We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



24

Poly (L-glutamic acid)-Paclitaxel Conjugates for Cancer Treatment

Shuang-Qing Zhang
National Center for Safety Evaluation of Drugs, National Institutes for Food and Drug Control, China

1. Introduction

One of the effective approaches to develop new anticancer drugs is to prepare polymer-anticancer drug conjugates. The polymer-anticancer drug conjugates include polymer-protein conjugates, polymer-drug conjugates and supramolecular drug-delivery systems. In 1975, the concept of a polymer-drug conjugate was first proposed by Ringsdorf (Ringsdorf, 1975). In his model, a bioactive anticancer agent was attached to a suitable polymeric carrier, directly or through a biodegradable linker. Currently developed delivery systems for anticancer agents encompass colloidal systems (liposomes, emulsions, nanoparticles and micelles), polymer implants and polymer conjugates. These delivery systems are able to provide enhanced therapeutic efficacy and reduce toxicity of anticancer agents mainly by altering the pharmacokinetics and biodistribution of the drugs (Kim & Lim, 2002). The idea is attractive and could form the basis of a new generation of anticancer agents (Sugahara et al., 2007).

Many polymers have been investigated as carriers for conjugates, including poly(glutamic acid), poly(L-lysine), poly(malic acid), poly(aspartamides), poly((N-hydroxyethyl)-L glutamine), poly(ethylene glycol), poly(styrene-co-maleic acid/anhydride), poly(N-(2-hydroxypropyl) methacrylamide) copolymer, poly(ethyleneimine), poly(acroloylmorpholine), poly(vinylpyrrolidone), poly(vinylalcohol), poly(amidoamines), divinylethermaleic anhydride/acid copolymer, dextran, pullulan, mannan, dextrin, chitosan, hyaluronic acid and proteins *etc.*. Coupling low molecular weight anticancer drugs to high or low molecular weight polymers is an effective method for improving the therapeutic index of clinically used agents.

Several candidates have been evaluated in clinical trials, such as N-(2-hydroxypropyl) methacrylamide conjugates of doxorubicin, camptothecin, paclitaxel, and platinum (II) complexes (Haag & Kratz, 2006). The conjugation of cytotoxic agents to a hydrophilic polymer may convey several advantages, (1) increased water solubility; (2) protection from hydrolysis and proteolysis; (3) prolonged half-life and enhanced bioavailability of drug; (4) reduction of toxicity, immunogenicity and antigenicity; (5) controlled release or specific targeting through an enhanced permeability and retention (EPR) effect. In the chapter, we will focus on poly (L-glutamic acid)-paclitaxel (PG-PTX), which can improve the therapeutic index, pharmacokinetic properties, safety and efficacy of paclitaxel (PTX).

2. The anticancer agent PTX

PTX, an anticancer agent isolated from the trunk bark of the Pacific Yew tree, Taxus brevifolia, shows a wide spectrum of anticancer activity for a variety of human cancers, including breast, ovarian, non-small-cell lung, prostate, head and neck, colon cancers and so on (Rowinsky, 1997). PTX can induce mitotic arrest and apoptosis in proliferating cells by targeting tubulin, which is a component of the mitotic spindle. PTX binds to the N-terminal 31 amino acids of the β-tubulin subunit and prevents depolymerization. As a result, the mitotic spindle is disabled, cell division can not be completed, and the cell replication in the late G2 or M phase of the cell cycle is inhibited. The cancer cells are killed by disrupting the dynamics necessary for cell division (Bhalla, 2003). The anticancer mechanism of PTX is shown in Fig. 1.

The clinical use of PTX is limited by its high hydrophobicity, low solubility, high systemic exposure, poor pharmacokinetic characteristics, and the lack of selective tumor uptake (Parveen & Sahoo, 2008; ten Tije et al., 2003). The clinical use of PTX also leads to many side effects. Side effects of PTX include nausea, vomiting, diarrhea, mucositis, myelosuppression, cardiotoxicity, neurotoxicity and hypersensitivity reactions, and the latter two are mainly owing to polyoxyethylated castor oil (Cremophor® EL) and ethanol used for solubilizing PTX (Rogers, 1993; Sugahara et al., 2007). PTX for injection is supplied in 50% Cremophor® EL and 50% dehydrated ethanol.

Despite premedication with corticosteroids and antihistamines, PTX still induces minor reactions (e.g., flushing and rash) in approximately 40% of patients and major potentially life-threatening reactions in 1.5%−3% of patients (Lemieux et al., 2008; Price & Castells, 2002). Hydrophobicity of PTX is also associated with unfavorable kinetics, high levels of protein binding, and high volumes of distribution often greatly exceeding total body water. Together, all these factors have a negative impact on the therapeutic index because only a small proportion of the drug administered actually reaches the tumor site (Singer, 2005). As mentioned above, the efficacy and tolerability of PTX are limited by its low solubility, high systemic exposure, and the lack of selective tumor uptake.

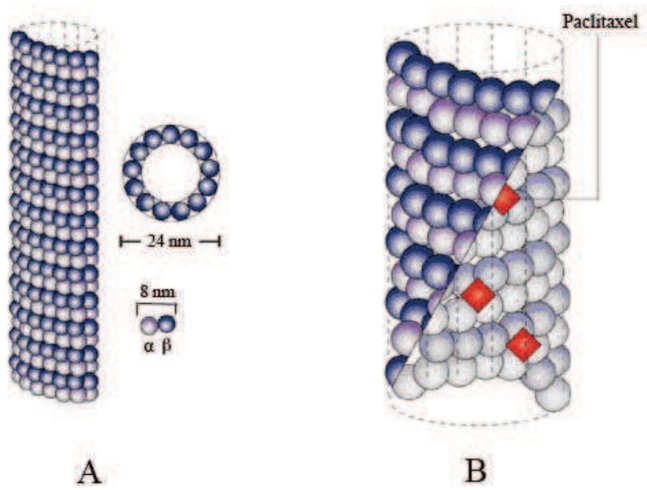


Fig. 1. Schematic illustration of PTX anticancer mode: heterdimers of α- and β-tubulin assemble to form a highly dynamic microtubule which plays an extremely important role in the process of mitosis (A); microtubule-targeted paclitaxel binds along the interior surface of the microtubule, suppressing its dynamics mitosis (B).

3. The EPR effect and endocytosis of polymer-drug conjugates

Anticancer polymer-drug conjugates can be divided into two targeting modalities: passive and active. While clinical anticancer activity has been achieved by passive macromolecular drug delivery systems, further selectivity is possible by active targeting (Luo & Prestwich, 2002). Polymer-drug conjugates can promote passive tumor targeting by EPR effect and allow for lysosomotropic drug delivery following endocytic capture of the drugs (Greco & Vicent, 2008).

The view that the polymer-drug conjugates passively accumulate in tumor tissues because EPR effect is clearly supported by the electron microscopic observation that the peripheral tumor vascular endothelium has quantitatively more fenestrations and open junctions than normal vessels (Li, 2002; Roberts & Palade, 1997). Tumor vasculature is more permeable to macromolecules than normal vasculature because the structures between the neovasculature in tumors and the mature vasculature in normal organs are different (Roberts & Palade, 1997; Singer, 2005). The paucity of lymphatic vessels in tumor tissues allows the retention of these macromolecules in the interstitial space, which leads to 10 to 100-fold increase in intratumoral drug concentrations for a prolonged time when compared with an equivalent dose of the anticancer drug given according to the conventional methods.

The phenomenon of EPR effect is applicable for almost all rapidly growing solid tumors and it has been widely used in cancer-targeting drug design (Iyer et al., 2007; Maeda et al., 2000; Reddy, 2005). The EPR effect is molecular weight (MW) - and size-dependent and is most effective with agents whose MWs are 50 000 or greater, which is above the threshold for renal excretion. Due to the different pathways to enter the cells between the small molecule drugs and the macromolecule drugs, multi-drug resistance (MDR) can be minimized at the same time (Boddy et al., 2005; Greish et al., 2003; Shaffer et al., 2007). Because of the stronger metabolic activity of the cancer cells, in addition to the EPR effect, cancer cells show a higher degree of uptake of macromolecules by endocytosis than normal cells (Li, 2002). The process of EPR and endocytosis is illustrated in Fig. 2.

4. PG-PTX conjugate

4.1 Modified formulations of PTX

Because of the unfavorable properties of PTX, it is urgent to develop a more effective strategy to improve its water solubility and selectivity towards tumor tissues (Maeda et al., 2009). Several approaches have been utilized to increase the therapeutic index of PTX. More water-soluble formulations of PTX have been investigated, including a nanoparticulate formulation (ABI-007), a polymeric micellar formulation (Genexol-PM), and a liposomal formulation and covalent linkage to macromolecule polymers that alter the pharmacokinetics of the parent drug (Ibrahim et al., 2002; Kim et al., 2004; Soepenberg et al., 2004).

4.2 The formation and the anticancer mechanism of PG-PTX

PG-PTX (paclitaxel poliglumex, CT-2103, Xyotax®, Opaxio®) is a water-soluble macromolecular conjugate that links PTX with PG (Li et al., 1996). PTX is conjugated by ester linkage to the γ-carboxylic acid side chains, leading to a relatively stable conjugate (Li

et al., 1998a). Because the conjugation site is the 2 hydroxyl group of PTX, which is a crucial site for tubulin binding, the conjugate does not interact with β-tubulin and is inactive (Li, 2002; Rogers, 1993). The median MW of PG-PTX is 38.5 kDa, with a PTX content of approximately 36% on a w/w basis, equivalent to about one PTX ester linkage per 11 PG units of the polymer (Fig. 3) (Bonomi, 2007; Rogers, 1993).

Morphological analysis and biochemical characterizations demonstrate that both PTX and PG-PTX are able to induce apoptosis in cells expressing wild-type p53 or mutant p53, to arrest cells in the G2/M phase of the cell cycle, and to down-regulate HER-2/neu expression. Furthermore, when PG-PTX is compared with other water-soluble derivatives of PTX, including small-molecular-weight sodium pentetic acid-PTX and polyethylene glycol-PTX conjugate (MW 5 kDa), they all show the same effects on telomeric association, mitotic index chromatin condensation, and formation of apoptotic bodies (Multani et al., 1999). These results indicate that PG-PTX has the same mechanisms of action as PTX.

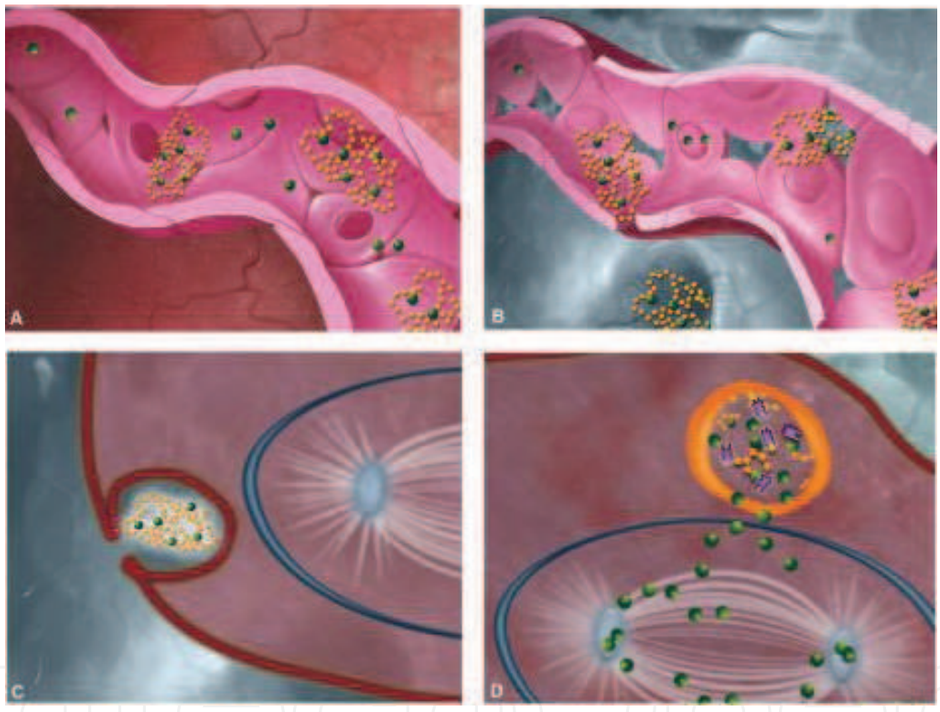


Fig. 2. Illustration of EPR effect and endocytosis. Different from blood vessels in normal tissue (A), those in tumor tissue (B) have porous openings, through which large-size conjugate leaks and is preferentially trapped and distributed to the tumor tissue. Once in the tumor tissue, the conjugate is taken up by the tumor cells through a cellular process called endocytosis (C). The conjugate releases active agent (D) via metabolism by lysosomal enzymes inside the lysosome of the tumor cell.

4.3 PG as the carrier of PG-PTX

Compared with other synthetic polymers that have been tested in clinical studies, PG is unique because it is composed of natural L-glutamic acid linked together through amide bonds rather than the nondegradable C-C backbone. The free γ-carboxyl group in each repeating unit of L-glutamic acid is negatively charged under a neutral pH condition, which

makes the polymer water-soluble. The carboxyl groups can also provide functionality for drug attachment. PG is not only water-soluble and biodegradable, it is also nontoxic. All these characteristics make PG a unique candidate as the carrier of polymer-drug conjugates for selective delivery of chemotherapeutic agents, especially for PTX (Parveen & Sahoo, 2008).

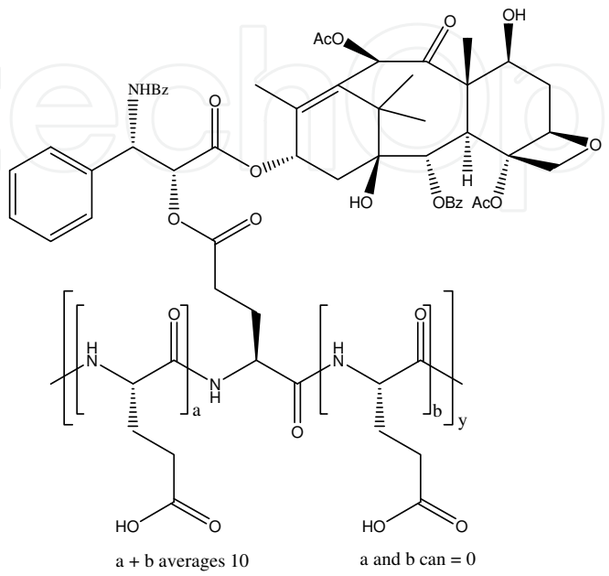


Fig. 3. Schematic representation of PG-PTX structure. The structure shown is illustration of a fragment of the molecule. On average there are approximately 10 non-conjugated monomer glutamic acid units (a + b) for every molecule conjugated to a PTX molecule (y).

4.4 The metabolism of PG-PTX

PG-PTX conjugate is stable in the systemic circulation but can be broken down by intracellular lysosomal enzymes to release the drug after entering cells by endocytosis. The proposed mechanism by which PG-PTX is metabolized includes endocytosis of the polymer-drug conjugate followed by intracellular release of active PTX by proteolytic activity of the lysosomal enzyme cathepsin B, an exocarboxydipeptidase, and diffusion of PTX into the nucleus (Turk et al., 2001). The process is presented in Fig. 4. This finding may have biological relevance as expression of cathepsin B is upregulated in malignant cells, particularly during tumor progression period (Podgorski & Sloane, 2003). These data support a model in which PG-PTX accumulates in tumor tissues through the EPR effect, followed by the cathepsin B-mediated release of PTX. The kinetics of intracellular formation of several PG-PTX metabolites have been quantified in vitro and have been found to be largely dependent on cathepsin B. Metabolites that have been detected in vivo include diglutamyl-PTX and monoglutamyl-PTX. Monoglutamyl-PTX is an unstable compound that can be nonenzymatically degraded to release free PTX. Specific enzyme inhibitors such as CA-074 methyl ester, a cell-permeable irreversible inhibitor of cathepsin B, and EST, a cell-permeable irreversible inhibitor of cysteine proteases, dramatically decrease the formation of monoglutamate PTX and unconjugated PTX in tumor cells that have been incubated with PG-PTX (Rogers, 1993).

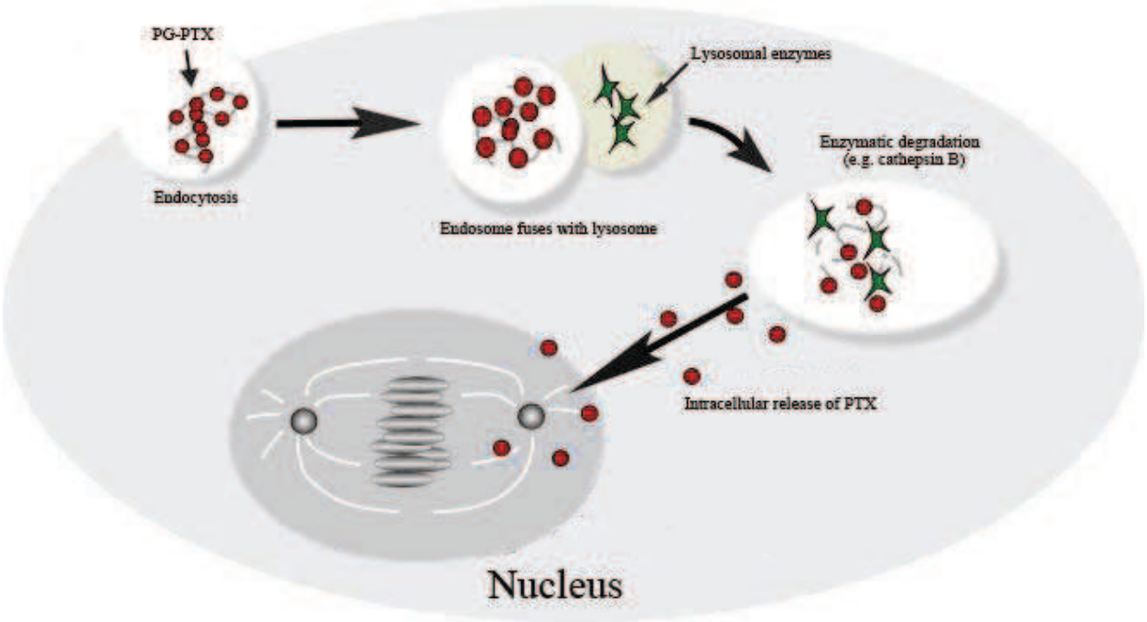


Fig. 4. Metabolism of PG-PTX by endocytosis and enzymatic degradation.

4.5 The advantages of PG-PTX

4.5.1 PG-PTX reduces the side effects of PTX in clinical application

Compared with PTX, the solubility, uptake, tumor retention, and anticancer efficacy of PG-PTX are increased. Many clinical studies so far have confirmed several advantages of PG-PTX in the treatment of cancer patients. This macromolecular conjugate PG-PTX eliminates the need for Cremophor® EL and, therefore, decreases infusion time and the risk of hypersensitivity. Compared to standard taxanes, PG-PTX in phase I and phase II studies shows encouraging outcomes with reduced neutropenia and alopecia, and allows a more convenient administration schedule without the need for routine premedications (Rogers, 1993). PG-PTX induces hypersensitivity reactions in less than 1% of patients, without premedication, and only rare severe reactions have been reported. Furthermore, patients undergoing PG-PTX therapy have a better quality of life, because there is no significant hair loss, nerve damage, or neutropenia at the current dose. PG-PTX is water-soluble and can be administrated rapidly as a 10 -20 min infusion rather than hours when administrating PTX. The recommended phase II dose of PG-PTX is 235 mg/m^2 every 3-week administered over a 10 min infusion without premedication (Sabbatini et al., 2004). Twenty-six patients were treated with PG-PTX in the Phase I study of PG-PTX administered weekly for patients with advanced solid malignancies. The recommended dose of PG-PTX for subsequent disease-directed studies is 70 mg/m^2 weekly. Most patients experienced at least one drug-related adverse event during the study (Table 1) (Mita et al., 2009). Ninety-nine patients were treated with PG-PTX in a multi-center phase II study of PG-PTX as an intravenous (i.v.) infusion (approximately 10 min) at a dose of 175 mg/m^2 on day 1 of each 3-week cycle. And the treatment-related adverse events including non-laboratory-based and laboratory-based maximum CTC toxicities in all cycles are listed in Table 2.

	Grade 1	Grade 2	Grade 3	Total
Adverse event -70 mg/m^2				
Neutropenia		1(13%)	1(13%)	2(25%)
Anemia	1(13%)	1(13%)		2(25%)
Peripheral neuropathy	2(25%)	2(25%)		2(50%)
Anorexia	1(13%)			1(13%)
Diarrhea			1(13%)	1(13%)
Nausea	1(13%)			1(13%)
Pain in limb	1(13%)			1(13%)
Fatigue		1(13%)		1(13%)
Adverse event-all cohorts				
Neutropenia		2(8%)	3(12%)	5(19%)
Anemia	1(4%)	1(4%)	2(8%)	4(15%)
Peripheral neuropathy	5(16%)	4(8%)	1(4%)	10(38%)
Anorexia	1(4%)	1(4%)		2(8%)
Diarrhea	3(12%)	1(4%)	1(4%)	5(19%)
Nausea	3(12%)	1(4%)		4(15%)
Rash	1(4%)	2(8%)		3(12%)
Myalgia	3(12%)	2(8%)		5(19%)
Pain in limb	1(4%)	1(4%)		2(8%)
Fatigue	4(15%)	3(12%)		7(27%)
Hypersensitivity	1(4%)	1(4%)		2(8%)

Table 1. Adverse events related to PG-PTX administration (n = 26).

	Grade 1	Grade 2	Grade 3	Grade 4
Non-laboratory-based maximum CTC toxicity, all cycles				
Neuropathy	20	15	15	0
Fatigue	10	19	5	0
Musculoskeletal	11	10	1	0
Myalgia/arthralgia	7	5	1	0
Nausea	21	4	1	0
Stomatitis/mucositis	7	1	1	0
Hoarseness	0	0	1	0
Drug hypersensitivity	5	8	1	0
Laboratory-based maximum CTC toxicity, all cycles				
Neutropenia	20	14	15	9
Leukopenia	13	18	18	0
Anemia	46	18	6	0

Abbreviation: CTC, National Cancer Institute Common Toxicity Criteria.

Table 2. Treatment-related adverse events (n = 99).

4.5.2 PG-PTX promotes anticancer efficacy and reduces toxicity by prolonging tumor exposure and minimizing systemic exposure to active drug

A single i.v. injection of PG-PTX at its maximum tolerated dose (MTD) equivalent to 60 mg of PTX/kg and at a lower dose equivalent to 40 mg of PTX/kg results in the disappearance of an

established implanted 13762F mammary adenocarcinoma (mean size, 2000 mm^3) in rats. Similarly, mice bearing syngeneic OCa-1 ovarian carcinoma (mean size, 500 mm^3) are tumor-free within 2 weeks after a single i.v. injection of PG-PTX at a dose equivalent to 160 mg of PTX/kg (Li et al., 1998b). MTD of PTX in rats and mice are 20 mg/kg and 60 mg/kg, respectively. In contrast, MTD of a single i.v. injection of PG-PTX in rats and mice are 60 mg/kg and 160 mg/kg, respectively. MTD of PG-PTX was approximately 160 mg/kg to 200 mg/kg in immunocompetent mice and 120 mg/kg to 150 mg/kg in immunodeficient animals. At their respective MTDs, single-dose PG-PTX is more efficacious than PTX in Cremophor® EL/ethanol (Li et al., 1999). PG-PTX has shown anticancer activity in preclinical studies with human tumor xenografts and in early phase I trials. MTD of PG-PTX as a single agent, based on the first cycle toxicity of patients, is 235 mg/m^2 (Verschraegen et al., 2009). Biodistribution in mice bearing OCa-1 tumor treated with i.v. injections of tritium-labeled PG-[^{3}H] PTX shows a five times greater distribution of PTX to tumor tissues than those treated with PTX (Li et al., 2000c), which was demonstrated by whole-body autoradiograph (Fig. 5).



Fig. 5. Whole-body autoradiographs of mice killed 1 day (A) and 6 days (B) after tail vein injection of PG-[^{3}H]PTX. Most radioactivity was localized to tumor periphery at 1 day after injection, but by day 6, radioactivity had diffused into the center of the tumor. L: liver; M: muscle; Arrow head: tumor.

Preclinical studies in animal tumor models demonstrate that PG-PTX is more effective than PTX and it is associated with prolonged tumor exposure but minimized systemic exposure to the active drug. The slow release of the active drug from a well-designed polymer carrier results in sustained high intratumoral drug levels and lower plasma concentrations of the

active drug. To accomplish this, the polymer conjugate should release the active drug in tumor tissues rather than in the plasma during circulation. As a result, exposure of normal tissues will be limited, which is potentially associated with a more favorable toxicity profile (Li et al., 2000c). Thus, enhanced tumor uptake and sustained release of PTX from PG-PTX in tumor tissues are major factors contributing to its markedly improved in vivo anticancer activities.

4.5.3 The favorable pharmacokinetic properties of PG-PTX

The superior anticancer activity of PG-PTX in preclinical studies suggests that PG-PTX might have favorable pharmacokinetic properties. Many studies suggest that PG-PTX exerts the anticancer activity by the continuous release of free PTX, and that the favorable pharmacokinetics of PG-PTX conjugate in vivo is likely the main cause contributing to its advanced anticancer activity (Oldham et al., 2000). Female mice with subcutaneous B16 murine melanomas are given PG-[^{3}H] PTX at the equivalent dose 40 mg/kg of [^{3}H] PTX i.v. infusion. Tumor samples are collected at regular intervals up to 144 h after infusion, and the concentrations of PG-PTX and PTX are determined by LC/MS analysis. Tumor exposure to total taxanes is increased by a factor of 3 (C_{max}) or a factor of 12 (AUC) in mice treated with PG-[^{3}H] PTX compared with the mice treated with [^{3}H] PTX (Table 3) (Chipman et al., 2006). PG-[^{3}H] PTX has a much longer half-life in plasma than [^{3}H] PTX (Fig. 6).

Whereas PTX has an extremely short half-life in the plasma of mice ($t_{1/2}$ = 29 min), the apparent half-life of PG-PTX is prolonged ($t_{1/2}$ = 317 min) (Li et al., 1998b). In clinical trials, PG-PTX is given as a 30-min infusion every 3 weeks. Patients were treated at dose levels ranging from 30 mg/m^2 to 720 mg/m^2. PG-PTX is detectable in plasma of all patients and has a long plasma half-life of up to 185 h, and the results are consistent with preclinical findings. Furthermore, concentrations of free PTX released from PG-[^{3}H] PTX remain relatively constant up to 6 d after infusing. Moreover, peak plasma concentrations of free PTX are less than 0.1 μM 24 h after PG-PTX administration at doses up to 480 mg/m^2 (176 mg/m^2 PTX equivalents) (Boddy et al., 2001).

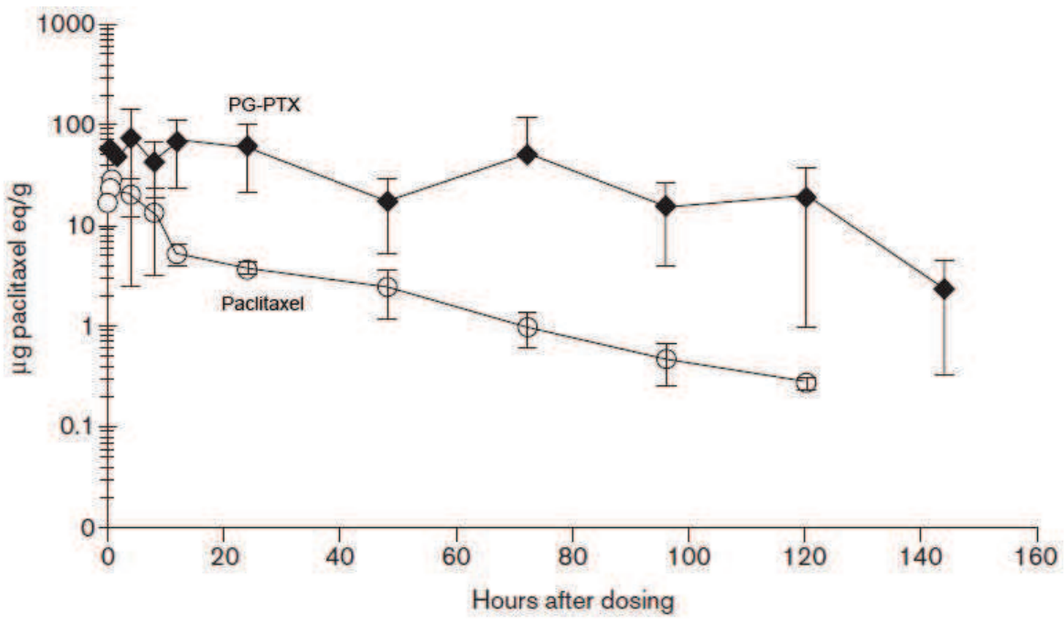


Fig. 6. Tumor concentration of [^{3}H]paclitaxel after treatment with PG-[^{3}H] PTX and [^{3}H] paclitaxel in female mice with s.c. B16 melanomas at a dose of 40 mg paclitaxel.

In another phase I study, PG-PTX is administrated at 70 mg/m^2. The mean maximal concentration (C_{max}) is 41.2 ± 8.60 μg/mL and the C_{max} is reached right after the end of the infusion. The plasma concentration declines with a mean terminal half-life of 15.7 ± 3.17 h. The mean AUC at the MTD is 455 ± 112 μg/h/mL and the mean average systemic plasma clearance is 0.16 ± 0.04 L/h/m^2 (Sabbatini et al., 2004). At the MTD, the mean volume of distribution at steady state and during the terminal phase are 1.41 ± 0.28 L/m^2 and 3.62 ± 1.13 L/m^2, the mean C_{max} of unconjugated PTX is 0.21 ± 0.07 μg/mL, the mean T_{max} is 0.56 ± 0.18 h, the mean terminal half life is 16.6 ± 7.85 h, and the mean AUC is 3.15 ± 1.16 μg/h/mL. The ratio of the free PTX AUC to the conjugated PTX AUC is 0.7%. The plasma concentration of PTX released from PG-PTX increases largely in proportion to the dose and remains similar after repeated administration (Sabbatini et al., 2004).

	C_{max} (μg/g)	T_{max} (h)	AUC (μg/h/g)	MRT (h)
PG-[^{3}H] PTX				
Total taxanes	72.0	4	4547	51
PTX	4.0	72	345	66
[^{3}H] PTX				
Total taxanes	26.7	1.5	384	23
PTX	22.4	1.5	261	17

Table 3. Preclinical tumor pharmacokinetics.

4.5.4 PG-PTX facilitates the radiotherapy and chemotherapy

Preclinical studies in animal tumor models demonstrate the enhanced safety and efficacy of PG-PTX relative to PTX when administered as a single agent or in conjunction with radiation. Studies show that PG-PTX given 24 h before or after radiotherapy enhances tumor growth delay significantly more than PTX. PG-PTX dramatically potentiates tumor radiocurability after single-dose or fractionated irradiation without affecting acute normal tissue injury. PG-PTX increases the therapeutic ratio of radiotherapy more than that previously reported for other taxanes (Milas et al., 2003). PG-PTX not only can produce a much stronger radiopotentiating effect than PTX, the kinetics of its radiopotentiating effect is also different from that of PTX. Delays in the growth of syngeneic murine ovarian OCa-1 tumors grown intramuscularly in C3Hf/Kam mice are used as the treatment end point.

PG-PTX given 24 h before tumor irradiation increases the efficacy of tumor radiation by a factor of more than 4 (Li et al., 2000a). Furthermore, the combination of radiation and PG-PTX can produce a significantly greater tumor growth delay than treatment with radiation and PTX when both drugs are given at the same equivalent PTX dose of 60 mg/kg 24 h after tumor irradiation (enhancement factors, 4.44 versus 1.50) (Li et al., 2000b). When the treatment end point is tumor cure, the enhancement factors are 8.4 and 7.2 of fractionated and single dose radiation, respectively. These values are greater than those produced by other taxanes or by any other chemotherapeutic drugs or radiosensitizer tested so far. PG-PTX may exert its radiopotentiation activity through increased tumor uptake of PG-PTX and sustained release of PTX in the tumor (Li et al., 2000a). To determine whether prior irradiation affects tumor uptake of PG-PTX, PG-[^{3}H] PTX is injected into mice with OCa-1

tumors 24 h after 15 Gy local irradiation (Li et al., 2000b). The uptake of PG-[^{3}H] PTX in irradiated tumors is 28%−38% higher than that in nonirradiated tumors at different times after PG-[^{3}H] PTX injection, indicating that tumor irradiation can increase the accumulation of PG-PTX in the tumors (Fig. 7).

Anticancer activity in patients who have failed previous chemotherapy, including PTX treatment, is observed with PG-PTX (Sabbatini et al., 2004). Ninety-nine patients in a multicenter phase II study treated with PG-PTX as an i.v. infusion approximately 10 min at a dose of 175 mg/m^2 on day 1 of each 3-week cycle have received at least one cycle of treatment. Response rates categorized by platinum sensitivity are shown in Table 4.

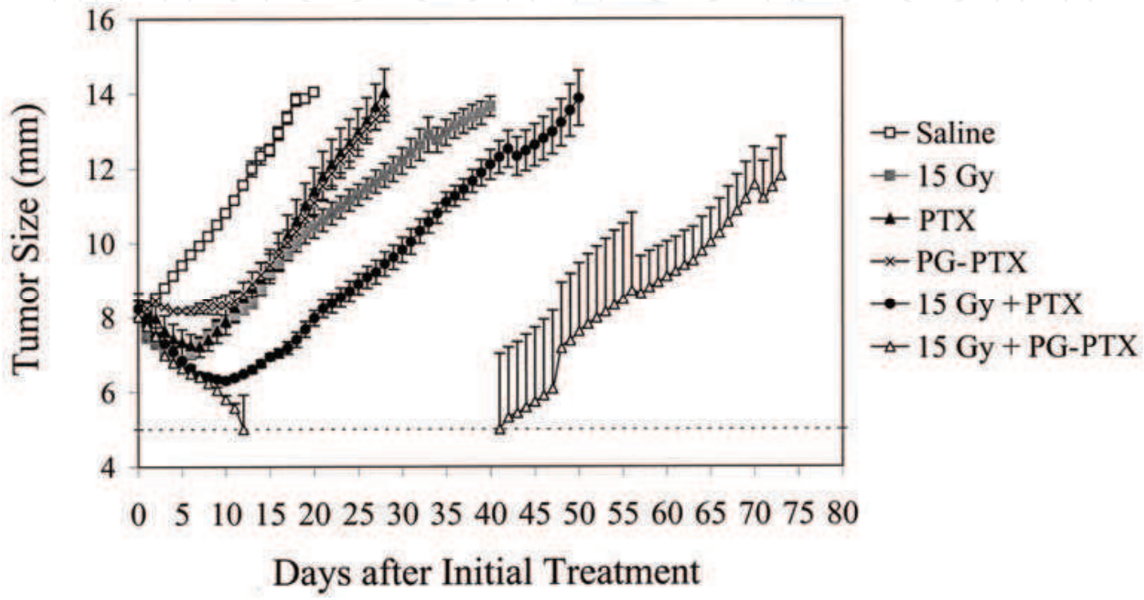


Fig. 7. Effects of combined radiation and PG-PTX and radiation and PTX on the growth of OCa-1 tumors in mice.

No. of Regimens	Response					
	PR		SD		PD	
	No. of Patients	(%)	No. of Patients	(%)	No. of Patients	(%)
Platinum-sensitive, *n* = 42						
1 or 2 prior regimens	5/18	28	6/18	33	7/18	39
≥3 prior regimens	1/24	4	11/24	46	12/24	50
Total	6/42	14	17/42	40	19/42	45
Platinum-resistant/refractory, *n* = 57						
1 or 2 prior regimens	2/21	10	4/21	19	15/21	71
≥3 prior regimens	2/36	6	11/36	31	23/36	64
Total	4/57	7	15/57	26	38/57	67

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Response by Platinum Sensitivity.

5. Summary

Clinical proof of concept for polymer conjugates has already been achieved over the last three decades, with a family of polymer-protein conjugates reaching the market and a growing list of polymer-drug conjugates currently in clinical studies. The application of polymer-anticancer drug conjugates in anticancer treatment is a promising field with growing opportunities to achieve medical treatments with highly improved therapeutic value (Vicent et al., 2008). PG-PTX conjugate can improve the anticancer activity, enhance the safety and efficacy, ameliorate the pharmacokinetic properties and so on. Therefore, the application of PG-PTX facilitates the clinical therapy of a variety of human cancers.

However, many challenges still exist, providing opportunities to improve this platform technology further. The clinical development of anticancer agents utilizing various delivery systems is actively undergoing. New technologies and multidisciplinary approaches to develop advanced drug delivery systems, applicable to a wide range of anticancer agents, may eventually lead to an effective cancer therapy in the future.

6. Acknowledgement

This work was supported by the National Key Technologies R & D Program for Drug Safety Evaluation (Grant No. 2008ZX09305-002) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry.

7. References

Bhalla, K. N. (2003). Microtubule-targeted anticancer agents and apoptosis. *Oncogene*, Vol. 22, No. 56, (December 2003), pp. 9075-9086, ISSN 0950-9232

Boddy, A. V.; Griffin M. J.; Sludden J.; Thomas H. D.; Fishwick K.; Wright J. G.; Plumner E. R.; Highley M. & Calvert A. H. (2001). Pharmacological study of paclitaxel duration of infusion combined with GFR-based carboplatin in the treatment of ovarian cancer. *Cancer chemotherapy and pharmacology*, Vol. 48, No. 1, (July 2001), pp. 15-21, ISSN 0344-5704

Boddy, A. V.; Plummer E. R.; Todd R.; Sludden J.; Griffin M.; Robson L.; Cassidy J.; Bissett D.; Bernareggi A.; Verrill M. W. and others. (2005). A phase I and pharmacokinetic study of paclitaxel poliglumex (XYOTAX), investigating both 3-weekly and 2-weekly schedules. *Clinical Cancer Research*, Vol. 11, No. 21, (November 2005), pp. 7834-7840, ISSN 1078-0432

Bonomi, P. (2007). Paclitaxel poliglumex (PPX, CT-2103): macromolecular medicine for advanced non-small-cell lung cancer. *Expert Review of Anticancer Therapy*, Vol. 7, No. 4, (April 2007), pp. 415-422, ISSN 1744-8328

Chipman, S. D.; Oldham F. B.; Pezzoni G. & Singer J. W. (2006). Biological and clinical characterization of paclitaxel poliglumex (PPX, CT-2103), a macromolecular polymer-drug conjugate. *International Journal of Nanomedicine*, Vol. 1, No. 4, 2006), pp. 375-383, ISSN 1176-9114

Greco, F. & Vicent M. J. (2008). Polymer-drug conjugates: current status and future trends. *Frontiers in Bioscience*, Vol. 13, No., 2008), pp. 2744-2756, ISSN 1093-4715

Greish, K.; Fang J.; Inutsuka T.; Nagamitsu A. & Maeda H. (2003). Macromolecular therapeutics: advantages and prospects with special emphasis on solid tumour targeting. *Clinical pharmacokinetics*, Vol. 42, No. 13, 2003), pp. 1089-1105, ISSN 0312-5963

Haag, R. & Kratz F. (2006). Polymer therapeutics: concepts and applications. *Angewandte Chemie*, Vol. 45, No. 8, (February 2006), pp. 1198-1215, ISSN 1433-7851

Ibrahim, N. K.; Desai N.; Legha S.; Soon-Shiong P.; Theriault R. L.; Rivera E.; Esmaeli B.; Ring S. E.; Bedikian A.; Hortobagyi G. N. and others. (2002). Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clinical Cancer Research*, Vol. 8, No. 5, (May 2002), pp. 1038-1044, ISSN 1078-0432

Iyer, A. K.; Greish K.; Seki T.; Okazaki S.; Fang J.; Takeshita K. & Maeda H. (2007). Polymeric micelles of zinc protoporphyrin for tumor targeted delivery based on EPR effect and singlet oxygen generation. *Journal of drug targeting*, Vol. 15, No. 7-8, (August-September 2007), pp. 496-506, ISSN 1061-186X

Kim, C. K. & Lim S. J. (2002). Recent progress in drug delivery systems for anticancer agents. *Archives of pharmacal research*, Vol. 25, No. 3, (June 2002), pp. 229-239, ISSN 0253-6269

Kim, T. Y.; Kim D. W.; Chung J. Y.; Shin S. G.; Kim S. C.; Heo D. S.; Kim N. K. & Bang Y. J. (2004). Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clinical Cancer Research*, Vol. 10, No. 11, (June 2004), pp. 3708-3716, ISSN 1078-0432

Lemieux, J.; Maunsell E. & Provencher L. (2008). Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. *Psychooncology*, Vol. 17, No. 4, (April 2008), pp. 317-328, ISSN 1099-1611

Li, C. (2002). Poly(L-glutamic acid)--anticancer drug conjugates. *Advanced Drug Delivery Reviews*, Vol. 54, No. 5, (September 2002), pp. 695-713, ISSN 0169-409X

Li, C.; Ke S.; Wu Q. P.; Tansey W.; Hunter N.; Buchmiller L. M.; Milas L.; Charnsangavej C. & Wallace S. (2000a). Potentiation of ovarian OCa-1 tumor radioresponse by poly (L-glutamic acid)-paclitaxel conjugate. *International Journal of Radiation Oncology, Biology, Physics*, Vol. 48, No. 4, (November 2000a), pp. 1119-1126, ISSN 0360-3016

Li, C.; Ke S.; Wu Q. P.; Tansey W.; Hunter N.; Buchmiller L. M.; Milas L.; Charnsangavej C. & Wallace S. (2000b). Tumor irradiation enhances the tumor-specific distribution of poly(L-glutamic acid)-conjugated paclitaxel and its antitumor efficacy. *Clinical Cancer Research*, Vol. 6, No. 7, (July 2000b), pp. 2829-2834, ISSN 1078-0432

Li, C.; Newman R. A.; Wu Q. P.; Ke S.; Chen W.; Hutto T.; Kan Z.; Brannan M. D.; Charnsangavej C. & Wallace S. (2000c). Biodistribution of paclitaxel and poly(L-glutamic acid)-paclitaxel conjugate in mice with ovarian OCa-1 tumor. *Cancer chemotherapy and pharmacology*, Vol. 46, No. 5, 2000c), pp. 416-422, ISSN 0344-5704

Li, C.; Price J. E.; Milas L.; Hunter N. R.; Ke S.; Yu D. F.; Charnsangavej C. & Wallace S. (1999). Antitumor activity of poly(L-glutamic acid)-paclitaxel on syngeneic and

xenografted tumors. *Clinical Cancer Research*, Vol. 5, No. 4, (April 1999), pp. 891-897, ISSN 1078-0432

Li, C.; Yu D.; Inoue T.; Yang D. J.; Milas L.; Hunter N. R.; Kim E. E. & Wallace S. (1996). Synthesis and evaluation of water-soluble polyethylene glycol-paclitaxel conjugate as a paclitaxel prodrug. *Anticancer Drugs*, Vol. 7, No. 6, (August 1996), pp. 642-648, ISSN 0959-4973

Li, C.; Yu D. F.; Newman R. A.; Cabral F.; Stephens L. C.; Hunter N.; Milas L. & Wallace S. (1998a). Complete regression of well-established tumors using a novel water-soluble poly(L-glutamic acid)-paclitaxel conjugate. *Cancer Res*, Vol. 58, No. 11, (Jun 1998a), pp. 2404-2409, ISSN 0008-5472

Li, C.; Yu D. F.; Newman R. A.; Cabral F.; Stephens L. C.; Hunter N.; Milas L. & Wallace S. (1998b). Complete regression of well-established tumors using a novel water-soluble poly(L-glutamic acid)-paclitaxel conjugate. *Cancer Research*, Vol. 58, No. 11, (June 1998b), pp. 2404-2409, ISSN 0008-5472

Luo, Y. & Prestwich G. D. (2002). Cancer-targeted polymeric drugs. *Current Cancer Drug Targets*, Vol. 2, No. 3, (September 2002), pp. 209-226, ISSN 1568-0096

Maeda, H.; Bharate G. Y. & Daruwalla J. (2009). Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. *European Journal of Pharmaceutics and Biopharmaceutics:*, Vol. 71, No. 3, (March 2009), pp. 409-419, ISSN 1873-3441

Maeda, H.; Wu J.; Sawa T.; Matsumura Y. & Hori K. (2000). Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *Journal of Controlled Release*, Vol. 65, No. 1-2, (March 2000), pp. 271-284, ISSN 0168-3659

Milas, L.; Mason K. A.; Hunter N.; Li C. & Wallace S. (2003). Poly(L-glutamic acid)-paclitaxel conjugate is a potent enhancer of tumor radiocurability. *International Journal of Radiation Oncology, Biology, Physics*, Vol. 55, No. 3, (March 2003), pp. 707-712, ISSN 0360-3016

Mita, M.; Mita A.; Sarantopoulos J.; Takimoto C. H.; Rowinsky E. K.; Romero O.; Angiuli P.; Allievi C.; Eisenfeld A. & Verschraegen C. F. (2009). Phase I study of paclitaxel poliglumex administered weekly for patients with advanced solid malignancies. *Cancer chemotherapy and pharmacology*, Vol. 64, No. 2, (July 2009), pp. 287-295, ISSN 1432-0843

Multani, A. S.; Li C.; Ozen M.; Imam A. S.; Wallace S. & Pathak S. (1999). Cell-killing by paclitaxel in a metastatic murine melanoma cell line is mediated by extensive telomere erosion with no decrease in telomerase activity. *Oncology Reports*, Vol. 6, No. 1, (January-February 1999), pp. 39-44, ISSN 1021-335X

Oldham, E. A.; Li C.; Ke S.; Wallace S. & Huang P. (2000). Comparison of action of paclitaxel and poly(L-glutamic acid)-paclitaxel conjugate in human breast cancer cells. *International Journal of Oncology*, Vol. 16, No. 1, (January 2000), pp. 125-132, ISSN 1019-6439

Parveen, S. & Sahoo S. K. (2008). Polymeric nanoparticles for cancer therapy. *Journal of drug targeting*, Vol. 16, No. 2, (February 2008), pp. 108-123, ISSN 1061-186X

Podgorski, I. & Sloane B. F. (2003). Cathepsin B and its role(s) in cancer progression. *Biochemical Society Symposium*, Vol. No. 70, 2003), pp. 263-276, ISSN 0067-8694

Price, K. S. & Castells M. C. (2002). Taxol reactions. *Allergy and Asthma Proceedings*, Vol. 23, No. 3, (May-June 2002), pp. 205-208, ISSN 1088-5412

Reddy, L. H. (2005). Drug delivery to tumours: recent strategies. *Journal of Pharmacy and Pharmacology*, Vol. 57, No. 10, (October 2005), pp. 1231-1242, ISSN 0022-3573

Ringsdorf, H. (1975). Structure and properties of pharmacologically active polymers. *Journal of Polymer Science: Polymer Symposia*, Vol. 51, No. 1, 1975), pp. 135-153,

Roberts, W. G. & Palade G. E. (1997). Neovasculature induced by vascular endothelial growth factor is fenestrated. *Cancer Research*, Vol. 57, No. 4, (February 1997), pp. 765-772, ISSN 0008-5472

Rogers, B. B. (1993). Taxol: a promising new drug of the '90s. *Oncology nursing forum*, Vol. 20, No. 10, (November-December 1993), pp. 1483-1489, ISSN 0190-535X

Rowinsky, E. K. (1997). The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. *Annual review of medicine*, Vol. 48, No., 1997), pp. 353-374, ISSN 0066-4219

Sabbatini, P.; Aghajanian C.; Dizon D.; Anderson S.; Dupont J.; Brown J. V.; Peters W. A.; Jacobs A.; Mehdi A.; Rivkin S. and others. (2004). Phase II study of CT-2103 in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. *Journal of Clinical Oncology*, Vol. 22, No. 22, (November 2004), pp. 4523-4531, ISSN 0732-183X

Shaffer, S. A.; Baker-Lee C.; Kennedy J.; Lai M. S.; de Vries P.; Buhler K. & Singer J. W. (2007). In vitro and in vivo metabolism of paclitaxel poliglumex: identification of metabolites and active proteases. *Cancer chemotherapy and pharmacology*, Vol. 59, No. 4, (March 2007), pp. 537-548, ISSN 0344-5704

Singer, J. W. (2005). Paclitaxel poliglumex (XYOTAX, CT-2103): a macromolecular taxane. *Journal of Controlled Release*, Vol. 109, No. 1-3, (December 2005), pp. 120-126, ISSN 0168-3659

Soepenberg, O.; Sparreboom A.; de Jonge M. J.; Planting A. S.; de Heus G.; Loos W. J.; Hartman C. M.; Bowden C. & Verweij J. (2004). Real-time pharmacokinetics guiding clinical decisions; phase I study of a weekly schedule of liposome encapsulated paclitaxel in patients with solid tumours. *European Journal of Cancer*, Vol. 40, No. 5, (March 2004), pp. 681-688, ISSN 0959-8049

Sugahara, S.; Kajiki M.; Kuriyama H. & Kobayashi T. R. (2007). Complete regression of xenografted human carcinomas by a paclitaxel-carboxymethyl dextran conjugate (AZ10992). *Journal of Controlled Release*, Vol. 117, No. 1, (January 2007), pp. 40-50, ISSN 0168-3659

ten Tije, A. J.; Verweij J.; Loos W. J. & Sparreboom A. (2003). Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clinical pharmacokinetics*, Vol. 42, No. 7, 2003), pp. 665-685, ISSN 0312-5963

Turk, V.; Turk B. & Turk D. (2001). Lysosomal cysteine proteases: facts and opportunities. *EMBO Journal*, Vol. 20, No. 17, (September 2001), pp. 4629-4633, ISSN 0261-4189

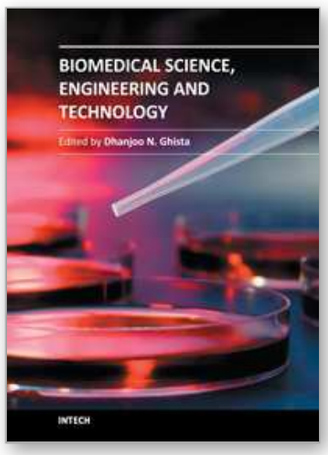
Verschraegen, C. F.; Skubitz K.; Daud A.; Kudelka A. P.; Rabinowitz I.; Allievi C.; Eisenfeld A.; Singer J. W. & Oldham F. B. (2009). A phase I and pharmacokinetic study of paclitaxel poliglumex and cisplatin in patients with advanced solid tumors. *Cancer*

chemotherapy and pharmacology, Vol. 63, No. 5, (April 2009), pp. 903-910, ISSN 1432-0843

Vicent, M. J.; Dieudonne L.; Carbajo R. J. & Pineda-Lucena A. (2008). Polymer conjugates as therapeutics: future trends, challenges and opportunities. *Expert Opinion on Drug Delivery*, Vol. 5, No. 5, (May 2008), pp. 593-614, ISSN 1742-5247

IntechOpen

IntechOpen



Biomedical Science, Engineering and Technology

Edited by Prof. Dhanjoo N. Ghista

ISBN 978-953-307-471-9
Hard cover, 902 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytomedicinal plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering coves topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Shuang-Qing Zhang (2012). Poly (L-glutamic acid)-Paclitaxel Conjugates for Cancer Treatment, Biomedical Science, Engineering and Technology, Prof. Dhanjoo N. Ghista (Ed.), ISBN: 978-953-307-471-9, InTech, Available from: http://www.intechopen.com/books/biomedical-science-engineering-and-technology/poly-l-glutamic-acid-paclitaxel-conjugates-for-cancer-treatment

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen