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Scientists test a 'bispecific' antibody that helps T cells zero in on treatment-resistant cancers

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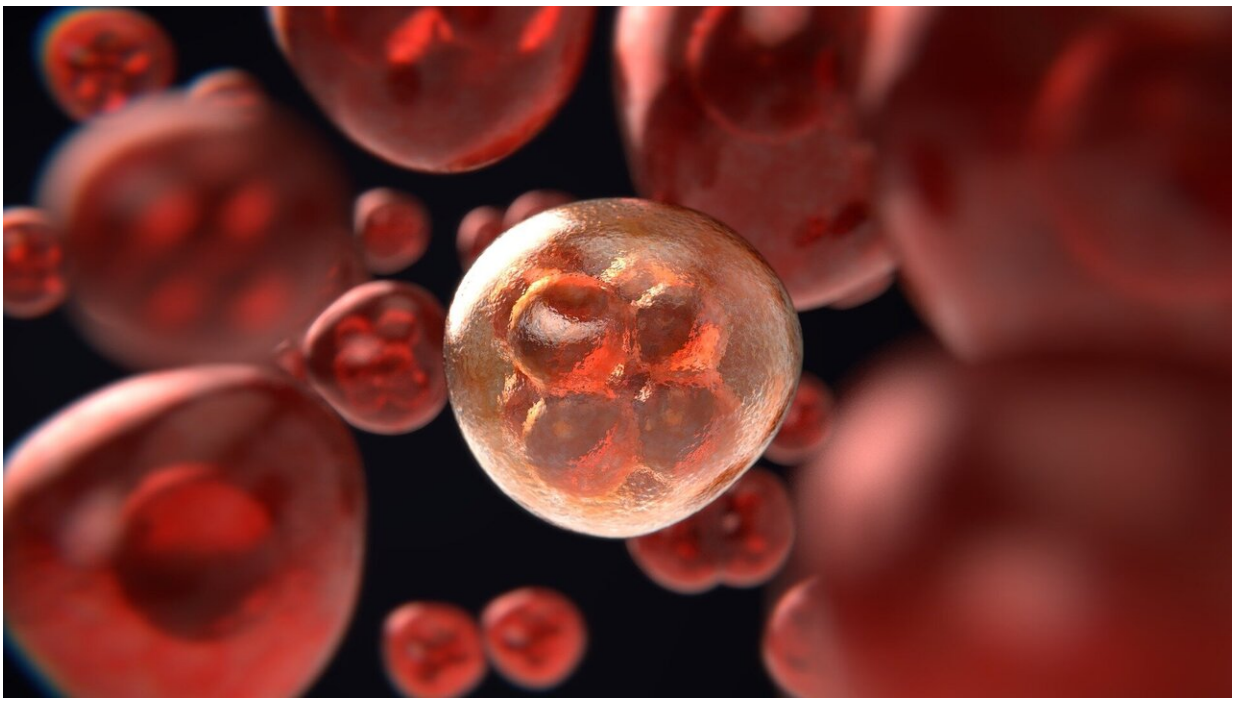

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Although immunotherapy has achieved increasing prominence in the panoply of innovative cancer treatments, it remains an imperfect tool—too many tumors simply do not respond.

To the rescue is an evolving class of engineered proteins that go by the unusual name of bispecific antibodies. As their name implies, these proteins have dual recognition capability: They are engineered to home in on a T cell surface receptor as well as bind to the surface antigen of a cancer cell itself. The aim is to bring the two types of cells together and to activate the tumor annihilating capability of T cells.

Research on bispecific antibodies is underway at Regeneron Pharmaceuticals, a leading biotechnology company in Tarrytown, New York. The company has garnered a spotlight for its development of REGN-EB3, a triple antibody cocktail, which outperformed other investigational treatments last year for Ebola. The drug is under review by the U.S. Food and Drug Administration and is expected to receive full approval later this year. Regeneron scientists are also conducting research on an antibody-based medication that can prevent or treat COVID-19, depending on the patient's need.

Regeneron's anticancer innovation, meanwhile, has grown out of a sobering reality: Certain cancers have developed deceptive strategies allowing them to resist immunotherapy. Resistance among cancers is as daunting a concern as infections caused by drug-resistant bacteria.

Several common cancers have a noteworthy history of thwarting checkpoint blockade immunotherapy, a treatment that relies on the strength of T cells to kill tumors. The investigational bispecific antibodies are designed to help overcome cancer-cell resistance.

Janelle Waite and Dimitris Skokos are part of a large Regeneron team testing a class of co-stimulatory CD28-bispecific antibodies to enhance antitumor activity. The scientists reported their advance in *Science Translational Medicine*.

Checkpoint blockade immunotherapy is itself an innovative form of

cancer therapy that relies on drugs known as immune checkpoint inhibitors. This class of therapeutics is designed to treat multiple forms of cancer by engaging the body's immune system—its T cells—to recognize and attack malignant cells. Keytruda, a medication that helped revolutionize the treatment of non-small-cell lung cancer, is a checkpoint inhibitor.

All checkpoint inhibitors are based on a deceptively simple principle: Cancer cells possess a protein dubbed PD-L1. T cells have a surface protein called PD1. Tricky cancer cells use their PD-L1 proteins to elude T cells, to get past the guards—the checkpoints—an activity that allows tumors to proliferate and spread.

Multiple cancers that range from Hodgkins lymphoma to lung, bladder, ovarian and kidney cancers may initially respond to checkpoint inhibitors, but soon develop resistance. The Regeneron team studied two bispecific antibodies that each target a T cell protein dubbed CD28. At the same time, they analyzed two tumor-specific antigens. The bispecific antibodies attracted both T cells and the cancer antigens, enhancing the potential of cancer cell death by T cells.

Waite and colleagues found that bispecific antibodies enhanced the effectiveness of treating the anti-PD-1 checkpoint blockade in mouse models. The scientists also say the combination sensitized, previously resistant tumors to treatment. The bispecific antibodies showed few signs of toxicity and did not provoke dangerous systemic responses from T cells.

"Monoclonal antibodies that block the programmed cell death checkpoint [PD-1] have revolutionized cancer immunotherapy," Waite wrote. "However, many major tumor types remain unresponsive to anti-PD-1 therapy, and even among responsive tumor types, most of the patients do not develop durable antitumor immunity."

In a series of animal studies, Waite and colleagues demonstrated that their experimental class of dual-affinity antibodies can safely boost the cancer-killing power of checkpoint blockade immunotherapy in mice. The animals had tumors that tend to resist immunotherapy treatments. The results represent a stride in creating safer cancer immunotherapy combinations, the team reported.

In addition to the mice, the antibodies were additionally well tolerated by long-tailed macaques and did not cause the severe immune side effects that have held back similar treatments in the past.

The research arrives amid worldwide efforts to address the obstacle of tumor cell resistance to checkpoint inhibition. Last year, scientists in France advanced the notion that rotavirus vaccines can be used to overcome the problem of cancer cell resistance to checkpoint blockade immunotherapy.

"We have found that rotavirus vaccines, Rotateq and Rotanix, have both immunostimulatory and oncolytic properties," Dr. Tala Shekarian of Center de Recherche en Cancérologie de Lyon told Medical Xpress. She added that the vaccines "can directly kill cancer cells with features of immunogenic cell death."

Shekarian, like Waite and colleagues, found a way to overcome tumor-cell resistance. The French team additionally underscored the importance of having an inexpensive off-the-shelf solution to a stubborn problem in cancer care.

More information: Janelle C. Waite et al. Tumor-targeted CD28 bispecific antibodies enhance the antitumor efficacy of PD-1 immunotherapy, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.aba2325