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Tamoxifen-resistant breast cancer reversed when drug paired with anti-malaria agent

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The inexpensive anti-malarial drug hydroxychloroquine (HCQ) reverses resistance to tamoxifen, a widely used breast cancer drug, in mice.

In the June 15 issue of *Clinical Cancer Research*, investigators from Georgetown Lombardi Comprehensive Cancer Center say adding HCQ to tamoxifen could provide a new treatment option for some women with advanced, postmenopausal estrogen receptor-positive (ER+) breast cancer. The ER+ subtype accounts for an estimated 70 percent of all breast cancers. While many of these women are treated with tamoxifen, which blocks estrogen from fueling the tumor, 50 percent of these cancers will either not respond or will become resistant to tamoxifen over time.

"Tamoxifen resistance when treating breast cancer is a big issue in the clinic, and we believe our findings provide a very promising fix to the problem," says the study's senior investigator, Robert Clarke, PhD, DSc, dean for research at Georgetown University Medical center, and co-director of the breast cancer program at Georgetown Lombardi.

Clarke adds that both drugs are inexpensive, on the market and have a well-defined safety profile.

HCQ was developed to treat malaria, but has since been repurposed as therapy for rheumatoid arthritis and lupus. The study is the first to test HCQ's ability to restore breast cancer cell sensitivity to tamoxifen or to a different anti-estrogen drug known as faslodex.

The research team, led by first author Katherine Cook, PhD, a postdoctoral research fellow in the tumor biology department at Georgetown Lombardi, purposely set out to test HCQ in mice with either tamoxifen or faslodex-resistant human breast cancer cells.

Previous research led by Clarke and Cook found that tamoxifen resistance occurs because a pro-survival pathway is switched on in breast cancer cells. HCQ functions by turning off that very same molecular pathway, Cook says.

The researchers found that the combination of tamoxifen and HCQ is more effective than faslodex and HCQ due to activities within the tumor's microenvironment. "Faslodex and tamoxifen, while both effective as antiestrogen therapies, have different effects on the immune system thus making the combination of faslodex and HCQ less effective," says Cook.

"Many people have been trying combinations of drugs to restore the ability of tamoxifen to fight breast cancer. We believe this pairing is very worthy of additional research, as well as clinical study," she says.

Provided by Georgetown University Medical Center

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