cer in the B14 trial died of the disease. This appears to support a finding by Lars E. Rutqvist of Sweden's Karolinska Institute, who reported in 1989 that breast cancer patients receiving doses of tamoxifen twice as large as those given to Fisher's group had an increased risk of dying of endometrial cancer. But it is at odds with the old consent forms, which noted that "no deaths from uterine cancers were reported," and uterine cancers that occurred in tamoxifen trials "have been caught at an early stage." Abrams and Fisher have now recommended that the forms should state that "uterine cancer is a potentially life-threatening illness," and that "the level of increased risk of uterine cancer associated with tamoxifen is still uncertain."

Fisher maintains that these changes are just routine revisions to the consent forms. "This would be done if aspirin were being used for this trial and something unexpected were seen with aspirin," says Fisher. This opinion is shared by NCI's Ford. But outspoken critics of the tamoxifen trial aren't likely to be mollified. Richard Love, a University of Wisconsin cancer researcher, says that in premenopausal women, the risks of lethal blood clots and endometrial cancer are likely to exceed expected benefits such as improved cardiovascular health and reduced osteoporosis. Younger women aren't normally at high risk for these ailments. The prevention trial, Love says, is "absolutely premature for premenopausal women."

Concerns about the risks involved in the trial, in fact, had already led some BCPT investigators to modify their recruitment policies and protocols. Carol J. Fabian of the University of Kansas says that her institution discourages premenopausal women from enrolling in the trial, but "we certainly wouldn't refuse" them. Victor Vogel, BCPT director at the M.D. Anderson Cancer Clinic in Houston, Texas, encourages all women in the trial with an intact uterus to have an annual endometrial biopsy.

Women participating in the trials won't know the complete details of the new B14 findings and the new risk-benefit calculations until they are published, however. And that concerns some researchers. Rutqvist, noting that Fisher last published data from the B14 trial in 1989, asks why the "largest double-blind tamoxifen study in the world [B14] does not publish its complete data on secondary cancers?" And toxicologist Michael DeGregorio of the University of Texas Health Sciences Center in San Antonio, who testified to Congress about the risks of tamoxifen, says that if the Fisher group has new data on secondary cancers, the information "should be published as quickly as possible so that all women can consider it before going on the preventive trial."

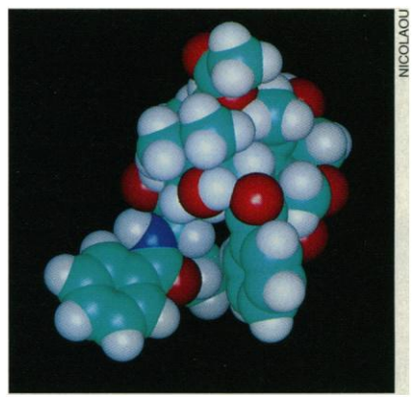
–Lisa Seachrist

DRUG DEVELOPMENT

Race to Synthesize Taxol Ends in a Tie

Two groups this week announced a complete synthesis of taxol, the extract of the Pacific yew tree that has been in the news as a promising but scarce cancer drug. The announcements, by groups led by K.C. Nicolaou of the Scripps Research Institute and Robert Holton of Florida State University, mark a photo finish to a race in which the stakes have changed repeatedly.

The complex structure of taxol (a name trademarked by Bristol-Myers–Squibb) has been a tempting goal for synthetic chemists ever since hints of its anti-cancer potential emerged more than 20 years ago. The promising results of 1991 clinical trials in breast cancer patients raised the stakes because, at that point, the only source of the drug was the bark of the endangered yew tree. Now, thanks to tree-sparing methods for extracting taxol precursors from needles instead of bark, then modifying them into taxol-like compounds, "there's plenty of taxol," says Holton (*Science*, 17 April 1992, p. 311). But there was still good reason to look for a synthesis technique: The ability to make the molecule from scratch means that chemists will be able to concoct modified "designer" taxols to pin down how the molecule works and improve on the natural version, say both Holton and Nicolaou. "Nature makes compounds for unknown reasons—and they are not necessarily the best drugs," says Nicolaou.



No need for yew. The taxol structure.

In this case, there are good reasons to improve upon nature. While natural taxol has been shown to shrink cancers of the ovary as well as the breast, it is far from a wonder drug. Poor solubility makes it hard to administer, and tumor cells tend to develop resistance to the drug. "We might find one that is less toxic and more effective than taxol," says Nicolaou. "There are a lot of advances to be made."

Before they could think about tinkering with the natural molecule, however, chemists first had to mimic it, and that was "a formidable synthetic challenge," as Nicolaou puts it. Chemist Paul Wender of Stanford University, who is also working on synthetic taxol, explains that the structure is "congested" with different functional groups, making it hard to predict the results of any given step. "Modifications in one part lead to problems and changes in a seemingly remote part," he says.

Holton started with the off-the-shelf compound camphor and Nicolaou with similarly simple ingredients. From there, the two techniques follow quite different pathways, but both take upwards of 30 steps. Following these tortuous paths was a matter of painstaking trial and error, redesign, and repeated failure.

At this early stage, neither group's method is likely to be commercially viable, says National Cancer Institute chemist Matthew Suffness. "Anything with more than 25 steps is not practical," he says. Even so, Holton argues that his technique, which he describes in next week's *Journal of the American Chemical Society*, is superior because its yield of synthetic taxol, equivalent to 4 to 5% of the starting materials, is much higher than the 0.05% reported by his competitor.

Nicolaou, who describes his achievement in this week's *Nature*, responds that he calculates the yield for every step while Holton calculates his at an intermediate point in the synthesis. A comparison made on the same basis, says Nicolaou, would show that both techniques give similar yields. In any case, he adds, yields are not important at this stage because both groups will be refining and modifying their processes, and it's not yet clear whose method has the most potential for improvement.

The next step, agree Suffness and Stanford's Wender, is to use the techniques to devise modified taxols, whose cancer-fighting ability can then be tested in cell culture. Once chemists know which parts of the molecule are crucial to its function, they could switch from a trial-and-error, empirical approach to a rational one as they attempt to make the drug more effective or less toxic. Suffness adds that researchers might also be able to design a "stripped-down model" of taxol that could be synthesized in a workable number of steps.

On the other hand, says Suffness, synthetic taxol might remain a research tool; even after the synthesis technique has been refined, it might still turn out to be cheaper to make commercial forms from natural sources. The real goal, says Wender, is to find a form of taxol that, whatever its source, is easy to make and effective against cancer. And in that race, the new results are "only the beginning."

–Faye Flam