Medical Xpress

New approach to shutting down breast cancer recurrence shows promise in mice

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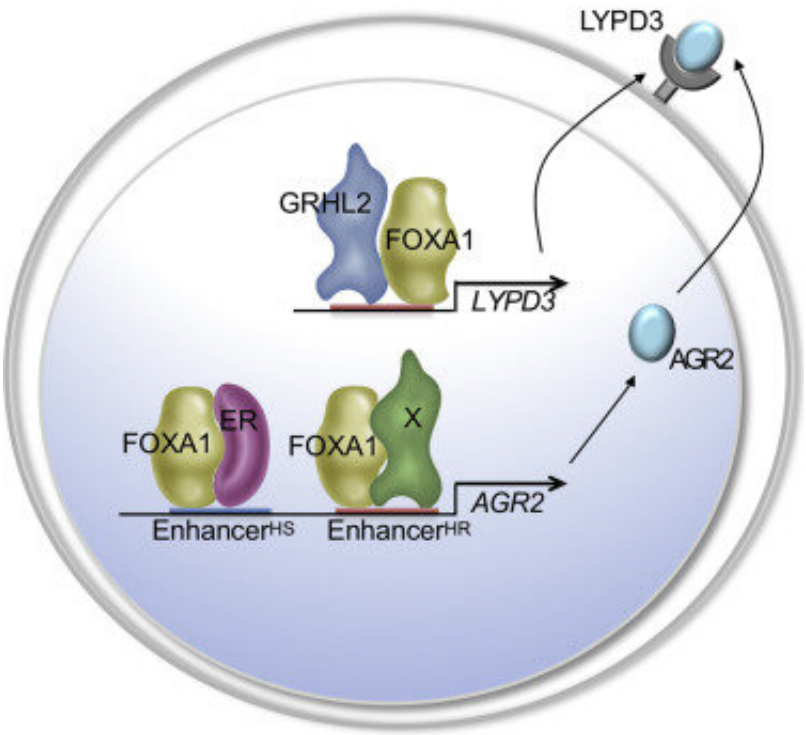

Graphical Abstract. Credit: *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.09.032

A new approach to treat advanced breast cancer shuts down the growth of cells that become resistant to standard hormone therapy, according to Duke Cancer Institute animal studies.

The research, which is likely to be tested in clinical trials within the year, identified and targeted vulnerabilities that appear in nearly all estrogen-positive breast cancers that develop resistance to current treatments.

"My father was an engineer and always said, 'Let the reproducible problem in a system be the first step in its solution,'" said Donald McDonnell, Ph.D., chair of the Department of Pharmacology and Cancer Biology at Duke and lead author of a study published online Oct. 22 in the journal *Cell Reports*.

"For breast cancer, the reproducible problem is the development of resistance to therapeutics," McDonnell said. "Rather than try to reverse or block the process of resistance, we took the approach that as tumors become resistant, they unwittingly expose new vulnerabilities that we can target."

McDonnell and colleagues analyzed cellular and mouse models of estrogen-positive breast cancer, which accounts for about 80 percent of all breast cancers. They identified a universal pathway used by tumors to outmaneuver both tamoxifen and aromatase inhibitors.

Using both pharmacological and biochemical approaches, they were able to inhibit the activity of this pathway and block the growth of recurrent breast tumors in mice. Humanized antibodies directed against these targets are in late-stage pre-clinical development and are expected to be in clinical trials shortly.

"This is a new approach," McDonnell said. "Typically we try to figure out what causes drug resistance and then develop ways to block these processes, but invariably another resistance mechanism kicks in and tumors continue to grow.

"In our study we looked for new therapeutic targets that emerged as

cancer cells tried to circumvent tamoxifen or aromatase inhibitors and used this information to develop two new approaches to inhibit the emergence of resistance or treat cancers that had already become resistant to standard endocrine therapies," McDonnell said.

More information: Kimberly J. Cocce et al. The Lineage Determining Factor GRHL2 Collaborates with FOXA1 to Establish a Targetable Pathway in Endocrine Therapy-Resistant Breast Cancer, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.09.032

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