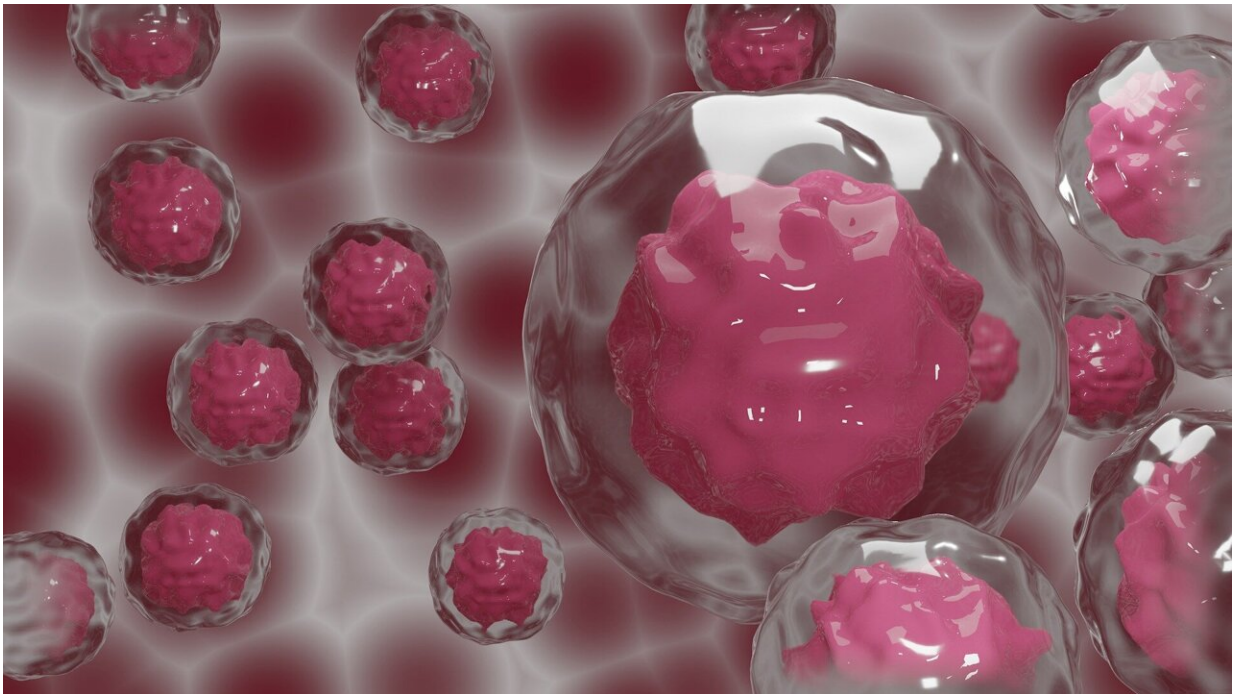


# Novel immunotherapeutic target against hepatocellular carcinoma

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HKUMed researchers at AIDS Institute, Department of Microbiology and Department of Surgery, School of Clinical Medicine, and School of Biomedical Sciences have discovered the role of an isoformic programmed cell death protein 1 (PD-1), namely  $\Delta 42$ PD-1, in suppressing the function of killer T cells, which are essential for killing cancer cells in hepatocellular carcinoma (HCC) patients.

The study is a breakthrough because it demonstrates that  $\Delta 42$ PD-1 causes stronger functional loss of killer T cells, revealing a [molecular mechanism](#) underlying the failure of PD-1-targeted immune checkpoint blockade (ICB) therapy. Moreover, an antibody drug targeting  $\Delta 42$ PD-1 inhibits HCC progression in animal models, which is independent of the PD-1 pathway. The full research article is now published online in the journal *Gut*.

HCC accounts for up to 92.3% of liver cancer cases in China. The 2018 Nobel Prize for Physiology or Medicine was awarded for the discovery of cancer ICB therapy by inhibition of negative immune regulation using PD-1-targeted antibodies, such as Nivolumab. ICB therapy has resulted in prolonged survival and even a cure in some cancer patients. However, ICB therapy is not effective for about 80% of HCC patients. Understanding the mechanism of unsuccessful ICB, therefore, would be essential for discovering a novel therapeutic target to save more lives of HCC patients.

## Research methods and findings

The research team found that human T cells, which express  $\Delta 42$ PD-1 but not PD-1, account for up to 71% of killer T cells in untreated HCC patients.  $\Delta 42$ PD-1 positive T cells are mainly found in tumor tissues, associated significantly with poor HCC prognosis. Moreover,  $\Delta 42$ PD-1 positive T cells have weaker killing function than PD-1 positive T cells. Treatment of HCC patients using Nivolumab, the PD-1-targeted ICB drug, even increases the number of  $\Delta 42$ PD-1 positive T cells especially in patients with tumor progression.

The researchers demonstrated that  $\Delta 42$ PD-1 positive T cells inside tumors promote HCC growth through activating toll-like receptor-4-mediated inflammation. Instead of Nivolumab, anti- $\Delta 42$ PD-1 antibody inhibits tumor growth in three HCC/humanized murine models

through blocking of the  $\Delta 42$ PD-1-TLR4 axis, reducing the number of  $\Delta 42$ PD-1 positive T cells and increasing functional killer T cells inside the tumor. These findings not only revealed a mechanism underlying the unsuccessful PD-1-targeted ICB therapy but also identified  $\Delta 42$ PD-1 as a novel therapeutic target for HCC immunotherapy.

This important discovery provides [scientific evidence](#) that  $\Delta 42$ PD-1 may serve as a novel drug target against HCC or other relevant cancers and may warrant the clinical development of a humanized  $\Delta 42$ PD-1-specific antibody for immunotherapy against HCC and related human cancers/diseases.

"We were the first research group in the world to discover the  $\Delta 42$ PD-1 protein," said Professor Chen Zhiwei, Director of AIDS Institute and Professor of the Department of Microbiology, School of Clinical Medicine, HKUMed, who led the study.

"In this study, we not only further discover the dual activities of  $\Delta 42$ PD-1 on human T cells in both suppressing anti-tumor [immune response](#) and promoting tumorigenesis, but also generate a potential anti- $\Delta 42$ PD-1 antibody drug for HCC treatment."

"Besides immunotherapy against HCC, the anti- $\Delta 42$ PD-1 antibody can also be used as a drug to prevent HCC recurrence without induction of graft rejection after [liver transplantation](#)," added Professor Nancy Man Kwan, Department of Surgery, School of Clinical Medicine, HKUMed.

**More information:** Zhiwu Tan et al, Isoformic PD-1-mediated immunosuppression underlies resistance to PD-1 blockade in hepatocellular carcinoma patients, *Gut* (2022). [DOI: 10.1136/gutjnl-2022-327133](#)

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