Experimental drug that boosts immunotherapy shows promise in bladder cancer study

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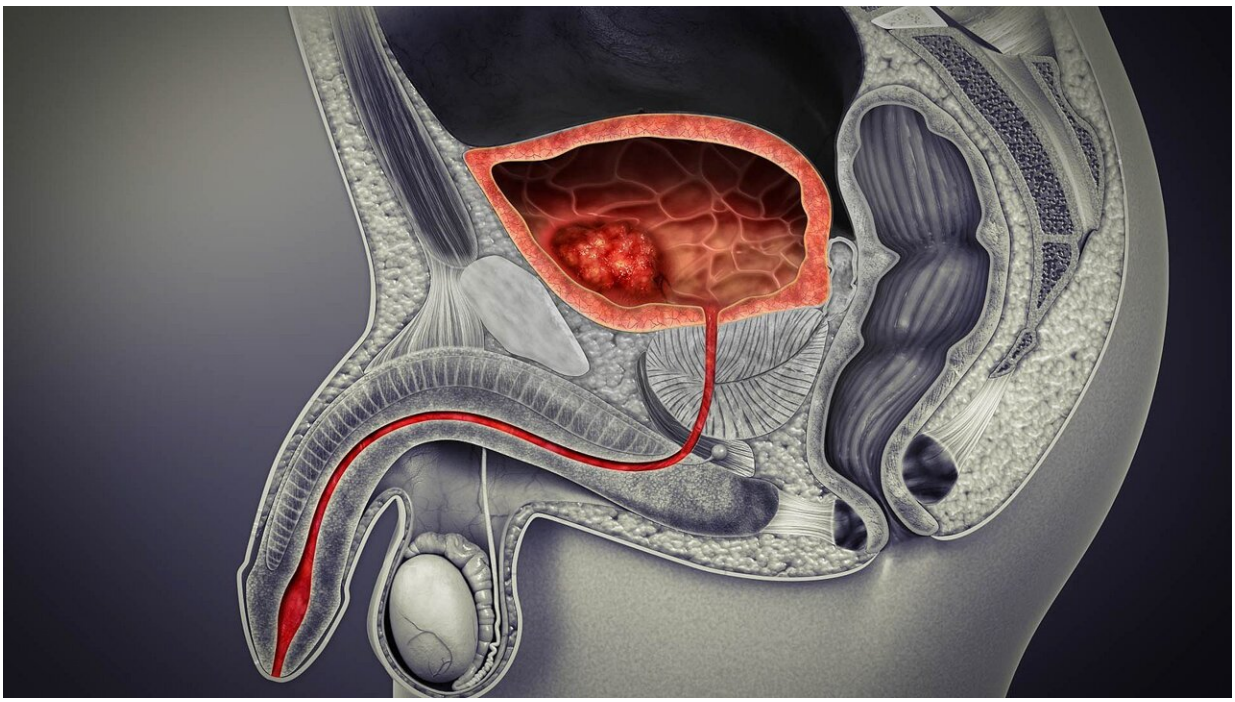

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A new study in mice found that adding the experimental drug entinostat to an immunotherapy-like treatment substantially boosted cancer remission. This approach shows such promise that it's already being tested in an ongoing clinical trial in people with advanced bladder

cancer.

This finding, led by scientists at the University of North Carolina Lineberger Comprehensive Cancer Center, was published August 16, 2021, in the *Journal of Clinical Investigation*.

"Bladder cancer rates in the United States have been stable or decreasing slightly over the past decade, but five-year survival rates have barely budged since the 1990s," said UNC Lineberger's William Y. Kim, MD, Rush S. Dickson Distinguished Professor of Medicine and professor of Genetics and the paper's co-corresponding author. "Hence our search for ways to improve treatments for a cancer that can be extremely difficult to treat in its advanced stages."

The FDA recently approved several immunotherapy treatments for bladder cancer, but these treatments shrink tumors in only approximately 15 percent of patients. With the goal of boosting response rates to immunotherapies, the researchers turned to histone deacetylase (HDAC) inhibitors in hopes that this class of drugs would result in expression of the immunotherapy targets that had previously been silenced during tumor evolution. In this study, the researchers used entinostat, a highly selective HDAC inhibitor being tested in late-stage clinical trials in various types of cancer.

"Importantly, neoantigen-specific T cells were increased in number after entinostat treatment. This means that the antigens unmasked by entinostat can be targeted by T cells already in the body that otherwise would not be activated to kill tumor cells," said UNC Lineberger's Benjamin Vincent, MD, assistant professor at the UNC School of Medicine and co-corresponding author. "We are excited about combining entinostat with therapies that boost T cell function in the future."

When treated with entinostat in combination with immunotherapy, two-thirds of mice had a complete disappearance of their tumors and none of the mice had relapse of their tumors when taken off the treatment.

"Use of entinostat alone in people has not led to effective reductions in tumor size," said UNC Lineberger's Tracy Rose, MD, MPH, assistant professor at the UNC School of Medicine. "We believe that neoantigens have to be unmasked, or made visible, at the same time that the brakes on T cells are released by immunotherapies."

Given the clear benefits of adding entinostat to immunotherapy in the lab, the investigators are conducting a clinical trial to test the benefit of the combination therapy with people who have advanced bladder cancer. That trial started in 2020 and its findings are expected to be reported in late 2022 (Clinical trial NCT03978624).

"For our next steps, we will wait until next year to see if the clinical results look promising, and if so, we will consider a larger trial," concluded Kim. "In the meantime, we would like to continue to improve the therapy and personalize it by adding a strategy called neoantigen vaccination to the entinostat plus immunotherapy regimen, to boost even further the chances for successful outcomes."

More information: Andrew S. Truong et al, Entinostat induces antitumor immune responses through immune editing of tumor neoantigens, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI138560

Provided by UNC Lineberger Comprehensive Cancer Center