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## Some Cancer Drugs May Block Cellular 'Cross Talk' but Not Kill Cancer Cells

***A class of drugs thought to kill cancer cells may in fact block "cross talk" between the cancer cell and normal immune cells, resulting in reduced cancer growth and spread -- a discovery that could significantly alter the way cancer drugs are evaluated in the future.***

Researchers at the University of Colorado Cancer Center demonstrated the discovery in bladder cancer, the fifth most common cancer in the United States. Bladder cancer will kill about 14,000 Americans this year, most of whom will die as a result of the disease's spread to other organs in a process called metastasis.

The scientists showed that endothelin-A receptor antagonist drugs are only effective at blocking the start of cancer spread to other organs, not treating large, established primary-or distant-site tumors. The study was published online Dec. 22, 2010, in the Journal of Clinical Investigation.

"We discovered that these drugs block the 'tumor host interactions' found at sites of metastasis, which is what reduces tumor growth at these sites," said Lead Author Dan Theodorescu, MD, PhD, Director of the University of Colorado Cancer Center and Professor of Surgery and Pharmacology at the University of Colorado School of Medicine. "However, unless the drugs are used early, they have minimal or no effect."

Endothelin-A receptor antagonist drugs block the action of a protein called endothelin 1 [ET-1], thought to be involved in stimulating cancer cell growth and spread. Theodorescu's lab discovered that ET-1 attracts immune cells called macrophages to cancer cells lodged in the lungs. The

macrophages start making factors that stimulate the cancer cells in the lungs to grow -- called metastatic colonization -- which significantly decreases the patient's chance of survival.

In the past decade, two endothelin-A receptor antagonist drugs -- Abbott's atrasentan and AstraZeneca's zibotentan - - have had difficulties in large phase 3 clinical trials. Both drugs were tested in a large number of patients with advanced cancer, and neither drug attained its desired effects. Most likely, Theodorescu said, the drugs were given after the window of opportunity for them to work had closed.

"Had we known this before the trials, we wouldn't have used them to try to reduce large, established tumors," he said. "We would have used them to try to suppress the appearance of metastasis. This new information has important implications for how we test drugs for effectiveness before human use and then on how we select patients in clinical trials with these agents, especially since many types of cancer secrete ET-1."

Neveen Said, Steven Smith, Marta Sanchez-Carbayo and Dan Theodorescu. Tumor endothelin-1 enhances metastatic colonization of the lung in mouse xenograft models of bladder cancer. J Clin Invest., December 22, 2010 DOI: 10.1172/JCI42912