

Targeted Nanotherapeutics for Ovarian Cancer: Advancing Treatment Through Smart Delivery

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The Importance of Study: Ovarian cancer remains a major global oncological burden due to its late-stage diagnosis and high mortality. Despite progress in surgery, chemotherapy, and targeted therapies, patient outcomes are often hindered by recurrence and chemoresistance. Early detection remains inadequate, emphasizing the need for innovative treatments.

Methods: Targeted nanotherapeutics offer a promising approach by enabling precise drug delivery through nanoscale carriers that enhance solubility, bioavailability, and tumor-specific accumulation while reducing systemic toxicity.

Results: Nanoscale drug carriers demonstrated enhanced bioavailability, with preferential tumor accumulation leading to improved therapeutic efficacy.

Conclusions: This review summarizes the current challenges in ovarian cancer management and highlights the potential of targeted nanodelivery systems to improve therapeutic efficacy and survival through controlled, cancer-specific drug-release mechanisms.

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INTRODUCTION

History: Ovarian cancer is the second most common gynecological malignancy in developed countries and the most lethal [1]. The incidence rate of ovarian cancer is escalating at an alarming pace in many parts of the world. The burden of this disease remains high, particularly in countries with a low Human Development Index. In these regions, access to quality cancer treatment and care is limited [2].

Anatomy and Physiology of the Ovary: The ovaries are a pair of oval structures, each approximately 1.5 inches (3.75 cm) in length, situated on either side of the uterus within the pelvic cavity (as depicted in Fig. 1). The ovarian ligament extends from the medial side of an ovary to the uterine wall; this ligament is essentially the peritoneum covering the ovaries. These

ligaments play a crucial role in maintaining the ovaries' proper position. The ovaries are paired reproductive organs responsible for oocyte production and the secretion of sex hormones, mainly estrogen, progesterone, and androgens. These hormones regulate the menstrual cycle, fertility, and secondary sexual characteristics. During the menstrual cycle, follicle-stimulating hormone (FSH) promotes follicle growth and estrogen production, while luteinizing hormone (LH) triggers ovulation and the formation of the corpus luteum, which secretes progesterone. Abnormal or prolonged hormonal stimulation, particularly excessive estrogen exposure or an imbalance between estrogen and progesterone, may contribute to ovarian epithelial cell proliferation and genetic instability, increasing the risk of ovarian cancer.

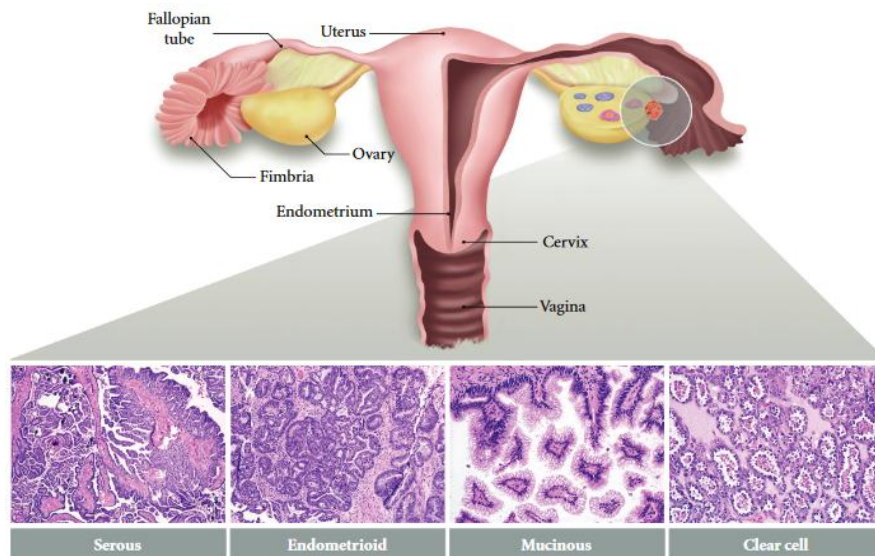


Figure 2. The major histologic subtypes of ovarian carcinoma. Serous carcinomas resemble fallopian tube epithelium, endometrioid carcinomas resemble endometrial glands, and mucinous carcinomas resemble endocervical epithelium. The shaded circle represents the general anatomical location from which ovarian carcinomas are thought to arise. The pink and blue entities within the cross-sectioned ovary represent maturing ovarian follicles [4].

High levels of gonadotropins (FSH and LH) have also been implicated in stimulating the ovarian surface epithelium, potentially causing cellular changes that lead to malignancy. Conversely, progesterone may protect by inducing apoptosis and limiting proliferation. Thus, the hormonal environment, especially chronic estrogen dominance and gonadotropin stimulation, plays a crucial role in the pathogenesis and progression of ovarian cancer [3].

Etiology and Pathophysiology of Ovarian Cancer:

The precise etiology of ovarian cancer, particularly regarding the progenitor cell populations implicated in epithelial ovarian carcinoma (EOC), remains under active investigation and debate. Historically, the ovarian surface epithelium (OSE) was theorized to be the primary origin of ovarian malignancies. This hypothesis was largely substantiated by the ‘incessant ovulation’ theory, which postulates that repetitive mechanical and biological alterations to the OSE, induced by the ovulatory process, contribute to an elevated risk of ovarian cancer. Factors implicated in this process include injury and subsequent repair of the OSE following follicular rupture, localized inflammatory responses within the ovarian microenvironment surrounding ruptured follicles, the encapsulation of OSE cells leading to the formation of

inclusion cysts, and the cumulative effects of high local concentrations of steroid hormones (progesterone, androgens, and estrogens) during each menstrual cycle. However, a growing body of contemporary evidence strongly indicates that a significant proportion of EOC cases do not originate in the OSE but rather in the distal segment of the fallopian tube, specifically the fimbrial epithelium. Ovarian cancer arises from complex molecular changes that affect cell growth, apoptosis, and DNA repair. Key mechanisms include mutations in tumor suppressor genes such as TP53, BRCA1, and BRCA2, which lead to defective DNA repair and genomic instability. Activation of oncogenic pathways (like PI3K/AKT, RAS/RAF/MEK/ERK, and NOTCH) enhances cell proliferation and survival. Additionally, epigenetic alterations, including abnormal DNA methylation and histone modification, silence critical regulatory genes. Angiogenesis and chronic inflammation further support tumor progression and metastasis. Together, these molecular events drive the initiation and advancement of ovarian cancer [4]. Current clinical guidelines set forth by the World Health Organization (WHO) recognize eight histologic tumor subtypes: serous, endometrioid, mucinous, clear cell, transitional cell, squamous cell,

mixed epithelial, and undifferentiated. The three most common—serous, endometrioid, and mucinous—are characterized by their morphological resemblance to various mucosal tissues of the female reproductive tract, all of which exhibit Mullerian differentiation (Fig. 2) [3]. Current research has robustly delineated two distinct classifications of EOC: Type I and Type II. Type I tumors, which encompass low-grade serous carcinoma, endometrioid carcinoma, and clear-cell carcinoma, typically develop through a well-defined progression from precursor lesions such as borderline serous tumors or endometriotic implants. In stark contrast, Type II carcinomas, which are more prevalent and predominantly consist of high-grade serous carcinomas (HGSC), appear to originate from the fimbrial epithelium in up to 60% of reported cases. The advanced clinical presentation of HGSC, frequently diagnosed at International Federation of Gynecology and Obstetrics (FIGO) stages III or IV, is consistent with the proposed mechanism of early peritoneal dissemination of malignant cells originating from the fimbriated end of the fallopian tubes [5].

Treatment Strategies for Ovarian Cancer

Conventional Treatments for Ovarian Cancer:

The cornerstone of ovarian cancer management, particularly for the most common type, epithelial ovarian cancer (EOC), involves a multimodal approach heavily reliant on cytoreductive surgery followed by systemic chemotherapy. **Cytoreductive Surgery:** Surgical debulking remains the single most important prognostic factor for advanced EOC. The goal is optimal cytoreduction, defined as leaving no residual disease or macroscopic disease measuring less than 1 cm, ideally less than 0.5 cm. Numerous studies confirm that the completeness of cytoreduction is significantly associated with longer progression-free survival (PFS) and overall survival (OS) in patients with advanced-stage disease (Stages III/IV) [6].

Systemic Chemotherapy: Systemic chemotherapy is administered either neoadjuvantly (before surgery to shrink the tumor bulk, making optimal cytoreduction feasible) or adjuvantly (after surgery to eradicate microscopic residual disease).

First-Line Chemotherapy: The universally accepted

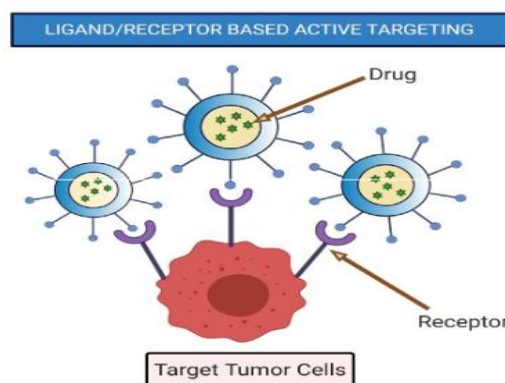


Figure 3. Depiction of active targeting/ ligand-based targeting approach [44].

first-line regimen for most EOC cases involves platinum-based doublets:

Platinum Agent: Carboplatin (often preferred over Cisplatin due to better tolerability, though efficacy is similar in many contexts) or Cisplatin.

Taxane Agent: Paclitaxel (Taxol) is the standard partner, administered concurrently or sequentially with the platinum agent (7). The patient's response to initial platinum-based therapy dictates subsequent treatment.

Platinum-Sensitive Recurrence: If the time to recurrence is ≥ 6 months after the last platinum dose, the cancer is considered sensitive, and re-treatment with platinum-based combination therapy is the standard approach.

Platinum-Resistant Recurrence: If the time to recurrence is < 6 months, alternative non-platinum agents (topotecan, liposomal doxorubicin, gemcitabine) are utilized, although overall response rates are lower.

Targeted/Maintenance Therapy: The introduction of targeted agents has significantly improved outcomes, particularly for patients with mutations or homologous recombination deficiency (HRD).

PARP (poly(ADP-ribose) polymerase) Inhibitors: Drugs such as Olaparib, Niraparib, and Rucaparib are standard maintenance therapy for patients with germline or somatic BRCA mutations and, in some cases, for those without BRCA mutations, following platinum-based chemotherapy. This strategy capitalizes on the concept of synthetic lethality [8, 9].

Active Targeting in Ovarian Cancer

Active targeting is a strategy in nanomedicine

designed to overcome the limitations of passive accumulation, which relies on the Enhanced Permeability and Retention (EPR) effect. In active targeting, the surface of the nanoparticle (NP) is modified with specific targeting ligands (molecules) that recognize and bind to overexpressed receptors on the surface of ovarian cancer cells (Fig. 3). This method significantly enhances the specificity of drug delivery, leading to higher intracellular drug concentrations within the tumor cells and minimizing off-target toxicity to healthy tissues [10, 11].

Mechanism and Key Targets in Ovarian Cancer:

This strategy relies on identifying unique biomarkers that are significantly upregulated in ovarian cancer cells compared to normal ovarian or stromal cells. Several receptors have been extensively studied for active targeting in ovarian cancer nanomedicine:

Folate Receptor Alpha (FR- α): This is one of the most promising targets. It is highly overexpressed in 90-100% of high-grade serous ovarian carcinomas (the most common and aggressive type) but is only minimally expressed in normal tissues [12, 13]. Folic acid (Vitamin B9) is the natural ligand used to coat the surface of nanoparticles (liposomes, polymeric micelles, or inorganic NPs). Folate-conjugated nanoparticles are rapidly internalized via receptor-mediated endocytosis, delivering their payload directly into the cancer cell. Folate receptor alpha (FR α) is overexpressed in a significant proportion of ovarian cancers, making it an attractive target.

Mirvetuximab Soravtansine (MIRV): An antibody-drug conjugate (ADC) consisting of a humanized FR α -binding antibody (mirvetuximab) conjugated to a maytansinoid payload (soravtansine). It targets FR α -expressing ovarian cancer cells, leading to their destruction [14].

Farletuzumab: A humanized monoclonal antibody targeting FR α . While it did not show sufficient efficacy as a monotherapy in earlier trials, it is being investigated in combination regimens [15].

Tissue Factor (TF): Tisotumab Vedotin (TV) targets Tissue Factor (TF), which is expressed on the surface of many solid tumors, including ovarian cancer, and plays a role in angiogenesis and metastasis [16].

Trop-2: Sacituzumab Govitecan (SG) targets Trop-2, a cell-surface glycoprotein expressed in various

epithelial cancers, including ovarian cancer. It delivers SN-38, an active metabolite of irinotecan [17].

Vascular Endothelial Growth Factor (VEGF):

While not “active targeting” in the sense of cell-specific binding, therapies targeting tumor angiogenesis are crucial. Bevacizumab, a monoclonal antibody targeting VEGF, inhibits VEGF, thereby blocking tumor angiogenesis. It is approved in combination with chemotherapy for advanced ovarian cancer [18].

Epidermal Growth Factor Receptor (EGFR): This receptor is frequently overexpressed in many epithelial cancers, including a subset of ovarian cancers, where it promotes proliferation and survival. Peptides (such as RGD sequences) or antibodies (such as Cetuximab) that bind to EGFR are used for surface functionalization.

Human Epidermal Growth Factor Receptor 2 (HER2/neu):

While less common than in breast cancer, HER2 amplification or overexpression is present in about 10-30% of ovarian cancers and is associated with poor prognosis. Small molecules or single-chain variable fragments of trastuzumab (Herceptin) can be used to target these receptors.

Specific Glycans and Other Markers: Other targets include hormone receptors (e.g., estrogen or progesterone receptors, though expression can be variable) and specific carbohydrate epitopes on the cell surface [19].

Passive Targeting in Ovarian Cancer: Passive targeting refers to the accumulation of systemically delivered agents (especially nanoparticles) in tumors

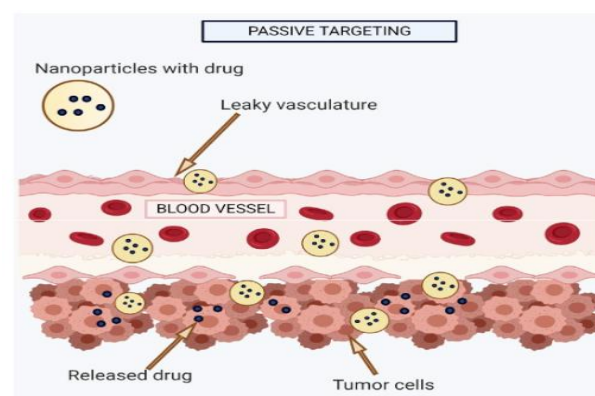


Figure 4. Representation of passive targeting by Enhanced Permeability and Retention effect [44].

via physicochemical phenomena rather than ligand-receptor recognition. The enhanced permeability and retention (EPR) effect (Fig. 4), caused by leaky tumor vasculature and poor lymphatic drainage, underlies passive targeting.

In ovarian cancer, passive targeting is attractive because many tumors and peritoneal metastases display abnormal vasculature and increased vascular permeability; intraperitoneal (IP) administration can further increase local retention of nanocarriers [20]. Passive delivery can improve drug pharmacokinetics, reduce systemic toxicity, and increase local drug concentration in tumor nodules. Limitations in ovarian cancer include heterogeneity of the EPR effect among patients and even within different tumor sites, dense stromal barriers, high interstitial fluid pressure, and rapid clearance by peritoneal macrophages or the mononuclear phagocyte system [21]. These factors reduce nanoparticle penetration into solid tumor masses and limit uniform drug distribution.

Strategies to enhance passive targeting in ovarian cancer include: optimizing nanoparticle size (typically 10–200 nm), shape, surface charge, and stealth coatings (PEGylation) to prolong circulation; utilizing intraperitoneal delivery for peritoneal metastases; modulating the tumor microenvironment (using vascular normalizing agents, enzymes to degrade extracellular matrix) to improve penetration; and combining passive targeting with stimuli-responsive release (pH, enzymes) to increase intratumoral drug availability. Several liposomal and nanoparticle formulations (e.g., pegylated liposomal doxorubicin) exploit passive targeting and show activity in ovarian cancer with reduced toxicity. However, the translation of newer nanomedicines is challenged by variable EPR and requires patient stratification, biomarkers of vascular permeability, and improved preclinical models that reflect human peritoneal disease [22]. Clinical Applications (or Late-Stage Clinical Trials) Related to Passive Targeting include:

Pegylated Liposomal Doxorubicin (PLD): Although not formally classified as an “active targeting” system, PLD’s liposomal formulation significantly increases the drug’s half-life in

circulation, promoting its accumulation in tumors via the EPR effect. This drug is widely used in the treatment of ovarian cancer, particularly in refractory or recurrent cases. (Approved and in widespread clinical use [23]).

Nanocarrier-Based Platinum Drugs (e.g., cisplatin, carboplatin): These are cornerstones of ovarian cancer treatment. Extensive research has focused on developing nanocarrier formulations of platinum drugs (such as nanoparticles and nanofibers) to improve tumor delivery and reduce toxicities like nephrotoxicity and neurotoxicity. These nanocarriers enhance drug accumulation in the tumor through the EPR effect. Several such formulations have progressed to clinical trials. (Under investigation and in clinical trials (Phase I/II) [24]).

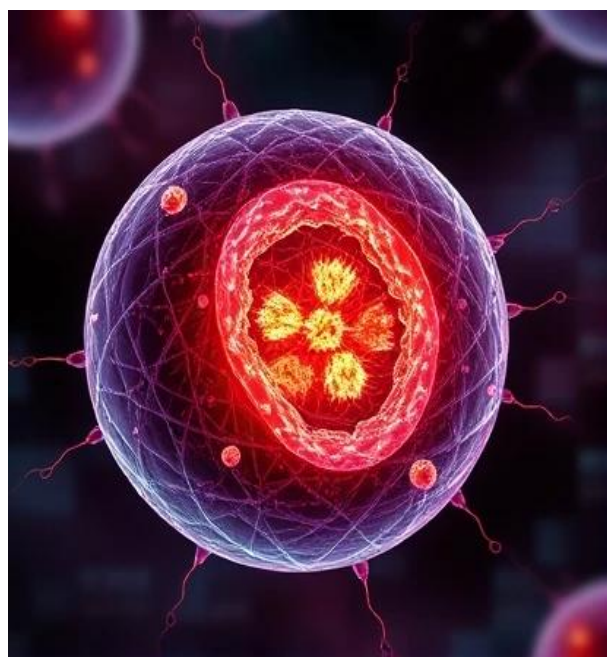


Figure 5. The detailed scientific illustration showing targeted payload delivery into the mitochondrial matrix of a stressed cancer cell. This delivery compromises the Electron Transport Chain (ETC), resulting in a dramatic, localized surge of orange-red Reactive Oxygen Species (ROS) within the inner compartment. Consequent outer mitochondrial membrane permeabilization leads to the release of pro-apoptotic factors, such as Cytochrome C, into the cytosol (Designed by AI).

Paclitaxel Nanocarrier Formulations: Another key drug in ovarian cancer therapy. Nanotechnology-based formulations of paclitaxel (such as nab-paclitaxel, which uses albumin, and other lipid- or polymer-based formulations) have been developed to

improve tumor distribution and reduce side effects (e.g., neuropathy). nab-Paclitaxel (brand name Abraxane) partially functions by enhancing tumor accumulation (EPR). (Approved and used for other cancers; studies have also been conducted for ovarian cancer. Other nanoformulations are in preclinical and early clinical trial stages [25]).

Dual-Function Nanocarriers (Theranostics): These are nanosystems designed for both imaging (tumor detection and localization) and therapeutic delivery. The accumulation of these nanocarriers in the tumor via the EPR effect enables more precise tumor imaging followed by targeted drug release. (Primarily in research and early clinical trial stages [26])."

Organelle Targeting in Ovarian Cancer

Organelle targeting refers to the design of therapeutics or delivery systems that selectively accumulate in specific intracellular compartments (e.g., mitochondria, nucleus, lysosomes, endoplasmic reticulum, Golgi apparatus) to improve efficacy and reduce off-target effects [27]. Targeting is achieved through small-molecule ligands, peptides, pH- and redox-responsive moieties, and nanocarrier surface modifications that exploit organelle-specific physicochemical cues. Ovarian tumor cells often exhibit organelle dysfunction, including mitochondrial metabolic reprogramming, altered lysosomal activity/autophagy, ER stress/unfolded protein response, and nuclear DNA repair defects. Directing drugs to these organelles can increase cancer cell killing, overcome drug resistance, and sensitize cells to chemotherapy or PARP inhibitors.

Mitochondrial Targeting (Fig. 5): Mitochondria are central to energy metabolism, apoptosis, and reactive oxygen species (ROS) production. Cancer cells often exhibit altered mitochondrial function and rely on them for survival. Exploiting the mitochondrial membrane potential and delivering pro-apoptotic agents or ROS-generating compounds to mitochondria enhances apoptosis in chemoresistant ovarian cancer cells [28, 29]. Cationic (positively charged) nanocarriers are often employed for this purpose due to the negative potential of the mitochondrial membrane [30, 31]. Triphenylphosphonium (TPP) and other lipophilic cations are common mitochondria-directing motifs.

Nucleus Targeting: The nucleus houses the cell's genetic material and controls key pathways for cell division and gene expression. Nuclear delivery of DNA-damaging agents or siRNA against DNA repair genes (e.g., BRCA pathway modulators) can

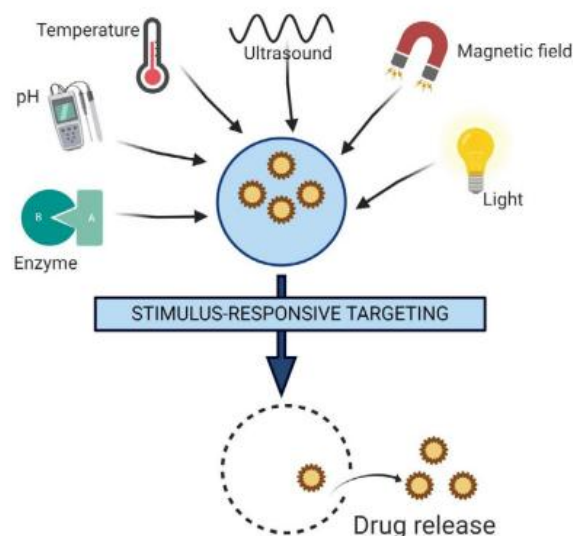


Figure 6. Illustration of stimulus-responsive targeting promoted by external and internal stimuli (Smart nanoparticles system) [67].

potentiate genomic instability in tumor cells. Targeting the nucleus with DNA-intercalating drugs or inhibitors of replication enzymes can effectively halt tumor growth. Delivery to the nucleus often requires nanocarriers capable of crossing the nuclear envelope; nuclear localization signals (NLSs) and small-sized vectors facilitate nuclear import [32].

Lysosome/Autophagy Targeting: Many ovarian cancers rely on autophagy to survive stress. Lysosomes are involved in cellular degradation and waste removal; in some cancer cells, they are utilized to evade apoptosis or degrade therapeutic agents. Targeting lysosomes with agents that induce lysosomal membrane permeabilization (LMP) and release hydrolytic enzymes into the cytoplasm can trigger cell death and overcome chemoresistance [33]. pH-responsive carriers are frequently used to exploit the acidic endo/lysosomal pH for cargo release.

ER/Golgi Targeting and Proteostasis: The endoplasmic reticulum (ER) is crucial for protein synthesis, folding, and lipid metabolism. ER stress and the unfolded protein response (UPR) are

implicated in drug resistance in ovarian cancer. Targeting ER stress pathways or protein processing (e.g., inhibiting chaperones) can preferentially kill tumor cells with a high secretory or proteotoxic



Figure 7. High-resolution, scientific illustration of a smart drug delivery system targeting ovarian cancer. A nanocarrier, equipped with tumor-specific targeting ligands, binds precisely to an ovarian cancer cell surface. Upon sensing the tumor microenvironment (e.g., low pH), the nanocarrier releases its anti-cancer drug payload directly into the cell, triggering apoptosis (Designed by AI).

burden [34, 35]. Organelle targeting utilizes ligands (peptides, small molecules), stimulus-responsive linkers (pH, redox, enzymes), and optimized nanocarrier characteristics. Various sophisticated strategies have been developed to enable nanocarriers to bypass endosomal entrapment and precisely target specific organelles [36]. Major challenges include intracellular trafficking barriers, endosomal escape, tumor heterogeneity, off-target toxicity, and translational gaps between preclinical models and patients. Nevertheless, organelle-targeted approaches can address platinum resistance and improve combination regimens—for instance, by combining organelle-targeted drugs with PARP inhibitors, anti-angiogenics, or immunotherapies. Finally, patient stratification based on organelle-related biomarkers (e.g., mitochondrial metabolism, autophagy flux, ER stress markers) may guide therapy selection [37].

Smart drug delivery systems in ovarian cancer: Smart nanocarriers (Fig. 6) are drug delivery systems engineered to respond to specific endogenous (pH,

redox, enzymes, hypoxia, ROS) or exogenous (light, heat, magnetic field, ultrasound) stimuli to trigger controlled drug release, enhance targeting, or modulate biodistribution.

Ovarian tumors and peritoneal metastases present distinct microenvironmental features (acidic pH, elevated glutathione, overexpressed enzymes, hypoxia) and an accessible intraperitoneal space, enabling stimulus-responsive strategies to increase local efficacy and reduce systemic toxicity. Key designs and mechanisms in smart drug delivery systems include pH-responsive carriers, such as polymers and liposomes, and acid-cleavable linkers that release payloads in acidic tumor/lysosomal compartments, thereby improving intratumoral drug availability. Redox-responsive systems: disulfide or thioether linkers cleaved by high intracellular GSH to release cytotoxic drugs or siRNA in tumor cells. Enzyme-responsive nanoparticles: substrates for MMPs, cathepsins, or hyaluronidase that trigger size/charge change or cargo release at tumor sites [38]. Thermo/photothermal and light-activated carriers: external triggers for spatiotemporal control (useful for peritoneal lesions accessible to local illumination). Magnetic and ultrasound-responsive platforms: for guided accumulation or sonoporation-enhanced penetration. The advantages of these smart systems (Fig. 7) include: Improved penetration and retention in peritoneal tumor nodules when combined with intraperitoneal delivery.

Overcoming drug resistance through intracellular, organelle-targeted release or co-delivery of chemosensitizers/siRNA. Heterogeneity of the tumor microenvironment and variable stimulus intensity among patients and lesions. Ensuring sufficient stability in circulation while enabling a rapid response at the tumor site. Manufacturing complexity, scalability, regulatory hurdles, and safety of stimulus modalities. Need for clinically relevant models of peritoneal disease and biomarkers to select responsive patients. Pegylated liposomal drugs set a precedent for nanoparticle oncology; several smart nanocarriers are in preclinical and early clinical studies for ovarian cancer (stimulus-responsive paclitaxel or siRNA formulations). Translation will require patient stratification based on microenvironmental markers

and demonstration of additional clinical benefit [39]. Stimuli-responsive nanoparticle systems are engineered to release their payload upon encountering specific stimuli present in the tumor microenvironment (TME) or within cancer cells. Common stimuli include pH changes (tumors are typically more acidic than normal tissues), specific enzymes (such as matrix metalloproteinases [MMPs]), or redox potential (higher glutathione levels in cancer cells) [40, 41]. Immune-Responsive Drug Delivery: These are designed to interact with or modulate the immune system at the tumor site. This can involve delivering immunoadjuvants, reprogramming tumor-associated macrophages (TAMs), or enhancing T-cell infiltration to promote an anti-tumor immune response alongside chemotherapy [42, 43]. Gene Delivery Systems are used to deliver nucleic acids (such as siRNA, miRNA, or plasmids) to silence oncogenes or to deliver therapeutic genes to ovarian cancer cells. These systems often incorporate specific targeting ligands to enhance uptake by cancer cells [44, 45]. Theranostic Nanoparticles combine diagnostic and therapeutic capabilities in a single platform. For ovarian cancer, these systems can simultaneously track drug delivery and tumor response (e.g., via MRI or fluorescence imaging) while delivering therapeutic agents. This allows for real-time monitoring and personalized treatment adjustments [46, 47].

Smart Drug Delivery Systems in Ovarian Cancer

Smart nanocarriers (Fig. 6) are drug delivery systems engineered to respond to specific endogenous stimuli—such as pH, redox conditions, enzymes, hypoxia, and reactive oxygen species (ROS)—or exogenous stimuli, including light, heat, magnetic fields, and ultrasound, to trigger controlled drug release, enhance targeting, or modulate biodistribution. Ovarian tumors and peritoneal metastases present distinct microenvironmental features, such as acidic pH, elevated glutathione levels, overexpressed enzymes, and hypoxia, as well as accessible intraperitoneal space, enabling stimulus-responsive strategies to increase local efficacy and reduce systemic toxicity. Key designs and mechanisms in smart drug delivery systems include:

pH-responsive carriers: Polymers, liposomes, or

acid-cleavable linkers that release payloads in acidic tumor or lysosomal compartments, thereby improving intratumoral drug availability.

Redox-responsive systems: Disulfide or thioether linkers cleaved by high intracellular glutathione (GSH) levels to release cytotoxic drugs or siRNA in tumor cells.

Enzyme-responsive nanoparticles: Substrates for matrix metalloproteinases (MMPs), cathepsins, or hyaluronidase that trigger size/charge changes or cargo release at tumor sites (38).

Thermo/photothermal and light-activated carriers: External triggers that provide spatiotemporal control, which is useful for peritoneal lesions accessible to local illumination.

Magnetic- and ultrasound-responsive platforms: Systems used for guided accumulation or sonoporation-enhanced penetration. The advantages of these smart systems (Fig. 7) include: Improved penetration and retention in peritoneal tumor nodules when combined with intraperitoneal delivery. The ability to overcome drug resistance through intracellular, organelle-targeted release or co-delivery of chemosensitizers/siRNA. However, several challenges remain: Heterogeneity of the tumor microenvironment and variable stimulus intensity among patients and lesions. The need to ensure sufficient stability in circulation while maintaining a rapid response at the tumor site. Manufacturing complexity, scalability issues, regulatory hurdles, and safety concerns related to stimulus modalities. The need for clinically relevant models of peritoneal disease and biomarkers to select responsive patients. Pegylated liposomal drugs have set a precedent for nanoparticle-based oncology; several smart nanocarriers are currently in preclinical and early clinical studies for ovarian cancer, including stimulus-responsive paclitaxel or siRNA formulations. Translation will require patient stratification based on microenvironmental markers and demonstration of added clinical benefit [39].

Additional categories of smart delivery systems:

Stimuli-responsive nanoparticles are engineered to release their payload upon encountering specific stimuli present in the tumor microenvironment (TME) or within cancer cells. Common stimuli include pH

changes (tumors are typically more acidic than normal tissues), specific enzymes such as matrix metalloproteinases (MMPs), and redox potential (higher glutathione levels in cancer cells) [40, 41].

Immune-responsive drug delivery systems are designed to interact with or modulate the immune system at the tumor site. This can involve delivering immunoadjuvants, reprogramming tumor-associated macrophages (TAMs), or enhancing T-cell infiltration to promote an anti-tumor immune response alongside chemotherapy (42, 43).

Gene delivery systems are used to deliver nucleic acids, such as siRNA, miRNA, or plasmids, to silence oncogenes or deliver therapeutic genes to ovarian cancer cells. These systems often incorporate specific targeting ligands to enhance uptake by cancer cells [44, 45].

Theranostic nanoparticles combine diagnostic and therapeutic capabilities in a single platform. For ovarian cancer, these systems can simultaneously track drug delivery and tumor response—for example, via MRI or fluorescence imaging—while delivering therapeutic agents. This allows for real-time monitoring and personalized treatment adjustments [46, 47].

FDA-approved drugs for ovarian cancer

Cytotoxic chemotherapy: Platinum agents such as carboplatin and cisplatin are the backbone of first-line and recurrent therapy, with carboplatin usually preferred because of better tolerability. Taxanes such as paclitaxel and docetaxel are combined with platinum agents for front-line treatment or used in recurrent disease. Other cytotoxic agents, including pegylated liposomal doxorubicin (PLD; Doxil/Caelyx), topotecan, gemcitabine, and cyclophosphamide, are used in recurrent or platinum-resistant settings. Anti-angiogenic agent: Bevacizumab (Avastin) is a monoclonal antibody against VEGF. It is approved in combination with chemotherapy and as maintenance therapy in selected settings, including front-line and recurrent disease.

PARP inhibitors: PARP inhibitors are targeted therapies for BRCA-mutated or HRD-positive tumors and are used in both maintenance and treatment settings. Olaparib (Lynparza) is approved for BRCA-mutated disease and in maintenance settings.

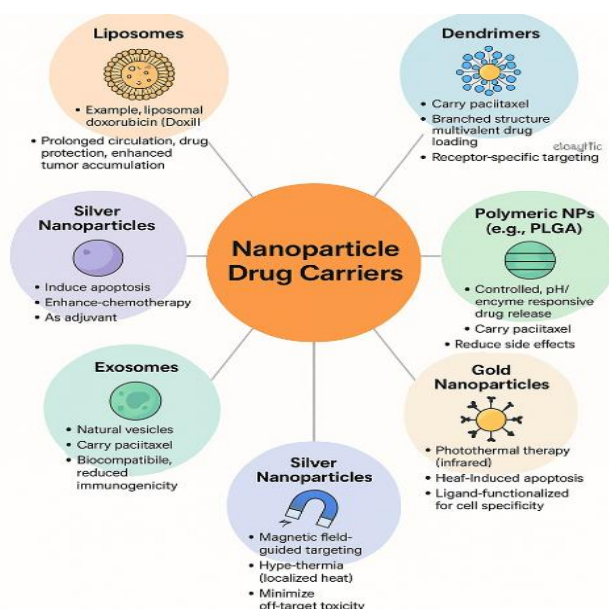


Figure 8. The classification of nanoparticle drug carriers used in cancer therapy [67].

Niraparib (Zejula) is approved for maintenance therapy after response to platinum, regardless of BRCA status, among other indications. Rucaparib (Rubraca) is approved for BRCA-mutated disease and as maintenance therapy in recurrent disease.

Antibody–drug conjugate: Mirvetuximab soravtansine-gxli (Elahere) is approved for FR α -high, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer after prior therapy.

Immunotherapy / biomarker-driven agents: Pembrolizumab (Keytruda) has tissue-agnostic FDA approvals for MSI-high/dMMR and high TMB tumors and may be used in biomarker-positive ovarian cancers according to the label and guidelines. Immune checkpoint inhibitors have limited single-agent approvals in ovarian cancer; their use is generally guided by biomarkers and clinical trials. Combination regimens and supportive formulations, such as chemotherapy with or without bevacizumab and PLD-based combinations, are commonly used. Several targeted agents and combinations are FDA-approved for specific molecular or clinical contexts. PARP inhibitors are central to maintenance therapy after a response to platinum-based therapy, especially in BRCA-mutated or homologous recombination-deficient (HRD) tumors. Treatment selection depends on stage, platinum sensitivity or resistance, BRCA/HRD status, FR α expression for Elahere, prior

therapies, and patient factors [48].

DISCUSSION

Nanoparticles, as fundamental components of nanomedicine, can be broadly categorized by composition into several principal types, each offering distinct advantages for biomedical applications [49]. These include lipid-based nanoparticles (e.g., liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs)), inorganic nanoparticles (such as iron oxides, gold nanoparticles, mesoporous nanoparticles, carbon nanotubes, and graphene oxide nanoparticles), polymeric nanoparticles (including polymeric nanoparticles, polymeric micelles, and dendrimers), and biological nanoparticles (exemplified by exosomes) (Fig. 8) [50]. Coating liposomes with synthetic polymers such as PEG is a crucial strategy for improving their performance as nanocarriers. The hydrophilic layer formed by the densely packed PEG head groups acts as a steric barrier, preventing interactions with plasma opsonins. This effectively increases nanoparticle longevity and prolongs circulation time [51]. In addition, zwitterionic coatings and albumin conjugation represent advanced stealth technologies that further help evade immune detection [52]. At their core, nanoparticles are defined as particles with dimensions typically ranging from 1 to 100 nm. Dendrimers are radially symmetric, spherical, and compact nanoscale structures that resemble tree-like architectures with branches and tunable surface groups, enabling drug conjugation, targeted delivery, and nucleic-acid complexation. Dendrimers consist of an inner and an outer layer. The outer layer contains functional groups essential for drug conjugation and targeting, whereas the inner layer is designed to improve drug encapsulation efficiency, reduce drug toxicity, and facilitate controlled-release mechanisms [53]. This nanoscale dimension provides critical physicochemical properties, particularly their remarkably large surface area, which enhances chemical reactivity. This increased reactivity—along with other characteristic physical properties—arises from quantum and surface-related phenomena that become prominent at the nanoscale [54].

Liposomes and PEGylated liposomes: Spherical lipid bilayer vesicles are used to encapsulate hydrophilic and lipophilic drugs. PEGylation prolongs circulation and enables EPR-based accumulation. PEGylated liposomal doxorubicin is used clinically. Polymeric nanoparticles / polymeric micelles are based on biodegradable polymers such as PLGA, PLA, and PEG-based block copolymers, which form solid nanoparticles or core-shell micelles for controlled release and improved stability. These systems are useful for delivering paclitaxel and siRNA. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) (55–58) are lipid-matrix particles that offer high drug-loading capacity, good stability, and suitability for intraperitoneal delivery in ovarian cancer. Inorganic nanoparticles, including gold, silica (such as mesoporous silica nanoparticles, MSNs), and iron oxide (magnetic) nanoparticles, are used for drug delivery, imaging, photothermal/photodynamic therapy, and magnetically guided delivery. Lipid-polymer hybrid nanoparticles [59] combine a polymeric core for controlled release with a lipid/PEG shell for biocompatibility, thereby optimizing pharmacokinetics and targeting. Exosomes and biomimetic/cell-derived vesicles are natural or engineered extracellular vesicles used for low-immunogenic delivery of drugs and siRNA, with inherent homing properties toward ovarian tumor cells. Stimuli-responsive or smart nanoparticles are pH-, redox-, enzyme-, temperature-, or light-responsive systems that enable triggered release in the tumor microenvironment or within intracellular compartments [60]. Targeted nanoparticles (active targeting) are surface-functionalized with ligands, antibodies, or peptides, such as folate, RGD, anti-HER2, and transferrin, to enhance uptake by ovarian cancer cells or the tumor vasculature. Pegylated liposomal doxorubicin is the most clinically established nanoparticle in ovarian cancer; however, many other platforms remain under preclinical or clinical evaluation [61, 62]. Heterogeneous tumor biology and the peritoneal microenvironment influence delivery efficacy. In recent years, biogenic nanocarriers have garnered significant interest because of their unique advantages in therapeutic

applications. A major benefit is their inherent biocompatibility, which is crucial for minimizing adverse effects in patients [63]. Studies consistently show that biogenic nanoparticles, especially those derived from natural sources such as plant extracts, can enhance drug efficacy while reducing systemic toxicity [64, 65]. In addition, recent interest in immunotherapy for ovarian cancer has increased substantially, particularly following studies demonstrating the positive impact of intra-tumoral (IT) T cells, especially CD8⁺ T cells, on clinical outcomes and survival in treatment-naïve ovarian cancer patients. Ovarian cancer (OC) remains a formidable challenge in oncology, characterized by late-stage diagnosis, rapid metastasis, and the development of therapeutic resistance. Conventional chemotherapy, while a cornerstone of treatment, is associated with significant off-target toxicities and limited... Efficacy against aggressive or recurrent disease remains limited. Consequently, advanced therapeutic strategies that emphasize precise drug delivery have attracted substantial research interest. Evaluations of key targeting modalities—including passive and active targeting, organelle targeting, and smart nanodrug delivery systems (SNDDS)—in the context of OC have highlighted their potential, limitations, and future directions. Although the EPR effect has been a foundational concept, its clinical translatability in OC has proven inconsistent. Tumor heterogeneity, varying degrees of vascularization, and interstitial pressure gradients can result in suboptimal and unpredictable nanoparticle distribution [66, 67]. This inherent variability underscores the need for more precise targeting mechanisms. Active targeting complements passive delivery by decorating nanocarrier surfaces with ligands (e.g., antibodies, peptides, and aptamers) that bind specifically to overexpressed receptors on OC cells (e.g., folate receptor alpha (FR α), epidermal growth factor receptor (EGFR), and integrins) [68, 69]. Receptor-mediated endocytosis can significantly enhance cellular uptake and increase intracellular drug concentration compared with passive accumulation alone. However, challenges persist, including receptor saturation, the immunogenicity of targeting ligands, and heterogeneity of receptor expression even within

the same tumor [70]. In addition, the dynamic nature of receptor expression during tumor progression and treatment can limit the long-term efficacy of active targeting strategies. Moving beyond cell-surface targeting, organelle targeting represents a sophisticated approach to exploit the specific metabolic and functional dependencies of cancer cells. By delivering therapeutics directly to critical organelles such as mitochondria, lysosomes, the nucleus, or the endoplasmic reticulum (ER), these strategies aim to induce targeted cell death or disrupt essential survival pathways [71]. The role of mitochondria in apoptosis and energy metabolism provides a promising avenue, particularly given the bioenergetic alterations observed in OC cells. Nanocarriers designed to accumulate in mitochondria can enhance drug efficacy and potentially overcome resistance mechanisms associated with mitochondrial dysfunction [72]. However, achieving high specificity while avoiding off-target effects on healthy mitochondria remains a critical hurdle [73]. Disrupting lysosomal function can trigger catastrophic cell-death pathways. While promising, the potential for lysosomal escape of drugs and the complex interplay between lysosomes and drug resistance pathways require careful consideration [74]. Direct targeting of the nucleus or ER offers additional opportunities to interfere with DNA. The disruption of replication, gene expression, or protein homeostasis are strategies of particular relevance for overcoming chemoresistance and modulating cellular stress responses common in ovarian cancer (OC) [75]. The major limitation across organelle-targeting approaches is the challenge of developing nanocarriers that can efficiently and selectively penetrate the cell membrane, navigate the complex intracellular environment, and release their payload specifically within the target organelle—all while maintaining biocompatibility. Smart nanodrug delivery systems (SNDDS) represent a paradigm shift by incorporating stimuli-responsive elements into nanocarrier design. These systems can be triggered by endogenous stimuli (e.g., low pH, high glutathione levels, specific enzymes) or exogenous stimuli (e.g., light, ultrasound, magnetic fields) prevalent in the OC microenvironment [76, 77]. pH- and enzyme-

responsive systems are particularly well-suited to the acidic tumor microenvironment (TME) and the enzyme-rich tumor interstitium of OC, facilitating controlled drug release and increasing local drug concentrations [78]. Redox-responsive systems exploit the elevated intracellular glutathione levels in cancer cells to enable targeted intracellular drug release [79]. Externally triggered systems offer spatiotemporal control over drug release, potentially reducing systemic exposure and enhancing therapeutic precision [80]. However, challenges such as deep tissue penetration of external stimuli and precise targeting remain significant hurdles. Despite substantial progress, the clinical translation of these sophisticated drug delivery systems for OC faces numerous obstacles:

Tumor heterogeneity: Both cellular and microenvironmental heterogeneity in OC limit the universal applicability of targeting ligands and stimuli-responsive triggers.

Biological barriers: Overcoming barriers such as peritoneal dissemination characteristic of OC, tumor penetration, and intracellular trafficking remains complex.

Immunogenicity and toxicity: The long-term biocompatibility and potential immunogenicity of nanocarriers and targeting ligands require thorough evaluation.

Manufacturing and scalability: Reproducible, large-scale production of complex nanocarrier formulations is a significant bottleneck.

Clinical trial design: Developing clinical trials that adequately assess efficacy and safety—considering patient selection and monitoring—is crucial. A primary challenge is achieving robust and specific tumor targeting while minimizing off-target toxicity. This is further complicated by the heterogeneous nature of ovarian tumors and the tumor microenvironment. Moreover, overcoming multidrug resistance (MDR)—a hallmark of OC progression and recurrence—remains a critical unmet need. This calls for nanocarriers that enhance drug accumulation and bypass efflux mechanisms. Biomimetic and “intelligent” nanosystems that respond to tumor-specific stimuli or actively engage with cellular machinery are still in the early stages of development.

Their full potential remains underexplored in preclinical and clinical settings. Addressing these gaps requires innovative nanodelivery strategies that improve pharmacokinetics, enhance cellular uptake, ensure sustained therapeutic release, and ultimately demonstrate superior clinical outcomes compared to conventional treatments.

Conclusion and Future Directions

Passive targeting, while conceptually important, often requires further augmentation. Active targeting can provide improved specificity, but its effectiveness is limited by tumor heterogeneity. Organelle targeting offers a highly precise strategy; however, it demands sophisticated nanocarrier engineering to achieve efficient intracellular delivery. SNDDS (smart nanodrug delivery systems) integrate “intelligence” into drug delivery, enabling stimuli-responsive release and theranostic capabilities. In the future, drug delivery in OC is likely to rely on multifunctional and combination-based strategies, including:

Synergistic combinations: Designing nanocarriers that co-deliver multiple agents (e.g., chemotherapy + immunotherapy + targeted agents) or combine different targeting mechanisms (e.g., active targeting with organelle-specific delivery).

Personalized nanomedicine: Tailoring nanodelivery systems based on individual patient tumor profiles (e.g., receptor expression, TME characteristics, and genetic mutations).

Advanced nanocarrier design: Developing novel materials and architectures that overcome biological barriers, enable robust organelle targeting, and provide reliable stimuli-responsive release.

Integration of imaging and therapy (theranostics): Leveraging theranostic platforms for real-time monitoring of drug delivery, therapeutic response, and adaptive treatment adjustments.

Addressing the peritoneal environment: Developing delivery systems specifically optimized for the unique challenges of the peritoneal cavity in advanced OC. Ultimately, bridging the gap between laboratory innovation and clinical success requires rigorous preclinical validation, well-designed clinical trials, and a deeper understanding of OC biology and its tumor microenvironment (TME). The convergence of nanotechnology, molecular biology, and clinical

oncology holds promise for revolutionizing OC treatment through highly targeted and intelligent drug delivery.

CONCLUSION

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

Not applicable.

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