

## New agent might control breast-cancer growth and spread

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The drug AS1411 works by blocking the cell's production of regulatory molecules called microRNA, some types of which are associated with cancer. Specifically, the drug inhibits a protein called nucleolin that plays a critical role in the microRNA maturation process. Left: Steps in the microRNA maturation process. Right: How AS1411 interferes with microRNA maturation. Credit: The Ohio State University Comprehensive Cancer Center



A new study led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) suggests that an unusual experimental drug can reduce breast-cancer aggressiveness, reverse resistance to the drug fulvestrant and perhaps improve the effectiveness of other breast-cancer drugs.

The findings of the laboratory and animal study, published in the *Journal of Experimental Medicine*, suggest a new strategy for treating breast cancer, the researchers say.

The drug, called AS1411, belongs to a class of agents called G-rich aptamers. The agent works by blocking the cell's production of molecules called microRNA, some types of which are associated with cancer. Specifically, the drug inhibits a protein called nucleolin that plays a critical role in the microRNA maturation process (See figure).

MicroRNA molecules help cells control the amount and kinds of proteins they make, and abnormal levels of certain microRNAs are a hallmark of many cancers.

"This study of the role of nucleolin in micro RNA regulation has clear clinical implications," says principal investigator Dr. Carlo M. Croce, director of Ohio State's <u>Human Cancer Genetics</u> program and a member of the OSUCCC – James Molecular Biology and Cancer Genetics program.

"It supports a novel treatment for breast cancer that reduces cancer aggressiveness and restores drug-sensitivity by inhibiting the processing of specific microRNAs that are highly expressed in cancers."

First author Flavia Pichiorri, assistant professor of hematology, notes that nucleolin is a promising <u>therapeutic target</u> for microRNA



modulation in <u>cancer cells</u>.

"To our knowledge, this is the first large study to show a clear association between nucleolin and specific microRNAs that are causally involved in cancer," she says. "We also believe it is the first study to show that targeting nucleolin with a G-rich <u>aptamer</u> can control breastcancer metastasis in an animal model through microRNA regulation."

The study's key technical findings include:

- Nucleolin is present at abnormally high levels in breast cancer cells.
- AS1411 reduces nucleolin levels and inhibits the processing of certain cancer-associated microRNAs, including miR-21, miR-103, miR-221 and miR-222, whose overexpression in breast cancer is associated with drug resistance and aggressiveness.
- AS1411 affects breast-cancer-cell motility and invasiveness by reducing the expression of several genes targeted by nucleolin-related microRNAs (e.g., PTEN);
- Impairing nucleolin in fulvestrant-resistant <u>breast-cancer</u> cells restores sensitivity to the drug, suggesting that agents targeting nucleolin can improve the effectiveness of conventional anticancer agents.

## Provided by Ohio State University Medical Center

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