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Dendritic cell engineering for selective targeting of female reproductive tract cancers

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Female reproductive tract cancers (FRCs) are considered as one of the most frequently occurring malignancies and a foremost cause of death among women. The late-stage diagnosis and limited clinical effectiveness of currently available mainstay therapies, primarily due to the developed drug resistance properties of tumour cells, further increase disease severity. In the past decade, dendritic cell (DC)-based immunotherapy has shown remarkable success and appeared as a feasible therapeutic alternative to treat several malignancies, including FRCs. Importantly, the clinical efficacy of this therapy is shown to be restricted by the established immunosuppressive tumour microenvironment. However, combining nanoengineered approaches can significantly assist DCs to overcome this tumour-induced immune tolerance. The prolonged release of nanoencapsulated tumour antigens helps improve the ability of DC-based therapeutics to selectively target and remove residual tumour cells. Incorporation of surface ligands and co-adjuvants may further aid DC targeting (*in vivo*) to overcome the issues associated with the short DC lifespan, immunosuppression and imprecise uptake. We herein briefly discuss the necessity and progress of DC-based therapeutics in FRCs. The review also sheds lights on the future challenges to design and develop clinically effective nanoparticles-DC combinations that can induce efficient anti-tumour immune responses and prolong patients' survival.

Key words Cancer therapy - dendritic cells - nanomedicine - translational oncology

Introduction

Cancer accounted for approximately 9.6 million deaths and 18.1 million new cases globally in 2018[1]. Among all female reproductive tract cancers (FRCs), the most common are the cancers of the cervix (cervical cancer), ovary and endometrium, which contribute to more than three-fourth of the total reported cases. Cervical cancer is the third most common malignancy in women which resulted in almost 300,000 deaths worldwide in 2018 (about 7.5% of all deaths from cancer in females)[1]. The overall mortality to incidence ratio of cervical cancer is almost 50 per cent due to which it

is a major problem in developing and underdeveloped countries[1,2]. Other frequently occurring FRCs also display a similar scenario, as cancers of endometrium and ovary, respectively, stand sixth and seventh most frequently occurring malignancies in women worldwide. Approximately, 382,069 and 295,414 new cases of endometrial and ovarian cancers, respectively, were reported worldwide in 2018. The occurrence rate of endometrial cancer in developing countries is more than three times to cervical cancer[1-4]. Despite several efforts, stage-dependent therapeutic response is considered as a major reason for the higher mortality rate observed in these cancers. This creates a pressing need to develop novel approaches for the prevention and treatment of FRCs.

Standard therapeutics and their limitations

The late detection and limited therapeutic options available for FRCs significantly contribute to the global rise in mortality due to these malignancies. Similar to other malignancies, the primary therapy of FRCs is the surgical tumour removal which may be used alone or with other therapies (radio- or chemotherapy). Occasionally, hormone therapy such as progestin (a synthetic drug similar to the hormone progesterone) is also administered. In general, the treatment option mainly relies on the tumour type, occurrence site and disease phase[5,6]. For instance, in endometrial cancers, radiation therapy may be given in combination to surgery if the disease is malignant and spreading to the nearby cervix, ovary or lymph nodes, which results in a better prognosis. Chemotherapeutic drugs such as carboplatin, cisplatin, doxorubicin and paclitaxel remain the choice of treatment if the disease is recurring or spreading beyond the uterus and cervix. These standard therapies have been shown to reduce the tumour size and control its spread; however, recurrence-induced toxicity and side effects remain severe issues[7,8]. Furthermore, a large number of female reproductive tract tumours metastasize before disease identification which significantly reduces the effectiveness of these traditional procedures[9]. For example, in cervical cancer, the disease starts as the growth of pre-cancerous lesions in the cervix region (stage I) and extends within pelvic cavity, side wall or lower vagina (stages II and III) and other body parts (stage IV)[10]. The prognosis after treatment gets even worse with increasing stages for advanced cancer; the cure rate (5 year survival) drops from about 45 per cent for earlier stages to as low as 15 per cent in advanced stages[11,12]. Due to various reasons including unawareness and fear, >80 per cent of affected population seeks help at later stages, thus worsening the disease outcomes. Moreover, the restricted response to high-dose standard therapies observed among different gynaecological malignancies increases the probability of disease recurrence as resistant disease. The unavailability of systemic therapies causes major harm to other normally growing cells of different vital systems including immune system, which may lead to an immunocompromised state, thereby increasing the probability of patients to develop various opportunistic infections[13].

Immunotherapeutics: An alternate strategy

Successful treatment of FRCs remains a major challenge and requires urgent attention for developing novel therapeutic strategies. In the past decade, significant efforts have been made to utilize immune cells and mechanisms to remove unwanted tumour cells. Normally, different components of immune system comprehensively check and remove unnecessary cells and other entities through a tightly regulated mechanism known as immune surveillance. This involves innate and adaptive immune responses which work under strict coordination to generate anti-tumour responses. The key for the generation of an immunotherapeutic strategy lies within these responses as these can be induced or modulated through a number of immunological agents. These strategies mainly depend on three basic strategies, *i.e.* increasing processing and presentation of tumour antigens (Ag), modulating T-cell responses and overcoming cancer cell-induced immunosuppression (Fig. 1). These strategies have been widely utilized to develop an effective anti-cancer therapy for gynaecological malignancies[14,15]. Among the various analyzed immune-based strategies, utilizing the ability of dendritic cells (DCs) to initiate immune responses makes these cells as appropriate therapeutic alternate for FRCs. Antigen presenting cells (APCs) such as DCs are one of the important constituents of immune mechanisms and possess the potential of being utilized for anti-cancer therapeutics. The superior capability of DCs to uptake, process and present foreign antigens holds optimum promise for utilizing these cells for developing a successful supportive care for gynaecological malignancies.

Dendritic cell immunotherapeutics for female reproductive tract cancers

DC, initially identified in 1973 by the pioneer work of R.M. Steinman and Z.A. Cohn, are the professional

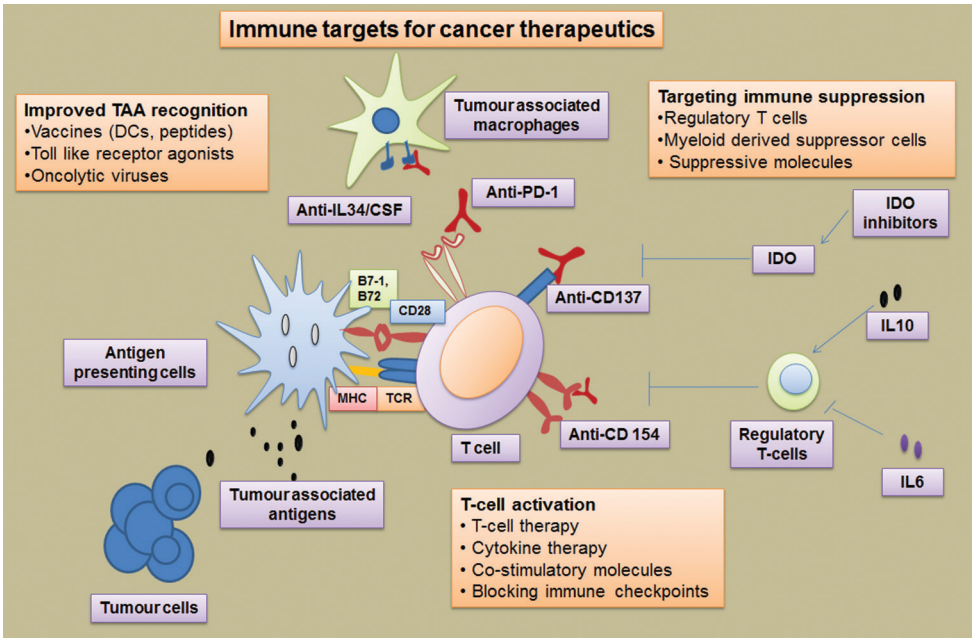

Fig. 1. An overview of widely used immune targets for cancer therapeutics. Different strategies utilizing antigen presenting cells, T-lymphocytes, macrophages and specific antibodies to specifically target tumour cells. CD, cluster of differentiation; DCs, dendritic cells; IL, interleukin; MHC, major histocompatibility complex; PD1, programmed cell death protein 1; TCR, T-cell receptor; IDO, indoleamine-pyrrole 2,3-dioxygenase.

APCs of our body. These cells possess a significant potential to initiate primary immunological responses. DCs identify and interact with foreign molecules through their pattern-recognition receptors to release different immunological mediators and trigger effective host immune responses[16]. This centralized role of antigen processing and presentation through specialized surface receptors makes DCs a key player in initiating and regulating responses against tumour cells. This vital role of DCs to regulate anti-tumour responses is being broadly utilized towards developing personalized cancer immunotherapeutics (Fig. 2). DCs take up foreign antigen, process through specialized major histocompatibility (MHC) complexes and present these processed antigen to T-cells for the generation of efficient immunological response. However, this also requires the appropriate presentation of different co-stimulatory and signalling molecules. Normally, after uptake, antigens are processed either via endogenous pathway in which intracellular antigens are processed through class-I MHC or by exogenous pathway whereas extracellular antigens are presented with MHC-II[17]. In endogenous pathway, the antigens are directed to proteasomal degradation through ubiquitination which helps them to fit in the peptide-binding region of MHC class-I. These peptides bind with a protein known as transport-associated protein-1 and 2 heterodimer, which aids their transfer to rough endoplasmic reticulum (ER)[18]. These peptides are co-presented with MHC-I on the DCs membrane. However, in exogenous pathway, the endocytosed antigens are degraded by endosomal proteases which then fuses with MHC class-II in the rough ER with the help of HLA-DM and the stable peptide-MHC composite is then presented on DCs[18]. The DCs also possess capability to cross-present exogenous antigens with class-I MHC to persuade a Th1-mediated response. In this pathway, the cells initiate antigen uptake in exogenous mode but later switches to the endogenous pathway. It involves the retrotranslocation of endosomal compartments and proteasomal complex to load exogenous antigens on class-I MHC[19]. This ability of DCs is important and has been widely assessed to develop a competent DC-based immunotherapy against FRCs.

Clinical efficiency and impediments

DC-based therapeutic vaccines for FRCs has undergone a series of *in vitro* examinations and now reached the stage of preclinical and clinical trials. A set of clinical considerations, including host- and tumour-related factors such as age, immunosuppression, stage of disease, HLA and co-infection have been recognized by the Cancer Vaccine Clinical Trial

Working Group to develop a successful DC vaccine[20]. It is also vital to have a standardized protocol for optimum DC culture and vaccination. Several ongoing and completed clinical studies have successfully established the clinical efficiency of DC-based vaccines in FRCs (Table I). A series of investigations conducted with the peptide-pulsed DCs has shown the generation of significant anti-tumour responses without any significant toxicity[32,33]. In one such phase II investigation among patients of ovarian cancer with elevated recurrence risk, it was reported that p53 peptide-pulsed DC vaccines were safe and efficient in generating specific responses against p53 peptide[23]. In another phase I trial, therapeutic

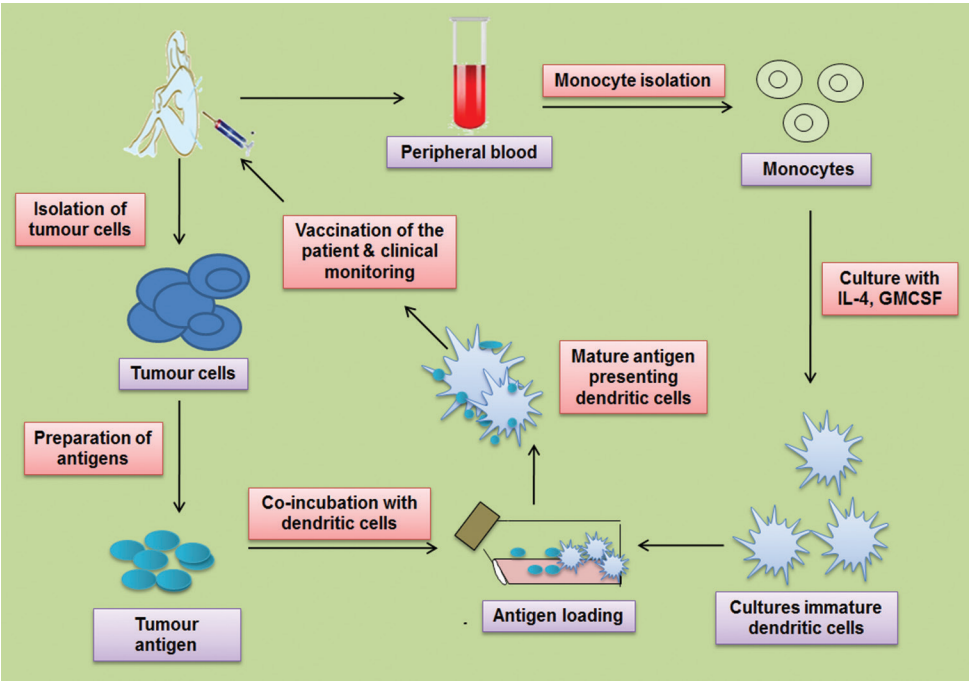

Fig. 2. A diagrammatic representation of developing dendritic cell vaccines for female reproductive tract cancers. Dendritic cells are isolated from peripheral blood and cultured with growth cytokines. These cultured dendritic cells are then pulsed with appropriate tumour antigens and administered to the patients. IL, interleukin; GM-CSF, granulocyte macrophage-colony stimulating factor; Ag, antigen.

Table I. Clinical assessment studies of dendritic cell immunotherapy in female reproductive cancers

Cancer	Strategy used	Reference
Ovarian	DCs loaded with peptides of MUC1/HER-2/NEU	21
Ovarian and uterine	DC pulsed with KLH and autologous tumour antigens	22
Ovarian	DCs pulsed with p53 peptide along with IL2	23
Ovarian	Chemotherapy followed by doses of TL-KLH co-loaded pulsed DCs followed by IL2 dosage as an immune adjuvant	24
Cervical	HPV protein loaded DC	25
Ovarian	DCs loaded with HER-2/NEU, hTERT, and PADRE peptides, with or without low-dose intravenous cyclophosphamide	26
Ovarian	TL co-incubated DCs	27
Uterine	DCs loaded with WT1-mRNA	28
Ovarian	DCs loaded with oxidized TL along with bevacizumab and cyclophosphamide	29
Ovarian and cervical	Autologous DC formulation	30
Cervical	TL primed DC followed by cisplatin	31

MUC1, mucin 1; HER-2, herceptin-2; KLH, keyhole limpet haemocyanin; DC, dendritic cells; TL, tumour lysate; HPV, human papiloma virus; IL, interleukin; h-TERT, telomerase reverse transcriptase; PADRE, pan HLA DR-binding epitope; WT1, wilms tumour 1

administration of DCs pulsed with the recombinant HER-2-granulocyte macrophage-colony stimulating factor (GMCSF) peptide blend to a group of patients comprising metastatic ovarian cancer was observed to generate a strong anti-HER-2 response[21]. Studies have also shown keyhole limpet haemocyanin (KLH) act as a vital antigen among different gynaecological malignancies. A phase I study conducted on patients suffering from uterine and ovarian cancers suggested that administration of KLH and whole T-lymphocytes (TLs) (autologous) activated DCs was safe and immunologically active[22]. Similarly, subcutaneous (s.c.) vaccination of KLH-loaded DCs to the patients resulted in significant induction of protein-specific cellular immune responses and delayed-type hypersensitivity reactions, which reaffirmed the safety and effectiveness of these vaccines[24].

To validate the clinical efficacy of this adjuvant therapy, the vaccines have been systematically administered and assessed in different combinatorial modes. In a randomized phase I trial, loaded DCs along with a chemotherapy drug cisplatin were administered to cervical cancer patients. Absolute clinical response with no recurrence for five years was reported in one of three individuals with the metastatic disease which suggested that the strategy might act as appropriate adjuvant therapy for advanced cervical cancers[31]. Similarly, a trial conducted on patients with recurrent ovarian cancers further reaffirmed the clinical efficiency of these vaccines. The study utilized DCs co-incubated with oxidized TL together with a chemotherapy drug, bevacizumab and observed strong anti-tumour response among the treated patients which later strongly correlated with the disease stability[29]. In one randomized trial vaccination of HER-2 + telomerase reverse transcriptase (h-TERT) + pan HLA DR-binding epitope (PADRE) peptides, pulsed DCs in combination with cyclophosphamide to the advanced ovarian cancer patients resulted in elicited tumour cell-specific responses with promising survival ability[26]. In a different strategy, treatment of WT1 mRNA electroporated DCs to ovarian cancer patients showed higher anti-tumour immunological responses which also correlated with the extended patient survival[28]. In the past decade, these clinical trials have shown promising results and suggested that the establishment of a successful DC-based approach requires utilization of synergistic therapy combinations and incorporation of novel modalities which can generate profound anti-tumour responses and prolong patients' survival in FRCs.

Immunosuppressive microenvironment

The efficiency of DC-based vaccines against FRCs has been assessed in several pre-clinical and clinical studies; however, the key problem in the clinical triumph of DC immunotherapy is the well-established immunosuppressive surroundings. These tolerogenic surroundings limit the immune activation ability of DCs and result in a limited therapeutic response[34]. Different mechanisms have been described which help tumour cells to manipulate host immune system and escape surveillance for progression. These mechanisms primarily aim to downregulate the expression of tumour antigens and MHC molecules, facilitating cancer cells to get away from infiltrating T-cells[34]. The immunosuppressive tumour cell surroundings primarily comprise numerous suppressive molecules and cells which jointly work to create a tolerogenic microenvironment[35]. These molecules suppress the secretion of inflammatory molecules and assist in recruiting Treg populations to downregulate the activity of T-cell subsets, natural killer cells and DCs[35]. Although exact molecular pathways and their inter-linking mechanisms are still a matter of investigation, evidence signifies the vital function of tumour growth factor (TGF)-β in tumour development and its metastatic progression[36]. Interleukin (IL)-10 has also been observed to significantly limit the appearance of different co-stimulatory molecules and inhibit the vital process of antigen processing and presentation[37]. T-cells interacting with IL-10 expressing DCs are shown to be functionally anergic[38]. Molecules such as vascular endothelial growth factor-A (VEGF-A) and prostaglandin E2 (PGE2) interfere with nuclear factor-κB, G protein-coupled receptor and other transcription factors to negatively influence DC maturation and function[39,40]. Moreover, PGE2 is also shown to influence the levels of an immunoregulatory enzyme, indoleamine-2,3-dioxygenase (IDO) which later suppresses the anti-tumour responses[41,42]. Tumours also release soluble Wnt ligands to actively tolerize DC populations within the tumour microenvironment. It has also been shown that the involvement of Wnt-β-catenin pathways have a vital role in suppression of pro-inflammatory cytokines and elevated expression of the immunosuppressive cytokines[43]. Different studies have shown that this tumour-associated immunosuppression is significantly linked to the aggressiveness and metastasis of different cancers of the female reproductive tract. Patients

with higher TGF expression are more closely related to the worse prognosis of post-surgical therapeutic interventions[44]. Similarly, differential expression of cell surface molecules such as intercellular adhesion molecule and MHC on tumour cells supports their escape from DC vaccine-generated specific immune responses[45,46]. Therefore, to develop clinically effective DC-based cancer therapeutics, it is important to design strategies which can potentially counter this immunosuppressive microenvironment.

Tumour-initiating cells

Tumour-initiating cells (TRICs) have a key function in developing therapeutic tolerance and progression of FRCs. This dedicated cell population functions as tumour stem cells and shows higher tendency for metastasis and increased therapeutic resistance. However, the exact mechanisms depicting the development of such resistive abilities of TRICs are largely unknown. It is assumed that the reciprocal crosstalk between the malignant cells and tumour-infiltrating leukocytes probably regulates the expansion of stem cell-like population and facilitates developing therapeutic resistance among these cells[47]. TRICs express membrane efflux transporters which further support their chemoresistance characteristics[46]. In addition, enhanced DNA repair and low mitotic index are other properties which contribute to the development of drug resistance. Further, these self-renewing malignant progenitors form a group of cells to regulate cellular differentiation[47]. TRICs are the major cause of clinical relapse as they escape the therapeutics and re-grow upon their cessation and can subsequently regenerate entire malignant phenotype[48-50]. The well-known immunosuppressive tumour microenvironment in patients and significant toxicity of traditional therapeutics further assist TRICs to escape the immunological surveillance[50]. This represents a decisive interface between vaccine effectiveness and tumour progression, so it is vital to devise and include new clinically effective approaches enabling DCs to overcome tumour-induced immunological suppression along with eliciting specific immune responses for removal of TRICs, a major cause of clinical relapse in gynaecological malignancies.

Dendritic cell nanoengineering: An approach to move forward

Nanotherapeutics offers an efficient inclusion in traditional DC-based vaccine to surpass the existing obstacle of immune suppressive microenvironment[51]. It has been shown that tumour antigens have limited ability to activate DCs; thus, co-encapsulating tumour antigens with different adjuvants such as micro-emulsions, lipopolysaccharides and bacterial CpG

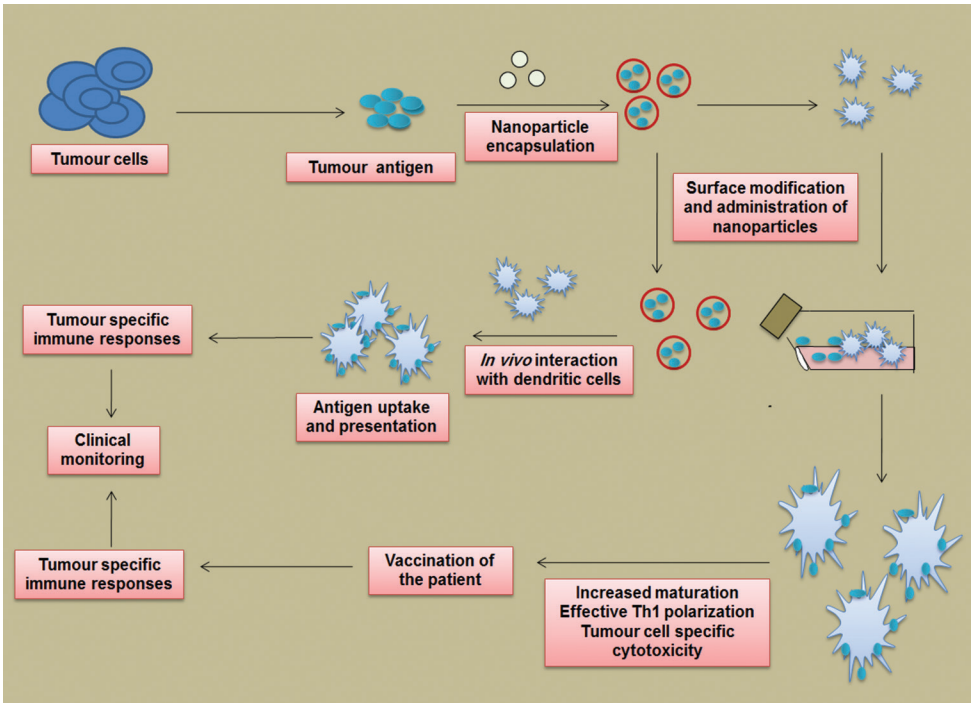

Fig. 3. Outline of using nanoencapsulated tumour antigens for dendritic cell engineering. The tumour antigens can be initially encapsulated and then utilized for pulsing the dendritic cells. These tumour antigen presenting dendritic cells can be administered to the patients. NPs, nanoparticles.

DNA may prove beneficial[51] (Fig. 3). Encapsulation of tumour antigens using different nanomaterials protects them from damage of proteases and assists in a prolonged and proscribed antigenic release to DCs. This increases the antigenic acquaintance to DCs and helps them to counter the suppressive microenvironment[34]. Incorporation of different surface modifiers and ligands may specifically direct nanocarriers to target cells and further aid the clinical and immune activation potential of DC vaccines. Earlier reports have shown that encapsulation of tumour antigens enhances the MHC-I-mediated antigen cross-presentation[34,50]. However, for efficient immune stimulation, different factors such as size, shape, surface chemistry, mode of administration, diffusion and solubility play an important role[52,53]. Evidence suggests that reduction in the ionic interaction of matrix material with the encapsulated protein significantly declines the burst effect and reduces the release rate[54]. Therefore, copolymers such as ethylene oxide-propylene oxide can be incorporated to a non-toxic polymer with appropriate molecular weight and chemically defined monomers to improve the efficiency of nanocarriers[54].

Vital factors for dendritic cell nanoengineering

The therapeutic efficiency of DC vaccines can be further modulated by the mode of uptake by DCs, which have a primary function in shaping the antigenic fate, *i.e.* either interact with MHC-I or with MHC-II. However, relying on the physical and chemical compositions of the encapsulated Ag the mode of uptake may be endocytosis, macropinocytosis and phagocytosis. A pre-requisite for successful DC-based therapeutic vaccines is their ability to generate a potent Th1-mediated cytotoxic response. It is suggested that larger nanoparticles (NPs) with size approximately 500 nm are preferably taken up through phagocytosis, a process which assists humoral immune responses[55]. The NPs with a smaller size (approximately 100 nm) are effectively taken up through endocytosis which generates a potent Th1 response[56]. Thus, the use of NPs with size less than 100 nm should be preferred to ensure the generation of an optimum cytotoxic immune response. The larger particles (500 nm) predominantly reside at the injection site while the smaller ones freely move to the lymph node area where these interact with resident DCs. Smaller particles also provide higher surface area and superior membrane permeability which support their efficient uptake[57]. A quick particle uptake and longer post-injection retention of smaller particles (<100 nm) have also been reported[58]. This suggests the suitability of these particles for designing future *in vivo* targeting strategies. In addition, maintaining the appropriate particle shape is also crucial as spherical particles are supposed to have less premature clearance, more circulatory halftime and good organ distribution[58,59].

Following size and shape of the particle, another vital factor for developing effective nanoengineered DC vaccines is the mode of administration. NPs injected through intraperitoneal mode interact with the macrophages, while, upon intradermal (i.d.) administration, NPs are taken up by DCs. It has been reported that i.d. injected particles move preferentially to lymphatics with an average 50 per cent higher bioavailability as compared to intramuscular (i.m.) mode[59]. Moreover, the kinetics and magnitude of tumour cell-specific Th1 responses were reported to be strongly influenced by the mode of administration [i.d., i.m., intralymphatic (i.l.) and s.c.]. Administration of different NPs such as chitosan, liposomes and poly(lactic-co-glycolic acid) (PLGA) through i.l. route induces a strong Th1-type immunological response which is a determining factor for therapeutic use of nanoengineered DCs[60].

Nanocarriers for dendritic cell nanoengineering

Different nanocarrier systems have been evaluated for the treatment of FRCs. These nanocarriers including lipid-based and/or polymer-based systems have been broadly used to deliver therapeutic drugs/tumour antigens and have also shown to possess the ability to target both tumour cells and microenvironment. The HPV16 E7 small interfering (si) RNA-loaded chitosan NPs were reported to successfully restrict the tumour cell proliferation and reverse the drug resistance of ovarian tumour cells, suggesting these nanocarriers as promising therapeutic mediators for treating gynaecological malignancies[61]. Similarly, cisplatin-loaded liposomal formulations effectively targeted cancer cells of the female reproductive tract. The observed growth inhibitory effects were better than that of free cisplatin[62]. The liposomal formulation comprising a new T7 peptide which exclusively attaches to the transferrin receptor, reported best *in vivo* growth inhibitory effect on ovarian carcinoma cells[63]. In addition, in comparison to the plain liposomal doxorubicin, peptide-conjugated liposomal doxorubicin was shown to be better in controlling tumours[64].

Polymeric NPs such as PLGA are also effectively analyzed for the release of therapeutic molecules. The delivery of tumour-associated antigens through PLGA-NPs enables DCs to proficiently trigger tumour-specific responses. The encapsulation

angiogenesis inhibitors (TNP-470-NP-APRPG) through PLGA showed promising results for utilizing the strategy for treating ovarian cancers[65]. Administration of short hairpin (sh) RNA encapsulated with PLGA showed significantly higher anti-tumour effects against ovarian cancer cells[66]. Therapeutic efficiency of novel folic acid decorated-PEG-PLGA NPs for targeting the drugs to cancer cells in endometrial cancers has also been shown[67]. The dosage of PLGA-PRINT NPs loaded with chemotherapeutic drug docetaxel and chitosan NPs containing mEZH2 siRNA was reported to be associated with considerable anti-angiogenic and pro-apoptotic consequences in tumour cells[68]. NPs carrying oligonucleotide duplexes dramatically raised the immune stimulatory activity of miR-155 in DCs related to ovarian cancers[69]. It has been shown that surface-modified PEG-poly caprolactin-NPs strongly activate DCs for antigen cross-presentation and thus can be used as a potent immune adjuvant[70].

A number of other NPs have been used for directing immune cells to target and increase the eradication of gynaecological tract tumours. Recently, the combination of NPs with albumin-bound paclitaxel and nedaplatin was observed to be active and well tolerable for treating cervical cancer patients with late-stage, frequent or metastatic disease[70]. Carbon NPs were shown to precisely envisage the pathological status of pelvic lymph nodes in early cervical tumours, suggesting their larger function towards generating DC immunotherapy against these cancers[71]. Synergistic combination of micellar-based telodendrimer nanocarrier systems with chemotherapeutic drugs paclitaxel and cisplatin resulted in a competent and targeted delivery of drug to tumour cells along with reduced toxicity and potent immunological effect[72]. The efficiency of this system has been re-validated with bortezomib and doxorubicin where these multifunctional telodendrimer nanocarriers were reported to restore therapeutic synergy with minimum cytotoxicity in ovarian cancers[73]. PEGylated peptide diaminocyclohexyl-platinum conjugates are suggested to be new prospective drug release method with enhanced anti-tumour efficacy and clinical possibility in treatment of ovarian cancer malignancies[74]. The superiority of cationic liposomes and Toll-like receptor (TLR)-3 agonist complexes towards improving the tumour-specific immune response has been attributed to the TLR3-interferon regulatory factor signalling within DCs[75].

Several NP formulations including polymeric formulations and lipid-based systems have been utilized for developing a successful nanocarrier system for efficient antigen delivery to DCs. Among the studied NPs, solid-lipid NPs (SLN) offer the most efficient delivery system. SLN systems initially prepared in the early 1990s belong to class of the standard colloidal systems which have a solid-lipid core making internal core minimally exposed to water, thereby possessing increased stability of the loaded material[76]. Besides, the surface of these NPs can be simply attached with appropriate ligands for targeting, has superior payload and is minimal toxic[52]. SLN is prepared by utilizing lipids such as triglycerides which have high melting points and their lipid core is stabilized by different emulsifiers. In addition, the ease of surface modification enables and ability to co-encapsulate adjuvants further improve their capability to activate DCs and provoke a strong anti-tumour response. These properties have been significantly supported by the reports which suggest SLN as an optimum nano-carrier system[77,78]. Cationic SLN loaded with STAT3 decoy oligodeoxynucleotides was reported to efficiently transfect genes, inhibit invasion and stimulate apoptosis in ovarian cancer cells[79]. Wang *et al*[79] suggested that SLN surface modified with hyaluronic acid act as a potential carrier to target tumour cells and overcome multidrug resistance associated with in cervical cancers. These studies provide a platform to utilize nanocarrier systems for developing optimum DC-based vaccines. However, the choice of an optimum system is vital but confusing. In a study, a relative evaluation of lipophilic NPs was performed to recognize and develop an optimum NP-based strategy for DC-based targeting of TRICS in gynaecological cancers. The study reported that in comparison to other studied lipid-based nanocarriers, mannosylated-SLN was a feasible and optimum approach. Mannosylated SLN-pulsed DCs were observed to be efficiently taken up by DCs, induced minimal toxicity and were more potent inducers of tumour cell-specific immune responses[50].

Nanocarriers for in vivo targeting

The limited existence of the administered DCs restricts their activity and not many of these reach to the lymph nodes which is a major reason for the observed limited effectiveness of these vaccines[45]. Therefore, focusing on the DCs within the body instead of culturing them *ex vivo* may be an option. This can be done using NP-mediated DC-targeting approaches which consist of a blend of antigens and other vaccine constituents. Further, addition of immune activating adjuvants may help generate a surrounding environment which aid effective DC recruitment and activation to increase the vaccine efficiency[80]. In addition, surface modification

of the NPs with ligands specific for DC membrane receptors enable the NPs to dynamically target DC with no or minimal non-specific uptake[81-83]. Upon administration, the NPs interact with the *in vivo* residing DCs, and due to the prolonged antigenic release, these cells come out of suppressive microenvironment and trigger tumour cell-specific immune responses[84-86].

Earlier evidence also suggests that *in vivo* DCs targeting is an efficient option with huge immunological prospective[87-89]. In this regard, C-type lectin receptors (CLR) is one of the vital ligands analyzed for precise DC targeting. CLR holds the ability to bind with the antigenic carbohydrates residues. Broadly, CLR is divided into two categories, *i.e.* type I and type II. Targeting DCs with DEC-205 and CD11c labelled liposomes showed significantly increased tumour-cell specific immune responses[90]. Perhaps preparing the blend of MHC-I and T-helper cell epitopes with CLR-specific molecules on NPs might hold as a promising approach for inducing a competent tumour cell-specific T-cell responses[56]. Similarly, liposomes surface modified with glycans exhibited an enhanced encounter with DCs[91]. Incorporating LPS additionally augmented T-cell activation signifying the anti-tumour potential of the approach[91]. Upon administration of the NPs (gold nanocarriers and liposomes) modified with Fc receptor, efficient interaction with DC receptor was observed which suggested their potential ability to target DCs and activating tumour cell-specific immune responses[92]. Investigations have also shown the ability of superoxide iron NPs towards DC targeting and inducing efficient migration *in vivo*, with superior bio-compatibility[93,94]. This ability of NPs can be further improved by including imaging mediators which enable simultaneous monitoring of nanocarriers and assist in further designing the improved targeted approaches[81]. Developing such DC targeting strategies will help towards overcoming immune suppressive tumour surroundings and designing efficient strategies

Table II. Nanoparticles for engineering dendritic cells to target tumour re-initiating cells in gynaecological malignancies

Nanoparticle	Properties	References
Liposomes	Non-toxic, biocompatible, biodegradable NP	51, 95
	Prompt RES clearance	
	Approved by FDA for clinical use	
Solid lipid nanoparticles	Non-toxic, biocompatible and biodegradable NP	32, 50, 96
	Long-term stable storage	
	Prompt surface modification	
	FDA approved for clinical use	
	Ease in higher pharmaceutical manufacturing	
Poly-(lactic-co-glycolic acid)	Non-toxic, biocompatible, biodegradable NP	97, 98
	Long-term stable storage	
	FDA approved for clinical use	
	Ease in higher pharmaceutical manufacturing	
Poly-ε-caprolactone	Non-toxic, biocompatible, biodegradable NP	99,100
Poly (propylene sulphide)	Non-toxic, biocompatible and biodegradable NP	101
	Long-term stable storage	
Poly (γ-glutamic acid) nanoparticles	Biocompatible and biodegradable NP	102
	Long-term stable storage	
Chitosan	Non-toxic, biocompatible, biodegradable NP	103, 104
	Long-term stable storage	
	Ease in surface modification	
Gelatin	Non-toxic, biocompatible, biodegradable NP	105
	Trouble-free manufacture	
	Prompt surface modification	

NP, nanoparticles; RES, reticular endothelial system; FDA, Food and Drug Administration

for cancer therapy in future. A brief detail of different NPs which can be used for generating nanoengineered DCs is provided in Table II.

Conclusion

DCs vaccines offer a potential therapeutic modality for FRCs. The promising results observed in pre-clinical and clinical studies encourage continuing efforts towards further optimizing these methodologies and validating combinatorial therapeutic approaches. A major effort must be dedicated towards designing approaches to overwhelm the well-identified issue of tumour-associated immunological suppression. In this regard, incorporation of nanoengineering approaches may prove vital as these possess the ability to enhance the immune activation property of DCs. These engineered DCs are suggested to be safe and hold significant potential to eradicate TRICs. Encapsulation helps DCs to overcome immune suppression which later initiates a cascade of tumour-specific immune responses. Designing multifunctional NPs may further open the opportunities of direct *in vivo* targeting and may be vital as it will help in overcoming some important concerns related to *ex vivo* tumour antigen loading, short life-span of loaded DCs and faulty migration. In addition, the presence of substantial amount of resident DCs in the lymph nodes will assist in the efficient antigen uptake, processing and its cross-presentation to the neighbouring T-cell population to generate specific immune responses. These nanotherapeutic approaches have profoundly worked under different *in vitro* and *in vivo* conditions, however; their successful clinical translation relies on the ability of these vaccines to overcome different limiting factors. The present article was an attempt to showcase the need and significance of developing nanoengineered approaches, likely to maximize the therapeutic success of DCs against different FRCs.

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***Conflicts of Interest*:** None.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; *68* : 394-424.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; *136* : E359-86.
3. Binesh F, Akhavan A, Behniafard N, Jalilian S. Endometrial adenocarcinoma: Clinicopathologic and survival characteristics in Yazd, Iran. *Asian Pac J Cancer Prev* 2014; *15* : 2797-801.
4. National Cancer Intelligence Network. *Cancer incidence and mortality by cancer network, UK, 2005*. London: National Cancer Intelligence Network; 2008. Available from: *http://www.ncin.org.uk*, accessed on January 3, 2018.
5. Cervera P, Fléjou JF. Changing pathology with changing drugs: Tumors of the gastrointestinal tract. *Pathobiology* 2011; *78* : 76-89.
6. Holman LL, Pal N, Iglesias DA, Soliman PT, Balakrishnan N, Klopp A, *et al.* Factors prognostic of survival in advanced-stage uterine serous carcinoma. *Gynecol Oncol* 2017; *146* : 27-33.
7. Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA, *et al.* Race and hormone receptor-positive breast cancer outcomes in a randomized chemotherapy trial. *J Natl Cancer Inst* 2012; *104* : 406-14.
8. Swier N, Versteeg HH. Reciprocal links between venous thromboembolism, coagulation factors and ovarian cancer progression. *Thromb Res* 2017; *150* : 8-18.
9. Kim HG, Ryu SY, Joo JK, Kang H, Lee JH, Kim DY, *et al.* Recurring gastrointestinal stromal tumor with splenic metastasis. *J Korean Surg Soc* 2011; *81* (Suppl 1) : S25-9.
10. Dasari S, Wudayagiri R, Valluru L. Cervical cancer: Biomarkers for diagnosis and treatment. *Clin Chim Acta* 2015; *445* : 7-11.
11. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. *Best Pract Res Clin Obstet Gynaecol* 2017; *41* : 3-14.
12. Corrado G, Salutari V, Palluzzi E, Distefano MG, Scambia G, Ferrandina G. Optimizing treatment in recurrent epithelial ovarian cancer. *Expert Rev Anticancer Ther* 2017; *17*: 1147-58.
13. Grossman SA, Ye X, Lesser G, Sloan A, Carraway H, Desideri S, *et al.* Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. *Clin Cancer Res* 2011; *17* : 5473-80.
14. Mookerjee A, Graciotti M, Kandalaft L. A cancer vaccine with dendritic cells differentiated with GM-CSF and IFNα and pulsed with a squaric acid treated cell lysate improves T cell priming and tumor growth control in a mouse model. *Bioimpacts* 2018; *8* : 211-21.
15. Uppendahl LD, Felices M, Bendzick L, Ryan C, Kodal B, Hinderlie P, *et al.* Cytokine-induced memory-like natural killer cells have enhanced function, proliferation, and *in vivo* expansion against ovarian cancer cells. *Gynecol Oncol* 2019; *153* : 149-57.
16. Dzopalic T, Rajkovic I, Dragicevic A, Colic M. The response of human dendritic cells to co-ligation of pattern-recognition receptors. *Immunol Res* 2012; *52* : 20-33.
17. Garg AD, Vara Perez M, Schaaf M, Agostinis P, Zitvogel L, Kroemer G, *et al.* Trial watch: Dendritic cell-based anticancer immunotherapy. *Oncoimmunology* 2017; *6* : e1328341.

18. Burgevin A, Saveanu L, Kim Y, Barilleau E, Kotturi M, Sette A, *et al.* A detailed analysis of the murine TAP transporter substrate specificity. *PLoS One* 2008; *3* : e2402.
19. Theisen D, Murphy K. The role of cDC1s *in vivo*: CD8 T cell priming through cross-presentation. *F1000Res* 2017; *6* : 98.
20. Murthy V, Moiyadi A, Sawant R, Sarin R. Clinical considerations in developing dendritic cell vaccine based immunotherapy protocols in cancer. *Curr Mol Med* 2009; *9* : 725-31.
21. Brossart P, Wirths S, Stuhler G, Reichardt VL, Kanz L, Brugger W, *et al.* Induction of cytotoxic T-lymphocyte responses *in vivo* after vaccinations with peptide-pulsed dendritic cells. *Blood* 2000; *96* : 3102-8.
22. Hernando JJ, Park TW, Kübler K, Offergeld R, Schlebusch H, Bauknecht T, *et al.* Vaccination with autologous tumour antigen-pulsed dendritic cells in advanced gynaecological malignancies: Clinical and immunological evaluation of a phase I trial. *Cancer Immunol Immunother* 2002; *51* : 45-52.
23. Rahma OE, Ashtar E, Czystowska M, Szajnik ME, Wieckowski E, Bernstein S, *et al.* A gynecologic oncology group phase II trial of two p53 peptide vaccine approaches: Subcutaneous injection and intravenous pulsed dendritic cells in high recurrence risk ovarian cancer patients. *Cancer Immunol Immunother* 2012; *61* : 373-84.
24. Baek S, Kim YM, Kim SB, Kim CS, Kwon SW, Kim Y, *et al*. Therapeutic DC vaccination with IL-2 as a consolidation therapy for ovarian cancer patients: a phase I/II trial. *Cell Mol Immunol* 2015; *12* : 87-95.
25. Santin AD, Bellone S, Palmieri M, Zanolini A, Ravaggi A, Siegel ER, *et al.* Human papillomavirus type 16 and 18 E7-pulsed dendritic cell vaccination of stage IB or IIA cervical cancer patients: A phase I escalating-dose trial. *J Virol* 2008; *82* : 1968-79.
26. Chu CS, Boyer J, Schullery DS, Gimotty PA, Gamerman V, Bender J, *et al.* Phase I/II randomized trial of dendritic cell vaccination with or without cyclophosphamide for consolidation therapy of advanced ovarian cancer in first or second remission. *Cancer Immunol Immunother* 2012; *61* : 629-41.
27. Zhang W, Lu X, Cui P, Piao C, Xiao M, Liu X, *et al*. Phase I/II clinical trial of a Wilms' tumor 1-targeted dendritic cell vaccination-based immunotherapy in patients with advanced cancer. *Cancer Immunol Immunother* 2019; *68* : 121-30.
28. Coosemans A, Vanderstraeten A, Tuyaerts S, Verschuere T, Moerman P, Berneman Z, *et al.* Immunological response after WT1 mRNA-loaded dendritic cell immunotherapy in ovarian carcinoma and carcinosarcoma. *Anticancer Res* 2013; *33* : 3855-9.
29. Kandalaft LE, Chiang CL, Tanyi J, Motz G, Balint K, Mick R, *et al.* A phase I vaccine trial using dendritic cells pulsed with autologous oxidized lysate for recurrent ovarian cancer. *J Transl Med* 2013; *11* : 149.
30. Ramanathan P, Ganeshrajah S, Raghanvan RK, Singh SS, Thangarajan R. Development and clinical evaluation of dendritic cell vaccines for HPV related cervical cancer - a feasibility study. *Asian Pac J Cancer Prev* 2014; *15* : 5909-16.
31. Chen B, Liu L, Xu H, Yang Y, Zhang L, Zhang F. Effectiveness of immune therapy combined with chemotherapy on the immune function and recurrence rate of cervical cancer. *Exp Ther Med* 2015; *9* : 1063-7.
32. Bhargava A, Mishra D, Khan S, Varshney SK, Banerjee S, Mishra PK, *et al.* Assessment of tumor antigen-loaded solid lipid nanoparticles as an efficient delivery system for dendritic cell engineering. *Nanomedicine (Lond)* 2013; *8* : 1067-84.
33. Peethambaram PP, Melisko ME, Rinn KJ, Alberts SR, Provost NM, Jones LA, *et al.* A phase I trial of immunotherapy with lapuleucel-T (APC8024) in patients with refractory metastatic tumors that express HER-2/neu. *Clin Cancer Res* 2009; *15* : 5937-44.
34. Bhargava A, Mishra D, Banerjee S, Mishra PK. Dendritic cell engineering for tumor immunotherapy: From biology to clinical translation. *Immunotherapy* 2012; *4* : 703-18.
35. Flavell RA, Sanjabi S, Wrzesinski SH, Licona-Limón P. The polarization of immune cells in the tumour environment by TGFbeta. *Nat Rev Immunol* 2010; *10* : 554-67.
36. Pang Y, Gara SK, Achyut BR, Li Z, Yan HH, Day CP, *et al.* TGF-β signaling in myeloid cells is required for tumor metastasis. *Cancer Discov* 2013; *3* : 936-51.
37. Mittal SK, Roche PA. Suppression of antigen presentation by IL-10. *Curr Opin Immunol* 2015; *34* : 22-7.
38. Huang FP, Chen YX, To CK. Guiding the "misguided" - Functional conditioning of dendritic cells for the DC-based immunotherapy against tumours. *Eur J Immunol* 2011; *41* : 18-25.
39. van Baren N, Van den Eynde BJ. Tumoral immune resistance mediated by enzymes that degrade tryptophan. *Cancer Immunol Res* 2015; *3* : 978-85.
40. Ji RC. Lymph nodes and cancer metastasis: New perspectives on the role of intranodal lymphatic sinuses. *Int J Mol Sci* 2016; *18* . pii: E51.
41. Jung ID, Lee JS, Lee CM, Noh KT, Jeong YI, Park WS, *et al.* Induction of indoleamine 2,3-dioxygenase expression via heme oxygenase-1-dependant pathway during murine dendritic cell maturation. *Biochem Pharmacol* 2010; *80* : 491-505.
42. Obermajer N, Wong JL, Edwards RP, Odunsi K, Moysich K, Kalinski P, *et al.* PGE(2)-driven induction and maintenance of cancer-associated myeloid-derived suppressor cells. *Immunol Invest* 2012; *41* : 635-57.
43. Xue G, Romano E, Massi D, Mandalà M. Wnt/β-catenin signaling in melanoma: Preclinical rationale and novel therapeutic insights. *Cancer Treat Rev* 2016; *49* : 1-2.
44. Taylor MA, Sossey-Alaoui K, Thompson CL, Danielpour D, Schiemann WP. TGF-β upregulates miR-181a expression to promote breast cancer metastasis. *J Clin Invest* 2013; *123* : 150-63.
45. Bhargava A, Mishra D, Banerjee S, Mishra PK. Engineered dendritic cells for gastrointestinal tumor immunotherapy:

Opportunities in translational research. *J Drug Target* 2013; *21* : 126-36.

46. Lacerda L, Pusztai L, Woodward WA. The role of tumor initiating cells in drug resistance of breast cancer: Implications for future therapeutic approaches. *Drug Resist Updat* 2010; *13* : 99-108.
47. Yamashina T, Baghdadi M, Yoneda A, Kinoshita I, Suzu S, Dosaka-Akita H, *et al.* Cancer stem-like cells derived from chemoresistant tumors have a unique capacity to prime tumorigenic myeloid cells. *Cancer Res* 2014; *74* : 2698-709.
48. Malanchi I, Santamaria-Martínez A, Susanto E, Peng H, Lehr HA, Delaloye JF, *et al.* Interactions between cancer stem cells and their niche govern metastatic colonization. *Nature* 2011; *481* : 85-9.
49. Baumann M, Krause M, Hill R. Exploring the role of cancer stem cells in radioresistance. *Nat Rev Cancer* 2008; *8* : 545-54.
50. Bhargava A, Mishra DK, Jain SK, Srivastava RK, Lohiya NK, Mishra PK, *et al.* Comparative assessment of lipid based nano-carrier systems for dendritic cell based targeting of tumor re-initiating cells in gynecological cancers. *Mol Immunol* 2016; *79* : 98-112.
51. Bhargava A, Bunkar N, Khare NK, Mishra D, Mishra PK. Nanoengineered strategies to optimize dendritic cells for gastrointestinal tumor immunotherapy: From biology to translational medicine. *Nanomedicine (Lond)* 2014; *9* : 2187-202.
52. Mishra D, Mishra PK, Dabadghao S, Dubey V, Nahar M, Jain NK, *et al.* Comparative evaluation of hepatitis B surface antigen-loaded elastic liposomes and ethosomes for human dendritic cell uptake and immune response. *Nanomedicine* 2010; *6* : 110-8.
53. Mishra D, Mishra PK, Dubey V, Nahar M, Dabadghao S, Jain NK, *et al.* Systemic and mucosal immune response induced by transcutaneous immunization using hepatitis B surface antigen-loaded modified liposomes. *Eur J Pharm Sci* 2008; *33* : 424-33.
54. Herzberger J, Niederer K, Pohlit H, Seiwert J, Worm M, Wurm FR, *et al.* Polymerization of ethylene oxide, propylene oxide, and other alkylene oxides: Synthesis, novel polymer architectures, and bioconjugation. *Chem Rev* 2016; *116* : 2170-243.
55. Rice-Ficht AC, Arenas-Gamboa AM, Kahl-McDonagh MM, Ficht TA. Polymeric particles in vaccine delivery. *Curr Opin Microbiol* 2010; *13* : 106-12.
56. Mottram PL, Leong D, Crimeen-Irwin B, Gloster S, Xiang SD, Meanger J, *et al.* Type 1 and 2 immunity following vaccination is influenced by nanoparticle size: Formulation of a model vaccine for respiratory syncytial virus. *Mol Pharm* 2007; *4* : 73-84.
57. Foged C, Brodin B, Frokjaer S, Sundblad A. Particle size and surface charge affect particle uptake by human dendritic cells in an *in vitro* model. *Int J Pharm* 2005; *298* : 315-22.
58. Manolova V, Flace A, Bauer M, Schwarz K, Saudan P, Bachmann MF, *et al.* Nanoparticles target distinct dendritic cell populations according to their size. *Eur J Immunol* 2008; *38* : 1404-13.
59. Kourtis IC, Hirosue S, de Titta A, Kontos S, Stegmann T, Hubbell JA, *et al.* Peripherally administered nanoparticles target monocytic myeloid cells, secondary lymphoid organs and tumors in mice. *PLoS One* 2013; *8* : e61646.
60. Mohanan D, Slütter B, Henriksen-Lacey M, Jiskoot W, Bouwstra JA, Perrie Y, *et al.* Administration routes affect the quality of immune responses: A cross-sectional evaluation of particulate antigen-delivery systems. *J Control Release* 2010; *147* : 342-9.
61. Yang Y, Wang Z, Li M, Lu S. Chitosan/pshRNA plasmid nanoparticles targeting MDR1 gene reverse paclitaxel resistance in ovarian cancer cells. *J Huazhong Univ Sci Technolog Med Sci* 2009; *29* : 239-42.
62. Ringhieri P, Pannunzio A, Boccarelli A, Morelli G, Coluccia M, Tesauro D, *et al.* Effect of cisplatin containing liposomes formulated by unsaturated chain-containing lipids on gynecological tumor cells. *J Liposome Res* 2016; *26* : 307-12.
63. Wu H, Yao L, Mei J, Li F. Development of synthetic of peptide-functionalized liposome for enhanced targeted ovarian carcinoma therapy. *Int J Clin Exp Pathol* 2015; *8* : 207-16.
64. Shen YA, Liu CS, Chang YH, Chen PH, He CL, Wu HC, *et al.* Subtype-specific binding peptides enhance the therapeutic efficacy of nanomedicine in the treatment of ovarian cancer. *Cancer Lett* 2015; *360* : 39-47.
65. Wang L, Shi C, Wright FA, Guo D, Wang X, Wang D, *et al.* Multifunctional telodendrimer nanocarriers restore synergy of bortezomib and doxorubicin in ovarian cancer treatment. *Cancer Res* 2017; *77* : 3293-305.
66. Zou L, Song X, Yi T, Li S, Deng H, Chen X, *et al.* Administration of PLGA nanoparticles carrying shRNA against focal adhesion kinase and CD44 results in enhanced antitumor effects against ovarian cancer. *Cancer Gene Ther* 2013; *20* : 242-50.
67. Liang C, Yang Y, Ling Y, Huang Y, Li T, Li X, *et al.* Improved therapeutic effect of folate-decorated PLGA-PEG nanoparticles for endometrial carcinoma. *Bioorg Med Chem* 2011; *19* : 4057-66.
68. Gharpure KM, Chu KS, Bowerman CJ, Miyake T, Pradeep S, Mangala SL, *et al.* Metronomic docetaxel in PRINT nanoparticles and EZH2 silencing have synergistic antitumor effect in ovarian cancer. *Mol Cancer Ther* 2014; *13* : 1750-7.
69. Cubillos-Ruiz JR, Baird JR, Tesone AJ, Rutkowski MR, Scarlett UK, Camposeco-Jacobs AL, *et al.* Reprogramming tumor-associated dendritic cells *in vivo* using miRNA mimetics triggers protective immunity against ovarian cancer. *Cancer Res* 2012; *72* : 1683-93.
70. Li P, Song H, Zhang H, Yang P, Zhang C, Huang P, *et al.* Engineering biodegradable guanidyl-decorated PEG-PCL nanoparticles as robust exogenous activators of DCs and antigen cross-presentation. *Nanoscale* 2017; *9* : 13413-8.
71. Lu Y, Wei JY, Yao DS, Pan ZM, Yao Y. Application of carbon nanoparticles in laparoscopic sentinel lymph node detection in

patients with early-stage cervical cancer. *PLoS One* 2017; *12* : e0183834.

72. Cai L, Xu G, Shi C, Guo D, Wang X, Luo J, *et al.* Telodendrimer nanocarrier for co-delivery of paclitaxel and cisplatin: A synergistic combination nanotherapy for ovarian cancer treatment. *Biomaterials* 2015; *37* : 456-68.
73. Pan D, She W, Guo C, Luo K, Yi Q, Gu Z, *et al.* PEGylated dendritic diaminocyclohexyl-platinum (II) conjugates as pH-responsive drug delivery vehicles with enhanced tumor accumulation and antitumor efficacy. *Biomaterials* 2014; *35* : 10080-92.
74. Wang C, Zhuang Y, Zhang Y, Luo Z, Gao N, Li P, *et al.* Toll-like receptor 3 agonist complexed with cationic liposome augments vaccine-elicited antitumor immunity by enhancing TLR3-IRF3 signaling and type I interferons in dendritic cells. *Vaccine* 2012; *30* : 4790-9.
75. Pandit AA, Dash AK. Surface-modified solid lipid nanoparticulate formulation for ifosfamide: Development and characterization. *Nanomedicine (Lond)* 2011; *6* : 1397-412.
76. Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid lipid nanoparticles for targeted brain drug delivery. *Adv Drug Deliv Rev* 2007; *59* : 454-77.
77. Bondì ML, Craparo EF, Giammona G, Drago F. Brain-targeted solid lipid nanoparticles containing riluzole: Preparation, characterization and biodistribution. *Nanomedicine (Lond)* 2010; *5* : 25-32.
78. Ma Y, Zhang X, Xu X, Shen L, Yao Y, Yang Z, *et al.* STAT3 decoy oligodeoxynucleotides-loaded solid lipid nanoparticles induce cell death and inhibit invasion in ovarian cancer cells. *PLoS One* 2015; *10* : e0124924.
79. Wang F, Li L, Liu B, Chen Z, Li C. Hyaluronic acid decorated pluronic P85 solid lipid nanoparticles as a potential carrier to overcome multidrug resistance in cervical and breast cancer. *Biomed Pharmacother* 2017; *86* : 595-604.
80. Fahmy TM, Demento SL, Caplan MJ, Mellman I, Saltzman WM. Design opportunities for actively targeted nanoparticle vaccines. *Nanomedicine (Lond)* 2008; *3* : 343-55.
81. Cruz LJ, Tacken PJ, Rueda F, Domingo JC, Albericio F, Figdor CG, *et al.* Targeting nanoparticles to dendritic cells for immunotherapy. *Methods Enzymol* 2012; *509* : 143-63.
82. Shen C, Li J, Zhang Y, Li Y, Shen G, Zhu J, *et al.* Polyethylenimine-based micro/nanoparticles as vaccine adjuvants. *Int J Nanomedicine* 2017; *12* : 5443-60.
83. Benson Z, Manjili SH, Habibi M, Guruli G, Toor AA, Payne KK, *et al.* Conditioning neoadjuvant therapies for improved immunotherapy of cancer. *Biochem Pharmacol* 2017; *145* : 12-7.
84. Ishii M, Kato C, Hakamata A, Kojima N. Targeting with oligomannose-coated liposomes promotes maturation and splenic trafficking of dendritic cells in the peritoneal cavity. *Int Immunopharmacol* 2011; *11* : 164-71.
85. Heit A, Schmitz F, Haas T, Busch DH, Wagner H. Antigen co-encapsulated with adjuvants efficiently drive protective T cell immunity. *Eur J Immunol* 2007; *37* : 2063-74.
86. Bourquin C, Anz D, Zwiorek K, Lanz AL, Fuchs S, Weigel S, *et al.* Targeting cpG oligonucleotides to the lymph node by nanoparticles elicits efficient antitumoral immunity. *J Immunol* 2008; *181* : 2990-8.
87. Cruz LJ, Tacken PJ, Fokkink R, Joosten B, Stuart MC, Albericio F, *et al.* Targeted PLGA nano- but not microparticles specifically deliver antigen to human dendritic cells via DC-SIGN *in vitro*. *J Control Release* 2010; *144* : 118-26.
88. Reddy ST, Rehor A, Schmoekel HG, Hubbell JA, Swartz MA. *In vivo* targeting of dendritic cells in lymph nodes with poly(propylene sulfide) nanoparticles. *J Control Release* 2006; *112* : 26-34.
89. Luo G, Yu X, Jin C, Yang F, Fu D, Long J, *et al.* LyP-1-conjugated nanoparticles for targeting drug delivery to lymphatic metastatic tumors. *Int J Pharm* 2010; *385* : 150-6.
90. Altin JG, van Broekhoven CL, Parish CR. Targeting dendritic cells with antigen-containing liposomes: Antitumour immunity. *Expert Opin Biol Ther* 2004; *4* : 1735-47.
91. Unger WW, van Beelen AJ, Bruijns SC, Joshi M, Fehres CM, van Bloois L, *et al.* Glycan-modified liposomes boost CD4+ and CD8+ T-cell responses by targeting DC-SIGN on dendritic cells. *J Control Release* 2012; *160* : 88-95.
92. Cruz LJ, Rueda F, Cordobilla B, Simón L, Hosta L, Albericio F, *et al.* Targeting nanosystems to human DCs via fc receptor as an effective strategy to deliver antigen for immunotherapy. *Mol Pharm* 2011; *8* : 104-16.
93. Mou Y, Hou Y, Chen B, Hua Z, Zhang Y, Xie H, *et al.* *In vivo* migration of dendritic cells labeled with synthetic superparamagnetic iron oxide. *Int J Nanomedicine* 2011; *6* : 2633-40.
94. Tavaré R, Sagoo P, Varama G, Tanriver Y, Warely A, Diebold SS, *et al.* Monitoring of *in vivo* function of superparamagnetic iron oxide labelled murine dendritic cells during anti-tumour vaccination. *PLoS One* 2011; *6* : e19662.
95. Rupaimoole R, Ivan C, Yang D, Gharpure KM, Wu SY, Pecot CV, *et al.* Hypoxia-upregulated microRNA-630 targets dicer, leading to increased tumor progression. *Oncogene* 2016; *35* : 4312-20.
96. Peira E, Chirio D, Battaglia L, Barge A, Chegaev K, Gigliotti CL, *et al.* Solid lipid nanoparticles carrying lipophilic derivatives of doxorubicin: Preparation, characterization, and *in vitro* cytotoxicity studies. *J Microencapsul* 2016; *33* : 381-90.
97. Han HD, Byeon Y, Kang TH, Jung ID, Lee JW, Shin BC, *et al.* Toll-like receptor 3-induced immune response by poly(d,l-lactide-co-glycolide) nanoparticles for dendritic cell-based cancer immunotherapy. *Int J Nanomedicine* 2016; *11* : 5729-42.
98. Yang M, Yu T, Wang YY, Lai SK, Zeng Q, Miao B, *et al.* Vaginal delivery of paclitaxel via nanoparticles with non-mucoadhesive surfaces suppresses cervical tumor growth. *Adv Healthc Mater* 2014; *3* : 1044-52.
99. Wang N, He T, Shen Y, Song L, Li L, Yang X, *et al.* Paclitaxel and tacrolimus coencapsulated polymeric micelles that

enhance the therapeutic effect of drug-resistant ovarian cancer. *ACS Appl Mater Interfaces* 2016; *8* : 4368-77.

100. Jones SK, Lizzio V, Merkel OM. Folate receptor targeted delivery of siRNA and paclitaxel to ovarian cancer cells via folate conjugated triblock copolymer to overcome TLR4 driven chemotherapy resistance. *Biomacromolecules* 2016; *17* : 76-87.
101. Dai L, Yu Y, Luo Z, Li M, Chen W, Shen X, *et al.* Photosensitizer enhanced disassembly of amphiphilic micelle for ROS-response targeted tumor therapy *in vivo*. *Biomaterials* 2016; *104* : 1-7.
102. Cho SH, Hong JH, Noh YW, Lee E, Lee CS, Lim YT, *et al.* Raspberry-like poly(γ-glutamic acid) hydrogel particles for pH-dependent cell membrane passage and controlled cytosolic delivery of antitumor drugs. *Int J Nanomedicine* 2016; *11* : 5621-32.
103. Yang Y, Zhao X, Li X, Yan Z, Liu Z, Li Y, *et al.* Effects of anti-CD44 monoclonal antibody IM7 carried with chitosan polylactic acid-coated nano-particles on the treatment of ovarian cancer. *Oncol Lett* 2017; *13* : 99-104.
104. Cheng B, Lu B, Liu X, Meng T, Tan Y, Zhu Y, *et al.* A pH-responsive glycolipid-like nanocarrier for optimising the time-dependent distribution of free chemical drugs in focal cells. *Int J Pharm* 2017; *522* : 210-21.
105. Madan J, Gundala SR, Kasetti Y, Bharatam PV, Aneja R, Katyal A, *et al.* Enhanced noscapine delivery using estrogen-receptor-targeted nanoparticles for breast cancer therapy. *Anticancer Drugs* 2014; *25* : 704-16.

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