A peptide-drug conjugate that targets the acidic environment of cancer cells may improve the efficacy of immunotherapy

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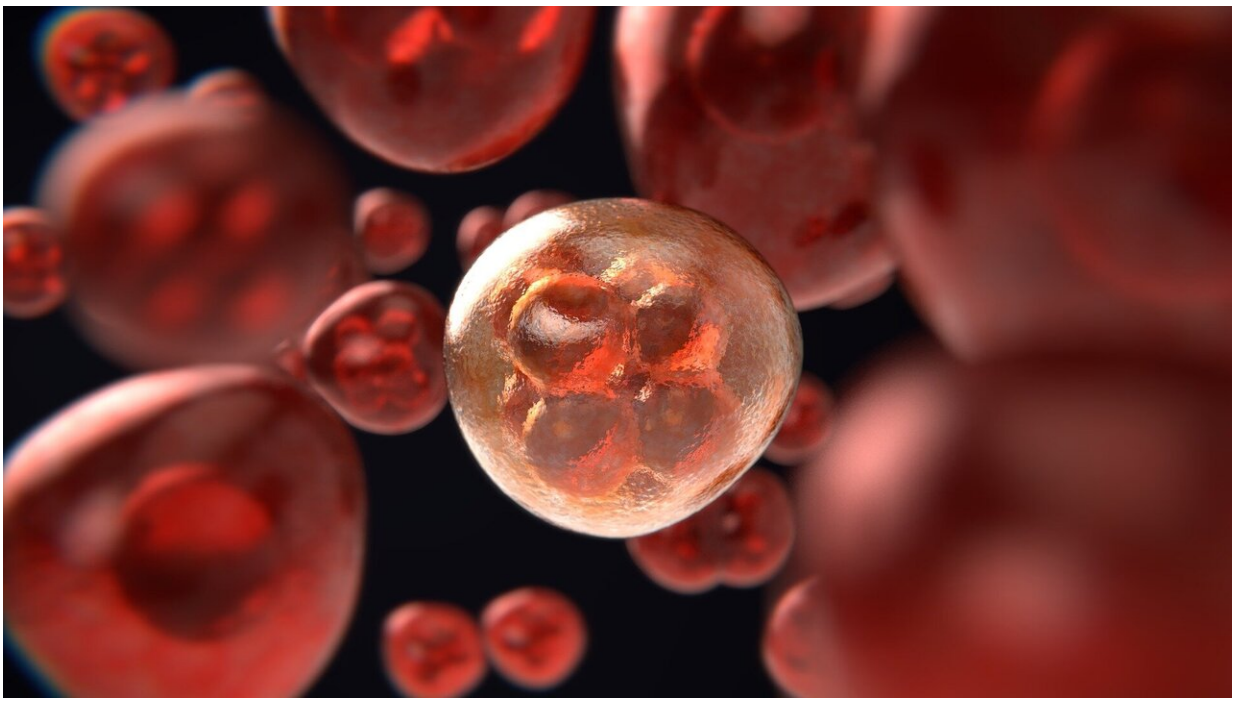

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A peptide-drug conjugate that targets the acidic environment of cancer cells enhanced the efficacy of immune checkpoint inhibitors in preclinical cancer models, according to results presented at the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and

Cancer Therapeutics, held October 7-10, 2021.

Immune checkpoint inhibitors are commonly combined with chemotherapy, but the myelosuppression associated with chemotherapy can reduce the efficacy of immunotherapy, explained presenter Sophia Gayle, Ph.D., an associate director of biology at Cybrexa Therapeutics. Chemotherapy is also associated with various toxicities, due to its effects on non-cancer cells.

CBX-12 is a peptide-drug conjugate that delivers exatecan, a potent cytotoxic agent, specifically to cells with low pH environments, a trait that is characteristic of all cancer types. CBX-12 utilizes a unique variant of a pH-low insertion peptide (pHLIP) that undergoes a conformational change in the presence of low pH, enabling the peptide to deliver exatecan into the cell.

"The novelty of CBX-12 is that it targets acidity, which is a universal feature of all tumors," said Gayle. "We are, therefore, able to deliver a potent anticancer therapeutic selectively to cancer cells in a much broader patient population, as opposed to antibody-drug conjugates that are restricted primarily to patients whose tumors express high levels of a target antigen."

The selective targeting of cancer cells also avoids the toxicities associated with other therapies that non-selectively affect normal cells, she added. Gayle and colleagues recently demonstrated that treatment with CBX-12 did not induce myelosuppression in preclinical cancer models. "Since CBX-12 does not lead to myelosuppression, we hypothesized that combining CBX-12 with immunotherapies could be a promising therapeutic strategy," she noted.

In this study, Gayle and colleagues used mouse models of colorectal cancer to evaluate the impact of CBX-12 treatment on the efficacy of

PD-1- and CTLA4-targeted immune checkpoint inhibitors. Mice receiving the combination treatment exhibited significantly delayed tumor growth, improved survival, and complete tumor regressions compared to mice treated with immune checkpoint inhibition alone. Tumor growth was delayed four times longer when CBX-12 was combined with a PD-1 inhibitor and 10 times longer when combined with a CTLA4 inhibitor.

In addition, mice that experienced complete tumor regressions demonstrated long-term immunological memory after tumor rechallenge. Injection of CBX-12-treated tumor cells into mice led to antitumor immunity upon tumor challenge, indicating that CBX-12 induced immunogenic cell death.

"Our results suggest that combining CBX-12 with immune checkpoint inhibition could extend the benefit of immunotherapies to tumors that do not normally respond to them," said Gayle, noting that this could benefit a wide range of patients, 80 percent of whom have tumors that do not respond to immune checkpoint inhibitors alone.

A limitation of the study is that all experiments were performed in preclinical models; thus, additional research is required to understand the impact of the treatment in patients. A phase I clinical trial to determine the safety and recommended phase II dose of CBX-12 is currently in progress.

More information: Conference: www.aacr.org/meeting/aacr-nci- … cancer-therapeutics/

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