

TECHNOLOGY RACES AGAINST DISEASE

CAR T-Cell Therapy Making Gains At Moffitt Cancer Center

By Ann Miller Baker

It started as a case of “physician, heal thyself.”

Jeff Backer, an Orlando emergency room physician, claims to have never been sick a day in his life. But during a 2014 visit with his daughter in New York City, their usual walks left him totally exhausted. He’d never felt this way before. Weeks later at home, when he couldn’t quite shake it, he decided to self-diagnose. Flu? No. Anemia? Possibly. Maybe a chest x-ray from his family physician would reveal a clue.

It showed shadows throughout his chest.

The straightforward diagnosis was later confirmed by CT scan and biopsy. Dr. Backer had a type of non-Hodgkin lymphoma called diffuse large B-cell lymphoma. Worse yet, he had a rare and aggressive subtype – double hit, which predicted that any response he might have to conventional therapy wouldn’t last long.

Multiple rounds of chemo in Orlando and a subsequent stem cell transplant at Moffitt both gained him remissions that lasted a matter of months.

But that last relapse had a silver lining. It meant he might finally qualify for a clinical trial he’d read about – the one that first brought Moffitt to his attention.

As Dr. Backer puts it, “The secret to being a successful cancer survivor is just stay alive long enough until technology catches up to your disease.” He was ready to pin his hopes on something that hadn’t been readily available when he was originally diagnosed – the latest development in cancer immunotherapy, called CAR T-cell therapy.

UNLEASHING THE LION

CAR T stands for chimeric antigen receptor T-cell therapy – quite the mouthful.

Those who study mythology know the Greek word chimera describes a fire-breathing monster with a lion’s head and a serpent’s tail. In science, chimeras are a mix of genetically different tissues – even molecules with parts derived from two or more organisms that are fused through laboratory manipulation.

The chimera in CAR T starts with the patient’s own natural defenders, the T cells. They are the immune system’s enforcers, taking out infections or anything “foreign” to the body. Since cancers are the body’s own cells growing out of control, T cells

don’t always target them for destruction. Cancers are notorious for cloaking themselves against the body’s defenses.

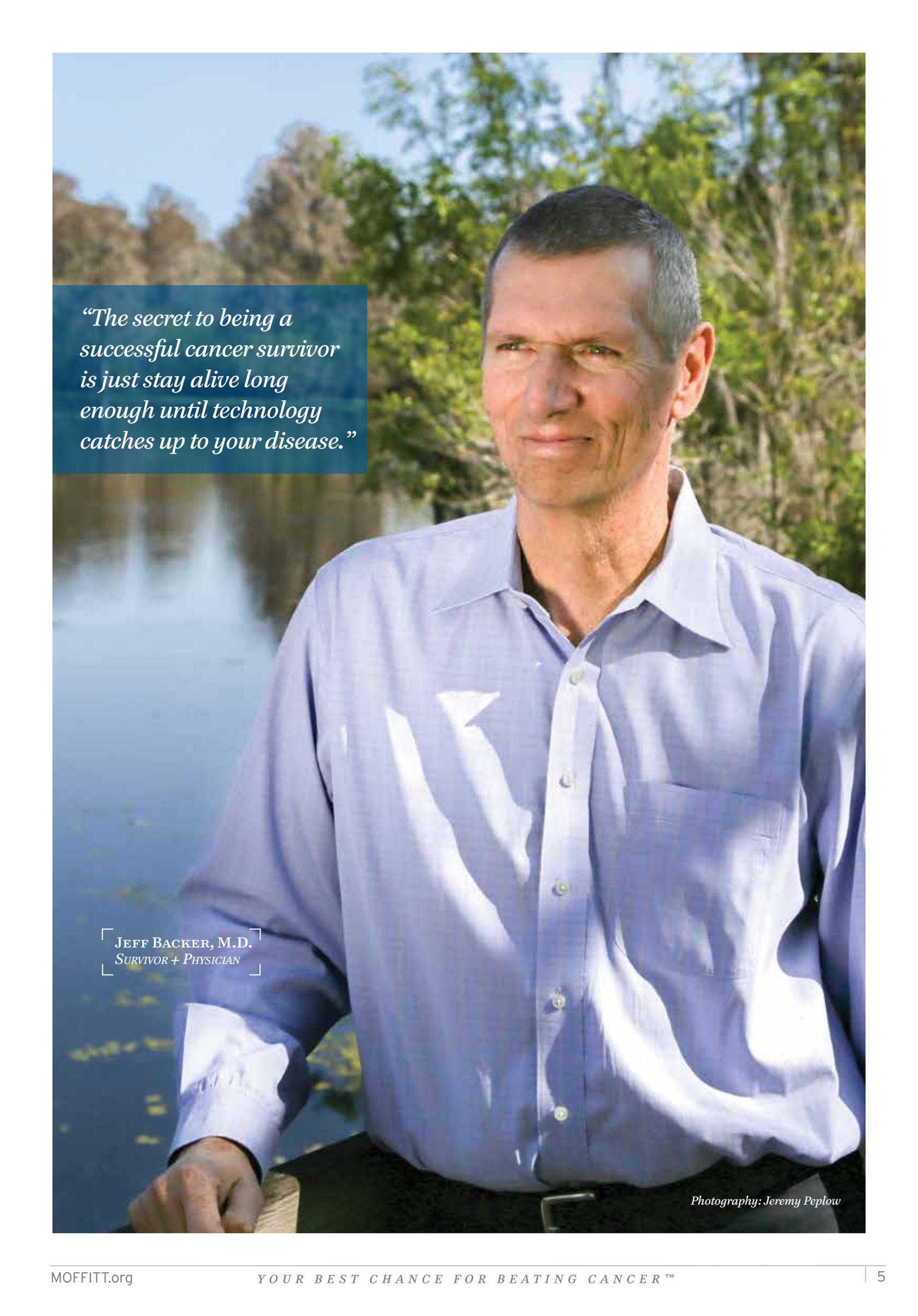
In the CAR T process, T cells are gathered from the patient’s blood and genetically manipulated in the laboratory, using a virus to add pieces that recognize the cancer. This chimera’s lion head is trained to pounce on a protein called CD19 that’s found on the surface of

certain cancer cells. And its serpent tail unleashes the T cell’s deadly force.

Moffitt has led several CAR T clinical trials sponsored by Kite Pharma, with its California manufacturing facility manipulating the patients’ T cells for multiple cancer centers across the nation. The studies’ co-lead principal investigator, Fredrick



Dr. Jeff Backer (left) participated in a CAR T-cell therapy clinical trial led by Moffitt’s Dr. Frederick Locke (right).



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JEFF BACKER, M.D.
SURVIVOR + PHYSICIAN

Photography: Jeremy Peplow

“I looked like elephant man.”



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Locke, M.D., is a medical oncologist and translational scientist in Moffitt’s Department of Blood and Marrow Transplant and Cellular Immunotherapy (BMT-CI). He also happened to be Dr. Backer’s treating physician for stem cell transplantation. And he has his own personal connection to research.

Dr. Locke first witnessed the lifesaving potential of clinical trials as a teen growing up in Michigan. His father had been diagnosed with a different type of lymphoma. After many rounds of chemotherapy failed, he was enrolled in a phase 2 clinical trial for a drug called Bexxar.

Decades later, he remains in remission.

It was an experience that Dr. Locke cites as a motivating factor behind his career choices. “Not only did I see how horrible cancer is,” he reflects, “but I could see how clinical trials can actually make a difference for people who are without other options.”

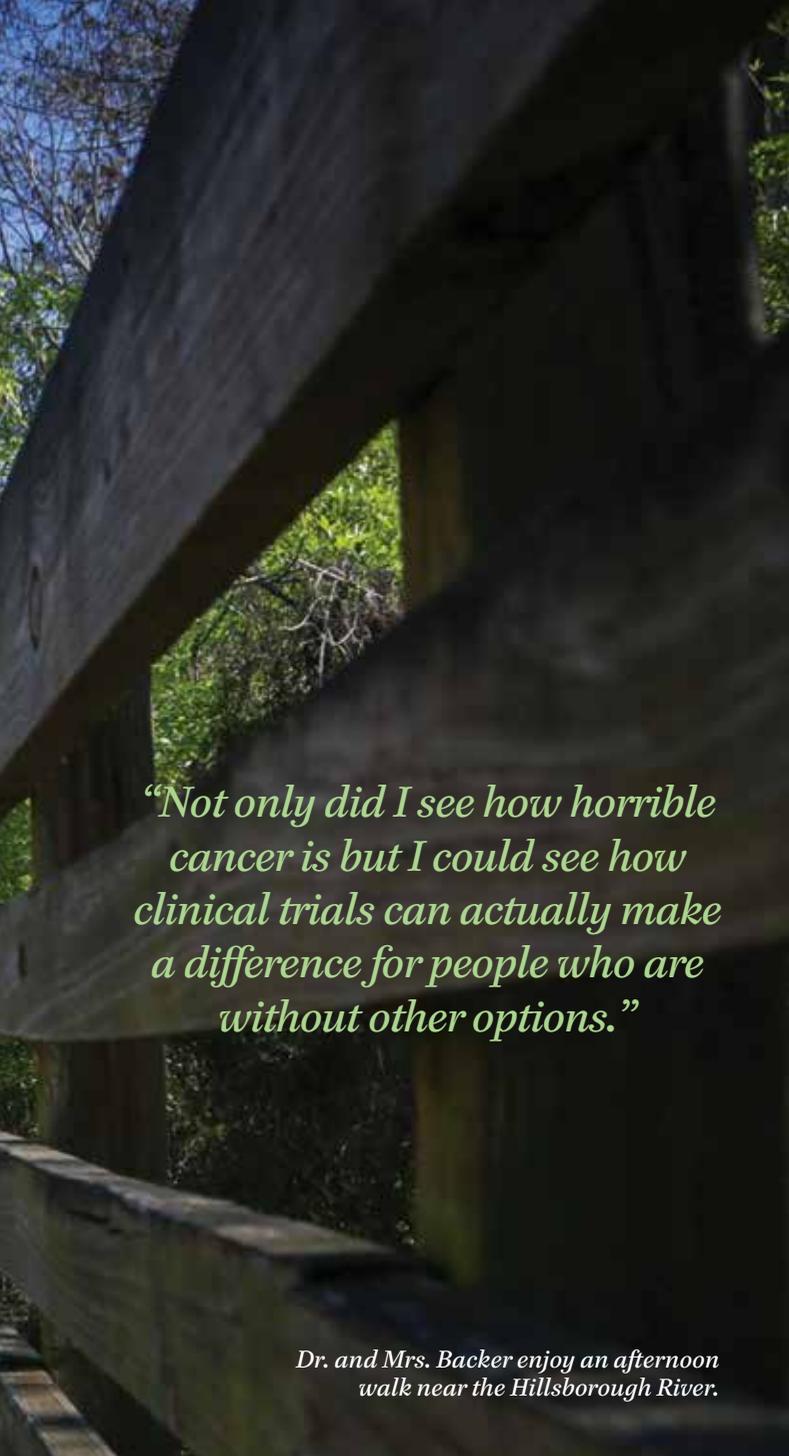
As many as 10,000 U.S. patients die each year of unresponsive aggressive B-cell related lymphomas. Dr. Backer pinned his

hopes of avoiding that fate on a clinical trial. He qualified for Moffitt’s phase 2 ZUMA 1 study of KTE-C19 in aggressive B-cell non-Hodgkin lymphoma in the spring of 2016.

THE ELEPHANT MAN ARRIVES

By the time Dr. Backer returned to Moffitt for collection of his T cells, he recalls ruefully, “I looked like the Elephant Man.” Nodules of the cancer were everywhere – on his face, his neck, and a fist-sized nodule in the middle of his back that kept him from sleeping. It would be a tough two weeks waiting for the cells to be processed at the Kite Pharma facility while Dr. Backer faced his own preparation – more chemo, to make room in his immune system for the CAR T-cell infusion.

The infusion itself isn’t much different from getting a blood transfusion, except this one is done as a hospital inpatient – a challenge in and of itself for Dr. Backer. “I’d never been in the hospital as a patient for extended periods of time, and it was just difficult. The good part about it is that I have really almost no recollection of that three weeks.”



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Dr. and Mrs. Backer enjoy an afternoon walk near the Hillsborough River.

ICE-T SETS MOFFITT APART

The idea behind ICE-T was to bring together Moffitt experts from across the institution who are interested in immunotherapies, to define best practices for both research and clinical care. It was founded more than two years ago by Dr. Locke and a few key individuals like his mentor, Moffitt BMT-CI Department Chair Claudio Anasetti, M.D.; Department Chair of Thoracic Oncology Scott Antonia, M.D., Ph.D.; Julio Chavez, M.D.; Bijal Shah, M.D.; and several senior faculty members who have since left Moffitt. Others would contribute as the idea took hold - Associate Center Director for Translational Science James Mulé, Ph.D., by working with industry partners; Associate Center Director for Clinical Science Daniel Sullivan, M.D., by providing resources; and Cell Therapy Facility Medical Director Marco Davila, M.D., Ph.D., who brought experience working with CAR T from his previous post at Memorial Sloan Kettering Cancer Center.

The results have established Moffitt as a leader in safely and successfully conducting early stage cellular immunotherapy trials. ICE-T includes a dedicated research group, with clinical trial coordinators and data managers familiar with cellular immunotherapies to serve all of Moffitt’s investigators. On the clinical side, ICE-T cares for patients in the outpatient and inpatient setting. Moffitt hematologists, solid tumor medical oncologists and BMT physicians direct care with staff and resources initially provided by the BMT program. “My boss and chair, Dr. Anasetti, said that this is a good idea and we should make it happen,” notes Dr. Locke, so they lectured the nursing staff, the advanced practice professionals and the faculty on what toxicities could happen.

“If you just put a CAR T patient on the floor and hope for the best without careful attention, bad things could happen. We started with a few nurses and doctors taking care of the first few patients and then slowly broadened the experience so more and more people could see how this therapy could work.”

For Dr. Backer, the effects were almost immediate. As soon as the CAR T-cells were infused, he developed high fevers. Then came the neurologic complications. “Now I know what stroke patients face,” says Dr. Backer. “The nurses would show me a clock and I would know what time it was. In my own mind, I knew exactly what I wanted to say, but I couldn’t say it. Luckily, that only lasted a couple of days.”

But what truly amazed Dr. Backer was what happened to those “Elephant Man” nodules. Within a week, they simply melted away.

“I was stunned,” recalls Dr. Backer, though fevers continued to make him feel horrible. His care team worried they might signal developing pneumonia or an infection, so they ordered a CT scan one week after the infusion. “And the scans demonstrated complete remission - in a week. It was absolutely amazing,” he says. “Psychologically, it boosted me to another level. I wanted to get better. I wanted to leave the hospital because I knew there was a light at the end of the tunnel.”

Good, because he developed almost all of the potential side effects that Dr. Locke had previously described. Most patients experience severe flu-like symptoms with high fevers and chills that can go on for days. Some also experience low blood pressure or shortness of breath. These are symptoms of cytokine release syndrome or CRS, and in severe cases, patients may need intensive care and steroids to reverse the effects. Moffitt’s care team developed algorithms to guide appropriate intervention.

But Dr. Locke says perhaps the most disconcerting side effect is neurologic toxicity. “These patients can become confused or sometimes even aphasic - they can’t come up with the words to describe things. But in almost all cases, these effects are reversible and go away within a few weeks of the treatment.”

CAR T patients can get very ill from the immune effects of the therapy, and specialized care is paramount. Dr. Locke says that’s where Moffitt has really distinguished itself from other research centers nationwide - by creating an innovative Immune Cell Therapy program, called ICE-T.



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Photography: Jeremy Peplow

A LIGHT OF HOPE

Results to date from the Moffitt-led ZUMA clinical trials offer that same hope for thousands of patients like Dr. Backer. Clinical trial patients from 22 centers nationwide with aggressive B-cell lymphomas showed significantly better response to the Kite Pharma-manufactured CAR T-cell therapy than what conventional therapies currently offer. At best, only eight percent of these patients could expect a complete remission with today’s standard therapies. With the trial’s CAR T therapy, about half the participants achieved complete remission, and over a third remain in complete remission six months after infusion of CAR T cells.

That’s groundbreaking according to Dr. Locke, who presented an interim analysis on a cohort of patients enrolled in the phase 2 trial to his peers at the American Society of Hematology meeting last December. “We have patients who really have no other treatment options now going into remission with sustained responses – some patients treated on the phase 1 portion of the study have no evidence of lymphoma at the one-year mark.”

The data put Kite Pharma and this CAR T therapy in place for a potential approval by the U. S. Food and Drug Administration sometime this year. If approved, Moffitt stands experienced and ready to offer this new hope to patients from across the state and around the world. Its experts are already running clinical trials with other cellular immunotherapies created in Moffitt’s Cell Therapies facility, including Dr. Locke’s NCI-supported trial utilizing patients’ dendritic cells as a vaccine against a key tumor target called survivin. Moffitt researchers are also developing their own studies for other possible CAR T therapies against some types of leukemia and solid tumors, with plans

underway to begin manufacturing these CARs at Moffitt’s Cell Therapies facility.

For Dr. Locke, whose father is alive thanks to a clinical trial for a similar cancer, these studies in some way bring him full circle.

“To open the door to future cellular immunotherapies that can be brought to patients across the world has been an amazing opportunity,” he says. “Great teamwork has led to the success of this trial and others like it. Here at Moffitt we’ve come together and worked across departments in order to make it happen, so that we can bring these therapies to our patients.”

And at least one patient knows just how lucky he is. Back home and back to work in his Orlando emergency room since last fall, Dr. Backer is relishing the opportunity to do what he loves. He and his wife are enjoying nature hikes. And he’s anxious to get back to kayaking – maybe even on the Hillsborough River close to Moffitt after one of his quarterly follow-up visits.

“I didn’t know if I was going to be alive six or eight months ago. I certainly never expected to be cured of this,” says Dr. Backer. “I expected to have a long, complicated course and ultimately succumb to cancer. This has been a blessing for me.”

A blessing in the form of technology that arrived at Moffitt in the nick of time for his cancer. “I never quite understood the value of a Comprehensive Cancer Center until I came to Moffitt. There’s no reason to go to New York or Houston with this type of center in your backyard. With the research and treatment that’s available at Moffitt, there’s no doubt that this is the future of cancer care.”

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