

Review

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Bench-to-bedside translation of podophyllotoxin-based nanomedicines for cancer treatment: utopias and reality?

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Abstract

Cancers represent a complex and multifaceted health challenge, marked by elevated disease burden and fatality rates stemming from both genetic alterations and epigenetic modifications. Nanomedicine, as an emerging field in oncological investigation, optimizes the site-specific delivery of chemotherapeutic compounds through innovative engineering approaches. This technological advancement enables the development of revolutionary strategies for designing precision-targeted treatments that maximize safety and effectiveness. Podophyllotoxin (PPT), a potent aryltetralin-class cytotoxic agent isolated from *Podophyllum* plants, has become a focal point in anticancer pharmaceutical development. Early research efforts focused on direct PPT administration for tumor management, yet clinical implementation through conventional delivery methods has been constrained by multiple factors



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including pronounced toxicity profiles, limited aqueous solubility, and narrow therapeutic windows. Advances in nanotechnology and biomaterials effectively enhance PPT therapy's potential for cancer treatment in clinical settings. Various PPT-based nanomedicines have been explored in recent years (2022-2025), including carrier-free nanodrugs, liposomes, polymeric micelles, polymer-drug conjugates, host-guest drug delivery systems, and peptide-based nanoparticles, which utilize passive targeting, active targeting, and stimulus-responsive targeting mechanisms to improve tumor-directed drug delivery. Nevertheless, due to the complexity of the tumor microenvironment, single PPT nanomedicine has suboptimal therapeutic efficacy. PPT-based "combo" drug delivery system facilitates innovative multi-dimensional therapies - such as chemotherapy combined with photodynamic therapy, photothermal therapy, immunotherapy, and chemodynamic therapy - to deliver superior therapeutic benefits and jump the "valley of death". This review explores delivery strategies of PPT-based nanomedicines and may spark new ideas for multimodal treatment protocols, providing an entry point for professionals to thrive in this exciting field.

Keywords: Cancers, podophyllotoxin, PPT-based nanomedicines, tumor-directed drug delivery, "Combo" drug delivery system

INTRODUCTION

Malignancy poses a significant threat to human health^[1,2]. Surgical intervention, chemotherapy, radiation therapy, and immunotherapy are frequently utilized modalities for cancer treatment, either in combination or as standalone approaches^[3-6]. Surgery serves as the primary approach for early-stage solid tumors; however, its efficacy in advanced stages, characterized by the presence of metastatic tumors, is considerably limited^[7,8]. In the 1940s, Louis Goodman and Alfred Gilman pioneered the use of nitrogen mustards in the treatment of non-Hodgkin's lymphoma, marking a significant milestone in the history of chemotherapy^[9]. Currently, chemotherapy (such as paclitaxel, vincristine, and irinotecan), an irreplaceable treatment, remains the most widely utilized therapeutic modality for various types of tumors due to its effectiveness in targeting both primary lesions and distant metastases^[10-13]. Despite notable advancements in treatment modalities, clinical outcomes associated with chemotherapy continue to be suboptimal^[14,15]. This is attributable to several factors, including narrow therapeutic windows, prominent tissue damage, inadequate curative effects, short circulation half-lives, suboptimal drug pharmacokinetics, and difficulties in achieving effective drug delivery within solid tumors^[16]. Consequently, there is a clear need for ground-breaking tactics and more effective therapies that focus on new mechanisms and enhanced drug delivery technologies.

Natural products have attracted considerable interest from chemists and pharmacologists due to their diverse chemical and biological activities^[17,18]. For years, researchers have explored natural products as solutions to diseases; healthcare professionals are increasingly recognizing the potential of plant secondary metabolites in diseases (including cancer) prevention and treatment^[19-25]. *Podophyllum* plants have long been used in traditional folk medicine for their notable medicinal properties^[26]. Podophyllotoxin (PPT, PODO, POD; $C_{22}H_{22}O_8$; [Figure 1A](#)) is an aryltetralin-type lignan derived from *Podophyllum* species, first described by Charles Linnaeus in 1753^[27]. PPT, one of the most promising chemotherapeutic agents, possesses a chemical structure characterized by cohesive ring systems and a distinctive spatial configuration. Its multiple chiral centers play a significant role in contributing to its optical activity and biological efficacy. This complex structure underlies its pharmacological effects and influences physical properties such as hydrophobicity, which affects its behavior and applications *in vivo*^[28,29]. PPT was added to the United States Pharmacopoeia in 1820 and is effective in treating venereal warts^[30]. Currently, pure PPT serves as an active ingredient in the product Podofilox, which contains 0.5% PPT and is utilized for the treatment of genital warts caused by human papillomavirus^[31]. Due to its significant antitumor efficacy, PPT, a tubulin inhibitor,

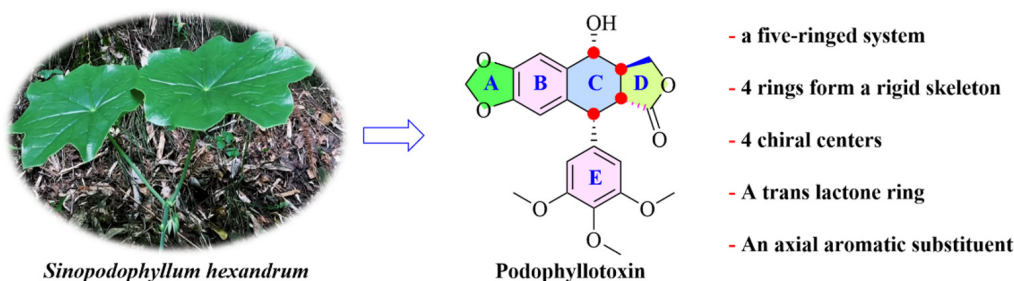
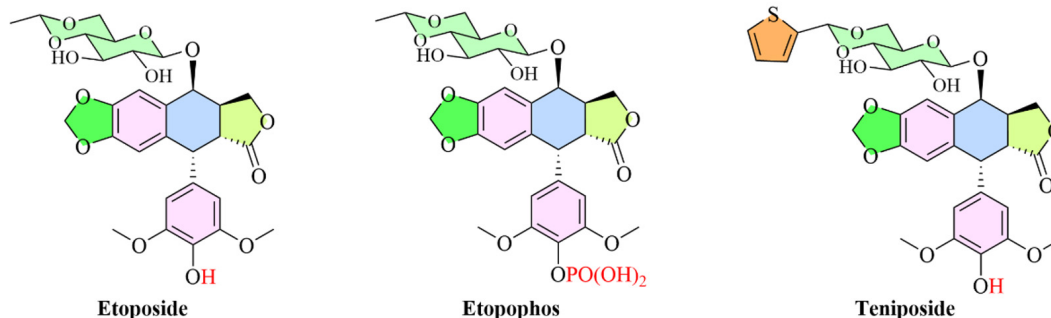
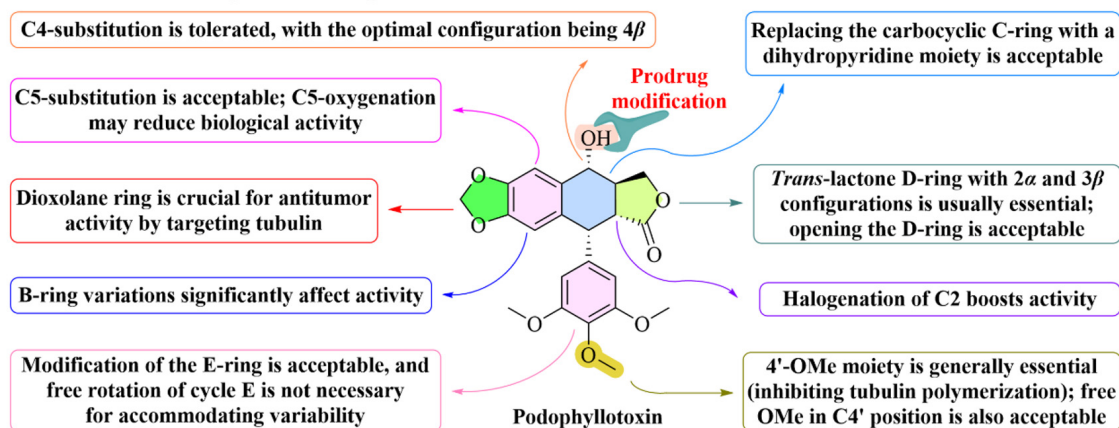
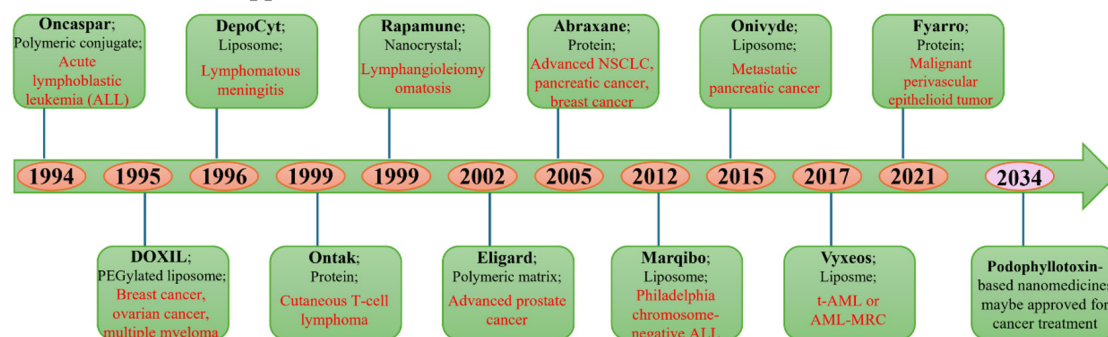
A: Chemical structure of podophyllotoxin (isolated from *Sinopodophyllum hexandrum*)**B: FDA approved anticancer drugs etoposide, etopophos, and teniposide****C: Structure–activity relationships****D: Timeline of FDA-approved landmark nanomedicines for cancer treatment**

Figure 1. Chemical structure of PPT (A); FDA-approved derivatives etoposide, teniposide, and etopophos (B); Structure-activity relationships pertaining to PPT (C); Timeline of FDA-approved landmark nanomedicines for cancer treatment (D).

has garnered substantial interest in research focused on targeting various cancers, including lung cancer, breast cancer, hepatocellular carcinoma, leukemia, and colorectal cancer^[32-36]. PPT inhibits cell growth by blocking tubulin polymerization, disrupting mitotic spindle formation^[37]. Initial studies aimed to use PPT directly for tumor treatment; however, various limitations (including poor water solubility, toxic side effects, and inadequate stability) hindered its effectiveness^[38-40]. To enhance the anticancer efficacy of PPT, structural modifications have been made to develop chemotherapy derivatives that exhibit reduced side effects and improved effectiveness^[41,42]. The main goal of altering the ring structure is to boost cytotoxic activity and inhibit topoisomerase II, primarily targeting the A, C, D, and E rings. Consequently, this effort has led to the development of etoposide, teniposide, and etopophos, all of which have been used in clinical settings^[43-45] [Figure 1B and C]. Nevertheless, these drugs continue to be associated with significant adverse effects, including nausea, cardiomyopathy, and myelosuppression^[46-48].

To address the limitations, there is a pressing need for drug targeting strategies that ensure tumor-specific delivery and improve the efficacy-toxicity balance of chemotherapeutic agents. As an emerging field within cancer research, nanomedicine paves the way for groundbreaking strategies in the design of effective and safe targeted therapies, and the demand for such advancements has never been greater^[49-55]. Nanotechnology-based drug delivery systems (DDSs) (mainly 10-200 nm) have been extensively explored for their potential in targeted chemotherapy, aimed at treating, monitoring, and diagnosing malignancies^[56-60]. To date, over 10 nanomedicines are approved by the U.S. Food and Drug Administration (FDA) for cancer treatment^[61,62] [Figure 1D]. Insights from these approved nanomedicines have prompted and inspired the exploration of PPT-based nanoplatfoms in cancer and beyond. Over the past few years, significant progress has been made in our understanding of the mechanisms, pharmacology, and therapeutic activities of PPT-based nanomedicines. An increasing number of PPT-based nanoplatfoms have been reported, overcoming the unfavorable pharmacokinetic characteristics, as well as toxicity and biosafety concerns of the parent PPT. We sincerely hope that PPT-based nanoplatfoms will be proven to be safe and effective anticancer drugs in the next decade. To move the field forward and ensure its transformative impact, it is crucial to consider various approaches. These PPT-based nanoplatfoms employ diverse methods - such as passive targeting, active targeting, and stimuli-responsive targeting - to deliver chemotherapy drugs directly to tumors while reducing exposure to non-target tissues^[63-65]. Conducting further fundamental research in this area may further clarify the potential applications of PPT-based nanomedicines in cancer treatment.

Advancements in nanotechnology and biomaterials significantly enhance the potential of PPT for cancer treatment within clinical settings^[66-70]. In recent years, a variety of PPT-based nanoplatfoms have been investigated, including carrier-free nanodrugs, liposomes, polymeric micelles, polymer-drug conjugates, host-guest DDSs, protein-based and peptide-based nanoparticles (NPs, Figure 2). Nanotechnology-based DDSs provide key advantages over traditional methods, such as enhanced bioavailability, increased stability, enhanced cellular uptake, extended vascular circulation, controlled release, improved therapeutic indices, and combination treatment^[71-76]. These benefits are particularly crucial for water-insoluble drugs (including PPT), offering a novel approach to their delivery^[77,78]. Meanwhile, due to the inherent complexity of the tumor microenvironment, single PPT nanomedicine exhibits suboptimal therapeutic efficacy. Combination therapies (and heterodimers) utilizing multiple treatment modalities can enhance anticancer efficacy synergistically while reducing the dosage of each drug, thus minimizing side effects^[79-85]. The PPT-based "combo" DDS enables innovative multi-dimensional therapies - such as chemotherapy in conjunction with photodynamic therapy (PDT), photothermal therapy (PTT), immunotherapy, and chemodynamic therapy (CDT) - thereby providing enhanced therapeutic benefits [Figure 2]. This comprehensive review explores delivery strategies for PPT-based nanoplatfoms (between 2022 and 2025^[86-105]; Table 1) and aims to inspire

Table 1. Representative paradigms of PPT-based nanoplatforms for cancer treatment

Type of nanoplatforms	Therapeutic agent	Size [nm]	PDI	Zeta [mV]	Therapy method	Results	Refs.
Carrier-free nanomedicines	PPT/Ce6 NPs	147	0.15	-	Chemotherapy, PDT	Enhancing chemo-photodynamic therapy for effective cancer treatment	[86]
	PPT/PPa NPs	130	0.17	-14.8	Chemotherapy, PDT	Superior tumor targeting, increased cytotoxicity, and improved PDT	[87]
	ECT Nano	84.1	< 0.2	-	Chemotherapy	Nanomedicine for dual inhibition of topoisomerase I and tubulin	[88]
	FAP NPs	96.4	0.08	-31.0	Chemotherapy	Improved blood circulation, greater tumor targeting, and enhanced <i>in vivo</i> antitumor efficacy	[89]
Liposomes	PSSF/BL-193 NAs	83.5	0.14	-25.0	Chemotherapy, Chemosensitization	Induces strong antitumor effects with reduced off-target toxicity	[90]
	PPT-SS1-PPT NPs	105.7	0.15	-35.8	Chemotherapy	Superior antitumor efficacy and reduced off-target toxicity	[91]
	PAG/Ce6 LPs	106	0.044	-18.8	Combined chemo-photodynamic therapy	Hypoxia-responsive, increased tumor accumulation, and enhanced efficacy	[92]
	MM-LPs-POD	101	0.129	-27.0	Chemotherapy, immune modulation	Enhanced tumor growth and lung metastasis suppression efficacy	[93]
	PPCNs	75	< 0.1	100	Chemotherapy, immunotherapy	Immunological and antitumor effects, along with improved targeting and reduced side effects	[94]
	miR-424@PPCNs	110	< 0.1	Positive	Chemotherapy, immunotherapy, and gene therapy	Reduced tumor growth and extended survival; decreasing immunosuppression	[95]
	Podo-NP	93	0.2	-1.65	Chemotherapy, immunotherapy	Regress tumors and reverse immunosuppressive microenvironments	[96]
	Lc-PTOX-Lps	169	0.19	-24.37	Chemotherapy	Improved effects on MCF-7 cells with lower toxicity to normal cells	[97]
Polymeric micelles	HA-S-S-PPT micelles	98.3	0.286	-44.67	Chemotherapy	pH/reduction dual-responsive, excellent antitumor efficacy, minimal systemic toxicity	[98]
	HP micelles	131	0.288	-50.37	Chemotherapy	pH-sensitive hyaluronic acid, improved chemotherapy	[99]
	FA-HA-SS-PPT NPs	69.7	0.252	-18.7	Chemotherapy	GSH-responsive, dual targeting of FR+CD44 overexpressing tumors	[100]
	MTX-PPT-micelles	107	0.235	-11.5	Chemotherapy, immunomodulatory	Inhibit proliferation, improve tumor immunosuppression	[101]
Polymer-drug conjugates	GBEPPT	52.8	0.116	-6.84	Chemotherapy	GGT-activated charge reversal and mitochondrial disturbance-induced mitocytosis	[102]
Peptide-based Nanoparticles	PEG-Pep-PPT NPs	108.7	0.295	-6.41	Chemotherapy	Improve <i>in vivo</i> inhibition of tumor growth, intratumoral microvessel density, and decrease systemic toxicity	[103]
Protein-based Nanoparticles	Nano-PPT	90.0	0.120	26.5	Chemotherapy, immunotherapy	Enhance antitumor immunity via mechanotransduction	[104]
Host-guest drug delivery systems	ACB-L/Fe-SS-PPT NPs	100	< 0.1	14.0	Chemo/chemodynamic/photothermal therapy	Targeting of cancer cells, NIR-enhanced Fe ²⁺ triggered •OH generation, and GSH consumption for cancer treatment	[105]

innovative ideas for multimodal treatment protocols. Major digital databases, including Web of Science, X-MOL, PubMed, Scopus, and Google Scholar, were perused using a series of search terms: podophyllotoxin, nanomedicines, nanoparticles, nanoplatform, co-assemblies, cancer, and antitumor.

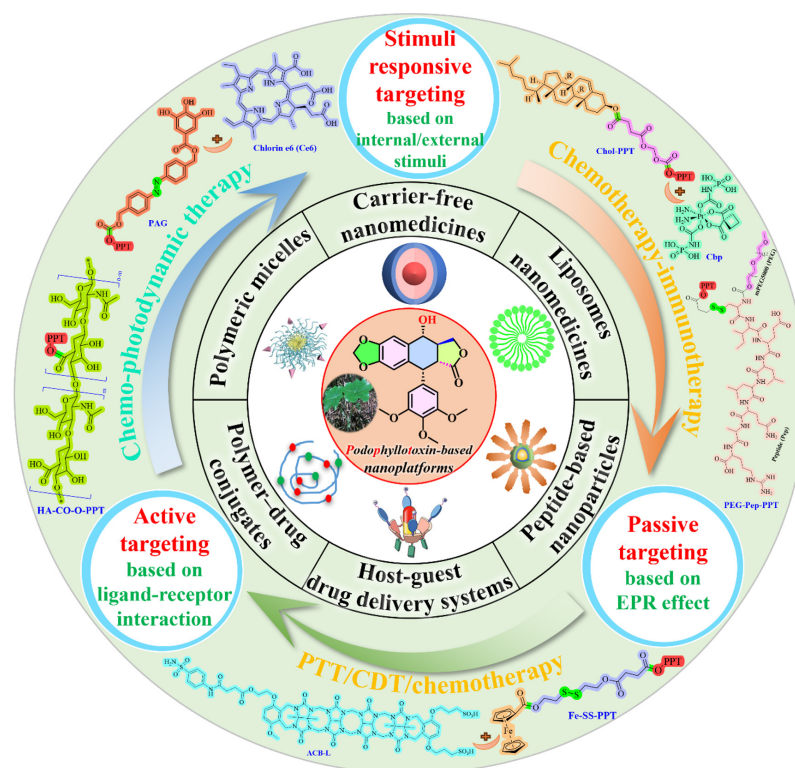


Figure 2. PPT-based nanoplatforms for multimodal cancer treatment.

CARRIER-FREE NANOMEDICINES

The clinical translation of nanomedicine delivery systems faces barriers due to complex preparation processes and low drug loading capacities^[106-110]. Since 2022, carrier-free nanomedicine has emerged as a cutting-edge research focus within the field of drug delivery, representing an innovative direction for drug development^[111-115] [Figure 3].

Unlike traditional DDS, carrier-free nanomedicines do not depend on additional carrier materials to encapsulate or transport the prodrugs or pure drugs (e.g., single or multiple drugs)^[116,117]. Instead, they primarily utilize the intrinsic physical and chemical properties of the drug molecules themselves to form nanoscale aggregates through self-assembly, with particle sizes typically ranging from 10 to 100 nanometers^[118,119]. During the preparation process, drug molecules spontaneously aggregate to create stable nanostructures via intermolecular interactions such as hydrogen bonding, hydrophobic interactions, and π - π stacking^[120,121]. This approach eliminates the need for supplementary carrier materials, significantly reducing potential risks associated with toxicity and immunogenicity linked to carriers while enhancing the biosafety profile of the drugs^[116,122-124]. From a pharmacokinetic perspective, the nanoscale dimensions of carrier-free nanomaterials facilitate favorable distribution characteristics *in vivo*. They can achieve passive targeted delivery more effectively to specific tissues or organs^[125,126]. Notably, in tumor tissues - where blood vessels exhibit high permeability and lymphatic drainage is often compromised - carrier-free nanomaterials can preferentially accumulate at tumor sites through enhanced permeability and retention (EPR) effects, thereby improving therapeutic efficacy^[127,128]. Regarding drug delivery mechanisms, carrier-free nanomedicines can be engineered as stimulus-responsive (acid-, redox-, or enzyme-sensitive) systems^[129,130]. For instance, leveraging low pH levels and elevated concentrations of glutathione (GSH) present within tumor microenvironments allows for structural transformation of these nanomedicines at tumor sites; this

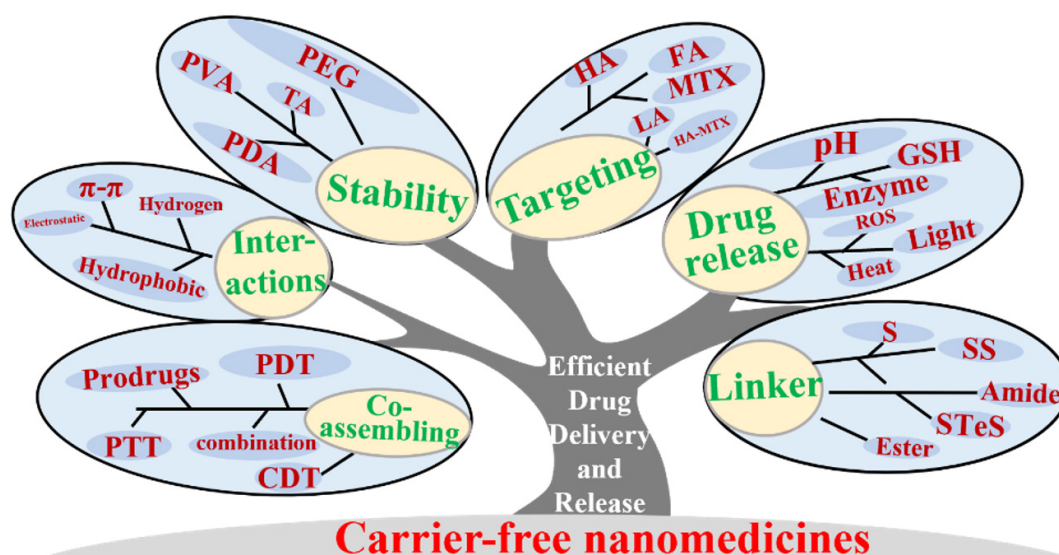


Figure 3. Schematic illustration of optimization strategies for carrier-free nanomedicines.

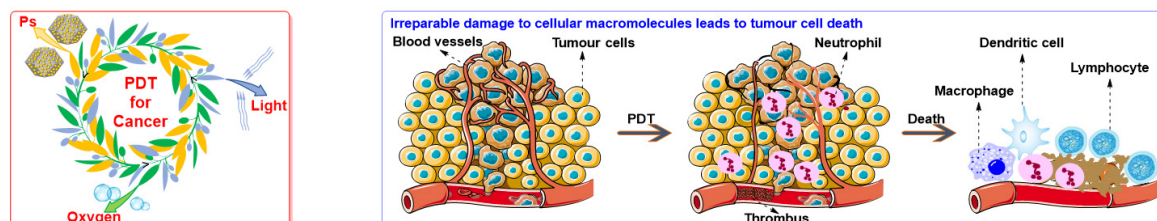
enables precise and controlled release of therapeutics^[131]. Co-assembling two or more chemotherapeutic agents enhances therapeutic efficacy and helps overcome multi-drug resistance (MDR) due to their synergistic antitumor mechanisms^[132-134]. Various therapeutic agents - such as photosensitizers or immunological agents - can also self-assemble based on specific antitumor therapy needs^[135-138]. In summary, the self-assembly process of carrier-free nanodrugs not only improves drug loading and reduces toxicity but also enables targeted and efficient drug delivery, making them particularly suitable for clinical translation.

Carrier-free, noncovalent NPs for chemo-photodynamic combination therapy

The complexity, diversity, and heterogeneity of tumors can significantly hinder the effectiveness of monotherapy, presenting substantial challenges in identifying optimal treatment strategies^[139,140]. Consequently, an increasing number of researchers have advocated for the combination of two or more therapeutic approaches to achieve enhanced antitumor effects^[141]. This strategy, which integrates multiple treatments for tumor management, is referred to as tumor combination therapy^[142]. Tumor combination therapy effectively addresses the limitations associated with single-agent therapies^[143,144]. PDT is a non-invasive cancer treatment that utilizes photosensitizers, light, and oxygen [Figure 4A]^[79,145-150]. PDT for cancer, a dynamic multi-stage procedure, typically consists of four components [Figure 4B]. The initial phase involves the administration of an inactive form of PS to the patient through topical application or systemic injection. Subsequently, PS can be selectively taken up by tumor cells or localized within tumor tissues. The third stage involves activating the PS by exposing the tumor site to the appropriate wavelength of light, which depends on the specific PS used. Finally, reactive oxygen species (ROS) are generated, which have cytotoxic effects on tumor cells and can induce oxidative damage to blood vessels and elicit an inflammatory response leading to targeted cell death or destruction within tumor tissue. However, the development of efficacious photosensitizers for PDT has encountered numerous challenges, including issues pertaining to poor solubility and non-specific tissue accumulation^[151,152]. The strategic combination of PDT with conventional chemotherapy holds potential to yield enduring and comprehensive treatment responses^[153,154].

Intrigued by this motivation, Zhang *et al.* proposed and successfully developed self-sensitive supra-molecular nanoassemblies that enhance antitumor efficacy by co-assembling PPT and chlorine e6 (Ce6)

A. Three elements of PDT



B. PDT for cancer treatment

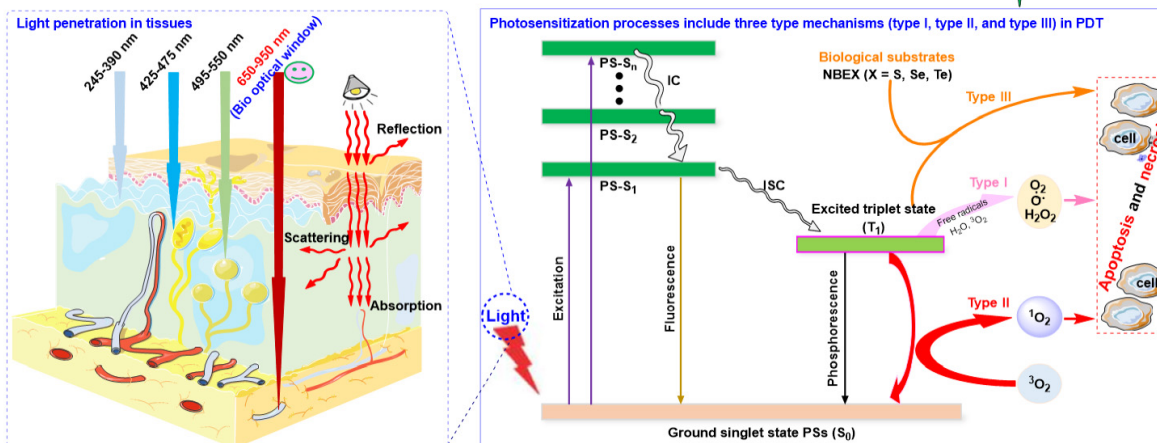
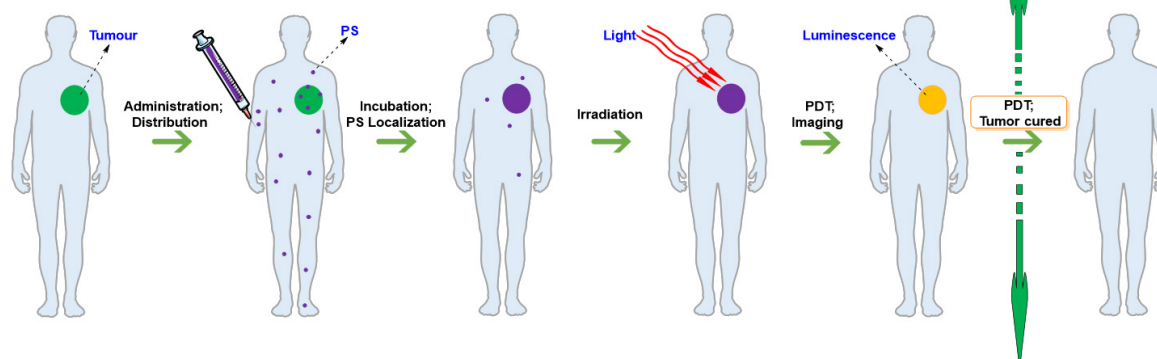


Figure 4. (A) Three key components of PDT. (B) The application of PDT in cancer treatment. Reproduced from Ref. [79] with permission from © 2024 The Authors. Published by Elsevier Ltd.

[Figure 5]^[86]. Achieving an ideal particle size and uniformity is essential for the effectiveness of DDS, particularly in enhancing therapeutic efficacy. This study determined that the optimal molar ratio of PPT to Ce6 is 3:1, resulting in a particle size of 147.4 nm and a low polydispersity index (PDI) of 0.146, which enhances therapeutic performance. During circulation, PPT is exposed to various physical influences, including shear stress from blood flow and fluctuations in temperature. These factors can contribute to the degradation of the drug and a subsequent loss of efficacy. The application of poly(ethylene glycol) (PEG) wrapping effectively isolates PPT from these external physical conditions, thereby minimizing their adverse effects on the drug. The PEG coating not only enhances the hydrophilicity and stability of PPT but also reduces interactions between blood-derived chemicals and the drug. Importantly, this protective layer helps maintain both the structural integrity and biological activity of PPT. The nanomaterials demonstrated stable co-assembly in simulated *in vivo* neural environments with a particle size of 150 nm and high co-loading capacities of 72.2 wt% for PPT and 27.8 wt% for Ce6. In concentrated solutions or polymerized states, the luminescence of photosensitizer molecules is frequently diminished or attenuated. This phenomenon results

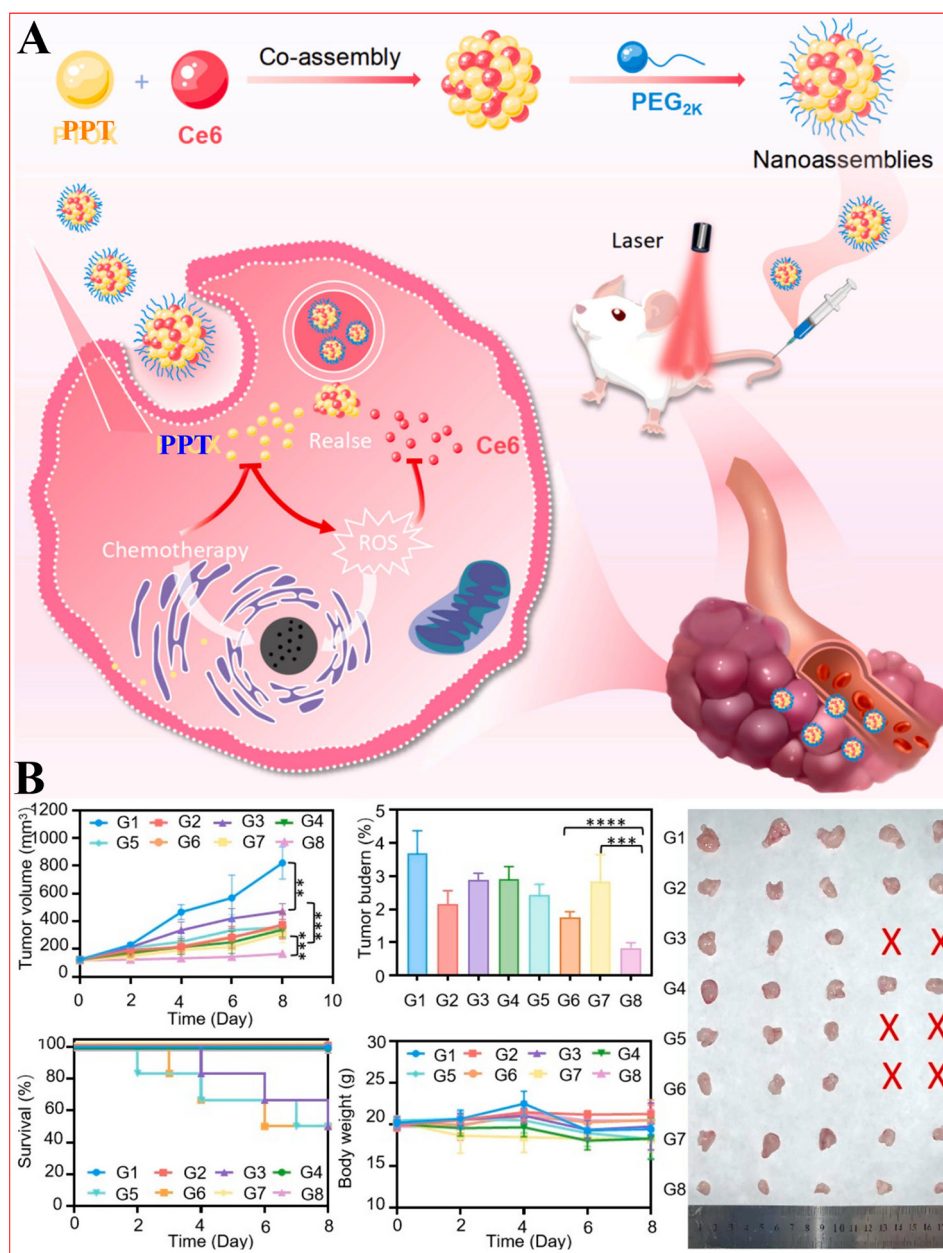


Figure 5. Illustration of the preparation process and the noncovalent NPs for combined tumor chemotherapy and PDT. (A) The preparation process of dual-drug nanoassemblies and its action mechanism; (B) *In vivo* therapeutic performances. ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$. Reproduced from Ref. [86] with permission from © 2024 Published by Elsevier B.V.

in “silent” formulations that reduce phototoxicity of Ce6 during circulation, contributing to enhanced safety and efficacy in PDT.

In experiments with 4 T1 breast tumor-bearing mice, combining nanoassemblies with laser irradiation resulted in smaller tumors and stronger antitumor effects, with negligible growth during treatment. The area under the drug-time curve (AUC) for the nanoassemblies was significantly increased, indicating prolonged circulation time and greater accumulation at the tumor site. Importantly, these nanoassemblies reduced toxicity associated with Ce6 and organic solvents while maintaining overall safety; liver and kidney

function indexes remained normal, and H&E staining revealed no significant tissue damage. Breast cancer remains the leading cause of malignancy-related deaths in women^[155,156]. These nanoassemblies present an efficient and safe platform for tumor therapy^[86].

The synergistic effect of PPT and Ce6 in nanoassemblies enhances the antitumor effect through multiple mechanisms. Specifically, the following points are key: (1) Enhanced cellular uptake: PPT/Ce6 NPs improve cellular uptake of drugs; (2) Synergistic generation of ROS: under laser irradiation, PPT and Ce6 work together to produce a number of ROS. This synergistic effect resulted in an increase in ROS levels within tumor cells, which enhanced the killing effect of the cells; (3) Pharmacokinetic advantages: compared with PPT/Ce6 solution, the area under the drug time curve (AUC_{0-24}) of nanoassemblies is significantly increased (2.6 times), and the half-life is extended (1.8 times); and (4) *In vivo* antitumor activity: compared with PPT alone or PPT/Ce6 mixtures, the nanoassemblies exhibited stronger tumor inhibition under laser irradiation, with the smallest tumor volume and the lowest tumor loading rate. The PPT/Ce6 nanoassemblies circulate in the blood for a longer time, increasing the probability of their accumulation at tumor sites. In summary, the synergistic effect of PPT and Ce6 in nanoassemblies significantly enhances the antitumor effect by enhancing cell uptake, enhancing ROS production, achieving self-sensitive release, and improving pharmacokinetic properties.

It is worth noting that the size of NPs significantly affects their behavior in the body after intravenous injection, influencing blood circulation, accumulation, and retention in tumors. Particles larger than 100 nm are typically taken up by organs such as the liver and kidney - areas with high blood flow and abundant mononuclear macrophages - and are then metabolically cleared from the body^[157]. Thus, there is an urgent need to establish guidelines for preparing carrier-free nanomedicine with optimized particle sizes for effective *in vivo* delivery. Meanwhile, preclinical animal models often fail to predict clinical outcomes accurately. Mouse models do not adequately replicate human tumors, increasing the gap between preclinical findings and patient data. Therefore, there is an urgent need for measurable changes in pharmacokinetics and biological distribution to enhance clinical translation.

Computer-aided, noncovalent NPs for chemo-photodynamic combination therapy

To achieve the optimal synergistic ratio of drugs in carrier-free supramolecular nanoassemblies, it is crucial to consider both the physicochemical properties of the drugs and their interactions within the nano-assembly^[158]. Computational simulations allow researchers to investigate atomic-level interactions among molecular components^[159,160]. These tools can analyze various parameters, including drug interactions, to simulate different combinations and their potential outcomes^[161,162]. By employing these methods, researchers can identify those combinations that maximize synergistic effects while ensuring stability and effective drug delivery by uncovering the driving forces behind NP formation.

The development of self-delivery NPs made from PPT and Pyrrolidine derivative (pyropheophorbide- α (PPa), a modified form of chlorophyll) offers a promising strategy for synergistic cancer therapy. Wang *et al.* explored compound dosage optimization through single-step nanoprecipitation, identifying a 1:2 molar ratio as optimal for 4T1 cancer cell cytotoxicity with $CI_{50} = 0.4951$, demonstrating superior combination effects [Figure 6]^[87]. Their computational analysis of PPa-PPT interactions revealed critical molecular engagements including hydrogen bonding, hydrophobic associations, and π - π stacking that stabilize NP formation. The research highlights the effective formulation of PPT/PPa NPs through systematic molar ratio optimization and computational insights into molecular dynamics, providing a strategic framework for combination therapy development.

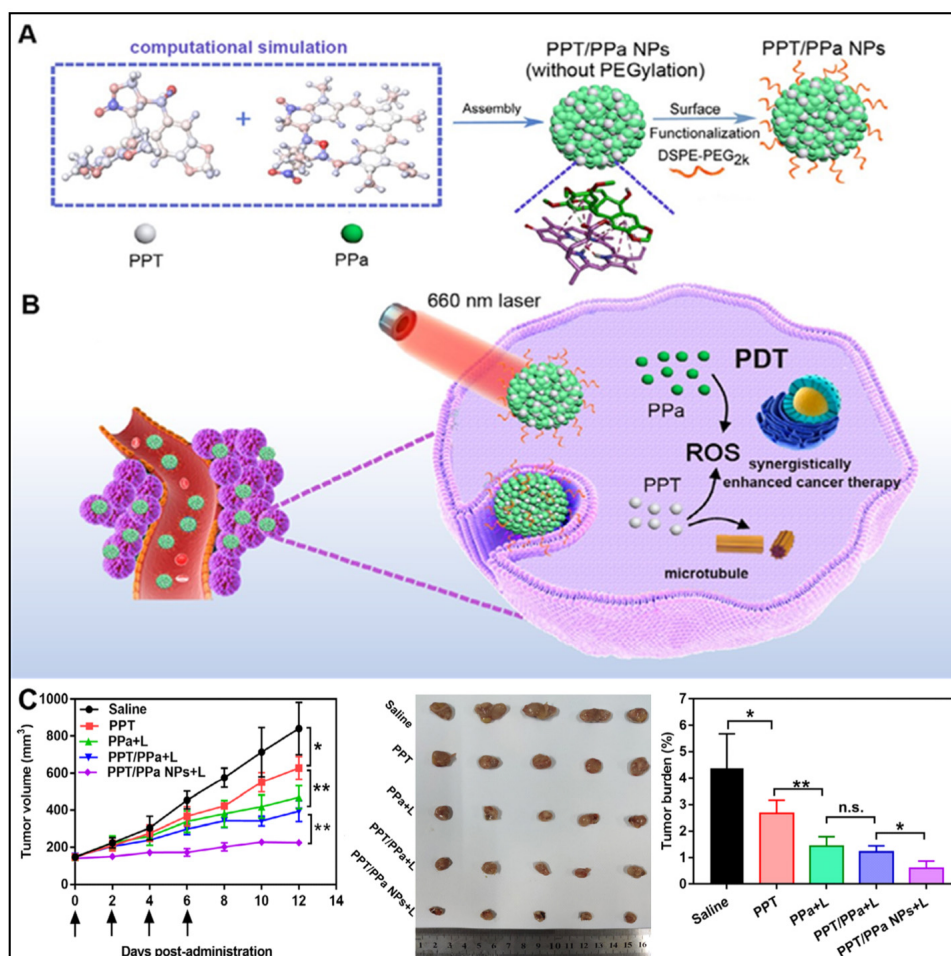


Figure 6. Illustration of the preparation process and chem-PDT synergistically enhanced cancer therapy of PPT/PPa NPs with computer-aided design. (A) The computer-aided design of PPT/PPa NPs; (B) Combination therapy of PPT/PPa NPs under 660 nm laser irradiation; (C) In vivo synergistic anti-tumor efficacy of PPT/PPa NPs under 660 nm laser treatment. * $P < 0.05$, and ** $P < 0.01$. Reproduced from Ref. [87] with permission from © 2020 Published by Elsevier B.V.

PEG chains are commonly attached to liposomes, providing "stealth" properties^[163,164]. This modification creates a hydrophilic barrier that enhances liposome stability and reduces protein adsorption, preventing rapid clearance by the reticuloendothelial system^[165,166]. The average diameter of PPT/PPa NPs is about 130 nm, with a low PDI of 0.172, indicating a uniform size distribution that enhances cell internalization and targeted delivery. Under physiological conditions, PPT/PPa NPs show good colloidal stability at 4 °C for up to 7 days^[87]. The therapeutic efficacy of PPT/PPa NPs was evaluated using a 4T1 xenograft tumor model, where they demonstrated the best antitumor effects among all tested formulations. The observed synergy in tumor ablation results from the co-delivery of PPT and PPa via NPs, enhancing pharmacological effects while their favorable size promotes high accumulation at the tumor site, leading to improved therapeutic outcomes^[87].

Advanced computational modeling has further accelerated NP optimization by elucidating structure-function relationships, informing design improvements for enhanced therapeutic performance. These collective results advocate for progressing PPT/PPa NPs toward clinical translation in oncology. It should be emphasized that the self-assembled PPT/PPa NPs maintain structural integrity through noncovalent

interactions, which may destabilize under physiological conditions. Such instability could lead to premature payload release during systemic circulation, potentially diminishing tumor-specific drug accumulation while increasing off-target toxicity risks. Current research focuses on developing stabilization strategies, including surface functionalization with amphiphilic polymers that reinforce NP integrity without impeding tumor penetration capabilities.

Natural product-empowered, GSH-responsive, covalent NPs for tumor chemotherapy

Natural products have been critical to the development of multi-drug regimens currently used in cancer chemotherapy and are used to treat a variety of malignancies^[167-173]. Meanwhile, the use of natural products as adjuvants or sensitizers for chemotherapy represents a promising strategy in cancer treatment^[174,175]. Lin *et al.* demonstrated that the natural compound BL-193 can selectively enhance the sensitivity of breast cancer cells to chemotherapy with PPT, even at low doses [Figure 7]^[90]. On the one hand, BL-193 establishes an ultra-low dose chemotherapy window that optimizes the antitumor effects of PPT. On the other hand, the design of the prodrug PSSF (linked by disulfide bonds) and precise hybrid nanoassemblies (PSSF/BL-193 NAs) effectively reduces non-targeted toxicity. Enabled by BL-193, PSSF/BL-193 NAs elicit strong antitumor responses, offering a novel approach to balance efficacy and toxicity in chemotherapy.

The study began with the observation that BL-193, when administered at a non-cytotoxic dose, significantly enhanced the sensitivity of breast cancer cells to PPT. BL-193 alone demonstrated minimal cytotoxicity, failing to induce substantial cellular death even at a concentration of 2 μM . Meanwhile, BL-193 can be safely utilized at higher concentrations without negatively affecting normal cell viability, rendering it an appealing candidate for combination therapy. The introduction of BL-193 at a non-cytotoxic concentration of 0.50 μM significantly enhanced PPT's cytotoxic effects on 4T1 breast cancer cells, indicating a synergistic effect with PPT. In non-cancer cell lines, mouse embryonic fibroblasts (3T3 cells) were used to assess the cytotoxicity of prodrug strategies. Prodrug PSSF exhibited significantly lower cytotoxicity than PPT, with its IC_{50} value increasing by over 40 times. Next, Lin *et al.* conducted a comprehensive study on various dose ratios (1:0 to 1:9) of PSSF combined with BL-193, using a one-step nanoprecipitation method to enhance therapeutic efficacy^[90]. The 1:5 molar ratio showed the strongest cytotoxic synergy in 4T1 cancer cells, achieving an IC_{50} value of 0.233 μM , which is 1.73 times lower than that of PSSF alone. For comparison, self-assembled PSSF NAs without BL-193 were prepared as controls. Both PSSF NAs (diameter = 87.60 nm, PDI = 0.13, Zeta = -25.38 mV) and PSSF/BL-193 NAs (diameter = 83.52 nm, PDI = 0.14, Zeta = -29.56 mV) exhibited uniform particle sizes and spherical structures with consistent PDI and Zeta values. High molecular weight (MW) PEG (> 2,000 Da) provides stealth and spatial stability. The incorporation of DSPE-PEG2K resulted in a negative zeta potential of approximately -25 mV, which helps reduce plasma protein adsorption and prolong blood circulation. Using a computer-aided approach, Lin *et al.* analyzed the molecular similarities and interactions between PSSF and BL-193, identifying key intermolecular interactions - such as π - π stacking and hydrophobic interactions - that are essential for forming PSSF/BL-193 NPs^[90].

BL-193 alone exhibited minimal cytotoxicity to 4T1 cells, but PSSF/BL-193 NAs (IC_{50} = 0.382 μM) showed more powerful cytotoxicity than PSSF NAs (IC_{50} = 1.120 μM), indicating that BL-193 enhances tumor-specific chemotherapy sensitization. Additionally, the cytotoxicity of PSSF NAs (IC_{50} > 2.0 μM) or PSSF/BL-193 NAs (IC_{50} > 2.0 μM) in normal 3T3 cells was lower than that of PPT solution (IC_{50} = 0.051 μM), highlighting the advantage of prodrug strategies in reducing PPT's toxic side effects. PSSF/BL-193 NAs exhibited superior antitumor efficiency compared to other controls (such as BL-193 solution, PSSF/BL-193 solution, and PPT solution). This enhanced efficacy is attributed to BL-193-mediated chemotherapy sensitization and increased tumor accumulation. During treatment, PSSF/BL-193 NAs did not significantly alter liver or kidney function parameters or damage major organs, showing lower systemic toxicity than the PPT solution group, which experienced notable weight loss and mortality^[90].

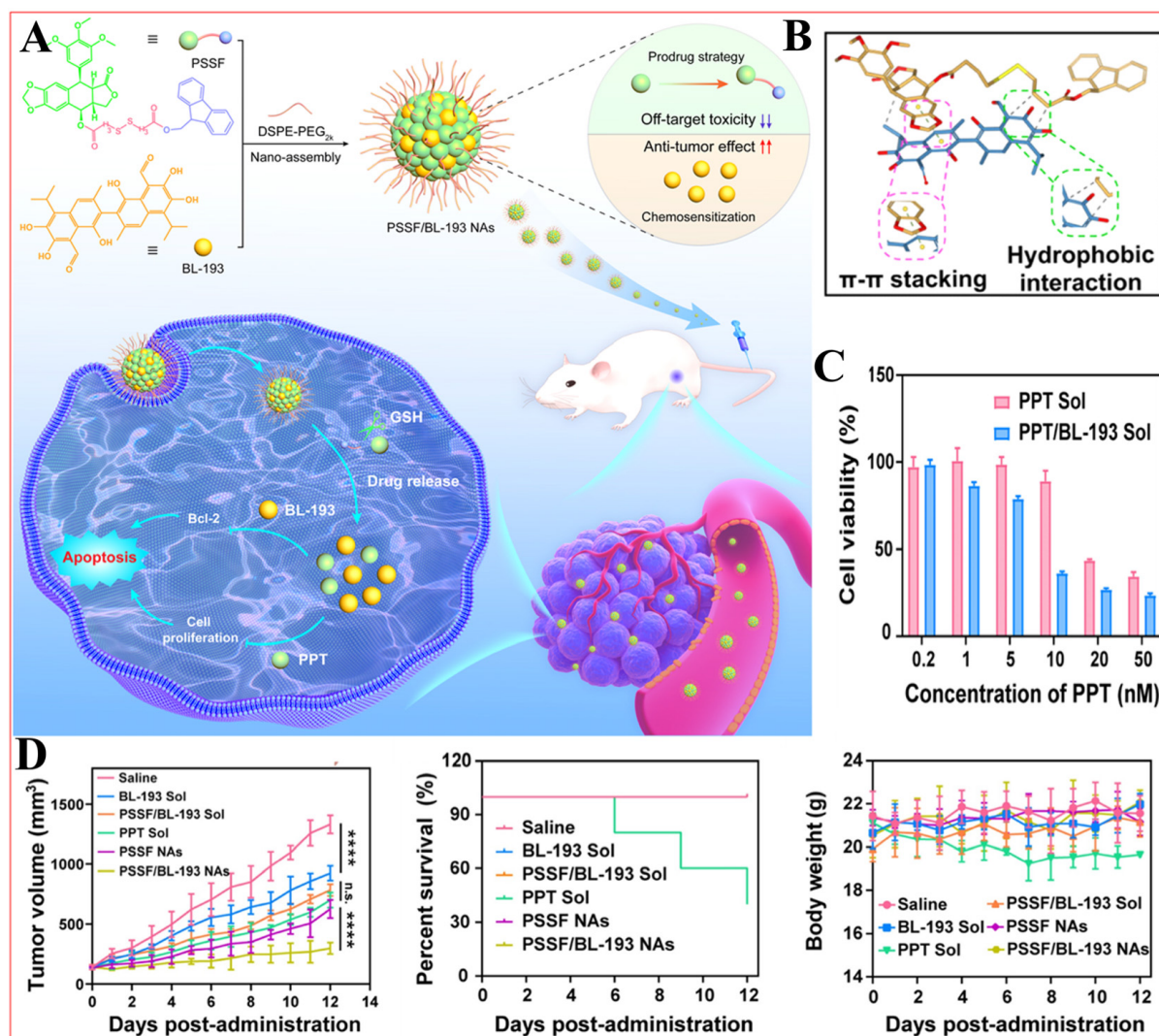


Figure 7. Schematic illustration of a BL-193 prodrug nanoassembly that elicits strong antitumor responses while minimizing off-target toxicity. (A) Preparation of PSSF/BL-193 NAs and its action mechanism; (B) Molecular docking simulation of PSSF and BL-193; (C) Cytotoxicity of PPT Sol or PPT/BL-193 Sol against 4T1 cells; (D) *In vivo* antitumor evaluation, **** $P < 0.0001$. Reproduced from Ref. [90] with permission from © 2024 Elsevier B.V.

This study combined the prodrug nanoassembly technology with a natural sensitizer (BL-193) to form a new chemotherapy regimen. This combination not only reduces the toxicity of prodrug, but also improves its therapeutic efficiency, especially in dealing with the delayed and insufficient activation of the prodrug. Although BL-193 as a chemotherapy sensitizer can open the window of ultra-low dose chemotherapy, in practical applications, accurately optimizing the ratio of PSSF and BL-193 to achieve optimal efficacy remains a challenge. Continued investigation into the specific mechanisms of action of BL-193 and its interactions with PPT will be critical.

Overall, carrier-free NP-based DDSs show promise in enhancing drug efficacy and reducing side effects. However, their clinical translation faces challenges, such as limited effectiveness compared to established formulations^[176,177]. Researchers have developed several strategies to address these issues. Additive and polymer modification^[178,179]: Adding small amounts of additives or modifying NPs with polymers can improve stability and extend *in vivo* circulation time, thus enhancing drug delivery efficiency. Introduction

of targeting agents^[180,181]: Attaching targeting molecules to NPs directs them to specific tumor sites, increasing local drug concentration while minimizing damage to healthy tissues. Responsiveness to linkers and external stimuli^[182,183]: Utilizing responsive linkers (e.g., amide bonds, ester bonds) or external stimuli (e.g., heat, light) allows for site-specific drug release at tumors, accelerating therapeutic effects. Adjustment of physicochemical properties^[184,185]: Optimizing the morphology, size, charge, or surface chemistry of NPs can enhance their *in vivo* behavior. Additionally, further investigation is needed on how additive and polymer modifications influence NP safety and the selection and design of targeting agents for improved specificity and effectiveness. By continuously optimizing carrier-free NP design and performance, it is hoped that current limitations will be overcome for broader clinical application.

LIPOSOMES NANOMEDICINES

The pioneering work by Alec D. Bangham in the development of liposomes in the mid-20th century has significantly shaped the landscape of modern medicine, offering innovative solutions for targeted drug delivery and personalized medical interventions^[186]. This enduring legacy continues to inspire ongoing research and innovation in the dynamic field of nanomedicine^[187-190]. Liposome therapy, characterized by its remarkable biocompatibility, degradability, and low immunogenicity, has significantly transformed the landscape of cancer treatment [Figure 8]^[191,192]. On the one hand, liposomes consist of one or more layers of concentric phospholipid bilayers that encase inner aqueous compartments. These nanocarriers markedly improve the dissolution properties and chemical integrity of various substances spanning low-molecular-weight compounds, nucleic acids, and protein-based molecules^[193,194]. This architectural design preserves the integrity and bioactivity of therapeutic compounds during systemic circulation until reaching pathological sites^[195]. Surface modifications employing diverse targeting moieties such as antibodies, aptamers, folate derivatives, and peptide conjugates demonstrate enhanced tumor specificity^[196-200]. Such molecular engineering improves cellular uptake efficiency and enables precision targeting through biological recognition mechanisms. Engineered release kinetics further allow temporal regulation of pharmaceutical agents, enabling prolonged therapeutic exposure through controlled liberation mechanisms^[201-203]. The amphiphilic nature of these vesicles enhances compound bioavailability while achieving spatial-temporal delivery control with reduced adverse reactions^[204,205]. Collectively, these nanoscale systems provide a versatile platform for oncological interventions through coordinated mechanisms of molecular stabilization, tissue-selective transport, and sustained release patterns. These characteristics establish lipid-based vesicles as sophisticated delivery vehicles capable of transporting bioactive compounds to malignant lesions with improved therapeutic precision. The unique amphiphilic structure permits PPT encapsulation within their aqueous core or incorporation into phospholipid membranes, forming a protective shield against destabilizing environmental factors while maintaining pharmacological activity.

Hypoxia-responsive dual-drug liposomes for combined tumor chemotherapy and PDT

The efficacy of PDT is considerably compromised by tumor hypoxia, which results from the consumption of oxygen during the therapeutic process^[206,207]. To improve the outcomes of PDT, various strategies have been developed to alleviate hypoxic conditions within tumors. These measures include supplemental oxygen, use of oxygen generators, downward adjustment of oxygen consumption and use of low-oxygen microenvironments^[208-211]. Utilizing hemoglobin as a carrier can effectively deliver oxygen to tumor sites. Hemoglobin has a high affinity for oxygen and can release it in the low pH environments typical of tumor tissues, thereby increasing local oxygen concentrations during PDT^[212-215]. Perfluorocarbons are another promising strategy for oxygen delivery; they can dissolve large amounts of oxygen and facilitate its transport to hypoxic areas within tumors, enhancing the efficacy of PDT^[216-219]. Catalase can decompose hydrogen peroxide (H₂O₂) into water and oxygen, providing an endogenous source of oxygen within the tumor microenvironment. By administering catalase, oxygen levels can be elevated, supporting the ROS generation necessary for effective PDT^[220-223]. Certain metal compounds have been explored for their ability to generate

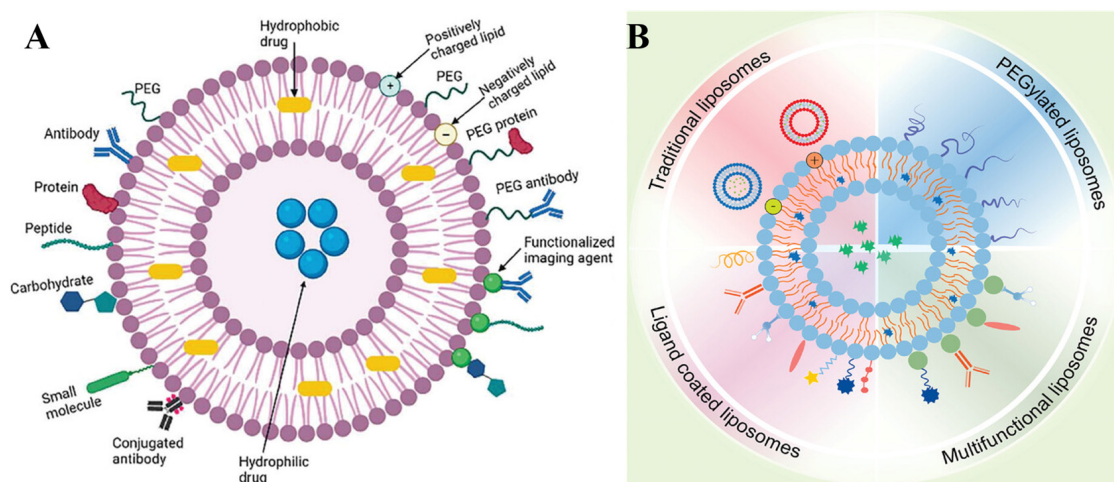


Figure 8. (A) Schematic of various liposome types and their functions. Reproduced from Ref.^[191] with permission from © 2023 The Authors. American Chemical Society; (B) Scheme of liposomal drug delivery system. Reproduced from Ref.^[192] with permission from © 2025 Wiley-VCH GmbH.

oxygen. Transition metal-based NPs, for instance, initiate oxygen-generating reactions to counteract hypoxic conditions in PDT settings^[224,225]. Approaches focusing on minimizing oxygen consumption of tumor cells may preserve elevated oxygen concentration. Such methods could involve disrupting oxygen-dependent biochemical processes, thereby creating optimal conditions for effective PDT implementation. Hypoxia-activated prodrug development embodies a novel strategy for targeted drug delivery within oxygen-deprived tumor microenvironments^[226-229]. Mitigating tumor hypoxia remains paramount for enhancing PDT treatment outcomes. The aforementioned techniques - including oxygen enrichment methods and hypoxia-targeted prodrug applications - offer viable pathways for optimizing PDT effectiveness. Continued research will be essential for optimizing PDT protocols and maximizing their clinical effectiveness in treating cancer.

Prodrug engineering has emerged as an innovative pharmaceutical strategy to enhance drug delivery parameters^[230,231]. Yu *et al.* developed a dual-drug liposome using the "turn enemy into friend" strategy to enhance synergistic chemotherapy and PDT [Figure 9]^[92]. They synthesized an anoxic-responsive prodrug (PAG) and incorporated it with the photosensitizer Ce6 in the liposome. By employing an active loading method based on a metal ion gradient, PAG and Ce6 were optimally loaded in a favorable synergistic ratio. In mouse models, PAG/Ce6 liposomes demonstrated notable antitumor efficacy by effectively inhibiting tumor growth without causing significant toxicity to normal tissues^[92]. The study highlighted the excellent biosafety profile of PAG/Ce6 liposomes; there were no significant changes in body weight during treatment, nor was there considerable damage observed in major organs upon histological examination. In summary, Yu *et al.* present a novel dual-agent liposome platform capable of efficiently releasing hypoxia-responsive prodrugs and photosensitizers in synergy for more effective tumor therapy^[92].

PAG/Ce6 LPs kill tumor cells through several mechanisms: (1) Production of ROS: Under laser irradiation, PAG/Ce6 LPs generate a significant amount of ROS, which directly induces tumor cell death; (2) Depletion of intracellular GSH: PAG/Ce6 LPs consume GSH in tumor cells, disrupting the REDOX balance and triggering apoptosis; (3) Exacerbating the hypoxic microenvironment: the action of PAG/Ce6 LPs intensifies the hypoxic conditions within tumor cells, promoting the release of antitumor drug PPT and enhancing chemotherapy effectiveness. These mechanisms interact synergistically to improve therapeutic outcomes.

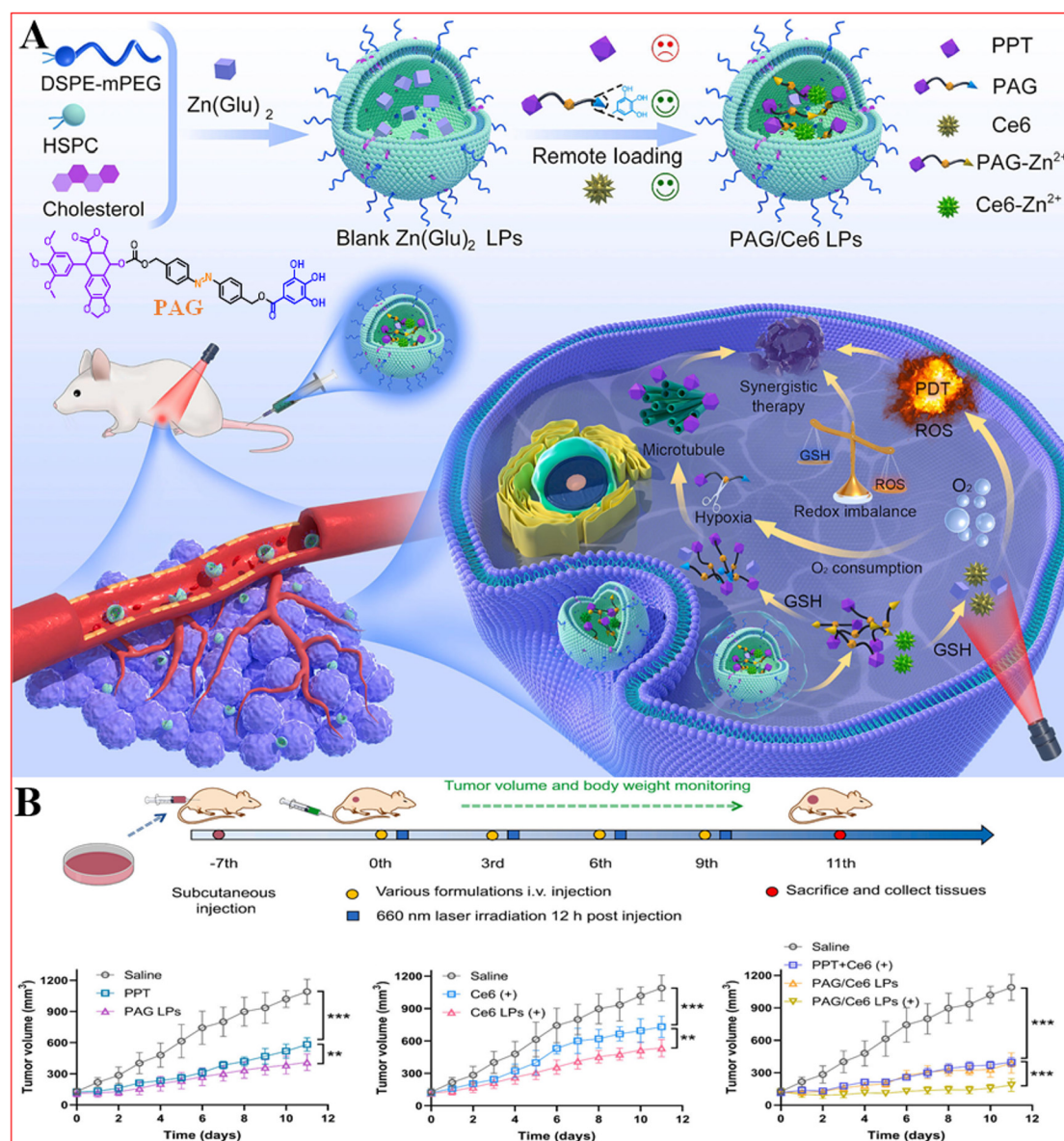


Figure 9. Schematic of PAG/Ce6 LPs for synergistic cancer therapy. (A) Preparation of PAG/Ce6 LPs and its action mechanism; (B) *In vivo* pharmacodynamics evaluation of PAG/Ce6 LPs, ***P* < 0.01, ****P* < 0.001. Reproduced from Ref. [92] with permission from © 2024 Elsevier B.V.

The "adversary to ally" tactic repurposes tumor hypoxia (traditionally viewed as a detrimental factor) into a beneficial element that amplifies pharmaceutical activation. This methodology integrates oxygen-sensitive prodrug formulations with light-activated compounds, capitalizing on the tumor's low-oxygen microenvironment to optimize treatment outcomes^[92]. Researchers demonstrated successful tumor cell eradication by developing hypoxia-activated polyphenolic prodrugs (PAG) combined with photosensitizing agents (such as Ce6), jointly encapsulated within lipid NPs (PAG/Ce6 LPs). This innovative approach presents three key therapeutic benefits: (1) Optimized pharmaceutical activation: The prodrug system specifically triggers drug release under oxygen-deprived conditions; (2) Multimodal tumor elimination:

Cancer cell destruction occurs through dual mechanisms involving ROS production and GSH depletion; (3) Enhanced pharmacokinetic performance: The nanoliposome delivery system prolongs systemic circulation duration while promoting tumor-specific aggregation, thereby maximizing therapeutic potential against malignancies. However, challenges remain: (1) Heterogeneity of tumor hypoxia: varying degrees of hypoxia may lead to inconsistent prodrug activation efficiency; (2) Phototoxicity: While liposomes maintain fluorescence quenching during circulation, photosensitizer activation at tumors may harm surrounding normal tissues; (3) Barriers to clinical translation: Despite their potential, hypoxia-activated prodrugs face limitations in clinical studies with no FDA-approved drugs yet.

MicroRNA-424-based, cationic lipids for combined chemotherapy and immunotherapy

The effectiveness of single-drug chemotherapy is limited by the complexity of the cancer ecosystem^[232-234]. Wang *et al.* proposed a NP system for simultaneous chemotherapy and gene therapy, developing a cationic lipid bilayer NP system (miR-424@PPCNs) for co-delivery of microRNA-424 (miR-424) and PPT as a multimodal anticancer treatment [Figure 10]^[95]. The combination enhances the sensitivity of non-small cell lung cancer cells to chemotherapy through multiple mechanisms. Specifically, miR-424 directly targets PD-L1 mRNA, reducing PD-L1 expression, an immune checkpoint protein that allows tumor cells to evade immune attacks. By decreasing PD-L1 production, miR-424 promotes T cell attack on tumor cells, enhancing the immune response^[235]. MiR-424 is a novel therapeutic target and prognostic factor in malignancies^[236]. This multimodal strategy results in higher efficacy with the miR-424@PPCN compared to using miR-424 or PPT alone.

In the control group, tumor volume rapidly increased to 2030 mm³, while mice treated with the miR-424@PPCN complex showed only 129 mm³, indicating a significant inhibitory effect^[95]. Additionally, mice receiving the miR-424@PPCN treatment had significantly longer survival compared to controls. The combination of miR-424 and PPT notably influenced tumor growth. The miR-424@PPCN achieved a mean tumor inhibition rate of 91%, surpassing that of miR-424 (42%) or PPCNs alone (67%)^[95]. This suggests that miR-424 enhances the inhibitory effects of PPT on tumor cells by potentially reversing chemotherapy resistance and promoting apoptosis. Although the study mentions the combined therapeutic mechanism of miR-424 and PPCNs, it does not deeply explore the specific molecular mechanisms and signaling pathways, potentially leading to an incomplete understanding of their therapeutic effects.

Bioresponsive liposome nanomedicines

In general, combination therapy surpasses monotherapy by enhancing efficacy and safety^[237-239]. This strategy has significantly improved clinical outcomes for tumor patients, including response rates and overall survival^[240,241]. Ling *et al.* investigate the application of bio-responsive NPs in antitumor immunity, specifically examining how these NPs can enhance antitumor immune responses through the integration of anti-angiogenic therapies and chemotherapy regimens [Figure 11]^[96]. Firstly, by introducing an alkanoyloxymethyl ester linkage between PPT and cholesterol, an esterase-cleavable PPT prodrug (Chol-Podo) was afforded. Then, two bio-responsive NPs were constructed: Podo-NP (prodrug containing PPT) and CbP-NP (prodrug containing carboplatin). By administering sequential treatment to tumors, these NPs promote an antitumor T-cell response. Notably, Podo-NP suppresses tumor angiogenesis through curtailing endothelial cell proliferation and motility, impeding neovascularization while reinforcing preexisting vasculature. Complementarily, CbP-NP augments therapeutic outcomes by disrupting tumor cell cycle progression and triggering programmed cell death. Concurrently, CD40 agonists prime antigen-presenting cells to present tumor-associated antigens derived from apoptotic cells, effectively counteracting immunosuppressive microenvironmental conditions^[242,243]. This sequential administration approach combining angiogenesis inhibitors with chemotherapeutic agents and immunomodulators demonstrated significant suppression of primary tumor growth and metastatic progression in murine lung carcinoma

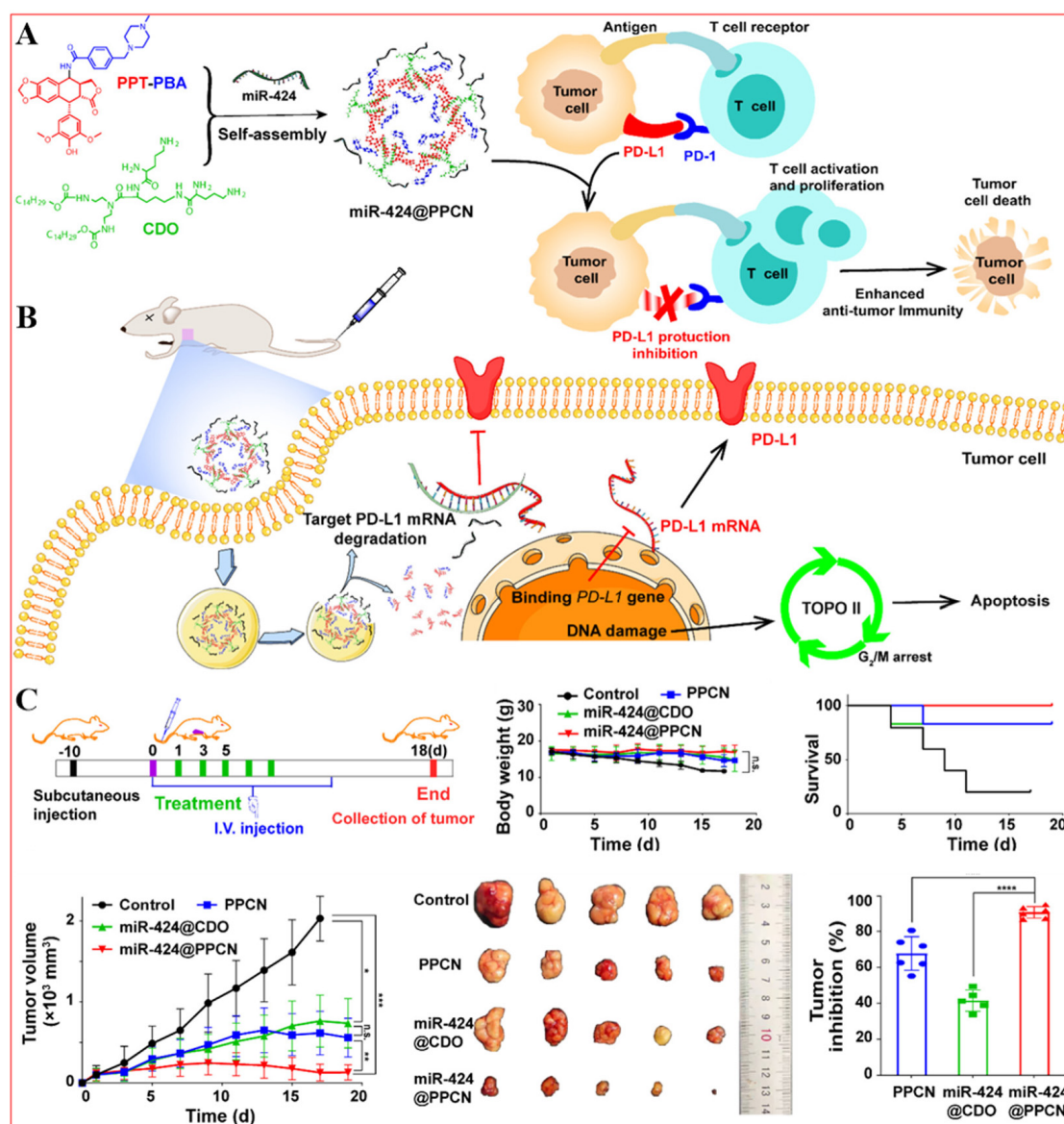


Figure 10. Preparation of miR-424@PPCN complexes and their mechanism of action on tumor cells. (A) Preparation of miR-424@PPCN complexes; (B) Action mechanism of miR-424@PPCN complexes; (C) *In vivo* antitumor effects of miR-424@PPCN complexes in tumor-bearing mice, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Reproduced from Ref.^[95] with permission from © 2022 American Chemical Society.

models. Both nanocarriers display optimal hydrodynamic diameters (93 nm for Podo-NP vs. 66 nm for CbP-NP) with narrow polydispersity indices (0.2 and 0.1, respectively), ensuring colloidal stability and therapeutic reliability. Stability assessments revealed both formulations maintained structural integrity at 4 °C, showing negligible changes in particle dimensions or surface charge over seven days^[96]. Intracellular concentrations of Podo and platinum derivatives from nanocarriers exceeded free drug levels by 83.8–108.5-fold and 116.9–118.4-fold respectively after 24-h exposure^[96], suggesting enhanced endocytic internalization mechanisms. Post-cellular entry, the nanovehicles respond to intracellular esterases and reducing agents to liberate therapeutic agents within cytoplasmic compartments.

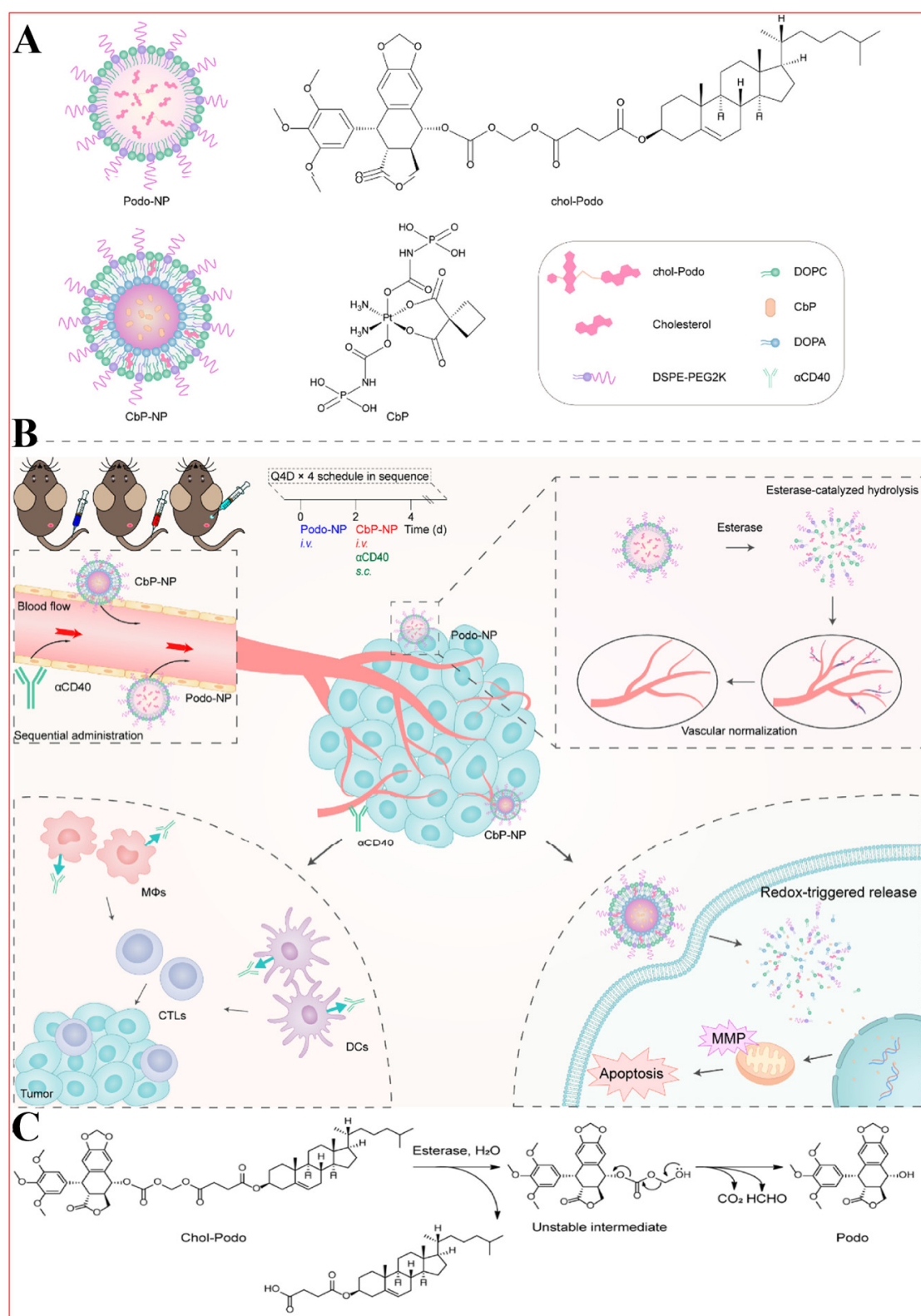


Figure 11. Sequential administration of esterase-responsive Podo-NP, redox-sensitive CbP-NP, and a CD40 agonist enhances the antitumor T cell response. (A) Bioresponsive Podo-NP and CbP-NP; (B) Improving immunotherapy outcomes with sequential antiangiogenesis and chemotherapy; (C) Proposed Podo prodrug bioconversion via esterase-catalyzed cascade hydrolysis. Reproduced from Ref. [96] with permission from © 2020 American Chemical Society.

CD40 is present on several APCs, and agonistic CD40 antibodies (α CD40) elicit broad immunostimulatory responses^[244]. CD40 agonists demonstrate substantial potential in amplifying immunotherapy outcomes through multifaceted modulation of the tumor microenvironment and immune cell dynamics^[245-247]. Key pathways involve dendritic cell activation, tumor niche remodeling, immune cell recruitment enhancement, and macrophage polarization control. Such activation drives the differentiation of naïve T cells into tumor-targeting cytotoxic effectors while potentiating systemic antitumor immunity^[96]. The immunomodulatory effects extend to converting suppressive tumor microenvironments into immune-permissive states. Combined regimens with angiogenesis inhibitors and chemotherapeutic drugs reveal synergistic effects, where CD40 agonists mitigate immunosuppression by altering T cell composition - suppressing regulatory T cell populations while expanding both CD4⁺ helper and CD8⁺ cytotoxic T cell infiltration. Marked increases in tumor-infiltrating CD4⁺ and CD8⁺ T lymphocyte populations post-treatment^[96], indicating enhanced immune cell trafficking to tumor sites that strengthens localized antitumor responses.

In different treatment groups, changes in tumor growth inhibition (TGI) rate reflect the effectiveness of each treatment strategy. Specifically, the TGI of Etop + Carb, CbP-NP, and Podo-NP alone was 44.7%, 48.1%, and 31.0%, respectively^[96]. Although these treatments have some tumor inhibition, the effect is relatively limited. However, when treated with Podo-NP in combination with CbP-NP, TGI was significantly increased to 70.6%. Furthermore, with the addition of α CD40, TGI was further increased to 89.9%^[96]. The strategy of combining Podo-NP and CbP-NP significantly enhances the antitumor effect, which is further enhanced by the addition of α CD40. In different treatment groups, measurements of tumor weight showed that the Podo-NP + CbP-NP + α CD40 group had significantly lower tumor weight than the other groups (0.08 ± 0.01 g), indicating the effectiveness of the combination therapy in inhibiting tumor growth. Collectively, the observed alterations in TGI rates and extended survival durations provide robust evidence for the therapeutic efficacy of the combination therapy approach.

Furthermore, the sequential therapeutic approach exhibits multiple benefits compared to single-agent treatments regarding tumor suppression effectiveness. These include amplified immune cell penetration, diminished immunosuppressive tumor microenvironment, and facilitated recruitment of M1-polarized macrophages. Experimental groups displayed marked increases in tumor-infiltrating CD3 ϵ +CD4⁺ helper T lymphocytes (Ths) and CD3 ϵ +CD8 α ⁺ cytotoxic T cells (Tcs) post sequential treatment. Quantitative analysis revealed the infiltration levels climbing to 24.4% in the triple combination group, in stark contrast to the 5.9% observed in phosphate-buffered saline (PBS)-treated counterparts. Tcs infiltration rates similarly demonstrated substantial elevation at 31.6%, vs. a minimal 2.0% in control groups. These metrics confirm the regimen's capacity to boost immune cell accumulation at neoplastic sites. The protocol effectively suppressed immunosuppressive Treg populations, with triple therapy groups showing 33.2% Treg levels compared to 93.2% in PBS controls^[96]. Sequential administration notably elevated CD86 expression (M1 macrophage marker) to 52.8%, dramatically exceeding the 2.7% baseline in PBS groups. Conversely, CD206 expression (M2 macrophage indicator) plummeted to 6.1% vs. 57.5% in controls, indicating successful macrophage repolarization toward antitumor phenotypes. Collectively, the Podo-NP/CbP-NP/ α CD40 regimen presents a multifaceted solution for immunologically inert tumors such as LL/2 Lewis lung carcinoma^[96]. By first addressing vascular abnormalities before modulating the tumor microenvironment and triggering comprehensive immune activation, this methodology shows promise for enhancing clinical outcomes in comparable malignancies, highlighting its value in multimodal therapeutic strategies.

Liposomal biomaterials offer promising opportunities for tumor treatment^[248,249]. As a nanodrug delivery system, liposomes effectively transport chemotherapy agents, genes, antibiotics, and other therapeutic compounds^[250-254]. Modifying the structures of liposomes can enhance drug delivery and targeted therapy while minimizing adverse effects. Current research highlights the potential of liposome-based nanomedicine in cancer; however, systematic studies are necessary to determine maximum tolerated doses, elucidate drug properties, and analyze metabolites. Furthermore, the complexity inherent in lipid nano-delivery systems presents challenges for mass production; clinical applications necessitate scalable manufacturing techniques that are both cost-effective and reliable while ensuring long-term storage and sterilization capabilities.

POLYMERIC MICELLES

Nanomicelles form through self-assembly of amphiphilic molecules such as block copolymers in aqueous environments^[255]. This structure provides excellent solubilization capabilities that substantially improve PPT's solubility. A nanomicelle's core consists of hydrophobic chain segments for encapsulating PPT, while its shell comprises hydrophilic chain segments that ensure good solubility and stability in water. The rational design of targeted micelles involves four endogenous targeting strategies [Figure 12^[255]]: (1) Modifying micelles with specific fragments to enhance drug delivery; (2) Developing stimulus-responsive micelles that release drugs in response to endogenous stimuli such as ROS; (3) Attaching ligands to micelles for high-affinity recognition of overexpressed receptors at target sites, improving tissue accumulation; (4) Surface modifications on micelles to evade immune detection within cells, enhancing targeting efficacy and therapeutic outcomes.

Active targeting incorporates specific antibodies, ligands, and other moieties into NP carriers by utilizing receptors that are highly expressed in tumor tissues or unique to these environments^[256,257]. This process leverages the precise binding interactions between receptors and ligands, as well as the efficient engagement between antibodies and antigens, facilitating targeted drug delivery. Commonly used targeting ligands include polysaccharides (such as hyaluronic acid (HA) and mannose), small molecular compounds (such as biotin), peptides (e.g., arginine-glycine-aspartic acid (RGD) peptides), and proteins (including antibodies and transferrin [Tf])^[258-264].

pH-sensitive, hyaluronan-targeted polymeric micelles

Tumor tissue has a weakly acidic environment, with a pH of 6.5 to 6.8, compared to the normal tissue pH of about 7.4^[265]. This difference is significant as tumor cells proliferate rapidly and often face inadequate blood supply, leading to hypoxia^[266]. Consequently, some tumor cells rely on glycolysis for energy, increasing lactic acid levels and contributing to the acidity^[267]. Intracellular compartments such as endosomes and lysosomes have even lower pH values (4.5 to 5.5)^[268]. Utilizing the pH gradient between tumor and normal tissues enables the development of pH-sensitive NP DDS that remain stable in circulation while reducing drug leakage^[269,270]. In response to acidic conditions in tumors, these systems can release antitumor drugs directly at the site, enhancing local drug concentration and improving therapeutic efficacy. At low pH, these linkages become unstable and undergo hydrolytic cleavage, resulting in drug release. Common acid-labile bonds include ester, amide, hydrazone, acetal or ketone groups, and borate esters^[271-274]. Another pH-sensitive DDS utilizes proton donor or acceptor groups, such as imidazole and acrylic moieties, to modify nanomedicine carriers^[275,276]. This modification results in drug carriers that can effectively respond to fluctuations in environmental pH levels. These protonic groups possess specific pKa values that determine their hydrophilic or hydrophobic state depending on the solution pH. When the pH exceeds the pKa of the proton group, the segment containing it becomes hydrophobic, promoting polymer self-assembly into micelles. As the pH gradually decreases, an increasing number of protonation sites become protonated;

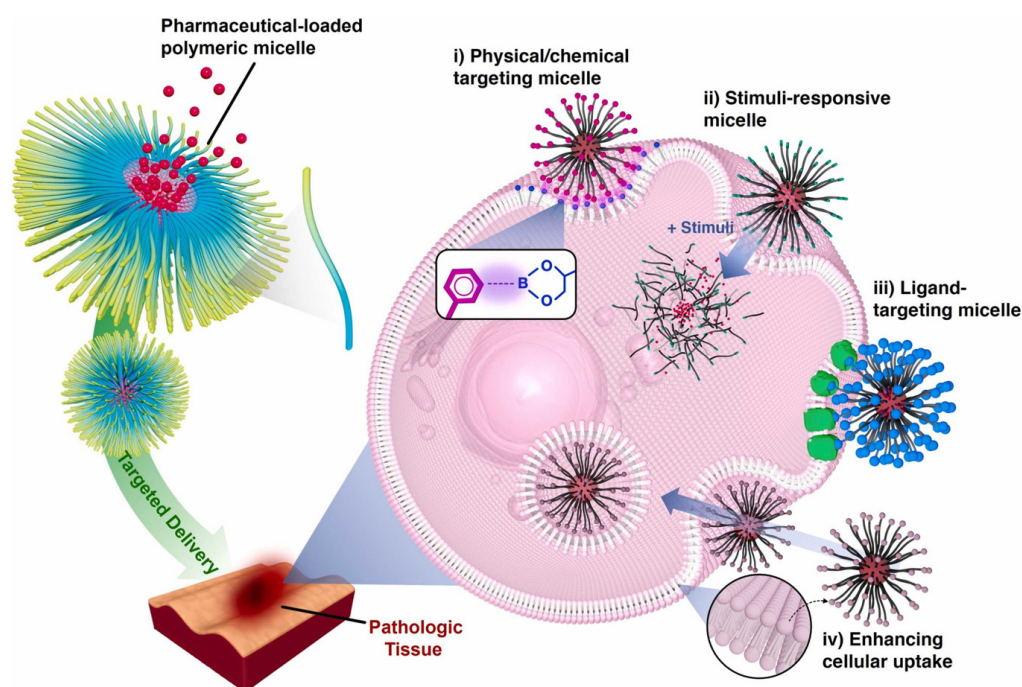


Figure 12. Designing polymeric micelles for targeted drug delivery. Reproduced from Ref.^[255] with permission from © 2024 Elsevier Ltd.

consequently, the hydrophilicity of the micelles is enhanced. This alteration leads to instability or dissociation of the micelles, resulting in drug release.

Li *et al.* developed a novel pH-sensitive HA-targeted prodrug micelle, named HA-CO-O-PPT, to enhance chemotherapy efficacy [Figure 13]^[99]. The pH-sensitive prodrug is synthesized by conjugating the hydrophobic antitumor agent PPT with hydrophilic HA via a one-step esterification reaction. In an aqueous environment, the prodrug self-assembles into nano-spherical micelles (HP micelles), exhibiting excellent serum stability and blood compatibility. Under simulated physiological conditions (pH = 7.4), HP micelles maintain their particle size even in media containing 10% fetal bovine serum (FBS), indicating structural integrity during circulation. They demonstrate a pH-responsive drug release mechanism in acidic tumor microenvironments, achieving an 81.2% drug release at pH 5.0. Additionally, these micelles facilitate targeted drug delivery and controlled release through efficient cellular uptake (over 97%)^[99]. Hemolysis tests showed a hemolysis ratio of less than 5%, confirming excellent blood compatibility and minimal blood damage when used *in vivo*, thereby reducing side effect risks.

In vivo experiments showed that MCF-7 cells implanted in Balb/c mice exhibited stronger fluorescence signals from fluorescein isothiocyanate (FITC)-labeled HP micelles compared to the control group^[99]. For antitumor activity, MCF-7 tumor-bearing Balb/c nude mice were divided into three groups and injected with normal saline, free PPT, or HP micelles (equivalent to a PPT dose of 15 mg/kg). Over 30 days of treatment, the saline group experienced significant tumor volume increase, while the free PPT group had a slight increase. In contrast, the HP micelles group showed no significant growth increase and achieved an 85% inhibition rate^[99]. TdT-mediated dUTP-biotin nick end labeling (TUNEL) experiments revealed the highest tumor cell apoptosis rate in the HP micelles group, indicating superior therapeutic efficacy against tumor growth. Further investigation is needed on the combination of HP microcapsules with other antitumor drugs to enhance therapeutic effects and reduce drug resistance. Meanwhile, to facilitate clinical

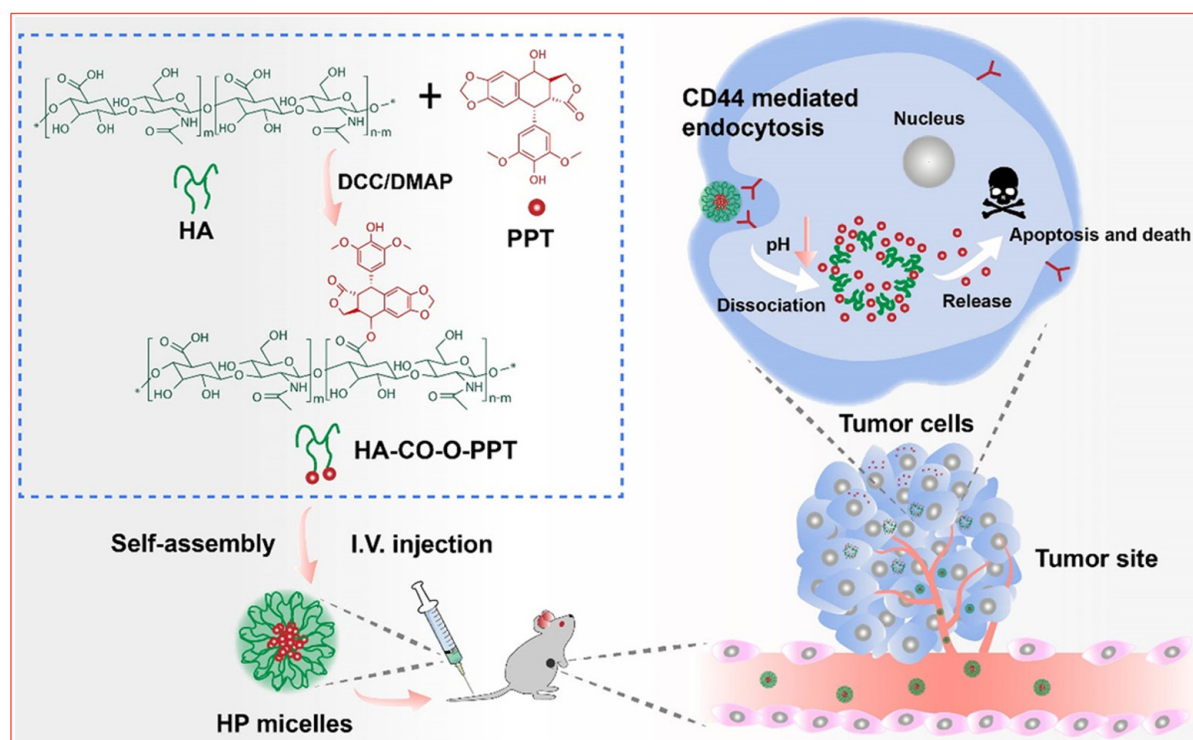


Figure 13. Illustration of the fabrication of pH-responsive HP micelles for the controlled and targeted delivery of PPT, enhancing cancer therapy. Reproduced from Ref. [99] with permission from © 2022 Elsevier B.V.

application, the following studies must be conducted: further investigation into the degradation mechanisms of targeted nano-delivery carriers in a simulated tumor microenvironment; and clarification of drug release sites, associated degradation processes, and the therapeutic effects of resulting degradation products.

Hyaluronan micelles targeting FR + CD44 overexpressing tumors

Small molecular substances such as folic acid (FA), anisamide, biotin, and phenylboric acid are favored as ligands for drug targeting vectors due to their stability, low cost, low toxicity, and ease of modification^[277-280]. FA is the most widely used targeting ligand; it is a vitamin with a natural affinity for folate receptor (FR) protein and can be converted to tetrahydrofolic acid in the body to participate in normal metabolism^[281]. FRs are highly expressed in tumor tissues, with levels in malignant cells being 20 to 200 times higher than in normal cells^[282]. The expression of FRs correlates with the severity of malignancy and metastatic potential - metastatic tumors express more FRs than localized tumors^[283]. Thus, FA is extensively utilized as an active targeting ligand for NPs in anticancer therapy. Zhang *et al.* have developed an innovative double-targeted nanodrug delivery system aimed at tumor cells that overexpress FRs and cluster determinant 44 (CD44) [Figure 14]^[100]. By conjugating PPT with FA to modify HA, they synthesized a prodrug, FA-HA-SS-PPT, which exhibits dual targeting capabilities. The hydration diameter of FA-HA-SS-PPT NPs is 69.66 nm, with a Zeta potential of -18.7 mV, exhibiting a small and uniformly distributed spherical structure. In contrast, FA-HA-CC-PPT NPs have a hydrodynamic diameter of 87.86 nm, a PDI of 0.192, and a zeta potential of -16.49 mV^[100]. Additionally, microwave radiation (MWR) techniques were used to improve the drug's binding efficiency to its carrier, ensuring stability and bioavailability *in vivo*. FA specifically directs towards FR, whereas HA interacts with CD44 molecules, both receptor types being abundantly expressed in particular malignant cell populations. This combined targeting mechanism significantly improves NP

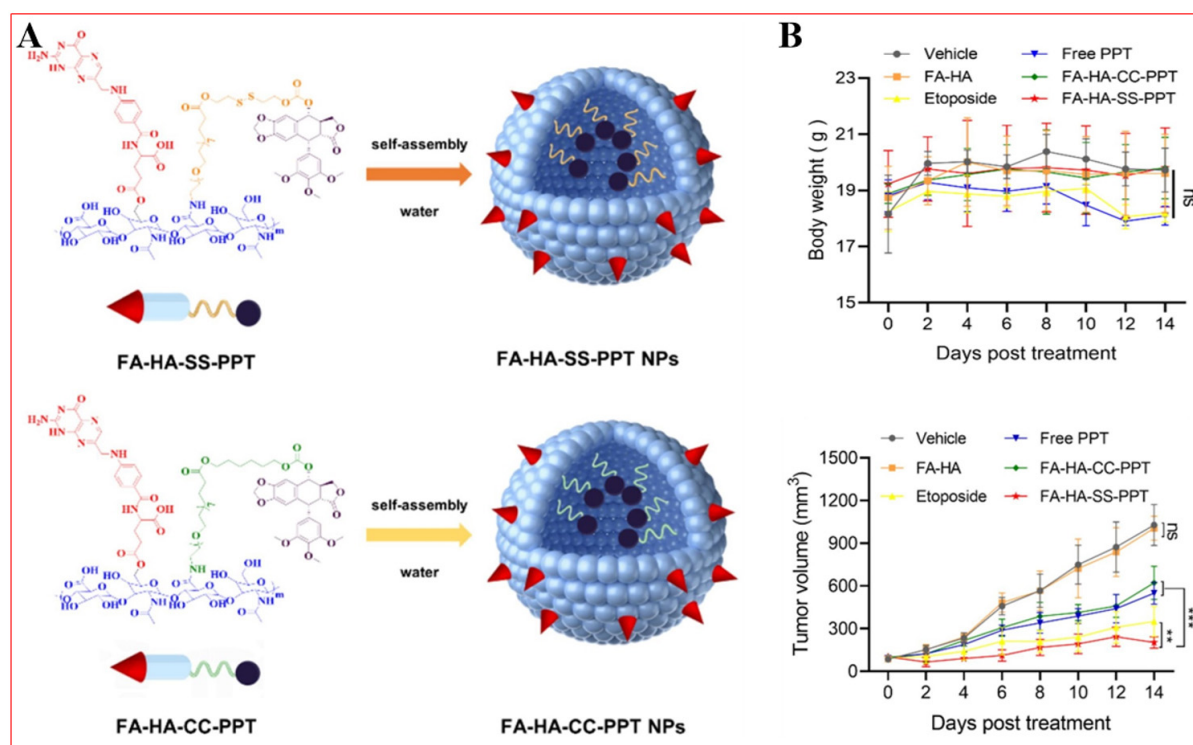


Figure 14. Preparation and biocompatibility of FA-HA-SS-PPT and FA-HA-CC-PPT NPs. (A) Preparation of FA-HA-SS-PPT and FA-HA-CC-PPT NPs; (B) Body weight and tumor volume after treatment with vehicle, free PPT, etoposide, FA-HA, FA-HA-CC-PPT, FA-HA-SS-PPT, ** $P < 0.01$, *** $P < 0.001$. Reproduced from Ref.^[100] with permission from © 2025 Elsevier B.V.

internalization efficiency within cancerous cells, consequently amplifying the concentration of therapeutic agents in neoplastic tissue regions through enhanced cellular absorption pathways.

In murine models, FA-HA-SS-PPT NPs achieved a TGI rate of 73.1%, surpassing both free PPT (43.5%) and FA-HA-CC-PPT NPs (41.5%)^[100]. Biodistribution studies further indicated 2.3-fold greater tumor accumulation of FA-HA-SS-PPT compared to Rh-PPT, confirming enhanced tumor-targeting characteristics. This improved targeting mechanism and therapeutic outcome primarily stems from the NPs' dual-targeting molecular architecture.

The fabrication of FA-HA-SS-PPT presents intricate challenges due to its multi-stage synthesis process, which poses obstacles for industrial-scale manufacturing. Streamlining the production pathway by minimizing procedural stages and improving operational efficiency may significantly advance its scalability. While existing investigations have predominantly utilized *in vitro* analyses and murine models, expanding preclinical evaluations to diverse cancer subtypes remains crucial for validating FA-HA-SS-PPT's therapeutic potential and biosafety profile. Although dual-targeting approaches have been implemented, variations in tumor biology might influence treatment outcomes, highlighting the necessity for comprehensive exploration of the compound's versatility across heterogeneous malignancies.

While considerable progress has been made in developing targeted polymeric micelles, their translation from experimental research to clinical implementation remains fraught with difficulties. Multiple barriers persist, including manufacturing scalability, unresolved safety profiles, insufficient pharmacokinetic characterization, and ambiguous biodistribution patterns post-administration. The intricate biological

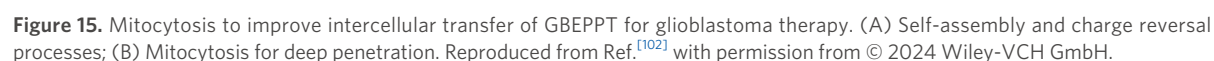
milieu further complicates clinical adaptation, as nanocarrier-biological component interactions frequently demonstrate unanticipated behaviors that may modulate immune activation pathways and metabolic processing. Future investigations should focus on three key areas: first, analyzing structural parameters including nanocarrier dimensions and surface functionalization in relation to biomolecular corona formation; second, deciphering immune-modulatory mechanisms of polymeric assemblies; third, improving the reliability of *in vitro* screening platforms for assessing batch-to-batch reproducibility and therapeutic performance predictability. In addition, although FA-HA-SS-PPT NPs have good biocompatibility, it is still necessary to ensure their long-term safety and non-toxicity in clinical applications, especially during metabolism and excretion in the body. Conduct larger animal experiments to evaluate the efficacy and safety of FA-HA-SS-PPT NPs to provide data support for clinical trials.

OTHER PPT-BASED NANOPLATFORMS

Polymer-drug conjugates

Polymer-drug conjugates, commonly termed polymer prodrugs, spontaneously form nanostructured particles when exposed to aqueous environments, facilitating tumor accumulation through EPR mechanisms^[284,285]. The covalent linkages bridging therapeutic agents with polymeric carriers are frequently designed to be sensitive to pathological conditions within tumor microenvironments. Such hybrid systems demonstrate enhanced stability and controlled release profiles in biological systems while preserving therapeutic efficacy^[286,287]. These systems serve as effective strategies to address challenges linked to PPT, particularly regarding biodistribution and site-specific activation^[288]. Glioblastoma (GBM) is a highly aggressive brain tumor that falls under the category of gliomas and primarily originates from astrocytes^[289-291]. The key characteristics of GBM include rapid proliferation, aggressiveness, high recurrence rates, and resistance to treatment^[292,293]. From a pathological perspective, GBM is typically associated with various genetic mutations and epigenetic alterations, such as abnormalities in the tumor protein P53 (TP53), epidermal growth factor receptor (EGFR), and phosphatase and tensin homolog deleted on chromosome ten (PTEN) genes, which facilitate the proliferation and survival of tumor cells^[294-296]. Treatment challenges for GBM are significant. One major obstacle is blood-brain barrier (BBB) penetration: effective therapies must be able to cross the BBB to reach the tumor site; however, this process poses considerable difficulties. Additionally, tumor heterogeneity complicates treatment efforts since the diversity among GBM cells often renders single-agent therapies ineffective. Although small molecules, peptides or proteins have been identified that can target DDS to enhance their accumulation within GBMs, achieving deep tissue penetration remains problematic.

Xiang *et al.* proposed that enhancing drug penetration and therapeutic efficacy for GBM can be achieved through the design of nanodrug carriers that are responsive to the unique microenvironment of tumors^[102]. This innovative approach in nanomedicine has the potential to demonstrate a remarkable capacity to effectively penetrate both the BBB and deeper layers within GBM tissues, thereby improving therapeutic outcomes while minimizing systemic toxicity. Consequently, Xiang *et al.* developed a novel polymer-drug conjugate known as GBEPPT (*p*GBEMA₂₂-*b*-pSSPPT₉), which responds specifically to overexpressed γ -glutamyl transpeptidase (GGT) [Figure 15]^[102]. The conjugate consists of PPT and a monomer (GBEMA) containing a GSH analogue for GGT cleavage. GBEPPT has a hydrodynamic size of 52.76 nm and a PDI of 0.116, allowing it to efficiently cross the BBB^[102]. The ideal size range for typical nanocarriers to penetrate the BBB is 20-70 nm, so GBEPPT meets this criterion, aiding its application in GBM therapy. In the mouse GBM model, mitocytosis facilitated the active delivery of GBEPPT within the GBM microenvironment, thereby achieving both BBB penetration and extensive infiltration into GBM tissues. The nanodrug showed strong tumor cell inhibition at low doses and showed significant anti-GBM effect *in vivo*, while alleviating systemic toxicity of PPT^[102]. These findings suggest that mitocytosis plays a key role in enhancing drug penetration into BBB and GBM tissues, providing a new pathway for active drug transport to brain tumors.



GBEPPT has demonstrated notable benefits in minimizing systemic toxicity during treatment. Through encapsulating the cytotoxic compound PPT within NP carriers, this formulation effectively alleviates the

toxicological effects commonly linked to PPT administration while maintaining therapeutic efficacy. While administration of PPT alone may lead to severe side effects, including liver damage, the use of GBEPPT has not resulted in any notable abnormalities in major organs. GBEPPT can effectively cross the BBB and remain at the tumor site for a longer time, thus achieving a higher concentration of the drug within the tumor tissue and reducing the impact on normal tissue.

The above advantages have important implications for the future treatment of GBM: The success of GBEPPT shows that the use of nanocarriers can effectively improve the targeting and penetration of drugs, thereby improving the therapeutic effect and reducing side effects, which provides a reference for the development of other types of nano-medical DDS; As an alternative or complementary treatment, GBEPPT may provide new treatment options for patients who do not respond well to existing chemotherapy regimens; By combining different therapeutic mechanisms, GBEPPT may provide new ideas for the design of personalized treatment options, especially in the face of drug-resistant tumors. Together, GBEPPT's findings provide a new direction for the treatment of GBM, highlighting the potential of nanotechnology to improve drug efficacy and reduce toxicity.

Peptide-based nanoparticles

Peptides are bioactive compounds recognized for their exceptional biocompatibility, low toxicity, and non-immunogenic properties^[297,298]. Polypeptide-mediated active targeted DDSs use small peptides of 2 to 50 amino acids to enhance drug delivery^[299,300]. They possess the ability to selectively target specific receptors and are frequently employed as active targeting ligands in cancer chemotherapy DDSs. Certain peptide receptors exhibit significantly higher expression levels on tumor cells compared to normal cells. Consequently, some short peptides can function as guiding agents to enhance the active targeting of cancer cells by delivery vectors. E-selectin plays a crucial role in the tumor microenvironment by facilitating the adhesion of circulating tumor cells to vascular endothelium, particularly in inflamed areas with elevated E-selectin levels^[301,302]. This selective expression positions E-selectin as a promising target for DDSs aimed at increasing therapeutic agent accumulation at tumor sites^[303,304]. Xiang *et al.* investigated a novel drug carrier, PEG-selectin peptide conjugate (PEG-Pep-PPT), designed to target cancer sites for enhanced tumor suppression and reduced side effects [Figure 16]^[103]. The PEG-Pep-PPT complex is formed by modifying PPT's structure, particularly by linking amino acids at the four positions of the C ring. This complex can be specifically cleaved by GSH in the tumor microenvironment to release PPT, which then attacks cancer cells. The short peptide (CIELLQAR) serves as an E-selectin ligand in the PEG-Pep-PPT conjugate, playing a crucial role in targeting tumor sites. Compared to traditional PPT and VP-16, PEG-Pep-PPT NPs demonstrated superior systemic toxicity reduction, highlighting their potential as an antitumor agent.

The PEG-Pep-PPT NPs had a size of 108.70 nm, a zeta potential of -6.41 mV, and a PDI of 0.295^[103]. *In vitro*, the MCF-7 cell line showed significant TGI with the PEG-Pep-PPT. At a dose of 10 mg/kg, it achieved a tumor volume inhibition (TMI) rate of 76.97 %, surpassing both free PPT (67.22%) and VP-16 (64.79%). Specifically, the conjugate effectively inhibited tumor cell lines while exhibiting significantly lower cytotoxicity towards normal endothelial cells (HUVEC, 90.76% viability for PEG-Pep-PPT vs. 21.02% for PPT at 1 μ M)^[103]. *In vivo*, PEG-Pep-PPT significantly differed from PPT regarding mouse body weight changes. Mice treated with PPT at doses of 5 and 10 mg/kg lost substantial weight, decreasing by 14.67% and 8.96%, respectively. In contrast, mice receiving both dosages of PEG-Pep-PPT did not experience any weight loss^[103]. This discrepancy highlights the safety profiles of the drugs; significant weight loss in PPT-treated groups indicates severe toxicity and side effects such as gastrointestinal reactions and bone marrow suppression - known limitations of PPT as an antitumor agent. Conversely, the lack of weight loss in PEG-Pep-PPT-treated mice suggests that this conjugate markedly reduces systemic toxicity compared to PPT, indicating it is safer for therapeutic use in antitumor treatments while potentially allowing for more effective dosing with fewer adverse effects.

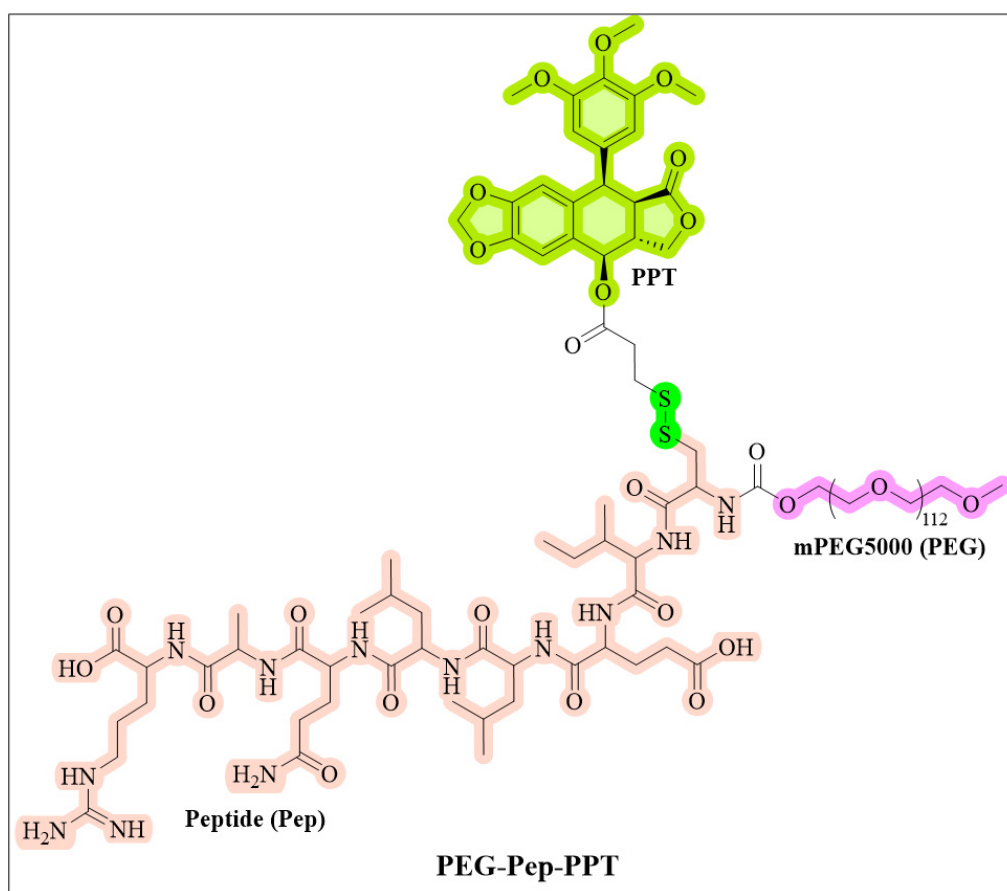


Figure 16. Chemical structure of E-selectin targeted PEG-Pep-PPT.

The enhanced pharmacokinetic profile of PEG-Pep-PPT - characterized by prolonged circulation and higher blood concentration - likely contributes to its improved effectiveness in treating tumors compared to traditional PPT, which suffers from rapid clearance and associated side effects. Specifically, while the distribution half-life of PEG-Pep-PPT is shorter (0.122 vs. 11.444 h), its elimination half-life is much longer (49.977 vs. 11.446 h)^[103]. Additionally, higher area under the curve (AUC) values indicate greater blood concentration, which may improve targeting and accumulation at the tumor site due to its E-selectin peptide ligand (CIELLQAR) designed for tumor vascular endothelial cells^[103]. In summary, due to its amphiphilic structure, PEG-Pep-ODO can form relatively uniform NPs in an aqueous environment. At the *in vitro* cellular level, it shows cytotoxic effects similar to those of PPT against multiple tumor cell lines; however, its toxicity to normal endothelial cells is significantly lower than that of PPT, demonstrating a certain "toxicity reduction" effect. Meanwhile, PEG-Pep-ODO exhibits significant E-selectin targeting at the cellular level and can effectively inhibit E-selectin-mediated cell adhesion. Its superior antitumor and targeting effects were further verified in tumor-bearing mice at the *in vivo* level, with a tumor inhibition rate of as high as 76.97%. The *in vivo* safety, pharmacokinetic properties, and tumor vascular targeting of PEG-Pep-ODO are significantly better than those of PPT monomer, confirming its potential as a targeted antitumor drug against E-selectin. While the PPT-loaded PEGylated E-selectin peptide conjugate demonstrates significant potential in targeting tumors and minimizing side effects, challenges must be addressed in future research. For example, the synthesis of this conjugate entails multiple steps, including

the formation of disulfide bonds and the coupling of various components. This complexity may present obstacles to scaling up production for clinical applications. Meanwhile, further investigation is needed to clarify the toxicity mechanisms of PEG-Pep-PODO in animal models for a comprehensive safety profile. Existing studies suggest that PEG-Pep-PODO's damaging effects are linked to apoptosis and cell cycle changes; however, specific cell signaling pathways mediating cytotoxicity have not been thoroughly examined. Additionally, it remains to be confirmed through further experiments whether the E-selectin peptide ligand formed upon binding with E-selectin can initiate a new mechanism of action following cysteine addition.

Host-guest drug delivery systems for combined chemotherapy, CDT, and PTT

Recently, the design of multifunctional NPs to improve PPT targeting and regulate its release through various stimulus-response mechanisms has garnered increasing interest from pharmaceutical researchers. Typically, a host-guest DDS is a host-guest complex comprising an artificial receptor and therapeutic agent that dissociates at the lesion site and releases the loaded therapeutic agent^[305,306]. Several artificial macrocyclic receptors, including cyclodextrins, calixarenes, cucurbiturils, and pillararenes, have been used as drug carriers to construct host-guest DDS to deliver small molecule drugs as well as large biomolecules such as proteins^[307-310]. These macrocyclic receptors have precise MWs, well-defined molecular structures, exact drug loading patterns, and quantifiable binding constants, providing theoretical feasibility to construct DDSs with good batch-to-batch reproducibility. Host-guest DDSs offer a range of notable benefits^[311,312]. The preparation of macrocyclic structures is relatively uncomplicated, while their remarkable chemical resilience ensures minimal breakdown under physiological conditions. These carriers exhibit accurate molecular masses and clearly delineated architectures, substantially reducing inconsistencies between manufacturing batches. Furthermore, the modular design principle of host-guest components permits flexible integration with diverse pharmaceutical compounds. This modularity is particularly advantageous in the context of personalized medicine, as it enables the adaptation of drugs to meet the specific needs of individual patients while maintaining consistent host molecules. However, for practical application of host-guest DDSs, a macrocyclic carrier should meet the following demands: (1) high binding affinity for a therapeutic agent with selectivity to biologically coexisting interferents to prevent off-target leakage; (2) broad-spectrum encapsulation capability to make it appealing in personalized medicine, where the same carrier could be used for delivering different drugs alone or in combination; and (3) stimuli-responsiveness to fulfill controlled release targeting the assigned lesion.

PTT is a promising tumor treatment method that utilizes photothermal conversion materials to generate heat when exposed to an external near-infrared (NIR) laser (650-900 nm)^[313,314]. This heat raises the temperature of tumor tissue, and if it exceeds 42 °C for a sufficient duration, it can cause significant damage or ablation of tumor cells. In addition to being non-invasive and highly controllable, research shows that the heat from photothermal materials can also inhibit tumor metastasis^[315]. These advantages have led to considerable interest in PTT among researchers. Good photothermal materials must meet several key criteria: (i) high photothermal conversion efficiency and stability; (ii) excellent biocompatibility and long-term biosafety; (iii) ease of surface modification. These features reduce laser power density, enhance treatment effectiveness, provide versatility, improve *in vivo* safety, and ensure safe tumor therapy. However, limited water solubility and non-specific targeting hinder further clinical use. Consequently, researchers have developed nanocarrier-based photothermal materials.

Li *et al.* developed and synthesized a novel supramolecular host, acyclic cucurbit [n]uril (ACB-L), to target carbonic anhydrase IX (CAIX) receptors on cancer cells [Figure 17]^[105]. ACB-L self-assembled with ferrocenyl disulfide-linked PPT into multifunctional supramolecular NPs through a host-guest mechanism. These NPs target cancer cells precisely *via* sulfanilamide groups, allowing for targeted tumor therapy. CAIX

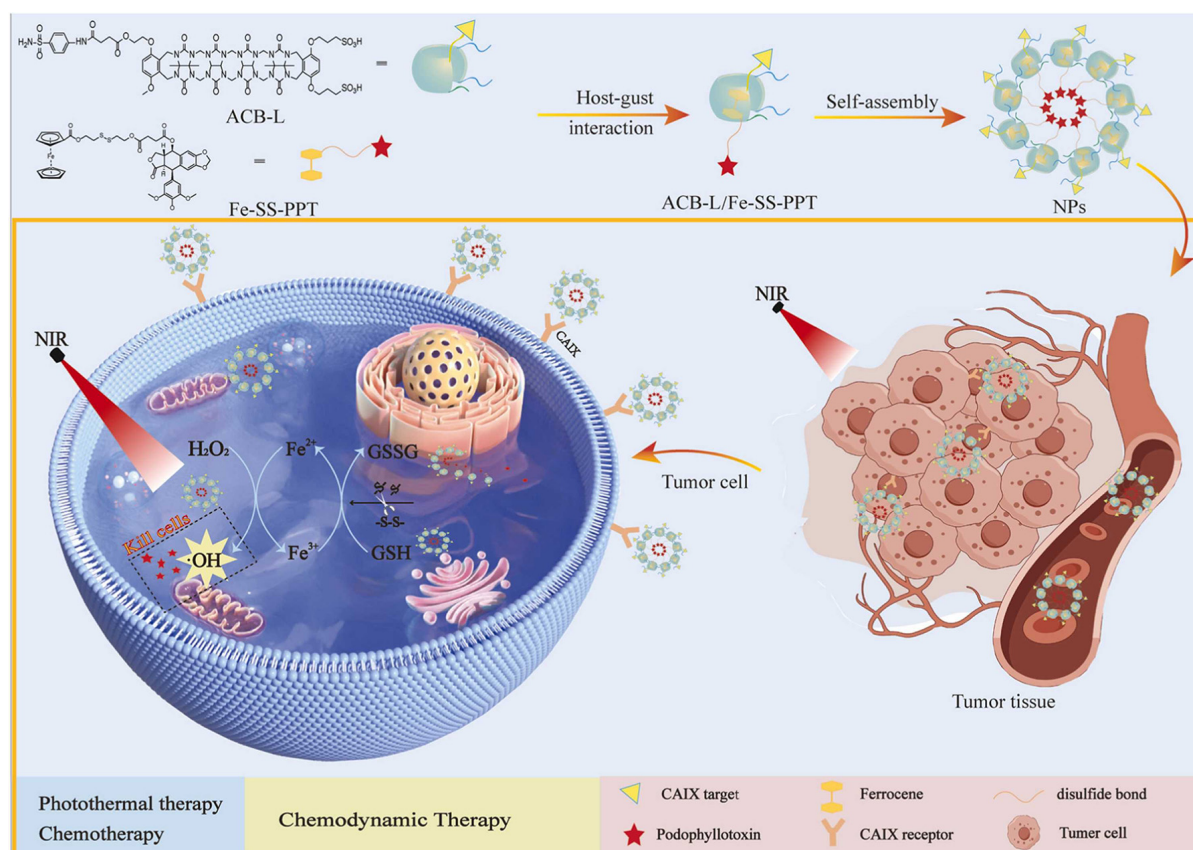


Figure 17. The diagram illustrates the preparation of supramolecular ACB-L/Fe-SS-PPT NPs and their roles in chemotherapy, CDT, and PTT. Reproduced from Ref. [105] with permission from © 2025 Elsevier B.V.

is highly expressed in various cancer cells, particularly in anoxic microenvironments. ACB-L, a novel supramolecular host, effectively binds to CAIX receptors on cancer cell surfaces. Its benzene sulfonamide group enters the pocket cavity of CAIX and binds with Zn²⁺, enhancing its affinity for CAIX. This binding allows ACB-L to target tumor cells precisely. When combined with CAIX, ACB-L induces the Fenton reaction through Fe²⁺ in its structure. By targeting CAIX, ACB-L not only promotes ROS generation but also facilitates chemotherapy by releasing the attached drug PPT^[105]. Additionally, NIR irradiation enhances oxidative stress and temperature within tumors while accelerating the Fenton reaction, achieving a triple therapeutic effect of chemotherapy, CDT, and PTT.

In vitro cytotoxicity assays demonstrated that the IC₅₀ values of the NPs under NIR irradiation against HepG2 and HeLa cells were 2.90 and 2.92 μM, respectively, which are lower than those of free PPT by 1.44 and 3.08 times^[105]. For A549 cells, a similar level of toxicity to PPT was observed, with IC₅₀ values recorded at 8.85 and 6.16 μM, respectively. In contrast, the NPs exhibited reduced toxicity towards normal 293 T cells, presenting an IC₅₀ value of 11.97 μM - significantly higher than that of free PPT by 2.62 times^[105]. Notably, in CDT, excess GSH in tumor cells can neutralize •OH, increasing tumor cell resistance to oxidative stress and diminishing CDT effectiveness^[105]. Due to the dynamic nature of host-guest recognition, preventing leaks in DDS is crucial. From a thermodynamic perspective, enhanced binding affinity is vital to resist dissociation from interference or dilution. Kinetically, increasing the energy barrier within these systems can effectively prolong dissociation time, minimizing leakage before reaching the target site. In addition, the absence of validation through animal experiments likely limits the effectiveness

and safety of these NPs in practical applications. Therefore, without animal studies, it may be challenging to fully understand NPs' performance and potential side effects *in vivo*.

CONCLUSION

The role of conventional chemotherapy is being reevaluated, with PPT-based nanoplateforms expected to become a new paradigm in cancer treatment due to their ability to (i) integrate multiple therapeutic molecules for synergistic antitumor effects; (ii) combine various mechanisms of action - such as chemotherapy and PDT; and (iii) enhance antitumor efficacy while minimizing drug dosage and toxicity. Furthermore, they can (iv) improve drug targeting and tissue permeability, overcome biological barriers, and regulate drug release at specific sites. However, its clinical translation faces significant challenges. First, bridging the gap between animal research and human trials remains a major obstacle. It is crucial to determine if the antitumor efficacy seen in preclinical studies can be replicated in humans. Second, while the toxicity of PPT-based drugs has been studied during nanotherapeutic development, there is an urgent need to further investigate potential toxicity and biosafety from carrier materials and excipients, along with adverse effects from drug interactions. Finally, the complexity of manufacturing and scaling up nanotherapies limits their industrial viability. To improve clinical translation efforts, it is essential that PPT nanotherapeutics are designed for reliability and simplicity rather than unnecessary complexity or extravagance. For instance, PPT-based multifunctional nanoplateforms can be efficiently produced via supramolecular self-assembly rather than through complex chemical reactions. This method can overcome the limitations of small-molecule drugs, including poor targeting and low bioavailability, while circumventing the challenges related to nanomedicine preparation and their low biocompatibility. To move PPT-based nanoplateforms forward and ensure translational impact, several prospective strategies are necessary to fully realize the potential of PPT-based nanoplateforms, particularly concerning safety concerns and clinical efficacy.

Navigating biological barriers

Achieving optimal therapeutic outcomes with minimal adverse reactions represents the paramount objective for PPT-derived nanoplateform development. Nevertheless, the intricate tumor microenvironment and cellular-level impediments pose significant challenges to nanomedicine efficacy. Anticancer agent delivery mechanisms typically involve five sequential phases: systemic circulation, tumor-targeted localization, tissue infiltration, cellular uptake, and controlled payload liberation^[316-320]. This sequence is crucial for intravenously administered nanomedicines to effectively reach the cytosol of tumor cells. Each step poses unique biological barriers; thus, conventional nanomedicines often struggle to overcome these challenges, leading to suboptimal therapeutic outcomes. Insufficient pharmacokinetic enhancement may be a key factor contributing to poor treatment outcomes, as complex biological barriers hinder the ability of drug carriers to improve pharmacokinetics and distribution. The mononuclear phagocytic system quickly eliminates foreign substances from circulation, reducing their half-life and bioavailability. One promising avenue to promote clinical transformation of PPT nanomaterials is to develop methods to increase the accumulation of nanocarriers in tumors. Among them, highly efficient adsorption-mediated endocytosis has been shown to be effective against tumor accumulation and nanomedicine penetration, independent of the action of EPR. Additionally, in tumors of various types, sizes, locations, and stages, each barrier - such as deep tissue-penetrating stimulation, the hypoxic tumor microenvironment, tumor penetration capabilities, resistance to apoptosis, immunogenicity, and drug resistance - exhibits differing levels of significance. Therefore, depending on the intended application, it is crucial to balance costs with synthesis challenges and potential practical advantages. For example, effectively delivering an adequate quantity of NPs to a palm-sized solid tumor requires a platform that possesses deep tissue penetration capabilities. In addition, when faced with the anoxic microenvironment of tumors, one strategy is to use preexisting species as a source of oxygen, while another involves precursors that generate oxygen. Additionally, hypoxia can be utilized to

treat tumors by activating specific prodrugs. Therefore, careful design strategies must be employed to ensure these vectors maintain satisfactory stability *in vivo* without compromising spatio-temporal responsive release of therapeutics. Note, for example, that at most three key obstacles to overcome should be addressed, and then a reasonable combination of modules needed to overcome these obstacles should be considered.

Leveraging "combo" drug delivery system

Targeting the dynamic nature and drug resistance of cancer, monotherapies often fail to address its versatility. Combination therapies utilizing multiple treatment modalities can enhance anticancer efficacy synergistically while reducing the dosage of each drug, thus minimizing side effects^[321-325]. Co-administering various therapeutic agents requires a delivery platform that normalizes pharmacokinetics and pharmacodynamics, prolongs circulation time, selectively accumulates at target sites, binds specifically to intended targets, and achieves controlled release. To achieve this goal, treatments should work synergistically across distinct yet interrelated carcinogenic signaling pathways. The nanoplatform enhances drug functionalities with specific cell targeting, imaging signal generation, and responsiveness to external triggers. "Combo" DDS enables innovative multi-dimensional therapies that integrate chemotherapy, gene therapy, PTT, PDT, and immunotherapy. This strategy shows promise in overcoming various forms of drug resistance. However, potential side effects linked to nanomaterials - such as oxidative stress, adverse inflammatory responses, and genotoxicity - must be carefully considered when designing multimodal treatment protocols. Meanwhile, the self-assembled nanostructures themselves could introduce new or different risks related to toxicity and immunogenicity. Specifically, it is crucial to further explore how these therapies synergize at the molecular level, particularly with respect to mechanisms such as free radical generation, tumor targeting, and immune modulation. Additionally, the design of combination drug delivery platforms must avoid introducing complexities in production or quality control procedures. Essential considerations such as chemical synthesis proficiency and industrial-scale manufacturing requirements - including batch consistency, scalability, material stability, economic viability, and self-assembly properties - require thorough attention during the development phase to ensure successful clinical translation.

Artificial intelligence enhances the clinical transition

The progression of nanomedicine represents an intricate and resource-intensive endeavor requiring coordinated efforts across scientific disciplines. Strategic interdisciplinary partnerships combined with systematic design methodologies are poised to expedite the clinical implementation of PPT-based therapies in forthcoming research cycles. Recent advancements in AI systems, especially sophisticated language processing architectures and creative artificial intelligence frameworks, present transformative opportunities for this domain^[326-330]. Machine learning algorithms are reshaping therapeutic innovation through sophisticated analysis of multi-dimensional health data, precise biomarker discovery, and anomaly detection capabilities. Specifically, AI-powered algorithms dramatically improve image analysis capabilities by enhancing resolution parameters and recognizing subtle diagnostic patterns. Such technological progress enables precise patient categorization through radiographic evidence, elucidates pharmacokinetic profiles of nanoscale therapeutics, guides personalized intervention planning - including optimal administration schedules and targeted delivery mechanisms - while supporting comprehensive treatment evaluation. Nevertheless, substantial obstacles must be overcome to fully actualize these computational advantages. Primary challenges include developing novel solutions for limited data availability in PPT research. Establishing collaborative data ecosystems, implementing uniform experimental guidelines, and creating adaptive machine learning architectures will prove critical for refining therapeutic efficacy metrics and ensuring pharmaceutical safety standards. Additionally, integrating multimodal analytical techniques can unlock synergistic insights from heterogeneous biological datasets to propel nanomedical innovations. Contemporary methodologies frequently emphasize isolated data streams while overlooking complex

systemic interactions within physiological networks. Consequently, designing next-generation AI platforms capable of constructing sophisticated digital twin simulations will deepen comprehension of oncological pathways, nanotherapeutic behaviors, and interpatient variability. For instance, machine learning models can be trained on multi-omics data (genomics, proteomics, metabolomics) from patient-derived xenografts to predict which tumor subtype responds best to a specific hypoxia-activated PPT prodrug.

Standardized protocols move the field forward

By establishing a standardized evaluation system framework and a long-term monitoring mechanism, the clinical transformation of PPT-based nanoplateforms can be facilitated, moving the field forward. Firstly, a standardized protocol should be established, including synthesis standards (clearly defining the synthesis methods of nanomaterials and the quality standards of raw materials used); characterization techniques (adopting unified characterization techniques to assess the physicochemical properties of nanomaterials); stability studies (ensuring that the drug does not degrade or become inactive under specified storage conditions, maintaining stability in terms of appearance, solubility, particle size and dispersion, and maintaining an effective concentration in the body); evaluation procedures (formulating a systematic safety and efficacy evaluation process to ensure the repeatability and reliability of clinical trials). Secondly, a complete regulatory framework should be established: carrier design (in the design of nanomedicine carriers, the impact on drug release rate, targeting ability and biodegradability should be considered); safety assessment (detailed assessment standards should be formulated, covering the synthesis process, physicochemical properties, biocompatibility and potential toxicity of nanomaterials); target specificity (assessing the selectivity of nanomedicines for specific target cells or tissues to reduce damage to normal cells). Finally, a long-term monitoring and evaluation framework should be improved: side effect monitoring (tracking the side effects of patients after using nanomedicines and their changes, and adjusting the treatment plan in a timely manner); long-term impact assessment (conducting long-term follow-up studies to evaluate the potential impact of PPT nanomedicines on health, such as immune response, organ function and tumor recurrence rate, *etc.*).

In summary, while translational hurdles continue to exist for PPT-based nanoplateforms in clinical applications, strategic emphasis must be placed on strengthening connections between preclinical research and human trials. Critical priorities involve comprehensive evaluation of carrier material toxicities, optimization of production protocols, and focused development of reliable, user-friendly systems with demonstrated therapeutic benefits. These innovations possess transformative potential for the field, ultimately enabling the successful transition of PPT-based nanoplateforms into clinical practice.

DECLARATIONS

Authors' contributions

Writing-original draft, writing-review & editing, funding acquisition, supervision, conceptualization: Wang, Z.

Writing-review & editing: Song, X.

Collecting the literature, Data curation: Sun, M.

Data curation: Zhang, R.

Conceptualization, Investigation, Writing-review & editing, Funding acquisition: Yang, L.

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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