Drug That Crosses Blood-Brain Barrier Reduces Formation of Brain Metastases in Mice

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(PhysOrg.com) -- The drug vorinostat is able to cross the blood-brain barrier and reduce the development of large metastatic tumors in mice brains by 62 percent when compared to mice that did not receive the drug, according to a new study. In humans, the drug has been approved by the U.S. Food and Drug Administration for the treatment of a cancer called cutaneous T-cell lymphoma but can be used experimentally to study its effectiveness against other cancers. This research, by investigators at the National Cancer Institute (NCI), part of the National Institutes of Health, and their collaborators, appears online Sept. 29, 2009, in *Clinical Cancer Research*.

For people, while various therapies are improving the survival of breast cancer patients, the incidence of breast cancer spreading to the brain is increasing. Brain metastases of breast cancer have proven to be largely untreatable because the blood-brain barrier, which arises from the specialized structure of blood capillaries in the brain, severely limits drug access and many drugs are actively transported out of brain at this barrier. Consequently, the one-year survival estimate for breast cancer patients after a diagnosis of brain metastasis is only about 20 percent.

Vorinostat has been found to slow the growth of primary tumors of several different types of cancer in mice. Previous studies have suggested that the drug can be taken up by the brain, although little was known about its effects on metastatic tumors. Therefore, to study the

effect of vorinostat on the formation of brain metastases, scientists used a mouse model of human breast cancer. Human breast cells were cultured in the laboratory and were injected into mice with compromised immune systems. The breast cancer cells then migrated to the brain, forming metastases.

"Drugs that can cross the blood-brain barrier and reduce the size and incidence of metastatic tumors are urgently needed," said Patricia S. Steeg, Ph.D., study author, Center for Cancer Research, NCI. The researchers found that vorinostat was absorbed readily into normal mouse brains, and accumulation of the drug was up to three-fold higher in some metastases treated with this drug when compared to surrounding brain tissue. Vorinostat also reduced the development of tiny tumors (micrometastases) in mice by 28 percent when compared with mice that did not receive this therapy.

The ability of vorinostat to reduce metastatic lesions in the brain was linked to a novel double-barreled mechanism — the drug can cause breaks in both strands of a DNA helix and can also lower the activity of a DNA repair gene called Rad52. The researchers hypothesize that the inability of the cancer cells to repair DNA damage would then slow the rate of tumor cell metastasis.

In June of this year, several researchers affiliated with this study published a paper in Molecular Cancer Therapeutics showing that vorinostat could enhance the effect of radiation therapy in mice with brain cancer metastasis. Mice that received implants of human breast tumors in their brains lived the longest after treatment with both vorinostat and radiation, demonstrating that the drug enhances the sensitivity of cancer cells to radiation therapy. "Taken together with our current finding, researchers have now established a preclinical basis for testing this drug in clinical trials in humans," said Steeg.