CANCER THERAPY

Surprise! A Fungus Factory For Taxol?

In a secret location in an old growth forest in northwestern Montana, there stands a yew tree unlike any ordinary yew. But wait. As trees go, even the ordinary yew is extraordinary: Its bark yields the anticancer drug taxol. Problem is, the quantities yielded are tiny compared to the potential market. Until recently, environmentalists have been concerned that the yew species could be wiped out for the sake of human lives. But thanks to alternative sources of taxol, such as synthesis of the drug from a chemical precursor found in the needles of European yews, the tree no longer is in danger of becoming extinct, says the company that sells taxol, Bristol-Myers Squibb of New York. Except that the new sources of taxol have done nothing to drive down the drug's price. Which brings us back to that extraordinary Montana yew.

WILLIAM HESS/BRIGHAM YOUNG UNIVERSITY

Plant pathologist Gary Strobel and chemist Andrea Stierle of Montana State University stumbled across the tree 2 years ago, and to their delight, nestled in the folds of the bark, they found a fungus that appeared to be producing taxol on its own. Indeed, after 2 years of careful work, the researchers report (see p. 214) that the fungus produces taxol even after it's been removed from its host. Assuming this discovery holds up, the end result could be enormous fermentation tanks producing vast quantities of (relatively) cheap taxol. Beams Gordon Cragg, chief of natural products development at the National Cancer Institute (NCI): "This is just an incredible discovery. It has quite tremendous implications for taxol production."

Cancer researchers will be excited by this study because in 1989 researchers at Johns Hopkins showed that taxol could greatly shrink tumors in about 30% of women whose ovarian cancers resisted other therapies. Just last January, the Food and Drug Administration (FDA) approved taxol for this treatment after only 5 months of study—a record. And taxol's promise extends beyond ovarian cancer to breast, head, and neck tumors. In fact, Bruce Chabner, director of NCI's division of cancer treatment, estimates that the number of U.S. patients receiving taxol could grow from 15,000 to more than 50,000, if FDA approves it as a treatment for breast cancer.

But if taxol is to reach that kind of a mass market, the price may have to come down. Representative Ron Wyden (D–OR), in a January hearing of the House subcommittee on regulation, business opportunities, and energy, attacked NCI and Bristol-Myers, which exclusively handles taxol, on the grounds that the price—$986 per treatment cycle—is too high. Consider this: Any patient following NCI guidelines would likely require a minimum of three treatment cycles simply to determine if the taxol was working, and if the taxol proved effective, as many as 10 cycles would be prescribed. Multiply this by the number of people worldwide who might receive taxol—Chabner estimates "several factors greater" than the 50,000 U.S. patients—and the total societal bill could be in the billions of dollars. Something had to be done.

DENNIS BODILY

Host and guest. A yew and its promising parasite *(left)* were found by Strobel and Stierle.

Anatomy of a breakthrough. Don't tell congressional research budget cutters, but nothing would have been done—in Strobel's shop, anyway—if he had been getting the funding he was used to. In July 1991, Strobel was running out of money to pay postdoc Andrea Stierle. Stierle had made a charmed discovery in the mid-1980s, when she found not 200 yards from her back door a fungus that produces a toxin that specifically kills the spotted knapweed, a pesky weed rampant in Montana. But now funding was looking so grim for Stierle that she was willing to try to beat the odds—she recalls thinking they were 10 million to 1—to find a taxol-producing organism.

Strobel has had plenty of experience ferreting out organisms that produce compounds capable of fighting plant diseases or killing weeds, and so he too knew the odds. But he also knew that the notion that both a fungus and a plant (a host and parasite) could produce taxol had several precedents. To name one, in the 1930s, Japanese plant scientists had discovered that a particular species of fungus, like its host (rice plants), could make gibberellins, diterpenoid hormones that regulate plant growth and development. Taxol, it turns out, also is a diterpenoid.

So Strobel gave Stierle a reluctant green light and that summer, Stierle and her husband, chemist Donald Stierle of the Montana College of Mineral Science and Technology, began taking strolls in the Montana woods. The result: samples of 50 fungi, including one from a certain yew tree whose location, not surprisingly, they won't reveal. Soon after Stierle began assaying the fungi for taxol, she thought she'd found a winner. Even Strobel, who hadn't worked much at the bench since the late 1970s, worked day and night to ensure that, among other things, the trace amounts of taxol in the fungal cultures weren't a contamination from the tree.

And when he wasn't in the lab, Strobel was out drumming up funding to keep the project going. The search was complicated by the fact that, to many in the scientific community, Strobel wears the tag "maverick." A respected plant pathologist, he became a national figure in 1987 when he ran afoul of the Environmental Protection Agency (EPA). Without obtaining an EPA permit, Strobel injected a genetically modified bacteria into elm trees as a potential cure for Dutch elm disease, which has ravaged U.S. elms. The incident, which stirred a debate over the scope of biotech regulations, ended when Strobel, weeping as he wielded a chain saw, cut down and burned his 14 experimental trees. Given this history, it may be no surprise that he struck out with NCI. But in early 1992 he managed to obtain small grants from the National Science Foundation and a local chapter of the American Cancer Society.

Several months later the Montana researchers had not only nailed down their discovery but triggered some fascinating speculation into fundamental ecological theory. Take taxol's chicken-or-egg question. NCI natural-products chemist Kenneth Snader puts it this way: "Nobody can demonstrate whether the fungus or tree had the machinery to produce taxol first." But, he adds, scientists speculate that because taxol has some antifungal properties, yew trees may produce it to ward off parasitic fungi. The fungus may have inadvertently picked up from the yew tree a copy of the gene (or genes) for taxol, Strobel says.

Speculations aside, Strobel and Stierle

have learned that their favorite fungus is an entirely new species with its very own genus. (The researchers named it *Taxomyces andreanae*, after codiscoverer Andrea Stierle.) They also learned that distantly related species of fungus couldn't produced taxol. Having resolved those questions, they moved on to the one that would be crucial if their find were ever to have any commercial significance: What if their fungus was incapable of manufacturing taxol when removed from its host?

Their concern was justified, since such an outcome isn't unheard of in fungi that live in a specific host. One example is a fungus that, when removed from its host—sugarcane—gradually loses its ability to produce a toxin that attacks sugarcanes. Mindful of this danger, Strobel's group stored their fungus on yew tree tissue. To their relief, over many fungal generations taxol production held stable.

Not all the news from Strobel's lab has been good, though. Cultures of the fungus so far produce only nanograms of taxol, while most other native wild strains of fungi that have been developed as drug sources started out producing milligrams of the target compound. Still, Arnold Demain, a Massachusetts Institute of Technology industrial microbiologist, argues that learning how to supply enough oxygen to the fungal cultures and improving the genetics of the strain are possible, and, depending "on who the sponsor is, and how much money somebody's willing to put into it," could produce a viable strain in about 5 years.

A hot commodity. That possibility had made the Montana group's fungus a hot commodity long before they'd even written their scientific paper. With a commercial payoff possible, in March 1992 the team filed patent applications on fungal production of taxol. In January of this year, Strobel and Roger Flair, president of the Bozeman-based Research and Development Institute, a nonprofit that handles Montana State University's patent negotiations, invited several pharmaceutical firms to negotiate licensing rights.

Among those bidding for the rights, *Science* has learned, are ESCAGenetics, Lederle Laboratories, Pharmagenesis, and the heavy hitter—Bristol-Myers. Since Bristol-Myers has a built-in conflict-of-interest where methods that might reduce the price of taxol are concerned, some researchers have tried to persuade Montana State to cut them out of the bidding. For the moment everyone's still in. But, as Flair says: "Our mission is not to let anyone quash this discovery." Given the discovery's potential, it's unlikely that anyone will be able to keep it down for long.

–Richard Stone

JAPAN

At Tokyo University, a Parting Shot

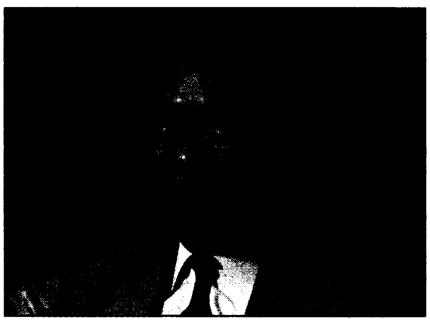
The recent retirement of the president of the University of Tokyo brought more than the usual warm, congratulatory sentiments. Along with warm feelings, departing president Akito Arima left behind a tough critique of the university's physics department, which he had commissioned from an international panel of scientists. Announced on 30 March, the report found that facilities at the university are "miserable and utterly unacceptable." The department's own structure and teaching style also came in for a stiff review.

Arima, himself a physicist, intended the report to be for the good of his university's physics department and other Japanese academic researchers. A long-time critic of the dismal funding levels and physical conditions at the national universities, Arima instigated the review late last year, expecting that the committee would echo his own complaints. The resulting publicity, he hoped, would goad the Ministry of Education, Science, and Culture (Monbusho) into finally doing something about Japan's neglected university system.

Arima opened his own department, the foremost in Japan, to scrutiny because he hoped its prominence would make the committee's findings all the more striking. The 10 prominent scientists—among them Jean Audouze, science adviser to the French government, physicist David Pines of the University of Illinois, biologist Sidney Brenner of Cambridge University, and several prominent Japanese researchers, including Nobel laureate Leo Esaki—agreed, calling the department "outstanding…in both quality and quantity of research output." It has achieved that status, says the report, "in spite of…handicaps and deficiencies" in research facilities and equipment and in teaching space.

The panel's criticisms of the physical plant were no surprise. Just last year analyses of conditions at the universities, published in special issues of *Science* (23 October 1992) and *Nature* (15 October 1992), prompted wrenching debates in Japan. But besides calling for more government investment, the committee identified some improvements the department could make on its own.

The panelists concluded, for example, that "the students' curriculum and research programs are too rigidly constrained, allowing little flexibility or freedom of choice. The interaction and communication within the department is also quite poor." Students should be given more freedom in their curricula, said the panelists; the best young researchers should be promoted quickly, and graduate students—most of whom have part-time jobs—should be awarded fellowships so they can concentrate on research. The committee also urged the department to open its doors to women and foreigners—there are none on the faculty—and internationalize itself by teaching some classes in English and encouraging students to travel abroad to conferences.



EISI MITAZAWA/BLACK STAR

Self-critic. Tokyo's Akito Arima.

This latest volley of criticism has shaken officials at Monbusho, says Ikuo Kushiro, the dean of the university's faculty of science, although the agency has not yet made a formal statement about the evaluation. Whatever the tone of the agency's response, however, Kushiro says a quick bailout for Tokyo and other universities looks unlikely in the face of Japan's deep recession.

Limitations on funds will also postpone some of the improvements suggested in the physics department, says Kushiro, including the creation of more assistant professorships and a substantial increase in the number of postdoctoral fellows. But he says the university will try to make the curriculum more flexible and encourage interactions between professors and students.

As the university and the government struggle to deal with the fallout from the evaluation, the Tokyo University faculty has just elected another researcher to succeed him: Hiroyuki Yoshikawa, an expert on intelligent manufacturing. To Genya Chiba, vice president of the Research Development Corp. of Japan, that move suggests that the university is serious about improving its research programs. "This is one of the first times that the presidency of [Tokyo University] has gone to people in technical fields two times in a row," says Chiba. And that departure from tradition in tradition-oriented Japan, says Chiba, may reflect the fact that faculty at Tokyo and other universities "feel that the universities are in the middle of a crisis." If so, it is a crisis Akito Arima's razor-sharp farewell message has only served to highlight.

–Fred Myers

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