

# Study shows why a common form of immunotherapy fails, and suggests solution

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Samir N. Khleif, MD, director of The Loop Immuno-Oncology Laboratory at Georgetown Lombardi, led the research team that published new research on checkpoint inhibitors. Credit: Georgetown University

New research has uncovered a mechanism thought to explain why some cancers don't respond to a widely used form of immunotherapy called "checkpoint inhibitors" or anti-PD-1. In addition, the scientists say they have found a way to fix the problem, paving a way to expand the number of patients who may benefit from the treatment.

Immunotherapy, which enables the body's own immune system to attack [cancer](#), has not yet met the promise it holds. While it has been a major

advance in the treatment of cancer, up to 85 percent of patients whose cancer is treated with checkpoint inhibitors don't benefit, according to estimates.

In a new study published online July 29 in *Nature Immunology*, a research team, led by Samir N. Khleif, MD, director of The Loop Immuno-Oncology Laboratory at Georgetown Lombardi Comprehensive Cancer Center show that the condition of immune cells (T cells) prior to anti-PD-1 therapy is a crucial determinant for the ability of cancer to respond.

"If the [immune cells](#) are not in the appropriately activated state, treatment with anti-PD-1 drives these T cells into a dysfunctional, non-reprogrammable state, inducing resistance to further immune therapy," Khleif explains.

In order to prevent the immune system from attacking [normal cells](#), the body has a way of protecting these cells from immune attack. Cancer cells often adopt this system of checkpoints in order to put the brakes on immune surveillance to protect themselves and grow. Checkpoint inhibitors release those brakes.

These inhibitors target molecules, such as PD-1 (programmed cell death 1), which sits on the surface of a T cell, and the molecule, PDL-1 (PD-ligand 1) that is present on [tumor cells](#) and bind PD-1. This PD-1/PDL-1 pairing inhibits the normal functioning of T cells known as (killer CD8+), which would otherwise attack the cancer cell. So drugs, in the form of antibodies that bind to either PD-1 or PDL-1, work to remove that protection, allowing T cells to recognize and attack the tumor.

Khleif says it has been known that the tumors that respond more readily to checkpoint inhibitors are those that have already engaged the immune system, such as melanoma and cancers that express a lot of mutations.

The question has been why the agents don't work on immunologically "quiet" tumors. This discovery now shed a light on the issue.

The team also was able to find a strategy to overcome such resistance to immunotherapy.

"When we first activate T cells by using a simple vaccine, or remove the dysfunctional T [cells](#), we found that the checkpoint inhibitor therapy works better," says Khleif, biomedical scholar and professor of oncology at Georgetown Lombardi.

He added that clinical trials are already being developed to confirm these findings in patients, which were made using animal models and patient tumor samples. Cancer vaccines, based on a patient's specific tumor, are being explored as a way to prime the tumors—to invigorate T-cell activity and to enhance PD-1 inhibitors.

"In the past, some of these vaccines have been used after checkpoint immunotherapy. Our findings suggest that the vaccines should be used first, or at least in conjunction with anti-PD-1 therapy," says Khleif.

By examining patient [tumor](#) samples from several [clinical trials](#), the researchers have also discovered a signature that identifies patients who would be resistant "biomarker."

"This might provide an easy and cost-effect prediction method of drug response," Khleif says.

**More information:** Vivek Verma et al. PD-1 blockade in subprimed CD8 cells induces dysfunctional PD-1+CD38hi cells and anti-PD-1 resistance, *Nature Immunology* (2019). [DOI: 10.1038/s41590-019-0441-y](https://doi.org/10.1038/s41590-019-0441-y)

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