Chemist has designs on drug-resistant breast cancer

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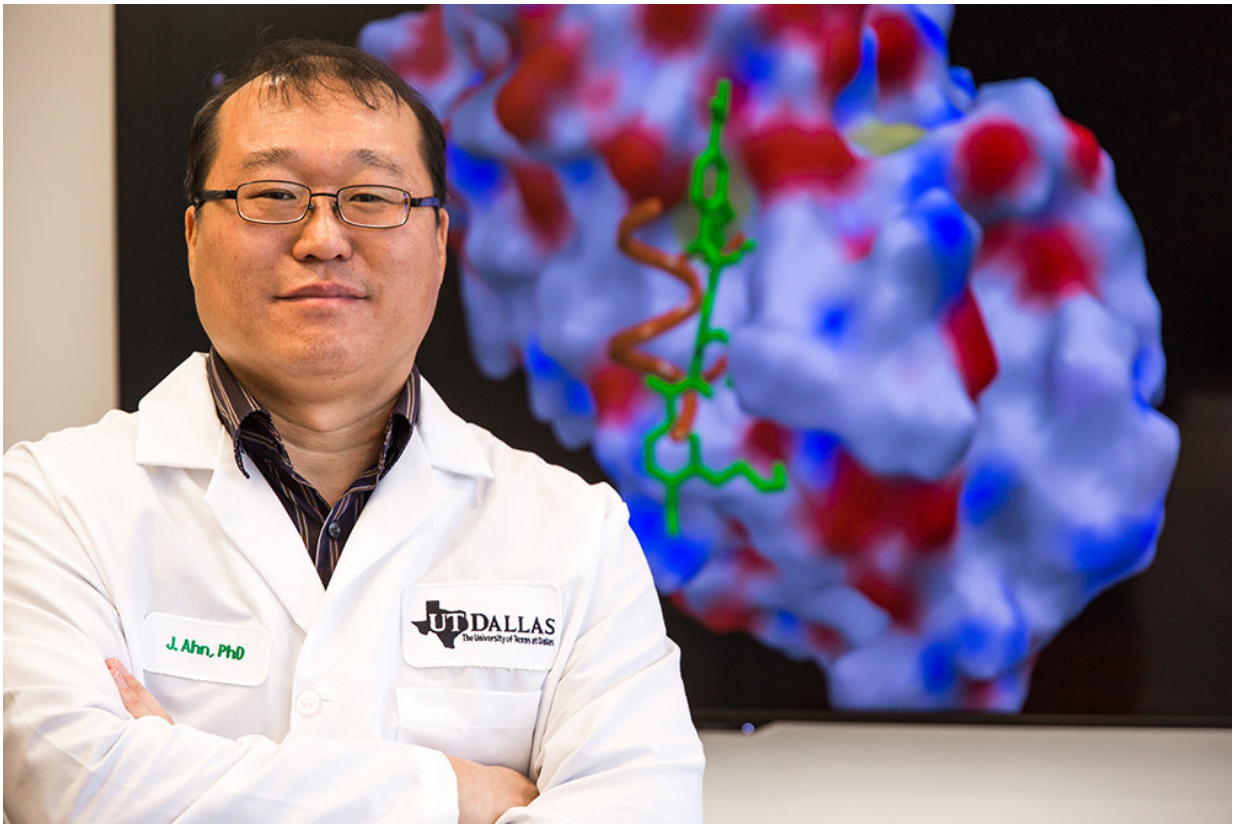

The compound Dr. Jung-Mo Ahn designed, called ERX-11, significantly and selectively disrupted the interactions of numerous co-regulators with estrogen receptors in breast cancer cells, including therapy-resistant cancer cells. The result was a halt to cancer proliferation and increased cancer-cell death. Credit: University of Texas at Dallas

Dr. Jung-Mo Ahn, associate professor of chemistry and biochemistry at The University of Texas at Dallas, has designed a small molecule that could help breast cancer patients for whom current treatments no longer work.

In a paper published recently in the online journal eLife, Ahn and his colleagues describe their approach to designing the molecule as well as experiments that show its effectiveness at stopping the progression of treatment-resistant breast cancer cells in isolation and in an animal model.

According to the National Cancer Institute, about 80 percent of breast cancers in women depend on the hormone estrogen to grow. Breast cancer cells in these patients contain proteins called estrogen receptors (ERs) that bind to the hormone and fuel cancer's growth.

For these ER-positive patients, treatment typically takes one of two tracks: drug regimens that stifle the body's production of estrogen, or drugs that bind to estrogen receptors and block the hormone from attaching.

In some patients, however, breast cancer becomes resistant to estrogen-blocking therapy. That happens when estrogen receptors in breast cancer cells mutate and change shape, leaving no place for the drugs to attach. With or without genetic mutations, the receptor still needs to recruit other proteins in the cell, called co-regulators, which promote tumor growth.

"Upon estrogen binding, estrogen receptors interact with other proteins like co-regulators to stimulate cancer cell growth," Ahn said. "Blocking these co-regulators is a new mode of action that could overcome treatment barriers."

Putting the Brakes on Cancer

The compound Ahn designed, called ERX-11, significantly and selectively disrupted the interactions of numerous co-regulators with estrogen receptors in breast cancer cells, including therapy-resistant cancer cells. The result was a halt to cancer proliferation and increased cancer-cell death.

Ahn, who has been investigating small molecules targeting protein-protein interactions for nearly a decade, developed ERX-11 using a structure-based rational design approach. His research group studied in detail the chemical structure of critical co-regulators at the surface where they associate with the estrogen receptor. They then designed a small-molecule "template" that fits like a bandage over the area on the receptor where the co-regulators dock.

"Basically, we were looking at a particular site where these proteins and the receptor shake hands," Ahn said. "We are not trying to reproduce the entire, large co-regulator proteins, just the small surface where they interface with the receptor. The idea was, even if the receptor mutates, these small surfaces still remain viable."

Rational Drug Design: A Streamlined Approach

To arrive at the design for ERX-11, Ahn's research group carried out computer simulations that narrowed the field to a small number of molecules that they predicted could work. His lab, including research scientist Dr. Tae-Kyung Lee and chemistry graduate student Bikash Manandhar, synthesized only a few candidate compounds before they found "a hit," Ahn said.

"The advantage of the rational design approach is that we are not starting

with thousands of compounds and screening them for their effectiveness," Ahn said. "Both biology and chemistry are involved in drug discovery, and our chemistry expertise was key to streamlining the process."

Ahn's group previously used the rational drug design approach to develop a potential therapeutic compound for prostate cancer.

To test the ERX-11 molecule, Ahn worked with collaborators including Dr. Ganesh Raj, professor of urology and pharmacology at the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center, as well as Dr. Ratna Vadlamudi, professor of obstetrics and gynecology at UT Health Science Center at San Antonio.

"Because of its unique design, ERX-11 operates very differently compared to other compounds currently in clinical trials, providing a potential alternate way of treating breast cancer," Ahn said. "Eventually we might be able to develop molecules similar to ERX-11 to treat other types of cancer as well."

Ahn and his colleagues have continued to improve ERX-11, and are evaluating a next-generation compound that Ahn hopes will be even more effective.

"Another beauty of this molecule is that it is not difficult to synthesize, so making this as a drug in large quantities for clinical testing is certainly feasible," he said.

More information: Ganesh V Raj et al. Estrogen receptor coregulator binding modulators (ERXs) effectively target estrogen receptor positive human breast cancers, *eLife* (2017). DOI: 10.7554/eLife.26857

Provided by University of Texas at Dallas