

HITTING THE TARGET

Dr. Mark Greene's pioneering discovery 25 years ago laid the foundation for a revolutionary breast cancer therapy. Can the same approach work for lung cancer? By Katie Sweeney

Cancer cells are formidable opponents. To defeat them, medicine must rely on its most powerful DNA-disrupting treatment weapons—sacrificing healthy tissue along the way. Even still, some cells refuse to surrender.

Recently, a new kind of cancer treatment has emerged that could change this paradigm: targeted therapy. A number of targeted drugs already are on the market, with more undergoing clinical trials. Kinder and gentler, targeted therapy has been widely hailed as the future of cancer treatment, with the potential to transform the nation's No. 2 killer into a manageable disease.

Behind these new drugs is an astonishing discovery made 25 years ago by Mark I. Greene, MD, PhD, a preeminent scientist in the field of cancer biology.

Then a professor at Harvard University, Dr. Greene discovered that administering a simple antibody delivered against a breast cancer-causing genetic protein essentially flipped an "on-off" switch. With the protein in the "off" position, malignant cells were transformed back into

essentially normal cells—a phenomenon previously thought impossible.

That discovery became the basis for a pioneering new breast cancer drug called Herceptin®, and also for nearly every targeted cancer drug developed since then (see sidebar page 24).

"Targeted therapy is not about killing cells; it is about turning off gene products, or proteins, that make cells malignant," explains Dr. Greene. "By transforming cancer cells into more normal cells, they become exquisitely sensitive to being killed—by chemotherapy and radiation, or even the body's own immune system."

While the DNA genome is the information archive, the work of the cell is controlled through proteins. Targeted therapy is a form of personalized medicine directed at proteins, not genes. It is not yet possible to easily target specific genes, although some DNA-based drugs are in the works. Dr. Greene believes DNA-targeting drugs could be developed eventually.

Targeting gene proteins has so far proven less harmful to normal cells, with fewer side effects than chemotherapy. Still, targeted drugs have

limitations. Herceptin, for example, is only applicable for about 25 percent of breast cancers—those with the HER2/neu protein. Targeted therapy is long-term; without the drug, those cancer-causing proteins turn back on.

"Targeted therapies allow us to convert cancer into a chronic disease that is manageable," says Dr. Greene. "In 10 to 15 years, I think we will treat all cancers this way."

Dr. Greene is now developing targeted therapies for advanced prostate cancer, as well as pancreatic and lung cancers. Current treatments target tumors with an epidermal growth factor receptor (EGFR) mutation—only about 8 percent of lung cancers. Dr. Greene is working on a drug that would make the other 92 percent sensitive to EGFR therapy by "tricking" proteins into acting like they have the mutation. The drug could be ready for Phase I clinical trials within two years. 🗨️

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—Mark Greene, MD, PhD



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