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POTENT EXPERIMENTAL DRUG SHOWN TO SLOW THE GROWTH OF BREAST AND PROSTATE CANCER TUMORS IN MICE

LOS ANGELES, CA (August 12, 2002) – In recent years, laboratory discoveries have led to the development of new drugs designed to target and attack cancer cells, leaving healthy ones intact. One key weapon in this arsenal of new therapies is called Herceptin, a drug that is currently used to treat breast cancer and works by targeting a specific protein that controls cell growth called *HER-2/neu*. But despite the drug's effectiveness, tumors shrink in only the small percentage of breast cancer patients whose cancer cells express an over-abundance of *HER-2/neu*.

Now, laboratory studies conducted by researchers at Cedars-Sinai Medical Center and Genentech have found that a potent experimental drug called 2C4 slows tumor growth in both breast and prostate cancer tumors in mice even when small amounts of *HER-2/neu* are expressed. The findings appear in the August issue of the journal, *Cancer Cell*, and may lead to a new way to treat breast and prostate cancers and other solid tumors.

“We found that 2C4 not only targeted *HER-2/neu*, but that it disrupted cell signaling among the entire HER family of proteins,” said Dr. David Agus, Research Director at the Cedars-Sinai Prostate Cancer Center and first author of the study. “As a result of these lab studies, clinical trials are currently underway to test the safety and effectiveness of 2C4 in patients with breast and prostate cancer, as well as other solid tumors.”

The drug, called 2C4, is a monoclonal antibody, or molecule that enlists the body's immune system to attack foreign invaders, such as viruses or bacteria. Produced by Genentech, Inc., 2C4 is similar to Herceptin in that it targets *HER-2/neu*, a member of the HER kinase family of proteins. The protein sits on the surface of cancer cells and receives signals from “growth factor” molecules within the HER family, which, in turn, stimulate tumors to grow.

“Although *HER-2/neu* is a major target because it plays an important role in tumor growth, it's the growth signaling process that we ultimately want to block,” commented Dr. Agus.

Earlier studies by Dr. Agus' research group had shown that 2C4 blocked signaling activity within the HER network in prostate tumors grown in mice and significantly reduced tumor growth. But in this study, the investigators wanted to see whether 2C4 would disrupt growth signals in breast cancer cells that did not express high levels of *HER-2/neu* and in prostate cancer tumors that were resistant to treatment with hormone blocking drugs.

In the study, the investigators evaluated the effectiveness of 2C4 both in cell-lines established in culture and in human tumors grown in mice. First, the investigators wanted to determine if 2C4 would block growth signaling between HER-2/*neu* and HER-3 as well as between Her-2/*neu* and the epidermal growth factor receptor (EGFR), which is a key growth-signaling pathway. To do this, the investigators first stimulated cancer cells by adding Heregulin or TGF-alpha, stimulants from the HER family of proteins, and then treated the cell lines with either 2C4 or Herceptin. They found that 2C4 was effective in disrupting communication among HER-2 and HER-3 and between EGFR and HER-2, but Herceptin was not.

“This means that 2C4 has the potential to turn off the entire HER-kinase signaling axis in solid tumors, as most solid tumors have some HER-2/*neu* on their cell surface, which is integral in the cell’s signaling apparatus,” commented Dr. Agus.

To determine whether 2C4 inhibited the growth of breast cancer, the investigators injected mice with tumors that expressed both high and low amounts of HER-2/*neu* with either Herceptin or 2C4. They found that Herceptin was just as effective as 2C4 to shrink tumors that expressed high levels of HER-2, in that Herceptin shrunk tumors by 77 percent, while 2C4 shrank them by 80 percent. However, in tumors that expressed low levels of HER-2/*neu*, the researchers found that Herceptin failed to slow cancer growth, while 2C4 inhibited tumor growth in this group by 59 percent.

“These findings suggest that 2C4 may work in breast cancers that do not express large amounts of HER-2/*neu*, which may ultimately mean that we can treat more patients with breast cancer,” said Dr. Agus.

In addition, the investigators studied prostate cancers that do not over-express HER-2/*neu* by evaluating 2C4 and Herceptin in prostate cancer that was either dependent on testosterone to grow or was the type that had become resistant to treatment and now grew independently of testosterone. In the prostate tumors that grew independently of treatment, the investigators found that 2C4 reduced tumor growth by 82 percent, whereas no reduction in tumor size was achieved in the Herceptin treated mice. Alternatively, the investigators found that Herceptin was as effective as 2C4 in significantly reducing tumor growth in testosterone dependent prostate tumors.

“The potential of a biologic agent, such as 2C4, to treat advanced prostate cancer is exciting, as there are presently few alternatives for treatment in these patients,” said Dr. Agus.

A Phase I clinical trial started in October, 2001 at Cedars-Sinai Medical Center to evaluate the safety and tolerability of 2C4 in patients with advanced cancers of the prostate, breast, ovary, lung, colon and other solid tumors. (Cedars-Sinai IRB No. 3691) Although Phase I trials are not designed to test the a drug’s effectiveness for treatment of a disease, results of the phase I study should tell investigators whether to proceed further with subsequent clinical trials.

Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For the fifth straight two-year period, Cedars-Sinai has been named Southern California’s gold standard in health care in an independent survey. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthrough in biomedical research and superlative medical education. Named one of the 100 “Most Wired” hospitals in health care in 2001, the Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.

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