BreakThroughs

Duke Cancer Institute

FALL 2017

LEAN ON ME

ESCAPING THE CANCER CARE BLACK HOLE

Duke is working to connect primary care physicians to the cancer-care team.

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On the case of inflammatory breast cancer.

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FROM THE DIRECTOR

Help Us Change the Rules on Cancer

JARED LAZARUS

MICHAEL KASTAN

ON THE COVER:
LEAN ON ME. Kris Wood, PhD, (right) has fought cancer on two fronts: as a researcher in the lab, and a patient in the hematological malignancies clinic. Pictured here with his physician, Joe Moore, MD, professor of medicine. Read more on page 10.

Four years ago, an energetic cancer researcher named Kris Wood, PhD, was going full steam, setting up his lab at Duke, when he was struck with non-Hodgkin's lymphoma.

Cancer is like that; it's always springing surprises. It doesn't obey the rules.

So we must beat it at its own game; we must change the rules. We are lucky that we have creative researchers like Kris who are helping us do that. Now cancer free thanks to treatment at Duke, Kris is making progress in understanding why perfectly good cancer treatments don't work for some patients, or they work at first, then suddenly stop.

One of the most important ways that Duke Cancer Institute (DCI) is faking out cancer is by nurturing creative collaborations. Earlier this year, DCI was fortunate to recruit a valuable teammate. In this issue, you'll meet Kevin Oeffinger, MD, who joined us specifically to draw in primary care physicians as partners with the cancer-care team, from screening, through treatment, and beyond, all with an eye toward improving the overall health of patients.

In yet another collaboration, Gay Devi, PhD, has won a $1.9 million "Breakthrough Award" from the Department of Defense to build upon her pilot work that improves understanding of and suggests new treatments for inflammatory breast cancer, a relatively rare but very aggressive subtype of the disease. Her partners in this work come from across Duke University Health System.

> "Cancer doesn't obey the rules. You can help us change them."
> Michael B. Kastan

These are just a few examples of the ways we at Duke are working every day to understand and defeat this terrible disease.

Please join us. Cancer doesn't obey the rules. You can help us change them.

Michael B. Kastan, MD, PhD
Executive Director, Duke Cancer Institute
William and Jane Shingleton Professor, Pharmacology and Cancer Biology
Professor of Pediatrics

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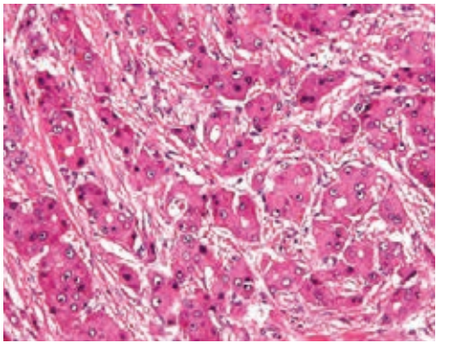
ANNA MAE DIEHL

CYNTHIA GUY

Diehl and Guy receive grant to study rare liver cancer

Two Duke researchers have been awarded a $125,000 grant by the Fibrolamellar Cancer Foundation to develop novel diagnostic tests and treatments for fibrolamellar liver cancer. Cynthia Guy, MD, associate professor of pathology, and Anna Mae Diehl, MD, Florence McAlister Professor of Medicine, are co-principal investigators of the project.

Fibrolamellar hepatocellular carcinoma (FHC) is relatively rare and generally strikes adolescents and young adults without known liver disease. The disease tends to be very aggressive and has often spread outside the liver by the time it is diagnosed, which means in those advanced cases, it cannot be cured by surgery.



2011 MICHAEL BONERT

FIBROLAMELLAR LIVER CANCER is often diagnosed in an advanced stage.

The Fibrolamellar Cancer Foundation provides support for researchers who have not previously worked on the disease, in hopes that they will bring new perspectives that will lead to more effective diagnosis and treatment approaches.

"The fact that fibrolamellar carcinoma contains large amounts of fibrous scar tissue and numerous stem-like cells suggested to us that attacking signaling pathways that promote liver scarring and stem cell accumulation might be a novel way to treat this cancer," Diehl says. "Our laboratory has studied these processes for many years, and we hope to apply this expertise to develop new treatments and diagnostic tests for advanced FHC."

Human-Derived Antibody Treatment Moves Forward

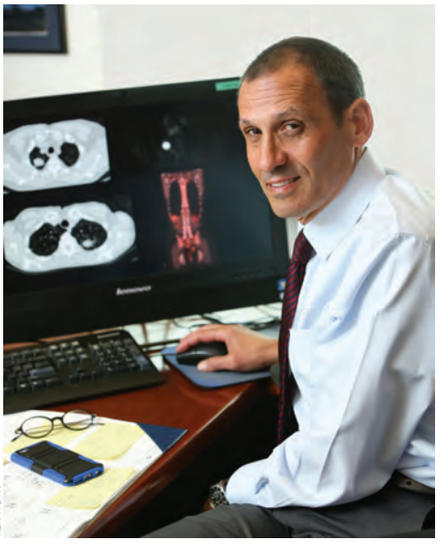
An antibody derived from cancer patients whose immune systems seemed to have a natural defense against the disease has been shown to make a leukemia treatment called rituximab work better.

The new drug was developed at Duke in the lab of Edward Patz Jr., PhD, who derived it from lung cancer patients whose tumors aren't aggressive. He traced that trait to a particular antibody unique to those patients, then developed a method for producing large quantities of it.

In the new work, Patz and colleagues tested the antibody in 11 patients with chronic lymphocytic leukemia. Normally, some leukemia patients respond to rituximab while some don't. In his study, 10 of the 11 patients were found to have no response to rituximab. But, when Patz's antibody was added, 5 of those 10 patients began showing a significant increase in death of cancer cells.

"This is a combination approach, and it appears to strip away immune protection of cancer cells," says Patz, the James and Alice Chen Professor of Radiology. "Patients who had been rituximab resistant became rituximab sensitive."

Patz is excited about the possibilities for the new antibody. He and others have begun a startup company, called Grid Therapeutics, to develop it and have begun manufacturing it. He expects to open a phase 1 clinical trial for cancer patients at Duke by the end of 2018, for patients with advanced lung, breast, and colon cancer.



KEN HUTH

EDWARD PATZ JR.

Duke and N.C. Central Work to Fight Cancer Health Disparities

Duke and nearby North Carolina Central University have been awarded a $2 million, four-year translational research partnership grant from the National Cancer Institute to fight cancer health disparities.

The grant aims to improve detection, treatment, and prevention of inflammatory breast cancer and prostate cancer, both of which are more common and more lethal in African Americans than in other racial and ethnic groups. The grant supports two research projects focused on understanding the molecular pathways that underlie these cancer health disparities, as well as a training program for minority graduate students and postdoctoral fellows in cancer disparities research.

The principal investigators are Steven Patierno, PhD, deputy director of Duke Cancer Institute, and Kevin Williams, PhD, an associate professor in the department of pharmaceutical sciences at North Carolina Central.

Gayathri Devi, PhD, an associate professor of surgery, will co-lead, with Williams, the project on inflammatory breast cancer and will work with Nadine Barrett, PhD, director of the Duke Cancer Institute Office of Health Equity and Disparities, and N.C. Central's Carla Oldham, PhD, in developing a cancer research education program for minority graduate students and postdoctoral fellows in cancer disparities research.

Jennifer Freedman, PhD, assistant professor of medicine, will co-lead the prostate cancer project with Patierno and Rob Onyenwoke, PhD, at N.C. Central.

ALEX NABAUM

DUKE AND N.C. CENTRAL have been awarded a grant to improve detection, treatment, and prevention of inflammatory breast cancer and prostate cancer, both of which are more common and more lethal in African Americans than in other racial and ethnic groups.

According to the American Cancer Society, mortality rates from prostate cancer in African Americans are more than twice as high as in other racial and ethnic groups. Inflammatory breast cancer is more common in African-American women than in other groups.

"This cancer health disparity is an extremely relevant and serious issue to the N.C. Central-Duke Cancer Institute partnership, as African Americans comprise 39 percent of the population of Durham and 22 percent of the population of North Carolina," says Patierno. "Although it is well documented that socioeconomic and sociocultural factors contribute heavily to cancer health disparities, they do not fully explain the differences in cancer incidence, aggressiveness, and mortality among racial and ethnic groups."

Campaign Raises $252 Million for Duke Cancer Institute

Duke Forward, the largest fundraising campaign in Duke University's history, concluded in June 2017.

Because of you, Duke Cancer Institute raised $252 million for the seven-year campaign.

103,800
Donors to the Duke Cancer Institute campaign

$252 million
Total raised to advance cancer research, care, and education.

PART OF
$1.4 billion
RAISED FOR DUKE HEALTH

THANK YOU FOR YOUR SUPPORT!

DCI FRIENDS

KAREN E. BUTLER

RIDING FOR RESEARCH. In July 2017, **Paul Rudershausen** began a solo bike ride across North America, in memory of his mom, who died five months after a lung cancer diagnosis. The ride benefits the research of **Jason Somarelli, PhD**. Somarelli (left), a faculty member in Duke Cancer Institute's Canine Comparative Oncology group, studies the genes that promote the spread of cancer in both dogs and humans. Paul (right), pictured with his dog Qualie, was riding about 100 miles a day, and as of mid September he has raised more than $9,000 toward his $20,000 goal. To donate and follow his ride, visit **riding4research.org**.

THE SECOND ANNUAL BIG BISCUIT SHOWDOWN on July 27, 2017, raised more than $15,000 for prostate cancer research at Duke Cancer Institute. The food competition featured 13 teams of chefs from Rise Biscuits and Donuts locations in Raleigh, Durham, and Chapel Hill, paired with a local brewery or beverage company. All proceeds benefited Duke through Give 1 for Dad, an effort to raise funds for a clinical trial of a novel treatment for advanced prostate cancer patients. The event launch introduced the first patient enrolled in the clinical trial, **Paul Gomulinski**. He will be treated with the Poley Protocol, named after **Sam Poley** (second from right), who launched Give1forDad in honor of his father, who died after a battle with prostate cancer. To donate, visit **give1fordad.com**.

THEY CRUSHED IT! Almost 400 runners competing in the 4th annual **Crush Colorectal 5K** in March 2017 raised $110,125 for colorectal cancer research at Duke as well as community outreach.

THE 24TH ANNUAL ANGELS AMONG US 5K, held in April 2017, raised more than $2.1 million for the Preston Robert Tisch Brain Tumor Center at Duke.

Escaping the Cancer Care Black Hole

BY **ANGELA SPIVEY**

People diagnosed with cancer enter a period of intense treatment at a cancer center, and it can seem to their primary care physicians that they have disappeared. The patient's overall health can suffer as a result. Duke's new Center for Onco-Primary Care aims to change that.

At age 49, Stacey Koplik has already had a mastectomy to prevent breast cancer, as well as two CT scans to screen for heart disease. When she was 18, she had large amounts of radiation to treat Hodgkin's lymphoma, which cured her cancer but increased her risk for heart disease, breast cancer, and skin cancers.

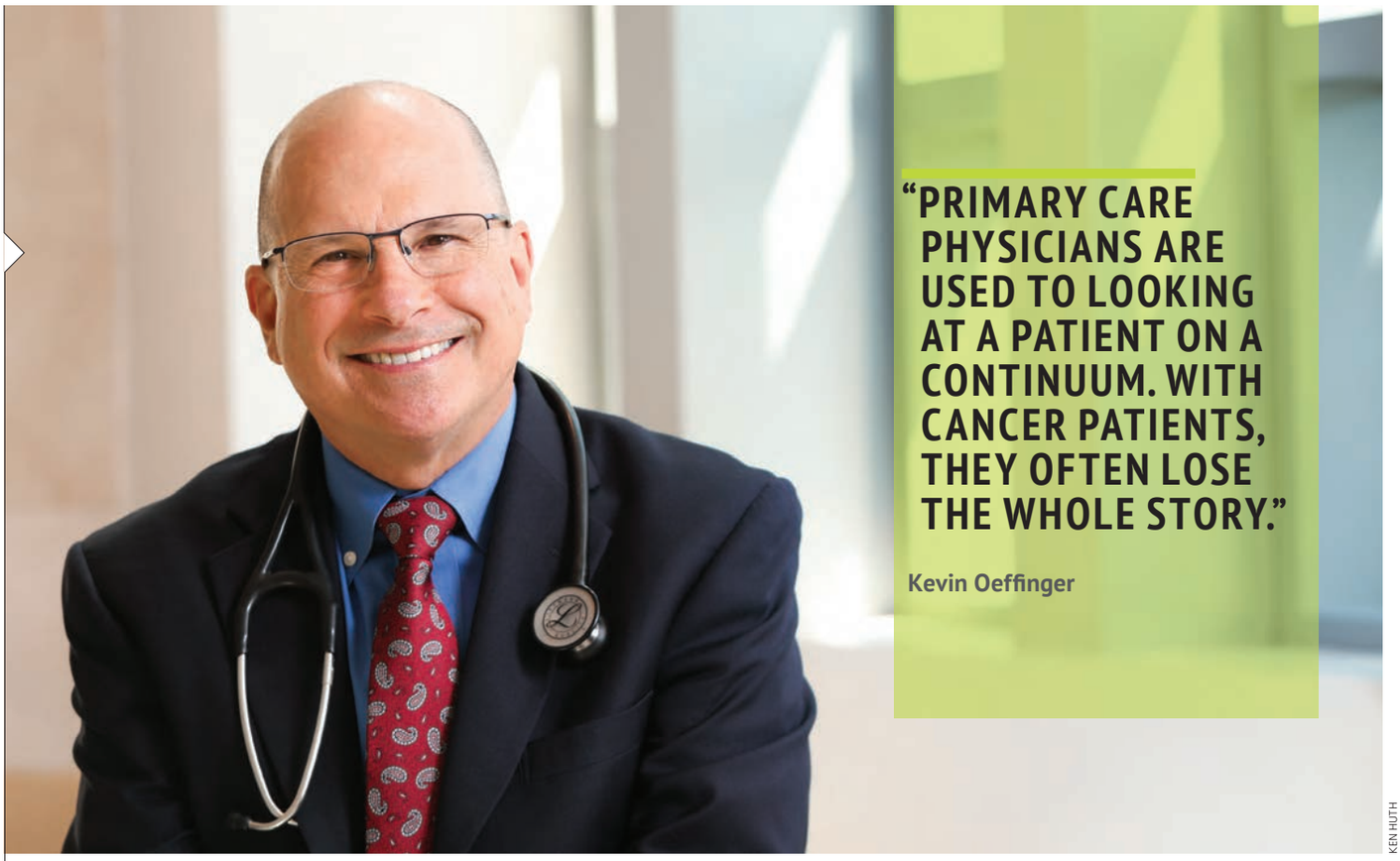
But when she finished cancer treatment almost 30 years ago, none of her oncologists said anything about her needing special care. Her thyroid no longer functioned, so when she moved to New York City after college, she saw an endocrinologist for yearly exams. But he didn't know anything about long-term side effects of radiation and was reluctant to order screening tests for her heart.

Soon after, Koplik found Kevin Oeffinger, MD, who at that time ran a cancer survivorship program at Memorial Sloan Kettering Cancer Center. "I wanted to be as healthy as I can be and live as long as possible, and I wanted someone who would understand what I should be looking for," says Koplik, a former lawyer. "I see Dr.

AURORA ROSE AND JOHN FREDRICKSON

Treatment for Hodgkin's lymphoma at age 18 left **STACEY KOPLIK** with increased risk of heart disease, breast cancer, and skin cancers.

KEN ORVIDAS



KEN HUTH

Oeffinger once a year, and he keeps track of what tests I should be having. He knows exactly what he's doing, and he patiently answers a gazillion questions in a language I can understand."

Oeffinger, who joined Duke Cancer Institute in 2017, is a family medicine physician who began treating and studying people with cancer in 1994, when an oncologist asked him to help start one of the first clinics in the country designed especially for adult survivors of childhood cancers.

Over more than 20 years, Oeffinger and other researchers have documented what they call the cancer treatment "black hole." A person diagnosed with cancer often disappears into intense treatment at a cancer center and may not see a primary care physician for years. When the patient emerges, their regular physician has no idea how the cancer treatment may have affected their overall health or whether common problems such as high blood pressure or high cholesterol have been properly managed. "Primary care physicians are used to looking at a patient on a continuum. With cancer patients, they often lose the whole story," Oeffinger says.

In March 2017, Oeffinger joined Duke Cancer Institute to lead a new clinical and research effort specifically to fix this problem. The Duke Center for Onco-Primary Care will formally link primary care physicians with the cancer care team in the care of patients before, during, and after cancer. In other words, it will aim to eliminate the black hole.

A NEW MODEL

Historically, many cancer survivors have simply visited their oncologist indefinitely, for everything. That practice is costly and inefficient, especially considering the expected shortage of oncologists in the next 10 years, says Steven Patierno, PhD, deputy director of Duke Cancer Institute. Patierno recruited Oeffinger to Duke to create a new model. They first worked together more than a decade ago, when Oeffinger helped train internal medicine physicians at the cancer survivorship clinic that Patierno started when he was executive director of the George Washington University Cancer Center. Patierno became interested in survivorship because of two patients who told him that the worst day of their cancer journey, aside from the day they were diagnosed, was the day they finished treatment. "Each patient, at different times, said to me, 'When I finished treatment, someone basically patted me on the back and said, 'Things seem to have gone well. See you later. Call us if you have any problems.' It hit me like a freight train; their entire lives had changed, and we did nothing for them," he says.

The onco-primary care model aims to improve care even before a cancer diagnosis—starting with helping primary care physicians and their patients make the best choices about screening. Prostate cancer screening is a prime example. "All of a sudden, the U.S. Preventive Services Task Force said 'Don't screen anymore.' And that didn't seem right,"

says John Ragsdale, MD, medical director of Duke Family Medicine Center. Now, the guidelines advise primary care physicians to talk to their patients to help them come to the decision that's best for them. Ragsdale is collaborating with another family medicine doctor to create and study a tool to guide primary care physicians in those conversations. "It's not black and white. It's really shades of grey now," he says.

Ragsdale also runs a once-a-week survivorship clinic for high-risk patients at the Duke Cancer Center. He's driven by conversations he has had with cancer survivors, including his sister, who was diagnosed with breast cancer at a young age. "I know the questions that need to be asked of her that aren't necessarily being asked all the time, and that bothered me," he says.

Over the next 10 years, cancer screening will become more personalized, based on individual risk, Oeffinger says. Rather than screening everyone with the same test at the same age, risk will be determined by tests of genetic markers and tests that detect circulating tumor cells. Primary care providers and oncologists will need to work together to implement those changes.

A DANGEROUS GAP

For people already diagnosed with cancer, the gap between cancer care and primary care is a dangerous one. For instance, studies have shown that women who are seven years out from a breast cancer diagnosis have a higher risk of dying from heart disease than women who have never had breast cancer. One of the reasons—a cancer care team may focus so intently on cancer therapy that risk factors for heart disease, such as high blood pressure and high cholesterol, aren't likely to be managed well. "If we don't keep the primary care physician involved during or soon after therapy, sometimes hypertension or lipid disorders actually increase the risk of dying more than the breast cancer," Oeffinger says.

KEN HUTH

JOHN RAGSDALE is creating a tool to help guide doctors and patients in their conversations about cancer screening.

Cancer treatments themselves can also increase the risk of many common diseases. "Many of our cancer treatments simply accelerate the aging process," Oeffinger says. "We know the agents that affect the heart, the lungs, the kidneys. So we just need to convey to the primary care physician, in a formal way, what they need to be watching out for."

HOW YOU CAN HELP

You can help us build new programs like the Center for Onco-Primary Care. To donate, use the enclosed envelope, or visit **bit.ly/dcifall2017.**

KEN HUTH

STEVEN PATIERNO on cancer survivors: "It hit me like a freight train; their entire lives had changed, and we did nothing for them."

ONLY AT DUKE?

Primary care doctors are actually already very good at the kind of thing that most cancer survivors need—managing multiple risk factors and conditions and diagnosing any new problems, Oeffinger says. They just need better communication from the cancer-care team. For high-risk survivors, such as those who have had bone marrow transplants or were diagnosed with cancer at a young age, long-term management may be needed from survivorship-trained health care workers in a cancer center survivorship clinic like those run at Duke by Oeffinger and Ragsdale. Nurse practitioners and physician assistants will also play a large role in these clinics.

Oeffinger says that Duke is one of the few places in the United States where he can carry out this vision, study the results, and then use what he finds to help patients around the country. "To study a patient from screening through cancer treatment and survivorship and even until end of life, I need a large health care center that has strong primary care, a strong cancer center, and a single electronic health record, so we can actually model where we are going over the next five to ten years in a diverse patient population."

As for Koplik, she is doing well, staying busy raising her two sons, who are 14 and 17. "My heart is—knock on wood—okay so far," she says. "I can't tell you how wonderful Dr. Oeffinger is. I've always felt like I was doing what I needed to do and that I was in good hands. Which is why I'm pretty sure I'm coming down to Duke. It's hard to find that in most doctors."

Oeffinger and team are working to make sure that for cancer patients, that kind of care will be easier to find. "We can do better," he says.

Why do perfectly good cancer treatments suddenly stop working?

Researcher and lymphoma survivor Kris Wood is finding answers.

Kris Wood, PhD, had been going full tilt for more than six months, ever since he'd been hired to the faculty in the Department of Pharmacology and Cancer Biology at Duke. He was working 12 stressful hours a day, adjusting to a new place, getting his lab up and running, training his research assistants, living on coffee. It was no surprise, he thought, that he felt exhausted and short of breath all the time.

But it kept getting worse. Finally, thinking he might have walking pneumonia, Wood went to a Duke clinic near his home in south Durham, where a doctor examined him and took a chest X-ray. When the doctor got the film back, he walked into the exam room and closed the door.

"He held the x-ray up in front of me," recalls Wood. "He said 'Kris, this is your heart; it looks fine. These are your lungs; those look fine too. Then he pointed to this cloudy shape in the middle and said, 'But this? I don't know what that is. But it is not good.'"

He was right. The mass, directly behind Wood's sternum, turned out to be a rare type of non-Hodgkin's lymphoma, a blood cancer.

More than most patients, Wood knew what he was up against. He has devoted his professional life to studying cancer, especially seeking to unlock the secrets of cancer's pernicious ability to thwart the drugs we use to try to kill it.

In the case of the type of non-Hodgkin's lymphoma that Wood had, we are winning that race; the standard therapy is extremely effective.

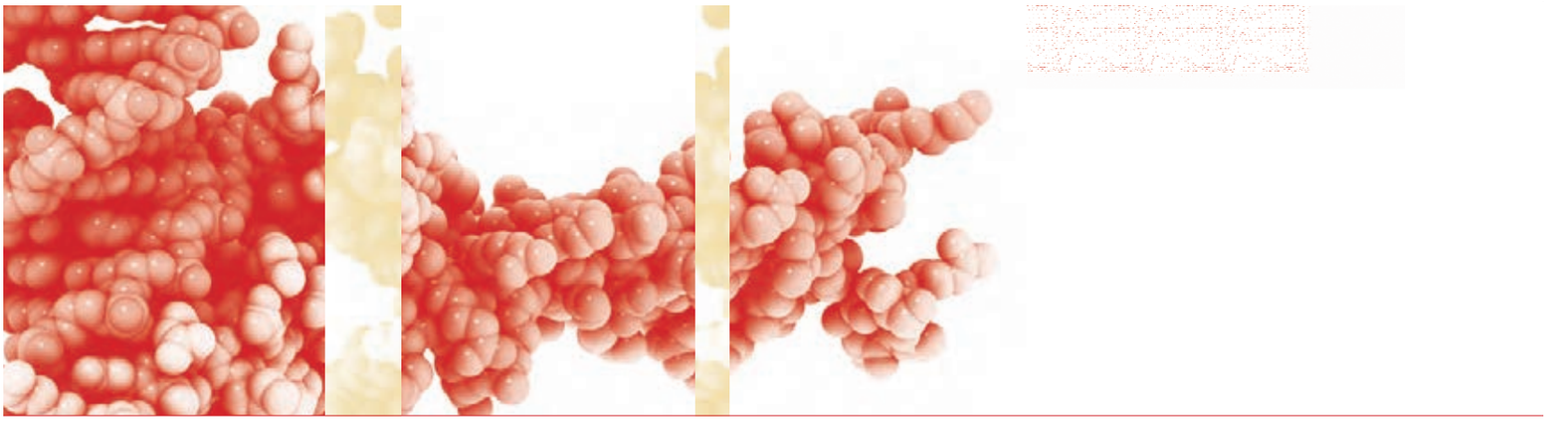
"Thirty or forty years ago, this type of lymphoma would have had a bad prognosis," Wood says. "Now, you get treated, and the overwhelming majority of people are cured."

The Duke community rallied to Wood's side— members of his department and lab staff even shaved their heads in solidarity when chemotherapy temporarily cost him his hair—and under the expert care of Joseph Moore, MD, Wood received swift and effective treatment.

BY **DAVE HART**

Fighting the

RESISTANCE



"Dr. Moore had an extraordinary impact on my life," says Wood. "Not only did he give me the therapy that cured me, he also cared for me in every sense: he gave me confidence and calmed my fears. He's a brilliant physician, a real gem here at Duke."

Four years on, Wood is cancer free.

"In one sense, the experience didn't really change how I feel about my work," Wood says. "I always thought cancer was important. That's why I study it. But my getting sick did bring it home to me. The therapy I received is the product of decades of research. And the research we do today will help somebody else with some other type of cancer down the line. I tend to be very optimistic about our chances. If I weren't, I wouldn't come to work every day."

WHACK-A-MOLE

Wood's research focuses on cancer resistance: the ability of cancer cells to activate effective biochemical defenses to protect themselves from the drugs we use to fight them.

"We have drugs that, in principle, should kill many cancers," Wood says. "But in practice, they don't. That's resistance. I would argue that it's as big a problem as any in cancer. Because if we could figure out what the cancer cells are doing to stay alive in the face of drugs that should kill them, then we could target those mechanisms. And then all of a sudden a drug that's currently pretty paltry would become one that's super potent."

"If we could figure out what the cancer cells are doing to stay alive in the face of drugs that should kill them, then we could target those mechanisms. And then all of a sudden a drug that's currently pretty paltry would become one that's super potent."
Kris Wood

In general, resistance happens by means of biochemical signaling pathways. Faced with an attack by anti-cancer drugs, certain molecules within cancer cells perform chemical reactions that activate other molecules to do the same, and so on down the line. The result is a complex chemical defense that enables cancer cells to overcome the toxic effects of drugs.

Resistance might not be such a difficult problem if a particular cancer deployed its defenses by activating only one or two signaling pathways: figure out how to block that pathway, and you overcome the cancer's resistance.

But in many cases, tumors employ a great many resistance pathways, each with a distinctive molecular mechanism. Trying to identify, characterize, and develop successful countermeasures to block each unique pathway is daunting almost to the point of futility.

"Even if you block one pathway, others will emerge," Wood says. "It's like a game of whack-a-mole, and there are just too many moles."

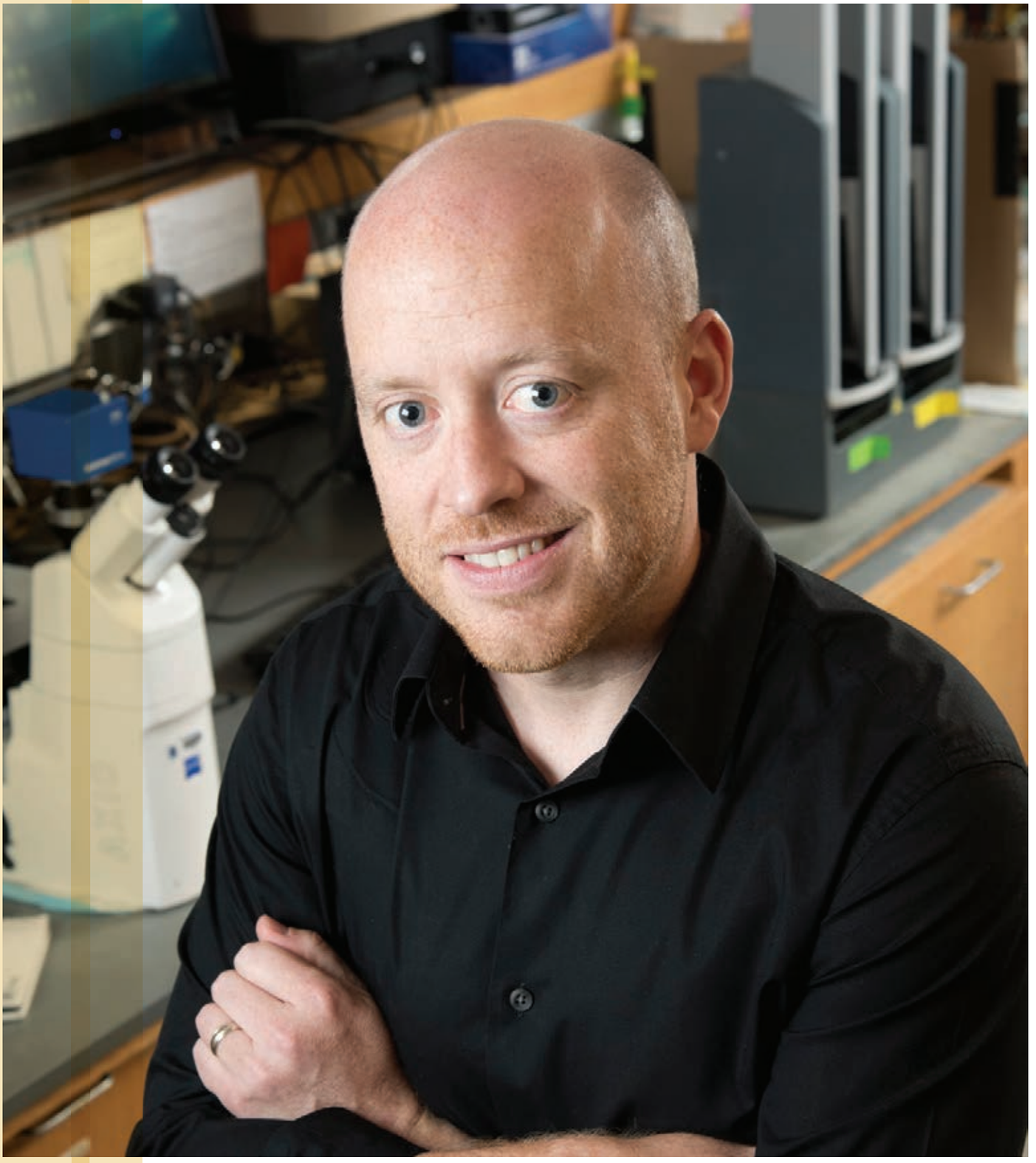
A POSSIBLE SOLUTION

Wood's lab analyzes very large sets of data to systematically identify and characterize the pathways of resistance, using a host of genomic, computational, and biochemical techniques. "We throw everything at it," he says.

And in doing so, they've discovered a possible solution to the whack-a-mole problem. Rather than isolate and block each pathway of resistance, Wood and his lab have homed in on the shared features of all those pathways. Successfully find and target a crucial common factor, and you might be able to clamp a lid over all the mole holes at once.

"We've found that in many cases the pathways of resistance funnel down to a common biological program," Wood says. "By blocking that program, you should be able to block the emergence of resistance."

Most recently, Wood has focused on resistance in a common type of melanoma characterized by a mutation in a gene called BRAF. In these cases—which constitute about



LES TODD

KRIS WOOD today, in the lab.

half of all melanomas—patients often initially respond well to treatment with BRAF pathway-inhibiting drugs. But very often, resistance emerges, driven by a whole series of different pathways, slowing and then completely reversing the effectiveness of treatment.

Wood and his lab have recently discovered that although many pathways can individually drive resistance to BRAF inhibitors, they all converge on a single gene, called MYC. Working in cell lines and mouse models, he has shown that administering a drug that blocks the activity of the MYC protein produced by the gene can prevent and even reverse resistance.

And because MYC activation is a cardinal feature of resistant melanoma cells, drugs that block it can selectively target drug-resistant melanoma cells without affecting other harmless ones.

> "Dr. Moore had an extraordinary impact on my life. Not only did he give me the therapy that cured me, he also cared for me in every sense: he gave me confidence and calmed my fears."
> Kris Wood

FROM ENGINEER TO CARD-CARRYING BIOLOGIST

Wood came to cancer biology, and to biomedicine in general, by a somewhat unorthodox route: engineering. He grew up on his grandfather's farm in Kentucky without any exposure to academic science, but as a kid he loved math, and as an undergraduate at the University of Kentucky he displayed a distinct talent for chemistry.

Math and chemistry converged in chemical engineering, and he followed up his undergraduate degree with a PhD in chemical engineering at the Massachusetts Institute of Technology. There he became intrigued by the potential of applying engineering tools and principles to medical problems. Cancer seemed the most interesting of those challenges.

"My hope was that I could eventually combine my engineering mindset with the knowledge of basic biology to innovate in ways that other people weren't, because the engineers were working on engineering problems and the biologists were working on biology problems," he says. "But toward the end of my PhD, I realized that I didn't know enough basic biology to really innovate as a cancer researcher."

So he spent five years as a National Institutes of Health postdoctoral fellow in a basic biology lab at

JOSEPH MOORE (left) treated researcher Kris Wood for non-Hodgkin's lymphoma.

LES TODD

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You can support research that leads to better treatments. Use the **enclosed envelope**, or visit **bit.ly/dcifall2017**.

the Whitehead Institute for Biomedical Research and the Broad Institute of Harvard and MIT. Then, as "a card-carrying biologist," he came to Duke in 2012.

"Duke was crazy enough to hire an engineer to work in a biology department," he says. "At the end of the day, although my career path went a bit off the usual track, I'm happy I did it that way. I can apply a systematic engineering mindset to really important questions in biomedicine and cancer."

A BRIGHT OUTLOOK

Everything Wood has seen in his field leaves him optimistic that the outlook is positive in the fight against cancer.

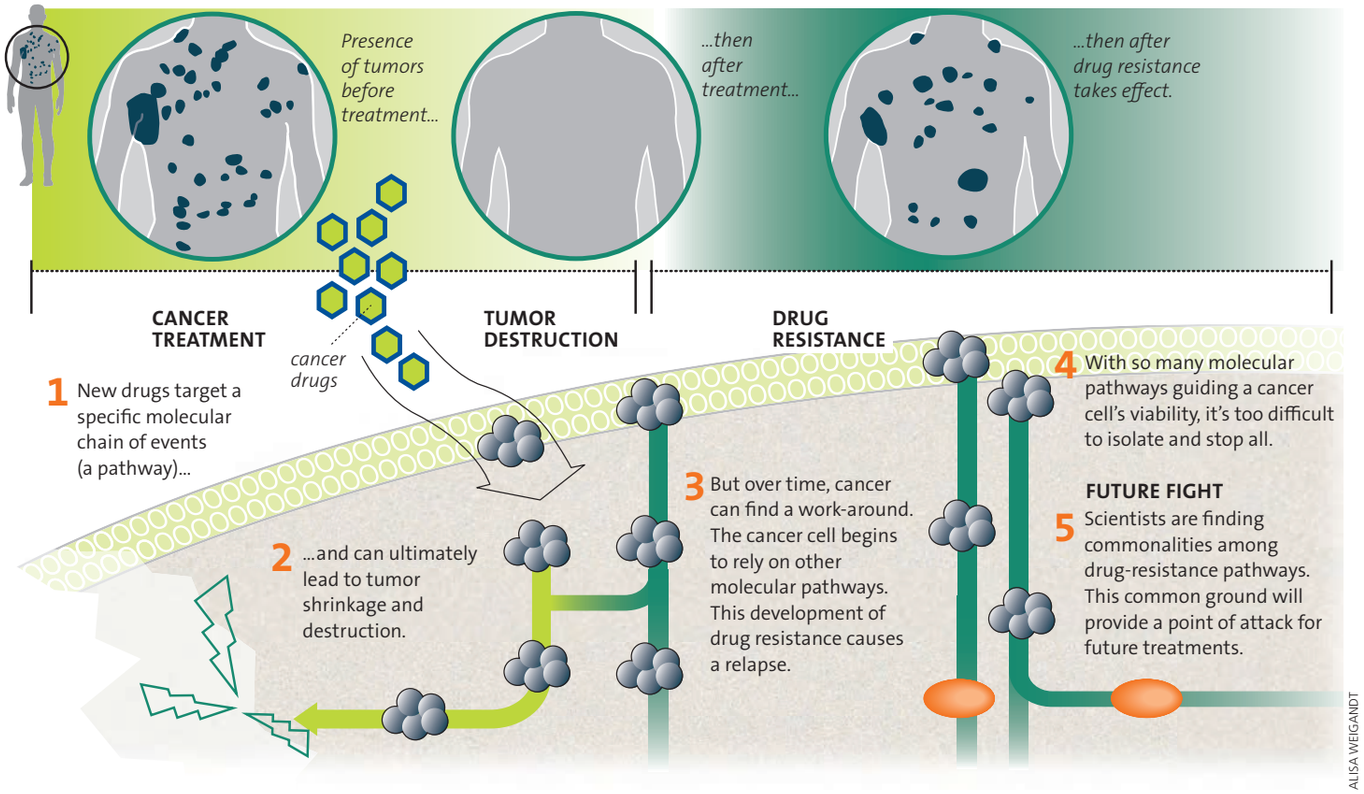
"Ultimately, we are working toward a future where cancers that kill people now can be managed so that people can live years and years with them, and in some cases even be cured," he says. "Where will that progress come from? It'll come from people like me who figure out how resistance works and how to overcome it. It will come from people who are developing entirely new types of drugs and therapeutic modalities. It will come from people who create early detection techniques that allow you to find the cancer early enough that you can remove it with a scalpel. It's going to be a combination of all these things. And we as a community are making enormous progress on all these fronts. That's why I can say with confidence that the future looks bright."

Kris Wood is an assistant professor of pharmacology and cancer biology in the Duke University School of Medicine.

Joseph Moore is a professor of medicine.

AN EVER-EVOLVING TARGET

As promising new drugs come into play, scientists must also tackle cancer's ability to navigate around them.



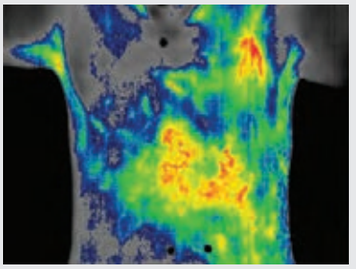
ALISA WEIGANDT

RARE AND DANGEROUS

It doesn't look or act like most breast cancers. But inflammatory breast cancer may just hold the secret to understanding what happens when any breast cancer turns deadly.

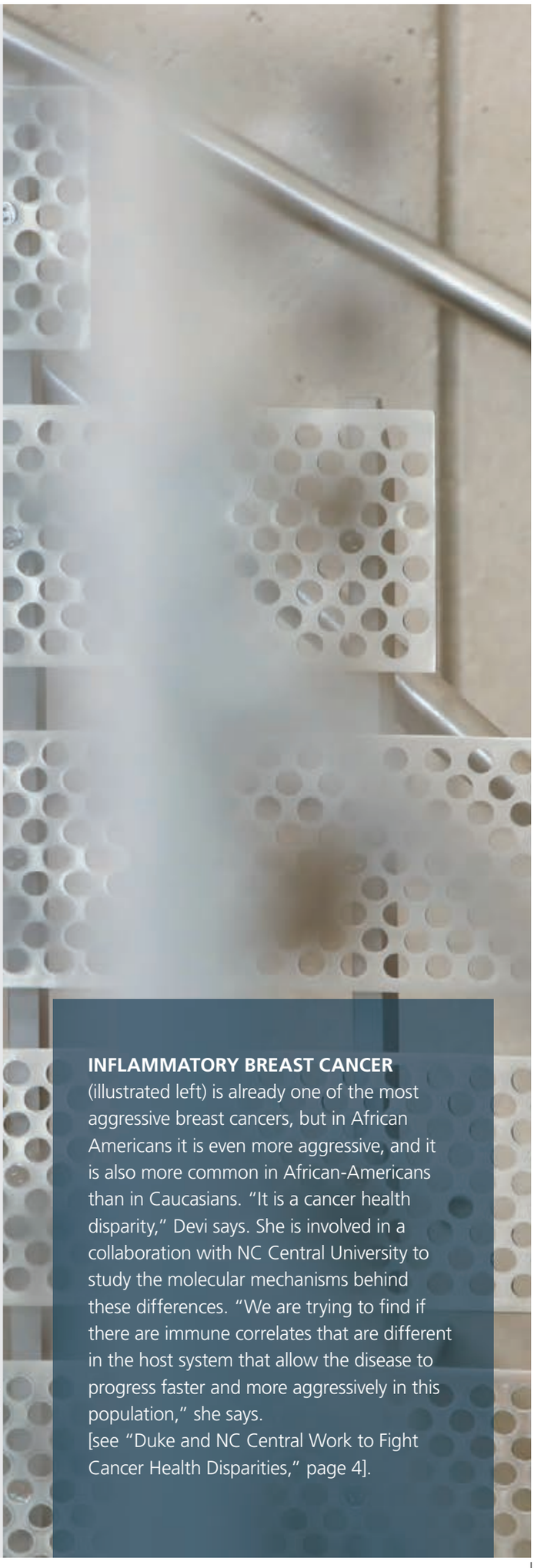
By Angela Spivey

When you think of breast cancer, you probably picture a telltale lump. Gayathri Devi, PhD, dispels that image with a few photos: a person's chest with what looks like a rash, then a thermographic version of the image showing the heat from elevated blood flow spread throughout the chest. This is inflammatory breast cancer (IBC).



Most patients with IBC don't have a single tumor mass that can be isolated and removed. Instead, the cancer appears as clusters of tumor cells called tumor emboli that infiltrate the skin and lymphatic vessels of the chest. "It's highly diffuse, so that even if you collect the tissue, there are hardly any tumor cells in the biopsy," says Devi, an associate professor of surgery and pathology. And, patients are treated with chemotherapy and radiation before surgery, which adds to the lack of tumor samples for research. Devi is developing better ways to sample, image, and understand IBC, enlisting help from researchers and clinicians in many other fields.

IBC is studied by only a handful of groups in the world, in part because it is rare. But it is the most aggressive form of breast cancer. IBC accounts for only about 6 percent of all breast cancers in the United States but causes 10 percent of the overall breast cancer deaths.



KEN HUTH

INFLAMMATORY BREAST CANCER (illustrated left) is already one of the most aggressive breast cancers, but in African Americans it is even more aggressive, and it is also more common in African-Americans than in Caucasians. "It is a cancer health disparity," Devi says. She is involved in a collaboration with NC Central University to study the molecular mechanisms behind these differences. "We are trying to find if there are immune correlates that are different in the host system that allow the disease to progress faster and more aggressively in this population," she says.
[see "Duke and NC Central Work to Fight Cancer Health Disparities," page 4].

GAYATHRI DEVI studies how inflammatory breast cancer cells are able to evade the body's programmed cell death mechanisms that normally get rid of damaged or abnormal cells. "We see that these cancer cells … are basically saying, 'Bring it on, I'm going to use this fundamental cellular process to my advantage.'"

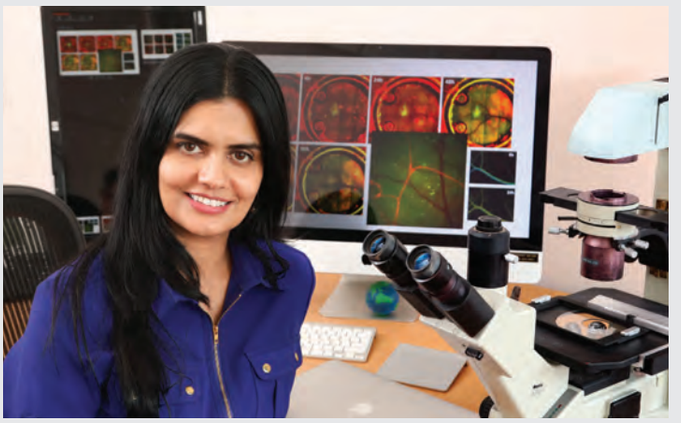
Because IBC is so dangerous—it resists treatment and easily spreads (metastasizes)—Devi thinks that what she learns can be applied to help fight other types of aggressive cancers. The Department of Defense agrees; in August 2017, they gave Devi and collaborators a $1.9 million "Breakthrough Award" to study why some breast cancers are more metastatic than others, based in large part on her pilot research with IBC. Collaborators include Mark Dewhirst, PhD, and Greg Palmer, PhD, who provide expertise in imaging; Mike Morse, MD, who helps with identifying immune biomarkers; and Shelley Hwang, MD, chief of breast surgery, and Shannon McCall, MD, Director of the Duke Biorepository and Precision Pathology Center, who work to increase banking of patient tumor samples.

It is IBC's differences that may hold the key to understanding all types of metastatic breast cancer. One characteristic that makes any breast cancer more likely to spread is if it invaded the lymphatic system. And about 95 percent of IBCs have already done that when diagnosed. Rather than spread through a single cell that travels the bloodstream, most IBC travels in clusters, via vessels in the skin that carry lymph—a fluid that contains immune system cells whose very job is to fight intruders. "How do these tumor clusters and tumor cells not only survive in that environment but also invade and go into different organs?" Devi says.

To study that question, Devi has developed some unique models; one takes cancer cells collected from patients and grows them in culture, and another in mice. "We aim to study the disease from bedside to bench, then back," she says. They take cell samples from patients, grow them in these models, then look for activation or inhibition of genomic and protein markers that regulate the cancer cells' ability to survive, proliferate, and become invasive. Then the team will determine if patients express those same markers. The hope is that the markers that ring true in both the models and in the patients will be targets for better treatment.

Inside the body, IBC cells are accustomed to the "shear stress" of the lymphatic system—the movement of lymph flowing through vessels in the skin. Devi's cell-culture IBC model uses machines to mimic that motion, enabling the researchers to study the actual formation of the tumor emboli—a hallmark of IBC.

Using these more realistic models, Devi has found that IBC is very good at escaping a tightly controlled process that our bodies use to get rid of abnormal cells, called programmed cell death. "To maintain homeostasis and cell populations in tissues, millions of our cells die every second and are replaced," she explains. To escape cell death, her laboratory has found, IBC cells take advantage of a process that normal cells use to survive during times of cellular stress, called the adaptive stress response. "The cancer cells are changing and adapting and signaling in the tumor microenvironment such that they are basically saying, 'Bring it on, I'm going to use this fundamental cellular process to my advantage.'" If Devi could shut down that ability, she could slow down IBC and make it more sensitive to anti-cancer drugs.



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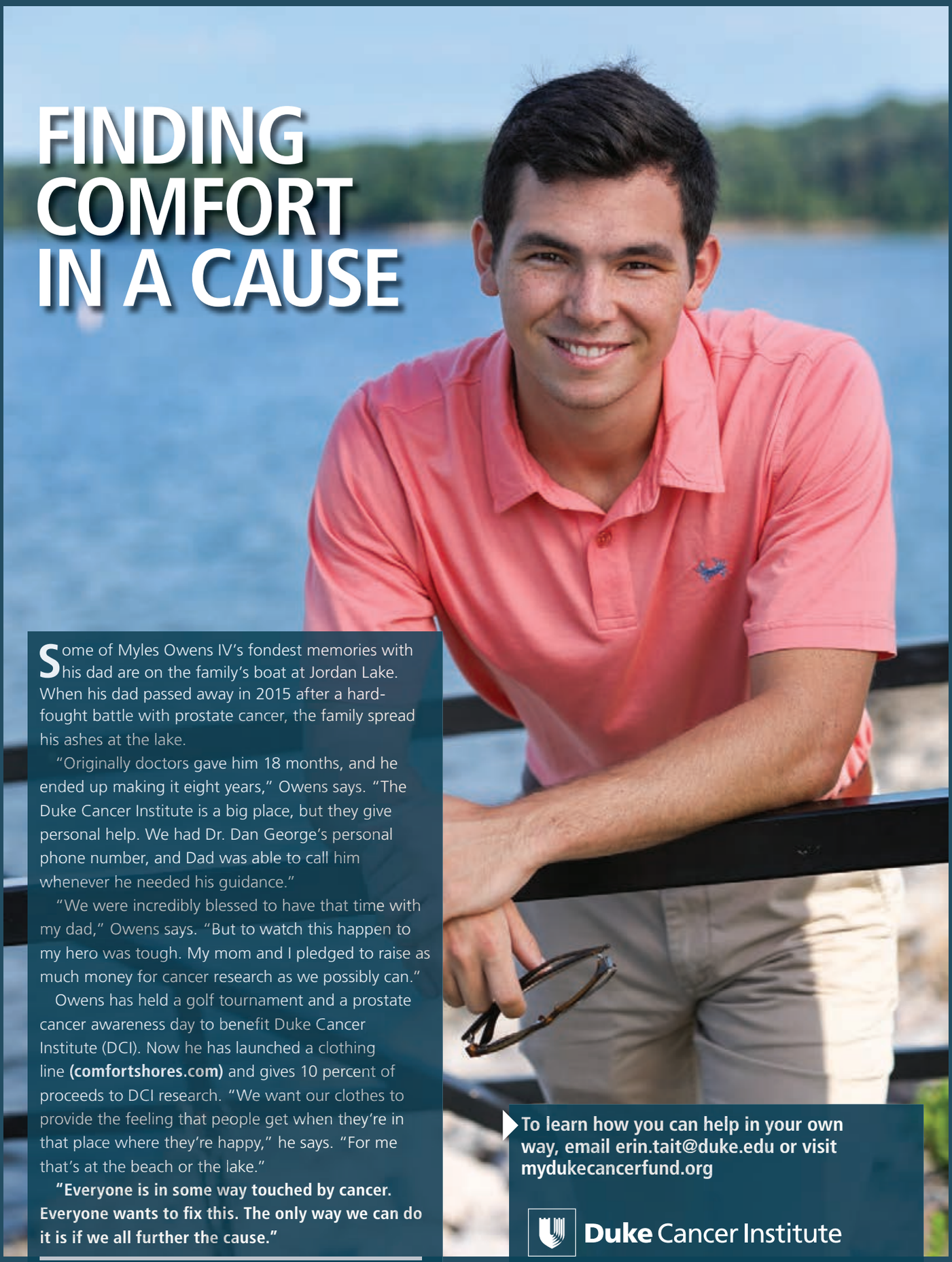
GAYATHRI DEVI is developing better ways to sample, image, and understand inflammatory breast cancer with help from researchers and clinicians in many other fields.

Devi's team recently found that IBC cells express high levels of proteins that inhibit programmed cell death. After screening drug and chemical libraries, her team tested an existing drug used to manage alcoholism, called disulfiram, and found that it can counteract those proteins. "We showed that disulfiram is able to override this adaptive stress response at multiple points," Devi says. "It was able to kill the cancer cells while sparing normal cells in IBC." When the researchers combined disulfiram with copper, it improved the ability of the drug to get inside the IBC tumor clusters. "It's very difficult to target and get all the way inside the tumor emboli, because it's a cluster of tumor cells that are constantly moving and have different features," Devi says. "Disulfiram in combination with copper provides a novel way to target and inhibit formation of the IBC tumor emboli directly."

Devi and collaborator Hwang (the breast cancer surgeon) are seeking funding for a clinical trial that adds disulfiram to IBC treatment. That isn't easy to get, because this treatment won't be a money-maker. "Disulfiram is a generic drug. It's very inexpensive to buy and therefore a challenge to get industry support for drug repurposing," Devi says. "We need to engage advocates and increase community awareness. This is the reality of trying to fight an orphan disease."

KEN HUTH

FINDING COMFORT IN A CAUSE



Some of Myles Owens IV's fondest memories with his dad are on the family's boat at Jordan Lake. When his dad passed away in 2015 after a hard-fought battle with prostate cancer, the family spread his ashes at the lake.

"Originally doctors gave him 18 months, and he ended up making it eight years," Owens says. "The Duke Cancer Institute is a big place, but they give personal help. We had Dr. Dan George's personal phone number, and Dad was able to call him whenever he needed his guidance."

"We were incredibly blessed to have that time with my dad," Owens says. "But to watch this happen to my hero was tough. My mom and I pledged to raise as much money for cancer research as we possibly can."

Owens has held a golf tournament and a prostate cancer awareness day to benefit Duke Cancer Institute (DCI). Now he has launched a clothing line **(comfortshores.com)** and gives 10 percent of proceeds to DCI research. "We want our clothes to provide the feeling that people get when they're in that place where they're happy," he says. "For me that's at the beach or the lake."

"Everyone is in some way touched by cancer. Everyone wants to fix this. The only way we can do it is if we all further the cause."

To learn how you can help in your own way, email erin.tait@duke.edu or visit mydukecancerfund.org

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Safe and Cared For

Breast cancer survivor Leslie Gartenberg (at left in photo) remembers a time not so long ago when she was so tired that she couldn't drive herself to Duke Cancer Center. Her friend Sharon Mills drove her to that chemotherapy treatment and all the rest: 17 rounds altogether. "I wouldn't have gotten through it without her," Gartenberg says.

Gartenberg also credits her entire treatment team at Duke. "Therapists, nurses, doctors—every single person I've met—does their best to help you feel safe and comforted and informed and cared for," she says.

Today, Gartenberg is finished with treatment and has no evidence of disease. "Just to see Leslie today is pretty remarkable," Mills says. "She ran up the steps and she drove. Thank you to Duke for taking such good care of my friend."

KEN HUTH

READ MORE about these two friends on **dukecancerinstitute.org** or **facebook.com/dukecancerinstitute**.

Share your own story with the hashtag **#MyDukeCancerStory**.

To learn more about sharing your #MyDukeCancerStory, email **dcidevelopment@duke.edu**.

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