

Nanoparticle-Based Combination Therapy for Ovarian Cancer

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Abstract: Ovarian cancer is one of the most common malignant tumors in gynecology with a high incidence. Combination therapy, eg, administration of paclitaxel followed by a platinum anticancer drug is recommended to treat ovarian cancer due to its advantages in, eg, reducing side effects and reversing (multi)drug-resistance compared to single treatment. However, the benefits of combination therapy are often compromised. In chemo and chemo/gene combinations, co-deposition of the combined therapeutics in the tumor cells is required, which is difficult to achieve due to dramatic pharmacokinetic differences between combinational agents in free forms. Moreover, some undesired properties such as the low-water solubility of chemodrugs and the difficulty of cellular internalization of gene therapeutics also hinder the therapeutic potential. Delivery of dual or multiple agents by nanoparticles provides opportunities to tackle these limits. Nanoparticles encapsulate hydrophobic drug(s) to yield aqueous dispersions facilitating its administration and/or to accommodate hydrophilic genes facilitating its access to cells. Moreover, nanoparticle-based therapeutics can not only improve drug properties (eg, in vivo stability) and ensure the same drug disposition behavior with controlled drug ratios but also can minimize drug exposure of the normal tissues and increase drug co-accumulation at targeted tissues via passive and/or active targeting strategies. Herein, this work summarizes nanoparticle-based combination therapies, mainly including anticancer drug-based combinations and chemo/gene combinations, and emphasizes the advantageous outcomes of nanocarriers in the combination treatment of ovarian cancer. In addition, we also review mechanisms of synergetic effects resulting from different combinations.

Keywords: ovarian cancer, nanoparticles, combination therapy, chemotherapy, gene therapy

Introduction

Ovarian cancer is one of the most common gynecologic malignancies with high morbidity.¹ Due to its relatively asymptomatic nature, about 70% of patients are diagnosed at an advanced stage and have poor prognosis, leading to high mortality rates.^{2,3} The clinical treatment of ovarian cancer mainly relies on chemotherapy after tumor debulking. Chemotherapy exerts the growth inhibition or control of cancer cells by utilizing a single chemotherapeutic drug. However, the therapeutic efficacy of monotherapy is compromised mainly due to the emergence of multidrug resistance (MDR) and undesired side effects.⁴

Since it can overcome the drawbacks of single drug treatment to some extent, combination therapy has been recommended for the treatment of ovarian cancer. Combination therapy is developed by combining two or more therapeutic agents in free forms and in a manner wherein anticancer mechanisms of action synergistically complement each other.⁵ Different combination strategies such as combinations of chemical drugs, combinations of chemo/gene therapy and combinations of chemo/immunotherapy have been explored for different purposes and applied in clinical

Table 1 Examples of Drug Combinations for the Treatment of Ovarian Cancer in Clinical Trials

Evaluable Patients	Combinations		Outcomes	References
n=410; advanced	Paclitaxel	Cisplatin	Median PFS in combo group: 18 months	[154]
n=672; platinum sensitive, recurrent	Liposomal doxorubicin	Trabectedin	Median PFS in combo group: 7.3 months (95% CI: 5.9–7.9 months) vs chemo alone group: 5.8 months (95% CI: 5.5–7.1 months)	[155]
n=566; platinum sensitive	Liposomal doxorubicin	Avelumab	Median PFS in combo group: 3.7 months (95% CI: 3.3–5.1 months) vs chemo alone group: 3.5 months (95% CI: 2.1–4.0 months)	[156]
n=631; advanced or recurrent	Cisplatin	Topotecan	Median PFS in platinum-sensitive group: 7.7 months vs platinum-resistant group: 2.5 months; Median OS in platinum-sensitive group: 46.6 months vs platinum-resistant group: 19.3 months	[157]
n=792; advanced	Carboplatin	Paclitaxel	Median PFS in Carboplatin and Paclitaxel group: 20.7 months vs Cisplatin and Paclitaxel group: 19.4 months; Median OS in Carboplatin and Paclitaxel group: 57.4 months vs Cisplatin and Paclitaxel group: 48.7 months	[158]

Abbreviations: PFS, Progression-free survival; OS, overall survival; CI, confidence interval.

practice (Table 1).^{6–8} Combinations of chemodrugs with various action mechanisms could exert antitumor effects cooperatively, which can reduce some cases of side effects.⁵ For instance, doxorubicin (DOX) in combination with free radical scavenger curcumin has been shown to reduce the cardiotoxicity side effect of DOX.⁵ In addition, the synergistic interactions of the combined drugs prevent cancer cells to form compensatory resistance mechanisms and thus improve the therapeutic efficacy.⁵ For instance, doxorubicin combined with Olaparib has been indicated against the drug-resistant ovarian tumor.⁹ However, the synergistic anticancer effects of combination therapy based on chemodrugs are highly dependent on the accurate molar ratio of the drugs accumulated in the targeted site. This is often limited by intrinsic differences between combinational therapeutic agents in free forms, thus resulting in dramatic pharmacokinetic differences, ie, the uncoordinated cellular uptake and distribution of various drugs at the targeted site, as presented in Figure 1. In addition, some undesired properties resulting from free forms of chemotherapeutic agents in systemic administration such as low-water solubility, instability in biological fluids, renal clearance and limited tumor specificity have to be optimized to fully exploit the therapeutic potential for the treatment of ovarian cancer.^{10–12} For instance,

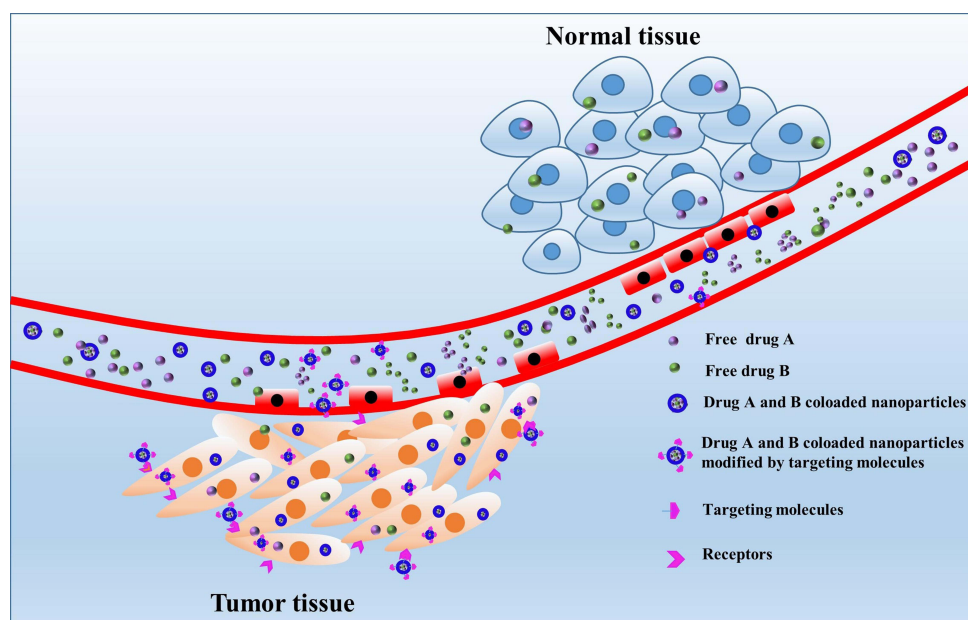


Figure 1 The schematic illustration of the advantages of codelivery of two drugs by nanoparticles over the combination of free drugs including improving drug water-solubility, controlling drug ratios, ensuring the same drug disposition behavior at the tumor site, decreasing non-specific toxicities and increasing drug co-accumulation at tumor via EPR effect and/or receptor-mediated endocytosis, ie, passive and/or active targeting.

paclitaxel (PTX) has poor water solubility requiring the use of toxic excipients, Cremophor EL, in clinical formulations, which can cause severe hypersensitivity reactions in patients.¹³

Because ovarian cancer is a disease with genetic and acquired genetic defects, gene therapy and chemotherapy can be combined to manipulate the gene content of tumor cells and kill cancer cells at the same time, thus improving the therapeutic outcomes. In addition, MDR in cancers can be caused by adaptive gene expression. For instance, P-glycoprotein (P-gp) as a typical drug efflux pump is usually overexpressed in drug-resistant cells and has become the main contributor to the reduced intracellular drug accumulation, especially for hydrophobic drugs like PTX. The co-administration of chemodrug and drug resistance related small interfering RNAs (siRNAs) targeting P-gp has been reported to restore the sensitivity of tumor cells to the used chemodrug and thus effectively reverse cancer resistance.¹⁴ To achieve the maximal synergetic effects, temporal colocalization of the combined drug and genes in the tumor cells is required. However, compared to chemodrugs, intrinsic differences between small molecular drugs and macromolecular gene therapeutics are even more prominent, making co-deposition of them more challenging. In addition, gene therapeutics are typically characterized by hydrophilicity, large molecular weight and negatively-charged, making them difficult to enter cells.¹⁵

Chemotherapy in combination with immunotherapy may improve the curative effect as chemotherapy can mobilize anticancer immunity and generate antigenic molecules while immunotherapy can evade immunological destruction and counterbalance the acute immunosuppression induced by chemotherapy.¹⁶ However, similar to chemotherapy, immunotherapeutic agents also face problems such as instability, immune-related adverse effects and inefficient delivery.¹⁶

Codelivery of dual or multiple agents by nanoparticulate drug delivery systems provides opportunities to tackle the limits above mentioned. A delivery system co-encapsulating different therapeutic agents can control drug ratios and ensure colocalization of the combined therapeutics at the tumor site.¹⁷ Nanoparticulate drug delivery systems can encapsulate hydrophobic therapeutic agent(s), such as PTX to yield aqueous dispersions facilitating its administration and/or to accommodate hydrophilic agent(s) such as RNA facilitating its access to cells.^{15,17-19} Nanoparticle-based therapeutics typically consist of nanosized particles with a diameter in the range of 10 to 200 nm, favorable for increasing accumulation of delivered cargoes in the tumor via passive targeting, ie, enhanced permeability and retention (EPR) effect (Figure 1).^{20,21} Nanoparticles can also be modified with targeting molecules such as growth factors, antibodies, antibody fragments, or peptides, which can specifically bind to receptors overexpressed by tumor cells, leading to enhanced internalization of drug loaded nanoparticles by targeted cells and thus improved selectivity and therapeutic response by so-called active targeting (Figure 1).²² In addition, by tailoring the type and characteristics, eg, molecular weight, compositions and architectures, of the nanoparticle-forming materials, nanoparticles can also be adjusted to improve their properties and thus their payload properties such as in vivo stability, drug retention, circulation time and renal clearance.¹⁷ Many studies on encapsulation of different therapeutic agents into various types of nanoparticles, eg, polymeric micelles, lipid-related nanoparticles, dendrimers, and liposomes (Figure 2) have been carried out and shown to be effective in the treatment of different cancers including ovarian cancer.²³⁻²⁵ Herein, this work summarizes nanoparticle-based combination therapies, mainly including anticancer drug-based combinations and chemo/gene combinations,

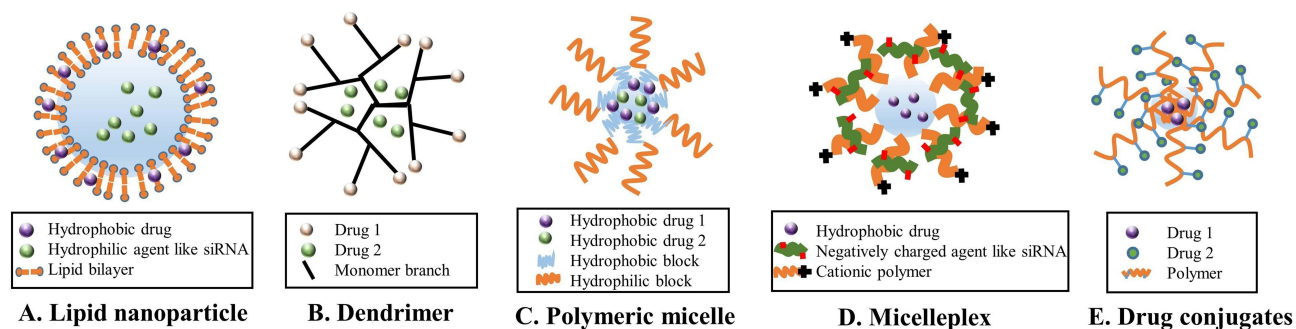


Figure 2 Different types of nanocarriers for codelivery of different therapeutic agents. (A) Lipid-based nanoparticle; (B) Dendrimer-based nanoparticle; (C) Polymeric micelle; (D) Cationic polymer coated complex; (E) Drug conjugates.

and emphasizes the advantageous outcomes of nanocarriers in the combination treatment of ovarian cancer. In addition, we also review mechanisms of synergetic effects resulting from different combinations. It is noted that combinations of chemo/immunotherapy are beyond our discussion because reports simultaneously involving combined chemo/immunotherapy, delivery systems, and ovarian cancer treatment are not found, which leaves room for investigation.

Anticancer Drug-Based Combinations

As combination chemotherapy is currently the first-line therapy for ovarian cancer, in this section combinational anticancer drug(s) and small molecule therapeutic agents with different action mechanisms by nanoparticulate delivery systems for the treatment of ovarian cancer are summarized (Table 2). In addition, mechanisms of synergetic effects resulting from different combinations are introduced.

Taxane-Based Combinations

Taxanes represented by PTX and docetaxel (DTX) are one of the most effective therapeutic agents in gynecological cancers including ovarian cancer.²⁶ Taxanes prevent depolymerization of the protofilament substructure within the microtubule by binding to and stabilizing the β -tubulin subunits, thus causing G2/M arrest and apoptosis through cell-signaling cascades.²⁷ Although taxanes are widely used in cancer treatment, the clinical application is limited by, eg, low water solubility, non-selective distribution and drug resistance.²⁸ Therefore, taxane-based combinations mediated by nanomedicines formed in an aqueous solution provide opportunities to overcome these obstacles and improve the therapeutic efficacy of taxanes (Table 2). For instance, to enhance specificity and therapeutic efficacy in ovarian cancer, Jain et al codelivered PTX and topotecan by liposomes consisting of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-methoxy(polyethylene glycol) (DSPE-PEG) dipalmitoylphosphatidylcholine (DPPC), dimyristoyl phosphatidylglycerol (DMPG).²⁹ The liposomes were decorated by folate acid facilitating folate receptor targeting, which is over-expressed more than 90% in ovarian cancer.^{29,30} In this combination regimen, PTX blocks cell division at the G2 and M phases by stabilization of microtubules whereas topotecan induces cell cycle arrest in the S phase by converting DNA topoisomerase I into a cellular toxin.²⁹ Indeed, the synergistic combination of PTX and topotecan mediated by liposomes exhibited superior therapeutic activities *in vitro* and *in vivo* compared to the combination of free PTX and topotecan and PTX and topotecan coloaded liposomes without folate modification.

One of the main contributors of MDR is related to P-gp, which is located in the cellular membrane and uses adenosine triphosphate (ATP) to actively pump cytotoxic drugs out from the cell.³¹ Therefore, PTX combined with P-gp inhibitor has been reported to overcome drug-resistance. For example, Zou et al reported the combination of PTX and Borneol, a natural compound with P-gp inhibition effect, using polyamidoamine (PAMAM) dendrimers as a nanocarrier for drug resistance reversal in ovarian cancer.^{32,33} As a result, when compared with PTX alone, nanoparticles containing PTX and Borneol exhibited higher cytotoxicity and apoptosis induction activity on drug-resistance A2780/PTX ovarian cancer cells *in vitro* and improved growth inhibition efficacy for drug-resistance A2780/PTX tumor *in vivo*. The synergistic effect of PTX and Borneol combination on drug-resistance reversal is attributed to decrease P-gp mediated drug efflux by P-gp inhibition activity of Borneol, thus leading to enhanced intracellular concentration of PTX in PTX-resistance A2780/PTX cells, as indicated in Figure 3.

Since it has been reported that curcumin as a natural polyphenol compound can suppress the expression of P-gp, Zhao et al designed hyaluronic acid decorated polyethyleneimine (PEI) nanoparticles for codelivery of curcumin and PTX to reverse the drug-resistance of ovarian cancer.^{34,35} In this system, hyaluronic acid as an active targeting ligand can target cancer cells with over-expressed CD44 on cancer cell membranes while the amphiphilic graft copolymer PEI-SA containing a hydrophobic segment of SA and a hydrophilic block of PEI self-assemble to nanoparticles.³⁶ Curcumin and PTX coloaded by the PEI-based nanoparticles exerted synergistic anticancer activities on chemosensitive SKOV3 and multidrug resistant SKOV3-TR30 ovarian cancer cells *in vitro* and had a good therapeutic effect on drug-resistant SKOV3-TR30 tumors *in vivo*. A clear synergistic effect against multidrug-resistant SKOV3-TR ovarian cancer cells *in vitro* and *in vivo* was also observed when curcumin and PTX were coloaded in micelles consisting of a mixture of DSPE-PEG and vitamin E.³⁷ In addition, codelivery of PTX and a synthetic analog of curcumin, namely di-fluorinated curcumin, by albumin-based nanoparticles also demonstrated a synergistic anticancer effect on SKOV3 ovarian cancer

Table 2 Summary of Anticancer Drug-Based Combinations Achieved by Various Drug Delivery Systems for the Treatment of Ovarian Cancer

Delivery System	Drug Combination	In vitro Cell Line	In vivo Animal Model	Targeting	Targeting Moiety	Advantage	Refs.
Liposomes consisting of DPPC, DMPG and DSPE-PEG	PTX Topotecan	OVCAR-3	OVCAR-3 ovarian cancer xenograft mouse model	Passive/Active	Folate acid	Improve efficacy and specificity	[29]
PAMAM-PEG nanoparticles	PTX Borneol	A2780 and drug-resistant A2780/PTX	Drug-resistant A2780/PTX ovarian cancer xenograft mouse model	Passive	–	Improve paclitaxel resistance	[32]
PEI-SA based nanoparticles	PTX Curcumin	SKOV3 and multidrug resistant SKOV3-TR30	SKOV3 tumor mouse model	Passive/Active	Hyaluronic acid	Reversing paclitaxel resistance	[34]
DSPE-PEG and Vitamin E based micelles	PTX Curcumin	SKOV3 and multidrug-resistant SKOV3-TR	SKOV3 and SKOV3-TR tumor models	Passive	–		[37]
Bovine serum albumin based nanoparticles	PTX Di-fluorinated curcumin	SKOV3	–	Passive/Active	Folic acid	Improve efficacy and specificity	[38]
PEG-PLA micelles	Docetaxel Curcumin	A2780	A2780 ovarian cancer xenograft mouse model	Passive	–	Improve efficacy	[28]
	DOX Chloroquine	SKOV3, A2780 and DOX-resistant A2780/DOX	Mice bearing SKOV3, A2780 or DOX-resistant A2780/DOX ovarian tumor	Passive	–	Improve efficacy and reduce toxicity	[61]
	DOX Verapamil	DOX-resistant A2780/DOX DOX-resistant SKOV3/DOX	A2780/DOX and SKOV3/DOX ovarian cancer xenograft mouse models	Passive	–	Significantly elevated the DOX accumulation	[64]
PLGA-PEG nanoparticles	PTX Cisplatin	SKOV3	SKOV3 ovarian cancer xenograft mouse model	Passive	–	Improve efficacy	[42]
	Cisplatin Wortmannin	A2780 and platinum-resistant A2780/cisplatin	A2780 and platinum-resistant A2780/cisplatin ovarian cancer xenograft models	Passive	–	Improves cisplatin sensitivity	[45]
	Cisplatin gemcitabine	IOSE-80, PA1, ES2, TOV-21G, TOV-112D, Caov-3, OVCAR3 and SKOV3	–	Passive	–	Overcoming drug resistance	[48]
	SH-aspirin Curcumin	ES2 SKOV3	–	Passive	–	Improve efficacy	[70]
P (MeOx-b-BuOx-b-MeOx) micelles	PTX Cisplatin	A2780 and cisplatin-resistant A2780/cisplatin	Cisplatin-resistant A2780/cisplatin ovarian xenograft tumor model	Passive	–		[43]
Liposomal nanoparticles based on DSPC, POPG and cholesterol	Cisplatin Olaparib or Talazoparib	COV362 OVCAR4 OVCAR8	COV362 and orthotopic OVCAR8 high-grade serous ovarian cancer xenograft tumor-bearing mouse models	Passive/Active	Hyaluronic acid	Improve efficacy and reduce toxicity	[41]

(Continued)

Table 2 (Continued).

Delivery System	Drug Combination	In vitro Cell Line	In vivo Animal Model	Targeting	Targeting Moiety	Advantage	Refs.
Micelles consisting of DOX conjugated PEG-PLA and docetaxel conjugated PEG-PLA	DOX Docetaxel	SKOV3	–	Passive/Active	Folate acid	Improve efficacy	[65]
Nanoparticles consisting of DOX conjugated DSPE-PEG and Rhein conjugated TPGS	DOX Rhein	SKOV3, DOX-resistant SKOV3/DOX, HOSEC	SKOV3/DOX tumor-bearing mouse model	Passive	–		[66]
Pluronic®F127 micelles	Curcumin Resveratrol DOX	SKOV3	–	Passive	–	Improve efficacy and reduce toxicity	[58]
	Quercetin Resveratrol DOX	SKOV3	Healthy Swiss Webster mice	Passive	–		[69]
	Quercetin Resveratrol Curcumin DOX	ES2 DOX-resistant A2780/DOX	ES2, A2780 and DOX-resistant A2780/DOX mouse xenograft models		–		[59]
PEG-DPPE/calcium phosphate hybrid nanoparticles	Curcumin Triptolide	SKOV3	SKOV3 tumor-bearing mouse	Passive			[74]

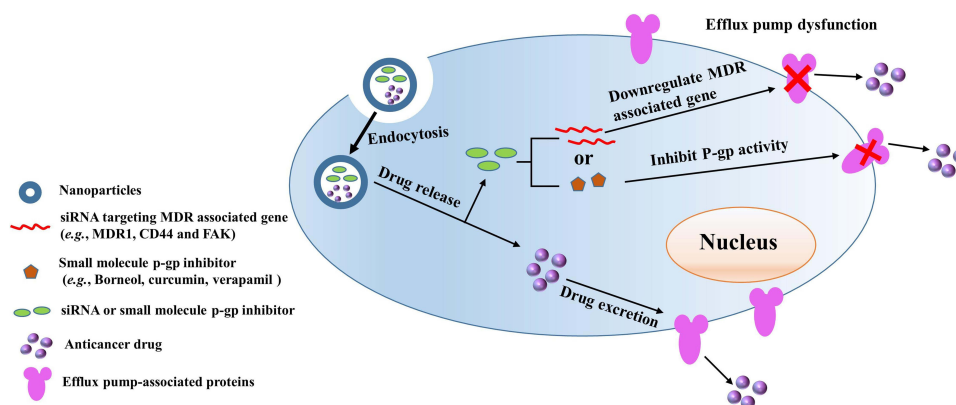


Figure 3 Codelivery of an anticancer drug and small molecule P-gp inhibitor or MDR related gene silencing siRNA to overcome pump-related resistance. In the combinational system, the activity of efflux pump-associated proteins is inhibited by small molecule P-gp inhibitor or siRNA targeting MDR associated genes, leading to increased drug accumulation in tumor cells and thus enhanced therapeutic response of anticancer drug on drug-resistant ovarian cancer cells.

cells.³⁸ In this system, the surface of the nanoparticles was modified by folic acid for actively targeting folate receptors, leading to improve tumor specificity. The mechanism of the synergistic effect is related to the fact that curcumin inhibits the drug efflux of P-gp and changes the paclitaxel signaling pathway, which increases the intracellular PTX concentration resulting in reversing the resistance and increasing anti-tumor activity of PTX.³⁴

In addition, although DTX as the second-generation anti-tumor taxane drug has some advantages over the first-generation taxane, ie, PTX, the bioavailability of DTX is still suboptimal due to the effect of cytochrome P450 (CYP3A) and P-gp. Considering that the activity of CYP3A enzyme and the expression of P-gp can be inhibited by curcumin, DTX was codelivered with curcumin by poly(ethylene glycol)-poly(L-lactic acid) (PEG-PLA) based polymeric micelles to improve therapeutic efficacy on ovarian cancer.²⁸ The DTX and curcumin coloaded micelles demonstrated stronger anti-proliferative and pro-apoptotic effects on A2780 ovarian cancer cells and significantly enhanced antitumor effects in terms of inhibiting tumor growth, suppressing tumor angiogenesis and promoting tumor cell apoptosis when compared to DTX or curcumin mono-loaded micelles.

Cisplatin-Based Combinations

Platinum-based anticancer drugs, such as cisplatin, are standard chemotherapeutic agents in ovarian cancer therapy.^{39,40} This class of drugs can penetrate the nucleus of cancer cells and form adducts with genomic or mitochondrial DNA to block the production of DNA, mRNA, and proteins, arrest DNA replication, and activate several transduction pathways, which finally lead to necrosis or apoptosis.⁴¹ Nanoparticle-mediated combination therapy based on cisplatin has been shown a promising strategy in improving water solubility, enhancing therapeutic potential, reducing side effects and reversing drug resistance (Table 2).⁶ For instance, Shen et al codelivered cisplatin and PTX using an injectable prodrug hydrogel based on poly(lactic-co-glycolic acid)-*b*-poly(ethylene glycol) (PLGA-PEG) polymer-platinum (IV) conjugate for ovarian cancer treatment.⁴² The dual-drug system exhibited a synergistic anticancer effect against SKOV3 ovarian cancer cells and excellent in vivo anticancer efficacy with significantly reduced side effects in SKOV3 ovarian cancer xenograft mouse model. Likewise, the synergistic anticancer effect was also found when PTX and alkylated cisplatin prodrug were coloaded in polymeric micelles based on poly(2-methyl-2-oxazoline-*b*-2-butyl-2-oxazoline-*b*-2-methyl-2-oxazoline) (P(MeOx-BuOx-MeOx)).⁴³ The PTX and cisplatin coloaded polymeric micelles exhibited superior antitumor activity in cisplatin-resistant A2780 ovarian xenograft tumor model in comparison with single drug loaded micelles.

In addition to combination with the classical anticancer drug PTX, cisplatin as a DNA-damaging agent in combination with drugs that interfere with DNA synthesis and/or DNA damage repair has been reported to exhibit synergistic effects on ovarian cancer treatment.³⁴ For example, Mensah et al used the electrostatic layer-by-layer liposomal nanoparticles based on 1,2-distearoylsn-glycero-3-phosphocholine (DSPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-(10-*rac*-glycerol) sodium salt (POPG) and cholesterol to codeliver cisplatin and poly(ADP-ribose) polymerase (PARP) inhibitors (Olaparib or Talazoparib) for the treatment of advanced ovarian cancers.⁴¹ The liposomal nanoparticles contain

a terminal hyaluronic acid layer for selective targeting of high-grade serous ovarian cancer cells with overexpressed CD44 receptors while both cisplatin and the PARPi drug were loaded within the liposomal core and bilayer. Compared to monotherapy, the combination therapy mediated by liposomal nanoparticles led to significantly reduced tumor metastasis, extended survival, and moderated systemic toxicity in orthotopic OVCAR8 high-grade serous ovarian cancer xenograft tumor-bearing mice. In this combination regimen, PARPs as a family of nuclear DNA damage repair enzymes are responsible for the repair of DNA single-strand breaks (SSBs). The inhibition of SSB repair by PARP inhibitors causes double-strand breaks (DSB) at replication forks, which induces synthetic lethality and confers sensitivity in cells with defective BRCA1- and BRCA2-mediated homologous recombination (HR)-directed DSB repair.⁴⁴ Therefore, cisplatin combined with PARP inhibitors exhibited synergistic activity by interfering with DNA repair and thus boosting the activity of the DNA-damaging agent. In addition, PLGA-PEG-based nanoparticles were used to encapsulate both cisplatin and wortmannin for the treatment of platinum-resistant ovarian cancer.⁴⁵ In this combination system, wortmannin, a phosphoinositide 3-kinase inhibitor, can potently block downstream DNA repair pathways that are involved in cisplatin resistance.^{46,47} As a result, wortmannin in dual-drug loaded PLGA-PEG nanoparticles synergistically enhanced the cytotoxicity of cisplatin on ovarian cancer *in vitro* and improved its therapeutic efficacy of cisplatin in both platinum-sensitive and platinum-resistant A2780/cisplatin ovarian cancer xenograft models as compared to combinations of free drugs or single-drug loaded nanoparticles.⁴⁵ Except for the inhibition of DNA repair resulting from wortmannin, the resistance reversal of cisplatin is partially attributed to improved cellular uptake of cisplatin resulting from PLGA-PEG nanoparticles. Besides, Hung et al also used PLGA-PEG-based nanoparticles to codeliver cisplatin and gemcitabine to overcome gemcitabine-chemoresistance in ovarian cancer subtypes.⁴⁸ The synergistic mechanism of both drugs is related to the fact that gemcitabine inhibition of ribonucleotide reductase leads to increased formation of platinum-DNA adduct, improved gemcitabine triphosphate incorporation into DNA, which hinders DNA replication and repair.^{49–53} The results suggest that compared to its free drug combination, nanoparticle mediated delivery of gemcitabine further enhanced synergistic interactions with cisplatin in different ovarian cancer subtypes including high drug-resistant cancer subtypes such as PA-1 teratocarcinoma and TOV-21G clear cell carcinoma. This improved synergistic effect is also partially attributed to the improved cellular accumulation of gemcitabine resulting from nanoparticle delivery that can bypass the inherent nucleoside transporters, required for intracellular delivery of gemcitabine in its free form but defective in high drug-resistant cancer subtypes such as teratocarcinoma.⁴⁸

Doxorubicin-Based Combinations

Doxorubicin (DOX) is an anthracycline anticancer antibiotic that is widely used for the treatment of various cancers including ovarian cancer.⁵⁴ The mechanisms for anticancer effects of DOX are involved in insertion into DNA to inhibit the production of topoisomerase II and production of reactive oxygen species (ROS), resulting in damage of the membrane of cell and mitochondria and apoptosis.^{55–57} Due to the undesired clinical effect of DOX alone, many researchers have explored the combined effect of DOX and other drugs by codelivering them with various nanoparticles for the treatment of ovarian cancer (Table 2).^{58–63} For example, Zheng et al encapsulated DOX and verapamil, a P-gp inhibitor, in PEG-PLA-based nanoparticles.⁶⁴ *In vitro* cytotoxicity shows that single DOX had limited intracellular concentration in DOX-resistant A2780/DOX and SKOV3/DOX ovarian cancer cells while the addition of verapamil significantly elevated the DOX accumulation in both cells due to inhibiting the DOX efflux induced by P-gp over-expression. More importantly, DOX and verapamil coloaded nanoparticles showed efficient drug resistance reversal in DOX-resistant A2780/DOX and SKOV3/DOX ovarian cancer both *in vitro* and *in vivo*, along with enhanced curative effects and reduced systemic toxicity when compared with single DOX and free verapamil and DOX combination of free verapamil and DOX. In addition, PEG-PLA nanoparticles simultaneously encapsulating DOX and chloroquine also led to significantly improved anticancer effects of DOX *in vivo* along with reduced side effects when compared with DOX alone regardless of its forms.⁶¹ The synergistic effect is contributed to the fact that chloroquine as a lysosome inhibitor efficiently reversed the DOX degradation and sequestration effects induced by lysosomes, leading to the enhanced tumor suppression of chemotherapeutic agents. Except for the physical loading of drugs in PEG-PLA nanoparticles, synergistic cytotoxic effects were observed by chemical conjugation of DOX and DTX to PEG-PLA polymeric micelles modified by folate acid that have targeting ability of folate receptors, as indicated by enhanced therapeutic efficacy *in vitro* at low

doses of each drug.⁶⁵ Similarly, DSPE-PEG conjugated with DOX and *d*-tocopheryl polyethylene glycol succinate (TPGS) conjugated a lipophilic anthraquinone Chinese herbal medicine, rhein, were mixed to form polymeric micelles for drug delivery.⁶⁶ Compared to the free DOX alone, free rhein and free DOX/rhein group, DOX and rhein loaded polymeric micelles elevated effects on cell cycle arrest in G0/G1 phase and apoptosis induction in DOX-resistant SKOV3/DOX ovarian cancer cells, which led to enhanced cytotoxicity in DOX-resistant SKOV3/DOX ovarian cancer cells. In vivo study shows that DOX and rhein loaded polymeric micelles had better cancer targeting and improved tumor efficacy without obvious toxicity on SKOV3/DOX tumor-bearing mice compared to free DOX/rhein combination group.

Cardiotoxicity is a major adverse effect of DOX, limiting its clinical use of DOX. It has been reported that the cardiotoxicity of DOX is associated with increased oxidative stress resulting from increased levels of ROS and lipid peroxidation.⁶⁷ Natural polyphenols such as quercetin, resveratrol, and curcumin are known free radical scavengers and have demonstrated cardioprotective effects through, eg, mechanisms of antioxidant and free radical scavenging.⁶⁸ In addition, these natural products have been reported to have chemosensitizing effects when used in combination with conventional chemotherapeutics.⁶⁰ Considering their low aqueous solubility and low oral bioavailability, and short half-lives, these free radical scavengers are usually delivered by nanocarriers when in combination with DOX to fully assess their capabilities of cardioprotection and chemosensitization in cancer treatment.⁶⁰ For instance, it has been demonstrated that curcumin and resveratrol coloaded Pluronic[®]F127 micelles in combination with DOX enhanced the antiproliferative effect of DOX on SKOV3 and DOX-resistant SKOV3/DOX ovarian cancer cells in vitro while mitigating doxorubicin-induced cardiotoxicity both in vitro and in vivo.^{58,59} In separate studies, they also show that combinatorial resveratrol and quercetin by Pluronic[®]F127 micelles when co-administered with DOX had cardioprotective effects in vitro and in vivo. Meanwhile, quercetin/resveratrol coloaded Pluronic[®]F127 micelles combined with DOX increased the DOX efficacy against DOX-sensitive (SKOV3 and ES2) and DOX-resistant (A2780/DOX) ovarian cancer cells in vitro and significantly lowered tumor growth in both ES2 and A2780/DOX mouse xenograft models when compared to DOX alone or quercetin/resveratrol loaded micelles alone.^{59,69}

Other Combinations

Except for combinations based on first-line chemodrugs, combinations between other drugs have also been studied for the treatment of ovarian cancer. For example, Zhou et al co-encapsulated a H₂S-releasing nonsteroidal anti-inflammatory prodrug, SH-aspirin, and curcumin in PEG-PLGA-based nanoparticles to solve their drawbacks such as the relatively low anticancer activity of SH-aspirin (eg, IC₅₀ of SH-aspirin were 56.1 µg/mL on SKOV3 cells) and poor water solubility of both drugs.⁷⁰ Codelivery of SH-aspirin and curcumin by nanoparticles led to better anticancer effects than SH-single aspirin or curcumin loaded nanoparticles on both SKOV3 and ES-2 human ovarian carcinoma cells in vitro due to the synergistic effects of both drugs. The synergistic anticancer effects are associated with the induction of apoptosis through activating caspase-3 and caspase-9 to trigger the mitochondria-dependent apoptotic signaling pathway.

Triptolide is a predominant active component of Chinese herbal medicine and has antitumor effects on ovarian cancer.⁷¹ However, the therapeutic potential is hindered by its high toxicity to the liver, kidney and reproductive system.⁷² It has been reported that curcumin can protect liver and kidney by resisting oxidative stress caused by chemodrugs.⁷³ Therefore, to enhance therapeutic effects and reduce the side effects of triptolide, nanoparticles composed of 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-*N*-methoxy(polyethylene glycol) and calcium phosphate (DPPE-PEG/calcium) were developed to codeliver triptolide and curcumin.⁷⁴ This study indicates that triptolide and curcumin coloaded nanoparticles exhibited synergistic in vitro proliferation inhibition effects on the SKOV3 cell line by arresting the cell cycle in the S and G2/M phases and inducing cellular apoptosis through inhibiting the expression of related heat shock protein in cells. In vivo study shows that nanoparticles loaded with both drugs could greatly reduce the toxicity of free triptolide to liver and kidney through anti-oxidative stress effects resulting from curcumin and exhibited favorable curative effects on the SKOV3 tumor-bearing mice (Table 2).

Combination of Chemotherapy and Gene Therapy

Gene therapy introduces exogenous genetic material(s), ie, nucleic-acid-based bioactives to regulate gene expression in specific cells and overcome the cellular pathways to treat diseases including cancers caused by aberrant gene expression.⁷⁵ Among nucleic-acid-based bioactive compounds, small interfere RNAs (siRNAs) are extensively studied as therapeutic agents, which can induce specific cleavage through its complementary pairing with mRNA, thus leading to degradation of mRNA and failure of the corresponding protein expression.⁴ Since naked-siRNA is difficult to enter cells due to its hydrophilicity, large molecular weight and negatively-charged feature resulting in low transfection efficiency, nanoparticle-based carriers are required for delivery of genes. Encouragingly, many siRNA-based therapeutic agents delivered by different nanocarriers have been developed and used for clinical trials.¹⁵ It has been demonstrated that a combinational therapy consisting of siRNA and chemotherapy is effective in the treatment of various cancers including ovarian cancer.^{4,19}

Codelivery of siRNA and Anticancer Drug for Overcoming Resistance

As the primary reason for the poor efficacy of ovarian cancer treatment, resistance to chemotherapy is related to abnormal gene expression. Expression of several genes such as MDR1 and Bcl-2 has been reported to be associated with the reduced sensitivity of cancer cells to anti-cancer drugs.⁷⁶ Therefore, chemotherapy in combination with siRNA-based gene therapy is shown to be effective in reversing MDR of ovarian cancer.^{4,19} In this section, we summarize nanoparticulate delivery systems for codelivery of different gene silencing siRNA and anticancer drug to treat ovarian cancer, especially MDR ovarian cancer (Table 3).

Codelivery of siRNA and Anticancer Drug for Overcoming Pump-Related Resistance

One of the main development mechanisms of MDR is associated with overexpression of ATP-binding cassette (ABC) transporter family of transmembrane proteins that can form membrane-bound ATP-dependent active drug efflux pumps (Figure 3).⁷⁶ ABC transporters utilize the energy of ATP to actively pump chemotherapeutic agents out of the cell, which can significantly decrease the intracellular accumulation of the drug and thereby increase the therapeutic efficacy. Suppression of the expression of MDR associated proteins can be achieved via selective silencing of the corresponding genes by siRNA, which is a promising approach to reverse the resistance of anticancer drugs (Figure 3).

Among MDR associated proteins, P-gp encoded by the ABCB1 or MDR1 gene is the first identified ABC transporter and is known to be the main protein that induces MDR in solid tumors.^{77–79} Therefore, many different nano-delivery systems have been developed to codelivery MDR1 gene silencing siRNA (MDR1 siRNA) and chemotherapeutics for overcoming MDR resistance of chemodrug(s) (Table 3).⁸⁰ For example, nanoparticles composed of poly(ethylene oxide)-*b*-poly(beta-aminoester) (PEO-PbAE) and poly(ethylene oxide)-*b*-poly(ϵ -caprolactone) (PEO-PCL) were developed to deliver MDR1 siRNA and PTX, respectively.⁸¹ Compared to PTX nanoparticles only, administration of MDR1 siRNA and PTX coloaded nanoparticles resulted in a significant increase in intracellular PTX levels, apoptotic rate and the cytotoxic chemotherapeutic effect in drug-resistant SKOV3-TR ovarian cancer cells. Wang et al designed a biomimetic lipid/dextran hybrid nanocarrier to coload MDR1 siRNA and PTX, which also showed better therapeutic effects on highly PTX-resistant OVCAR-3 ovarian cancer cells both in vitro and in vivo as compared to PTX-only system did.⁸² The synergistic effects were also found when MDR1 siRNA delivered by hyaluronic-acid-based PEI/PEG nanoparticles in combination with PTX.¹⁴ It is shown that compared to treatment of the PTX alone, administration of nanoparticles loaded with MDR1 siRNA followed by PTX effectively downregulated P-gp expression, potentially increased apoptosis and significantly inhibited tumor growth in MDR SKOV3-TR ovarian cancer mice model. In addition, He et al reported a self-assembled core-shell nanoscale coordination polymer-based nanoparticles for the codelivery of MDR1 siRNA with cisplatin or cisplatin plus gemcitabine, in which siRNAs were located in the lipid layer and chemotherapeutic agent(s) was loaded in the core. Strong synergic effects among chemotherapeutic agent(s) and MDR1 siRNA in the nanoparticles were indicated by, eg, efficiently induced cell apoptosis and drastically enhanced anticancer efficacy in subcutaneous and intraperitoneal xenograft mouse models of cisplatin resistant ovarian cancer, as compared to that provided by mono-chemotherapeutic nanoparticles or free drug(s).⁸³ Joshi et al delivered DOX and MDR1 siRNA using a novel hypoxia-sensitive nanoparticle system composed of PEG, azobenzene (Azo), polyethyleneimine (PEI) and

Table 3 Summary of Combination of Chemotherapy and Gene Therapy

Delivery System	siRNA Targeted Gene	Drug	In vitro Cell Line	In vivo Animal Models	Targeting	Targeting Moiety	Advantage	Refs.
PEO-PbAE and PEO-PCL based nanoparticles	MDR1	PTX	SKOV3 and multidrug resistant SKOV3-TR	–	Passive	–	Significantly improves paclitaxel efficacy	[81]
DOPE and DOTAP lipid-coated dextran nanogels	MDR1	PTX	OVCAR-3 and highly PTX-resistant OVCAR-3/PTX	OVCAR-3/PTX tumor-bearing mouse model	Passive	–	Improve efficacy	[82]
Nanoparticles consisting of mixed hyaluronic acid -PEI and hyaluronic acid -PEG	MDR1	PTX	Multidrug resistant SKOV3-TR and OVCAR8-TR	Multidrug resistant SKOV3-TR ovarian cancer mouse model	Passive/Active	Hyaluronic acid		[14]
Nanoscale coordination polymer-based nanoparticles coated with DOPA, DOPC, cholesterol and DSPE-PEG	MDR1	Cisplatin	SKOV3, A2780 and cisplatin-resistant A2780/cisplatin	SKOV-3 subcutaneous xenograft mouse model and A2780/cisplatin intraperitoneal xenograft mouse model	Passive	–		[83]
PEG- azobenzene-PEI-DOPE nanoparticles	MDR1	DOX	DOX-resistant A2780/DOX	–	Passive	–		[84]
PMMA-PEG-DOPE nanoparticle	MDR1	DOX	DOX-resistant A2780/DOX	–	Passive	–		[85]
PPI nanoparticles	CD44	PTX	Human ascitic cancer cells obtained from the peritoneum area of the patients with ovarian cancer	Mice bearing xenografts of human cancer cells isolated from malignant ascites from patient with advanced ovarian carcinoma	Passive/Active	LRHR peptide	Improve efficacy and specificity	[90]
	DJ-1	Cisplatin	ES2, IGROV1, SKOV3 and A2780/cisplatin	–	Passive/Active	Folate acid		[105]
PLGA nanoparticles	FAK	PTX	A2780, cisplatin-resistant A2780/cisplatin, SKOV3, PTX-resistant SKOV3-TR, HeyA8 and multidrug resistant HeyA8/MDR	Multidrug-resistant HeyA8/MDR and PTX-resistant SKOV3-TR xenograft mouse models and drug-resistant ovarian cancer patient derived xenograft model	Passive/Active	Hyaluronic acid		[97]

(Continued)

Table 3 (Continued).

Delivery System	siRNA Targeted Gene	Drug	In vitro Cell Line	In vivo Animal Models	Targeting	Targeting Moiety	Advantage	Refs.
Mesoporous silica nanoparticles	Bcl-2	DOX	A2780/DOX	–	Passive	–	Improve efficacy	[99]
PEG–PEI–PCL based cationic micelles	Bcl-2	DOX	SKOV3	–	Passive	–		[102]
Cholesterol, DOPE and DSPE-PEG based cationic liposomes	KSP	PTX	HeyA8/MDR	HeyA8-MDR tumor bearing mouse model and mice bearing xenografts of human cancer cells derived from the patient with platinum-resistant epithelial ovarian cancer	Passive/ Active	LHRH peptide	Improve efficacy and specificity Reverse cisplatin resistance	[112]
Chitosan coated PLA nanoparticles	P62/pβ5 ^a	Cisplatin	Cisplatin-resistant 2008/C13	–	Passive	–		[116]
Nanoscale coordination polymer-based nanoparticles coated with DOTAP, cholesterol and DSPE-PEG	Bcl-2/P-gp/survivin	Cisplatin	SKOV3, ES2, OVCAR-3, A2780 and A2780/cisplatin	Cisplatin-resistant SKOV3 ovarian cancer mouse model	Passive	–	Enhanced therapeutic efficacy of cisplatin	[117]

Note: ^aIs Plasmid DNA.

1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) units (PEG-Azo-PEI-DOPE), where Azo imparts hypoxia sensitivity.⁸⁴ The treatment of PEG-Azo-PEI-DOPE nanoparticles containing MDR1 siRNA and DOX significantly enhanced the cytotoxicity effect of DOX on the DOX-resistant A2780/DOX ovarian cancer cells. For instance, cell viability was approx. 90% at DOX monotherapy of 3 μ M whereas only 25% cell viability was observed when MDR1 siRNA (500 nM) was combined with DOX (3 μ M) under hypoxia. Dendrimer micelles composed of polyamidoamine-*g*-1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-(methoxy (polyethylene glycol)) (PMMA-PEG-DOPE) and PEG-DOPE were developed to codeliver MDR1 siRNA and DOX to the tumor, in which siRNA was loaded in PAMAM moieties and hydrophobic DOX were encapsulated into the lipid core.⁸⁵ Dendrimer micelles loaded with both DOX and MDR1 siRNA led to significantly higher cytotoxicity on DOX-resistant A2780/DOX cell lines compared to micelles containing DOX only and free DOX due to MDR1 siRNA induced downregulation of the P-gp efflux pump and thus increased amount of DOX inside cells.

In addition, CD44 as a cell-surface glycoprotein involves in cell interactions, cell adhesion, and migration.⁸⁶ It has been reported that CD44 expression is related to the expression of P-gp, resistance to chemotherapy, and progression of metastases.^{87–89} Therefore, Shah et al established a polypropylenimine (PPI) dendrimer-based drug delivery system consisting of the mixture of PTX conjugated PPI (PTX-PPI) and CD44 targeted siRNA-PPI complexes (CD44 siRNA-PPI), which simultaneously deliver PTX and CD44 siRNA to ovarian cancer cells to induce cell death and prevent metastases.⁹⁰ In this system, PPI dendrimers were decorated by luteinizing hormone-releasing hormone (LHRH) peptide for active targeting LHRH receptor that is overexpressed in ovarian cancer cells.^{91,92} The results show that the delivered siRNA targeting to CD44 effectively suppressed CD44 mRNA and MDR1 mRNA, primarily responsible for multidrug resistance in ovarian cancer cells. Such inhibition significantly improved the potent of PTX to induce cell death by apoptosis and, as a result, the PTX-PPI and CD44 siRNA-PPI exhibited significantly enhanced antitumor efficiency *in vitro* and *in vivo* while preventing adverse side effects on healthy organs. For instance, within the 28-day study period, when treated by monotherapy, ie, PTX-PPI or CD44 siRNA-PPI alone, the tumor derived from ovarian cancer cells isolated from malignant ascites from patients with advanced ovarian carcinoma continued growth whereas the combination of PTX and CD4 siRNA delivered by the nanocarrier led to the almost complete tumor shrinkage.

In addition to MDR1 gene encoding P-gp, other genes encoding drug efflux pump-related proteins such as focal adhesion kinase (FAK) can also regulate the drug efflux pump, thus serving as an important defense mechanism for ovarian cancer resistance (Figure 3).^{93–95} It is reported that down-regulation of FAK can restore the sensitivity of tumor cells to chemotherapy.⁹⁶ Therefore, Byeon et al designed hyaluronic acid modified PLGA nanoparticles to encapsulate PTX and siRNA inhibiting FAK expression (FAK siRNA), in which hyaluronic acid can actively target CD44 over-expressed ovarian cancer cells.⁹⁷ When compared with those without FAK siRNA loading, the nanoparticles loaded with both PTX and FAK siRNA induced a significant increase in cell death and apoptosis in multidrug-resistant HeyA8-MDR and PTX-resistant SKOV3-TR cells. *In vivo* study shows that the combined delivery of PTX and FAK siRNA resulted in significant inhibition of tumor growth not only in drug-resistant HeyA8-MDR and SKOV3-TR xenograft mouse models but also in a drug-resistant, patient-derived xenograft model.

Codelivery of siRNA and Anticancer Drug for Overcoming Nonpump-Related Resistance

Except for the above-mentioned efflux pump-based resistance, non-efflux pump resistance also play an important role in drug resistance.⁹⁸ This resistance is involved in various proteins like MCL-1, Bcl-2, Toll-like receptor 4, surviving and vascular endothelial growth factor (VEGF).⁹⁹ Instead of affecting the accumulation of drugs in tumor cells, nonpump resistance protects tumor cells from anticancer drugs by altering the checkpoints in the cell cycle, activation of detoxifying systems, the escape from drug-induced apoptosis and impaired DNA repair.⁹⁹ Among the aforementioned mechanisms, the proteins associated with the antiapoptotic defense are extensively studied to overcome cancer resistance. For instance, Bcl-2 protein encoded by the Bcl-2 gene is a well-known anti-apoptotic protein that is an activation of cellular anti-apoptotic defense to prevent cell death.⁹⁹ Overexpression of Bcl-2 protein in MDR cancer cells can cause the formation of a large number of Bcl-2/Bcl-2 homodimer on the surface of mitochondria, which inhibits the formation of apoptosomes in the external membrane of mitochondria and thus results in bypassing the regular apoptotic pathway in

tumor cells.^{100,101} Therefore, Chen et al designed mesoporous silica nanoparticles to coload DOX and siRNA targeting the Bcl-2 gene (Bcl-2 siRNA) for overcoming drug resistance in ovarian cancer.⁹⁹ The result showed that due to the significant suppression of Bcl-2 mRNA by Bcl-2 siRNA, simultaneously delivered Bcl-2 siRNA and DOX by the silica nanoparticles resulted in a 64- and 132-fold increase in cytotoxicity of DOX on multidrug-resistance A2780/DOX human ovarian cancer cells as compared to that of mono-DOX loaded nanoparticles and free DOX alone (IC₅₀: 0.017 μM vs 1.07 μM and 2.25 μM), respectively. In addition, Zou et al developed a folate-targeted nanocarrier based on PEG–PEI–PCL triblock copolymer for codelivering DOX and Bcl-2 siRNA into folate receptor overexpressed SKOV3 ovarian cancer cells.¹⁰² Upon the codelivery of Bcl-2 siRNA and DOX using the folate-targeted nanocarrier, DOX-induced apoptosis in the SKOV3 cells significantly enhanced through downregulating the antiapoptotic protein Bcl-2, while simultaneously upregulating the proapoptotic protein Bax. As a result, siRNA and DOX codelivered by the folate-targeted PEG–PEI–PCL nanocarrier exhibited higher cytotoxicity on the SKOV3 cells than a single therapeutic agent loaded targeting nanoparticles or dual-agent loaded nontargeting nanoparticles.

Another example of acting on the anti-apoptotic pathway is DJ-1 protein that can bind to p53 tumor suppressor protein, thereby impeding the cell cycle arrest function of p53 and facilitating the enhanced expression of various anti-apoptotic proteins.^{103,104} Given the role of the DJ-1 protein, Taratula group constructed the PPI dendrimer-based nanoplatfrom to deliver DJ-1 targeted siRNA (DJ-1 siRNA), which is combined with a low dose of cisplatin for the treatment of platinum-resistant ovarian cancer.¹⁰⁵ It is shown that the combinatorial approach is superior to both siRNA-mediated DJ-1 knockdown and cisplatin treatment alone in therapeutic response, especially in the platinum-resistant A2780/cisplatin cancer cells characterized by the highest basal level of DJ-1 protein. In addition to being an anti-apoptotic agent in cancer cells, it has been reported that DJ-1 is associated with invasion and metastasis by modulating different oncogenic pathways.^{103,104} Therefore, in the follow-up study, Schumann et al demonstrated the synergistic effects of combinatorial DJ-1-siRNA delivered by PPI nanoparticles and cisplatin at low dose on the treatment of metastatic ovarian cancer.¹⁰⁵ For example, compared to incomplete remission of cancer in mice treated by DJ-1 siRNA or cisplatin monotherapy, complete eradication of ovarian metastatic tumors with no cancer recurrence during the 35-week trial was observed in mice with metastatic ovarian cancer treated by sequentially intraperitoneal injection of DJ-1 siRNA loaded nanoparticles and low-dose cisplatin.

In addition to the anti-apoptotic defense mechanism, the development of nonpump-related MDR can also be due to ineffective induction of cell death by, eg, affecting the cell cycle.⁷⁶ For instance, kinesin spindle protein (KSP), a member of kinesin superfamily, facilitates bipolar spindle assembly during an early stage of mitosis and eventually leads to centrosome separation.¹⁰⁶ KSP inhibitors as therapeutic agents can cause cell cycle arrest during mitosis by inhibiting KSP function, ultimately leading to cell death. However, a different endogenous kinesin Kif15 is capable of driving bipolar spindle assembly/maintenance in the absence of KSP activity, which leads to resistance against KSP inhibitors.^{106–108} It has been reported that Kif15 behavior is associated with dynamic microtubules, ie, Kif15 motility is suppressed by the reduction of microtubule growth with a microtubule-directed antimitotic agent like PTX.^{109–111} Therefore, Lee et al paired KSP silencing siRNA (KSP siRNA) as KSP inhibitor with PTX as Kif15 inhibitor by PEGylated cationic liposomes composed of cholesterol, DOPE, and DSPE-PEG to overcome KSP resistance and enhance the therapeutic effects of PTX in drug-resistant ovarian cancer.¹¹² The results show that combined KSP siRNA and PTX in liposomes completely blocked bipolar spindle assembly in mitosis through simultaneous down-regulation of KSP and Kif15. This dual action led to the synergistic therapeutic efficacy of combined therapy in vitro and in vivo. This is supported by the fact that siKSP/PTX coloaded liposomes inhibited cell proliferation more potently, induced cell death more prominently on drug-resistant HeyA8-MDR cells and suppressed tumor growth more efficiently in the drug-resistant in vivo models, including drug-resistant cell line and patient-derived xenografts when compared to mono PTX or KSP siRNA loaded liposomes and free PTX alone.

Reduced expression of the β5 subunit of the proteasome and/or enhanced expression of the autophagy regulatory protein P62/SQSTM1 (P62) protein have been demonstrated to contribute to cancer drug resistance in ovarian cancer cells.^{113–115} To reverse cisplatin resistance, Babu et al developed multifunctional nanoparticles based on chitosan coated poly (D, L -lactide) (PLA) to codeliver cisplatin, siRNA for P62/SQSTM1 gene silencing (P62 siRNA) and a plasmid DNA for restoring β5 expression (pβ5).¹¹⁶ In the nanoparticles, cisplatin was loaded in the inner core formed by PLA

while the negatively charged P62 siRNA and p β 5 were located at the outer layer of the cationic chitosan polymer through electrostatic interactions, as indicated by Figure 2C (the third nanoparticles). Codelivered P62 siRNA and p β 5 by the nanoparticles caused P62 knockdown and restored expression of β 5 in cisplatin-resistant 2008/C13 ovarian cancer cells, resulting in restoration of sensitivity to cisplatin and enhanced cell killing as evidenced by a marked decrease of IC₅₀ value of cisplatin on 2008/C13 cells compared to single P62 siRNA or p β 5 and cisplatin coloaded nanoparticles, single cisplatin loaded nanoparticles and free cisplatin.

Codelivery of Multiple siRNAs and Anticancer Drug for Overcoming Both Pump and Nonpump-Related Resistance

Targeting a single factor responsible for drug resistance is often insufficient in reversal MDR due to the simultaneous activation of both pump and non-pump resistances in heterogeneous tumors. Therefore, He et al developed a nanoscale coordination polymer system consisting of cisplatin prodrug, 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), cholesterol and DSPE-PEG for codelivery of cisplatin and pooled siRNAs targeting three MDR genes including anti-apoptotic proteins (Bcl-2 and survivin) and P-gp to overcome drug resistance of ovarian cancer.¹¹⁷ The resulting siRNAs and cisplatin loaded particles promoted cellular uptake of cisplatin in cisplatin-resistant ovarian cancer cells, which is attributed to the decreased nanoparticle/drug efflux pump by downregulating the P-gp expression. Codelivery of cisplatin and pooled siRNAs significantly enhanced the chemotherapeutic efficacy of cisplatin as indicated by the drastically decreased IC₅₀ values of cisplatin in different types of cisplatin-resistant ovarian cancer cell lines (ES2, OVCAR-3, SKOV3, and A2780/cisplatin cells) compared to either free cisplatin or cisplatin coordinated particles. For instance, in ES2 and SKOV3, the IC₅₀ of cisplatin induced by siRNAs and cisplatin loaded nanoparticles showed a 102- and 140-fold decrease compared to single cisplatin coordinated particles. In addition, the codelivery of cisplatin and pooled siRNAs drastically enhanced the in vivo chemotherapeutic effects in cisplatin-resistant SKOV3 ovarian cancer mouse model while no side effects such as immunogenic response and nephrotoxicity were observed. The drastically enhanced anticancer efficacy of the combination treatment benefits from the synergy between downregulation of MDR genes by pooled siRNAs and chemotherapeutic effects of cisplatin.

Codelivery of Viral Gene and Anticancer Drug

Viral-mediated gene therapy (virotherapy) is an approach to cancer treatment, in which the replicating virus itself is the anticancer agent and exploits the lytic property of virus replication to kill tumor cells. A variety of viral species have been adopted as virotherapy agents, such as Adenoviruses, retroviruses, lentiviruses, and herpes simplex viruses (Figure 4).^{118–121} It has been reported that virotherapy combined with chemotherapy is a potential therapeutic modality for the improvement of transfection efficiency and therapeutic efficacy for ovarian cancer.^{122,123} Zhang et al demonstrated a synergistic effect in the combination of a novel surviving promoter-based conditionally replicating adenovirus and cisplatin in the enhancement of the antitumor efficacy in ovarian cancer while Franke et al reported that tobacco mosaic virus delivered cisplatin restored efficacy in platinum-resistant ovarian cancer cells.^{122,124} In addition, It is reported that some microtubule-disrupting drugs, such as PTX, can improve gene transfection efficiency at a non-cytotoxic dosage.^{125–129} Therefore, Long et al reported that the

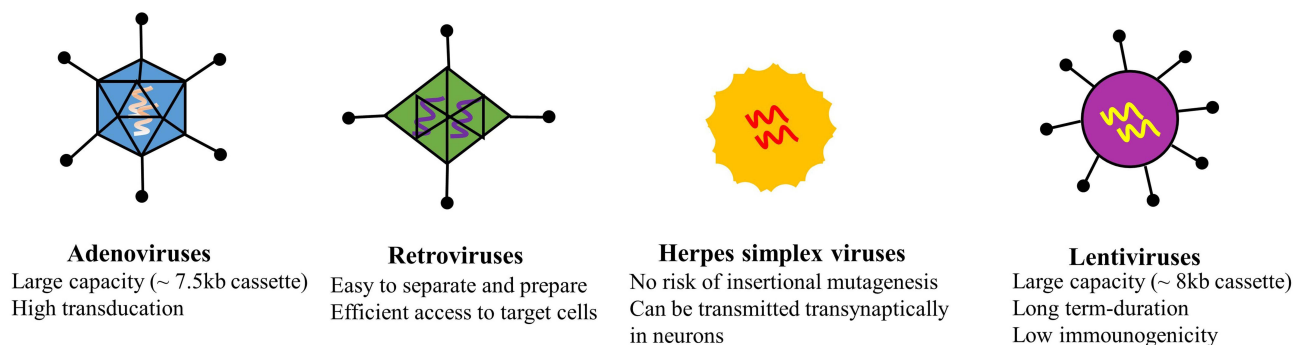


Figure 4 Representative images of the viral vectors with their features including genome sizes and advantages for virotherapy.

therapeutic gene targeting vesicular stomatitis virus matrix protein (VSVMP), ie, VSVMP gene, was codelivered with low-dosage of PTX by nanoparticles composed of DOTAP and PEG-PLA for combinational treatment of ovarian cancer.¹¹⁶ Vesicular stomatitis virus (VSV) is an oncolytic virus that preferentially replicates in various tumor cells and has antitumor effects.^{118,130–132} VSVMP as a key structural component of the virion is the main contributor to VSV-induced antitumor activities, which has exhibited antitumor effects in multiple tumor-bearing models.^{133–136} As expected, VSVMP gene and low-dosage PTX coloaded in nanoparticles exhibited synergistic anticancer effects in SKOV3 ovarian cancer treatment.¹³⁷ The results show that in the codelivery system, the PTX significantly improved the gene delivery efficiency of VSVMP gene, leading to enhanced VSVMP expression and VSVMP-induced anti-proliferation and apoptosis in SKOV3 cells. Intraperitoneal injection of nanoparticles coloaded with VSVMP and PTX more effectively inhibited the intraperitoneal metastasis of SKOV3 ovarian cancer, as compared to that delivered either VSVMP or PTX only.

Combination of Other Therapies

Photodynamic therapy (PDT) is an emerging non-invasive treatment modality that is based on a photochemical reaction between a light-activable molecule, namely photosensitizer, and light to generate ROS to kill cancer cells (Figure 5).^{138–141} Current research reveals that the combination of PDT and chemotherapy is a feasible and effective strategy for the improvement of the therapeutic outcomes of ovarian cancer therapy due to the synergistic effect as presented in Figure 5.¹⁴² For instance, a reduction-sensitive drug codelivery system based on polymeric prodrug poly(ethylene glycol)-*b*-poly(5-methyl-5-propargyl-1,3 dioxan-2-one)-*g*-paclitaxel (PEG-*b*-PMPMC-*g*-PTX) was constructed to coload a near-infrared (NIR) fluorophore, 4,8-bis((2-ethylhexyl)oxy)benzo[1,2-*b*:4,5-*b'*]dithiophene-1,1,5,5-tetraoxide (BDTO) derivative (namely, DEB) and tariquidar to treat drug-resistant ovarian cancer.¹⁴³ In this codelivery system, DEB functions as a photosensitizer for image-guided PDT, while PTX and tariquidar act as a cytotoxic agent and a drug-resistant (P-gp) inhibitor, respectively. In vitro study shows that DEB and tariquidar loaded in PEG-*b*-PMPMC-*g*-PTX prodrug formed micelles substantially increased the accumulation of PTX in drug-resistant SKOV3/MDR ovarian cancer cells due to the suppression of P-gp by tariquidar and displayed a prominent synergistic enhancement effect of PDT and chemotherapy in terms of anti-proliferation of SKOV3 and SKOV3/MDR cells. In the SKOV3/MDR tumor-bearing mouse model, the multidrug resistance of tumors was successfully reversed and the tumor growth was significantly inhibited by combining PDT and chemotherapy. Moreover, Pan et al reported nanoparticles based on poly- ϵ -caprolactone using bovine albumin as a stabilizer to coload IR780, a hydrophobic NIR photosensitizer, and PTX for combinational PDT and chemotherapy.¹⁴⁴ IR780 and PTX coloaded nanoparticles demonstrated an excellent synergistic therapeutic effect against PTX-resistant

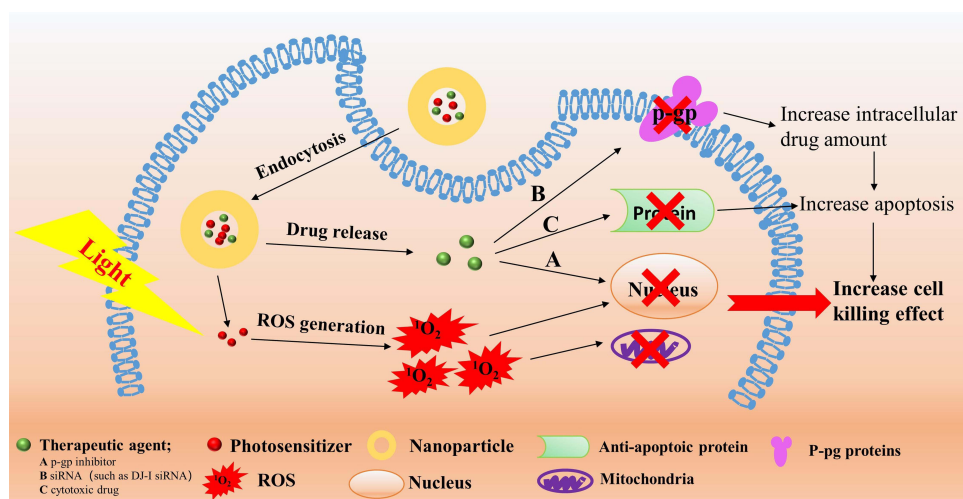


Figure 5 PDT based combination therapy. In the process of PDT, the harmless photosensitizer is activated by light of the absorbed wavelength. The activated photosensitizer subsequently transfers its energy to nearby molecular oxygen, producing oxygen radicals and other ROS. These formed ROS are highly reactive with cellular components such as nucleic acids, proteins and lipids, leading to direct damage to cells. PDT in combination with (non)cytotoxic drug and/or P-gp inhibitor and/or siRNA (eg. targeting anti-apoptotic DJ-1 protein) can exert the synergistic effect to improve cell killing effect.

SKOV3-TR30 cells *in vitro*, which is evident by a substantial decrease in the IC_{50} value (19.8 nM) compared to that of the corresponding monotherapy (IC_{50} of chemotherapy only and PDT only was 1285 and 158 nM, respectively). In drug-resistant SKOV3-TR30 tumor-bearing mice treated simultaneously with NIR light-induced PDT and chemotherapy (ie, IR780-PTX loaded nanoparticles + light group), tumors were completely eradicated without recurrence in the entire experimental period and the survival of mice was greatly prolonged to over 65 days. In contrast, after treatment with one of the corresponding two therapies, the tumors were destroyed at the beginning but followed by regrowth and tumor-bearing mice had a medium survival rate of 35–37 days.

In addition to the advantages for MDR ovarian cancer, cooperative therapy of chemotherapy and PDT also provides a great opportunity for metastasis, which is one of the major obstacles to the successful treatment of ovarian cancer.¹⁴⁵ Many small molecule inhibitors, such as KBU2046, BENC-511, MPT0G211, DSHN, BDP5290 and BMS-777607, have been reported for effectively inhibiting the metastasis of primary tumors.^{146,147} However, no cytotoxic effect of these inhibitors, responsible for continuous proliferation of tumor cells *in situ*, is a defect in the treatment of tumors. Cooperative therapy through the introduction of PDT provides a possibility to compensate for their congenital defects. Dai et al used DSPE-PEG-based nanoparticles to codeliver small molecule inhibitor (KBU2046) and a photosensitizer, BDT0 derivative (namely TB), in which the former drug has the effect of anti-metastasis of the primary tumors and the latter photosensitizer can suppress the growth of the primary tumors under irradiation.¹⁴⁸ *In vitro* studies show that KBU2046 and TB coloaded nanoparticles exhibited the anti-migration and anti-proliferation for SKOV3 cells under irradiation. In line with this, *in vivo* study shows that cooperation therapy achieved anti-tumor growth and anti-metastasis in the subcutaneous SKOV3 tumor model and effectively suppressed the recurrence and metastasis of tumor after surgery in an orthotopic ovarian tumor model.

In addition to the combination of PDT and chemotherapy, chemotherapy associated with ultrasound or tumor treating fields has also been demonstrated to enhance therapeutic outcomes of ovarian cancer.^{149,150} For example, Baghbaniet al demonstrate that DOX and curcumin coloaded alginate/perfluorohexane nanodroplets in combination with ultrasound irradiation led to significantly increased drug internalization in a very short time and cytotoxicity on DOX-resistant A2780/DOX ovarian cancer cells compared to the non-sonicated group. *In vivo* study shows that DOX and curcumin coloaded nanodroplets resulted in complete eradication of DOX-resistant A2780/DOX ovarian tumors while tumor growth was only inhibited to some extent in the non-ultrasound irradiation group.¹⁴⁹

Except for the combination of chemotherapy and PDT, PDT is also reported to have synergistic effects when in combination with gene therapy (Figure 5). For instance, Clements et al exploited Generation 4 PPI dendrimer-based nanoplatforms for the sequential delivery of a NIR photosensitizer, phthalocyanine, and siRNA targeting DJ-1 gene (as a DJ-1 gene suppressor), a key player in protecting cancer cells from ROS mediated apoptosis.^{104,151,152} It is validated that compared to that provided by PDT alone, the anticancer activity and intracellular ROS levels induced by phthalocyanine mediated PDT in combination with siRNA delivery dramatically increased in DOX-resistant A2780/DOX human ovarian carcinoma cells characterized by higher basal levels of DJ-1 due to siRNA mediated silencing of DJ-1 expression. In A2780/DOX ovarian cancer mice model, after the treatment with PDT alone, tumors were almost eliminated but followed by relapse while tumors were completely eradicated and, importantly, no evidence of cancer recurrence was exhibited when treated with a single dose of a combinatorial therapy (PPI-siRNA followed by PPI-phthalocyanine).

Conclusion and Perspective

Combined different therapy modality by nanomedicine has advantages in terms of improving drug water-solubility, controlling drug ratios, ensuring the same drug disposition behavior at the tumor site, decreasing non-specific toxicities and increasing drug co-accumulation at tumor sites, which provides an unprecedented opportunity for the treatment of ovarian cancer. Various nanocarriers have been developed for different combination purposes and nanoparticle-based combinations indeed have been demonstrated the outperformed therapeutic outcomes in ovarian cancer treatment compared to drug alone or free drug combination. Codelivery of chemodrugs with other small molecule drugs by nanoparticles solves the problems of conventional combinations such as low-water solubility, non-specific distribution, and different pharmacokinetics of combined drugs. As a result, the synergistic interactions of the different combinations

are dramatically enhanced, leading to improved antitumor effects, increased tumor targeting and reversed MDR. Combination delivery of chemodrug and siRNA using nanoparticles minimizes the accumulation of the drug/siRNA in the normal tissues, achieves temporal co-deposition of the combined agents in tumors and efficient delivery of siRNA into cells. Combined with the fact that gene therapy can tune the expression of proteins (eg, P-gp, Bcl-2) by manipulating the gene content of tumor cells, the drug/gene combination leads to the excellent performance of anticancer drug(s) in overcoming MDR and enhancing therapeutic response. In addition, other combinations like PDT in combination with chemotherapy or gene therapy also exhibit superior therapeutic outcomes compared to single therapy alone.

Although nanoparticles as codelivery systems are extensively used for the combination treatment of ovarian cancer, they are still challenged by their instability in circulation, which often leads to premature drug release, diminished ability to selectively reach target sites, and suboptimal therapeutic efficacy. In addition, concerns regarding drug loading capacity, flexibility in changing the drug ratio, release timing of different therapeutic agents (mainly for chemo/gene combination) and biosafety of the delivery materials also remain in the field of nanoparticle-based combination therapies. Therefore, future work should concentrate on optimizing carrier systems or implementing innovative delivery strategies such as carrier-free drug delivery systems to address these challenges and thus generate a maximum effect of the combination therapy in the preclinical trials.

Despite the superior advantages of nanomedicine in the combination treatment for ovarian cancer compared to traditional therapy, the number of nanomedicines used clinically is rare, let alone as first-line treatment options. The clinical translation failure of many nanomedicines is partially due to a lack of understanding of the different physiology and pathology between animal models and humans.¹⁵³ Except for the differences across species, heterogeneity amongst patients is another contributor to hindering the clinical translation of nanomedicines. Therefore, future research can explore how the gap between animals and humans and how heterogeneity resulting from, eg, the growth, structure and physiology of pathological tissue amongst patients influence the behavior, distribution, functionality and efficacy of nanomedicines in the human body. This research will provide an important reference for the rational design of nanomedicines. On the other hand, the current nanoparticle design mainly focuses on developing delivery systems with a one-size-fits-all solution. Considering the heterogeneous barriers, future research also should focus on advanced intelligent nanoparticle design, which can utilize tailored designs for precision applications while improving therapeutic effects in conventional delivery applications, ultimately enhancing the overall therapeutic outcomes in patients.

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Disclosure

The authors declare no conflict of interest.

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