

Development and Preclinical Trials of Genexol[®]

Sung Chul Kim

Samyang R&D Center, Samyang Corporation

Nature has provided many excellent medicines to benefit the human health. There are many effective anti-cancer agents in current use originating from nature, such as the microbially derived drugs; dactinomycin, bleomycin and doxorubicin and the plant-derived drugs; vinblastine, irinotecan, topotecan, etoposide, and paclitaxel.

Paclitaxel may be one of the most important anticancer agents to be developed over the past two decades. With its unique mechanism of action as an inducer of stable microtubules assembly and inhibitor of depolymerization¹⁾, paclitaxel has demonstrated significant activity in clinical trials against a wide variety of tumors, including ovarian, breast, NSCLC and AIDS-related Kaposi's sarcoma since paclitaxel (Taxol[®], Bristol-Myers Squibb; BMS) was firstly marketed in the U.S. (December 1992) for the treatment of ovarian cancer after failure of first-line chemotherapy²⁾.

Paclitaxel is a hydrophobic drug that is poorly soluble in water but has a high efficacy for cancer. Because paclitaxel has limited solubility in water, current clinical dosage form of paclitaxel consists of a 5 and 16.7 milliliter size vial, with each milliliter of solution containing 6 mg of paclitaxel, 527 mg of Cremophor[®] EL and 49.7% dehydrated ethanol (1:1, v/v) and must be further diluted before administration for I.V. injection in cancer treatment^(3,4,5). This current clinical dosage form of paclitaxel, however, is associated with a number of concerns including filtering requirements, use of non-plasticized solution containers and administration sets.

Early marketing of Taxol[®] using natural paclitaxel extracted from the bark of Pacific yew tree was limited by a restricted supply due to the several difficulties including productivity

and high cost in obtaining the drug. Since 1994, BMS has scaled up a process for commercial production by semi-synthesis from 10-deacetylbaccatin (10-DAB) III, isolated from needles and twigs of the European yew tree, a renewable source due to the use of limited resources. Patients were received investigational semi-synthetic Taxol in 1994 and FDA approved semi-synthetic Taxol in 1994. Although current semi-synthetic paclitaxel will no longer harvest yew bark from public lands, it is still associated with reproducibility and high manufacturing cost.

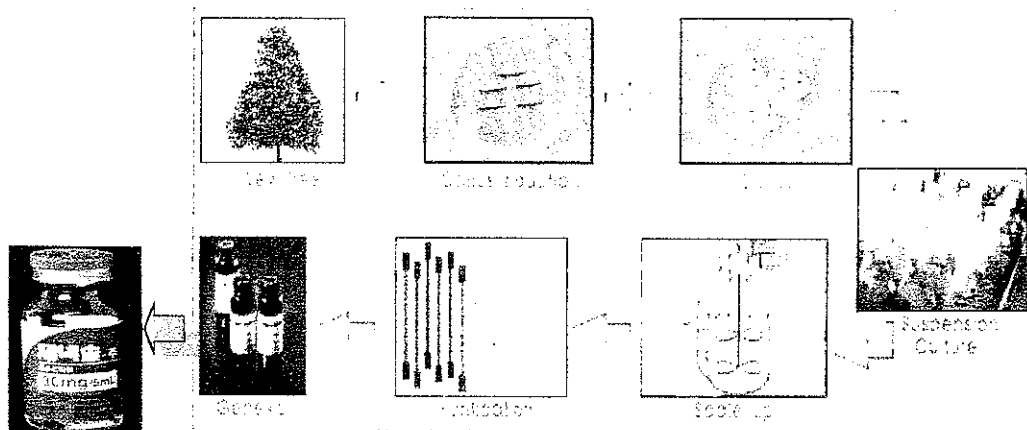
To overcome a limitation of resources, Samyang Genex Corporation developed an advanced plant cell and tissue culture technology (Fig. 1) to produce pure Genexol® (paclitaxel) from the explants of *Taxus chinensis* in 1997. The advanced plant cell and tissue culture technology of Samyang Genex Corporation assures no negative environmental problems, native friendly and unlimited supply of high quality paclitaxel with very competitive cost, high productivity, low purification cost and constant yield. Scientific evidences confirmed that Genexol® contains >99.0% of pure paclitaxel, the highest quality of paclitaxel product.

Genexol® Injectable (which contains paclitaxel fermented from *Taxus chinensis*) is a generic formulation of Taxol® which was self-developed by Samyang Corporation for the clinical use of various human cancers in Korea and other countries.

In human cancer cell line model, Genexol® Injectable and Taxol® showed comparable in vitro cytotoxicity against human ovarian cancer cell line (OVCAR-3) and breast cancer cell line (MCF7). The Maximum Tolerated Dose (MTD) of Genexol® Injectable and Taxol® in beagle dogs after I.V. infusion was determined to be 0.2 and 0.1 mg/kg, respectively. The median lethal dose (LD₅₀) in Sprague-Dawley rats was 9.9 mg/kg (male) and 11.9 mg/kg (female) for Genexol® Injectable, while 8.3 mg/kg (male) and 8.8 mg/kg (female) for Taxol®. The in vivo antitumor efficacy of Genexol® Injectable as measured by reduction in tumor volume of human breast cancer MX-1 implanted in nude (nu/nu) athymic mice was similar to Taxol® at a dose of 8, 16 and 24 mg/kg.

In March 2001, KFDA approved the use of Genexol® Injectable for patients with metastatic breast cancer after failure of first-line chemotherapy based on the pre-clinical trials and clinical trials for the treatment of advanced breast cancer. Subsequently, Genexol® Injectable will be approved in 2002 for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Fig. 1. Typical Production Method of Genexol® Using Plant Cell Culture Technology



References

1. Huizing, M. T., Sewberath Misser, V. H., Pieters, R. C. et al. Taxanes: a new class of antitumor agents. *Cancer Invest.* 13: 381-404 (1995)
2. Holmes, F. A., Kudelka, A. P., Kavanagh, J. J. et al., in: G.I. Georg (Ed.), *Taxane Anticancer Agents*, ACS, Washington DC, 1995, pp. 31-57.
3. Straubinger, R. M., *Taxol Science and Applications*, CRC, New York, 1995, pp. 237-258
4. Adams, J. D., Flora, K. P., Goldspiel, B. R. et al. Taxol: a history of pharmaceutical development and current pharmaceutical concerns. *J. Natl. Cancer Inst.* 15: 141-147 (1993)
5. Panchagnula, R., Pharmaceutical aspects of paclitaxel. *Int. J. Pharm.* 172: 1-15 (1998)