

Giving CAR T Cells a Portable Pit Crew to Fuel Their Fight Against Cancer

Fred Hutch scientists dig deep into CAR T-cell exhaustion and examine a strategy to improve the immunotherapy for solid tumors.

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Over the last decade, the cellular cancer immunotherapy known as [CAR T-cell therapy](#) has roared to the rescue of many blood cancer patients. The engineered immune cells revolutionized treatment of certain leukemias and lymphomas, but have mostly stalled out in test drives against solid tumors like lung and breast cancer.

It turns out that the synthetic CAR molecule that guides them straight to tumors may be a weakness nearly as much as a strength. Focused on the tumor, CAR T cells zip past key sources of support that our natural T cells rely on to sustain a fight against disease. Without natural pit stops to refuel and rejuvenate, CAR T cells end up running on fumes.

In [new work](#) published March 6 in Science Immunology, Fred Hutch Cancer Center scientists show there may be a way to give CAR T cells their own portable pit crew. This allows CAR T cells to rejuvenate on the go (without the need for a side trip to a lymph node) and transforms them into a type of T cell that can support long-term immune responses against tumors.

“We’re able to rewire the CAR T cells to mimic the signals that they might get from those niches to now maintain the subset, but in a totally different location,” said Fred Hutch immunologist [Shivani Srivastava, PhD](#), who spearheaded the work with University of Washington MD/PhD student Andrew Snyder.

In a preclinical model of [lung cancer](#), Srivastava and Snyder found that boosting expression of a gene called c-Jun could equip CAR T cells with a portable “pit crew,” helping them live longer and stay healthier inside tumors.

But the extra support wasn’t enough to win the race: the boosted gene alone didn’t help CAR T cells fight tumors better. But there was a secret benefit: c-Jun had rewired the CAR T cells to respond better to checkpoint inhibitors, a type of immunotherapy that releases immune brakes. Checkpoint inhibitors enabled the CAR T cells to tap into c-Jun’s added support and mount a far more durable attack on tumors.

The researchers also uncovered how the tumor microenvironment works to keep T cells exhausted and ineffectual and how CAR T cells could be redesigned to overcome these defenses. The strategy is several steps away from the clinic but reveals basic biological principles that could help improve the design of future cellular immunotherapies, Srivastava said.

CAR T cells go their own way

CAR T cells were developed to take advantage of T cells' ability to orchestrate immune responses and kill diseased cells, including cancer cells. But in natural immune responses, T cells don't work alone: They receive critical information and support from a bevy of other immune cells. Many of these interactions occur in lymph nodes, small immune organs scattered throughout our bodies.

"The lymph node is the safe spot, where the immune system really arms up. It's the training ground," Srivastava said. "We tend to look at the literature on endogenous T cells and apply it one-to-one to CAR T cells, but we're beginning to understand that CARs are their own immune context. They ignore a lot of the niches that really help sustain T-cell responses."

Guided by their CARs (short for chimeric antigen receptor), CAR T cells bypass lymph nodes and head straight for tumors. But after an initial burst of anti-tumor activity, CAR T cells lose steam and become, in scientific parlance, "exhausted." They're sprinters, not marathoners.

Usually, T cells go to lymph nodes to get the training they need to build the stamina for a long-lasting immune response. Marathon-ready T cells aren't found deep within tumors, likely because tumors find ways of preventing their formation, Srivastava said. These T cells share some qualities with stem cells: the ability to self-renew and the ability to turn into different types of cells. This allows this T-cell subset to seed repeated forays against tumors while maintaining a long-lived pool of battle-ready cells.

Researchers have tried various strategies to boost CAR T-cell anti-cancer activity — but these often just make them better sprinters. In complex preclinical models that mimic the tumor and immune environment inside patients, these CAR T cells eventually crash and burn, Srivastava said.

Scientists have also tried adding checkpoint inhibitors, a class of immunotherapy that removes hurdles (an interaction between molecules called PD-1 and PD-L1) that solid tumors erect to block T cell function. But CAR T cells don't always get the boost investigators expected.

"That's been puzzling because normally, a lot of these studies show that when people don't respond to checkpoint inhibitors, it's because they don't have enough T cells in their tumor, or they're not PD-1 positive or PD-L1 isn't up," Srivastava said. "But the CAR T cells are all PD-1 positive. There's lots of PD-L1. This axis is very strongly activated."

Srivastava and Snyder had two goals: to learn more about the molecular basis of CAR T-cell exhaustion and to see if they could provide some critical lymph node-type support sans lymph

node.

A portable pit crew, ready and waiting

Srivastava and her team collaborated with Lyell Immunopharma, a CAR T cell-focused biotech company co-founded by Fred Hutch's [Stanley Riddell, MD](#), which was exploring whether forcing CAR T cells to overexpress the c-Jun gene could help. The c-Jun protein turns on genes that give T cells the "stemness" they need to prevent burnout and maintain stamina. Prior work had shown that overexpressing c-Jun could keep CAR T cells from becoming exhausted.

But these CAR T cells were tested in mice that don't have an immune system. CAR T-cell therapy must contend with a patient's immune system, which is often coopted by tumors to ward off T-cell attack. Srivastava hoped to better understand how c-Jun-overexpressing CAR T cells would work in a patient.

She and Snyder developed CAR T cells that target a protein called ROR1, found at higher levels in certain tumors than in healthy tissue, and which also overexpress c-Jun. They tested these CAR T cells in a mouse model of lung cancer in which tumors co-evolve naturally with an intact immune system, similar to how they grow in a patient.

The researchers found that forcing expression of the c-Jun gene led to only a slight improvement in CAR T-cell proliferation and anti-cancer activity. The CAR T cells, with or without a ramped-up c-Jun gene, eventually lost steam.

Turning on a gene is only the first step: it's the protein it encodes that does the work. Unexpectedly, Snyder found that ramping up expression of the c-Jun gene did not lead to higher levels of c-Jun protein.

"Basically, we found that even though c-Jun is overexpressed, something happens to its regulation where the protein levels go down and that really seems to compromise its activity and beneficial effects," Srivastava said.

But cells with higher c-Jun expression did show molecular markers (including PD-1 and TCF1) similar to those seen in stemlike T cells usually found in lymph nodes. These T cells are the major responders to checkpoint inhibitors.

When Snyder and Srivastava added a checkpoint inhibitor, the c-Jun-overexpressing CAR T cells roared to life: After five days, the number of these cells within tumors had increased more than ten-fold. Boosted by the checkpoint inhibitors, they achieved near-complete tumor clearance. In contrast, checkpoint inhibitors had no effect on CAR T cells lacking engineered c-Jun.

It appears that signals from the microenvironment, acting in part through PD-1 on CAR T cells, lead to reduction of c-Jun protein. Checkpoint inhibitors, which disrupt this signal, allow c-Jun to rebound and rejuvenate exhausted CAR T cells.

The team is currently working to better understand the source of the signal that promotes c-Jun reduction and also how c-Jun protein is handled within CAR T cells. These insights could inform strategies to maintain c-Jun levels, Srivastava said. The team is also exploring whether checkpoint inhibitors help CAR T cells by acting on other immune cells, including natural T cells.

For now, the work shows that CAR T cells can be encouraged to take on critical characteristics outside of the lymph node environment.

“By rewiring the CAR T cells in this way, we actually are able to get them to maintain the subset now, right at the site of action where you need them,” Srivastava said. “It’s a weird hybrid: We’re now able to fix a defect, but also we’re now imparting new biology into them.”

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