



Dr. Dennis Slamon's development of Herceptin revolutionized breast cancer treatment and accelerated research into therapies customized for each individual patient.

# The Personal Approach

# Winning Endeavor

The development of the breast cancer drug Herceptin has earned Dr. Dennis Slamon a number of research awards, including the 2007 Gairdner International Award, the most prestigious award for outstanding discoveries in medical science, and a 2004 American Cancer Society Medal of Honor. The Society's support of Slamon began in 1988 and, including his current ACS-Cissy Hornung Clinical Research Professorship, totals \$505,000 in grant funds.

**Current Positions**

Director, Clinical/Translational Research, UCLA's Jonsson Comprehensive Cancer Center; and Director, Revlon/UCLA Women's Cancer Research Program, to name just two.

**Education**

MD and PhD, University of Chicago, 1975



**W**hen Dennis Slamon, MD, PhD, first began his work identifying unique molecular changes in tumors, none of the federal funding agencies would give him money. "People didn't think our approach would work," he says. Slamon was hoping to find genetic alterations that could be targets for new drugs.

The American Cancer Society, however, saw the potential in Slamon's research, which resulted in the 1998 U.S. Food and Drug Administration's (FDA) approval of the drug Herceptin for breast cancer that had spread to other parts of the body, turning one of the deadliest forms of the disease into one of the most treatable. Herceptin goes to work in those breast tumors with an overabundance of the protein HER2, which affects 15% to 25% of women diagnosed with breast cancer.

Slamon led the research to identify HER2 as a cancer target while at the University of California, Los Angeles Jonsson Comprehensive Cancer Center where he today is director of clinical/translational research. He also worked with the biotechnology company Genentech on clinical trials proving the effectiveness of Herceptin.

**Q: What does the HER2 protein do in the cell?**

**A:** HER2 sits on the outside of the cell like an antenna, detecting growth signals from the cell's surroundings. In normal quantities HER2 plays an important role in maintaining the breast cell's growth.

But breast cancer cells in about one third of all women make extra copies of the HER2 gene. Those extra copies result in excess HER2 protein on the

surface of the cell. Cells with an overabundance of HER2 protein amplify the growth signals from the environment and, as a result, divide more rapidly than normal and propagate the tumor. It's that extra protein that doctors look for when deciding whether women will respond to Herceptin.

**Q: Are tumors with the HER2 mutation different from other tumors?**

**A:** When we began our work, women with HER2 alterations had among the worst survival rates. Their tumors were more likely to spread and less likely to respond to treatment. With the advent of Herceptin, things have reversed. Patients with HER2 now have among the best survival rates. This is an example of how a pretty aggressive cancer can become quite treatable.

**Q: How does Herceptin work?**

**A:** Herceptin binds to the HER2 protein and prevents it from relaying a signal that stimulates the cancer cell to divide. It has far fewer side effects than standard chemotherapy because it only disrupts cancerous cells containing HER2. Standard chemotherapy damages cells that are dividing rapidly throughout the body, causing the side effects most people associate with cancer treatment such as hair loss and nausea.

**Q: Herceptin is often considered to be among the first forms of personalized medicine for cancer treatment. Is this a glimpse at the future of cancer treatment?**

**A:** There's no question that personalization is where cancer treatment is going. The "one size fits all" approach

is starting to ebb. In the past, all people with a particular type of tumor would receive the same treatment. In the future, a person will receive the treatment that is most appropriate for the genetic changes present in his or her tumor. That doesn't mean if you treat 100 patients they'll all be treated differently. It means that those tumors will break down into seven or so classes depending on the alterations they contain, and the class will determine which treatment will be most effective. This personalized approach will revolutionize the way that we treat cancer.

**Q: So not all tumors in a particular tissue are the same.**

**A:** No. The challenge for doctors is losing the assumption that cancer treatment is "one size fits all." Breast cancer is not one disease. It's a multiplicity of diseases depending on how the cell became altered. There are many roads that can lead to cancer, which results in many subclasses of cancers. This model will pretty much be the case in most cancers including lung, ovarian, prostate,



Dr. Slamon and his laboratory team work together to merge clinical and basic research to develop new cures and cancer control strategies.

**HER2 that detect growth signals in other types of tumors?**

**A:** Yes. Some lung cancers make an excess of a protein called epidermal growth factor receptor, or

**treatment prohibitive?**

**A:** No, the methodology is moving at a breakneck speed and the costs are dropping for doing this sophisticated technology. By the time researchers have found genetic alterations in many different tumor types, making widespread personalized cancer treatment possible, the technology will be affordable.

**Q: When you began this work did you know that tumors would break down into these genetic subclasses?**

**A:** We didn't know, but we suspected. We started out by investigating genetic alterations that were thought to be oncogenes—genes that, when altered, could promote cancer. Our job was to see if any of those

"American Cancer Society money allowed us to take the first steps to convince federal funders that our approach could work."

colon and others. Each of these is really five or 10 different diseases depending on the genetic alteration present in those cells.

**Q: Are there other proteins like**

EGFR, which is quite similar to HER2.

**Q: Will the cost of finding those genetic alterations in each person's tumor make personalized**

potential oncogenes were altered in tumors from different tissues. If yes, did those alterations correlate with any aspect of the disease? For example, did those genetic changes make the tumor more aggressive or more likely to metastasize?

When HER2 was identified, it looked like it might be a receptor that detects growth signals from the cell's environment. We thought we'd look in the major cancers to see if any carried alterations in that gene. We didn't see anything until we got to a group of breast cancer specimens that contained too many copies of the gene. We found that the tumors containing the HER2 alteration were much more aggressive than normal tumors, making that protein an excellent drug target.

**Q: That's the work that was funded by your first American Cancer Society grant.**

**A:** That's right. That kick-off grant was very small but also very timely. It was Society money that allowed us to do the first work to convince the major federal funders that our approach could work to identify genetic alterations in tumors that could be drug targets. I now have an American Cancer Society Clinical Research Professorship, which is more of a career award to fund ongoing research.

**Q: Herceptin received FDA approval in 1998. How has your work progressed since then?**

**A:** We've taken the same approach to other tumor types, looking for genetic alterations that we can target with drugs. We're looking for

these alterations in several different tumor types, including ovarian and lung. I also think there are still places to go with the HER2 work. HER2 doesn't cause dramatic change all by itself. It's the instigating event but it engages other genes and other pathways in the cell. The question is what are those other genes and pathways and can they be added to Herceptin treatment.

**Q: You have an interest in promoting translational medicine. What does that mean?**

**A:** Translational research marries the clinical medicine with the basic research. In the case of our Herceptin work, the clinical researchers knew that tumors with excess HER2 didn't

behave the same as other tumors, but the question was why. That's where the basic research comes into play. When the basic and clinical researchers worked together, we were able to understand the basic biology and devise an effective new treatment. That type of work translates the basic science into clinical cures and/or cancer control.

This type of translational work has always been my interest and the interest of our lab. It's what made our success with Herceptin a reality. I also think it's where the future of medicine is going.

The American Cancer Society is currently funding 199 breast cancer research grants worth \$109.4 million.

Tubes of HER2-positive breast cancer tissue are prepared for testing. Herceptin prevents the HER2 protein from stimulating cancer cell division.

