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Strategies for the drug discovery and development of taxane anticancer therapeutics

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Abstract

Introduction: As epoch-making anticancer drugs, paclitaxel and docetaxel have been extensively used in the clinic over the past three decades. Although the patents of these first-generation taxanes have expired, their clinical applications, particularly new formulations and combination therapies are under active investigations. Inspired by the notable success of Abraxane and Lipusu, new formulations have been extensively developed. In parallel, to overcome multidrug resistance (MDR) and to eradicate cancer stem cells, immense efforts have been made on the discovery and development of new-generation taxanes with improved potency and superior pharmacological properties.

Areas Covered: Starting from three taxanes used in clinic, this review covers (a) natural sources of advanced intermediates used for semi-synthesis of taxane API, (b) new formulations, (c) the major issues of FDA approved taxanes, (d) the design and development of next-generation taxanes, particularly those already in clinical trials or advanced preclinical development, (e) new mechanisms of action, and (f) a variety of taxane-based drug delivery systems. In particular, the next-generation taxanes are not only highly potent and capable of overcoming MDR, but also critically important as the payloads of efficacious tumor-targeted drug delivery systems.

Expert Opinion: As the highly potent next-generation taxanes can eradicate cancer stem cells and overcome MDR, the priority is to develop these superior compounds as an integral part of cancer therapy, especially for the treatment of pancreatic, colon and prostate cancer patients who hardly respond to checkpoint inhibitors. In order to mitigate undesirable side effects, the

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Declaration of Interest

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exploration of effective nanoformulations and tumor-targeted drug delivery systems are essential. Therefore, it is expected that these research programs will be the major focus in taxane-based drug development for years to come.

Keywords

paclitaxel; cancer; next-generation taxanes; nanoformulation; drug delivery system

1. Introduction

Since approved by the U.S. Food and Drug Administration (FDA), paclitaxel and docetaxel (Figure 1A) have been used extensively as front-line anti-cancer drugs for treatment of most solid tumors over the past three decades. Their manufacturing and clinical use have been continuously expanding through the generic drug market, especially in countries such as China and India. The exploration of their newer clinical applications is also actively ongoing, especially through new formulations and combination therapies.

Although new strategies in cancer treatment, such as cancer immunotherapy, have been explored to bring in success and hope, these applications have also shown serious and sometimes fatal adverse effects among cancer patients [1,2]. Accordingly, established chemotherapies such as taxane-based chemotherapy will continue to play a major role in the foreseen future. Noteworthy is the expansion of potential indications of new-generation taxanes to triple-negative breast, prostate, pancreatic, colon and gastric cancers and even neurodegenerative diseases. The development of new-generation taxanes with superior pharmacological properties and higher potency against multi-drug resistant cancers and cancer stem cells are expected to meet the medical needs, especially with new nanoformulations. These new taxanes will also be critically important as the payloads of tumor targeting drug conjugates [3].

2. FDA approved first-generation taxane anticancer drugs: paclitaxel, docetaxel and cabazitaxel

Taxane anticancer drugs stabilize microtubule assembly by binding β-tubulin thereby preventing depolymerization, and this results in blocking cell division at G2/M phase, followed by apoptosis [4]. Paclitaxel is a naturally occurring diterpenoid, approved by FDA in 1992. Both docetaxel and cabazitaxel (Figure 1A) are semi-synthetic taxanes developed by Rhone-Poulenc Rorer (now Sanofi). Docetaxel exhibited better efficacy than paclitaxel in stabilizing microtubule [5]. Although used for limited tumor types, the market of cabazitaxel has kept increasing since its approval in 2010, reaching $606 million in 2020 [6].

2.1. Commercial production of the active pharmaceutical ingredients (APIs) of taxane anticancer drugs

In the 1980's the only known source of paclitaxel was from the bark of Pacific yew (*taxus brevifolia*) [7] and persistent over-harvesting of this slow growing tree once resulted in serious environmental issues [7]. Fortunately, this problem was resolved by the development of practical semi-synthesis of paclitaxel from 10-deacetylbaccatin III (10-DAB III), which

is much more abundant in the needles of European yew (*Taxus baccata*), up to ~1g/kg of fresh biomass, and these yew needles are renewable. Thus, abundantly culturable European yew secured the production of paclitaxel and docetaxel [5,7], which allowed INDENA SpA, Italy to supply 10-DAB III to most of the global market [7]. Now, the “South No.1 Yew”, an elite clone from *Taxus wallichiana* Zucc var *mairei*, the fastest growing species of *Taxus* spp. that is endemic to China, is widely cultivated in Fujian and Yunnan provinces of China to produce 10-DAB III (0.9–1% of dry biomass) at much cheaper cost [8].

2.2. Major issues of the FDA approved taxanes

Several issues with the taxanes already in clinic have been identified. One of these is the use of excipients which is required to overcome their very poor aqueous solubility [9]. There have been some cases in which the use of these excipients have led to serious side effects. Once this happens, the patients must be removed from the treatment immediately [9]. The second problem is multidrug resistance [10,11]. There are quite a few major mechanisms for multidrug resistance (MDR): 1) Overexpression of efflux pumps, especially P-glycoprotein (Pgp) and multidrug resistance-associated proteins 1 (MRP1); 2) Decrease in the cellular uptake of drug by overexpression of plastin-3, decrease of organic anion transporting polypeptide 1B3, and changing membrane compositions mostly *via* increasing cholesterol percentage; 3) Changing apoptotic pathways by overexpression of Bcl-2 protein that strongly binds to paclitaxel; 4) Point mutation of tubulin, particularly the expression of βIII isoform in β-tubulin; 5) Widely existing hypoxic microenvironment in solid tumors; and 6) Metabolism-based resistance [9,11,12].

Another major issue is due to the presence of cancer stem cells (CSCs) [13,14]. Growing evidence indicates that CSCs play a key role in tumor development, metastasis, MDR and relapse. The expression of many stem cell-related genes endow CSCs with tumor initiating capacity in most cancer types, making it notoriously malignant [13,14]. The inefficiency of taxane-based treatment is partially attributed to these relatively rare, quiescent or slowly proliferating CSCs. Moreover, the current taxane-based drugs have very limited efficacy in treating melanoma, pancreatic, triple-negative breast, gastric, brain and renal cancers.

2.3. New formulations of paclitaxel and docetaxl

Inspired by the successful development of Abraxane (albumin-bound paclitaxel) and Lipusu (paclitaxel liposome injection), new paclitaxel formulations have been developed and approved in different countries. For example, 7-oligo(lactic acid)-paclitaxel, o$(LA)_8$-PTX (Figure 1A), in poly(ethylene glycol)-block-poly(D,L-lactide) (PEG-*b*-PLA) micelle is a micellar formulation of paclitaxel approved for treating metastatic breast cancer and advanced lung cancer in South Korea [15]. Samyang Biopharm uses its own plant cell culture technology for API supply. Various clinical investigations for other types of cancers are ongoing in several countries [15].

Polymeric micellar paclitaxel developed by Shanghai Yizhong Pharmaceutical was recently approved by SFDA to treat patients with advanced non-small cell lung cancer (NSCLC) [16]. In comparison with the standard combination of paclitaxel and cisplatin, the Phase III clinical data of this micellar formulation indicated that progress free survival (PFS)

is increased to 6.4 months from 5.3 months with reduced adverse effects. Combination therapy of polymeric micellar paclitaxel and PD-1 for the treatment of breast and gastric cancers is also under clinical evaluation [16]. Additionally, polymeric micellar docetaxel and cabazitaxel are projected to be filed for IND in 2023 [16].

Oral formulations have also been intensively studied. For example, DHP107 (Liporaxel), developed by Daehwa Pharmaceutical based on their "DH-LASED technology", was approved in South Korea for treatment of advanced gastric cancer with similar efficacy and safety to paclitaxel (i.v.) [17,18]. The phase III study in China is close to completion and its clinical trials for metastatic breast cancer and other tumors are ongoing [19].

New formulations of paclitaxel and docetaxel approved or in clinical development in the last 5 years are summarized in Table 1, wherein Abraxaneand Lipusu are included for comparison. The tumor-targeted delivery, including nanoformulations of paclitaxel and docetaxel, will be discussed in Section 6.

2.4. Combination therapy

To enhance the overall efficacy and to overcome MDR of taxane-based treatment, hundreds of clinical studies, taking advantage of the synergy of taxane-including combination chemotherapies are underway [12]. Paclitaxel and carboplatin are one of the earliest combination treatments for diverse solid tumors. To date there are still numerous ongoing clinical trials of this combination therapy [24]. After approved by the FDA in 2013, the combination of Abraxane and gemcitabine (Figure 1A) is one of the most frequently used therapy for metastatic pancreatic cancer treatment [29]. Athenex's clinical trials of "oral paclitaxel" plus encequidar (P-glycoprotein inhibitor, Figure 1A) (Oraxol) for the treatment of metastatic breast cancer [28] revealed some issues, particularly the neutropenia-related sequelae, and this was raised as a potential safety risk by the FDA. To address these issues, another round of Phase III clinical trials is planned [30].

Combinations of taxanes with immunotherapy are recently attracting considerable interest. For example, paclitaxel with ramucirumab, approved by the FDA in 2014 for the treatment of progressed advanced gastric carcinomas after the first line chemotherapy, is one of the most successful combinations [31]. Other combinations include paclitaxel-carboplatin-bevacizumab for non-small cell lung cancer (NSCLC) [32], paclitaxel-carboplatin-bevacizumab-atezolizumab for NSCLC [33], paclitaxel-carboplatin-pembrolizumab for squamous head and neck carcinoma [34], paclitaxel-cetuximab for squamous head and neck carcinoma [35], and paclitaxel-gemcitabine-pamrevlumab for pancreatic cancer [36].

4. Development of new-generation taxanes

Since other review articles have covered the new-generation taxanes derived from 10-deacetylbaccatin III, 14β-hydroxy-10-deacetylbaccatin III and C-*seco*-baccatins [3,10,37,38], this review focuses on the newer taxanes disclosed during the last 5 years, which are under recent clinical or advanced preclinical development.

4.1. New-generation taxanes developed from 10-deacetylbaccatin III and 14β-hydroxy-10-deacetylbaccatin III disclosed in the last 5 years

Recently, a library of new 3rd-generation taxanes by incorporating $OCHF_2$ and OCF_3 groups at the C2-benzoate position were developed and evaluated (Figure 1B) [39,40]. These fluoromethoxy groups are not only well tolerated, but also enhanced potency, especially against the MDR cancer cells. For drug-sensitive cancer cell lines MCF7 and LCC6-WT, these newer taxanes exhibited up to 2–3 orders of magnitude higher potency than that of paclitaxel against drug-resistant ovarian, breast and colon cancer cell lines with MDR-phenotype (NCI/ADR, LCC6-MDR and LDL-1), as well as pancreatic cancer cell line, CFPAC-1 [39]. The introduction of a difluorovinyl (DFV) group at the C3' position exhibited synergistic effect with the OCF_3/OCF_2H group at the 3-position of C2-benzoate moiety [40]. These DFV-taxanes not only exhibited subnanomolar IC_{50} values against drug-sensitive human cancer cell lines, A549, HT29, Vcap and PC3, as well as CFPAC-1, but also exhibited 2–4 orders of magnitude greater potency against extremely drug-resistant cancer cell lines, LCC6-MDR and DLD-1 as compared to that of paclitaxel. Furthermore, they exhibited excellent metabolic stability [40].

Molecular modeling analysis of the 3rd-generation fluorine-containing taxoids indicated that both 3-CF_3O/3-CHF_2O group of the C2-benzoate moiety and the 3'-DFV moiety are well accommodated in the deep hydrophobic binding pocket of β-tubulin [40]. Compared to the previously reported taxoids, there is an extra hydrogen bond between a fluorine of the OCF_3 group and the NH of His229 (C-F---H-N), or between the hydrogen in the $OCHF_2$ group and the nitrogen of His229 (C-H---N). These unique features may be contributing to the 10–100 pM IC_{50} values displayed by some of these newer fluorine-containing taxoids.

As a DFV-analog of ortataxel, which has advanced to Phase II clinical trials for the treatment of breast, NSCL cancers and glioblastoma, DFV-ortataxel (Figure 1B) was developed and its potency and efficacy examined [41]. DFV-ortataxel exhibited higher potency and better efficacy than ortataxel in taxane-resistant MCF-7R and MDA-MB-231R tumor xenografts in mice, wherein MDA-MB-231R cells overexpress ABCB1/ABCG2 efflux pumps [41]. A recent study on newer DFV-taxanes against anaplastic thyroid cancer also exhibited excellent potency *in vitro* and promising efficacy *in vivo* [42].

Two recent Chinese patent applications disclosed different libraries of newer taxanes. One library was made by incorporating water-soluble modules such as a trimethylammonium group to produce paclitaxel and docetaxel prodrugs (Figure 1B) [43]. These modules not only increase aqueous solubility, but also possess targeted antitumor activity. Once metabolized, free paclitaxel or docetaxel is released in tumor tissues. Thus, the potency is comparable to paclitaxel against drug-sensitive tumors, but much more potent against MDR tumors with reduced toxicity [43]. The other library was created by modifying the C7 and/or C10-hydroxyl groups with various arylcarbamoyl groups, e.g., DTX3-01, DTX3-08 and DTX3-20 (Figure 1B), which exhibit higher potency and better pharmacological properties than docetaxel [44].

4.2. New-generation taxanes in clinical trials and advanced preclinical development

Tesetaxel (Figure 2), derived from 9-dihydro-10-DAB III (9-DHB), was originally developed by Daiichi-Sankyo until 2006. However, the death of a patient due to severe neutropenia led to the suspension of its clinical trials [45,46]. After tesetaxel failed to exhibit superior efficacy over existing therapies in its Phase II clinical studies for the treatment of metastatic colorectal cancer and advanced gastric cancer, combination therapy became the hope for its further development [45,46]. Odonate Therapeutics continued its development and expected a 3.5 month extension benefit in its Phase III “Contessa” study against metastatic breast cancer. However, the combination therapy of oral tesetaxel and capecitabine only achieved a modest 2.9 month improvement as compared to capecitabine alone [47]. Furthermore, neutropenia was observed in 71.2% of patients, while the control group treated with capecitabine only exhibited 8.3% [47]. Consequently, after development for over 10 years, Odonate Therapeutics failed to get its FDA approval in March, 2021 [45–48].

Ortataxel (SB-T-101131, IDN5109) (Figure 2) is an early new-generation taxane that was synthesized from 14-OH-DAB III. Ortataxel is an effective modulator of ABC transporters, and is also orally active [38]. To date, ortataxel completed three Phase II clinical trials for the treatment of taxane-resistant breast cancer, NSCLC [38] and recurrent glioblastoma [49]. Similar to paclitaxel in toxicity profile, ortataxel exhibited encouraging, but still rather limited efficacy against paclitaxel/docetaxel-resistant advanced breast cancer and NSCLC [38]. It failed to meet the expected progression-free survival (PFS) in the treatment of glioblastoma [49].

Abeotaxane, TPI287 (Figure 2), is the first taxane advanced to human clinical trials for treating diseases other than cancer [50]. Although it is in phase I and II clinical trials for a range of cancers, including glio-, neuro- and medulloblastoma [51,52], those for breast cancer and metastatic melanoma [53,54] were suspended. However, its clinical investigation against tauopathies deserves attention [50]. Similar to ortataxel, TPI287 can cross the the blood brain barrier (BBB) [55] and thus, TPI-287 was primarily evaluated for treating brain cancer and a variety of tumors metastasized to the brain [55]. Since microtubule stabilization of cytoskeletal components favors the physiological function of protein tau, whose dysfunction could lead to neuronal death. Cortice Biosciences assessed the safety, tolerability and pharmacodynamics of TPI287 in Alzheimer’s disease, corticobasal degeneration and progressive supranuclear palsy in humans and further clinical trials are in planning [55].

Among the new-generation taxanes developed by Ojima et al., SB-T-1214 (Figure 2) is the most extensively investigated in preclinical studies. It exhibited remarkable efficacy in various tumor xenografts in mice [56] and impressive activity against CSCs [57]. SB-T-12854 (Figure 2) is a 2nd-generation 3′-DFV-taxane, exhibiting excellent metabolic stability, particularly against CYP3A4 enzyme [58,59] and showed superior efficacy to paclitaxel in suppressing rat lymphoma [58,59]. It was found that treatment of tubulins with DFV-taxanes led to the formation of uniquely thinner, shorter and straight microtubules as compared to paclitaxel [59]. These differences of taxanes-tubulin/microtubules interactions

is likely a critical contribution factor for the enhanced potency and efficacy of 2nd-generation DFV-taxanes [10].

Derived from cephalomannine, aziditaxel (Figure 2) has a better microtubule-binding affinity than paclitaxel enabling it to overcome drug resistance [60,61], and results in its much better efficacy than that of paclitaxel in BGC-823 human gastric carcinoma and A549 human non-small cell lung carcinoma xenografts in mice models [62]. After being formulated with human serum albumin, the aziditaxel nanoparticles efficiently inhibited the proliferation, migration and invasion of triple negative breast cancer cells *in vitro* [63]. Aziditaxel is currently under advanced preclinical development.

5. Novel mechanism of actions

Many studies have shown that taxanes mainly function by binding to β-tubulin, triggering mitotic arrest at G2/M phase through suppressing the dynamics of microtubule and this leads to apoptosis [4,10]. However, more studies, particularly with newer generation taxanes are uncovering other mechanisms of action (MOA).

5.1. Induction of multipolar division to cause chromosomal instability

Substantial amount of work has been focusing on determining and understanding the taxane binding site [10]. However, a study using a breast cancer model argues the intratumoral paclitaxel concentration produced by standard paclitaxel treatment regimen is not sufficient to initiate mitotic arrest of breast cancers [64]. It was suggested that it is likely the clustering of multipolar spindles into bipolar spindles that is responsible for paclitaxel resistance, rather than the lower intratumoral paclitaxel concentration. It was shown that longer duration of multipolarity increased instability of chromosome and conversely decreasing its duration increased cell survival and decreased sensitivity to paclitaxel treatment. Thus, the level of chromosomal stability of breast cancer patients was shown as a biomarker to determine whether they are sensitive to multipolar divisions triggered by paclitaxel treatment [64].

5.2. Suppression of CSCs genes, blockage of Hedgehog signaling and PI3K/Akt pathway

It has been demonstrated that new-generation taxanes are capable of enacting other MOA such as suppressing the cancer stem cell genes [13,14], repressing Hedgehog signaling pathway [65] and blocking the PI3K/Akt pathway [66].

As CSCs are critically important for maintenance, resistance to treatment, metastasis, and recurrence of tumor, the suppression of their stemness genes is critical to eradicate these relatively rare, highly drug-resistant, quiescent or slowly proliferating tumor-initiating cells [67]. A new generation taxane, SB-T-1214 exhibited remarkable efficacy in the treatment of CSC-enriched tumors not only by inhibiting the expression of stemness genes, but also by waking up gene expressions to reverse drug-resistance [13].

Significant enhancement of Hedgehog (HH) signaling pathway is critical for the development and metastasis of pancreatic ductal adenocarcinoma (PDAC) [68]. SB-T-1216 was shown to (Figure 2) suppress the HH pathway by down-regulating most of the tested downstream genes in the Paca-44 pancreatic cancer cells, as well as in tumor xenografts in

mice [65]. This discovery provides another possibility to treat aggressive pancreatic cancer with new-generation taxanes such as SB-T-1216 [65].

Another new-generation taxane, SB-T-121205 (Figure 2) was found to block the PI3K/Akt pathway by downregulating the expression of transgelin 2, p-Akt and p-GSK-3β, as well as upregulating the expression of tumor-suppressor PTEN in highly taxane-resistant MCF-7/PTX cells [66]. SB-T-121205 not only inhibited proliferation, migration and invasion of paclitaxel resistant cells by suppressing epithelial–mesenchymal transition, but exhibited less toxicity towards BEAS-2B nontumorigenic human bronchial epithelial cells, as compared to paclitaxel [66].

6. Tumor-targeted drug delivery of taxanes

To mitigate undesirable side effects, especially for the rapidly proliferating noncancer cells in certain tissues like bone marrow, extensive efforts have been made on taxane-based tumor-targeting chemotherapy [69–78]. Along this line, the development of “tumor-targeting prodrugs” has been a promising approach [72,73,77,78]. Methods such as new liposomal nanoformulations [79,80], peptide-drug conjugates (PDC) [81–86], “TumorSelect” technology [87], omega-3 polyunsaturated fatty acids (PUFAs) [71,88], vitamin Bs [72,73,77], poly(2-oxazoline)s micelles [9], monoclonal antibodies (mAbs) [78], hyaluronic acid (HA) [89,90], single-walled carbon nanotubes [76], and PAMAM dendrimers [77] have been used as tumor-specific targeting modules for the development of taxane-based tumor-targeting prodrugs and each of these will be briefly presented here.

6.1. Liposomal nanoformulations

Liposomal formulations have been extensively explored for taxane development. Constructed with dioleoyl-3-trimethylammonium propane/dioleoyl-sn-glycero-3-phosphocholine, a cationic liposomal formulation, “EndoTAG®−1”, has exhibited good efficacy against pancreatic cancer and advanced breast cancer by targeting the negatively charged surface of newly formed epithelial cells of tumor vasculature [79]. Phase III clinical trials in pancreatic cancer, as a first-line therapy, is currently underway in China and as a second-line therapy in a number of other countries [91].

Another very promising formulation is ginposomal paclitaxel, prepared by replacing liposomal cholesterol and PEG with a ginsenoside Rh2 [80]. Ginsenoside is the major bioactive substance obtained from ginseng and is responsible for a variety of pharmacological functions, including anticancer activity [92]. Ginsenoside can promote the cytotoxic and apoptotic effects of paclitaxel through inhibiting the NF-κB signaling pathway and regulating the Bax/Bcl-2 expression in breast cancer [93]. Relative to cholesterol, Rh2 can stabilize the liposome, prolong its blood circulation, and enhance its accumulation in tumors by targeting the glucose transporters of tumor cells. Moreover, ginposome works well in tumor microenvironment where the clinical therapeutic efficacy of liposome is limited [80]. Ginposomal paclitaxel exhibited much better efficacy than Abraxane in preclinical studies [94], and is currently in Phase I clinical trial. The ginposomal formulation of docetaxel and cabazitaxel are also under preclinical development.

6.2. Peptide-taxane conjugates (PDCs) and FK506-taxane conjugate

Two taxane-based peptide drug candidates, ANG-1005 and TH1902 (Figure 3) have advanced to human clinical trials [85,86]. ANG-1005 was designed and developed by linking three molecules of paclitaxel to Angiopep-2 (AP-2), a flexible peptide-based drug delivery platform for transporting drugs across the BBB. It efficaciously decreased ovarian cancer originated metastatic tumors within the brain. Although it failed to meet expectations in a phase II breast cancer metastasis study, clear improvement and prolonged overall survival were observed in patients with leptomeningeal carcinomatosis [85]. For further evaluation of the patients with poor prognosis, a randomized Phase III clinical trial is underway [85].

Based on its own “SORT1+ Technology”, TH1902 was designed and developed by Theratechnologies to treat patients with recurrent sortilin tumors that are refractory to normal therapy. It is a docetaxel linked to a sortilin receptor targeting peptide, and is currently under Phase I evaluation as a single agent treatment for all sortilin receptor positive advanced refractory solid tumors [86].

To increase aqueous solubility and for tumor targeting, oligopeptides are used to develop taxane-based prodrugs [82,95] (Figure 3). Poly(L-glutamic acid)-paclitaxel (PG-TXL) was advanced to Phase III clinical trial for the treatment of non-small cell lung cancer (NSCLC), ovarian cancer and glioblastoma [37]. Similarly, paclitaxel has also been conjugated to oligoarginine with a disulfide linker at the C2’ or C7 position to overcome the efflux-based MDR in human ovarian carcinoma [83]. Another example, to reduce taxane neurotoxicity, an immunosuppressive and neuroprotective agent FK506 was conjugated to docetaxel via a PEG_3 linker (Figure 3). This conjugate exhibited high potency in SKOV3 ovarian, PC3 prostate and MCF7 breast cancer cell lines [84].

6.3. ART-207 using TumorSelect® technology

Taking advantage of an emerging anticancer technology, “TumorSelect”, ART-207 (Figure 4) was recently reported as a promising chemotherapy [87]. As tumor cells are voracious for cholesterol and very lipophilic molecules, ART-207 incorporates an acid-labile lipophilic chain on the C2’-OH of paclitaxel for recognition by tumor cell LDL receptors. This allows ART-207 to selectively accumulate in tumor tissues, get internalized and hydrolyzed in acidic environment of the cancer cell to release free active paclitaxel in a controlled manner. Consequently, this prodrug shows long-lasting effect with greatly decreased collateral damage to normal tissue. In a xenograft model of ovarian cancer in SCID mice, ART-207 exhibited an obviously better efficacy relative to Abraxane with minor weight loss [87].

6.4. Taxane conjugates with omega-3 polyunsaturated fatty acids (PUFAs) and their nanoemulsion formulation

Omega-3 polyunsaturated fatty acids (PUFAs) often exhibit synergistic effects with cytotoxic drugs and of these, DHA-paclitaxel, was advanced to Phase III clinical study against metastatic melanoma and pancreatic cancer [96]. Following up on the promising feature of DHA-paclitaxel, PUFA conjugates of much more potent new-generation taxanes have been extensively explored (Figure 4) [56]. As anticipated, the new-generation derived

PUFA, DHA-SBT-1214, exhibited a remarkable antitumor effect [38]. It achieved complete eradication of pancreatic (PANC-1) and colon (DLD-1) tumor xenografts in mouse models [88]. Comparably, α-LNA-SBT-1214 (Figure 4) also demonstrated similar efficacy to that of DHA-SBT-1214 [97].

To enhance therapeutic efficacy and bioavailability, DHA-SBT-1214 was formulated as a nanoemulsion. Taking advantage of the "enhanced permeability and retention (EPR) effect", taxane nanoemulsion, NE-DHA-SBT-1214, exhibited substantially improved pharmacokinetic and pharmacodynamic properties as well as reduced systemic toxicity [98]. In mice implanted with patient-derived prostate cancer stem cells PPT2, NE-DHA-SBT-1214 exhibited much better efficacy than Abraxane without causing significant weight loss [98]. Moreover, no CSCs were detected or found viable in the NE-DHA-SBT-1214 treated tumors. In contrast, the viable cells that survived Abraxane treatment still induced a substantial amount of floating spheroids and holoclones [98]. NE-DHA-SBT-1214 is well positioned for development as a comprehensive targeted therapeutic modality for both de-bulking tumor and for eradicating cancer stem cell (CSC) populations in multidrug-resistant cancers [98].

6.5. Vitamin B-taxane conjugates

Tumor cells are particularly voracious for certain vitamins, especially vitamin Bs such as folate (vitamin B9), biotin (vitamin B7) and cobalamin (vitamin B12) [75]. Receptors of these vitamins are often highly overexpressed on the surface of cancer cells [99]. These receptors are widely used for tumor-targeting taxane delivery [100]. The anti-angiogenic efficacy of a paclitaxel-cobalamin conjugate (Figure 4) was shown to be effective in the treatment of eye diseases [101]. A biotin-docetaxel conjugate, IDD-1010, exhibited remarkable efficacy in the PC3 prostate tumor xenograft in mice [102]. A folate-linker-taxane conjugate, FLT-1 (Figure 4), displayed excellent selectivity for ID8 ovarian and MX-1 breast cancer cells in comparison with normal lung fibroblast cells [103].

In addition to folate-linker-taxane conjugates (FLTs) and biotin-linker-taxane conjugates (BLTs) such as IDD-1010, FLT-1 and BLT-1 (Figure 4), a dual-warhead biotin-conjugate bearing camptothecin (CPT) and SB-T-1214 (1:1) was also developed [73] (Figure 4). This unique conjugate as a combination therapy displayed over 100 times higher selectivity for cancer cells over human normal cells [73].

6.6. Taxane conjugates with hyaluronic acid

Hyaluronic acid or hyaluronan (HA), a water-soluble polysaccharide, is used to target the CD44 marker of cancer stem cells (CSCs) [89,90]. HA is very common in the extracellular tissue matrix and is important for cell proliferation [104]. Additionally, HA-based nanoparticles have been shown to accumulate in tumor tissue and exhibit prolonged circulation by taking advantage of the enhanced permeability and retention (EPR) effect [105]. Accordingly, HA can be an excellent vehicle for drug delivery through the attachment of drugs to its hydroxyl or carboxyl groups. Thus, a hyaluronic acid-linker-taxane conjugate, HALT (Figure 4), was constructed by attaching SB-T-1214 *via* a self-immolative disulfide

linker to ensure the release of the drug only after internalization [106]. The biological evaluations of HALT showed promising activity against CSC spheroids [106].

6.7. EPR-based tumor-targeted taxane delivery using poly(2-oxazoline)-based micelles

A series of new-generation taxanes were successfully encapsulated in micelles of doubly amphiphilic poly(2-oxazoline)s (POx) with high loading capacity for EPR-based tumor-targeted drug delivery [9]. Among these POx-taxanes, POx-SB-T-1214 exhibited up to 100 times higher activity than the corresponding POx-paclitaxel against LCC6/MDR human breast cancer cell line *in vitro* [9]. Furthermore, POx-SB-T-1214 also exhibited impressive suppression of the growth of LCC6/MDR and T11 orthotopic tumors in mouse models [9].

6.8. Monoclonal antibody-taxane conjugates

The first antibody drug conjugate (ADC) using paclitaxel as a payload only exhibited limited cytotoxic activity *in vivo*, even though it was better than paclitaxel *in vitro* [107]. In pioneering work of Chari and Ojima, highly efficacious EGFR-targeting ADCs using 2^{nd}-generation taxanes as warheads were developed (Figure 5). These early ADCs were not only highly selective to cancer cells *in vitro*, but also exhibited excellent efficacy in the treatment of A431 human squamous tumor xenografts in mice without showing systemic toxicity [78]. Considering the loss of potency from C10 modification of the original taxane structure, highly efficient self-immolative disulfide smart linkers were developed to release the original taxane without compromising potency [75].

6.9. Taxane conjugates with surface-modified single-walled carbon nanotubes

Chen *et. al.* successfully attached 178 molecules of biotin and 71 molecules of SB-T-1214-fluorescein to single-wall carbon nanotubes (SWNTs) of 250 nm in length and average diameter of 1 nm to produce a novel SWNT-taxane conjugate, SWNT-SB-T-1214 (Figure 5) [76]. Subsequent confocal fluorescence microscopy (CFM) analysis indicated this huge tumor targeting drug carrier “Trojan horse” was completely internalized *via* receptor-mediated endocytosis (RME). SWNT-SB-T-1214 exhibited remarkable cytotoxicity and selectivity (>150) against biotin-receptor expressing (BR^+) cancer cells compared to normal human cells (BR^-) [76].

6.10. Asymmetric bow-tie poly(amidoamine) (PAMAM) dendrimer-taxane conjugates

The well-defined structure and functionalization feature of dendrimers make it a promising drug delivery system [77,108]. Starting from poly(amidoamine) dendrimers with cystamine cores, Wang *et. al.* successfully constructed an asymmetric bowtie dendrimer (ABTD)-tumor-targeting conjugate (TTC) (Figure 5). ABTD-TTC, for biotin receptor recognition, bears 16 biotins in the G3 half-dendron moiety and 4 taxanes connected to self-immolative linkers in the G1 half-dendron moiety [77]. This dendrimer exhibited an extraordinary cancer cell specificity of 1,000–5,000 times more selective for ID-8 ovarian (BR^+) and MX-1 breast (BR^+) cancer cells than to WI38 human lung fibroblast cells (BR^-) [77].

7. Summary

This review has covered the exploration and development of new formulations of FDA approved taxanes, and the new-generation taxanes that possess superior pharmacological properties and higher potencies than the parent taxanes. The new-generation taxanes, other than initiating tubulin polymerization much faster than the 1st-generation taxanes, also revealed new mechanisms of action [109]. Favorably, the new-generation taxanes are able to eradicate CSCs *in vivo* by suppressing "stemness genes" and promoting cell differentiation [13]. Furthermore, the taxane SB-T-121205 can overcome MDR by blocking the invasion and metastasis, as well as the epithelial-mesenchymal transition of cancer cells by suppressing the PI3K/Akt pathway[66]. These are previously unknown MOA of taxanes.

Starting from three 1st-generation taxanes used in the clinic, this review also covered the supply of API intermediates, new formulations, the major issues of FDA-approved taxanes, the design and development of new-generation taxanes, particularly those already in clinical trials or advanced preclinical development, and a variety of taxane-based drug delivery systems. Considering that efficacious tumor-targeted drug delivery systems are the key to advance the new-generation taxanes to become clinical drugs, this account covered taxane-based delivery systems, especially nanoparticle formulations.

8. Expert opinion

It is expected that the three FDA-approved taxane drugs, paclitaxel, docetaxel and cabazitaxel will continue to be used as first line chemotherapies in the foreseen future. The heavily invested cultivation of yew trees in China will keep supplying substantial amounts of API intermediates for the global market. The extraordinary efficacy of Abraxane, specifically its combination therapy with gemcitabine for pancreatic cancer patients indicates that one future for taxane drugs will be in combination therapies. Additionally, there is continuous exploration and development of tumor targeting drug delivery systems, especially highly efficacious formulations that spare normal cells and are superior to Abraxane. These show promise to produce single agent taxane drugs with less toxic side effects.

To overcome multi-drug resistance, eradicate cancer stem cells, solve aqueous solubility issues, development of new-generation taxanes with superior pharmacological properties and higher potencies are extremely important, especially for pancreatic and colon cancer patients who do not respond to checkpoint inhibitors well. New-generation taxanes are also expected to expand their applications to treating prostate cancer, triple-negative breast, gastric, melanoma, brain and renal cancer patients on whom currently used taxanes have very limited efficacy. Highly potent new-generation taxanes will be critical as the payloads/warheads of efficacious tumor-targeted drug delivery systems and are expected to be developed as an integral part of cancer therapy.

Usually, improved clinical efficacy of taxane-based treatments are achieved by increasing the dosage through formulation, however, the raised systemic exposure also increases incidence of undesired toxic side effects. Ortataxel, for example, failed to realize its optimal

efficacy partially because of dose-limiting toxicity resulting from the conventional Tween 80/ethanol/saline formulation. If maximum tolerated dose (MTD) can be raised by using a new drug delivery formulation and higher doses can be achieved, with minimal side effects, its efficacy would be substantially improved, like in the case of Abraxane. Similarly, to obtain the FDA approval, a new drug delivery formulation is also the most practical and efficient strategy for tesetaxel and other new-generation taxanes already in clinical trials.

The progression of new-generation taxanes heavily relies on the exploration of ideal formulations and drug delivery systems. It is one of the major fields of taxane-based drug development. Certain vitamins like folate and biotin, PUFAs especially DHA, hyaluronic acid, peptides, antibody as well as various nanoscale vehicles are all promising as tumor-targeting modules. Particularly, taxane-based liposomal formulations are expected to be a hot field in drug development.

To date, no taxane-ADCs have been advanced to clinical studies, simply because the cytotoxicity level was not high enough. For the first-generation taxane-ADCs, the payload needed to be in the 10–100 pM IC_{50} range. However, in more recently developed second-generation taxane-ADCs a 1 nM level IC_{50} is acceptable, due to the “bystander effects” in which delivered free drug diffuses from antigen positive to neighboring antigen negative cancer cells and so contributes to the efficacy.

Alternatively, small molecule drug conjugates (SMDCs) are also highly specific and smaller in size, as well as have shorter retention time, better penetration, and are capable of delivering cytotoxic agents selectively to cancer cells, thereby reducing the off-target side effects observed with traditional chemotherapy [110]. Owing to their low molecular weight, SMDCs are excreted with significantly faster kinetics than the large ADC counterparts [110]. By minimizing the time spent in circulation, the probability of premature drug release in healthy tissues is reduced, and thereby the likelihood of mitigating off-target toxicities is improved [110].

Results from recent studies indicate that investigations into the new mechanisms of action of taxanes are important for taxane-based drug development, specifically for combination therapies. The disclosed new mechanisms of action of new-generation taxanes include overcoming MDR by suppressing CSC genes, as well as blocking Hedgehog and PI3K/Akt signaling pathways. Paclitaxel was also reported to destabilize chromosomes by inducing multipolar division. These new MOA may help to expand utility to other cancers and disease indications in which taxanes are currently not used.

Further exploration of broader applications of taxanes beyond cancer is an interesting and promising field of research. As indicated by TPI-287, an abeotaxane in clinical trials for the treatment of Alzheimer’s disease, corticobasal degeneration and progressive supranuclear palsy, tubulin related diseases like neural system disorders would be a field for further investigation with taxanes.

Lastly, it is very important to emphasize that the library of fluorine-containing 3rd-generation taxanes is a very valuable asset for drug development, particularly those bearing the DFV moiety in the isoserine side chain. Endued with excellent pharmacological

properties, these extremely potent taxanes are highly promising as payloads/warheads of ADCs and SMDCs or for various emerging new tumor-targeted drug delivery systems and nanoformulations.

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Abbreviations:

10-DAB III	10-deacetylbaccatin III
9-DHB	9-dihydro-10-DAB III
14-OH-DAB III	14 β-hydroxy-10-deacetylbaccatin III
ABTD-TTC	asymmetric bowtie dendrimer tumor-targeting conjugate
ADCs	antibody-taxane conjugates
AP-2	Angiopep-2
APIs	Active Pharmaceutical ingredients
BBB	Blood Brain Barrier
BLTs	biotin-linker-taxane conjugates
BR^+	biotin-receptor expressing
CFM	confocal fluorescence microscopy
CSC	cancer stem cell
CPT	camptothecin
DFV	difluorovinyl
DHA	docosahexaenoic acid
EGFR	epidermal growth factor receptor
EPR effect	enhanced permeability and retention effect
FDA	Food and Drug Administration, U.S.A.
FLTs	folate-linker-taxane conjugates
G2/M phase	growth 2/mitotic phase

HA	hyaluronic acid or hyaluronan
HALT	hyaluronic acid-linker-taxane conjugate
mAbs	monoclonal antibodies
MDR	multidrug resistance
MRP1	multidrug resistance-associated proteins
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
o(LA)$_8$-PTX	7-Oligo(lactic acid)-paclitaxel
PAMAM	asymmetric bow-tie poly(amidoamine)
PDAC	pancreatic ductal adenocarcinoma
PDC	peptide-drug conjugates
PEG-*b*-PLA	poly(ethylene glycol)-block-poly(D, L-lactide)
PFS	progress free survival
Pgp	P-glycoprotein
PG-TXL	Poly(L-glutamic acid)-paclitaxel
PI3K/Akt pathway	phosphoinositide 3-kinases/protein kinase B pathway
POx	poly(2-oxazoline)s
PUFAs	omega-3 polyunsaturated fatty acids
RME	receptor-mediated endocytosis
SFDA	State Food and Drug Administration, China
SMDCs	small molecule drug conjugates
SWNTs	single-wall carbon nanotubes

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Article Highlights:

- The FDA approved taxanes will continue to play significant roles in a foreseen future as the first-line drugs for cancer chemotherapy.
- Efficacious drug delivery systems, especially nanoformulations, are the promising directions of taxane-based drug development.
- Next-generation taxanes are critically important as the payloads of efficacious tumor-targeted drug delivery systems.
- Next-generation taxanes overcome MDR, suppress CSC genes, block Hedgehog signaling and PI3K/Akt pathway.
- Highly potent fluorine-containing 3rd-generation taxanes exhibit excellent pharmacological properties for development.
- TPI-287, an abeotaxane in clinical trials for brain cancers, also exhibited efficacy in Alzheimer's disease, corticobasal degeneration and progressive supranuclear palsy.

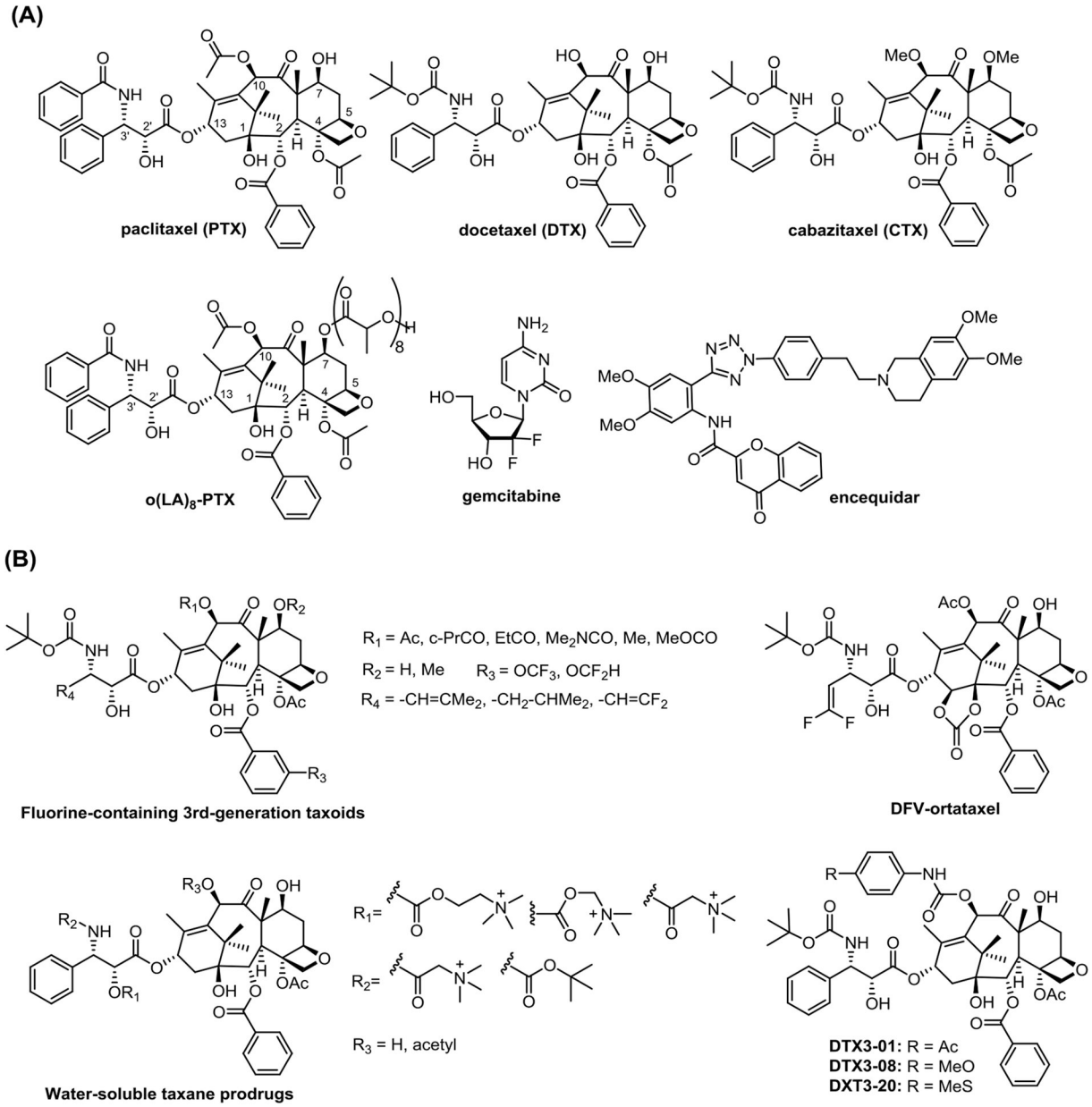

Figure 1.

(A) Structures of 1st-generation taxanes, o(LA)$_8$-PTX, gemcitabine and encequidar; (B) Selected next-generation taxanes disclosed in the last 3 years

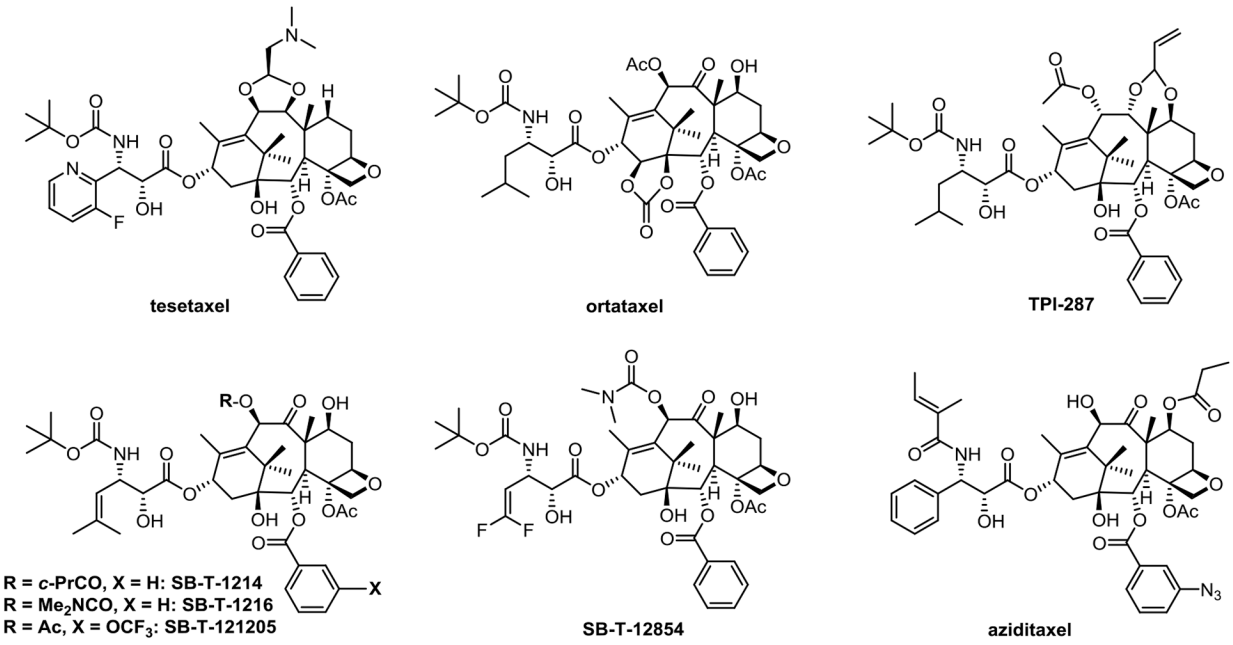

Figure 2.
New-generation taxanes in clinical trials or advanced preclinical development

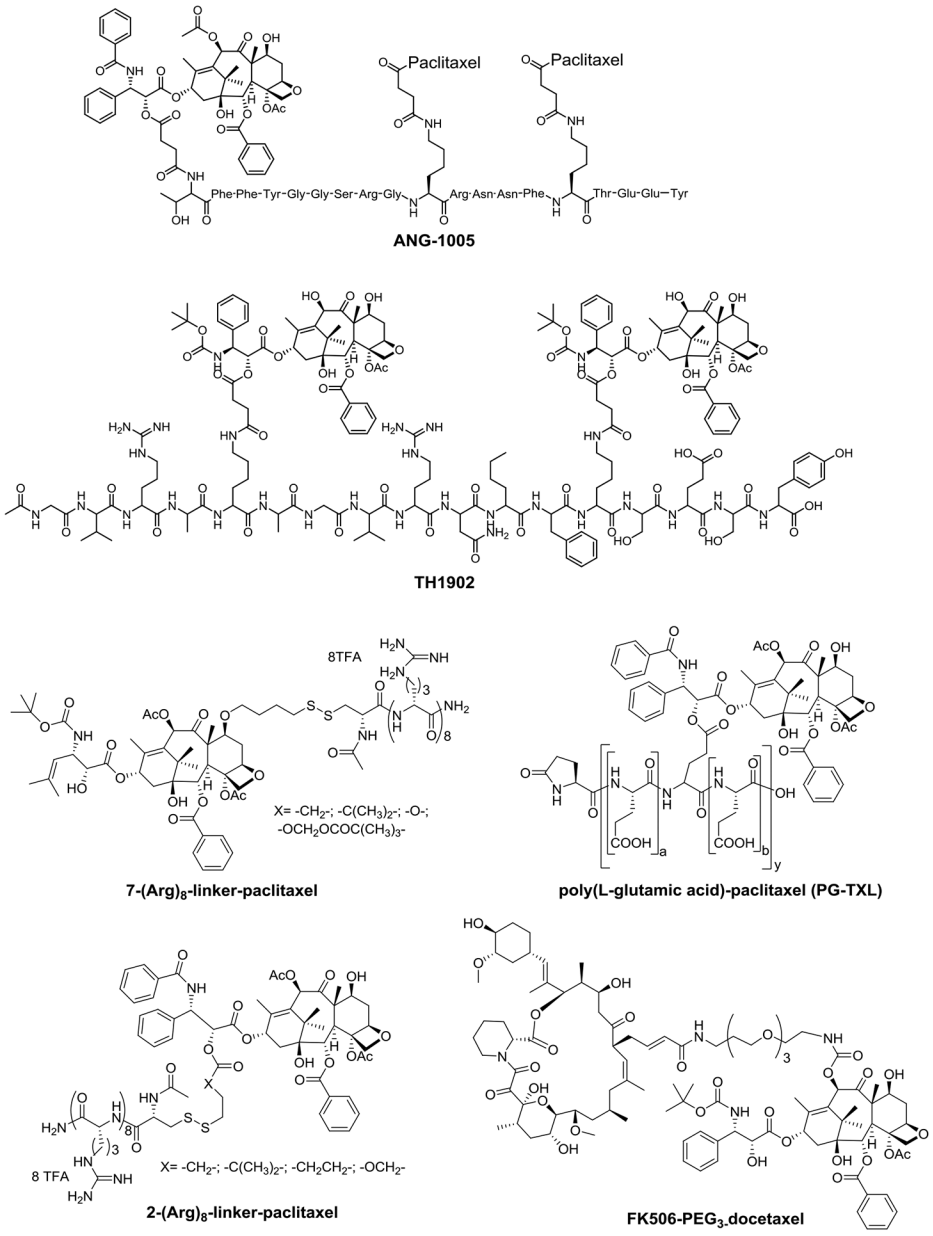

Figure 3.

ANG-1005, TH1902, C2'-/C7-polyarginine-paclitaxel, poly(glutamic acid)-paclitaxel (PG-TXL) and FK506-PEG_3-docetaxel

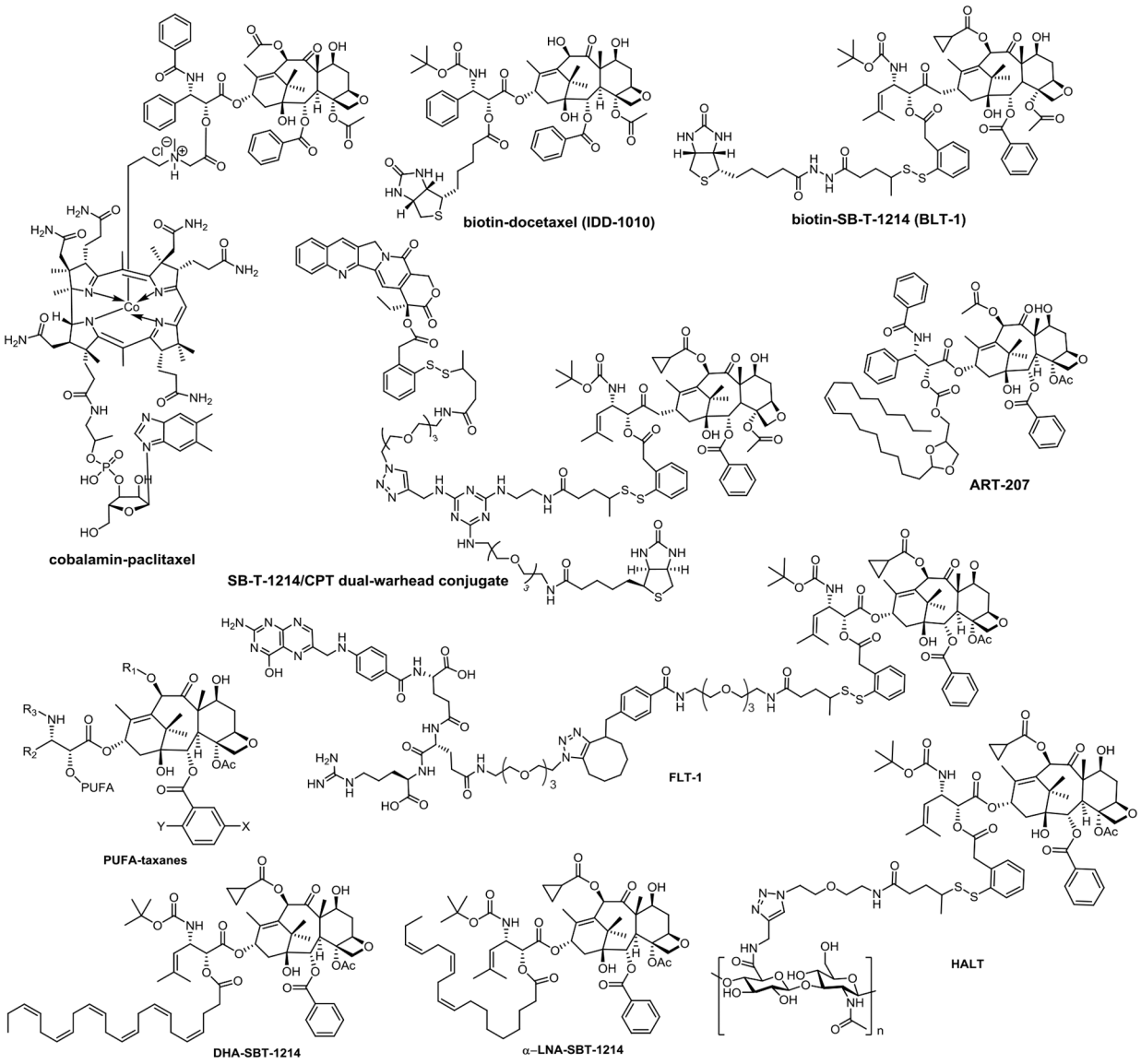

Figure 4.

Structures of FLT-1, HALT, PUFA-taxane conjugates, DHA-SBT-1214, α-LNA-SBT-1214 and ART-207

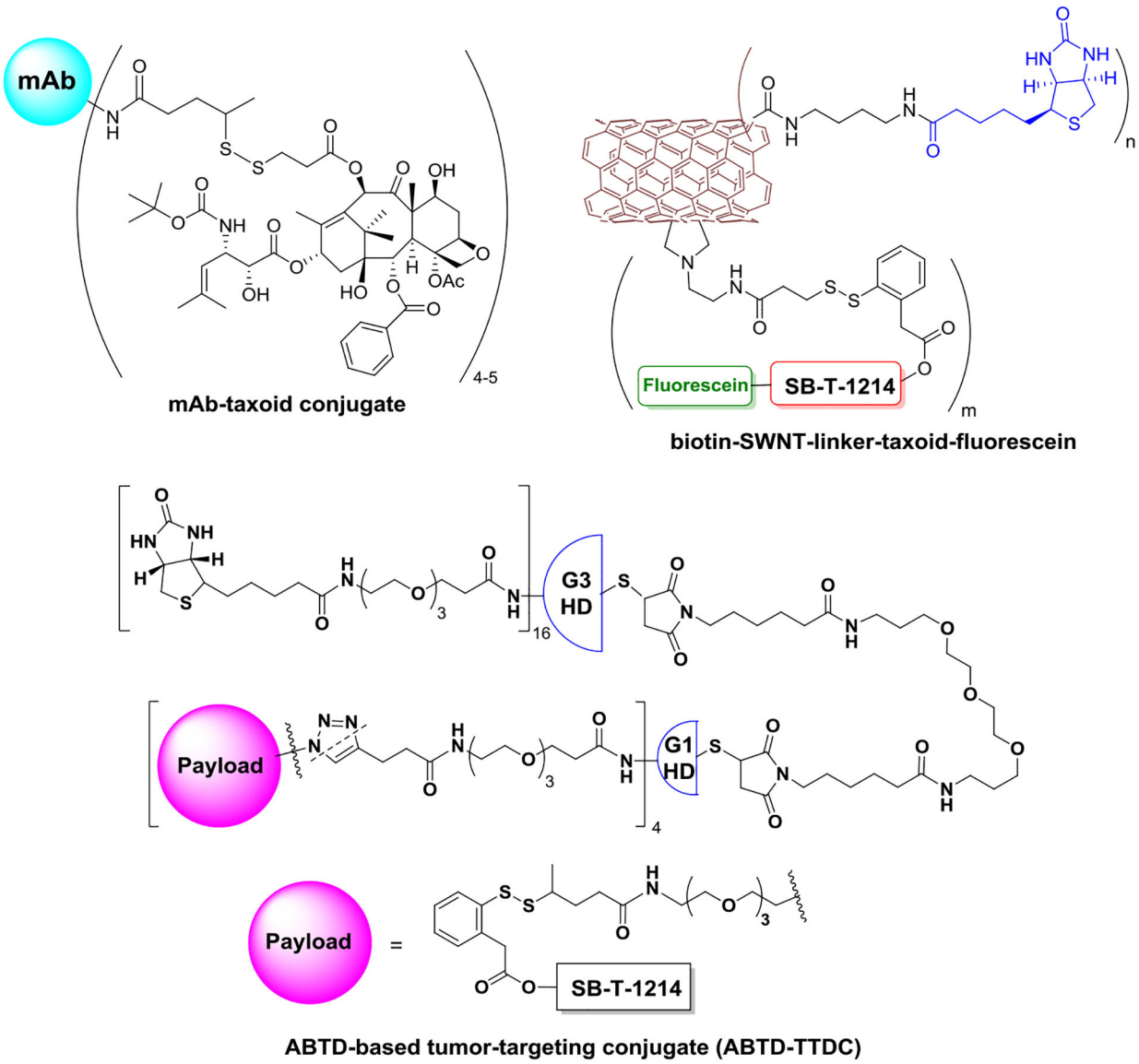

Figure 5.
EGFR-mAb-taxoid conjugate, vitamin-SWNT-taxoid conjugate, and ABTD-TTDC-taxoid.

Table 1.

New formulations of paclitaxel and docetaxel approved or in clinical development

Product	Developer	Taxane	Formulation	Administration	Ref.
Abraxane	Abraxis BioScience	paclitaxel	HSA nanoparticle	i.v.	[20]
Lipusu	Luye Pharmaceuticals	paclitaxel	Liposome lecithin and cholesterol	i.v.	[21]
Genexol-PM	Samyang Corp.	paclitaxel	o$(LA)_8$-PTX, PEG-*b*-PLA micelle	i.v.	[15,22]
Nanoxel	Samyang Corp.	docetaxel	PEG-*b*-PLA micelle	i.v.	[23]
LEP-ETU	Insys Therapeutics	paclitaxel	Liposome dioleoyl-sn-glycero-3-phosphocholine, cholesterol, and cardiolipin	i.v.	[21]
EndoTAG-1	Medigene AG	paclitaxel	cationic liposome (dioleoyl-3-trimethylammonium propane/dioleoyl-sn-glycero-3-phosphocholine)	i.v.	[24]
PTX-LDE	Palantir Technologies	paclitaxel	Lipid core nanoparticle protein-free liposome phosphatidylcholine, cholesterol and triolein), mimicking LDL	i.v.	[25]
LE-DT	NeoPharm	docetaxel	Liposome dioleoyl-sn-glycero-3-phosphocholine, cholesterol, cardiolipin, alpha-tocopheryl succinate	i.v.	[26]
ATI-1123	Azaya Therapeutics	docetaxel	Liposome phospholipids, cholesterol, human serum albumin, saccharose	i.v.	[24]
Paclical	Oasmia Pharmaceutical	paclitaxel	Polymeric micelle N-retinoyl-L-cysteic acid methyl ester sodium salt, retinoid derivatives	i.v.	[27]
Paclitaxel polymer micelles	Shanghai Yizong	paclitaxel	Polymeric micelle mPEG-PDLLA (methoxy polyethylene glycol 2000-polylactide amphiphilic block copolymer)	i.v.	[16]
Liporaxel (DHP107)	Daehwa Pharmaceutical	paclitaxel	lipid-based oral formulation monoolein, tricaprylin, polysorbate 80	oral	[17,18]
Oraxol	Athenex	paclitaxel	lipid-based oral capsule combination with encequidar	oral	[28]