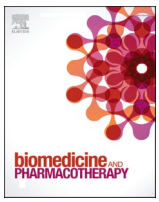
Biomedicine & Pharmacotherapy 165 (2023) 115151

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Review

Targeted drug conjugate systems for ovarian cancer chemotherapy

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ARTICLE INFO

Keywords:
Ovarian cancer
Chemotherapy
Targeted drug conjugates

ABSTRACT

Ovarian cancer is a highly lethal disease that affects women. Early diagnosis and treatment of women with early-stage disease improve the probability of survival. Unfortunately, the majority of women with ovarian cancer are diagnosed at advanced stages 3 and 4 which makes treatment challenging. While the majority of the patients respond to first-line treatment, i.e. cytoreductive surgery integrated with platinum-based chemotherapy, the rate of disease recurrence is very high and the available treatment options for recurrent disease are not curative. Thus, there is a need for more effective treatment options for ovarian cancer. Targeted drug conjugate systems have emerged as a promising therapeutic strategy for the treatment of ovarian cancer. These systems provide the opportunity to selectively deliver highly potent chemotherapeutic drugs to ovarian cancer, sparing healthy normal cells. Thus, the effectiveness of the drugs is improved and systemic toxicity is greatly reduced. In this review, different targeted drug conjugate systems that have been or are being developed for the treatment of ovarian cancer will be discussed.

1. Introduction

Ovarian cancer is the most lethal of gynecological cancers globally [138,41,44,75]. It is estimated that 19,710 women in the United States will be newly diagnosed with ovarian cancer and 13,270 of these women will die of the disease by the end of 2023 [106]. Approximately 1 in 78 women will develop ovarian cancer in their lifetime, and a woman's lifetime risk of dying as a result of the disease is about 1 in 108 [44,81]. Over the past three decades, there has been an increase in cancer survival rates due to advances in screening, diagnosis, and therapy [86]. However, the overall 5-year relative survival rate for ovarian cancer in the United States is 50.8% [106]. This is attributed to its late diagnosis and high recurrence rate [3,32,81]. Non-specific symptoms associated with ovarian cancer which are very difficult to distinguish from less serious abdominal symptoms include abdominal pain, bloating, early satiety, and urinary urgency [100,34,75]. These symptoms, in addition to the lack of routine screening tests for ovarian cancer, make the disease to be easily missed at the early stages, thereby making treatment challenging [138,75,81].

In the United States, ovarian cancer is more common among non-Hispanic White women compared to Hispanic, Asian, or African American women [88]. However, African-American women continue to bear the largest and most disproportionate burden of ovarian cancer of all racial and ethnic groups in the United States, largely due to structural disparities in clinical trial participation and access to cutting-edge therapies [43]. This claim is corroborated by the African American Cancer Epidemiology Study (AACES), which is probably the largest cohort study of African-American women with epithelial ovarian cancer [128]. According to the AACES report, 45% of the women evaluated earn < $25,000 annually, 51% have a post-high school education, and 32% have no standard insurance. Additionally, [104], in their study, reported that non-Hispanic African-American patients have a 26% higher risk of death from ovarian cancer compared with non-Hispanic White patients [104]. Over the past three decades, deaths from ovarian cancer have narrowly dropped [138]. Also, the overall prognosis for ovarian cancer, irrespective of race, is still poor [75]. Thus, many unmet needs in ovarian cancer treatment require urgent attention.

1.1. Overview of ovarian cancer

The pair of ovaries in the adult female reproductive system (Fig. 1) serves the essential roles of ovulation and the production of reproductive hormones [20]. A normal ovary is made up of three major cell types, namely; the epithelial cells, stromal cells, and germ cells. The epithelial cells form the epithelium that envelops the ovary; the germ cells form the ova; and the stromal cells form the ovarian connective and structural tissues. Each of these ovarian cell types can produce benign and malignant tumors, with the tumor being named after the cell type from

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https://doi.org/10.1016/j.biopha.2023.115151
Received 25 May 2023; Received in revised form 30 June 2023; Accepted 7 July 2023
Available online 18 July 2023

which it arises [124]. Accordingly, ovarian cancer is an umbrella name for malignant ovarian tumors that can either be epithelial, germ cell, or stromal tumors [88].

Ovarian cancer, like other types of cancer, can metastasize to other organs, including the liver, lungs, and brain, through the blood and lymphatic vessels [124]. Fig. 2 depicts the four main clinical stages of ovarian cancer. Early stage 1 disease is confined to the ovaries, however as the cancer progresses to advanced stages (stages 2, 3, and 4), the cancer has spread to other body organs. When diagnosed early, greater than 90% of ovarian cancer patients survive for at least five years after treatment [75]. Unfortunately, the majority of ovarian cancer patients are diagnosed when the disease has spread to other parts of the body, including the bowel, lymph nodes, liver, and lungs. Ovarian cancer can also spread within the abdominal cavity, forming nodules on the surface of the peritoneum, including the omentum [124]. Ascites, a common feature of advanced ovarian cancer, is caused by the buildup of fluid in the peritoneal cavity. This occurs due to the obstruction of lymphatic vessels in the diaphragm during the later stages of the disease [124]. According to Ray et al. (2022), malignant bowel obstruction is a prevalent complication of recurrent ovarian cancer and a significant contributor to mortality [119].

Approximately 90% of ovarian cancer cases are epithelial and are highly heterogeneous at both cellular and molecular levels [121,34,82]. Five identified subtypes of epithelial ovarian cancer include low-grade serous, high-grade serous, endometrioid, clear cell, and mucinous carcinoma [3,83]. The most aggressive subtype, high-grade serous ovarian carcinoma (HGSOC) [5], is responsible for the majority of ovarian cancer cases, making epithelial ovarian cancer the most clinically important ovarian malignancy [82,83].

Low-grade serous ovarian carcinomas develop slowly, are confined to the ovary, and resist conventional chemotherapy [124,73]. The most common ovarian cancer type, HGSOC, develops quickly and is rarely confined to the ovary. HGSOC is believed to have initiated from the fallopian tube and metastasized to the ovary [100,88]. The shedding of invasive serous lesions known as 'serous tubal intraepithelial carcinoma (STIC)' from the fallopian tube into the ovary has been commonly reported as the origin of HGSOC ([31,69,83]). A microRNA called miR-181a has been recently identified as being responsible for the transformation of fallopian tube secretory epithelial cells to STIC by inhibiting tumor suppressor genes Rb1 (retinoblastoma 1) and STING (stimulator-of-interferon genes) [69]. The exact mechanism of this transformation is still relatively unknown. While HGSOC originates from the epithelium of the fallopian tube, the other major epithelial ovarian cancer histotypes originate from the ovarian surface epithelium [41].

High-grade serous ovarian carcinoma is primarily clinically distinguished by alterations in TP53, the gene that encodes the tumor protein, p53 [100,88]. In normal cells, p53 is activated when there is DNA damage to stop cell cycle progression and allow damage repair. If the damage is irreparable, p53 triggers the affected cells' death by apoptosis [70]. Hence, the mutation or loss of p53 function as the "keeper of the genome" leads to genomic instability and the accumulation of toxic DNA lesions [42]. TP53 mutations drive oncogenesis by activating pathways such as the Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) pathways. MAPK promotes cell survival and resistance to apoptosis through the activation of PI3K [124, 70].

Approximately 15–20% of women with HGSOC have germline mutations in BRCA1 and BRCA2 proteins, which are involved in the repair of DNA double-strand breaks through the process of homologous recombination [83]. The efficient repair of DNA double-strand breaks is crucial for maintaining genomic stability and preventing harmful mutations. Homologous recombination repair (HRR) is error-free and very essential for maintaining genomic stability; thus, BRCA1/2 proteins act as tumor suppressors. HGSOCs with mutations in BRCA1/2 genes (*BRCAness*) typically have homologous recombination deficiency (HRD) [70,83]. HGSOCs are characterized by *BRCAness* and TP53 mutations, resulting in high copy number alterations. Copy number aberrations and marked genomic instability present in HGSOC make its treatment very challenging [124]. In addition, features of the ovarian tumor microenvironment such as dense extracellular matrix, activated fibroblasts, tumor-associated macrophages, and cancer-associated adipocytes contribute to the development of chemoresistance and metastasis of

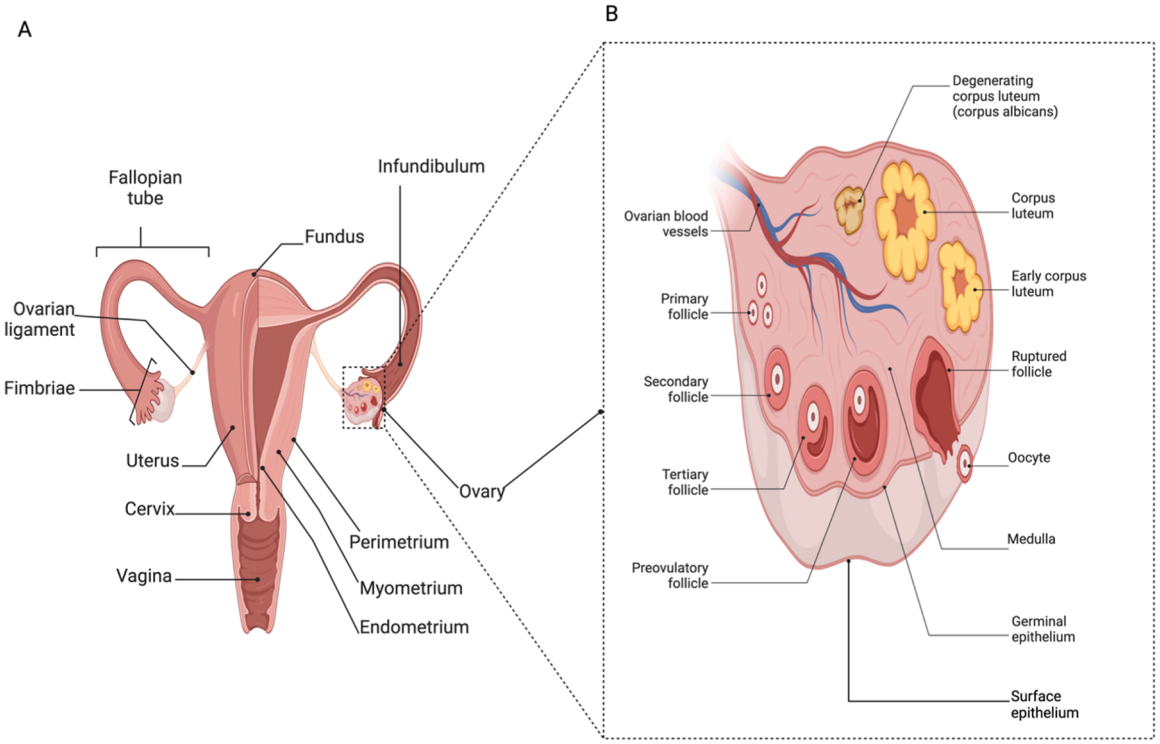

Fig. 1. (A) Anatomy of the female reproductive system (B) Anatomy of the human ovary. Created with BioRender.com.

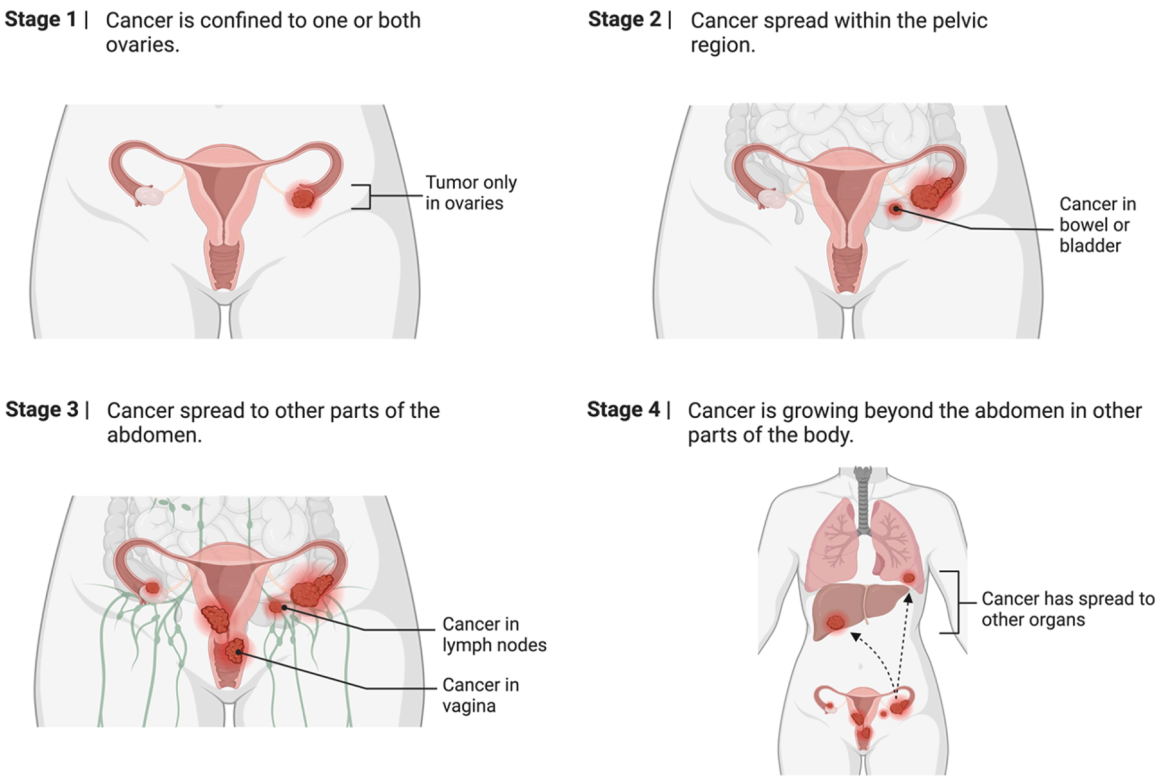

Fig. 2. Ovarian cancer staging. Created with BioRender.com.

ovarian cancer to distal organs [100].

1.2. Treatment of ovarian cancer

1.2.1. Systemic chemotherapy

The primary treatment of ovarian cancer, in most cases, integrates cytoreductive surgery with systemic chemotherapy [3,75]. The standard chemotherapy for the treatment of epithelial ovarian cancer was a single alkylating agent, such as cyclophosphamide and melphalan, until cisplatin/carboplatin combination therapy showed superior results over single agents [83,86]. The current standard first-line chemotherapy for epithelial ovarian cancer is intravenously co-administered carboplatin/cisplatin and paclitaxel, given every three weeks over six cycles [3,83]. Doxorubicin, gemcitabine, irinotecan, and etoposide, 5-fluorouracil, among others, are also approved by the US Food and Drug Administration (FDA) for the treatment of ovarian cancer [78,88]. While most ovarian cancer types are sensitive to chemotherapy, the majority of ovarian cancer patients suffer relapse and die quickly [126,88]. This is attributed to resistance to chemotherapy and the inability to eliminate the disease completely with the available standard treatment [100,22,23].

The treatment of recurrent ovarian cancer is rarely curative, with patients surviving for no more than 24 months after recurrence [75]. Epithelial ovarian cancer that is resistant to the first-line treatment is treated with a sequence of single chemotherapeutic agents like paclitaxel, liposomal doxorubicin, topotecan, and gemcitabine until subsequent progression to advanced stages or unacceptable toxicity takes place [84,88]. To overcome chemoresistance and improve therapeutic efficacy, the combination of two or more chemotherapeutic agents is the most effective strategy for ovarian cancer treatment [78,88]. The idea is that a broader cytotoxic effect can be achieved by simultaneously administering multiple chemotherapeutic agents that work in different ways, thereby decreasing the likelihood of resistance [150,78]. Some examples of combination drugs approved for the treatment of advanced ovarian cancer include cyclophosphamide/doxorubicin and gemcitabine/cisplatin combination regimens [88].

Despite the benefit of combination drugs in improving therapeutic efficiency in ovarian cancer care, pharmacologic or toxicity issues have limited their efficacy. For instance, cisplatin and paclitaxel have a synergistic effect when co-administered, but only if they are given in a specific order, at specific intervals, and specific concentrations [9]. Paclitaxel is used at a much higher dose than cisplatin, although it is about 1000 times more potent than cisplatin. The reason for this is that, at the same dose, paclitaxel has faster clearance than cisplatin [9]. The extensive binding of cisplatin to some serum proteins results in its very slow clearance, resulting in long-term exposure of both normal and cancer cells to the drug. This explains its significant acute and chronic systemic toxicities [9]. The varying pharmacokinetic properties of both drugs make their dosing and scheduling optimization difficult. Their relative lack of water solubility also limits their administration at high doses [145].

1.2.2. Targeted therapy

In addition to chemotherapy, other agents, such as bevacizumab and poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors, that target specific cancer features are approved by the FDA for ovarian cancer treatment [3,83]. Bevacizumab is a monoclonal antibody that has been humanized through recombinant technology. It is designed to target vascular endothelial growth factor (VEGF), which is frequently overexpressed in ovarian cancer [86]. It is added as a third agent to platinum-based chemotherapy as the standard of care for women at high risk of disease progression [3,75]. Additional toxicities related to bevacizumab, when used, include delayed wound healing, hypertension, and bowel perforation [75,83].

PARP inhibitors (olaparib, rucaparib, and niraparib) are used as maintenance monotherapies for recurrent epithelial ovarian cancer in women who have BRCA1 / BRCA2 mutations [105,126,23,86]. BRCA1 and BRCA2 genes are involved in the repair of DNA double-strand breaks through the process of homologous recombination [70]. Ovarian cancers with BRCA1 / BRCA2 mutations depend on error-prone

alternative pathways like the base excision pair (BER) pathway to repair single-strand breaks in DNA damage [101,39]. PARP is a family of DNA-repairing enzymes significantly involved in DNA damage repair via BER [101]. PARP inhibitors kill cancer cells via synthetic lethality when given to patients who have BRCA1 / BRCA2 mutations by blocking the BER pathway and causing an accumulation of toxic double-strand breaks within cancer cells [130,91]. The use of PARP inhibitors has been reported to improve progression-free survival but not overall survival [23]. In addition, the concurrent use of olaparib, the first approved PARP inhibitor, with platinum-based chemotherapy is limited by overlapping hematologic toxicities, which necessitates drug dose reduction (Lhereux et al., 2019a). Furthermore, acquired drug resistance mechanisms such as BRCA mutation reversions and ABCB1 fusions have been described for PARP inhibitors treatment resistance in some patients (Lhereux et al., 2019b).

Pembrolizumab and nivolumab, two immune checkpoint inhibitors, have showed promise in clinical trials with a limited number of ovarian cancer patients when used in combination with PARP inhibitors or bevacizumab [137,175]. However, the response rate of ovarian cancer patients to immunotherapy is still limited, mainly due to the inherently immunosuppressive tumor microenvironment in ovarian cancer [86]. In addition, immunotherapy is not yet approved for use in the treatment of ovarian cancer because of a lack of sufficient experimental evidence of its effectiveness [137]. Treatment-induced hypertension caused by VEGF inhibitors (e.g. bevacizumab) limits their use in hypertensive patients [113]. Also, a small proportion of ovarian cancer patients can benefit from PARP inhibitors since only 5–10% of them carry mutations in the BRCA1 / BRCA2 genes [66]. These limitations of targeted therapies leave chemotherapy as the major option for the treatment of metastatic or advanced ovarian cancer.

The myriads of adverse side effects and non-specific toxicity to normal cells limit the therapeutic efficiencies of existing chemotherapeutics. Strategies that can enhance the therapeutic efficacy of chemotherapeutics and reduce their non-specific biodistribution are therefore needed. The most common of such strategies is the encapsulation of one or more chemotherapeutic agents in nanoparticles for controlled drug delivery to specific sites [86]. Another approach is the development of cytotoxic drugs as targeted drug conjugates, which is the highlight of this review. Similar to nanoparticles, targeted drug conjugates embody Paul Ehrlich's "magic bullet" application in cancer therapy by selectively killing cancer cells while sparing healthy cells [114,15,65]. In these systems, the active drug is presented as a prodrug that remains inactive during its delivery to the site of action and is activated by specific conditions in the targeted site [4,40,64].

1.3. Targeted drug conjugates for ovarian cancer treatment

Drug conjugates are compounds that are formed by chemically joining a drug with another molecule or compound to enhance its therapeutic effect, increase its selectivity, or improve its pharmacokinetic properties [1]. The other molecule can be a protein, peptide, antibody, or other biologic entity that specifically targets a cell or tissue type or a chemical compound that improves drug stability or solubility, or facilitates drug delivery to the target site [1]. Targeted drug conjugates are different from general drug conjugates because of the presence of one or more targeting moieties in their design, and can be broadly categorized into antibody-, peptide-, polymer-, and small molecule-drug conjugates, depending on the targeting molecules that are conjugated with the drug [107]. These conjugate systems exploit one or more specific tumor microenvironment conditions including, acidic pH, enhanced permeability and retention effect, overexpression of glutathione, certain surface receptors, surface proteins, and proteolytic enzymes for their activation and subsequent drug release. Table 1 highlights many target molecules that have been explored for the development of targeted drug conjugates for ovarian cancer treatment.

Folate receptor-alpha (FR-α) is one of the most targeted antigens in the development of targeted drug delivery systems for ovarian cancer treatment [118]. This is because approximately 90% of patients with ovarian cancer overexpress FR-α [150]. In addition, the expression of FR-α increases as the disease progresses; making FR-α an excellent target for advanced disease [150]. FR-α is a cell membrane-bound receptor with a very high affinity for folate and its derivatives, which are transported into the cell via endocytosis [17]. As the density of FR-α surges with cancer progression, it loses its polarized cellular localization and becomes distributed over the cancer cell surface, making numerous FR-α accessible drug-containing macromolecules in the blood circulation [38]. It should be noted that FR-α is also expressed in normal cells, although to a lesser extent (100 – 300 times) compared to cancer cells [38]. This expression in normal cells is limited to the apical surfaces of the organs expressing the receptors except for the kidney [17,74]. These sites are inaccessible to FR-α-targeted drug conjugates administered parenterally because intercellular junctions prevent such molecules from crossing the epithelium [38]. As a result of this specific orientation, FR-α-targeted therapeutics cannot bind to folate receptors on normal cells but only to those on malignant cells [176,94]. Also, it has been reported that folic acid retains its ability to bind to the folate receptor after conjugation with drugs or other carrier systems [176]. It is thus capable of eliciting receptor-mediated endocytosis of FR-α-targeted drug conjugates for selective drug delivery to cancer cells.

Mirvetuximab soravtansine (Elahere™) is an antibody-drug conjugate comprising of an anti-FR-α monoclonal antibody that is linked with DM4, a maytansinoid microtubule inhibitor, through a gluthathione-reducible disulfide linker [52]. The anti-FR-α monoclonal antibody present in mirvetuximab soravtansine targets and binds to FR-α, a cell surface antigen that is commonly overexpressed in epithelial ovarian cancer [150]. The specific binding of the monoclonal antibody with FR-α facilitates receptor-mediated internalization of mirvetuximab soravtansine, followed by cleavage of the disulfide linker and subsequent drug release in the tumor [15]. It received approval in the USA in November 2022 for the treatment of adult patients who have FR-α positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer and have undergone up to three prior systemic

Table 1
Molecular targets and their reported overexpression in ovarian cancer.

Target molecules	Reported overexpression	Reference
Folate receptor-α	60 – 100%	[15]
Sortilin-1	52 – 100%	[25]
Tumor-associated glycoprotein-72	88%	[103]
Cluster of differentiation 70	70%	[135]
Human epidermal growth factor receptor-2	Up to 50%	[99]
Mesothelin	55 – 100%	[15]
Trophoblast-antigen-2	47 – 89%	[111]
Type II sodium–phosphate cotransporter	95%	[15]
Mucin-16	70 – 90%	[15]
Tissue factor	25 – 100%	[15]
Cadherin 6	65%	[134]
Wnt/β-Catenin signaling pathway	16 – 54%	[142]
Lipolysis-stimulated lipoprotein receptor	50 – 70%	[60]
Type-I 15-leucine–rich repeat-containing-membrane protein (LRRC15)	16% of HGSOC	[119]
Nectin-2	50%	[109]
Gonadotropin-releasing hormone receptor	78%	[90,129]
Permeability glycoprotein	~ 0% chemo-naive cells; 8% chemoresistant cells	[46,170]
Nuclear factor erythroid 2-related factor 2 Kelch-like ECH-associated protein 1	95% 72%	[18]
Cluster of differentiation-44	55 – 64%	[61]
Ephrin receptor A2	> 75%	[77]

treatment regimens [52]. Other drug-conjugate systems that have been or are being clinically developed for the treatment of ovarian cancer are highlighted in Table 2.

2. Antibody-drug conjugates (ADCs)

An antibody-drug conjugate (ADC) is a drug conjugate system comprising a cytotoxic agent which is conjugated through a linker with an antibody that targets specific tumor-associated antigens (Fig. 3) [98,114]. Extensive reviews on ADCs for targeted cancer therapy have been done elsewhere ([114,47,65], and [27]), and the readers are referred to them. Chimeric or humanized antibodies, approximately 150 kDa in size and belonging to the immunoglobulin G1 class, are generally used to make ADCs [114,47]. The Fab region, which is responsible for antigen recognition by these antibodies, is also used for the design of smaller

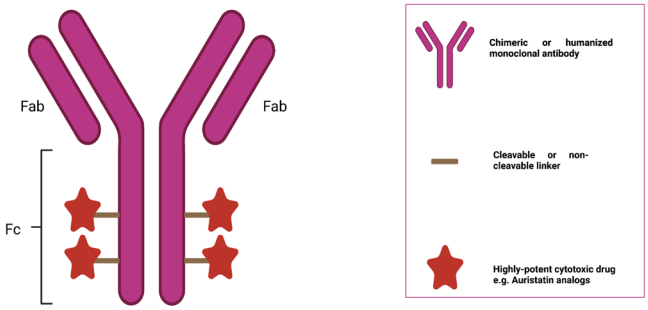

Fig. 3. Representation of an antibody-drug conjugate. Created with BioRender.com.

Table 2
Targeted drug conjugate systems in or through clinical development for the treatment of ovarian cancer.

Conjugate (Cytotoxin)	Target antigen	Linker	Status	ClinicalTrials.gov identifier
Nanoparticle-drug conjugate				
ELU001 (Exatecan)	FR-α	Protease-cleavable	Phase 1/2	NCT05001282
CRLX101 (Camptothecin)	None	Ester bond	Phase 2[c]	NCT01652079
EP0057 (Camptothecin)	None	Ester bond	Phase 2	NCT04669002
Peptide-drug conjugate				
TH1902 (Docetaxel)	Sortilin	Ester bond	Phase 1	NCT04706962
BT5528 (MMAE)	EphA2	Cleavable linker	Phase 1/2	NCT04180371
Small molecule-drug conjugate				
EC1456 (Tubulysin B hydrazide)	Folate receptor	Disulfide	Phase 1[c]	NCT03011320
Antibody-drug conjugate				
Lifastuzumab vedotin (MMAE)	NaPi2b	Maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyl carbamate	Phase 1[c] Phase 2[t]	NCT01363947; NCT01995188 NCT01991210
XMT-1536 (Auristatin F-HPA)	NaPi2b	Dolaflexin platform	Phase 3	NCT05329545
XMT-1592 (Auristatin F-HPA)	NaPi2b	Dolasynthen platform	Phase 1b	NCT04396340
Dato-DXd (Exatecan derivative)	TROP2	Lysosomal enzyme-cleavable tetrapeptide	Phase 2	NCT05489211
XB002 (Auristatin)	Tissue Factor	ZymeLink	Phase 1	NCT04925284
A166	HER2	Valine-citrulline	Phase 1/2	NCT03602079
STRO-002 (SC209)	FRα	DBCO-valyl-citrullinyl-*p*-amino benzyl carbamate	Phase 1	NCT03748186
TORL-1–23	Unknown	Unknown	Phase 1	NCT05103683
AZD5335	Unknown	Unknown	Phase 1/2a	NCT05797168
ASN004 (Auristatin moiety)	5T4	Dolaflexin	Phase 1	NCT04410224
MORAb-202 (Eribulin)	FRα	Maleimido-PEG2-valyl-citrullinyl-*p*-aminobenzyl carbamate	Phase 1/2 Phase 2	NCT04300556 NCT05613088
AZD8205 (novel TOP1i)	B7-H4	Unknown	Phase 1/2a	NCT05123482
IMMU-132 (SN-38)	TROP2	pH-sensitive	Phase 1/2[c]	NCT01631552
SKB264	TROP2	Unknown	Phase 1/2	NCT04152499
Anetumab ravtansine (DM4)	Mesothelin	Reducible SPDB	Phase 1[c]	NCT02751918
Mirvetuximab Soravtansine (DM4)	FRα	Sulfo-SPDB	Phase 2 Phase 3[c] Phase 3	NCT05041257 NCT04296890 NCT04209855
Vobramitamab duocarmazine (Duocarmycin analog)	B7-H3	Maleimido valine-citrulline type	Phase 1	NCT05293496
Tisotumab vedotin (Monomethyl auristatin E)	Tissue factor	Maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyl carbamate	Phase 2[c]	NCT03657043
Enapotamab vedotin (Monomethyl auristatin E)	AXL receptor tyrosine kinase	Maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyl carbamate	Phase 1/2[c]	NCT02988817
CX-2009 (DM4)	CD166	Reducible SPDB	Phase 1/2[c]	NCT03149549
IMGN151 (DM21)	FRα	Cleavable peptide	Phase 1	NCT05527184
PRO1184 (Exatecan)	FRα	Cleavable hydrophilic	Phase 1/2	NCT05579366
CDX-014 (Monomethyl auristatin E)	TIM-1	Maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyl carbamate	Phase 1[t]	NCT02837991
SC-003 (SC-DR002)	Dipeptidase 3	Protease-cleavable linker	Phase 1[t]	NCT02539719
SGN-15 (Doxorubicin)	Lewis Y	Hydrazone	Phase 2[t]	NCT00051584
HKT228 (DM4)	Cadherin-6	Sulfo-SPDB	Phase 1[t]	NCT02947152
SYD985 (Duocarmycin)	HER2	Valine-citrulline	Phase 1[w]	NCT04602117

FRα: folate receptor-α; NaPi2b: type II sodium–phosphate cotransporter; TROP2: trophoblast cell surface antigen 2; HER2: human epidermal growth factor receptor 2; B7-H4: B7 homolog 4; B7-H3: B7 homolog 3; CD166: cluster of differentiation 166; TIM-1: transmembrane protein T-cell immunoglobulin mucin-1; DBCO: dibenzocyclooctyne; PEG: poly(ethylene glycol); SPDB: succinimidyl 4-(pyridin-2-yl)disulfanyl; [c]Completed; [t]Terminated; [w]Withdrawn. *Sources: ClinicalTrials.gov; adcreview.com; NCI's Drug Dictionary*

antibody fragments-drug conjugates [114].

ADCs facilitate the targeted delivery of cytotoxic drugs to cancer cells by selectively binding to a specific antigen that is either exclusively expressed or overexpressed on the surface of cancer cells while having low expression in healthy tissues. [15]. ADCs possess unique characteristics as they are biocompatible proteins with high molecular weight, that exhibit extended plasma circulation and efficient accumulation in solid tumors through the enhanced permeability and retention (EPR) effect [114]. EPR effect is the preferential accumulation of macromolecules in tumors relative to healthy tissues due to leaky vasculature and a defective lymphatic drainage system present within the tumor microenvironment. These two characteristics—leaky vasculature and a faulty lymphatic drainage system—are unique to cancers and distinguish them from healthy tissues, thereby allowing for selective drug delivery to cancer cells [140,35,96]. The leaky tumor blood vessels increase tumor vascular permeability to circulating macromolecules, which are also not efficiently removed from the tumor microenvironment by the defective lymphatic drainage system, thus allowing the macromolecules to passively accumulate in the tumor. In particular, the medulla of the ovary (Fig. 1B) comprises abundant blood and lymphatic vessels [68]. Rapid angiogenesis in the ovarian tumor will therefore present higher tumor vascular permeability, making ovarian cancer prone to targeting by the EPR effect.

2.1. Linker

The primary function of the linker between the monoclonal antibody and the cytotoxic drug in an antibody-drug conjugate (ADC) is to facilitate the selective release of the cytotoxic drug within the tumor environment [12,55]. The linker should have good plasma stability such that the ADC can undergo prolonged circulation without nonspecific drug release and ultimately accumulate in the tumor where selective drug release is facilitated. Linker stability is essential to prevent the premature release of the cytotoxic payload, which could cause off-target toxicity. It has been reported that whether the ADC is internalized or not, the drug release is dependent on the type of linker used, which may be cleavable or non-cleavable [47,55].

Cleavable linkers utilize characteristic tumor properties such as acidic pH, redox, and proteolytic enzymes for the selective release of the cytotoxic drug from the antibody-drug conjugate [55]. The utilization of pH-sensitive linkers is based on the pH gradient between the acidic tumor microenvironment and the general blood circulation (pH = 7.4) [1]. The observed acidity in the tumor microenvironment is a result of energy production by anaerobic glycolysis, a process that leads to the production of lactic acid [21]. Several drug conjugates have been designed using acid-sensitive linkers that contain hydrazone [1]. An example is Mylotarg®, an ADC comprising gemtuzumab ozogamicin conjugated to calicheamicin through an acyl hydrazone linkage [93]. Hydrolysis of the hydrazone in the lysosome (pH ~4) induces the selective release of calicheamicin, which causes cytotoxic double-strand breaks, within the cancer cells [123]. The disadvantage of ADCs that are designed using acid-labile linkers that contain hydrazones, imines, or acetals, is low plasma stability [21,47] which could cause non-specific drug release and systemic toxicity. Mylotarg® was marketed in the US for the treatment of acute myeloid leukemia from 2000 until 2010 when it was withdrawn due to multiple toxicity reports [93]. The instability of hydrazone-containing linkers is believed to have played a role in this [55].

Redox-sensitive linkers, which include disulfide bonds, utilize elevated levels of glutathione within the intracellular environment compared to the plasma [55]. Drugs that are linked by disulfide bonds exhibit resistance to reductive cleavage in the bloodstream due to the comparatively lower concentration of glutathione in the blood (5 μmol/L) as compared to the cytoplasm (1–10 mmol/L) [114]. This differential in reductive potential between the plasma and cytosol facilitates the selective release of the cytotoxic drug in the reductive intracellular environment. Additionally, glutathione concentration in cancer cells is approximately 1000-fold higher than that observed in normal cells [147]. Thus, the site-specific release of drugs in cancer cells is enabled by the use of glutathione-cleavable linkers.

due to low levels of glutathione in healthy tissues. Succinimidyl 4-(pyridin-2-yl) disulfanyl (SPDB), a glutathione-sensitive cleavable disulfide linker used in mirvetuximab soravtansin, prevents cleavage of the ADC in the bloodstream where the glutathione level is low, and on the other hand facilitates cleavage in the cancer thereby enhancing its targeting efficacy [15].

Enzyme-sensitive linkers utilize proteases, predominantly cathepsin B, that are present in the lysosomes of tumor cells to identify and cleave particular peptide sequences within the linker [55]. Cathepsin B is constitutively expressed in all tissues for cellular housekeeping functions [29], and it is localized to the lysosome [13]. Cathepsin B overexpression, as seen in ovarian cancers, is often accompanied by its migration to the plasma membrane where it is secreted into the extracellular environment [13]. Cathepsin B in blood circulation is not active due to the plasma pH and the presence of protease inhibitors in the plasma [160,85]. Normal tissues have very low expression of cathepsin B and the enzyme has often been targeted for enzyme-triggered tumor-specific drug delivery [133,167,172]. Maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate (Fig. 4) is a chemically modified form of the cathepsin B-cleavable dipeptide, valine-citrulline, that is utilized in Tisotumab vedotin to link monomethyl auristatin E (MMAE) to an anti-tissue factor antibody [50]. Following the cleavage of the valine-citrulline dipeptide by cathepsin B, *p*-aminobenzyl carbamate (PABC) derivative of MMAE is released. This is followed by a spontaneous 1,6-elimination of PABC, leaving the free drug molecule and carbon dioxide as the release products [110]. The stability of valine-citrulline in the plasma is higher compared to acid-based linkers, owing to the presence of protease inhibitors. However, upon internalization, valine-citrulline is rapidly hydrolyzed by lysosomal cathepsin B [47].

For ADCs that use non-cleavable linkers, the linker is part of the payload [139]. The release of the cytotoxic drug from such ADC is contingent upon the degradation of the ADC within the lysosome after its internalization [55]. The predominant non-cleavable linkers employed in the synthesis of ADCs are typically of alkyl or polymeric composition, and commonly feature a thioether or maleimidocaproyl moiety [1,114].

2.2. Mechanism of action of antibody-drug conjugates

Most ADCs are designed to target specific internalizing antigens, such as surface receptors, with subsequent internalization of the ADCs, intracellular cleavage of the linker, and subsequent direct release of the drug in the tumor cells to elicit cytotoxicity (Fig. 5) [12,26]. Non-internalizing ADCs, on the other hand, are designed to selectively release the cytotoxic drugs in the tumor extracellular space through the cleavage of the linker by proteolytic enzymes or redox conditions in the tumor microenvironment [114,12]. The liberated drug could then enter the tumor cells by mechanisms such as diffusion and pinocytosis [114]. Some ADCs, in addition to killing cells that express the targeted antigen, also kill neighboring cells that may not express that antigen by "bystander effect" [47]. This happens when the cytotoxic drug molecules are either expelled from the target antigen-expressing cells following internalization and degradation of the ADC or are released from non-internalizing ADCs following the cleavage of the ADC linker within the tumor microenvironment [47]. Further, ADCs also kill tumors by the activation of the immune response through antibody-dependent cellular toxicity or complement-dependent cytotoxicity by tumor-infiltrating immune cells [15,47,58].

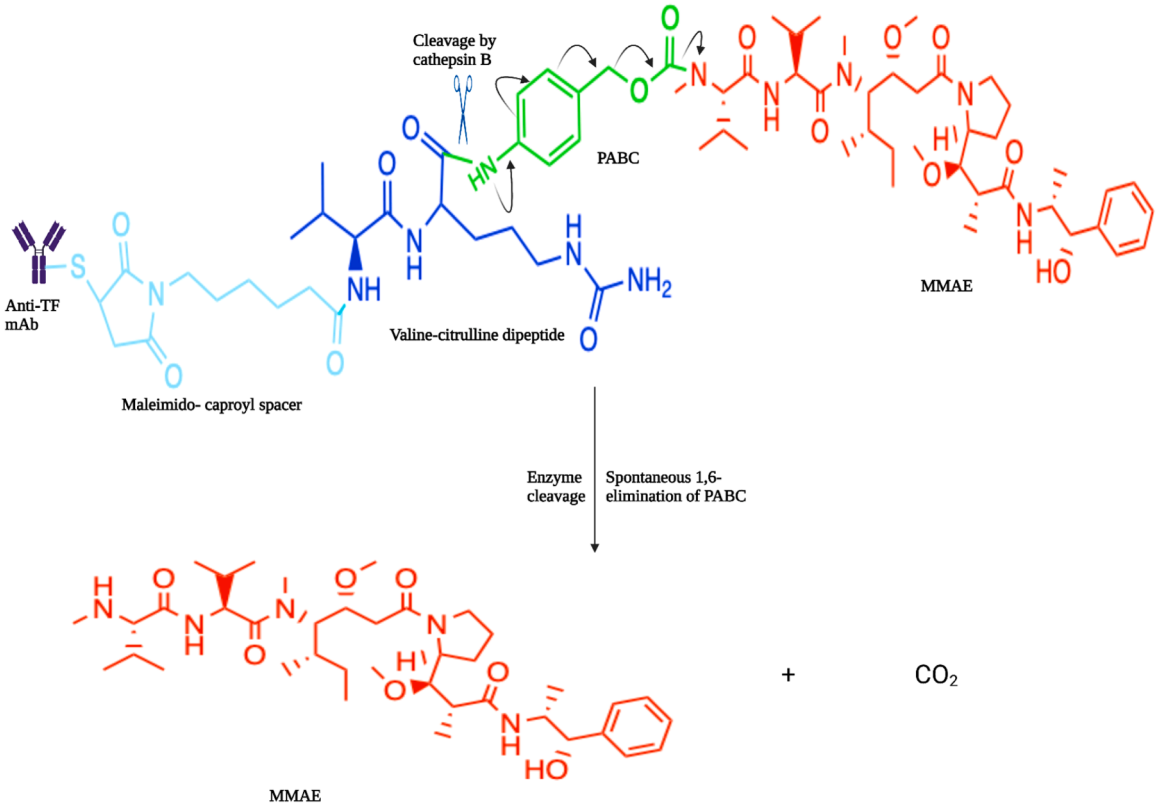

Fig. 4. Representation of the chemical structure of Tisotumab vedotin [50]. The self-immolation of the *p*-aminobenzyl carbamate (PABC) group following the cleavage of valine-citrulline by cathepsin B results in the release of the free drug and carbon dioxide (CO_2).

2.3. Antibody-drug conjugates developed for ovarian cancer

The first FDA-approved ADC for human use was gemtuzumab ozogamicin (Mylotarg) for acute myeloid leukemia in 2000 [36]. More than two decades later, the first ADC for ovarian cancer, Mirvetuximab soravtansine, was approved by the FDA [52]. More than 150 ADCs have now been evaluated in clinical trials [60]; however, the number of clinically tested ADCs for the treatment of ovarian cancer is still limited. About twenty-seven ADCs have been clinically evaluated for the treatment of ovarian cancer since 2003 (Table 2). Out of these, four (clinicaltrials.gov identifiers: NCT0283799; NCT02539719; NCT00051584; NCT02947152) were terminated, and one (clinicaltrials.gov identifier: NCT04602117) was withdrawn from clinical development. Despite this low representation, significant efforts are being made in the preclinical development of novel ADCs for the targeted chemotherapy of ovarian cancer.

While most ADCs in clinical development for ovarian cancer (MIRV, IMGN151, PRO1184, MORAb-202, and STRO-002) target the FR-α antigen, there is a continuous search for newer target antigens to expand the targeting effectiveness of ADCs. Kanda et al. (2023) recently identified the lipolysis-stimulated lipoprotein receptor (LSR) as a new tumor antigen of epithelial ovarian cancer. The overexpression of LSR has been linked with the proliferation and metastasis of different cancer types [60]. Approximately 70% of serous ovarian carcinoma overexpress LSR, and high LSR expression has been correlated with poor prognosis in these cancer subtypes [60]. Kanda et al. (2023) also demonstrated that while LSR is widely expressed in epithelial ovarian cancer patient tissues and cell lines, LSR expression in normal tissues is very low, making LSR a good candidate for an antibody-based therapy against epithelial ovarian cancer. They prepared an anti-LSR mAb and reacted it with maleimidocaproyl-valyl-citrullinyl-PABC-MMAE to yield the LSR-ADC with a drug-to-antibody ratio of 2.8. The LSR-ADC was efficiently internalized within 1 h, and subsequent trafficking to the lysosomal compartment was confirmed by immunofluorescence. The LSR-ADC selectively inhibited the proliferation of LSR-expressing ovarian cancer cell lines (NOVC-7 C and OVCAR3) compared to LSR-negative ES2 cell lines. However, the in vivo cytotoxicity of the LSR-ADC in OVCAR3 and primary patient-derived xenograft models was not the same, although both tumors are highly LSR-expressing. At a dose of 3 mg/kg, significant tumor growth suppression by LSR-ADC was observed in the OVCAR3 and primary patient-derived xenograft models after day 7 and day 21, respectively. This observed slower inhibitory effect of LSR-ADC on the primary patient-derived xenograft models raises concerns about the direct extrapolation of preclinical animal studies to clinical models.

LRRC15, a type-I 15-leucine–rich repeat-containing membrane protein, is another novel ADC target in ovarian cancer [119]. The functional association of LRRC15 with the regulation of cell-cell and cell-extracellular matrix interactions has been established [119]. These are believed to be achieved through LRRC15 interaction with various extracellular matrix proteins such as fibronectin, laminin, and collagen IV, facilitated by its extracellular leucine-rich repeats. Ray et al. (2022) demonstrated that LRRC15 is highly over-expressed in ovarian cancer cells compared to normal ovarian cells; significantly promotes adhesion to mesothelial cells and extracellular matrix proteins, implicating LRRC15 as a potent driver of omental metastasis [119]. They targeted LRRC15 with ABBV-085, an antibody-drug conjugate consisting of an anti-LRRC15 humanized IgG1 antibody linked with MMAE through a protease-cleavable valine-citrulline linker. ABBV-085 showed a dose-dependent reduction in cell viability for LRRC15-expressing OVCAR5 NTC cells but not in cells where LRRC15 has been knocked down. They also showed that therapeutic targeting of LRRC15 led to suppression of both tumorigenesis and metastatic spread in xenograft models of ovarian cancer. ADCs targeting other antigens including, trophoblast-antigen-2 [111], type II sodium–phosphate cotransporter (NaPi2b) [8], cluster of differentiation 70 [135], Wnt signaling receptors [33,95], and nectin-2 [136], have also shown promising activities

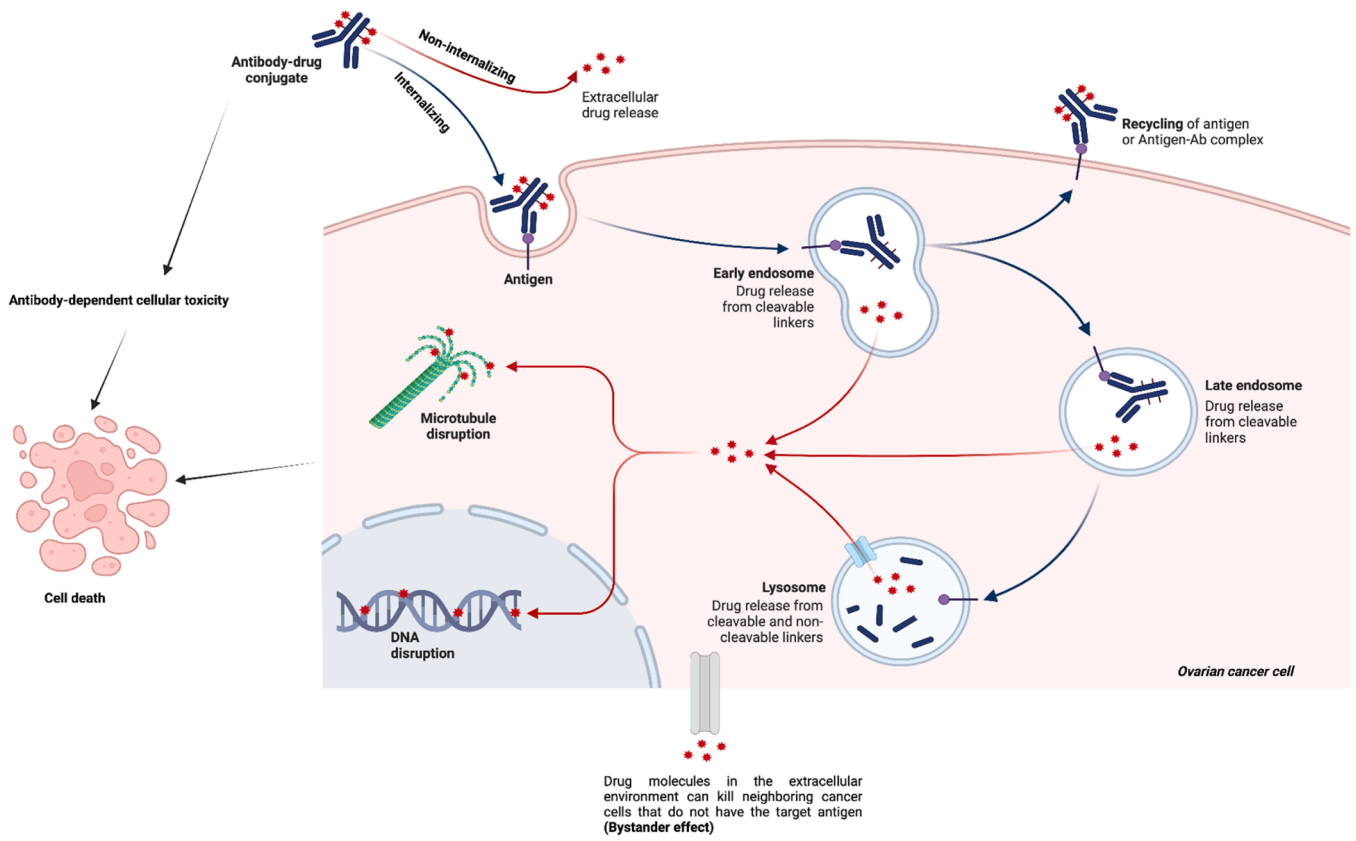

Fig. 5. Schematic representation of the mechanisms of action of ADCs. The cleavage of ADCs with cleavable linkers starts in the early endosome. The cleavage of ADCs with non-cleavable linkers, on the other hand, is a complex proteolytic process involving cathepsin B and plasmin and occurs in lysosomes [47]. Created with BioRender.com.

against ovarian cancer in vitro and in vivo. The common denominator for these antigens is their overexpression in ovarian cancer cells with little or no expression in normal cells.

One limitation of many developed ADCs is that the drug-to-antibody ratio for most of them is limited to between 3 and 4 [165]. A higher drug load is essential to retard the development of chemotherapeutic resistance by cancer cells. However, increasing the drug load can alter the targeting ability of the antibodies that are used in designing the ADCs, or lead to an increase in the molecular size of the ADCs, causing rapid clearance by the reticuloendothelial system [165,92]. This seems to not be a problem for XMT-1536, a NaPi2b-targeting ADC comprising of a humanized antibody (Rebmab200) conjugated with 10–15 auristatin F-hydroxypropyl amide payload molecules using a flexible poly--L-hydroxymethylethylene hydroxymethylformal platform called Dolafexin [165,8]. The Dolafexin platform is a linker platform with high hydrophilicity and polyvalency, and allows for the preparation of antibody-drug conjugates with high drug-antibody ratios [165]. Compared with another NaPi2b-targeting ADC that has a drug-antibody ratio of 3.5, XMT-1536 showed superior antitumor activity in both ovarian cancer and non–small cell lung cancer primary patient-derived xenograft models [8]. This superior activity was attributed to the higher drug-antibody ratio of the XMT-1536. It is currently in phase 3 clinical trials for platinum-resistant ovarian cancer and metastatic non-small cell lung cancer (clinicaltrials.gov identifier NCT05329545).

Other challenges of ADCs include the risk of antibody-induced immunogenicity [11], and alterations in antigen recognition by the ADC antibody [26]. To address these, antibody fragments or formats that can simultaneously target multiple antigens are now being employed in the development of ADCs [26,27]. Overall, ADCs are the foremost drug conjugate systems that have made considerable clinical success in ovarian cancer-targeted chemotherapy. Preclinical evaluation of monoclonal antibody immunogenicity and ADC resistance mechanisms is critical to optimizing ADC development and improving clinical benefit [26]. For more detailed information on ADCs for the treatment of ovarian cancer, readers are referred to the reviews by [10,101,37,102]; and [16].

3. Small molecule-drug conjugates

Small molecule ligands (with molecular weight < 0.5 kDa) [21] are fast-becoming attractive alternatives to antibodies for cancer-targeted drug conjugates owing to their non-immunogenicity tunable synthesis, and better cell penetration due to their low molecular weights [118, 174]. Folate and glutamic acid urea derivatives designed for targeting FR-α and prostate-specific membrane antigen, respectively, are probably the most used small molecule ligands for the selective delivery of cytotoxic drugs to tumors [12,118,171]. The use of small molecules for the development of drug conjugates has been reviewed in detail and the reader is referred to it [174]. Typically, small molecule-drug conjugates (SMDCs) are drug conjugate systems that contain a therapeutic agent that is covalently attached to a small molecule targeting ligand through a cleavable linker (Fig. 6). A spacer is usually inserted between the targeting ligand and the cleavable group in the linker for enhanced target binding or improved cleavage rate and plasma stability of the SMDCs [174].

FR-α-targeted SMDCs have been widely investigated for the treatment of different types of cancer [118]. EC1456 is an FR-α-targeted small molecule drug conjugate consisting of folic acid covalently attached to tubulysin B hydrazide through a disulfide linker (Fig. 6). It also contains a hydrophilic spacer, 1-amino-1--deoxy-glucitolyl-γ-glutamate residues, separated by *d*-Glu residues and terminated with *d*-Cys, between the folic acid targeting ligand and the

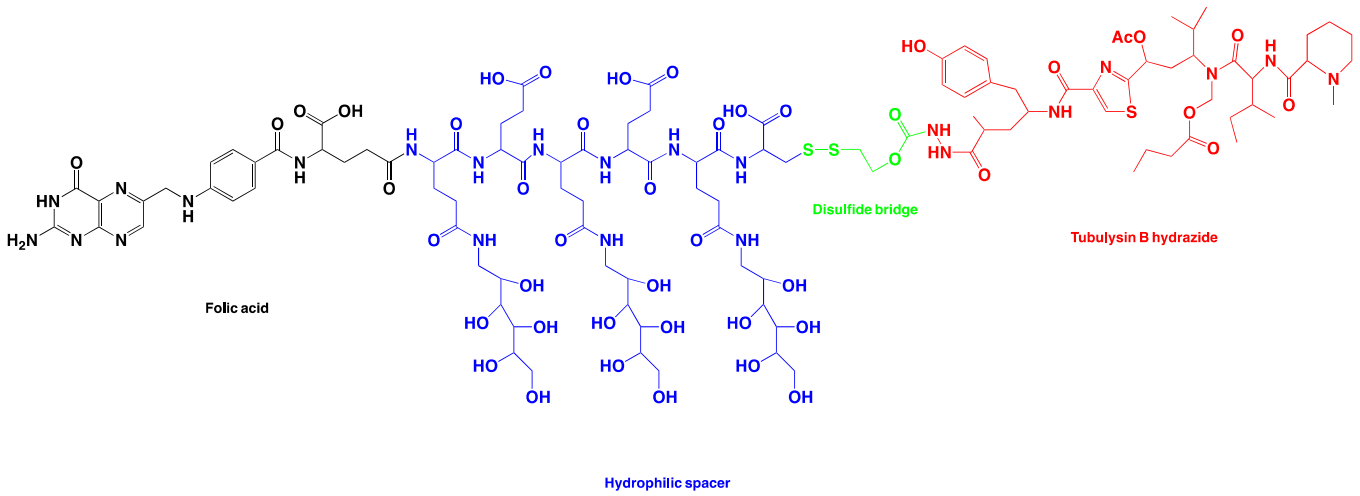

Fig. 6. Representation of the chemical structure of EC1456 consisting of folic acid as the targeting ligand for FR-α, a hydrophilic spacer, reducible disulfide bridge, and tubulysin B hydrazide as the cytotoxic drug.
Adapted from [120].

cleavable disulfide linker [120]. The importance of the hydrophilic spacer is to prevent non- FR-α-mediated cellular uptake by other FR-α-expressing cells [120]. Tubulysins are a family of tetrapeptide products that cause cell death by disrupting microtubule dynamics [24]. They are highly potent against many cancer cell lines, including multidrug-resistant cells; but are not selectively toxic to cancer cells [120,24]. The pre-clinical assessment of EC1456 exhibited a dose-dependent response and shows approximately 1000-fold specificity in FR-α-expressing cells [120]. A phase one study of EC1456 in ovarian cancer patients undergoing cytoreductive surgery (ClinicalTrials.gov Identifier: NCT03011320) was completed in 2018 but the outcome has not been released. The major limitation of SMDCs is their low molecular weights, which makes them undergo rapid renal clearance, and hence do not accumulate in solid tumors by the EPR effect [174].

4. Peptide-drug conjugates

Peptide-drug conjugates (pDCs) are drug delivery systems that are formed by the covalent attachment of drug(s) to a peptide sequence through a suitable linker (Fig. 7) [107]. They are now gaining more attention as a means of cancer targeting owing to their advantages over the well-known antibody-drug conjugates [1,21,53]. Peptide-drug conjugates have simpler designs, cheaper synthesis, decreased immunogenicity, and offer a multifunctional approach to cancer targeting [21]. The average molecular weight of a monoclonal antibody and that of a peptide used in cancer targeting is 150 kDa and 0.5–5 kDa, respectively [21,53]. The smaller size of peptides enables them to better penetrate primary tumor and metastatic tumor sites than larger-sized antibodies [107]. Both the N-terminus and the C-terminus of the amino acid residues present in a given peptide provide attachment sites for drugs, linkers, and other targeting moieties. This has made pDCs extensively studied for targeted delivery of drugs to cancers [133,167,172,21]. Readers are referred to reviews by [55] and [163] for detailed reviews on pDCs for general cancer targeting.

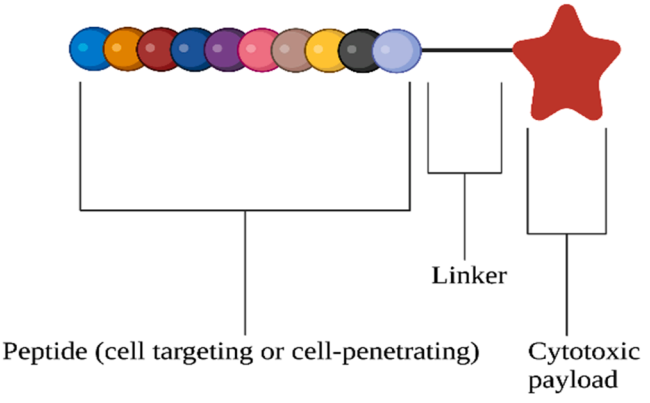

Fig. 7. Representation of a peptide-drug conjugate. Created with BioRender.com.

Similar to ADCs, the linker used for the design of pDCs can be cleavable or non-cleavable. Two categories of peptides employed in the design of pDCs can be identified and these include cell-targeting peptides and/or cell-penetrating peptides [21,53]. Cell-penetrating peptides (CPPs) mainly transport cytotoxic payloads across the cell membrane into the cytoplasm by energy-independent transmembrane mechanisms [157]. Oligoarginine is a cell-penetrating peptide that has been reported to facilitate intracellular delivery of paclitaxel by rendering it water-soluble and evading p-glycoprotein-mediated efflux [151]. HIV transactivator of transcription peptides and transportan are other examples of CPPs that have been used to improve the internalization of anticancer agents [107]. The use of CPPs is, however, limited due to their low selectivity [53]. Most CPPs cannot target and bind to specific cell types and may enter cells indiscriminately [122].

Cell-targeting peptides, on the other hand, can selectively bind with specific receptors that are overexpressed on the cancer cell surface, and facilitate receptor-mediated endocytosis of the conjugated cytotoxic drugs [144]. Peptides that can bind specifically with somatostatin, epidermal growth factor, and gonadotropin-releasing hormone (GnRH) receptors on ovarian cancer cell surface have been commonly used as targeting peptides for the design of peptide-drug conjugates developed against ovarian cancer [144,53]. Schuster et al. (2022) prepared GnRH-drug conjugates by covalently linking paclitaxel and daunorubicin with a GnRH analog, GnRH III, via cathepsin-B cleavable dipeptides. The conjugates exhibited significant growth inhibition in GnRH-receptor-overexpressing A2780 ovarian cancer cells compared with pancreatic cancer cells that express GnRH receptors at low levels.

Compared with ADCs, only a few pDCs have been tested clinically for the treatment of cancer. Melphalan flufenamide (melflufen) is a peptide-drug conjugate that is made up of a lipophilic dipeptide formed by an ester linkage of melphalan with para-fluoro-L-phenylalanine. Following administration, melflufen rapidly penetrates cell membranes because of its high lipophilicity and is quickly hydrolyzed into the more hydrophilic melphalan by aminopeptidases in aminopeptidase-positive tumor cells

[30]. This results in the specific release and accumulation of melphalan in the tumor cells. Melphalan is an alkylating agent that induces the cross-linking of DNA strands leading to cell death. The delivery of melphalan as melflufen thus allows for improved efficacy and reduced off-target toxicity [87]. In 2021 melflufen (ClinicalTrials.gov Identifier: NCT04534322) received accelerated FDA approval for the treatment of multiple myeloma but was withdrawn from the US market following multiple deaths in a phase 3 clinical trial the same year [108].

A novel peptide-drug conjugate, TH1902, is currently undergoing a phase one clinical trial in patients with advanced solid tumors, including ovarian cancer (ClinicalTrials.gov Identifier: NCT04706962). TH1902 is a sortilin-targeted peptide-drug conjugate comprising two docetaxel molecules linked to the peptide, TH19P01, through an ester linkage [25]. SORT1 is a key scavenger receptor that plays a dual role in endocytosis and receptor trafficking, facilitating the transfer of many peptides and proteins, including proneurotrophins, from the cell surface to specific intracellular locations [14,25]. SORT1 is associated with cancer cell proliferation, migration, and invasion, and its expression is significantly higher in ovarian cancer compared to healthy ovarian tissue. [14]. In a preclinical investigation conducted by Currie et al. (2022), TH1902 reduced ovarian cancer cell growth and induced more SORT1-dependent cell death than unconjugated docetaxel. This was a result of TH1902's potential to leverage SORT1's ligand internalization ability.

While it is possible to generate high-affinity human monoclonal antibodies against almost any protein target, isolating small ligands to target proteins of pharmacological interest is not always feasible [12]. Also, the problem of fast clearance of small peptides, either by the kidney or enzymatic degradation leading to non-specific drug release, is a major limitation of pDCs [21]. A detailed review of the efforts made to improve plasma stability and circulation of peptides including cyclization, peptide stapling, and conjugation of peptides with macromolecules with sizes above the renal filtration threshold (>50 kDa) has been published [21]. One example of such stabilized peptides is the 'bicycle' peptide, which has an average of 15 amino acids with 3 cysteine residues in its sequence [21]. Covalent linking of the cysteine residues results in the rigid 'bicycle' conformation of this peptide [21]. BT5528 is a bicyclic peptide-drug conjugate consisting of an EphA2-targeting peptide covalently linked to MMAE through a cleavable linker [7]. EphA2 is a receptor tyrosine kinase that is involved in cancer spread and survival and is overexpressed in > 75% of ovarian cancer cases [77]. High anti-tumor activity in pre-clinical animal models has been reported for BT5528 without the adverse effect of bleeding associated with earlier EphA2-targeting antibody-drug conjugate [7]. A Phase 1/2 clinical study of BT5528 patients with EphA2-expressing cancers, including ovarian cancer, is currently ongoing (ClinicalTrial.gov Identifier: NCT04180371).

Additionally, elastin-like polypeptides (ELPs), which are synthetic derivatives of tropoelastin, are recently gaining attention in cancer therapy [57]. The basic structural unit of ELPs consists of linearly-repeating pentapeptides. These pentapeptides consist of the amino acid sequence (Val-Pro-Gly-*X*-Gly)*n*, where the variable *X* can be any amino acid except for proline [117]. ELPs are biocompatible, degradable, temperature-responsive, have tunable structures, and can be used to improve the physical properties and in vivo fate of anticancer agents [57]. For example, gemcitabine-conjugated ELPs developed by Ramamurthi et al. (2022) showed significant cytotoxicity in ovarian cancer cell lines. Also, the pH-sensitive hydrazone linker used in the design of the ELPs facilitated the in vitro release of gemcitabine in the acidic tumor microenvironment. Moreover, the block architecture of ELPs enables them to undergo self-assembly into drug-encapsulating nanoparticles; with the drugs being chemically conjugated to the ELPs before self-assembling or physically adsorbed to the self-assembled ELPs [57]. Self-assembling pDCs have been reported to passively target and enhance the accumulation of loaded drugs in ovarian cancer via the EPR effect [67,87].

5. Nanoparticle-drug conjugates

The term 'nanoparticles' refers to small molecules in the nanometer size range that are made from a variety of materials including inorganic materials, naturally-occurring polymers, and synthetic polymers (Fig. 8) [35]. Various ovarian cancer chemotherapeutics have been developed as polymeric nanoparticles [28], micelles [48], and liposomes [149]. These nanoparticle platforms offered the advantages of enhancing the water-solubility of hydrophobic drugs, active targeting of cancer cell surface receptors, prolonged blood circulation, tissue penetration, and enhanced tumor accumulation [63,86]. Also, as a result of their nano-size range, they are not susceptible to plasma membrane-bound transporters that efflux small drug molecules from cancer cells [159]. While so much effort has been directed towards the development of nanoparticle drug delivery systems, the nanoparticle-based chemotherapeutics that have been approved for the treatment of ovarian cancer - Doxil® (liposomal doxorubicin), Genexol-PM® (polymeric micellar paclitaxel formulation), and Abraxane® (albumin-bound paclitaxel nanoparticle) - are those based on conventional methods of drug encapsulation [125,158,86]. These conventional nanoparticles have been reported to improve the toxicity profiles, but not the therapeutic efficacy of the drugs incorporated in them [116]. Additionally, since the drugs are simply encapsulated within the nanocarriers, they are susceptible to 'burst-release' in blood circulation causing off-target toxicity in healthy cells [116].

Nanoparticle-drug conjugates (NpDCs) can be defined as drug delivery systems in which active drug molecules are covalently attached to natural or synthetic materials to form a nano-sized 'prodrug' that is activatable by target-specific conditions [154]. To improve the safety and effectiveness of cytotoxic drugs, it may be best to chemically conjugate them with nanoparticles using suitable linkers that are selectively degraded in the tumor microenvironment. This approach has been used for the selective delivery of highly potent anticancer drugs to ovarian cancer cells without 'burst release'. [116] covalently conjugated MMAE to a triblock copolymer of methoxy poly (ethylene glycol)-block-poly (carbobenzyloxy-L-lysine)-block-poly(N-[N-(2-aminoethyl)-aminoethyl]aspartamide) through a disulfide linker. The triblock copolymer can self-assemble in aqueous solutions into polymeric nanoparticles. Further complexation of methoxy poly(ethylene glycol)-block-poly (glutamic acid) with the nanoparticle produced 'stealth' nanoparticle-MMAE conjugate by conferring a steric hydrophilic barrier on the MMAE-conjugated nanoparticle (Fig. 9a). This approach enables longer blood circulation of the nanoparticle by evading the reticuloendothelial system, leading to passive tumor accumulation by the EPR effect [107]. The polymer coat of the MMAE-conjugated nanoparticle was designed to be degraded in the acidic tumor microenvironment, escape the endo-lysosome, and selectively deliver the drug component in the cytoplasm where the reduction of the disulfide linker by high intracellular glutathione concentrations triggers the release of the cytotoxic MMAE. *In vitro* studies show that the MMAE-conjugated nanoparticle gradually released MMAE over a period of time in the presence of exogenous glutathione, but remained stable over 7 h at pH 7.4 without glutathione. This shows that the conjugate system can circulate longer in the plasma (pH 7.4) without releasing the incorporated drug until it reaches the tumor site. In addition, the conjugate exhibited cytotoxicity comparable to free MMAE in OVCAR8 cell lines and demonstrated no toxicity in animal models at a dose of 3 mg/kg [116].

The conjugated drug in NpDCs can also be covalently attached to the surface of nanoparticles instead of self-assembling (Fig. 9b). Recently, Wu et al. (2022b) developed a small (6.4 nm) targeted nanoparticle-drug conjugate (EC112002) comprising a stealth C'Dot nanocarrier that is linked to multiple folic acid and exatecan molecules via non-cleavable and cathepsin B-cleavable dipeptide linkers, respectively (Fig. 9b). A C'Dot nanocarrier is a PEGylated silica nanoparticle in which one to two Cy5 fluorescent dyes molecules are covalently

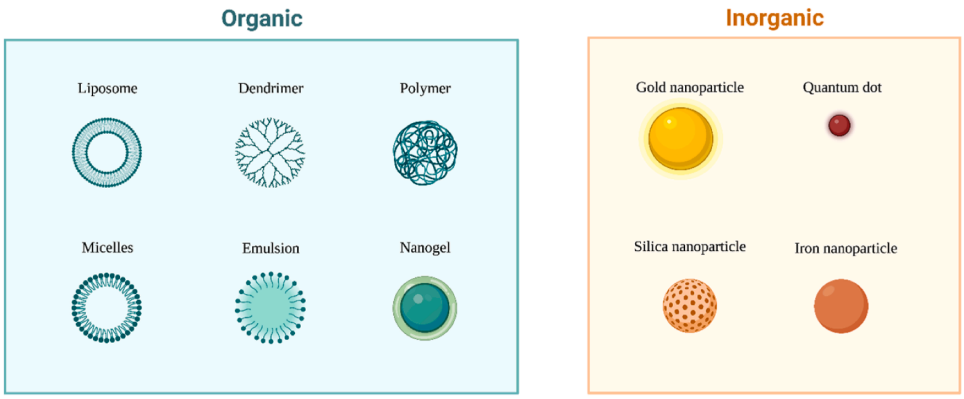

Fig. 8. Different types of nanoparticles. Created with BioRender.com.

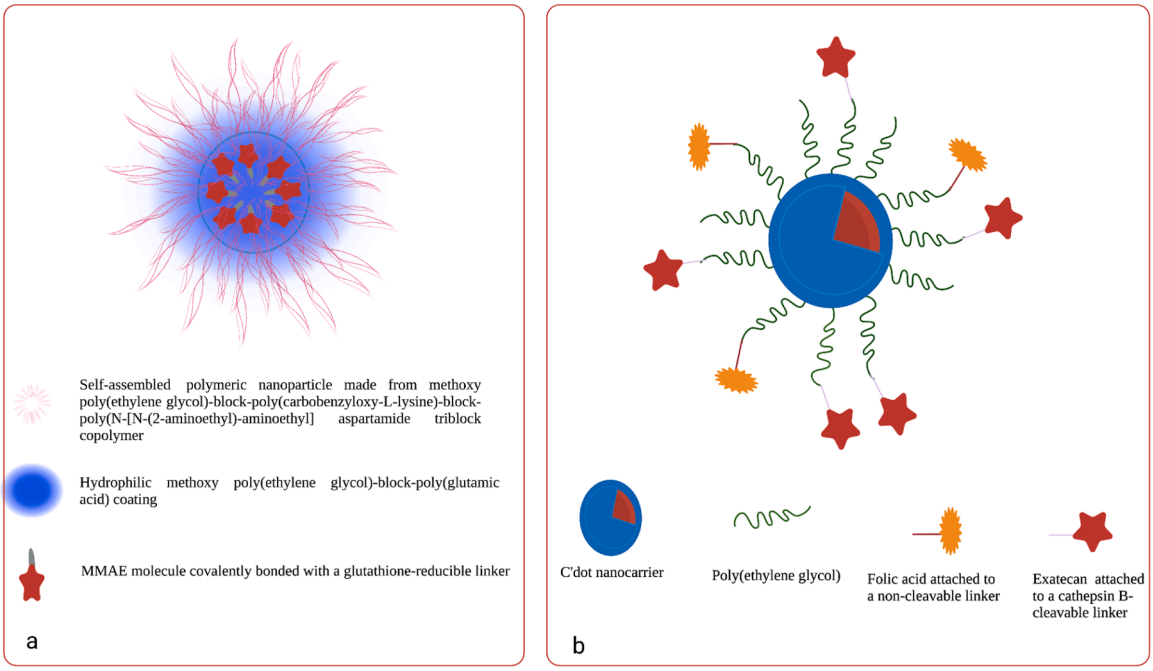

Fig. 9. Representation of a nanoparticle-drug conjugate where (a) the drug is conjugated to a self-assembling polymeric backbone, and (b) the drug is conjugated to the surface of a stealth nanocarrier through a cleavable linker. Created with BioRender.com.

attached to the silica network [155]. EC112002 contains approximately 13 folic acid molecules linked to the C'Dot via DBCO-azide click chemistry [155]. Approximately 21 molecules of exatecan, a topoisomerase 1 inhibitor, are also covalently linked to the C'Dot by click chemistry. The folic acid enables FRα-mediated endocytosis and lysosomal trafficking of EC112002 in the tumor cells where cathepsin B-cleavage of the dipeptide linker releases free exatecan to elicit its cytotoxic effect. EC112002 was stable in human plasma for over 48 h and released about 80% of the drug after 24 h in vitro in the presence of exogenous cathepsin B at pH 5.0. An IC_{50} range of 160pM to 17.6 nM was established for EC112002 in 3D platinum-resistant ovarian cancer models. EC112002 demonstrated dose-dependent and FR-α-expression-dependent cytotoxicity in vivo and was tolerated in animal models at doses up to 0.48 mg/kg [155].

Compared with ADCs, only a few NpDCs have been clinically developed. ELU001, a C'Dot drug conjugate that is similar in design to EC112002, is currently undergoing a phase 1/2 clinical trial in patients who have advanced, recurrent, or treatment-resistant FRα-expressing tumors, including ovarian cancer (ClinicalTrials.gov identifier: NCT05001282). In another development, the initial phase of the clinical development of CRLX101, a self-assembled cyclodextrin-based nanoparticle-drug conjugate of camptothecin was completed (ClinicalTrials.gov identifier: NCT00333502). CRLX101 was administered as monotherapy to 29 patients with relapsed platinum-resistant ovarian cancer [72]. The study reported that CRLX101 was generally well-tolerated by the patients except for nausea, fatigue, and anemia. The patients received a median of 3 treatment cycles and showed a clinical benefit rate of 68% and an overall response rate of 11% [72]. The polymeric nature of the nanoparticle-drug conjugate enabled it to accumulate preferentially in tumor tissues by the EPR effect, such that intact conjugate was still present in the tumor up to 48 h after intravenous administration in animal models [19]. The conjugate system was reported to exhibit a sustained slow release of camptothecin in the tumor while limiting unwanted toxicity in healthy cells [112]. Another phase 2 clinical trial to evaluate the safety and efficacy of CRLX101 (under the code name, EP0057), in combination with olaparib in women with advanced ovarian cancer is ongoing (ClinicalTrials.gov Identifier: NCT04669002).

6. Polymer-drug conjugates

Polymer-drug conjugates (PDCs) are probably the commonest macromolecules that are used for EPR-based passive targeting of cancer [2,37]. By definition, PDCs are drug conjugate systems in which active drugs with or without targeting moieties are covalently attached to a polymeric backbone (Fig. 10a) [56]. Conjugation to water-soluble polymers is one strategy that has the potential to boost the clinical utility of chemotherapeutic drugs. For example, the formulation and administration of many chemotherapeutic drugs, are complicated by the fact that they are poorly water-soluble. A significant increase in aqueous solubility can be achieved without the use of organic solvents or surfactants through the process of conjugation to water-soluble polymers [107]. Second, the conjugated system's biodistribution and pharmacokinetics can be modulated by linking it to a hydrophilic polymer carrier [78]. Several PDCs have been used to improve the stability of plasma-labile drugs [78], provide ultra-sustained drug delivery [131], EPR-based passive targeting [153] and combined active/passive targeting [6,79] in human ovarian cancer cells (Table 3).

Recent reviews on the structure and design of PDCs were done by [2] and [56], and the readers are referred to them. The polymers selected for the design of PDCs should have suitable functionalities such as the carboxyl, hydroxyl, amino, or thiol functional groups suitable for covalent bonding with drugs and targeting ligand molecules. They should also be biodegradable or degraded to components that are completely excreted from the body after drug release [2]. Ideally, such polymers and their metabolites should not elicit toxicity or immune response; be easily synthesized using reproducible methods; have uniform molecular-weight distribution, and be water-soluble [45]. For the general synthesis of PDCs, the drug may be conjugated to a pre-formed polymer or a polymer-intermediate for subsequent polymerization. The latter method circumvents the problem of uncontrolled conjugation of drugs to the polymer backbone that may occur with the former method, resulting in controlled drug loading [2]. Polymers that have been used for the synthesis of PDCs can be broadly classified as linear and branched polymers (Figs. 10b, 10c, & 10d). Such linear polymers include poly (N-(2-hydroxypropyl) methacrylamide) (HPMA), poly (malic acid) (PMA), and poly (ethylene glycol) (PEG), and branched polymers include poly(amidoamine) (PAMAM) and poly(ethyleneimine) (PEI) polymers [2].

Linear, water-soluble synthetic non-biodegradable polymers, such as N-(2-hydroxypropyl) methacrylamide (HPMA) polymers, have been mostly employed in the synthesis of PDCs because of their wide molecular weight range, biocompatibility, non-immunogenicity, and relative ease of incorporating one or more drug molecules and targeting agents [37,71,78]. First-generation HPMA-based PDCs were non-biodegradable with macromolecular sizes below 40 kDa. Since their sizes fall below the renal threshold, they were suboptimal due to rapid renal elimination [161]. For example, PK-1, a conjugate of doxorubicin and a first-generation HPMA copolymer was synthesized with a molecular weight of 28 kDa to facilitate renal elimination of the conjugate. PK-1 showed limited effectiveness when evaluated in Phase 2 clinical trials [161]. This is attributable to the rapid elimination of the conjugate and its inability to fully exploit the EPR effect. Second-generation HPMA-based PDCs comprised high molecular weight multiblock copolymers of HPMA that contain enzyme-degradable sequences to make the PDCs biodegradable [78]. Such conjugates were shown to have longer blood circulation times, higher tumor accumulation, and no adverse effects in A2780 human ovarian carcinoma xenografts, compared with the low molecular weight PDCs [161,78].

Dendrimers are another polymer-based system utilized in the synthesis of PDCs. Dendrimers are well-defined, three-dimensional, multibranched macromolecules with a central core surrounded by building units of several layers known as generations [10,152,54,89]. They have attracted notable attention in drug delivery owing to their unique properties and versatility including biocompatibility, polyvalency, solubility, and monodispersity [146]. In addition, their nanometer size makes them applicable in cancer passive targeting via the EPR effect, exploiting the tumor microenvironment, as well as in active targeting. Dendrimers afford versatility in drug delivery as drugs can be encapsulated within the inner core or conjugated to the surface of the dendrimers [97,143,146].

Different types of dendrimers including polyamidoamine (PAMAM), glycodendrimers, poly amidoamine-organosilicon (PAMAMOS),

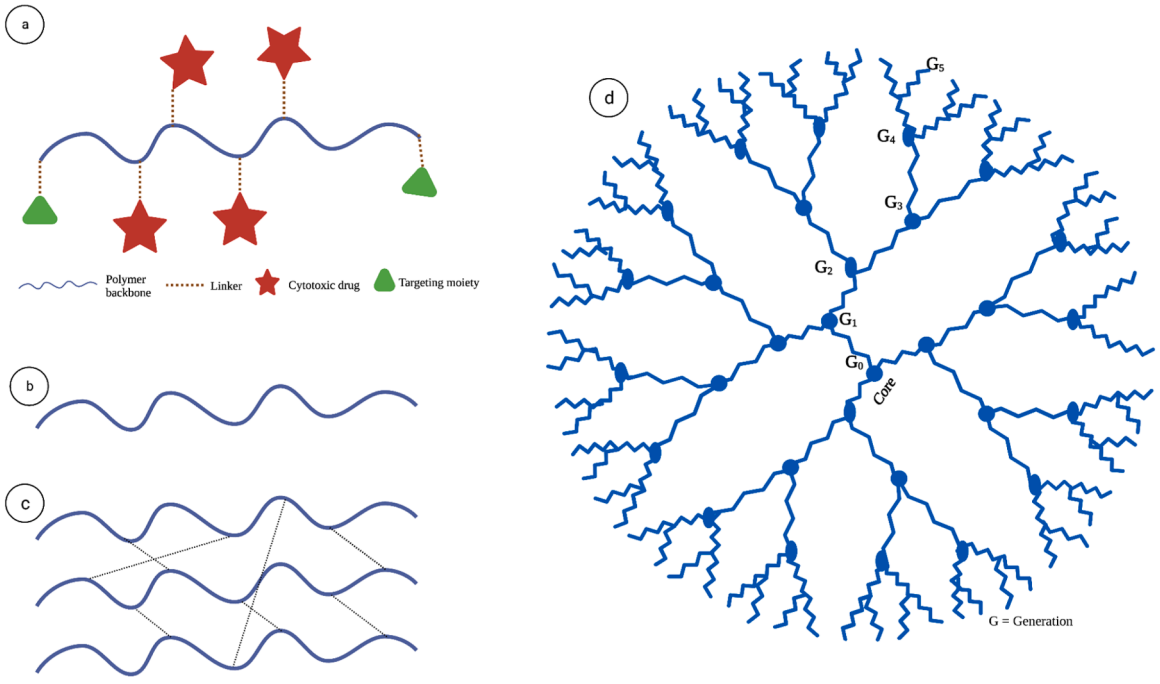

Fig. 10. Representation of: (a) polymer-drug conjugate (b) linear polymer, (c) cross-linked linear polymer, and (d) a 5th-generation dendritic polymer. Created with BioRender.com.

Table 3
Examples of polymer-drug conjugates developed for targeting ovarian cancer.

Polymer	Anticancer agent (s)	Linker	Targeting strategy	Study model	Summary	Reference
Polylysine dendritic polymer	Cisplatin	pH-sensitive	EPR effect	SKOV-3 cells	Exhibited increased tumor uptake, accumulation, and anticancer activity compared with the free drug	[173]
HPMA copolymer	Doxorubicin	GFLG tetrapeptide	EPR effect	A2780 & resistant A2780/AD cells	Conjugate decreased tumor size by 28X and 18X in the sensitive and resistant cells, respectively, compared to the free drug.	[102]
PolyHPMA	Gemcitabine Paclitaxel	GFLG tetrapeptide	EPR effect	A2780 cells	Conjugates showed moderate stability at pH 7.4 and fast drug release in the presence of exogenous cathepsin B at pH 6.0.	[78]
PolyHPMA	Gemcitabine Paclitaxel	GFLG tetrapeptide	EPR effect	A2780 xenografts	Increased Mw of the conjugates resulted in enhanced drug exposure to tumor cells by prolonging the blood circulation time.	[169]
PolyMPC	Doxorubicin	Hydrazone	EPR effect	SKOV-3 xenografts	Drug loading was ~19%; Tolerated maximum conjugate dose was > twice free drug dose; Reduced systemic toxicity and improved drug accumulation in tumor cells.	[153]
PolyHPMA	Epirubicin	GFLG tetrapeptide	EPR effect	A2780 xenografts	Four-fold increase in the drug half-life attributable to the conjugate's molecular weight (106 kDa)	[162]
PolyHPMA	Gemcitabine Paclitaxel	GFLG tetrapeptide	EPR effect	A2780 xenografts	Conjugates ~ 100 kDa in size had the best antitumor activity compared to those with Mw of 200 kDa and 300 kDa.	[163]
Bi-(mPEG-PLGA)	Cisplatin Paclitaxel	Ester bonds	EPR effect	SKOV3 cells & xenografts	Reported a synchronous and sustained in vitro release of both drugs over 2.5 months; a single injection of the conjugate in mice showed enhanced efficacy and reduced side effects compared with multiple injections of the free drug combination.	[131]
PolyHPMA	Aminohexyl-geldanamycin Docetaxel	GFLG tetrapeptide	EPR effect & αvβ3 integrins targeting	A2780 cells	Targeting of αvβ3 integrins significantly improved tumor regression	[79]
Pullulan	Doxorubicin	Primary amide bonds	EPR effect & folic acid receptor targeting	A2780 cells	Exhibited moderate stability at pH 7.4 and gradually increasing in vitro drug release at acidic pH. *In vitro*, the cytotoxicity of the conjugate (IC_{50} 0.036 mg/L) was greater than free doxorubicin (IC_{50} 0.15 mg/L).	[166]
HPMA copolymer	Paclitaxel	Hydrazone	EPR effect & CD44 targeting	SKOV3 cells	Hyaluronic acid-modified conjugate demonstrated 50X higher in vitro cytotoxicity towards CD44-overexpressing cells compared to unmodified conjugate.	[59]
PolyHPMA	Doxorubicin Zosuquidar	GFLG tetrapeptide Hydrazone	EPR effect & P-gp inhibition	A2780 & resistant A2780ADR cells	Early cleavage of the hydrazine linker in an acidic tumor environment inhibited P-gp resulting in enhanced doxorubicin cytotoxicity in resistant A2780ADR cells.	[6]

MPC: methacryloyloxyethylphosphorylcholine; HPMA: N-(2-hydroxypropyl) methacrylamide; GFLG: glycyl phenylalanyl leucyl glycine; mPEG-PLGA: methoxylpoly (ethylene glycol)-poly(lactide-co-glycolic acid; P-gp: permeability glycoprotein

polyester, polypropylene imine, and peptide dendrimer have been evaluated [97,132]. Yellepeddi et al. (2011) developed biotinylated PAMAM dendrimers loaded with cisplatin. The formulation reduced the toxicity associated with cisplatin and exhibited increased intracellular uptake, accumulation, and in vitro cytotoxicity compared to the free drug [164]. Also, Lee et al. (2022) modified the surface of a dendrimer encapsulating a doxorubicin-containing gold nanoparticle with hyaluronic acid, facilitating the active targeting of CD44 [80]. The nanoformulation facilitated enhanced cellular uptake and cytotoxicity in SKOV-3 xenograft models, compared to free doxorubicin [80]. The major concern with the use of dendrimers in drug delivery is toxicity, which has been reported to be dependent on the generation of dendrimers, size, and surface charge/functionality [127,62]. For example, positively charged dendrimers unlike those with neutral or anionic charge may cause cell disruption and lysis [132,62].

Polymer-drug conjugates containing various degradable linkers (acid-sensitive, enzyme-cleavable, hydrolysis-sensitive) have been described in the literature for ovarian cancer targeting and treatment (Table 3). A lot of these studies used GFLG, a tetrapeptide-specific substrate for cathepsin B enzyme that is overexpressed in many solid tumors, including ovarian cancer. Proteolytic enzymes, such as cathepsin B, possess extensive active sites that can bind with multiple amino acid residues [71]. Hence, the peptide linker's length plays a crucial role in drug attachment. Typically, a peptide linker composed of four amino acid residues is involved in the interactions that govern the creation of the enzyme-substrate complex, leading to the eventual release of the drug [71]. Furthermore, the incorporation of oligopeptide linkers at the termini of polymer chains serves to mitigate steric hindrance effects that may impede the formation of enzyme-substrate complexes [71]. Another cathepsin B peptide substrate, Val-Cit, which is very popular in ADCs development [55], is known to exhibit widespread sensitivities to a variety of cathepsins and could induce non-specific drug release causing off-target toxicity in normal cells [139]. GFLG, on the other hand, is more specific for cathepsin B and is stable in the plasma [141,168,76]. Challenges with the use of GFLG include hydrophobicity and very long cleavage times, which may lead to slower drug release and a consequent reduction in cytotoxic efficacy [115].

Pechar et al. (2022) covalently attached doxorubicin with HPMA polymer using Val-Cit-PABC, Val-Cit, and GFLG linkers and compared the in vitro cathepsin-B-mediated drug release and in vivo cytotoxicity of the three HPMA-doxorubicin conjugates in sarcoma S-180 mice models [110]. The GFLG-containing conjugates exhibited a 'linear' drug release (~20% at 48 h) while the Val-Cit-PABC-containing conjugates exhibited a very fast initial drug release (~30% at 8 h) followed by a gradual 'linear' drug release (~55% at 48 h) in the presence of exogenous enzyme at pH 6.0. The Val-Cit-PABC-containing conjugates, however, showed degradation at this pH in the absence of cathepsin B, releasing about 17%w/w of doxorubicin in 48 h. The Val-Cit-containing conjugates (not containing the self-immolative PABC), on the other hand, only released < 5%w/w of the drug at pH 6.0 in the presence of the cathepsin B. Despite differences in the in vitro drug release profiles, there was no significant difference in the inhibition of tumor growth between the conjugates containing GFLG or Val-Cit-PABC linkers. This

similarity in effect is thought to be due to the similar pharmacokinetics of the PDCs, resulting in similar accumulation in the tumor tissue and exposure to a similar dose of chemotherapeutics. Additionally, complex enzymatic activity may lead to similar drug release rates from the conjugates in a living organism. Although the Val-Cit-PABC linker showed higher drug release within 48 h in vitro, the GFLG linker demonstrated a linear release property that may result in increased release over a longer incubation period, leading to similar cumulative drug release in the tumor tissue [110]. A similar sustained slow drug release exhibited by GFLG-containing conjugates was also reported for CRLX101 which was discussed in the previous section. In contrast to GFLG-, and Val-Cit-PABC-containing conjugates, the conjugate that contains just Val-Cit without PABC is not cleaved by cathepsin B and exhibited insignificant effects on tumor growth [110]. This study may prove the importance of the self-immolative PABC spacer in drug-conjugated systems that contain Val-Cit as the linker.

Although a large macromolecular size that can exploit the EPR effect has been the selling point of PDCs, the molecular weight of a polymer-drug conjugate must be optimized for it to be most effective [163]. An increase in the size of PDCs of gemcitabine and paclitaxel from < 50 kDa to ~100 kDa resulted in higher drug loading, improved tumor accumulation, and antitumor activity [163,162,169,78]. Further increase in molecular weight, however, resulted in decreased antitumor activity [163]. This is attributed to the complexity of water-soluble polymers that bear hydrophobic drugs (e.g. paclitaxel) at their terminal side chains. The hydrophobic moieties can undergo hydrophobic interactions leading to conformational changes in the macromolecules which subsequently impact water solubility, tumor penetration, enzymatic drug release, and antitumor activity [163]. Additionally, the architecture of PDCs impacts cellular internalization [71]. Linear HPMA copolymer-meso-tetra (4-carboxyphenyl) porphyrin conjugate exhibited higher internalization rates and light-induced cytotoxicity than meso-tetra (4-carboxyphenyl) porphyrin attached to hyperbranched amine-terminated PAMAM dendrimer [71]. Complex architectures may therefore impede the enzyme-substrate complex formation and slow-down drug release, and ultimately decrease cytotoxic activity [71].

Considerable efforts have been made by researchers in the development of PDCs for cancer targeting and treatment. In addition to monotherapy, PDCs have been used for combination drug delivery and have shown promising results in ovarian cancer targeting. Combination chemotherapy using two drugs with distinct mechanisms of action, serves as a good strategy for reducing the development of chemoresistance [131,163,169,79,78]. PDCs that are fabricated as nanoparticles, for instance, CRLX101, have shown effectiveness in patients with advanced solid tumors, including ovarian cancer [112,19]. Also, the use of polymer platforms, Dolaflexin and Dolasynthen, in the ADCs, XMT-1536 and XMT-1592, respectively, have enabled the synthesis of novel ADCs with higher drug loading compared to conventional ADCs [165]. The clinical translation of polymer-drug conjugates themselves, is, however, still very limited as no polymer-drug conjugate has been approved for cancer treatment yet [148]. The major limiting factors responsible for this include safety concerns over cumulative polymer accumulation throughout the body [78], structure complexity, and lack of batch-to-batch synthetic reproducibility [161]. An ideal polymer-drug conjugate for ovarian cancer treatment should be rationally designed to circulate longer in the blood without releasing the active drug, sufficiently accumulate in the tumor microenvironment, be internalized whether by fluid-phase, adsorptive or receptor-mediated endocytosis, and efficiently release the drug in the cancer cells [110,148]. It is also important that a higher drug loading and optimal release characteristics are achieved to minimize the development of chemoresistance. In addition, the polymer carrier should be completely cleared from the body once the drug payload is released [148].

7. Miscellaneous conjugates: affibody-drug conjugates and aptamer-drug conjugates

Although larger than small molecules, affibodies and aptamers are also used for the development of small-sized targeted drug conjugates (Fig. 11) [27]. Their use as targeting ligands leverages the approximately 10-fold size decrease of these molecules compared with monoclonal antibodies. Affibodies, which are ~ 7 kDa affinity proteins folded into stable three-helix bundle structures, can be tailored to selectively bind to a variety of target structures, including tumor cell surface receptors [87]. They can also be produced quickly and cheaply through microbial fermentation. Xia et al. (2022) designed an affibody and conjugated it to MMAE through a maleimido valine-citrulline type linker to form an amphiphilic affibody-drug conjugate [156]. When dispersed in water, the conjugate self-assembled into nano micelles due to its amphiphilic nature. The nano-aggregation prolonged the plasma circulation of the conjugate by 8 h following intravenous administration leading to an enhanced tumor accumulation and antitumor activity in HER2-positive ovarian and breast xenograft models. A reported limitation of affibodies is their short biological half-lives [156]. This limitation can be circumvented by developing affibody-drug conjugates into nanoparticles as described above.

Aptamers are chemically synthesized oligonucleotides (5–30 kDa) that can bind with a target molecule with specificity and affinity that is equal to that of antibodies but with little or no immunogenicity. They are being increasingly used for cancer targeting [49,51,85]. [49,85] prepared an aptamer, NucA, to target nucleolin protein, which facilitates cancer proliferation and metastasis [16]. Nucleolin is mainly found in the nucleus but is also found on the cell surface of various cancers including ovarian cancer [85]. The covalent linkage of paclitaxel to NucA using a valine-citrulline-p-aminobenzyl carbonyl linker rendered the hydrophobic drug water-soluble. The NucA-paclitaxel conjugate was also reported to facilitate the selective accumulation of paclitaxel in ovarian tumor tissue compared with normal tissues in SKOV3 and OVCAR3 xenograft models of ovarian cancer. This resulted in enhanced anticancer activity and reduced toxicity of paclitaxel in the animal models. Similarly, Henri and colleagues (2023), also prepared an aptamer that specifically targets epithelial cell adhesion molecule (EpCAM) on ovarian cancer cell surface and conjugated it with doxorubicin. The aptamer-doxorubicin conjugate demonstrated in vitro cytotoxicity similar to free doxorubicin in ovarian cancer cells. While aptamers are promising targeting moieties for drug conjugates in cancer therapy, there is concern regarding how much drug can be conjugated to them without losing targeting capacity [49]. As the drug loading increases, the targeting ability of the aptamer may be compromised due to the reduction in the size of the aptamer relative to the drug load. The steric hindrance caused by the drug has the potential to obstruct the aptamer, leading to a loss of its targeting efficacy. Insufficient drug loading may also result in ineffective drug delivery [49].

8. Conclusion

Drug conjugate systems are promising effective treatment options for advanced, recurrent, or platinum-resistant ovarian cancer. This article is distinct from other published reviews on drug conjugate systems for the treatment of ovarian cancer in that it discusses the progress and limitations of targeted drug conjugate systems, including antibody-drug conjugates, in ovarian cancer treatment.

The overexpression of different molecules that can serve as therapeutic targets in ovarian cancer (Table 1) opens up great opportunities to selectively deliver highly potent cytotoxic drugs to cancer cells with little or no systemic toxicity. While a lot of efforts have been made by researchers in the area of targeted drug conjugate systems, only Mirvetuximab Soravtansine, an antibody-drug conjugate system carrying DM4 as the cytotoxic payload, has been approved for the treatment of FR-α-overexpressing ovarian cancer that is resistant to first-line

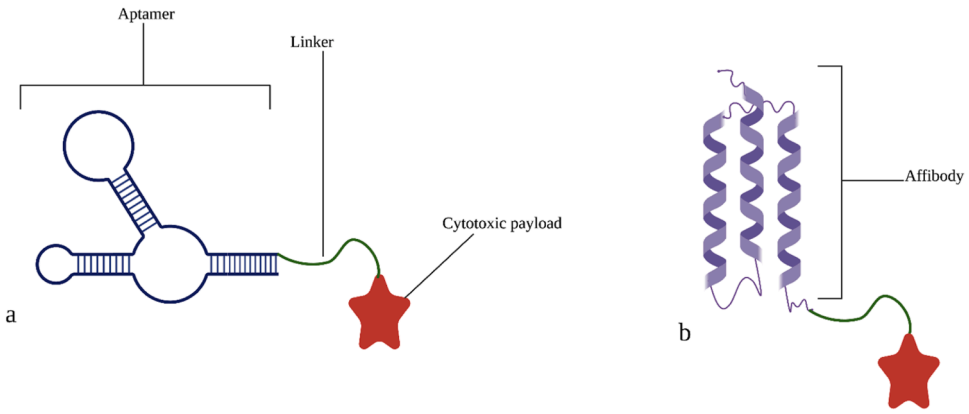

Fig. 11. Representation of an aptamer-drug conjugate (a) and affibody-drug conjugate (b). Created with BioRender.com.

chemotherapy. Other drug conjugate systems, including polymer-, peptide-, small molecule-, and nanoparticle-drug conjugates, are not as successful as ADCs in terms of clinical development. In addition to the active targeting to overexpressed target molecules in ovarian cancer, EPR-based passive targeting is the mechanism of targeted macromolecule drug conjugate systems, especially polymer- and nanoparticle-drug conjugates, that have been developed for ovarian cancer treatment. The paucity of patient-based experimental data on the EPR effect limits the extrapolations from studies in pre-clinical models to clinical patients. To promote the clinical translation of these drug conjugate systems, it is important to develop and utilize improved pre-clinical tumor models that more accurately mimic ovarian tumors in humans during the pre-clinical phase of drug development.

CRediT authorship contribution statement

Simeon K. Adesina and Omotola D. Ogundipe participated in conceptualization of the manuscript. Simeon K. Adesina, Omotola D. Ogundipe and Oluwabukunmi Olajubutu participated in writing, review and editing. Omotola D. Ogundipe was responsible for visualization. All authors contributed to the final version. Simeon K. Adesina was responsible for supervision of manuscript. All authors read and approved the article. The manuscript has not been submitted for consideration elsewhere.

Funding

Support for S.K.A. is provided by the HRSA Center of Excellence Grant under award number 6 D34HP16042-14-01.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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