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Researchers identify new pathway, enhancing tamoxifen to tame aggressive breast cancer

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Tamoxifen is a time-honored breast cancer drug used to treat millions of women with early-stage and less-aggressive disease, and now a University of Rochester Medical Center team has shown how to exploit tamoxifen's secondary activities so that it might work on more aggressive breast cancer.

The research, published in the journal *EMBO Molecular Medicine*, is a promising development for women with basal-like breast cancer, sometimes known as triple-negative disease. This subtype has a poor prognosis because it is notoriously resistant to treatment. In fact, basal-like cancers lack the three most common breast cancer biomarkers – the estrogen receptor, the progesterone receptor, and theHer2/neu receptor – and without these receptors, the usual front-line treatments are not effective.

Until recently, tamoxifen was known primarily for its ability to block estrogen receptors on the outside of cancer cells. However, new studies have suggested that when tamoxifen is given in higher doses, it works through a second mechanism of action independent of the estrogen receptor. This second mechanism was the focus of the Rochester laboratory.

Led by doctoral student Hsing-Yu Chen and Mark Noble, Ph.D., professor of Biomedical Genetics at URMC, the team studied the molecular mechanism that allows basal-like breast cancer cells to escape the secondary effects of tamoxifen, and discovered that two proteins are

critical in this escape. One protein, called c-Cbl, controls the levels of multiple receptors that are critical for cancer cell function. A second protein, Cdc42, can inhibit c-Cbl and is responsible for the tumor's underlying resistance.

The team also discovered that targeting Cdc42 – and thus inhibiting the inhibitor - with an experimental drug compound known as ML141 restored c-Cbl's normal function. Through additional work in animal models and in human cell cultures, the team demonstrated that when ML141 is paired with tamoxifen, it enhances the ability of tamoxifen to induce cancer cell death and suppress the growth of new cancer cells. Neither drug alone had the same effect on basal-like breast cells.

Noble believes there is considerable value to targeting Cdc42, because elevated levels of the protein have been observed in multiple types of cancer. (In this context, scientists are also studying the potential for tamoxifen as a therapy for other cancers.)

The powerful ML141-tamoxifen drug combination looks like it has two more important features: It selectively targets cancer cells while sparing normal, healthy cells; and it appears to cripple cancer stem cells, the primitive cells responsible for initiating new tumors and for fueling the bulk of the tumor cell population.

"Our work is very exciting because our approach simultaneously addresses two of the most critical challenges in cancer research—to increase the utility of existing therapies and to discover new vulnerabilities of cancer cells," said Noble, who also is a leader at UR's Stem Cell and Regenerative Medicine Institute. "Based on these discoveries, we are already pushing forward with new compounds and with new approaches that might make clinical translation of this discovery much more rapid than would occur with traditional drug-discovery approaches."