0273-2289/95/5401-03—0133$05.60

Taxol® (Paclitaxel)

Strategies to Increase the Supply of a New Anticancer Drug

DEAN P. STULL,* THOMAS A. SCALES, RANDY DAUGHENBAUGH, NEIL A. JANS, AND DAVID T. BAILEY

Hauser Chemical Research, Inc., 5555 Airport Blvd., Boulder, CO 80301

ABSTRACT

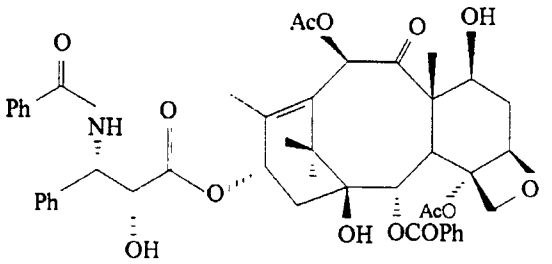
Taxol® (paclitaxel) has been hailed by many as the most promising new cancer treatment in two decades. The FDA requires that paclitaxel intended for human consumption be obtained only from the bark of *Taxus brevifolia,* the Pacific yew. As this may become increasingly uneconomical, new strategies must be explored to ensure the continued availability of taxol and related molecules. This article examines the planning that must be engaged in and the contingencies that must be prepared for in this changing arena.

Index Entries: Taxol®; paclitaxel; cancer treatments; antitumor.

INTRODUCTION

Taxol® (paclitaxel) (Scheme 1) is an exciting new drug that recently received Food and Drug Administration (FDA) approval for the treatment of refractory ovarian cancer and refractory breast cancer and that has strong indications of efficacy in the treatment of other cancers, including those of the colon and lung, as well as melanoma and lymphoma. The active agent, paclitaxel, is known to be a promoter of microtubule assembly, which is the likely source of its antitumor activity. Many oncologists have hailed taxol as the most promising new cancer treatment in two decades.

*Author to whom all correspondence and reprint requests should be addressed.



Scheme 1. Taxol® (Paclitaxel).

Currently, the FDA requires that paclitaxel intended for human consumption be obtained only from the bark of *Taxus brevifolia*, the Pacific yew. Hauser's experience has shown that this tree is underappreciated, but not particularly rare in the forests of the Pacific northwest of the United States and Canada. Nevertheless, because continued harvest from the wild is likely to become increasingly uneconomical, Hauser is looking toward new strategies to ensure the continued availability of paclitaxel and related molecules.

We offer this article as a case study of the depth of the planning that must be engaged in and the contingencies that must be prepared for in this rapidly changing arena. Paclitaxel continues to be an exciting and fulfilling story and a daily challenge. We have never been involved before with a project for which one of the primary journals for publication of scientific results has been *The Wall Street Journal.*

Paclitaxel is present at the 0.001–0.05% level in the species, hybrids, and cultivars of the *Taxus* genus of the Taxaceae family. These plants are primitive evergreens found in widely scattered locations around the world. Some have been extensively hybridized and many are valued as ornamentals. *T. brevifolia* is a thin-barked, small, slow-growing tree found in the understory of the old growth forests, as well as new forests in the Pacific Northwest. Hauser collects its bark from private land in areas that are scheduled for timber harvest and in which these trees are usually destroyed by the logging operations.

THE PACLITAXEL PROJECT

Paclitaxel was originally identified by the National Cancer Institute (NCI) drug discovery program in the late 1960s, and its structure was reported in 1971 by Wani and coworkers, who named it taxol (*1*). Hauser became involved in 1988, when the NCI needed kilogram quantities for clinical trials. Since that time, Hauser has produced paclitaxel for both the NCI and American Home Products Bristol-Myers Squibb and has primarily focused its efforts in these areas:

- Develop analytical methods—at the onset of Hauser's involvement, the assay methods available for paclitaxel and its impurities were problematic at best, and their continued use resulted in considerable misinformation in the press and in the chemical literature. Hauser has contributed to the development of effective analytical methods for the analysis of paclitaxel and taxanes (2).
- Develop isolation methods—isolation methods suitable for large-scale manufacturing of paclitaxel and related molecules were not available at the onset of this project (*1*). Existing methods had either an excessive number of steps or steps that could not be scaled up sufficiently to meet the needs of the project. Hauser has developed several effective and efficient large-scale paclitaxel isolation methods.
- Build an FDA-approved manufacturing facility—the FDA was involved from the beginning with the design of Hauser's large-scale paclitaxel production facility.
- Develop sufficient raw material capacity—about 1500 permanent and seasonal employees in Washington, Oregon, California, Idaho, and Montana have collected, dried, ground, and shipped approx 1.5 million pounds of bark/yr in recent years.
- Bring all processes and facilities into full current Good Manufacturing Practices (cGMP) compliance—this has been a multiyear program that brought every aspect of the paclitaxel manufacturing process under regulatory control.
- Meet all FDA requirements, and gain its approval of the facility and the process—Hauser's large-scale paclitaxel isolation facilities have been thoroughly inspected by the FDA. Currently, Hauser has the only FDA-approved process and facility for the manufacture of human-grade paclitaxel and is producing in excess of 200 kg/yr.

STRATEGIES TO INCREASE THE FUTURE SUPPLY OF PACLITAXEL

Find a Better Plant Source

Other parts of the *T. brevifolia* plant have been found to contain potentially useful quantities of paclitaxel and taxanes (Table 1). For example, much attention has been focused on *Taxus* clippings as an attractive source because their harvest would not require the death of the tree. Paclitaxel isolation from parts of the plant other than bark will require somewhat modified isolation procedures. Because the FDA is very concerned with

Table 1
Paclitaxel in Wild *Taxus brevifolia*

Biomass	Dry weight (%)
Bark	0.02–0.04
Clippings	<0.005–0.015
Wood	<0.003
Total plant	0.02

Table 2
Paclitaxel in Whole-Plant *Taxus* Species

Species	Dry weight (%)
T. brevifolia	0.02
T. × *media* "Hicksii"	0.05
T. × *media* "Runyan"	0.03
T. cuspidata	0.03
T. baccata	0.01

the profile of trace impurities that are present with the paclitaxel, a different starting material or isolation method will likely need additional clinical trials and require an extensive review by the FDA before this type of paclitaxel can be made available for human use.

Other related *Taxus* species and hybrids have also been examined for their paclitaxel and taxane content (Table 2). Some contain useful amounts of paclitaxel, and some have lower quantities of certain difficult-to-remove impurities. To recover paclitaxel from an alternate plant will require harvesting steps, extraction steps, purification steps, and production costs similar to those experienced in the purification of paclitaxel from *T. brevifolia* bark, so a substitute raw material likely will not dramatically affect the overall paclitaxel production costs. In addition, there is the lingering concern that the use of an alternative species may only exchange the problems inherent with *T. brevifolia* bark for new problems as yet unappreciated. It is clear that FDA approval will be necessary for the sale of human-grade paclitaxel from an alternate raw material because of the likelihood of a different taxane impurity profile.

Some *Taxus* species are plentiful in the wild, but some are rare enough to be essentially unavailable. *Taxus* hybrids and cultivars are generally available only from nursery stock. Consequently, a plantation system seems to be a possible scenario. This approach is made particularly attractive by the freedom that it permits in the selection of the plant type(s) with the most desirable paclitaxel characteristics. A plantation also allows the use of modern plant-growing methods; can be located for optimal

climate, drainage, soil conditions, and so forth, and can allow a less costly and a more manageable harvest.

There are also disadvantages with the plantation scenario: many years are required to establish a sustained yield program; plantation plants are costly to grow and maintain; they may be more vulnerable to localized crop disasters; and the paclitaxel from the harvest of alternate species will surely require FDA approval. Whereas the costs to grow and manage wild trees are considered to be almost negligible, these costs for a plantation are very real. On the other hand, harvesting costs for wild trees are likely to far exceed those costs from a plantation.

There are also negative biological and political implications for the environment from the harvesting of a wild population. Hauser has no desire to threaten the viability of this or any other species, and is keenly aware of the dangers of excessive harvesting. Consequently, Hauser has adopted the approach that we will collect bark only from areas that are designated for timber harvest on private land. For the future, the remote and sometimes difficult access to many timber harvest areas and the dispersed growth pattern of these trees combine to make continued total reliance on the wild material unreasonable. Considering all of this, Hauser has surveyed the available species, hybrids, and cultivars within the *Taxus* genus and has established a plantation program to supplement its successful bark harvesting program.

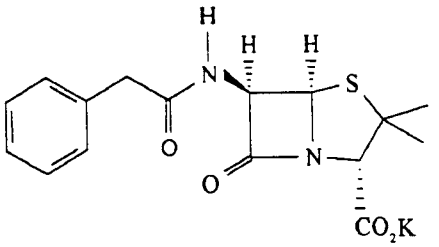
Alternate Routes to Paclitaxel

Several other solutions to the paclitaxel supply problem are under investigation.

Total Synthesis

Modern organic chemistry offers many tools and strategies to synthesize complex organic molecules. The challenges posed by this molecule and the need for the product have prompted many workers to pursue the synthesis of paclitaxel. Total synthesis offers the opportunity not only to produce paclitaxel, but also to access unnatural paclitaxel-like molecules, perhaps with similar structures, that may have interesting pharmaceutical properties.

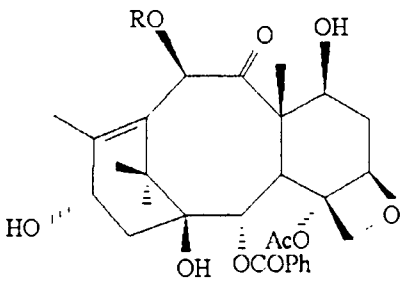
To date, a total synthesis of paclitaxel has not been reported. Its structure has 11 chiral centers and other challenging characteristics, and will likely require a large number of synthetic steps. Consequently, for a synthetic process to be competitive with isolation from a natural source, it must have great economy with all reagents and high yields at every step. It is noted that, although the total synthesis of penicillin (Scheme 2), which has only three chiral centers, has been known for many years, it is still prepared by isolation from a biological source. Should paclitaxel eventually yield to economical total synthesis, then this type of paclitaxel will also require in-depth FDA approval before it can be allowed for human use, in



Scheme 2. Penicillin G potassium.

Table 3
Theoretical Yield of Natural and Semisynthetic Paclitaxel per Metric Tonne of *T. brevifolia* Bark

Natural paclitaxel	300 g
Natural paclitaxel plus synthetic paclitaxel	1800 g



R = H 10-Deacetylbaccatin II
R = Ac Baccatin III

Scheme 3. 10-Deacetylbaccatin III and baccatin III.

part because of its considerably different impurity profile. Although the total synthesis of paclitaxel has significant academic interest, Hauser has elected to leave this work to others.

Semisynthesis

Semisynthesis attempts to make paclitaxel from naturally available sister molecules also present in *Taxus*. This approach has the potential to increase substantially the total recovery of paclitaxel from the same quantity of raw material (Table 3).

It would seem then that a cost-effective paclitaxel production scenario would be to isolate the natural paclitaxel, as well as to recover and convert as many sister molecules as possible into paclitaxel. Most examples (3) of paclitaxel semisynthesis begin with 10-deacetylbaccatin III and baccatin III (Scheme 3), molecules with the diterpene portion already performed, but without the side chain. In addition to these two molecules, the *Taxus* species contains a number of other molecules that might be interconverted to paclitaxel.

Even if the semisynthetic starting molecules are available in large quantities in the plant, this approach still must include the costs associated with both isolation and synthetic steps. Semisynthesis allows structural modification only to certain specific sites on the sister molecules, so some natural taxanes may not be cost-effectively converted to paclitaxel. Paclitaxel produced via this approach will also require in-depth FDA scrutiny and approval. Hauser can produce the paclitaxel-like sister molecules in quantity at its large-scale paclitaxel isolation facility, and has an active and productive semisynthesis development program.

Plant Cell Culture and Plant Fungal Growth

The production of paclitaxel via plant cell culture (*4*) and plant fungal growth (*5*) has been reported, and may offer the opportunity to provide this molecule and perhaps other valuable taxanes in a convenient manner, reducing the paclitaxel supply difficulties. The large-scale production of paclitaxel by either of these methods has yet to be reported, but is under active investigation in several laboratories. There are always problems associated with trying to implement young and emerging technologies, and so, although great strides are being made, the eventual outcome of these efforts cannot yet be seen. Again, paclitaxel from either of these sources will require FDA approval. Hauser has been part of an NCI-supported consortium (*6*) of universities and private companies working to produce paclitaxel via cell culture techniques.

Develop a Paclitaxel-Like Analog

This strategy seeks a paclitaxel-like molecule that has improved pharmaceutical properties or economic benefits, and avoids the difficulties inherent in the paclitaxel supply issue. Such an analog might:

1. Have a higher water solubility to improve its clinical deliverability;
2. Be capable of achieving a different distribution within the body;
3. Be capable of being effective for tumor types for which there is no adequate chemotherapy; and
4. Have an improved safety and toxicity profile.

In addition, the analog should be a patentable compound and have good availability of the necessary starting materials. The likely approaches to such a new analog come from the isolation of other natural molecules, total synthesis, or semisynthesis. Once again, such an analog will be a completely new drug and will need full approval by the FDA. Hauser has patented compounds that are more active in tubulin binding and cytotoxicity than paclitaxel is and that are undergoing in vivo testing at this time.

We would like to close with this thought: One must always be mindful that there is more than one way to do almost any job, including the production of paclitaxel. Economics will eventually intercede to sort out the

wisdom and success of the various approaches. Hauser looks to the future with optimism in its ability to be the low-cost producer of paclitaxel and paclitaxel-related compounds.

ACKNOWLEDGMENT

We thank the organizing committee for the opportunity to present these comments.

REFERENCES

1. Wani, M. C., Taylor, H. L., Wall, M. E., Coggon, P., and McPhail, A. T. (1971), *J. Am. Chem. Soc.* **93,** 2325.
2. Richheimer, S. L., Tinnermeier, D. M., and Timmons, D. W. (1992), *J. Anal. Chem.* **64,** 2323.
3. Denis, J.-N., Greene, A. E., Guenard, D., Gueritte-Voegelein, F., Mangatal, L., and Potier, P. (1988), *J. Am. Chem. Soc.* **110,** 5917.
4. Gibson, D. M., Ketchum, R. E. B., Vance, N. C., and Christen, A. A. (1993), *Plant Cell Rep.* **12,** 479.
5. Stierle, A., Strobel, G., and Stierle, D. (1993), *Science* **260,** 214–216.
6. Manipulation of *T. brevifolia* Physiology in Tissue Culture, Grant No. 5 RO1 CA55138, National Cancer Institute, Bethesda, MD.