

The Story of Taxol



Pacific Yew

© 1995-2003 [Missouri Botanical Garden](#)

One plant collected as part of the NCI program was the Pacific yew, *Taxus brevifolia* Nutt., a small understory tree from the Pacific Northwest forests. Three-quarters of a pound of stem bark of the Pacific yew was collected August 21, 1962 by a team of botanists led by [Arthur Barclay](#) at a site 7 miles north of Packwood, Washington, in the [Gifford Pinchot National Forest](#). The extract was confirmed as active in an animal test system, and by September of 1964 a larger recollection was made to facilitate isolation of the active compound from the extract.



Pacific Yew bark

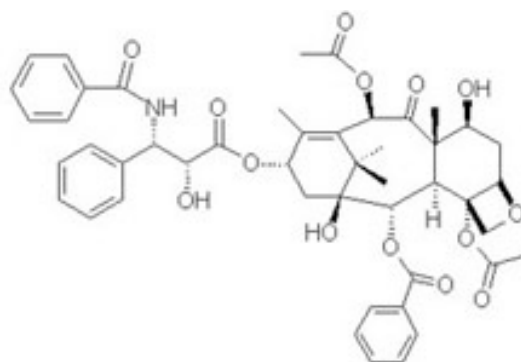
In the early 1960's, Jonathan Hartwell of the United States [National Cancer Institute](#) organized collection of plants from the U.S. for evaluation as potential sources of anticancer drugs. These collections were conducted by botanists from the U.S. [Department of Agriculture](#), including Robert Perdue and James Duke. Plants were shipped from the field to chemistry laboratories where they were extracted with solvents to dissolve agents present in the plant for testing as possible cancer drug candidates. Monroe Wall, Morris Kupchan, Jack Cole, Norman Farnsworth, and G. Robert Pettit were some of the chemists involved.



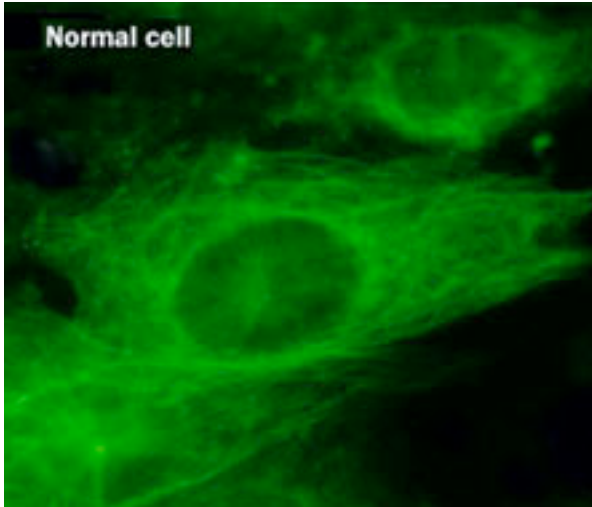
RTI photo

The next step was to determine its structure. With the tools available at that time, this was not a simple task, but by 1971, the team had obtained a crystalline derivative of taxol which could be examined by X-ray crystallography, and the insights from this data helped to solve the structure of taxol. While taxol was a novel compound, related compounds had been previously obtained from other yew species, though none had been shown to have anticancer activity. No patent was filed because it was felt that the amounts of taxol obtained were too small to justify the compound's development. Nonetheless, with the small quantities in hand, NCI pressed on to further explore the potential of taxol as a cancer treatment. Matthew Suffness of the NCI was a key advocate for the compound's development.

The [Natural Products Laboratory](#) of [Monroe Wall and Mansukh Wani](#) at the [Research Triangle Institute](#) in North Carolina was assigned the task of identifying the active substance in Pacific yew, among other promising projects. By repetitively partitioning the extract and testing each fraction for bioactivity, the RTI team was able to identify a pure substance responsible for the anticancer activity in the text systems. They named the substance "taxol", referring to the botanical name of the yew, *Taxus*.



Many different animal cancer models were used to evaluate taxol's actions, and in some of them, taxol demonstrated good activity. Yet there was little understanding of the way that taxol killed tumor cells.

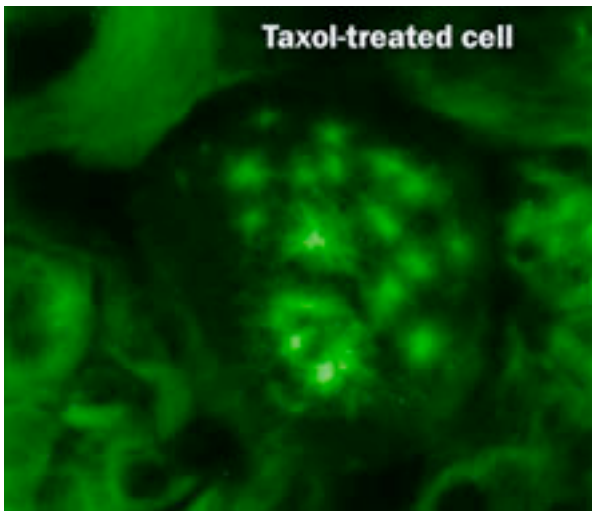


This gap was filled in 1977, when [Susan Horowitz](#) and coworkers at [Albert Einstein College of Medicine](#) in New York City discovered that taxol interfered with cell division by binding to the protein tubulin, which is a key factor in mitosis.

Unlike some other cancer drugs which *prevented* tubulin from assembling into microtubules, taxol bound to assembled microtubules and blocked them from disassembling.

In either case, the process of cell division and growth is stopped, but the difference from previous drugs meant that taxol might have different properties as a drug.

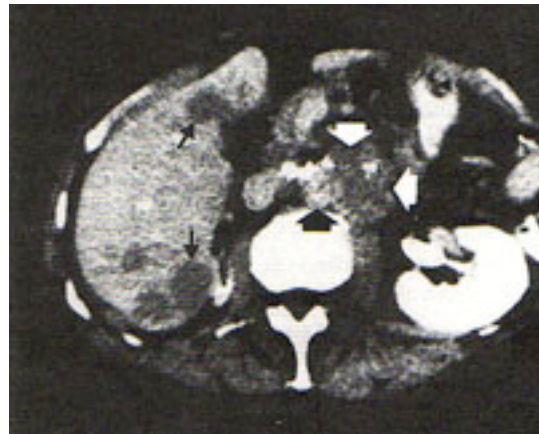
Taxol-treated cells courtesy Dr. Ernest Hamel, NCI



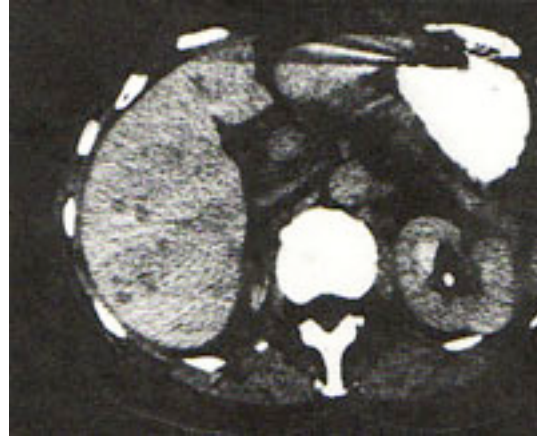
Before Taxol

Animal tests had indicated that taxol might be useful against cancers such as breast, and once the limited supplies of taxol permitted, studies in human cancer patients were begun at [Johns Hopkins University](#) in Baltimore, and at Albert Einstein in New York.

Initial trials at JHU in patients with ovarian cancer showed significant responses for about a third, including dramatic improvement with some who had failed to benefit from any previous therapies.



After Taxol



The cost of drug development rises steeply once human trials begun, and in an effort to accelerate the progress of taxol's development as a drug, the NCI signed a cooperative agreement with the pharmaceutical company [Bristol Myers](#) to fund and carry out further work, including securing a larger supply of drug. In return, the NCI provided Bristol Myers with the data it had assembled to that point in time. The collection of yew bark from Oregon and Washington was expanded so that more trials could be run. At their peak, Pacific yew bark collections were several hundred thousand pounds of bark per year. The bark from a single tree only yielded enough taxol for about one dose of the drug.

Bristol Myers addressed the supply problem by finding an alternative source of the compound. The common yew, *Taxus baccata*, which is widely grown as an ornamental, contains a taxol relative, 10-deacetyl baccatin III, which is relatively more abundant, and which can be converted to taxol by chemical manipulation. A process invented by [Robert Holton](#) of [Florida State University](#) was licensed and developed to produce taxol by Bristol Myers. Currently a cell culture method developed by Phyton Catalytic [now a division

of [DFB Pharmaceuticals](#)] is used by BMS to produce taxol. Taxol has also been found to be useful in therapy of breast cancer, non-small-cell lung cancer, and Kaposi's sarcoma. Current sales are over a billion U.S. dollars per year. Several generic brands are now available.