industry if they were found patentable. The move infuriated scientists, who feared that licensing battles over sequences with no known function would slow research for little or no benefit.

Once NIH made its move, others felt compelled to follow. In July 1992 the British Medical Research Council (MRC) filed applications on some 1,200 partial sequences, even as MRC officials argued that the applications should not be granted. MRC later decided not to file for any new patents, however, and last week it, too, withdrew its existing applications.

Although many patent attorneys believed the uncharacterized gene fragments would ultimately be found unpatentable on the grounds they were of little value by themselves, few companies in the gene sequencing business were willing to take the risk and forgo filing applications. For example, Human Genome Sciences of Gaithersburg, Maryland—the commercial arm of a nonprofit research institute launched by Venter when he left NIH in 1992—has filed for 9,900 sequences, according to a recent prospectus. And Incyte, a Palo Alto, California, biotech company, has filed for 40,000 more (*Science*, 15 January, 1993, p. 302). However, given the amount of time and money spent on pursuing the patents, most companies were happy to have NIH lead the way in trying to resolve the issue of patentability as quickly as possible.

Varmus says he and his advisers decided that playing such a role didn't justify pursuing the patents. "Although an appeals process by NIH would probably have provided some decision earlier than would have been possible if we had to wait for other applicants, it was unlikely to be a solid or definitive decision," he explains. He notes that the cDNAs underlying the application were not the best range of sequences on which to base a claim. In addition, he says, "if we had failed in the appeals process, it is unlikely that the decision would have been considered solid, because we might have been perceived as half-hearted in our attempts; certainly the motivation to succeed will be higher in the private sector."

David Galas, the former head of the Department of Energy's share of the human genome project and now scientific director of Darwin Molecular in Seattle, Washington, agrees with those arguments. "If [NIH officials] didn't think that the granting of the patents was in the public interest, then they were put in the position of pursuing with public funds something they hoped they'd lose," he says.

Academic scientists also appear pleased with NIH's decision. James Sikela, a University of Colorado geneticist, says his team has obtained some 3,000 cDNA sequences but has not pursued patents because he believes such sequences should be available to all researchers. "There's a sense of relief that NIH is not pursuing these partial sequences," he says. "It makes things a little less complex."

Varmus says his decision was heavily influenced by Rebecca Eisenberg, a University of Michigan law professor who was part of a panel Varmus convened on 20 December to advise him. Varmus intends to flesh out last week's statement in the next several weeks with a legal brief written by outside patent experts. He says NIH may participate in a forum on the issue under the auspices of the PTO, as well as convening a meeting to discuss the international aspects of the subject. "We do not believe we have settled any questions," he says, "but a brief can serve as a point of reference" for others.

–Christopher Anderson

CANCER PREVENTION

Restating the Risks of Tamoxifen

A much-debated trial of the anticancer drug tamoxifen is heading into stormy seas once again. Prescribed for more than a decade to treat women with breast cancer, the drug is to be given to 8,000 healthy women who have a high risk of breast cancer to see if it can prevent the disease. Some critics fought this trial before it began in April 1992, arguing that this experimental use is too risky because tamoxifen appears to increase the odds of getting other diseases, such as endometrial cancer and deep vein thrombosis. But proponents countered that the endometrial cancer risk is acceptable, partly because tamoxifen appears to reduce breast cancer risk dramatically and partly because uterine cancers can be remedied with surgery if detected early. Now, new data on endometrial cancer mortality among breast cancer patients in one tamoxifen study may rekindle this controversy.

"We have conducted risk-benefit analyses, and we still find that there is a benefit of going ahead with the trial."

—Bernard Fisher

The information has already prompted the National Cancer Institute (NCI) to instruct clinics conducting research on tamoxifen to rewrite consent forms and ask participants to sign again. NCI has also started an "ancillary study" to monitor 800 healthy women in the preventive tamoxifen trial. Researchers will be looking for signs of endometrial cancer, and NCI will pay the costs of following these women closely and giving them yearly biopsies. This is "an encouraging sign," says Trudy Bush, an epidemiologist at the Johns Hopkins University who's concerned about tamoxifen risks. To her, it looks as though NCI is becoming more "responsive."

The complete data on which these actions are based haven't been made public, however, because they are awaiting publication in the scientific literature. Leslie Ford, NCI's project coordinator for the prevention trial, told *Science* she couldn't release the information because it belongs to Bernard Fisher, a surgeon at the University of Pittsburgh and one of NCI's senior extramural researchers. Fisher declined to release the data because he has sent a paper to NCI, which is still in the peer-review process for potential publication in the *Journal of the National Cancer Institute*. Fisher would only say that the new data don't undermine the rationale for the prevention study: "We have conducted risk-benefit analyses," he says, "and we still find that there is a benefit of going ahead with the trial."

Fisher oversees a study of tamoxifen therapy for cancer patients that began in 1981 (the B14 trial), and he serves as principal investigator on the prevention study, known as the Breast Cancer Prevention Trial (BCPT). In December, Fisher's group sent out an alert to all participating BCPT clinics, noting in general terms that "updated information regarding the risk of uterine cancer" from the B14 trial would require a revision of consent forms. The recommended new wording went out on 14 January. Two days earlier, NCI had sent out a more detailed advisory to doctors using tamoxifen in treatment trials.

Both the letter from Fisher's group and the NCI's letter, written by Jeffrey Abrams, senior investigator at the Clinical Trials Evaluation Program, indicate that patients in the B14 trial appear to have a risk "approximately three times greater than that of a similar group of women in the general population" of contracting endometrial cancer. This is at the high end of the range researchers had predicted. But there were more deaths than expected: Abrams' letter says four of the 23 women with uterine can-

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."

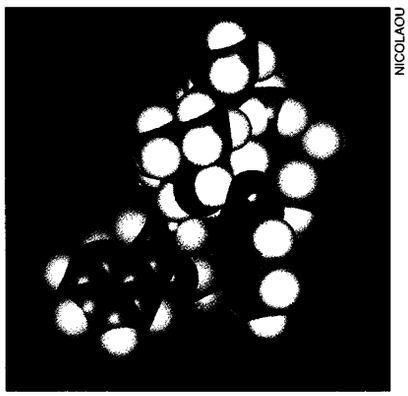
–Lisa Seachrist

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.



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