When cancer immunotherapy works, it’s swift and brawny like a lumberjack. Stage IV melanoma? Whomp. Felled. That was the case for President Jimmy Carter, who remarkably recovered in 2016 from melanoma that had spread to his brain and liver. He was treated with a PD-1 blocker, an immunotherapy drug that recruited his own immune system to chop down all the cancerous cells.

President Carter was lucky. A minority of cancer patients respond to this therapy despite it’s becoming a first-line treatment for melanoma and lung cancer since the FDA approved it in 2014. Most don’t get any benefit. Why is it a windfall for only a few?
Pitt immunologist Greg Delgoffe has figured out a big part of the reason why. Even if a patient’s immune cells have been nudged by PD-1 blockers or other immunotherapy drugs to prune away cancer cells, they may struggle to use their axes once inside the peculiar world of a tumor, a space that scientists refer to as the tumor microenvironment. Delgoffe’s team has shown that when immune T cells enter the tumor microenvironment, their mitochondria begin to shrink and disappear, indicating that the T cells are starving and don’t have enough energy to fell tumor cells. (See the write-up in August 2016 Immunity.)

“We found that T cells are not only in a nutrient-dearth environment, but they also start to suppress the ability to even process those nutrients,” says Delgoffe, a PhD assistant professor of immunology who specializes in the subfield of immunometabolism. (“It’s a five-dollar word, but we go with it,” he says of the subfield’s name.)

Immunologists “always ask T cells how they do their job,” says Delgoffe, but he also asks sidekick rather than a blue ox. The Seahorse XFe96 Analyzer is what his team uses to evaluate cell metabolism. Put any cell into the machine, and it’ll offer a report on the cell’s respiration and glycolysis.

The Seahorse is also helping Delgoffe meet others around campus. It’s an “instrument of collaboration” that various researchers use to gain insight into metabolism, he says. “People are like: ‘Hi, I want to study my cell type.’”

Delgoffe bought the Seahorse soon after he came to Pitt in 2014. He was drawn to Pitt, in part, because of the University’s strong foundation in immunology, dating back to the “dark ages” of the 20th century when the medical community largely doubted the viability of immunotherapy. Luminaries like Olivera Finn—founding chair of Pitt’s immunology department who, by the way, won the 2017 Cancer Immunology Prize from the American Association for Cancer Research—kept the candles burning despite skepticism. Finn welcomed scientists exploring the newest areas of immunology. (Hello, immunometabolism!) “We need to bring people here who do immunology just for the hell of it,” Finn told Pitt Med in 2002.

Delgoffe, who started college as a mathematics major (though he wasn’t sure how he’d use the major), is that kind of person. His helluva interest in T cells began when his molecular biology professor at Western Michigan University hired him to help unearth what the plague bacterium *Yersinia pestis* does to the immune system. When Delgoffe got to Johns Hopkins University for graduate school, he was surprised to learn that when T cells first encounter disease cells, their immediate reaction isn’t to chop them down. “The first signal is not to turn on. It’s to turn off,” he says reiterating his disbelief. He quickly learned that’s a good thing—for gathering intel to mount bigger attacks or to prevent autoimmune diseases. But that also presented a challenge. How could he make T cells turn on? And what better way to lure them than with food?

At Johns Hopkins, Delgoffe ultimately explored how T cells sniff out nutrients in their environment and how that affects their behavior. He coauthored studies that not only explained the importance of nutrient sensing in T cell function but also forged the subfield of immunometabolism.

Along the way, Delgoffe got curious about another type of T cell: regulatory T cells that serve an immunosuppressive role to keep the common T cells (the cytotoxic, ax-wielding ones) from overrunning healthy tissue. For his postdoc, he headed to St. Jude Children’s Research Hospital in Memphis, where he trained with Dario Vignali, who is now the Frank Dixon Professor of Cancer Immunology at Pitt. They reported in *Nature* in 2013 on a signaling pathway for regulatory T cells that, when blocked, can lead to complete tumor regression in mice. Preliminary clinical trials are expected to begin later this year.

In his Pitt lab, Delgoffe is investigating the metabolism of both types of T cells in the tumor microenvironment. His team has found that tumors not only starve T cells (remember those shrinking mitochondria), but they also

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them metabolic questions, like whether they’ve eaten lunch so they can stay energized. He and his team are uncovering a surprising number of metabolic problems in the tumor microenvironment—and they are learning what can be done to fix them so that immunotherapies can help more people with cancer.

If you enter Delgoffe’s microenvironment of suite 2.19 in the research wing of the UPMC Hillman Cancer Center, four out of five scientists are likely to be wearing plaid.

“Plaid is in,” insists Delgoffe, who says labmates dressing alike was at first a coincidence, then a look they embraced. They even posted a photo of themselves in plaid shirts on the lab Twitter account to announce their trip to the latest Society for Immunotherapy of Cancer meeting. Their hashtag? #lumberjackscientists.

Delgoffe denies that his lab’s penchant for plaid has anything to do with his upbringing in Michigan’s Upper Peninsula, though if one were to tell a tall tale about this lumberjack scientist, he’d probably have a seahorse as his sidekick rather than a blue ox. The Seahorse XFe96 Analyzer is what his team uses to evaluate cell metabolism. Put any cell into the machine, and it’ll offer a report on the cell’s respiration and glycolysis.

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umber of ways to metabolically reprogram the tumor microenvironment. They’re genetically modifying T cells to make them super lumberjacks who can work long hours with little food. They’re trying out oncolytic viruses (viruses that infect and kill cancer cells) to see whether they’re good tools for reprogramming tumor cell metabolism. They’re taking T cells modified by CAR T–cell therapy (a means of adding receptors directly to a patient’s T cells) and looking at what happens to the metabolism in the tumor microenvironment of individual patients, investigating whether reprogramming would be beneficial. Their March 2018 report in the Journal of Experimental Medicine demonstrates that activating 4-1BB proteins on the surface of T cells (which tend to lie dormant in the tumor microenvironment) enables the T cells to increase their mitochondria and regain their energy. And combining that 4-1BB therapy with a PD-1 blocker in mice is particularly effective for equipping T cells to do their cancer-felling job. On the regulatory T cell front, the team has assisted Vignali’s lab with showing that an interferon protein that causes immunosuppressive cells to become more fragile could also make a PD-1 blocker therapy more effective. Those findings, first-authored by Abigail Overacre-Delgoffe, Delgoffe’s wife and a trainee working in Vignali’s lab, were published in Cell in June 2017.

There’s more good news. Delgoffe’s lab (with help from the trusty Seahorse) has shown that the tumor microenvironment not only starves T cells of nutrients, but oxygen, too. They’ve found that metformin—a drug typically used for type 2 diabetes that’s also promising for cancer treatment—has the ability to reoxygenate the tumor microenvironment and can reduce tumors in mice if given in combination with PD-1 blockers. When Delgoffe talked about these findings at a campus grand rounds soon after they were reported in Cancer Immunology in 2016, he was approached afterwards about teaming up for a clinical trial to see whether this tack might benefit the majority of patients who don’t respond to the PD-1 blockade.

The clinical trial for skin cancer is now open, just a year and a half later, which Delgoffe thinks is pretty phenomenal. “This is exactly why I came here: to get involved,” he says of the translational research infrastructure in place at Pitt. He’s partnering on the trial with Yana Najjar, an MD assistant professor of medicine, and John Kirkwood, MD director of the Skin Cancer SPORE, a National Cancer Institute Specialized Program of Research Excellence at the UPMC Hillman Cancer Center. Delgoffe is looking to rev up more bench-to-bedside projects as a member of the new UPMC Immune Transplant and Therapy Center announced in February. (See story on page 16.)

Delgoffe is proud that his team’s work may generate more solutions for cancer. “We can do all sorts of things to give T cells back their mitos to allow them to compete better,” he says. “I don’t think we’re going to fix the antitumor responses by just changing metabolism, but we have to be thinking about it. We have to think about it in order for us to realize the potential of these awesome immunotherapies.”