# Gaining Ground on Breast Cancer

## The newest targeted therapies are helping doctors to tailor increasingly effective treatments to individual patients

BY FRANCISCO J. ESTEVA AND GABRIEL N. HORTOBAGYI

**KEY CONCEPTS**

- Breast cancer survival rates have been steadily climbing in North America and Europe, thanks to increased early detection and novel treatment options.
- Many new treatments target specific molecules on tumor cells, allowing doctors to tailor medication to an individual patient's tumor profile.
- Breast cancer was the first solid-tumor type for which molecular-targeted therapy became available, and the success of the approach promises further dramatic advances.

*—The Editors*

Breast cancer is the most commonly diagnosed malignancy among women and, after lung cancer, the second leading cause of cancer-related deaths in North America. Yet unlike the survival rate for individuals diagnosed with lung cancer, the rate for women diagnosed with breast cancer has been rising dramatically over the past decade—to the point where breast cancer could soon lose its ranking as the second-greatest cancer killer. Nothing would delight clinicians like us more.

This improvement in overall outlook for women diagnosed with breast cancer is attributable in part to earlier detection, which results from greater awareness of, and access to, regular breast screening. But breast cancer patients are also benefiting from accelerated research that has led to a much better understanding of the disease and a wider variety of treatment choices that doctors can mix and match to tailor therapy for a particular patient. In just the past decade, it has even become possible to target drugs to specific molecules within tumors that help to drive the disease.

Breast cancer was, in fact, the first type of solid-tumor cancer to be treated with this molecular-targeting therapeutic approach, when the drug trastuzumab (Herceptin) was approved in 1998. The protein that trastuzumab was designed to attack, called HER2, promotes aggressive tumor growth. Before trastuzumab, diagnosis with a tumor that overproduces HER2 was dreaded news for patients. Now it can be one of the tumor types with the best prognosis, because doctors have an increasing number of effective weapons against HER2.

The next decade promises to be an exciting and productive time in the field of molecular-targeted cancer therapy: additional drugs currently being tested in people and animals are making it possible to go after an increasing variety of molecular tumor features that play a critical role in the initiation and survival of malignancies and in the cancers' progression to increasingly threatening stages. Along with improvements in older therapies and supportive care, this newer generation of drugs gives doctors more options for customizing treatment to cope with a tumor's particular suite of molecular characteristics and reflects our growing realization that breast cancer is not a single disease.

### Evolving Treatment Approaches

Although the prospect of tailoring treatment to the molecular features of individual tumors is incredibly encouraging, prior advances are also contributing to the declining mortality rate for women diagnosed with breast cancer. Improved screening techniques, for instance, are definitely helping to catch and confirm more cases at an earlier stage, which is a boon, because breast cancer is highly curable if detected early. Newer imaging methods include digital mammography (which produces a clearer picture than screen-film mammography), ultrasound and magnetic resonance imaging (MRI). Women at high risk of developing breast cancer because of family history or mutations in one of the *BRCA* genes are now offered annual MRI breast screening, although ultrasounds are usually reserved for following up on abnormal findings in a mammogram or physical exam.

JAMES PORTO

In addition, surgical approaches to tumor excision have changed over the past 20 years from radical tissue removal in women whose tumor appears confined to a small part of the breast to breast-conserving therapy. More focused radiation is also less damaging to normal tissues such as those of the heart and lungs. These changes have made treatment less destructive, with equally successful results.

Besides these refinements in the detection and local management of breast tumors, the use of systemic therapies as supplementary, or adjuvant, treatments has become more sophisticated thanks to the availability of new drugs, improvements in their delivery, and management of side effects. Such treatments aim to eradicate any malignant cells not eliminated by surgery or radiation. The approach is often warranted because even tumors that are tiny and apparently self-contained can already have quietly spawned microscopic metastases, undetectable tumors at distant sites in the body. By attacking these invisible tumors, adjuvant chemotherapy can prolong disease-free intervals and overall survival rates.

Adjuvant chemotherapy is also improving the odds for those with more advanced tumors. In the 1970s our clinical group and others began developing multidisciplinary treatment programs for patients with so-called locally advanced breast cancer, which has invaded neighboring tissue. Such patients are often not diagnosed until their cancer is incurable with surgery alone. Our approach is to treat them with preoperative, or neoadjuvant, chemotherapy to shrink their tumors to operable size, after which surgery is performed, followed by additional chemotherapy and radiation therapy. Using this sandwich approach over the past three decades, specialized teams of doctors, nurses and other health professionals have greatly enhanced the cure rate for these patients. Even those whose breast tumor has already metastasized to other organs now have access to novel therapies that prolong their survival and to supportive care that increases their quality of life.

Another mainstay of breast cancer treatment, at least for patients with tumors that are determined to be dependent on estrogen or progesterone, is endocrine therapy. Indeed, hormonal manipulations to treat breast cancer date as far back as the 1890s, when doctors observed tumors regressing after they had removed the ovaries of premenopausal women with advanced breast disease. In 1966 researchers identified hormone receptors—molecules that bind to specific hormones—in various tissues, including that of the breast. Subsequent studies showed that a significant number of invasive breast cancers—as many as 75 percent—contain estrogen receptors or progesterone receptors, or both, causing these molecules to quickly become therapeutic targets.

The antiestrogen drug tamoxifen was first approved in the U.S. in 1977 to treat advanced breast cancer in postmenopausal women. The drug molecule binds to the estrogen receptor, preventing estrogen from doing so. Tamoxifen has since proved effective for patients with localized breast tumors that display estrogen or progesterone receptors and as a preventive therapy in healthy women who are at high risk for breast cancer. Meanwhile newer drugs that inhibit the aromatase enzyme, suppressing natural estro-

## FAST FACTS

Inherited mutations in the *BRCA1* gene can multiply lifetime breast cancer risk by 10 times, but only in the past year have researchers discovered why. *BRCA1* is involved in DNA repair, so its malfunction makes errors in other cancer-promoting genes more likely.

Following a 2002 report that hormone replacement therapy (HRT) increased breast cancer risk in postmenopausal women, HRT use fell. The next year there was a dramatic drop in the incidence of both invasive (7.3 percent) and noninvasive (5.5 percent) breast cancers in the U.S.

## [TREATMENT MILESTONES]

Doctors started aggressively treating breast cancer in the 19th century, with the first mastectomy performed in 1882. But insights into mechanisms driving the disease that would lead to increasingly targeted therapies began with discoveries in the 1950s.

**1880s–1890s**

George T. Beatson

Hormonal cancer connection suggested when physicians report significant regression of breast cancer tumors following ovary removal or onset of menopause.

**1896:** First ovary removal performed as a breast cancer treatment by George T. Beatson.


**RAISING AWARENESS of the importance of early detection, as well as raising funding for research, has paid off in notable declines in breast cancer mortality in the developed world.**

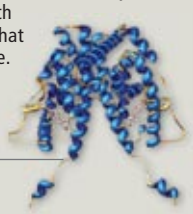
ANGELA ROWLINGS *AP Photo (racers)*; LISA APFELBACHER *(all pills)*; TIMELINE: WELLCOME LIBRARY, LONDON *(Beatson)*; MARK J. WINTER *Photo Researchers, Inc. (estrogen receptor)*; SCIENCE MUSEUM *(tamoxifen)*; P. MARAZZI *Photo Researchers, Inc. (Herceptin)*

## 1950s–1960s

**1951:** Estrogen and testosterone found to drive the growth of breast and prostate cancers, respectively.

**1958:** Cancer researchers identify additional "growth factor" proteins that help tumors thrive.

**1966:** Estrogen receptor identified.



Estrogen receptor protein structure

## 1970s–1980s

**1976:** Cancer-promoting "oncogenes" first discovered in mammals.

Tamoxifen, a selective estrogen receptor modulator

**1976:** Clinical trials begin to show that lumpectomy with radiation can be as effective as mastectomy.

**1977:** Hormone-blocking drug tamoxifen approved in U.S. for treatment of breast cancers sensitive to estrogen or progesterone.

**1988:** Trial results show that preoperative chemotherapy shrinks tumors, making less invasive surgeries possible.

## 1990s–2008

**1994:** *BRCA1* gene, known to increase susceptibility to breast cancer, is isolated.

**1997:** Letrozole, which blocks estrogen synthesis, approved in U.S. for patients whose cancer did not respond to tamoxifen.

**1998:** Trastuzumab, the first molecular-targeted cancer therapy, approved in U.S. for use in breast cancer.

**2007:** Lapatinib, an inhibitor of growth signaling, approved in U.S. for use in breast cancer.

**2008:** Bevacizumab, an inhibitor of blood vessel formation in tumors, approved in U.S. for use in breast cancer.


Trastuzumab, also known by the trade name Herceptin

gen manufacture in the body, have proved superior to tamoxifen in postmenopausal women.

In a sense, then, estrogen and progesterone receptors became the first molecular features of tumors that could be directly targeted by drugs, although an important distinction should be noted between these targets and newer ones identified in the past decade. The sex steroid receptors promote cell proliferation, or growth, in healthy tissues as well as in tumors, so suppressing their ability to transmit growth signals does help to check tumor enlargement. And changes to the receptors' shape or function may sometimes contribute to the general malignant characteristics of tumor cells. But the gene encoding the estrogen receptor is rarely mutated in breast cancers, which means that it is not a true cancer-causing gene.

Perhaps the most important realization in cancer research since the era when sex hormone receptors were discovered is that particular genes, when they become mutated, can cause a normal cell to turn cancerous. Such genes, once they do mutate, are referred to as oncogenes, and they are believed to be responsible both for initiating the transformation of a normal cell into a cancerous one and for driving tumor growth. That is why breast cancer (like all cancers) is described today as fundamentally a disease of genes. An oncogenic mutation, such as a small change in the DNA nucleotide sequence of a gene, might disable a protective gene or boost the activity of a tumor-promoting one. In some cases, entire genes are deleted or duplicated [*see sidebar on page 63*].

Tumors can now be classified according to the genes that are overactive or suppressed in their cells and according to the resulting changes in the manufacture and function of proteins encoded by those genes. The damaged genes can vary from tumor to tumor, and this heterogeneity at the genetic level explains why the breast cancers of individual patients might behave differently. Some cancers have limited invasiveness and metastatic potential, for instance, whereas others spread quickly to distant organs. Knowing the molecular profile of a patient's tumor should permit a doctor to focus on inhibiting the mechanisms driving that particular tumor, one day choosing from an arsenal of drugs a set that will interfere with the specific molecules involved in the initiation, growth and spread of the cancer. The success of trastuzumab and other HER2-targeted therapies illustrates the potential of this approach in combating breast cancer.

## Targeting HER2

In the early 1980s the gene that gives rise to HER2 was first discovered in mutated form in rat neural tumors by investigators at the Massachusetts Institute of Technology, who named that oncogene *Neu*. Soon researchers realized that the gene was a mammalian version of one previously identified in viruses called *ERBB*, so *Neu* also came to be known as *ERBB2*. This gene was not done accumulating names, however. When scientists identified the protein encoded by *ERBB2*, they realized that it was closely related to a cell-membrane protein called epidermal growth factor receptor (EGFR). Thus, when they finally isolated the human version of the *ERBB2* gene, they named it human epidermal growth factor receptor 2 (*HER2*).

As it turns out, the entire EGFR family of proteins has proved important to tumor cell growth in a variety of cancers. When activated by specific molecules that bind to them (their ligands), such receptors transmit a proliferation signal to the cell by initiating a cascade of internal molecular interactions—spurring activity by genes whose encoded proteins regulate the activity of still more "downstream" genes. Shortly after the *HER2* gene was discovered, scientists noted that

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MEDICAL GRAPHICS & PHOTOGRAPHY/UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER (*left*); JOHN SMALLWOOD (*right*)

it was frequently duplicated in breast cancer cells and that having multiple copies of the gene was associated with a poor prognosis.

Laboratory studies confirmed that adding copies of the *HER2* gene to a normal cell could transform it into a cancer cell—a hallmark ability of oncogenes. Because 20 percent of breast cancer tumors overproduce the HER2 protein, it became a therapeutic target for drug researchers. Genentech scientists created trastuzumab in the late 1980s by manufacturing so-called monoclonal antibodies that bind to the HER2 receptor, preventing it from being activated. In clinical trials, it was found that trastuzumab could lengthen the survival of patients with both early-stage and metastatic breast cancer.

The success of trastuzumab has led to the development of similar antibody-based therapies, such as pertuzumab, which binds to HER2 at a different site than trastuzumab and has the added effect of preventing the receptor from interacting with other members of its family in the cell membrane, such as EGFR and HER3. Blocking such interactions reduces growth signaling along the intracellular pathways of molecular communication downstream of these receptors. Pertuzumab can even disrupt certain types of HER2 activation in tumor cells that have become resistant to trastuzumab. Moreover, we have shown that combining trastuzumab with pertuzumab can boost the rate of cell death in breast cancer cells overproducing HER2.

Still another method of wielding antibodies against the HER2 receptor is to attach a potent toxin to them, which the antibodies then transport into the cancer cell. After the toxin-antibody pair is internalized by a cell, the toxin detaches and kills the cell. This approach has been successful in other types of cancer, such as acute myeloid leukemia, and clinical trials are under way in patients with metastatic breast cancer to determine the safety and efficacy of such trastuzumab-based conjugates.

To send a growth signal into a cell, the intracellular region of the EGFR family of proteins must first be acted on by tyrosine kinases, enzymes that chemically modify a segment known as the tyrosine kinase domain. Tyrosine kinases can thus act as growth-stimulating factors, and inhibiting them directly is another way of squelching EGFR-mediated growth signaling in cells. That is why pharmaceutical companies are avidly pursuing the clinical development of such drugs. Lapatinib (Tykerb) is a dual EGFR/HER2 tyrosine kinase inhibitor that has shown remarkable laboratory results, leading to growth arrest and cell suicide in breast cancer cell lines that overproduce HER2.

One way to improve the effectiveness of HER2-targeted therapy is, therefore, to combine a drug such as trastuzumab with a tyrosine kinase inhibitor such as lapatinib. In breast cancer cell lines, that combination produces greater synergistic growth inhibition and higher rates of cell suicide. Even in cell lines that have developed resistance to trastuzumab after long-term treatment, lapatinib has proved just as effective at inducing cell suicide. A recent large (phase III) clinical trial among patients with HER2-overproducing metastatic breast cancer, whose disease had become resistant to trastuzumab, demonstrated that lapatinib plus capecitabine chemotherapy doubled the median time to progression as compared with capecitabine alone. On the basis of these results, in 2007 the U.S. Food and Drug Administration approved the use of lapatinib combined with capecitabine for treating metastatic disease. Clinical trials to determine lapatinib's value as an adjuvant treatment in a wider variety of circumstances are

JEN CHRISTIANSEN

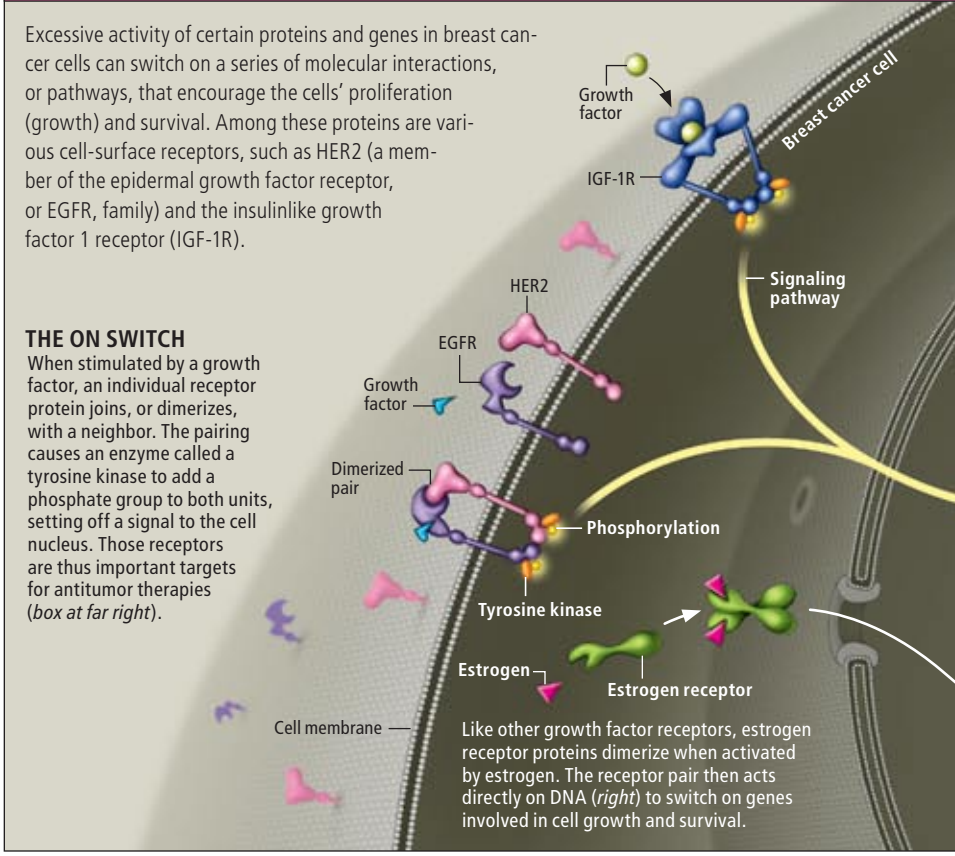
[TARGETS]

## TUMOR PATHWAYS

Excessive activity of certain proteins and genes in breast cancer cells can switch on a series of molecular interactions, or pathways, that encourage the cells' proliferation (growth) and survival. Among these proteins are various cell-surface receptors, such as HER2 (a member of the epidermal growth factor receptor, or EGFR, family) and the insulinlike growth factor 1 receptor (IGF-1R).

**THE ON SWITCH**

When stimulated by a growth factor, an individual receptor protein joins, or dimerizes, with a neighbor. The pairing causes an enzyme called a tyrosine kinase to add a phosphate group to both units, setting off a signal to the cell nucleus. Those receptors are thus important targets for antitumor therapies (*box at far right*).

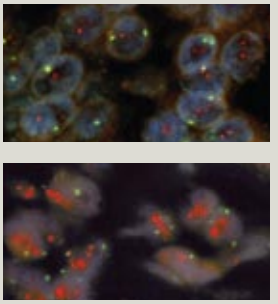


ongoing, as are trials of several other tyrosine kinase inhibitors that target HER2 and EGFR.

Finding alternative means of interfering with the same growth pathways is important because, as can happen with trastuzumab, cancer cells often do eventually find ways to evade individual drugs. Also under way is research into how and why cancer cells develop resistance to trastuzumab, so that investigators can use those insights as a guide to designing more effective combinations or new agents for patients whose tumors overproduce HER2.

In studies of cell cultures and animals, for instance, our laboratory has discovered that cancer cells employ many different mechanisms to survive in the presence of trastuzumab, including increasing their production of other growth factor receptors, either from the EGFR/HER family or from other families, such as the insulinlike growth factor 1 (IGF-1) receptor. The cells may also lose or inactivate the tumor suppressor gene *PTEN*. This gene normally blocks a survival pathway involving the enzyme phosphotidylinositol 3-kinase (PI3K), which allows damaged cells to ignore signals telling them to commit suicide. We have even seen cells lose or disable the extracellular binding site that trastuzumab attaches to on the HER2 receptor.

In light of these observations, identifying additional molecular targets to attack in cells that overproduce HER2, as well as targets in the other 80 percent of tumors that do not have *HER2* mutations, is a high research priority.



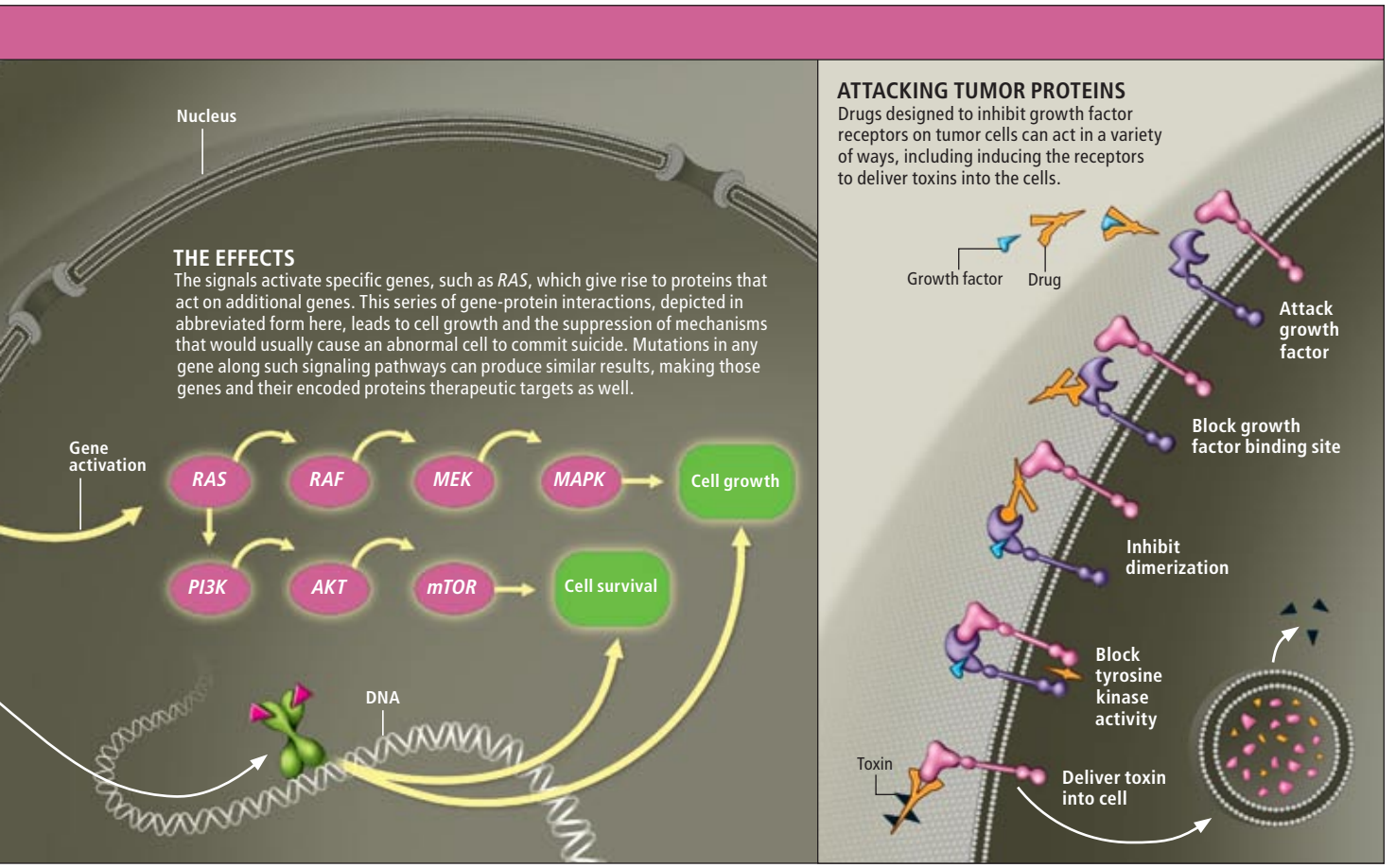
COURTESY OF FRANCISCO J. ESTEVA

## HER2 AMPLIFICATION

**A gene encoding the HER2 growth factor receptor is tagged with red fluorescence in breast cancer cells (*top*). In HER2-positive cancer cells (*bottom*), the gene is duplicated many times over, leading to overproduction of HER2 proteins that cause the cells to receive excessive growth signals.**

## Expanding the Arsenal

Among the most promising new targets for breast cancer therapy is the IGF-1 receptor as well as the growth hormone molecules that activate it, IGF-1 and IGF-2. High levels of IGF-1 in the bloodstream have been linked with increased risk of breast cancer, and many laboratory and clinical studies have implicated its receptor in the development, maintenance and progression of multiple cancer types. Signaling by the IGF-1 receptor regulates a variety of cellular processes, including growth, motility and protection from cell suicide. In fact, such signals have been shown to protect tumor cells from the effects of chemotherapy and radiation therapy. Conversely, inhibiting IGF-1 receptor activity during radiation therapy or



chemotherapy has been found to enhance tumor cell suicide rates in animal studies.

In addition to exploring IGF-1 receptor inhibition as a direct therapeutic tool for breast cancer, scientists are evaluating ways to apply it toward preventing or reversing resistance to other treatments, such as endocrine therapies, trastuzumab and lapatinib. Cross talk between the IGF-1 receptor and the various other growth factor receptors—including estrogen, HER2 and additional EGFRs—is a key mechanism for the growth and survival of breast cancer. This codependence and communication between different intracellular pathways is thought to play an important role in drug resistance. Our research group has shown, for example, that blocking the IGF-1 receptor with a monoclonal antibody restores the sensitivity of resistant cells to trastuzumab and disrupts the interaction between the IGF-1 and HER2 receptors. Suppressing the IGF-1 receptor also kills the resistant cells. Furthermore, lapatinib appears to have inhibitory effects on IGF-1 signaling in the trastuzumab-resistant cells, suggesting that its ability to limit tumor cell proliferation may result not only from its anti-EGFR/HER2 activities but also from direct IGF-1 receptor inhibition.

The tangle of signaling pathways leading from the receptors we have been describing to the cellular processes that actually cause a cell to divide or to resist suicide despite DNA damage is highly complex. But scientists are finding that key genes along those pathways are also frequently mutated or dysregulated in tumor cells. Among the best characterized examples is the *PI3K* gene, whose encoded protein chemically modifies another protein known as AKT, which in turn modifies a complex called the mammalian target of rapamycin (mTOR). This PI3K/AKT/mTOR pathway plays a critical role in the body's use of glucose for energy and other important physiological processes in normal cells, but it is pathologically overactivated in cancer cells, prolonging their survival. Because the pathway's effects are ubiquitous in the body, delivering drugs that inhibit it could disrupt healthy cells as well as cancerous ones—a drawback that has so far limited the use of such agents.

Several mTOR inhibitors are nonetheless being tested in clinical trials, both as single agents and combined with other therapies. At the moment, studies using the mTOR-suppressing antibiotic rapamycin, along with an inhibitor of the IGF-1 receptor, suggest that such combinations yield additive antitumor effects as compared with single agents—and that, further, clinically evaluating combined inhibition of both pathways may be a good idea.

Another approach showing great promise is combining direct antitumor agents with compounds that target elements in a tumor's environment. Cancers secrete a variety of growth factors to attract the endothelial cells that build new blood vessels in a process called angiogenesis. Overproduction of the most important of these, vascular endothelial growth factor (VEGF), is thought to make tumors more dangerous, and high levels correlate with worse survival rates in human invasive breast cancers.

## TARGETED THERAPIES

A growing list of drugs designed to inhibit specific tumor proteins are approved to treat breast cancer patients (*bold*) or are undergoing clinical trials.

**DRUG TYPE**

- **Aromatase inhibitor** (blocks an enzyme involved in estrogen and progesterone synthesis)
- **Monoclonal antibody** (impedes activation of cellular receptors)
- **Kinase inhibitor** (inhibits signaling by cellular receptors)
- **Vaccine** (stimulates production of antibodies specific to tumor proteins; can be composed of cells or peptide molecules)
- **Other** (includes direct inhibitors of other molecules or gene therapy to alter cellular protein manufacture)

| TARGET | DRUG |
|---|---|
| Estrogen/ progesterone receptor proteins | **Anastrozole**<br>**Letrozole**<br>**Exemestane**<br>**Tamoxifen**<br>**Fulvestrant** |
| HER2 receptor protein | **Trastuzumab**<br>**Pertuzumab**<br>**Lapatinib**<br>NeuVax<br>dHER2<br>MVF-HER-2<br>E1A (gene therapy) |
| IGF-1 receptor protein | IMC-A12<br>CP-751, 871<br>AMG 479<br>h7C10<br>OSI-906 |
| PI3K/AKT/mTOR cell survival pathway | BGT226<br>BEZ235A<br>RAD001<br>Rapamycin |
| VEGF receptor protein (involved in forming tumor blood vessels) | **Bevacizumab**<br>Sunitinib<br>Vatalinib<br>Pazopanib<br>AZD2171<br>AMG706<br>AMG386<br>PTC299 |
| Other targets | Dasatinib (SRC inhibitor)<br>THERATOPE<br>Dendritic cell vaccines<br>P53 peptide vaccine<br>ALT801 (p53 inhibitor)<br>Ad5CMV-p53 (gene therapy)<br>Anti-p53 T-cell reinfusion<br>AZD2281 (PARP protein inhibitor)<br>BSI-201 (PARP inhibitor) |

## Global Power

Targeted therapies will be most powerful, in principle, when they are used together in combinations tailored to the tumor features driving an individual patient's cancer. Clinical trials to test specific drug combinations provide critical information about which treatments work most effectively on different tumor profiles and reveal unexpected interactions between drugs. But trials take time, often years, to enroll a sufficient number of participants to generate statistically significant results. That is why multinational research consortia based in Europe and the U.S. are pooling resources to conduct a 50-country trial, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Study (ALTTO), which has just begun recruiting in the U.S.

Some 1,500 testing sites will treat patients with early (stage I or II) breast cancers that overproduce the HER2 protein, giving them chemotherapy and either trastuzumab or lapatinib alone, or one of those drugs followed by the other, or both drugs together. The trial will provide the first side-by-side comparison of these HER2-targeted treatments that work by different mechanisms.

With a goal of including as many as 8,000 women on six continents, ALTTO has the potential to quickly generate results that can then be applied to patients everywhere. Moreover, this global data-sharing model can highlight differences in treatment responses or toxicity among different ethnic groups, a phenomenon observed with certain types of chemotherapy because of genetic variations that affect the way the drugs are metabolized by patients' bodies. Having such information about the newer targeted therapies will help doctors to further personalize treatment, tailoring it to both the tumor and the patient. ***—The Editors***

Genentech's bevacizumab (Avastin) is a monoclonal antibody directed against VEGF that was first approved for use in colon cancer in 2004. In more recent clinical trials among patients with heavily treated metastatic breast cancer, bevacizumab alone had limited activity, but certain patients who received it in combination with capecitabine chemotherapy showed improved responses [see "Taming Vessels to Treat Cancer," by Rakesh K. Jain; Scientific American, January]. In another study, HER2-negative metastatic breast cancer progressed more slowly in patients who received paclitaxel chemotherapy with bevacizumab than it did in patients who received paclitaxel alone. Based on such results, bevacizumab was recently approved for use in breast cancer patients, and other VEGF inhibitors are also in development, such as Pfizer's sunitinib (Sutent), a tyrosine kinase inhibitor targeted against the VEGF receptor.

At the same time, very basic biology research is continuing to turn up new molecular targets that both reveal more about the underlying mechanisms of cancer and provide potential leads for drug development. Terumi Kohwi-Shigematsu of Lawrence Berkeley National Laboratory and her colleagues announced one such discovery earlier this year. They identified a gene called *SATB1* as the "master regulator" of activity for more than 1,000 genes involved in breast cancer metastasis. Kohwi-Shigematsu showed that the influence of the SATB1 protein encoded by the gene is both necessary and sufficient for breast cancer cells to become metastatic, which makes it an appealing therapeutic candidate. Her research group is already working on an inhibitor of the SATB1 protein, which could be ready for clinical trials within a few years.

Progress in the molecular targeting of breast cancer and individualized therapy will generally rely on the continuing development of profiling tools to determine whether a patient's tumor overproduces proteins such as HER2, SATB1 and others that might be direct drug targets. In addition, genetic testing can help to characterize a tumor's overall gene activity patterns—a potential signature of a good or poor prognosis. Still other tests already available or nearing approval can help to profile the patient herself to establish whether she has genetic variations that might make her body process a medication more slowly than average—a situation that can be problematic with a drug such as tamoxifen that depends on the body to convert it to active form.

Meanwhile further clinical trials of various drug combinations are needed to validate the effectiveness of attacking multiple targets at once. A 50-country trial has recently begun recruitment in the U.S., for example, to test lapatinib and trastuzumab alone and in combination with each other and with traditional chemotherapies [*see box on this page*].

Such a large international trial exemplifies the considerable resources and attention focused on breast cancer research, in recognition of its importance as a global health threat. The intensive scientific investigation and heightened awareness are certainly bearing fruit. When breast cancer is compared with other types of cancer, such as malignancies of the lung or brain, advances over the past decade have been impressive. Doctors' ability to profile a tumor and tailor treatment to fight it with a growing arsenal of weapons is already making a difference in the survival rates of breast cancer patients, and the coming decade promises even more dramatic progress. ■

### MORE TO EXPLORE


**Molecular Oncology of Breast Cancer.** Edited by Jeffrey S. Ross and Gabriel N. Hortobagyi. Jones and Bartlett Publishers, 2005.

**Long-Term Cardiac Tolerability of Trastuzumab in Metastatic Breast Cancer: The M.D. Anderson Cancer Center Experience.** Valentina Guarneri et al. in *Journal of Clinical Oncology,* Vol. 24, No. 25, pages 4107–4115; September 1, 2006.

**Trastuzumab: Triumphs and Tribulations.** Rita Nahta and Francisco J. Esteva in *Oncogene,* Vol. 26, No. 25, pages 3637–3643; May 28, 2007.

**Advances in the Treatment of Breast Cancer.** Stacy Moulder and Gabriel N. Hortobagyi in *Clinical Pharmacology & Therapeutics,* Vol. 83, No. 1, pages 26–36; January 2008.

**Breast Cancer.** Second edition. Edited by Kelly K. Hunt, Geoffrey L. Robb, Eric A. Strom and Naoto T. Ueno. Springer, 2008.