Drug combo breaks down cancer resistance to immunotherapy

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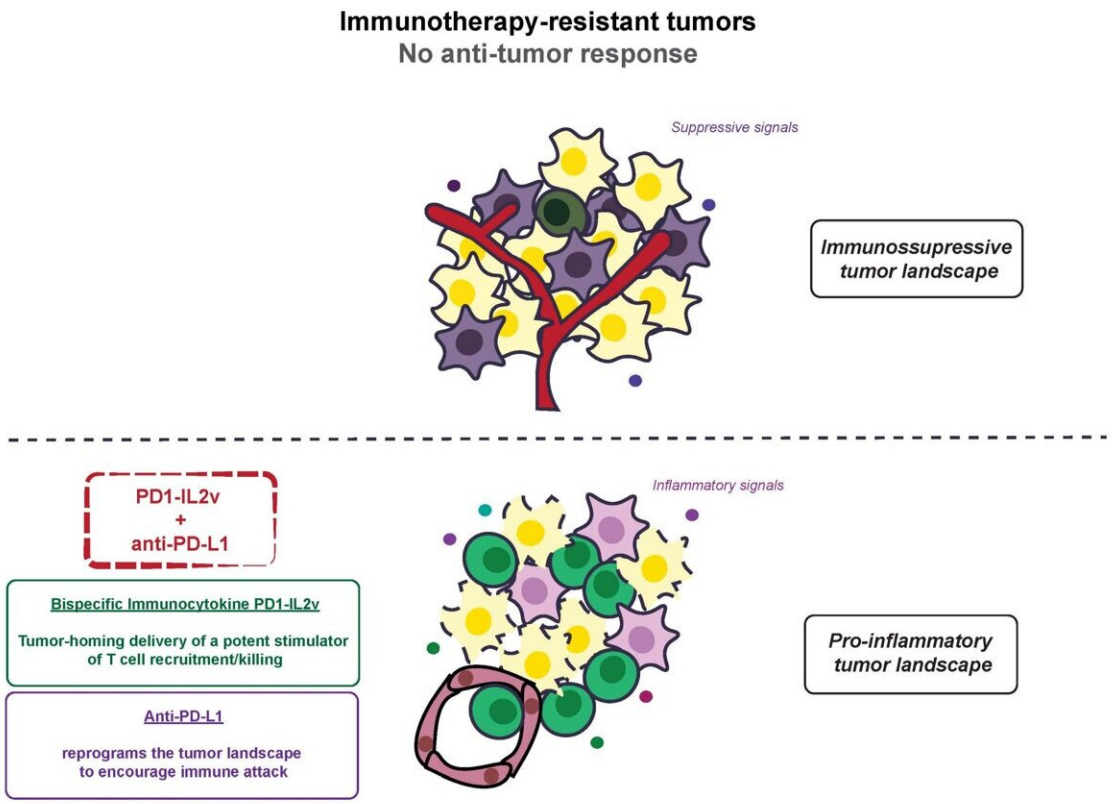


A schematic summary of the study. Credit: Douglas Hanahan (EPFL)

Immunotherapy is a way of treating cancer by reprogramming the patient's immune system to attack their tumor. This cutting-edge approach has significantly impacted the treatment of cancer patients, and

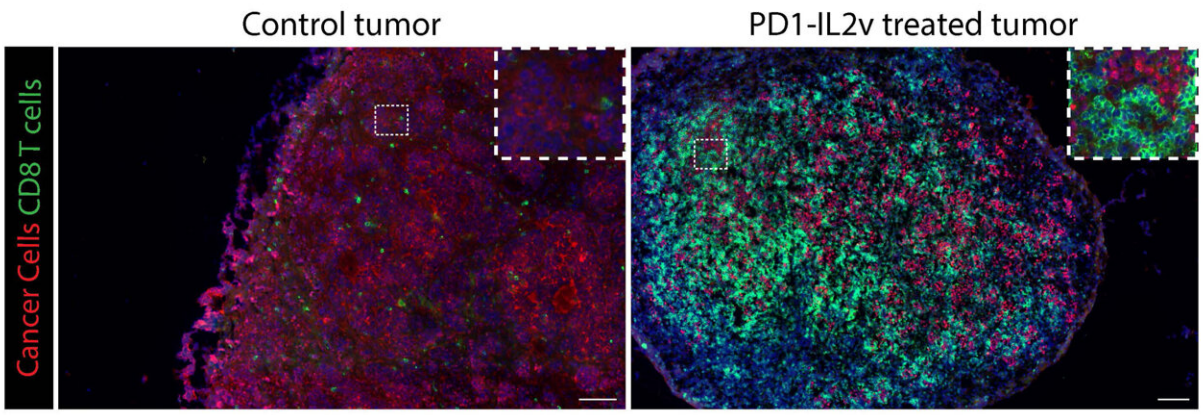
already boasts cases of long-term remission.

Nonetheless, many patients either don't respond to immunotherapy, or if they do, the effects are temporary, which highlights how crucial it is that we better understand the mechanisms leading to cancers resisting this kind of treatment.

In a new study, scientists have found a way to break down the resistance of mice with neuroendocrine pancreatic cancer. This cancer is very resistant to a type of immunotherapy called checkpoint blockade, where the patient receives a drug (a checkpoint inhibitor) that blocks proteins that normally keep immune responses from being too strong, but can also prevent immune cells (T cells) from killing cancer cells.

The study was led by the group of Douglas Hanahan at EPFL's Swiss Institute for Experimental Cancer Research, with the Ludwig Institute for Cancer Research, the Lausanne University Hospital (CHUV), the Swiss Institute for Bioinformatics, and Roche.

The scientists evaluated a type of engineered protein-antibody fusion called an immunocytokine, which is increasingly used in immunotherapy. They focused on the bispecific immunocytokine PD1-IL2v, which is newly developed by Roche and can home in on tumors, wherein it activates killer T cells to attack the cancer cells driving tumor growth.



Fluorescence microscopy of a control tumor vs a PD1-IL2v treated tumor. Credit: Tischet et al.

The researchers combined the immunocytokine PD1-IL2v with the immune checkpoint inhibitor anti-PD-L1, thereby enhancing anti-tumor immunity against immunotherapy-resistant tumors. "[PD1-IL2v] is even more effective when combined with an immune checkpoint inhibitor, anti-PD-L1," write the authors.

"PD1-IL2v induces stronger and more specific expansion of anti-tumor T cells compared to conventional anti-PD-1 therapy by stimulating a specific subtype of T cells, whereas anti-PD-L1 targets and disrupts barriers erected in the tumor microenvironment, namely pro-tumoral macrophages and tumor vasculature, which collaborate to counteract the anti-tumor immunity."

Combining the two molecules resulted in increased survival rates in tumor-bearing mice, producing a more sustained therapeutic effect than just the bispecific immunocytokine by itself. The combination improved therapeutic efficacy by reprogramming immunosuppressive tumor-

associated macrophages and tumor vasculature to render the cancer easier to detect by immune cells.

"This innovative immunotherapeutic combination sensitizes immunotherapy-resistant tumors infiltrated with PD-1^+ stem-like T cells, which have recently been found to be important for sustaining efficacious anti-tumor immune responses, leading to tumor destruction with consequent survival benefit," says Douglas Hanahan.

"These provocative results present a rationale for clinical trials aimed to evaluate the combination therapy of PD1-IL2v and anti-PD-L1, perhaps initially in immunotherapy-resistant cancer patients with T cell infiltrated tumors."

The research is published in the journal *Immunity*.

More information: Douglas Hanahan, Bispecific PD1-IL2v and anti-PD-L1 break tumor immunity resistance by enhancing stem-like tumor-reactive CD8+Â T cells and reprogramming macrophages, *Immunity* (2023). DOI: 10.1016/j.immuni.2022.12.006.
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