

## Dynamic HER2 Switch Discovered in Circulating Breast Cancer Cells

**Can understanding plasticity of HER2 protein states in breast cancer cells of treatment-resistant tumors lead to better treatments?**

**H**ER2 proteins—human epidermal growth factor receptors 2 that control breast cell growth—are intimately connected to the growth of breast cancers. About 15 percent to 25 percent of breast cancers exhibit amplification of the gene that codes for the HER2 protein,<sup>1</sup> and these cancers are known as “HER2-amplified breast cancers.” The rest are considered to be HER2-negative cancers because they have few or no HER2 receptors. HER2-amplified breast cancers are dependent on HER2 activity for growth and survival, and they are often susceptible to treatment with HER2 inhibitors. Therefore, identification of HER2 subtypes is considered standard clinical practice in breast cancer.

While HER2-positive tumors are traditionally identified based on tissue analysis of the primary tumor, some HER2-negative tumor cells, upon being treated with multiple therapies, can start expressing the HER2 protein. The levels of the HER2 protein in HER2-positive breast cancer cells are much lower compared with HER2-amplified breast cancer cells. Yet, the appearance of HER2-positive

breast cancer cells could have major implications for therapeutic decision-making and therapy selection.

Researchers Shyamala Maheswaran, PhD, Aditya Bardia, MD, and Nicole Vincent Jordan, PhD, of Massachusetts General Hospital Cancer Center, along with Daniel Haber, MD, PhD, director of Mass General Cancer Center, using ex vivo cultures of circulating tumor cells derived from breast cancer patients, have shown that breast cancer cells can spontaneously switch from a HER2-negative to a

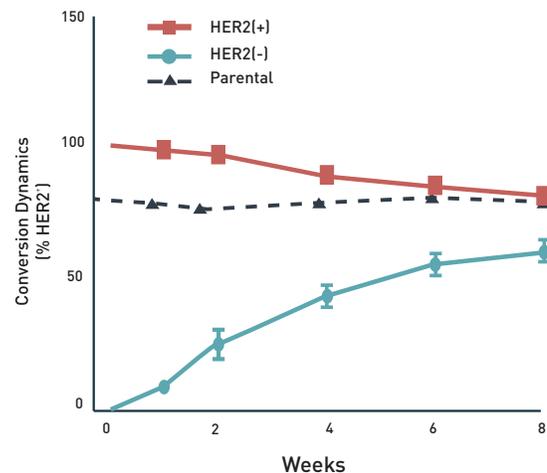
HER2-positive state and vice versa. These two populations have different molecular pathways that drive their growth. Several growth-factor-driven pathways are active in the HER2-positive cells, and one pathway, called Notch, is active in the HER2-negative cells.

As a result, these two populations are sensitive to different drugs: The growth of HER2-positive cells is blocked by chemotherapy as well as a mixture of inhibitors that suppress growth-factor-driven pathways; the HER-negative cell growth is suppressed by Notch inhibitors. The team found that breast tumors, consisting of HER2-positive and -negative populations, grown in mice are effectively suppressed by treating them with a combination of chemotherapy and Notch inhibitors, compared with treating them with either agent alone.

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### Interconversion of HER2-Positive and HER2-Negative Cells

Time course of HER2-positive and HER2-negative interconversion following fluorescence-activated cell sorting isolation of HER2-positive and HER2-negative cells. Parental cultured circulating tumor cells (black dotted line) are shown as control.



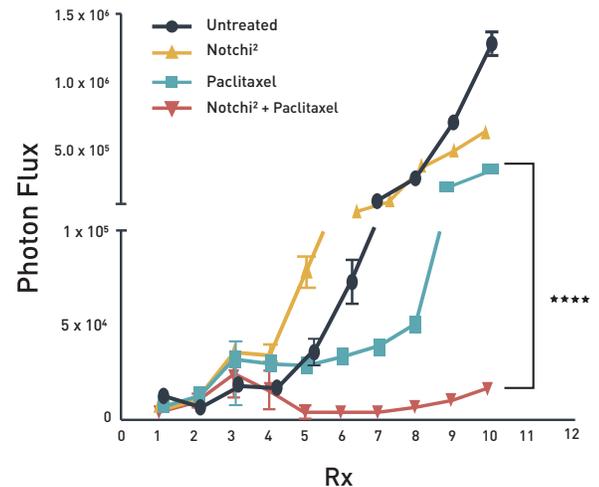
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“Other teams have described that HER2-positive circulating cells can be detected in traditional HER2-negative tumors, and there has been interest in targeting them with anti-HER2 drugs,” Bardia said. “However, these HER2-positive cells are not responsive to classical HER2-targeting therapy, and what is very striking is the plasticity and the dynamic interplay, where they can actually switch from one state to another. The two states are responsive to different drugs, suggesting that combination therapy is warranted to treat these tumors.” Their findings were published in the September 1, 2016, issue of *Nature*.<sup>2</sup>

Future avenues of research will include experiments to understand the mechanisms by

## Combination Therapy

Simultaneous treatment of breast cancer xenografts for four weeks using the chemotherapy drug paclitaxel, a Notch inhibitor, and both combined. The combination therapy suppressed tumor growth more effectively than paclitaxel or the Notch inhibitor alone.



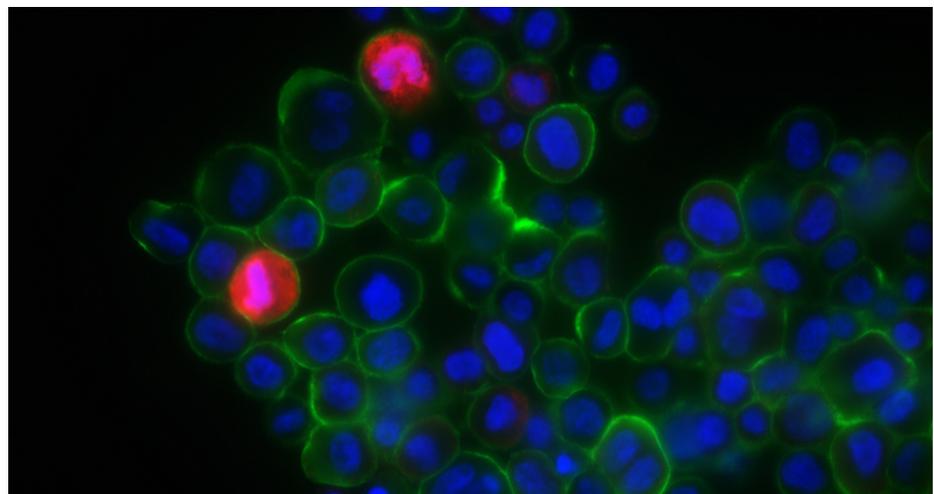
which these HER2-negative cells gain HER2 expression so that researchers can better define the plasticity of these cells. “Ideally, you want to be able to lock that switch, so the cells can’t hide in one state or another in response to a particular kind of therapy,” said Maheswaran.

<sup>1</sup>Piccart-Gebhart JM, Procter M, Leyland-Jones B, et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. *N Engl J Med*. 2005; 353: 1659-1672.

<sup>2</sup>Jordan VN, Bardia A, Wittner SB, et al. HER2 expression identifies dynamic functional states within circulating breast cancer cells. *Nature*. 2016; 537: 102-106.

## Circulating Tumor Cells

Ex vivo cultures of circulating tumor cells isolated from breast cancer patients express HER2 protein (those stained in green are HER2-positive). Note the absence of HER2 in some cells (HER2-negative). The blue and red stains mark the nucleus and dividing cells, respectively.



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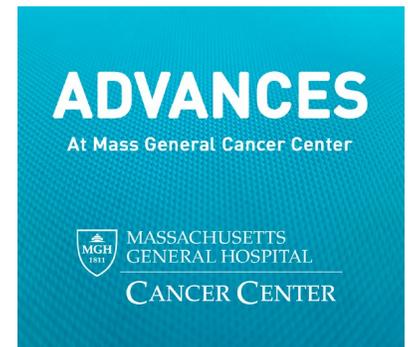
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