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REVIEW

Nanotechnology-Assisted Co-Delivery of Immunotherapeutic Agents for Targeting Ovarian Cancer: Prospects and Challenges

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Background: Ovarian cancer is one of the most lethal gynecologic malignancies, mainly due to late diagnoses and chemoresistance. The immune checkpoint inhibitors and other immunotherapies achieve very low response rates in ovarian cancer. Nanotechnology-assisted co-delivery can helpful by simultaneously delivering multiple therapeutic agents together with their collective advantages.

Methods: This review documents recent advances in nanocarrier-based co-delivery of immunotherapeutics for ovarian cancer, including organic (liposomes, Polymeric nanoparticles, dendrimers), inorganic (gold nanoparticles, mesoporous silica nanoparticles, and metal-organic frameworks), and hybrid (polymer-drug conjugates combined with gene vectors, polymer-lipid nanoparticles) nanocarrier systems. Early clinical trial data show that such systems can reprogram the myeloid cells in ovarian cancer. Key co-delivery strategies covered include combinations of chemotherapy with checkpoint inhibitors, cytokines with adjuvants, and gene therapies with conventional drugs.

Results: Nanocarrier-based co-delivery enables synergistic therapy by simultaneously targeting tumor cells and the immune microenvironment. The co-delivery of chemotherapeutics with immune checkpoint inhibitors promotes antigen expression by relieving immune suppression within the tumor microenvironment, hence improving the subsequent immune activation while increasing the infiltration of T-cells. Similarly, nanoparticle delivery of immunostimulatory cytokines produces local immune activation with reduced systemic toxicity, and gene-editing nanotherapies have also emerged.

Conclusion: Nanotechnology-assisted co-delivery strategies overcome the immunotherapy limitations in ovarian cancer. Preclinical and early clinical outcomes are encouraging, with some challenges in safety, synthesis, and regulatory concerns. Continued innovation in biodegradable nanocarriers and rigorous clinical evaluation are crucial to fully realize the clinical impact in ovarian cancer.

Keywords: ovarian cancer, co-delivery, nanotechnology, nanocarriers, immunotherapy

Introduction

Ovarian cancer is one of the deadliest malignancies affecting women worldwide and remains a major health burden.[1–3] It is known as one of the most lethal gynecologic cancers, accounting for approximately 5% of all female cancer deaths on a global scale.[1,4] A key reason for such a high mortality rate is the inability to be detected until it has spread beyond the ovaries.[5] Due to the lack of reliable early symptoms and effective screening tools, about 70–75% of ovarian cancer cases are diagnosed at a late stage, where prognosis is very poor, with only around 30% five-year survival.[5–7] Another major clinical challenge posed by this disease is its high rate of recurrence and chemoresistance.[8–11] The current standard treatments can initially produce remissions in a majority of patients.[8] Over 80% of women with late-stage ovarian cancer usually achieve a complete or partial response after first-line surgery and chemotherapy.[8,12] However, 70–80% of patients relapse within a few years of initial therapy, with the consequence that the recurrent tumors are often resistant to chemotherapy due to the cancer cells adapting to evade the cytotoxic

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effects of drugs.[13,14] As a result, the treatment options for relapsed ovarian cancer are very limited. The late diagnosis, in combination with frequent relapse and drug resistance, means an unfortunately low chance of long-term survival.[8]

The standard ovarian cancer therapy relies on a combination of surgery and cytotoxic chemotherapy, an approach that has modestly improved survival over the past decades, but it has significant limitations.[15,16] Surgery is essential for reducing the tumors, yet it is rarely curative when solely applied at late stages, as the microscopic tumor deposits almost always remain.[16–18] Additionally, platinum-based chemotherapy, eg, carboplatin combined with paclitaxel, can kill many of the remaining cancer cells but often induces remission.[12] Chemotherapy causes the dying tumor cells to display calreticulin on their surface and secrete ATP and HMGB1, which recruit and mature the dendritic cells (DCs) and the prime T cells.[19,20] Following that, the checkpoint inhibitors enhance the newly activated T cells to kill the cancer cells. Nanocarrier-based co-delivery enhances this synergy by co-encapsulating the chemo and checkpoint antibodies that induce immunogenic cell death.[19,20] Nonetheless, chemotherapy lacks selectivity for tumor cells and causes substantial toxicity to normal tissues with severe side effects.[21,22] Even in the initially successful treatments, drug-resistant clones of cancer cells eventually emerge and lead to the regrowth of tumors.[21] Thus, conventional platinum/taxane regimens often fail to completely eradicate the disease, and recurrence is very usual rather than the exception in ovarian cancer.[8,13] The currently applied diagnosis strategies (including biomarkers, biosensors, tissue biopsy, and serum, as well as imaging techniques) and therapeutic approaches in ovarian cancer[23] are schematically represented in Figure 1.

In recent years, targeted therapies have been introduced to tackle these issues in ovarian cancer, but these also have many shortcomings.[25] For example, the anti-angiogenic antibody bevacizumab and PARP inhibitors have shown benefit in prolonging remission in patients.[26,27] However, PARP inhibitor resistance has been frequently seen via restoration of homologous DNA repair in cancer cells.[8] Furthermore, targeted agents can bring their own toxicities; for example, bevacizumab can lead to hypertension, bleeding, or thromboembolic events, and is typically not recommended for prolonged durations.[8,21] So, conventional therapies and current targeted drugs have many limitations, which underscore the need for new therapeutic modalities that can more specifically eradicate the ovarian cancer cells and overcome resistance mechanisms, without adding undue harm to the patient.

Over the past decade, cancer immunotherapy has revolutionized the treatment of several malignancies by enhancing the immune system of the patients themselves to fight against cancer.[28] Such innovative approaches, like immune checkpoint inhibitors (ICIs), cancer vaccines, and adoptive cell therapies, have achieved remarkable successes in diseases like melanoma, lung cancer, and some types of leukemia.[29] Thus, researchers have tested ICIs in ovarian cancer to reinvigorate exhausted

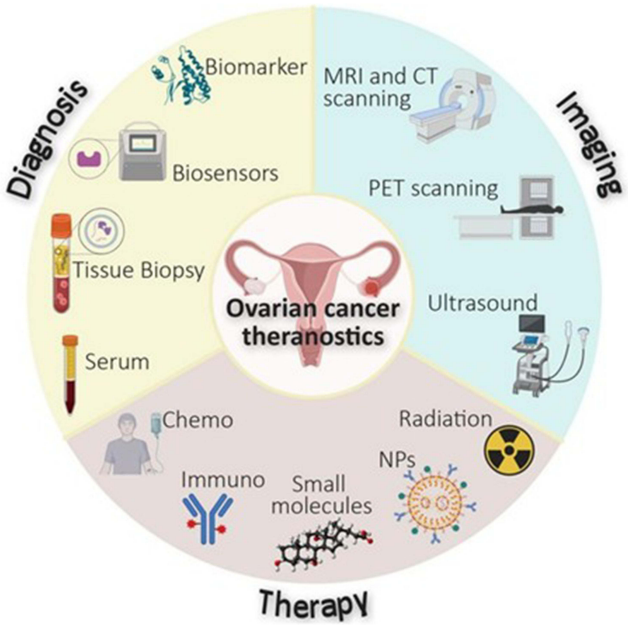

Figure 1 The currently applied diagnosis strategies and therapeutic approaches in ovarian cancer.[24]

T cells and unleash anti-tumor immunity, eg, antibodies against PD-1/PD-L1 and CTLA-4.[30,31] Unfortunately, the ovarian tumors have so far shown only a limited response to such immunotherapies, with objective response rates often in the order of only 5–15%.[32,33] Likewise, adoptive T cell therapies and vaccine approaches have faced challenges, with most studies reporting modest clinical activity. This lack of efficacy of immunotherapy for ovarian cancer is attributed to its immunosuppressive microenvironment,[33] where the effector T cells are countered by a variety of suppressive cells and checkpoints.[34] The nanotechnology-based co-delivery platforms are intended to provide a solution by precisely targeting and releasing combinations of the immunotherapeutic agents. The nanoparticle platforms can co-encapsulate the checkpoint-blocking antibodies, the pro-inflammatory cytokines, adjuvant vaccines, mRNA constructs, siRNA, and chemo-drugs in a nanocarrier.[35,36] Early clinical trial data shows that such systems can reprogram the myeloid cells in the advanced epithelial and ovarian cancers.[37] Many studies are evaluating the nanoparticle vaccine or cytokine-nanogel systems. While the clinical progress faces many challenges, yet it offers innovative ways to simultaneously deliver the immunotherapeutic agents to support the immune system in ovarian cancer.[38] Nonetheless, the immunotherapy for ovarian cancer is still in its early stages, and the limited success so far indicates that ovarian cancer likely requires innovative approaches to activate immune responses and deliver immunotherapeutic agents more effectively to tumor sites.

Given the need for combination therapies and the limitations of the available drug delivery approaches, nanotechnology offers a promising solution to enhance the treatment strategies in ovarian cancer by the application of engineered nanoparticles as vehicles for co-delivery of multiple therapeutic agents directly to the tumor.[39,40] Among the various types of nanotechnology-driven co-delivery platforms are organic, inorganic, and hybrid nanocarrier systems. A co-delivery mechanism via a single nanocarrier can create a combined interplay between treatment strategies, which would be otherwise difficult to achieve with separate administration methods.[22,41] For example, in chemo-immunotherapeutic combinations, a nanoparticle can simultaneously release a chemotherapeutic agent that induces cell death in immunogenic tumors and an immunostimulatory molecule that activates immune cells.[22,42] This approach has the advantages of both chemotherapies to expose tumor antigens and mobilize the T-cells by the immunotherapy to attack the exposed tumor cells, leading to a potentiated immune-mediated anti-tumor strategy. Studies have shown that such nanoscale co-delivery systems can enhance the sensitivity of cancer cells to drugs and lower the required doses with better tumor inhibition.[18,41] This synergistic immunomodulation is especially attractive for ovarian cancer, where mediating a robust immune response within the tumor could actively target the immunosuppressive microenvironment.[22,42]

Another major advantage of nanotechnology-assisted co-delivery is improved drug targeting and controlled release.[39–41] Nanoparticles can be engineered with sizes and surface properties to preferentially accumulate at tumor sites.[18] This leads to a higher percentage of dose to reach the ovarian cancer lesions and less to normal tissues, thereby improving the therapeutic index. Such controlled release of drugs maintains effective drug levels in the tumor sites over time.[18,41] Importantly, co-delivered nanoparticles homogenize the biodistribution of combined agents, which travel together and penetrate tumor tissue together.[41] In practical terms, a well-designed nanoparticle can deliver combination therapy more evenly and efficiently, reaching tumor cells in regions that might be inaccessible to free drugs and releasing the payload in situ to maximize the tumor cell death.[18,41] In addition, the targeted nanocarriers significantly reduce systemic toxicity by avoiding high systemic concentrations of free drugs until the nanoparticle reaches the tumor.[18,22] Along with its advantages in drug delivery, nanotechnology also offers smart approaches to overcome drug resistance and immune evasion, two of the key factors involved in the treatment failure in ovarian cancer. For instance, nanocarriers have been used to deliver immunostimulatory cytokines (eg, IL-12). A study shows that IL-12-loaded nanoparticles concentrated the cytokine in metastatic ovarian cancer nodules and induced a robust accumulation of T-cells by sensitizing the previously refractory tumors to PD-1 blockade and leading to cures in mouse models.[42] Similarly, co-delivery nanoparticles can carry small interfering RNAs or inhibitors to block specific resistance mechanisms within tumor cells.[18] Hence, this strategy leads to the integration of multiple functions in the nanocarriers to hit the tumor on multiple fronts.

Nanotechnology-enabled co-delivery has the potential to tackle the dual challenges of ovarian cancer. It can not only attack the tumor directly but also rally the immune system with greater precision and fewer side effects than conventional methods.[22,42] This review rationally summarizes the prospects and challenges growing in the area of ovarian cancer research for designing multifunctional nanoparticles for co-delivery of chemotherapeutic and immunotherapeutic agents to overcome therapeutic resistance and immune escape and improve survival in a disease that has long been in need of better solutions.

Immunotherapeutic Agents Applied in Ovarian Cancer

As discussed above, ovarian cancer is a highly lethal malignancy often diagnosed at advanced stages, with most patients eventually relapsing after standard surgery and chemotherapy.[5,7,16] These conditions have ignited intense interest in immunotherapy as an alternative treatment approach.[43] A range of immunotherapeutic modalities are under investigation for application in ovarian cancer, including ICIs, immunomodulatory cytokines and adjuvants, adoptive cell therapies, and gene-based strategies, as shown in Figure 2.[44] Below, we discuss each category, highlighting its rationale, current progress in ovarian cancer, and the challenges faced.

Immune Checkpoint Inhibitors (ICIs)

These are monoclonal antibodies to block the inhibitory receptors, such as PD-1, PD-L1, and CTLA-4, and restore T-cell activity against cancer cells.[45,46] Multiple trials in ovarian cancer have reported no significant survival benefit from checkpoint blockade alone, and some were halted early due to lack of efficacy or excessive toxicity.[47,48] To improve the outcomes, combination strategies are being explored, eg, combining ICIs with chemotherapy, anti-angiogenic agents like bevacizumab, or PARP inhibitors have shown slightly higher response rates and prolonged disease control than ICIs alone.[47,48] Unfortunately, these combinations can increase toxicity, with less median progression-free survival benefits.[49] Another approach is dual-checkpoint blockade, eg, an anti-CTLA-4 agent (ipilimumab) added to anti-PD-1 agents has been tested in platinum-resistant ovarian cancer, which showed that some patients achieved partial responses or disease stabilization, while with limited overall survival gains, and severe immune-related adverse events.[49,50] However, selecting the right patients and targets could improve efficacy, eg, tumors with mismatch-repair deficiency or high TMB may respond better.[49] In one study of nivolumab in ovarian/uterine cancers with mismatch-repair deficiency, an ORR of 57% was observed with prolonged progression-free survival in responders.[49] Furthermore, novel bispecific antibodies are also in trials (eg, ivonescimab) to tackle multiple immunosuppressive pathways (PD-1 and VEGF-A) simultaneously.[49,51]

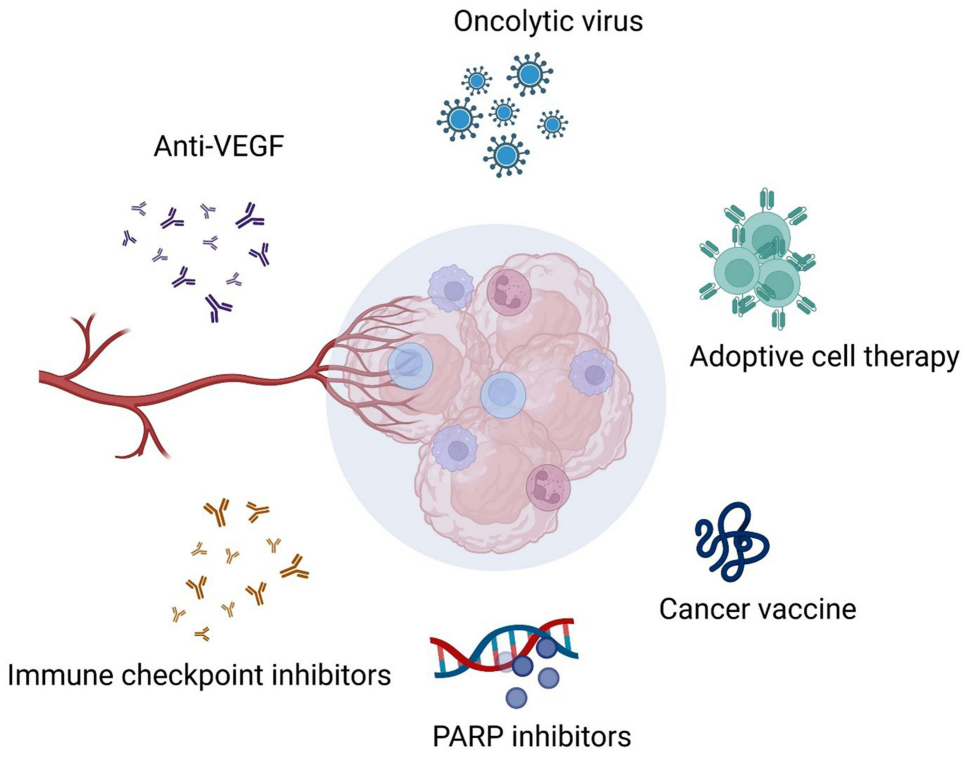

Figure 2 A representation of immunotherapeutic strategies in ovarian cancer.[44]

Cancer Vaccines

Cancer vaccines aim to elicit a targeted immune attack on ovarian tumor cells by exposing the immune system to tumor-linked antigens and are given to cancer patients to induce the tumor-specific T-cells and antibodies.[49,52] Several vaccine platforms, including peptide vaccines, nucleic-acid (DNA or mRNA) vaccines, and dendritic cell-based vaccines, are under investigation in ovarian cancer. The peptide vaccines consist of short peptides derived from tumor-associated antigens mixed with an immune adjuvant.[49,53,54] In ovarian cancer, peptides from the cancer-testis antigen NY-ESO-1 and mutant tumor suppressor p53 have been used in early trials to induce T-cell responses in patients.[55] A peptide called E39, derived from overexpressed folate-binding protein, has shown promising results in Phase I/IIa clinical trials by improving 2-year disease-free survival to 90% in vaccinated ovarian cancer patients.[49,56] However, peptide vaccines alone often yield only transient tumor responses and hence may be most useful as boosters to maintain immunity by their delivery in combination with other therapies.[49]

The DNA vaccines use plasmid DNA encoding a tumor antigen to be taken up by cells to produce the encoded tumor antigen internally.[49] A study used a synthetic consensus DNA vaccine against the follicle-stimulating hormone receptor (FSHR) in the ovarian tumor microenvironment, which successfully broke immune tolerance to FSHR in mice by inducing strong $CD8^+$ and $CD4^+$ T-cell responses and antibodies to significantly delay tumor progression in an aggressive ovarian cancer model.[57] In addition to encoding multiple epitopes, a practical advantage of DNA vaccines is their stability and ease of manufacturing. However, low immunogenicity has long been a concern in humans; thus, strategies like incorporating immune-stimulatory sequences (CpG motifs) or using delivery via viral vectors are being explored to enhance the potency of DNA vaccines.[49] Similarly, the mRNA vaccines consist of messenger RNA encoding one or more tumor antigens, typically formulated in a lipid nanoparticle for delivery.[49,58] In silico studies have identified promising targets, eg, a multi-epitope mRNA vaccine for targeting the CA-125 ovarian cancer antigen (MUC16), which showed its ability to induce strong immune responses.[49,59,60] An mRNA vaccine encoding neoantigens was given to patients after ovarian cancer surgery, resulting in the expansion of T-cells that recognized the tumor.[61] However, a challenge for ovarian cancer is the typically immunosuppressive peritoneal environment.[62] In the DC vaccines, the DCs of the patients are harvested, loaded with tumor antigens ex vivo, and then matured and injected back into the patient.[48] An autologous DC vaccine pulsed with whole tumor lysate given after chemotherapy significantly improved progression-free and overall survival in Phase II clinical trials.[48]

Cytokines and Immune Adjuvants

The tumor microenvironment in ovarian cancer is rich in immunosuppressive cytokines (eg, IL-10, TGF-β) and often lacks pro-inflammatory signals, so adding the stimulatory cytokines or adjuvants can help in tilting the balance toward tumor rejection.[63] A classic example is Interleukin-2 (IL-2), a T-cell growth factor, which was one of the first immunotherapies to show efficacy in metastatic cancer.[64] High-dose IL-2 can induce durable remissions by massively expanding $CD8^+$ T-cells and NK cells, which can attack tumors.[64] However, IL-2 therapy in ovarian cancer has been limited by severe toxicity caused by the capillary leak syndrome and extreme inflammatory reactions.[64] Interleukin-12 (IL-12) is another potent cytokine, which can bridge the innate and adaptive immunity by activating the NK cells and cytotoxic T-cells and inducing the production of interferon-gamma (IFN-γ).[65,66] Recombinant IL-12 was tested in cancer patients (including ovarian cancer) and showed some anti-tumor immune effects, but dose-limiting toxicities were a major hurdle.[67] Many patients experienced high-grade liver toxicity, hematologic suppression, and cytokine release syndrome due to systemic IL-12 exposure.[67] These trials showed that although IL-12 can stimulate immunity, the tumor microenvironment barriers and systemic side effects prevented its applicability in clinical settings.

Beyond interleukins, other cytokines and adjuvants are also being explored in ovarian cancer immunotherapy. An example is interferon-alpha (IFNα), which has been used intraperitoneally in the past to treat minimal residual ovarian cancer due to its antiviral and immunostimulatory properties. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is frequently used as an immune adjuvant because it recruits and matures dendritic cells.[49] Toll-like receptor (TLR) agonists are another class of adjuvants being tested, which can activate dendritic cells and macrophages in the tumor, thereby facilitating a more inflamed microenvironment in ovarian cancer.[49] The cytokine and adjuvant therapies in

ovarian cancer make a viable immunologic option. By supplying activating signals (via IL-2, IL-12, IFNα) or removing inhibitory signals (via TLR agonists), these approaches aim to make the ovarian tumor vulnerable to the immune system.[63] The major challenge in this regard is achieving enough immune stimulation at the tumor to be effective, but not so much systemic spillover that the patient suffers severe toxicity.[63]

Adoptive Cell Therapy and Gene-Based Immunotherapies

Adoptive cell therapy involves the infusion of immune cells engineered outside the body to fight cancer. In ovarian cancer, two main approaches have been studied, including chimeric antigen receptor (CAR) T-cell therapy and tumor-infiltrating lymphocyte (TIL) therapy.[49] CAR-T cells are a kind of living drug, where T-cells are genetically modified to express CAR to target a specific tumor antigen.[68] The CAR T-cell therapy has achieved remarkable success in certain leukemias and lymphomas, but this approach faces major challenges in solid tumors, like ovarian cancer, such as finding the right target antigen.[49,69] On the contrary, the TIL therapy takes advantage of a patient's own T-cells that have been naturally homed to the tumor. This approach involves surgically resecting a tumor deposit, isolating the lymphocytes from it, expanding them massively in the lab, and then infusing the TILs back into the patient after a lymphodepleting chemotherapy regimen.[70,71] This personalized cell therapy has shown success in melanoma and is being applied to other cancers, including ovarian. In the 1990s, a Japanese study reported that patients who received TILs after surgery/chemo had 82% 2-year survival rate compared to those who did not had 55% 2-year survival rate.[71] Additionally, a case (in 2022) described two ovarian cancer patients who had long-term tumor control after TIL therapy combined with an anti-PD-1 checkpoint inhibitor, which highlighted the potential of combination approaches to sustain TIL function in vivo.[71]

On the other hand, the emerging gene-based therapies seek to modulate the immune response to ovarian cancer at the genetic level, either by silencing or editing the genes to enhance the immune function. This technique leverages the modern molecular tools, including small interfering RNAs (siRNAs) and CRISPR, to address the mechanisms of immune evasion in ovarian cancer.[72] The siRNAs are double-stranded RNA molecules that can specifically bind and induce the degradation of a target mRNA to effectively knock down the expression of a gene.[72,73] In ovarian cancer, this strategy has been explored to silence immunosuppressive factors in the tumor and its microenvironment. One prominent target is the ligand on tumor cells, PD-L1, that binds PD-1 on the T-cells to turn them off. A study has demonstrated that folate receptor-targeted nanoparticles loaded with PD-L1 siRNA could suppress PD-L1 expression on ovarian cancer cells, thereby promoting T-cell mediated tumor killing.[73] In the context of immunotherapy, CRISPR can be used to enhance the function of immune cells or sensitize tumor cells.[49] Beyond checkpoints, CRISPR can remove intrinsic negative regulators in T-cells, eg, by dual knockout of DGKα and DGKζ in CAR T-cells, which improved their anti-ovarian cancer activity by enhancing the T-cell receptor signaling. While direct in vivo CRISPR editing of tumors still remains futuristic, some preclinical studies use this technique to screen new target genes in ovarian cancer cells, which, when knocked out, make the tumor more susceptible to T-cells or visible to the immune system.[74] Such genes then become candidates for drug or gene therapy targeting.

Nucleic Acid-Based Cargos

The nanotechnology also enables the delivery of antigens, cytokines, and genome editors to target cells mediated by the nucleic acids (mRNA, DNA) with the benefits of protecting from degradation, cellular uptake, and endosomal escape for cytosolic release.[75,76] The nanoparticles act as the adjuvants to enhance the immunogenicity of the delivered cargos and also enable cytokine gene delivery.[77–79] The gene editing cargos, eg, CRISPR/Cas9, can be delivered via plasmid DNA, mRNA, or the ribonucleoprotein.[20,76] The nanocarriers, such as lipid nanoparticles, liposomes, polymeric nanoparticles, and the exosome-like vesicles, can co-encapsulate the CRISPR/Cas9 components as well as the immunomodulators eg, checkpoint inhibitors, cytokines, and siRNAs. For example, the ionizable lipid nanoparticles have delivered Cas9 mRNA and sgRNA along with an EGFR-targeted ligand. This yielded more than 90% editing and tumor suppression in the ovarian xenografts.[20,80] Currently, such approaches are in the preclinical stages, while some studies have reported that over 80% editing in the ovarian cancer cell models.[20,80] The nanoparticles condense or encapsulate the negatively charged nucleic acids, eg, via the ionizable lipids or cationic polymers, and enter cells through the endocytosis mechanism and the endosomal acidification triggers the cargo release.[76,81] The plasmid DNA moves to the nucleus,

while the mRNA and ribonucleoprotein act in the cytosol.[20,76] Targeted nanoparticles being used in this approach help deliver folate, antibodies, and peptides that can bind the overexpressed receptors on the ovarian cells.[82] This delivery approach confines the cytokines to the tumor microenvironment and boosts the efficacy while reducing the risk of toxicity.

Nanotechnology-Based Co-Delivery Platforms

In the nanotechnology-based co-delivery systems, nanocarriers enable precise control over where and when therapeutic agents are to be released.[83] By encapsulating multiple payloads in a single vector, nanocarriers ensure both agents co-localize at the targeted tumor site instead of dispersing to off-target tissues.[84] This targeted delivery increases drug concentration in ovarian tumor tissue while minimizing systemic exposure and toxicity. In addition, the nanoparticle formulations can also be designed for sustained or sequential release of two drugs, maintaining an optimal timing and ratio for synergy.[84] Studies indicate that adjusting the sequence or schedule of drug release via nanocarriers can further enhance combination efficacy in ovarian cancer.[18] Co-delivery platforms are motivated by the synergistic interactions observed with combination therapy in ovarian cancer. Delivering two or more agents simultaneously can activate multiple anticancer pathways with enhanced activity.[18,84] Nanocarriers keep the therapeutic agents at a fixed, optimized ratio as they travel to and enter cancer cells, promoting synergy and reducing the likelihood of one drug being metabolized or effluxed before the action of the other.[85] A co-delivery approach can overcome resistance mechanisms in ovarian cancer by concurrently attacking distinct survival pathways and preventing cancer cells from easily adapting.[84] Among various types of nanotechnology-driven co-delivery platforms, some of the recent effective examples of organic, inorganic, and hybrid nanocarriers are discussed below. Figure 3 illustrates some of the nanocarrier systems, therapeutic strategies, and targeting mechanisms used in cancer immunotherapy.

Organic Nanocarriers

The organic nanocarrier systems have the ability to exploit the enhanced permeability and retention effect and ligand targeting to accumulate in the ovarian tumors.[86] These nanocarriers are biodegradable and are generally well tolerated due to their less cardiotoxic characteristics.[87] Also, their physicochemical stability is good, which allows longer shelf life. Among the organic nanocarriers, the liposomal co-delivery systems are widely explored in ovarian cancer for their biocompatibility and ability to carry both hydrophilic and hydrophobic drugs.[88] For example, a recent study conducted by Parsa et al formulated a liposome co-loaded with cisplatin (hydrophilic) and doxorubicin (lipophilic) to overcome chemoresistance in ovarian cancer.[89] This co-loaded liposome achieved high encapsulation efficiencies of about 85% and 74% for cisplatin and doxorubicin, respectively, and showed faster pH-sensitive release in the acidic tumor microenvironment. Besides this, another major advantage of their co-delivery approach via liposomes was that it attenuated the typical toxicities of each drug by enabling dose reduction and tumor-targeted release.[89] In another study, Jain et al loaded paclitaxel and topotecan together in PEGylated liposomes decorated with folic acid to target folate receptors.[90] This innovative folate-targeted co-loaded liposome achieved superior in vitro and in vivo tumor killing compared to free paclitaxel and topotecan or non-targeted liposomes due to enhanced cancer cell uptake and the synergistic action of the two drugs.[90] In 2022, Tang et al developed an estrone-conjugated PEGylated liposome co-loaded with paclitaxel and carboplatin, in which the estrone ligand on the liposome binds estrogen receptors on ovarian cancer cells for enhanced targeted delivery.[91] This co-delivery system presented improved pharmacokinetics and tumor targeting, resulting in the inhibition of 81.8% tumor growth in mice while significantly reducing the systemic toxicity as compared to the free drugs.[91] Another notable example is PEGylated liposomes containing kinesin spindle protein siRNA alongside paclitaxel loaded into cationic PEGylated liposomes by Lee et al to overcome mitotic resistance in ovarian cancer.[92] This study showed that the siRNA knocked down kinesin spindle protein while paclitaxel blocked an alternate mitotic pathway (Kif15), completely disabling cell division. The co-delivered liposomes significantly inhibited the proliferation of drug-resistant ovarian cancer cells and reduced the size of tumors in resistant xenografts.[92]

Polymeric nanoparticles (PNPs) present another organic nanocarrier platform for co-delivery in ovarian cancer, which are made from biocompatible polymers, for example, poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG) derivatives, or polysaccharides, and are sub-200 nm carriers.[18,84,93] The PNPs can be formulated as nanospheres or

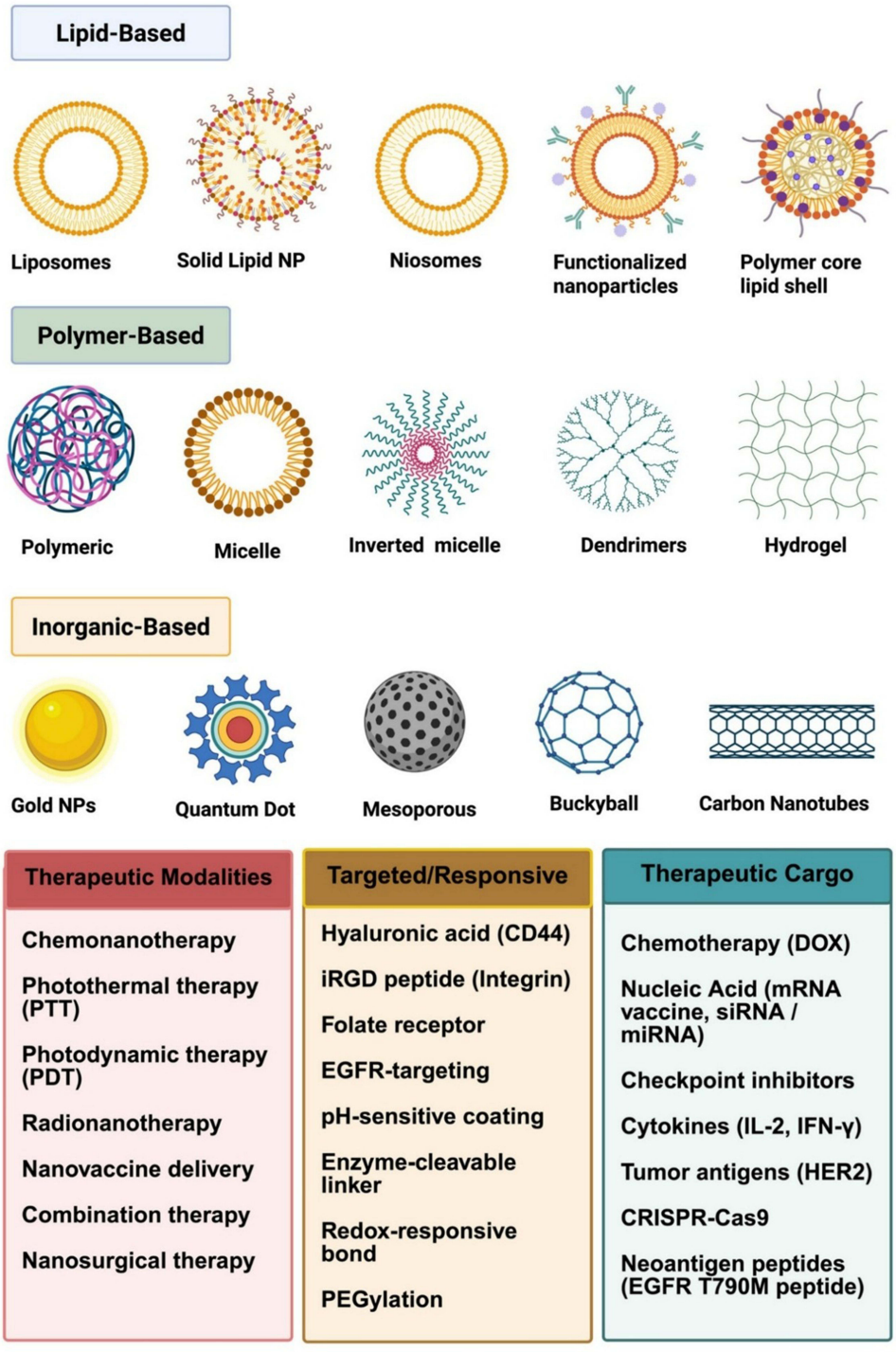

Figure 3 Representation of different nanocarrier systems for co-delivery of immunotherapeutics, along with therapeutic strategies and targeting mechanisms.[38]

hydrogels with the advantage of controlled release of therapeutics, and co-delivery with this platform has yielded promising results in ovarian cancer.[84] For example, Shen et al developed a co-formulation of cisplatin and paclitaxel in an injectable PLGA-PEG hydrogel system, where cisplatin was chemically conjugated as a platinum(IV) prodrug to the polymer, and paclitaxel was physically encapsulated.[94] This dual-drug polymeric system showed synergistic anticancer effects against SKOV3 ovarian cancer cells with significant inhibition of tumor growth in an ovarian xenograft model, with the advantage of markedly reduced side effects compared to free cisplatin and paclitaxel chemotherapy.[94]

Similarly, in a study conducted by Zhao et al, paclitaxel and curcumin were loaded together into an amphiphilic PEI-SA copolymer nanoparticle coated with hyaluronic acid to target CD44 receptors overexpressed on ovarian cancer cells and inhibit the P-glycoprotein drug efflux pump with curcumin.[95] This nano-formulation achieved synergistic cytotoxicity in both chemosensitive and multidrug-resistant ovarian cancer cell lines, and significantly regressed paclitaxel-resistant ovarian tumors in mice.[95]

Another category of organic nanocarriers as a co-delivery platform for immunotherapeutic agents in ovarian cancer is dendrimers, which are highly branched, tree-like polymers with a central core and branches in multiple surface groups.[96] Their well-defined architecture and high functionality make them attractive nanocarriers for co-delivery. Zou et al co-delivered paclitaxel along with borneol, a small-molecule P-glycoprotein inhibitor, using a poly(amidoamine) (PAMAM) dendrimer to reverse paclitaxel resistance.[97] Another example is a combination of chemotherapy with gene therapy co-delivered through a dendrimer, where Shah et al developed a polypropylenimine dendrimer system by conjugating dendrimers with paclitaxel complexed with siRNA. This approach achieved potent anti-tumor activity wherein the siRNA suppressed CD44, sensitizing the cells to paclitaxel-induced apoptosis.[98] Furthermore, the dendrimer platforms have also been applied to deliver drug-siRNA combinations to deal with specific resistance pathways, demonstrating the potential of this platform to co-deliver chemotherapeutics and immunotherapeutic agents simultaneously. However, the organic nanocarriers can trigger complement activation-related pseudoallergy, anti-PEG, or anti-lipid antibodies. For example, the PEGylated liposomes often induce anti-PEG IgM and the complement release, while cationic polymers and lipids may activate NLRP3 inflammasomes via cell stress.[99]

Inorganic Nanocarriers

The inorganic nanocarriers usually depend on the enhanced permeability and retention effect and can include active targeting.[100] For example, gold nanoparticles (AuNPs), mesoporous silica nanoparticles (MSNPs), and metal-organic frameworks (MOFs) have been extensively utilized for delivering combinatorial therapies in ovarian cancer.[101] Their high surface area and facile conjugation of multiple agents make them ideal for co-loading of immunotherapeutics along with chemotherapeutics or other modulators.[102] In ovarian cancer therapy, AuNPs have primarily been studied for photothermal ablation and drug delivery, with emerging work incorporating immunotherapies.[100] For example, a study conjugated anti-PD-L1 antibodies and doxorubicin to AuNPs for combined checkpoint blockade and chemotherapy. This co-delivery system was able to significantly enhance tumor cell killing in vitro and improve antitumor immune responses under the laser irradiation.[100] While this system was utilized in a colorectal model, it illustrates a principle applicable to ovarian cancer, where AuNPs bearing anti-PD-1 agents could localize immunotherapy to the tumor site and simultaneously deliver cytotoxic drugs.

On the other hand, the MSNPs-based nanocarriers have a well-defined porous structure that can encapsulate drug molecules, proteins, and siRNAs.[103] In ovarian cancer, MSNPs are being engineered for co-delivery of immunomodulators for reversing local immunosuppression. A study conducted by Lu et al documents loading the MSNPs with indoximod, an indoleamine 2,3-dioxygenase (IDO) pathway inhibitor, and a PD-L1 siRNA.[104] This approach achieved a synergistic immune effect where indoximod blocked the IDO enzyme, which promotes regulatory T-cells, while PD-L1 gene silencing restored activity of T-cells, resulting in enhanced antitumor responses in preclinical models.[104] In another representative study, Lee et al developed folate-targeted upconversion MSNPs loaded with the T-cell chemoattractant CCL21. This strategy targeted the folate receptor-positive ovarian cancer cells (OVCAR-3) and released CCL21, which successfully induced the migration of T lymphocytes toward the tumor in an in vitro endothelial co-culture model.[105] These studies demonstrate the potential of silica nanocarriers to carry cytokines and/or chemokines into the tumor microenvironment to recruit immune cells.

The MOF-based co-delivery systems have porous crystals made of metal nodes and organic linkers with tunable porosity, which have been applied to deliver combination immunotherapies due to their high loading capacity and stimuli-responsive disassembly.[106] A recent study reported a MOF-based nanoreactor for co-loading of glucose oxidase (GOx) enzyme with an IDO inhibitor, 1-methyltryptophan.[107] The GOx enzyme catalyzes the depletion of glucose and generation of reactive oxygen species, inducing immunogenic tumor cell death and T-cell infiltration. In the meantime, the IDO inhibitor blocks a key immunosuppressive pathway used by tumors to inactivate the T-cells.[107] These examples

demonstrate the diversity of inorganic nanocarriers and their potential applications for co-delivery of the chemotherapeutics with immunotherapeutic agents targeting immune checkpoints (eg, PD-L1), immunosuppressive enzymes (IDO), or by carrying immune stimulants (cytokines, chemokines) for combating the ovarian cancer on multiple fronts, from directly killing tumor cells to simultaneous mobilization of the immune system. However, the inorganic nanocarrier systems usually have low acute toxicity but they have long-term accumulation.[108] They may persist in the tissues and can generate reactive oxygen species and cause DNA damage and chronic inflammation if not cleared. They may activate complement and cause hypersensitivity or immunosuppression.[99] Therefore, standardized testing for chronic toxicity and monitoring of their biodistribution are essential.[99,109] The long-term toxicity issues include biodistribution to the liver, spleen, kidneys, and reproductive organs, and chronic inflammation. Long-term accumulation may also impair the function of organs, eg, gold and silica nanoparticles induce hepatic oxidative stress and nephrotoxicity.[99]

Hybrid Nanocarriers

Hybrid nanocarriers are composite nanoparticles that combine two or more materials, eg, liposomes, polymeric nanoparticles, and inorganic nanoparticles, to reinforce the potential of each component for improved co-delivery of therapeutics, with combined features like improved stability and loading.[110,111] In ovarian cancer immunotherapy, the hybrid nanosystems allow simultaneous delivery of the immunotherapeutic agents, for example, nucleic acids, drug molecules, and proteins in a single platform, with the collective advantages of the combined treatment strategies. A strategy of the hybrid nanocarriers employs polymer-drug conjugates combined with gene vectors for co-delivery of chemotherapy and immune gene therapy.[112] For instance, an acid-responsive polymeric nanoparticle was developed by Xu et al to carry three payloads, including a carboplatin prodrug, a plant-derived cardiac glycoside (digitoxin), and a PD-L1 silencing siRNA.[102] In this hybrid nanocarrier system, the carboplatin prodrug provided direct cytotoxicity by releasing platinum in the tumor cells, while digitoxin induced immunogenic cell death, exposing tumor antigens and releasing danger signals. Whereas the siRNA suppressed the expression of PD-L1 on cancer cells to overcome immune evasion by preventing engagement of PD-1 on T-cells.[102] The hybrid co-delivery systems can also include polymer-lipid nanoparticles by combining the stability of polymeric particles with the excellent encapsulation of the drug by liposomes.[113] Li et al recently utilized a cRGD peptide-decorated lipopolymeric nanoparticle for co-delivery of PD-L1 siRNA and anemoside B4, a natural triterpenoid.[114] The lipid-polymer hybrid provided a stable carrier with flexibility, anemoside B4 was incorporated to promote immunogenic cancer cell death, and the PD-L1 siRNA knocked down the immune checkpoint on cancer cells, to ultimately boost the T-cell response. In comparison to either agent alone in the ovarian cancer models, this combination significantly enhanced infiltration of cytotoxic T-lymphocytes and reduced tumor growth, yielding improved efficacy of this combinatorial immunotherapy approach.[114]

Preclinical and Clinical Progress

In vitro and in vivo Studies

Nanotechnology-driven immunotherapeutic strategies have shown promising anti-tumor activity in controlled in vitro and in vivo experiments against ovarian cancer.[115] A variety of nanoparticle platforms, including liposomes, polymeric nanoparticles, and biomimetic nanovaccines, have been engineered to deliver immunotherapeutic agents (discussed in Immunotherapeutic Agents Applied in Ovarian Cancer) directly to the target cells. These studies aim to overcome the immunosuppressive tumor microenvironment of ovarian tumors, which typically hinders T-cell infiltration and reduces the efficacy of immunotherapy.[36] By concentrating immunostimulatory agents in the peritoneal tumors, nano-immunotherapy strategies seek to boost the anti-tumor immunity.[36] Recent in vitro studies have demonstrated that nano-delivery can effectively modulate the interactions between the cancerous and immune cells. For example, Teo et al showed that folate-targeted polymeric nanoparticles delivering PD-L1-specific siRNA to ovarian cancer cells achieved 45% PD-L1 protein knockdown in vitro, which doubled the susceptibility of cancer cells to cytotoxic T-lymphocyte killing.[72] Similarly, biomimetic nanocarriers coated with tumor-derived vesicles have been used to present a broad array of tumor antigens to CDs, which effectively strengthens the T-cells in vitro.[116] These findings confirm the feasibility of using nanoparticles to manipulate the immune pathways in ovarian cancer cells and immune cell co-cultures. Notably,

in vivo preclinical models have provided the most compelling evidence of the potential of nanotechnology-assisted immunotherapies. In immunocompetent mouse models of ovarian cancer, nanoparticle systems have achieved enhanced tumor targeting, immune activation, and improved survival. Table 1 summarizes some of the recent preclinical studies highlighting their design and therapeutic outcomes.

Translational Challenges and Clinical Trials

Ovarian cancer is still one of the few malignancies that do not have an FDA-approved immunotherapy due to multiple challenges.[121] As already discussed, the immunosuppressive microenvironment in ovarian cancer fails the immune therapies in patients, even when they showed efficacy in mouse models. Various single-agent checkpoint inhibitors have yielded low response rates and no survival benefit in platinum-resistant ovarian cancer.[121] Releasing the inhibitors on immunity is insufficient because, unlike other cancers, baseline immune infiltration is minimal.[36] Thus, a translational challenge is how to effectively enhance the immune responses in ovarian tumors as was done in mice, but within the complex physiology of human patients.[122] Another hurdle is the delivery and safety concerns of nanomedicines in humans. Systemic administration of immune stimulants, eg, cytokines and TLR agonists, can cause off-target inflammation and toxicity. Although the nanocarriers promise more localized delivery, their poor biodegradability and complement immune activation can limit their clinical translation.[43] As such, manufacturing high-quality, reproducible nanoparticles for human use is also non-trivial. These practical issues have slowed the entry of nanotechnology-based immunotherapies into clinical trials, despite strong preclinical validation.[121]

Table 1 Representative Preclinical Nanotechnology-Driven Immunotherapy Studies in Ovarian Cancer

Study Model	Summary	Animal Model	Route of Administration	Reference
ID8 syngeneic ovarian cancer in mice	Large anionic liposomes delivering a TLR7/8 agonist (R848) to TAMs, which repolarized the M2 macrophages to M1 with increased infiltration of $CD8^+$ and $CD4^+$ T-cells. Combined with the PD-L1 antibody, it achieved complete tumor rejection with long-term immunity.	Athymic nude mice, C57/B6 mice	Injected intraperitoneally	[117]
Intraperitoneal ovarian tumor xenograft	Calcium-alendronate nanoparticles engineered to co-display tumor (HER2) and T-cell (CD3) ligands in a bispecific mimic fashion by inducing polyclonal T-cell activation, significantly delaying the progression of the tumor in mice.	NOD/SCID mice	Injected intraperitoneally	[118]
ID8 ovarian cancer in mice	PLGA nanoparticles loaded with CpG (TLR9 agonist) and coated with ID8 tumor cell membrane as antigens to formulate a nanovaccine, which reprogrammed the tumor-linked macrophages to M1 via Gbp2/Pin1–NFκB signaling. This approach inhibited the tumor growth and counteracted chemo-induced immunosuppression.	C57BL/6 mice	Intraperitoneal	[119]
HM-1 ovarian cancer in mice	Liposomal nanoparticles covalently conjugated with IL-12. This study localized IL-12 in peritoneal tumors to promote the infiltration of T-cells and extended the median survival, with 30% of mice achieving complete tumor clearance and developing protective immune memory against rechallenge. In combination with the checkpoint inhibitors, 80% of treated mice eradicated metastatic tumors while resisting recurrence.	HM-1-luc-tumour-bearing mice	Intraperitoneal administration	[36]
Cell therapy in mice with a hydrogel	Injectable hydrogel loaded with engineered immune cells for local immunotherapy, which showed improved polarization of macrophages and activation of T-cells in the peritoneal cavity by bridging the cell therapy with biomaterials.	C57BL/6mice	Intraperitoneal injection	[120]

Abbreiations: TAM, tumor-associated macrophage; CpG, CpG oligodeoxynucleotide (TLR9 agonist); PLGA, poly(lactic-co-glycolic acid).

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Despite these co-occurring challenges, the past few years have seen some encouraging results of the first clinical trials of nanotechnology-based immunotherapy in ovarian cancer.[123] One landmark example is IMNN-001, a gene-mediated IL-12 immunotherapy delivered via a non-viral nanoparticle, consisting of a plasmid encoding IL-12, formulated with a synthetic polymeric lipid complex to be injected intraperitoneally to transfect local cells.[124] In a Phase II trial for a newly diagnosed advanced case of ovarian cancer, adding IMNN-001 to standard carboplatin-paclitaxel chemotherapy led to significantly improved patient outcomes compared to chemo alone.[125] Notably, this combination was well tolerated with no serious immune-related adverse events, due to the localized IL-12 expression from the nanoparticle vector.[124,125] Given this promising Phase II data, a Phase III trial of IMNN-001 is planned, potentially making it the first nanoparticle immunotherapy to become part of the standard of care for ovarian cancer.[124] Another notable example is maveropepimut-S (DPX-Survivac), a lipid-based nanoparticle cancer vaccine encapsulating peptides from a tumor antigen (survivin) and an immune adjuvant.[126] In the Phase II study, it was given with low-dose cyclophosphamide to enhance T-cell activity in advanced recurrent ovarian cancer. The vaccine induced survivin-specific T cells in 87% of patients and achieved a 79% disease control rate. Interestingly, 21% of patients had a partial response with about 30% tumor shrinkage, and some responses lasted over a year, with 66% 12-month overall survival rate.[126–128] While DPX-Survivac is not yet approved, its clinical activity suggests that nanotechnology-formulated vaccines could become a viable immunotherapy approach for ovarian cancer, especially when co-delivered with checkpoint inhibitors or other therapies.

In addition, several other early-phase trials are also exploring nanotechnology-assisted immunotherapeutic concepts in ovarian cancer. For example, investigators are evaluating intraperitoneal nanoparticle drug depots for the release of immune modulators to stimulate local immunity in refractory.[121] Another approach in trials is adoptive cell transfer augmented by nanomaterials like CAR T-cells co-delivered with nanoparticle cytokines to improve their persistence and efficacy.[121] While such studies are in Phase I stages, they exemplify the push to bridge the gap by leveraging nanotechnology to address known hurdles like poor immune cell trafficking and immunosuppressive signals in the peritoneal tumor environment.

Emerging Trends and Challenges

The landscape of nanotechnology-assisted co-delivery for ovarian cancer immunotherapy is rapidly evolving, and new approaches and obstacles are shaping the future. Despite promising preclinical outcomes, the regulatory challenges are a major barrier to translating nanocarrier co-delivery systems to clinical use.[129,130] The existing drug regulations are mainly designed for conventional single-agent therapies and often do not adequately address the complex nature of nanoparticle-based combinations.[130] In addition, demonstrating the bioequivalence is particularly challenging for generic versions of nanocarriers due to their complex structures and behaviours.[131] The regulatory authorities often have to apply existing rules to nanocarriers, which may not fully address the associated risk factors.[38] Hence, there is a growing consensus that new regulatory standards for nanomedicine-based co-delivery systems are to be devised. Luckily, many collaborative efforts are underway to develop such guidelines and emphasize agreement with regulatory agencies during nanoparticle design.[38] Next to the regulatory barriers are the scalability and manufacturing challenges of nanocarrier-driven co-delivery systems. Many of the well-performing nanoparticle formulations in the laboratory settings are difficult to reproduce on large scales with the same quality.[38] For instance, polymeric nanoparticles such as PLGA have shown great promise in delivering combinations of drugs and immune modulators in ovarian cancer models, but they can suffer from batch inconsistencies when scaling up the production on a large scale that affect drug release profiles.[132] To deal with the inconsistencies of the batch processes, continuous manufacturing processes are being explored to provide more uniform production conditions compared to traditional batch methods.[38,132]

With the scientific advancement, several emerging trends and technologies are on the way to revolutionize nanocarrier co-delivery of immunotherapeutics for ovarian cancer, for example, the design of smart multifunctional nanocarriers endowed with the ability to simultaneously perform therapeutic and diagnostic functions.[133] These next-generation nanoparticles are being engineered to respond to the unique characteristics of the ovarian tumor microenvironment.[38] The novel nanocarrier systems can enhance the output and persistence of the transgene even at lower doses.[134,135] For example, the cytidine substitutions in the poly(A) tail of mRNA extended its half-life and yielded higher protein output in cells and mice.[136] Similarly, a 5′ cap analog resisted decapping and produced three times more protein in vivo.[137] Gene

circuits are also among the recent trends that have been encoded into DNA/mRNA to lock the immunotherapy to the cancer cells. For example, Liang et al designed a VPg-capped mRNA with an aptamer for sensing a molecule and bidirectionally tuning two reporters for the identification of a target cell.[138] Similarly, Abe et al utilized split-intein RNA logic triggered by miR-21/miR-302a with ON-switch and leak-suppressing OFF-switch modules.[139] Also, Masaki et al built a hybrid miRNA-responsive mRNA for only cells with the target miRNA expressing protein in vivo, which cut background expression and boosted the ON/OFF ratio.[140]

The innovation of personalized medicine in nanotechnology is another perspective to be fulfilled in the future. Ovarian cancer is heterogeneous, and the tumors are often patient-specific, which may vary in antigen profile and immune landscape. Advances in omics are enabling the identification of patient-specific tumor markers and unique peptides from the tumor of a patient, known as the neoantigens. An emerging strategy is to develop personalized nanovaccines for the co-delivery of tumor neoantigens along with immune adjuvants to the antigen-presenting cells of the patient.[141] Interestingly, the bioengineered nanoparticles carrying neoantigen peptides have already shown the ability to develop strong personalized T-cell responses in preclinical models.[141,142] The circulating tumor DNA may further guide these efforts by revealing mutations and the evolution of the tumor over time.[38] Another transformative trend is the application of artificial intelligence (AI) and machine learning (ML) to facilitate the development of an optimal co-delivery nanocarrier by balancing multi-dimensional factors. In silico models have the potential to accurately predict how a given nanocarrier will distribute in the body or interact with the immune system, allowing researchers to virtually screen formulations before ever developing them.[38] The AI-driven algorithms have already been used to identify nanoparticle designs that improve their pharmacokinetics and tumor accumulation while reducing the off-target toxicity.[143,144] Such computational strategies could be especially useful for co-delivery systems to optimize the simultaneous delivery of two or more therapeutic agents. Furthermore, the ovarian tumors present delivery barriers, including a dense extracellular matrix, immunosuppressive cells, and ascitic fluid, which hinder the penetration of nanoparticles. To overcome this issue, the nanoparticles should be very small and neutral or weakly positive to traverse the extracellular matrix and avoid rapid clearance.[145] In this regard, the co-delivery agents aim to reprogram the suppressive cells. For example, the mannose-coated nanoparticles delivering NF-κB siRNA reprogram to an M1.[145] In addition, the immunocompetent orthotopic and ascites-bearing mouse models can be used along with the patient-derived ovarian organoids with immune cells to test the nanoparticles.[19]

Conclusion

Ovarian cancer poses global severe health concerns and life-threatening risks to women. For the treatment of this deadliest cancer, several immunotherapeutic co-delivery strategies have been developed in combination with chemotherapies, cytokine-adjuvant pairings, and gene-drug therapies, which have demonstrated synergistic anti-tumor effects. Moreover, the early clinical findings are also promising; for example, a recent trial combining an IL-12 gene nanoparticle with chemotherapy has shown a notable improvement in median survival without increasing toxicity. Numerous nanocarrier platforms have been investigated for the co-delivery of therapeutics in ovarian cancer immunotherapy. Among them, the conventional organic nanocarriers offer biocompatible vehicles capable of co-encapsulating chemotherapeutics and immunomodulators, while the inorganic nanocarriers provide stable, multifunctional cores for combination therapy. The hybrid nanocarrier systems combine the advantages of each component to enhance tumor targeting and immune evasion. However, translating the co-delivery of immunotherapeutics into routine clinical care requires addressing regulatory challenges. The existing drug regulations are mainly designed for conventional single-agent therapies and often do not adequately address the complex nature of nanoparticle-based combinations. In addition, demonstrating the bioequivalence is particularly challenging for generic versions of nanocarriers due to their complex structures and behaviors. Additionally, the synthetic scalability is another challenge due to the complexity of combined nanomedicines, but the emerging smart materials and techniques are evolving to further enhance efficacy by tailoring co-delivery strategies to individual patients. Nanotechnology-assisted co-delivery of immunotherapeutic agents represents a transformative approach for ovarian cancer, enabling synergistic multi-modal therapy and offering potential improvements in treatment approaches. The emerging novel strategies in nanomedicine should focus on the multi-pronged immunotherapy payloads and optimized delivery systems to reprogram the tumor microenvironment in ovarian cancer

for a more durable response. In this regard, future directions include integrating the novel immunomodulatory payloads with precisely engineered nanoparticle carriers, and addressing the translational, safety, and regulatory challenges.

Data Sharing Statement

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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