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# Researchers identify genetic markers that predict efficacy of novel cancer drug

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Researchers at the University of Southern California (USC) and USC/Norris Comprehensive Cancer Center have identified genetic markers in cancer cells that predicted the benefit of a novel cancer drug prior to chemotherapy.

Researchers looked at the effect of the drug PTK/ZK--a novel therapy designed to inhibit the development of cancer blood vessels--in combination with chemotherapy. The findings suggest that patients with tumors with a specific gene expression profile may benefit most from the incorporation of this drug into their treatment.

The results of the study will be presented as an oral presentation Saturday, May 31, at the 2008 annual meeting of the American Society of Clinical Oncology (ASCO), held at McCormick Place in Chicago.

"Our research shows that tumor blood vessel formation is critical for tumor growth and that the mechanisms in place controlling tumor blood vessel development are complex," says Peter M. Wilson, senior post-doctoral research fellow at the Keck School of Medicine of USC and lead author of the study. "When we understand how drugs like PTK/ZK work, we can develop treatment strategies to maximize their impact by identifying patients who will benefit most from their use."

The drug regulates angiogenesis, a process of blood vessel formation that provides nutrients and oxygen to cancerous growths, says Wilson. As tumor cells grow, they increase the levels of a key protein called

Hypoxia-Inducible Factor 1Î± (HIF1Î±) in order to deal with the oxygen depletion. HIF1Î± results in the tumor cell producing a number of other proteins that assist in promoting blood vessel growth. One of the most important of these is the vascular endothelial growth factor (VEGF) that is released by the tumor and binds to receptors on blood vessels, promoting their growth toward the tumor.

Disrupting the growth of new blood vessels toward a growing tumor will effectively slow tumor growth and spread, he says.

The PTK/ZK was tested in two large clinical trials in patients with metastatic colon cancer. The drug appeared to work well in a subset of patients who had high levels of serum lactate dehydrogenase (LDH)--one of the major targets of HIF1Î± signaling. Researchers successfully associated genes within this pathway with increased patient benefit from PTK/ZK treatment.

"It is important to note that this is the first study in which we were able to show that gene expression levels (markers) predict efficacy of novel agents targeting tumor blood vessel formation," says Heinz-Josef Lenz, M.D., professor of medicine at the Keck School and the principal investigator on the study. "These markers need to be validated in other clinical trials but are the first step to developing a diagnostic test for clinicians to decide which patients will benefit from inhibitors of the VEGFR."

The data also provides insight into the importance of regulating angiogenesis, and the mechanisms of resistance against new drugs, Lenz says. This information is critical in order to develop more effective and novel drugs using genes as a target.

"The future of colorectal cancer treatment will incorporate such markers in â€˜individualized treatment' where a patient will receive an effective

chemotherapy based on their own genetic makeup and genetic markers within their tumors," Wilson says.

Source: University of Southern California