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First-in-class targeted microRNA therapy slows cancer tumor growth

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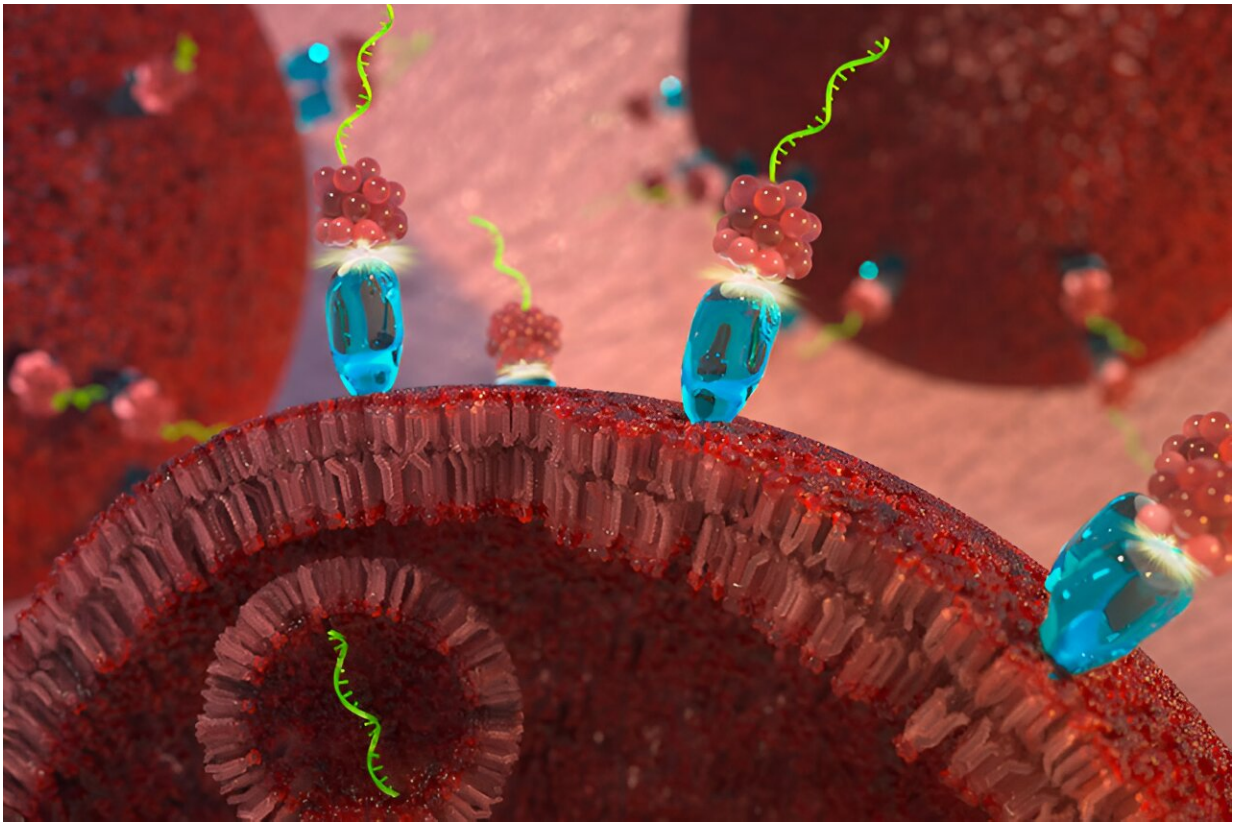

A new therapy targets cancer cells with a modified strand of micro-RNA that naturally blocks cell division. Credit: Second Bay Studios/Purdue University

A new cancer therapy developed by Purdue University researchers attacks tumors by tricking cancer cells into absorbing a snippet of RNA

that naturally blocks cell division. As reported in *Oncogene*, tumors treated with the new therapy did not increase in size over the course of a 21-day study, while untreated tumors tripled in size over the same time period. The paper is tiled "A first-in-class fully modified version of miR-34a with outstanding stability, activity, and anti-tumor efficacy."

Cancer can begin almost anywhere in the human body. It is characterized by cells that divide uncontrollably and that may be able to ignore signals to die or stop dividing, and even evade the immune system. The therapy, tested in mouse models, combines a delivery system that targets cancer cells with a specially modified version of microRNA-34a, a molecule that acts "like the brakes on a car," slowing or stopping cell division, said Andrea Kasinski, lead author and the William and Patty Miller Associate Professor of biological sciences at Purdue University.

In addition to slowing or reversing tumor growth, the targeted microRNA-34a strongly suppressed the activity of at least three genes—MET, CD44 and AXL—known to drive cancer and resistance to other cancer therapies, for at least 120 hours. The results indicate that the patent-pending therapy, the newest iteration in more than 15 years of work targeting microRNA to destroy cancer, could be effective on its own and in combination with existing drugs when used against cancers that have built drug resistance.

"When we acquired the data, I was ecstatic. I am confident that this approach is better than the current standard of treatment and that there are patients who will benefit from this," said Kasinski, a member of the Purdue Institute for Cancer Research.

MicroRNA-34a is a short double strand of ribonucleic acid—a string of ribonucleic acids attached like the teeth of a zipper along the length of a sugar-phosphate chain. The two strings of the microRNA are unevenly zipped together, with one string acting to guide a protein complex to the

worksite in the cell while the other string is destroyed.

In healthy cells, microRNA-34a is abundant, but its presence is dramatically reduced in many cancer cells.

While the idea of reintroducing microRNA-34a to cancer cells appears simple, the research team had to overcome many challenges in crafting an effective therapy. Naturally occurring RNA breaks down rapidly, so to improve the durability of the therapy, the team stabilized microRNA-34a by adding several small clusters of atoms along the length of the strand.

The team modeled its modifications on an FDA-approved chemical structure that researchers at the biotechnology company Alnylam used on similar short interfering RNAs. Experiments on mouse models show the modified microRNA-34a endures for at least 120 hours after being introduced.

As a bonus, the fully modified microRNA-34a is invisible to the immune system, which would ordinarily attack double-stranded RNA introduced to the body.

To ensure the modified microRNA-34a makes it to cancer cells, the team attached the double strand to a molecule of the vitamin folate. The surfaces of all cells in our body have receptors that bind to folate and draw the vitamin into the cell, but the cells in many cancers—breast, lung, ovarian and cervical—have far more folate receptors on their cell surface than do healthy cells.

The tiny microRNA-34a and folate compound penetrates the dense tissue of tumors and binds to the folate receptor on the cell surface. It is then drawn inside in a little bag of cell membrane called a vesicle. Once inside the cell, some of the microRNA-34a is able to escape the vesicle

and slows cell division.

The targeted specificity of the therapy reduces the amount of the compound that must be administered to be effective, which in turn reduces potential toxicity, side effects and cost. The team can also prepare a separate version, which targets a different cell surface receptor, for prostate cancer cells, which do not produce excessive folate receptors. Kasinski and her team are confident in the value of the most recent iteration and will prepare for clinical trials.

At Purdue, Kasinski was joined in the research by Philip S. Low, Presidential Scholar for Drug Discovery, Ralph C. Corley Distinguished Professor of Chemistry, and inventor of the FDA-approved drug Cytalux; Nadia A. Lanman, a research assistant professor; Ahmed M. Abdelaal, first author and a graduate student in Kasinski's lab; and researchers Harish Kothandaraman, Kasireddy Sudarshan, Shreyas Iyer and Ikjot S. Sohal.

Kasinski disclosed the innovation to the Purdue Innovates Office of Technology Commercialization, which has filed a patent application on the IP.

More information: A first-in-class fully modified version of miR-34a with outstanding stability, activity, and anti-tumor efficacy, *Oncogene* (2023). DOI: 10.1038/s41388-023-02801-8 , www.nature.com/articles/s41388-023-02801-8

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