Tamoxifen clears hurdle to preventive use

Healthy women at high risk of developing breast cancer should be allowed to take the drug tamoxifen as a means to cut the short-term risk that they will develop the malignancy. That was the recommendation last week of an 11-member expert panel convened by the Food and Drug Administration.

Some European researchers view the approval as premature, however, and worry that it might jeopardize evaluations of long-term risks of the treatment.

Currently, the only approved use for tamoxifen is to prevent tumor recurrence following breast-cancer surgery. However, tamoxifen's manufacturer—Zeneca Pharmaceuticals of Wilmington, Del.—recently petitioned FDA for approval to label and market the 25-year-old synthetic hormone for a new use, citing a recent 4-year, $50 million National Cancer Institute (NCI) cancer prevention trial.

Some 6,600 women took the drug. Though all were healthy, each faced a high risk of breast cancer because of age, family history, or premalignant breast changes. Compared with an equal number of at-risk women who got a placebo, women in the treatment group developed 45 percent fewer breast cancers (SN: 4/11/98, p. 228). FDA's Oncologic Drugs Advisory Committee (ODAC) reviewed these data before advising FDA to approve tamoxifen for prophylactic use.

Panel member Kathy S. Albain, a medical oncologist from Loyola University Medical Center in Maywood, Ill., says ODAC's acceptance of prophylactic use of tamoxifen "was a landmark vote," clearing the major hurdle to FDA approval. "There are sufficient numbers [of women] at increased risk that we wanted to make sure that [the drug] was available for them."

However, she adds emphatically, her panel's endorsement comes with major qualifications. The panel found insufficient data to demonstrate that tamoxifen can prevent breast cancer—despite claims to the contrary earlier this year. The drug may only delay a nascent tumor's growth.

Also, the panel couldn't define which women stood to benefit from the drug. Nor could it assess whether treating cancerfree women offers "a favorable benefit-risk ratio." There has not been long enough follow-up of the treated women to resolve this, Albain says.

Several researchers argue that in the absence of longer follow-up, it is premature to prescribe tamoxifen for healthy women.

Many studies have shown that tamoxifen, which has been used against breast cancer in a variety of prophylactic and therapeutic trials, spawns increased rates of endometrial cancer (SN: 2/26/94, p. 133). Among women who take tamoxifen before menopause, these cancers often appear long after treatment is over—as much as 8 years later, according to a new 14-center study led by surgeon Hervé Mignotte of Centre Léon Bérard in Lyon, France. These women had "lower survival rates" because their endometrial cancers were "more advanced" than those in women treated with other therapies, according to a report in the July JOURNAL OF CLINICAL ONCOLOGY.

Previously, two U.S. research groups had also found hints that the drug causes unusually aggressive endometrial cancers (SN: 9/25/93, p. 207).

Mignotte expects French demand for tamoxifen by healthy women to grow if FDA approves the new use—despite a recommendation by two French cancer-research societies that doctors should resist prescribing the drug prophylactically.

Moreover, notes Trevor J. Powles at the Royal Marsden NHS Trust hospital in Surrey, England, the excess breast cancers in the nontamoxifen group in the NCI trial tended to be treatable—"and curable." In that case, he asks, does it pay to expose large numbers of women to the drug treatment's side effects—which include blood clots, loss of bone density, and eye and memory problems—so that a few are spared a treatable cancer?

His research suggests that women who face the highest genetic risk of breast cancer, owing to BRCA-gene mutations (SN: 6/21/97, p. 386), may be helped least by the drug.

Without long-term follow-up, which the NCI study was not designed to offer, there will be no assurance that a short-term reduction in cancer incidence doesn't revert to "unacceptable" treatment-related mortality down the road, says Powles. He also worries that European funding for his ongoing, long-term study (SN: 7/18/98, p. 37) may dry up if FDA is already satisfied that the drug is safe enough for healthy women. *—J. Raloff*

A sugarfree beet that tastes just as sweet

Dutch researchers have grown genetically engineered sugar beets that transform their sucrose into fructan molecules, which serve as a low-calorie sweetener. The beets could become an inexpensive way to manufacture fructans commercially.

Fructans are polymer chains of the sugar fructose, but human enzymes can't easily digest them, so they contribute few dietary calories. Today, manufacturers either synthesize fructans biochemically or isolate them from plants such as chicory and Jerusalem artichokes. Fructans haven't found a large market, however, because the manufacturing methods are expensive and the plants yield little product.

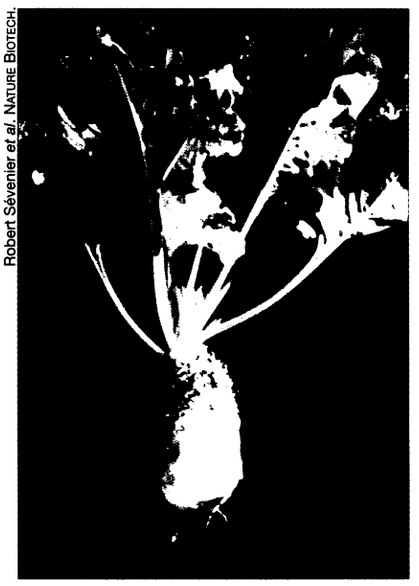
Sugar beets, on the other hand, churn out lots of sucrose. Hoping to take advantage of the beets' efficient biochemical machinery, researchers from the Netherlands Organization for Agricultural Research in Wageningen transplanted the Jerusalem artichoke gene for making fructans into the sugar beet. The gene codes for an enzyme that converts molecules of sucrose, each consisting of one glucose and one fructose unit, into fructan polymer chains. The team reports its achievement in the September NATURE BIOTECHNOLOGY.

The genetically altered beets transform 90 percent of their sucrose into short fructans, each being two to four fructose units in length, the ideal size for sweeteners. "Through addition of extra fructan genes, sugar beets can also be induced to synthesize other fructans, like long-chain, branched fructans," says study coauthor Andries J. Koops. "All these fructans may have different applications or market potentials."

Larger fructans "have an interesting mouth feel, so you can use them in emulsions instead of fat," says Martina McGloughlin, director of the biotechnology program at the University of California, Davis. They could find uses in low-calorie ice cream and spreads, she suggests (SN: 9/5/98, p. 157).

The Dutch team also is pursuing the "plant as factory" concept for other food products and chemicals, Koops says.

It remains to be seen whether fructan beet production can be scaled up to commercial levels, McGloughlin cautions, but getting efficient synthesis is "a big step forward." *—C. Wu*



Robert Sévenier *et al.*, NATURE BIOTECH.

A genetically engineered sugar beet that makes fructan, a low-calorie sweetener.