A CHINK IN BREAST CANCER'S ARMOR

Tamoxifen is a mainstay of treatment for many women with breast cancer, but when the drug stops working, tumors can progress rapidly. In a recent study that could lead to new options for such patients, Ludwig Chicago Director Geoffrey Greene and his colleagues discovered why some of the most advanced cases of breast cancer become resistant to this drug.

Tamoxifen binds the estrogen receptor, and in so doing blocks its activity, choking off the ability of estrogen to fuel tumor growth. Many late-stage, metastatic tumors contain the estrogen receptor but fail to respond to tamoxifen. Greene asked why by closely looking at a battery of 36 such tumors.

He and his colleagues found that about one-quarter of the tumors contained mutations that made the receptor hyperactive. The hyperactive receptors drove tumor cell proliferation even in the absence of estrogen.

In cell culture experiments, the researchers found that it took extremely high doses of tamoxifen—doses too toxic for patients—to shut down metastatic tumors containing the mutations. The findings suggest that compounds that block the estrogen receptor more potently, gram for gram, than tamoxifen may keep breast cancer at bay for longer. The findings were bolstered by similar findings last year by other groups.

"Drug companies and researchers are now actively developing and testing next-generation compounds," says Greene,

whose collaborators in the study included José Baselga and Sarat Chandarlapaty at Memorial Sloan Kettering Cancer Center in New York. Baselga is also a member of Ludwig's Scientific Advisory Committee.

Greene brings decades of experience to the project. His team, for instance, helped determine, at the atomic scale, how tamoxifen binds to the estrogen receptor. This research propelled the development of other hormone-blocking drugs. Yet, even in a terrain so familiar to Greene, cancer biology serves up its surprises. "This was an unexpected result," he says of the team's recent discovery, "and it is making quite an impact on our field."

REFERENCE

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ESR1 ligand-binding domain mutations in hormone-resistant breast cancer.

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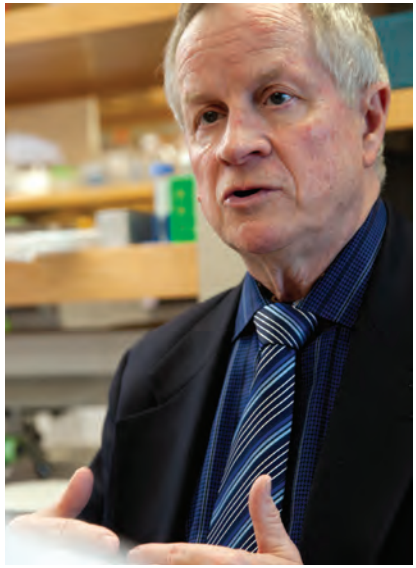

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