Boosting anti-cancer antibodies by reducing their grip

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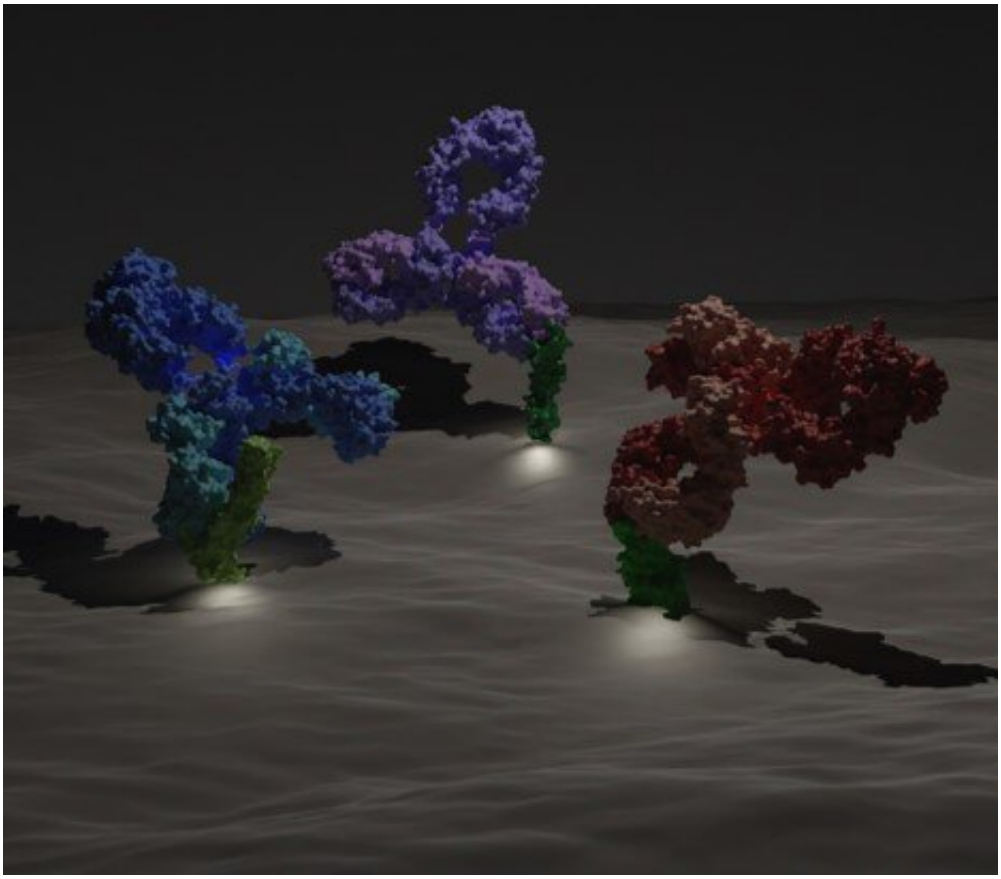

Illustration of antibodies binding receptors and stimulating them. Credit: University of Southampton

New research from the Centre for Cancer Immunology at the University of Southampton, published ahead of World Cancer Day (February 4),

has shown that changing how tightly an antibody binds to a target could improve treatments for cancer.

Antibodies detect and tag viruses and bacteria so the body's immune system can destroy them. To help prevent a second infection our immune system fine-tunes these antibodies to have a tighter grip on these targets, known as higher affinity.

Immunotherapy treatments for cancer use the same concept—direct targeting antibodies are designed to find and bind tightly to the cancer cells so the immune system can kill them. These antibody treatments have proved successful for some cancers over the last few years, but many cancer patients still do not respond or become resistant to them.

In a new study, published in *Nature*, Southampton researchers have shown that a different type of therapeutic antibody, called "immunomodulatory antibodies," are successful in treating cancer when they have a looser grip.

Changing the tightness of binding is known as affinity engineering and the research team believes this could offer an efficient, more flexible, opportunity to treat cancer.

Immunomodulatory antibodies bind to receptors on immune cells rather than tumor cells and work by altering the signals that are transmitted into the immune cells to make them more active and better at killing cancer cells.

In the study, the team examined three separate receptors (CD40, 4-1BB and PD-1), and showed there was better clustering of the receptors and signaling into the immune cells was improved when the binding was looser. For one of these, CD40, it showed better killing of tumor cells.

Professor Mark Cragg, from the Centre for Cancer Immunology, said, "Although the number of approved antibody drugs is continually increasing, with over 100 now in clinic, some patients remain unresponsive to the treatment. Therefore, developing new strategies to super-charge our antibodies through techniques such as affinity engineering is key to providing better treatments for patients."

"Our study suggests that by changing the affinity we can effectively fine tune the antibody to the desired level and activity."

"Importantly, immunomodulatory antibodies target the same receptor on immune cells and so can in theory be used for very many different types of tumors, opening up more treatment opportunities for more people. The main applications currently are in oncology, but in principle the same approach could be used for antibodies treating autoimmune disorders and inflammatory diseases."

Dr. Xiaojie Yu, first author of the study and now assistant professor at the School of Life Sciences at Westlake University, said, "High affinity binding has been the mantra of therapeutic antibody development for decades. The finding that low affinity was conducive to antibody-mediated cellular signaling by the immunomodulatory antibodies presents a powerful tool for developing new and more effective antibodies for treating cancer and autoimmunity."

Katherine de Retuerto, Associate Director of Development at the University of Southampton, said, "This exciting work is exactly what we hoped would happen when we were fundraising to build the Centre for Cancer Immunology. The many generous donors whose philanthropy contributed to the Centre, including those who funded a key piece of equipment used in these experiments, should feel great pride at the progress the Southampton team is making."

Dr. Iain Foulkes, Executive Director of Research and Innovation at Cancer Research UK, said, "Cancer is a master of the art of evading the immune system. We need to try many different tactics to help our bodies unmask tumors and attack them."

"Immunomodulatory antibodies are one of the cornerstones of immunotherapy, which is fast becoming a staple treatment in the clinic. But immunotherapy doesn't always work for everyone, and we need to keep refining it to ensure it gives patients the best chance of a good outcome."

"This research offers an exciting new approach to making antibody treatments work better and in the future we hope to see it reach its full potential in the clinic."

More information: Mark Cragg, Reducing affinity as a strategy to boost immunomodulatory antibody agonism, *Nature* (2023). DOI: 10.1038/s41586-022-05673-2.
www.nature.com/articles/s41586-022-05673-2

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