THE FOX GOT YOU

Art and science project by
photography artist Françoise Sergy

The drugs PACLITAXEL / DOCETAXEL

Most yew tree species are poisonous. This is caused by a toxic compound called taxine B which is present in all parts of the plant except in the ripe seed coat (the red aril). It affects the heart and the nervous system, causing death by heart failure. Most domesticated animals will be poisoned by it but wild animals such as deer will not - their grazing of young saplings is a major reason for the tree's decline in its natural forest habitats.

The anticancer properties of the yew come from another set of compounds called taxanes, which are not soluble in water and therefore are not absorbed by the body. This non-solubility aspect may explain why the yew tree has not been used to treat cancer until very recently. The only historical reference comes from the Bower manuscript, an ancient Ayurveda text of Indian medicine dating to the 6th cent. A.D., in which yew was mixed with clarified butter to treat abdominal cancer. The butter may have made the active compound more soluble. However, over the ages, the potent toxicity of the tree gave it its reputation as a poison and it has been used as a remedy for all sorts of ailments, for which it has no effect. Many people have died of lethal doses, including countless pregnant women during the 18th and 19th centuries when it was used to induce abortion (the tree was then considered effective in regulating the menstrual flow).

The modern story of the anticancer drug starts in the United States. In 1960 the Department of Agriculture (USDA) and the National Cancer Institute (NCI) began a programme to find and test plant products with the hope of developing anticancer drugs. In 1962, random plant collections included samples of the Pacific yew (Taxus brevifolia), a very slow growing tree situated in the understorey of giant conifers, ranging from northern California to Alaska. At the time the tree was considered a 'trash tree', with no commercial value except for firewood and fence posts. The plants programme ran until 1981. During this time, it collected and tested six percent of the world's plant species. Just over four percent of these plants were confirmed to have molecules active against cancer. Of these compounds, only Paclitaxel made it into a drug.

In 1964 the Pacific yew extracts were found to have confirmed anticancer activity by Monroe Wall at the Research Triangle Institute in North Carolina. The isolation of the active compound took another three years. In 1967 Wall and his co-worker Mansukh Wani gave it the name of taxol, from the tree's genus Taxus and the fact that the compound was an alcohol. In 1970 they finally determined its true molecular formula and published the results in 1971 in the Journal of the American Chemical Society. They had taken six years to elucidate the structure of a very unusual and complex compound, one that could only be found in nature. More recent research has established that the compound is not actually made by the yew but by a fungus living inside the tree (an endophytic fungus). The fungus uses the tree's own taxanes to make an even more complex molecule.

At that stage of the research, the active ingredient came from the bark of the Pacific yew. This meant that in order to harvest it, the tree had to be killed, as it cannot regrow its bark. Also, the compound was found in minute amounts: With hindsight, the felling of six mature trees would be required to treat a single patient. It became apparent that the harvesting of the Pacific yew would render it extinct, which obviously defeated the whole purpose. Realisation of the problem was slow however: No studies existed of the tree's presence within the forest, as logging companies had no tradition of growing or exploiting it commercially. The supply problem considerably slowed the progress of the research, with companies unable to harvest enough bark. In the 1980s environmental and conservation groups highlighted the importance of the forest where the Pacific yew grew: This forest is a truly ancient woodland. As well as the yew, a main concern was the plight of another forest resident, the spotted owl. The issue was eventually addressed in the 1990s but not without a considerable loss of yews in the wild, not only in the States but also in India and China.

Between 1976 and 1983 taxol was screened and studied at the NCI to see if the compound was good enough to make it to phase I clinical trials, which would involve it being tested on people. At the start of this initial stage, it had only a four percent chance of success. In 1977 and 1979 two separate groups of scientists elucidated taxol's mechanism of action in cancer cells. David Fuchs and Randall Johnson published the first study and Susan Horwitz and colleagues the second study (you can read a description of how the compound works in page 33 of this exhibition's book "Visits to Biomedical Research Laboratories"). One of the problems which had to be resolved before trials could begin was how to make the compound soluble in water. This was initially worked out in 1980. Success came and approval to commence clinical trials was given by the Food and Drug Administration (FDA) in 1984.

However, an other player had by now entered the field: Pierre Potier, of the Centre National de la Recherche Scientifique (CNRS) in France. Whilst taxol was found mostly in the Pacific yew, scientists knew that taxanes as a group were present in all the yew species. Potier was aware of the supply problem in the States. The European yew (Taxus baccata) happened to be growing outside his lab windows. He decided to search for a compound in this tree which would act as a precursor to taxol and also offer a good yield. Using a different approach to that of the American chemists, his team focused on a taxane known as 10-deacetylbaccatin III or 10-DAB for short, which is abundant in the leaves of Taxus baccata and could be used to make taxol through a semi-synthetic route. Teaming up with another French lab, that of Andrew Greene, and the pharmaceutical company Rhône-Poulenc, they published their findings in 1988. A path to the production of taxol using a renewable source had been found.

Chemists in the States had meanwhile focused on making taxol entirely from scratch, by pure synthesis. This was achieved in the mid 1990s by four different labs, including that of Bob Holton at Florida State University. The process involved at least 40 steps and had an abysmal yield. In the end, total synthesis was not used to produce the drug. It did however allow chemists to understand how the compound was constructed and to explore ways of modifying it and creating derivatives with improved qualities. This is how Docetaxel (brand name Taxotere) was developed by Potier and approved for use in breast cancer in 1995. Several taxol derivatives have since being researched and some are now coming onto the market.

Back in 1984, clinical trials were started on taxol in the States. So far all the costs of developing the drug had been paid for by the state, through the NCI, and this would remain so until the successful end of the trials in 1989, when the contract to commercialise the drug was given to the pharmaceutical company Bristol-Myers Squibb. By then the research had cost the American government $32 million. In 1990 Bristol-Myers Squibb applied to have the name taxol patented, even though this name had been used for several years by the research community. Taxol became Taxol® and the compound's generic name became Paclitaxel. Over the subsequent years, Bristol-Myers Squibb and its partners were to make considerable profits from the sale of the drug.

Once a semi-synthesis route had been found by French chemists, Americans got persuaded to develop their own approach and in 1989 Bob Holton was successful. In partnership with Florida State University, he teamed up with Bristol-Myers Squibb to make Taxol®. The drug finally entered the markets in 1993, 31 years after the original Pacific yew bark collection. By 1998 it had become the best-selling anticancer drug ever. Huge plantations of yew trees were set up in the Pacific north-west and in Asia. By using taxanes in the leaves as a precursor to the drug, the semi-synthetic route had enabled the sustainable production of the drug. The taxanes are now harvested from three different sources: the plantations, the collection of leaves from gardens in Europe and the newest method which uses plant cell tissue culture.

Paclitaxel / Docetaxel are used for a range of cancers, often in combination with other drugs. Although a very effective treatment, they are no panacea. No doubt one day better drugs will be found but right now we have an ancient tree to thank for saving the lives of many.

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