

## Prostate enzyme triggers cancer drug

Using a new drug that enlists the aid of an enzyme naturally abundant in the prostate gland, researchers have reversed advanced prostate cancer in mice. If the drug similarly thwarts the cancer in men, it would be the first to employ the enzyme, called prostate-specific antigen (PSA), as anything more than a blood-test indicator of cancer risk.

Prostate cancer persists in many patients after radiation treatment and surgery to remove tumors. Because the male hormone androgen seems to abet prostate-tumor growth, physicians frequently administer hormone suppressants as well. But the drugs' effectiveness wanes after a year or so, often leaving a patient defenseless against the disease's spread.

Researchers at Merck Research Laboratories in West Point, Pa., tested the new drug, called L-377,202, on 110 mice in which they had implanted tumor cells already resistant to hormone suppressants. When these cells grew into tumors weighing 1 gram, some mice received a 5-week course of injections of the new drug and others received doxorubicin—a potent cancer fighter.

Doxorubicin kills tumor cells but also can cause heart damage. L-377,202 is a combination of doxorubicin and a protein fragment called leucine-doxorubicin, a less-harsh chemical. Because PSA cleaves L-377,202 into these components, Merck scientists suspected the new drug could be a better-targeted, safer form of doxorubicin.

In the new study, reported in the November *NATURE MEDICINE*, the tumors in 50 mice shrank slightly over 11 weeks following treatment with conventional doxorubicin. However, 28 of these mice died from side effects of the drug, says study coauthor Raymond E. Jones, a molecular biologist at Merck.

In contrast, 60 mice given L-377,202 showed a sharp reduction in average tumor size. Overall, L-377,202 was about 15 times better than doxorubicin at inhibiting tumor growth in the mice, the researchers report. None of the mice treated with L-377,202 died.

The researchers expected doxorubicin produced from L-377,202 to materialize mostly near tumor cells, where PSA is most abundant. This apparently happened, says study coauthor Deborah DeFeo-Jones, also a molecular biologist at Merck. The minimal heart damage observed in the mice suggests that L-377,202 produced little doxorubicin in the blood, she says. This makes sense because PSA's action in the blood is inhibited by other chemicals, says DeFeo-Jones.

"I think this is potentially a major development," says Stephen B. Strum, an oncologist and medical director of the Prostate Cancer Research Institute in Los Angeles. "The whole idea of PSA as a functional substance has been pretty much downplayed," he says.

The technique might work especially well in early prostate cancers, says Herbert A. Fritsche, a clinical chemist at the M.D. Anderson Medical Center in Houston. However, he notes that while these implanted tumor cells secreted PSA, some aggressive prostate cancer cell lines don't, and that could limit the drug's utility.

Merck has now begun testing L-377,202 on prostate cancer patients.

—N. Seppa