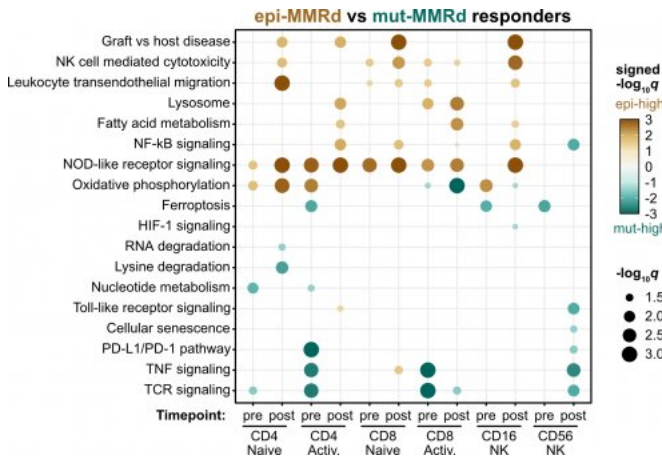


# Study finds a possible explanation for why immunotherapy works well for some cancer patients, but not others

27 October 2022



"We wanted to understand why some patients respond better than others to immunotherapy," said co-corresponding author Ryan Chow, an M.D./Ph.D. candidate working in Yale's Department of Genetics and the Systems Biology Institute.

For the study, the Yale team focused on the failure of a process known as "mismatch repair." When cells divide, errors often arise in their DNA. Through mismatch repair, a special group of proteins recognizes and corrects errors in the DNA. A breakdown in this editing process occurs in many different types of [cancer](#), however, leading to high mutation levels.

Credit: *Cancer Discovery* (2022). DOI: 10.1158/2159-8290.CD-22-0686

Immunotherapy, a biotherapy that boosts the ability of the immune system to recognize and attack mutant tumor cells, has transformed the treatment landscape for patients battling cancer, which emerges from the progressive accumulation of DNA mutations. However, many patients do not respond to immunotherapy. For instance, among highly-mutated colorectal and endometrial cancers, research has shown that only half will show a response to immunotherapy.

A new study by Yale School of Medicine researchers published Oct. 27 in the journal *Cancer Discovery* has identified a possible explanation for why this happens. In an analysis of a phase 2 trial investigating the immunotherapy drug pembrolizumab in 24 patients with [endometrial cancer](#), the Yale team identifies a specific mechanism of faulty DNA repair in tumors as a key factor in determining patient outcomes.

The research team—led by Chow, Dr. Eric Song, an ophthalmology resident and former M.D./Ph.D. student at Yale, and Dr. Alessandro Santin, a professor of obstetrics, gynecology, and reproductive sciences—zeroed in on the fact that mismatch repair deficiency can result from two distinct mechanisms.

In one, mutations occur in the DNA repair machinery itself, leading to the production of defective repair proteins; in the second, production of the DNA repair machinery is halted entirely. In both cases, the tumors accumulate very high levels of mutations that would be expected to make them good candidates for immunotherapy.

"An analogy would be a dysfunctional toy factory," Chow said. "Maybe the factory makes broken toys that don't work, or the factory has no personnel and stops producing toys altogether. Either way, kids won't be happy."

However, the researchers found that tumors with defective DNA repair proteins had significantly better responses to immunotherapy than those in which the production of DNA repair proteins had

been silenced. These differences could ultimately be traced to changes in the [immune response](#) that was mounted against each of the two classes of tumors, they said.

"When it comes to immunotherapy, it seems that the journey—in this case, the underlying cause of [mismatch repair](#) deficiency—may be just as important as the destination," Chow said.

Song added that "the innovative use of clinical trial data can guide our understanding of how [immunotherapy](#) manipulates the [immune system](#) and ultimately improve how we treat patients."

**More information:** Ryan Chow et al, Distinct mechanisms of mismatch repair deficiency delineate two modes of response to PD-1 immunotherapy in endometrial carcinoma, *Cancer Discovery* (2022). [DOI: 10.1158/2159-8290.CD-22-0686](#)

Provided by Yale University

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