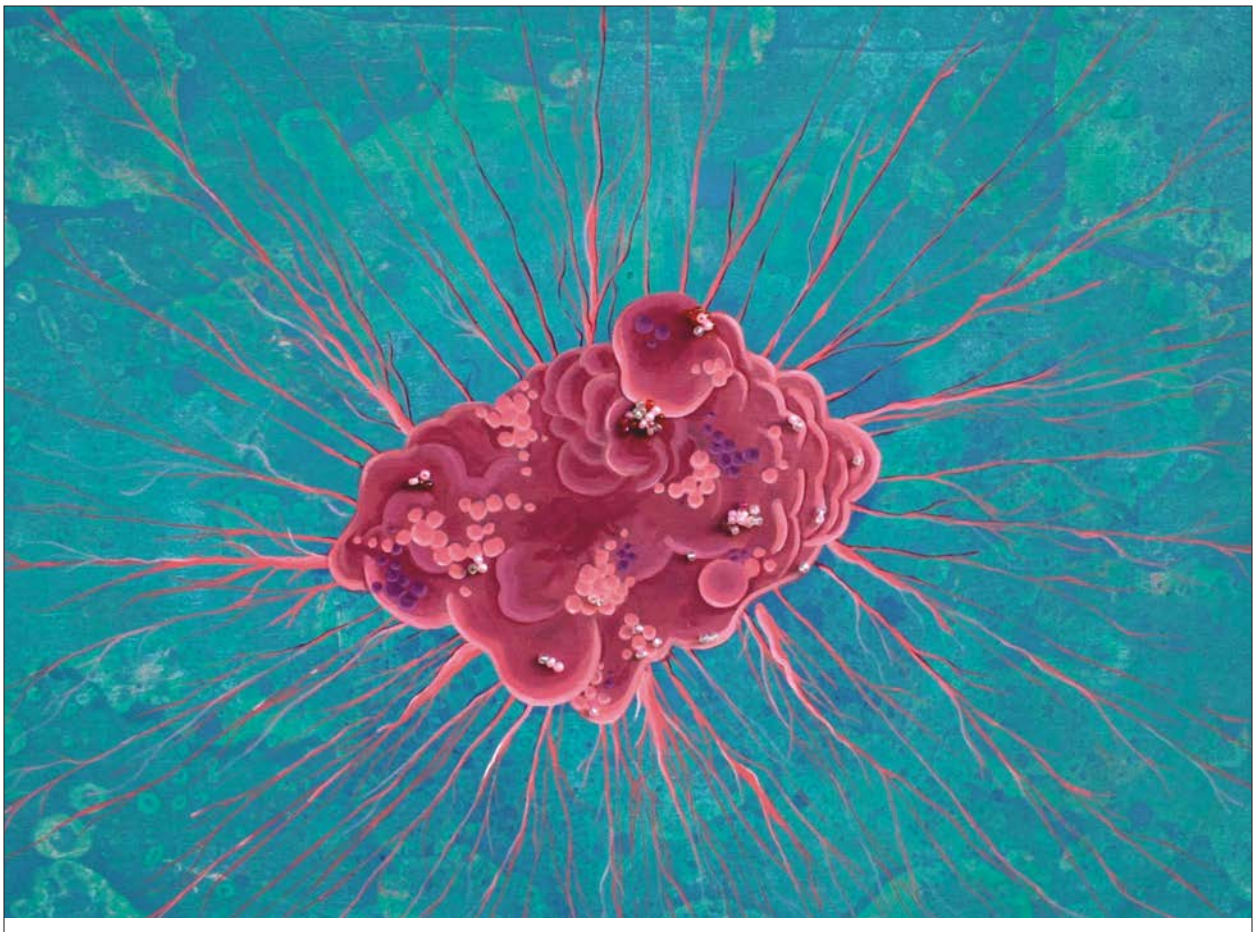

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Molecular Rationale for Combining Targeted Agents to Treat Breast Cancer

A new study by Ohio State University cancer researchers provides a rational for treating breast cancer by combining two kinds of targeted agents, one that inhibits an overactive, cancer-causing pathway in cancer cells and one that reverses changes that silence genes that normally prevent cancer. Both types of agents are currently available and being evaluated individually in clinical trials, the researchers note.

The findings, published online in the journal Cancer Research, show that abnormal activation of the PI3K/AKT signaling pathway leads to the silencing of a number of tumor-suppressor genes that regulate cell proliferation, survival and motility and angiogenesis.

The laboratory and animal study also shows that combining an agent that inhibits PI3K and a drug that reverse the epigenetic changes that cause gene silencing significantly slows tumor growth.

"The link we have uncovered between PI3K/AKT signaling and epigenetic silencing offers a new therapeutic strategy for breast cancer that combines a PI3K/AKT inhibitor and agents that target epigenetic changes," says study leader Tim H-M Huang, professor of molecular virology, immunology and medical genetics at the Ohio State University Comprehensive Cancer Center -- Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

"Our studies show that, in models, these agents work together synergistically to reverse gene silencing and suppress cancer-cell growth, suggesting that combining these targeted agents might improve breast-cancer therapy."

Cancer development typically involves the abnormal activation of genes that regulate cell growth and the silencing of genes that normally prevent cancer development. The activation of one or more "oncogenes" and the silencing of tumor-suppressor genes are usually considered separate events that together lead to cancer. This and earlier studies led by Huang show that the two events are sometimes linked.

Huang and his colleagues are now planning a clinical trial for patients with metastatic breast cancer that will investigate the use of combined targeted drugs.

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Other researchers involved in this study were Tao Zuo, Ta-Ming Liu, Xun Lan, Yu-I Weng, Rulong Shen, Fei Gu, Yi-Wen Huang, Sandya Liyanarachchi, Daniel E. Deatherage, Pei-Yin Hsu, Cenny Taslim, Bhuvaneswari Ramaswamy, Charles L. Shapiro, Huey-Jen L. Lin and Victor X. Jin of Ohio State University; and Alfred S. L. Cheng of The Chinese University of Hong Kong.

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