Cancerous tumors are hostile environments where T cells fight to kill cancer cells, which in turn try to kill or silence the T cells. “That’s where we started,” said Nikhil Joshi, PhD, Assistant Professor of Immunology. “We figured that if T cells inside the tumor constantly get killed or shut off, how are there still enough of them in there to get activated when a patient receives immunotherapy?”

The answer surprised him and Kelli Connolly, PhD, a postdoctoral associate in his lab. Using a mouse model, they found that dead or exhausted T cells in the tumor were constantly replenished by a slow trickle of fresh T cells that infiltrate the tumor from reservoirs in nearby tumor-draining lymph nodes. These T cell reinforcements fight the progression of the disease and likely boost the tumor’s response to immunotherapy. Drs. Joshi and Connolly’s findings were reported in September 2021 in Science Immunology.

Researchers previously knew that lymph nodes contain T cells that are activated to invade when tumor cells develop nearby. “What wasn’t understood,” said Dr. Connolly, “is that this migration continues as the tumor progresses, which could be for years.”

“It never made sense to look for T cells in the lymph nodes,” added Dr. Joshi, “because once they were activated, why would they stay in the lymph node and not go to the tumor? It’s clever that the immune system hangs on to these cells off site and sends them out later.”

In fact, noted Dr. Connolly, clinicians often see these lymph nodes as places where the tumor might spread, so clinicians sometimes remove them, thus eliminating the reservoir of T cells. Dr. Connolly hopes the new paper shifts that perspective.

The discovery of this unknown migration was a breakthrough, but Drs. Joshi and Connolly are more energized by its implications for cancer treatment. Most tumors—typically about 80 percent—do not respond to immunotherapy. What would happen, wonder Drs. Joshi and Connolly, if the reservoir of T cells in the lymph nodes could be induced to migrate en masse into a tumor? Current immunotherapies do not seem to prompt the T cells to leave the lymph nodes.

“I would say the most exciting part of our findings is that we suggest you can target T cells in the draining lymph nodes to make some immunotherapies more effective,” said Dr. Connolly.

Drs. Joshi agrees. In the future, cancer patients whose tumors don’t contain enough T cells to fight the disease might be able to tap a reservoir close by. By figuring out how to make that happen is the next task for Drs. Joshi and Connolly.

“They suspect that the T cells in the lymph nodes get a signal telling them to migrate. If the researchers can detect and mimic that signal, they could induce migration.”

“We continue finding the mechanisms that get T cells out of the lymph nodes and into the tumor,” said Dr. Connolly. “I think that’s what we see as most promising therapeutically. That could help the large group of patients who don’t respond to immunotherapy.”

They envision finding the mechanism that gets T cells out of the lymph nodes and into the tumor. It was a big reason Dr. Connolly wanted to work at Yale, which is known for its research in immunology.

“This is the most exciting part of our findings,” said Dr. Joshi. “There are a lot of people here eager to collaborate to solve these problems. So, the chances are high that this discovery gets translated into meaningful gains for patients.”

Their paper also drew attention to Dr. Joshi’s advanced mouse model, which took him eleven years to develop. It was a big reason Dr. Connolly wanted to work at Yale, and other researchers are requesting it from all over, which delight Dr. Joshi. “We’re not telling it,” he said, “and hoping that people will use it to achieve breakthroughs in their own work.”