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Clinical trial hits new target in war on breast cancer

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Breast cancers are defined by their drivers – estrogen and progesterone receptors (ER and PR) and HER2 are the most common, and there are drugs targeting each. When breast cancer has an unknown driver, it also has fewer treatment options – this aggressive form of breast cancer without ER, PR or HER2, which was thought not to be driven by hormones, is known as triple negative. A decade ago, work at the University of Colorado Cancer Center added another potential driver to the list – the androgen receptor – and this week marks a major milestone in a clinical trial targeting this cause of breast cancer growth.

In fact, 75 percent of all breast cancers and about 20 percent of triple negative cancers are positive for the androgen receptor. Blocking the androgen receptor may stop the growth of some triple negative breast cancers – these aggressive cancers for which chemotherapy, radiation, surgery and hope have long been the only treatments.

"This work is a concise example of modern cancer science in action. We noticed something in the clinic, worked on it in the lab, and now are happy to report the lab work is once again back in the clinic where it has the very real potential to benefit patients," says Anthony Elias, MD, breast cancer program director at CU Cancer Center.

The work started in 2001 when Elias took the clinical observation of estrogen-positive breast cancers that responded poorly or only very temporarily to estrogen-blocking treatments, to colleague Jennifer Richer, PhD, co-director of the CU Cancer Center Tissue Processing

and Procurement Core. In these cases, something else was driving the cancer. What was the pathway? Richer showed that it was the androgen receptor.

Androgens including testosterone have long been implicated as a driver of prostate cancer and so drugs targeting both the body's production of androgens and cancer cells' ability to use the hormone were already in the development pipeline. Richer started with cell culture and animal model work on a then-experimental drug by the company Medivation known as MDV-3100.

"Normally, the way these hormones work is by attaching to receptors in the cell cytoplasm, at which point the receptor draws itself and the hormone molecule inside the nucleus where it regulates genes," Richer says. The genes regulated by these hormones tell breast cancer cells to survive and reproduce beyond control. The drug MDV-3100, now known as Enzalutamide, which recently gained FDA approval for use with prostate cancer, makes androgen receptors unable to go into a cell's nucleus – and so the message of growth never gets delivered.

"Interestingly, it seems that estrogen-positive breast cancers are susceptible to the same drug," Richer says, explaining that something about the way the signal of estrogen is transmitted inside a cell's nucleus requires the (counterintuitive) presence of androgen receptors in the nucleus, too.

And so Enzalutamide has many potential uses in the treatment of breast cancer: as a first-line drug against androgen receptor-positive cancers with or without additional hormonal drivers, as a second-line drug against tumors that have mutated away from estrogen- or HER2 -dependence by adopting androgen-dependence, in combination with drugs that target these other hormones to disallow cancer from mutating toward androgen-dependence in the first place, or perhaps in addition to

or instead of existing treatments for estrogen-positive breast cancers – which seem susceptible to this anti-androgen therapy.

This week, after seeing, "no additional toxicities," Elias expects an ongoing Phase I clinical trial of Enzalutamide for triple-negative breast cancers to flip to a Phase II trial – from proving safety to demonstrating results. In addition to the CU Cancer Center, the trial is being offered at Memorial Sloan-Kettering Cancer Center and the Karmanos Cancer Institute. Richer and Elias will present additional findings from their work with androgen-positive breast cancer at the San Antonio Breast Cancer Symposium in December and will hear about a major invited grant proposal to the U.S. Department of Defense the same month.

"It's an exciting time for breast cancer research," Elias says. "We should know soon if we have a viable new target in breast cancer treatment."

Along with validating a new target, Richer and Elias may soon provide a powerful new treatment for breast cancers that evade current therapies.

Provided by University of Colorado Denver

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