

AZT shows promise as breast cancer fighter

The anti-AIDS drug AZT functions like a Trojan horse. Once inside a rapidly dividing HIV-infected cell, it prevents the virus from making a copy of its genes. AZT displaces thymidine, one of the four building blocks used to construct the virus' DNA. Thus, the invading virus cannot use such a cell to spread.

A similar strategy would seem to work against cancer cells, which also synthesize DNA to divide rapidly, but scientists have had only spotty success using AZT against the disease in lab studies. Now, a study in rats indicates that AZT may have another Trojan horse in its army: The drug also appears to substitute for uridine, another component of the cell's genetic machinery. When AZT displaces both compounds, it seems to fight breast cancer.

That's the hypothesis raised by chemist Carston R. Wagner of the University of Minnesota in Minneapolis. Wagner was using AZT last year as a control substance in tests of new compounds against breast cancer, when he found, to his surprise, that AZT worked better than the compounds he was studying.

Subsequent tests using AZT against breast cancer cells in test tubes and then in rats with breast cancer are showing the same outcome. The drug homes in on the cancer cells and stymies their growth. "It is quite amazing," Wagner says.

The reason for AZT's attraction to breast cancer cells remains a mystery, but if further study supports these findings, the drug will have come full circle. Discovered by biochemist Jerome Horwitz in 1964, AZT, also called zidovudine, initially seemed like a natural cancer fighter. Despite its ability to infiltrate cells, however, the drug proved useless against leukemia in mice.

It was ignored until the AIDS epidemic erupted in the 1980s, when AZT was found to have potent antiviral properties.

In the last 7 years, AZT has occasionally been tested against cancers. It was used against colon cancer in the laboratory in combination with other drugs, with mixed results. In three other, small-scale studies, patients took AZT mixed with other medications to fight advanced cancer, including breast cancer. These tests showed somewhat positive, but inconclusive, results and attracted scant attention.

"I just couldn't believe this compound had been around for so long and hadn't been tested [specifically] on breast cancer," says Wagner. He then collaborated with Yusuf J. Abul-Hajj and others at Minnesota to do just that. Their study appears in the June 15 *CANCER RESEARCH*.

In their initial test-tube experiments, AZT failed against leukemia cells but worked against breast cancer cells. The researchers then injected 20 rats with a cancer-causing agent called N-MNU. The rats developed breast cancer. Of the 10 that developed small tumors, half were given a small dose of AZT—equivalent to the minimum amount per kilogram of body weight that AIDS patients typically get—and half got five times that dose. The five rats that developed larger tumors got the higher dose. The remaining five rats received placebo injections containing no AZT.

Striking differences emerged. Tumors doubled in size weekly in the rats getting the placebo, leading to death after 3 weeks. In the rats with small tumors, AZT at either dose cut the rate of tumor growth by 80 percent after 1 week and almost completely by 7 weeks. Some of the tumors even shrank. The tumor growth rate slowed markedly in the rats with larger tumors.

While research in rats doesn't always translate directly to people, Wagner's team has come up with "intriguing results," says Robert Yarchoan, chief of the HIV and AIDS malignancy branch of the National Cancer Institute in Bethesda, Md. "Given the doses [of AZT] he's using, it

would be worth exploring further.”

The Minnesota researchers are now trying to synthesize compounds similar to AZT in hopes of learning why it seems to work better on breast cancer than on other cancers.

—*N. Seppa*