

# Immune-cell population predicts immunotherapy response in melanoma

August 16 2016, by Leigh Beeson

---

The abundance of a subtype of white blood cells in melanoma tumors can predict whether or not patients will respond to a form of cancer immunotherapy known as checkpoint blockade, according to a new study led by UC San Francisco researchers and physicians. The research offers the beginnings of a solution to a puzzle that has vexed oncologists: Though many patients with previously untreatable cancers are in remission after receiving checkpoint-blockade drugs, only about 20 percent of patients who receive them respond.

UCSF's Michael Rosenblum, MD, PhD, assistant professor of dermatology and senior author of the new study, said that the new work has generated insights that may help bring the benefits of checkpoint inhibitors to a greater number of patients. Though the study was done in melanoma patients, Rosenblum said that the findings should apply to other types of cancer as well.

As reported online in the Aug. 15, 2016, issue of the *Journal of Clinical Investigation*, the research team analyzed tumors from 40 patients, and found that the relative size of a population of T [cells](#) known as partially exhausted CD8+ cells in the tumors accurately predicted most patients' responses to immunotherapy drugs that target a protein called PD-1. If 30 percent or more of the [immune cells](#) in a given patient's tumor before treatment were of the proper subtype, that patient responded to therapy; if fewer than 20 percent were such cells, there was no response.

Intriguingly, the CD8+ cells that predicted response to anti-PD-1 therapy

expressed high levels of PD-1 and also of CTLA-4, another well-known immune checkpoint protein targeted by immunotherapy drugs. The cells are called "partially exhausted" because they can't produce certain cytokines, signaling molecules that regulate the body's immune response, and as a result aren't able to adequately respond to antigens present in tumors.

PD-1 acts as a "brake" that shields cells from an overzealous immune system. Over the past decade it has been found that drugs that inhibit PD-1's ability to tamp down the immune response unleash T cells to recognize [tumor cells](#) as aberrant and to destroy them, effectively enabling the body's immune system to kill cancers.

These drugs, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), have none of the usual side effects of chemotherapy, radiation, or traditional targeted drugs, and they have led to remarkable cancer remissions, even in advanced metastatic disease, and especially in late-stage melanoma.

But only a fraction of patients respond to anti-PD-1 therapy, and scientists have been eager to devise a method to predict which patients will respond, and why.

"People had concluded that there was never going to be an accurate test that could tell you the difference between responders and non-responders," said Adil Daud, MD, director of Melanoma Clinical Research at the UCSF Helen Diller Family Comprehensive Cancer Center. "They've just assumed that there's no way you could take a tiny piece of tissue and determine who will and won't respond with high predictability," said Daud, also a member of the UCSF Parker Institute for Cancer Immunotherapy. The best tests available so far, which measure levels in tumor tissue of a PD-1-related protein called PD-L1, only modestly discriminate between responders and non-responders, so

they have seen limited use in clinical situations, Daud said.

In the new research, funded by grateful patients of Daud's, the research team analyzed tumor samples from a "discovery cohort" of 20 patients who had received PD-1 inhibitors and were thus known responders or non-responders, employing a technique known as multiparameter flow cytometry. In this method, proteins such as PD-1 and CTLA-4 can be tagged with labels that emit fluorescent signals as they move single-file through transparent tubes past laser beams, allowing scientists to precisely count and sort cells according to their characteristics.

The team focused on a population of "killer" T cells within patients' tumors known as CD8+ cells, and examined these cells to see whether they expressed PD-1, CTLA-4, and other proteins. They found that the number of partially exhausted CD8+ cells in tumors that expressed high levels of both PD-1 and CTLA-4 was a reliable biomarker of response to anti-PD-1 therapy: the more of these cells in the tumor, the more likely patients were to respond, with response defined as at least a 30 percent reduction in melanoma lesions.

The potential clinical usefulness of this observation was then tested in a "validation cohort" of 20 patients not yet treated with anti-PD-1 therapy, and the results held up. Moreover, the researchers were able to quantify the biomarker's predictive power: every patient in whom at least 30 percent of tumor-infiltrating immune cells were the newly characterized CD8+ cells responded to therapy; those in whom fewer than 20 percent were such cells had no response. No reliable prediction could be made for patients in between.

In a new project partially funded by UCSF's Parker Institute, Rosenblum, Daud, and colleagues hope to find a way to increase populations of these "good" CD8+ T cells in non-responders, with the objective of turning them into responders.

For this phase, the researchers have partnered with Berkeley Lights, a company that is pioneering the use of nanofluidic technology to analyze and manipulate [single cells](#). Using this technology, the researchers hope to be able to remove CD8+ cells with the right characteristics from patients, multiply them outside the body, and then return them to patients to change the [patients'](#) immune profiles and encourage response to therapy.

**More information:** Adil I. Daud et al. Tumor immune profiling predicts response to anti-PD-1 therapy in human melanoma, *Journal of Clinical Investigation* (2016). [DOI: 10.1172/JCI87324](https://doi.org/10.1172/JCI87324)

Provided by University of California, San Francisco

Citation: Immune-cell population predicts immunotherapy response in melanoma (2016, August 16) retrieved 20 April 2024 from <https://medicalxpress.com/news/2016-08-immune-cell-population-immunotherapy-response-melanoma.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--