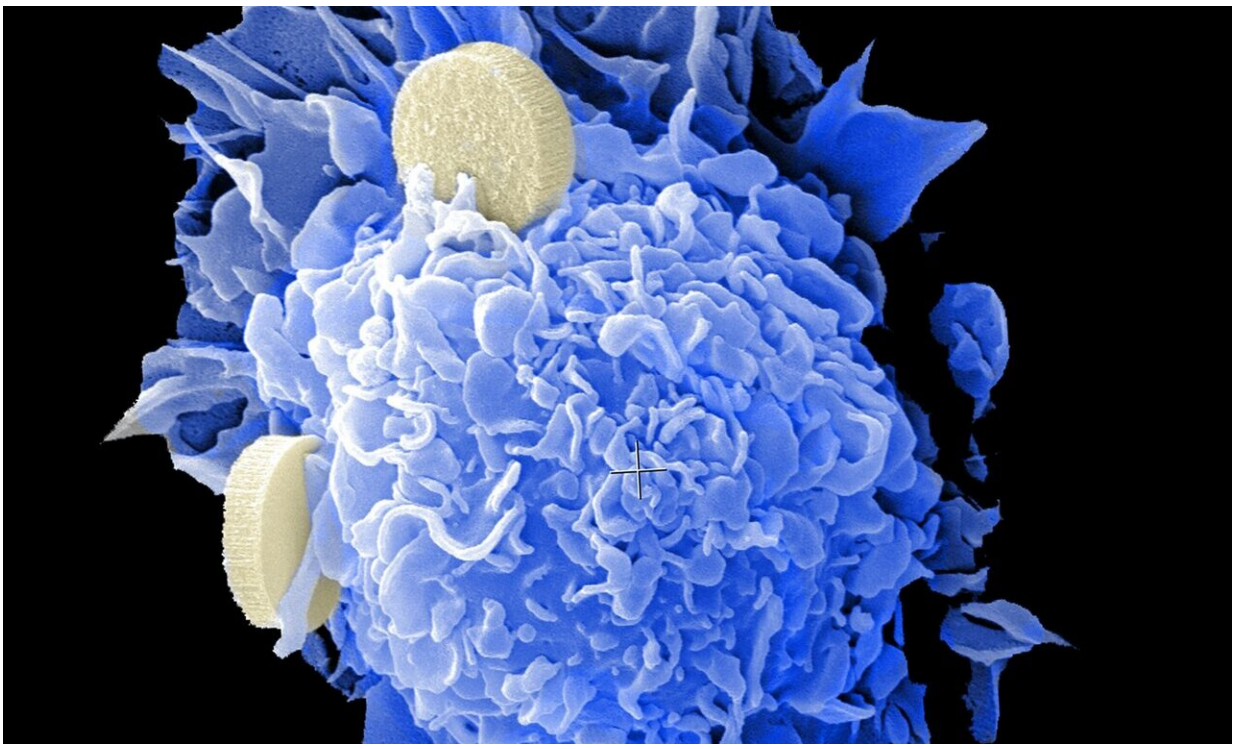
Promising compound kills range of hard-to-treat cancers by targeting a previously undiscovered vulnerability

June 2 2022



Credit: Unsplash/CC0 Public Domain

A compound, developed by a team including scientists from The University of Texas Health Science Center at San Antonio, kills a range of hard-to-treat cancer types in petri dishes and animal models by

targeting a previously unexploited vulnerability, a new study reports. The findings, published in *Nature Cancer*, could eventually lead to new drugs to fight these cancers, which currently have few effective treatments.

"We identified a critical vulnerability in multiple cancers and have validated our findings in multiple cancer cell types and animal models," said study leader Ratna Vadlamudi, Ph.D., professor of obstetrics and gynecology at UT Health San Antonio and a member of the Mays Cancer Center, home to UT Health San Antonio MD Anderson Cancer Center. "The range of cell lines and xenografts in which the compound has been shown to work is compelling and indicates that it is targeting a fundamental vulnerability in cancer cells." Xenografts are human tumors grown in mouse models for research purposes.

The Vadlamudi lab studies breast and ovarian cancer progression, including in therapy resistance, with a goal to developing small-molecule inhibitors for therapy-resistant cancers. In 2017, he and his colleagues identified a compound called ERX-11 that targets the estrogen receptor (ER), a protein that drives the vast majority of breast cancers. From a screen of chemical analogs of ERX-11, the researchers identified that a compound called ERX-41 not only killed ER-positive cancers in petri dishes, but also readily killed triple-negative breast cancers (TNBCs), including more than 20 distinct TNBC cell lines. TNBC is a cancer subtype lacking receptors for estrogen, progesterone and human epidermal growth factor 2, and for which there is a paucity of targeted treatments.

The researchers expanded these studies to show ERX-41 had activity against a large number of human tumors grown from several of these cell lines in mouse models. In addition, ERX-41 was potent against patient-derived xenografts, as well, causing shrinkage of these human tumors grown in mouse models without affecting normal breast cells or causing any discernible toxicity in these animals. "The safety profile and high

therapeutic index of this compound is particularly notable and bodes well for clinical translation," Dr. Vadlamudi said.

Other experiments showed that in addition to ER-positive breast cancers and TNBC, ERX-41 is also effective against other cancer types with elevated endoplasmic reticulum stress, including pancreatic, glioblastoma and ovarian cancers, which all have few effective treatments. The endoplasmic reticulum is a structure in many cell types that performs assorted functions, including manufacture of proteins.

This work was performed in collaboration with scientists at UT Dallas (led by Dr. JungMo Ahn) and UT Southwestern Medical Center at Dallas (led by Dr. Ganesh Raj). ERX-41 and the related portfolio have been licensed to Dallas-based EtiraRx, which plans to move these drugs into clinical trials in early 2023.

Other researchers from UT Health San Antonio who contributed to this study include Drs. Suryavathi Viswanadhapalli, Mengxing Li, Gangadhara R Sareddy, Uday P Pratap, Zexuan Liu, Hui Yan, Zhenming Xu, Susan E Weintraub and Rajeshwar Rao Tekmal.

More information: Ratna Vadlamudi, Targeting LIPA independent of its lipase activity is a therapeutic strategy in solid tumors via induction of endoplasmic reticulum stress, *Nature Cancer* (2022). DOI: 10.1038/s43018-022-00389-8.
www.nature.com/articles/s43018-022-00389-8

Provided by University of Texas Health Science Center at San Antonio

Citation: Promising compound kills range of hard-to-treat cancers by targeting a previously undiscovered vulnerability (2022, June 2) retrieved 10 May 2024 from

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.