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Antibiotic slow growth of bladder, breast cancer cells

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Researchers at the Johns Hopkins University School of Medicine have discovered that nitroxoline, an antibiotic commonly used around the world to treat urinary tract infections, can slow or stop the growth of human breast and bladder cancer cells by blocking the formation of new blood vessels. The results, appearing in the Dec. 15 issue of the *Journal of the National Cancer Institute*, suggest that nitroxoline shows promise as a potential therapeutic agent.

“Angiogenesis, the growth of new blood vessels, plays an important role in tumor growth and metastasis, so inhibiting angiogenesis is a promising strategy for developing new anticancer drugs,” says Jun O. Liu, Ph.D., a professor of pharmacology and molecular sciences at Johns Hopkins.

The research team tested more than 177,000 chemical compounds and drugs for their ability to block the activity of a protein—called MetAP2—implicated in the formation of new blood vessels. Previous research had shown that inhibiting MetAP2 leads to a cascade of molecular events that ultimately prevents vessel-forming cells from growing. The team first tested 175,000 chemicals for their ability to block MetAP2 activity. Of the 294 chemicals found to reduce MetAP2 activity by at least half, nitroxoline stood out in its ability to inhibit MetAP2 by more than 99 percent at low and safe concentration. “It was one of the most potent hits we identified from this chemical compound library,” says Liu.

At the same time, the team also tested 2,687 FDA-approved or

commonly used drugs in the Johns Hopkins Drug Library for their ability to stop blood vessel-forming cells from growing. The research team grew human umbilical vein endothelial cells, or HUVEC, in tiny wells and treated each well with a different drug from the Library. Of the 210 drugs that inhibited HUVEC growth by at least half, nitroxoline again stood out; it inhibited cell growth by 95.5 percent at the same concentration that blocked MetAP2.

The team then tested nitroxoline for its ability to stop blood vessel growth in mice. They treated 10 mice with growth factors that encourage new vessel growth, then treated half with nitroxoline and the other half with only salt solution for comparison. After 10 days they discovered that untreated mice on the average developed 48.6 new vessels per microscope field — the area visible when looking at the tissue through a microscope — --whereas nitroxoline-treated mice on average developed only 20 new vessels per microscope field.

“Because nitroxoline showed such a substantial inhibitory effect, we moved on to see if it would have an effect on tumors in mice,” says Liu.

Mice carrying transplanted human breast or bladder cancer cells were treated with nitroxoline injections every other day for a month in the case of breast cancer or every day for two weeks in the case of bladder cancer. Nitroxoline treatment reduced breast cancer cell tumor volume by 60 percent and bladder cancer cell tumor by more than 50 percent.

“There are limitations of this study, but we find the results encouraging enough to pursue further study of nitroxoline for preclinical and clinical use in treating bladder carcinomas,” says Liu.

Provided by Johns Hopkins University

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