggested two new possible treatments for a rare cancer that often strikes children. Thanks to the help of pet dogs with cancer, researchers have, in just one short year, ruled one drug out and are taking the other on to the next step.

BY WHITNEY J. PALMER

JIM ROGALSKI

Duke oncologist and veterinarian **WILL EWARD** (right) with veterinary oncologist **STEVEN SUTER** and cancer patient **DEUCE.**

WALKS IN THE PARK, A STRESS-RELIEVING GAME OF FETCH, AFFECTIONATE BELLY RUBS. "Man's best friend" brings us all that and more.

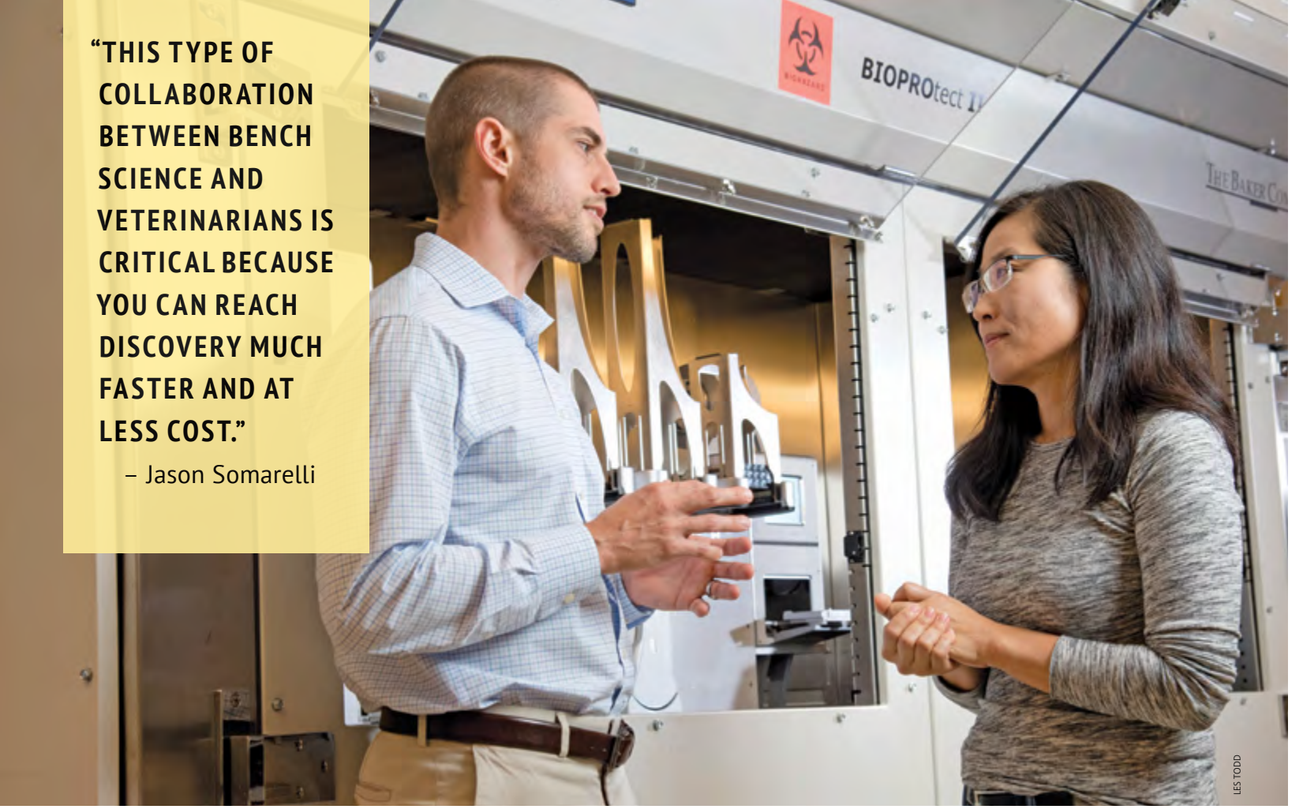
But, in the case of bone cancer (osteosarcoma), dogs are proving, again, that they can benefit their humans' lives in a substantial way. Duke orthopedic oncologist Will Eward, MD, DVM, and colleagues are investigating how this link could improve health outcomes for children stricken by this disease.

THE CASE FOR OSTEOSARCOMA AND DOGS

Osteosarcoma rarely occurs in humans, accounting for less than one percent of all diagnosed cancers. However, when it appears, it impacts children most heavily as the third most commonly occurring pediatric cancer after lymphoma and brain cancer.

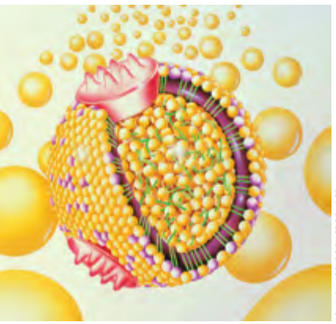
"THIS TYPE OF COLLABORATION BETWEEN BENCH SCIENCE AND VETERINARIANS IS CRITICAL BECAUSE YOU CAN REACH DISCOVERY MUCH FASTER AND AT LESS COST."

– Jason Somarelli



LES TODD

Researcher **JASON SOMARELLI** in the lab with **SO YOUNG KIM, PHD**



JOHN BAVOSI/SCIENCE SOURCE

A drawing of low-density lipoprotein (a naturally produced substance in the body that cancers eat). Duke engineer **DAVID NEEDHAM** used nanotechnology to encapsulate an existing drug into a tiny particle that mimics low-density lipoprotein, making it easier for it to get into the bloodstream, where it can help kill cancer. The treatment, niclosamide stearate pro-drug therapeutic, is showing promise for treating osteosarcoma (bone cancer) in pet dogs.

Treating it is difficult, though, because there's been lack of therapeutic advancements.

"With osteosarcoma, I'm telling parents exactly what was told to them in the 1980s," Eward said. "We can't keep driving the 1984 Datsun forever. We have to do better because pediatric oncology occupies a special place in medicine. Kids shouldn't get cancer."

The small number of children developing osteosarcoma has been a barrier to improving care. That's where dogs come in, he says. Veterinarians diagnose roughly 4 million dogs with cancer annually, and osteosarcoma accounts for approximately 15 percent of those cases. Not only are most of their tumors identical to those in humans, but their immune systems are also similar, and they share the same food, air, and water exposures. Additionally, the natural survival time for a dog with osteosarcoma is approximately 18 months, making it quicker to find out if treatments prolong life.

To test the viability of new drugs, Eward is partnering, via the Consortium for Canine Comparative Oncology, with veterinary oncologist, Steven Suter, VMD, PhD, medical director of North Carolina State College of Veterinary Medicine's canine/feline molecular oncology diagnostic lab. Through a canine clinical trial, funded by a $250,000 grant from Hyundai Hope on Wheels to specifically target links between canine and human sarcomas, they are investigating whether two existing medications can combat osteosarcoma in dogs, potentially opening the door for use with children.

"These are dogs that just happen to get osteosarcoma like we do," Eward says. "This is a clinical trial for dogs just like it would be for humans. Their owners have asked for their pets that have osteosarcoma to be included, and we're treating them the same as we would in a human clinical trial even though that group has two legs and this group has four legs and wags their tails."

HOW YOU CAN HELP

You can accelerate innovations like this one. Use the enclosed envelope, or make a gift online at **bit.ly/dcifall2019**

TESTING THERAPIES

The clinical trials test two existing medications approved for other uses—bortezomib and niclosamide. The team designed these trials based on predictive work conducted in mice. Using immunosuppressed mice, researchers Jason Somarelli, PhD, and David Hsu, MD, PhD, created dog avatars, called xenografts, by injecting cells from dog tumors into the mice to prompt tumor growth. Doing so allowed researchers to more quickly see the drug's effect.

"Using these xenografts, we demonstrated on a small scale that the drugs could work and could be scaled up for use from a 30-gram mouse to a 150-pound dog," Somarelli says. "This type of collaboration between bench science and veterinarians is critical because you can reach discovery much faster and at less cost. We haven't spent time or millions of dollars going down the rabbit hole."

In the first trial, after seeing strong efficacy with the xenografts, the team examined how well bortezomib, a drug used to treat multiple myeloma cancer in humans, would work in dogs. While other chemotherapy agents attack cells indiscriminately, causing toxic side effects, bortezomib avoids those responses by only targeting how the cancer packages proteins. Consequently, this trial enrolled 10 dogs who received standard amputation but whose owners did not want to pursue subsequent chemotherapy.

"This is a clinical trial for dogs just like it would be for humans. Their owners have asked for their pets that have osteosarcoma to be included, and we're treating them the same as we would in a human clinical trial even though that group has two legs and this group has four legs and wags their tails."

—Will Eward

Despite high expectations, Suter says, bortezomib has performed poorly, introducing neurological side effects, such as limb weakness and an inability for the dogs to walk. In addition, the dogs who received the drug didn't fare any better than those who received standard chemotherapy. While it's disappointing that bortezomib doesn't work as anticipated, Eward says, the trial results are still critical.

"If we've found that bortezomib has no role for treating osteosarcoma, we've figured that out by treating 10 dogs for $90,000 in one year rather than treating five to 10 children in a trial that cost over $1 million," he said. "We've saved doctors from using something that's not effective."

The second trial is focused on niclosamide, a drug traditionally used to treat intestinal parasites. Although existing evidence revealed it had some efficacy against osteosarcoma, as an oral drug, it wasn't a viable treatment option because it can't dissolve in the blood to reach the tumors. So David Needham, Ph.D., Duke professor of mechanical engineering and material science, created a version of niclosamide that could be intravenously administered, called niclosamide stearate pro-drug therapeutic (NSPT). He used nanotechnology to encapsulate niclosamide into a particle that mimics low-density lipoprotein (a naturally produced substance in the body that cancers eat).

Ten enrolled dogs have received amputation, four standard chemotherapy treatments, and four doses of the modified niclosamide. To date, Suter says, the results have been promising, with no organ toxicity, no neurological impacts, and only some allergic reactions that can be treated with antihistamines.

THE IMPORTANCE OF COLLABORATION

Ultimately, Eward says, the partnership between Duke and N.C. State has been crucial in moving osteosarcoma research forward. In emerging from their individual silos, bench scientists, oncologists, and veterinarians are charting new territory in cancer treatment. Much work still needs to be done in determining how NSPT kills cancer, providing the therapy to more dogs, and testing NSPT in other solid tumors, but it is clear the potential exists for this drug to combat additional cancers, including breast, prostate, and pancreatic.

"This is kind of like *A Tale of Two Cities*, only it's a tale of two drugs," Eward says. "We had two promising therapies based on the results of mice trials, and now we're putting effort into moving NSPT to the next step to, one day, be available to humans with this disease."

Accelerating Immunotherapy

BY ANGELA SPIVEY

Translating findings from a lab into patients in a clinic can be a long slog up a steep hill. The new DCI Center for Cancer Immunotherapy helps researchers with the climb.

It's August 2019, and Duke Professor of Immunology and Pediatrics Tom Tedder, PhD, is excited; a drug initially developed in his research lab is under review by the US Food and Drug Administration for approval to treat a rare autoimmune disease that affects the central nervous system (neuromyelitis optica.)

THIS EXCITEMENT WAS A LONG TIME IN THE MAKING. The drug, now called inebilizumab, came out of discoveries his lab made more than 15 years ago, about a new way to inhibit immune system cells. Tedder founded a private startup company to develop the drug because, he says, moving it forward using only federal funding "was so slow that I thought I would die before it got to patients."

Various researchers have estimated that it takes industry an average of 17 years to translate a promising laboratory finding to the clinic. And the average cost to develop a new prescription medication is $2.6 billion, according to a study from the Tufts Center for the Study of Drug Development.

Scott Antonia, MD, PhD, aims to speed up this process for scientists across all departments at Duke who have made discoveries that show promise for developing new immunotherapies—treatments that boost the immune system's ability to kill cancer. Antonia, who joined Duke in February 2019, is a lung cancer physician who spent years at Moffitt Cancer Center developing immunotherapies to fight lung cancer, including one that in June 2019 changed the standard of care for stage III non-small-cell lung cancer.

ANTONIA AND COLLEAGUES WHO LEAD THE NEW DUKE CANCER INSTITUTE CENTER FOR CANCER IMMUNOTHERAPY LOOK FOR CANCER IMMUNOTHERAPY DISCOVIERIES THAT SHOW PROMISE, NO MATTER THE CANCER TYPE.

Antonia and colleagues who lead the new Duke Cancer Institute (DCI) Center for Cancer Immunotherapy look for cancer immunotherapy discoveries that show promise, no matter the cancer type. Then they form a team that works with the original investigator to accelerate the finding into a drug that can be tested in a clinical trial. The team

THE CONNECTORS. **Scott Antonia** and **Mustafa Khasraw** look across Duke for new discoveries they can translate into clinical trials of treatments that use the body's immune system to fight cancer.

ALEX BOERNER

members will help accomplish all the tasks required to take a finding to human trials, from conducting additional lab studies, to designing a clinical trial, and even manufacturing a drug (see "DCI Center for Immunotherapy Fast Facts, below).

Currently, a dozen or so findings from Duke investigators are under development with the new center. One of those is new work from Tedder's lab, showing that a particular antibody can selectively decrease a subset of regulatory B cells to ramp up the immune system against cancer. As part of the collaboration, he's working with physician Neal Ready, MD, PhD, to study the antibody's activity in cells obtained from human lung cancer patients. "Scott's new center solidifies everybody's focus in a common way, and that's something that is really needed," Tedder says.

Other findings now in development by the center suggest immunotherapies that will fight head and neck cancer, upper gastrointestinal cancer, colorectal cancer with metastasis to the liver, melanoma, bladder cancer, and lung cancer. Antonia says they will eventually have immunotherapy clinical trials under development for all cancer types.

Mustafa Khasraw, MD, FRCP, FRACP, deputy director of the center, is newly arrived at Duke from the University of Sydney (Australia) and brings expertise in designing and leading large clinical trials. "There is enormous hope in the field of cancer research that we can help patients who are now not benefiting from immunotherapy," he says. Immunotherapies have shown success for some patients with certain cancers, such as melanoma, but not for others. "I think this is the next page in curing cancer. With a lot of us working together, we will get there."

Antonia says that Duke's wealth of talent and the willingness of investigators to collaborate is what brought him here. "The science is already here at Duke," he says. "We just need to accelerate it. We've been able to accomplish here in six months what might take years at another institution."

> "THE SCIENCE IS ALREADY HERE AT DUKE, WE JUST NEED TO ACCELERATE IT. WE'VE BEEN ABLE TO ACCOMPLISH HERE IN SIX MONTHS WHAT MIGHT TAKE YEARS AT ANOTHER INSTITUTION."
>
> – Scott Antonia

DCI CENTER FOR IMMUNOTHERAPY
FAST FACTS

There are a lot of steps to turn a discovery in an animal or cells into a therapy that can be tested in humans. The new Duke Center for Cancer Immunotherapy will partner with Duke investigators to:

- Conduct additional studies in animals or cells
- Obtain or manufacture a new immunotherapeutic treatment
- Design a clinical trial and write the clinical protocol
- Obtain regulatory approvals
- Oversee the clinical trial
- Study tissue or blood samples from patients to understand how the therapy is working

The center is led by:

- **SCOTT ANTONIA, MD, PHD,** Director
- **MUSTAFA KHASRAW, MD, FRCP, FRACP,** Deputy Director
- **BRENT HANKS, MD, PHD,** Associate Director for Basic/Translational Science
- **ANDREW NIXON, PHD,** Associate Director for Correlative Science
- **JENNIFER CHOE, MD, PHD,** Associate Director for Clinical Science
- **JOANNE KURTZBERG, MD,** Associate Director for Cell Based Immunotherapeutic Manufacturing
- **AHMED GALAL, MD,** Associate Director for Cell Based Immunotherapy


ANTONIA


KHASRAW


NIXON


HANKS


CHOE


KURTZBERG


GALAL

FIGHTING SIDE EFFECTS

Stephen Totty thought he had simply pulled a pectoral muscle while moving furniture. But the soreness lingered. Then a painful "water balloon" full of blood developed on the right side of his chest. An orthopedist drained it several times, and then an MRI revealed cancer.

Totty, a software engineer who lives in Rolesville, North Carolina, came to Duke, where Brian Brigman, MD, performed surgery. He removed a large part of Totty's pectoral muscle and a muscle in his back, along with 99 percent of the cancer. But scans showed it had already spread to Totty's liver and lung.

The cancer turned out to be melanoma, not sarcoma as doctors had originally thought. Totty's wife, Heather, had lost her father to ocular melanoma just six months earlier. So the couple and their two sons were scared. But Brent Hanks, MD, PhD, gave them hope. "He didn't sugarcoat it," Heather recalls. "He said, 'This can be beat. I can't promise you it *will* be, but it *can* be.' He told us that with Stephen's health and his age, it was statistically in his favor that he could beat it."

"Dr. Hanks educated us so we knew what to expect every step along the way," Stephen says. "With education, the fear goes away."

Stephen began infusions of two different immunotherapies—nivolumab (Opdivo) and ipilimumab (Yervoy). But he was hit with some severe gastrointestinal side effects, and his thyroid gland quit working. He stopped taking ipilimumab after just one dose.

Hanks, assistant professor of medicine, is trying to understand why some patients on immunotherapy develop such side effects, which are caused by an immune system that's suddenly more active than normal. Some patients develop autoimmune responses that inflame the gastrointestinal tract, lungs, liver, or lead to the destruction of endocrine glands, including the thyroid and pituitary.

As part of the new Duke Center for Cancer Immunotherapy, Hanks will be banking blood and tissue samples from Duke patients treated with immunotherapy for a wide variety of cancer types, along with data on what sort of reactions, if any, the patients experienced. Also working on the repository are Andrew Nixon, PhD, professor of medicine, and Jennifer Choe, MD, PhD, assistant professor of medicine.

The data from this project will help predict which patients are at risk for side effects so they can be proactively managed or even prevented. "These therapies are fairly new, and in terms of side effects we're early in the process," Hanks says. "There's a lot we don't understand about toxicities and how we can separate those toxicities from the efficacy. Moving forward, we're going to be more in tune in managing those side effects."

Costs to get the biobank up and running for a couple of years will range from $300,000 to $1 million, Nixon says.

Though he had to stop the one immunotherapy, Stephen continued to take nivolumab, and after six months, the tumors in his liver and lungs were almost gone. The fast response was unusual; Hanks had told him not to expect results for two years.

As of his 43rd birthday in September 2019, PET scans of Stephen's liver and lungs show no evidence of disease. He continues to take nivolumab every two weeks. After a year and a half of physical therapy, he can play baseball with his sons again.

Unfortunately, the thyroid damage from one dose of the other therapy was permanent. He will have to take thyroid medication every day for the rest of his life. "The good news is they have pills for that," Stephen says. "In the grand scheme of things, it's not that big of a deal. I could be dead from cancer."

— Mary-Russell Roberson and Angela Spivey


ALEX BOERNER

Melanoma survivor Stephen Totty with his wife, Heather, and sons Craig, 13; and Harrison, 10. "Dr. Hanks cared for Stephen but he also cared for me. His nurses and whole office staff were that way. They very much took the approach of, this is happening to Stephen, but this is also happening to your whole family," Heather says.

Overcoming Resistance

Can research make immunotherapies work better, for more people?

BY MARY-RUSSELL ROBERSON

Some patients experience amazing results from new immunotherapy treatments, including unprecedented long-term remission. However, most patients don't. And that bothers Brent Hanks, MD, PhD.

"THERE IS A LOT OF ROOM FOR IMPROVEMENT," HANKS SAYS. "We want to broaden the population that is capable of responding and benefiting from these treatments."

Hanks is assistant professor of both medicine and pharmacology and cancer biology. In 2019, he received the ASCI Young Physician-Scientist Award from the American Society of Clinical Investigators, one of only 35 such accolades awarded nationwide.

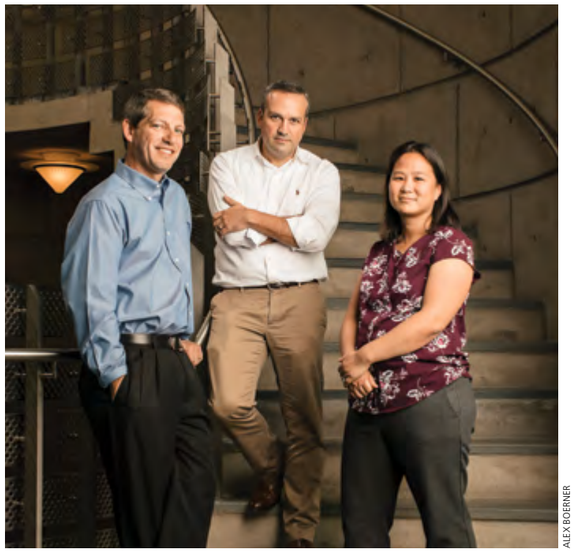
Hanks focuses on understanding how some cancers resist immunotherapy treatments called checkpoint inhibitors. His goal is to design new pharmaceuticals or deploy existing ones to disrupt that resistance.

Immunotherapy works by unleashing the immune system's cell-killing power on cancer. It's not easy to do that, because cancer has mechanisms to outsmart the immune system, often by co-opting signals that healthy cells use to persuade the immune system not to attack. "The tumors have essentially usurped these mechanisms and use them to their advantage," Hanks says.

Our bodies have dozens of different ways to help the immune system tone down its killer instincts and leave healthy tissue alone. These mechanisms are called checkpoints because they keep the immune system in check. For example, a protein called PD-L1 on the surface of healthy cells interacts with a protein called PD-1 on the immune system's T cells to send the message: "Hey, I'm friendly. Don't kill me."

Cancer cells also have PD-L1 proteins, which fool the T cells into passing them by. Pharmaceuticals that prevent this from happening, called anti-PD-1 therapies, essentially remove cancer's disguise.

In melanoma, anti-PD-1 therapies like pembrolizumab (Keytruda) and nivolumab (Opdivo) work for about 40 percent of patients. The other 60 percent are said to have primary resistance. And among those who initially responded well, some will later develop adaptive resistance and relapse. Hanks is seeking to discover the exact biological mechanisms that cause the different responses in different patients.



ALEX BOERNER

COLLABORATORS. Basic scientist **Andrew Nixon** (left), clinician and translational scientist **Brent Hanks,** and clinician **Jennifer Choe** work together as part of the new DCI Center for Immunotherapy.

"We feel like understanding the mechanism is actually very important," Hanks says. "If you are able to understand these mechanisms of resistance then you can reverse those processes."

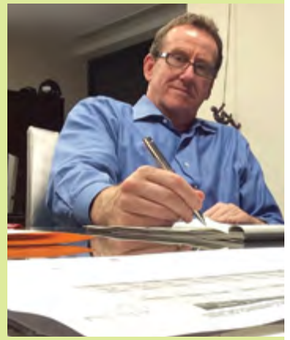
Understanding the biological pathways of resistance could also make it possible to identify proteins or other molecules in the blood or tumor that could serve as biomarkers to guide decisions about treatment.

The approach Hanks takes in the lab begins with identifying a possible molecular mechanism that cancer might be using to outsmart the immune system. He's not just looking for the presence or absence of a particular receptor or cell type, but a progression or cascade of biological signals that leads to resistance.

If the mechanism seems promising in theory, he then studies it in mice that are genetically engineered to develop melanoma. Is there evidence that the mechanism is active in mice that don't respond well to anti-PD-1 therapy? He can also run experiments in which some mice receive both anti-PD-1 therapy plus another pharmaceutical that disrupts the mechanism of resistance.

If the mouse studies support the theory, the next step is to check for clinical relevance. Hanks turns to a bank of tissue samples from melanoma patients who were treated with anti-PD-1 therapies (see "Crucial Support," below). The samples are anonymous, but each is linked to data about how that donor responded to the therapy.

CRUCIAL SUPPORT



As a Duke alumnus, Ross Bierkan has long supported efforts at his alma mater. But he decided to give to melanoma research because of personal experience; he was diagnosed with melanoma in 1999 and has had four recurrences. "I firmly believe that when you catch things early you can intercede and expect a reasonably good outcome," he says. "But the fact that it's recurring just points out the importance of not only maintaining vigilance but seeking answers to longer-term solutions."

Bierkan made a gift that supports the research of April Salama, MD, and Brent Hanks, MD, PhD, who are working to understand why some patients with melanoma respond to immunotherapy and some don't, and why some respond initially and then develop resistance.

The support from Bierkan has helped Hanks collect tissue specimens from patients and analyze them to discover pathways and mechanisms that may be involved when immunotherapies stop working. The work is painstaking and time-consuming and isn't likely to be funded by large federal agencies. "Philanthropic donations like Mr. Bierkan's are absolutely critical in order to keep this process going," Hanks says. "This is the only way that we're going to be able to identify clinically significant mechanisms of resistance to immunotherapy and the only way we will ultimately get better therapeutics into the clinic."

For this part of his work, Hanks collaborates with Andrew Nixon, PhD, professor of medicine. Nixon has been the director of Duke's Phase I Biomarker Laboratory since 2004. He and his team have the expertise and technology to detect the presence of a wide variety of proteins and other molecular markers in blood and other tissue samples.

"We are undertaking novel approaches to building better assays for molecules that are typically undetectable in blood," Nixon says. "We work with investigators to try to bring new and better technology to biomarker questions that have not been able to be properly addressed yet." Nixon and his team in the biomarker lab collaborate with partners nationwide.

In the research he's doing with Hanks, Nixon analyzes patient blood samples and develops techniques to detect specific molecules associated with one or more pathways of resistance that Hanks is investigating. Nixon then works with the Center for Biostatistics and Bioinformatics to see if there is a statistically relevant correlation between the presence of those biomarker molecules and immunotherapy resistance in the patient.

This painstaking and multi-step process is paying off. "We've identified two bona fide treatment strategies to overcome resistance to anti-PD-1 therapy," Hanks says.

One of the strategies involves dendritic cells, which are like generals in charge of soldier T cells. Cancer uses a signaling pathway called WNT to convince dendritic cells not to activate cancer-killing T cells. Disrupting the WNT pathway could provide a way to improve the effectiveness of anti-PD-1 therapy.

The other strategy focuses on preventing a buildup of immune-suppressing cells called myeloid-derived suppressor cells (MDSC) in cancer tumors. Hanks and his team believe they have identified a molecular mechanism that leads to the MDSC buildup in response to anti-PD-1 treatment. They have found evidence of the mechanism in both mice and patients that developed adaptive resistance to anti-PD-1 therapy.

Although both of these strategies have been confirmed in mouse models and clinical specimens, they need to be validated in a larger group of patient specimens, and ultimately, clinical trials. "It's an iterative process, a back and forth," Hanks says. "We keep searching and keep digging and finding things."

Hanks is motivated to keep digging by his patients. The science intrigues him, but the clinical relevance drives him.

Although he focuses on melanoma in his clinic and in his research, Hanks believes that some of these mechanisms that he has identified can also be applicable to other tumor types.

JOIN THE FIGHT

You can help us make immunotherapy work better for more people with cancer. To give, please use the enclosed envelope, or visit **bit.ly/dcifall2019.**

CAR-T Therapy: A Living Drug

BY MARY-RUSSELL ROBERSON

There's new hope for some lymphoma patients who've run out of options. Called a "living drug," the treatment involves removing white blood cells called T cells from a patient's body, genetically modifying the cells in a lab, and then infusing them back into the patient.

UNLIKE A PHARMACEUTICAL WITH A DEFINED CHEMICAL FORMULATION, each batch is made from living cells from an individual patient.

It's approved for people who have failed at least two lines of treatment for several kinds of non-Hodgkin's lymphoma: diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Richard Carroll, a retired deputy sheriff from Moore County, North Carolina, received the treatment at the Duke Adult Bone and Marrow Transplant Clinic last year.

He watched while his T cells were collected during a procedure that took several hours. Blood flowed out of his body through an IV tube, and into a machine that removed T cells. Then the blood flowed back into his body through another IV tube. His T cells were frozen and shipped to a lab in California. There, they were "infected" with a specially designed virus that inserts receptors on the surface of T cells to help them recognize cancerous blood cells.

After his engineered cells were shipped back to Duke, Carroll underwent a few days of mild outpatient chemotherapy to optimize the environment in his body for the modified cells. Two days after completing the chemotherapy, Carroll was admitted to the hospital and received an infusion of his new and improved T cells.

"They are supposed to seek out and destroy cancer and apparently they have done that," Carroll says. A PET scan several months after the treatment showed no evidence of cancer.

The therapy is called chimeric antigen receptor T-cell therapy, or CAR-T for short. In ancient Greece, a chimera was a fire-breathing monster made of a mix of animal parts—a lion's head, a goat's body, and a snake for a tail. A CAR-T cell is a chimera, too—a combination of a T cell with a synthetic receptor that recognizes cancer. That cancer-seeking receptor is key because although natural T cells are capable of killing cancer cells, they are often fooled by cancer's disguises.

ALEX BOERNER

CELL THERAPY. Ahmed Galal is Duke's clinical lead for CAR-T therapy, which is made from the patient's own cells. **Joann Kurtzberg** will lead manufacturing of new cell-based immunotherapies developed from Duke discoveries.

"It overcomes the way the tumor tries to hide from the immune system," explains Ahmed Galal, MD, who is Carroll's physician. Galal is a specialist in hematologic malignancies and cellular therapy and the clinical lead for CAR-T therapy at Duke.

"We have about 54 percent complete remission rates," Galal says, referring to national results for axicabtagene ciloleucel (Yescarta), which is the CAR-T therapy Carroll received. "It looks like when they go into complete remission their chance of continuing is very high. It looks very promising."

The stunning results of the therapy can come with serious side effects. "These are reversible side effects that don't leave permanent damage, but they can be life threatening," Galal says. For that reason, patients stay in the hospital for a week after the infusion, and must commit to staying within a half hour of Duke for a month after that. They are seen daily during that time, and can be hospitalized quickly if needed.

A common side effect is neurotoxicity, which can cause confusion and problems with balance. Carroll felt unsteady while he was in the hospital following the infusion and even walked into a wall. "It threw my equilibrium off. I was uncoordinated," he says. "But I got over all that."

Many patients also develop a condition called cytokine release syndrome, which can vary from mild to severe. When T cells kill cancer cells, proteins called cytokines are released into the body. The sudden influx can cause fever, nausea, and low blood pressure. Carroll fainted a couple of times after he left the hospital due to low blood pressure. He was readmitted until his blood pressure could be stabilized with medication.

In addition, the engineered T cells can kill healthy B cells (white blood cells that produce antibodies) along with the cancerous B cells. Sometimes patients become immunocompromised and need infusions of antibodies.

> "IT LOOKS LIKE WHEN THEY GO INTO COMPLETE REMISSION THEIR CHANCE OF CONTINUING IS VERY HIGH. IT LOOKS VERY PROMISING."
>
> – Ahmed Galal

Carroll was first diagnosed in 2012 with large B-cell non-Hodgkin's lymphoma. An initial course of chemotherapy appeared to be successful. Then, in 2017, he noticed a lump on his neck, which turned out to be a return of the cancer. "It was everywhere from my neck down to below my waist," he says. After some more chemotherapy, Galal suggested CAR-T therapy.

Carroll says of Dr. Galal, "I wouldn't take anything for him. He's a good man. I hope [the cancer] doesn't come back, but if it does I want to see him because he's looking after me. Dr. Galal stays on top of it."

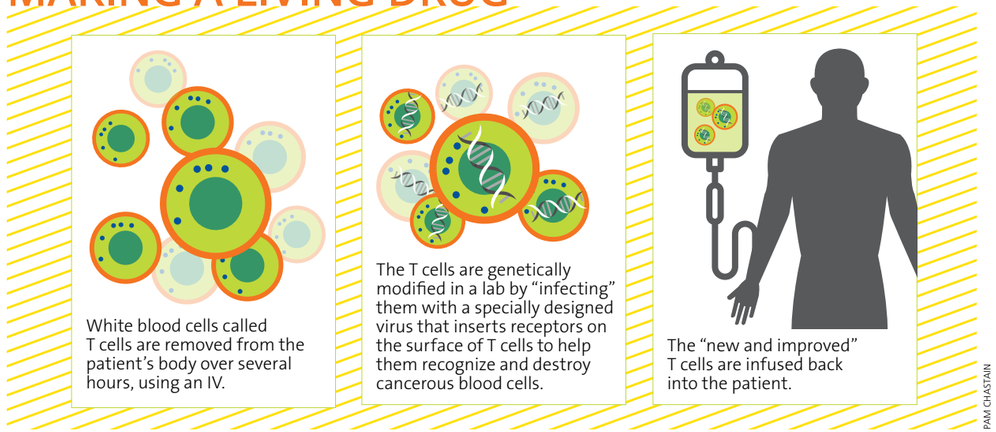
Duke Cancer Institute was one of the earliest treatment centers certified to administer Yescarta. It was approved by the FDA in October of 2017, and Duke was certified to use it three months later. Duke is also certified to administer the other FDA-approved CAR-T therapy, called tisagenlecleucel (Kymriah). It is approved for use in pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL) as well as adults with some types of large B-cell lymphoma. Almost 20 patients with blood cancers have been treated with CAR-T therapy at Duke, not including those who've been treated as part of clinical trials.

CAR-T therapies for solid tumors are not as far along in development as those for blood cancers, but some are in clinical trials. The Preston Robert Tisch Brain Tumor Center at Duke is studying a CAR-T therapy for glioblastomas, a type of brain cancer.

Galal is also excited about a different new approach for patients with blood cancer. He's seeing promising results in a clinical trial he's leading in which patients receive an infusion of specially treated stem cells from a donor in combination with an immunotherapy drug called nivolumab (see page 14 for more information about nivolumab and other similar immunotherapies).

"It is an exciting time for lymphoma and leukemia," Galal says. "I'm fortunate to be part of this era. There's nothing compared to having a patient [on the way] to hospice bounce back and go back to full-time work."

MAKING A LIVING DRUG



Duke was one of the first centers in the United States approved to offer axicabtagene ciloleucel (Yescarta), a brand of CAR-T therapy approved for people who have failed at least two lines of treatment for several kinds of lymphoma.

STRIKE OUT FOR SARCOMA. The Duke Multidisciplinary Sarcoma Program raised $41,425 at its 10th Annual Strike out for Sarcoma 4K and Family Fun Walk in September 2019. (See "A Tale of Two Drugs," page 7, to read about Duke's efforts to develop new treatments for osteosarcoma, which forms in the bones.)

DUKE ATHLETICS

LAXERS AGAINST CANCER. Abby Johnson, an eight-year-old cancer survivor, was drafted as an honorary captain by the Duke women's lacrosse team at their "It Takes a Team–Duke WLAX for DCI" game in April 2019. Johnson is cancer free after fighting a brain tumor at Duke Children's at the age of five. The game raised $8,920 for DCI.

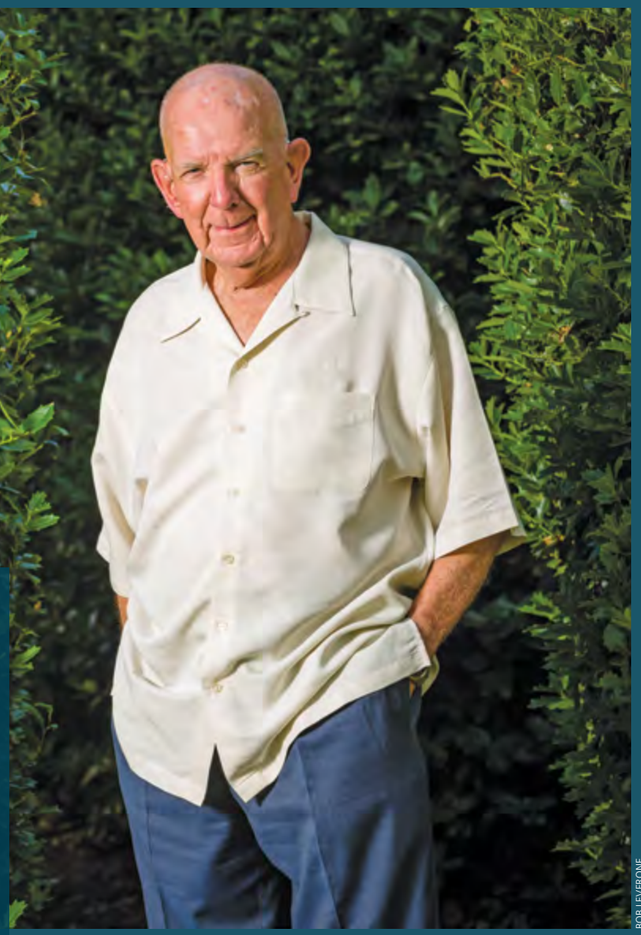
SHAWN ROCCO

DOCS GOT DUNKED. Eighteen doctors, including obstetrician and gynecologist Rebecca Previs, MD, pictured, took their chances in a dunking booth on the lawn across from Duke Cancer Center on May 16, 2019. The "Dunk a Doc" event raised $5,618 for the DCI Center for Prostate and Urologic Cancers.

CREATIVE INSPIRATION. Thanks to AC Moore and the Alicia Rose Victorious Foundation for donating and stocking an Alicia's Art Cart to the Duke Teen and Young Adult Oncology Program. Geoffrey Vaughn, medical family therapist and art therapist, (at left in photo, with Kassandra from AC Moore) will use the portable cart to help provide creative expression for teens and young adults with cancer in both inpatient and outpatient settings.

KRISTY EVERETTE

THE MIRACLE MAN



BOB LEVERONE

Bob Porter of Greenville, South Carolina, met a lot of doctors in his 28-year career working in health care management in the U.S. and worldwide. But he has found none other who compared to Joe Moore, MD, professor of medicine and a cell therapy and hematologic malignancies specialist at Duke Cancer Institute and Duke Raleigh.

Over the past 13 years, Moore has managed Porter's care through treatment for six different types of cancer, including Hodgkin's lymphoma, non-Hodgkin's lymphoma, kidney cancer, and Merkel cell carcinoma (a rare skin cancer). Moore often introduces Porter to trainees as "the miracle man."

"I have found Dr. Joe Moore to be the most caring physician I have ever met," Porter says. He exudes confidence and a no-rush philosophy. He has become a friend and a confidant."

Porter speaks as highly of all the people involved in his care, from the technician who conducts his PET scans to receptionists in the nephrologist's office. "Everyone I have met at Duke has been professional, helpful, and has gone beyond the call of duty," Porter says.

In gratitude for the care he has received, Porter made a gift to establish an endowed fund in Moore's honor—the Duke Cancer Institute Leukemia/Lymphoma Endowed Research Fund. He has continued to contribute to the endowment, as have other donors who want to honor Moore. Upon Moore's full retirement, the fund will be named for him.

To sum it up, Porter says, "If it wasn't for Dr. Moore, I wouldn't be here today."

"I have found Dr. Joe Moore to be the most caring physician I have ever met. He exudes confidence and a no-rush philosophy. He has become a friend and a confidant."

To learn more about how you can honor a doctor who has been special to you, please contact Executive Director of Development Michelle Cohen, 919-385-3124, or michelle.cohen@duke.edu.

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A Family Says Thank You

When Monica Crooks was diagnosed with breast cancer, her whole family (husband Rodolfo and children Kadyn, Kylah, and Kaleb) were shocked and scared.

The Crooks family found peace of mind from support groups offered by the Duke Cancer Patient Support Program. "I did not feel alone," Monica says.

Monica is now cancer free. Her daughter Kylah, says, "I would like to give a big thank you to Duke for helping our family get through one of the roughest years of our lives."

YOUR GIFT CAN HELP MORE FAMILIES.
Please use the enclosed envelope, or visit **bit.ly/dcifall2019**

To watch a video about the Crooks family, visit **bit.ly/CrooksFamily**

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