Investigators build a better targeted drug therapy using the power of computation

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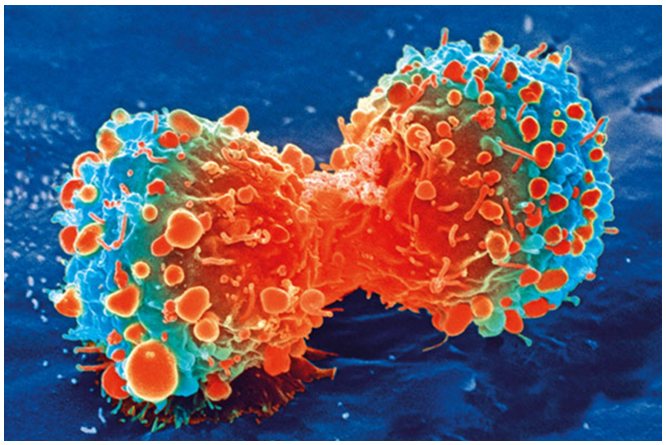

Cancer cell during cell division. Credit: National Institutes of Health

Antibody drug conjugates (ADCs)—cancer drugs that are designed to target and destroy cancerous tissue while leaving healthy cells intact—represent a long sought-after advancement in cancer therapy. ADCs work by attaching a cancer drug to an antibody that is unique to a specific type of tissue, allowing ADCs to deliver treatment directly to the site of a tumor rather than throughout the body.

To date, five ADCs have received Federal Drug Administration approval for treating cancer and 56 drug companies are developing ADCs. However, ADCs currently have substantial limitations. They can have unpredictable effects and may be unstable, losing their payloads and producing toxicity. Investigators from Brigham and Women's Hospital set out to design more stable and predictable ADCs by using computer simulations to predict and plan out how the drug payload and antibody can stay linked to each other. The team tested out their predictions in human and mouse plasma and in a model of human lung adenocarcinoma. Their findings are published in *Nature Biomedical Engineering*.

"The goal of this technology is to empower currently used antibodies in cancer treatment, making them more effective against cancer," said corresponding author Shiladitya Sengupta, Ph.D., an associate professor of medicine in the Division of Engineering in Medicine at the Brigham. "We designed a LEGO-like linker that just clicks a drug payload to any antibody we want. That means we can deliver a drug specifically to any tissue that expresses the target of the antibody."

Sengupta and colleagues used computational docking molecular simulations to create prototype that could link an antibody and drug payload. They mapped the binding sites to determine how ligand-drug pairs would bind to different antibodies. They synthesized the various components and showed that when they were incubated together, they could self-assemble into ADCs, like magnets that find one another. Inspired by this observation, the team named this approach MAGNET ADCs, which stands for multivalent and affinity-guided antibody empowerment technology.

The team reports that MAGNET ADCs could be generated rapidly and did not require modifying antibodies. The MAGNET ADCs showed long-term stability in plasma, lasting 14 days and showing low toxicity. The team tested MAGNET ADCs in a model for human lung cancer, but the authors note that this technology could be adapted to a variety of therapeutic or diagnostic uses.

"We envisage that the MAGNET-ADC approach can be extended to a wide range of therapeutic molecules as well as to diagnostics, with potential uses beyond the treatment of cancer," the authors write.

More information: Nimish Gupta et al, Computationally designed antibody–drug conjugates self-assembled via affinity ligands, *Nature Biomedical Engineering* (2019). DOI: 10.1038/s41551-019-0470-8

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