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REVIEW

Engineering Nanoparticles for Gynecologic Cancer Therapy

Amanda M. Murray, Kelsey L. Swingle,* and Michael J. Mitchell*

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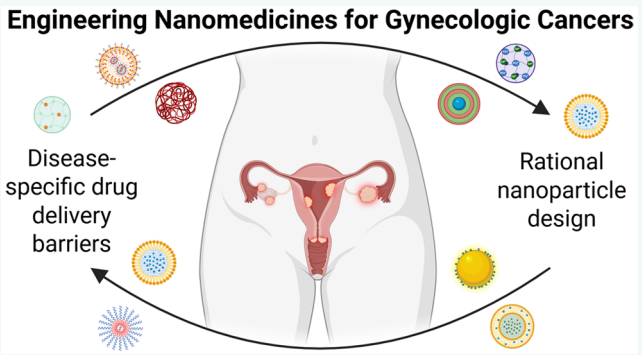
ABSTRACT: The significant morbidity and mortality of gynecologic cancers places a substantial burden on global healthcare and creates an urgent need for new treatment modalities. Here, we explore the emerging role of nanoparticles in treating gynecologic cancers, specifically ovarian, cervical, and endometrial cancers. These diseases are often diagnosed after they have metastasized, developed multidrug resistance, and formed immunosuppressive tumor microenvironments, hampering the effectiveness of traditional debulking surgery and chemotherapy. We first discuss the gynecologic cancer-specific barriers to nanoparticle drug delivery, including systemic and off-target toxicity, peritoneal fluid shear and convective forces, stromal fibrosis, and immunosuppressive tumor microenvironments. We then comprehensively analyze how various nanoparticle drug delivery platforms, such as liposomes, ionizable lipid nanoparticles, and layer-by-layer nanoparticles, have been engineered preclinically to selectively target tumor cells and increase retention within tumor lesions. Additionally, we examine the application of nanoparticles in delivering nucleic acids and immunotherapies, which can heat up immunologically cold tumors and tumor microenvironments to restore antitumor immune function. Despite promising preclinical results, additional efforts are needed to optimize nanoparticle design and ensure safe and effective translation into the clinic for all gynecologic cancers, and we conclude by discussing potential solutions to these barriers. Overall, this review explores the latest preclinical studies and emerging frontiers in nanoparticle therapies for gynecologic cancers, with a focus on efforts to overcome the disease-specific delivery challenges to effectively treat these lethal diseases.



KEYWORDS: *nanoparticles, gynecologic cancers, ovarian cancer, cervical cancer, chemoresistance, active targeting, passive targeting, nucleic acids, immunotherapy*

Gynecologic cancers—encompassing ovarian, cervical, endometrial, vulvar, and vaginal cancers—represent a significant global health burden. In the United States alone, it is estimated that nearly 119,000 women will be diagnosed with a gynecologic cancer in 2025, with a resulting 35,000 deaths from these malignancies.[1] While these distinct organs give rise to equally distinct diseases, gynecologic cancers collectively exhibit common pathological complexities that limit treatment efficacy, including distant metastatic spread, resistance to chemotherapeutics, and complex stromal and immune tumor microenvironments.

Currently, gynecologic cancers are treated with a combination of surgical, chemotherapeutic, and radiotherapeutic interventions; combinations of these treatments are often tailored to the specific type and stage of a patient's cancer.[2−4] Cytoreductive surgery is often the first course of treatment and can range from minimally invasive operations, which aim to remove only diseased tissue, to wide-ranging operations, such as radical hysterectomies.[5,6] If gynecologic tumors cannot be resected with surgery alone or if the cancer has metastasized beyond its organ of origin, second-line chemotherapy and/or radiotherapy are employed. Unfortunately, many patients who initially respond to chemotherapy do not experience lasting remission. Often, recurred disease becomes chemoresistant, which drastically decreases a patient's five-year chance of survival.[7] In recent years, traditional chemotherapeutic regimens, which consist of platinum- or taxane-based drugs,

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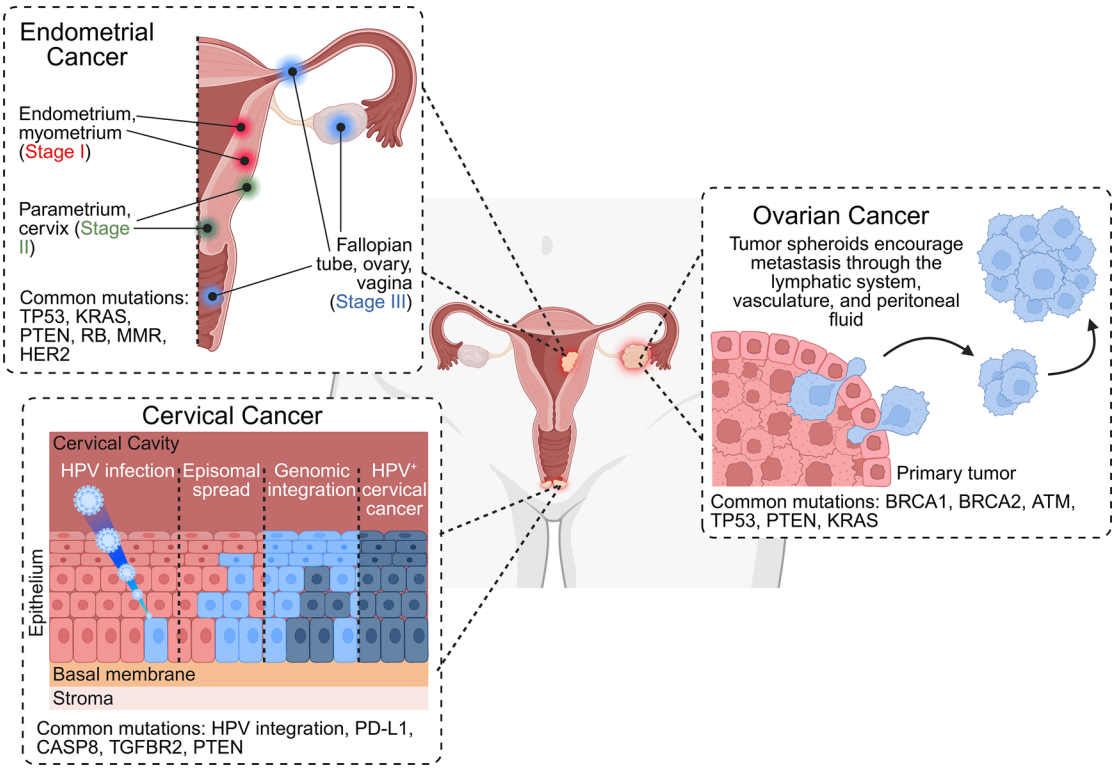

Figure 1. Pathogenesis of cervical, endometrial, and ovarian cancers. Cervical cancer is often a result of infection with human papillomavirus (HPV), which integrates into cervical epithelial cells and gives rise to a rapidly invasive disease.[320] Ovarian cancer often metastasizes within the intraperitoneal space by generating small tumor spheroids that can survive without vasculature or a basal membrane.[321,322] Endometrial cancer arises from the thin layer of endometrial tissue that lines the inner uterus; however, it can spread throughout the reproductive system as it metastasizes.[323] (TP53, tumor protein P53; KRAS, Kirsten rat sarcoma viral oncogene; PTEN, phosphatase and TENsin homologue; RB, retinoblastoma; MMR, mismatch repair; HER2, human epidermal growth factor 2; HPV, human papillomavirus; PD-L1, programmed death ligand 1; CASP8, caspase 8; TGFBR2, transforming growth factor-β receptor type 2; BRCA1/2, breast cancer gene 1/2; ATM, ataxia telangiectasia mutated gene).

have been supplemented with mutation-specific targeted therapies, which are designed to attack cancer cells by exploiting their genetic mutations and sparing healthy cells from off-target toxicity. In gynecologic cancers, successful targeted therapies include poly(ADP-ribose) polymerase inhibitors (PARPi), antiangiogenic therapies, tyrosine kinase inhibitors, and antibody-drug conjugates; advancements in the preclinical investigation and clinical application of these therapies have been comprehensively reviewed elsewhere.[7,8] Despite these promising advancements, there remains an urgent need for new gynecologic cancer treatments that overcome drug delivery barriers common to these diseases, such as systemic and off-target toxicity, chemoresistance, dense stromal fibrosis, peritoneal fluid shear and convective forces, and immunosuppressive tumor microenvironments.

Nanoparticles have gained significant attention in the field of cancer therapy because they can be engineered to overcome common drug delivery limitations, such as poor drug solubility, stability, and bioavailability.[9] Nanoparticles can also evade immune detection, avoid renal clearance, and mediate improved cell entry and endosomal escape.[10] Doxil, the first US Food and Drug Administration (FDA)-approved cancer nanomedicine, exemplifies the advantages of chemotherapeutic loading within a nanoparticle formulation; by encapsulating doxorubicin within poly(ethylene glycol) (PEG)-modified phospholipid and cholesterol liposomes, the plasma half-life of the drug was significantly increased and its renal clearance was drastically reduced.[11,12] Since Doxil's 1995 approval, it has demonstrated success in the treatment of ovarian and cervical cancers, and preclinical nanoparticle-mediated drug delivery research for gynecologic cancers has expanded greatly.[13−16]

Herein, we review the design and implementation of nanoparticle platforms to circumvent the specific delivery challenges associated with treating gynecologic cancers, specifically ovarian, endometrial, and cervical cancers (Figure 1). After discussing the drug delivery barriers unique to gynecologic tumors, we examine (i) nanoparticle strategies that reduce chemotherapy-associated toxicity, (ii) platforms that overcome multidrug resistance, (iii) nucleic acid nanomedicines targeting previously undruggable pathways, (iv) the rationale of and recent advances in intraperitoneal delivery of nanoparticles, (v) immunomodulatory strategies that reshape the immune landscape within the gynecologic tumor microenvironment, and (vi) the current landscape of nanoparticle-based gynecologic cancer clinical trials. We conclude with an outlook on the future of gynecologic cancer nanomedicine, including important regulatory and funding considerations that must be made early during nanoparticle platform development to encourage successful clinical translation.

DELIVERY BARRIERS TO GYNECOLOGIC TUMORS DICTATE DESIGN CRITERIA FOR NOVEL NANOMEDICINES

Gynecologic tumors present many obstacles to any therapeutic approach, including anatomic, cellular, and immunologic

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Table 1. Receptor Targets for Gynecologic Cancer Nanomedicines[a]

Receptor	Gynecologic cancer with receptor overexpression	Ligand(s) of receptor	Receptor-targeting nanoparticle studies
Folate receptor α (FRα, FOLR-1)	Ovarian, endometrial, cervical[38]	Folate/folic acid	Nanostructured lipid carriers[39]
			Liposomes[40]
Luteinizing hormone-releasing hormone receptor (LHRHR)	Ovarian, endometrial[41]	LHRH-mimetic peptide (also called gonadorelin[42])	Tandem peptide complexes[43]
			Liposomes[44]
Integrin $\alpha v\beta 3$ receptor	Ovarian[45]	RGD peptide motif	Liposomes[44]
	Cervical[46]		Heparin-based nanoparticles[47]
CD44	Ovarian[48]	Hyaluronan	Layer-by-layer nanoparticles[51,52]
	Endometrial[49]	Anti-CD44 antibody	Ionizable lipid nanoparticles[53]
	Cervical[50]		PLGA nanoparticles[54]
			Chitosan nanoparticles[55]
Human epidermal growth factor receptor 2 (HER2)	Ovarian, endometrial, cervical, vulvar[56]	Chitosan	PLGA nanoparticles[57]
Glucose transporter protein type 1 (GLUT1)	Ovarian[58]	*N*-acetyl-D-glucosamine (GLcNAc)	Solid lipid nanoparticles[61]
	Endometrial[59]		
	Cervical[60]		
Ephrin type-A receptor 2 (EphA2)	Ovarian, cervical[62]	Ephrin A-mimetic peptide	Nanogels[64]
	Endometrial[63]		
Mesothelin (MSLN)	Ovarian, endometrial[65]	MSLN-targeting nanobody	Organic nanoassemblies[66]

[a]An overview of receptors that are overexpressed or solely expressed on the surface of gynecologic malignancies and have been used in preclinical studies as targets for ligand-functionalized nanoparticles. (PLGA, poly(lactic-*co*-glycolic acid); RGD, arginine-glycine-aspartic acid).

barriers. Understanding how each of these barriers operates and the design space that each creates is essential for engineering nanoparticle platforms that can endure systemic circulation, reach poorly vascularized metastatic lesions, and remain therapeutically potent once they have reached their target gynecologic tumor or immune cell.

Systemic and Off-Target Toxicity. Currently, most gynecologic cancers are treated with platinum- or taxane-based chemotherapeutics, such as cisplatin (Platinol) and carboplatin (Paraplatin) or paclitaxel (Taxol), respectively.[2,17] These drugs are administered systemically through intravenous injections, allowing their cytotoxic functions to affect not only gynecologic cancer cells but also healthy tissue.[18,19] This results in widespread systemic toxicity—with side effects such as alopecia, nausea, fatigue, and immunodeficiency—which severely detriments patient quality of life.[20,21] Additionally, many chemotherapeutics are poorly water-soluble and are often formulated with a surfactant, such as Kolliphor EL (formerly Cremophor EL), that improves water solubility by reducing the surface tension between water and nonpolar substances.[22] While this excipient improves the intravenous administration of paclitaxel, it is an additional source of toxicity, causing hyperlipidemia, peripheral neuropathy, and axonal demyelination.[23]

While off-tumor toxicities of chemotherapeutics are not unique to gynecologic cancers, it is still important to design nanoparticle platforms that reduce off-tumor toxicity when engineering gynecologic cancer nanomedicines. This engineering begins with size considerations: nanoparticles with hydrodynamic diameters between 50 and 120 nm are large enough to evade renal filtration (<5.5 nm) yet small enough to evade splenic filtration (>200 nm), allowing them to maximize their circulation and persistence within the bloodstream if delivered intravenously.[24,25] Nanoparticles within this size range will also take advantage of the Enhanced Permeation and Retention (EPR) effect, allowing them to be retained within tumor tissue far longer than in healthy organs; more detailed discussion of the EPR effect can be found in the Nanoparticles for Passive Targeting to Gynecologic Tumors section.[26]

Next, steric stabilization of nanoparticle surfaces can further prolong their circulation within the blood. *In vivo*, nanoparticles accumulate readily in the liver and spleen due to the adsorption of serum proteins, such as apolipoproteins E and A-1, to their surface.[27,28] In recent years, the nanoparticle drug delivery field has focused on antifouling strategies, such as modifying nanoparticle surfaces with PEG or by conferring a zwitterionic, net-neutral charge to nanoparticle surfaces.[29,30] While PEGylated therapeutics have long been approved by the U.S. FDA, administration of PEG-containing biomaterials, including ionizable lipid nanoparticles (LNPs) and liposomes (Figure 3), results in the production of anti-PEG antibodies by the adaptive immune system.[31] Upon repeated administration of these PEGylated therapies, an immunogenic response known as the accelerated blood clearance phenomenon clears the therapies more rapidly from circulation after each dose and hinders their efficacy.[32] Given the heavy metastatic tumor burden and the recurrent nature of many gynecologic cancers, researchers should consider this PEGylation design constraint when designing novel nanomedicines that might require repeated dosing to completely eradicate gynecologic tumors. Alternatively, zwitterionic nanoparticles have been shown to circumvent this PEG-associated clearance while still preventing serum protein adsorption, and thus may be a better avenue for steric stabilization of future nanoparticle technologies for gynecologic cancers.[33−36]

Once systemic nanoparticle filtration has been avoided and circulation time has been extended, nanoparticle platforms can be engineered to actively target receptors that are solely or overly expressed on gynecologic tumor cells; this engineering takes advantage of the Active Transport and Retention (ATR) effect, which is discussed in more detail in the Nanoparticles for Active Targeting to Gynecologic Tumors section.[37]

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Previously reported receptor targets for gynecologic cancer nanomedicines are summarized in Table 1, and collectively, they support a precision-targeting landscape in which ligand-functionalized nanoparticles can be matched to tumor type, disease stage, and chemoresistance phenotype of gynecologic cancers.

Finally, intraperitoneal drug depots have been increasingly studied in recent years as a way to avoid systemic circulation and promote sustained, nanoparticle-mediated drug release adjacent to metastatic gynecologic tumors.[67] These depots, often biocompatible hydrogel scaffolds filled with therapeutic-encapsulating nanoparticles, are thermosensitive, allowing for injection of a liquid that solidifies *in situ* and releases nanoparticles over the course of days to months.[68] This sustained drug release is not only physically close to disseminated gynecologic tumor lesions, but it also maintains low systemic levels of the therapeutic, avoiding the high-dose intravenous chemotherapy regimens needed to achieve sufficient tumor delivery.[69] The hydrogels used in previous studies have been biodegradable, to prevent additional surgery to remove the scaffold and to allow for the potential of repeat dosing.[70,71] Future studies could also investigate the feasibility of engineering hydrogel scaffolds that degrade into cancer-fighting components, such as by the addition of a chemotherapeutic prodrug in the scaffold, or investigate the detection of hydrogel degradation through urine-detectable byproducts, allowing clinicians to noninvasively monitor hydrogel degradation to inform when patients should be administered a second dose.[72,73] Additionally, hydrogel degradation could advance these therapies into theranostics: if the hydrogel could respond to tumor stimuli, such as hypoxia or acidity, and degrade into urine-detectable components, clinicians could potentially track tumor regression through noninvasive urinalyses.[74,75]

These gelling nanoparticle depots also provide promising avenues for the local treatment of endometrial, cervical, and vaginal cancers. Endometrial tumors develop inside an enclosed uterine cavity that can be reached directly with transcervical catheters; cervical and vaginal cancers arise on a thin, visually accessible mucosal surface that is both drug-permeable and enriched with antigen-presenting dendritic cells.[76−78] The shallow stromal depth and routine colposcopy-mediated surveillance of some lower-genital-tract tumors also open opportunities for image-guided intra- or peri-tumoral injection of muco-adhesive vaginal gels for the sustained release of cytotoxic agents.[79−81] Together, the lumenal access of the uterus and the feasibility of repeated localized dosing provide a distinctive therapeutic window in which nanoparticles can outperform conventional systemic chemotherapy and radiation in treating gynecologic cancers.[82]

Peritoneal Fluid Shear and Convective Forces. In a healthy adult, between 5 and 20 mL of fluid (or between 50 and 75 mL during a normal menstrual cycle) is constantly produced and filtered in the peritoneal cavity to lubricate the abdominal and pelvic organs and prevent friction during respiration and digestion.[83] In advanced ovarian and endometrial cancers, metastatic tumors throughout the peritoneal cavity disrupt lymphatic drainage and the steady-state balance between fluid production and filtration, leading to the development of up to 8 L of malignant ascites.[84] This pathological accumulation of protein-rich peritoneal fluid contains tumor cells, tumor spheroids, and pro-tumor immune cells, and during normal activity, ascitic fluid circulates throughout the peritoneal cavity, subjecting free-floating tumor cells and spheroids to chronic, low-level shear stress (~0.02 to 0.1 dyn cm^{-2}) (Figure 2).[85,86] This shear not only physically removes unanchored nanoparticles from mesothelial surfaces, but it also reprograms ovarian tumor cells, triggering cytoskeletal remodeling, spheroid compaction, and activation of pathways that boost stem cell-like traits, encourage epithelial-to-mesenchymal transition, and increase efflux pump expression.[87]

To prevent the shearing of nanoparticles from mesothelial surfaces and increase intraperitoneal residence time, nanoparticles can be surface-modified with muco-adhesive catechol or chitosan moieties.[88,89] Furthermore, to evade the convective clearance of nanoparticles due to circulating ascitic fluid, researchers can also consider encapsulating their nanomedicines within aforementioned thermoresponsive hydrogels, which solidify *in situ* and could resist movement from shear forces.[72,73] These nanoparticle design considerations build on the clinical success of intraperitoneal chemotherapy, which has significantly improved progression-free survival and decreased systemic toxicities compared to intravenous cisplatin in a recent trial of stage III ovarian cancer patients with large residual tumors following cytoreductive surgery.[90]

Lastly, researchers should consider the physiochemical changes a nanoparticle undergoes during convection within ascitic fluid, specifically in terms of the proteins that adsorb to their surface. Initial studies of liposomes within ovarian cancer ascites showed that protein corona composition was highly heterogeneous between patients and was compositionally distinct from coronas formed in patient-matched serum samples; proteomic analyses showed an overrepresentation of tumor-secreted and extracellular matrix-associated proteins, including Mucin-16/Cancer Antigen-125 (CA-125), vitronectin, fibronectin, and complement C3 fragments.[91,92] While these heterogeneous protein coronas are not ideal when designing nanomedicines for broad gynecologic cancer patient populations, it provides an interesting avenue to explore toward personalized cancer therapies: could patient-specific protein coronas determined from ascitic fluid samples inform the rational design of a nanoparticle therapy that optimally targets an individual patient's peritoneal tumors? Additionally, if a patient's ascitic protein corona is composed more abundantly by complement fragments or immunoglobulins, nanoparticles are more likely to be phagocytosed and cleared by peritoneal macrophages; this may indicate that a nanoparticle-based therapy might not be as effective for that specific patient.[93,94]

Stromal Fibrosis and Elevated Interstitial Pressure. Another drug delivery barrier to gynecologic tumors is dense desmoplastic stromal fibrosis.[95,96] Ovarian, endometrial, and recurrent cervical tumor nodules are encased in a lattice of collagen-I/III and hyaluronan which is produced by myofibroblast-like cancer-associated fibroblasts (CAFs).[97] This cross-linked matrix elevates interstitial fluid pressure within tumors and narrows tumor pore diameters to less than 40 nm, preventing immune cells and larger nanoparticles from penetrating to tumor cores.[98−100]

When engineering nanoparticles to overcome this physical barrier, researchers could consider designing small nanoparticles or decorating their surface with matrix-binding peptide motifs to encourage nanoparticle infiltration.[101−103] When engineering the therapeutic payload within a nanoparticle, combination therapies could promote further nano-

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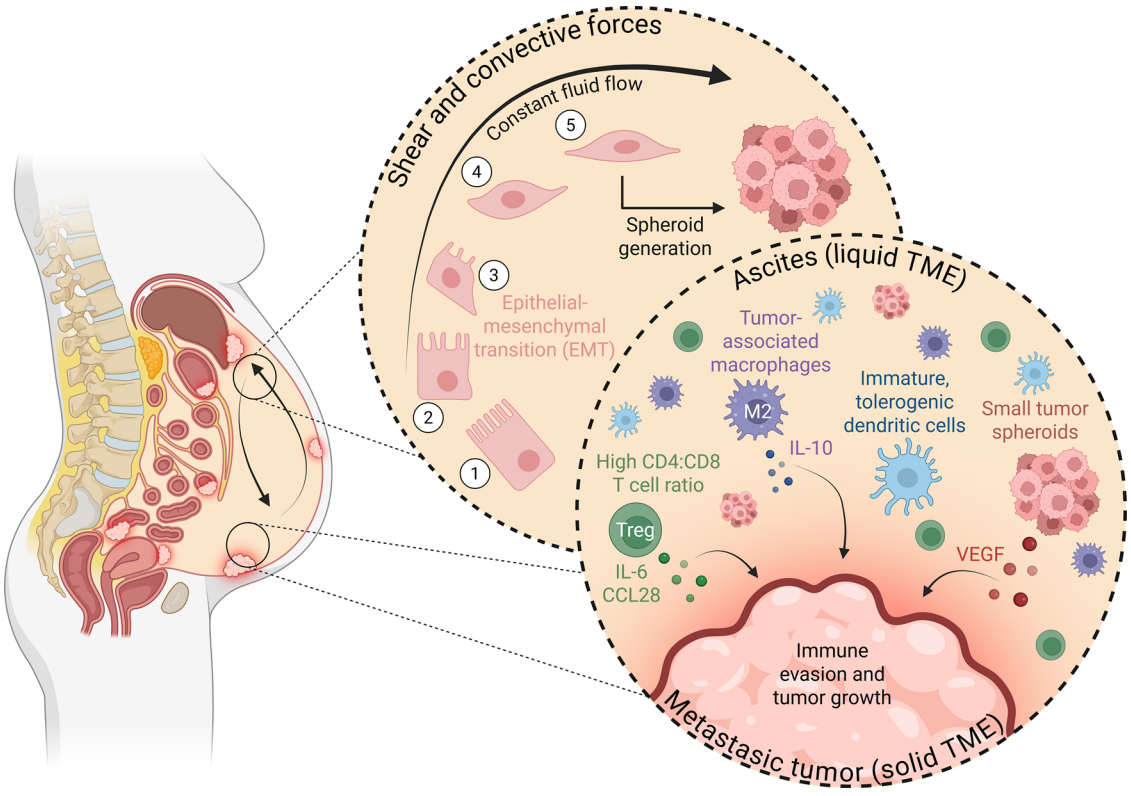

Figure 2. Dynamic tumor microenvironment within malignant ascites. In late-stage metastatic ovarian and endometrial cancers, tumor lesions impede lymphatic drainage of peritoneal fluid, causing the accumulation of malignant ascites. This protein-rich fluid is filled with pro-tumor, suppressive immune cells, and normal digestion and respiration causes convective fluid flow within the peritoneal cavity. (TME, tumor microenvironment; Treg, regulatory T cell; IL-6, interleukin 6; IL-10, interleukin 10; CCL28, chemokine ligand 28; VEGF, vascular endothelial growth factor).

particle penetration within tumors by delivering a collagenase or other antifibrotic agents along with a tumor cell-specific therapeutic, such as a chemotherapy.[104] Nanoparticles that allow for time-dependent therapeutic release, such as layer-by-layer (LbL) nanoparticles (Figure 3), could be especially useful here to provide a two-prong mechanism of action: nanoparticles first release their stroma-degrading component to decrease the barrier to entry for the later-released chemotherapeutic.[105] Recently, CAF-targeted or collagenase-releasing nanomedicines have resensitized tumors to chemotherapeutics in preclinical studies of pancreatic and breast cancers, underscoring fibrosis as a nanoparticle design target rather than a fixed anatomical barrier, and these techniques should be further validated in dense gynecologic tumors.[106,107]

Chemoresistance. One hallmark of gynecologic cancers is multidrug resistance; this chemoresistance is responsible for up to 90% of mortality in patients with recurrent, late-stage ovarian, endometrial, or cervical cancers.[108−111] Chemoresistance often develops after multiple rounds of chemotherapy, as cancer cells adapt and resist its cytotoxic effects; dose-limiting toxicities prevent the administration of enough chemotherapy to effectively clear tumors.[112] While chemoresistance is not unique to gynecologic cancers, nanoparticle therapeutics should be designed with the specific pathways involved in gynecologic tumor chemoresistance in mind. Some of these pathways are illustrated in Figure 4; however, there are many more mechanisms in which cancer cells become resistant to chemotherapeutics. For a comprehensive overview of these pathways, readers may reference previous literature reviews.[113−115] Broadly, the mechanisms of chemoresistance in gynecologic cancers include the overexpression of drug efflux and antiapoptotic proteins (P-glycoprotein, Pgp; Caspase 8 and FADD-like Apoptosis Regulator, CFLAR), the restorative mutation of DNA repair pathways (Breast Cancer Susceptibility Genes 1 and 2, BRCA1/2), and the promotion of cell-survival pathways (Signal Transducer and Activator of Transcription 3, STAT3).

To circumvent excessive therapeutic efflux, nanoparticles can mediate the codelivery of two therapeutics in a single injection: one that is cytotoxic to gynecologic tumor cells and one that inhibits a mechanism of chemoresistance. For example, nanoparticles can mediate the controlled release of a drug efflux pump inhibitor, such as verapamil or tariquidar, followed by the release of a chemotherapeutic, which will then remain in the cell without being actively exported.[116−120] Another class of experimental efflux pump inhibitors includes lipid-based compounds, which can be directly embedded within nanoparticles during their formulation, such as a vitamin E surfactant (TPGS) or complex glyceride (Gelucire 44/14).[120,121] Additionally, many protein mediators of gynecologic chemoresistance have long been "undruggable" with small molecules, but the recent regulatory and clinical success of nanoparticles encapsulating nucleic acids has allowed for novel cancer nanomedicines that attack the chemoresistance at the genomic level.[122,123] Nanoparticle-mediated nucleic acid delivery is discussed in further detail in the Nucleic Acid Nanoparticles: An Emerging Class of Gynecologic Cancer Therapies section, but overall, these platforms greatly expand the therapeutic space that conventional chemotherapies cannot reach within gynecologic tumors.

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Immunosuppressive Tumor Microenvironment. Peritoneal metastases of late-stage ovarian and endometrial cancers are surrounded by ascitic fluid that contains a host of suppressive immune cells which favor tumor survival (Figure 2). This cell population is dominated by regulatory $FoxP3^+CD4^+$ T cells and tumor-associated macrophages (TAMs) that secrete interleukin 10 (IL-10) and transforming growth factor β (TGFβ) cytokines and dampen tumor infiltration of cytotoxic $CD8^+$ T cells.[124−126] Additionally, many myeloid-derived suppressor cells (MDSCs) produce reactive oxygen species that prevent $CD8^+$ T cell proliferation. The imbalance of pro-tumor regulatory T cells and antitumor cytotoxic T cells can actually be used as a prognostic indicator in the clinic; a low CD4:CD8 T cell ratio (<1.6) in ovarian cancer-derived ascites has been shown to correlate with significantly longer overall survival.[127] Finally, ascitic fluid also contains immature and tolerogenic dendritic cells that poorly present antigens and secrete additional immunosuppressive cytokines.[128]

When designing nanomedicines for late-stage gynecologic tumors that reside within this immunosuppressive niche, researchers can consider two approaches: targeting the immune cells themselves or releasing immunostimulatory cargoes that will recruit antitumor immune cells to the tumor microenvironment. For the former, many nanoparticle platforms have been engineered to actively target and alter the phenotype of immune cells, including T cells, dendritic cells, and B cells.[129,130] Specifically, researchers can target nanoparticles to TAMs by conjugating mannose or CD206-binding antibodies or peptides to their surface, by conferring an anionic surface charge, or by creating large (>200 nm) particles.[131] TAM-targeted nanoparticles should also contain different therapeutic payloads, shifting from cytotoxic molecules to immunostimulants, such as interleukin 2 and 12 (IL-2, IL-12). These cytokines repolarize TAMs to an antitumor, M1 phenotype and recruit more cytotoxic $CD8^+$ T cells to the ascitic microenvironment. Immunomodulation via messenger RNA- (mRNA-) loaded nanoparticles is also a promising therapeutic mechanism for nanoparticles that are not targeted specifically to tumor or immune cells; mRNA-induced secretion of cytokines or chemokines from peri-tumoral healthy tissue could reshape the immune microenvironment without the need for complex active targeting moieties.[132,133] Additionally, combining immunomodulatory cargo with aforementioned stroma-remodeling cargo within one nanoparticle platform could promote antitumor immune cell infiltration within gynecologic tumors by modulating local immune cell phenotypes while degrading the physical barrier to immune cell infiltration.

NANOPARTICLES TO MITIGATE CHEMOTHERAPY-ASSOCIATED SYSTEMIC TOXICITY

Nanoparticles for Passive Targeting to Gynecologic Tumors. Passively, nanoparticles accumulate in solid tumors due to the aforementioned EPR effect.[134] This phenomenon arises from the leaky vasculature and impaired lymphatic drainage in tumor tissue: as tumors grow rapidly, their vasculature must also grow rapidly, leading to structures that are leakier and more permeable than healthy vasculature.[134,135] The small size of nanoparticles allows them to readily permeate this impaired tumor vasculature, and the lack of sufficient lymphatic drainage within the tumor allows nanoparticles to reside within the tumor, avoiding the rapid lymphatic clearance that occurs in healthy tissues.[136−138]

To take advantage of the EPR effect, investigators have utilized liposomes to shuttle azelnidipine, an FDA-approved calcium channel blocker, to endometrial tumors, which rely on high intracellular calcium levels to grow and metastasize.[139] Although this drug potently kills endometrial cancer cells *in vitro*, its off-target effects on the cardiovascular system and poor water solubility limit its application in systemic cancer therapies.[140] To improve these biosafety concerns and target tumors *in vivo*, investigators have encapsulated azelnidipine within methoxy-PEG_{2000}-DSPE liposomes (NP@AZL) (Figure 3).[141] In healthy BALB/C nude mice, NP@AZL treatment exhibited a milder effect on hematologic and hepatic leukocyte, monocyte, and lymphocyte counts compared to soluble azelnidipine, indicating improved systemic tolerability. In mice bearing subcutaneous endometrial tumors from human Ishikawa cells, NP@AZL homed to tumors within 6 h and were retained for up to 48 h postintravenous injection; however, significant nanoparticle signal was also detected in the liver and kidneys. After five intravenous doses, NP@AZL significantly reduced tumor weight and volume compared to the saline control and performed similarly to the soluble azelnidipine control. While the results of this study are promising in decreasing the systemic toxicities associated with intravenous azelnidipine via liposomal encapsulation, it would be informative to test whether a more concentrated dose or more doses of NP@AZL would have conferred more significant tumor reduction while maintaining their mild effect on blood and liver immune cell counts compared to naked azelnidipine.

Additionally, it is important to note that current animal models for endometrial cancer are limited to xenografts, such as the human Ishikawa and nude BALB/C model utilized in the previous study, because there are no commercially available syngeneic endometrial cancer cell lines (Figure 5).[142−144] There is one murine-derived, syngeneic cervical cancer cell line available, called U14; however, these cells are not human papillomavirus-positive (HPV^+), thus leading many researchers to use human xenografts *in vivo* to recapitulate the majority of cervical cancers that are associated with HPV infection.[145] These xenograft models allow for tumor engraftment and growth; however, the use of immunodeficient nude mice prevents researchers from studying the effects of nanoparticle drug delivery platforms on the innate and adaptive immune responses in their studies.[146] To circumvent this modeling limitation, nanoparticle researchers should prioritize establishing collaborations with biologists and physician-scientists who have published data describing in-house syngeneic models of endometrial and cervical cancers who might be willing to share their immortalized syngeneic cell lines for more accurate disease modeling *in vivo*.[147,148]

Also in the context of endometrial cancer, encapsulation within poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles (Figure 3) improved the tolerability and decreased the off-target effects of a paclitaxel (PTX) and angiokinase inhibitor (BIBF1120) combination therapy (PTXp+BIBFp).[149] While the PLGA nanoparticles homed to subcutaneous endometrial tumors following intravenous administration in BALB/C mice, some off-tumor signal was detected in the liver and spleen; however, *in vitro* analyses demonstrated that concomitant treatment with PTXp+BIBFp induces cytotoxicity only in cells containing a loss-of-function P53 mutation, such as endome-

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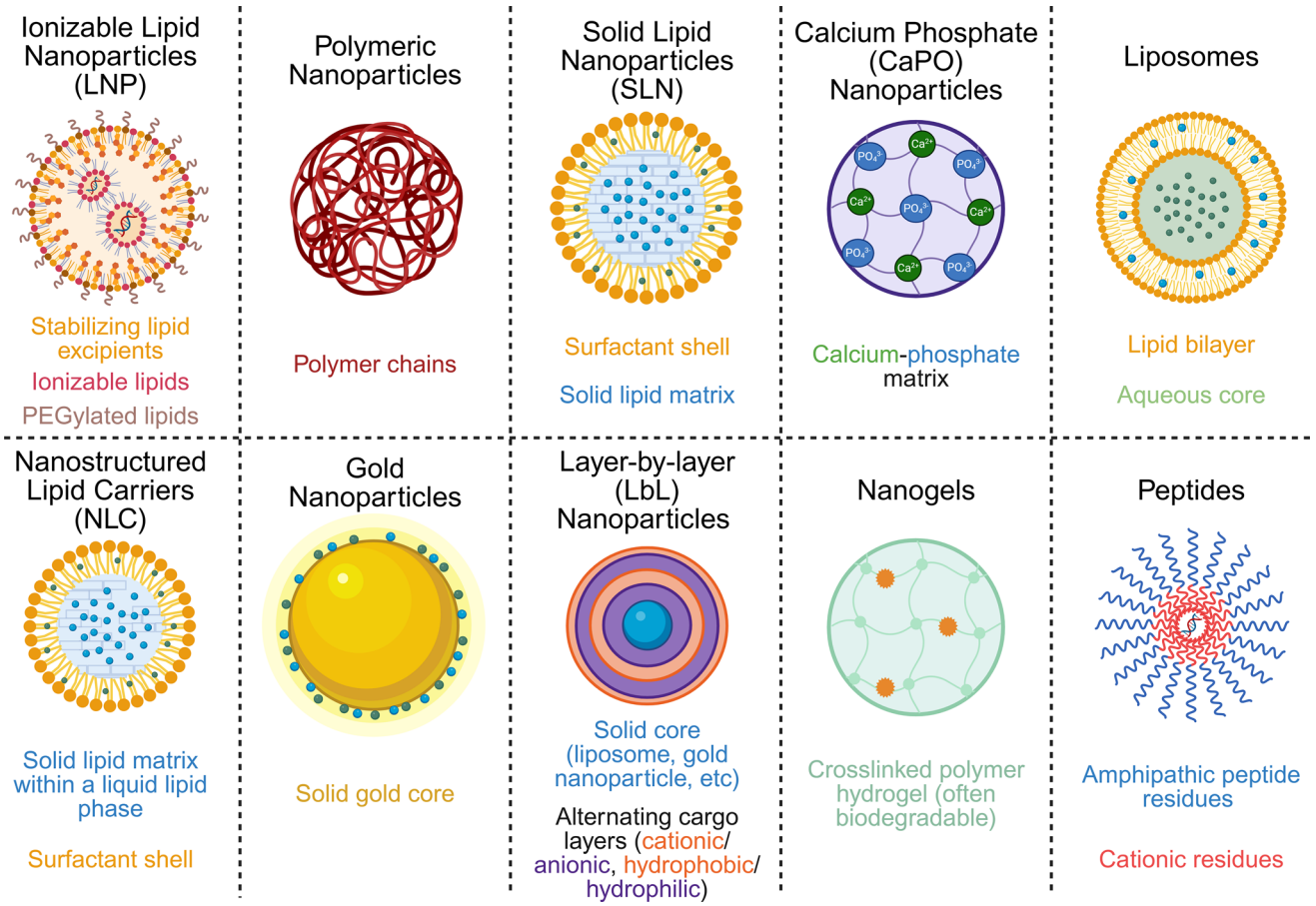

Figure 3. Preclinical nanoparticle drug delivery systems for gynecological cancers. Nanoparticle drug delivery systems are nanoscale biocompatible materials whose physicochemical properties allow them to be loaded with therapeutic payloads, such as nucleic acids and both hydrophilic and hydrophobic drugs.

trial tumor cells. In an athymic, subcutaneous murine xenograft model using P53 mutant Hec50co endometrial cancer cells, intravenous PTXp+BIBFp demonstrated a significant decrease in tumor volume and increase in overall survival compared to soluble paclitaxel and PTXp alone.[143] It would be interesting to compare these results to a heterogeneous endometrial tumor model, with cells that both contain and do not contain the P53 mutation, as endometrial cancers often have intertumoral heterogeneity in their morphologic and molecular profiles.[150] The PLGA nanoparticles also significantly increased drug retention within tumors for 12 h, demonstrating the advantages of nanoparticle-encapsulated chemotherapeutics compared to individual soluble drugs. The PTXp+BIBFp treatment also did not induce any toxicity compared to saline- or soluble PTX-treated mice, as shown by a lack of morphological differences in hematoxylin and eosin staining of major organs and no significant changes in mouse body weight after treatment.

PLGA nanoparticles encapsulating paclitaxel have also been researched in the context of ovarian cancer; however, the chemotherapeutic agent was engineered, rather than its nanoparticle carrier. While prior studies have investigated the incorporation of paclitaxel within PLGA after nanoparticle formulation, chemical modification of the paclitaxel allowed for its conjugation with PLGA prior to nanoparticle formation, which increases the amount of paclitaxel in the final nanoparticle structure compared to the former drug-loading strategy.[151,152] By reacting two of the paclitaxel carbon residues with a succinic anhydride linker, easily accessible carboxyl groups are produced on the drug, allowing for enhanced coupling to the hydroxyl group in PLGA. The PLGA−PTX hybrid nanoparticles were also coated with phospholipid-PEG to deter protein adsorption and subsequent recognition and clearance by the reticuloendothelial system in the blood.[153] *In vitro* assays using seven immortalized ovarian cancer cell lines and three patient-derived tumor cell lines demonstrated cytotoxicity equal to that of free paclitaxel at all tested doses, even in platinum-resistant cells. Further testing is required to validate biological efficacy *in vivo*, and this testing could also provide insight into the proposed reduced systemic toxicity that the PLGA−PTX hybrid nanoparticles confer compared to soluble paclitaxel. Additionally, these tests should be conducted using the more traditional paclitaxel-loaded PLGA nanoparticles as a control.

Chemotherapeutic encapsulation has also been investigated in cervical cancer, evaluating cisplatin loaded within chitosan-coated solid lipid nanoparticles (SLNs) (Figure 3).[154] *In vitro*, the encapsulation of cisplatin within SLNs significantly increased HeLa cell death compared to soluble cisplatin, even at drastically reduced dosages. The authors propose that the chitosan-coated SLNs had the greatest cytotoxic effect as their coating decreased the release rate of cisplatin from the nanoparticles; however, further mechanistic studies are needed to confirm this effect and to determine the therapeutic efficacy *in vivo*. As mentioned previously, syngeneic HPV^+ cervical cancer animal models are not yet commercially available, but

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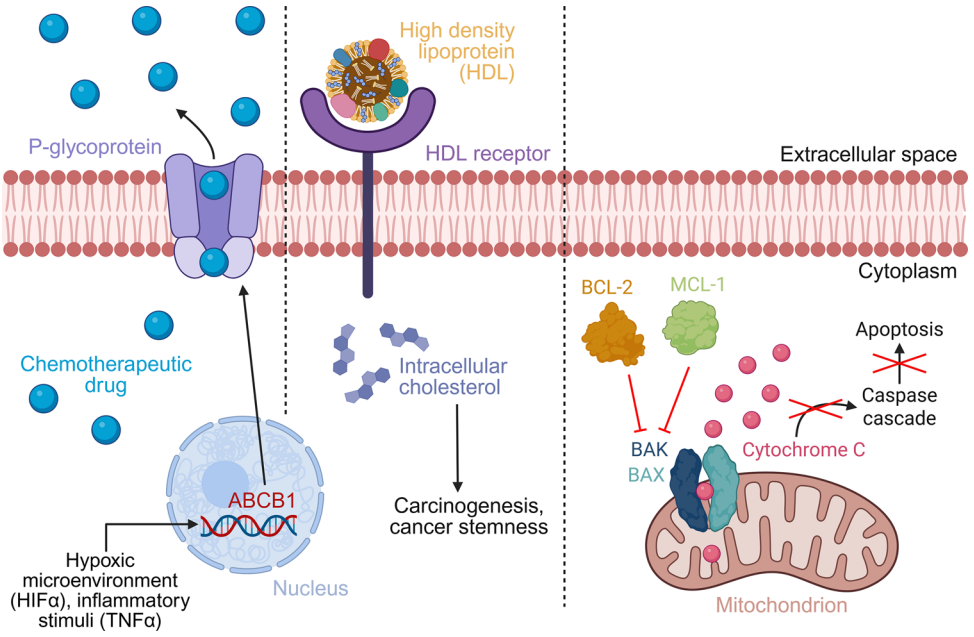

Figure 4. Selected mechanisms of gynecologic cancer chemoresistance. Gynecologic cancers acquire multidrug resistance following treatment with chemotherapeutics that do not eradicate tumors; the remaining tumor cells adapt and mutate to resist the cytotoxic effects of platinum- and taxane-based drugs. In this scheme, we have depicted chemoresistance pathways that have been studied in the context of nanoparticle drug delivery to gynecologic tumors. (ABCB1, ATP binding cassette subfamily B member 1 gene; BCL-2, B-cell lymphoma 2 protein; MCL-1, myeloid cell leukemia 1 protein; BAK, BCL-2 homologous antagonist/killer protein; BAX, BCL-2 associated X protein)

cisplatin is a common chemotherapeutic among many gynecologic cancers; it may be valuable to evaluate these chitosan-coated SLNs in a murine model of other gynecologic malignancies, such as the well-established syngeneic ID8 model, which recapitulates the lesion dissemination and immune landscape of metastatic ovarian cancer better than subcutaneous tumor models, both syngeneic and xenographic.[155]

Nanoparticles for Active Targeting to Gynecologic Tumors. While the EPR effect has been widely exploited in solid tumor drug delivery research, EPR-based drug delivery can be limited by tumor heterogeneity, high interstitial pressures, and dense stromal networks often seen in gynecologic tumors, leading to inconsistent therapeutic accumulation.[156,157] In contrast, the ATR effect is an emerging concept in nanoparticle-based drug delivery that challenges the passive nature of the EPR effect.[37] The ATR effect relies on active vascular and cellular transport processes, such as transendothelial pathways and receptor-mediated endocytosis, respectively.[158] The tunability of nanoparticles makes them an exciting therapeutic solution in this regard, as they can be engineered to display antibodies, peptides, or other ligands on their surfaces, which can specifically bind to receptors that are overexpressed on cancer cells.[159] This binding triggers cellular internalization of nanoparticles and their cargo, facilitating delivery of the therapeutic directly into target cells.

To exploit the ATR effect, LNPs and LbL nanoparticles (Figure 3) have been coated with hyaluronan to target CD44-overexpressing ovarian cancer cells.[51−53] In this application, CD44 targeting provides a two-pronged mechanism of action; it allows nanoparticles to have preferential affinity to CD44-expressing ovarian cancer cells compared to healthy cells, and it allows nanoparticles to competitively inhibit CD44, preventing it from enacting its cellular adhesion functions and thereby inhibiting tumor growth.

Hyaluronan-coated LNPs (tLNPs) demonstrated prolonged functional small interfering RNA (siRNA) delivery and promoted dissociation in spheroid cultures of human OVCAR-8 ovarian cancer cells compared to non-targeted LNPs.[53] Spheroids are three-dimensional cultures of cancer cells that better recapitulate the hypoxic core, acidic microenvironment, and increased cell-to-cell interactions of tumors within a patient, and their small size makes them highly relevant models of disseminated ovarian tumors, especially in the context of tracking nanoparticle penetration.[160,161] *In vivo*, tLNPs increased nanoparticle uptake within tumors along the ovaries, uteri, and omentums of athymic nude mice bearing intraperitoneal luciferase-expressing OVCAR-8 xenograft tumors, compared to uncoated LNPs, after intraperitoneal administration.

In the LbL study, nanoparticles were engineered to target CD44 by the addition of a terminal hyaluronan coating during their formulation (HA-LbLs). When tested in both NCr Nude and NSG mice bearing intraperitoneal luciferase- and GFP-expressing OVCAR-8 or DF09 xenograft tumors, fluorescent Cy7-labeled HA-LbLs colocalized with luminescent tumors, including metastatic tumor nodules on the omentum, pancreas, ovaries, and uterus, following intraperitoneal administration.[51] This tumor-nanoparticle colocalization was more prominent in the OVCAR-8 model; however, this was expected as CD44 is only overexpressed on human OVCAR-8 cells and not on high-grade serous ovarian cancer (HGSOC) patient-derived DF09 cells, indicating that the hyaluronan coating on LbL nanoparticles does promote CD44-specific binding *in vivo*.[162,163] Additionally, these two tumor models were chosen for biodistribution studies due to the differences in tumor development: the OVCAR-8-Nude model forms solid tumor lesions, whereas the DF09-NSG model forms thin layers of tumor cells along peritoneal structures. It is important to note that both of these models are immunodeficient, and future

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studies should prioritize selecting *in vivo* models that accurately emulate the native immune landscape during ovarian cancer progression, such as with syngeneic cancer cell lines.

LbL nanoparticles have also been used to decode the role that nanoparticle surface chemistry plays in the preferential uptake of nanoparticles by ovarian cancer cells. Following intraperitoneal administration in NCr Nude mice bearing peritoneal OVCAR-8 xenograft tumors, LbL nanoparticles modified with carboxylated surface chemistries displayed strong and lasting affinity for tumors with little to no accumulation in the liver and spleen over 72 h after treatment.[164] The authors acknowledge that further mechanistic work is required to determine the exact binding pathway between the carboxylated LbL nanoparticles and HGSOC cells; they hypothesize that it may be due to active targeting of overexpressed mucins on the surface of these cells, as carboxylated polymers have been shown to exhibit mucoadhesion.[165,166]

Another reporter cell surface target for ovarian cancer is the luteinizing hormone-releasing hormone receptor (LHRHR) which is overexpressed on up to 80% of human ovarian cancers and minimally expressed in healthy tissues.[167] Using a multifunctional tandem peptide (Figure 3) that includes an LHRHR-targeting domain and a fusogenic domain to aid in endosomal escape, Cy5-tagged siRNA was delivered intact within OVCAR-3 and CAOV3 cells *in vitro*.[43] It is important to note that both of these cells express LHRHR, and uptake of the siRNA-peptide complex was not compared with a cell line that does not express LHRHR. Nonetheless, LHRHR has also been shown to be overexpressed on the surface of early-stage endometrial tumors in the clinic, and thus it could be of future interest for researchers to investigate the application of these targeted siRNA-peptide complexes in additional gynecologic cancers, both *in vitro* and *in vivo*.[168]

Nanoparticles have also been designed to target the overexpressed ephrin type-A receptor 2 (EphA2) on the surface of ovarian tumor cells.[64] Nanoscale hydrogel particles, called nanogels (Figure 3), were functionalized with an ephrin A1-mimetic peptide and loaded with anti-epidermal growth factor receptor (EGFR) siRNA. In a xenograft model, luciferase-expressing Hey A8 human ovarian cancer cells were intraperitoneally inoculated into NOD-SCID mice, and nanogel particles were administered intravenously. Targeted nanogels colocalized with tumor luminescent signal as soon as 6 h postadministration and decreased tumor EGFR mRNA expression at 24 and 48 h after injection, with a return to pretreatment mRNA levels at 72 h. EGFR protein levels were reduced at 24 h, were essentially negligible at 48 h, and elevated back to baseline expression at 72 h. It is important to note that these EphA2-targeting nanogels were not evaluated against nontargeted nanogels for tumor homing or retention *in vivo*; however, combinatory therapy of intravenous targeted, siEGFR nanogels and intraperitoneal cisplatin did mediate significant decreases in tumor luminescence and tumor weight compared to intravenous non-targeted, noncoding siRNA nanogels with intraperitoneal cisplatin.

Lastly in the context of ovarian cancer, PLGA nanoparticles have been engineered to target the human epidermal growth factor receptor 2 (HER2).[57] Following PLGA nanoparticle formulation with cisplatin, the PLGA nanoparticle surface was modified with chitosan to facilitate the conjugation of trastuzumab, an anti-HER2 monoclonal antibody, via carbodiimide chemistry. This nanoparticle platform decreased the half maximal inhibitory concentration (IC_{50}) of $HER2^+$ SKOV-3 ovarian cancer cells compared to soluble cisplatin after 48 h of treatment. When comparing nanoparticle-induced cytotoxicity between $HER2^+$ SKOV-3 cells and $HER2^-$ HCC70 breast cancer cells *in vitro*, non-targeted cisplatin-loaded nanoparticles mediated a ~25% reduction in cell viability, whereas targeted cisplatin-loaded nanoparticles decreased cell viability by ~60%, but only in $HER2^+$ cells. This result implies that HER2-targeting nanoparticles could enhance the cytotoxic effects of chemotherapeutics in $HER2^+$ ovarian tumors, but this platform requires further *in vivo* validation.

For targeted treatment of cervical cancer, nanostructured lipid carriers (NLCs) (Figure 3) have been loaded with cisplatin and surface-modified with folate to target overexpressed folate surface receptors on cancer cells.[39] In a subcutaneous tumor model using HeLa cells and BALB/C nude mice, targeted NLC treatment decreased tumor growth compared to soluble cisplatin and non-targeted NLC controls following three intravenous doses. The targeted NLC treatment also minimized changes in mouse body weight and physical activity observed in the soluble cisplatin and non-targeted NLC control groups, suggesting that nanoparticle targeting reduced the systemic toxicity of cisplatin. However, it is important to note that the mice in this study did not receive a folate-depleted diet, as dietary folate has been shown to alter the progression and recurrence of many cancers.[169] Future studies utilizing folate-based targeting for gynecologic cancers should take this into consideration and try to ensure that targeted nanoparticles are tested in models that stably express folate receptors, regardless of dietary intake.

Overall, preclinical nanoparticle therapeutics have successfully utilized both the EPR and ATR effects for mitigating off-target toxicity associated with systemically administered chemotherapeutics for gynecologic cancers. The ATR effect enhances cellular uptake and prolongs retention at tumor sites through receptor-mediated endocytosis, complementing the EPR effect by increasing nanoparticle internalization rather than relying solely on passive accumulation. Utilizing both effects synergistically can improve nanoparticle delivery efficiency in gynecologic tumors that are well vascularized. However, many gynecologic tumors, such as metastatic ovarian and endometrial tumors, are not well vascularized and thus require researchers to engineer nanoparticles for tumor-localized drug delivery.

Local Nanoparticle Administration for Delivery to Gynecologic Tumors. Local delivery of nanoparticle therapeutics allows them to avoid systemic circulation and first-pass hepatic clearance, and it can also increase and sustain nanoparticle retention in malignant lesions. This effect is exemplified in cervical cancer, where the ability of nanoparticles to overcome biological barriers is particularly advantageous for penetrating the cervicovaginal mucus, which lines the area between the vagina and cervix and acts as a natural barrier to drug delivery.[170] This mucus is composed of water, mucin fibers, antimicrobial peptides, and electrolytes which create a hydrogel-like material of varying viscosity, depending on menstrual cycle phase.[171] Encapsulation of drugs and other therapeutics in nanoparticles for cervicovaginal delivery is also advantageous, as it can protect therapeutic cargo from the harsh cervicovaginal mucus environment, characterized by low pH and the presence of digestive enzymes.[172,173]

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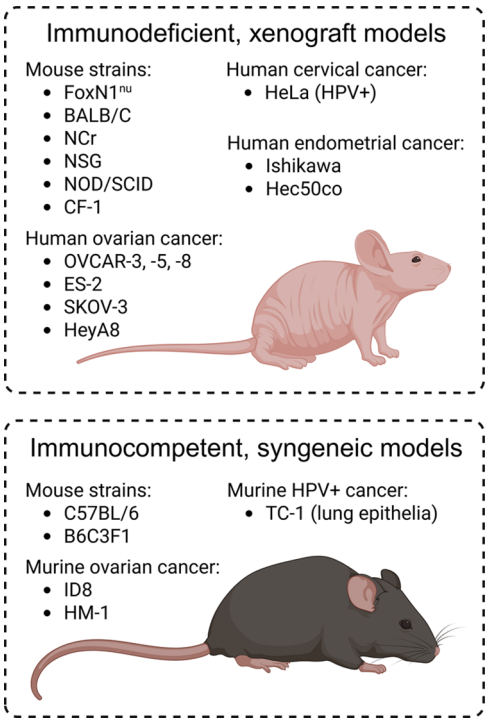

Figure 5. Common *in vivo* models of gynecologic cancers. To recapitulate gynecologic cancers *in vivo*, researchers commonly use murine models. Tumors can be xenographic, meaning that immunodeficient mice are inoculated with human-derived cancer cells, or syngeneic, meaning that immunocompetent mice are inoculated with mouse-derived cancer cells. In all models, tumor cells can be inoculated intraperitoneally to model orthotopic metastases, intravaginally to model cervical and vaginal cancers, or subcutaneously. Subcutaneous tumor models are not reflective of how gynecologic tumors grow in patients; however, these tumors are facile to track for survival studies as they can be measured noninvasively with calipers. Orthotopic tumor models often require luminescent or fluorescent imaging systems and cell lines that have been transduced to express firefly luciferase, mCherry, or green fluorescent protein (GFP).

Early investigations into the mechanisms of cervicovaginal mucus penetration found that virus-like particles (VLPs), such as HPV and Norwalk virus, diffuse as rapidly in human cervical mucus *ex vivo* as they did in saline, indicating that small capsid viruses (less than ∼60 nm and ∼20,000 kDa) can diffuse through mucus unhindered, compared to larger VLPs such as herpes simplex virus (∼180 nm).[174] VLPs are virus-derived structures that contain a viral protein capsid but not a viral genome, preventing them from infecting a host cell, and they are strongly immunogenic due to their surface antigen expression and are thus often used for engineering nanoparticle-based vaccines.[175,176]

However, for applications in which immunogenicity is not favored, such as nonvaccine cancer nanomedicines, PLGA nanoparticles have been designed to mimic the small size and net-neutral charge of VLPs, allowing them to easily maneuver through the mucin fiber mesh and avoid ionic interactions with anionic mucus glycans. Specifically, negatively charged PLGA nanoparticles have been surface-functionalized with biotinylated PEG to not only rapidly penetrate and be retained within cervical mucus but to penetrate mucosal epithelial cells.[177] Researchers found that PEG−PLGA nanoparticles formulated with low-molecular-weight PEG at a high surface density diffused the fastest within samples of human cervicovaginal mucus, identifying PEG molecular weight and degree of PEGylation as key nanoparticle design criteria to promote mucus penetration.[178] Further studies then demonstrated the ability of these PEG−PLGA nanoparticles to improve vaginal retention compared to bare PLGA nanoparticles after intravaginal administration in CF-1 mice; PEG−PLGA nanoparticles were also found at higher concentrations in the underlying epithelial cells, submucosal stroma, and vaginal fibroblasts.[179] While these studies lay the groundwork for engineering nanoparticles capable of cervicovaginal mucus penetration, when applying these results to gynecologic cancer nanomedicine, it is important to note that these *in vivo* studies were performed in healthy, nontumor-bearing mice. As cervical and vaginal cancers are known to alter the metabolomic, proteomic, and physical properties of cervicovaginal mucus, it is important for these PEG−PLGA nanoparticles to be validated in tumor-bearing animals.[180−182]

Additionally, Pluronic F127 has been shown to promote nanoparticle penetration and diffusion within cervicovaginal mucus, both as a hydrogel pretreatment and through formulation within nanoparticles themselves. Pluronics are a family of amphiphilic triblock copolymers that are used to form hydrogels, and they have been broadly investigated in many drug delivery applications.[183] Pluronic F127 is a highly hydrophilic formulation, and when human cervicovaginal mucus was preincubated with its hydrogel form *ex vivo*, PEGylated polystyrene nanoparticles suspended in Pluronic F127 diffused faster and deeper in comparison to nontreated mucus.[184] It has been hypothesized that the F127 hydrogel, which is poorly bioadhesive, prevents nanoparticles from adhering to mucins and thus allows their diffusion through the mucus to underlying epithelial cells.[185] Other mechanisms of nanoparticle mucus penetration have been reviewed elsewhere, such as particle shape, diameter, and poly(vinyl) alcohol inclusion, yet these design parameters have not been investigated with regard to gynecologic cancers.[186]

Applying these principles to an *in vivo* model of advanced cervical carcinoma, PLGA nanoparticles have been coated with both low-molecular-weight PEG and Pluronic F127.[187] In C57BL/6 mice treated with contraceptive Depo-Provera, luciferase- and GFP-expressing TC-1 cells were inoculated by vaginal instillation and monitored for tumor growth with bioluminescent imaging. While TC-1 cells are derived from mouse lung epithelial cells rather than the cervix, they have been modified to express the HPV viral oncogenes E6 and E7 that are often critical for cervical cancer development and progression, and thus these cells allow for an immunocompetent, syngeneic *in vivo* cervical cancer model.[188] Following daily intravaginal administration, empty F127-PLGA nanoparticles penetrated deeper within the cervicovaginal mucus than bare PLGA nanoparticles, and when loaded with paclitaxel, the F127-PLGA nanoparticles were retained at the tumor site for up to 24 h, extended mouse survival, and did not induce significant toxicity to the cervicovaginal epithelium. It is interesting to consider the effect of contraceptives on the efficacy of nanomedicines for gynecologic cancers, as some, such as progestin-based Depo-Provera and levonorgestrel intrauterine devices, work by thickening the cervical mucus barrier to physically limit sperm from reaching an egg during ovulation.[189,190]

Additionally, local delivery of paclitaxel and B-cell lymphoma 2 protein siRNA (siBCL-2) to cervical cancer has

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been explored; this combination therapy was encapsulated within SLNs which were then suspended in a PEG suppository.[191] The SLNs reduced HeLa cell viability *in vitro*, and their loading within the PEG suppository allowed for sustained siBCL-2 and paclitaxel release over the course of 4 h in an *in vitro* drug release study using a vaginal fluid simulant. While these results are promising, further animal studies should be completed to determine the safety and feasibility of these suppository-embedded nanoparticles. Vaginal suppositories are an exciting local delivery option for gynecologic cancers due to the current FDA approvals and clinical successes of suppositories and creams for vaginal dryness and yeast infections.[192−194]

Another promising method of local delivery of nanoparticle therapies to gynecologic cancers lies within their encapsulation and controlled release from larger macromolecular biomaterials that are administered via intratumoral or peri-tumoral injections.[195,196] These local injections offer promising approaches for treating gynecologic cancers, particularly in cases of unresectable or recurrent disease where systemic toxicity and poor drug accumulation limit traditional intravenous therapies. By delivering therapeutics directly into or near tumors, these injections enable high local drug concentrations, reduced systemic exposure, and the potential to modulate the tumor microenvironment locally, while concomitantly bypassing the limitations of poor tumor vascularization and dense stromal barriers which often limit the effectiveness of systemic therapies in gynecologic cancers.

Among local delivery strategies, injectable hydrogels incorporating nanoparticles have emerged as powerful platforms, combining the advantages of local depot formation with nanoparticle-mediated control over drug encapsulation and release kinetics. These hydrogels, which are often formed with biocompatible polymers such as alginate, hyaluronic acid, or gelatin, can be engineered to solidify *in situ* following injection, forming a reservoir for sustained drug release within or near gynecologic tumors.

For example, a recent study explored the sustained release of cationic diblock polymeric nanoparticles complexed with siRNA (polyplexes) following encapsulation within an injectable, thermosensitive triblock polymeric hydrogel that transitions to a gel state at body temperature.[197] Naked polyplexes demonstrated tumor accumulation following intraperitoneal administration into BALB/C athymic nude mice bearing intraperitoneal luciferase-expressing SKOV-3 xenograft tumors. After polyplex encapsulation within the polymeric hydrogel (polyplex hydrogel) and intraperitoneal injection within the aforementioned ovarian cancer xenograft model, the hydrogel enabled progressive intra-abdominal release of the polyplexes, driven by hydrogel erosion, resulting in nanoparticle accumulation within disseminated ovarian tumor nodules throughout the peritoneal cavity. In therapeutic studies, the polyplexes were formulated using siRNA against signal transducer and activator of transcription 3 (siSTAT3). STAT3 is a signaling protein that encourages cell growth and survival, and it is constitutively active and aberrantly overexpressed in many gynecologic cancers.[198−201] The therapeutic polyplex hydrogel mediated significant tumor growth delay after 4 weeks of hydrogel implantation compared to saline, naked siSTAT3 polyplex, and noncoding siRNA polyplex hydrogel controls; however, tumor growth resumed by week 8, indicating that the polyplexes had been completely released by this time and that the hydrogel conferred no therapeutic effect on its own. This limitation leaves room for future studies optimizing the timing of hydrogel injections (early- versus late-stage disease) and the possibility of repeated hydrogel doses, to renew the local presence of therapeutic siRNA polyplexes. Additionally, given the prolonged hydrogel deposition within the peritoneal cavity, there is potential for adverse host immune responses against or fibrous encapsulation of the hydrogel, both of which could impede nanoparticle release; in future, this polyplex hydrogel platform should be validated in an immunocompetent ovarian cancer model.

Another study has investigated the sustained codelivery of cisplatin and paclitaxel against ovarian cancer using an injectable hydrogel.[202] The coadministration of these chemotherapeutics is used clinically to synergistically target both platinum-resistant and taxane-resistant cells in one treatment; however, cisplatin is hydrophilic and is quickly released from previous hydrogel systems within a matter of hours, whereas paclitaxel is hydrophobic and is released slowly over the course of weeks.[203,204] After optimizing the relative drug-loading concentrations of the final codelivery hydrogel *in vitro* to overcome this difference in release kinetics (cisplatin loaded at ∼3× the dose of paclitaxel), a thermosensitive polymer-platinum conjugate was developed by covalently linking two PEG−PLGA diblock copolymers onto a Pt(IV) prodrug, which is reduced to cisplatin intracellularly. These amphiphilic conjugates (PtGel) then self-assemble into micelles, which encapsulate hydrophobic PTX within their cores (PtGel +PTX). This concentrated micelle solution exhibits a reversible sol−gel transition as temperature increases, allowing for liquid injection and subsequent gelation within the body. In a xenograft model of ovarian cancer, BALB/C nude mice were subcutaneously inoculated with SKOV-3 cells in the mammary fat pad. Fluorescent imaging displayed PtGel hydrogel retention at the tumor site for 3 weeks following intratumoral injection, with degradation beginning at week four. Therapeutically, the PtGel+PTX hydrogel significantly reduced tumor weight at sacrifice compared to saline, PtGel, and PtGel with intravenous paclitaxel. Notably, all hydrogel-based treatment groups conferred protection from the systemic toxicity induced by intravenous paclitaxel and cisplatin combination therapy, as measured by change in mouse body weight over time.

While this indication of decreased systemic toxicity is promising, the intratumoral injection of the PtGel+PTX therapy exhibited in this study might not translate into clinical studies of ovarian cancer, as it would only be available for patients with metastatic lesions that are visible, palpable, or detectable by ultrasound imaging; this intratumoral therapy may be more suited for cervical or vaginal cancers that can be accessed intravaginally.[205−207] In future, it would be informative to test this PtGel+PTX hydrogel as a peri-tumoral therapy in an immunocompetent model of metastatic ovarian cancer; this model could also inform researchers of the stability and degradation rate of the hydrogel in protein- and cell-rich ascites fluid.

Lastly, a glycol-chitosan hydrogel has been developed for the local delivery of paclitaxel complexed with β-cyclodextrin (GC/CD/PTX).[208] β-Cyclodextrin is known to improve the water solubility of paclitaxel, and this complexation increased the *ex vivo* release of paclitaxel from the hydrogel over 7 days compared to nonmodified paclitaxel.[209] In a subcutaneous xenograft model of ovarian cancer using SKOV-3 cells inoculated in BALB/C mice, peri-tumoral administration of

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the GC/CD/PTX hydrogel significantly reduced tumor volume and increased tumor necrosis compared to saline, soluble PTX, and GC/PTX controls. However, it is important to note that these therapeutic studies were conducted in male BALB/C mice; future studies should be conducted in an immunocompetent syngeneic model with female mice.

Overall, local drug delivery techniques using intra- or peritumoral injections combined with biomaterial-embedded nanoparticles provide a promising strategy for advancing gynecologic cancer nanomedicine. By leveraging high local drug concentrations and sustained drug release kinetics while circumventing systemic circulation, these delivery modalities help fulfill the urgent need for innovative, novel approaches for patients with advanced or recurrent gynecologic malignancies.

NANOPARTICLE THERAPEUTICS TO COMBAT CHEMORESISTANCE

One hallmark of gynecologic cancers is multidrug resistance; this chemoresistance is responsible for up to 90% of mortality in patients with recurrent, late-stage ovarian, endometrial, or cervical cancer.[108−111] Chemoresistance often develops after multiple rounds of chemotherapy, as cancer cells adapt and resist its cytotoxic effects; dose-limiting toxicities prevent the administration of enough chemotherapy to eradicate tumors.[112] Herein, we have chosen to highlight a limited number of chemoresistance mechanisms, as these specific pathways have been investigated in the context of nanoparticle therapies for gynecological cancers, both at the transcriptomic and proteomic levels (Figure 4).

SLNs have been previously shown to improve the *in vitro* kinetics and retention of paclitaxel in ovarian cancer cells; however, a recent study investigated the coencapsulation of paclitaxel and verapamil, an inhibitor of the drug efflux protein P-glycoprotein (PgP).[210] Nanoparticle-mediated codelivery conferred higher cellular uptake and cytotoxicity when chemoresistant MCF-7 cells were treated with paclitaxel-verapamil SLNs, compared to soluble paclitaxel and verapamil. While the MCF-7 cell line is derived from human breast cancer, the authors note that this technology could be expanded to any cancer that overexpresses PgP as a mechanism of chemoresistance, such as ovarian and cervical cancers.[211,212] This strategy has also yet to be tested *in vivo*, and future studies could prioritize evaluating its therapeutic potential in murine models of gynecologic cancers.

Additionally, platinum-resistant ovarian cancer cells increase their intracellular cholesterol levels using a high-density lipoprotein (HDL) receptor.[213] To block this receptor and starve cancer cells of their cholesterol needs, HDL-mimetic gold nanoparticles (Figure 3) were engineered through surface-functionalization with apolipoprotein AI, a major protein component of plasma HDL particles.[214] In a xenograft model of peritoneally metastasized ovarian cancer with platinum-resistant OVCAR-5 cells and FoxN1^{nu} mice, the HDL-nanoparticles reduced tumor burden and total number of tumors, and *in vitro*, the HDL-nanoparticles also resensitized chemoresistant ovarian cancer cells to cisplatin. In future, this resensitization should be validated *in vivo*, by assessing the tumor-reducing effect of cisplatin after treatment with the HDL-nanoparticles.

Ovarian cancer chemoresistance is also mediated by the overexpression of antiapoptotic proteins, such as BCL-2 and myeloid cell leukemia-1 (MCL-1). Co-inhibiting BCL-2 and MCL-1, via the pharmaceutics ABT-236 and S36845, respectively, exhibits potent cytotoxicity in chemoresistant ovarian cancer cell lines. However, the use of this treatment is limited clinically; coadministration of these drugs *in vivo* is thought to be toxic. To ameliorate this toxicity and enhance their synergy, ABT-326 and S36845 have been encapsulated within LbL nanoparticles.[51] In a xenograft model of peritoneally metastasized ovarian cancer using luciferase-expressing OVCAR-8 cells and nude NCr mice, daily injections of coloaded LbL nanoparticles eliminated almost all metastatic lesions with no discernible toxicities, compared to LbL nanoparticles loaded with ABT-236 or S36845 alone.

NUCLEIC ACID NANOPARTICLES: AN EMERGING CLASS OF GYNECOLOGIC CANCER THERAPIES

While chemotherapeutics are the current standard for treating gynecologic cancers, recent FDA approvals of nucleic acid−based therapies have spurred a new focus on ameliorating the mutated transcriptomes and proteomes of gynecologic tumors.[215,216] Nucleic acids, such as siRNA and mRNA, can restore the expression of tumor-suppressive proteins or silence oncogenic proteins; however, they are very fragile and risk rapid degradation by ribonucleases found throughout the body and within endosomes.[217,218] Nucleic acids are also large and negatively charged, limiting their transport across negatively charged cell membranes.[219−222] Thus, delivery systems, such as nanoparticles, are required to effectively protect and transport nucleic acids into the cytoplasm *in vivo*.

The most commonly delivered nucleic acid for cancer therapies is siRNA, as it prevents the translation of oncogenic proteins through RNA interference.[223] RNA interference has been heavily investigated in the field of nucleic acid therapy following the 2018 FDA approval of patisiran (Onpattro), an siRNA LNP formulation for the treatment of hereditary transthyretin-mediated amyloidosis.[224] Since this approval, LNPs have been studied for the delivery of siRNA to gynecologic cancers. As discussed previously, hyaluronan-coated LNPs (tLNPs) homed preferentially to the tumor-laden ovaries and omentums of immunodeficient, OVCAR-3 tumor-bearing mice. In the same murine tumor model, tLNPs were then coloaded with siRNAs for polo-like kinase-1 (PLK1) and eukaryotic translation initiation factor 3c (eIF3c), creating eP-tLNPs; these proteins are implicated in the malignant transformation and mTOR pathway-related tumorigenesis of cancer cells, respectively.[225,226] The eP-tLNPs downregulated the expression of both PLK1 and eIF3c mRNA within the ovaries, omentum, and ascitic fluid following intraperitoneal administration. Therapeutically, this combinatory eP-tLNP treatment also increased median and overall mouse survival, in the same mouse model used for nanoparticle biodistribution studies, compared to the saline control.[53] While not statistically significant, the eP-tLNP treatment also improved overall survival percentage compared to mice receiving only one siRNA (PLK1-tLNP or eIF3c-tLNP), highlighting the power that nanoparticle platforms hold to not only safely deliver nucleic acids, but to deliver combinations of synergistically paired nucleic acids at once.

For the treatment of cervical cancer, LNPs have also been used to encapsulate siRNA against oncogenic HPV proteins E6 and E7 (ENB101-LNPs), both of which play important roles in the malignant transformation and progression of HPV-infected cervical cancer cells.[227] In a subcutaneous xenograft model using HPV+ human cervical cancer cells (CaSki) and nude BALB/C mice, intravenous administration of ENB101-

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LNPs significantly decreased tumor volume and weight compared to the saline control, and combinatory therapy of intravenous ENB101-LNPs and intraperitoneal cisplatin further decreased tumor weight.

Similarly, PEG-decorated, siRNA-encapsulating liposomes have been designed to encapsulate siE7 and siMCL-1 for the local treatment of cervical cancer.[228] *In vitro*, the liposomes decreased the viability of HPV^+ cervical cancer (SiHa) cells while not affecting the viability of HPV^- control cell lines. To assess the effect of PEGylation on nanoparticle penetration of cervical lesions, the researchers assembled a three-dimensional model, where SiHA cells were grown with fibroblasts in a collagen gel. In this model, PEGylated liposomes loaded with a fluorescent siRNA penetrated deep into the collagen-cell construct and were observed intracellularly after 2 h of treatment, compared with non-PEGylated liposomes and free siRNA controls, which penetrated slowly and inhibited intracellular siRNA delivery, respectively. These penetration results were also observed in explanted samples of porcine vaginal mucosa. Similarly, liposomes loaded with siRNA against HPV protein E6 (siE6) have significantly reduced E7 protein levels and restored P53 protein expression in CaSki cervical cancer cells *in vitro*.[229] The tumor-reducing therapeutic potential of both nanoparticle platforms should be further validated *in vivo*, as siRNA-loaded liposomes and PLGA nanoparticles have been shown previously to effectively penetrate the vaginal mucus accumulated within the uterine horn, cervix, and vaginal tract of mice for up to 7 days, following topical intravaginal delivery.[230,231]

Fusogenic peptide nanocarriers (Figure 3) have also been used to deliver casein kinase 2 α 1 siRNA (siCSNK2A1) for the treatment of ovarian cancer; siCSNK2A1 prevents the translation of a kinase which regulates practically all malignant hallmarks in many cancers, such as cell migration, proliferation, and invasion.[232,233] *In vitro*, siCSNK2A1-peptide complexes decreased both mRNA and protein expression of siCSNK2A1 and functionally decreased the cell migration and colonization abilities of both OVCAR-3 and SKOV-3 ovarian cancer cells. In a subcutaneous xenograft model using OVCAR-3 cells and athymic $FoxN1^{nu}$ mice, intratumoral administration of reporter siRNA-peptide complexes led to strong nanoparticle accumulation in tumors, and therapeutically, siCSNK2A1-peptide complexes significantly reduced tumor volume following four intratumoral administrations over 14 days.

While many of the nanoparticle platforms studied for gynecologic cancers are synthesized with organic and inorganic components to facilitate nucleic acid encapsulation during the formulation process, a recent study investigated the loading of patient-derived exosomes with siRNA *ex vivo via* electroporation.[234] Exosomes are naturally occurring extracellular vesicles that cells use to package nucleic acids and proteins for cell-to-cell communication within the body, and while many researchers choose to engineer exosome-mimetic nanoparticles for improved tumor drug delivery, the current study aimed to harvest and isolate endogenous exosomes.[235,236] During initial cytoreductive surgery, ovarian cancer patients often undergo a partial or complete omentectomy to remove the apron-like fold of visceral peritoneum that serves as a common site of tumor nodule formation; the excised omental tissue contains fibroblasts from which exosomes can be isolated.[237,238] Leveraging their natural tropism for peritoneal tumor nodules, the researchers electroporated the omental exosomes with siRNA against cellular-mesenchymal epithelial transition factor (sic-Met), a protein that promotes carcinogenesis and aberrant cell proliferation when overexpressed.[239] Upon intraperitoneal delivery in a xenograft model of peritoneal metastases using luciferase-expressing SKOV-3 ovarian cancer cells and athymic BALB/C mice, sic-Met exosomes decreased tumor radiance and volume and the accumulation of ascitic fluid. While these preclinical results are exciting, this platform should be validated using murine-derived exosomes in an immunocompetent ovarian cancer model, to ensure that *ex vivo* electroporation does not preclude exosomes from naturally homing to peritoneal tumors. However, barring adverse immunogenic effects, this platform offers a promising and novel use for the often-discarded tissue removed during frontline cytoreductive surgeries.

The aforementioned studies demonstrate the powerful implications of siRNA-mediated oncogene silencing for treating gynecologic cancers, but nanoparticles can also deliver mRNA to encode for tumor-killing or -suppressive proteins, opening a promising new avenue for gynecologic cancer nanomedicine.[240] Recent work has described the first protein-coding, nanoparticle-mediated mRNA therapy for metastatic ovarian cancer.[241] Follistatin mRNA was encapsulated within LNPs and administered intraperitoneally to a xenograft model of metastatic ovarian cancer using luciferase-expressing ES-2 cells in athymic $FoxN1^{nu}$ mice. While the LNPs homed to tumor sites in biodistribution studies, the LNPs reduced tumor burden in combination with cisplatin, indicating a potential synergistic lethal effect. While this research is an exciting step forward in the application of mRNA therapies to treat gynecologic cancers, it leaves room for continued research toward a more efficacious stand-alone mRNA therapy, such as with powerful tumor suppressive (i.e., P53, PRB) or proapoptotic (i.e., BAX, BMF) cargo.[242−244]

LNPs have also been engineered to deliver CRISPR/Cas9 gene editing machinery to treat ovarian cancer by coencapsulating Cas9 mRNA and sgRNA targeting PLK1.[245] Additionally, these LNPs were surface-functionalized with antibodies for the epidermal growth factor receptor, which is overexpressed on ovarian cancer cells. In a xenograft model of metastatic ovarian cancer using athymic $FoxN1^{nu}$ mice and mCherry-expressing OVCAR-8 cells, the targeted LNPs decreased tumor burden and improved overall survival following intraperitoneal administration. While PLK1 gene editing proved successful in this application, this work also opens the door for precision medicine in gynecologic cancer treatments, allowing for the nontoxic delivery of sgRNAs for patient-specific oncogene mutations or the delivery of sgRNAs that use patient-specific mutations to induce synthetic lethal interactions.[246]

NANOPARTICLES AS INTRAPERITONEAL GYNECOLOGIC CANCER THERAPIES

Late-stage ovarian and endometrial cancers often metastasize within the peritoneal cavity, forming widespread tumor nodules on peritoneal surfaces and causing the accumulation of malignant ascitic fluid. Traditional intravenous delivery of nanoparticles is limited in these settings due to first-pass hepatic clearance and inadequate peritoneal penetration. As a result, intraperitoneal nanoparticle delivery has emerged as a targeted strategy to improve therapeutic concentration directly at peritoneal lesions of gynecologic cancers.

One recent study compared the intraperitoneal delivery of albumin-bound paclitaxel with polymer micelle-encapsulated

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paclitaxel in two xenograft models (SKOV-3 and OVCAR-3) of metastatic ovarian cancer in athymic FoxN1^{nu} mice.[247] Both formulations decreased tumor burden and increased survival compared to a saline control; however, the micelles achieved the most sustained levels of paclitaxel within the disseminated tumors, underscoring the importance of formulation-dependent pharmacokinetics, even within the intraperitoneal space.

Another recent study investigated intraperitoneal delivery of a doxorubicin prodrug nanoparticle. Upon conjugation to a cathepsin B-specific cleavable peptide (FRRG), doxorubicin self-assembles into nanoparticles (FRRG-DOX) upon formulation with Pluronic F68, and within the intracellular endosome, cathepsin B cleaves the peptide residues to release active doxorubicin.[248,249] In cathepsin B-overexpressing SKOV-3 cells, FRRG-DOX nanoparticles decreased cellular viability and the IC_{50} compared to free doxorubicin. Despite these promising results *in vitro*, the FRRG-DOX nanoparticles were only tested *in vivo* in a xenograft model of peritoneal colon cancer metastases, where their intraperitoneal administration demonstrated significant tumor regression and survival extension while decreasing off-tumor delivery in the liver and spleen, compared to soluble doxorubicin. In future, these cleavable prodrug nanoparticles should be evaluated in an immunocompetent model of ovarian or endometrial metastases within the intraperitoneal cavity.

Additionally, active nanoparticle targeting has been combined with intraperitoneal administration to enhance therapeutic delivery to disseminated ovarian tumor nodules. Calcium phosphate nanoparticles (Figure 3) were loaded with doxorubicin and modified with a PEGylated arginylglyclyaspartic acid (RGD) peptide motif (RGD-CaPO/Dox) to provide synergistic tumor cell killing: the PEG moiety shields nanoparticles from nonspecific protein adsorption; the RGD peptide targets the overexpressed integrin $\alpha v\beta 3$ on ovarian tumors; doxorubicin induces endoplasmic reticular stress and high intracellular calcium levels, and the calcium-based nanoparticles further raise intracellular calcium to the point of tumor cell apoptosis.[250] In a model of intraperitoneal ovarian metastases with luciferase-expressing SKOV-3 cells in BALB/C nude mice, intraperitoneally injected RGD-CaPO/Dox nanoparticles colocalized with tumors for up to 72 h and extended survival and reduced tumor luminescence compared to nontargeted, empty CaPO nanoparticles and soluble doxorubicin. These promising preclinical results emphasize the versatility that nanoparticle-based therapies can provide for the treatment of gynecologic cancers with rational engineering of their structure, cargo, and surface properties, coupled with potent delivery via intraperitoneal injection.

Overall, these findings suggest that intraperitoneal nanoparticle delivery provides more direct access to metastatic gynecologic tumors and enhances the efficacy of many therapeutics compared to when they are administered intravenously. When choosing this intraperitoneal delivery route for future studies, researchers should consider the effect of ascitic fluid volume on nanoparticle dilution and thus dosing regimens. Clinically, late-stage ovarian cancer patients have been reported to have between 1 and 8 L of ascitic fluid during the progression of their disease; depending on a patient's specific ascitic burden, they may need to receive a higher dose of an intraperitoneally delivered nanomedicine. Very few studies have explicitly explored the dilution of nanoparticles within ascitic fluid; however, it has been shown that nanoparticle uptake within cells *in vitro* is greatly impeded after nanoparticles have been incubated in human ascitic fluid *ex vivo*, highlighting one more design constraint that must be accounted for when engineering nanomedicines for late-stage gynecologic tumors.[251]

GENERATING AN ANTITUMOR IMMUNE RESPONSE

While traditional cancer therapies, such as chemo- and radiotherapeutics, aim to kill cancer cells by inducing apoptosis via DNA repair and cell division pathway disruption, a new class of therapies have been designed to attack cancer cells by activating the phagocytic and inflammatory mechanisms of the immune system. In recent years, immunotherapies have led to complete tumor eradication and durable remission in cancers such as melanoma, lymphoma, and leukemia, but have largely failed to provide meaningful results in gynecologic cancers, especially ovarian cancer.[252] This is a consequence of highly immunosuppressive, or "cold," tumor microenvironments (TME) within gynecologic cancers (Figure 2).

One promising therapeutic avenue to improve the response of gynecologic cancers to immunotherapies is by counteracting the immunosuppressive TME through the production of pro-inflammatory, antitumor cytokines.[253−256] While this is an attractive strategy, efficacy has been limited in previous clinical trials due to severe toxicity; the cytokines must be delivered as recombinant proteins and therefore face rapid degradation in physiological environments, meaning that toxic large quantities must be infused to confer therapeutic benefits.[257] Promisingly, the encapsulation of recombinant IL-12 protein within LbL nanoparticles has been shown to successfully drive immune infiltration in a syngeneic model of peritoneal metastases using HM-1 ovarian cancer cells and B6C3F1 mice. Additionally, body weight measurements throughout treatment indicated that cytokine-associated toxicity was not observed following intraperitoneal administration of IL-12 LbL nanoparticles.[258] While IL-12 is not FDA-approved for the treatment of cancer, this LbL nanoparticle approach demonstrates significant potential for clinical translation to decrease the adverse toxicity of FDA-approved IL-2 and interferon α (IFNα) protein therapies.[259]

To circumnavigate the toxicity associated with recombinant protein cytokines altogether, PEG nanoparticles have also been surface-functionalized with folic acid to codeliver IL-12 plasmid DNA (pIL12) and a PD-L1 inhibitor (iPDL1).[260] The latter was included because IL-12 induces IFN-γ release, leading to increased PD-L1 expression on tumor cells and inhibition of the immune system against the tumor cells.[261] Following intraperitoneal administration in a syngeneic murine model of peritoneal metastases using ID8 ovarian cancer cells (the strain of mice used in this study was not specified; however, the ID8 cell line was derived from C57BL/6 mice), folate-targeted pIL12-iPDL1 nanoparticles inhibited tumor growth and ascitic fluid development, demonstrating the efficacy of both folate receptor targeting and the synergistic effect of IL-12 upregulation and PD-L1 inhibition. Targeted pIL12-iPDL1 nanoparticles also did not significantly increase serum levels of IL-12 nor IFN-γ, demonstrating that while nanoparticles led to higher tumor concentrations of these immunoeffectors, they reduced the potential for an adverse systemic inflammatory response. However, as previously mentioned, these results should be corroborated in mice with a folate-depleted diet to remove the interference of dietary folate on the expression of folate receptors on tumor cells.

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Table 2. Nanoparticle- and Mutation Target-Based Clinical Trials in Gynecologic Oncology[a]

Category	Identifier	Title	Year	Stage	Disease	Intervention
Nanoparticle-based therapies	NCT03742713 (previously NCT0371243)	Efficacy Study of CPC634 (CriPec Docetaxel) in Platinum Resistant Ovarian Cancer (CINOVA)[273,274]	2018–2020	Phase IIa	Advanced epithelial ovarian cancer	CPC364 (Polymeric micelle- encapsulated docetaxel)
	NCT00753740	Efficacy Study of Maintenance IT-101 Therapy for Ovarian Cancer Patients[276]	2008–2010	Phase II	Platinum-sensitive ovarian cancer	IT-101 (cyclodextrin-PEG polymer encapsulating camptothecin)
	NCT01591356	EphA2 siRNA in Treating Patients With Advanced or Recurrent Solid Tumors[278]	2015 - present	Phase I	Advanced or recurrent solid tumors	Liposomes encapsulating EphA2 siRNA
	NCT05739981	Phase II IMNN-001 (Also known as GEN-1) on SLL With BEV and NACT, Newly Diagnosed Advanced Ovarian, Fallopian Tube or Primary Peritoneal Cancer (MRD)[279]	2023 - present	Phase I/II	Advanced ovarian, fallopian tube, or primary peritoneal cancer	Chemotherapy and bevacizumab in combination with IMNN-001 (Lipopolymer encapsulating IL-12 plasmid)
Targeted/precision therapies	NCT04065269	ATr Inhibitor in Combination With Olaparib/Durvalumab (MEDI4736) in Gynaecological Cancers With ARId1A Loss or no Loss (ATARI)[282]	2019 - present	Phase II	Relapsed, ARID1A-deficient gynecologic cancers	Ceralasertib (ATR inhibitor), alone or in combination with Olaparib (PARP inhibitor)
	NCCH1615	Trastuzumab Deruxtecan for Human Epidermal Growth Factor Receptor 2–Expressing Advanced or Recurrent Uterine Carcinosarcoma: The STATICE Trial[283]	2023	Phase II	Advanced or recurrent HER2-expressing uterine carcinosarcoma	Trastuzumab deruxtecan (antibody-drug conjugate; delivers topoisomerase I inhibitor and targets HER2)
	NCT03675893	RESOLVE: Abemaciclib + Letrozole ± Metformin or Zotatifin in Endometrial or Low-Grade Serous Ovarian Cancer[284]	2018 - present	Phase II	ER-positive endometrial cancer and low-grade serous ovarian cancer	Combination of abemaciclib (CDK inhibitor), letrozole (aromatase inhibitor), metformin (glucose production inhibitor), and zotatifin (eIF4A inhibitor)
	NCT05761951	Phase 2 Study Evaluating the Efficacy of the Combination of DKN-01 (DKK1 Inhibitor, Leap Therapeutics) and Pembrolizumab in the Treatment of Advanced or Recurrent Endometrial Cancer[285]	2023 - present	Phase II	Advanced or recurrent endometrial cancer with a Wnt/β-catenin activating mutation	DKN-01 (DKK1 inhibitor) in combination with pembrolizumab (monoclonal antibody targeting PD-1)

[a]An overview of select past and current clinical trials involving nanoparticle or precision medicine approaches for gynecologic cancers, including endometrial, ovarian, uterine, and fallopian tube malignancies (PEG, polyethylene glycol; EphA2, Ephrin type-A receptor 2; siRNA, small interfering RNA; IL-12, interleukin 12; ATR, ataxia telangiectasia and Rad3-related gene; PARP, poly(ADP-ribose) polymerase; HER2, human epidermal growth factor receptor 2; CDK, cyclin-dependent kinase; eIF4A, eukaryotic translation initiation factor 4A; DKK1, Dickkopf-1 gene; PD-1, programmed cell death protein 1).

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One hallmark of the immunosuppressive ovarian, endometrial, and cervical cancer TMEs is the high presence of tumor-promoting TAMs and M2-polarized macrophages.[262−265] These macrophages enhance the development of tumor extracellular matrix and angiogenesis, compared to the antitumor properties of M1 macrophages, which phagocytose cancer cells and trigger antitumor inflammatory responses.[266,267] As such, one method of reversing the immunosuppressive TME is repolarizing TAMs into M1 macrophages. This has been demonstrated using mannose-decorated polymeric nanoparticles (MnNPs) (Figure 3) to deliver siRNA for the inhibitor of nuclear factor κBα (iNF-κBα) to target CD206 on TAMs.[268−270] After intraperitoneal administration to C57BL/6 mice bearing intraperitoneal ID8 ovarian tumors, MnNPs decreased the M2:M1 macrophage ratio within murine ascitic fluid and reduced tumor burden without evidence of systemic toxicity. Additionally, the mannosylated carriers decreased ascitic fluid development in tumor-bearing mice, positing potential synergistic effects of iNFκBα siRNA with MnNPs to improve patient quality of life during ovarian cancer treatment.

Furthermore, resiquimod is a toll-like receptor agonist that can induce macrophage polarization toward an M1 state through the activation of the NFκB pathway.[271] To address the systemic toxicity of resiquimod, liposomes have been designed to facilitate its delivery to ovarian cancer TAMS and avoid systemic circulation via intraperitoneal dosing.[272] In a syngeneic model of peritoneally metastasized ovarian cancer using GFP- and luciferase-expressing ID8 cells in C57BL/6 mice, combination therapy of resiquimod-liposomes and PD1 blockade appeared to be equally or more effective at tumor clearance compared to soluble resiquimod and PD1 blockade treatment. Additionally, the liposome+blockade-treated mice were rechallenged with tumors 250 days later, and all mice prevented engraftment for up to 50 days, suggesting that this treatment results in long-term, protective immunity against ovarian cancer cells. These results are especially promising in their application to other hard-to-resect cancers, such as uterine and cervical cancer.

ADVANCING NANOPARTICLES TO THE CLINIC: PAST AND ONGOING CLINICAL TRIALS IN GYNECOLOGIC ONCOLOGY

Building upon promising results from preclinical studies, researchers have begun translating nanoparticle-based therapies for gynecologic cancers into clinical trials, aiming to bring these innovative drug delivery approaches to patients (Table 2). As the transition to clinical trials progresses, researchers face new challenges in scaling up these therapies and ensuring consistent, reproducible results in patient populations with heterogeneous tumors. By exploring the insights gained from preclinical studies and addressing obstacles in the clinical setting, such as metastatic spread and poor tumor vascularization, these trials are a critical next step in advancing nanoparticle therapies for gynecologic cancers from the laboratory to real-world applications.

The majority of nanoparticle-based clinical trials for gynecologic cancers involve the encapsulation of small-molecule drugs. A Phase IIa trial in the Netherlands is investigating the response rate of CriPec docetaxel, a polymeric micelle-encapsulated formulation of the drug, against platinum-resistant ovarian cancer.[273,274] While 35% of patients had stable disease at first evaluation, the trial was stopped prematurely due to gastrointestinal adverse events in many participants. The intratumoral accumulation of this micellar docetaxel formulation was also studied compared to free drug in patients with solid tumors; CriPec docetaxel resulted in higher intratumoral drug concentration and had a lower peak plasma concentration, underscoring the tumor-homing capabilities of nanoparticles.[275] Another withdrawn study sought to determine the efficacy of maintenance IT-101 therapy for delaying the progression of platinum-sensitive ovarian cancer.[276] IT-101, also referred to as CRLX101, is a cyclodextrin-PEG polymer that self-assembles into nanoparticles and encapsulates camptothecin, an inhibitor of DNA topoisomerase I.[277] CRLX101 has also been investigated in a Phase II study in combination with bevacizumab, leading to an improvement in both progression-free survival and overall response rate of recurrent ovarian cancer.

Other nanoparticle-based clinical trials investigate the encapsulation of more modern cargoes, such as nucleic acids. From the Department of Gynecologic Oncology at MD Anderson Cancer Center, promising toxicity studies performed in rhesus macaques led to a Phase I study of liposomes encapsulating EphA2 siRNA to treat advanced or recurrent solid tumors, including ovarian cancer.[278] While this trial is ongoing without posted results, it is expected that EphA2 silencing may slow the growth of tumor cells by reducing the proliferative effects of EphA2. Nanoparticle-mediated nucleic acid delivery has also been investigated clinically to modulate the immunosuppressive tumor microenvironment of gynecologic cancers. A phase II trial is currently recruiting to investigate the efficacy of GEN-1, an IL-12 plasmid encapsulated within a lipopolymer, alone or in combination with chemotherapy and bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), for patients who are newly diagnosed with advanced ovarian, fallopian tube, or primary peritoneal cancer.[279] This nonviral delivery system is formulated with cholesterol, PEG, and polyethylenimine (PEI), and it aims to induce local production of IL-12, a powerful antitumor cytokine, within the ovarian cancer TME. In a previous Phase I study, recurrent platinum-resistant epithelial ovarian cancer patients were treated with GEN-1 and PEGylated liposomal doxorubicin; no dose-limiting toxicities were found, and IL-12 levels were increased in ascitic fluid following intraperitoneal GEN-1 administration.[280]

Despite these promising nanoparticle-mediated results, nanoparticle approaches for gynecologic cancers remain in their infancy at the clinical stage. Currently, the majority of clinical trials in gynecologic oncology are focused on mutation-targeted therapies for precision medicine approaches, which have generated promising improvements in patient survival compared to chemotherapies alone (Table 2). While we have discussed many therapeutic cargoes that are currently undergoing preclinical studies for gynecologic cancer nanomedicines, perhaps one avenue for advancing nanoparticle drug carriers clinically is to focus on encapsulating some of the mutation-targeting therapeutics that are currently under clinical investigation.[281]

CONCLUSIONS AND FUTURE DIRECTIONS

The drug delivery benefits conferred by nanoparticles have allowed researchers to preclinically circumvent specific delivery challenges associated with gynecologic cancers, including decreasing the systemic toxicities of chemotherapeutics, reversing cellular chemoresistance, mediating efficient delivery

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of nucleic acids, improving intraperitoneal drug retention, and regenerating antitumor immune responses. Alas, there is still much ground to cover in the development of nanoparticle treatments for gynecologic cancers as there is a very limited number of clinical trials investigating these approaches (Table 2). Additionally, while the research endeavors covered in this review offer preclinical hope for the treatment of ovarian, cervical, and endometrial cancers, there are few reports of nanoparticles applied to vaginal and vulvar cancers. While the latter malignancies are the least common gynecologic cancers, they still represent significant portions of gynecologic cancer mortality, and they are often caused by the same HPV infection that induces cervical cancer (Figure 1). Future efforts should be made to test the preclinical efficacy of nanoparticle-based cervical cancer therapeutics on vaginal and vulvar cancers as well.[286,287]

Overall, despite the promise of nanoparticle-based drug development, there remains a relative lack of research specifically investigating gynecologic cancers compared to cancers affecting both sexes or only males. For instance, when reviewing cancer nanomedicine publications over the past decade, there is a disproportionate focus on cancers such as lung, colorectal, and hematological, with significantly fewer studies addressing ovarian, endometrial, and cervical cancers.[288,289] This disparity mirrors broader funding inequities in women's oncology research, where cancers solely affecting women receive substantially less investment than other cancers despite having comparable or higher mortality rates.[290,291] A particularly alarming comparison can be made between ovarian and prostate cancers. While prostate cancer diagnoses are more common, with almost 315,000 new cases predicted in 2025 in the United States compared to 21,000 new ovarian cancer diagnoses, the latter has a dismal 5-year survival rate of 51%, compared to prostate cancer's 97%.[1,292−294] Yet, from 2019 to 2024, ovarian cancer research received between 29 and 44% less funding from the National Institutes of Health (NIH) annually compared to prostate cancer.[295] This underinvestment limits the development of therapies designed for gynecologic cancers from the start, preventing research ranging from basic science to the development of more biologically relevant *in vivo* models to translational therapeutic studies. Addressing these funding and research disparities is essential to advance equitable therapeutic innovation for patients with gynecologic cancers, and while much preclinical research is funded governmentally, such as by the NIH in the United States, it will be imperative in the coming years for researchers to explore nongovernmental funding agencies. Optimistically, the overarching goal of many gynecologic cancer advocacy and awareness organizations is to fund novel approaches for gynecologic cancers that may be deemed high risk to governmental agencies, such as new nanoparticle-based therapies.

Additionally, a major barrier to the efficacious treatment of gynecologic cancers is early detection, as these cancers often exhibit nonspecific symptoms, such as pelvic pain, bloating, vaginal bleeding or spotting, and changes in urination. These symptoms, if present at all, can be clinically misattributed to the menstrual cycle, menopause, or hormonal imbalances, thus leading to late diagnoses for gynecologic cancers, often once the diseases have already metastasized and spread throughout the reproductive system and beyond to the peritoneal cavity and lymph nodes.[296−299] Furthermore, as gynecologic cancers can be difficult to confirm or even detect using traditional imaging modalities, such as ultrasound or magnetic resonance imaging (MRI), many patients undergo invasive tissue biopsies to confirm their diagnoses and/or stage of their disease, some of which may affect their future fertility.[300,301] Recent studies have made efforts to elucidate biomarkers for gynecologic cancers that can be detected in noninvasive "liquid biopsies," such as urine or blood samples; however, these markers, such as CA-125 and folate receptor α (FRα, FOLR-1), are often only minimally expressed during the early stages of these diseases.[302−305] While nanoparticle trafficking to tumor sites via the aforementioned EPR and ATR effects is advantageous for the delivery of therapeutics, these drug delivery phenomena should also be exploited for improving early-stage diagnostics or theranostics.[306,307] For example, nanoparticles that traffic to tumors could be engineered to respond to stimuli within the tumor microenvironment, such as acidic pH or hypoxia, and release a molecule that can be detected within liquid biopsies, such as fluorescent dyes or nucleic acid barcodes.[308−310]

Although cytoreductive surgery is often the first course of treatment for gynecologic cancers, the female reproductive system is anatomically complex, and gynecologic tumors often develop in areas that are not easily accessible by surgery. While these surgeries aim to only remove tumor lesions, surgeons recommend radical operations, such as oophorectomies, hysterectomies, and salpingectomies, which remove the origin organs as well, therefore sterilizing patients.[311] While most gynecologic cancers occur in women of postmenopausal age, a recent study found that for the 20% of gynecologic cancer patients who are of childbearing age, fertility preservation is their utmost concern after receiving their diagnosis.[312] Nanoparticles provide a promising avenue of fertility preservation for gynecologic cancer patients, as they can mediate tumor-specific delivery; in tumors that are unable to be surgically resected, tumor cells could be eradicated without removing any reproductive organs. In the future, it would be interesting for researchers developing nanoparticle-based treatments for gynecologic cancers to consider the effects their nanoparticles have on the fertility of animals used during *in vivo* studies. In animals that survive long-term with treatment, further studies could track the resumption and regularity of their menstrual cycles, the genetic health of their oocytes, or their ability to procreate and produce viable offspring compared to healthy, wild-type controls.

Lastly, several limitations hinder the clinical application of nanoparticles to gynecologic cancers. First, nanoparticle-based therapies for many cancers demonstrate promising preclinical efficacy, yet relatively, few have been approved by global regulatory agencies.[313] Nanoparticle-based therapies struggle in scaling their production from laboratory *in vitro* and *in vivo* batches to good manufacturing practice (GMP)-compliant, large-scale batches that would be required for dosing in clinical trials. GMP also requires stringent control over physicochemical properties, such as nanoparticle size, surface charge, drug- or nucleic acid-loading efficiency, and stability, to ensure batch-to-batch reproducibility.[314−316] Overall, there is a current lack of universally accepted guidelines for regulatory-grade characterization and production of nanoparticle-based therapeutics, and while some researchers have proposed frameworks and processes to accelerate the clinical translation of a nanomedicines, they have yet to be used in clinical practice outside of lipid- or polymer-based nanoparticles (Table 2).[317,318] For now, researchers should focus on nanoparticle technologies that have been granted regulatory approval and

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have been successfully produced, packaged, and distributed on a global scale, such as the nucleic acid-loaded ionizable lipid nanoparticle platform utilized in Pfizer and Moderna's COVID-19 vaccines.

In gynecologic oncology specifically, these challenges to nanoparticle production and regulatory approval are compounded by the relative rarity and heterogeneity of gynecologic tumors, limiting patient populations for trials and subsequently complicating trial design for the evaluation of nanomedicine efficacy across different subtypes of disease and after intravenous versus intraperitoneal administration. Additionally, gynecologic cancer patients recruited for nanomedicine-based clinical trials have failed to respond or stopped responding to prior, FDA-approved treatments, such as cytoreductive surgery, chemotherapy, targeted small-molecule drugs, and immune checkpoint inhibitors. Despite failing to reduce tumor burden, this myriad of treatments could distort the genotype or microenvironment of a tumor in a noncytotoxic way, which could then affect the efficacy of a nanomedicine, especially if that nanomedicine has only been tested as a frontline therapy preclinically. In future, it may be important for researchers to mimic FDA-approved, clinically relevant frontline therapies in their *in vivo* tumor models before administering their novel therapeutic approaches. Overall, collaborative and multidisciplinary efforts will be critical to transition engineered nanoparticle systems from bench to bedside for women suffering from gynecologic cancers worldwide.[319]

ASSOCIATED CONTENT

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current review.

AUTHOR INFORMATION

Corresponding Authors

Kelsey L. Swingle − *Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States;* orcid.org/0000-0001-8475-9206; Email: kswingle@seas.upenn.edu

Michael J. Mitchell − *Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States; Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States; Penn Institute for RNA Innovation, Perelman School of Medicine,, Philadelphia, Pennsylvania 19104, United States; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States; Institute for Immunology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States; Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States; Institute for Regenerative Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States;* orcid.org/0000-0002-3628-2244; Email: mjmitch@seas.upenn.edu

Author

Amanda M. Murray − *Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States;* orcid.org/0009-0000-2124-351X

Complete contact information is available at: https://pubs.acs.org/10.1021/acsnano.5c07748

Author Contributions

A.M.M.: Conceptualization, visualization, writing—original draft, writing—review and editing. K.L.S.: Conceptualization, writing—review and editing. M.J.M.: Writing—review and editing, funding acquisition.

Notes

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VOCABULARY

Gynecologic cancers: malignant tumors that affect the female reproductive system, including ovarian, uterine, vaginal, cervical, and vulvar cancers; Chemoresistance: the ability of cancer cells to withstand the effects of chemotherapy drugs through acquired mutations, also known as multidrug resistance; Active targeting: enabling cell- or tissue-specific drug delivery by modifying the surface of a nanoparticle with specific ligands which interact with receptors on target cells; Passive targeting: a strategy of nanoparticle drug delivery systems which leverages physiological differences between healthy and diseased tissues to concentrate the nanoparticulate at a target location in the body; Immunotherapy: a class of therapeutics which stimulate the immune system to initiate an antidisease response, often used in anticancer regimens

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