Breast cancer drug pushes colon cancer cells to their death

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A new treatment for colon cancer that combines a chemotherapy agent approved to treat breast cancer and a cancer-fighting antibody is ready for clinical trials, according to Penn State College of Medicine researchers.

More than 150,000 cases of colorectal cancer are diagnosed each year, and about 50,000 people die from colorectal cancer yearly. Currently there are limited chemotherapy treatments for colorectal cancer with little that has been in the pipeline in recent years.

Wafik S. El-Deiry, M.D. Ph.D., American Cancer Society Research Professor and Rose Dunlap Professor and chief of hematology/oncology, and his team have tested lapatinib, a targeted chemotherapy agent currently approved for breast cancer treatment, in a new combination with artificial antibodies that mimic a natural cancer-fighting protein produced in the human body. The monoclonal antibodies mapatumumab and lexatumumab act similarly to TRAIL -- tumor necrosis factor [TNF]-related apoptosis-inducing ligand -- a naturally occurring molecule in the body that tells a cell it is time to die. TRAIL sets a process in motion that targets and shuts down tumor cells and keeps them from spreading.

"These are therapeutic antibodies that are manufactured very efficiently, and given to patients," said El-Deiry, who is also the associate director for translational research, Cancer Institute.

The TRAIL receptors -- death receptors -- on the cancer cells respond to TRAIL by dying. The artificial antibodies act as surrogates of TRAIL by activating the same signaling pathway resulting in tumor cell death.

The monoclonal antibodies have an advantage over TRAIL because they remain active in the body for a longer period of time. TRAIL receptor antibodies last for less than 30 minutes, while the artificial monoclonal antibodies last for about nine days. Although the antibodies can act similarly to TRAIL, they do not completely substitute for TRAIL and ultimately which one gets used in what situation is still being tested in clinical trials. But for the purpose of these new advances either one works.

Lapatinib increases the amount of "death receptor" protein available for TRAIL to do its job -- killing off cancerous cells -- El-Deiry and his colleagues report in this week's issue of *Science Translational Medicine.*

The researchers tested the lapatinib and monoclonal antibody combination in mice. Separately, the two treatments did not increase tumor cell suppression -- but when the drugs were administered together, the researcher found that cell death escalated.

"We have discovered a mechanistic basis for combining these drugs that says one drug upregulates the receptor for the other drug, and maybe now when we combine these two drugs we'll get an even better synergy between them," said El-Deiry. "I think that's probably the most exciting result, to be able to provide a molecular rationale for a new treatment combination for difficult-to-treat advanced colorectal cancers."

The Food and Drug Administration approved lapatinib in 2007 for use as a breast cancer chemotherapy. It blocks two specific types of proteins located on tumor cell surfaces from causing tumors to grow. These proteins are a potent way that tumors are signaled to grow -- and if the

proteins are blocked, there is one less mechanism for tumors to proliferate. However, in the treatment El-Deiry has proposed, lapatinib would be used off-label by increasing a different tumor cell death-inducing protein to help colon cancer patients.

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