Medical Xpress

New cancer drug shows promise targeting genetic weakness in tumors

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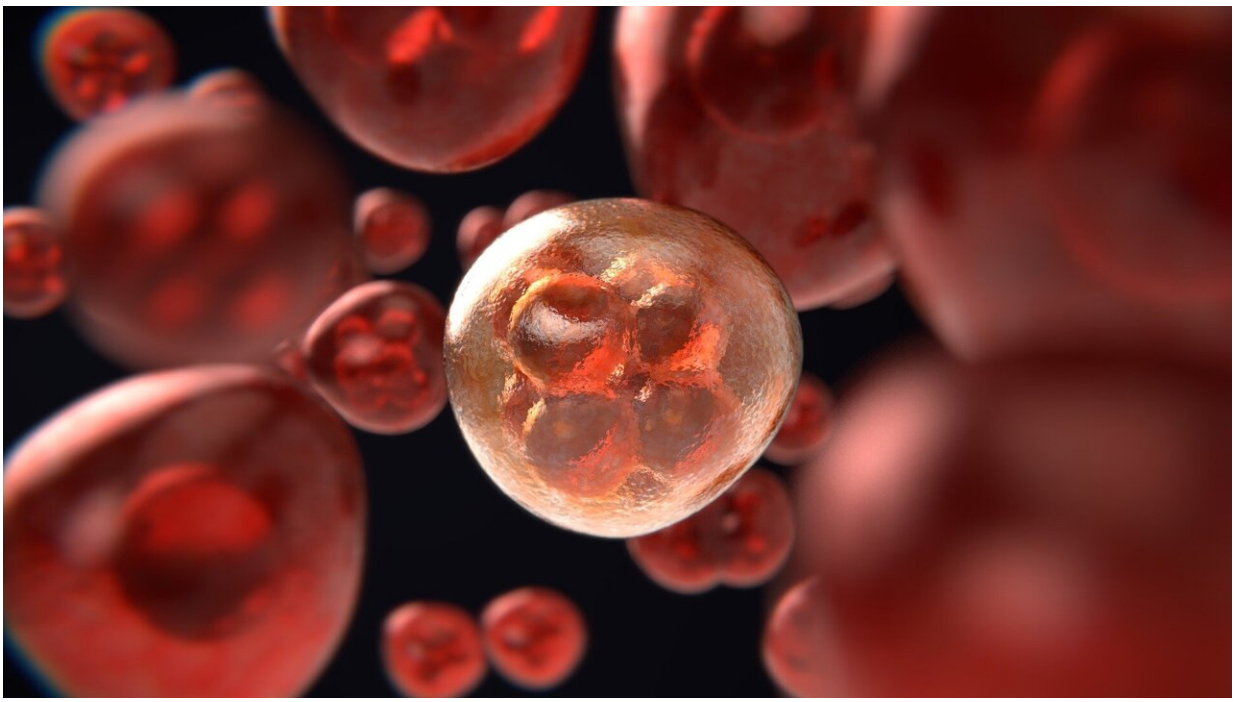

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Imagine the body's cells are well-behaved students in the classroom. The "teachers" are tumor suppressor genes, and they make sure cells follow the rules. But when tumor suppressor genes are away, cells may go astray.

With cells, this is a serious matter. Unregulated behavior can lead to

uncontrolled growth, and ultimately, the development of cancer.

In a new invited review article in *Cancer Discovery*, Kathleen Mulvaney, assistant professor with the Fralin Biomedical Research Institute at VTC, talks about the potential of a new drug called MRTX1719 that has shown early promise in clinical trials for solid tumors by killing cancer cells with that lack specific tumor suppressor genes.

"This is an updated version of an important new class of drugs targeting the PRMT5 enzyme, which is the target protein we study in my lab," said Mulvaney, a Virginia Tech cancer researcher who is not affiliated with Mirati Therapeutics Inc., the biotechnology company that published clinical results in *Cancer Discovery*.

Mulvaney accepted the invitation to write the commentary because of her enthusiasm for the new class of drug and its potential to help the 10–15% of human cancer patients who could benefit from these drugs based on their genetic deletion status.

The MRTX1719 drug targets cancers with a genetic vulnerability—the absence of tumor suppressor gene CDKN2A and its neighbor gene, MTAP. These missing genes can lead to uncontrolled cell growth, but the drug exploits this weakness to fight the cancer.

"This drug is an improvement because it binds to a specific part of the PRMT5 protein in a manner unique to cancer cells with the CDKN2A/MTAP gene deletion," said Mulvaney, who is also an assistant professor in the Department of Biomedical Sciences and Pathobiology in the Virginia-Maryland College of Veterinary Medicine. "The data from early testing looks promising for using this drug either alone or in combination with others in the future."

In the Phase 1 and Phase 2 stages of clinical testing, researchers reported

positive results in patients with specific types of cancer with the MTAP gene missing, including melanoma, gallbladder cancer, mesothelioma, lung cancer, and a type of nerve cancer called MPNST (Malignant Peripheral Nerve Sheath Tumor).

"What's remarkable is that it took just a few years to go from discovering the genetic issue in these cancers in 2016 to having a hopeful drug in clinical trials by 2023," Mulvaney said. "This shows how genetic research and smart drug development can create effective cancer treatments. Through genomic screens, we can identify cancer's Achilles heels and develop small molecules to target them."

Earlier versions of PRMT5 inhibitors that reached clinical trials from 2016 to 2019 struggled with issues of toxicity in patients before the drugs could reach a therapeutically helpful dose, Mulvaney said.

But with the improvements, she said it is important to draw the field's attention to a new class of MTA-cooperative PRMT5 inhibitors, which includes the drug MRTX1719 and others, because they are demonstrating they can effectively help in killing tumors while leaving the normal human cells unharmed.

Mulvaney's lab is part of the Fralin Biomedical Research Institute in Washington, D.C., on the Children's National Research and Innovation Campus. Her lab is part of a growing collaborative research program between Fralin Biomedical Research Institute and Children's National Hospital. She is also a member of the Virginia Tech Cancer Research Alliance.

More information: Early clinical success of MTA-cooperative PRMT5 inhibitors for the treatment of CDKN2A/MTAP deleted cancers, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-CD-0951

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