

FEATURE STORY

Targeted Therapy: Hope or Hype?

BY LAURA BEIL

With all the excitement surrounding targeted cancer drugs, what's the reality of these "magic bullets"?

Here's a quiz: Targeted drug therapy has been one of the most promising approaches to cancer treatment in the past decade. What do we mean by "targeted"?

- A. A drug hits a bull's-eye on a malignant cell; the cancer goes kabloolie.
- B. Normal tissue does not contain the target.
- C. We know where the target is.
- D. We know what the target is.

The answer is ... all of the above. And none of the above. Which makes "targeted therapy" one of the most used and least understood phrases in the modern cancer vocabulary.

Around a decade ago, targeted therapy rose to stardom on the hope of providing powerful cancer treatment with fewer side effects than chemotherapy. It made the cover of *Time* magazine in 2001, and experts—those who normally talk in cautious terms—started using words like *miracle*.

So what is it? In its simplest sense, a targeted therapy drug is developed from scratch with the target in mind. The idea is that scientists discover a molecule critical to a tumor's operation, but not important to normal cells, and design a medicine to short circuit that molecule. It's kind of like stopping a car by just disconnecting the spark plugs from the engine. But the excitement also comes from what targeted therapy doesn't do. By zeroing in on genetic flaws unique to a tumor, targeted therapy has the potential to leave normal tissue unscathed. One early report called it "a smart bomb pill."

But after years of high expectations, reflection, and plenty of sticker shock, targeted therapy met reality. In many ways, the love affair with targeted therapy has been like any other romance. At first sight, it was new and exciting. Lots of

people became starry-eyed over the possibilities. But as time passed, researchers began to see that targeted therapy was more complex and flawed than everyone first thought. The love isn't gone, just settled.

"I think what's happened now is we've grown more sophisticated," says lung cancer specialist Martin Edelman, MD, of the University of Maryland Greenebaum Cancer Center in Baltimore, who warned in 2003 that targeted therapy would be the victim of its own press. "The whole concept of 'targeting' has taken on a greater degree of nuance."

He and other researchers point out that some of the earliest cancer treatments were actually targeted therapies that came along before anyone had a catchy term for them. Women have taken the hormonal agent tamoxifen, which targets estrogen receptors in breast cancer, for four decades. Scientists didn't understand the role of estrogen in cancer when the drug first entered the market, but that didn't make tamoxifen any less targeted. A more traditional chemotherapy drug, Adriamycin (doxorubicin), was given to patients starting in the 1960s, even before doctors knew it disrupted a particular enzyme necessary for cell division, particularly rapidly dividing cancer cells.

"Any treatment that works hits a target," says James Armitage, MD, a lymphoma expert at the University of Nebraska Medical Center in Omaha. "If you give somebody doxorubicin, and the cancer goes away, it's a targeted therapy. The fact that we didn't know the target prospectively didn't change that."

Rituxan (rituximab), an immunotherapy drug that targets a protein called CD20, was approved for non-Hodgkin lymphoma in 1997, but it took more glamorous entries such as Herceptin (trastuzumab) and Gleevec (imatinib) to bring targeted therapy into its own.

When Herceptin made its debut, reports heralded a new era in cancer treatment. Herceptin is designed to treat tumors that produce too much of a protein called HER2, which occurs in about 20 percent of women with breast cancer. First approved for metastatic breast cancer in 1998, Herceptin's second approval followed in 2006 after research showed Herceptin plus chemotherapy cut the recurrence rate in early-stage breast cancer by half compared with chemotherapy alone.

Words like *breakthrough* and *cure* were used for Gleevec, which treats chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). Gleevec interferes with the production of an enzyme that certain cancer cells need to survive. Shortly after its approval for leukemia in 2001, one doctor told the *New York Times* that Gleevec was "not much short of miraculous."

Jim Guzzi agrees wholeheartedly. For three years after his diagnosis of leukemia in 1998, the 65-year-old painting contractor from Florham Park, New Jersey, used interferon. The drug kept him alive, but drained so much energy he could hardly climb the stairs of his home. After his doctor switched him to Gleevec in 2001, he says, "I got back to work within three months or so. It's a godsend."



Jim Guzzi says he's "back to normal" thanks to the targeted drug Gleevec. Photo by Ryan Ashby.

But in the everyday world, miracles get complicated—and expensive. Scientists now realize targeted therapy is a much messier undertaking than the approach first seemed. Herceptin was supposed to seek only breast cancer cells, but clinical trials revealed a very small percentage of women suffered heart complications. (Stopping the drug may reverse the effect.) Gleevec can keep CML under control, but patients may have to stay on the drug indefinitely at a cost of thousands of dollars each month.

Other targeted drugs came along that were not the slam dunks they should have been, or had more side effects than anticipated. “The problem is that the reality often has not met the high expectations,” says Neil Spector, MD, co-director of the program on experimental therapies at Duke Comprehensive Cancer Center in Durham, North Carolina.

Targeted therapy is still considered the future of cancer treatment. In fact, so powerful is the phrase that new drugs almost must be called “targeted,” regardless of how they came to be. “It’s become, for many, a marketing term,” Edelman says. Nonetheless, doctors have a greater appreciation of the challenges in targeted drug development. Among them:

Cancers will most likely have many targets, not just one. Cancers keep themselves alive with more than one mechanism, each of which is a potential target. Some targets will be more important than others. The trick is to find a target that remains narrowly focused on a tumor, but not so narrow that the cancer can survive without it. This is why many researchers believe that most cancers will not be wiped out by one wonder drug that does the heavy lifting, but by combinations of drugs that work together.

View Illustration : Taking Aim

Gleevec is a noted exception. It is highly effective even though it only has a single target—the bcr-abl gene located on the abnormal Philadelphia chromosome that causes certain white blood cells to become malignant.

In general, though, solid tumors are a more treacherous terrain, says Thomas

Lynch, MD, director of Yale Cancer Center in New Haven, Connecticut. “The genetically complex cancers, you’re going to have to find a way to take out all the pathways,” he says. Chances are, no one medicine will have such talent.

Even a drug that hits a very specific target on a cancer cell may still affect normal tissue. We like to think of a targeted drug fitting cancer like a puzzle piece—it has a shape that only matches its mate on the tumor, and the fit is exact. In truth, the biology is never as tidy as we would like. The molecular target on the tumor may be so similar to a target on normal tissue that the drug can’t tell the difference. Thus, a drug can hit the target on a tumor and still have side effects on other tissues.

Herceptin, for example, can cause heart damage in a rare number of cases. The antiangiogenic drug Avastin (beva-cizumab), which blocks a tumor’s ability to feed itself with new blood vessels, can lead to high blood pressure. “I don’t think it’s wrong to call them targeted therapies,” says Spector, who helped develop a HER2-targeted drug called Tykerb (lapa-tinib). “The question becomes, how selective are these targeted therapies? It may be a misnomer to say they are hitting a single target when they are actually hitting multiple targets.”

The narrowest target might not necessarily be the best one. Tumors have wired themselves for one purpose: survival. And they have survived despite the body’s attempts to crush them from the earliest signs of abnormality. This means any malignancy is supported by intricate and genetically volatile circuitry, and we don’t yet understand all the wiring. “Cancer is hugely complicated,” says Edward Chu, MD, section chief of medical oncology at Yale Cancer Center. “The cancer cell is far more brilliant than the most brilliant scientist we have.”

So a drug might hit a target, but the target could be too narrow to do little more than make a dent in the cancer. Knocking out one mechanism in the tumor circuitry may not be good enough if the tumor has any number of backups.

The key to success will be matching the right drugs and the right targets to the right patient. Doctors are starting to argue that cancer treatment should consider the tumor’s molecular properties, not just location. This concept would not only change the practice of cancer treatment, but it would mean, for example, that cancers would be tested for their drug susceptibility from the outset. A tumor’s particular molecular hallmarks could also change the way drugs are tested and approved.

Proponents of the idea liken the approach to infectious disease treatment. For a stubborn infection, doctors take a sample of the bacterium to grow in a culture dish, checking to see which drugs the germ is susceptible to. “We need something like an antibiotic sensitivity test,” says Nebraska’s Armitage.

In some cases, this is already happening. For example, since 2004, patients with metastatic colorectal cancer have been treated with Erbitux (cetuximab), a drug that zeroes in on the epidermal growth factor receptor on the surface of the malignant cell. But about 40 percent of tumors have no response to Erbitux; studies have found that these unresponsive tumors have a mutated (as opposed

to normal) form of a gene called KRAS (see "[Bittersweet Gene](#)"). A mutation in the KRAS gene enables the tumor to resist the drug, which is why the American Society of Clinical Oncology now recommends that doctors determine a tumor's KRAS status before prescribing treatment. "What we're doing is instead of looking at a particular target, we're looking at profiles," says Chu.

View Chart : Agents in the Pipeline

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Yet some doctors are concerned about the accuracy of the genetic profile results. Consider Herceptin: Determining whether a breast cancer is of the HER2 variety isn't like a test for a KRAS mutation, where the answer is either yes or no. A "positive" HER2 tumor is one that has a certain density of HER2 on the cell surface, but recent studies have questioned the threshold for interpreting the results.

Studies suggest that some women who are technically negative might benefit from Herceptin, although these observations are not conclusive. Researchers are now discussing a trial for "HER2-low" patients. (See "A Patient's Guide to HER2-Positive Breast Cancer," at www.curetoday.com/patient_guides)

There will probably be no wonder drug, but there will be wondersCancer researchers are used to measuring progress in increments: months of added life, not cures; cancers controlled, but not gone. Targeted therapy, despite its days as a cover celebrity, will be no different, researchers say. Each gene, each target, and each drug tells scientists something they might one day use against a tumor. Over time, these small improvements will hopefully result in significant cure rates.

Guzzi will tell you that without Gleevec, he would not have been able to return to work or care for his wife, who lost her sight 40 years ago. Now he runs his business, with enough energy left over to volunteer for the local Leukemia and Lymphoma Society. "I am back to normal."

Progress will come as it always has—one molecule and one patient at a time.