Scientists reengineer cancer drugs to be more versatile

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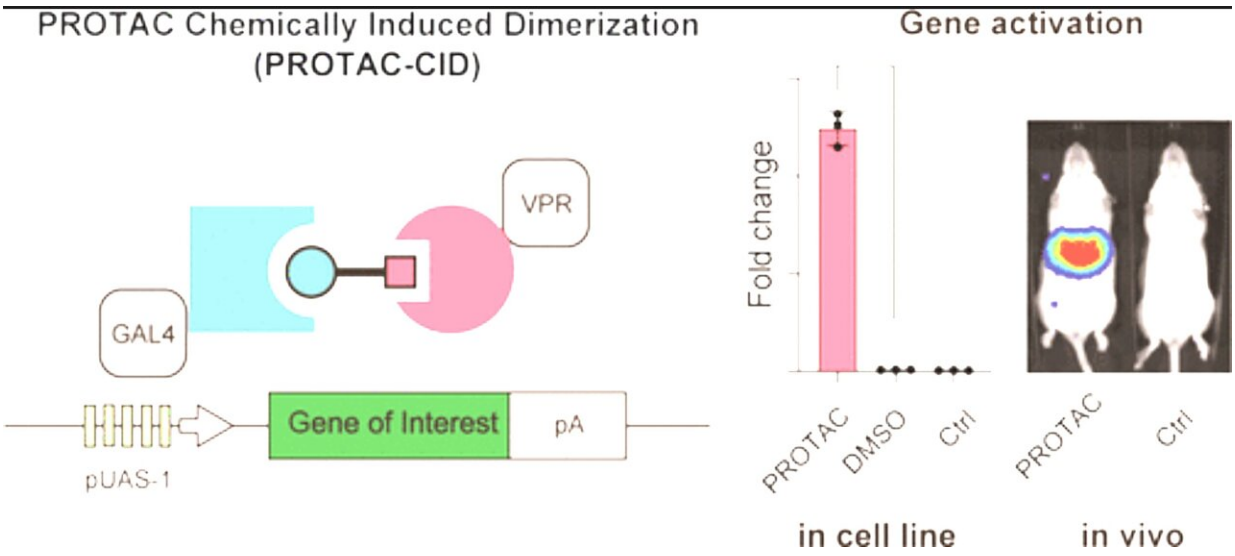

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Rice University scientists have enlisted widely used cancer therapy systems to control gene expression in mammalian cells, a feat of synthetic biology that could change how diseases are treated.

The lab of chemical and biomolecular engineer Xue Sherry Gao discovered a way to further tap the therapeutic potential of proteolysis targeting chimeras (PROTACs), small molecules that are used as effective tools for treating cancer, immune disorders, viral infections

and neurodegenerative diseases.

Gao and collaborators reengineered the PROTAC molecular infrastructure and showed it can be used to achieve chemically induced dimerization (CID), a mechanism by which two proteins bind together only in the presence of a specific third molecule known as an inducer. The research is described in a study published in the *Journal of the American Chemical Society*.

"The novelty of this is the extent of control that combining these two mechanisms gives us over inducing gene activation at desired locations in the body and for desired durations," Gao said.

"Small molecules can act as a switch to turn gene expression on and off," she said. "Temporal control is a result of the fact that small molecules are metabolized by living organisms. What this means is that you can schedule for a certain gene to be expressed for a certain amount of time."

"In terms of spatial control, we can deliver the system only to the organ or site of the body where it is needed," Gao continued. "You don't need to have the medication go through your whole body and generate unnecessary and harmful toxicity."

The CID mechanism is a key part of many biological processes, and over the past two decades scientists have devised a host of ways to engineer it to serve medical, research and even manufacturing needs. The development highlights the growing impact of synthetic biology, which takes an engineering approach to biological systems, repurposing their mechanisms to harness new resources.

Sirolimus, formerly known as rapamycin, is an example of a molecule that can act as an inducer and form CID systems with multiple cell

pathways in the body. Discovered in 1972 in soil bacteria on Easter Island, the compound has been used as an antitumor and immunosuppressant drug. More recently, it was touted as a potential anti-aging drug after researchers discovered it could interfere with a cellular pathway that activates lysosomes, organelles responsible for cleaning up damaged cells.

"CID systems are attractive tools because they enable precise control over molecular interactions, which in turn can activate or inhibit biological outcomes, such as, for example insulin production in a diabetic patient or tumor growth in a cancer patient," Gao said.

"Right now there are only a limited number of functional and efficient CID systems," she added. "I wanted to address this unmet need. I saw PROTACs, which are already being used with good results as therapies, as an opportunity to expand the CID toolbox."

PROTACs work by targeting specific proteins, such as those found in a tumor, causing them to disintegrate. One side of the molecule binds to a targeted harmful protein, another side flags down a specific enzyme that initiates protein degradation and a third element connects the two sides together.

"You can think of this mechanism as similar to a smart missile that relies on a sensor to track its target," Gao said. "The vocabulary is suggestive in this sense, too, since the protein you want to destroy is called a 'target protein,' and the part of the PROTAC system that binds to the target protein is called a 'warhead.' We are hijacking this system to control gene expression instead."

The advantage of PROTACs over other drugs is that they can be effective in small doses and do not lead to the development of drug resistance. There are over 1,600 PROTAC small molecules approved for

cancer therapy, acting on more than 100 human protein targets.

"PROTACs are very efficient and act with great specificity against oncogenic proteins, which are proteins encoded by certain activated or dysregulated genes that have a potential to cause cancer," Gao said. "We wanted to harness that efficiency and precision and put it to work in a new way. We redesigned PROTAC from a protein-degradation system to a gene-activation system.

"Ultimately, I hope this will prove useful in the context of treating real diseases," she continued. "The ability to regulate when and where genes are activated in the body could help solve a wide range of medical problems. My main goal with this project is to have a small molecule-controlled gene expression system, including the CRISPR genome editors."

More information: Dacheng Ma et al, Engineered PROTAC-CID Systems for Mammalian Inducible Gene Regulation, *Journal of the American Chemical Society* (2023). DOI: 10.1021/jacs.2c09129

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