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REVIEW ARTICLE

Co-delivery systems: hope for clinical application?

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Abstract

Cancer is a multidimensional and challenging disease to handle. Current statistics reveal that we are far from satisfying cancer treatment. Taking advantage of different therapeutic agents that affect multiple pathways has been established as highly productive. Nevertheless, owing to several hindrances to conventional combination therapy, such as lack of tumor targeting, non-uniform pharmacokinetic of the combined drugs, and off-target side effects, it is well documented that this treatment approach is unlikely to address all the difficulties observed in monotherapy. Co-delivery systems could enhance the therapeutic efficacy of the combination therapy by targeting cancer cells and improving the pharmacokinetic and physicochemical properties of the therapeutic agents. Nevertheless, it seems that present knowledge in responding to the challenges in cancer treatment is still inadequate and far from optimal treatment, which highlights the urgent need for systematic studies direct to identify various aspects of co-delivery systems. Accordingly, to gather informative data, save time, and achieve superior results, the following steps are necessary: (1) implementing computational methods to predict drug-drug interactions (DDIs) in vitro and in vivo, (2) meticulous cancer studies at the cellular and molecular levels to obtain specific criteria for selecting preclinical and clinical models, (3) extensive physiological and pharmacokinetic study of nanocarriers behavior in preclinical models, and (4) finding the optimal formulation and analyzing its behavior in cellular and animal models facilitates bridging in vivo models to clinical trials. This review aims to deliver an overview of co-delivery systems, rationales, and suggestions for further studies in this field.

Keywords Combination therapy · Co-delivery systems · Nanomedicine · Drug development · Targeting therapy

Introduction

Despite new methods of diagnosing and treating cancer, a recent WHO forecast shows that by 2040, more than 16 million cancer deaths are expected each year [1]. The high mortality rate of cancer indicates that the current treatment approach is questionable to bring about promising tumor inhibition. The primary cancer treatment in the current practice is limited to surgical resection, radiotherapy, immunotherapy, and predominantly chemotherapy. The first option is mostly workable in the primary stages of cancer treatment. Despite the fact that surgical resection is still used in the treatment and control of most solid cancers, it has long been reported that surgery may accelerate tumor recurrence, the concept states that tumor resection may increase tumor recurrence [2]. To sum up, a growing body of evidence suggests that surgery may provide an appropriate environment for tumor progression. According to the in vivo studies, sites of injury provide desired site for tumor growth and that surgical trauma increases local metastases [3]. Besides, several experimental findings showed the tumor growth acceleration after surgery in distant locations [4]. On top, some studies show that open cancer resections are associated with shorter survival rate for patient compared to minimally invasive resections, a concept that is strongly corroborated by experimental data [5].

The unsuccessfulness of current therapies can be attributed to pharmacological and formulations issues [6]. Non-selective therapeutics specially in the case of chemotherapy and radiation [7–9], intrinsic/acquired resistance [10, 11], and mutations in the cancer cells [12, 13] have been observed in most of the conventional treatments. Moreover, the complexity of the tumor microenvironment (TME) limits

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drug delivery to the target site [14]. The poor solubility of chemotherapeutics, inappropriate and toxic excipients [15], short blood circulation time [16], and short half-life [17] of some therapeutic agents can decrease drug delivery to the tumor site. The findings of the long-term study in the cancer field confirm that the current treatments are not well-armed [18].

Combination therapy has been represented as simultaneous/sequential administration of the therapeutic agents that enhance the overall therapeutic outcome compared with the administration of the individual therapeutic agents. Combination therapy has shown advantages and merits over monotherapy. In the case of cancer, this hypothesis is somewhat plausible as combination therapies are used in the clinic frequently [19–21].

In general, combination therapy includes the following approaches: firstly, targeting multiple signaling pathways to overcome the cascade of mechanisms employed by cancer cells to counter therapeutics [22]; secondly, drug repositioning by reusing existing generic drugs for the alternate indication, which is an excellent approach for cancer treatment that can reduce the required dose of both individual drugs and shorten clinical translation and post-marketing process [23]; and thirdly, medicine personalization by developing new drugs based on the bimolecular characteristics of the tumor and genetic distinctions in humans can help to patient selection for a specific treatment [24]. Medicine personalization tailored to the tumor molecular characteristics is one of the topics of interest in current cancer treatment, which aims to target specific signaling pathways based on the individuals' genetic profile [25].

Despite recent achievements in this field, there are few numbers of targeting therapeutic agents such as small molecules designed for targeting HER2 on breast cancer (BC) cells [26], BRCA mutations in breast and ovarian cancer [27], BRAF mutations in melanoma [28], and EGFR mutations in lung cancer (LC) cells [29]. The findings of the clinical studies indicated the low efficacy of these therapeutic agents to bring about favorable outcomes [30]. It was reported that some of the targeting agents do not just act on the cancer cells; in other words, the targets of these therapeutic agents can be found in healthy tissues [31]. However, combination therapy presented noteworthy benefits over monotherapy; disappointing results usually accompany it due to the dissimilarities in the physicochemical and pharmacokinetics of drugs and distinctive action sites of the therapeutics [32].

In light of the necessity for optimal treatments, drug delivery systems (DDSs) are based on the unique characteristics of the TME, such as enhanced permeability and retention (EPR), hypoxia, and overexpressed ligands in the tumor have been designed [33–36]. DDSs present benefits by protecting drugs, increasing drug blood circulation [37], reducing side effects [38], and drug targeting [39, 40]. Co-delivery of anticancer agents exhibited superiority over the cocktails of a combination of anticancer [41, 42]. Co-delivery system design is extremely challenging cause besides adjusting the dose of therapeutic agents and their ratio; it is essential to determine the location [43], sequence [44], and release rate of both therapeutics [45]. In recent years, a variety of co-delivery systems have been designed in preclinical studies, while few of them exist on the market. The first part of this review aims to provide a brief overview of the reasons for the importance of co-delivery systems, followed by discussion over benefits, challenges, and opportunities in this field.

Combination therapy considerations

Therapeutics combination ratio: there is no general principle

In theory, when two therapeutics are administrated simultaneously, the combination effectiveness may be less (antagonistic), equal (additive), or higher (synergism) than the summed effect of the individual drugs [46]. Nevertheless, the difference between drug interactions, e.g., synergism and additive, is practically indistinguishable in pharmacotherapy. In other words, the principle to the best choice of regimen and drug combinations in the clinic is not well-known, and there is no mathematical formula to find the exact relationship between therapeutic agents in practice [18]. According to a recent analysis of human clinical trials (phases II and III) over a simulated population that implicated all possible combination therapies from patient-derived tumor xenograft models (PDX) data [47], $<5\%$ of potential combination therapies presented superior outcomes and improved progression-free survival, compared to monotherapy of individual drugs [48]. This unexpected report proved that most of the preclinical studies fail to show promising effects in the clinical trials, and there is an urgent need to employ a suitable strategy to match appropriate therapeutic agents.

Pharmacokinetic considerations

Drug-drug interactions (DDIs) are concerned to be one of the critical factors in designing combination therapies. These interactions affect not only the pharmacodynamics but also the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the individual drugs. The combination of the free form of therapeutic agents does not show satisfying outcomes due to the distinctive properties (solubility, permeability, stability, half-life, distribution) and non-uniform distribution [49]. Several databases have valuable information for checking DDIs such as Drug-Bank and the databases,

which are beneficial to check adverse effects such as FDA Adverse Event Reporting System (FAERS) [50]. The accurate computational prediction of cancer patients' responses is necessary to find the optimal combination therapy. Computational models are widely used to facilitate finding appropriate candidates for combination therapy [51]. These models utilize bio/chemo informatics information (physicochemical, pharmacodynamics, and pharmacokinetics) and clinical information (indications, safety information, drug interactions) from a variety of sources and make it possible to predict the behavior of drugs in combination [23]. Therefore, novel promising combinations can be recognized through high throughput and systematic approaches [52].

Cell and animal models

A fundamental issue in developing practical combination therapy is the mismatch between in vitro and in vivo test outcomes. The fact of the matter is that the simple methods of examining the effect of therapeutic agents in combination, which usually take place in a culture medium, do not provide accurate and reliable results [53]. Numerous reasons are associated with this consequence. The complex physiopathological condition in cancer which cannot be studied in the culture medium [54, 55], genetic differences in individuals [56], and the insufficient animal models to simulate genetic variations and carcinogenesis in humans [57] result in difficulties in the toxicity–efficacy studies of combinations therapies.

Recent findings have documented that TME in human tumor tissues contains dense stroma remarkably higher than the stroma observed in the tumor xenograft models. Besides, animal models cannot simulate drug pharmacodynamics accurately due to the lack of molecular characteristic simulation [58–61]. Preclinical outcomes are often meaningfully far from the clinical studies [62], and just about 8% of animal studies are translated into clinical trials [57]. Ultimately, roughly one-third of clinical trials successfully pass phase I [63]. These surprising results showed that the main reason for the poor translation of animal studies to clinical trials is the biological differences between models, which highlights the importance of developing reliable preclinical models.

Numerous studies conducted to determine if PDX mouse models could serve as a reliable model to simulate treatment response in individual cancer patients. These tumor models are developed by implantation of tumor cells or parts of a patient's tumors into the host mice [64]. One of the advantages of patient-derived models is the facilitation of molecular mechanism studies such as resistance of the tumor to the therapeutic agents. In a recent study, a set of PDX ovarian cancer models were generated from patients under the clinical procedure. These models simulate patients' responses to the standard chemotherapy treatment which is beneficial to a better understanding of the molecular-level mechanism of the therapeutic agents in ovarian cancer tumors [61]. In a new research on the mechanism of alkylating agents and PARP inhibitors, a triple-negative BC patient xenograft model was generated which uncovers a new resistance mechanism in BRCA1-methylated models [65]. One of the approaches to examine this is to treat PDX models with the therapeutic agents. For examples, Zhang et al. designed patient-derived human BC xenograft models to achieve in vivo models that reflect the complexity of BC pathophysiology particularly in the primary stages. This research showed strong correlation between PDX models and clinical response [66]. In this regard, a number of prospective studies used PDX models to guide clinical treatment decisions in a small number of patients. There are studies that have shown the strong correlation between PDX and clinical results [67]; for example, the research by Stebbing's et al. showed that 20.1% (6/29) of the patients with advanced, metastatic sarcoma received direct clinical benefits in from PDX-guided therapy [68]. Taken together, these models can mimic molecular characteristics of cancer cells and the TME, which present a great platform for drug development studies.

Why co-delivery systems?

Rational

Even though valuable, traditional combination therapy faces several limitations. For instance, differences in pharmacological fate and pharmacokinetic profile of individual therapeutic agents may cause serious side effects and systemic toxicity. When the therapeutic agent is loaded in a DDS, its pharmacokinetics are enclosed by the carrier; thus, the physicochemical properties of the delivery system determine the biological fate of the therapeutic agent [35, 39]. Co-delivery systems can unify the pharmacokinetic behavior of the therapeutic agents, improve physicochemical properties, increase biodistribution time, and enhance selectivity to the tumor [69]. The remarkable advantage of nanosystems is the ability to release therapeutic agents in a controlled manner in terms of location, time, amount, and sequence [33, 41, 42, 70–73]. Therefore, co-delivery systems can be considered potential candidates to maximize treatment efficiency, minimize side effects, and improve the pharmacokinetic profile of combined therapeutic agents (Fig. 1). Design and fabrication of the co-delivery system for cancer treatment are extremely complicated process. There are three major strategies to co-deliver therapeutics which combine chemotherapy with immunotherapy and/or gene therapy. Table 1 summarizes the rationales of designing co-delivery systems.

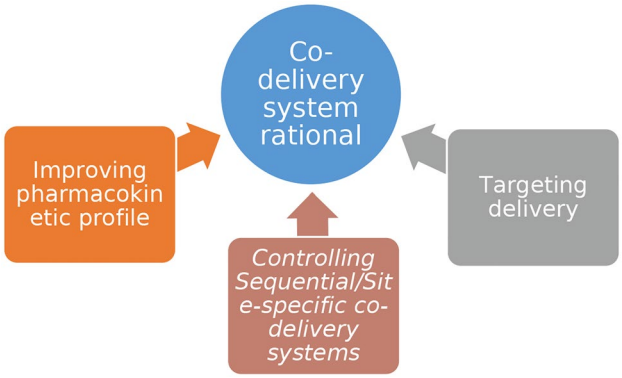

Fig. 1 Rational of designing co-delivery systems

Targeting delivery

The pathophysiological condition in solid tumors is very complicated. Since cancer cells need high energy to multiply actively, their demand for oxygen and nutrients is excessive [33]. These features contribute to an abnormal condition that significantly differs from healthy tissues. Extreme angiogenesis, hypoxia, and acidity eventually lead to a condition in which the vessels and the lymphatic drainage are impaired, which contributes to the interstitial fluid pressure elevation [54, 86].

The concept, EPR, which is known to exist to some degrees in solid tumors, is the main positive point about the tumors that explains why DDSs can penetrate the tumors efficiently [87]. Passive targeting, the primary evidence-based targeting delivery mechanism in the clinic [34, 88], relies on the EPR effect and facilitates tumor delivery of particles with specific features [89]. Another way to target tumors is by taking advantage of ligands that are overexpressed in the tumor cells or TME. This strategy, active targeting, is implemented in several clinical studies and seems to be in collaboration with passive targeting [35, 40, 90]. Here, some of the examples of targeting delivery are elaborated.

Anthracyclines are known to be the core stone of several cancer treatments [91]. Despite the usefulness of these therapeutic agents in cancer, several side effects limit their use in the clinic [92, 93]. According to the previous studies, doxorubicin administration as the first-line therapy in BC [94] showed irreversible cardiac dysfunction, which is exacerbated in combination with HER2-suppressing agents administrated in HER2-positive BC [95]. Even though advantageous, the doxorubicin and trastuzumab (HER2 targeting agent) combination failed to get FDA approval.

Various studies have surveyed the efficacy of receptor targeting liposomes in comparison to conventional therapies [96, 97]. Research studies have shown that liposomes can increase the therapeutic effect of highly potent drugs, specially chemotherapeutics [98, 99]. PEGylated liposomal formulation improved doxorubicin pharmacokinetics and showed less cardiac dysfunction compared with conventional doxorubicin or its combination with trastuzumab [100]. The relying mechanism of this result can be attributed to the particular characteristics of TME, such as abnormal vasculature that support nanosystems delivery into the tumor through the EPR effect [91]. However, there is some consideration in the combination of liposomal doxorubicin and trastuzumab, as trastuzumab may cause cardiac dysfunction by targeting HER2 receptors expressed in cardiomyocytes [31]. To take the most benefit and the fewer side effects of doxorubicin and trastuzumab-like agents, HER2-targeted liposomal doxorubicin was designed. Several preclinical models exhibited HER2-targeted liposomal doxorubicin superiority to non-targeted ones [90, 101]. The mechanism of this targeting doxorubicin-loaded liposome has shown in Fig. 2 [90].

Despite these reports, it was necessary to evaluate whether HER2-targeted liposomal doxorubicin is uptaken by cardiomyocytes or not. The findings of a recent study indicated that the uptake of HER2-targeted liposomal doxorubicin is negligible [102]. According to this research, slight or no cardiomyocyte cell death or dysfunction was observed. As HER2-targeted liposomal doxorubicin showed a promising effect in preclinical studies, it was entered into clinical studies. In a clinical dose-escalation study performed on patients who had metastatic BC, no cardiac adverse event in HER2-targeted liposomal doxorubicin monotherapy was reported, and progression-free survival increased about 3 months compared with conventional treatment regime [103]. These findings highlighted the potential of targeting co-delivery system application to reduce off-target side effects and increase selective toxicity in the target site.

Improving pharmacokinetic profile

There are various methods for co-delivery of the chemotherapeutics; some of them are easy to implement, such as coencapsulation into the polymeric core, which suffers from poor release kinetics of the individual drugs and inefficiency in loading hydrophilic therapeutic agents [104]. In contrast, this method showed promising results in the case of lapatinib and paclitaxel combination, which are hydrophobic chemotherapeutics [105]. There are alternative methods to deliver therapeutics with distinctive physicochemical prosperities such as polymer-drug conjugation [106]. The pH-responsive supramolecular hydrogel was designed, which could deliver NPOD, a hydrophobic molecule, by conjugation with PEG and doxorubicin as a hydrophilic molecule [107]; this co-delivery system showed a higher cytotoxicity effect in comparison with monotherapy.

Table 1 Rationales of designing co-delivery systems

Strategy	Rational	NC	Mechanism and results	Ref
Chemo + Chemo	Overcoming P-gp	Lapatinib and paclitaxel coloaded micelle	- P-gp inhibition by lapatinib and pluronic micelle - Reduced paclitaxel IC_{50}	[74]
	Overcoming genetic mutations	Gefitinib and vorinostat coloaded liposomal	- TAM repolarization through histone deacetylase inhibition - Resensitization of resistant tumor cells to gefitinib	[75]
	Increasing tumor delivery and accumulation	Doxorubicin and metformin loaded liposome	- Increased metformin accumulation in the tumor site - TME modulation through oxidative phosphorylation suppression induces by metformin	[76]
	Decreasing systemic toxicity	Gemcitabine and olaparib coloaded active targeting peptide nanoparticle (NP)	- Synergistic actions in vitro - Half-life prolongation of both drugs - Significant tumor suppression in vivo	[77]
	Overcoming TME barrier	Dexamethasone and docetaxel coloaded liposome	- Dexamethasone released before docetaxel results in vasculature normalization and decreased interstitial	[44]
	Impaired vascular and tumor cells	Combretastatin A4 and SN38	- Fluid pressure hence enhanced the therapeutic effect of docetaxel - Antiangiogenic effect of combretastatin A4 which was released SN38 before enhanced tumor inhibition	[78]
Chemo + Gene	Gene delivery and improving pharmacokinetic profile	ALN-VSP02 (a lipoplex that loads two different siRNA)	- Cell proliferation inhibition and vascular endothelial growth factor (VEGF) targeting	[79]
		P-gp siRNA and mitochondria complex polymeric prodrug carrier	- Antitumor activity in patients with solid tumors - Down-regulating of resistance-related proteins - Enhanced drug delivery and tumor accumulation in vivo	[80]
	Synergistic effect	miR122 and sorafenib coloaded micelle	- Increased cellular uptake efficiency - Decreased migration and invasion	[81]
	Controlled release at the target site	IKKβ-siRNA and DOX layer peeling co-delivery system	- Improved antitumor - Efficiency with macrophage-type re-polarization ability	[82]
Chemo + Immune	Effect on the TME	Checkpoint inhibitor NLG919 and doxorubicin polymeric prodrug carrier	- Increased immunoactivity in the TME - Increased tumor growth inhibition in vivo	[83]
		Mitoxantrone and a Cholesteryl Indoximod liposome	- Animal survival extension-induced chemo-immunotherapy responses by natural killer cells participation	[84]
		Doxorubicin and Interferon-γ Thermosensitive NP	- Synergistic antitumor efficiency - Combinational antitumor immune responses	[85]

The efficacy of co-delivery systems has been long-established in several clinical trials (Table 3). Vyxeos® is a liposomal formulation that combines daunorubicin and cytarabine (1:5 molar ratio), which received approval for acute myeloid leukemia (AML) [108]. The traditional regimes for AML consisted of cytarabine infusion for 1 week and doxorubicin bolus administration in the first 3 days. In contrast, this delivery system is infused in 1, 3, and 5 days [109]. As the clinical benefit of this co-delivery system was remarkable, which exhibited superior activity compared to the combination of bared drugs and patient compliance improvement, Vyxeos® was approved by the FDA for AML treatment in 2017 [110]. Switching genes on and off is one of the promising tools for cancer treatment as

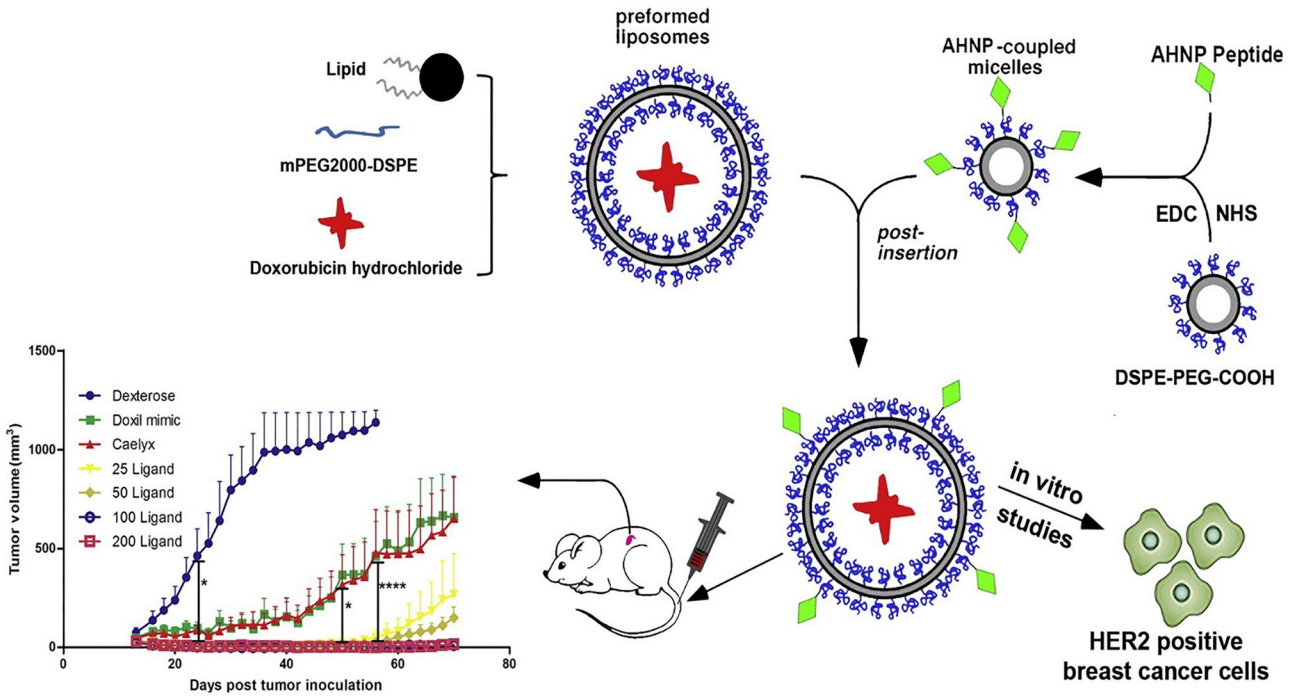

Fig. 2 Schematic illustration of improved drug delivery of doxorubicin by targeting anti-HER2 peptide in murine breast tumor model [90]. Reprinted with permission from Elsevier, June 2021

it enables treatment at the molecular level. However, using these strategies is challenging due to systemic toxicity, stability issues, low circulation time, and low cellular uptake of genetic materials [111]. Therefore, choosing the appropriate delivery system to take advantage of gene therapy is vital [112]. The first dual-targeted siRNA drug (ALN-VSP02) is a lipoplex that loads two different siRNA, one for kinesin spindle protein (KSP) targeting, which is responsible for cell proliferation, and the other one for vascular endothelial growth factor (VEGF) targeting. The clinical trial showed antitumor activity in patients with solid tumors [79]. It was observed that hypoxia-induced factor 1α (HIF-1α) is overexpressed in cancer cells. Several studies confirmed the correlation between hypoxia and cancer development and progression [113, 114]. Metformin is an antidiabetic medicine that showed potential anticancer effects by intervention in the hypoxic process [115, 116]. However, short blood circulation time, low tumor accumulation, poor bioavailability, and short half-life limit metformin application in the clinic as evidence-based researches are indicating low tumor accumulation of metformin [117]. The findings of a study that designed a liposomal co-delivery system for metformin and doxorubicin indicated the faster release of the metformin from the liposome, which could increase doxorubicin cytotoxicity in drug-resistant BC cells. This result is in accordance with the hypoxia improvement caused by doxorubicin and metformin coloaded liposome [76].

Controlling sequential/site-specific co-delivery systems

Individual therapeutic agents present diverse pharmacodynamics, so it is necessary to control the release sequence, site, and rate of each therapeutic. As mentioned in the previous section, the sequence of drug administration is an important factor in the combination of therapy regimens. To achieve this goal, sequential and site-specific DDSs are designed. Generally, site-specific DDSs target tumor tissue and TME entities, such as vascular endothelial cells [118], tumor associated fibroblasts, tumor associated macrophage [119], and cancer stem cells [120] or affect cellular/subcellular mechanisms such as mitochondria [121, 122] and nuclei [123] related pathways. To the purpose, various DDSs are designed which can be triggered to release load in response to defined pH, temperature, enzyme activity, redox potential, and the external triggers such as light irradiation, magnetic, and electric fields [124]. There are mainly three strategies in this area:

Increasing NC penetration into the tumor Recent studies aim to target TME components included but are not limited to vascular endothelial cells [125], immune cells [126], and cancer stem cells [127]. Studies have confirmed that dexamethasone showed TME modulating effect, which is attributed to interstitial fluid pressure reduction [14]. Docetaxel and dexamethasone liposomal co-delivery system showed

promising effect in BC mice. It was reported that dexamethasone release before docetaxel release increased docetaxel delivery to the tumor, which resulted in an enhanced therapeutic effect in vivo [44].

Increasing therapeutic efficacy by targeting extracellular and intracellular cell death pathways Doxorubicin and TNF-related apoptosis-inducing ligand (TRAIL) hybrid NP was designed in which TRAIL was crossed linked to the outer shell of the NP and doxorubicin was encapsulated in the liposome core [128]. The extracellular release of TRAIL-induced cell death by targeting cell death ligand expressed in the cancer cell membrane beside increased doxorubicin uptake through cell-penetrating peptide modification on liposome showed promising cytotoxicity effect in the PDX model.

Reducing side effects Most cancer treatment regimens include protocols to prevent or reduce complications which are not specified to prevent off-target site effects in some of the cancer cases [129, 130]. It seems that the use of new methods such as simultaneous released co-delivery system may reduce the drugs side effects administrated in the cancer therapy protocols. In a recent study, a disulfide cross-linked low-generation peptide dendrimer-based nano polymer conjugate was designed (Fig. 3) [131]. This delivery system could increase doxorubicin release in the colon cancer cells due to the high concentration of glutathione in the cancer cells, while the presence of nattokinase, a thrombolytic drug [132], could reduce thrombolytic side effects in vitro [131].

Challenges in co-delivery systems: are we doing right?

Despite extensive studies at the academic centers and pharmaceutical companies, few DDSs enter clinical trials and many of which fail in the early phases. There is a considerable gap between enormous articles published in this field and nanomedicine on the market. As it can be seen (Table 2), there are few co-delivery DDSs in the market. Finally, the question arises as to what is the promising procedure for developing a co-delivery system which will be discussed in the following section.

DDS design

Carrier exploration in the body

Physicochemical properties of components of delivery systems including compatibility between all the materials and their ratio, shape, size, and surface charge of the NP should be optimized to achieve an ideal DDS that can inhibit cancer cell proliferation noticeably. In reality, DDSs do no show promising results in the clinic. It was reported that only about 0.7% of the injected NPs delivered into the tumor [144].

Size Further, a recent quantitative study showed that a tiny portion (< 0.0014%) of active targeting NPs could target cancer cells [145]. In addition, a recent study from 2015 to 2018

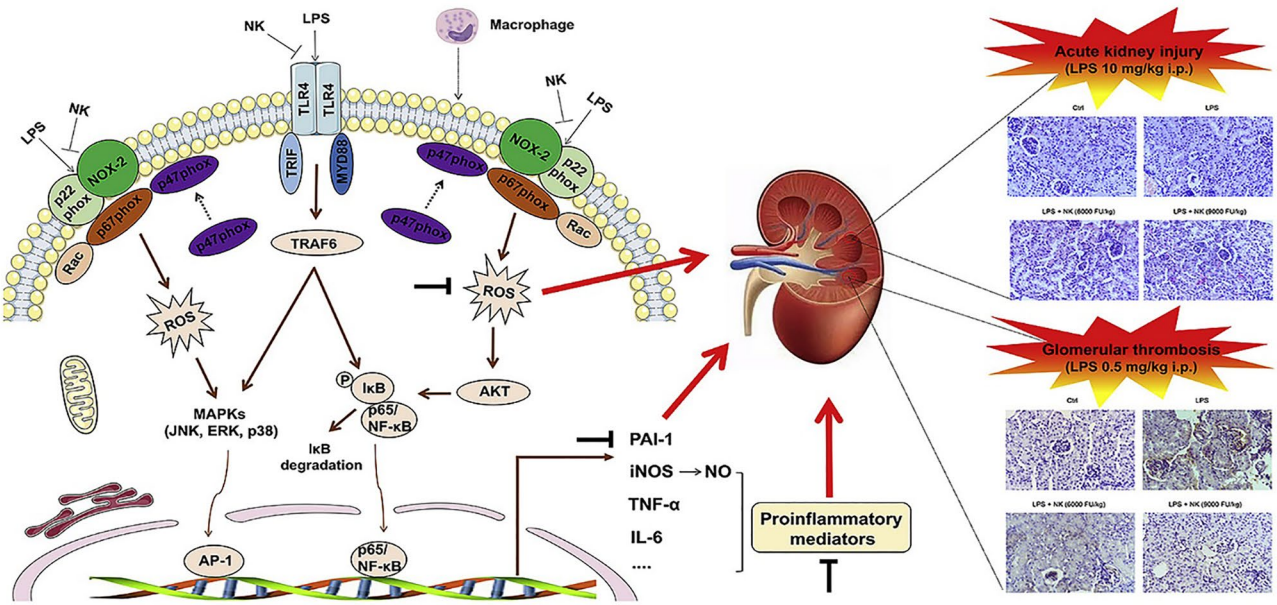

Fig. 3 Schematic illustration of the doxorubicin and nattokinase co-loaded DDS action on cancer cells [131]. Reprinted with permission from Elsevier, June 2021

Table 2 Some of the Approved nanomedicines for cancer treatment

Nanomedicine	Composition	Investigated application/indication	Ref
Doxil®	Liposomal doxorubicin	HIV-related Kaposi's Sarcoma, metastatic BC, advanced ovarian cancer, Multiple myeloma	[91]
Daunoxome®	Liposomal daunorubicin	HIV-related Kaposi's Sarcoma	[133]
Onivyde®	Liposomal irinotecan	Pancreatic cancer	[134]
Mepact™	Mifamurtide incorporated into large multilamellar liposomes	Non-metastasizing osteosarcoma	[135]
Eligard®	Leuprolide acetate incorporated in NPs	Advanced prostate cancer	[136]
Gendicine®	A recombinant adenovirus engineered to express wild-type p53	Treat patients with tumors that have mutated p53 genes	[137]
Rexin-G®	Gene inserted into the retroviral core of viral genes	Metastatic cancers	[137]
Genexol PM	Polymeric micelle paclitaxel	Metastatic BC, advanced LC	[138]
Abraxane®	Albumin NP paclitaxel	BC, NSCLC, pancreatic cancer	[139]
Marqibo®	Vincristine sulfate liposomes	Relapsed aggressive non-Hodgkin's lymphoma	[140]
VYXEOS®	Liposomal formulation of Cytarabine and daunorubicin	Acute myeloid leukemia	[141]
Mylotarg®	Monoclonal anti-CD33 antibody and calicheamicin	CD33-positive AML patients	[142]
Kadcyla®	Antibody–drug conjugate (ADC) trastuzumab emtansine	BC	[143]

revealed that only 2.23% (mean) and 0.76% (medium) of the injected dose could be delivered to the tumor site. According to the analysis of this study, the NPs having hydrodynamic sizes lower than 10 nm showed higher tumor delivery efficacy than the NPs with a size smaller than 10 nm [146]. This report is in agreement with the recent study, which showed that the 12-nm size NPs target tumors more selectively than the larger NPs, which were found in the off-target sites (liver, lung, and pancreas) [147]. Since nanosystems are known to be alien by the body's immune system, the other fraction of these particles taken up by the macrophages or filtered by the kidney, especially if the hydrodynamic diameter of the NP is lower than 5 nm, the other extraction way for NPs is through the liver in which NPs over ≈ 10–20-nm hydrodynamic diameter is eliminated [148].

Shape In terms of particle shape, several studies showed that nonspherical NPs could penetrate tumors more effectively than spherical NPs, as a study suggested that rod NPs are more promising for drug delivery purposes than the disc and sphere form NPs [149]. The results of a study indicated that nanorod gold NP tumor accumulation was higher than gold nanospheres [150]. Findings of another study which compared tumor penetration of nanorod and nanosphere particles showed that nanorods could penetrate tumor about 1.7 times more than nanospheres with the same hydrodynamic diameter [151].

Surface charge The other factor that controls NP delivery to the tumors is the surface charge, which plays a critical role in the absorption of biomolecules. Positive charge NPs have higher tumor delivery efficacy in comparison to negative charged NPs, which can be associated with the electrostatic interactions between the negative charge surface of cells and the NPs. During DDSs' circulation in the bloodstream, they are covered with a layer called "biocorona" that may lead to the rapid elimination of NPs [79]. The composition of the biocorona is significantly linked to the NP physicochemical properties (size, shape, charge, …). Studies have shown that the size of the NPs affects the composition and thickness of the biocrona layer [152]. The DDS type can affect the amount of biocorona composition and the toxicity of the DDS to the body. For example, the results of a study suggest that regardless of physicochemical properties, the adsorption of biocorona by AUNP is significantly influenced the biological effect of NP through the reduction of sole NP-negative hemotoxic [153]. Other findings suggest that regardless of NP chemical composition, proteins interact differently with NP, and some proteins, such as HSA, interact more strongly with the NP. The HAS-NP complex showed higher cellular uptake in comparison to fibrinogen-bound NP [154].

Safety

Despite numerous studies in nanotechnology, achieving effective and safe DDS remains a major challenge. The specific physical and chemical properties of NPs can lead to serious and unpredictable side effects in the human body [155]. Safety of a novel DDS must be strictly analyzed to prevent development of side effects in clinic which maybe the first step toward developing a successful DDS from the discovery phase to its entry into clinical trials [156]. Inorganic DDSs are amazing DDS of choice as they can overcome some of the inherent drawbacks of conventional organic DDSs [157], such as multidrug resistance due to the compositional properties such as high stability. In a recent

study, a mesoporous silica-based targeting nanocarriers could circumstance multidrug resistance efficiently [158]; however, there was some unsolved matters such as toxicity and side effects which are the major drawback of inorganic DDS which may be lessen by some modifications in their structure by application of biocompatible polymers [156]. Polymer-based NPs can be consisting of biodegradable and nonbiodegradable parts. Due to the chronic toxicity and high immunological response of nonbiodegradable polymeric NPs, biodegradable NPs are more promising for application as DDSs. [159]. The results of a recent study showed the efficacy of biodegradable thermo-sensitive copolymer hydrogel for the co-delivery of gemcitabine and cis-platinum to inhibit cellular proliferation synergistically and promote apoptosis in pancreatic cancer Bxpc-3 cell [159]. Extracellular vesicle DDSs have shown unique properties which make them promising DDSs. Extracellular vesicle carriers participate in important physiological and pathological processes such as of intercellular communication, cell maintenance, tissue repair, immune modulation, and tumor growth [159]. The results of Pei et al. on the tumor immune microenvironment after administration of cRGD-modified coloaded siFGL1 and siTGF-β1 showed tumor infiltration CD8 + T cells increase and immunosuppressive cells decrease, which can be conclude as the promoted antitumor immunity in the TME [160]. Although effective, the complex manufacturing process of this DDSs limits application of these DDSs in the clinic [161]. Most of the DDSs of interest in the clinical trials and also in the clinic are lipid-based NPs. Lipid-based DDSs that present interesting benefits include but not limited to biocompatibility, simple to synthesis, and capable to deliver various therapeutic agents (chemotherapeutics, siRNA, polyphenols, peptides) [39].

Co-delivery systems in the clinical trials

As mentioned above, to deliver drugs simultaneously, several DDSs are employed, including liposomes [42], micelles [162], dendrimers [163], hydrogels [164], and antibody–drug conjugates (ADCs). Regarding trends in the delivery systems for cancer therapy (Table 3), it can be found that liposome has received more attention [100]. These spherical structures composed of phospholipid and cholesterol are highly compatible and safe with the human body [165]; also, the structure of these DDSs allows the simultaneous transport of drugs with different physicochemical properties [166].

Liposomes can be called as the simplest forms of DDSs that can protect loaded drugs from external media, which can reduce systematic toxicity and loss of drugs in off-target

Table 3 Some of the co-delivery systems in the clinical trials

Name	Composition	Investigated indication	Clinical trial status	Outcome	Ref
MM-302	HER2-targeted liposomal doxorubicin (PEGylated)	BC	Early Phase 1/withdrawn/2018	Positive	[103]
Targomirs	Anti-EGFR bispecific antibody minicells (Mir-16 based microRNA payload)	Mesothelioma and non-small cell LC	Phase 1/completed/2017	Acceptable safety profile and signs of activity	[167]
C225-ils-dox	Doxorubicin-loaded anti-EGFR Immunoliposomes	Advanced triple-negative EGFR positive BC High-grade gliomas	Phase 1/recruiting/2021	Promising antitumor activity The relationship between antibodies and targeting immunoliposome effectiveness was not established	[168]
CPX-1	Irinotecan and floxuridine (1:1) Liposome	Colorectal cancer	Phase 2/completed/2008	CPX-1 superiority above FOLFIRI used after FOLFOX (Tournigand)	[97]
ALN-VSP02	Liposomal KSP/VEGF siRNAs	Advanced tumors	Phase1/completed/2012	The anti-VEGF effect was confirmed 1.25 mg/kg q2wks is the recommended phase II dose	[79]
DPX-0907	Liposomal 7 tumor-specific HLA-A2-restricted peptides and a polynucleotide adjuvant	Ovarian, breast, and prostate cancer	Phase1/completed/2011	Positive outcome High immunogenicity and adjuvant properties	[169]
Dher2 + AS15	Truncated HER2 protein in combination with the immunological Liposomal AS15 adjuvant	BC	Phase 2/completed/2009	Immunization of metastatic BC patients with the HER2 minimal toxicity	[170]

tissues [171]. Despite several advantages of liposomes, several studies showed high liver and spleen accumulation of these DDSs, which results in poor delivery into the target site [172]. Besides, it was found that the reticuloendothelial system eliminates liposomes rapidly [173]; to solve this problem, PEGylated liposome was introduced; however, PEGylation results in lower cellular uptake [174]. To address these issues, the natural carriers are introduced based on cell compositions. These carriers are safe as they are body-originated; they can cross physiological barriers and induce particular responses in target cells. Despite their superiority to synthetic delivery systems, no vesicle-based co-delivery system has been passed clinical trials, and more meticulous studies are needed to take advantage of these promising carriers. Elsharkasy et al. have discussed about extracellular vesicles in detail recently [175]. Conjugation of the drug molecule with an antibody, called "antibody–drug conjugates" (ADC), combines the characteristics of antibodies and drugs [176]. The presence of antibodies in these DDSs reduces the nonselective effect of the drug, minimizing side effects, and increasing tolerability and efficacy compared to the free drugs [36]. These appropriate characteristics make them interesting for combination therapy. Today, there are nine approve ADCs for cancer therapy in the clinic [177]. Between several co-delivery Emtansine is a potent antimicrotubule derivative of maytansine, and trastuzumab is a HER2 binding monoclonal antibody, which enables ADC uptake through receptor-mediated endocytosis. Kadcyla® is a coupling-based combination therapy consisting of trastuzumab and Emtansine. Clinical trials have shown the superior supporting effect of Kadcyla® compared to trastuzumab in HER2- positive BC patients [178]. Thus, it has been approved for the treatment of advanced BCs, mainly positive for HER2 [143].

Manufacturability and clinical translation: suggestions

Although nanotechnology has provided a worthy platform for the design of DDSs, due to technological limitations, such as loading method of the therapeutics (hydrophobic [179], electrostatic interaction [180] and chemical conjugation [181]), and DDIs, it is very difficult and challenging to predict nano-biological interactions in such a complex field [182]. Experimental and computational studies have enriched our knowledge of physicochemical properties of DDSs and the loaded therapeutic agent, the mechanism of action between them and nano-biological interactions including interactions with biological membranes and other biological molecules generally [183]. Theoretically, these models are based on primary screening of variables to predict appropriate conditions for successive experiments. Besides, these methods generally examine variables in detail are precious tools for high efficiency DDSs investigation [184]. Consequently, application of computational and experimental methods may be one of the best ways to proceed in the experimental process in the shorter time. Various types of computational models are presented to facilitate achieving DDS of interest considering size and continuum, which are generally employed to predict kinetics nano-biointeractions, biodistribution, and DDS penetration into target-site. Shamsia et al. discussed the recent advancements in computational modeling for nano-engineered DDSs [185]. Taking advantage of the experimental method, it is imaginable to determine the interaction effects of variables on response simultaneously [184]. In previous studies, the use of this method has been effective in accomplishing the optimal ratio and amount of formulation components to achieve the maximum drug load in the paclitaxel and lapatinib in the co-delivery system [105, 186]. Notwithstanding clear guidelines for nano medicine approved by the FDA, the growing transfer of DDSs from paper to the trials is increasing the application of nanomedicine in the clinic [187], the pharmaceutical industry is a potential barrier to combination therapy implementation. Many pharmaceutical companies are hesitant to cooperate in the clinical trials and marketing of combination therapies, which can be attributed to financial and insurance issues. On the other hand, the use of combination therapies requires special care and consideration because there are always concerns about controlling therapeutics dose in a combination and avoid side effects by such co-delivery systems [188, 189]. These studies are time-consuming due to the complicated process needed to prove the superiority of co-delivery systems to the bare form combination therapies. Therefore, combination therapy by co-delivery systems seems more expensive than the traditional treatment approaches. On the other hand, recent findings suggest that the extraordinary advantages of co-delivery systems are worth the short-term cost of these studies [190–192]. From this point of view, designing co-delivery systems for cancer treatment is of utmost prominence.

Conclusions and suggestions

An expanding understanding of cancer physiopathology offers considerable advances and accomplishments in cancer treatment. In light of various studies, the superiority of combination therapy is concluded. Co-delivery systems hold countless promises in improving the pharmacokinetics of the therapeutics and control release properties. Far too frequently, the wide gap separating preclinical research and approved co-delivery systems indicated that in vitro and in vivo studies fail to simulate human physiopathology. Despite the variety of DDSs, few co-delivery systems enter clinical trials, and a negligible number of them successfully pass the phases of clinical trials. Thus, the design of DDSs

in this area requires careful and original studies. First of all, the choice of the appropriate drug combination should be made by computational designs: Furthermore, basic research is needed to achieve the optimal combination index based on the DDIs and pharmacokinetics of each drug. Additionally, in vitro models should be harmonious with animal models, and the selected animal models should be able to simulate human tumor histopathology to bridge preclinical and clinical models. Predictive biomarkers can facilitate patient preselection for delivering specific and personalized treatment. In the formulation part, DDS design should be based on the computational studies to find the optimal formulations regarding physicochemical properties, pharmacokinetics, loading capacity, targeting the ability, and controlled release profile of the NP. Most importantly, experimental designs should be employed to ensure the proper drug ratio, pharmacokinetics, biological distribution, and adequate drug concentration at the tumor site to fulfill enhanced therapeutic efficacy. In the end, it should be noted that manufacturability, a limiting factor in developing co-delivery systems, should be considered by implementing simple, straightforward, and affordable preparation methods to translate lab studies to industrial-scale fabrication.

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Declarations

Competing interests The authors declare no competing interests.

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