

Immune Cells vs. Cancer Metastasis: “It’s a Numbers Game” [VIDEO]

Fred Hutch scientists prevent metastasis by boosting cancer-killing T cells in patients, primarily those with breast cancer.

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New research published January 8 in the [journal Cancer Cell](#) cracked an important code in the quest to prevent metastatic cancer.

Co-led by Fred Hutchinson Cancer Center’s metastasis researcher [Cyrus Ghajar, PhD](#), and immunotherapy expert [Stanley Riddell, MD](#), the research explains why the body’s natural immune system doesn’t eliminate disseminated tumor cells lying dormant in bone marrow or other sites and offers three potential T-cell immunotherapies that actually do.

“If a tumor just stayed in the breast it wouldn’t kill anybody, but tumor cells leave the breast and destroy vital organs like the liver or brain or lungs and that’s what causes the vast majority of breast cancer deaths,” said Ghajar, whose research focuses primarily on metastatic breast cancer. “This process can take a very long time and it doesn’t happen in the majority of people, thankfully. But it does happen.”

Ghajar leads Fred Hutch’s Center for Metastasis Research Excellence, or [MET-X](#), a multidisciplinary research program focused exclusively on metastatic cancer. Previous research by others, including Julio Aguirre-Ghiso, PhD, who wrote a [commentary on the new paper](#), has shown that single disseminated tumor cells, or DTCs, can break off from a tumor site even before a tumor has formed — whether in the breast or another organ. These cells then find a tumor-friendly environment — often in the bone marrow — where they can lie dormant for 5, 10, 15, 20 years or more before something wakes them up and they begin to replicate, eventually forming metastatic tumors.

Somewhere between 20% to 30% of early-stage breast cancer patients go on to develop metastasis, or stage 4 disease, after early-stage treatment (others, known as de novo metastatic patients, are diagnosed stage 4 from the start). And while metastatic cancer is treatable — sometimes giving patients many extra years — it is still not curable.

“We’re trying to stop this from happening by keeping these cells asleep or by taking them out of the equation altogether,” said Ghajar, who holds the Peter S. Lefkarites Memorial Endowed Chair.

“We need a way to selectively kill them — and only them — so patients don’t have to look over their shoulder wondering if or when their cancer is going to come back.”

Ghajar, Riddell and other MET-X researchers hope to change the metastatic playbook by zeroing in on the hows and whys of the metastatic cascade — and coming up with tangible solutions. In this case, they’re engineering a handful of immunological workarounds to basically smother tumor cells in their sleep.

“A numbers game”

Our immune system continually surveils our bodies for threats — from viruses, bacteria and our own mutated cells — in order to destroy them and keep us healthy. But that doesn’t always happen when it comes to disseminated tumor cells.

“We find these cells in the bone marrows of breast cancer patients, so we know they haven’t been surveilled and destroyed by T cells,” Ghajar said. “We wanted to know how these cells persist.”

Ghajar, Riddell and their laboratories — led by postdoctoral fellows Erica Goddard, PhD, and Miles Linde, PhD — ran a number of experiments to figure out why T cells don’t seek out and destroy mutated tumor cells lying dormant in bone marrow and lung.

A few years later, they reached a stunningly simple conclusion.

In order to destroy threats, the immune system first has to find them. But there are so few DTCs — and so few T cells capable of destroying them — that never the twain shall meet.

“It’s basically a numbers game,” Ghajar said. “Dormant tumor cells are very rare — one in a million, maybe one in 10 million in the human body. And T cells that can recognize antigens present on the DTCs — are equally rare. So you have two one-in-a-million populations trying to find each other. And you’re expecting that to happen not just once or twice, but hundreds or thousands of times.”

Ghajar compared the likelihood of the body’s T cells finding and killing off all dormant DTCs to the likelihood of a person winning the lottery again and again and again.

“The only way you could win the lottery over and over again is if you cheat,” he said. “How are we cheating? Not by upping the number of tumor cells, but by upping the number of T cells that can surveil that tumor.”

Boosting T-cell surveillance

This insight didn’t happen overnight.

The prevailing theory was that dormant tumor cells were somehow able to evade surveillance by T

cells by downregulating something known as MHCI or major histocompatibility complex type 1, a diverse set of molecules expressed on the surface of all human cells that serve as beacons for T cells. The team believed the low levels of MHCI on DTCs would allow them to evade adoptive therapy with either TCR-engineered T cells or a vaccine designed to elicit MHC-restricted T cells. T cells use T-cell receptors, or TCRs, to home in on tumor-associated antigens displayed by MHC.

Co-investigator Riddell, who holds the Burke O'Reilly Family Endowed Chair in Immunotherapy, said that's why they first tested T cells engineered with synthetic chimeric antigen receptors, or CARs, that can recognize tumor cells independent of MHCI.

"When we started this work, our hypothesis was that CAR T cells, which are highly effective for eliminating both minimal residual disease and advanced disease in blood cancers, would more likely be effective for DTCs," Riddell said.

So the investigators were surprised when the TCR-engineered T cells and the vaccine were just as effective as CAR T cells. This led them to realize that MHCI wasn't the issue; it was the scarcity of the disseminated tumor cells — and of T cells that could recognize them — that allowed DTCs to persist.

It was just a numbers game.

"When we boosted the T cells, we saw definitively that there was a threshold," Ghajar said. "Once you crossed the threshold, you went from having DTCs to not having DTCs. That, to us, was our 'this is what's going on!' moment."

They now have three separate immunotherapies capable of reaching an "effector-to-target ratio" powerful enough to clear out dormant tumor cells.

"We showed that adoptive immunotherapy — that is, the infusion of T cells engineered to express a T cell receptor (TCR) or a chimeric antigen receptor (CAR) that recognized antigens expressed on the DTCs — would eliminate DTCs," Riddell said. "We also found that a vaccine that stimulated endogenous T cells against tumor antigens was effective in eliminating DTCs."

And the results, tested so far in culture models and mice, have been impressive.

"When we added in millions of these T cells capable of recognizing and killing dormant tumor cells, we found they could effectively surveil and eliminate up to 98% of them," Ghajar said.

From mouse models to clinical studies

Now, the team is moving the research into humans, specifically early-stage breast cancer patients.

Ghajar believes these patients generally fall into two camps. One is patients with enough natural immunity to their breast tumor to successfully surveil the whole body, including the marrow and

other DTC sites, and destroy whatever tumor cells found.

“These are going to be the patients without disseminated tumor cells,” he said. “These are the patients who will do really well.”

The other group of patients, he said, don’t develop that strong of an immune response to their primary tumor, or the immunity doesn’t transmit throughout their body. These patients will have DTCs, he said, and will have a higher risk of recurrence.

Riddell, Ghajar and the rest of their team are already working with newly diagnosed breast cancer patients to determine their DTC and immune status. Currently, there are 900 patients at three sites: Fred Hutch, Huntsman Cancer Institute in Utah and Washington University in St. Louis, Missouri. [Read more about the TRANCE study, funded by the Department of Defense.](#)

“We have one of the only studies in the world where we’re matching primary tumors with bone marrow biopsies and profiling the tumor antigens, the immune response to primary tumor, and correlates within the bone marrow,” Ghajar said. “We want to know how the numbers of antigen-specific T cells in the breast and bone marrow relate to the presence or absence of disseminated tumor cells, and how all of this relates to recurrence.”

Fred Hutch’s [Christopher Li, MD, PhD](#), holder of the Helen G. Edson Endowed Chair for Breast Cancer Research, is leading the epidemiologic endeavor to determine if there are lifestyle or environmental reasons why some patients have a better immune response than others.

“The mere presence of DTCs is not predictive of recurrence,” Ghajar explained. “There are additional factors and those factors are what Chris Li and his team are trying to uncover.”

Ghajar said the game plan is to engineer a hardier T cell response for those who need it.

“Our lab continues to be deeply involved in engineering T cells to target tumor antigens,” added Riddell. “The key is to identify targets that are expressed commonly on patient DTCs. But we’re also profiling the immune cells in these patients to determine if there are characteristics that might be predictive of patients that have — or don’t have — these disseminated tumor cells.”

What about current metastatic patients?

As for patients who are currently dealing with metastatic tumors (as opposed to single metastatic cells here or there in their marrow), Ghajar said so far, engineered T-cell therapies haven’t worked as well on metastatic breast tumors as they have in other cancers.

But that doesn’t mean the team is stymied.

“We’re not giving up just because the setting is more difficult,” Ghajar said. “We want to figure out how we can make immunotherapies function well in a stage 4 setting.”

He and Riddell believe their approach might work now in patients with oligometastatic disease, that is, metastatic cancer in just one or two distant sites.

“Most patients present with a metastasis at one site,” Ghajar said. “It’s the downward spiral of additional metastases that make the problem less tractable, leading to organ dysfunction and ultimately death. Maybe we can prevent additional metastases by enhancing surveillance of other sites that harbor dormant cells with potential to become a new met. What we’ve uncovered here could apply in those settings.”

He also believes the principle will hold true for other solid tumors, not just breast cancer.

Eventually, Ghajar envisions this new understanding of metastasis will help create a protocol in the early-stage breast cancer setting where clinicians not only test the bone marrow of patients for DTCs but will be able to identify those at the highest risk of recurrence.

“We need to define which patients are at higher risk and have a treatment for those patients,” he said. “But beyond this, we lack truly curative treatments in the stage 4 setting. And it’s a real need.”

It’s also a need that’s being directly addressed through Fred Hutch’s new MET-X project.

“We have a unique ecosystem here,” Ghajar said. “We have a core of metastasis researchers, and incredible depth in basic sciences, data science and immunology. The infrastructure we’ve established to bring these people together via MET-X is only going to help.”

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