Antibody drug conjugates may help personalize radiotherapy for patients with cancer

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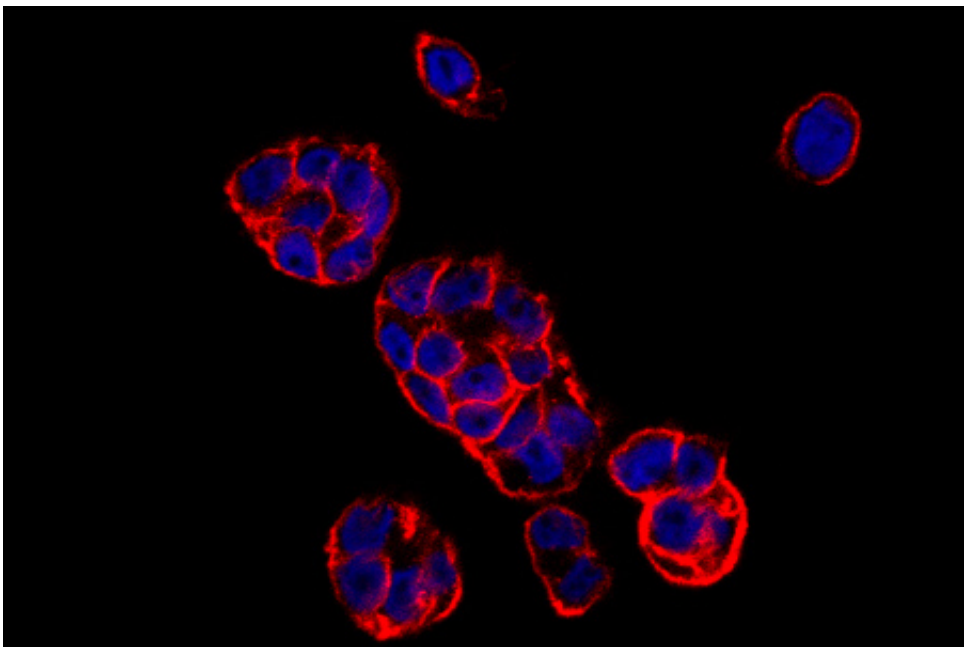

UC San Diego School of Medicine and Moores Cancer Center researchers report that in mouse models tumors testing positive for a protein called human epidermal growth factor receptor 2 (HER2) were sensitized to a combination of radiation therapy and an antibody drug conjugate (ADC), called ado-trastuzumab emtansine (T-DM1) pictured here in red binding to tumor cells. Credit: UC San Diego Health

Many types of cancer become drug resistant, making them difficult to treat. Researchers with University of California San Diego School of

Medicine and Moores Cancer Center have identified a strategy to selectively sensitize certain cancer cells to radiation therapy that may improve tumor control and reduce treatment-related side effects.

In a paper published October 4 in *Nature Communications*, researchers report that in mouse models tumors testing positive for a protein called human epidermal growth factor receptor 2 (HER2) were sensitized to a combination of radiation therapy and an antibody drug conjugate (ADC) called ado-trastuzumab emtansine (T-DM1). ADC is a new technology that chemically links an antibody to a targeted cell receptor to deliver a drug to specific cells—in this case a very potent chemotherapy to HER2 positive tumors—while sparing normal tissue.

"A biomarker-driven, tumor-targeted radiosensitization approach to treating cancer is a potentially significant advancement from current chemotherapy and radiation therapy," said Sunil J. Advani, MD, associate professor in the Department of Radiation Medicine and Applied Sciences and the paper's senior author. "Non-targeted, highly toxic chemotherapies continue to remain the most effective treatments for patients treated concurrently with chemotherapy and radiation, but these treatments have significant toxicity and we need alternatives that are molecularly guided based on mutations found in specific patients. Our approach is to use antibodies to restrict delivery of powerful drugs to cancer cells that sensitize tumors to radiation therapy."

The study shows promise in HER2 cancers, which occur in a percentage of lung, esophageal, gastric and bladder cancers.

T-DM1 is already approved for use in metastatic HER2 positive breast cancer treatment. Researchers repurposed the existing drug to sensitize cancer cells to radiation therapy among patients who simultaneously receive chemotherapy and radiation therapy at the beginning of the treatment process, instead of waiting until the cancer spreads or becomes

resistant to treatment.

Intensifying a dose of non-targeted chemotherapies increases normal tissue toxicities, often precluding further radiation therapy or chemotherapy escalation. Using targeted ADC with radiation therapy would reduce toxicity, reduce the risk of tumor resistance and attacks both known tumors as well as cancer cells that may have metastasized, while sparing normal tissue.

"Our hope is that the results can transition to clinical studies quickly to help patients with advanced cancers that are difficult to treat with standard therapies," said Stephen R. Adams, PhD, project scientist in the Department of Pharmacology and first author on the paper.

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