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Recent advances in engineering prodrug-based nanomedicines for cancer therapy

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Despite substantial progress, nanomedicines still face numerous obstacles in cancer therapy. The combination of prodrugs and nanoparticle drug delivery systems has cooperatively led to unprecedented levels of control over the pharmacological properties of antitumor drugs, which gained significant attention a decade ago and is believed to propose pioneering clinical outcomes. Manipulating the matter within the nanoscale, prodrug-based nanomedicines are unified in classification and categorized by promoiety size and nanoconstruction formulation in the review. In addition, we focus on the updates of a broad spectrum of fabrication advances and applications in the field of prodrug-based nanotechnologies in multiple cancer therapeutic strategies in response to the tumor microenvironment, with special emphasis on chemotherapy and immunotherapy. Finally, the prospects and the potential threats of prodrug-based nanoassemblies toward the market and clinical uses are highlighted.

1. Introduction

The field of anticancer drug delivery has seen a growing interest in the use of drug nanocarriers to improve therapeutic efficacy and to reduce the risk of adverse reactions due to the inherent toxicity of these molecules. As concluded by Shen *et al.*, the successful delivery of nanomedicine involves five steps, including blood circulation, tumor accumulation, tumor penetration, cellular internalization, and drug release (also called the CAPIR cascade).[1] Each step exhibits distinct biological barriers, and the inability of conventional nanomedicines to efficiently circumvent all of these barriers results in their unsatisfactory therapeutic outcomes. The physicochemical features of nanomedicines including size, shape, surface charge and composition all play essential roles in each step and determine *in vivo* interaction with biomolecules, especially with proteins.[2,3]

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The proteins adsorbed onto the nanoparticle surface (also called, protein corona) were found in a recent study to perturb proteostasis and disrupt the cellular metabolism pathway, including glycolysis and lipid metabolism in cancer cells.[4] As a result, thorough comprehension of the biological effects and the structure–function relationship of nanomaterials is crucial for designing effective and safe nanoplatforms with optimal physicochemical properties and tumor-oriented capabilities.[5–7]

Ideally, the delivery of drugs loaded into nanodevices should:[8–10] (i) protect the drug from degradation/metabolization, (ii) deliver the pharmacologically active molecule to the target tissue or cell, (iii) reach the specific subcellular organelles (*e.g.*, cytoplasm, lysosomes, mitochondria, and nucleus), (iv) control drug release with the help of exogenous (*i.e.*, temperature, magnetic field, and light) or endogenous (*i.e.*, pH, enzymes, and redox) stimuli, and (v) even combine a therapeutic functionality with an imaging capability (the so-called ''nanotheranostic'' approach). However, the direct physical encapsulation of antitumor drugs into nanocarriers during nanoformation often faces serious challenges such as the burst release of encapsulated drug before reaching tumors upon systemic administration. The overuse of organic co-solvents during the formulation process to stabilize the poorly-soluble drugs leads to low activity and severe side effects. For all these reasons, developing nanoplatforms that accomplish improved physicochemical properties, prolonged systemic circulation, controlled drug release, and lessened drug toxicity is critically required.[11,12]

As an alternative strategy, the prodrug-based nanomedicine approach has found wide application to alleviate or even suppress the aforementioned limitations of nanomedicine.[13] A prodrug is formed by the covalent linkage between a drug and a (macro)molecule that is further metabolized (*e.g.*, hydrolytic degradation) to release the active form *in vivo*.[14,15] The covalent modification of a drug molecule into an inactive precursor from which the drug will be subsequently freed after administration offers several benefits, including:[16] (i) sustained and tumor microenvironment responsive drug release, (ii) reduced toxicity before the metabolization occurs, (iii) increased drug chemical stability and solubility, and (iv) facile encapsulation by nanocarriers or self-assembly into nanoparticles (NPs). To date, plenty of prodrug strategies, such as antibody–drug conjugates (ADCs) that target the over-expressed cancer-specific antigens, account for momentous positions in oncotherapy.[16,17] Researchers including Satpathy *et al.* demonstrated that Her-2 targeted ADC self-assembled nanoparticles presented long-time retention in tumor tissues, which induced a strong therapeutic response in breast and ovarian tumor models.[18,19] Thus, the combination of a prodrug strategy and nanotechnology is supposed to take advantage of the merits of both strategies and to achieve a potent synergetic effect for cancer therapy.

The prodrug nanocarriers can be roughly divided into organic and inorganic delivery systems.[19] However, the classification of prodrug-based nanodrug delivery systems (nano-DDS) hasn't been further reasonably unified for cancer therapy. Luo *et al.* first categorized prodrug nano-DDS into polymer–drug conjugates, self-assembling small molecular weight prodrugs and prodrug-encapsulated nanoparticles for cancer chemotherapy in 2014.[9] Meng *et al.* classified that solely by the structure and the constitution of prodrugs in 2019.[14] Zhang *et al.* further introduced prodrug-based nano-DDS using small molecule based, polymer–drug conjugate based and biomacromolecule-drug conjugate based prodrug nanoformulations in 2021.[20] In this review, we unified the classification and categorized the prodrug platforms according to the promoiety size and nanoconstruction formulation. Prodrug-based nanomedicines can be divided into small molecular prodrug (SMP)-based or macromolecular prodrug (also described as polymer prodrug, PP)-based Nano-DDS according to the molecular weight of the prodrug.[14,21] The SMP-based Nano-DDS with promoieties such as lipid fatty acids and cholesterol derivatives have been extensively used, which are further discussed in this review. Furthermore, according to the formulation and the construction approach, the prodrug-based Nano-DDS could be distinguished as self-assembled prodrug nanosystems and prodrug-encapsulated NPs.[22,23]

The prodrug-based system has become a notable trend in recent years to facilitate more efficient delivery of anticancer drugs and has been extensively explored in various cancer therapies. Our previous study demonstrated that reconstructing chemotherapeutics cabazitaxel (CTX) and 7-ethyl-10-hydroxy camptothecin (SN38) with a polyunsaturated fatty acid (*i.e.*, docosahexaenoic acid, DHA) and cholesterol *via* hydrolyzable ester bonds confers the generated prodrugs with sustained drug release profiles and improved pharmacokinetics for systemic chemotherapy *in vivo*.[24,25] The targeted drug delivery systems based on prodrug nanocarriers for cancer chemotherapy were also summarized in several published studies.[23,26,27] For example, Sun *et al.* recently introduced the latest updates of taxane prodrug-based nanomedicines (TPNS) and discussed the new trends of tumor stimuli-responsive TPNS.[26] In addition, prodrug-based nanomedicines have also been substantially exploited for cancer immune and combination therapy, which were also discussed in several review papers.[14,28,29] For instance, Yang *et al.* introduced prodrug nanomedicines as a promising strategy to improve cancer immunotherapy.[28]

In this review, we summarize the current emerging research studies and applications of prodrug nanomedicines as efficient strategies to improve multiple common cancer therapies, including chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), molecular-targeting therapy, immunotherapy, and combination therapy. We are the first to summarize the self-assembled nanomedicines based on photosensitizer (PS) or photothermal agent (PTA) prodrugs for PDT and PTT. Specifically, the applications of prodrug nanomedicines in cancer immunotherapy are introduced by the mechanism of action in this review, which can probably inspire the design of prodrug nanoparticles that can specifically target the corresponding tumor immuno-microenvironment. We also discuss the principles, challenges, clinical and commercial perspectives related to the development of nanomedicine-based prodrug approaches toward cancer therapy.

2. Classification of prodrug-based nanomedicines

Prodrug-based Nano-DDS consist of SMP- or PP-based Nano-DDS on the basis of their molecular weights (Fig. 1). Both SMPs or PPs can self-assemble into NPs or be encapsulated in nanocarriers (organic or inorganic carrier) by noncovalent interactions (*e.g.*, hydrophobic forces and electrostatic interactions). The nanosystems based on those two prodrugs are reviewed in the following section.

2.1 SMP-based Nano-DDS

SMP-based Nano-DDS are formed by self-assembly of the SMP or loading of nanocarriers (*e.g.*, liposomes or micelles) with SMPs. The SMP-based nanostrategy utilizes properties of the conjugates, such as high solubility and pharmacokinetics properties, that are more suitable for biological applications than those of a single drug molecule.[13]

The self-assembly of SMPs can be divided into the nanoassembly of homodimer/oligomer and heterodimers/oligomer according to their chemical structure.[30] Researches on the self-assembly of homodimeric chemotherapeutics into NPs for cancer therapy are summarized in Table 1. Mostly focusing on the construction of homodimeric taxanes or camptothecin (CPT), those studies reported self-assembled SMP nanoplatforms with high drug loading and tumor responsive drug release for cancer chemotherapy. Small changes in the length or the adjustment of linkages exert great influences on the antitumor activity of homodimeric prodrug nanoassemblies. The generated dimeric anticancer drug ligand *via* a ROS activatable thioketal linkage is often coassembled with photosensitizers to form colloidal-stable nanoassemblies and to achieve synergistic chemo-photodynamic therapy.[31–33]

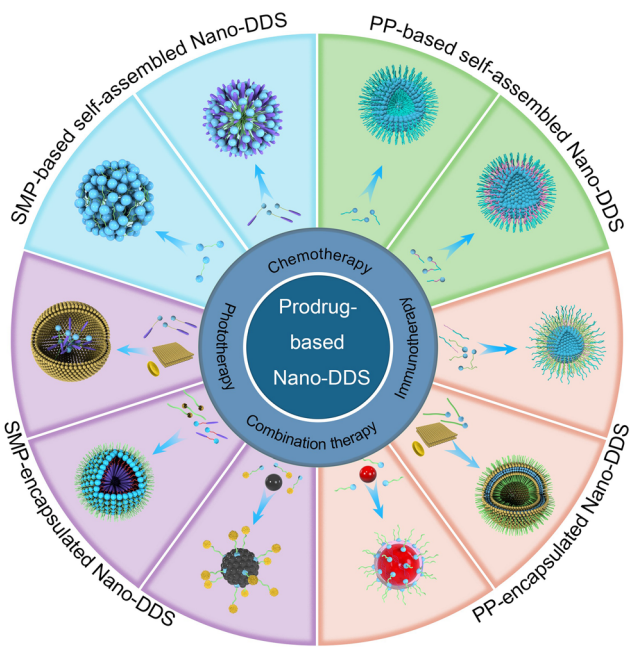


Fig. 1 Schematic of the formulation of prodrug-based nanoparticulate drug delivery systems (Nano-DDS) for cancer therapy. SMP: small molecular prodrug; PP: polymer prodrug.

For heterodimer/oligomer formulation, the side chain conjugated to the therapeutic drug can be hydrophilic (*e.g.*, lactose, folic acid, or a peptide) or hydrophobic (*e.g.*, a lipid or fatty acid). The self-assembly of SMPs into nanostructures often produces considerably high drug-loading efficiency and avoids issues encountered in nanocarrier binding and excipient-trigged adverse reactions, making SMP-based Nano-DDS a promising platform for anticancer drug delivery.[34]

In addition, the simple and reproducible one-step nanoprecipitation preparation methods used for SMP-based NPs are beneficial for scaling-up to industrial production and clinical translation.[35] However, the short blood circulation time caused by the lack of a dense shield layer (*e.g.*, a long chain polyethylene glycol [PEG]) and poor structural stability due to a relatively higher critical micelle concentration significantly hamper their drug potency, safety, and eventually hinder their clinical application.[23] Therefore, nanosystems self-assembled from SMPs are usually stabilized with a small amount of amphiphilic block copolymer containing a long PEG chain to achieve both a higher drug-loading efficiency and structural stability.[36,37] For example, a paclitaxel (PTX)-based self-assembled prodrug was developed by conjugating oleic acid to paclitaxel, and then a small amount of amphiphilic block copolymer tocopheryl PEG_{2k} succinate was selected as a surface active agent.[38] Impressively, PEGylated nanoassemblies exhibited higher stability compared with that of PTX self-assembled naked NPs. These PEGylated NPs achieved significantly high drug loading (56% of PTX, w/w), and the anticancer activity of this hybrid nanocarrier in a human epidermoid carcinoma murine model was significantly higher than that of the conventional clinical formulation (Taxol).

SMP entrapment into nanocarriers (*e.g.*, liposomes, solid lipids, polymeric NPs, and cell membranes) for tumor delivery is another strategy to achieve valid therapy with increased SMP stability, improved bioavailability, enhanced targeting to tumor cells, and increased capacity for encapsulation efficiency of both lipophilic and hydrophilic prodrugs.[52–54] The NPs used for SMP loading can be divided into organic and inorganic delivery systems. Organic nanocarriers, including polymer NPs, micelles, liposomes, dendrimers, and nanoemulsions have been studied for drug delivery,[55,56] while inorganic NPs, including silica, gold, silver, iron, and quantum dots, have favorable properties for extensive diagnostic and therapeutic use.[57–59] However, the main disadvantage of this entrapment strategy is related to the relatively low drug loading caused by using a high proportion of carrier materials during preparation.

2.2 PP-based Nano-DDS

Unlike SMPs, PPs refer to the conjugates where the carrier materials usually have a macromolecular weight and occupy a large portion of the nanostructure, and the polymers themselves play an important role in adjusting the hydrophilic–lipophilic balance of the conjugates.[60] The most widely used

Table 1 Research on the self-assembly of homodimeric chemotherapeutics into NPs for cancer therapy

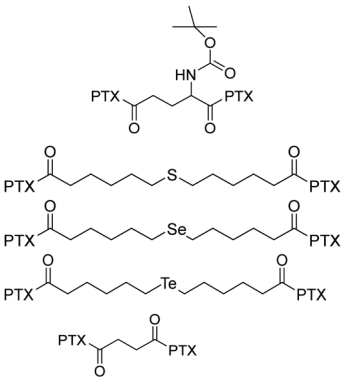
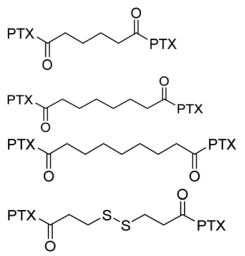
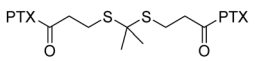
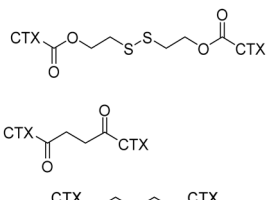
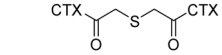
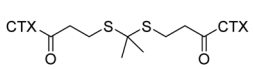
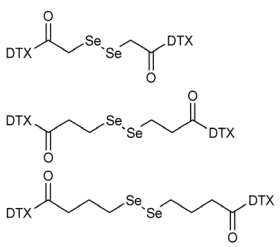
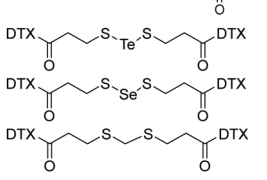
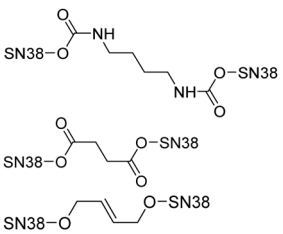
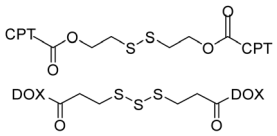
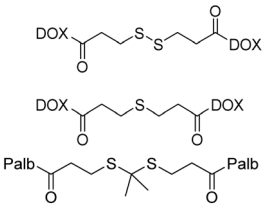
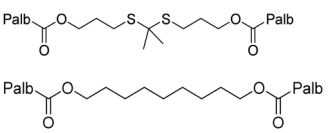
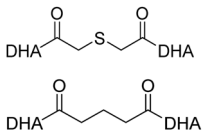
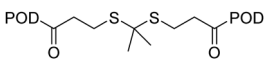
Chemotherapeutics	Drug	Structure	Findings	Ref.
Antimitotic agents	Paclitaxel (PTX)		Glu-PTX2 NPs could be internalized by cancer cells and exert potent cytotoxicity toward HeLa and MCF-7 cells.	39
			Among three dimers, the PTX2-Te dimer exhibits preferable cytotoxicity on HeLa cells, which is comparable to Taxol.	40
			PTX-SS-PTX dimer formed nanoparticles exhibited the most efficient endocytosis and cytotoxicity on HeLa cells and B16F10 cells.	41
			Nanoparticles coassembled from dimeric PTX prodrugs and porphyrin achieved synergistic chemo-photodynamic therapy.	31
	Cabazitaxel (CTX)		Self-assembled dimeric CTX preserves inherent pharmacologic efficacy while reducing *in vivo* systemic and immune toxicity.	42 and 43
			Driven by a photosensitizer, PPa, CTX-S-CTX self-assembled into nanoparticles and demonstrated potent antitumor activity in a 4T1 mice model.	44
			Coassembly with a photosensitizer, chlorin e6 (Ce6), CTX-TK-CTX self-assembled into nanoassemblies and produced durable tumor regression and low systemic toxicity in an orthotopic patient-derived xenograft (PDX) model of malignant melanoma.	32
	Docetaxel (DTX)		The longest diselenide bond-containing linkage facilitated the self-delivery of DTX prodrugs and achieved the maximum accumulation of DTX in tumor cells.	45
			DTX-STeS-DTX NPs resulted in the improved antitumor efficacy of DTX with satisfactory safety on the 4T1 tumor mice model.	46
Topoisomerase inhibitors	7-Ethyl-10-hydroxy camptothecin (SN38)		SN38 dimer self-assembled nanoparticles possess potent cytotoxic activity.	47

Table 1 (*continued*)

Chemotherapeutics	Drug	Structure	Findings	Ref.
	Camptothecin (CPT)		CPT-dimer self-assembled nanoparticles could be internalized by cancer cells and exert potent cytotoxicity on HeLa and HepG2 cells.	48
DNA intercalators	Doxorubicin (DOX)		Trisulfide bond-bridged prodrug nanoassemblies exhibit high selective cytotoxicity on tumor cells, notably reducing the systemic toxicity of DOX.	49
Cyclin dependent kinase inhibitor	Palbociclib (Palb)		The carrier-free nanomedicine self-assembled from Palb-TK-Palb and Ce6 showed high cellular uptake and *in vitro* antitumor activity on MDA-MB-231 cells.	33
NF-κB inhibitor	Dihydroartemisinin (DHA)		Ce6&DHA-*S*-DHA@CMN NPs enabled higher tumor accumulation, inhibited tumor metastasis, and achieved favorable chemo-photodynamic combination therapy.	50
Insulin-like growth factor-1 receptor	Podophyllotoxin (POD)		Incorporating VK3 and F127 into POD dimer self-assembled nanoparticles increased the therapeutic efficacy in MCF-7 tumor-bearing mice.	51

polymers in formulating PPs include PEG block copolymers (BCPs), polypeptides, polyaminoacids, and polysaccharides.[61–64] Each type of polymer offers distinct benefits for drug delivery. For example, the stretched PEG in the outer shell plays an important role in avoiding the elimination of Nano-DDS by the mononuclear phagocytes in the reticuloendothelial system, and polymers including polypeptides and polysaccharides usually have a large number of active groups (*e.g.*, hydroxyl, amino, and carboxyl) for easier chemical modification and higher drug-conjugating efficiency.[65,66]

PP-based Nano-DDS can also be distinguished by the self-assembly of PPs or PP-encapsulated nanoscaffolds. As elaborate nanoformulations, self-assembly of drug-conjugated polymers (usually amphiphilic copolymer) to form polymeric micelles possess several potential advantages,[67–69] including: (i) increased chemical stability due to the protection by the nanostructures, (ii) facilitated codelivery of different therapeutic agents for combinational therapy, and (iii) easier subsequent functionalizations on the surface of NPs for enhanced drug delivery efficiency. Conversely, although the loading of PPs in various nanocarriers can compromise the drug-loading efficiency to a degree, it often ensures higher stability and longer blood circulation time of the nanosystem.[70]

As depicted in Fig. 2, according to the construction of macromolecular prodrugs, the PP-based platform can be divided into a pure prodrug platform (PPP) or a combinative prodrug platform (CPP).[14] PPP refers to the direct use of drugs as a building unit in the polymer backbone, which is usually designed to ensure that drug molecules have longer persistence

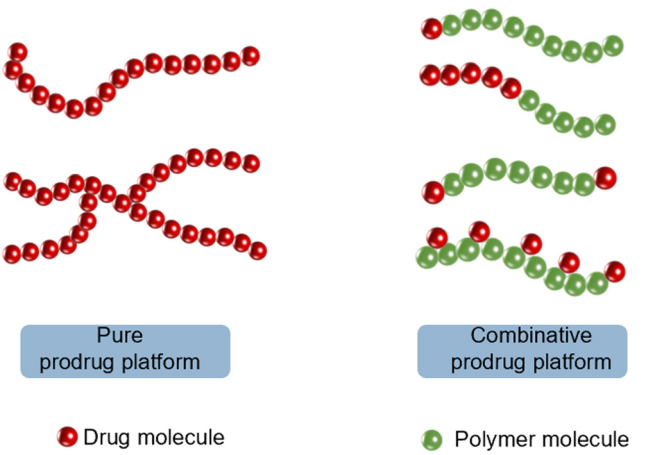


Fig. 2 Classification of polymer prodrug platforms. PP based on a pure prodrug platform and combinative prodrug platform.

during *in vivo* circulation, as well as to increase the drug loading and drug type to achieve a combination therapy. CPP mostly consists of polymer–anticancer drug conjugates for improved drug solubility and bioavailability. As shown in Fig. 3, the synthesis of drug–polymer conjugate can consist of three strategies:[60,65] (i) conjugating a drug to a presynthesized polymer, (ii) conjugating a drug to a monomer prior to polymerization, and (iii) growing a polymer chain initiated from a functionalized drug. The "conjugation to" approach is the most widely employed approach to achieve drug–polymer nanoparticulate systems.

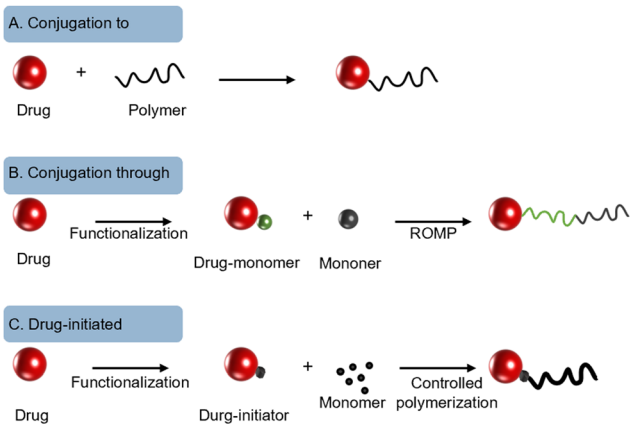


Fig. 3 Three main strategies for the synthesis of drug–polymer conjugates. (A) "Conjugation to" refers to conjugating a drug to a presynthesized polymer. (B) "Conjugation through" refers to conjugating a drug to a monomer prior to polymerization. ROMP: ring-opening metathesis polymerization. (C) "Drug-initiated" refers to growing a polymer chain initiated from a functionalized drug.

3. Prodrug-based Nano-DDS approaches for anticancer therapies

Prodrug-based Nano-DDS, which integrate the advantages of both prodrug and nanomedicines into a single nanoplatform, have been developed for effective drug delivery and have multiple advantages for high drug loading, enhanced stability, tumor targeting ability, and safety. This strategy has been widely studied for cancer therapy. In this section, the latest updates in prodrug-based Nano-DDS for various anticancer approaches are reviewed.

3.1 Prodrug-based Nano-DDS in chemotherapy

Chemotherapy remains an essential tool in cancer therapy. Although considerable efforts have been made toward the high-efficiency delivery of chemotherapeutic agents (CAs), several obstacles still limit the curative effect of chemotherapy, including:[71,72] (i) the inferior physiochemical properties of anticancer drugs, (ii) their poor metabolic stability and the quick clearance from the body of the CAs, (iii) undesirable distribution and tumor accumulation of the CAs, and (iv) inefficient cellular uptake of the CAs. These disadvantages contribute to the limited therapeutic efficiency and severe toxicity of chemotherapy. In response, the formulation of prodrug (SMP or PP)-based nanomedicines has been widely designed and studied to overcome the delivery barriers of CAs that include the inferior chemical stability, limited tumor targeting, poor tumor accumulation, and low cellular uptake.[23,73]

3.1.1 SMP-based nanomedicines for chemotherapy. Among the rational design of SMP-based nanomedicines, the direct self-assembly of homodimeric chemotherapeutics into NPs produces high drug loading, high self-assembly stability, high tumor selectivity, and low excipient-related toxicity. The linkers in the formulation of homodimeric CAs for efficient self-assembly into nanosystems are shown in Table 1. For example, Yang *et al.* separately introduced disulfide, thioether bonds, and trisulfide bonds for the construction of a doxorubicin (DOX) dimer (Fig. 4).[49] Only the trisulfide bond could effectively convert DOX homodimeric prodrugs into self-assembled NPs, and the trisulfide bond insertion showed higher glutathione (GSH) sensitivity compared with that of the disulfide bond. Therefore, the trisulfide bond-bridged prodrug nanoassemblies exhibited high drug-loading efficiency (67.24%, w/w) and tumor selective cytotoxicity, notably reducing the systemic toxicity of DOX.

Nano-DDS based on a lipid–CA conjugate has also attracted attention for cancer chemotherapy. Lipids such as fatty acids, cholesterol derivatives, phospholipids, and triglycerides, have been extensively used as promoieties covalently conjugated to CAs.[24,74] The lipid conjugation and subsequent nanosystem formulation helped to:[75,76] (i) resolve the poor solubility of several CAs, (ii) increase their biocompatibility with biomaterials approved by the Food and Drug Administration (FDA), and (iii) be readily internalized by cancer cells because of their lipophilic nature. Motivated by this concept, Wang and colleagues exploited a combinational strategy that involved a structure-guided prodrug formulation and a sequential prodrug-induced self-assembly process by conjugating the chemotherapeutic CTX with several lipids including DHA, linolenic acid, linoleic acid, oleic acid, stearic acid, and heptanoic acid. The resulting prodrug amphiphiles spontaneously formed nanocrystals in aqueous solutions.[12] The DHA modification on CTX produced enhanced *in vivo* stability, pharmacologic efficacy, therapeutic efficacy, and safety in comparison with conjugation with other lipids.

In addition to the self-assembled systems, structural similarities between lipid prodrugs and lipid-based nanocarriers may facilitate prodrug loading or insertion, for instance *via* simple nanocarrier membrane anchoring.[77] As shown in Fig. 5(A), our work demonstrated that the conjugation of cholesterol with therapeutic SN38 substantially increased the miscibility with a liposomal scaffold.[25] Our esterase-activatable prodrug (Chol-SN38)-based nanoassemblies exhibited elevated therapeutic efficacy in a human lung carcinoma murine model and improved drug tolerability in mice in comparison to the SN38 clinical counterpart irinotecan (Fig. 5(B) and (C)).

Lipid–CA based nanosystems have also been substantially applied to deliver inorganic therapeutics including the platinum (Pt) family.[78] For instance, a lipid-based Pt prodrug was formulated to grow alkyl chains at the axial positions and to ensure the stability in the hydrophobic core of the NPs for increased cancer therapy in the serial studies of Farokhzad *et al.*[79–81] Their recent research showed that both the Pt prodrugs and cysteine-based poly-(disulfide amide) (Cys-PDSA) polymers that readily react with GSH were formulated together with lipid–PEG to generate Pt(IV) prodrug-loaded Cys-PDSA NPs (CP5 NPs) for efficient Pt delivery and reversal of drug resistance (Fig. 6(A)). Prodrug-based NP formulation and tumor microenvironment responsive release of Pt showed prolonged persistence of Pt in systemic blood circulation and achieved tumor specific drug release of the payload in the redox tumor microenvironment (Fig. 6(B)). The resulting CP5 NPs displayed substantial growth inhibition of

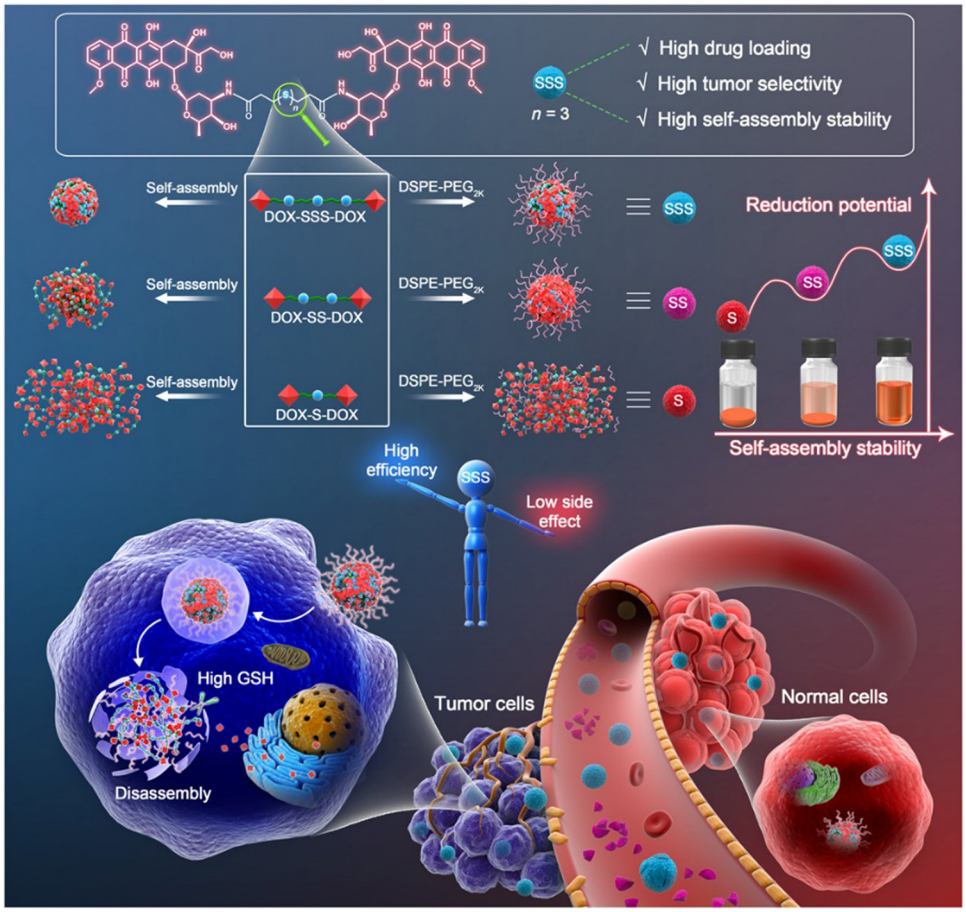


Fig. 4 Construction of nanoassemblies based on trisulfide bond-bridged doxorubicin (DOX) for cancer therapy. Reproduced from reference 49 with permission from Science, copyright 2020.

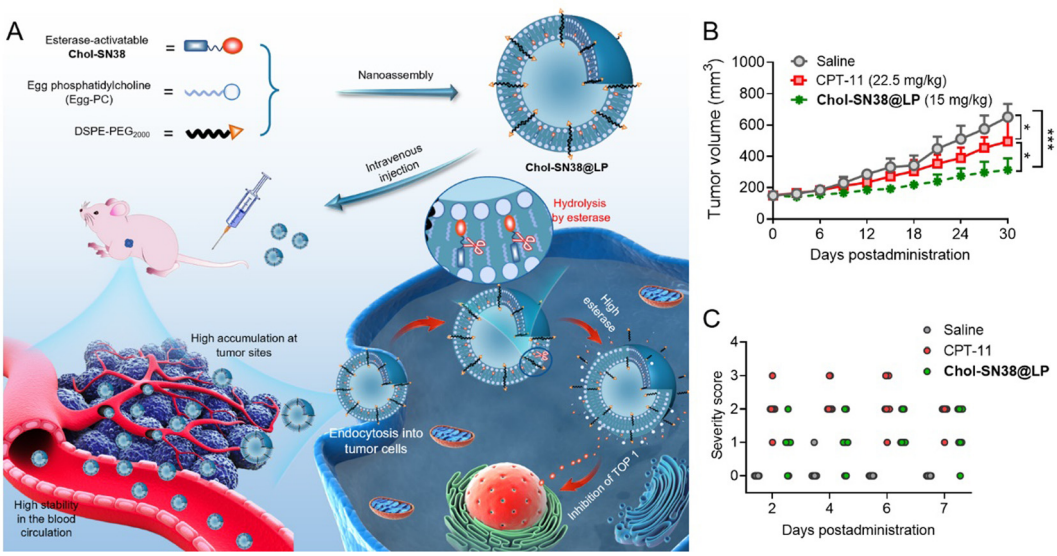


Fig. 5 *In vivo* delivery of esterase-activatable SN38 prodrug-based NPs Chol-SN38@LP. (A) Schematic illustration of the preparation and intravenous administration of Chol-SN38@LP for cancer therapy. Tumor growth curves of mice (B) and the bloody diarrhea severity score in mice (C) after treatment with Chol-SN38@LP and irinotecan (CPT-11). Reproduced from reference 25 with permission from The Royal Society of Chemistry, copyright 2022.

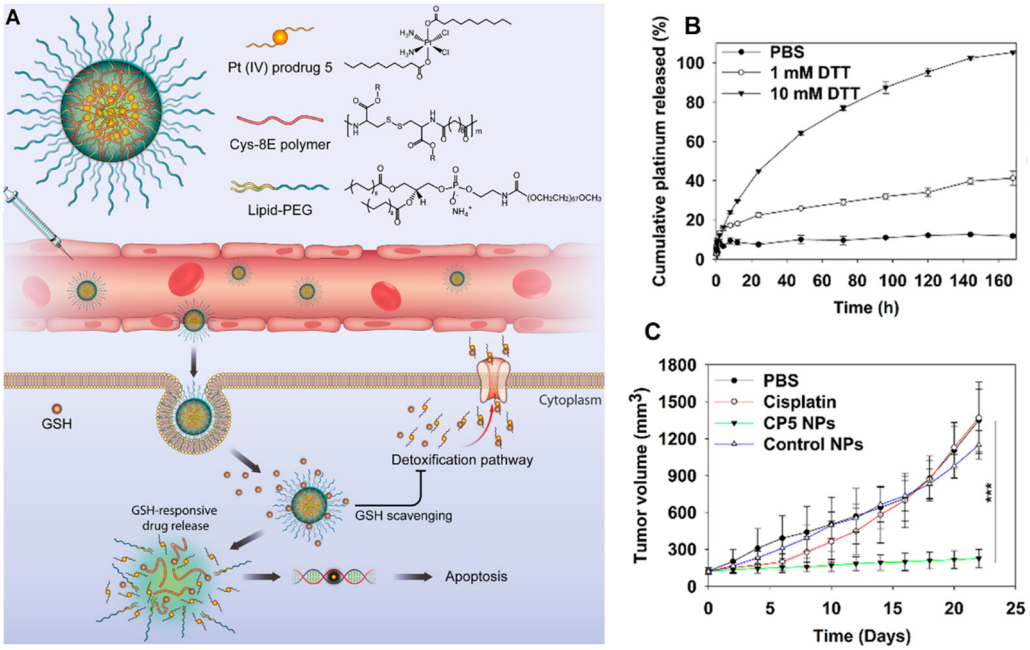


Fig. 6 Study of Cys-PDSA NPs (CP5 NPs). (A) Illustration of the Pt(IV) prodrug-based nanoplatform for treating cisplatin-resistant tumors. (B) Drug release profile of CP5 NPs upon redox stimuli with dithiothreitol (DTT). (C) Tumor volumes of A2780cis tumor-bearing mice after treatment with CP5 NPs. Reproduced from reference 81 with permission from American Chemical Society, copyright 2018.

cisplatin-resistant A2780cis xenograft tumors and negligible systemic toxicities compared with those of the conventional form (Fig. 6(C)).[81]

3.1.2 PP-based nanomedicines for chemotherapy. Polymeric nanosystems are the most popular and widely used nanoplatforms for treating malignancies. The excellent properties of polymeric nanocarriers enable tailored control to a suitable size for tissue penetration and specific cellular intake *via* sophisticated material modification.[82] Various polymers have been successfully used to synthesize polymer–drug conjugates for cancer therapy. Nanosystems self-assembled from amphiphilic polymer–CA conjugates or formulated from the encapsulation of polymer–CA conjugates with nanocarriers each have specific advantages. BCPs have been the most commonly used polymers to synthesize self-assembling NPs based on polymer–drug conjugates *via* "conjugation to".[83,84] The hydrophobicity of the drug is of crucial importance as this will govern the self-assembly of the conjugate into nanocarriers. Various CAs have been conjugated with BCPs to form self-assembled micelles and successfully achieved higher water solubility and drug payloads with sustained drug release in the circulation than seen with the traditional system containing physically entrapped CAs.[85–87] For example, block copolymer poly(ethylene glycol)-*block*-poly(pyridyldisulfide ethylmethacrylate) (PEG-PDSEMA) was conjugated to thiolactone functionalized drug (PTX, CPT) to produce imidazole and disulfide bonds-incorporated BCPs, which subsequently self-assembled into stable micellar NPs (Fig. 7(A) and (B)).[85] The resulting

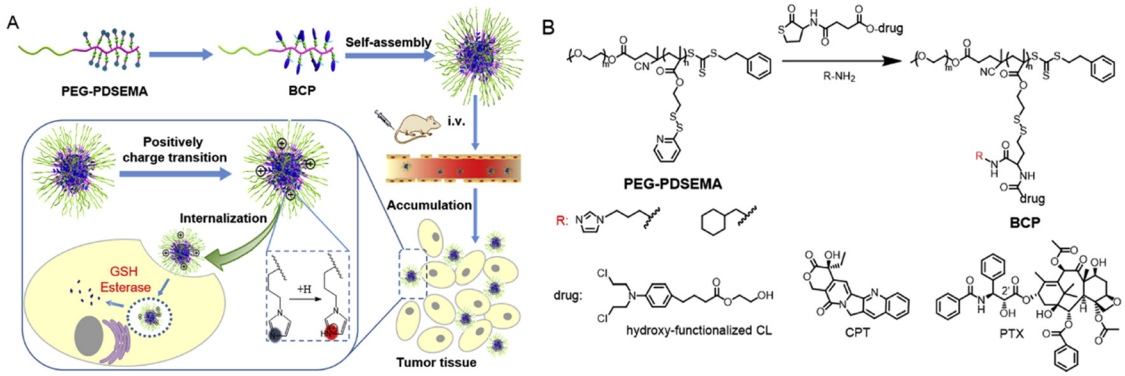


Fig. 7 Preparation and study of block copolymer prodrug (BCP) NPs. (A) Schematic illustration of the construction of BCPs, self-assembly into micellar NPs, and intratumoral delivery process. (B) Chemical synthesis of BCPs *via* thiolactone chemistry reaction. Reproduced from reference 85 with permission from Elsevier Ltd, copyright 2017.

CA-BCP polymer-based self-assembled NPs achieved extremely high drug loading (>50%), pH-sensitive charge transition for cellular internalization, and GSH-responsive drug cleavage for precise drug release inside cancer cells. Finally, those two NPs exhibited complete tumor completion in tumor murine models.[85]

In comparison with self-assembled nanomedicines based on polymer–CA conjugates, the encapsulation of the PP with carriers (*i.e.*, biphilic polymer carrier or liposomes) can enhance chemical stability because of the miscibility with the scaffold and the protective effect of the nanostructures. This facilitated the codelivery of different therapeutic agents in the same vehicle for combinational therapy and facile functionalization on the surface of Nano-DDS for enhanced drug delivery.[70,88] Polymer materials, such as poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA), polystyrene, polyvinylalcohol, polyglycolic acid, polyethyleneimine, poly(acrylic acid), poly(glutamic acid), and cellulose, are employed for the polymer–drug conjugation and subsequent polymeric NP fabrication for drug delivery.[89] Wang *et al.*, recently reported a simple and rational design for the conjugation of SN38 to oligo-ε-caprolactone (oligoCL) *via* an esterase-activatable linkage to form oligoCL$_n$-SN38 conjugates that were subsequently encapsulated by structurally similar matrices (*i.e.*, PEG-*block*-poly(ε-caprolactone) copolymers (PEG-*b*-PCL)) to form injectable NPs.[90] Compared with treatment using the clinical counterpart CPT-11, oligoCL$_n$-SN38 conjugate-based Nano-DDS administration achieved 62.8% (p = 0.001, *versus* CPT-11) reduction in terms of tumor number in orthotopic colonic cancer.

3.2 Prodrug-based nanomedicines in phototherapy

PDT and PTT are light-regulated, noninvasive medical technologies that have been widely studied in cancer treatment. They use irradiation with PSs to generate reactive oxygen species (ROS) or PTAs to generate local hyperthermia (>50 °C) for destroying cancer cells.[91–93] In recent years, PSs and PTAs have been conjugated with multiple components including lipids, drugs or polymers to formulate PS/PTA-based prodrugs that can self-assembled into micelles or be delivered by nanoscaffolds.[94,95] The reports on self-assembled nanoparticles based on PS or PTA prodrugs for cancer PDT and PTT are summarized in Table 2. Chlorin e6 (Ce6) is the most studied photosensitizer in the prodrug formulation and subsequent self-assembly into nanoparticles for cancer PDT therapy.[97,99,108]

PDT therapy often results in the exhaustion of oxygen and the over production of ROS, and most studies therefore combine PDT therapy with hypoxia- or ROS-activated therapy.[32,96,97] For example, Feng *et al.*, prepared a multifunctional liposome by simultaneously loading hydrophobic hexadecylamine-conjugated chlorin e6 (hCe6) and hydrophilic hypoxia-activated prodrug AQ4N, and a ^{64}Cu isotope was also chelated to Ce6 for *in vivo* PET imaging.[98] Post-iv injection of the AQ4N-hCe6-liposome after irradiation could induce severe tumor hypoxia, which was favorable for the activation of AQ4N and producing effective tumor regression in 4T1 tumor-bearing mice. Another study adopted a similar concept for combinative therapy by formulating a PS prodrug by the ligation of hypoxia-activated prodrug PR104A to PS using a ROS sensitive thioether or thioketal linkage. Both two heterodimeric prodrugs self-assembled into high drug coloading combinative NPs, which efficiently generated ROS under light irradiation for PDT (Fig. 8(A)). Meanwhile, the ROS sensitive linkers rapidly underwent cleavage to release PR104A, which was then further activated by the hypoxia in the tumor for synergistic antitumor efficacy (Fig. 8(B)). Such PS prodrug-based NPs successfully facilitate specific drug release, showing high-efficiency synergy

Table 2 Self-assembled nanomedicines based on photosensitizer or photothermal agents conjugate for photodynamic therapy (PDT) and photodermal therapy (PTT) based antitumor therapy

Photosensitizer	Prodrug conjugate	Therapy	Findings	Ref.
Pyropheophorbide-a (PPa)	PR104A-S-PPa PR104A-TK-PPa	PDT/ chemotherapy	Nanoplatforms self-assembled from PR104A-TK-PPa exhibited higher tumor accumulation and better combination therapy efficiency in 4T1 tumor-bearing mice.	99
Chlorin e6 (Ce6)	Ce6-linolenic acid	PDT/ chemotherapy	Coassembly with photoactivatable LTK-cabazitaxel prodrug, Ce6-LA achieved a dramatic shrinkage of tumors in a melanoma PDX mouse model.	95
	Ce6-R9-125I-RGD	PDT/radiotherapy	Self-assembled with miR-139-5p, Ce6-R9-125I-RGD-MNPs formed nanoparticles inhibited growth of HeLa cells and tumors.	106
	PEG-Poly(Ser-Ce6)	PDT/ chemotherapy	Coassembly of PTX2-Azo and PEG-Poly(Ser-Ce6) induced synergistic antitumor effect in HeLa tumor bearing mice.	97
Methylene blue (MB)	MB-SS-biotin-azide (MBP)	PDT	MBNPs, self-assembled from MBP, showed remarkable PDT efficacy and negligible toxicity in HeLa tumor model.	107
Methylene violet (RAX)	RAX-perylene diimide (PRX)	PDT/PTT	Nanoparticles self-assembled from PRX exhibited high phototoxicity against A549 cells *in vitro*.	108
Diketopyrrolopyrrole (DPP)	Diketopyrrolopyrrole-benzothiazole-triphenylamine (DPP-BT-TPA)	PTT/chemotherapy/anti-angiogenic therapy	Coassembly of DPP-BT-TPA with CPT-SS-CA4 exhibited improved combinative antitumor efficacy in 4T1 tumor-bearing mice.	94
Cypate	Cypate-Phe-Phe-Lys(SA-HCQ)-Tyr(H_2PO_3)-OH (Cyp-HCQ-Yp)	PTT/autophagy inhibition	Under sequential catalysis of ALP and CES, Cyp-HCQ-Yp is converted to Cyp-Y, which self-assembles into its nanoparticle Cyp-NP and showed enhanced cancer therapy in HepG2 tumor-bearing mice.	105

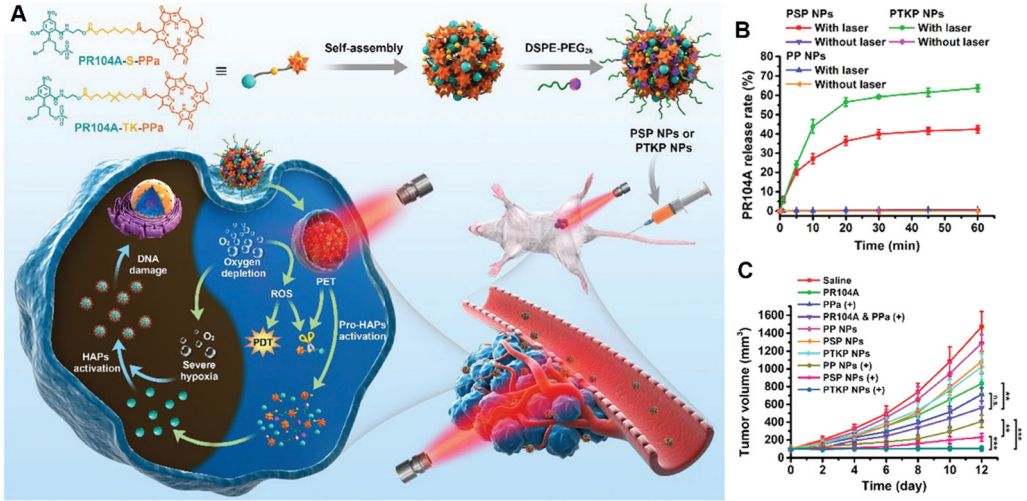


Fig. 8 Use of self-assembled heterodimeric prodrug-based NPs. (A) Schematic of the preparation of self-assembled heterodimeric prodrug-NPs (PSP NPs or PTKP NPs). (B) *In vitro* PR104A release of prodrug-NPs under laser irradiation. (C) Tumor growth curves. Reproduced from reference 99 with permission from The Royal Society of Chemistry, copyright 2020.

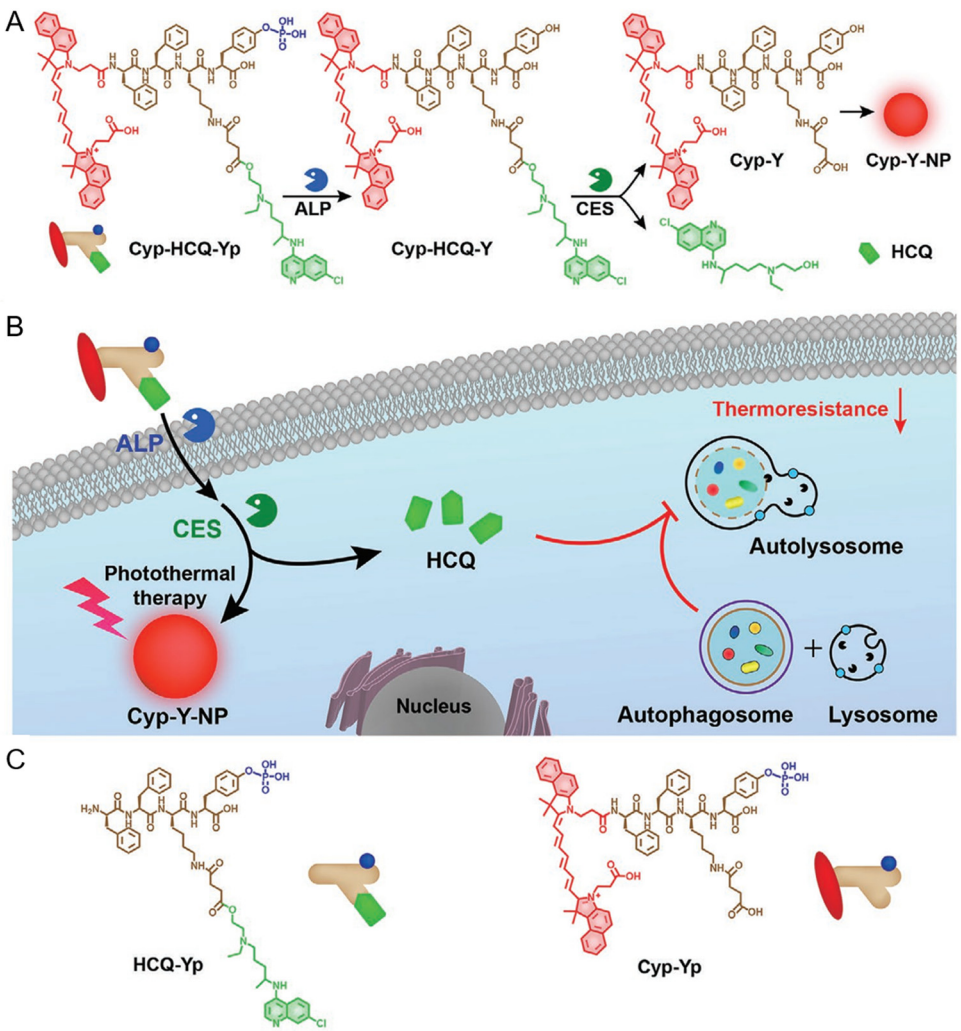


Fig. 9 A "smart" prodrug Cyp-HCQ-Yp for autophagy-inhibited mild-temperature photodermal therapy. (A) The enzymatic transformation of Cyp-HCQ-Yp into Cyp-Y which self-assembles into Cyp-Y-NPs. (B) Schematic of the working mechanism of Cyp-HCQ-Yp. (C) Chemical structures of two control agents HCQ-Yp and Cyp-Yp. Reproduced from reference 105 with permission from Wiley, copyright 2021.

in combination with PDT and hypoxia-activated therapy (Fig. 8(C)).[99]

PTT, which relies on local hyperthermia generated by PTAs under near-infrared (NIR) laser irradiation is an attractive alternative approach to PDT.[100,101] The heat induces cell death by apoptosis or necrosis for efficient tumor eradication, conferring noninvasiveness and reduced side effects. Unfortunately, it may cause severe collateral heating damage to neighboring healthy tissues, which can induce serious side effects and unendurable heat pain to patients. Hence, to perform PTT at a mild local temperature (<45 °C) is of clinical significance.[102] However, mild-temperature PTT alone exhibits a limited anticancer ability in most cases, thereby necessitating adjuvant strategies (*e.g.*, chemotherapy, gene therapy, or immunotherapy) to enhance its therapeutic efficacy.[103,104]

Inspired by these studies, a study proposed an alkaline phosphatase (ALP) and carboxylesterase (CES) dual-responsive prodrug to enhance the therapeutic efficacy of mild-temperature PTT through autophagy inhibition. Under sequential enzymatic catalysis by ALP and CES, this prodrug (Cypate-Phe-Phe-Lys(SA-hydroxychloroquine)-Tyr(H_2PO_3)-OH) (Cyp-HCQ-Yp, Fig. 9(A)–(C)) is converted into Cyp-Y which self-assembles into Cyp-Y-NPs in tumor cells, accompanied with release of the autophagy inhibitor HCQ.[105] The exceptional therapeutic antitumor effect of Cyp-HCQ-Yp *in vivo* was achieved by the dual-enzyme-controlled intracellular NP formation and autophagy inhibition in tumors.

3.3 Prodrug-based nanomedicines in molecular-targeting therapy

Distinct from traditional cytotoxic chemotherapy, targeted therapy efficiently inhibits cancer proliferation by interfering with the specific signaling pathways and relevant kinases involved

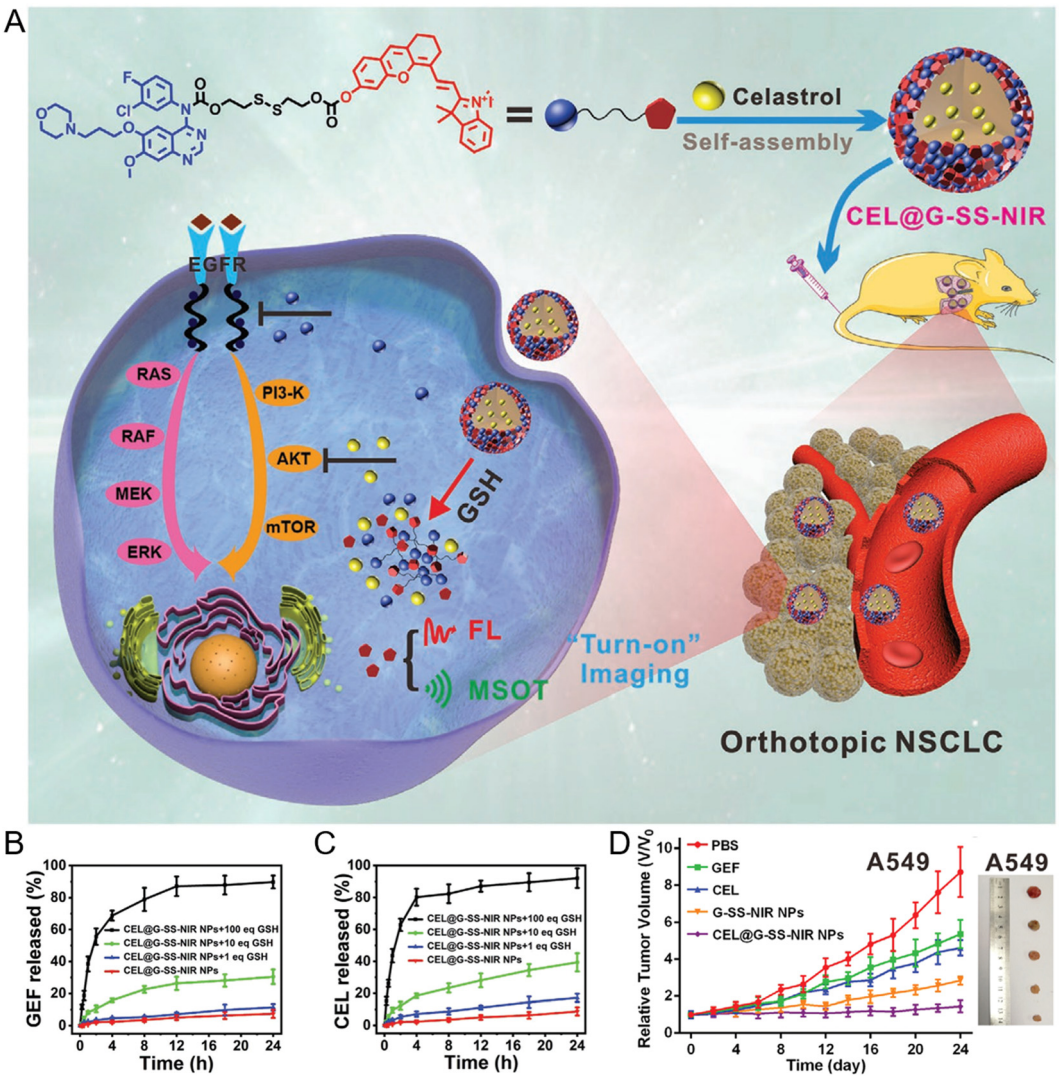


Fig. 10 Formation and *in vivo* delivery of a gefitinib prodrug-based nanodrug (CEL@G-SS-NIR NPs). (A) Schematic illustration for the formation of CEL@G-SS-NIR NPs and the therapeutic action on non-small cell lung cancer (NSCLC). Drug release profile of gefitinib (B) and celastrol (CEL) (C) from nanodrugs treated with various equivalents of GSH. (D) Tumor volume of NSCLC-bearing mice treated with different drug formulations. Reproduced from reference 113 with permission from Wiley, copyright 2020.

in tumor development and metastasis.[109] Small molecular inhibitors (SMIs), including tyrosine kinases inhibitor (TKI), represent a major portion of targeting agents used for targeted therapy.[110] However, many existing SMIs have extremely low water solubility and require oral medication in large doses that may produce poor biodistribution and severe systemic toxicities. The chemical modification of such inhibitors is a viable way to increase self-assembly or loading by nanocarriers in water. TKIs are widely studied for prodrug formulation.[111] Li *et al.* synthesized a redox-sensitive prodrug polymers poly(oligo(ethylene glycol) methacrylate) (POEG)-*b*-PSSDas and a redox-insensitive POEG-*b*-PCCDas that comprise POEG hydrophilic blocks and oncogenic TKI dasatinib (DAS, the inhibitor of Src/Bcr-Abl)-conjugated hydrophobic blocks to form mixed micelles with DOX. The system substantially enhanced the solubility of DAS and facilitated the intravenous delivery of DAS.[112] The incorporation of disulfide linkages into the codelivery system facilitated efficient cleavage of DAS from prodrug micelles in tumor tissues, generating increased tumor inhibition and survival rate in an aggressive 4T1.2 tumor mice model.

Another study designed a TKI-based prodrug that covalently linked epidermal growth factor receptor (EGFR)-TKI gefitinib with a NIR chromophore *via* a cleavable disulfide bond. This prodrug (G-SS-NIR) could readily self-assemble into NPs driven by the insertion of disulfide bonds and intermolecular π–π interaction in aqueous media (Fig. 10(A)).[113] The Akt inhibitor celastrol (CEL) is encapsulated into the NPs to form a nanodrug (CEL@G-SS-NIR). Upon the overexpression of GSH in the tumor, the nanodrug is activated and releases two inhibitors to exert a tumoricidal effect and enable NIR for both fluorescence and multispectral optoacoustic tomography (Fig. 10(B) and (C)). Furthermore, the strong "turn-on" fluorescence caused by aggregation-induced emission and multispectral optoacoustic tomography imaging inside the tumor allows for precise monitoring of the drug release. The study validated that the nanodrug containing two inhibitors exhibits high inhibition efficacy against orthotopic nonsmall cell lung cancer in murine models (Fig. 10(D)).

3.4 Prodrug-based nanomedicines in immunotherapy

Immunotherapy has shifted the clinical paradigm of cancer management. Recently, prodrug-based nanoplatforms have been widely used for efficient delivery of immune modulators and to integrate multiple immune regulators with variable chemophysical properties and pharmacokinetic profiles into a single nanoplatform to provide synergistic immunotherapy.[28,114,115] In this section, we summarize the major applications of prodrug nanomedicines as strategies to improve cancer immunotherapy.

3.4.1 Immunogenic cell death (ICD)-based prodrug Nano-DDS for cancer immunotherapy. Both chemotherapy (*e.g.*, DOX, oxaliplatin, PTX) and PDT can enhance antitumor immunity by inducing ICD.[116,117] Tumor cells undergoing ICD will release immune-stimulatory damage-associated molecular patterns (*e.g.*, calreticulin, ATP, and high mobility group protein B1) that are recognized by antigen-presenting cells (APCs; *e.g.*, dendritic cells) and thus initiate their activation.[118] Activated APC cells encounter tumor-associated antigens (TAAs) and present these to T lymphocytes, eliciting a protective T-cell immune response. The ICD inducer-based NPs can considerably

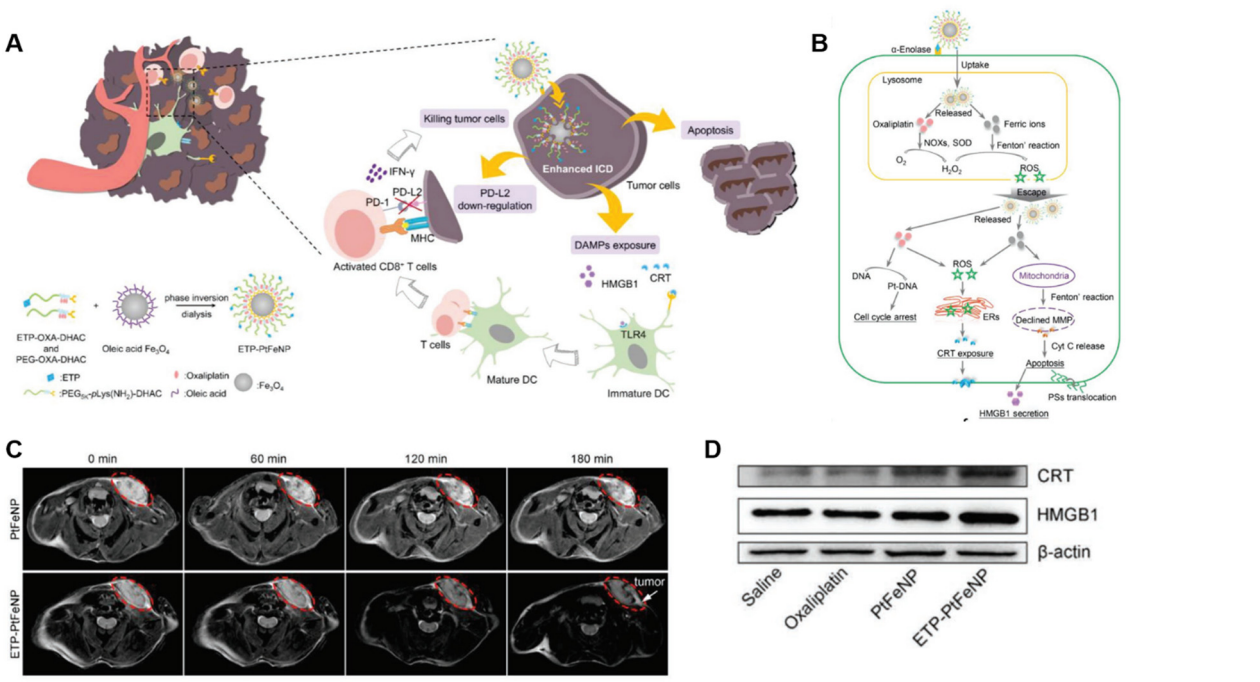


Fig. 11 Study of ETP-PtFeNP formulations. (A) The preparation of ETP-PtFeNP and representation of elevated antitumor immune responses with ETP-PtFeNP treatment. (B) Illustration of ETP-PtFeNP modulation *via* three pathways for ICD induction. Magnetic resonance images (C) and western blotting analysis of CRT and HMGB1 expression (D) for mice bearing 4T1 breast tumors following treatment with ETP-PtFeNP. Reproduced from reference 120 with permission from WILEY, copyright 2019.

improve solubility and stability for systemic injection, which ultimately induces potent ICD effects for anticancer therapy.[119] Chen *et al.* designed a core–shell prodrug-based magnetic NP (ETP-PtFeNP) that contained polymeric shells of an oxaliplatin prodrug modified with an α-enolase-targeting peptide and a core made of oleic acid–Fe_3O_4[120] (Fig. 11(A)). They showed that peptide-modified shell caused substantial tumor accumulation and subsequent endocytosis, and the Pt(IV) prodrugs were activated to specifically release oxaliplatin in the highly reductive conditions inside tumor cells. In addition, the Fe_3O_4 in the NP core can be activated to release ferric ions to generate cytotoxic ROS in the acidic tumor microenvironment (Fig. 11(B) and (C)). Thus, the released oxaliplatin and ferric ions synergistically induced strong ICD-associated immunogenicity and antitumor immune responses *via* both endoplasmic reticulum (ER) and non-ER associated pathways (Fig. 11(D)).

3.4.2 Immunosuppression inhibition-based prodrug nanomedicines for attenuating immune tolerance. Immune checkpoints play essential roles in immunotolerance in cancer immunotherapy.[121,122] In recent years, immune checkpoint

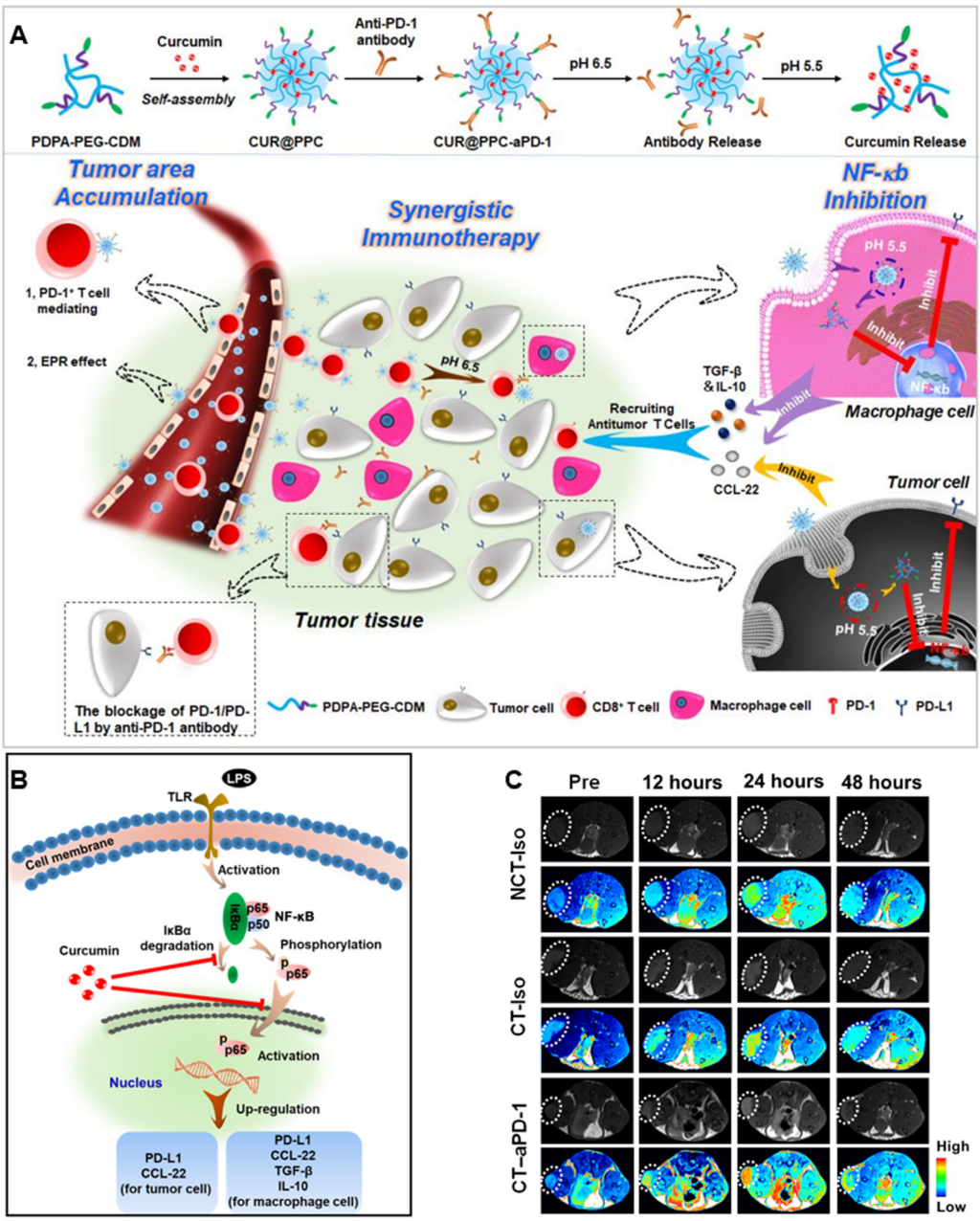


Fig. 12 Study of nanodrug PDPA-PEG-CDM. (A) Preparation and tumor-targeted delivery of a dual pH-sensitive nanodrug. (B) Schematic of curcumin to suppress cytokine secretion and PD-L1 expression by inhibiting the NF-κB pathway. (C) *In vivo* T_1-weighted magnetic resonance imaging (T1WI) of mice bearing B16F10 tumors after iv injection of MnO_2@PPC-αPD-1 or MnO_2@PPC-Iso. Reproduced from reference 130 with permission from Science, copyright 2020.

blockade (ICB) has reached a milestone in cancer therapy. However, those therapeutic inhibitors, including targeting peptides, antibodies, and SMIs, block immune cell checkpoints that are both important and irrelevant to cancer therapy.[123] Such an indiscriminate blockade on immune cells limits their efficacy and readily causes the autoimmune toxicity of the therapy.[124] Thus, constructing prodrugs by chemical modification and delivering them *via* nanocarriers to target immune checkpoints of cancer-reactive immune cells may be beneficial. To illustrate this concept, substantial efforts have been devoted to developing immune checkpoint inhibitors based prodrugs and nonosystems for efficient targeting and delivery.[125,126]

Recently, monoclonal antibody-based ICB therapy has significantly advanced cancer immunotherapies in the clinic. For example, antibodies to PD-L1, PD-1, or CTLA-4 have been conjugated to lipid components to form antibody functionalized lipid NPs or have been conjugated to biodegradable polymer (PLGA, poly(amidoamine) dendrimers) (PMLA/LLL) to form polymeric NPs for ICB therapy.[127–129] As evidence of this, Xiao *et al.* developed a dual pH-sensitive prodrug-based NP (CUR@PPC-αPD-1), formed by the conjugation of the antibodies to PD-1 (αPD-1) with di-block copolymer (CDM-PEG-PDPA) *via* an ammonolysis reaction and loaded curcumin in their core[130] (Fig. 12(A)–(C)). The antibody-modified NPs specifically bound the circulating PD-1$^+$ T cells, producing effective tumor accumulation. Afterward, the pH-sensitive linker in the surface of αPD-1-modified NPs was cleaved in the acidic tumor microenvironment to release αPD-1 at the tumor site. After being internalized by tumor cells, the pH-responsive nanomedicine disassembled under the acidic condition of lysosomes, causing a rapid release of the encapsulated curcumin, which inhibited the nuclear factor kappa B (NF-κB) pathway and enhanced the effect of anti-PD-1/PD-L1 immunotherapy. This combination enabled the simultaneous blockade of the PD-1/PD-L1 pathway and tumor infiltration by antitumor T cells enabled by curcumin delivery, causing impressive antitumor efficiency.[130]

Except for immune checkpoints, several other factors also cause strong local immunosuppression, including indoleamine 2,3-dioxygenase (IDO),[131] interleukin 10 (IL-10),[132] TGF-β,[133] NF-κB,[134] and CD47.[135] Thus, strategies are also needed to block these immunosuppressive factors. IDO is a key negative feedback protein that acts by suppressing the activity of the effector T cells and recruiting regulatory T cells, thus inhibits the activity of infiltrating cytotoxic T lymphocytes (CTLs) and produces an immunosuppressive tumor microenvironment (ITM). The IDO pathway inhibitors (*e.g.*, NLG919) have shown encouraging clinical outcomes.[136] However, the commonly used small-molecule drugs have shown poor pharmacokinetic effects when administered in free form. Therefore, IDO inhibitors formulated prodrug-based nanomedicines have recently been investigated for combating IDO-induced immune tolerance. Han *et al.*, recently constructed a peptide–drug conjugate for IDO-1-induced immune resistance inhibition.[137] First, a peptide–drug conjugate was synthesized by conjugating the hydrophilic targeting motif arginylglycyl-aspartic acid (RGD) with a potent IDO-1 inhibitor NLG919, *via* two protonatable histidines, and then self-assembled into NPs. The NLG919 prodrug has several significant advantages, including specific tumor targeting *via* modification of RGD, pH-responsive disassembly by protonatable histidines, and controllable esterase-catalyzed drug release of NLG919 (Fig. 13(A)). The NLG919 prodrug had enhanced inhibition of intratumoral IDO to considerably improve the therapeutic efficacy in the combination of PD-L1 blockade therapy and reduce the systemic toxicity (Fig. 13(B)).

3.4.3 Cancer vaccine-based prodrug formulated nanomedicines for cancer immunotherapy. Vaccination therapy is an attractive strategy for tumor immunotherapy.[138] The vaccination therapy starts with the release of TAAs and costimulation signals (adjuvants), which are internalized and processed by APCs in secondary lymphoid organs. The antitumor immunotherapy is thereby enhanced by cross-presentation of tumor epitopes by APCs to naive or memory T cells.[139] The ICD therapy can be categorized as an endogenous vaccination therapy as this generated endogenous TAAs by the tumor to activate APCs and initiate antitumor immunotherapy. However,

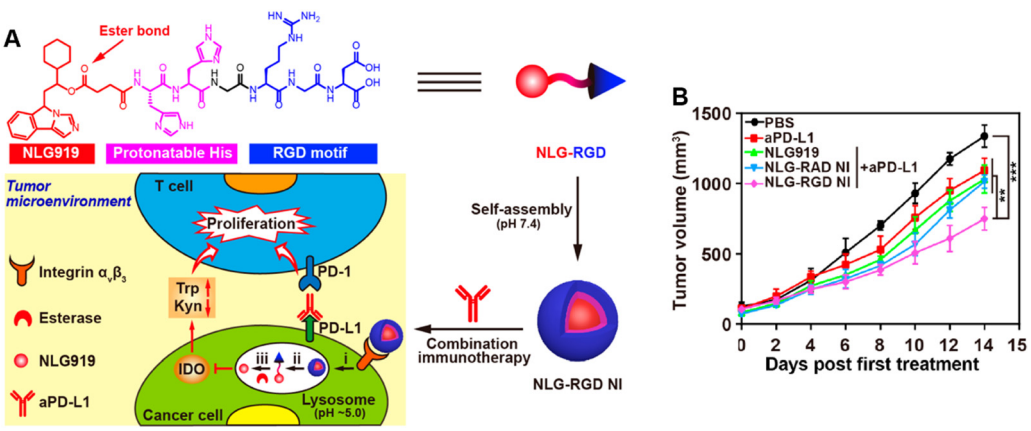


Fig. 13 Preparation and antitumor study of a prodrug-based nanomedicine NLG-RGD. (A) Schematic of the self-assembly of NLG-RGD and the mechanism of combination therapy using NLG-RGD NI and aPD-L1. (B) Tumor growth curves of Pan02 tumors in mice using NLG-RGD NI and aPD-L1. Reproduced from reference 137 with permission from American Chemical Society, copyright 2020.

the majority of cancer vaccination is realized by the exogenous administration of such TAAs (*i.e.*, peptides, cell membrane.) together with adjuvants, which are generally defined as "exogenous vaccination".[115]

Despite considerable advances having been made in cancer exogenous vaccines, several disappointing studies have hindered their widespread use.[140] These obstacles may be ascribed to unsynchronized delivery of the neoantigens and adjuvants to the tumor draining lymph nodes (dLNs) in a traditional drug delivery platform, causing immune tolerance and decreased proliferation of tumor-cytotoxic CTLs. Nanoplatforms are the best tools to address these challenges. They can encapsulate antigens and adjuvants to prevent degradation and achieve stable codelivery.[141] For example, Kuai *et al.* designed novel vaccine high-density lipoprotein-mimicking nanodiscs that coupled with redox responsive antigen and CpG oligonucleotide adjuvant (TLR-9 agonist) for antigen/adjuvant codelivery (Fig. 14(A) and (B)).[142] Strikingly, the authors revealed that the vaccine nanodiscs produced up to 47- and 31-fold greater frequencies of neoantigen-specific CTLs than those produced by soluble vaccines and the strongest adjuvant in clinical trials (CpG in Montanide), respectively. More importantly, when combined with ICB therapy, the nanovaccine eliminated the growth of both MC-38 and B16F10 tumors (Fig. 14(C)–(E)).

Another major challenge for vaccination therapy is to prime a strong and effective immune response of effective CTLs through cross-presentation of the antigens.[143] Ideally, the antigens should successfully escape from the lysosomes of APCs and be loaded onto MHC-I molecules for presentation to $CD8^+$ T cells instead of being loaded onto MHC-II for presentation to $CD4^+$ T cells. Wei *et al.*[144] addressed this challenge by preparing a redox-sensitive polycondensate neoepitope (PNE) to deliver neoantigens and adjuvants for tumor vaccination immunotherapy. The PNEs were constructed by crosslinking neoantigen

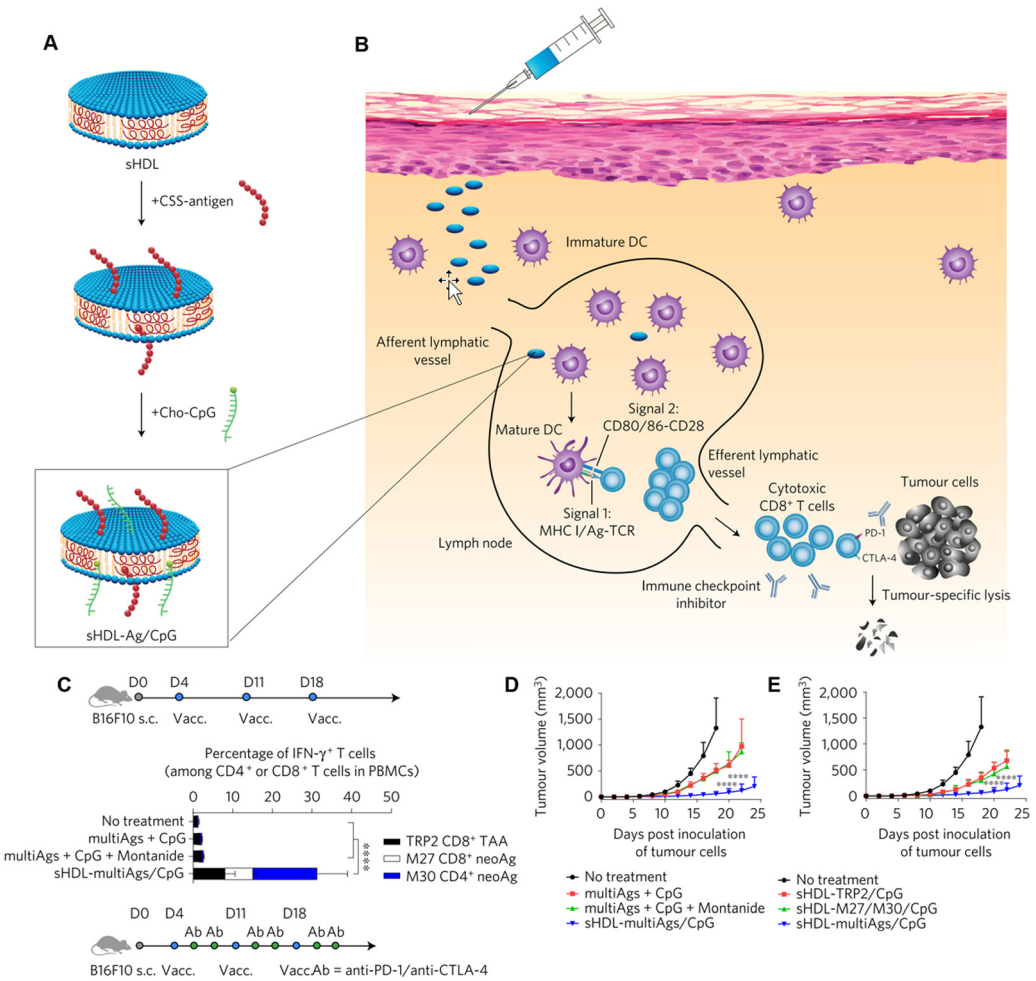
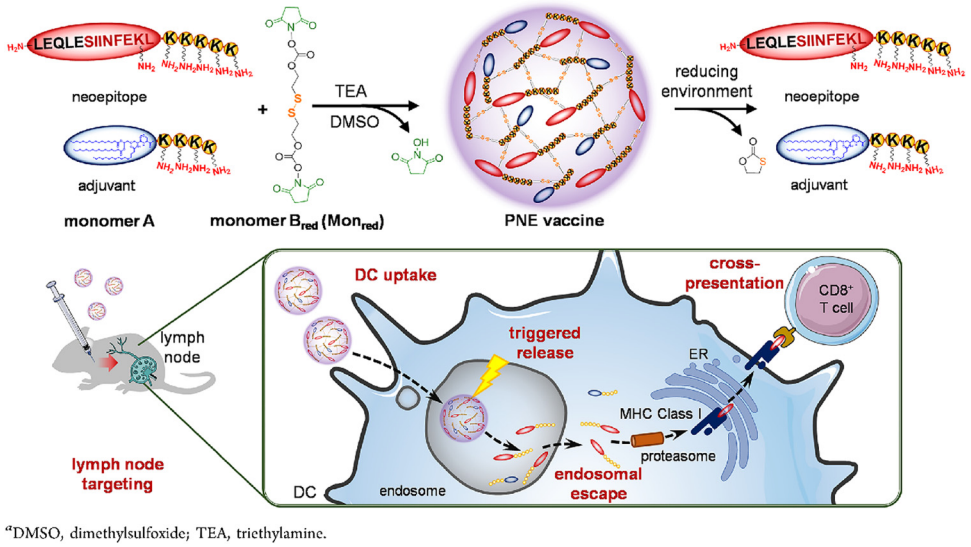


Fig. 14 Design of high-density lipoprotein (sHDL)-mimicking nanodiscs that coupled with redox responsive antigen peptide (Ag) and adjuvant CpG for codelivery. (A) sHDL nanodisc platform engineered for codelivery of Ag peptides and adjuvants. (B) Ag and CpG were efficiently codelivered to draining lymph nodes by nanodiscs, promoting strong Ag presentation by dendritic cells (DCs) (Signal 1), inducing DC maturation (Signal 2) and causing the activation of Ag-specific $CD8^+$ cytotoxic T-lymphocyte (CTL) responses. Activated CTLs recognize and kill their target cancer cells. The combination with ICB further amplifies the potency of nanodisc vaccination. (C) The schedule of tumor eradication by combination immunotherapy with multiepitope vaccine and ICB. (D) and (E) The tumor growth curves of B16F10 tumor-bearing mice after various drug formulations. Reproduced from reference 142 with permission from Springer Nature, copyright 2016.

peptides (monomer A) and amphiphilic adjuvants (monomer B) with a redox-liable linker (Fig. 15). The PNEs showed an efficient LN accumulation and DC uptake. More importantly, the intracellular reduction in APCs could trigger rapid release of neoantigens from PNEs to facilitate endosomal escape and cross-presentation of neoantigens by MHC-I, thereby considerably improving the immune response in a prophylactic mouse model.

3.4.4 Immune adjuvant-based prodrug nanomedicines for adoptive cell therapy of tumors. Various costimulating pathways have been identified, and corresponding agonists that function as vaccine adjuvants have been developed.[145] The adjuvants are critical components of many vaccines and can enhance the magnitude, breadth, quality, and longevity of the immune response to the antigens. One widely used immune adjuvant, Toll-like receptor agonists (TLRa) have been shown to be the most potent adjuvants discovered to effectively stimulate APCs for antigen presentation and T-cell immune responses.[146] A TLR-9a based on a CpG-motif oligonucleotide has been widely investigated in preclinical trials.[147] However, because of their working mechanism and high toxicity when administrated in a free form and subsequent spread into the systemic circulation,



[a]DMSO, dimethylsulfoxide; TEA, triethylamine.

Fig. 15 Schematic of the synthesis, responsive release, and *in vivo* efficacy of redox-sensitive polycondensate neoepitope (PNE) vaccines. Reproduced from reference 144 with permission from American Chemical Society, copyright 2020.

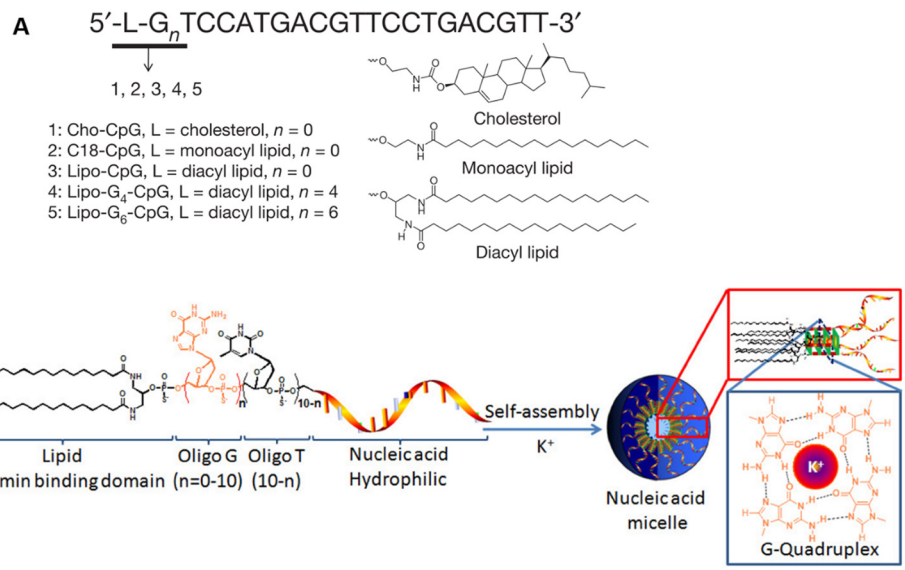


Fig. 16 Construction and characterization of lymph node-targeted G-quadruplex-stabilized CpG adjuvants. (A) Structure of Amph-CpGs. (B) G-quadruplex-stabilized CpG micelles self-assembled from amphiphiles. Reproduced from reference 148 with permission from Springer Nature, copyright 2014.

the novel drug formulations need to be exploited. Although polymeric carriers have a potential for improved TLR delivery by integrating both TLRa and antigens into one vector, non-covalent encapsulation of TLRa often causes burst release of payloads after administration.

To facilitate efficient dLN-targeted delivery of immune adjuvants, Irvine and colleagues designed an "albumin hitchhiking" approach.[148] Dyes with certain hydrophobic moieties can efficiently bind to endogenous albumin, and the albumin/dye compounds can then be transferred to LNs in patients with cancer. Inspired by this phenomenon and the role of albumin as a fatty acid transporter, the TLR9 agonist CpG was modified with selected hydrophobic chemical groups (cholesterol, monoacyl lipid, and diacyl lipid) that bind to albumin, which facilitates transportation of CpG to LNs (Fig. 16(A)). These amphiphiles can self-assemble into three-dimensional spherical micelles with a CpG corona and a lipid core in aqueous solutions (Fig. 16(B)). With the optimized lipophilic moiety-diacyl lipid tail, the CpG trafficking to LNs was significantly enhanced compared with that of native CpG or CpG with suboptimal modifications. The optimized amphiphilic CpG self-assembled micelles had a 30-fold increase in T-cell priming and tumoricidal efficacy. Furthermore, this "albumin hitchhiking" approach greatly reduced the toxicities of CpG.

In comparison with TLR-9a, TLR-7/8a (such as imiquimod, R848) have better potential for clinical translation since all APCs in humans express both TLR-7 and TLR-8.[149,150] To facilitate the LN drainage and intracellular release of TLR7/8 agonists, De *et al.* synthesized an IMDQ prodrug based on the conjugation with acid-activatable amphiphilic block copolymer.[151] The IMDQ-conjugated amphiphilic block polymer could successfully self-assemble into micellar NPs ($Amph^{IMDQ}$) to reduce what was described as "wasted inflammation" during systemic circulation (Fig. 17(A)). $Amph^{IMDQ}$ provoked a significantly stronger LN-localized response compared with that of soluble IMDQ and hydrophilic block copolymer-assembled IMDQ micelles (Hydro), causing strong activation of DCs (Fig. 17(B)). $Amph^{IMDQ}$ also showed excellent acid sensitivity in

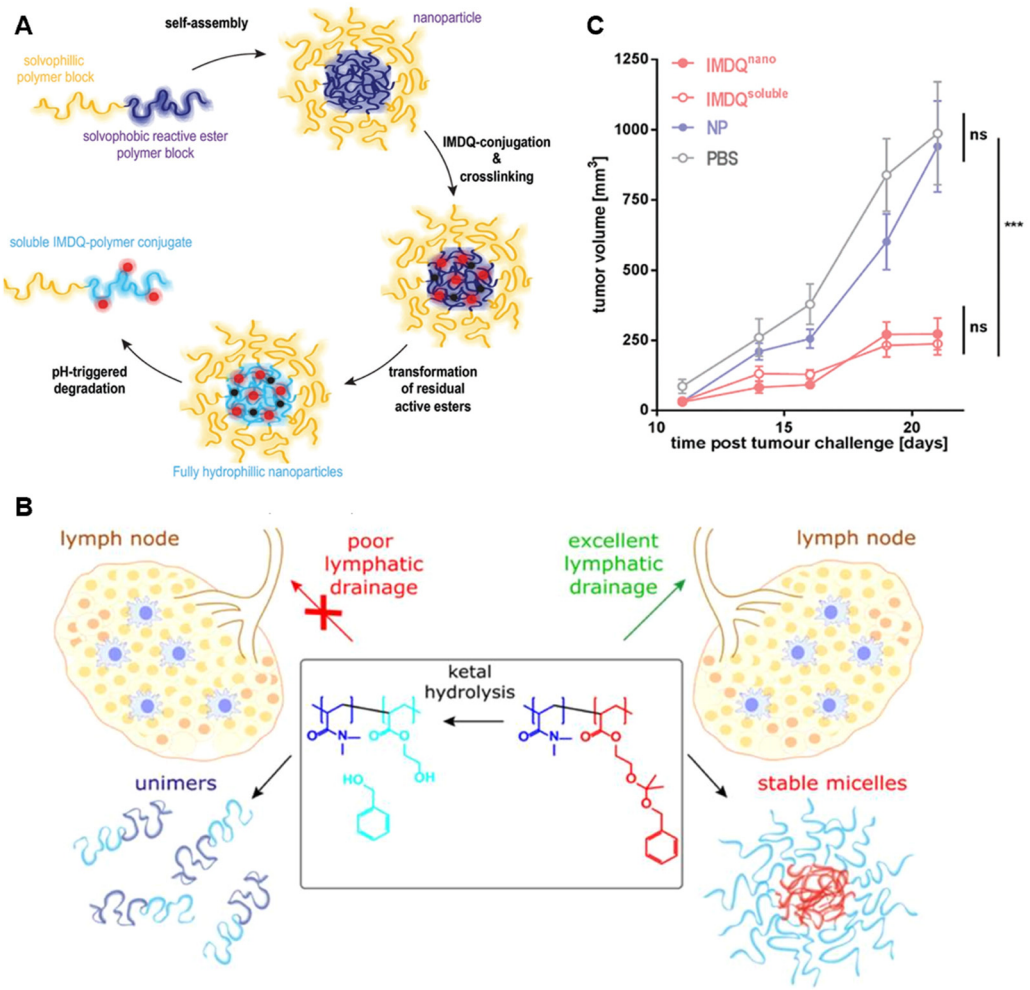


Fig. 17 Assembly, fabrication, and efficacy evaluation of $IMDQ^{nano}$. (A) Schematic of the fabrication of $IMDQ^{nano}$. Reproduced from reference 152 with permission from WILEY, copyright 2018. (B) Concept of localized tumor treatment with $IMDQ^{nano}$ in draining lymph nodes. Reproduced from reference 151 with permission from American Chemical Society, copyright 2018. (C) Tumor growth of B16F10 tumors in mice, in response to treatment with soluble IMDQ and nanoformulated IMDQ. Reproduced from reference 152 with permission from WILEY, copyright 2018.

the endosomal compartment, causing hydrolysis into the unimer fraction by cleaved ketal bonds but remained highly stable under physiological conditions representing systemic circulation. Localized treatment with a NP-conjugated IMDQ was confirmed to potently activate DCs in the sentinel LN and promote proliferation of tumor antigen-specific $CD8^+$ T cells, which considerably improve the therapeutic effect upon combination with anti-PD-L1 checkpoint inhibition and Flt3L, a growth factor that expands and mobilizes DCs from the bone marrow (Fig. 17(C)).[152]

4. Prodrug-based combination nanotherapy

The heterogeneity and complexity of tumors often results in the emergence of drug resistance and tumor relapse following cancer treatment *via* a single agent strategy. Therefore, using a single chemotherapy agent is less common in actual clinical applications. Combination therapies help to overcome the limitations encountered with each therapy alone and has shown enhanced tumor responses in patients.[153] However, the therapeutic challenges of combination chemotherapeutic therapy include unsatisfactory therapeutic effects and unfavorable toxicities caused by incorrect choice of dosages, incorrect ratio of drugs, and inaccurate drug release. Prodrug-based Nano-DDS has shown considerable benefits in combination therapy in comparison with conventional nanocarriers (*e.g.*, micelles, liposomes, and polymeric NPs).

Combination drug therapy based on a prodrug nanoplatform can be categorized into three types:[154] (i) all drugs are bound together to construct a prodrug for nanoformulation; (ii) some of the free therapeutic drug is encapsulated in the anticancer prodrug assembled nanosystem; and (iii) some of the free therapeutic drug is used as additive therapy but not included in the prodrug-based antitumor nanosystem. The combinative prodrug nanosystem also could be divided into a self-assembled system from prodrugs or a prodrug-encapsulated system by nanocarriers. These hybrid nanocarriers based on anticancer prodrugs could:[155] (i) enhance

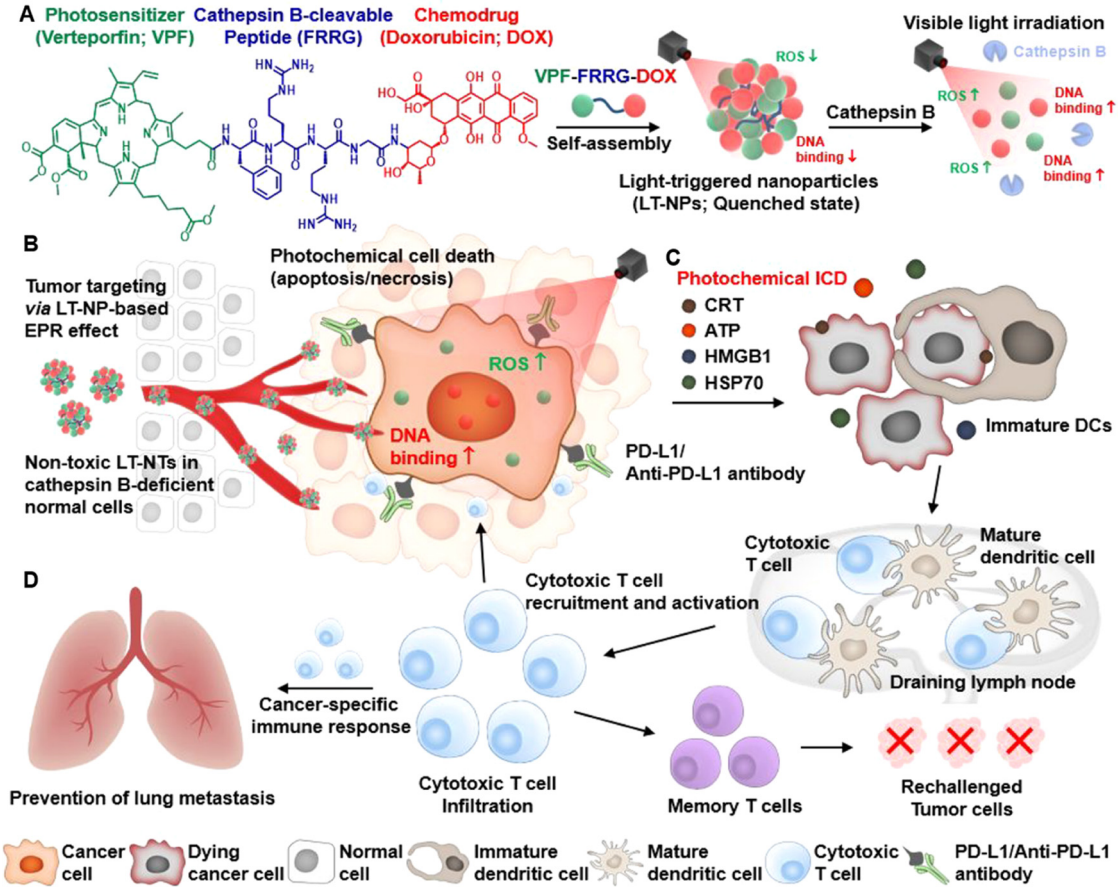


Fig. 18 Schematic of light-triggered chemodrug–photosensitizer conjugate–based NPs (LT-NPs) to potentiate cancer ICB. (A) LT-NPs are prepared by self-assembly of cathepsin B-specific cleavable, light-trigged prodrug VPF-FRRG-DOX. (B) LT-NPs accumulated in tumor tissues specifically release VPF and DOX in cathepsin B-overexpressing cancer cells, generating ROS upon visible light irradiation. (C) Synergy of photochemotherapy by LT-NPs causes a strong ICD effect for dendritic cells (DCs) and cytotoxic T-cell activation. (D) Combinatorial LT-NP treatment with anti-PD-L1 antibody induces complete tumor regression of both primary tumors and distant pulmonary metastatic tumors by effective antitumor immune responses. Reproduced from reference 159 with permission from American Chemical Society, copyright 2021.

the assembly stability of nanostructures and prolong blood circulation time and (ii) achieve targeting therapy (improving the uptake efficiency by tumor cells or release the functional drug in the specific site inside tumor cells). Since drugs are distinctive in physiochemical characteristics and mode of action, evaluating the specific contribution of each component in multifunctional nanoformulations in cancer therapy is of importance in order to optimize drug selection, drug ratio and to control the drug release of multiple drugs according to their molecular and pharmacodynamic mechanisms.[14,154,156]

Recently, according to the logical design and the specific function of each component, the rational combination of chemotherapeutics, PS and ICB drugs has shown a high-efficiency synergy in prodrug-based Nano-DDS.[157,158] For example, as shown in Fig. 18, Choi *et al.* designed light-triggered chemodrug–photosensitizer conjugate–based NPs (LT-NPs) for reversing ITM into high immunogenic tumors to potentiate the antitumor efficacy of ICB. The conjugate of photosensitizer (verteporfin; VPF), DOX, and cathepsin B-specific cleavable peptide (FRRG) are prepared *via* a one-step amide bond reaction and can self-assemble into LT-NPs. Upon visible light irradiation, the LT-NPs specifically release VPF and DOX in cathepsin B-overexpressing cancer cells and induce effective ICD and maturation of DCs to stimulate cross presentation of cancer specific antigens to T cells in tumor models. Furthermore, the combination of iLT-NPs with PD-L1 blockade has shown strong immune responses and has considerably inhibited tumor growth, tumor recurrence, and lung metastasis.[159]

5. Summary and outlook

The past several years have witnessed the rapid development of nanomedicines. Approved by the FDA in 2005, the albumin bound PTX self-assembled nanoparticle nab-Paclitaxel (Abraxane®) is the most successful nanomedicine in the market utilized for cancer therapy at the current stage. The billion-dollar market achieved by Abraxane® has spurred researchers to further focus their efforts in this area.[160,161] Considering the tumor is heterogeneous and evolutionary in divergent tumor types and distinct tumor development stages, the existing strategy is far from perfect. More rational and efficient Nano-DDS have to be exploited to facilitate the highly efficient delivery of anticancer agents in multiple cancer therapies. Prodrug-based nanomedicines can be decorated with any logical design and can be integrated with combinative therapeutic regimens for targeting multiple singling pathways.[162]

Despite the significant number of promising prodrug-based nanoformulations undergoing clinical development, a few formulations are expected to quickly enter the market for cancer therapy. The patents and clinical trials available related to prodrug-based nano-drugs for cancer therapy are discussed and reviewed in several papers.[27,163] Nanoformulations self-assembled from both DHA–paclitaxel conjugate and poliglumex paclitaxel conjugate have been evaluated in phase III clinical studies, which has achieved minimal hypersensitivity reactions and improved therapeutic effect for cancer therapy.[164,165] The accomplishments in clinical translation of those paclitaxel prodrug-based nanoformulations are supposed to threaten the position of Abraxane® in the marketing of cancer chemotherapy in the future. However, compared to the rapid FDA approval and the great achievement made by Abraxane®, those formulations struggle in marketing and clinical translation. Among them, insufficient improvements in pharmacokinetics while adding the preparation complexity might explain the unsatisfactory therapeutic outcomes and delayed industrialization of those prodrug-based nanomedicines. The more functionalities conferred to the nanocarriers, the greater difficulty that pharmaceutical development will face and the greater costs the patients will bear.

The great achievements of prodrug-based nanoparticulate drug delivery strategies in various cancer therapies have been presented in this review. The marketing potential and current barriers to clinical translation of this platform are also introduced. The clinical translation of prodrug nanomedicine will benefit from the effective communication between the medical care, academia, industry, and drug administration of government. Green and cost-effective chemistry is key to scale up the prodrug-NPs. Furthermore, developing preclinical mice models that recapitulate human cancers and conducting studies under the guideline of drug administrations will be helpful for generating reliable data sets for clinical translation of prodrug nanomedicine for cancer therapy.

Abbreviations

NPs	Nanoparticles
ADCs	Antibody–drug conjugates
nano-DDS	Nanodrug delivery system
SMP	Small molecular prodrug
PP	Polymer prodrug
DHA	Docosahexaenoic acid
CTX	Cabazitaxel
SN38	7-Ethyl-10-hydroxy camptothecin
TPNS	Taxanes prodrugs-based nanomedicines
PDT	Photodynamic therapy
PTT	Photothermal therapy
PSs	Photosensitizers
PTAs	Photothermal agents
PEG	Polyethylene glycol
PTX	Paclitaxel
DTX	Docetaxel
CPT	Camptothecin
DOX	Doxorubicin
Palb	Palbociclib
POD	Podophyllotoxin
BCPs	Block copolymers
PPP	Pure prodrug platform
CPP	Combinative prodrug platform
CAs	Chemotherapeutic agents
GSH	Glutathione

FDA	The food and drug administration
DHA	Docosahexaenoic acid
Pt	Platinum
Cys-PDSA	Cysteine-based poly-(disulfide amide)
PLA	Poly(lactic acid)
PLGA	Poly(lactic-*co*-glycolic acid)
PEG-*b*-PCL	PEG-*block*-poly(ε-caprolactone)
hCe6	Hexadecylamine-conjugated chlorin e6
NIR	Near-infrared
ALP	Alkaline phosphatase
CES	Carboxylesterase
Cyp-HCQ-Yp	(Cypate-Phe-Phe-Lys(SA-hydroxychloroquine)-Tyr(H_2PO_3)-OH)
SMIs	Small molecular inhibitors
TKI	Tyrosine kinases inhibitor
DAS	Dasatinib
EGFR	Epidermal growth factor receptor
CEL	Celastrol
NSCLC	Non-small cell lung cancer
ICD	Immunogenic cell death
APCs	Antigen-presenting cells
TAAs	Tumor-associated antigens
ER	Endoplasmic reticulum
ICB	Immune checkpoint blockade
NF-κB	Nuclear factor kappa B
IDO	Indoleamine 2,3-dioxygenase
IL-10	Interleukin 10
CTLs	Cytotoxic T lymphocytes
ITM	Immunosuppressive tumor microenvironment
dLNs	Draining lymph nodes
DCs	Dendritic cells
PNE	Polycondensate neoepitope
TLRa	Toll-like receptor agonists
VPF	Verteporfin

Author contributions

L. Shi and J. Zhang are responsible for the concept development, writing, revision, and review of the manuscript. S. Lin is responsible for collecting the reference for the manuscript. F. Zhou and H. Jiang are responsible for the collation of the manuscript. All authors contributed to the article and approved the submitted version.

Conflicts of interest

The authors declare no conflicts of interest.

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