# Targeting drug-resistant breast cancer with estrogen

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Todd Miller, PhD (left), and Nicole Traphagen, a PhD candidate in the Miller Laboratory, have found a method for long-term control of drug-resistant breast cancer growth in preclinical models by switching between estrogen and anti-estrogen therapies. The strategy is now in human clinical trials at Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center. Credit: Mark Washburn

Researchers at Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center (NCCC) hope to make estrogen therapy a more accessible treatment option for breast cancer patients who could benefit from it. Anti-estrogen treatments, which block growth signals from estrogen receptors (ER) in tumors, are effective treatments for ER+ breast cancer. But it is common for breast tumors to become resistant to anti-estrogen treatments over time. The research team, led by molecular biologist Todd Miller, Ph.D., and Nicole Traphagen, a Ph.D. candidate in the Miller Laboratory, found that in mice, cycling between estrogen treatment and anti-estrogen treatment at a specific point in time can dramatically increase the duration of tumor regression.

The team's unconventional approach has exciting implications for breast cancer patients by suggesting that treating short-term with estrogen before anti-estrogen therapy resistance occurs, and then switching back to a more standard anti-estrogen therapy can better control tumor growth long-term. Traphagen and Miller have newly published their findings, entitled "High estrogen receptor alpha activation confers resistance to estrogen deprivation and is required for therapeutic response to estrogen in breast cancer," in *Oncogene*.

"Although we typically think of estrogens as feeding breast cancer growth, treatment with estrogens can actually induce tumor regression in some patients with anti-estrogen resistant breast tumors," says Miller. Despite the fact that estrogen treatment is effective in some patients, estrogen therapy is rarely used. An ongoing clinical trial at NCCC (POLLY; NCT0218875) will determine whether the strategy of cycling between estrogen therapy and anti-estrogen therapies is effective in human patients with advanced breast cancer.

"Tumors that initially respond to estrogen therapy eventually develop resistance to it by decreasing the amount of estrogen receptors in the tumor cells. Once these tumors become resistant to estrogen therapy,

they can be successfully treated with anti-estrogen therapies," says Traphagen. "This finding suggests that treatment with estrogen can re-sensitize patients' tumors to anti-estrogen therapies, even if those tumors had previously acquired resistance to anti-estrogen treatments."

Miller and Traphagen will also study the molecular characteristics of breast cells that respond to estrogen therapy. The goal is to use this information to predict and improve selection of patients who may respond to estrogen therapy and inform development of new drug combinations to optimize the anti-cancer effects of estrogen therapy.

**More information:** Nicole A. Traphagen et al, High estrogen receptor alpha activation confers resistance to estrogen deprivation and is required for therapeutic response to estrogen in breast cancer, *Oncogene* (2021). DOI: 10.1038/s41388-021-01782-w

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