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*Review*

# Drug Delivery Systems for Enhancing Cancer Chemotherapy

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**How To Cite:** Yi, S.; Ren, X.; Liu, J.; et al. Drug Delivery Systems for Enhancing Cancer Chemotherapy. *Medical Materials Research* **2025**, *1*(1), 4.

Received: 24 February 2025
Revised: 12 March 2025
Accepted: 24 March 2025
Published: 2 April 2025

**Abstract:** Cancer chemotherapy remains one of the most effective treatment strategies, but its clinical success is often limited by challenges such as poor drug bioavailability, non-specific toxicity, and drug resistance. Drug delivery systems (DDSs) have emerged as a promising solution to overcome these barriers, offering enhanced efficacy and reduced side effects. For instance, liposomal doxorubicin (Doxil®) has significantly improved treatment outcomes in triple-negative breast cancer (TNBC) by reducing cardiotoxicity, while albumin-bound paclitaxel (Abraxane®) enhances drug solubility and tumor targeting in glioblastoma. This review focuses on the classification of DDSs, drug loading methods, and surface functionalization strategies, which enable targeted drug delivery, controlled release, and improved cellular uptake. Additionally, we explore the integration of stimuli-responsive systems that can release chemotherapeutic agents in situ in response to endogenous or exogenous stimuli. The potential of multifunctional DDSs to combine chemotherapy with radiotherapy, phototherapy, ultrasound therapy, immunotherapy, and imaging is also discussed. Despite promising results, the clinical translation of these systems faces challenges, including manufacturing scalability, regulatory approval, and safety concerns. Future directions for the development of more efficient and personalized DDSs for cancer treatment are also proposed.

**Keywords:** nanoparticles; drug delivery systems; cancer therapy; targeted therapy; nanotechnology

## 1. Introduction

Cancer, as a malignant disease, continues to be one of the leading causes of morbidity and mortality worldwide, with 20 million new cases and alongside 9.7 million deaths reported this year [1]. The global burden of cancer is projected to increase in the coming decades due to factors such as aging populations, lifestyle changes, and environmental influences [2,3]. This rising incidence underscores the urgent need for effective and sustainable treatment strategies to manage and reduce the impact of this malignant diseases [2]. Despite chemotherapy has been a crucial approach in cancer treatment for decades [4,5], traditional chemotherapy faces significant limitations that compromise its overall effectiveness. One of the primary challenges is the lack of selectivity, where chemotherapeutic agents not only target cancer cells but also harm healthy, rapidly dividing cells, leading to severe side effects such as immunosuppression, gastrointestinal disturbances, and alopecia [4,6]. This non-selective action often necessitates dose reductions or treatment delays, which can negatively impact the therapeutic efficacy. Additionally, the formation of multidrug resistance (MDR) in cancer cells is a major obstacle in chemotherapy [7]. MDR arises through various mechanisms, including the overexpression of drug efflux pumps, alterations in drug targets, and changes in cellular metabolism, which collectively reduce the intracellular concentration of

chemotherapeutic agents and render them less effective [8,9]. This resistance mechanism leads to treatment failures and disease recurrence, posing a significant challenge in achieving long-term remission and improving survival rates. The tumor microenvironment (TME) further complicates the efficacy of chemotherapy. The heterogeneous nature of tumors, characterized by variations in cell types, genetic mutations, and local environmental conditions, creates a dynamic and often hostile environment that can promote cancer progression and resistance to treatment [10]. The complex interplay between cancer cells and their surrounding stroma, immune cells, and extracellular matrix components can shield tumors from the effects of chemotherapy, contributing to treatment resistance and disease persistence [9,11].

In response to these challenges, nanotechnology has emerged as a transformative approach in the field of oncology, particularly through the development of nanomaterial-based drug delivery systems (DDSs). These systems are designed to enhance the delivery and efficacy of chemotherapeutic agents by leveraging the unique properties of nanoparticles (NPs), such as their small size, large surface area, and the ability to be engineered for specific targets [12,13]. NPs can be functionalized with targeting ligands (e.g., antibodies, aptamers) that bind overexpressed receptors on cancer cells, such as human epidermal growth factor receptor 2 (HER2) in breast cancer or nucleolin in glioblastoma, thereby increasing drug accumulation in tumor tissues while minimizing exposure to healthy cells. This targeted approach not only improves the therapeutic index of chemotherapeutic agents but also reduces the incidence and severity of side effects, thereby enhancing patient quality of life [13]. Moreover, MDR in cancer poses a significant challenge to chemotherapy, and DDSs offer innovative strategies to overcome this issue [14]. One major mechanism of MDR is the overexpression of drug efflux pumps like P-glycoprotein (P-gp), which expel chemotherapy agents from cancer cells [15]. DDSs can address this by co-delivering P-gp inhibitors with drugs or using NPs that inhibit P-gp function. For example, lipid NPs delivering paclitaxel alongside the P-gp inhibitor Tariquidar can increase drug accumulation in tumor cells, enhancing therapeutic effectiveness [16]. Polymeric NPs, like those made from poly(lactic-co-glycolic acid) (PLGA), can also be surface-functionalized with Vitamin E-TPGS, which inhibits P-gp activity, helping to reverse resistance in colon cancer [17].

Additionally, the TME, characterized by acidity and hypoxia, creates conditions that promote resistance. DDSs can exploit these conditions by releasing drugs in response to the TME. For instance, pH-responsive DDSs, such as those using polyhistidine, release doxorubicin in the acidic TME, improving drug delivery to cancer cells [18,19]. NPs like manganese dioxide ($MnO_2$) can also release oxygen to alleviate tumor hypoxia, enhancing drug efficacy and overcoming resistance [20]. Another challenge is cancer stem cells (CSCs), which are resistant to conventional therapies and drive tumor recurrence [21]. DDSs can target CSCs by using ligands like anti-CD44 antibodies, which promote drug delivery specifically to CSCs and enhance their apoptosis [22]. Co-delivery of Wnt pathway inhibitors, such as LGK974, alongside chemotherapeutics can block CSC self-renewal, further reducing resistance [23]. Also, the capability to modulate drug release in response to specific stimulus, such as pH fluctuations or enzymatic activity within the TME, as well as external triggers like ultrasound (US) or laser irradiation, further enhances the precision of tumor targeting, minimizes the adverse effects of chemotherapeutic agents, and opens new avenues for synergistic combination therapies. This advancement significantly expands the therapeutic potential and applicability of DDSs (Figure 1) [24–26].

Due to the aforementioned advantages, combined with the inherent properties of nano-carriers, such as photothermal conversion ability, imaging performance, and piezoelectric effects, DDSs have demonstrated great potential in overcoming the limitations of conventional cancer chemotherapy, enhancing antitumor efficacy, and enabling precision diagnosis and therapy. Herein, this review aims to comprehensively retrospect recent advancements in DDSs design and antitumor applications, and provide a thorough understanding of how DDSs are poised to revolutionize cancer therapy (Figure 1). Unlike prior reviews focusing on conventional organic or inorganic carriers, this work critically examines emerging hybrid systems (e.g., metal-organic frameworks (MOFs), cell membrane-coated NPs). We further emphasize recent breakthroughs in clinical translation, such as macrophage-mediated drug delivery and stimuli-responsive systems validated in Phase II trials.

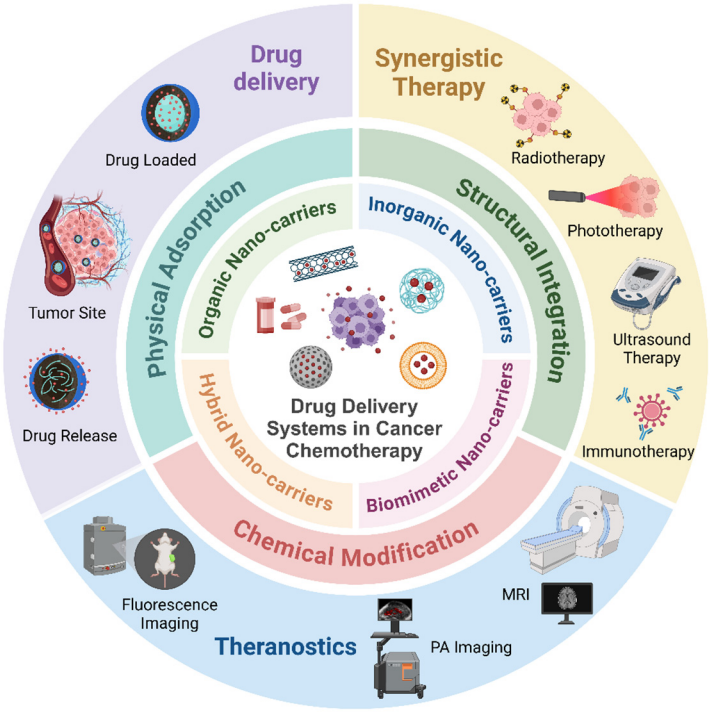


**Figure 1.** Schematic diagram of DDSs classification, construction methods, and potential tumor therapeutic applications drawn by Biorender.

## 2. Classification of NPs-Based DDSs

As mentioned above, NPs-based DDSs have emerged as a promising platform for enhancing the precision, efficacy, and stability of therapeutic agents [24,27,28]. These systems are broadly categorized into four groups based on material composition and functional capabilities: organic nano-carriers, inorganic nano-carriers, hybrid organic-inorganic carriers, and biomimetic nano-carriers (Figure 2). Each category leverages distinct advantages to address challenges such as drug solubility, stability, targeted delivery, and controlled release.

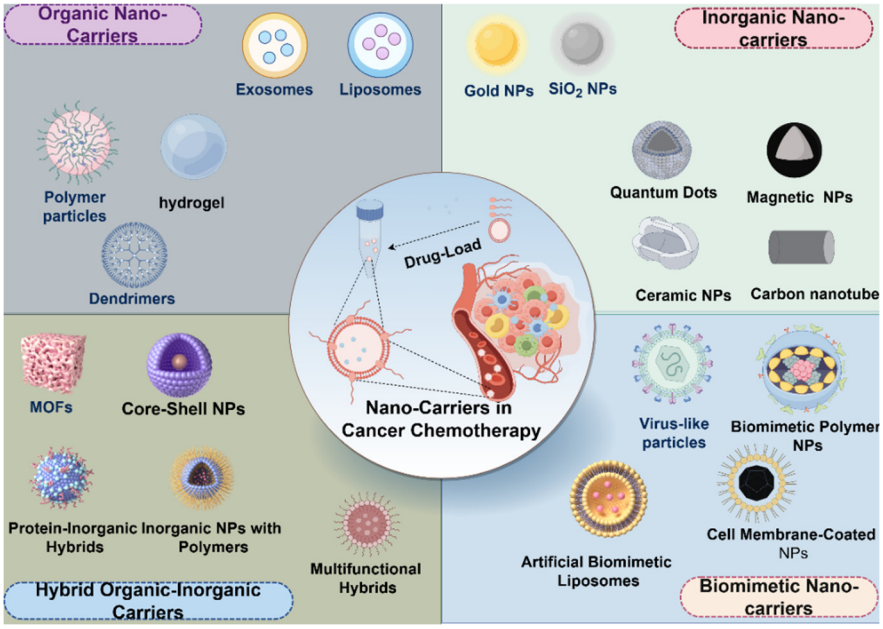


**Figure 2.** Classification of nanoparticle-based DDSs in cancer chemotherapy**.** This diagram categorizes various nano-carriers into four groups based on their material composition and functional capabilities: Organic nano-carriers, Inorganic nano-carriers, Hybrid organic-inorganic carriers, and Biomimetic nano-carriers. Organic nano-carriers include liposomes, exosomes, hydrogels, and dendrimers, which are composed of biocompatible materials like lipids and polymers, offering versatile drug encapsulation and controlled release. Inorganic nano-carriers, such as gold NPs (Au NPs), silica NPs ($SiO_2$ NPs), and quantum dots, provide unique physicochemical properties,

including magnetic and optical features for targeted delivery and imaging. Hybrid organic-inorganic carriers combine the advantages of both organic and inorganic materials, with examples like MOFs and core-shell NPs, enhancing drug loading and stability. Biomimetic nano-carriers, including virus-like particles, cell membrane-coated NPs, and artificial biomimetic liposomes, replicate natural biological systems for improved biocompatibility, immune evasion, and precise targeting. This classification highlights the potential of these systems to address challenges in drug solubility, stability, and targeted delivery. Image created with Figdraw.com.

### *2.1. Organic Nano-Carriers*

Organic nano-carriers are DDSs composed of organic materials, typically biodegradable and biocompatible. They mainly include polymeric NPs, lipid-based NPs, dendrimers, micelles, and cubosomes. Polymeric NPs such as PLGA-based systems enhance the solubility and tumor accumulation of cisplatin, with encapsulation efficiency exceeding 85% [29]. Liposomes, exemplified by polyethylene glycol (PEG) modified doxorubicin (Doxil®), reduce cardiotoxicity and are Food and Drug Administration (FDA)-approved for ovarian cancer [29]. Cubosomes, a class of bicontinuous cubic phase NPs, enable controlled release of hydrophobic drugs like docetaxel through thermoresponsive gel systems, achieving sustained release over 12 h [29,30]. Dendrimers (e.g., Polyamidoamine Dendrimers PAMAM) allow precise drug loading via terminal functional groups, while micelles (e.g., Distearoylphosphatidylethanolamine-Polyethylene Glycol 2000, DSPE-PEG~2000~) improve the delivery of mitoxantrone by combining chemotherapy and photothermal therapy [30,31]. Among them, liposomes are the most well-established organic nano-carriers, used to deliver both hydrophilic and hydrophobic drugs [28]. Their bilayer structure allows for efficient drug encapsulation, while modifications such as PEGylation enhance stability and circulation time. Liposome-based DDSs efficiently encapsulate hydrophilic and hydrophobic agents and enhance targeting through surface modifications, but their stability is limited by oxidation and enzymatic degradation. In contrast, polymer NPs offer superior stability, controlled release, and enhanced targeting via surface engineering, although their complex fabrication may hinder broader application. Exosomes, naturally secreted vesicles, mimic intercellular communication pathways and are increasingly explored for their biocompatibility and targeting capabilities [32]. Hydrogels, with their tunable porosity and biodegradability, enable controlled release mechanisms, while dendrimers, with their highly branched architecture, allow for precise drug loading and multifunctionality [33].

Organic nano-carriers are highly regarded for their excellent biocompatibility and are particularly effective in minimizing immune responses. However, challenges such as stability in the bloodstream and limited drug loading capacity remain critical barriers [34]. Research is focused on enhancing these properties through surface modifications and material optimization.

### *2.2. Inorganic Nano-Carriers*

Inorganic nano-carriers are mainly composed of metals, metal oxides, or other inorganic frameworks [12,35]. These nano-carriers are particularly valued for their unique physicochemical properties, such as optical, magnetic, and structural tunability. Gold NPs (Au NPs) are widely studied for their ability to combine photothermal therapy and drug delivery in cancer treatment [36]. Their functional versatility is enhanced by ligand conjugation, enabling precise targeting. Mesoporous silica NPs (MSNs), known for their high surface area and tunable pore sizes, facilitate efficient drug loading and release [37]. Magnetic NPs enable site-specific delivery through external magnetic fields, while quantum dots are utilized for simultaneous imaging and therapeutic delivery [38]. Metal oxide nano-carriers with controllable morphology and multifunctional properties, such as enzyme-like activity and photothermal effects, hold great potential for combined tumor therapy. Compared to organic nano-carriers, inorganic nano-carriers offer enhanced stability, well-defined surface properties, high loading capacity, and multi-functionality. However, their clinical translation is hindered by challenges such as limited biodegradability, manufacturing difficulties, interactions with the immune system, and issues with aggregation.

### *2.3. Hybrid Organic-Inorganic Carriers*

Hybrid organic-inorganic carriers combine the biocompatibility of organic materials with the functional versatility of inorganic components, offering more options for drug delivery [39,40]. MOFs represent an innovative class of hybrid carriers, characterized by high porosity and tunable chemical properties [41]. These structures enable high drug-loading capacity and responsive release of drugs. Core-shell NPs integrate the structural strength of inorganic cores with the flexibility of organic shells, enhancing stability and functionality [42]. Protein-inorganic hybrids and polymer-inorganic composites offer additional versatility, allowing for targeted delivery and responsiveness to external stimuli [43]. Leveraging the benefits of both organic and inorganic materials, hybrid

organic-inorganic carriers present a promising strategy for drug delivery, offering enhanced stability, multi-functionality, and improved targeting capabilities. However, challenges related to the complexity of fabrication, potential toxicity, and regulatory hurdles must be overcome to fully unlock their clinical potential.

### *2.4. Biomimetic Carriers*

Biomimetic carriers are DDSs designed to mimic biological structures or functions found in nature. These carriers are engineered to replicate the function of natural biomolecules, such as lipids, proteins, or polysaccharides, to enhance the delivery and release of therapeutic agents. Owing to their improved targeting, stability, controllable drug release, and minimized toxicity, biomimetic carriers have gained widespread attention and rapid development in recent years. Given that their composition includes both inorganic-organic hybrid systems as well as pure organic systems, they cannot be easily classified into the aforementioned categories. Therefore, they are categorized and discussed separately here. Liposomes, micelles, and other typical biomimetic carriers also defined as organic nano-carriers. Here, we primarily focus on live cells or extracted cell membrane-modified nano-carriers, such as red blood cells (RBCs) membrane-coated NPs, exosome-mediated drug delivery, and other similar delivery systems. Particularly, virus-like particles exploit the structural features of viruses for drug delivery, without the associated pathogenic risks [44–46]. Cell membrane-coated NPs, which integrate natural cell membranes with synthetic NPs, enable immune evasion and tumor-specific targeting [44]. Artificial biomimetic liposomes replicate the structure of natural lipid bilayers, enhancing stability and reducing immunogenicity [47]. These systems are particularly promising in cancer therapy and immune modulation. Biomimetic carriers represent a significant advancement in nanoparticle-based drug delivery, offering unmatched precision and biocompatibility. However, their complex design and high production costs hinder large-scale application. Streamlining manufacturing processes and enhancing the reproducibility of these systems are key areas for future research [45,48].

In addition to using biomimetic NPs as drug delivery carriers, recent studies have also explored the use of natural circulating cells, such as macrophages, as vehicles for tumor-targeting drug delivery (Figure 3A) [49]. Macrophages are attracted to tumor sites via various cytokines secreted by cancer cells and can effectively transport liposomes loaded with chemotherapeutic agents. By leveraging the biotin-avidin binding system, researchers have successfully attached drug-loaded liposomes to macrophages (Figure 3B,C), resulting in efficient delivery of chemotherapy agents directly to tumors. This innovative approach not only improves drug delivery efficiency but also harnesses the natural capabilities of immune cells to navigate complex TME (Figure 3D). Overall, the use of modified liposomes in conjunction with cellular carriers represents a significant advancement in the field of cancer therapy, offering promising new strategies for more effective and targeted treatment options.

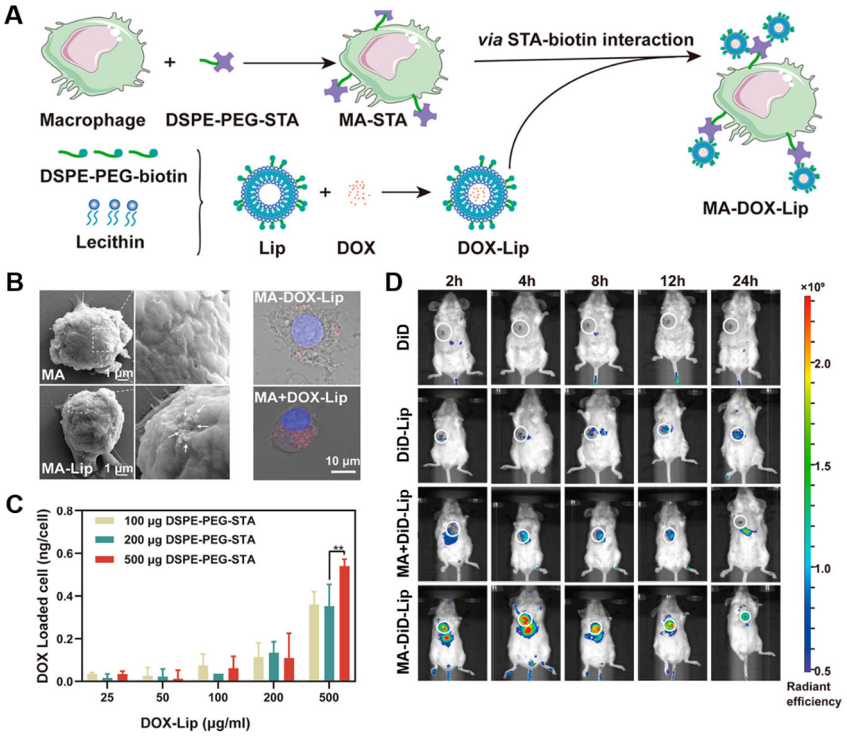


**Figure 3.** Live macrophage-delivered doxorubicin-loaded liposomes effectively treat TNBC. (**A**) Schematic representation of the macrophage-liposome fabrication process. (**B**) Representative SEM images of macrophages

(MA) and macrophage-liposome complexes (MA-Lip), showing attached liposomes on the macrophage surface. (**C**) Native or STA-modified macrophages were incubated with DOX-Lip for 5 min and imaged using CLSM. Most liposomes were rapidly endocytosed by non-modified macrophages, while STA-modified macrophages retained liposomes on their surface. (**D**) In vivo fluorescence images captured at various time points following the intravenous injection of free DiD, DiD-Lip, MA + DiD-Lip, or MA-DiD-Lip in tumor-bearing mice, with tumor sites indicated by white circles [49]. Copyright 2022, American Chemical Society. MA-STA: Macrophage-DSPE-PEG3400-streptavidin; Lip: Liposome; DOX: Doxorubicin; DiD: 1,1′-Dioctadecyl-3,3,3′,3′-Tetramethylindodicarbocyanine,4-Chlorobenzenesulfonate Salt.

## 3. Construction Strategies for Nano-Drug Carriers

The construction strategy of nano-drug carriers could be broadly categorized into three approaches: physical adsorption, structural integration, and chemical modification. Each strategy offers unique mechanisms to enhance drug encapsulation and delivery while overcoming biological barriers.

### *3.1. Physical Adsorption*

Non-covalent physical adsorption employs non-covalent interactions—such as Van der Waals forces, hydrogen bonding, and electrostatic interactions—to load drugs onto nano-carriers. This method is advantageous due to its simplicity, compatibility with various drugs, and minimal alteration to drug structure. MSNs are extensively utilized as a versatile platform for targeted and controlled drug delivery in cancer therapy due to their large surface area, tunable pore sizes, and ability to carry high drug loads [50]. For instance, Cheng et al. reported the delivery of chemotherapy drug paclitaxel (PTX) using silica-based nano-carriers, achieving improved therapeutic effects in tumor models due to the enhanced drug bioavailability [50,51]. The pre-loaded PTX or other chemical drugs in the mesoporous pores of MSNs via physical adsorption can be released in response to the pH in TME due to the disruption of pH-sensitive physical adsorption, thereby enabling controlled drug release (Figure 4A) [52]. Although the drug delivery method via physical adsorption is simple and applicable to a variety of drugs, the instability of physical adsorption forces in physiological microenvironments poses a risk of premature drug leakage due to weak non-covalent interactions. The implementation of core-shell nanostructures or hollow mesoporous architectures in nanoparticle design has demonstrated promising potential in partially addressing this challenge. For instance, PLGA-PEG NPs loaded with cisplatin showed <5% leakage over 72 h in serum [53].

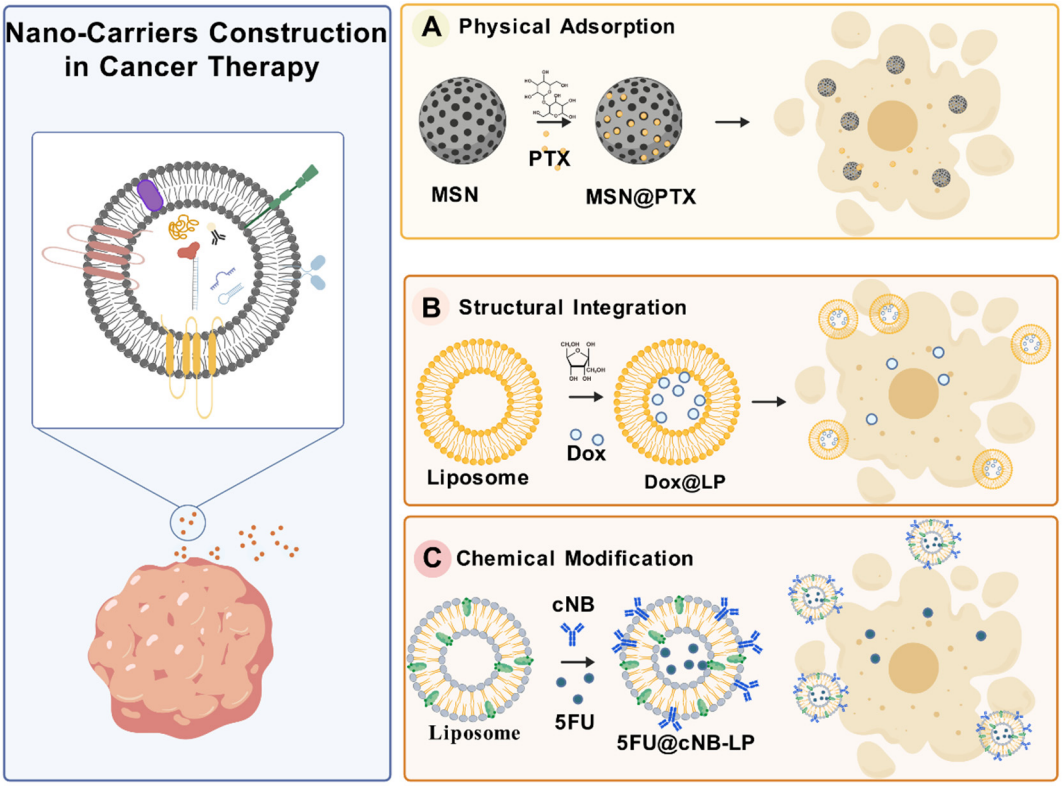


**Figure 4.** Construction strategies for nano-drug carriers in cancer therapy. (**A**) Physical adsorption: Non-covalent interactions, such as van der Waals forces and electrostatic interactions, are used to load drugs (e.g., paclitaxel,

PTX) onto MSNs, creating MSN@PTX for targeted drug delivery. (**B**) Physical encapsulation: Drugs, such as doxorubicin (Dox), are encapsulated within the internal structure of nano-carriers like liposomes (Dox@LP), enabling controlled release and protection from degradation. (**C**) Chemical modification: Functionalization of nano-carrier surfaces, such as chimeric nano-body-decorated liposomes (5FU@cNB-LP), enhances targeting, stability, and circulation time, improving tumor specificity and reducing immune clearance.

### *3.2. Physical Encapsulation*

Structural integration involves encapsulating drugs within the cavities of nano-carriers (Figure 4B), such as liposomes, solid lipid NPs (SLNs), and polymeric NPs. This approach protects drugs from degradation, increases loading efficiency, and enables controlled release. Recent innovations include US-mediated delivery, which further enhances the efficiency of this strategy by enabling targeted delivery through external stimulus. An important advancement in this field is the use of US-mediated liposomal delivery of doxorubicin for glioma treatment. This approach demonstrated enhanced drug delivery across the blood-brain barrier (BBB) and improved immune responses to PD-1 blockade therapy [54]. Additionally, SLNs and polymeric NPs have shown promise in improving drug solubility and overcoming drug resistance, making them effective platforms for cancer therapy [55,56].

### *3.3. Chemical Modification*

Nano-carriers can also load drugs through chemical bonding, which involves the formation of covalent or non-covalent bonds between the drug and the carrier. This method offers greater stability compared to physical adsorption, as the drug is more tightly bound to the carrier. The chemical bonding can be designed to be responsive to specific stimuli, such as pH, temperature, or enzymes, enabling controlled and targeted drug release in desired environments, such as tumor sites. Beyond drug loading via chemical bonds, chemical modification also encompasses the functionalization of the nano-carrier surface to improve targeting, stability, and circulation time. This can be accomplished by conjugating specific ligands, antibodies, or peptides to the surface, enabling the nano-carriers to selectively bind to target cells or tissues (Figure 4C). Moreover, surface modifications can enhance the stability of nano-carriers in the bloodstream and extend their circulation time, thereby promoting more efficient delivery of therapeutic agents [57,58]. This strategy is particularly effective in improving tumor specificity and reducing immune clearance. Recent breakthroughs include the development of chimeric nano-body-decorated liposomes, which integrate nano-bodies targeting HER2 receptors into liposomal bilayers. This method achieved precise delivery to HER2-overexpressing cancer cells while maintaining high encapsulation efficiency. Similarly, PEGylation has been extensively used to prolong circulation time and reduce premature drug clearance [59].

## 4. Targeting Modifications of DDSs

DDSs hold great promise for cancer therapy but are limited by poor targeting efficiency, uneven drug distribution, low specificity, and rapid immune clearance. These challenges lead to suboptimal efficacy and off-target side effects. To improve tumor targeting and accumulation, recent nanoparticle engineering has focused on enhancing cancer cell affinity and reducing non-specific interactions and immune clearance. Two key strategies have emerged in this regard. The first strategy involves functionalizing nanoparticle surfaces with targeting ligands, such as peptides or antibodies, which specifically bind to overexpressed receptors on cancer cells (Figure 5A), thereby improving targeted delivery and minimizing off-target effects [60–62]. The second strategy employs biomimetic systems, using natural cells, cell membranes, or extracellular vesicles as carriers to enhance biocompatibility and evade immune clearance (Figure 5C) [63,64]. These approaches significantly improve tumor-specific drug delivery, increase drug concentrations within tumor tissues, and reduce systemic toxicity.

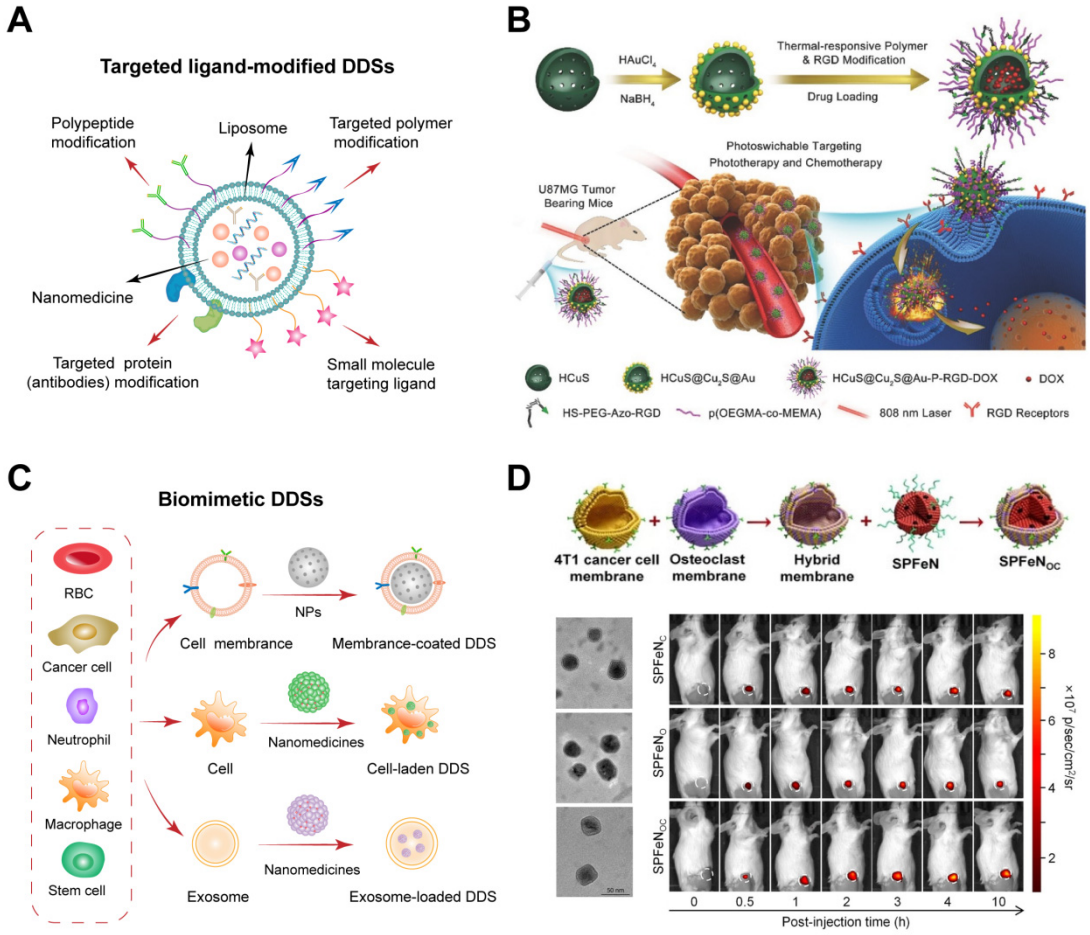


**Figure 5.** Schematic representation of ligand-targeted modifications on liposomal NPs. (**A**) Targeting ligand modifications include polypeptide-based targeting, polymer-based targeting, small molecule-based targeting, and protein-based targeting. (**B**) Synthesis of thermosensitive polymer- and Arginine-Glycine-Aspartic (RGD)-modified HCuS@$Cu_2S$@Au-P-RGD-DOX NPs and their proposed mechanism for tumor-targeted therapy. Copyright 2017, Wiley-VCH [65]. (**C**) Illustration of the construction strategies for biomimetic DDSs, including cell membrane-coated nano-carriers, cell-based nano-carriers, and exosome-based nano-carriers. (**D**) TEM images and tumor fluorescence imaging in tumor-bearing mice of biomimetic semiconducting polymer nanocomposites $SPFeN_C$, $SPFeN_O$ and $SPFeN_{OC}$ coated with cell membranes [66]. Copyright 2024, Wiley-VCH.

### *4.1. Targeted Ligand Modification*

Ligand-functionalized DDSs offer a versatile and precise strategy for targeted cancer therapy by exploiting specific interactions between ligands and overexpressed receptors or antigens on tumor cells. Ligands used in these systems can be grouped into four categories: small molecule ligands (e.g., folic acid (FA) and mannose), polymeric ligands (e.g., PEG) [67] and hyaluronic acid (HA) [68], peptide ligands (e.g., RGD and trans-activator of transcription (TAT) peptides) [69,70], and protein ligands (e.g., transferrin and epidermal growth factor receptor (EGFR) antibodies) [71,72]. When selecting ligands, it is essential to choose ligands with high affinity based on the characteristics of different types of cancer. For example, FA is primarily used to target cancer cells that overexpress FA receptors, such as those in ovarian cancer, lung cancer, and breast cancer [73–75]. Mannose is commonly used to target cells expressing mannose receptors (CD206), particularly immune system cells such as macrophages and dendritic cells [76]. HA is frequently used to target cancer cells that overexpress HA receptors (CD44), such as those in gastric cancer, breast cancer, and glioblastoma [77]. RGD peptides target cancer cells that overexpress integrin αvβ3, a receptor typically highly expressed in the angiogenesis of tumor cells, and are commonly found in lung cancer, liver cancer, and gastric cancer [69,70].

Recent studies highlight the transformative potential of these delivery systems in cancer chemotherapy. For example, Xiao and colleagues developed an antigen-capturing nanoplatform using mannose as a targeting ligand to co-deliver tumor-associated antigens and m6A demethylase inhibitors to tumor-infiltrating dendritic cells, enhancing thermal ablation and immune checkpoint blockade therapy [78]. Similarly, Deng and co-workers created

a thermosensitive polymer-based nanohybrid system, CuS@$Cu_2S$@Au-P-RGD-DOX, functionalized with an RGD peptide. Upon 808 nm laser exposure, the system's photothermal properties triggered polymer shrinkage, releasing the RGD peptide to target integrin $\alpha_v\beta_3$ on tumor cells, thereby enhancing chemotherapy efficacy (Figure 5B) [65]. In addition, Oh and co-workers synthesized MOFs conjugated with targeting antibodies, such as anti-CD44, HER2, and EGFR, achieving improved specificity against cancer cell lines like HeLa, SK-BR-3, and 4T1 [79]. Ligand-modified DDSs enhance tumor specificity, reduce systemic toxicity, improve cellular uptake, and offer versatile drug-loading capabilities. These attributes collectively enhance the therapeutic index of chemotherapeutic agents, representing a promising advancement in cancer treatment strategies. Nevertheless, the efficacy of ligand-functionalized DDSs is strongly dependent on ligand stability and receptor availability, both of which must be carefully addressed to optimize their clinical application.

### *4.2. Biomimetic Modification*

Biomimetic modification refers to incorporating biological elements or structures into synthetic DDSs to enhance their performance, functionality, or targeting ability, by mimicking natural biological systems or processes. These typical biological elements or structures include RBCs, cancer cells, neutrophils, immune cells such as macrophages and T cells, and stem cells, which preserve their biological molecules—such as receptors and ligands—to enhance targeting efficacy within tumor environments. Certain natural cells, including cancer cells, macrophages, and neutrophils, exhibit innate abilities to migrate to tumor sites or inflammatory areas, facilitating precise drug delivery [80]. Compared to traditional nanodrug platforms, biomimetic systems offer enhanced biocompatibility, immune evasion, and targeting efficacy, while improving drug delivery efficiency and versatility [81,82]. For instance, Zhang and colleagues developed a biomimetic semiconductor polymer nanocomposite (SPFeNOC) designed to dual-target osteoclasts and tumor cells, aiming to improve the diagnosis and treatment of bone metastases [66]. SPFeNOC, composed of a semiconductor polymer and iron oxide ($Fe_3O_4$) NPs, is cloaked in a mixed membrane of cancer cells and osteoclasts to enable homologous targeting and boost nanoparticle accumulation in tumors. In vivo bioimaging demonstrates its superior targeting efficacy in murine tumors when encapsulated by both membranes of cancer cells and osteoclasts (Figure 5D). In addition, macrophages are promising carriers in biomimetic nanodrug delivery for oncology, neurology, and inflammatory diseases due to their biocompatibility, high drug-loading capacity, and ability to penetrate tumor matrices [83]. Macrophage-based systems effectively overcome tumor-associated physiological barriers, offering substantial clinical translation potential. Wang and collaborators developed a tumor-targeting system using M1 macrophages and hyaluronic acid-modified, drug-loaded carbon NPs (M@C-HA/ICG), which exhibit synergistic effects via photothermal, photodynamic, and immune responses [84]. By integrating nanomedicine properties with macrophage functions, this approach introduces a novel paradigm in cell-mediated biomimetic drug delivery and multimodal anticancer therapy.

## 5. Controlled Drug Release Strategies

In addition to reduced efficacy due to inadequate drug targeting and resistance mechanisms, the failure of cancer chemotherapy in clinical settings is often attributed to premature drug release and insufficient delivery at the target site [85]. Developing responsive DDSs with controlled release strategies could enhance the efficacy of cancer treatments while minimizing side effects, optimizing drug utilization, and ensuring precise therapy. Current strategies for effective responsive-drug release within tumors are primarily classified into two categories. Endogenous stimuli include tumor-specific triggers such as acidic pH, elevated glutathione (GSH), and hypoxia. Exogenous stimuli utilize external energy sources like near-infrared (NIR) light, US, and magnetic fields. For example, pH-sensitive polymers release drugs in the acidic TME (pH 6.5–6.8), while NIR-activated gold NPs enable spatiotemporal control of drug release. The first relies on endogenous stimulus from the TME, such as hydrogen peroxide ($H_2O_2$), GSH, intracellular enzymes, acidic pH, and hypoxic conditions [86–90]. The second involves exogenous stimulus, utilizing external energy sources like lasers, thermal effects, US, X-rays, and magnetic fields to trigger drug release (Figure 6) [86,91–94].

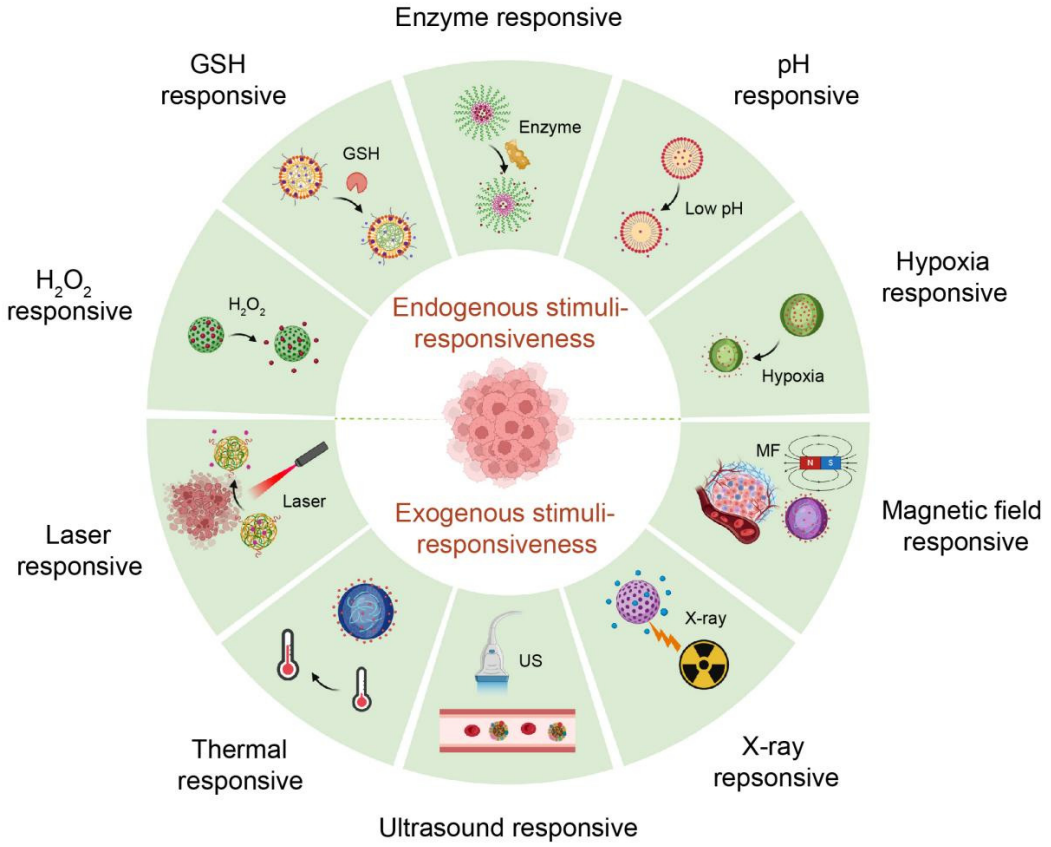


**Figure 6.** Controlled release strategies for nanomedicines encompass both endogenous stimulus-responsive approaches and exogenous stimulus-responsive approaches. Endogenous stimuli include elevated levels of $H_2O_2$, GSH, specific enzymes, acidic pH, and hypoxia within the TME. Exogenous stimuli encompass laser irradiation, photothermal effects, US, X-rays, and magnetic fields. Created with BioRender.com.

### *5.1. Endogenous Stimulus-Responsive Drug Release*

Internal triggers that respond to specific TME conditions are also widely employed in DDSs. These include pH, redox conditions, and enzymes, which provide a more selective release of drugs. For instance, pH-sensitive DDSs exploit the acidic conditions found in tumor tissues, releasing encapsulated drugs when the pH decreases below a certain threshold. Redox-sensitive DDSs make use of the high levels of reducing agents, such as GSH, in tumor cells to trigger the drug release via a redox reaction. Additionally, enzyme-sensitive DDSs can be designed to release drugs in response to the presence of specific enzymes (e.g., cathepsins) that are overexpressed in cancer cells, further enhancing the specificity of the DDSs [95]. For example, Yang and colleagues developed a biodegradable hollow manganese dioxide (H-$MnO_2$) nanoplatform modified with PEG and co-loaded with chlorin e6 (Ce6) and doxorubicin (DOX) (H-$MnO_2$-PEG/Ce6&DOX). Under the dual stimuli of GSH and acidic pH, H-$MnO_2$ gradually degrades, releasing DOX, Ce6, and oxygen, alleviating tumor hypoxia and enhancing both chemotherapy and photodynamic therapy (PDT) efficacy [96]. Liu et al. reported a GSH-responsive cancer cell membrane-wrapped mesoporous copper/manganese silicate nanospheres (mCMSNs) system that releases $Cu^{2+}$ and uses the $Mn^{2+}$-mediated Fenton reaction to generate reactive oxygen species (ROS), enabling a synergistic chemodynamic therapy (CDT) and PDT [97]. Additionally, Li and collaborators designed an enzyme-responsive mesoporous silicon quantum dot nanoparticle (CPP-QDs@m$SiO_2$-DOX) that activates cell-penetrating peptides (CPPs) and proteases in the TME, enhancing nuclear delivery of DOX and chemotherapy efficacy [98]. This system demonstrated limited drug accumulation and low cytotoxicity in non-enzyme-expressing cells, whereas drug-resistant tumor cells expressing the target enzyme showed increased DOX accumulation and enhanced tumor inhibition.

Tumor hypoxia can also be leveraged as endogenous stimuli to trigger drug release in tumor tissue from the designed DDSs. Recently, hypoxia-responsive polymeric NPs (HR-NPs) were developed for targeted drug delivery to hypoxic tumor tissues, which are typically associated with treatment resistance in cancers (Figure 7) [99]. The HR-NPs, synthesized by conjugating a hydrophobically modified 2-nitroimidazole derivative to carboxymethyl

dextran, encapsulated the model anticancer drug doxorubicin and demonstrated sensitivity to hypoxic conditions, facilitating selective drug release under hypoxia. In vitro cytotoxicity tests showed increased toxicity to hypoxic cells, and in vivo biodistribution studies in tumor-bearing mice revealed prolonged circulation and selective accumulation of HR-NPs in tumor tissues. The in vivo antitumor efficacy of doxorubicin-loaded HR-NPs resulted in minimal tumor growth, highlighting their potential as effective nano-carriers for treating hypoxia-associated diseases such as cancer. This research provides a significant advancement in hypoxia-targeted cancer therapies, showcasing HR-NPs as a promising tool for specifically release hydrophobic drugs within the hypoxic TME.

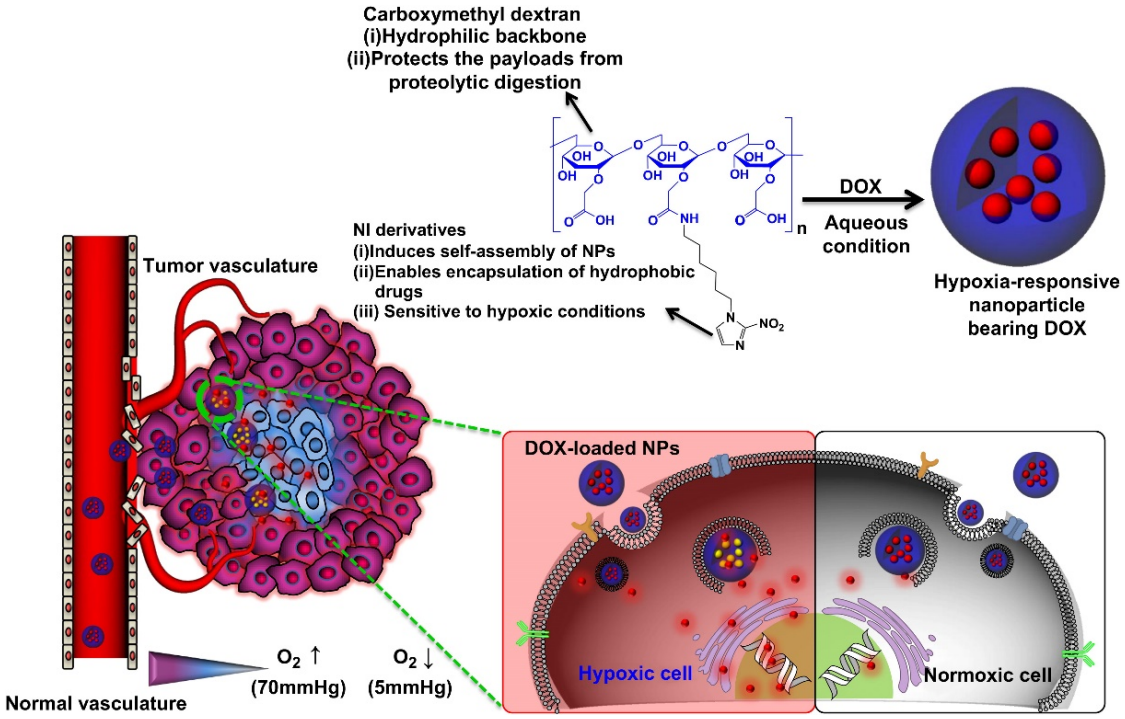


**Figure 7.** The creation of drug-loaded HR-NPs and the mechanism for targeting tumors. The HR-NPs reach the tumor site through the enhanced permeability and retention (EPR) effect, leading to intracellular drug release in hypoxic tissue [99]. Copyright 2014, Elsevier.

Endogenous stimulus-responsive DDS utilize the unique characteristics of the TME, such as elevated levels of $H_2O_2$, GSH, acidic pH, and hypoxia, to achieve selective drug release. However, these systems are subject to several limitations. Tumor heterogeneity poses a significant challenge, as variations in the TME, even within the same cancer type, complicate the development of universal systems, potentially resulting in insufficient or unpredictable drug release. Moreover, drug release driven by endogenous stimuli is often difficult to control and predict due to fluctuations in the concentration of these stimuli within the TME. This can lead to issues such as premature drug release before reaching the target site, particularly if similar stimuli are present in non-tumor tissues. Furthermore, these systems may face stability challenges, as they may degrade too quickly or lack the necessary durability for sustained drug release in complex biological environments [95,97,99].

### *5.2. Exogenous Stimulus-Responsive Drug Release*

Exogenous stimulus-responsive drug release strategies utilize external energy sources—such as light, heat, US, magnetic fields, and ionizing radiation—to precisely control drug release, enhancing cancer treatment efficacy. These approaches offer superior controllability compared to endogenous stimuli, enabling precise regulation of release timing and rate, high adaptability, localized action with minimal side effects, and real-time imaging monitoring. For example, light-responsive DDSs can be activated by NIR light, generating heat or chemical reactions to trigger the release of chemotherapeutic agents at specific tumor sites. Similarly, magnetic field-sensitive DDSs, often employing magnetic NPs, offer precise control over the drug release at targeted sites under an external magnetic field. US-responsive DDSs leverage mechanical effects or cavitation to trigger drug release and enhance drug accumulation in tissues, making them ideal for deep tissue drug delivery, especially for brain tumors [100]. For instance, Li and co-workers developed a light-responsive liposome (Lip-DTI/NO) that, upon 808 nm laser irradiation, generates peroxynitrite anions ($ONOO^-$) within tumors to degrade the extracellular matrix, improving drug delivery and phototherapy efficacy. Lei and colleagues created an US-responsive MOF nanodrug

system (MFePCN@1-MT) that induces reactive oxygen species (ROS) generation and ferroptosis, enhancing osteosarcoma treatment through immunogenic cell death (ICD) and ROS-amplified ferroptosis [93]. Chen and collaborators reported an X-ray-responsive gold nanocluster-platinum prodrug system that converts Pt (IV) prodrugs into cytotoxic Pt (II) drugs, enabling synergistic radiotherapy and chemotherapy in breast cancer [101]. This strategy demonstrates enhanced antitumor efficacy and safety through spatiotemporal synergy, overcoming chemoresistance while offering precision and controllability in tumor treatment.

Exogenous stimulus-responsive DDSs also encounter several challenges. The penetration depth of these external stimuli is often limited, particularly in the case of light-based systems, which are typically effective only in superficial tissues, restricting their use for deep-seated tumors. Additionally, there is the potential risk of over-stimulation, where excessive drug release or damage to surrounding healthy tissue may occur if the external stimulus is not accurately controlled. The need for precise calibration of external energy sources, such as lasers or magnetic fields, presents regulatory and safety concerns that must be addressed. Finally, the reliance on complex equipment for the generation of external stimuli increases both the complexity and cost of these treatment modalities, thereby limiting their widespread clinical applicability [100–102].

## 6. Antitumor Applications of DDSs

The development of DDSs has significantly enhanced the therapeutic efficacy of chemotherapy, providing new opportunities to improve treatment precision and effectiveness. These systems have notably improved cancer treatment outcomes by increasing drug bioavailability, enhancing targeting efficiency, reducing toxicity, and enabling the combination of multiple therapeutic approaches [28,103,104].

### *6.1. Delivery of Chemotherapy Drugs*

The primary function of DDSs is to improve the delivery and release of chemotherapy drugs at tumor sites while minimizing systemic side effects. Traditional nano-carriers can effectively encapsulate hydrophobic or poorly soluble drugs, enhance drug bioavailability, prolong circulation time, and could be accumulated in tumors through the EPR effect. Due to the limited EPR effect, even after targeted modification, the effective accumulation of these DDS systems in tumor tissues remains limited. Clinically, Doxil® has been approved for Kaposi's sarcoma and ovarian cancer, reducing cardiotoxicity by 50% compared to free doxorubicin [105,106]. Similarly, Abraxane® improves survival in metastatic breast cancer and pancreatic adenocarcinoma, with ongoing trials exploring its synergy with immunotherapy [107,108].

To further improve the targeted delivery efficiency of chemotherapeutic drugs, the engineering of endothelial leakiness using NPs (NanoEL) recently has emerged as a promising strategy for enhancing therapeutic access to tumors [36,109,110]. The study effectively demonstrates that varying sizes and surface characteristics of gold NPs (AuNPs) can induce a controllable leakiness effect in vivo, as shown through intravital imaging in cancer models. They synthesized a library of AuNPs consisting of two size series (Au30 and Au70) and four distinct surface roughness groups (smooth, R0; low roughness, R1; mid roughness, R2; and high roughness, R3), as shown in the transmission electron microscopy (TEM) images (Figure 8A). Upon exposing these NanoEL Au particles to a monolayer of endothelial cells, we observed leakiness gaps ranging from approximately 5 to 20 μm. Notably, the smaller-sized NPs exhibited a greater number and wider gaps, particularly those with increased surface roughness (Figure 8B). This approach successfully increases the permeability of tumor vasculature, facilitating the migration of larger therapeutic agents from the bloodstream into the tumor interstitial space (Figure 8C,D). Significantly, the induced leakiness led to complete regression of primary tumors in certain instances without an increase in metastasis, highlighting the potential of this strategy in treating advanced malignancies (Figure 8E,F). Furthermore, the application of NanoEL to micrometastases illustrated its versatility in combating secondary tumors, emphasizing its utility in a clinical context. Importantly, the findings suggested that NanoEL did not adversely impact healthy vascular structures, positioning this method as a transformative engineering strategy that could also be applicable to other diseases related to the vasculature. However, the study's focus on short-term outcomes and the need for broader validation across diverse tumor types and microenvironments warrant further exploration to enhance the clinical applicability of this innovative approach.

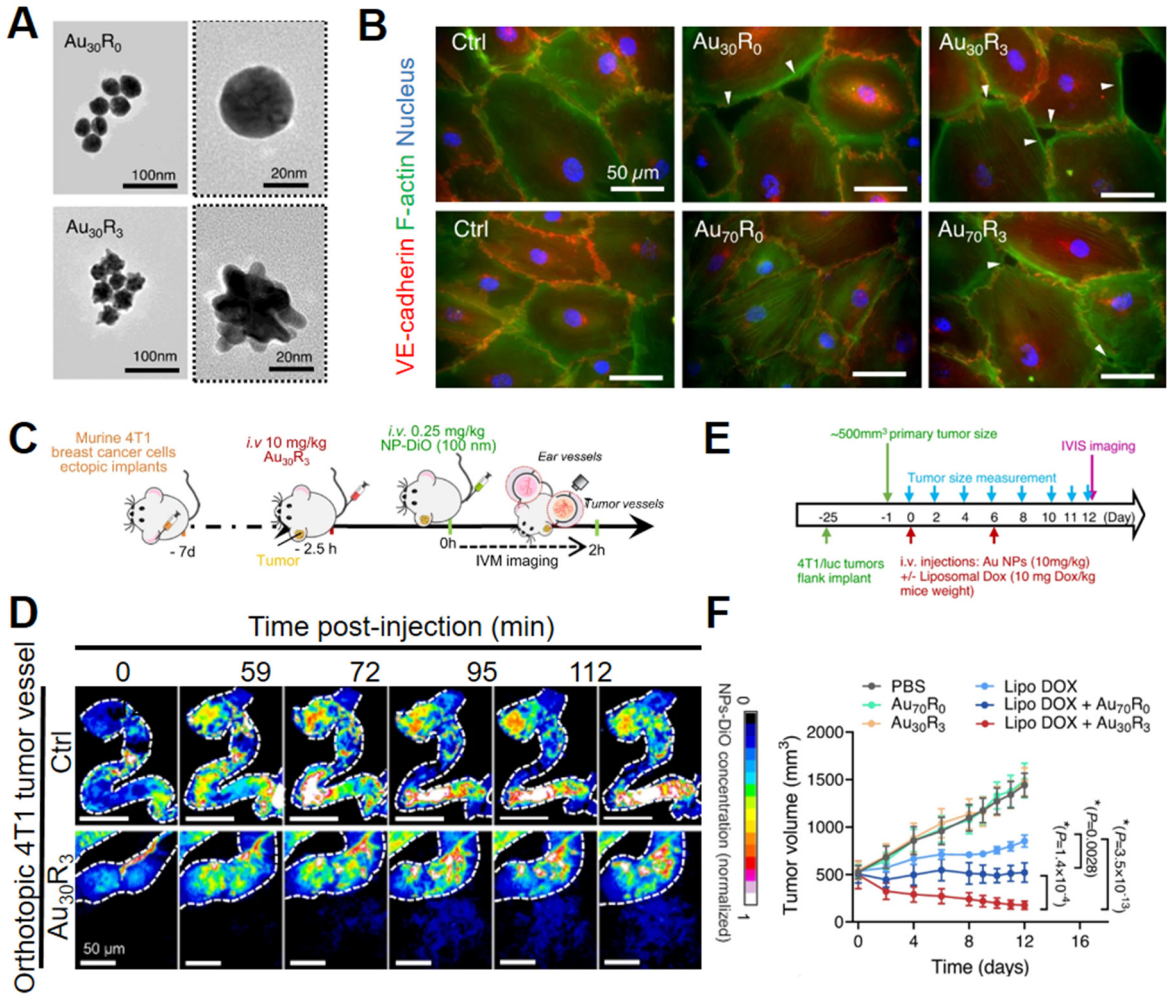


**Figure 8.** Engineering tumoral vascular leakiness with gold NPs. (**A**) TEM images depict the surface roughness of 30 nm gold NPs (Au30). (**B**) Immunofluorescence images illustrate the formation of intercellular gaps within an endothelial cell monolayer following treatment with these NPs. High-magnification details are provided, showcasing staining for VE-cadherin (red), F-actin (green), and nuclei (blue). Scale bar: 50 μm. (**C**) A schematic representation of intravital imaging (IVM) of ear flap vasculature ectopically implanted with 4T1 breast tumor cells (n = 3 mice per group). Multicolor imaging reveals increased vascular permeability into the interstitial space within the 4T1 tumor model treated with Au30R3 NPs. (**D**) Time-lapse analysis depicts changes in permeability within a localized region of the 4T1 orthotopic tumor vasculature. Scale bar: 50 μm. The images shown are representative of three independent experiments. (**E**) Treatment schema for mice utilizing NanoEL particles, including Au30R3 and Au70R0, with n = 6 mice per group. Treatment commenced when tumors reached an approximate volume of 500 $mm^3$ and was administered exclusively on Days 0 and 6. (**F**) Tumor growth profile over the 12-day treatment period demonstrates that the administration of AuNPs enhanced the delivery efficacy of liposomal doxorubicin (Dox). Data are expressed as mean ± SEM, with n = 6 mice per group. Statistical analysis was conducted using two-way repeated measures analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) post-hoc test; * indicates significance relative to the Lipo-Dox group ($p < 0.05$). At the conclusion of the 12-day treatment period, mice were injected with luciferin, and the 4T1/luc tumors were imaged using the IVIS system. Mice were subsequently euthanized, and the tumors were excised for size-sorting [36]. Copyright 2023, Springer Nature.

### *6.2. Synergistic Therapy*

As the understanding of cancer treatment mechanisms deepens, the limitations of monotherapy have become increasingly evident. Compared to monotherapy, combination therapy can result in enhanced efficacy, reduced resistance, and broader coverage of different types of tumors. With multi-functionality, DDSs can facilitate the combination of chemotherapy with other therapeutic modalities to achieve synergistic effects, enhance treatment efficacy, and reduce drug resistance.

### 6.2.1. Radiotherapy Combined with Chemotherapy

The combined use of radiotherapy and chemotherapy is a common clinical strategy to enhance the overall therapeutic efficacy of cancer treatment. NPs containing high atomic number elements can simultaneously serve as radiotherapy sensitizers and nano-carriers, thereby enabling the combination of radiotherapy with chemotherapy.

Nanoscale MOFs based on heavy metals have emerged as excellent radiosensitizers by increasing energy deposition and ROS generation. Lin and colleagues reported a novel nMOF design, Hf-TP-SN, which is capable of releasing the X-ray-triggered prodrug 7-ethyl-10-hydroxycamptothecin (SN38) for combined radiotherapy and chemotherapy (Figure 9) [111]. The authors connected SN38 to Hf-TP-OH nMOF through 3, 5-dimethoxyphenyl carbonate, forming Hf-TP-SN, and this linkage can be cleaved by hydroxyl radicals (·OH) (Figure 9A). Under X-ray irradiation, the Hf structural units act as radiosensitizers, enhancing ·OH production and promoting the release of SN38 from Hf-TP-SN, which not only enhances radiotherapy but also achieves a chemotherapy effect through SN38. TEM images show that both Hf-TP-OH and Hf-TP-SN have a nanosheet morphology, with diameters around 70 nm (Figure 9B). The in vivo anticancer effect of Hf-TP-SN (+) was evaluated using subcutaneous CT26 and 4T1 tumor mouse models. The results showed that Hf-TP-SN (+) strongly inhibited CT26 and 4T1 tumor growth, with tumor growth inhibition (TGI) indices of 0.965 and 0.889, respectively (Figure 9C–F). The significant therapeutic effect of Hf-TP-SN (+) is attributed to the synergistic effect of the radiosensitization mediated by nMOFs and the X-ray-triggered release of SN38. This combined chemoradiotherapy strategy effectively reduced the radiation dose required for tumor regression and minimized the side effects of chemoradiotherapy by the burst release of SN38 within cancer cells.

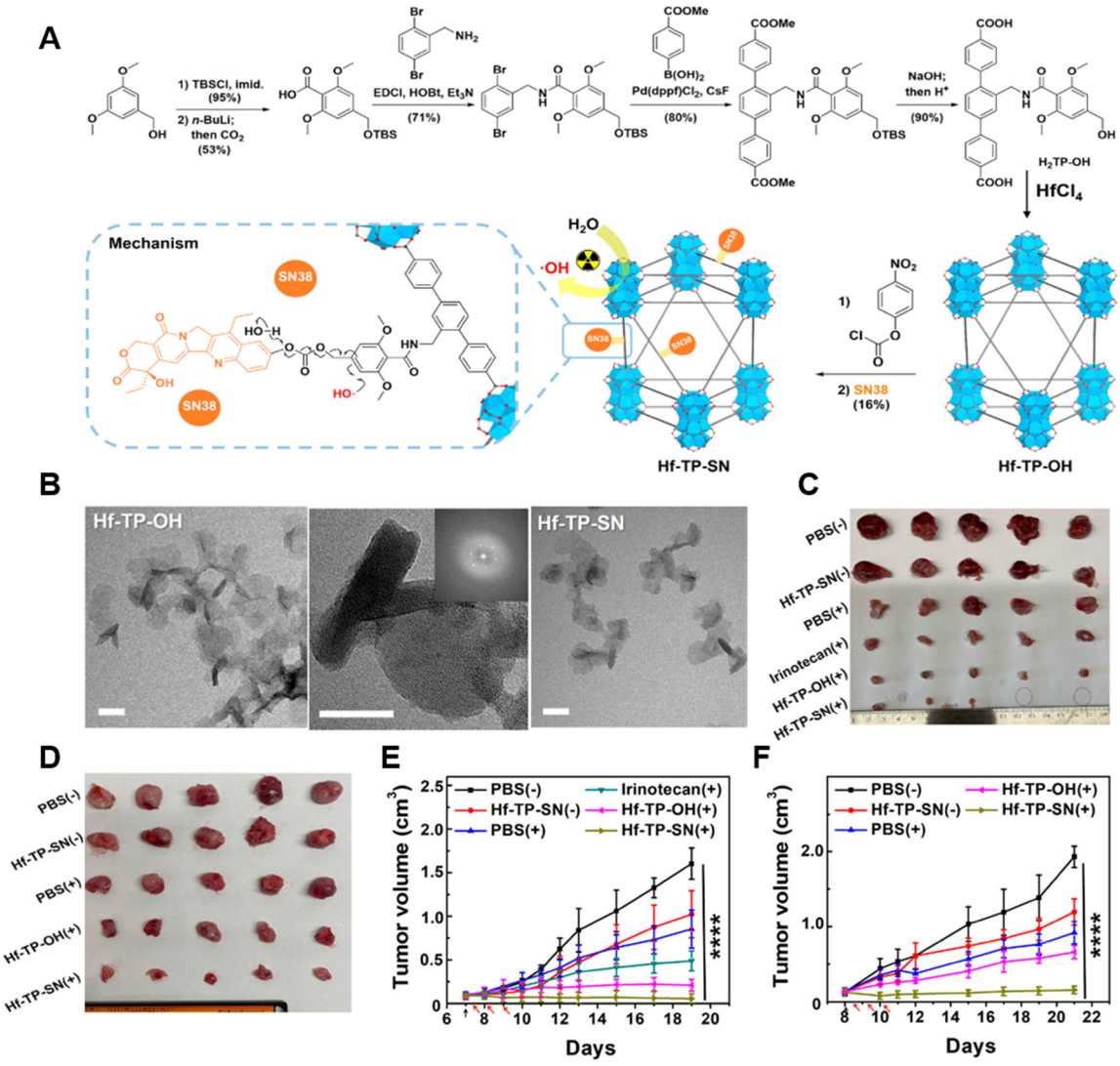


**Figure 9.** nMOFs with X-ray-triggered prodrug release for synergistic radiotherapy and chemotherapy**.** X-ray-triggered prodrug release of nMOFs for synergistic radiotherapy and chemotherapy. (**A**) Synthesis of Hf-TP-OH nMOF and Hf-TP-SN nMOF, along with the X-ray-triggered SN38 release mechanism. (**B**) TEM image of Hf-TP-OH, high-resolution transmission electron microscopy (HRTEM) image (with inset FFT pattern), and TEM image

of Hf-TP-SN. Scale bar: 50 nm. (**C**) Tumor images of CT26 tumors in BALB/c mice after different treatments. (**D**) Tumor images of 4T1 tumors in BALB/c mice under different treatments. n = 5. (**E**) Tumor growth curves of CT26 tumors after different treatments. (**F**) Tumor growth curves of 4T1 tumors after different treatments [111]. Copyright 2023, American Chemical Society.

### 6.2.2. Phototherapy Combined with Chemotherapy

Phototherapy primarily includes PDT and Photothermal therapy (PTT), which respectively generate ROS through the activation of photosensitizers (for PDT) or induce local hyperthermia through the activation of photothermal agents (for PTT) for tumor ablation upon light exposure. The combination of phototherapy and chemotherapy is an emerging therapeutic strategy. On one hand, light exposure can enhance the precise release of chemotherapeutic drugs at the tumor site, while on the other hand, the action of chemotherapy can, in turn, increase the sensitivity of tumor cells to phototherapy.

Xiao et al. developed a multifunctional DDS (mitoxantrone (MTO) micelles) based on the chemotherapy drug mitoxantrone (MTO) and the amphiphilic polymer DSPE-$PEG_{2000}$, to realize synergistic mild PTT (Figure 10A) [112]. MTO serves not only as a chemotherapy agent but also as a photothermal transducer, exhibiting excellent NIR absorption and high photothermal conversion efficiency (η = 54.62%). Under near-infrared irradiation, mild high temperatures promote the binding of MTO to tumor cell DNA, enhancing chemotherapy sensitivity. Furthermore, the increased DNA damage results in the downregulation of heat shock protein 70 (HSP70) expression, which further diminishes tumor thermotolerance and enhances the efficacy of mild PTT. TEM images and dynamic light scattering (DLS) data show that the MTO micelles are spherical with an average size of 15–20 nm (Figure 10B,C). Over four heating/cooling cycles, the temperature of the MTO micelles steadily rises, indicating good photothermal stability (Figure 10D). Western blot (WB) results demonstrate that mild photothermal combined chemotherapy (MTO + laser) increases DNA damage and reduces HSP70 expression, thereby lowering tumor cell thermotolerance and enhancing the therapeutic effects of mild PTT (Figure 10E,F). This multifunctional MTO micelle system effectively eliminates tumors under mild thermal therapy and demonstrates significant clinical potential.

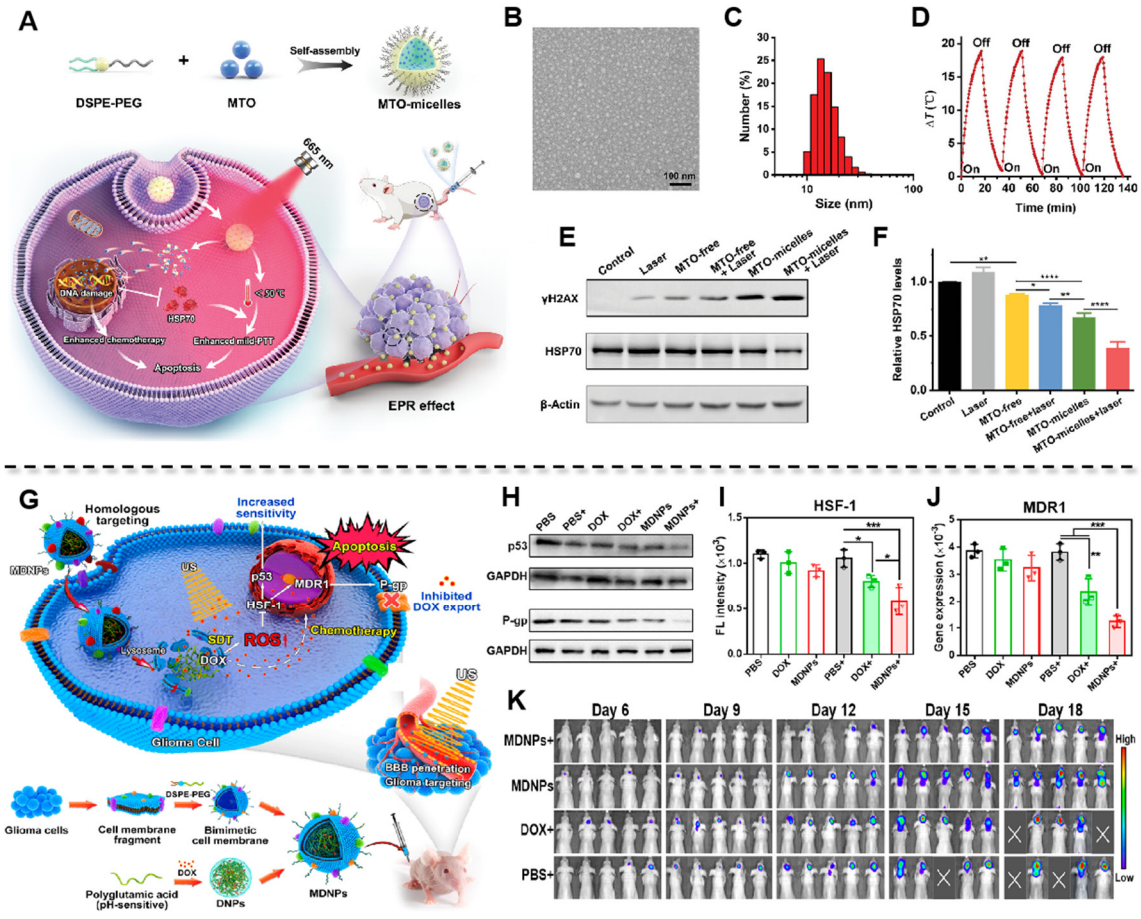


**Figure 10.** Phototherapy or Sonodynamic therapy combined with chemotherapy. (**A**) Schematic illustration of the multifunctional MTO micelles for synergistic mild photothermal chemotherapy in TNBC. (**B**) TEM image of MTO micelles. (**C**) DLS measurements of MTO micelles. (**D**) Photothermal stability of MTO micelles exposed to 665 nm

laser. (**E**) Western blot analysis of γH2AX and HSP70 proteins. (**F**) Relative expression levels of HSP70 in 4T1 cells from different treatment groups [112]. Copyright 2023, Wiley-VCH. (**G**) Preparation process of MDNPs and the release of DOX in endosomes/lysosomes, with ROS generation under US assistance to downregulate drug resistance markers for sonodynamic therapy (SDT) combined with chemotherapy. (**H**) Western blot analysis of mutant p53 and P-gp proteins. (**I**) Flow cytometry analysis of HSF-1 protein expression in U87 cells under different treatments. (**J**) qRT-PCR results showing MDR1 gene expression in U87 cells after different treatments. (**K**) In vivo bioluminescence images showing tumor progression after different treatments. "×" denotes mouse mortality [113]. Copyright 2023, American Chemical Society.

#### 6.2.3. Sonodynamic Therapy Combined with Chemotherapy

Compared to phototherapy, US-mediated therapy combined with chemotherapy is a more promising therapeutic strategy, due to the deeper tissue penetration of US compared to laser. The application of US enhances the permeability of tumor blood vessels, increasing the uptake of NPs at the tumor site. Furthermore, US-induced bubble rupture can trigger the release of chemotherapy drugs encapsulated within nano-carriers, enabling localized drug delivery. Concomitantly, the utilization of chemotherapeutic drugs may potentiate the susceptibility of neoplastic cells to US-based treatment, thereby resulting in synergistic therapeutic effect.

Cai and colleagues developed a biomimetic nanosonosensitizer systems, consisting of membrane-coated DOX NPs (MDNPs), driven by noninvasive US for targeted delivery and sonodynamic-enhanced chemotherapy for glioblastoma (GBM) (Figure 10G) [113]. MDNPs are composed of polyglutamic acid (PGA) encapsulating the chemotherapy drug and sonosensitizer DOX, with an outer membrane derived from human glioblastoma multiforme (GBM) U87 cell membranes. Under US assistance, MDNPs can effectively cross the BBB to reach the in situ GBM site. Membrane-coated MDNPs are internalized by GBM cells via endocytosis, and due to the pH-responsive characteristics of the PGA carrier, DOX is rapidly released in endosomes/lysosomes, entering the nucleus to induce apoptosis. Moreover, US activation of MDNPs generates intracellular ROS, which inhibit drug efflux by downregulating HSF-1 expression and suppressing the production of P-gp encoded by MDR1, thereby reversing chemotherapy resistance (Figure 10H–J). The downregulation of HSF-1 also inhibits the production of mutated p53, preventing tumor cells from evading apoptosis and enhancing chemotherapy sensitivity. The antitumor efficacy of MDNPs assisted by US was further validated in a BALB/c nude mouse orthotopic GBM model (Figure 10K). On day 6, one day after treatment, the MDNPs+ group showed no bioluminescent signal, while the other groups exhibited noticeable bioluminescence. At day 12, the bioluminescence intensity in the MDNPs+ group indicated moderate tumor growth, and even after treatment cessation, the bioluminescence remained lower than the other groups. These results demonstrate that MDNPs may represent a promising nanoplatform for combating brain tumors through the synergistic effects of sonodynamic therapy (SDT) and chemotherapy.

#### 6.2.4. Immunotherapy Combined with Chemotherapy

Immunotherapy aims to harness the body's immune system to target and eliminate cancer cells. By using DDSs to directly deliver immune checkpoint inhibitors, cytokines, or tumor-associated antigens together with chemotherapeutic drugs to the TME, the combination of immunotherapy and chemotherapy can be achieved. DDSs not only deliver chemotherapy drugs to the tumor site but also enhance its therapeutic efficacy in improved immune microenvironment by reducing immunosuppressive cells and promoting antitumor immunity. This synergistic treatment approach holds promise for overcoming drug resistance and improving clinical outcomes.

Polysaccharides, a class of biomacromolecules with various immune activities, have excellent biocompatibility, biodegradability, and ease of modification, making them ideal drug delivery carriers for synergistic chemotherapy and immunotherapy [114–116]. Yu et al. cleverly constructed a multifunctional nanoplatform based on sodium alginate, a biotinylated aldehyde alginate-doxorubicin nano micelle (BEA-C=N-DOX-M), for the synergistic chemotherapy and immunotherapy of hepatocellular carcinoma (HCC) (Figure 11A) [117]. This platform utilizes the β-D-mannuronic acid (M) units of alginate to specifically bind to the mannose receptors (MRs) and provide natural immune effects, while the α-L-guluronic acid (G) units serves as reactive sites for coupling with biotin (Bio) and DOX. The nano micelles combine the natural immune effects of alginate and the ICD induction capability of DOX, enabling dual-targeting of HCC cells through MRs and bioreceptor-mediated endocytosis for efficient chemotherapy and immunotherapy.

The antitumor immune effects of BEA-C=N-DOX-M nano micelles were validated in vivo using Hepa1-6 tumor-bearing C57BL/6J mice (Figure 11B). The tumor-bearing mice were treated with physiological saline, ASA, BEA, DOX, ASA-C=N-DOX-M, and BEA-C=N-DOX-M respectively. The results showed that BEA-C=N-DOX-M exhibited the best performance in inhibiting rapid tumor growth and reducing early tumor volume (Figure 11C).

To further explore the immunomodulatory effects of BEA-C=N-DOX-M, flow cytometry was used to assess the maturation of dendritic cells (DCs) and the polarization of M1-type tumor-associated macrophages in tumor tissues (Figure 11D–F). The results revealed that the BEA-C=N-DOX-M treatment group had the highest proportion of mature DCs and the highest relative number of M1 macrophages, with the lowest relative number of M2 macrophages, indicating effective polarization of tumor-associated macrophages by BEA-C=N-DOX-M. The nanomicelles cleverly integrate the advantages of DOX and alginate, stimulating a strong immune response in vivo, thereby enhancing the antitumor effects.

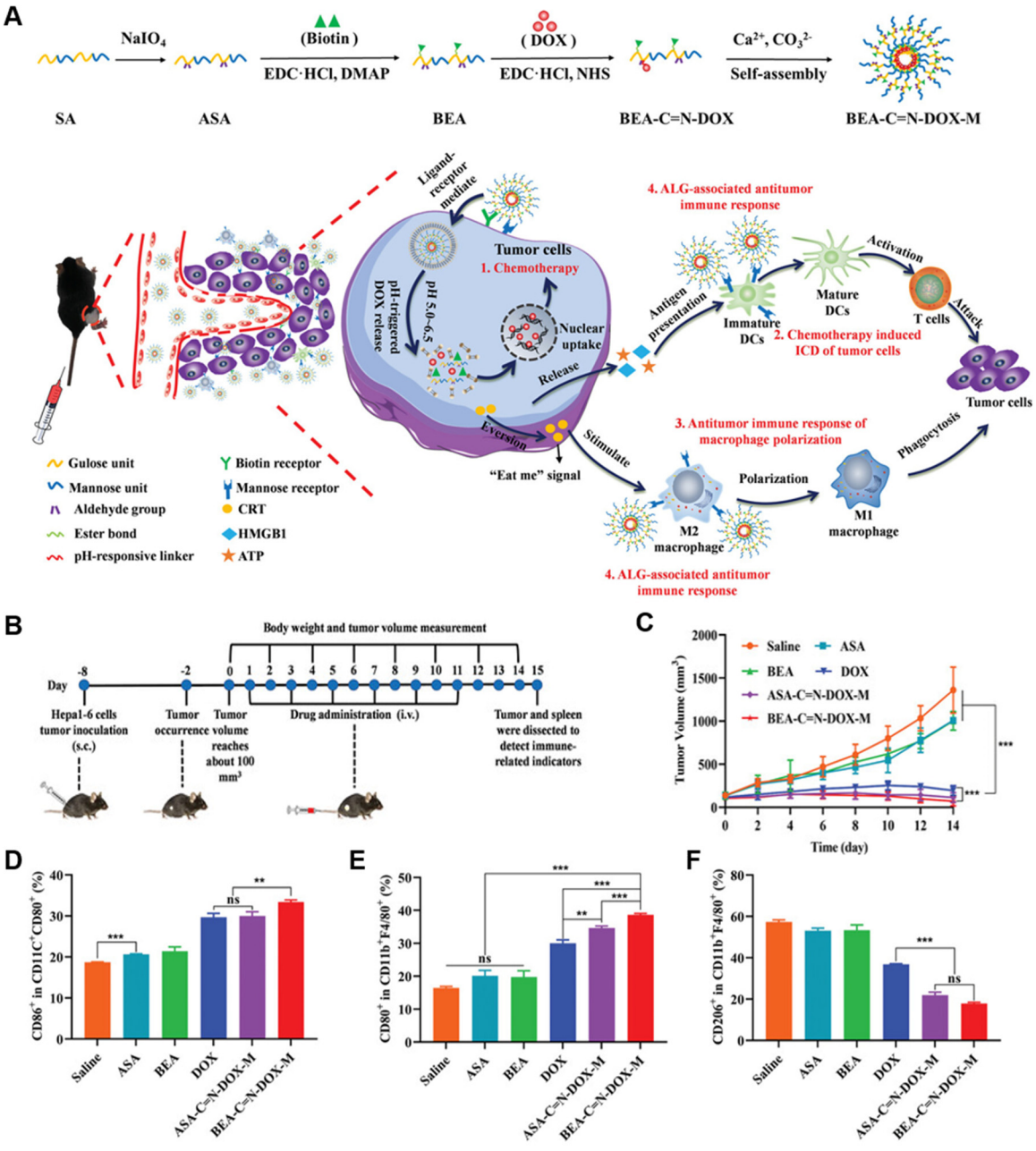


**Figure 11.** Multifunctional nanoplatform based on sodium alginate for synergistic chemotherapy-immunotherapy in hepatocellular carcinoma. (**A**) Preparation of BEA-C=N-DOX-M and its synergistic chemo-immunotherapy for hepatocellular carcinoma. (**B**) Schematic of chemo-immunotherapy in Hepa1-6 tumor-bearing C57BL/6J mice. (**C**) Tumor volume change curve of Hepa1-6 tumor-bearing C57BL/6J mice after different treatments. (**D**) Flow cytometry quantification of the maturation rate of dendritic cells in tumor tissues after different treatments. (**E**) Proportion of M1 macrophages in tumor tissues after different treatments. (**F**) Proportion of M2 macrophages in tumor tissues after different treatments [117]. Copyright 2023, Wiley-VCH.

### *6.3. Theranostics*

Integration of diagnosis and therapy is an emerging field that combines diagnostic and therapeutic functions into a single platform. DDSs are ideal for this purpose, as they not only deliver drugs but also enable imaging functions for monitoring treatment efficacy.

#### 6.3.1. Fluorescence Imaging Integrated with Chemotherapy

Fluorescence imaging is a powerful tumor visualization tool that allows real-time monitoring of treatment responses. NPs with fluorescent properties can be designed to co-deliver chemotherapy drugs while also providing imaging functionality. These NPs enable non-invasive tracking of drug distribution within the body, thereby facilitating precise drug delivery and assessment of therapeutic outcomes.

Tang and colleagues developed a photodynamic-enhanced chemotherapy strategy (PECC) based on aggregation-induced emission (AIE) materials, aimed at improving chemotherapy efficacy for bladder cancer while reducing the toxic side effects of cisplatin [118]. The study utilized biocompatible and biodegradable bovine serum albumin (BSA) as a nanocarrier, loaded with AIE molecule BITT and cisplatin (IV) prodrug Pt-2COOH (DSP), to construct a second NIR fluorescence imaging (NIR-II FL)-guided PECC drug for bladder cancer treatment. The results showed that BITT facilitated the binding of BSA with cisplatin (IV) to self-assemble into stable NPs without the need for additional crosslinkers. Due to the excellent properties of the BITT aggregates, the drug exhibited synergistic effects in NIR-II fluorescence emission, ROS generation, and photothermal conversion efficiency. In vitro and in vivo experiments demonstrated that BITT@BSA–DSP NPs not only effectively visualized the tumor region but also significantly inhibited bladder tumor growth. This PECC strategy proved to be highly effective against various cancer cells. Therefore, this study not only provides an optimized strategy for reducing chemotherapy drug doses while achieving significant efficacy but also guides the clinical translation of AIE-based phototherapeutic diagnostic agents.

#### 6.3.2. Photoacoustic (PA) Imaging Integrated with Chemotherapy

PA imaging combines the high spatial resolution of US with the molecular specificity of optical imaging. NPs designed for PA imaging can absorb light and generate US signals for tumor detection and monitoring. By integrating chemotherapy drugs into these NPs, it is possible not only to diagnose cancer but also to provide concurrent treatment. This imaging technology enables real-time monitoring of drug accumulation at tumor sites and offers valuable feedback for optimizing therapeutic strategies.

Huang et al. reported a smart integrated therapeutic diagnostic nanoprobe (PEG/αCD25-Cy7/TMZ) for precise delivery of temozolomide (TMZ) for localized chemotherapy, while real-time tracking of regulatory T cells (Treg cells) in the TME using PA-fluorescence imaging (Figure 12) [119]. This nanoprobe carries TMZ and is encapsulated with the optical dye αCD25-Cy7, targeting Treg cells through a GSH-responsive DSPE-SS-$PEG_{2000}$. The probe enhances drug accumulation in the TME by extending circulation time, enabling precise localized chemotherapy. Cy7-based PA-fluorescence signals are used to monitor drug release, tumor growth, and changes in Treg cells, providing an effective way to assess immune responses. TEM analysis showed that the nanoprobe is uniform and spherical, with the outer shell being disrupted and aggregated under GSH influence (Figure 12A). TMZ in PEG/αCD25-Cy7/TMZ released less than 15% without GSH, but after the addition of 10 mM GSH, the release increased to 74%, reflecting the redox-responsive degradation of DSPE-SS-$PEG_{2000}$ (Figure 12B). After a single laser pulse exposure, intense PA signals were observed, confirming the nanoprobe's PA imaging capability (Figure 12C).

The therapeutic, imaging, and immune tracking effects of the nanoprobe were validated in a C57BL/6J mouse orthotopic GBM model. Fluorescence signal biodistribution was detected at various time points after intravenous injection of PBS, αCD25-Cy7, and PEG/αCD25-Cy7/TMZ. The results showed that the fluorescence signal in the tumor region gradually increased over time, indicating its accumulation in the tumor (Figure 12D). Photoacoustic computed tomography (PACT) experiments measured the accumulation of PEG/αCD25-Cy7/TMZ in the mouse body. The focus area, marked by a circle, showed stronger PA signals than surrounding regions, indicating that PEG/αCD25-Cy7/TMZ could accumulate in the tumor area (Figure 12E). Both fluorescence and PA imaging can provide precise guidance for subsequent chemotherapy, assisting both diagnosis and treatment.

In GBM, CD25CD4FoxP3 Treg cells promote tumor growth by suppressing immune responses. The study used dual-wavelength (532 and 770 nm) photoacoustic microscopy (PAM) to monitor Treg cell infiltration in GBM and assess immune responses (Figure 12F). The results showed that Treg cell infiltration increased 1.5 times after chemotherapy, while injection of indoleamine-2,3-dioxygenase (IDO) inhibitors gradually reduced Treg cell infiltration (Figure 12G). Tracking the dynamic distribution of Treg cells to monitor immune responses and their combination with IDO inhibitors provides important guidance for GBM treatment and prognosis evaluation.

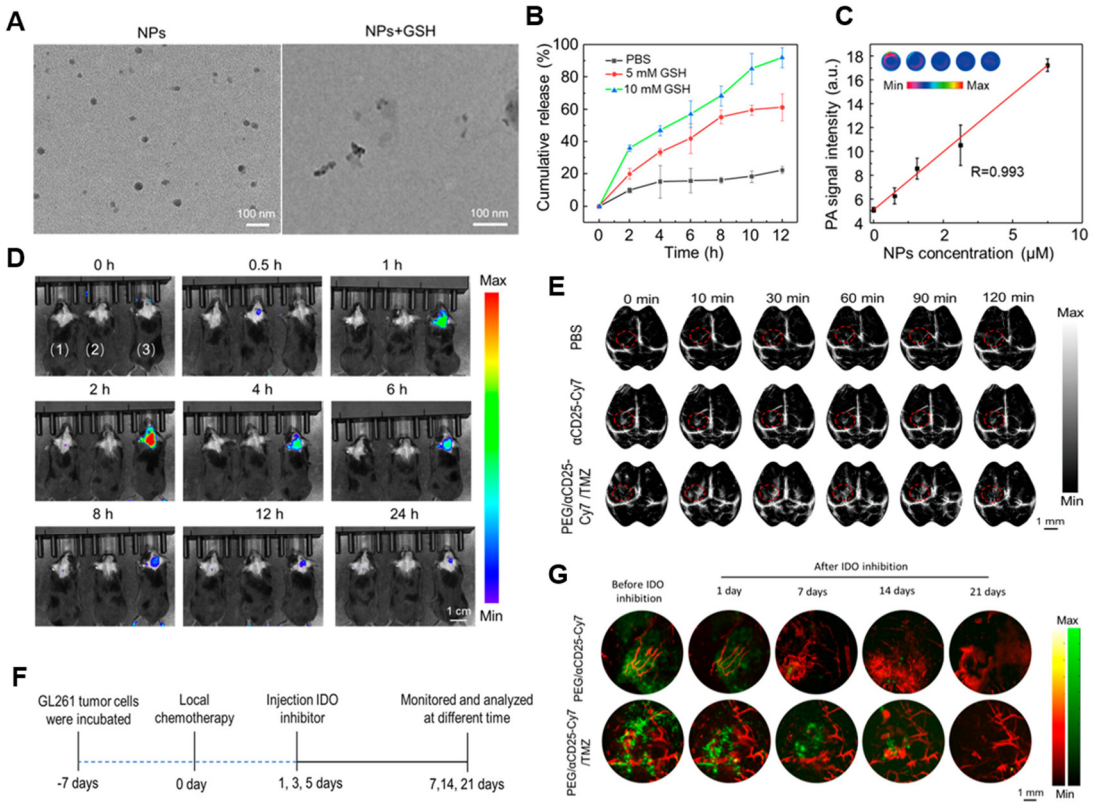


**Figure 12.** TME activated PA-fluorescence bimodal nanoprobe for chemo-immunotherapy and immune response tracing of GBM. (**A**) TEM images of PEG/αCD25-Cy7/TMZ and PEG/αCD25-Cy7/TMZ treated with GSH. (**B**) Release of TMZ from PEG/αCD25-Cy7/TMZ after treatment with PBS and GSH. (**C**) PA signals of PEG/αCD25-Cy7/TMZ at different concentrations under laser irradiation. (**D**) In vivo fluorescence imaging of orthotopic GBM mice treated with PBS, αCD25-Cy7, and PEG/αCD25-Cy7/TMZ at different time intervals. (**E**) In vivo PACT of orthotopic GBM mice after treatment with PEG/αCD25-Cy7/TMZ at different time intervals. (**F**) Experimental schematic design for visualizing Treg cells infiltration in vivo after chemotherapy combined with IDO inhibitor. (**G**) Monitoring Treg cells infiltration using PA imaging [119]. Copyright 2023, American Chemical Society.

### 6.3.3. Magnetic Resonance Imaging Integrated with Chemotherapy

Magnetic resonance imaging (MRI) is a widely used imaging technique for cancer diagnosis due to its high resolution and soft tissue contrast. NPs combined with magnetic materials can serve as MRI contrast agents while also delivering chemotherapy drugs to tumor sites. This dual function not only enables detailed imaging of tumor location and size but also allows for real-time tracking of drug delivery. The combination of MRI and DDSs enhances the precision of chemotherapy, enabling personalized treatment while minimizing side effects.

MRI is superior to other diagnostic methods in preoperative evaluation, and cisplatin-based chemotherapy is the preferred treatment for cancer. Wang and colleagues combined these two rapidly developing fields by using the metal coordination bonds formed between cisplatin prodrug (Pt-COOH), $Fe^{3+}$, and natural polyphenol (gossypol) to construct a composite nanocarrier (HA@PFG NPs) [120]. In the acidic TME, HA@PFG NPs release $Fe^{3+}$, Pt-COOH, and gossypol. The Pt-COOH and cisplatin-based chemotherapy, along with the pro-apoptotic effects of gossypol, create a synergistic effect that enhances tumor cell killing. Additionally, the release of $Fe^{3+}$ promotes ferroptosis and enables MRI imaging of ovarian cancer. After being coated with HA, HA@PFG NPs exhibit specific targeting, strong penetration, controllable drug release properties, and outstanding in vitro and in vivo imaging contrast. TEM images show that HA@PFG NPs are spherical with a particle size of 105.47 ± 0.28 nm (Figure 13A). HA@PFG NPs are relatively stable at pH 7.4, but under acidic conditions, the release rate of gossypol significantly increases, with approximately 80% being released within 72 h (Figure 13B). At low pH, the release of $Fe^{3+}$ from the disrupted NPs significantly enhances the T1-weighted MRI signal, indicating their potential for in vivo T1-weighted MRI (Figure 13C). Further in vivo experiments in mice confirmed the tumor accumulation and MRI capability of HA@PFG NPs. Six hours after intravenous injection of HA@PFG NPs, enhanced T1-weighted MRI contrast was observed in the tumor region, demonstrating their potential for in vivo tumor MRI (Figure 13D). A patient-derived xenograft (PDX) mouse model was established to evaluate the in vivo

therapeutic effect of HA@PFG NPs (Figure 13E). The results showed that HA@PFG NPs significantly inhibited tumor growth in mice (Figure 13F,G). This work combines MRI with cisplatin-based chemotherapy, offering great potential for the diagnosis and synergistic treatment of ovarian cancer.

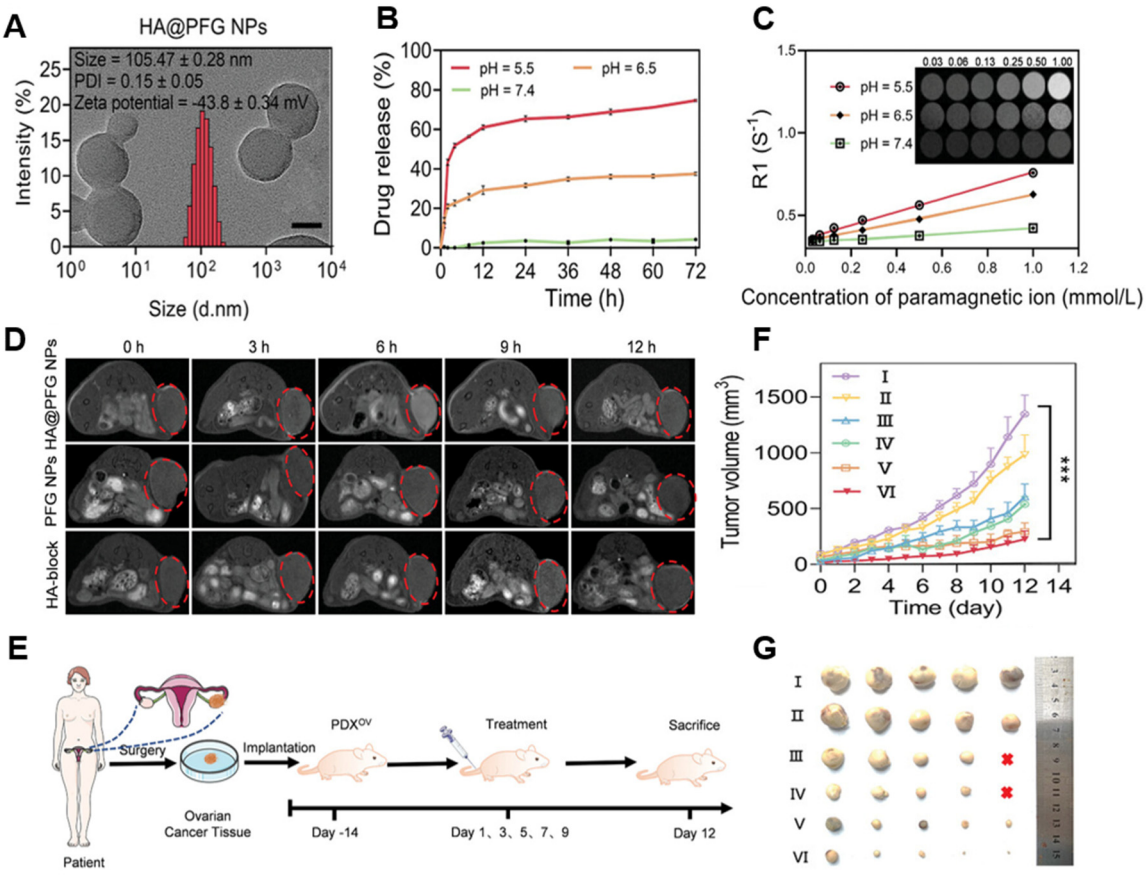


**Figure 13.** Efficient synergistic chemotherapy and MRI targeted ovarian cancer treatment using HA-coated coordination polymer NPs. (**A**) TEM image of HA@PFG NPs. (**B**) Drug release behavior of HA@PFG. (**C**) T1-weighted MRI and relaxation rates of HA@PFG NPs. (**D**) T1-weighted MRI images of PDX tumor-bearing mice at different time points after intravenous injection of different materials. (**E**) Schematic illustration of PDX model establishment and in vivo treatment process. (**F**) Tumor growth curves of mice after different treatments. (**G**) Tumor images of mice after different treatments [120]. Copyright 2024, Wiley-VCH.

## 7. Challenges and Future Perspectives

### *7.1. Challenges in DDSs Application*

DDSs hold significant potential for advancing synergistic therapies, yet their clinical translation faces several hurdles. One of the primary challenges is the increased complexity that arises when integrating multiple components into a single system [14,121]. For example, the development of core-shell NPs that combine imaging agents like $Fe_3O_4$ (for MRI) with therapeutic payloads such as doxorubicin requires precise control over each layer's assembly to maintain both stability and functionality [122,123]. This intricate design often leads to substantial manufacturing challenges, as batch-to-batch variability can reach up to 30%, making large-scale production difficult and inconsistent.

Another major concern is the risk of immune reactions. Multifunctional NPs may unintentionally trigger immune responses that compromise their effectiveness and safety [21,35]. For instance, cationic lipid-based carriers, like LNPs, can activate the complement system, which may result in hypersensitivity reactions [124]. In a Phase I trial, 20% of patients treated with PEGylated liposomes developed anti-PEG antibodies, which caused accelerated clearance of subsequent doses from the bloodstream. Additionally, targeting ligands used in antibody-conjugated NPs (such as anti-HER2 liposomes) can provoke the formation of neutralizing antibodies. Preclinical studies have shown that repeated administration of trastuzumab-decorated NPs led to a 50% reduction in targeting efficiency due to immune recognition, undermining their therapeutic potential [31,125].

Regulatory approval poses another significant obstacle for multifunctional DDSs. Regulatory agencies like the FDA and european medicines agency (EMA) require rigorous validation of each component within a multifunctional system, which involves detailed safety profiling and combinatorial testing [126]. Each individual element, such as the polymer, targeting ligand, or drug, must be carefully assessed for toxicity, and their interactions must be evaluated to ensure the overall safety of the system. A notable example is the withdrawal of Resovist® (an iron oxide MRI contrast agent) due to its long-term accumulation in organs, underscoring the importance of conducting comprehensive biodistribution studies [127]. Moreover, the lack of standardized characterization protocols for hybrid systems, such as exosome-lipid hybrids, further complicates the regulatory approval process. Variability in the surface protein composition of such systems (sometimes deviating by more than 15% between batches) makes it difficult to meet regulatory requirements, hindering the widespread adoption of multifunctional DDSs [32,40].

### *7.2. The Targeting Efficiency of DDSs*

Despite the promising advancements in DDSs, especially tumor-targeting DDSs designed via ligand-receptor interactions, antibody-drug conjugates, and mixed targeting strategies, the accumulation efficacy of DDSs in tumor tissues still limited due to tumor heterogeneity [128,129]. Additionally, NPs can disrupt cell membrane function and alter cellular processes post-internalization, potentially hindering their absorption [130]. Moreover, once in the bloodstream, NPs may become coated by biomacromolecules, leading to changes in their properties that can adversely affect therapeutic outcomes.

Moving forward, there is an urgent need to enhance surface targeting modifications and functionalization strategies of DDSs to improve the identification of specific lesions [107]. Additionally, exploring new stimulus-responsive DDSs could significantly bolster their stability and effectiveness in vivo. Designing biodegradable DDSs that can integrate multiple targeting strategies with intelligent release mechanisms holds great promise for improving the efficacy and safety of cancer chemotherapy [131]. Furthermore, the combination of advanced imaging technologies with dynamic monitoring will enable real-time tracking of nanoparticle distribution and efficacy, facilitating the optimization of drug delivery protocols and ultimately improving treatment outcomes [92]. The approval process for DDSs involves preclinical studies, clinical trials, market application, and post-market surveillance. Key regulatory challenges include their multicomponent interactions, drug release mechanisms, cytotoxicity, complexity of manufacture process, and the lack of specialized guidelines in existing regulatory frameworks.

### *7.3. DDSs for Personalized Therapy*

As personalized medicine gains traction, DDSs are emerging as crucial tools for achieving precision in treatment. These systems allow for the customization of drug formulations based on a patient's genetic and phenotypic characteristics, optimizing therapeutic effectiveness while reducing adverse effects [92,130]. Recent advancements in genomics and proteomics facilitate the identification of specific biomarkers linked to various cancer types, enabling the design of NPs that can accurately target a patient's unique pathological state [129]. This tailored approach enhances the effectiveness of drugs against specific cancer cells, leading to improved treatment outcomes and minimized side effects during chemotherapy [132].

Jia et al. developed a microchip-based personalized nanodrug delivery platform using patient-derived tumor extracellular vesicles (PT-EVs) [133]. The microchip design features a micropillar array made from polydimethylsiloxane (PDMS), effectively capturing microspheres of various sizes and functionalized magnetic beads (MBs). It integrates multiple functions such as capture, enrichment, drug loading, and elution of PT-EVs. This platform allows for the customization of personalized nanodrugs based on PT-EVs and their use to treat matched homologous tumors, providing strong support for personalized and precision medicine. Minko et al. proposed and validated a personalized ovarian cancer treatment approach based on nanotechnology, tailored to the genetic profile of the patient's tumor [134]. By analyzing the expression of predefined genes and proteins in each patient sample, a complex nanocarrier system containing drugs/siRNA/targeted peptides is selected, and in vivo testing is conducted using a murine cancer model, with cancer cells isolated from each patient's tumor. The study provides an innovative approach to personalized ovarian cancer treatment and evaluates the potential benefits and prospects of this method.

Implementing personalized therapy through DDSs also necessitates the integration of advanced bioinformatics and big data analytics, with artificial intelligence (AI) playing a key role in the design process. AI-driven design predicts optimal nanoparticle parameters (e.g., size, surface charge) for tumor penetration, while 3D-printed scaffolds enable patient-specific drug release profiles. For instance, AI-designed dendrimers targeting

EGFRvIII mutations improved survival in glioblastoma models [107,135–137]. By collecting and analyzing patient clinical data, imaging profiles, and treatment responses, strategies for nanoparticle design and administration can be continuously refined [107]. AI algorithms and machine learning techniques can predict the most effective drug delivery plans, further enhancing the precision and efficiency of treatment [131]. Innovations in nanoparticle technology are poised to significantly enhance the efficacy and safety of cancer chemotherapy, ushering in a new era of personalized and precise cancer treatment [138].

### *7.4. Clinical Translation Prospects of DDSs*

Currently, several chemotherapy DDSs have entered the clinical translation stage, such as Doxil® and Abraxane®, but the number is very limited. In the future, to enable widespread clinical translation of DDSs, several challenges still need to be overcome. The first challenge is the variability in research models. Numerous studies have investigated DDSs for chemotherapy, primarily using mouse models. However, significant differences between these animal models and human patients pose challenges for clinical translation. A notable example is the EPR effect, observed in animals but rarely demonstrated in clinical settings [138].

The safety of DDSs in humans remains unverified, as drug dosages effective in animal studies may lead to adverse effects when applied to humans. Factors such as the absorption, distribution, metabolism, and elimination of NPs can significantly impact their efficacy and safety, with potential organ accumulation resulting in varying side effects [132]. Thus, in vivo distribution and pharmacokinetics must be considered in the design and clinical development of these systems, alongside the pursuit of new biodegradable options.

Additionally, preclinical studies often involve small-scale nanoparticle production, which can lead to issues like low yields and variability between batches during mass production, ultimately affecting stability and functionality. Standardizing and scaling production processes is crucial for the successful clinical application of nanomedicine [139]. Economic considerations, such as treatment costs for patients, also play a critical role [61]. Regulatory approval represents another vital step in bringing nanomedicine to clinical practice. Current regulatory standards are still being refined, necessitating clear guidelines to ensure safety and efficacy. Future efforts should prioritize expediting the approval of new nanomedicines while adhering to regulatory requirements, fostering their broader application [130]. As nanomedicine continues to advance, DDSs are expected to play an increasingly significant role in cancer chemotherapy, overcoming current clinical challenges and offering new hope for cancer patients [138].

## Author Contributions

S.Y., J.L., X.R. and L.Y. wrote the manuscript, S.Y., J.L. and X.R. illustrated the figures. All authors have read and agreed to the published version of the manuscript.

## Funding

This research received no external funding.

## Institutional Review Board Statement

This study does not involve humans or animals.

## Informed Consent Statement

This study does not involve humans.

## Data Availability Statement

No new data were generated or analyzed in this study.

## Acknowledgments

Because of space limitations, we sincerely apology to colleagues in the field whose work was not mentioned.

## Conflicts of Interest

The authors declare no competing interests.

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