UT SOUTHWESTERN MEDICAL CENTER NEWS

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Radiation and drug combo helps boost efficacy of lung-cancer treatment

DALLAS – Sept. 1, 2007 – Combining radiation therapy with a drug that helps destroy blood vessels nourishing malignant tumors has been shown in mice to be significantly more effective in treating lung cancer than either approach alone, researchers at UT Southwestern Medical Center have found.

The study, involving human lung-cancer cells implanted in mice, appears in the Sept. 1 issue of *Clinical Cancer Research*.

In the study, Dr. Philip Thorpe, professor of pharmacology at UT Southwestern, and his colleagues found that radiation generates a chemical reaction in the membranes of endothelial cells, which line the blood vessels that feed tumors. The reaction causes membrane components called anionic phospholipids to flip inside out, exposing them. In normal blood vessels, they face the interior of the cell.

Dr. Thorpe's previous research has shown that anionic phospholipids, particularly one called phosphatidylserine, are already flipped inside-out on tumor endothelial cells.

"The flipping is likely due to stress conditions present in the tumor micro-environment, and radiation increases the number of exposed phospholipids," said Dr. Thorpe.

Once they induced more flipping with radiation, the researchers administered bavituximab, a monoclonal antibody that homes in on tumor vessels by selectively binding to the inside out phospholipids. The binding signals white blood cells from the immune system to attack and destroy the vessels feeding the tumor.

In their study of mice, the researchers found that radiation increased the percentage of phospholipids that flip inside out from 4 percent to 26 percent. Treating the mice with bavituximab and radiation therapy together reduced tumor growth by 80 percent and was more effective than administering either treatment by itself.

"About 30 percent of all lung-cancer patients receive radiation and, in this animal model of lung cancer, we found that this monoclonal anitbody improves the efficacy of radiation therapy without the toxicity seen in other chemotherapeutic drugs," said Dr. Thorpe. "It's a win-win."

Bavituximab was created in Dr. Thorpe's lab is currently being tested in clinical trials in the

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U.S. and India for its effectiveness against solid-tumor cancers.

Peregrine Pharmaceuticals Inc. has exclusively licensed bavituximab from UT Southwestern and has a sponsored research agreement to further explore clinical uses of the drug. Dr. Thorpe is a consultant to and has an equity interest in the company.

Lung cancer is the leading cause of cancer death in the U.S. About 213,000 cases of lung cancer will be diagnosed this year and 160,000 people are expected to die from the disease, according to the National Cancer Institute.

"Although there are current therapies, the five-year survival rate for lung-cancer patients remains at only 15 percent," Dr. Thorpe said. "This tells us that there is an urgent need to develop new treatment strategies."

Vascular targeting agents such as bavituximab kill tumors without causing damage to surrounding healthy tissue. They cause fewer side effects than conventional cancer drugs that kill rapidly dividing normal cells along with the cancer cells.

Because Peregrine is already testing bavituximab in cancer patients, Dr. Thorpe said he expects new clinical trials using a combination of bavituximab and radiation therapy to start soon.

Other UT Southwestern scientists involved in the study were Drs. Jin He and Troy Luster, both postdoctoral researchers in pharmacology.

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