

Extending Efficacy for CAR T-Cell Therapies in Cancers

Shivani Srivastava receives NCI MERIT Award to investigate how to improve engineered cancer immunotherapies against solid tumors through reservoirs of self-renewing immune cells.

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Efforts to develop cellular cancer immunotherapies against solid tumors like breast and prostate cancer have run aground against tumor defenses.

Research into our natural anti-cancer immune defenses has shown that a self-renewing pool of anti-cancer cells sustains long-term immune attacks against tumors. Could this type of perpetual anti-cancer attack be recreated to improve immunotherapy?

Fred Hutchinson Cancer Center immunotherapy researcher [Shivani Srivastava, PhD](#), recently received a National Cancer Institute MERIT Award to study whether genetically engineered CAR (chimeric antigen receptor) T cells have the [ability to form such self-renewing reservoirs](#), and how to encourage their formation to improve CAR T-cell therapy for solid tumors.

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“The basis of the proposal was to determine for engineered T cells, do they form reservoirs?” Srivastava said. “Maybe they do, but by different rules than endogenous [natural] T cells. And the second part is to see if we can fix this gap.”

The NCI’s [Method to Extend Research in Time Awards](#) are designed to offer early-career investigators a longer-term funding opportunity. After the grant’s initial five-year term, awardees can apply for a funding extension to support a further two years of investigation.

Lessons From Natural Anti-Tumor Immunity

Our immune system doesn't just fight infection; many of the cells that ward off bacteria and viruses can also attack cancer cells. This includes T cells, which can recognize and kill diseased cells. Several cancer immunotherapies take advantage of T cells' natural abilities.

Immune checkpoint inhibitors, or ICIs, interfere with molecular brakes that hold anti-tumor T cells in check, allowing them free rein to attack the tumor. ICIs like [pembrolizumab](#) (Keytruda) and [ipilimumab](#) (Yervoy) are now FDA-approved for a range of tumor types. Scientists have also used genetic engineering to encourage patients' T cells to attack a specific target. CARs guide engineered T cells to home in on tumor cells carrying a specific molecule on their surface. Currently, all the CAR-T cell therapies on the market target B cell leukemias and lymphomas.

ICIs have transformed the treatment of solid tumors like melanoma, and CAR T-cell therapies have had incredible success against so-called "liquid" tumors like leukemias and lymphomas. Scientists hope to deploy these cellular therapies against "solid" tumors—but it turns out that these tumors erect barriers that liquid tumors don't.

In leukemia, cancer cells are spread through the circulatory system. CAR-T cells also circulate through the blood, making it easier for them to find and destroy leukemia cells.

But solid tumors localize to specific tissues, like the breast or lung, where they may be able to hide from T cells circulating in the blood. Solid tumors can also recruit cells that suppress immune attack and may prevent T cells from entering. To fight against this, T cells must engage in siege warfare. But this is exhausting. Eventually, T cells burn out and die or become lethargic.

Research into ICIs showed how natural T cells can sustain an attack against aggressive solid tumors. They're not merely reinvigorating tired or suppressed T cells.

"For a long time, we thought it was simple: there are T cells trying to kill the tumor, and they get blocked. All we do is release the brakes and unleash the T cells," Srivastava said. "It's a lot more complex than that."

It turns out that there's a pool of anti-tumor T cells with the ability to renew themselves. They're fresh and energetic and can produce new T cells that fight the tumor with vigor. These T cells with stem cell-like properties are mostly found on the outer edges of tumors or in lymph nodes, way stations along our lymphatic vessels that allow immune cells to co-mingle, communicate and orchestrate our immune defenses.

"Being away from the action allows [the stem-like T cells] to maintain quite a bit of function, and the closer you get to the tumor, the more that function goes down," Srivastava said. ICIs "do unleash some of the cells in the tumor—but they are really short-lived. It's the stem-like T cells that drive the response to checkpoint inhibitors."

After ICI treatment, T cells at the tumor attack and die. Self-renewing anti-tumor T cells in the lymph nodes expand in number and generate a fresh wave of reinforcements that can sally forth to the tumor. Some number stay behind, ready to answer the next call to battle.

“You can think of the lymph node as a reservoir tank,” Srivastava said. “It’s sustaining the long haul—and you really need that for a long-lived response.”

Patients who have more stem-like anti-tumor T cells tend to respond better to ICI treatment than people with fewer self-renewing immune cells, highlighting their importance in the immune system’s battle against the tumor.

“But engineered T cells are very, very different,” than home-grown T cells, Srivastava said. “So we had this theory that maybe CAR-Ts are disadvantaged in two ways.”

While their CAR guides them to the tumor and activates their deadly instincts, it doesn’t help them reach the lymph node and form a self-renewing reservoir.

“We had this theory that, maybe they’re really good in the first wave: they get into the tumor, but as those cells die off, there’s no reservoir to replenish them,” Srivastava said. Lymph nodes offer native-born T cells a safe space to arm up before attacking the tumor, but CAR T cells bypass this respite.

“We wondered if this is a crutch that’s unique to CAR T cells,” she said. “It’s great that we’ve put this receptor in that gets them to the tumor, but [scientists have been] so focused on the tumor, we’ve ignored these other sites that might really be important.”

Expanding Focus to Improve CAR T-Cell Performance

Srivastava has shown that CAR T cells don’t go to lymph nodes, and her data suggest that reservoirs are critical to the strength and longevity of T-cell responses.

“What we’re learning is that you can’t compare CAR T-cells with endogenous [natural] T cells one-to-one,” Srivastava said. “The way those cells behave is going to be completely different than endogenous T cells. The [biological] rules that define whether those cells can form reservoirs—and how you enhance them—may be totally different.”

Her goal is to discover if CAR T cells do have the capacity to form a self-renewing reservoir—whether it’s in a lymph node or elsewhere. Perhaps they can be encouraged to make a pit stop in a lymph node on their way to the tumor, or perhaps there are ways to help them create a reservoir at the tumor itself. Srivastava will learn whether CAR T cells are being blocked from forming reservoirs, or whether this capacity must be engineered into them along with the CAR itself.

Once Srivastava has figured out the biological rules governing reservoir formation in CAR T cells,

her next goal will be to develop strategies to create the reservoir that CAR T-cells need in their long-term fight against the tumor.

“It’s a very basic spin on adoptive T-cell therapy,” she said. “Our whole field looks to endogenous T cells for answers, but what we’re uncovering is that engineered T cells are their own context.”

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