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REVIEW

# Polymer Nanoparticles Advancements for Gynecological Cancers

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**Abstract:** Gynecological cancers represent one of the leading causes of death in women and pose a critical global health challenge. While surgery and chemotherapy remain the first-line therapies for gynecological cancers, the persistently high morbidity and mortality rates have driven the urgent exploration of novel theranostic strategies. In recent years, polymer nanoparticles (PNPs) have gained increasing attention in the diagnosis and treatment of cancer due to their superior targeting ability and delivery efficiency. This review provides an overview of PNPs and their role in tumor diagnosis and treatment, with a strategic focus on their utility in gynecological cancers. It covers drug delivery, imaging, combination therapy, and theranostic integration in gynecological cancers, and summarizes the composition, principles and characteristics of diverse polymers and their cargoes. Furthermore, this work highlights innovative applications of PNPs in gynecological cancers management, spanning chemotherapy, immunotherapy, PARPi therapy, phototherapy and other therapies. Despite promising preclinical advancements in PNPs, formidable challenges persist in their clinical translation. This review serves as a comprehensive resource for researchers and clinicians aiming to optimize gynecological cancers theranostics as well as accelerate the development and clinical translation of PNPs.

**Keywords:** polymer nanoparticles, gynecological cancer, theranostics, nanoparticles, ovarian cancer, cervical cancer, endometrial cancer, nanomedicine

## Introduction

Nanoparticles (NPs) are solid colloidal particles, usually between 10–1000 nm in size,[1] which can be composed of lipids, metals, metal oxides, polymers and other materials.[2] Polymer nanoparticles (PNPs) is a collective term for nano-sized particles made of polymer,[3] with the optimal size of 10–200 nm for their in vivo application.[4] PNPs have superior biocompatibility and drug-loading flexibility compared to other NPs. PNPs are mainly prepared by self-assembly, nanoprecipitation, dialysis, solvent evaporation, salting-out, based on preformed polymers or on monomers.[1,3–5] The circulation time of PNPs in vivo is determined by their physicochemical properties, while their controllable shape, size, and surface modifications allow them to be a promising therapeutic carrier.[4] PNPs can encapsulate various cargoes to improve their solubility, bioavailability, biocompatibility, half-life, etc.[6] Then they deliver and release the cargoes precisely to exert therapeutic or diagnostic effects. Therefore, PNPs have undergone extensive research in the treatment and prevention of tumors,[7–9] cardiovascular diseases[10,11], and infectious diseases.[12,13]

Cancer is one of the most important risk factors for human mortality in modern society. According to Global Cancer Observatory, about 9.7 million people died of cancer worldwide in 2022.[4] Gynecological cancers, including ovarian, cervical, endometrial, vulvar, and fallopian tube cancers, are the leading causes of death in women.[14] For now, the major therapies for gynecological cancers are still surgery and chemotherapy.[15–17] However, the recurrence, metastasis, chemoresistance, and the still-growing global burden of gynecological cancers highlight the urgent need to develop novel precision-based strategies. Recently, polymeric nanosystems for combination therapy and diagnostic and therapeutic integration have been developed to increase the therapeutic efficiency of gynecological cancers. Particularly, the

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potential of PNPs in gynecological cancers therapy is gradually being realized. Since different gynecological cancers vary significantly in their pathogenesis, target expression, drug sensitivity, etc, the design of PNPs needs to be differentiated according to the cancers. Researchers have designed many novel PNPs to deliver therapeutic agents or adjuvants required for chemotherapy, immunotherapy, phototherapy, gene therapy in gynecological cancers.

Although many studies are underway, very few PNPs have been successfully translated into clinical practice. The clinical application of these PNPs still faces many challenges, such as biosafety, heterogeneity of clinical effects, targeted delivery efficiency, and scale-up production.[18]

# The Mechanism of PNPs in Cancer Diagnosis and Treatment

## Cargoes Loaded with PNPs

PNPs produce effects in the diagnosis and treatment of tumors primarily by loading different cargoes. Among them, chemotherapeutic agents (CTAs) are one of the most common cargoes. Many PNPs have been developed to address their drawbacks such as premature drug release, difficulty in targeted delivery, low bioavailability, side effects and toxicity, and drug resistance[19,20] enhancing the efficacy of oncology chemotherapy. Other strategies with PNPs including the application of prodrugs,[21] the combination of two drugs,[22] and synergistic treatment with other therapies[23,24] are constantly being investigated.

RNA-based drugs such as small interfering RNAs (siRNA), mRNAs, antisense oligonucleotides, microRNAs, etc, are increasingly explored for tumor therapy.[25] mRNA-based therapies deliver genetic instructions for therapeutic protein production without nuclear entry, minimizing genotoxicity risks compared to DNA-based approaches.[26,27] However, siRNA silences oncogenes via RNA interference but faces challenges like poor stability, rapid renal clearance, and inefficient cellular uptake in its free form.[28,29] The protection of the polymer keeps these nucleic acids from being degraded during delivery to tumor cells and promotes cellular uptake.[30]

PNPs can also deliver phototherapeutic agents such as photothermal agents (PTA) for photothermal therapy (PTT) and photosensitizers (PS) for photodynamic therapy (PDT)[4] as well as contrast agents for magnetic resonance imaging (MRI),[31,32] photoacoustic imaging (PAI),[33] etc. This capability enhances both therapeutic precision and diagnostic accuracy. Compared to conventional therapies, phototherapy (including PTT and PDT) offers non-invasive treatment with minimal trauma.[23] PTT generates localized heat to eliminate cancer cells[34] and remodel the TME,[35] while PDT relies on light-activated PS to produce cytotoxic reactive oxygen species (ROS), inducing tumor cell apoptosis or necrosis.[23,36,37]

## Targeted Drug Delivery

Targeted drug delivery of PNPs is categorized as active targeting and passive targeting. Controllable surface modifications are the basis for active targeting. Active targeting mainly occurs through the binding of ligands on the surface of PNPs to receptors on the surface of tumor cells or tumor vascular endothelial cells. Therefore, the tumor cell receptors selected for designing PNPs are supposed to be specifically overexpressed on the tumor surface but not in healthy cells.[4] Commonly overexpressed target receptors in tumors include human epidermal growth factor receptor 2 (HER2), CD44 receptor, folic acid (FA) receptor, vascular endothelial growth factor (VEGF) receptor, and others.[30,38] For example, Sader et al[39] utilized dermatan sulfate, which can target the CD44 receptor, to design PNPs capable of actively targeting triple-negative breast cancer. The site-specific binding of the ligands to the receptors decreases the probability of off-targeting during delivery.

However, passive targeting is achieved by enhanced permeation and retention (EPR) effects and does not require ligand-receptor binding. Nano-sized particles preferentially enter tumor cells but are difficult to exit due to leaky vasculature and poorly developed lymphatic drainage of the tumor,[6] which allows them to accumulate and prolongs their sustained release within the tumor cells.[40] (Figure 1) Although the theory of the EPR effect is widely recognized, it has not been successful in clinical translation. That might be related to the heterogeneity of the EPR effect in different tumors or individuals. Thus several researchers are exploring this area and trying to guide the application of nanomedicines through patient stratification.[41]

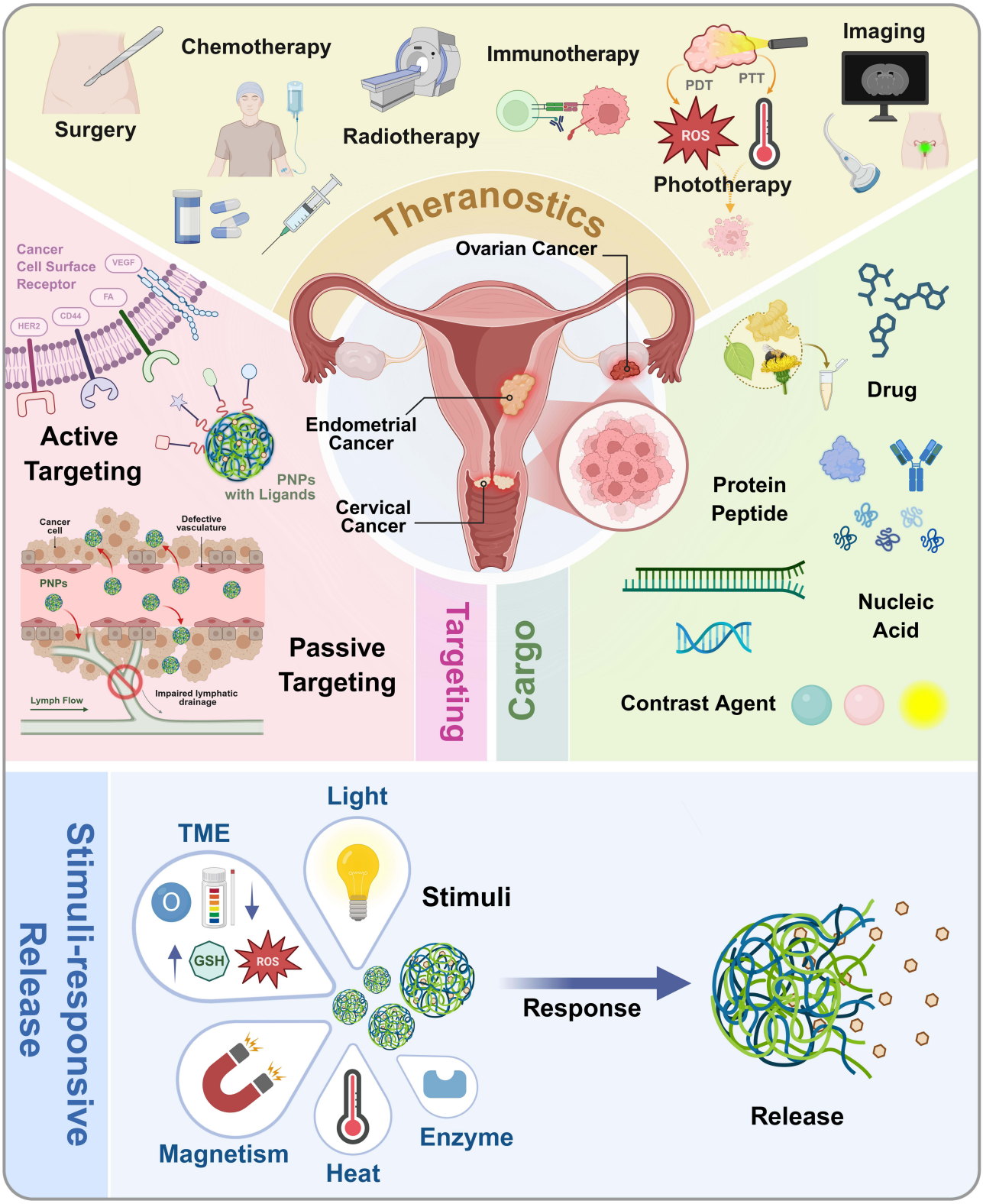


**Figure 1** The mechanism of PNPs in the theranostics of gynecological cancers. Created in BioRender. Lin, X. (2025) https://BioRender.com/wlprr14.
**Abbreviations**: PNPs, polymer nanoparticles; PDT, photodynamic therapy; PTT, photothermal therapy; ROS, reactive oxygen species; TME, tumor microenvironment; GSH, glutathione.


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## Stimuli-Responsive Release

The tumor microenvironment (TME) is remarkably different from the environment in which healthy cells live. Acidic pH, high levels of glutathione (GSH), specific enzymes, ROS, hypoxia, and other stimuli unique to TME offer opportunities to design stimuli-responsive PNPs.[42–44] In addition, in vitro physical stimuli such as light, heat, ultrasound, magnetic fields and so on can also mediate drug release.[43] PNPs can release the cargoes they carried when they encounter the specific stimulus in the target site. This process is known as stimuli-responsive release. For example, as an important reducing agent in tumors, GSH can break disulfide bonds in the backbone of redox-responsive polymers, leading to the degradation of the polymer and the release of its loaded drug.[45,46] This capacity to locally release the drug only in response to the specific stimulus effectively minimizes the loss of the drug in the circulation and the side effects of systemic administration (Figure 1).

# Commonly Used Polymers

As the core of PNPs, the characteristics of the various polymers themselves cannot be ignored. The polymers used to design PNPs for drug delivery share the general characteristic of biocompatibility, which can be classified into natural and synthetic polymers[47,48] (Table 1).

## Natural Polymers

### Chitosan

Chitosan (CS) is the most widely used natural polymer as a drug carrier which is found in large quantities in nature.[48] CS can be extracted from crustacean shells or fungi,[54] and it is a copolymer of $\beta$-(1,4)-linked D-glucosamine and *N*-acetyl-D-glucosamine.[50] The cationic nature is one of the advantages of CS, which facilitates its binding to anionic molecules such as nucleic acids and cell surface macromolecules, and also enhances adhesion to negatively charged mucous membranes.[49,50] Other advantages of CS include lower toxicity and immunogenicity, excellent biocompatibility and biodegradability, and potential for antimicrobial, antioxidant and anticancer activity.[49,54,59] Ali et al[60] designed chitosan/tannic acid nanoparticles (CS/TAN NPs) for loading loratadine (LOR), which exhibited stronger cytotoxicity than free loratadine, to enhance the anticancer activity of the antihistaminic agent LOR against MCF-7 breast cancer. Together with the ability of tannic to promote apoptosis in MCF-7 breast cancer cells, this demonstrates the great potential of LOR-CS/TAN NPs as a novel antiproliferative agent for breast cancer therapy.

The disadvantages of CS are also well defined, such as poor water solubility and inefficient endosomal escape ability,[49] which prevent it from achieving clinical translation. In this regard, scientists have explored multiple approaches to overcome its shortcomings by adding various structural modifications. Among them, polyethylene glycolylation

**Table 1** Commonly Used Polymers

| Category | Abbreviation | Full Name | Main Characteristics |
|---|---|---|---|
| Natural polymers | CS | Chitosan | Cationicity, solubility in aqueous acidic medium[49,50] |
| | – | Albumin | Solubility[48] |
| | – | Polyphenols | Fast metabolism, limited bioavailability[51] |
| | – | Gelatin | Hydrophilicity, near-body-temperature melting[52] |
| Synthetic polymers | PEG | Poly (ethylene glycol) | Hydrophilicity,[4] escape MPS recognition and clearance[53] |
| | PLGA | Poly (Lactic-*co*-Glycolic Acid) | Hydrophobicity, tunable physicochemical properties[54,55] |
| | PCL | Poly-$\varepsilon$-Caprolactone | Hydrophobicity, slow degradation[6,56] |
| | PLA | Poly(lactic acid) | Hydrophobicity[57] |
| | PEI | Polyethyleneimine | Cationicity, non-degradability[58] |

(PEGylation) is one of the reliable strategies to improve CS nanoparticles (CS-NPs) drug delivery.[61,62] Coating the surface of CS-NPs with PEG, covalent conjugation of CS with PEG to form self-assembled NPs, or linking CS-NPs with drugs via PEG-linker are all used as means to form PEGylated CS-NPs. PEGylation improves CS solubility, inhibits mononuclear phagocytic system (MPS) clearance to prolong plasma circulation time, and enhances CS stability and anticancer ability in biological fluids.[63]

### Albumin

Albumin is a protein-based polymer that has also been used to engineer PNPs. Albumin NPs are considered as excellent drug carriers due to their biological origin, lack of toxicity and immunogenicity, good water solubility, and the ability to accumulate at the tumor site. According to its source, albumin can be classified as human serum albumin, bovine serum albumin (BSA), etc.[48] Its most classical application case is albumin-bound paclitaxel (Abraxane). Paclitaxel (PTX) is a Taxanes with well-defined tumor inhibitory properties, however, high insolubility has hindered its clinical development. Earlier, researchers had developed solvent-based PTX (Taxol®) with Cremophor EL as an excipient, but the risk of inducing hypersensitivity reactions, neutropenia and peripheral neuropathy was identified in subsequent clinical applications. In order to avoid the Cremophor EL-related toxicities, researchers developed Abraxane.[64,65] Abraxane avoids solvent-related toxicity and has better response rates, tumor uptake, and tolerability.[64] Clinical trials have shown that Abraxane can significantly improve the toxicity and efficacy of the drug, with higher volume of distribution and clearance, as well as significant linear pharmacokinetics compared to Taxol®.[66]

### Other Natural Polymers

Owing to their natural abundance, low toxicity, biodegradability and biocompatibility, these natural polymers, including polysaccharide-based polymers (CS, hyaluronic acid (HA), alginate, starch, agarose, etc) and protein-based polymers (albumin, gelatin, collagen, etc), are widely used for drug delivery.[48] For example, gelatin was used to load PTX for EPR effect and slow release of the drug.[52] In addition, some teams have also designed PNPs with natural polyphenol Gossypol as the polymer backbone to promote anti-tumor effects utilizing its pro-apoptotic ability.[67]

## Synthetic Polymers

### Poly (Ethylene Glycol)

Poly (ethylene glycol) (PEG) is a hydrophilic polymer with high stealth properties in vivo and is the most common polymer used to produce PNPs.[4] PEG shows excellent biocompatibility, drug encapsulation efficiency and non-toxicity.[68] What's more, it has the capacity to escape recognition and clearance by MPS, therefore breaking the limitation of circulation time.[53] In addition, using PEG as a surface coating for NPs, PEGylation can also prolong its in vivo circulation time.[53] However, other studies have reported that in vivo PEG antibody production and pre-existing PEG antibodies can induce accelerated blood clearance, negatively affecting the safety and efficacy of PEGylated drugs.[69]

### Poly (Lactic-co-Glycolic Acid)

Poly (Lactic-*co*-Glycolic Acid) (PLGA), a polyester polymer approved for medical applications by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), has received extensive attention in the design of PNPs.[70] PLGA is hydrolyzed in vivo to lactic acids and glycolic acids, which are degradable metabolite monomers that can be metabolized in the tricarboxylic acid cycle, thus making PLGA a polymeric material with minimal toxicity.[56,70] The physicochemical properties such as hydrophobicity, mechanical strength, and degradation speed can be controlled by adjusting the ratio of lactic acid and glycolic acid content in PLGA.[54,55] This allows PLGA to be utilized better for encapsulation of different drugs as well as treatment of different diseases.

### Poly-ε-Caprolactone

Poly-ε-Caprolactone (PCL) is also a polyester polymer approved by the FDA that can be hydrolyzed or enzymatically cleaved to caproic acid and excreted in urine or feces without accumulation in the body,[6,71] so it is considered a reliable synthetic polymer. PCL is a hydrophobic polymer that degrades slowly in vivo,[56] and the encapsulated drug can be released slowly and gradually once it is applied.[6] Some teams have utilized its controlled-release property to design

drugs[72,73] to prolong the duration of effects or to achieve long-term administration in vivo.[56,71,74] Abriata et al[75] utilized polycaprolactone (PCL) as a delivery vehicle for PTX and demonstrated its potential to optimize treatment protocols for ovarian adenocarcinoma in vitro.

### Other Synthetic Polymers

Similar to PLGA and PCL, Poly(lactic acid) (PLA) is also one type of the hydrophobic polyesters, yet water molecules can break its ester bonds leading to hydrolysis.[57] Its degradation product, lactic acid, can be metabolized by the body, making PLA also a suitable polymer for the production of PNPs.[76,77] Polyethyleneimine (PEI) is a cationic synthetic polymer that encapsulates negatively charged DNA to protect it from degradation.[58] It also has great transfection ability and has been extensively studied as a gene delivery carrier.[4,26] However, its non-degradability can lead to cytotoxic effects,[58] which limits its application. Therefore, researchers have attempted to synthesize some biodegradable polymers with similar functions to PEI. For example Poly(β-amino esters) (PBAE) synthesized by Jordan J Green et al[78] for the delivery of DNA for the treatment of glioblastoma. Additionally, disulfide-bonded derivatives of PEI (*l*-PEIS) synthesized by Yan Lee et al[79] which showed high transfection efficiency and low toxicity.

Combining the advantages of different polymers to form new copolymers is also an important research trend. For example, the PLGA introduced previously is a commonly used copolymer. The amphiphilic PNPs prepared using PEG-PCL featured both PCL as the hydrophobic core and PEG as the hydrophilic shell, which enhances the water solubility while protecting the physicochemical properties of the cargo.[33] The mPEG-PEI copolymer NPs were utilized for the delivery of short hairpin RNA (shRNA) for the treatment of chemoresistant prostate cancer, taking advantage of the high transfection efficiency of PEI while incorporating PEG to reduce the toxicity of the NPs and enhance their stability.[80] Coating CS and PEG on the outside of PLA-based NPs can inhibit the phagocytosis of PNPs by the reticuloendothelial system, facilitate the penetration of macromolecules across the mucosal surface and form a hydrated shell to prolong the in vivo circulation time of PNPs.[81]

## Polymer-Hybrid Nanoparticles

In order to overcome the disadvantages of homopolymer, another strategy is to combine it with other kinds of materials (such as lipids, metals, inorganic compounds, etc) to form new polymer-hybrid nanoparticles (PHNPs).[82] Farinha et al[83] designed a novel targeted hybrid nanosystem consisting of a pH-sensitive lipid bilayer and a PLGA core in order to improve the effects of targeted therapeutics selumetinib and perifosine in combination with the tumor suppressor gene transgene for the treatment of hepatocellular carcinoma (HCC). They endowed this nanosystem with many advantages, including the capability of PLGA to load different therapeutic molecules, easy adjustment of the degradation rate, the stimulus responsiveness of lipids and reduced therapy-related side effects. Kong et al[84] also designed a lipid-PHNP using PLGA with the incorporation of redox-responsive polymer for the delivery of mRNA encoding the tumor suppressor p53, to treat the patients with p53-deficient HCC and non-small cell lung cancer. Le's team[85] utilized PBAE combined with bioactive lipids, forming PBAE-lipid hybrid NPs that encapsulate the mRNA encoding bevacizumab, which is preferentially targeted to the pulmonary endothelial cells in systemic administration. There are many other studies that have demonstrated that the application of PHNPs can contribute to improving the blood circulation time of NPs, increasing the encapsulation rate, and optimizing the specific release.[82]

# Novel Polymer Nanoparticles for Drug Delivery in Gynecological Cancers

Focusing on the field of gynecological cancers, although surgery and chemotherapy remain the mainstream treatment options, scientists are also attempting to leverage the unique advantages of PNPs to provide new strategies for gynecological cancers theranostics (Table 2).

## Ovarian Cancer

Ovarian cancer (OC) is a common malignant tumor of the female reproductive system that lacks effective diagnostic strategies in the early stages, therefore most of the patients are already in advanced stages when they are diagnosed.[116] According to the survey data of the World Health Organization (WHO), in 2022, there were 6.65

**Table 2** Novel Polymer Nanoparticles for Gynecological Cancers

| Cancer | Polymer | Active Substance | Surface Targeting Ligand | Cell Line/ In-vivo Model | Reference |
|---|---|---|---|---|---|
| Ovarian Cancer | PLA | PTX | HA | SKOV3; SKOV3 xenograft tumor model | [86] |
| | PLGA-b-PEG | Platin-C | TPP | A2780/CP70 | [21] |
| | PEI, PEG | siRNA | FA | SKOV-3-Luc | [87] |
| | PBAE | mRNA | Di-mannose | C57BL/6 mice | [88] |
| | PLGA | aEP2/4 | - | A375; patient-derived ascites | [89] |
| | BSA | Olaparib, $Ga^{3+}$ | - | SKOV3, OVCAR3 | [90] |
| | MESOPOROUS polydopamine | Olaparib, adavosertib | TMTP1 | OVCAR8, SKOV3; patient-derived xenograft models | [91] |
| | PLA | JQ1 | - | OVCAR8, SKOV3 | [92] |
| | $PEG_{5000}$ | Ki16425; CBZ | - | A2780, OVCAR3, SKOV3 | [93] |
| | PLA | Brazilian red propolis extract | - | OVCAR3 | [94] |
| | PLGA-PEG-PLGA | Genistein | FA | SKOV3 | [95] |
| | PCL | PTX | - | SKOV3 | [75] |
| Cervical Cancer | Polymeric gemini, PEG | Ir(III) complexes, BODIPY | - | HelaDDP; HelaDDP tumor-bearing mouse | [96] |
| | chitosan | DOX | HA | HeLa, HEK | [97] |
| | l-tyrosine poly (ester-urethane) | DOX, CPT | - | HeLa, WT-MEFs | [98] |
| | PDMS | DOX | - | HeLa | [99] |
| | Thiolated chitosan | NDV | HA | HeLa | [100] |
| | PLGA | Antigenic peptide HPV16 $E7_{44-62}$, ATP | - | TC-1; C57BL/6 mice | [101] |
| | Polystyrene | Lead vaccine antigens HPVE7, Survivin and WT1 | - | HLA-A2/Kb | [102] |
| | PEG-b-P(MNT-r-StSi) | α-Mangostin-rich extract, TEMPO | - | HeLa | [103] |
| | PLGA | Coumarin derivative **21** | - | HeLa | [104] |
| | PGS | Curcumin | - | HeLa | [105] |
| | PMBA | Curcumin | FA | HeLa | [106] |
| | Chitosan | Syringaldehyde | - | HeLa | [107] |
| | PBAE | CRISPR/ shRNA | - | SiHa, HeLa, CaSki, S12, HEK293; C57BL/6 mice, SiHa and HeLa cells xenografts models | [108] |

(*Continued*)


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**Table 2** (Continued).

| Cancer | Polymer | Active Substance | Surface Targeting Ligand | Cell Line/ In-vivo Model | Reference |
|---|---|---|---|---|---|
| Endometrial Cancer | PEG–PLGA | PTX | FA | HEC-1A | [109] |
| | PEG-PDPA | DOX, navitoclax | - | Ishikawa; Ishikawa xenograft models | [110] |
| | PLGA | CIP2b, PTX | - | Hec50co | [111] |
| | PLGA | PTX, BIBF-1120 | - | Ishikawa, Hec50co, KLE | [22] |
| | PCL-PEG-PCL | CRZ, GEM | - | Ishikawa, KLE | [112] |
| | Reduction-sensitive polymer P1 | JX06 | - | Ishikawa, patient-derived EC cells | [113] |
| Uterine Sarcoma | Poly(l-glutamic acid), poly(l-leucine), PEG | PTX | - | MES-SA/DX5 | [114] |
| Choriocarcinoma | PEG-PLA | Methotrexate | HCG | JEG-3, JAR | [115] |

new cases of OC and 3.97 deaths due to OC per 100,000 women, and the incidence and mortality rates of ovarian cancer ranked 7th and 6th among women.[117] OC is the most lethal gynecological cancer, while surgery and chemotherapy are the major therapies for OC. However, most patients relapse after chemotherapy or surgery.[116] The high invasiveness, metastases and drug resistance of OC result in high mortality rates.[102,118–120] Therefore new OC treatments still urgently need to be developed. In recent years, with the development of pharmaceutical research, the status of new modalities, such as immunotherapy, targeted therapy and hormonal therapy, has been rising in the management of OC. Notably, the development of PNPs has also provided an efficient strategy for the application of these new therapeutic molecules.

## Chemotherapy

Chemotherapy is one of the most common treatments for OC. Neoadjuvant chemotherapy and postoperative adjuvant chemotherapy both belong to the first-line chemotherapy; while second-line approaches are usually applied in patients with OC recurrence or deterioration during the first-line chemotherapy.[121]

PTX has been the first-line drug for OC treatment in recent decades. Several formulations, such as Abraxane, have been put into use to deal with the problem of adverse reactions or low solubility of PTX.[122] However, how to overcome its short half-life in vivo remains a focus of scientific inquiry, and PNPs have certain advantages in this field.[123] Xiang Sun et al[86] designed HA-PLA-PTX NPs, which took advantage of HA to bind to CD44 overexpressed on the surface of OC, used HA to surface-modify PNPs synthesized by PLA and PTX. They also PEGylated the surfaces of the PNPs in the process of preparation. The HA on the surface of HA-PLA-PTX NPs provides the ability to actively target OC, and the PEGylation provides the stealth ability to avoid being cleared by MPS. This facilitates the solution of the premature release of PTX and the improvement of the therapeutic targeting and killing efficiency of ovarian tumors in vivo.

Platinum is another chemotherapy drug that is frequently used. Banik's team[21] reported a novel platinum (IV) prodrug, Platin-C, a combination of curcumin and cisplatin, which is recognized as a promising drug to enhance the cytotoxic activity of platinum drugs. In order to deliver Platin-C to mitochondria directly, they used triphenyl phosphonium (TPP) cation-modified PLGA-b-PEG as a carrier for PNPs and validated its mitochondria-targeting activity in the cisplatin chemotherapy-resistant human OC cell line A2780/CP70.

## Immunotherapy

Immunotherapy achieves its anti-tumor effects through enhancing the immune response.[124] Interaction of programmed death 1 (PD-1) protein overexpressed in OC cells with its ligand PD-L1 decreases T-cell responsiveness in epithelial OC. Therefore, using siRNA to inhibit PD-1 expression is a viable immunotherapy for OC. However, PD-1 can also be

expressed in healthy cells, so it is necessary to improve the specificity of siRNA delivery. Teo et al[87] designed PNPs that use FA and PEG to modify the surface of PEI bound to siRNA, which can specifically bind to the FA receptors overexpressed in epithelial OC cells to enhance its uptake. The combination of PEI with siRNA can improve its stability by protecting siRNA from enzymatic degradation through the "proton sponge hypothesis".

Tumor-associated macrophages (TAM) have anti-tumor properties when they express the M1-like phenotype. However TAMs usually express the M2-like phenotype, which means it has a pro-tumorigenic effect to reduce inflammation and promote tissue repair, leading to tumor progression, metastasis, and drug resistance.[125,126] For reprogramming TAM into the M1-like, Zhang's team[88] developed IRF5/IKKβ NPs choosing mRNA-PBAE as the core of PNPs. In order to enable mRNA-PBAE to specifically target TAM and improve its stability, Di-mannitol-functionalized polyglutamic acid was coated on the outer side, and in vitro-transcribed mRNA that encodes the M1-polarizing transcription factors were delivered to M2-like macrophages. Through experiments in OC, glioblastoma and melanoma models, they confirmed the efficacy of IRF5/IKKβ NPs in inducing TAM reprogramming to antitumor, as well as the safety of repeated administration.

Tumor-derived Prostaglandin E2 (PGE2), along with its receptors EP2 and EP4, forms a PGE2-EP2/4 signaling axis, which has been proven to affect the immune function of dendritic cells (DCs) in the tumor microenvironment.[127] Clinical trials have been conducted to study the efficacy of EP2/EP4 antagonists (aEP2/4) in the treatment of cancer.[128] In order to address the possible off-target effects and premature degradation, Jorge Cuenca-Escalona et al[89] used PLGA to encapsulate aEP2/4, which can be phagocytosed by DCs and inhibit the signal transduction involved in PGE2 to protect conventional type 2 DCs from inhibition and promote anti-tumor immune responses of DCs. This concept was validated in experiments with ascites from OC patients.

## PARP Inhibitor

Poly (adenosine diphosphate ribose) polymerase inhibitor (PARPi) induces DNA strand breaks and shows synthetic lethality in homologous recombination deficiency (HRD) cells to exert anti-tumor effects.[129,130] Clinical evidence supports PARPi's role in improving overall survival (OS), particularly in patients with newly diagnosed OC and BRCA gene mutations,[131,132] leading to FDA approval for OC maintenance therapy.[129] However, PARPi also faces problems of poor long-term tolerability as well as acquired resistance.[92]

DNA repair consists of both single-stranded and double-stranded, which are handled by two enzymes, PARP and BRCA, separately. Therefore, the use of PARPi in BRCA-mutated HRD OCs results in the failure of both types of repair. In this case, tumor cells are unable to repair themselves in the event of genetic errors, inhibiting cell proliferation.[90] The low rates of BRCA gene mutations in OC and the limited effects of PARPi in promoting apoptosis in non-HRD cells have restricted the clinical benefit of PARPi in the treatment of OC. Hence, a new combination strategy is needed to improve the sensitivity of OC to PARPi. Yangyang Li et al[90] utilized gallium(III), which can disrupt cellular iron homeostasis and thus inhibit DNA, in combination with PARPi to improve the therapeutic efficacy of PARPi. However, gallium (III) ions ($Ga^{3+}$) have low solubility and bioavailability in vivo and are associated with a risk of nephrotoxicity, so they developed olaparib-Ga nanomedicines composed of NPs with an average size of ~7 nm to deliver PARPi and $Ga^{3+}$ simultaneously. Firstly, BSA-$Ga^{3+}$ was formed based on the natural polymer BSA, then gallic acid (GA) was mixed to form stable GA-$Ga^{3+}$, and then hydrophobic PARPi (olaparib) was attached to BSA and self-assembled to form pH-responsive releasing nanodrugs. The synergistic therapeutic effect of gallium (III) and olaparib was demonstrated in SKOV3 and OVCAR3 homologous recombination-proficient (HR-proficient) OC cells, and its inhibitory effect on tumor growth was proved in vivo in xenograft models.

The combination of PARPi and WEE1 inhibitor (WEE1i) can provide more effective inhibition of ovarian tumor growth, but it is not widely used in clinical practice because it is poorly tolerated.[133] Therefore, Chaoyang Sun's team[91] designed a type of PNPs called TPNPs based on mesoporous polydopamine NPs modified with a tumor-targeting peptide (TMTP1), for the delivery of WEE1i (adavosertib) and PARPi (olaparib), reducing the side effects of the combination through precise delivery of PNPs.

It has been reported that the bromodomain and extra terminal inhibitors (BETi) can specifically regulate oncogene expression and enhance the therapeutic efficacy of PARPi when co-applied with olaparib in HR-proficient OC.[134] Juan et al[92]

utilized PLA-based NPs encapsulating JQ1, a BETi, to form JQ1-NPs. The use of JQ1-NPs together with olaparib in OVCAR8 and SKOV3 OC cell lines showed an enhanced synergistic interaction as well as stronger ability to induce cell death than free JQ1. In addition, JQ1-NPs used alone also showed similar or slightly stronger antiproliferative effects than free JQ1.

### Other Therapeutic Modalities and Medications

There are many signaling pathways dysregulated in OC. The widely recognized ones include the VEGFR and LPA pathways, whose dysregulation can stimulate tumor growth, adhesion, migration, invasion and angiogenesis and also lead to chemoresistance.[93,135–137] VEGF and lysophosphatidic acid (LPA) secreted by OC cells are important signaling molecules involved in the above-mentioned signaling pathways. Ozel et al[93] designed a targeted polymer-drug conjugate nanoparticles loaded with LPA receptor inhibitor (Ki16425) and VEGFR inhibitor (CBZ), using O-(2-Carboxyethyl) polyethylene glycol ($PEG_{5000}$) as a carrier to inhibit the growth of OC.

As a natural product, propolis has been reported to have anticancer effects in OC, including inhibition of tumor angiogenesis, metastasis, as well as inhibition of anti-apoptotic proteins and activation of cysteine-containing aspartic protein hydrolases caspases that promote apoptosis.[138] Justino's team[94] encapsulated Brazilian red propolis extract, which shows cytotoxicity against drug-resistant OC cells,[139] in PLA to form PNPs for the treatment of OC. The use of polymer for loading this promising natural antitumor drug overcomes the disadvantages of its instability, low solubility and low bioavailability. Patra et al[95] designed folate-targeted PLGA nanoparticles for delivery of Genistein (GEN), which has therapeutic potential for OC, to improve GEN's water solubility and bioavailability, as well as to overcome its disadvantages that lack of targetability and rapid in vivo metabolism.

## Cervical Cancer

Data from WHO surveys indicate that cervical cancer (CC) is the fourth most common cancer in women, with approximately 14.12 and 7.08 new cases or deaths per 100,000 women worldwide in 2022 respectively.[117] CC is an infection-associated cancer and the majority of CC is caused by human papillomavirus (HPV) infection, while about 5% of cases are HPV-independent, and the latter is often associated with a poor prognosis.[140] As for treatment, regular therapy for CC includes surgery, radiotherapy, chemotherapy, or a combination of these therapies. For recurrent or metastatic CC, first-line therapy involves platinum-containing combination regimens of chemotherapy as well as pembrolizumab in combination with chemotherapy. While for patients with progression after first-line therapy, other regimens like immunotherapy, pembrolizumab, tisotumab vedotin-tftv and cemiplimab are available as second-line treatment. However, the response rate is low, with a median progression-free survival (PFS) of only 3–6 months.[16] Therefore, a number of PNPs for the treatment of CC are also being developed.

### Chemotherapy

Platinum-containing chemotherapy is the standard regimen for CC treatment, but the risk of tumor progression and drug resistance should not be ignored.[16,141] The use of synchronized radiotherapy is considered to bring additional clinical benefits,[16,142] while there are many teams attempting to optimize CTAs and their carriers to improve the chemotherapeutic efficacy in CC.

Ir (III) complex is an antitumor agent that has received widespread attention for its excellent photophysical and photochemical properties as well as its ability to overcome the drawbacks of the commonly used CTA cisplatin. However, many studies have shown unsatisfactory therapeutic efficacy and severe side effects of Ir (III) complexes, which are related to their poor accumulation in tumors.[96,143,144] Therefore Liang et al[96] designed NPIr@Bp, a PNPs formed by self-assembly of Ir(III), dipyrromethene boron difluoride (Bp) (a type of near-infrared PS) added to polymeric gemini NPs, and terminally capped PNPs with PEG. NPIr@Bp generates single-linear oxygen under near-infrared (NIR) light, which triggers the dissociation of nanostructures and activates the prodrug to achieve mitochondrial targeting. The CTA Ir accumulates in the mitochondria and thus achieves induction of apoptosis. In the cisplatin-resistant human CC mouse model, the application of 808 nm light irradiation of NPIr@Bp shows 95% tumor inhibition.

HA-modified PNPs can target CD44 receptors overexpressed on the surface of solid tumors, and the strong attraction of HA to CD44 promotes the internalization and retention of PNPs within tumor cells.[97] And as a multifunctional transmembrane cell surface adhesion receptor, CD44 is involved in tumor progression by regulating signal transduction pathways and enhanced invasion.[145] Anjum et al[97] utilized HA-coated CS NPs loaded with CTA adriamycin (DOX) to overcome the systemic toxicity, lack of targeting, and other drawbacks of free DOX as well as to optimize the efficacy of DOX in CC therapy. Aluri's team[98] developed an l-tyrosine-based PNPs, which encapsulated DOX and camptothecin utilizing l-tyrosine-based amphiphilic poly(ester-urethane) self-assembled enzyme-responsive NPs. It was confirmed in CC HeLa cells that such l-tyrosine PNPs increased drug uptake and internalization by tumor cells compared to free DOX. Polydimethylsiloxane (PDMS) is one of polymers with organelle-targeting properties. Maparu et al[99] proposed a novel strategy to use PDMS to produce soft NPs with a size of about 30 nm. They successfully utilized these NPs to deliver DOX to the nucleus and mitochondria of CC cells, and the IC50 value was reduced by more than four times compared with that of free DOX. The anticancer potential of PDMS NPs to specifically deliver drugs to the mitochondria and nucleus was also demonstrated by a series of experiments.

### Immunotherapy

As an emerging therapeutic approach, some studies have suggested that immunotherapy has superior effect to surgery and radiotherapy in recurrent CC, however, the low tumor immunogenicity and targeting efficiency pose challenges for the application of immunotherapy in CC.[146]

Oncolytic virotherapy is a promising immunotherapy for CC. To address the rapid clearance of the virus by immune-neutralization in vivo, Kousar et al[100] used thiolated CS NPs to encapsulate Newcastle disease virus (NDV) and modified the surface of the PNPs to attain active targeting of CD44 on the surface of CC cells. They found that such PNPs not only actively targeted cargo delivery, but also kept NDV away from the immune system and prolonged the release of NDV in the TME.

Therapeutic vaccines are also recognized as a promising therapy for HPV infection and CC. HPV E6 and E7 are ideal antigens to activate cell-mediated immune responses, but such peptide vaccines usually require adjuvants to attain the ideal efficacy.[147] It has been reported that extracellular adenosine triphosphate (ATP) promotes DC recruitment as well as antigen uptake and presentation. And the binding of ATP to receptors on the surface of DCs can lead to the release of immunomodulators. Besides, ATP facilitates the maturation and homing of DCs. All of the above suggests that ATP has the potential to act as an adjuvant for therapeutic vaccines.[101] In addition, particles with a size <500 nm are more easily internalized by DCs and more likely to stimulate $CD8^+$ T cell responses.[148] Therefore, Qishu Zhang et al[101] used PLGA to encapsulate E7 peptide and carry the adjuvant ATP to form ATP-adjuvanted PNPs vaccine, which showed potent anti-tumor cellular immunity. The NPs formed by polymer PLGA in this nanovaccine play an important role in enhancing the stability, DC uptake, and lymph node accumulation of E7 peptide.

Polystyrene nanoparticles (PSNPs) are polymeric carriers with self-adjuvanting properties that induce antigen-specific $CD8^+$ and $CD4^+$ T cells. Moreover, it does not induce inflammation, pro-inflammatory cytokines, and expansion of inflammation reactive regulatory T cells, and can show superiority over conventional pro-inflammatory adjuvants in delivering protein-based antigens. Xiang et al[102] utilized PSNPs to study peptide-based nanovaccines for CC and OC therapy.

### Other Therapeutic Modalities, Medications

α-Mangostin is a natural product that derives from pericarps of mangosteen and is cytotoxic to a wide range of cancer cells. However, it has poor water solubility as well as a risk of oxidative degradation surrounding solid tumors. Therefore Suttithumsatid et al[103] used TEMPO (a nitrogen oxide) with antioxidant properties as the side chain of amphiphilic copolymers and added silanol moiety to improve the encapsulation efficiency, self-assembled to form $Nano^{AOX}$ NPs for the delivery of α-Mangostin-rich extract (AME). It was proved that this PNPs could effectively inhibit the growth of HeLa cell lines and had a better safety profile than free AME.

In an attempt to develop anticancer drugs with higher efficacy and fewer side effects, six coumarin derivatives were designed by Arvas et al.[104] And PLGA NPs were utilized as carriers to deliver compound 21 which has the lowest IC50

value among the six derivatives. The use of PLGA carriers provided better drug loading and controlled release of compound 21.

Curcumin is a plant-derived chemical with anticancer activity, but its drawback of poor water solubility should not be ignored. Poly(glycerol sebacate) (PGS) is another FDA-approved polymer made from the condensation of sebacic acid and glycerol and is biodegradable. Massironi et al[105] encapsulated curcumin in PGS NPs to improve its bioavailability and absorption by oral administration, which showed higher ability to anti-HPV, cytotoxicity and activation of apoptosis in HeLa cells. Instead, Kavya et al[106] utilized poly(methacryloyl beta-alanine) (PMBA) as the carrier to deliver curcumin. In this study, PMBA was polymerized from radicals in supercritical CO(2) and treated with FA. Both curcumin and Bcl2 siRNA were encapsulated in PMBA to form Poly@Cur-FA NPs for co-delivery of drugs and genes. Poly@Cur-FA stimulates autophagy and inhibits the growth of CC cells through activation of Bcl2 and multiple other signaling pathways, which may provide an idea for overcoming tumor drug resistance.

Ahmed et al[107] studied CS and butyraldehyde together to form new modified CS derivative NPs called CS-3NPs in the presence of cross-linking agents. This new CS derivative has a size of less than 100 nm with a wide range of applications, an ideal stability with a zeta potential of 20±5.98 mV, an improved crystallinity, as well as the ability to induce apoptosis in Hela cells to achieve antitumor effects. And it shows therapeutic potential for CC.

Zhu et al[108] developed gene-targeting technology-based PNPs for the treatment of CC. They utilized shRNA and CRISPR/Cas targeting to silence and knockdown the HPV16 E7 gene and delivered the associated nucleic acids using PBAE NPs. Their PNPs are intended for vaginal administration for the treatment of HPV infections, providing new ideas for the prevention and treatment of CC.

## Endometrial Cancer

Endometrial cancer (EC) or more broadly known as carcinoma of the uterine corpus[17] is an epithelial malignant tumor that occurs in the endometrium, which is also one of the three most common malignant tumors of the female reproductive system. The incidence of EC has been on the rise in recent years, with 420,368 newly diagnosed patients worldwide in 2022.[117,149] As far as therapy is concerned, EC is usually treated with surgery, supplemented by a comprehensive approach of radiotherapy, chemotherapy and hormone therapy. It has also been reported that adding immunotherapy to chemotherapy for advanced or metastatic EC is beneficial for improving OS in patients.[150]

Earlier, Changyan Liang et al[109] created a folate-modified PLGA NPs using PEG as a coupling agent to connect folate with PLGA, and encapsulated the CTA PTX in it. The modification of folate allows this PNPs to be internalized into EC cells through a folate receptor-mediated mechanism. And it was experimentally confirmed that PTX-loaded folate-targeted PNPs showed higher anti-tumor efficacy than free PTX, and the tumor inhibition rate of targeted PNPs was higher than that of non-targeted ones. Subsequently, there have also been many studies combining PNPs with CTAs used to improve the therapeutic efficacy of EC.

Jie Ding et al[110] combined the CTA DOX with an anti-apoptotic gene Bcl-2 inhibitor (navitoclax) encapsulated in pH-sensitive poly(ethylene glycol)-poly(diisopropylamino)diethyl methacrylate (PEG-PDPA) NPs (NP@DOX/Nav) for the treatment of EC and delivered them to the tumor site through enhanced permeability and TME effects. And the NP@DOX/Nav showed a higher level of pro-apoptotic effects in the Ishikawa xenograft model than DOX or Nav alone.

Loss of function (LOF) p53 occurs in 80% of type II EC, may lead to EC resistance to chemotherapy. Recent studies have shown that CIP2b, a derivative of the fluoroquinolone antibiotic ciprofloxacin (CIP), exhibits cytotoxicity against various cancer cells. Its combination with PTX increases the accumulation of PTX in tumors and inhibits tumor growth.[151] Naguib's team[111] designed CIP2b-NPs that encapsulate CIP2b in PLGA and use TPGS containing hydrophilic PEG chains as a surfactant, which aggregates at the tumor site through the EPR effect. The CIP2b-NPs were confirmed to increase the accumulation and cytotoxicity of PTX in Hec50co cells of EC. Moreover, the CIP2b-NPs were able to maintain a higher concentration in tumors for a longer period of time than soluble CIP2b alone, demonstrating its ability to synergize with PTX in the treatment of LOF p53 type II EC and to reduce chemotherapy resistance.

Kareem Ebeid's team[22] developed a PNP utilizing the combination of PTX and a tyrosine kinase inhibitor to synergistically induce LOF p53 cancer cell death by abrogating the G2/M checkpoint. The PNP was PLGA-based and

carried PTX and the triple angiokinase molecular inhibitor (BIBF) to achieve co-delivery and increase the synthetically lethal to uterine serous carcinomas (USC) (a type II EC with low differentiation) cells. The application of these PNP carriers overcame the drawbacks of the low water solubility of PTX and BIBF, reduced the side effects due to off-target effects, and improved the pharmacokinetics.

Jiaolin Yang's team[112] designed NPs (CRZ@GEM-NPs) of a PCL-PEG-PCL triblock copolymer coupled with the CTA gemcitabine (GEM) and the protease inhibitor crizotinib (CRZ) to reduce the side effects of chemotherapy and improve their anti-tumor capabilities.

Hyperglycemia is associated with EC invasion and progression.[152] Xiao Yang et al[113] found that a high glucose environment could promote glucose metabolism reprogramming in EC cells by promoting the expression of pyruvate dehydrogenase kinase 1 (PDK1), while down-regulation of PDK1 significantly inhibited EC proliferation and invasion. Therefore, a reduction-sensitive polymer (P1) encapsulating a PDK1 inhibitor (JX06) was designed to form PNPs called JX06-NPs. JX06-NPs deliver small molecules of JX06 with limited water solubility to the tumor site via GSH-triggered release in TME. JX06 synergistically enhances antitumor effects with metformin, providing a novel adjuvant for the management of patients with both diabetes and EC.

## Other Gynecological Cancers

Uterine sarcoma (US) is a very rare gynecological cancer that develops in the uterus. Compared to other uterine tumors, it has a poorer prognosis.[153] Mostoufi et al[114] designed a type of PTX-PNPs for multidrug-resistant US. They utilized the pH-responsive polymer poly(l-glutamic acid), the hydrophobic polymer poly(l-leucine), and PEG to form pH-sensitive copolymer NPs. This PNPs showed a 10-fold lower IC50 than free PTX in multidrug-resistant US cell line, as well as the ability to inhibit drug efflux and induce lysosomal membrane permeability.

Choriocarcinoma is a gynecological cancer that occurs after childbirth, miscarriage or gravida. Chemotherapy remains its first-line therapy, yet the non-selective drug distribution leads to serious side effects.[153,154] The HCG81-NP created by Cong et al[154] was aimed at solving this problem. The characteristic of choriocarcinoma overexpressing human chorionic gonadotropin (HCG) receptor was utilized by them to achieve targeted delivery of PNPs. They loaded CTA methotrexate using PEG-PLA and modified the PNPs with HCG. It was confirmed that the uptake of this PNPs was significantly increased in choriocarcinoma cell lines and showed higher inhibition of cell proliferation.

## Polymer Drug Delivery Systems for Combination Therapy

In addition to the development of novel medicines, how existing therapies and drugs can be combined and reused is also an important research area. Evidence suggests that combination therapies work better against advanced tumors than single drugs or sequential drug combinations. On top of that, the heavy financial burden of new drug innovation and the uncertainty of efficacy have shifted our focus to the development of combination therapy strategies, even though this may contradict the interests of pharmaceutical companies.[155,156] Although combination therapy is not a totally novel concept, its progress has been hampered in the past because of non-specific delivery of drugs, different pharmacokinetics of various agents, and other problems.[157] With the increasing development of nanomedicine, chemotherapy, phototherapy, immunotherapy and other proven effective tumor therapies are combined to form new dual-mode or multi-mode therapeutic nano-systems, and the synergistic effects of tumor therapy are significantly improved.[158] In the field of gynecological cancers treatment, several teams have created nanoplatforms for combination therapy such as chemotherapy and immunotherapy,[159] chemotherapy and PDT[160] or two-drug combination[161], etc. Similarly, polymer-based nanosystems have been studied for gynecological cancers therapy, most of which are synergistic drug combinations,[162] while several studies have involved combinations of diverse therapies.

High levels of nitric oxide (NO) gas on the one hand can react with ROS to produce tumor-killing reactive nitrogen species, and on the other hand may increase tumor sensitivity to chemotherapy, which provides a novel idea for synergistic treatment with chemotherapy and NO therapy.[163–165] Based on the above, Guang Li's team[165] designed PSSP@ART-ISMN PNPs using GSH-responsive PNPs loaded with isosorbide 5-mononitrate (ISMN), a NO donor that can release NO, as well as a traditional Chinese medicine extract that promotes apoptosis and increases the concentration

of ROS called Artesunate (ART). The synergistic therapeutic effect of PSSP@ART-ISMN was confirmed via in vivo experiments in SKOV3 tumor-bearing mice, which provides an innovative combination therapy strategy for OC.

PDT can be difficult to attain satisfactory efficacy because of insufficient ROS generation due to hypoxia in the TME. In this situation, it is necessary to combine PDT with other therapies, such as cold atmospheric plasma (CAP) therapy, to enhance the efficacy.[36] CAP is an ionized gas near room temperature.[166] Its antitumor effects through oxidative damage to DNA and cell membranes are most likely related to high concentrations of ROS and reactive nitrogen.[36] Some studies have reported that CAP has a promising future in the treatment of gynecologic tumors.[167,168] Ha and Kim[36] prepared a PNPs named PPHE, which was formed by self-assembly of (Pheo a)-conjugated poly(γ-glutamic acid) and mPEG-PLGA to form the core of the PNP, and encapsulated the core with targeting ligand-modified HA (HA-EAE7). PPHE was released more readily in the acidic pH of the cellular lysosome than in the physiologic pH environment of blood, and showed enhanced phototoxicity against the CC CaSki cell line. They subsequently applied this HER3/CD44 dual-targeting PPHE in an in vitro experiment with combined PDT/CAP treatment, which showed enhanced ability to induce apoptosis in HPV-positive CC cells compared to free Pheo a or PDT alone.

## Synthesis of Functional Polymers for Tumor Imaging and Therapy

Theranostics derives from the words diagnostic and therapeutic.[169] Progress in nanomedicine has also made it possible to integrate the diagnosis and therapy of diseases on a single platform. In the last section, it was introduced that PNPs achieve synergistic treatment by carrying multiple therapeutic cargoes; similarly, co-delivery of therapeutic agents with contrast agents allows the integration of tumor treatment and imaging, as well as the simultaneous monitoring of treatment efficacy.[158] The characteristics of PNPs, which can be easily modified, and their high drug-carrying capacity enable them to be a promising carrier for tumor theranostics. The strategy of integrating therapy with diagnosis is expected to provide novel personalized solutions with higher efficacy and safety for the treatment of tumors.[170]

In recent years, PAI has gained increasing attention in tumor detection due to its superior contrast, temporal and spatial resolution.[171] The combination of phototherapy and PAI is one of the most widely studied strategies for the integration of diagnosis and therapy. PAI often can be applied concurrently with PTT, and PTA is usually suitable for PAI as well.

In PTT, the protective mechanisms of cancer cells are triggered at high temperatures. Therefore, to achieve cancer cell killing, heating above 50°C is required, but this can easily damage normal tissues. However, the milder conditions of 40–45°C may also increase the risk of tumor recurrence and spread.[172] The efficacy of PTT is also influenced by the ability of the laser to penetrate tissues. The near-infrared-I (NIR-I) window (650–950 nm) has been studied a lot; while the near-infrared-II (NIR-II) window (1000–1700 nm) laser has attracted attention due to its deep-tissue penetration and less damage to normal tissues, and many related PTAs have been developed.[35,173,174] In addition to the deep tumor treatment, NIR-II fluorescence imaging (FL) can also guide PTT through precise imaging.[172]

Lorenz's team[33] designed a novel PNP carried contrast agent to increase the diagnostic accuracy of PAI. They encapsulated two dyes that show excellent photoacoustic peaks in specific NIR regions in PEG-PCL NPs, which were intravenously injected and delivered to primary and metastatic lesions of OC. These PNPs produced well-separated absorption peaks when irradiated with 770 nm and 860 nm laser light, which could clearly distinguish the tumor from other tissues in the background; and when irradiated with 808 nm NIR laser light, PNPs can heat up the tumor to ≈49°C and kill the tumor, which enabled both PAI diagnosis and PTT treatment can be realized. Similarly, the PD-FA NPs prepared by Qiu et al[175] enabled both NIR imaging and PAI-guided PTT.

Indocyanine Green (ICG) is an FDA-approved PTA as well as an excellent NIR fluorescent contrast agent, yet its poor stability limits its clinical application. Nuernisha's team[176] encapsulated ICGs with amphiphilic poly(styrene-co-maleic anhydride) (PSMA) to form PNPs and demonstrated its favorable biocompatibility and enhanced PTT efficiency in CC Hela cells. (Figure 2) Another study from this team[177] utilized PSMA to encapsulate a new ICG (IR-820) that acts as a PTA and NIR fluorescent probe to enhance its biocompatibility. This IR-820@PSMA NP was confirmed to be uptaken by Hela cells under confocal microscopy and obtained a PTT efficiency of 77%. Their study suggests that theranostics PNPs can also be prepared with a single multifunctional cargo.

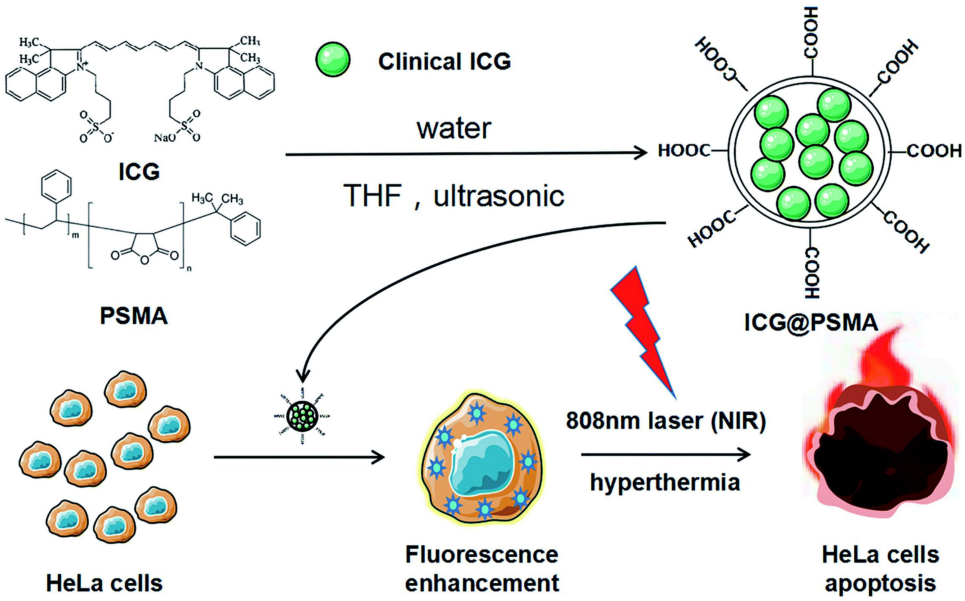


**Figure 2** Schematic illustration of the synthesis process and PTT effect. Reprinted with permission from Chen S, Zhu L, Du Zet al Polymer encapsulated clinical ICG nanoparticles for enhanced photothermal therapy and NIR fluorescence imaging in cervical cancer. *RSC Adv.* 2021;11(34):20,850–20858. Copyright 2021 Royal Society of Chemistry.[176]

Apart from integration with phototherapy, PNPs have been developed in relation to other therapies. Guang Li's team[67] designed a nanoparticle called HA@PFG NPs, whose core is a PNP composed of Gossypol, a type of natural polyphenols, together with $Fe^{3+}$ and Pt-COOH, a prodrug of the CTA cisplatin; and coated the outside of the PNP with HA, which can target tumor cells. When HA@PFG NPs were delivered into the TME, the acidic environment stimulated the breakage of pH-sensitive linkages to release $Fe^{3+}$ and Pt-COOH. HA@PFG NPs exert cytotoxicity to suppress tumors through chemotherapy, $Fe^{3+}$-induced iron death, and promotion of apoptosis by Gossypol. $Fe^{3+}$ can also act as a contrast agent to enhance MRI visualization, allowing HA@PFG NPs to play a role in both diagnosis and treatment for OC.

Dragulska's team[178] has also developed a PNP that combines diagnostic imaging with targeted therapy, called the RGDFFF-CA4 NP. This PNP has a PLGA core, carries the vascular disrupting agent combretastatin A4 (CA4) used for OC treatment. Additionally, replaces the popular PEG coating on the surface of the PNPs with a short arginine-glycine-aspartic acid-phenylalanine x3 (RGDFFF) peptide to diminish immunogenicity and achieve targeting. What's more, they also modified the surface of PNPs with NIR fluorophore label Cy7 for tumor imaging.

## Challenges in Clinical Translation of PNPs

For clinical translation, in addition to Abraxane, which has been approved by the FDA for oncology treatment,[179] few PNPs have been in clinical practice. For example, Paclical is approved by the EMA for OC therapy, as well as Genexol-PM is approved in South Korea for the treatment of breast cancer and non-small cell lung cancer.[4] Besides, only a limited number of studies that have entered clinical trials, for example, CRLX101, a cyclodextrin-based PNP, whose first Phase 1/2a clinical trial results in OC were published in 2013,[180] with several subsequent clinical trials completed alone or in combination.[181,182] A systematic review showed that CRLX101 may bring higher efficacy and lower systemic toxicity to cancer therapy, but its safety and efficacy are still influenced by multiple factors.[183] While another meta-analysis showed that CRLX101 improved patients' median PFS compared to the control group, but delivered poorer median OS.[184] Issues such as biological barriers, plasma stability, and immune clearance preventing the drug from reaching the desired therapeutic dose at the lesion site;[185] as well as challenges in synthesizable scale-up such as production stability, green nanotechnology,[18] are the core barriers faced by the clinical translation of PNPs.


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## Conclusions and Future Prospect

In conclusion, polymer is a promising material to prepare nanoparticles for tumor theranostics. The preparation of novel PNPs involves not only the modification and combination of the polymers themselves to optimize the circulation time, release mechanism and action site of the PNPs in vivo; but also the use of the polymers' advantages to carry the freshly developed cargoes for improving the water solubility, biocompatibility, bioavailability and other properties of the cargoes. These advantages of PNPs could meet the urgent need for precision strategies in the management of gynecologic cancers. Especially in chemotherapy and immunotherapy for gynecological cancers, lots of novel regimens of PNPs have been proposed, which provide possibilities to better the prognosis of advanced gynecological cancers. In addition, PNPs can realize co-delivery by storing different agents in different layers/chambers in the particles respectively. These strategies for combination therapy as well as diagnostic and therapeutic integration will contribute to higher efficiency and lower economic burden for gynecological cancers theranostics.

Despite demonstrated preclinical success of several PNPs in cellular and animal models, their clinical translation remains challenging, with few candidates progressing to human trials. To bridge this translational gap, critical parameters must be addressed during PNP design and development: (1) Biosafety assurance and scalable synthesis protocols; (2) Wider therapeutic window and lower dosing frequency; (3) Tumor-selective targeting with mitigated off-tissue effects.

Future target of design PNPs could be shifted to the early diagnosis of tumors, especially for OC, which is diagnosed at advanced stages in most patients.[186] PNPs carry contrast agents to precisely target tiny malignant lesions and provide imaging evidence for very early diagnosis of gynecological cancers. In terms of gynecological cancers, the female reproductive tract, as a unique route of administration, perhaps can replace the traditional ones to enhance gynecological cancers therapeutic efficiency. For example, the intrauterine device (IUD) is a common controlled release device for drugs used in ovarian endocrine disorders. Corrie et al[187] proposed the concept of controlled release of PS-loaded PNPs through IUDs for PDT and FL. Similarly, such integration of gynecological cancers-targeted PNPs with IUD-based delivery platforms may establish a clinically viable strategy for precision intervention. Furthermore, the versatile surface functionalization capacity of PNPs provides a robust foundation for the further development of personalized therapy and intelligent NPs.

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