New agent overcomes drug resistance in HER2-positive breast cancer, preclinical study shows

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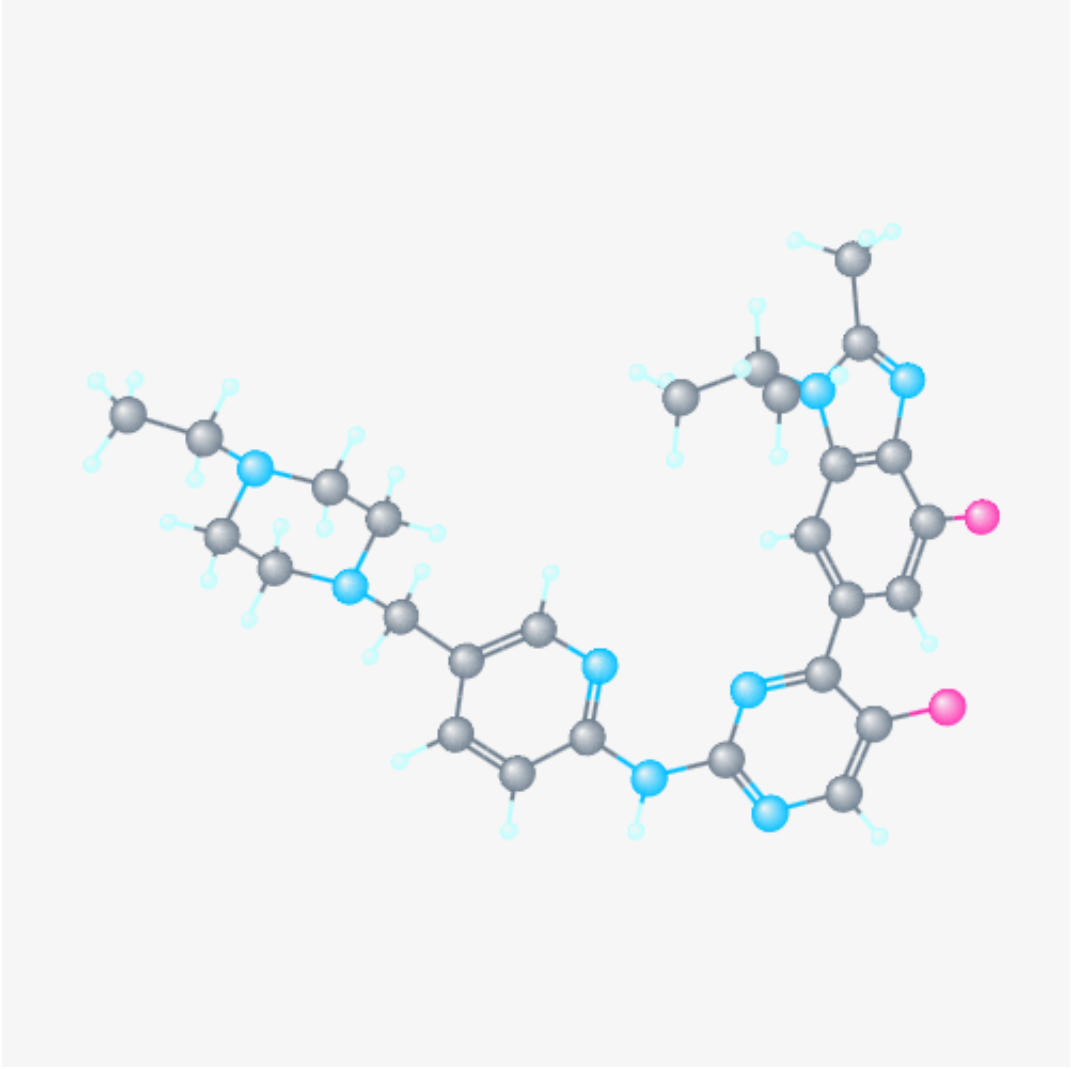

Chemical structure of the the CDK4/6 inhibitor, abemaciclib. Credit: Shom Goel

A type of breast cancer that often develops resistance to targeted therapies was driven back into remission in mice by a drug that blocks the division of cancer cells, a new study led by researchers at Dana-Farber Cancer Institute has found. The results, reported today in *Cancer Cell*, prompted investigators to launch a clinical trial of the new agent in women with a metastatic form of this cancer, known as HER2-positive breast cancer.

The study demonstrates the potential of new agents known as CDK4/6 inhibitors to overcome drug resistance in patients with HER2-positive breast tumors, which carry an excess of the human epidermal growth factor receptor 2 (HER2) protein. Although HER2-blocking drugs such as Herceptin often halt the growth of these tumors, many patients' cancers become resistant, leading to a resurgence of tumor growth. This is particularly true in patients with metastatic tumors.

"Finding ways to resensitize drug-resistant tumors - to restore their vulnerability to front-line agents - is a critical priority for cancer researchers," says the study's first author, Shom Goel, MD, PhD, of the Susan F. Smith Center for Women's Cancers at Dana-Farber. "In this study, we sought to understand how HER2-positive breast tumors - which account for 15-20 percent of all breast cancers - become resistant to targeted therapies, and whether we can use that knowledge to reverse such resistance."

To probe how resistance occurs, researchers created a strain of genetically modified, "transgenic" mice that carry a genetic switch for turning production of the HER2 protein on and off. With the switch on, the animals developed human-like HER2-positive breast tumors; after it was turned off, the tumors shrank away, only to return months later in about two-thirds of the animals.

Researchers examined tissue samples from original and recurrent tumors

to determine how they differed. Using RNA-sequencing techniques, they found that certain genes that control cell division and the cell cycle were overactive in recurrent tumors. Notably, cells from these tumors had abnormally high levels of two proteins associated with the cell cycle: cyclin D1 and CDK4.

"In HER2-positive breast cancer, cyclin D1 partners with CDK4 to drive cell proliferation," Goel explains. "We hypothesized that cyclin D1 and CDK4 might also enable tumors to become resistant to HER2-targeted treatments and eventually recur."

He and his colleagues conducted a series of experiments in cells and mice to confirm that that is indeed the case. The results suggested that drugs targeting CDK4 could defeat the resistance mechanism and reinstate tumors' original susceptibility to HER2 blockers.

"In cells, we found that the drug abemaciclib - which inhibits CDK4 and the related protein CDK6 - was active against HER2-positive breast tumor cells that were resistant to standard treatments," Goel remarks. "Strikingly, when we added a HER2-targeting drug to abemaciclib, we saw even greater efficacy. This means that abemaciclib restored the cancer cells' sensitivity to HER2-directed agents." Studies in mouse models showed the same benefit: the combination of abemaciclib and a HER2-blocking drug was more effective in halting HER2-positive tumor growth than either drug was alone. In their paper, the team also describes the molecular basis by which abemaciclib can reverse drug resistance.

Finally, the investigators explored whether abemaciclib alone could delay the recurrence of HER2-positive breast cancers in mice. They found that the combination of abemaciclib and HER2-blocking strategies was able to significantly delay the time it took for breast cancers to recur. "This result is particularly exciting as it leads us to speculate the CDK4/6 inhibitors might not only help patients with

metastatic breast cancer, but could potentially help in earlier stages of the disease where we aim to prevent recurrence of cancer," says Goel.

On the strength of these findings, investigators will open a randomized clinical trial across the United States and Europe later this year. It is designed to determine whether abemaciclib is an effective treatment for patients who cancers have developed resistance to standard HER2-targeted drugs. Goel and his Dana-Farber colleague Sara Tolaney, MD, MPH, will lead the trial. "Our preliminary experience in patients has certainly been very encouraging," remarks Goel.

"Our goal as scientists is to anticipate the questions clinicians will be asking in the future, so we begin doing the basic research necessary to answer them now," says Jean Zhao, PhD, of Dana-Farber, whose co-senior author is Ian Krop, MD, PhD, of the Susan F. Smith Center at Dana-Farber. "This study is a prime example of how we can apply what we learn in the laboratory to improve the treatment of patients."

Provided by Dana-Farber Cancer Institute

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