SOUTHWESTERN NEWS

Media Contact: Toni Heinzl
214-648-3404
toni.heinzl@utsouthwestern.edu

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Antibody combined with cancer drug shows promise against breast tumors

DALLAS – May 15, 2005 – An antibody that targets the blood vessels nourishing tumors significantly reduced breast cancer formation and growth in mice when combined with a current cancer drug, according to researchers at UT Southwestern Medical Center.

Their work appears in today's issue of *Cancer Research*.

"This antibody could enhance the therapeutic efficacy of the drug docetaxel in breast cancer patients," said Dr. Philip Thorpe, professor of pharmacology at UT Southwestern and senior author of the research. "The combination merits further scrutiny as a potential treatment for human cancer."

Docetaxel is one of the most effective chemotherapeutic drugs for treating breast, ovarian and prostate cancer, but its use in treating other cancers is limited by its toxicity.

In their study of mice, Drs. Thorpe and Xianming Huang, assistant professor of pharmacology in the Harold C. Simmons Comprehensive Cancer Center, found the antibody compound 3G4 was effective as a vascular targeting agent (VTA) when used with docetaxel. VTAs are designed to find and destroy blood vessels within cancerous tumors, cutting off their blood supply.

Specifically, mice with human breast tumors treated with 3G4 and docetaxel had a 93 percent reduction in overall tumor growth. The injected breast cancer cells also stimulated the growth of tumor colonies in the lungs, and the drug combination reduced the average number of those colonies by 93 percent, with half of the mice not developing any lung tumors.

The combination of 3G4 and docetaxel was much better than either compound used by itself, Dr. Thorpe said. In mice with breast cancer tumors, growth was suppressed by 50 percent using 3G4 alone and 70 percent for docetaxal alone. The reduction in lung tumor colonies was 82 percent with 3G4 alone and 78 percent with docetaxal alone.

Peregrine Pharmaceuticals is developing a version of 3G4 called Tarvacin for cancer treatment and recently received approval from the Food and Drug Administration for a phase I clinical trial. The compound was discovered by Dr. Thorpe's lab, and Peregrine has a sponsored research agreement with UT Southwestern to further develop the drug.

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"We are currently investigating whether the enhanced therapeutic efficacy with 3G4 and docetaxel extends to other tumor models and other conventional therapies," Dr. Thorpe said.

VTAs like 3G4 target tumor vessels by selectively binding to a certain component in the membranes of endothelial cells that line tumor blood vessels. This component, called an anionic phospholipid, faces the interior of cells in normal blood vessels.

In tumor blood vessels, however, changes in the tumor environment cause the phospholipid to flip inside out and be positioned on the external surface. VTAs then can bind to this exposed phospholipid, causing the body's white cells to attack and destroy the vessels feeding the tumor.

By targeting receptors unique to tumor vessels, vascular targeting agents kill tumors without causing damage to surrounding healthy tissue. They also reduce the risk of side effects by operating at lower doses than traditional cancer therapies because they are effective without needing to penetrate the innermost layer of a tumor.

And, while drug resistance caused by the instability and mutability of cancer cells is a significant problem with conventional therapies that target tumor cells, cells targeted by VTAs do not mutate to become drug resistant, Dr. Thorpe said.

Tarvacin itself has shown promise in mice against cancers in the fibrous tissues, brain cancers and Hodgkin's disease.

Mary Bennett, a UT Southwestern technician, also contributed to the *Cancer Research* study.

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