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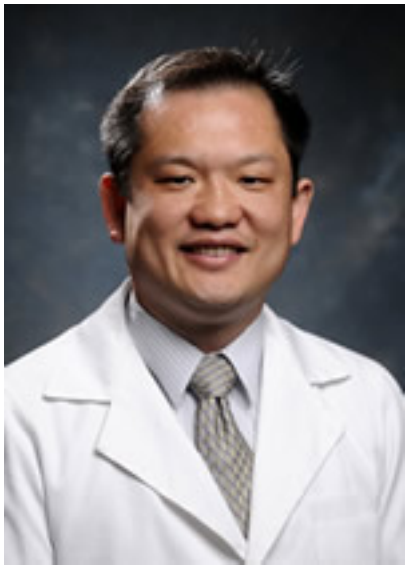
New research from the University of Alabama at Birmingham shows that a class of drugs with clinical activity in familial breast and ovarian cancers may be useful in treating women with another, aggressive disease subtype known as HER2-positive breast cancer.



Poly ADP ribose polymerase (PARP) inhibitors interfere with a cancer cell's ability to repair DNA damage, hastening cell death. This class of drugs is currently in clinical trials to treat breast and ovarian cancers linked with inherited mutations in the BRCA genes, which are particularly prone to DNA damage. But only about 5 to 10 percent of all breast and ovarian cancers are BRCA-associated familial cancers. And since PARP inhibitors are generally well tolerated and have relatively few side effects, researchers at UAB and elsewhere have been trying to expand the patient population that might benefit from the drugs.

"To do this, we have been attempting to render nonfamilial cancers deficient in DNA repair," says Eddy S. Yang, M.D., Ph.D., assistant professor in the UAB Department of Radiation

Oncology and an associate scientist in the experimental therapeutics program at the UAB Comprehensive Cancer Center.

But in a new study that was published Sept. 17, 2012, in *Cancer Research*, a journal of the American Association for Cancer Research, Yang's lab found that this step may not be necessary in the case of an aggressive subtype of breast cancer known as HER2-positive tumors, which account for about 20 percent of breast-cancer cases.

Once a tumor is determined as HER2-positive, women are treated with very specific HER2-positive breast-cancer therapies. However, many women with this form of cancer either fail to respond to these targeted therapies, or initially respond to them but then become resistant to their effects.

In prior studies, the Yang lab found that inhibiting the epidermal growth factor receptor (EGFR) pathway, which is commonly overactive in many tumor types, resulted in a DNA repair defect similar to that seen in familial cancers. They subsequently showed that this "forced" DNA repair defect increased tumor sensitivity to PARP inhibitors. Because HER2 and EGFR are in the same family of proteins, Yang and his team theorized that HER2-targeted therapies might force a similar DNA repair defect in HER2-positive tumors, increasing their sensitivity to PARP inhibitors.

In this current study, Yang found that HER2-positive breast cancer cell lines were indeed sensitive to PARP inhibitors, both in culture and when transplanted into mice. “However, the surprise was that these HER2-positive tumors were sensitive to PARP inhibitors alone, independent of a DNA repair defect,” says Yang. “This means that there may be other mechanisms, outside of DNA repair, that dictate the sensitivity of a tumor to PARP inhibitors.”

The researchers hope to further map out the reason why HER2-positive tumors are sensitive to PARP inhibitors. If better defined, the knowledge could ultimately broaden the clinical application for PARP inhibitors.

“These findings will allow us to potentially uncover other targets that may lead to future therapeutic strategies and ultimately improve outcomes and patient quality of life,” says Yang.

The UAB Comprehensive Cancer Center is among the 41 cancer centers in the nation to meet the stringent criteria for the National Cancer Institute's comprehensive designation. The center is a leader in groundbreaking research, reducing cancer disparities and leading-edge patient care.