

New Biomarker Could Help Tailor Immunotherapy for Merkel Cell Carcinoma

Findings help explain why only certain patients respond to immune checkpoint inhibitors and could point toward new strategies to improve treatment response.

March 5, 2024 By Fred Hutch News Service and Sabrina Richards

It's the cancer-fighting immune cells in a Merkel cell carcinoma patient's blood — not their tumor — that best predicts whether a certain type of immunotherapy will work, according to new work from two teams of scientists at [Fred Hutchinson Cancer Center](#) and the [University of Washington School of Medicine](#).

In back-to-back papers published February 9 in [Cell Reports Medicine](#), the researchers showed that the frequency of circulating battle-ready anti-cancer immune cells can act as a biomarker in patients with this aggressive skin tumor: MCC patients with higher levels in their blood are more likely to respond to immune checkpoint inhibitors, or ICIs. The findings are a step toward the development of a clinical test that could someday guide MCC treatment.

"These data have implications for how we manage patients, both in making early treatment decisions and how we overcome non-response," said Fred Hutch and UW Medicine dermatologist [Paul Nghiem, MD, PhD](#), who treats patients with MCC and [works to develop better therapies](#). He and Fred Hutch immunologist [Evan Newell, PhD](#), led the teams that independently uncovered the biomarker.

Because these cells are the cells that ICIs help fight cancer, the results also suggest strategies scientists could use to improve patients' chances of responding to ICIs, the researchers said. One potential treatment, in which patients receive immune cells called T cells that have been genetically engineered to help attack their tumor, are already being tested in clinical trials.

Known as adoptive cell therapies, these engineered immune cells "could increase the number of anti-tumor T cells in the blood," said graduate student Saumya Jani, who helped spearhead the Nghiem Lab project during the PhD portion of her medical scientist training program. "This would allow the immune checkpoint inhibitors to do their job — keep these cells in healthy, fighting shape — and lead to disease regression."

A virus-driven tumor

Merkel cell carcinoma is a rare and aggressive skin cancer. About 20% of cases are caused by exposure to UV light, while about 80% are caused by the Merkel cell polyomavirus. Most cases occur in older adults. Based on data reported [between 2012 and 2018](#), patients diagnosed with localized, early-stage MCC are about 70% as likely to survive five years as people without MCC. But if a patient's MCC is diagnosed after it's metastasized, or spread through the body, their relative five-year survival rate drops to 24%.

But these numbers don't reflect a recent sea change in MCC treatment: immune checkpoint inhibitors. In 2018, two clinical trials in which Nghiem played a lead role showed that ICIs [pembrolizumab](#) and avelumab [dramatically improved survival rates](#) for patients with MCC. Fred Hutch and UW Medicine clinicians and researchers [updated MCC treatment guidelines](#) published later that same year.

Immune checkpoint inhibitors improve MCC treatment outcomes by helping patients' immune systems fight off the tumors. Tumors can deflect immune attack by turning on molecules that act like brakes on immune cells, slowing them down. Immune checkpoint inhibitors help release these brakes. Three ICIs have been approved for MCC patients: pembrolizumab (Keytruda), avelumab (Bavencio) and retifanlimab (Zynyz).

"Immunotherapy has been a big revolution, but there has not been a good way to figure out who's going to respond and who's not," Nghiem said. "The odds are a little better than 50% that an ICI will work in any given patient."

Patients and doctors need more than a coin flip to guide treatment, he said. So he, Newell and their research groups went in search of a biomarker that could predict response to ICI treatment in MCC patients.

Revealing an ICI barometer: T cells in blood

Fellow MSTP student Thomas Pulliam and Jani co-led the project in Nghiem's lab, and postdoctoral fellow Heeju Ryu, PhD, led the work in Newell's lab. Ryu studied MCC patients treated with pembrolizumab and Pulliam and Jani studied patients who received nivolumab, which was being assessed for efficacy against MCC in an international [clinical trial](#) co-led by the Seattle team. Both teams arrived at the same answer: the blood level of a key type of anti-tumor immune cell best predicts MCC patients' ICI responses.

The answer came after many other hypotheses related to a tumor's potential ability to trigger an immune response had been ruled out.

The two teams' findings focused on immune cells called killer or CD8 T cells, which can seek out and kill off infected or cancerous cells. CD8 T cells use a specialized type of molecule, the T-cell

receptor, or TCR, to target diseased cells. Anti-cancer T cells pursue snippets of proteins produced by tumor cells. In most cases, these are only slightly different than the proteins made by healthy cells.

But T cells that target polyomavirus-driven MCC cells have clear targets that aren't found anywhere else in a patient's body: viral proteins. Through an ongoing collaboration with [David Koelle, MD](#), a UW Medicine immunologist who studies viruses in the skin, these teams took advantage of this unique aspect of MCC biology to develop methods to easily detect anti-cancer T cells in MCC patients' blood and tumor samples.

Together, the two studies included 44 patients. The researchers measured the frequency of anti-MCC CD8 T cells in patients' blood and tumor samples and looked at which frequencies correlated with positive responses to an ICI. Even though T cells must reach tumors to attack them, the patients most likely to respond to ICIs were those with high levels of anti-MCC cytotoxic T cells in their blood.

This is because a successful immune invasion of a tumor isn't a skirmish — it's a siege.

"It's really about how many new soldiers you can import onto the battlefield over time, rather than what their number is on the battlefield or with their number is on the battlefield at any given moment," Nghiem said.

Ryu and Newell's project also underlined how a fresh set of anti-tumor T cells is critical to the success of ICIs. T cells are powerful warriors against cancer, but eventually the battle within the tumor leaves them too "exhausted" to attack — even if an ICI has removed the barriers holding them back.

T cells at different stages of an immune response turn on different molecules that scientists can use to categorize them. The scientists found that if an important subset of the patient's T cells appeared more battle-worn, the patient was less likely to respond well to ICIs even if they had detectable anti-MCC T cells in their blood. But patients whose blood samples contained T cells that appeared to have spent less energy attacking tumor cells were more likely to respond to ICIs.

Moving toward the clinic

In theory, the findings could form the basis of an easy blood test to help tailor MCC patients' treatment — but there's a long way to go to translate the results into a routine clinical test, Nghiem said.

"This is not ready for prime-time clinical use right now," he said.

Jani has initiated an effort to transform the complex, highly technical methods she and Pulliam used to detect anti-tumor T cells into a simplified and consistent clinical test. Because the T cells she's trying to detect all target the same two polyomavirus proteins, their TCRs share structural

similarities, which may give Jani a leg up in developing a test to quantify the cells in a patient's blood that carry those TCRs, she said.

Ryu and Newell's strategy to identify more energetic anti-MCC T cells relies on less finicky methods that could be more quickly turned into a clinical test once they're validated, Newell said. Validation will include confirming that the cells they've identified are as predictive of response in an independent study, and as active against MCC tumors as they appear.

To further validate these cells as a predictive biomarker, Jani is leading an additional collaboration between the Nghiem and Newell labs to study them in a trial of MCC patients who received retifanlimab, an ICI similar to nivolumab and pembrolizumab.

Once a biomarker test exists, Nghiem envisions it being used to identify who should receive ICIs, or help figure out why a patient didn't respond to an ICI as expected. In these cases, he said, if the test shows that a non-responding patient lacked the right T cells, their oncologist could use this information to direct them to a clinical trial designed to help overcome this hurdle.

Clearing this hurdle will likely involve a strategy to boost a patient's battle-ready anti-tumor T cells. Fred Hutch/UW Medicine scientists, led by [Aude Chapuis, MD](#), and [Josh Veatch, MD, PhD](#), recently opened a [clinical trial](#) testing the efficacy of adoptively transferred T cells genetically engineered to express an anti-MCC TCR.

The findings may have biological relevance beyond MCC, the researchers said. Active anti-tumor T cells outside a tumor are likely to help ICIs work against cancers like melanoma and lung cancer, but it will be more difficult to develop a biomarker test for tumors driven by a complex set of mutations rather than a virus, the scientists noted. The Newell Lab is also actively testing whether their methods for predicting response to immunotherapy in MCC could be applicable to other cancers.

But the primary importance of the papers' findings is that they create a foundation from which scientists can now build, the teams said.

"We believe we're finally really understanding why people do and do not respond, and that this is going help us have better treatments in the future," Nghiem said.

These studies were supported by the National Institutes of Health, the National Cancer Institute, the Fred Hutch Immunotherapy Integrated Research Center, a Kelsey Dickson Team Science Courage Research Award, the National Foundation for Cancer Research, the National Research Foundation of Korea, the UW Merkel cell carcinoma patient gift fund, Merck & Co. and Bristol Myers Squibb.

[This article](#) was originally published February 9, 2024, by Fred Hutch News Service. It is republished with permission.

