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# Personalized medicine for breast cancer: it is a new day!

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**Abstract** Breast cancer remains the most common cancer diagnosed in women in the United States and is second only to lung cancer as a cause of cancer mortality. Breast cancer has become the prototypical solid tumor where targets have been identified within the tumor allowing for a personalized approach of systemic therapy.


Breast cancer continues to be the most common cause of cancer in women and the second most common cause of cancer death. Breast cancer will account for 29% of all newly diagnosed cancers and for 14% of cancer deaths in women in 2013.[1] Although the incidence of breast cancer has remained relatively flat since 2005, the mortality rate has dropped about 2% per year since 1998. These improvements in breast cancer mortality can be attributed to both improved early detection from screening and to improvements and access to treatment. Breast cancer, more than any other female cancer, has been recognized as having identifiable targets for therapy. With the discovery of these various targets, new methods for identifying the targets and new agents that recognize them have been created.

Sir George Beatson, a surgeon in Glasgow, United Kingdom, published the often-quoted article in *The Lancet* in 1895 with the following title: "On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases."[2] He described performing an oophrectomy on 3 women with advanced breast cancer, all of whom experienced dramatic regression of their cancer. But what if these 3 women had been postmenopausal or had cancers that did not express an estrogen receptor (ER)? Although this was a targeted therapy, it was not a personalized medicine.

## Estrogen Receptor

The ER was the first of many targets that has been described in most breast cancers. It is a target that is most commonly assessed by immunohistochemical staining of breast cancer tissue. About 75% of newly diagnosed breast cancers are estrogen receptor positive (ER+), and ER status is a modest predictor of disease-free and overall survival. More importantly, ER strongly predicts for benefit from hormonal manipulation. A National Comprehensive Cancer Network task force in association with a panel of the College of American Pathologists has issued recommendations on

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ER and progesterone receptor testing for breast cancer.[3] Multiple studies have been published that demonstrate that the percentage and intensity of cells staining positive correlates with long-term clinical outcome.

The function of the ER is similar when comparing the interaction of estrogen versus tamoxifen.[4] Estradiol binds to the ER and recruits activation factor (AF)-1. Subsequently, the bound ER dimerizes with another ER, and AF-2 is activated. The dimerized complex moves into the nucleus, binds to ER elements, and recruits multiple coactivators. This complex leads to transcription and cell division. In contrast, when tamoxifen binds to the ER, there is a reduction in both transcription and cell division. Tamoxifen binds to the ER in the same manner as estrogen, but the tamoxifen–ER complex has only activation function AF-1. The ER dimerizes, and only AF-1 is active and AF-2 remains inactive. There is nuclear localization of a partially active ER and a reduced amount of coactivator function. Thus, there is reduced transcription and cell division when compared with estrogen, which explains the partial agonist effect of tamoxifen and other selective ER modifiers. Despite the recognition that ER+ breast cancers can be treated with estrogen or ER blockade, the timeline for approval of various therapies has spanned multiple decades, with modest improvements in outcome.

The US Food and Drug Administration approved Tamoxifen in 1977 for women with advanced breast cancer. No new agents were introduced in the subsequent 18 years until the aromatase inhibitor, anastrozole, was approved in 1995. Since then, 2 other aromatase inhibitors and the ER downregulator, fulvestrant, have been approved. The aromatase inhibitors function by blocking the conversion of adrenal androgens into estrogen in postmenopausal women. Thus, rather than competing with estrogen for binding to the ER as do the selective ER modifiers, the aromatase inhibitors completely block the production of estrogen. Fulvestrant, approved in 2002, forms a complex with the ER, and neither AF-1 nor AF-2 is active. The complex does not dimerize, and localization to the ER element is markedly reduced. There is no coactivator recruitment and no estrogen-dependent cell division. In addition, the fulvestrant–ER complex rapidly degrades, resulting in "downregulation" of the ER.

The options for hormone manipulation in women with a hormonally sensitive breast cancer must take into consideration the woman's menopausal status. Women who are premenopausal may undergo modulation of estrogen synthesis either through the administration of luteinizing hormone releasing hormone (LHRH) or through an oophrectomy. Tamoxifen is equally effective regardless of menopausal status. Postmenopausal women may block estrogen conversion via the use of aromatase inhibitors or may be placed on the ER downregulator, fulvestrant. Up to 80% of women with advanced breast cancer treated with estrogen blockade will have either a clinical response or stable disease for a minimum of 24 weeks. With each subsequent hormonal therapy, the clinical benefit will be reduced by 25% to 30%. Ultimately, malignant breast cancer cells will develop resistance, which represents an unmet need for personalized therapy.[5]

## HER2 neu

The second most commonly described target in breast cancer is the HER2 protein. The *HER* family of genes and their HER transmembrane proteins were first described in 1978, when *ErbB-1* was discovered.[6] The derivation of the term Erb-b originated with the *Erb-b* gene, which is responsible for the avian erythroblastosis virus. The human gene *ErbB-1* is also known as *HER1* or epidermal growth factor receptor. Subsequently, the neu oncogene was discovered in 1982, and *HER2* was cloned in 1984.[7] Work was subsequently initiated on the development of a monoclonal antibody against the HER2 receptor. In 1992, humanized HER2 monoclonal antibody was created, and clinical trials in humans were subsequently initiated.[8] Trastuzumab was approved in 1998 for use in women with metastatic HER2+ breast cancer, and in 2006, the antibody was approved for use in women with HER2+ early breast cancer when given with chemotherapy.

HER2 positivity can be described in 1 of 2 ways. Normal breast ductal epithelial cells have 1 copy of the *HER2* gene on each chromosome 17. Thus, each normal breast cell and each "normal" breast cancer cell should have 2 copies of each, maintaining a 1:1 ratio. The *HER2* gene encodes for a 185-kDa HER2 protein, which is a transmembrane receptor with cytoplasmic tyrosine kinase activity.[9] There are approximately 20,000 HER2 receptors in each normal breast epithelial cell. The *HER2* gene may be amplified in up to 25% of cases of metastatic breast cancer. Amplification refers to an increased number of *HER2* gene copies in relationship to the cell's chromosome 17. If the ratio rises to more than 2 copies of *HER2* gene to each chromosome 17, then the gene is amplified. As a consequence of this gene amplification, the HER2+ breast cancer cell may have up to 2 million receptors on the cell surface. This is referred to as HER2 overexpression. There are 2 common methods used to test for the HER2 status of a breast cancer cell. Immunohistochemistry (IHC) is used to detect the HER2 receptor and the expression is subjectively measured as 0, 1+, 2+, or 3+, depending on the percentage of cells staining. IHC 3+ usually corresponds to gene amplification, whereas 0 or 1+ rarely does. Tumors with 2+ expression are usually tested by fluorescent in situ hybridization. Alternatively, the tumor cells can be tested by the fluorescent in situ hybridization method, which directly stains both the *HER2* gene and the centromeres on chromosome 17. The *HER2* ratio is the expression of the *HER2* gene copies/chromosome 17 centromere copies. A ratio $\geq 2.0$ is considered amplified.

HER2 is a member of the human epidermal growth factor family of receptors. This family consists of 4 transmembrane proteins (HER 1 to 4) each of which has different properties,