On September 10, 2019, the Albert and Mary Lasker Foundation announced that H. Michael Shepard of San Diego-based Biooncology Consultants, Dennis J. Slamon of the University of California, Los Angeles (UCLA), and Axel Ullrich of the Max Planck Institute of Biochemistry in Martinsried, Germany had been awarded the 2019 Lasker–DeBakey Clinical Medical Research Award for their development of the drug Herceptin. Approved in 1998, Herceptin was the first drug of its kind: a monoclonal antibody treatment for cancer. Since its release, Herceptin, which blocks the activation of the \(\text{HER2}\) oncogene and can significantly extend lifespan, has helped treat more than 2.3 million women across the globe whose breast cancers are positive for the \(\text{HER2}\) gene. PNAS spoke with Shepard, who was at the biotechnology company Genentech during the drug’s development, and Slamon about their achievements.

**PNAS:** Dr. Slamon, you graduated with MD and PhD degrees from the University of Chicago in 1975, in part inspired by your family’s pediatrician. How did you get interested in cancer biology?

**Slamon:** At the time, a special virus cancer program at [the] NCI [National Cancer Institute] had begun to identify that there were viral-oncogenes that were carried by a family of acutely transformed retroviruses. These were... potent carcinogenic agents. You could take a healthy animal, inject them with one of these viruses, and they would have tumors, in some cases overwhelming tumors, in 14 days. These oncogenes were fascinating to me, so I decided what I’d start to study was the potential role of these genes in human cancer (1).

**PNAS:** Dr. Shepard, you studied molecular, cellular, and developmental biology at the University of California, Davis and then did your doctoral research at Indiana University. What were you working on when you first joined Genentech?

**Shepard:** When I joined Genentech everybody was cloning genes that could be immediately applied to human health, like insulin and human growth hormone. Around 1984 or 1985, it started to become apparent that those so-called “low-hanging fruit” were getting harder to find, and the company was trying to figure out how to deal with that. They happened to let me initiate a research program that was focused on how tumor cells become resistant to killing by the host immune system.

It was about this time that I learned about the terrible toxicities of therapeutics for brain cancer, in particular carmustine, mustard gas. It dissolves cells. We decided that we wanted to create a cancer drug that would specifically target cancer cells and not normal cells. During our early work, we discovered that most tumor cells are resistant to an anticancer cytokine called tumor necrosis factor (TNF). We were able to link this resistance to the immune system when we showed, together with Hans Schreiber at The University of Chicago, that TNF is the means by which...
macrophages conduct early surveillance against tumor cells (2). Subsequently, we showed this resistance results from overexpression of tyrosine kinases in tumor cells (3).

PNAS: What was your entry point for working with HER2? How did the collaboration begin in the mid-1980s?

Shepard: I gave a seminar on our work relating TNF resistance, macrophages, and tyrosine kinases. Afterward, Robert Hudziak from Axel Ullrich’s [laboratory], showed up in my office one night. He started telling me about this great receptor tyrosine kinase that they had just discovered called HER2 (3).

We screened Hudziak’s monoclonal antibodies and found one (4D5) that could inhibit the growth of HER2-overexpressing tumor cells, and also induce sensitivity to TNF (4). Then, at almost exactly the same time, Dennis published a paper in Science about how overexpression of HER2 can predict shorter survival in breast and ovarian cancer (5). We thought we knew how that happened. Dennis and I got together at that point because by then Axel had left Genentech for the Max Planck Institute. Dennis and I carried that project forward, and it turned out to be successful. My goal was to discover a way to kill tumor cells without hurting the patients and, at this point, I think we had achieved it.

Slamon: We had started to bank tissue collections from various human cancers that were being removed for therapeutic purposes and began molecular analysis on those tumors with, what was at the time, pretty primitive techniques. We were using good old Southern blots and Northern blots and Western blots to study DNA, RNA, and protein extracted from these tumors (6).

We were looking at breast tumors and lymphomas and colon and lung cancers. So, as new probes came in, we would query the new probes against our banks of tumors. I went to a seminar that Axel gave, and he was talking about a couple of new genes that he had recently cloned, HER2 being one of them.

So I met with him afterward for dinner and said, “Would you be interested in a collaboration?” We did not know that we’d find what we found in breast cancer. We just started to walk through the DNA, RNA, and protein from tumor tissue banks and saw an occasional alteration: a deletion here, a rearrangement there, but it wasn’t until we got to the breast cancer panel that we saw this significant signal in about 27% of the cases that indicated that they were seeing an amplification of HER2, and that’s how things got kicked off (5).

PNAS: Did you immediately think about drug development implications, Dr. Slamon?

Slamon: Oh, there was no question that was a thought, and we said so at the conclusion of that first paper in 1987 (5).

PNAS: Were there moments that you felt you were swimming against the tide and had to persist?

Slamon: Mike deserves a lot of credit for keeping the drug alive in the company after Axel left. There was not a lot of enthusiasm in the company at the time. But Mike and a small cohort of his colleagues, a handful of maybe 10 or 12 people, really kept it alive until we kept producing enough data in our [laboratory] and in the company that, ultimately, it convinced people that perhaps it should get another look.

Shepard: The general feeling at the time was that antibodies just could not penetrate solid tumors; they were just too big. It was very important then to show that it was possible. So in collaboration, again with Dennis, we made an FDA [Food and Drug Administration]-approved mouse 4D5, and we brought it down to UCLA. We radiolabeled it in the basement there, and then Dennis administered it to amazing patient volunteers. We did autoradiograms and showed that after a certain amount of time the antibody did localize in patient tumors. Once we saw that, the project team decided to go for it. Between November and January, we had cloned the mouse antibodies, designed, made, and expressed the human antibodies (7).

PNAS: Once you had the human antibody, what were the challenges in scaling up production?

Shepard: At one point, the only thing that was holding up approving the drug was inventing a way to make that much antibody for a global supply. A whole new plant was built, but before that plant was built, the plant in South San Francisco was making the supply, and the guy who was trying to figure out how to manufacture it according to very stringent FDA guidelines was working 18 hours a day, every day, just to make sure it was reproducible.

PNAS: What was the role of patients in developing Herceptin? How did you convince patients to be part of a trial?

Slamon: That’s absolutely the case. As I’ve said, and will continue to say, those patients that participate,
they’re not research subjects or study patients, they’re colleagues in every sense of the word.

Remember, the receptor is a normal gene, and it’s expressed almost everywhere in the body, not just in normal breast tissue, but more importantly in lung, in colon, in kidney, in liver. The concern, quite correctly, is if we start to inhibit this receptor, we would have toxicity.

When we do the informed consent process, we have to tell patients, “We don’t know that this is likely to help you. In fact, the dose is so small, we’re not sure it would help. But it could hurt you because all these normal, critical tissues express the gene.” So, we have to go through this very carefully, trying to do it in a compassionate way and explaining it. Many of the patients would interrupt me and say, “Look. I understand what you’re saying. You’re saying this may not help me, but it could help women later.” And I said, “Yeah, basically.” They all agreed.

3 L. Coussens et al., Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 230, 1132-1139 (1985).