A faster way to make antibody-drug conjugates

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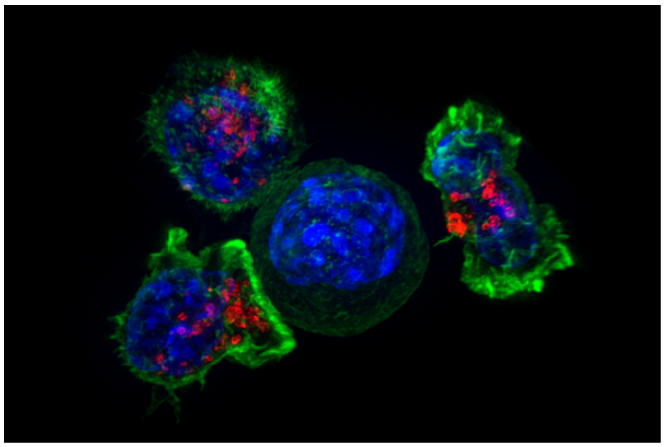

Killer T cells surround a cancer cell. Credit: NIH

A USC School of Pharmacy-led team has engineered a new, faster way to make drugs that precisely target malignant cells—while leaving healthy tissue undamaged—that could lead the way to better treatments for numerous types of cancer.

The drugs, called antibody-drug conjugates or ADCs, belong to a relatively new class in which drug molecules are attached to antibodies which zero in on and attach to the surface of cancer cells. As of May 2020, eight ADCs have been approved by the U.S. Food and Drug Administration, and more than 100 clinical trials are underway studying their effectiveness in treating blood, lung, breast, brain and other cancers.

In a study published today in *Science Advances*, USC scientists describe a new technology to rapidly create a homogeneous type of ADC, which attaches to a specific site on the cancer cell, with improved efficiency and potentially enhanced stability, effectiveness and safety.

ADCs consist of an antibody for seeking out a cancer cell, a drug for killing it and a chemical "linker" uniting them. However, currently used ADCs are manufactured through a process that yields varied products of limited stability and efficacy.

Homogenous ADCs therefore carry more potential for clinical effectiveness. But current technologies for making this type of ADC require multiple steps or long reaction times due to inefficient chemistries. Many homogenous ADCs can also trigger immune responses that hamper their use.

The USC team may have solved these issues. "Using our approach, homogenous ADCs could be made through a single-step reaction in less than two hours, much faster and more efficiently than conventional approaches," says the study's Principal Investigator, Yong (Tiger) Zhang, Assistant Professor of Pharmacology and Pharmaceutical Sciences at the USC School of Pharmacy.

"Our technology features a designer 'linker' component exclusively recognized by a human enzyme that can rapidly catalyze the conjugation of drug molecules to the antibodies at a defined position," he says. "In addition to its fast rate and high efficiency, our ADC technology offers a new type of linker for connecting the drugs to antibodies. This designer linker ensures stable attachment of the drug and rapid release of the drugs into target cells, making the generated ADCs safer and more efficacious."

Using this technology, the USC team generated an ADC that can effectively block the growth of breast cancer tumors in animals. These promising results provide a strong basis for translation of this ADC into clinical studies, the investigators say.

More information: "Synthesis of site-specific antibody-drug conjugates by ADP-ribosyl cyclases" *Science Advances* (2020). advances.sciencemag.org/content/6/23/eaba6752