**URL**: http://www.iupac.org/symposia/proceedings/phuket97/venkat.html


# Paclitaxel Production Through Plant Cell Culture: An Exciting Approach to Harnessing Biodiversity

**K. Venkat**

*Phyton, Inc., 95 Brown Road, Ithaca, NY USA and Rutgers University, New Brunswick, NJ USA.*

The plant kingdom has historically been a major source of valuable medicinal compounds and healing agents. Unfortunately, these compounds often occur in low yields in nature; furthermore, they require complex isolation and purification procedures. Plant cell culture technology offers a potential means to address these problems. Although elements of this technology have been around for many years, its widespread commercial use has not been possible owing to a number of factors. Recent developments have brought this technology into the commercial arena for both drug discovery and large scale manufacturing of therapeutic compounds.

Phyton has invested more than 200 man-years of effort to address the commercial issues of plant cell culture technology. Under a long-term collaborative relationship with Bristol-Myers Squibb Company (BMS), Phyton has developed and is commercializing a plant cell culture process for the production of paclitaxel (the active ingredient of Taxol$^{R}$; Taxol is a registered trademark of BMS). Through its wholly owned subsidiary, Phyton Gesellschaft für Biotechnik mbH (Phyton GmbH), the Company operates the world's largest dedicated plant cell culture production facility in Germany. This highly-automated and computer-controlled facility has large-scale fermentor capacity of up to 75,000 liters. It is being used for paclitaxel production under current Good Manufacturing Practice (cGMP) conditions.

The discovery of Taxol and its potential anti-cancer activity was first reported in the mid-1970's. Taxol was originally isolated from the bark of the Pacific Yew tree. Although a relatively small molecule, Taxol's highly complex structure does not lend itself to easy chemical synthesis. Lack of adequate supply of Taxol hampered further development until the mid-1980's when there was renewed interest. Early clinical trials were conducted by the National Cancer Institute (NCI), and the results were exceedingly promising. BMS entered into a collaborative arrangement with NCI to commercialize Taxol based on these results. Following FDA approval of Taxol for the treatment of refractory ovarian cancer, BMS commenced marketing of this product based on material derived from the Pacific Yew tree. Taxol has currently been approved in numerous countries worldwide and is being used for the treatment of advanced breast cancer and other indications in addition to ovarian cancer. Applications in several other indications are also being developed. Current worldwide sales of Taxol are estimated to be in the range of $900 million per

*Invited lecture presented at the International Conference on Biodiversity and Bioresources: Conservation and Utilization, 23–27 November 1997, Phuket, Thailand. Other presentations are published in *Pure Appl. Chem.*, Vol. 70, No. 11, 1998.

year. Phyton's proprietary plant cell fermentation (PCF) process is a more reliable and cost-effective source for Taxol.

We embarked on a comprehensive program to address numerous technical and commercial development issues. The natural genetic diversity of the *Taxus* genus was employed, along with appropriate environmental conditions to develop elite Taxol-producing cell lines.

Phyton has collected and screened every known species of *Taxus*. In addition to high productivity of Taxol, several other commercially important performance parameters, such as high growth rate, reproducibility, and stability of cell lines, were critically assessed, and several elite cell lines were developed. A number of scale-up issues were examined and resolved, resulting in a commercially attractive performance in large scale fermentors. The productivity of Taxol was enhanced by several orders of magnitude through a combination of genetic and environmental approaches. A number of cGMP manufacturing problems were also addressed and resolved, including establishment and certification of production strain banks, proper downstream processing methods, isolation and characterization of impurities, and demonstration of product equivalence compared to the bark-derived material. Engineering problems such as oxygen transfer, optimum aeration rates, mangement of sheer stress, and the like were also studied, and appropriate solutions were developed. The resulting process for this large production of paclitaxel appears to be quite robust.

The plant kingdom is characterized by a tremendous biodiversity arising out of a large pool of genetic information which, in turn, encodes for a broad spectrum of phytochemicals. Plant cell culture technology can be used effectively to tap into this chemical diversity, resulting in a large array of potentially useful pharmaceutical product leads. Application of this approach to the discovery of novel taxanes is illustrated.

Phyton has also developed a number of supporting technologies and related capabilities as part of its technology platform. A proprietary cryopreservation technology is being employed to store and retrieve plant germplasm and elite cell lines reliably. Such new techniques combined with natural biodiversity present unique opportunities to develop new therapeutic products.