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REVIEW

# Self-Assembled Nanoparticles: Overcoming Limitations of Conventional Nanomedicines for Enhanced Tumor Therapy

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**Abstract:** The high mortality rate associated with cancer presents a significant clinical challenge, necessitating breakthroughs to overcome the limitations of traditional therapies, which often entail substantial side effects, as well as the complexities associated with existing nanodelivery systems (NDDS) that lack adequate targeting capabilities. Self-assembled nanoparticles (SANs) form spontaneously through weak interactions between drugs and functional molecules, such as hydrogen bonds and hydrophobic interactions. They exhibit revolutionary advantages, including ultra-high drug loading capacity, stimulus responsiveness, precise drug release, self-driven targeting capabilities, and a straightforward preparation process that does not require complex carrier synthesis. This review systematically summarizes the latest advancements in SANs for tumor therapy, emphasizing their molecular design principles and mainstream preparation strategies, while detailing their efficacy in multi-modal synergistic therapies, including chemotherapy, photodynamic/photothermal therapy, immunotherapy, and gene therapy. The technology of SANs establishes a robust foundation for the development of highly efficient and low-toxicity anti-cancer strategies, demonstrating significant potential to offer a transformative new paradigm for clinical precision therapy. We believe that the continued evolution of SANs holds great promise for clinical translation, potentially offering transformative solutions for personalized oncology in the near future.

**keywords:** self-assembled nanoparticles, tumor therapy, molecular design, non-covalent interactions, nanodrug delivery system

## Introduction

Currently, despite continuous advancements in the field of medicine, the high mutability of cancer cells has led to a sustained increase in overall cancer incidence rates and persistently high mortality rates, severely impacting global human health. Common treatment methods currently include surgery, chemotherapy, and radiotherapy, but these approaches often carry significant side effects, necessitating the development of safer and more effective treatment strategies.[1–5]

Nanodrug delivery systems (NDDS) offer a new approach to addressing the limitations of traditional therapies by encapsulating drugs within nanoscale carriers, demonstrating potential to enhance drug stability, bioavailability, and targeting. However, traditional NDDS face challenges such as complex preparation processes, risks related to biocompatibility and immunogenicity, scalability and cost issues, and limitations in targeted delivery efficiency.[6–8]

To overcome the limitations of existing NDDS, self-assembled nanoparticles (SANs) based on intermolecular weak interactions have emerged as a highly promising strategy in recent years. SANs refer to drug molecules or drugs combined with other functional molecules, such as carrier materials, targeting ligands, or responsive elements, which spontaneously aggregate through intermolecular noncovalent interactions like hydrogen bonds, π-π stacking, hydrophobic interactions, or electrostatic interactions to form ordered nanostructures. For instance, in the crystallization-driven self-assembly of homopolymers, the synergistic action of van der Waals and electrostatic forces precisely regulates the morphological evolution of hexagonal nanosheets, profoundly revealing the central role of molecular design and

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noncovalent interactions in self-assembly processes.[9] In the self-assembly of camptothecin and antisense DNA amphiphilic molecules, hydrophobic interactions and π-π stacking synergistically complete the entire process from driving hydrophobic collapse nucleation to consolidating internal structural stability.[10]

This property, where the function of the assembly is directly determined by its molecular structure, endows self-assembled nanodelivery systems with advantages such as high drug loading capacity, low toxicity, sustained release, high stability, targeted delivery, and simple preparation methods.[11–14] This integrated "structure-self-assembly-function" design philosophy was perfectly demonstrated in a doxorubicin (DOX) prodrug study: by precisely controlling the length of the hydrophobic fatty acid chain (eg, C16) in the prodrug molecule, a highly efficient nanocarrier system was successfully constructed that remains stable in the bloodstream while rapidly releasing the drug in response to high concentrations of glutathione within tumor cells.[15]

In the construction of SANs, the rational selection of preparation methods is crucial for regulating nanoparticle size, drug-loading capacity, and response characteristics. Commonly used preparation strategies include template-assisted methods, solvent-driven approaches, microfluidic techniques, and emulsification methods. These methods not only facilitate the controlled self-assembly of nanostructures but also lay the foundation for their subsequent large-scale production.

Currently, SANs have demonstrated significant therapeutic effects in tumor treatment, antibacterial, and anti-infective applications. This paper aims to systematically review the latest research progress of SANs in tumor treatment. We will delve into their molecular design principles, focus on analyzing the key non-covalent interactions driving self-assembly and their regulatory mechanisms, detail mainstream preparation strategies, and comprehensively review their application examples and synergistic effects in tumor treatment modalities such as chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), immunotherapy, and gene therapy. Finally, we will discuss the current challenges and outlook for future development directions.

# Design Principles of Self-Assembled Nanoparticles

## Molecular Interactions

The formation of SANs is essentially a spontaneous process driven and balanced by the synergistic interaction of various noncovalent interactions, such as hydrophobic interactions, hydrogen bonds, π-π stacking, electrostatic interactions, and van der Waals forces. Under thermodynamic driving, these forces precisely regulate the recognition, orientation, and ordered arrangement of molecular building blocks, not only determining whether nanoparticles can spontaneously form and their core structural characteristics—such as morphology, size, and hierarchical order—but also profoundly influencing their stability and stimulus responsiveness, thereby determining their ultimate functional expression. It is precisely these relatively weak but highly synergistic and dynamically characteristic non-covalent bonds that endow self-assembly technology with the unique ability to construct complex, precise, and intelligent nanostructures. Therefore, understanding and manipulating these non-covalent interactions constitutes the core foundational principle for designing functionalized self-assembled nanostructures.

Hydrophobic interactions refer to the tendency of nonpolar molecules or groups to aggregate in aqueous environments, a phenomenon driven by the increase in entropy resulting from structural changes in water molecules near hydrophobic surfaces. These interactions play a crucial role in processes such as protein folding and micelle formation.[16] Hydrophobic interactions are not only ubiquitous among nonpolar substances but also profoundly influence various interfacial phenomena. They serve as a key factor in regulating intermolecular recognition, driving the formation of self-assembled structures—such as nanoparticles and micelles—and maintaining their stability. During self-assembly, hydrophobic molecules or molecular segments tend to aggregate to minimize contact with water, thereby promoting the ordered arrangement of molecules and the formation of structures.[17] This interaction is particularly critical for the self-assembly of biomolecules, including peptides, proteins, and lipids, as it facilitates the creation of biocompatible and functional nanostructures. For instance, hydrophobic interactions drive the entropically favorable tight binding between the aromatic ring of ferulic acid and the Phe/Leu/Pro residues of casein peptides, leading to an increased β-sheet content and a 70% reduction in particle size while encapsulating bitter sites within the core. This process achieves multifunctionality in self-assembly, including bitterness masking and digestive timing regulation.[18] Furthermore, hydrophobic interactions can regulate nanoparticle self-assembly; researchers have successfully assembled gold nanoparticles into three-dimensional clusters and confirmed the dominant role of hydrophobic interactions in this process through theoretical models and experiments.[19]

Hydrogen bonds represent the strongest and most directional noncovalent interactions in water. Although their nature involves multiple contributions, such as electrostatic forces, polarization, and weak charge transfer, they are distinctly classified as noncovalent interactions in chemical terminology. The ionic structure of water causes the hydrogen atoms in O−H bonds to carry a greater positive charge, generating an electric field at interfaces, such as the surfaces of water droplets or when in contact with hydrophobic media. This phenomenon is crucial for understanding water's behavior in chemistry, biology, and materials science.[20,21] Hydrogen bonds facilitate not only molecular recognition but also the self-assembly of complex structures, which have potential applications in catalysis and materials science. By designing building blocks with specific hydrogen bond sites, the self-assembly process can be controlled to yield ring-shaped, linear, or capsule-shaped structures.[22] Researchers have investigated hydrogen bond-induced polymer-grafted nanoparticles (PGNPs), where hydrogen bonds serve as the key driving force for PGNP self-assembly. The strength and dynamic properties of these bonds render the assembly process reversible: hydrogen bonds weaken at elevated temperatures, leading to dissociation, and reform at lower temperatures, resulting in particle aggregation.[23]

Van der Waals forces represent a prevalent form of non-covalent interaction in molecules and materials, significantly influencing their structure, stability, dynamics, and functionality. These forces play a crucial role in the self-assembly of nanomaterials and drug delivery systems, impacting the self-assembly process and aiding in the stabilization of nanoparticle structures. In superfluid helium environments, Van der Waals forces are markedly enhanced, dominating the self-assembly process of nanoparticles. They guide gold atoms to preferentially adsorb at specific binding sites on molecular templates, thereby determining the spatial arrangement and assembly structure of nanoparticles.[24] Furthermore, Van der Waals forces are instrumental in the self-assembly of quasi-two-dimensional graphene and quasi-one-dimensional nanofibrillated cellulose hybrid interfaces, facilitating the binding of nanoparticles at specific sites on the template and controlling the structure and size of the assembly. Additionally, these forces can functionalize nanomaterials through non-covalent interactions, thereby enhancing their mechanical, electrical, and thermal properties and expanding their application potential.[25]

Electrostatic interactions arise from fixed or induced charges on particle surfaces, which are a result of external electric fields. In non-polar media, charges are generated through electrostriction or ionization, while in polar media, they primarily arise from the adsorption of ions, ionic surfactants, and polyelectrolytes, as well as the dissociation of surface ionic groups. The Coulomb forces produced by these surface charges serve as the fundamental mechanism driving the attraction between oppositely charged particles and the repulsion of similarly charged ones, exerting a decisive influence on the structure and dynamics of the self-assembly process. Furthermore, electrostatic interactions not only facilitate the initial binding of building blocks during self-assembly but also precisely regulate the structure, size, and shape of assemblies through synergistic interactions with other forces, such as π-π stacking and hydrogen bonding. These interactions are critically important in self-assembly technologies, particularly in the context of DNA-nanoparticle (NP) self-assembly. By manipulating cation concentration and temperature, the bonding efficiency can be significantly enhanced.[26]

π-π stacking, as a key non-covalent interaction, plays a foundational role in both natural and artificially synthesized molecular structures. This interaction is highly sensitive to the spatial orientation of participating molecules, exhibiting significant directional anisotropy, which is a core factor in regulating molecular self-assembly pathways and structural stability.[27] Researchers ingeniously utilized π-π stacking as the core driving force to successfully construct π-1, a porous supramolecular framework based on a Zn(II) mononuclear complex, through self-assembly. Single-crystal X-ray diffraction analysis confirmed that the formation and stability of this three-dimensional framework primarily depend on precisely localized intermolecular π-π stacking interactions. The rigid three-dimensional porous skeleton stabilized by π-π stacking contains one-dimensional channels, with suspended thiol groups modified within the channels. This unique structure enables π-1 to efficiently capture $Hg^{2}$+ ions within the channels, demonstrating excellent mercury removal performance.[28]

The self-assembly process is fundamentally a result of a dynamic equilibrium among various non-covalent interactions. Quinoa protein effectively encapsulates quercetin, curcumin, luteolin, and resveratrol through hydrophobic interactions and hydrogen bonds, leading to the formation of stable nanomicelles.[29] The interplay of electrostatic interactions and π-π stacking facilitates the self-assembly of collagen into nanospheres, offering new insights for the development of functional materials.[30] Van der Waals forces and cation-π interactions are crucial in self-assembly, with van der Waals forces providing the foundational stability, while cation-π interactions significantly enhance intermolecular packing, resulting in self-assembled molecules with high thermal stability in aqueous environments.[31] PTX-PBA,

a boronic acid-modified paclitaxel derivative, forms reversible dynamic borate ester bonds with fructose (Fru), generating PTX-PBA-Fru complexes. Under the influence of hydrogen bonds, π–π stacking, and van der Waals forces, these complexes self-assemble into PTX-PBA-Fru nanoparticles,[32] as illustrated in Figure 1.

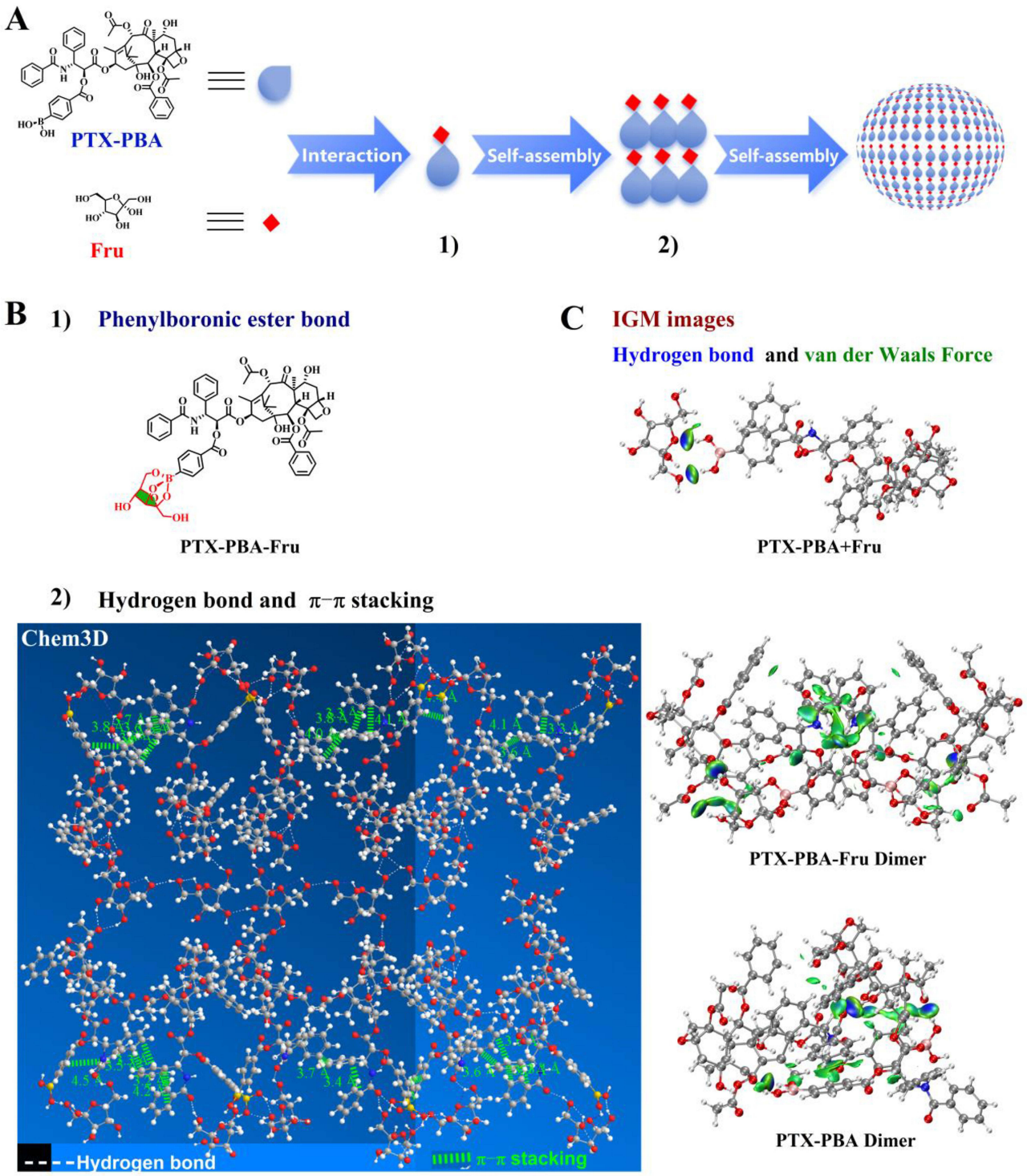


**Figure 1** Mechanism of self-assembly of PTX-PBA-Fru NPs. (**A**) Schematic representation of the self-assembly process of PTX-PBA-Fru NPs. 1) Interactions between PTX-PDA and Fru 2) Self-Assembly of PTX-PDA and Fru (**B**) Driving forces behind self-assembly: 1) The pH-responsive dynamic borate ester bond (verified by TLC and $^{11}$B-NMR); 2) Hydrogen bonds formed between PTX-PBA and PTX-PBA/Fru, as well as the π-π interactions between PTX-PBA molecules, simulated using Chem 3D. (**C**) Weak interactions among PTX-PBA +Fru, PTX-PBA-Fru dimer, and PTX-PBA dimer were analyzed using the Independent Gradient Model (IGM). Reproduced with permission.[32] Copyright 2025 Elsevier.

## Mechanisms of Molecular Interactions in the Regulation of Structural Dynamics

External environmental factors (including temperature, pressure, solvent type, pH value, and ionic strength) have a significant impact on noncovalent forces. An increase in temperature typically weakens van der Waals forces and electrostatic forces, leading to hydrogen bond breakage and affecting the flexibility and mobility of polymer chains. High pressure causes molecules to arrange more closely, enhancing van der Waals forces and electrostatic forces. The polarity of the solvent affects intermolecular interactions; polar solvents weaken hydrogen bonds and electrostatic forces, while non-polar solvents promote van der Waals forces and hydrophobic interactions. Changes in pH and ionic strength alter the ionization state of charged groups and the intensity of electrostatic forces, thereby influencing intermolecular interactions.[33] The combined effects of these factors can significantly alter the strength and behavior of non-covalent bonds.

Researchers have investigated the effects of temperature, pH, and ion concentration on the self-assembly properties of acid-soluble collagen extracted from sheepskin. Increasing the temperature from 25°C to 37°C accelerates self-assembly; however, temperatures exceeding 37°C lead to collagen denaturation due to excessive heat, thereby inhibiting fiber formation. pH values near the isoelectric point of acid-soluble collagen (ASC) promote self-assembly, as the net charge of the molecules is neutral at this point, which weakens electrostatic repulsion and enhances intermolecular interactions and assembly. Appropriate ion concentrations can enhance the assembly rate of ASC by shielding the surface charges of collagen, thereby reducing electrostatic repulsion and promoting aggregation.[34] Yosuke et al investigated the self-assembly process of the amphiphilic 4-aminoquinoline (4-AQ)-tetraphenylethylene conjugate. This conjugate demonstrates a gradual self-assembly behavior at room temperature, with 4-AQ monomers responding within the weakly acidic to neutral pH range, exhibiting different self-assembly time scales at varying pH levels. At pH 5.5, the 4-AQ monomers are diprotonated, resulting in strong electrostatic repulsion, which necessitates an increase in NaCl concentration for effective shielding. Conversely, at pH 7.4, the monomers are monoprotated, leading to weak electrostatic repulsion and facilitating self-assembly.[35]

## Influence of Molecular Interactions on Nanostructure

Noncovalent interactions significantly influence the nanostructure of complexes, promoting their expansion from one-dimensional chain-like structures to two-dimensional networks and three-dimensional supramolecular networks, thereby enhancing the stability and complexity of crystal structures. Additionally, these interactions affect the thermal stability of complexes, altering their decomposition temperature and process during thermal analysis.[36] Researchers prepared composite nanoparticles of deamidated gliadin (DG) and TA. Studies showed that non-covalent interactions promoted the formation of nanoparticle networks, increased the viscosity and elasticity of the emulsion, and enhanced nanoparticle stability.[37] DNA nanostructures can be successfully modified with DNA aptamers through non-covalent interactions to achieve targeted functionalization. The modified DNA nanostructures demonstrated good biocompatibility and targeting in cell uptake experiments.[38] The synergistic effects of multiple non-covalent interactions can achieve multi-level assembly of molecules from the microscopic to the macroscopic scale. For example, hydrogen bonds first form molecular dimers or oligomers, which are then further assembled into larger supramolecular polymers or hierarchical structures through π-π stacking or van der Waals forces, thereby endowing the nanostructures with more complex morphologies and higher orderliness.

In summary, noncovalent interactions are crucial in regulating molecular self-assembly, nanostructure formation, and material stability, demonstrating complex and diverse functionalities and regulatory mechanisms. To elucidate these relationships clearly, the functionalities and regulatory mechanisms of the primary types of noncovalent interactions are compared below (see Table 1).

**Table 1** Comparison of Functions and Regulatory Mechanisms of Non-Covalent Interactions

| Molecular Force | Driving Mechanism | Nanostructure Effects | Co-Assembly Case | Ref |
|---|---|---|---|---|
| Hydrogen bond | Electrostatic dominance, polarization contribution | Constructs precise rings/ capsules; confers reversibility | Synergistic driving of collagen → nanospheres with electrostatic forces | [29] |
| Van der Waals force | Transient dipole-induced dipole | Enhanced mechanical/thermal properties; guided template positioning for assembly | Synergy with cation-π → highly thermally stable assemblies | [31] |
| Electrostatic force | Coulomb attraction, repulsion | Tuning size/form; realizing long-range ordered structures | Synergy with π-π stacking → control of supramolecular frameworks | [30] |
| π-π stacking | Directed coupling of aromatic ring exotic electron clouds | Construction of porous channels; exposure of functional sites | Synergy with hydrogen bonding → multistage supramolecular polymerization | [32] |
| Hydrophobic force | Entropy-driven | Forms micelles/vesicles; enhances thermal stability; promotes biocompatible structures | Synergistic encapsulation of polyphenols (quercetin, etc.) with hydrogen bonding → stabilization of nanomicelles | [29] |

# Preparation of Self-Assembled Nanoparticles

## Anti-Solvent Precipitation

The antisolvent precipitation method is a commonly used technique for preparing SANs. Its core principle involves adding an antisolvent to the solvent system, causing the solubility of the drug molecules to sharply decrease, thereby precipitating and forming nanoparticles. After nanoparticle formation, impurities are typically removed through methods such as dialysis and ultrafiltration purification. This method offers advantages such as simple and rapid preparation, low preparation temperature, ease of controlling nanoparticle size, and energy efficiency. However, due to the difficulty in uniformly controlling the precipitation rate, the reproducibility of the preparation is poor.[39,40] Huang et al dissolved Glycosylated Stearyl Sulfate Ferulic acid (GSSF) and Docosahexaenoic Acid (DHA) in DMSO, slowly added it to water, stirred, and dialyzed to obtain DHA@GSSF nanoparticles, which were encapsulated in A549 cell membranes and exhibited excellent tumor suppression and anti-tumor metastasis capabilities.[41] Zuo et al prepared Rg3-Rb1 NPs via Rg3/Rb1 co-mixing (DMSO/water system), dialysis, and freeze-drying. Compared to free ginsenosides, Rg3-Rb1 NPs exhibited stronger antitumor and anti-invasive effects on TNBC cells,[42] as shown in Figure 2.

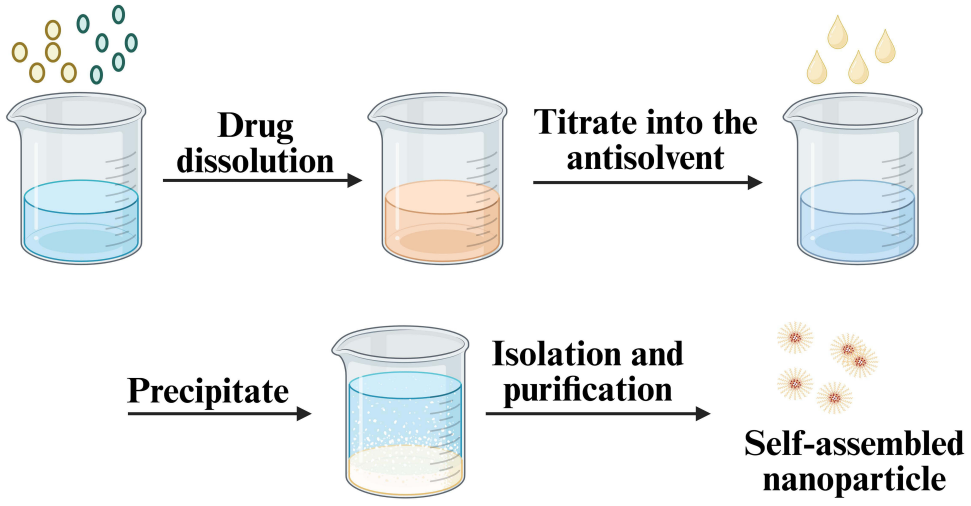


**Figure 2** Antisolvent precipitation method for preparing self-assembled nanoparticles (figure was created in https://BioRender.com).

## Template-Assisted Method

Template-assisted methods are a technique for preparing self-assembled nanostructures (SANs) by using template materials to guide the self-assembly of drug molecules or nanomaterials into specific structures. These methods leverage the structural characteristics of templates (such as pores, shape, or surface properties) to direct the self-assembly process of drug molecules or nanomaterials. By selecting appropriate template materials (such as mesoporous silica, metal-organic frameworks, polymers, etc)., the size, morphology, and composition of nanodrugs can be precisely controlled.[43] Gong et al used human serum albumin (HSA) as a template, which contains abundant active groups and binds to calcium ions at a ratio of 1:2.32. Hydrogen peroxide was then added to obtain calcium peroxide nanoparticles ($CaO_2$–HSA), which exhibit excellent antitumor efficacy and biosafety.[44] Magneto-plasmonic nanoparticles ($Fe_3O_4$@Au core-shell structure) guided by an external magnetic field can be co-assembled via non-covalent forces and arranged in an ordered structure within the template,[45] as shown in Figure 3.

## Microfluidics

Microfluidic technology enables precise control of fluid behavior (such as laminar flow, turbulent flow, interfacial tension, etc.) within micron-scale channels, thereby achieving precise regulation of nanoparticle synthesis. In recent years, it has been widely applied in the preparation of SANs. Microfluidic technology can control the size, morphology, and distribution of nanoparticles by adjusting microfluidic parameters, making it suitable for large-scale production and reducing raw material waste. However, equipment costs and the establishment of standardized production processes remain challenges for the current application of microfluidic technology.[46–50] In nanoparticle preparation, Camptothecin (CPT) and PTX were dissolved in acetone via disulfide bonds to obtain a CPT-S-S-PTX acetone solution. This was injected at a constant flow rate into a microfluidic chip assembled with a coaxial nested structure, along with an aqueous solution containing 0.1% Pluronic® F-127 (external flow). By adjusting the flow ratio between the inner and outer streams and the drug concentration, the acetone-to-water phase migration process was driven, enabling the drugs to self-assemble into nanoparticles.[51]

## Supramolecular Self-Assembly

Supramolecular self-assembly refers to the aggregation of two or more molecules through weak intermolecular interactions (such as hydrogen bonds, van der Waals forces, π-π interactions, electrostatic interactions, etc.) to form supramolecular structures with specific structures and functions.[52–54] KASHAPOV et al achieved nanoparticle self-assembly under mild conditions through synergistic supramolecular interactions between RNA and cuprophane (including electrostatic and hydrophobic interactions).[55] SUN et al developed a nanomedicine preparation technology combining hydrogen bond-driven supramolecular self-assembly with reactive oxygen species (ROS)-responsive design. The core of this approach involves the spontaneous formation of nanoparticles through intermolecular hydrogen bonds between FEGCG and MPI, coupled with hydrophobic interactions of fluorinated chains, and the utilization of ROS sensitivity via a chlorobenzoyl chloride linker to achieve intelligent drug release.[56]

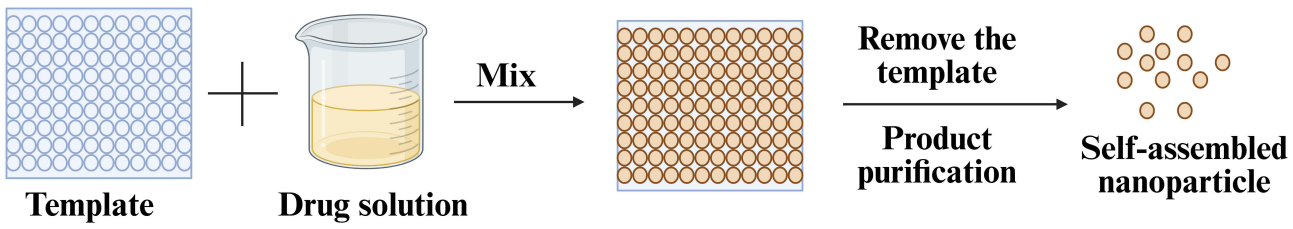


**Figure 3** Template-assisted preparation of self-assembled nanoparticles (figure was created in https://BioRender.com).


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## Emulsification Technology

Emulsification technology involves mixing two immiscible liquids (such as an oil phase and a water phase) to form a stable emulsion, thereby inducing the self-assembly of drug molecules or carrier materials. Emulsification technology is simple and efficient to prepare, but suffers from poor stability. Delamanid is a hydrophobic small-molecule drug whose hydrophobicity and crystallinity result in poor solubility in water. To improve its solubility and bioavailability, researchers employed emulsification for nanoencapsulation, dissolving it in a dichloromethane dispersion phase to obtain suitable nanoparticles.[57]

## Spray Drying Technology

Spray drying technology involves atomizing a liquid into small droplets and rapidly drying them into micron-sized particles (1–100 μm). It is suitable for industrial production and can process solutions or suspensions, with a yield typically below 70%. Nano-spray drying is a novel technology that uses vibrating screens and electrostatic collectors to prepare submicron or nanoscale particles (as low as 100 nm), with yields exceeding 90%, making it suitable for small-scale laboratory production.[58] However, there is a risk of thermal sensitivity. Using nano spray drying technology (Nano Spray Dryer), carrier-free dual-drug nanocrystal self-assembled microspheres were prepared, with nicotinamide riboside and resveratrol loaded into the microspheres for oral administration.[59]

## Ultrasound-Assisted Method

The ultrasound method is a commonly used technique for preparing SANs, based on the cavitation effect and mechanical stirring action of ultrasound to promote the mixing and self-assembly of drug molecules with carrier materials. However, it requires precise control of ultrasound intensity and has a limited scope of application. Zhu et al used calorimetric ultrasonic treatment to induce acoustic assembly and synthesize doxycycline nanoparticles (DoxyNPs). Compared to unmodified doxycycline, DoxyNPs exhibited selective toxicity toward cancer cells.[60]

## In vivo Self-Assembly

The core of in vivo SANs lies in utilizing specific physiological or pathological conditions within the body, such as enzymes, pH, reactive oxygen species, etc., to trigger the self-assembly process of nanomaterials, thereby achieving targeted drug delivery, controlled release, and therapeutic functions. However, there are issues such as complex design and dependence on external environments. Gao et al demonstrated that GNPs self-assemble into larger aggregates within immune cells through host-guest interactions. This self-assembly process not only reduces GNP exocytosis but also activates their photothermal properties through plasma coupling effects, enhancing drug targeting to tumor cells.[61] Researchers utilized bioorthogonal chemistry to develop an in vivo self-assembling protein degradation targeting chimera (PROTAC) technology, decomposing high-molecular-weight traditional PROTACs into two smaller drug-like precursors. These precursors can self-assemble into functional PROTACs through bioorthogonal reactions in vivo, enabling precise cancer therapy and addressing the limitations of traditional PROTACs.[62] In drug-resistant breast cancer cells, the peptide precursors Fmoc–FF–YP and NBD–FF–YP assemble into nanofibers under the action of the EYA (Eyes absent) tyrosine phosphatase, significantly enhancing the efficacy of DOX.[63]

# Emerging Designs and Intelligent Strategies

The core of stimulus-responsive self-assembly lies in utilizing specific signals from the tumor microenvironment (such as overexpressed enzymes) to trigger in situ drug assembly and functional transformation, thereby achieving precise drug enrichment and activation. A classic approach is enzyme-controlled cascade self-assembly: the system initially forms a stable nanoscale precursor (eg, micelle) in the bloodstream. Upon reaching the target site, specific enzymes cleave responsive peptide segments on the precursor, disrupting its initial stability and triggering morphological changes or the formation of larger-scale aggregates. For instance, in myocardial infarction treatment, amphiphilic peptide-polymer molecules initially self-assemble into approximately 15 nm micelles. Upon encountering MMP-2/9, enzymatic cleavage disrupts their amphiphilic equilibrium, leading to reassembly into micrometer-scale aggregates. This enables specific

**Table 2** Common Preparation Methods of Self-Assembled Nanoparticles, Their Advantages, and Disadvantages

| Preparation Method | Advantage | Disadvantage | Ref |
|---|---|---|---|
| Anti-solvent precipitation | Simple and fast, Easy to regulate, Low energy consumption | Poor reproducibility | [41, 42] |
| Template-assisted method | Precise control of the size, morphology, and composition of nanomedicines | Cumbersome steps Limited applicability | [44, 45] |
| Microfluidics | Suitable for mass production, | High equipment costs | [51] |
| Emulsification technology | Simple and efficient | Poor stability | [57] |
| Supramolecular self-assembly | Preparation conditions are mild, and Dynamic regulation | Poor stability Complex design | [55, 56] |
| Spray drying technology | Suitable for small-scale production in the laboratory | Thermal sensitivity risk | [59] |
| Ultrasound-assisted method | Preparation of efficient dispersion | Ultrasound intensity needs to be preciseNarrow scope of application | [60] |
| In vivo self-assembly | Favors targeted drug delivery | Design Complexity Dependency Environment | [61–63] |
| Stimulus-responsive self-assembly | Precise Targeting and Enrichment High Biosafety | Complex design Individual differences | [64, 65] |
| Co-assembly of dual-drug /multi-drug systems | Achieving Synergistic Therapy Vector-free with high drug loading efficiency | Molecular Compatibility Design Major Challenges in Complex Control | [66] |

retention and enrichment of drugs within the infarct zone.[64] Alkaline phosphatase (ALP) catalyzes the dephosphorylation of phosphopeptide precursors. This process enhances molecular hydrophobicity, triggering self-assembly on tumor cell surfaces to form nanofibers. These fibrous structures disrupt cell membrane integrity and interfere with lipid metabolism, inducing apoptosis. Combining this strategy with metabolic inhibitors demonstrates significant synergistic effects.[65]

Molecularly engineered co-assembly of two or more therapeutic agents into a single nanomaterial—the co-assembled dual-drug system—represents a cutting-edge strategy for enhancing therapeutic efficacy. One study exemplifies this paradigm shift from "drug loading" to "functional unit construction." Researchers directly co-assembled three functionally complementary drugs as building blocks into carrier-free nanoparticles targeting the myocardium. This ingenious design enables the nanoparticles to perform dual tasks in vivo: reversing DOX toxicity in cardiac tissues (by modulating multiple pathways including ROS, apoptosis, autophagy, and inflammation) while simultaneously enhancing anticancer efficacy in tumor sites. This ultimately achieves synergistic effects in cardiac protection and tumor treatment, overcoming limitations of traditional drug delivery.[66]

The various preparation methods for the aforementioned self-assembled nanoparticles each possess distinct characteristics and applicable scenarios. Table 2 summarizes and compares the principles, advantages, and limitations of these common preparation methods.

# Self-Assembled Nanoparticles in Tumor Therapy

## Chemotherapy and Synergistic Therapy

Chemotherapy is a cancer treatment method that uses chemical drugs to kill cancer cells or inhibit their proliferation. These drugs can act through single-agent or combination therapy regimens, killing cancer cells or preventing their proliferation by damaging DNA, interfering with DNA and RNA synthesis, or generating ROS.[67] Chemotherapy can lead to drug resistance in cancer cells[68] and may cause mild side effects such as nausea, vomiting, taste disorders, and hair loss, as well as more severe complications, including potentially life-threatening bone marrow suppression.[69] In recent years, researchers have discovered that combining chemotherapy with self-assembly technology can effectively mitigate severe side effects. Self-assembly technology enables precise delivery of chemotherapy drugs to tumor sites, reducing drug distribution in normal tissues and thereby minimizing damage to normal cells, lowering the risk and severity of side effects, and providing new therapeutic strategies for chemotherapy, as shown in Figure 4.

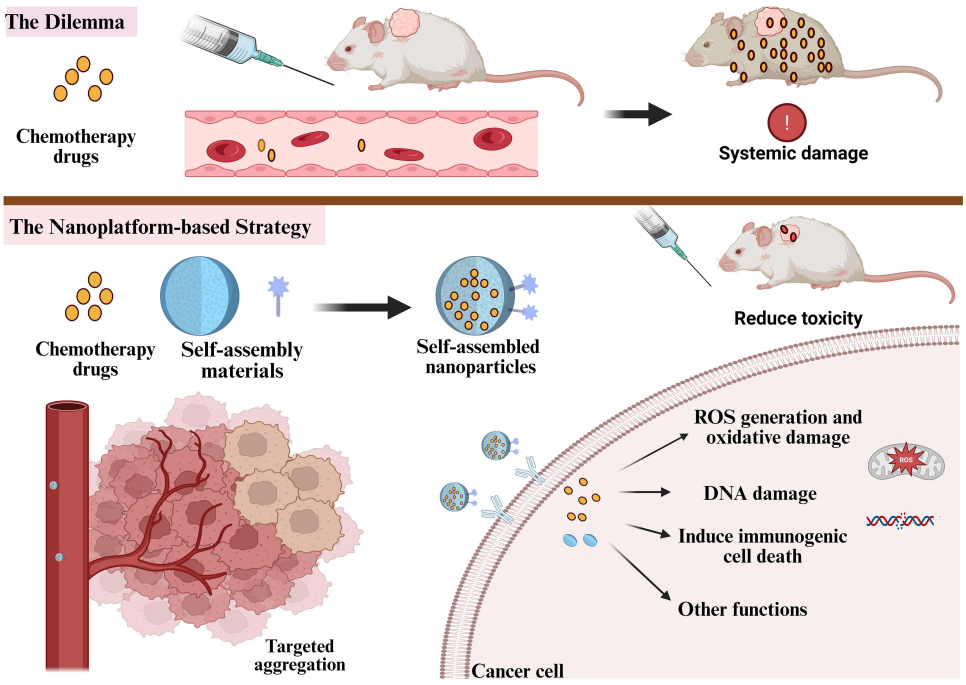


**Figure 4** Chemotherapeutic drugs for self-assembled cancer treatment (figure was created in https://BioRender.com).

DOX is one of the most effective chemotherapy drugs. DOX can induce DNA damage, exerting direct cytotoxic effects on tumor cells and activating immune CD8+ T cell responses. However, DOX has significant side effects that affect normal cells, leading to bone marrow suppression, nephrotoxicity, and cardiotoxicity.[70] Zhao et al utilized DOX and the BRD4 degrader dBET57 to self-assemble into 75 nm nanodrugs, referred to as DdLD NPs. This approach simultaneously achieves chemotherapy and immune regulation: DOX induces immunogenic cell death, while dBET57 degrades BRD4, inhibiting c-Myc-mediated glycolysis and downregulating PD-L1. Consequently, this strategy effectively reverses the immunosuppressive microenvironment. This strategy significantly inhibits primary colorectal cancer tumors and lung metastases while exhibiting low systemic toxicity. It provides new insights for the clinical translation of PROTAC and the enhancement of tumor immunotherapy through chemotherapy.[71] Spherical nucleic acids (SNAs) composed of monophosphoryl lipid A (MPLA) and CpG oligonucleotides (CpG ODN). DOX is linked to the surface of SNAs via the substrate peptide (sMMP9) of matrix metalloproteinase-9 (MMP-9). Through self-assembly, these components form MCMD nanoparticles (MPLA-CpG-sMMP9-DOX, MCMD NPs). Under the influence of MMP-9 in the tumor microenvironment, MCMD nanoparticles (NPs) can rapidly release DOX, facilitating targeted drug delivery. This process enhances the direct cytotoxic effect of DOX on tumor cells and amplifies the anti-tumor immune response induced by ICD. Consequently, this approach achieves synergistic therapeutic effects between chemotherapy and immunotherapy while minimizing off-target toxicity.[72] Zhang et al used carbon dots (CDs) as carriers, single-atom catalysts (SACs), and single-atom nanozymes (SAzymes) to self-assemble Pt SAzymes driven by DOX, constructing CDs@Pt SAs/NCs@DOX with biomimetic enzyme activity. This improved the enrichment efficiency in tumors, significantly reduced the in vivo toxicity caused by free DOX, and amplified oxidative stress reactions in tumors. As illustrated in Figure 5, the tumor inhibition rate of the nanomedicine was significantly improved compared to free DOX (G3/G4). Additionally, mice exhibited steady weight gain, normal ALT/AST levels, no signs of bone marrow suppression, and a 100% survival rate at 15 days. Furthermore, when compared to CDs@Pt SAs/NCs without DOX (G5/G6), the incorporation of DOX further enhanced tumor inhibition. ICP-OES and fluorescence imaging confirmed larger particle size and improved EPR, with higher tumor Pt enrichment, reduced retention in the pulmonary reticuloendothelial system, and local tumor temperatures reaching 45.5 °C after laser irradiation, with prolonged circulation. In contrast, the tumor exhibited rapid growth in the laser-only and buffer solution (G1/G2) treatment groups, with no observed weight loss. This further underscores that the synergistic advantages of CDs@Pt SAs/NCs@DOX prevail in terms of both efficacy and safety.[73]

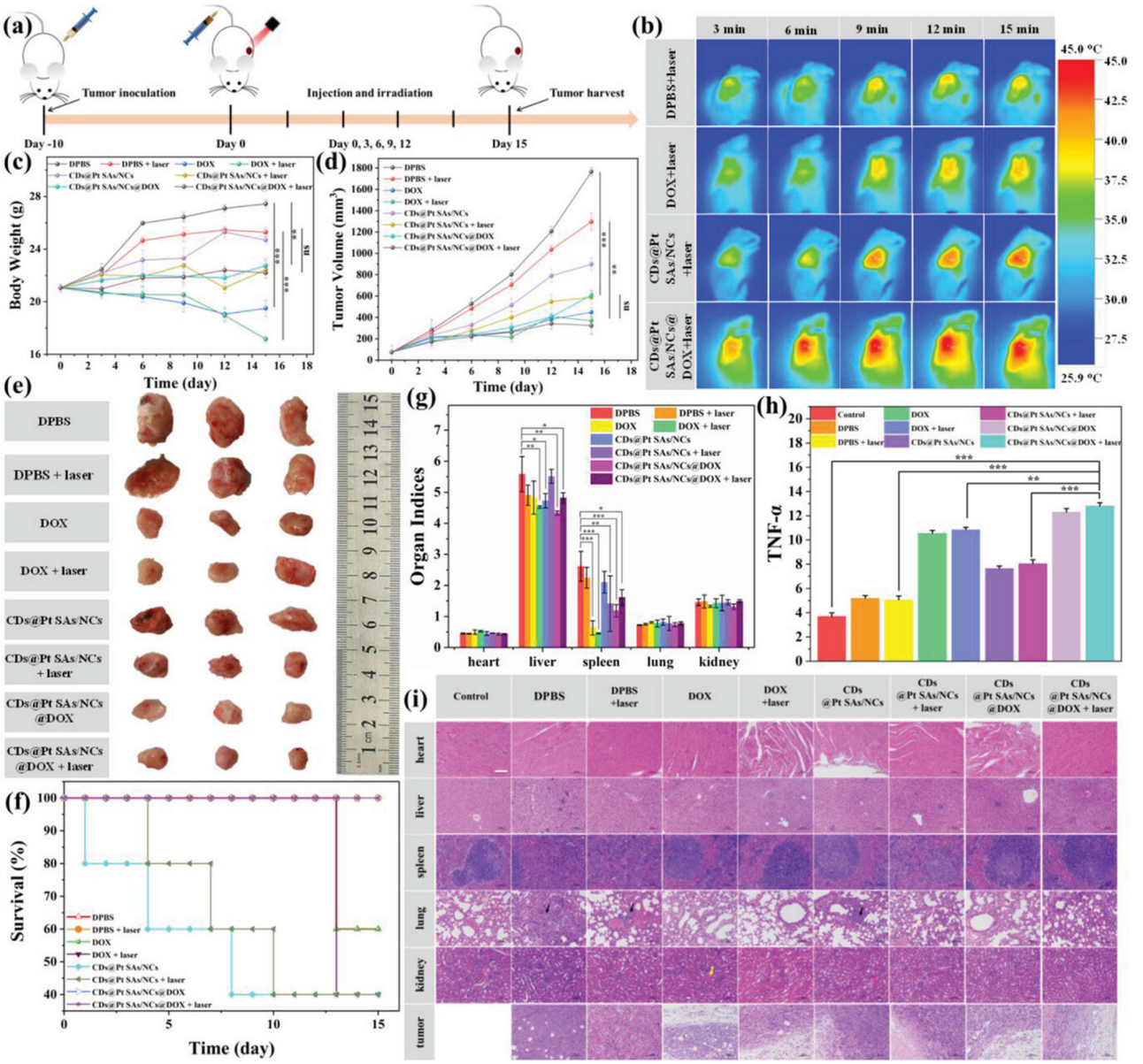


**Figure 5** In vivo tumor suppression study. (**a**) Schematic illustration of the treatment protocol. (**b**) Thermographic images of 4T1 tumor-bearing mice with different treatments. (**c**) The body weight and (**d**) tumor volume of the mice in all groups during the treatment for 15 days. (**e**) Representative digital photos of excised tumors in all treatment groups. (**f**) Survival rate of the mice in all treatment groups during 15 days. (**g**) Comparison of the organ indices of the mice after 25 days of inoculation. (**h**) TNF-α level of mice after various treatments. The presence of arrow markings in the pulmonary regions was only observed in the control and some treatment groups, indicating that these groups had developed lung metastases. (**I**) H&E staining of main organs and tumors after different treatments (Scale bar: 100 μm). (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, *ns*: not significant). Reproduced from Gong et al, Adv. Sci. 2023, 10, 2302703[73] Licensed under CC BY.

Nayak et al developed a cysteine-core diphenylalanine peptide (SN) that self-assembles into nanocarriers for the delivery of DOX in aqueous solutions. This system demonstrates redox responsiveness, triggered by glutathione (GSH), and exhibits aggregation-induced emission (AIE) properties, which enhance antitumor activity while facilitating real-time monitoring of drug release, thereby effectively integrating therapeutic intervention with monitoring.[74] Bellavita et al designed a modular amphiphilic peptide capable of co-assembling into nanofibers (NF). By introducing an EGFR-targeting peptide at its terminus, linked via an MMP-9-cleavable spacer to the transmembrane peptide gH625 and DOX, they constructed the intelligent delivery system NF-Dox. These fibers synergistically promote rapid cellular internalization via surface positive charges and targeting peptides, while escaping lysosomes through transmembrane peptides. Within the tumor microenvironment, MMP-9 cleavage of the linker enables precise in situ DOX release. This design


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achieves integrated "self-assembly-targeting-on-demand drug delivery," effectively killing triple-negative breast cancer cells at extremely low doses while significantly reducing toxicity to normal cells.[75]

PTX is a tricyclic diterpenoid compound used to treat various cancers, such as breast cancer, glioma, and abdominal aortic aneurysm, and is a common chemotherapy drug. While PTX therapy can inhibit tumor growth, it may fail to effectively eliminate cancer stem cells (CSCs) and may even promote metastasis. Additionally, it is associated with low drug utilization and adverse off-target toxicity.[76–78] To address the challenges posed by triple-negative breast cancer, which is characterized by a high propensity for metastasis, recurrence, and the absence of targeted therapies, Lu et al developed PTX-ICG self-assembled carrier-free nanoparticles (IP NPs). They combined these nanoparticles with FA-modified MK-2206 liposomes (MK-2206NPs) to achieve spatiotemporal synergy among chemotherapy, PTT, and AKT-targeted therapy. Mechanistically, this combination significantly inhibits the AKT/MAPK/NF-κB axis and blocks EMT. More importantly, a postoperative re-inoculation model demonstrated that it can activate CD8+ T cell memory, preventing tumor recurrence.[79] To address chemotherapy resistance and immune evasion caused by breast cancer stem cells, Wei et al developed an RGD-modified, acid-responsive amphiphilic peptide nanocarrier, PA/Pep1, co-delivering PTX and all-trans retinoic acid (ATRA). In the tumor's acidic microenvironment, the nanocarrier transforms from spherical to high aspect ratio nanofibers, significantly prolonging drug retention and inhibiting efflux. By downregulating the TGF-β/IL-6/PD-L1 axis to weaken immune suppression, while inducing BCSC differentiation and apoptosis, the tumor inhibition rate in the 4T1 model reached 75.8%, with metastasis almost completely blocked. This study provides a modular paradigm for "shape-immunity-stem cell" triple-synergistic nanodrug design.[80] Hydrophilic Rb1, hydrophobic PPD and PTX, along with SDS, can be effectively assembled into GPP NPs. The in vivo antitumor activity of GPP NPs is ten times greater than that of PTX injection, significantly enhancing antitumor efficacy, reducing TGF-β levels, inhibiting tumor angiogenesis, and consequently improving the tumor microenvironment.[81]

By leveraging multiple molecular interactions between PTX and polyphenolic compounds, structurally stable co-assembled nanoparticles can be constructed and further integrated with stimulus-responsive drug delivery mechanisms. Researchers polymerized resveratrol (RES) via a disulfide linker (DTPA) to form the prodrug PRES, which then co-precipitated with DSPE-$PEG_3$k to self-assemble into nanoparticles (PTX@PRES NPs). This system achieved a high paclitaxel (PTX) loading capacity of 7.2% and exhibited redox responsiveness, releasing over 86% of the drug within 60 hours under 10 mM GSH conditions. These nanoparticles effectively reversed multidrug resistance in A549/PTX-resistant cells, achieving an 82% tumor inhibition rate in in vivo models without systemic toxicity, fully demonstrating the combined therapeutic advantages of prodrug co-assembly-reductive release-synergistic sensitization.[82]

Platinum-based anticancer drugs include cisplatin (CDDP), carboplatin, and oxaliplatin. CDDP is the first-generation platinum-based anticancer drug and a commonly used drug for treating malignant tumors, including breast cancer and ovarian cancer. However, cisplatin can cause systemic toxicity, including renal toxicity, neurotoxicity, ototoxicity, and bone marrow suppression, which can severely harm normal tissues.[83–86] CDDP, tolfenamic acid (Tolf), and linoleic acid (LA) can self-assemble into TPNPs in aqueous environments. Within the tumor microenvironment, these nanoparticles can release drugs in a responsive manner, significantly improving drug delivery efficiency, reducing drug toxicity, inhibiting COX-2 expression, and inducing both DNA and mitochondrial damage. This mechanism exerts synergistic antitumor effects and enhances overall antitumor efficacy.[87] The PARP inhibitor olaparib (Olaparib, OLA) and CDDP self-assemble into nanoparticles via hydrogen bonding, targeting drug release under the acidic conditions of the tumor microenvironment. This inhibits DNA repair, increases DNA damage, activates the mitochondrial apoptosis pathway, induces tumor cell apoptosis, achieves efficient anticancer effects, and reduces side effects.[88] CDDP, hyaluronic acid (HA), and methoxy polyethylene glycol (mPEG) self-assemble to form HA-mPEG-Cis NPs, which exhibit pH-responsive drug release characteristics. HA-mPEG-Cis NPs exert antitumor effects through the PI3K/AKT/mTOR signaling pathway, enhancing stability and circulation time while reducing side effects associated with CDDP loading.[89]

Other chemotherapeutic drugs, such as irinotecan and docetaxel (DTX), can also be used in self-assembly technology to improve bioavailability and enhance therapeutic efficacy. Irinotecan and niraparib (Nir) can be co-assembled into nanoparticles, overcoming irinotecan resistance and enhancing antitumor effects against colorectal cancer.[90] (Ac)FRRF peptide and DTX can be assembled into (Ac)FRRF-DTX nanoparticles, leveraging the enhanced penetration and retention (EPR) effect in tumor tissues to selectively accumulate in tumor tissues, reduce drug toxicity, and enhance

antitumor efficacy.[91] DTX and CXCR4 antagonist peptides (CTCE) can self-assemble into CTCE-DTX NPs, specifically targeting CXCR4-upregulated metastatic tumor cells. This self-assembly enhances the efficacy of DTX while inhibiting both bone-specific and lung metastasis in triple-negative breast cancer.[92]

## Photodynamic Therapy and Synergistic Therapy

PDT is a minimally invasive therapeutic technique combining photosensitizers and specific wavelength light sources, which precisely targets diseased tissues through photochemical reactions to achieve therapeutic effects.[93] PDT combats tumors through the following three mechanisms: (1) ROS generated by photosensitization reactions mediate oxidative damage within tumor cells, triggering apoptosis. (2) Disruption of the tumor vasculature indirectly inhibits tumor growth by interrupting local blood supply and causing oxygen depletion. (3) Activation of the immunogenic cell death pathway to initiate systemic antitumor immunity.[94–96] However, PDT faces challenges such as uneven distribution of photosensitizers, limited light penetration, tumor recurrence, and insufficient antitumor immune effects.[97,98] The application of self-assembled nanotechnology to PDT can enhance tumor treatment efficacy, improve tumor targeting, and enable synergistic therapy combining photodynamic, photothermal, chemotherapy, and immunotherapy.

Among chlorophyll-based photosensitizers, chlorin e6 (Ce6) is the most commonly used in SANs. Ce6 is a highly efficient second-generation photosensitizer and sonosensitizer that generates ROS under near-infrared (NIR) light or ultrasound activation, directly killing tumor cells. It has high light conversion efficiency and can absorb longer-wavelength light (such as red light), enabling deeper tissue penetration.[99] Ce6, DOX, and HA can self-assemble into HA-DOX-Ce6 NPs without a carrier. HA specifically binds to the CD44 receptor on tumor cells, promoting drug accumulation in tumor tissue while reducing systemic toxicity. This nanoparticle exhibits pH responsiveness, enabling precise drug release in the tumor microenvironment. DOX kills tumor cells by inhibiting DNA synthesis, while Ce6 generates ROS under light exposure, inducing cell apoptosis. The synergistic action of the two, combined with PDT, demonstrated significant tumor growth inhibition and low toxicity in in vivo experiments.[100] HA, DOX, CE6, and CuNC can self-assemble into HA-CuNCs@DC nanoparticles. Under neutral conditions, HA-CuNCs@DC induces fluorescence quenching of DOX and Ce6, while the drugs are released under acidic conditions to restore their fluorescence, enabling targeted therapy and enhancing chemotherapy and PDT.[101] Beta-hydroxybutyrate (BA), water-soluble chitosan oligosaccharides (COS), and Ce6 can self-assemble into BA/Ce6 NPs. Based on the enhanced permeability and retention (EPR) effect, BA/Ce6 NPs can achieve efficient accumulation at tumor sites. Under light irradiation, the Ce6 component significantly enhances ROS generation, effectively inducing ICD in tumor cells, thereby activating anti-tumor immune responses. Additionally, this nanomaterial system can be rapidly metabolized and cleared in vivo, significantly reducing the potential risk of long-term toxicity.[102] Ce6 and $Cu^{2}$+ can self-assemble into Ce6@Cu NPs (as illustrated in Figure 6). This assembly can trigger the production of reactive oxygen species (ROS) under ultrasound conditions, oxidize unsaturated fatty acids, and simultaneously induce ferroptosis and copper-dependent apoptosis, thereby comprehensively targeting tumor cells.[103] In addition to Ce6, PheoA, and peptides KLVFF, GRGDLGRL, and GGK can assemble into GRGDLGRL-KLVFF-GGK-PheoA. The nanofibrillar aggregation state of PheoA facilitates light energy conversion efficiency, ROS generation, and tumor retention, thereby enhancing tumor suppression.[104]

Porphyrin compounds are common photosensitizers in SANs, and their tunable aromaticity and NIR absorption properties make them an ideal choice for highly efficient photosensitizers in SANs, particularly for PDT of deep-seated tumors.[105] Lu et al prepared a water-soluble porphyrin photosensitizer, 5,10,15,20-tetra-(4-pyridyl, N-β-bromomethylnaphthalene) porphyrin (TPOR), and self-assembled the DOX/TPOR4@$CB^{7}$ 4 dual-loaded compound. Through self-assembly, the production of ROS was significantly enhanced, improving the therapeutic efficacy for neuroblastoma while reducing side effects.[106] The self-assembly strategy can significantly enhance the PDT efficacy of phthalocyanine photosensitizers. Zinc(II) phthalocyanine-based amphiphilic molecules (ZnPc 1) that self-assemble into ZnPc 1 NPs demonstrate superior PDT effectiveness compared to their monomeric counterparts, resulting in a more effective inhibition of tumor growth.[107] Similarly, carrier-free nanoparticles (KPF NPs) constructed by self-assembly of CM, protoporphyrin IX (PP), and $Fe^{3}$+ ions can efficiently generate ROS and inhibit HIF-1α protein under 650 nm laser irradiation. Compared to individual components, KPF NPs significantly enhance the inhibition rate of tumor cells.[108] Verteporfin and Torin 1 can be assembled into carrier-free nanomedicines with good long-term stability. As shown in

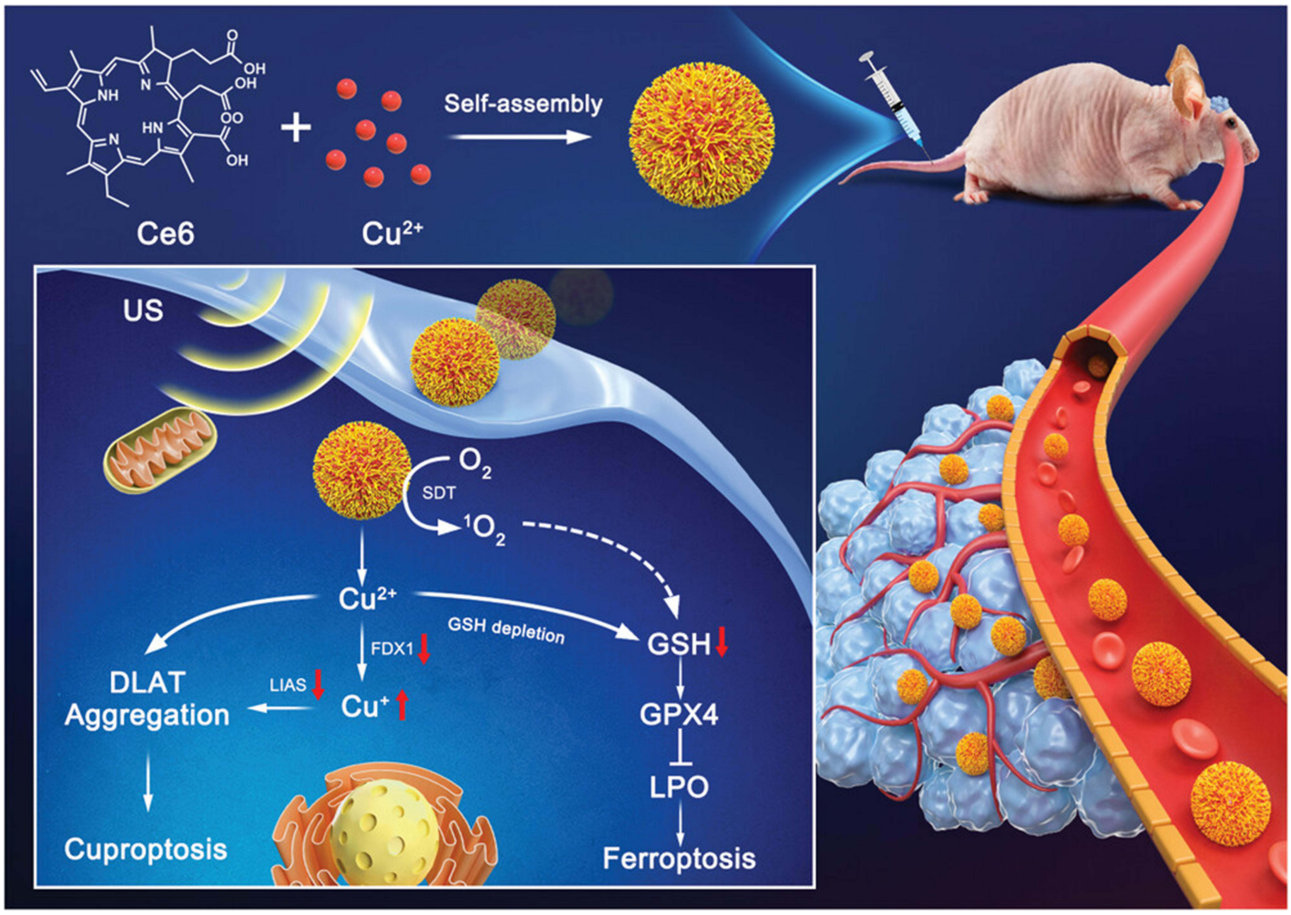


**Figure 6** Carrier-Free Self-Assembly Nano-Sonosensitizers for Sonodynamic-Amplified Cuproptosis-Ferroptosis in Glioblastoma Therapy. Reproduced from Zhu et al, Adv. Sci. 2024, 11, 2402516.[103] Licensed under CC BY.

Figure 7, compared with free Verteporfin, the cellular uptake of VP-Torin1 NPs increased by 1.27–1.38 times, leading to a significant increase in intracellular ROS levels after light irradiation, thereby enhancing PDT killing. Elevated levels of ROS facilitate the lysosomal escape of nanoparticles, evidenced by a reduction in colocalization observed three hours post-irradiation. This process is accompanied by the release of Torin 1, which further inhibits the mTOR and induces autophagy. Consequently, this interaction creates a synergistic amplification effect between PDT and chemotherapy.[109]

In addition to chlorophyll-based and porphyrin-based photosensitizers, other types of photosensitizers also exist. 3,6-Bis(2-thienyl)-2,5-dihydropyrrolo[3,4-c] pyrrole-1,4-dione (DPP) and the photosensitizer BODIPY, when combined with polyethylene glycol (PEG), can be assembled into DPBDP NPs. These NPs exhibit effective photodynamic and photothermal effects under 690 nm laser irradiation, demonstrating significant phototoxicity toward HeLa cells.[110] Irinotecan and the photosensitizer curcumin can form an ionic pair complex (ICN), showing significant antitumor efficacy against the HT-29 cancer cell line, achieving synergistic therapy combining chemotherapy and phototherapy.[111] Researchers designed and synthesized a novel hydrophilic phthalocyanine derivative (PcN8O), which can self-assemble into nanoparticles (NanoPcN8O) of approximately 6 nm in size in vivo. This material can be specifically reduced by the CYP450 enzyme + NADPH system in hypoxic tumor microenvironments, converting it into the active form NanoPcN8 with electron-rich tertiary amine groups. This marks the first achievement of oxygen-independent photodynamic + photothermal synergistic therapy, demonstrating high specificity, low toxicity, and clinical translational potential.[112]

PTT is a tumor treatment method that uses photothermal agents to convert light energy into heat energy, killing tumor cells through local heating and triggering biochemical processes.[113] When used for tumor treatment, PTT has the characteristics of high efficacy, low side effects, metastasis inhibition, and high selectivity.[114] However, PTT for tumor

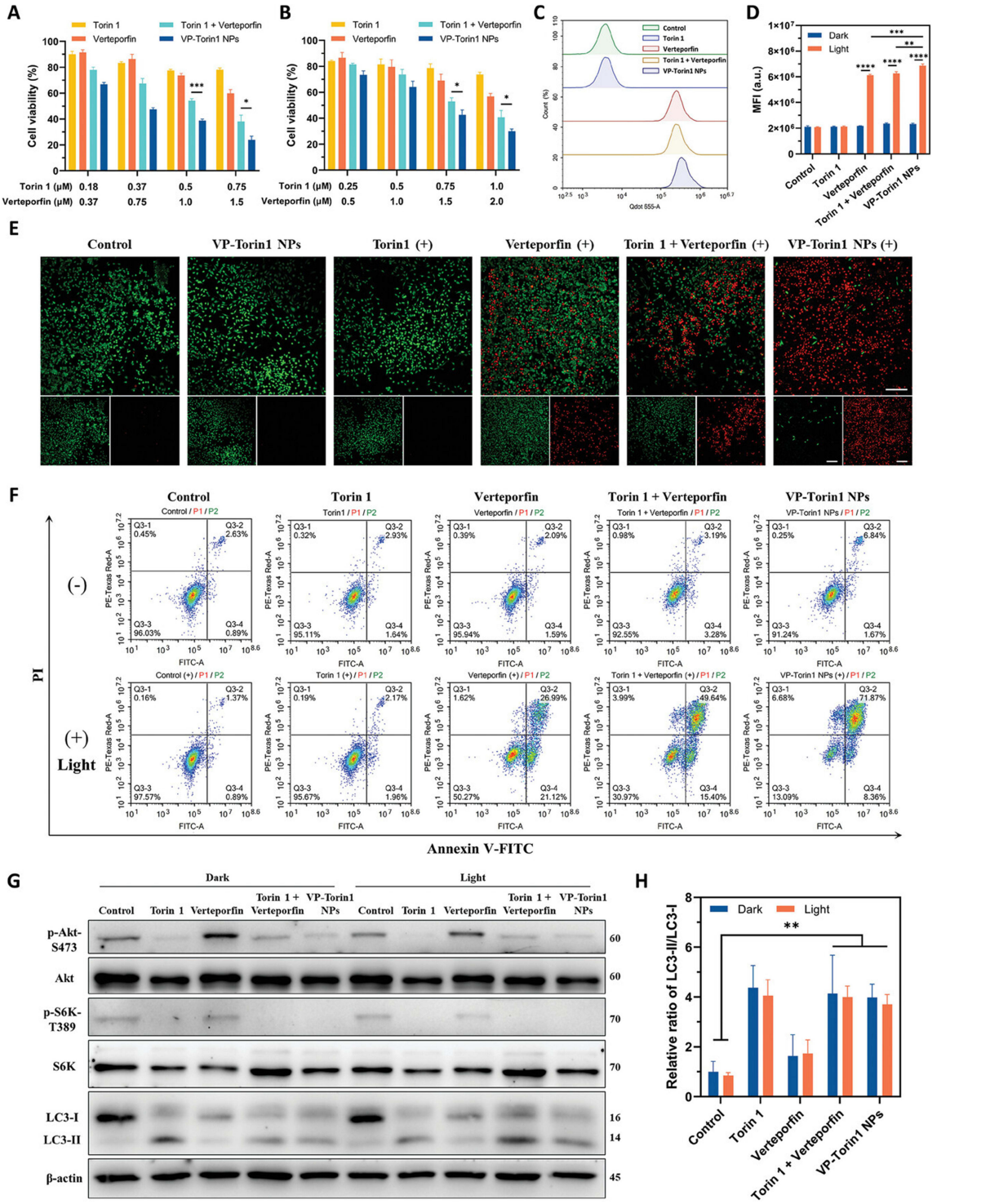


**Figure 7** Cytotoxicity and mTOR inhibition effect of VP-Torin1 NPs. Cell viability of 4T1 cells (**A**) and MDA-MB-231 cells (**B**) after the treatment of gradient concentrations of Torin 1, Verteporfin, Torin 1 plus Verteporfin, or VP-Torin1 NPs in the presence of light irradiation (n = 3, Xe lamp, 690 nm, 2.7 mW cm− 2, 2 min). (**C**) Flow cytometric analysis of cellular uptake behavior in 4T1 cells treated with Torin 1, Verteporfin, Torin 1 plus Verteporfin, or VP-Torin1 NPs for 4 h. (**D**) ROS generation level of 4T1 cells after treatment with Torin 1, Verteporfin, Torin 1 plus Verteporfin, or VP-Torin1 NPs with or without light irradiation (n = 3, Xe lamp, 690 nm, 2.7 mW cm− 2, 10 min). DCFH-DA was used as the indicator. (**E**) Representative confocal microscopy images of Calcein AM (green fluorescence, indicating living cells) and PI (red fluorescence, indicating dead cells) staining in 4T1 cells after treatment with Torin 1, Verteporfin, Torin 1 plus Verteporfin, or VP-Torin1 NPs with or without light irradiation (Xe lamp, 690 nm, 2.7 mW cm − 2, 2 min, Scale bar: 200 μm). (**F**) Flow cytometric apoptosis analysis of 4T1 cells treated with Torin 1, Verteporfin, Torin 1 plus Verteporfin, or VP-Torin1 NPs with or without light irradiation (Xe lamp, 690 nm, 2.7 mW cm− 2, 2 min). (**G**) Western blot analysis of mTOR downstream protein levels (p-Akt, Akt, p-S6K, S6K, and LC3-I/II) in 4T1 cells receiving indicated treatments with or without light irradiation (Xe lamp, 690 nm, 2.7 mW cm− 2, 90s). (**H**) Quantitative Western Blot analysis of LC3-II/LC3-I. Data were shown as mean ± SD. "(+)" represents the application of light irradiation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Reproduced from Liu et al, Adv. Healthcare Mater. 2024, 13, 2402357.[109] Licensed under CC BY.


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treatment often suffers from drawbacks such as uneven heat distribution and the complexity of combination therapy. Traditional photothermal materials face issues like difficulty in degrading within the body, leading to long-term toxicity. New materials like indocyanine green (ICG) also have problems such as water instability, photodegradation, thermal degradation, and photobleaching.[115] Combining self-assembly technology with photothermal materials can enhance photothermal efficacy and biosafety, effectively addressing the challenges faced by photothermal materials, and enabling synergistic therapy combining photothermal, photodynamic, immunotherapy, and chemotherapy.[116,117]

ICG is a commonly used photothermal agent. ICG is an anthocyanin compound that exhibits strong light absorption in the NIR region and has fluorescent properties. When irradiated, it exerts a photothermal effect to induce cancer cell death.[118] ICG and PTX can be co-assembled into PTX@ICG. In vitro and in vivo experiments have demonstrated that assembling into PTX@ICG enhances the bioavailability of the single drug, enabling tumor-targeted therapy and synergistic photothermal and chemotherapy.[119] ICG and the chemotherapy drug SN38 were loaded onto (TA)-$Fe^3$+-metal-phenol formaldehyde networks (MPNs), which were modified with hydroxyethyl starch (HES). Subsequently, these were encapsulated with macrophage membranes (CM) and surface-modified with Angiopep-2 peptides to prepare AM-NP. The AM-NP employs a dual-targeting strategy utilizing both Angiopep-2 peptides and CM to efficiently penetrate the blood-brain barrier (BBB) and actively target GBM. After accumulation at the tumor site,NIR light (808 nm) excites the photosensitizer ICG to generate localized high heat, achieving PTT while triggering the rapid release of the chemotherapy drug SN38. The released SN38 inhibits topoisomerase I to induce DNA damage and apoptosis in tumor cells, ultimately producing a synergistic antitumor effect with PTT, significantly inhibiting tumor growth.[120] L-arginine (L-Arg), the ferroptosis inducer sorafenib (SRF), ICG, and MPN (composed of TA, $Fe^3$+, and hydroxyethyl starch) can be assembled into IS@ATF. This assembly triggers a cascade reaction enhanced by NIR laser irradiation to promote tumor ferroptosis. Under NIR irradiation, the ROS generated by the ICG photosensitizer oxidize L-Arg, leading to the release of NO, while simultaneously depleting glutathione (GSH) and accumulating lipid peroxides (LPO). Meanwhile, SRF disrupts the ferroptosis defense system by inhibiting GSH biosynthesis. Additionally, TA-$Fe^3$+-MPNs continuously generate hydroxyl radicals (·OH) via the Fenton reaction, which synergistically enhances radical-mediated killing alongside ICG's PTT. Ultimately, this multi-faceted approach amplifies the effects of ferroptosis through various mechanisms.[121] 3′,5′-Dioleoyl gemcitabine (DOG), γ-octadecyl folate (MOFA), and ICG are assembled into DOG/MOFA/ICG NPS. The thermal effect generated by ICG under NIR irradiation directly kills tumor cells, triggering pH/light-responsive drug release from the nanoparticles, promoting DOG absorption, and achieving synergistic chemotherapy and PTT.[122] The tyrosine kinase inhibitor pyrotinib and ICG can be assembled into PIGNPs, significantly improving ICG stability and circulation time. PIG nanoparticles can specifically accumulate in HER2-positive tumor tissues through surface modification (eg, HER2-targeted ligands), activating ferroptosis in HER2-positive breast cancer with drug resistance, overcoming drug resistance.[123] ICG, the oxygen donor $MnO_2$, the IDO inhibitor NLG919, and the toll-like receptor 4 agonist monophosphoryl lipid A (MPLA) assemble into multifunctional polymeric micelles RIMNA (as shown in Figure 8). PTT/PDT directly kills tumor cells, leading to the release of damage-associated molecular patterns (DAMPs) from tumor cells, promoting the maturation of dendritic cells (DCs), and achieving photothermal/photodynamic/immune synergistic therapy for colorectal cancer.[124]

## Immunotherapy and Synergistic Therapy

Immunotherapy is a treatment method that utilizes the body's immune system to combat disease. Immunotherapy is increasingly being applied in cancer treatment, with the core of cancer immunotherapy being the activation of the immune system to recognize and attack tumor cells. Currently, immunotherapy faces challenges such as tumor cell resistance, lack of biomarkers, and immune-related toxicity.[125] Self-assembly technology applied to immunotherapy can reverse the tumor microenvironment, co-load immunomodulators with targeted drugs, undergo in situ self-assembly in response to the tumor microenvironment, serve as a vaccine carrier, and enable multi-modal synergistic therapy combining photothermal, photodynamic, and immunotherapy.[53,126–128] Therefore, with technological advancements, self-assembly technology demonstrates increasing potential in immunotherapy.

Ursolic acid (UA) and Lentinan (LNT) can self-assemble into LNT-UA, which exhibits high drug bioavailability and anticancer activity, inducing the ICD response to enhance tumor immunogenicity.[129] Peptide PROTACs and DSPE-PEG can

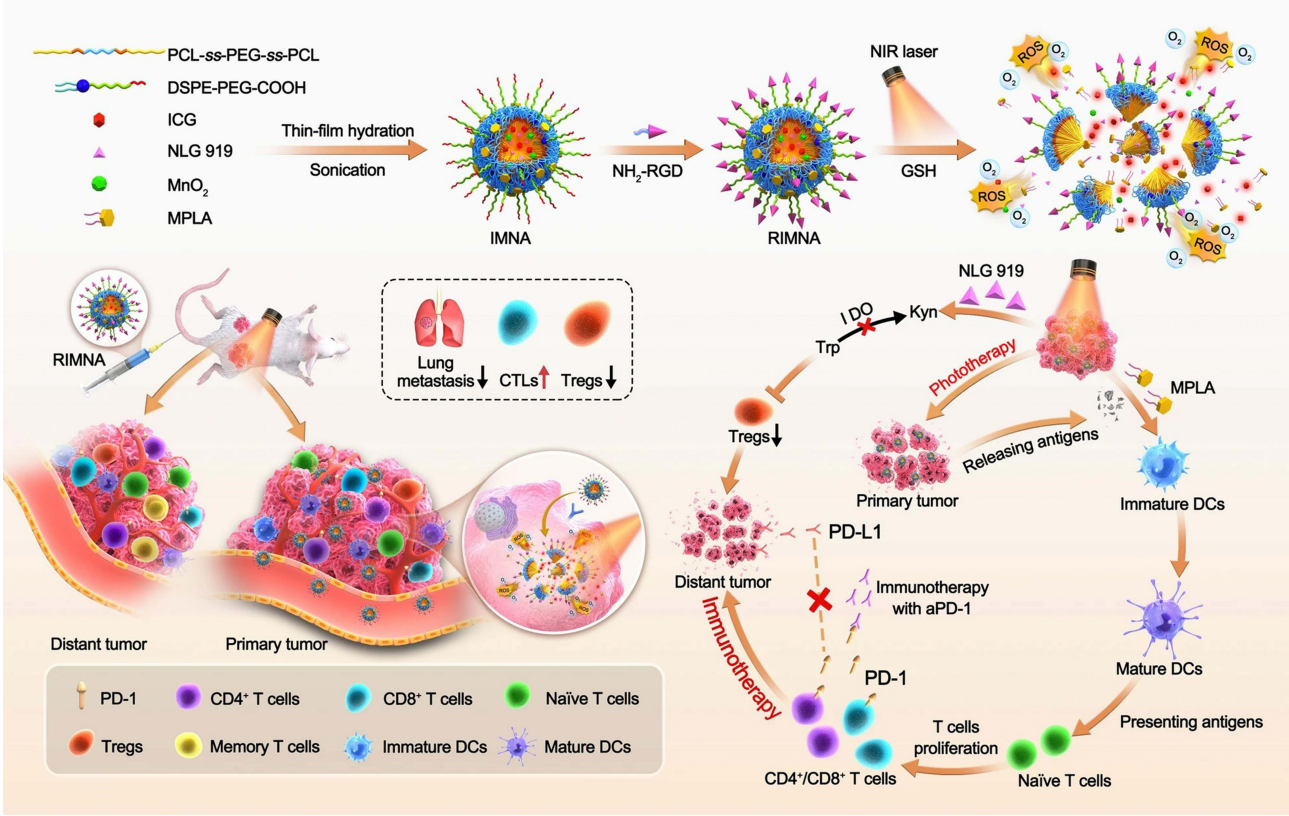


**Figure 8** GSH-responsive polymeric micelles-based augmented photoimmunotherapy synergized with PD-1 blockade for eliciting robust antitumor immunity against colon tumor. Reproduced with permission.[124] Copyright 2025 Springer Nature.

self-assemble into NP-PROTACs, enhancing CD103+ DC infiltration and T-cell cytotoxicity, and alleviating the β-catenin /STAT3-induced immunosuppressive microenvironment in CRC.[130] Immunomodulatory metformin (Met) and 7-ethyl-10-hydroxycamptothecin (SN38) can self-assemble into MS NPs, reducing PD-L1 levels to achieve immunotherapy, inhibiting tumor metastasis, and used in combination therapy for immunotherapy and chemotherapy.[131] HAS, IR780, and zinc sulfide (ZnS) can self-assemble into IR780-ZnS@HSA, inducing ICD and pyroptosis in tumor cells and enhancing immune responses.[132] The self-assembled nanovaccine MEAO-Z, composed of mannose-modified protein antigens, significantly promotes antigen cross-presentation, triggers strong cytotoxic T cell responses, and exhibits potent antitumor effects.[133] Using cytosine-phosphate-guanine oligodeoxyribonucleotides (CpG ODN) as a framework, self-assembled CpG NPs can induce the production of pro-inflammatory cytokines, promote the conversion of immunosuppressive M2 macrophages to immune-activated M1 macrophages, enhance the antigen presentation capacity of mature DCs, and activate T cells at the tumor site, thereby achieving antitumor immunotherapy.[134] Triphenylphosphine (TPP), tamoxifen (TAM), and albumin (Alb) self-assemble to form TPP-TAM@Alb nanoparticles. These NPs target mitochondria to inhibit oxidative phosphorylation (OXPHOS) and glycolysis, thereby activating the AMPK signaling pathway. This activation reduces the expression of PD-L1 and TGF-β in tumor cells, decreases collagen secretion, and improves the tumor immune microenvironment. Additionally, TPP-TAM@Alb enhances the accumulation of PTX@Alb in tumors, promotes T cell infiltration, thereby enhancing the efficacy of chemotherapy and immunotherapy, ultimately achieving effective inhibition of chemotherapy-resistant tumors.[135] Researchers have designed a novel construct known as CPM, which involves the self-assembly of $Fe^{3}$+-TA metal–polyphenol networks to form core nanoparticles (CP). This is followed by a surface coating with CM, resulting in an integrated approach that combines "self-assembly" with "biomimetic camouflage." CPM effectively inhibits SerpinB9, thereby releasing its blockade on Granzyme B and amplifying the apoptotic effects of CTL/NK cells. Cholesterol oxidase COD depletes cholesterol, increases ROS, and downregulates GPX4/FSP1, triggering ferroptosis, while also driving dendritic cell maturation, macrophage M1 polarization, and CD8+ T cell infiltration, comprehensively reversing the immunosuppressive


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microenvironment.[136] $Cu^{2}$+, ICG, CpG, and FA are assembled into a CICF system, which synergistically triggers CDT, PTT, PDT, and immune activation under 808 nm laser irradiation. This process ICD, significantly inhibiting the growth of 4T1 breast cancer and preventing lung metastasis. The tumor inhibition rate of the CICF combined with NIR irradiation exceeds 90%, demonstrating substantial potential for clinical translation.[137] Atorvastatin calcium (AC) and polydopamine (PDA) were assembled into nanoparticles encapsulated by CM, yielding AC@PDA@CM (APM). This composite inhibits the COX-2/$PGE_2$ pathway, promotes DC maturation, enhances effector T cell function, and establishes a positive feedback loop between PTT-induced ICD and COX-2 inhibition, thereby activating systemic antitumor immunity.[138] Peptides targeting HER2, when combined with phorbol-a (Pha), were assembled into nanoparticles (as illustrated in Figure 9). This assembly enhances immune induction and activates a robust immune response in CD8+ T cells, thereby initiating a potent tumor immune cycle. Additionally, it improves the effects of PDT and exerts anti-breast cancer activity.[139]

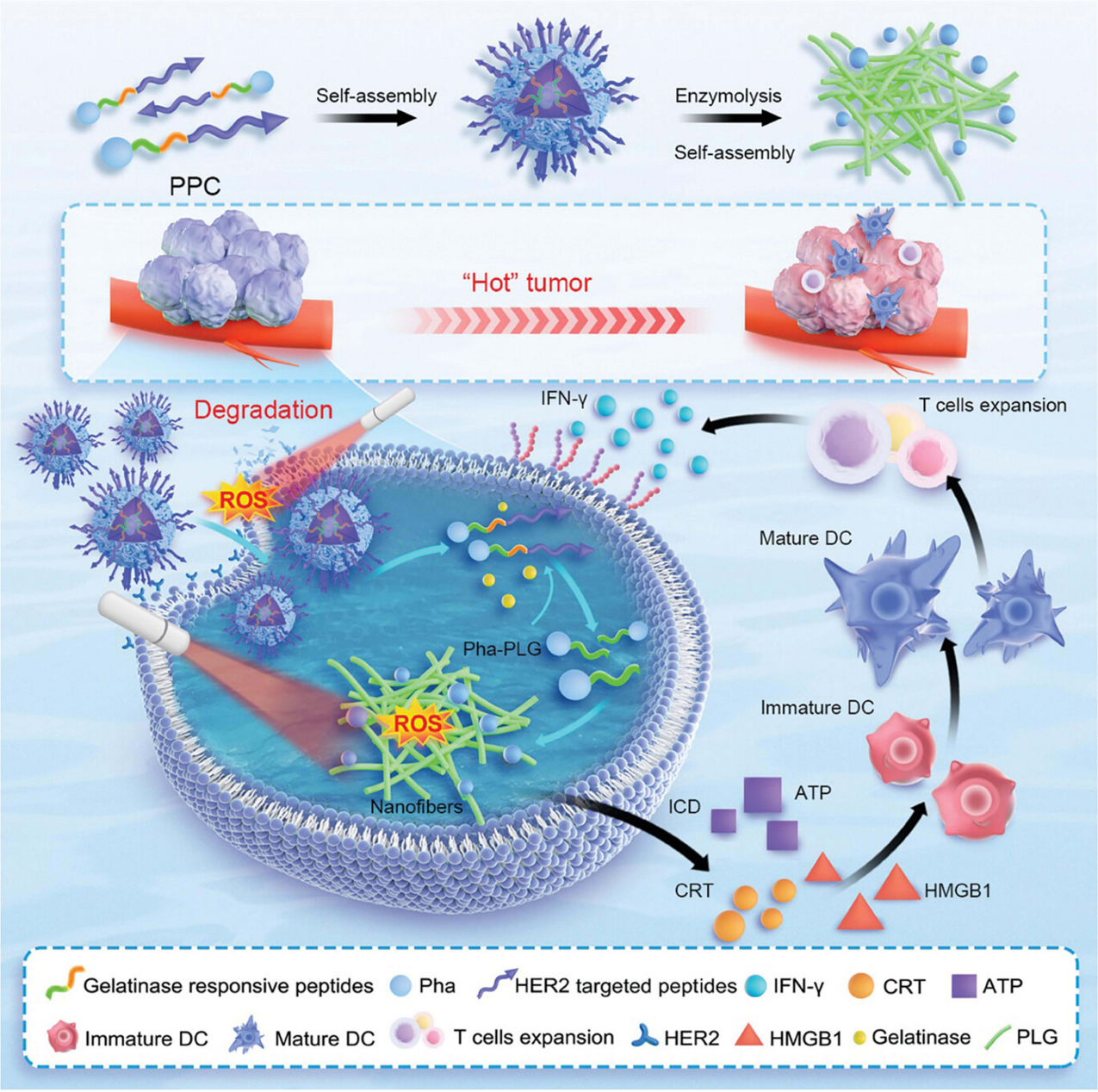


**Figure 9** Precise HER2 Protein Degradation via Peptides-Conjugated Photodynamic Therapy for Enhanced Breast Cancer Immunotherapy. Reproduced from Guo et al Adv. Sci. 2025, 12, 2410778.[139] The phrase "HER2 targeted pepides" in the legend has been corrected to "HER2-targeted peptides." Licensed under CC BY.

## Gene Therapy and Synergistic Therapy

Gene therapy, as an emerging cancer treatment technology, is being applied in an increasingly wide range of applications. Gene therapy is a biomedical technology that treats and prevents diseases by modifying or regulating gene expression. Its core objective is to correct abnormal gene function, replace defective genes, suppress harmful gene expression, or influence specific signaling pathways through gene regulation, thereby achieving intervention in diseases.[140–143] The application of self-assembling nanotechnology in gene therapy can enhance therapeutic efficacy against tumors, improve tumor targeting, prolong circulation time in the bloodstream, and reduce toxic side effects.[144–147]

IR780 derivatives (PTA), 2-methylimidazole (2-MIM), and siRNA, along with $Zn^2$+, can be assembled into siRNA@PT-ZIF-8. This assembly overcomes the limitations of short half-life and weak stability of free genes in the bloodstream, thereby achieving a synergistic effect in gene therapy and PTT.[148] PLL modified with fluorinated chains and CRISPR-Cas9 plasmids can be assembled into PLLF/Cas9-sgDAD1. This construct exhibits high cellular and mucosal permeability, effectively targets the DAD1 gene to inhibit its expression, and simultaneously influences the MAPK signaling pathway to induce apoptosis in bladder cancer (BCa) cells.[149] Amphiphilic peptides modified with N-acetylgalactosamine (GalNAc) bind to the sialic acid glycoprotein receptor (ASGPR) on the surface of hepatocytes, forming a nanocore. This nanocore subsequently combines with the CD24 antibody to create LYTAC, which intervenes in the CD24/Siglec-10 signaling pathway and inhibits tumor growth.[150] Researchers have designed a VEGFR2 siRNA that self-assembles within the host and is encapsulated in small extracellular vesicles (sEV) secreted by the liver. This innovative approach enables sustained delivery of siRNA to target organs, effectively inhibiting lung metastasis and tumor angiogenesis, thus providing a novel strategy for treating lung metastatic osteosarcoma.[151] Glucuronic acid self-assembles with siRNA to form SMS2 siRNA gene expression plasmids, which inhibit SMS2 expression. This process promotes M1 polarization, suppresses M2 polarization, enhances the antitumor activity of immune cells, regulates the NF-κB/CXCL5 pathway, and exerts antitumor effects.[152] Cen et al self-assembled the (LLHH)3-Acp-2[mini-PEG]-GRRRRRRRG-2[mini-PEG]-Acp-cRGD peptide (cRGD-GR9G-(LLHH)3) with siRNA to form peptide/nucleic acid nanoparticles. This approach enables siRNA to specifically target GBM, thereby enhancing treatment precision and stability. The delivery of siRNA effectively silences the EGFR and RELA/P65 genes, obstructs DNA damage repair pathways such as non-homologous end joining (NHEJ) and homologous recombination (HR), increases GBM sensitivity to radiotherapy, and ultimately improves treatment efficacy.[153]

The flexibility of SANs enables their adaptation to a wide range of cancer treatment strategies, from traditional chemotherapy to emerging approaches such as photodynamic, photothermal, and immunotherapy. To gain deeper insights into their design principles and application efficacy across different therapeutic scenarios, Table 3 presents a multidimensional analytical framework. This framework serves as a valuable reference for guiding future nanomedicine design tailored to specific therapeutic needs.

**Table 3** Multidimensional Analysis of Self-Assembled Nanoparticles in Cancer Therapy

| Therapy Modality | Nano System | Core Components | Core Mechanism & Strategy | Ref |
|---|---|---|---|---|
| Chemotherapy | DdLD NPs | DOX, dBET57 (PROTAC) | Chemo-protein degradation synergy: DOX induces ICD, dBET57 degrades BRD4 to downregulate PD-L1, reversing immunosuppression. | [71] |
| Chemo/ Immunotherapy | MCMD NPs | MPLA, CpG, DOX | Enzyme-responsive chemo-immunotherapy: MMP-9 triggers DOX release for direct killing and enhanced ICD; immune adjuvants activate immunity. | [72] |
| Chemo/Photothermal Therapy | CDs@Pt SAs/ NCs@DOX | Carbon dots, Pt single-atom enzymes, DOX | Self-assembled catalytic therapy: Enhanced tumor accumulation, synergistic amplification of oxidative stress, combined with photothermal therapy. | [73] |
| PTT | HA-DOX-Ce6 NPs | Hyaluronic acid (HA), DOX, Ce6 | Targeted chemo-PDT: HA targets CD44, pH-responsive drug release; synergy between DOX and ROS generated by Ce6. | [100] |

(*Continued*)

**Table 3** (Continued).

| Therapy Modality | Nano System | Core Components | Core Mechanism & Strategy | Ref |
|---|---|---|---|---|
| Photodynamic/ Sonodynamic Therapy | Ce6@Cu NPs | Ce6, $Cu^{2}$+ | Inducing novel cell death: Ultrasound-triggered ROS synergistically induces ferroptosis and cuproptosis. | [103] |
| Photothermal Therapy | PTX@ICG | Paclitaxel (PTX), ICG | Chemo-photothermal synergy: Co-assembly improves bioavailability and tumor targeting for synergistic therapy. | [119] |
| Photothermal/ Ferroptosis | IS@ATF | L-arginine, Sorafenib, ICG, MPN | NIR-triggered cascade reaction: Photothermal therapy synergizes with multiple mechanisms (NO generation, GSH depletion, Fenton reaction) to amplify ferroptosis. | [121] |
| Photothermal/ Photodynamic/ Immunotherapy | RIMNA | ICG, $MnO_2$, NLG919, MPLA | Multimodal immunotherapy: PTT/PDT directly kills tumor cells, combined with immune adjuvants to activate anti-tumor immunity. | [124] |
| Immunotherapy | NP-PROTACs | Peptide PROTACs, DSPE-PEG | Nano-PROTAC: Remodels the immune microenvironment, enhances DC infiltration, and T cell cytotoxicity. | [130] |
| Immuno/ Chemotherapy | MS NPs | Metformin, SN38 | Chemo-immunomodulation: Co-delivery to reduce PD-L1 levels and inhibit metastasis. | [131] |
| Immunotherapy | CPM | TA-$Fe^{3}$+, Macrophage membrane | Biomimetic immune reversal: Alleviates immunosuppression, triggers ferroptosis, and drives immune cell activation. | [136] |
| Gene Therapy | siRNA@PT-ZIF-8 | IR780 derivative, siRNA, $Zn^{2}$+ | Gene-photothermal synergy: Metal-organic framework co-delivery for gene silencing and photothermal therapy. | [148] |
| Gene Therapy | LYTAC | GalNAc, Peptide, CD24 antibody | Targeted protein degradation: Intervenes in immune checkpoint signaling pathways to inhibit tumor growth. | [150] |
| Gene/Radiotherapy | Peptide/siRNA Nanoparticles | cRGD peptide, (LLHH)3 peptide, siRNA | Radiosensitization: Targeted delivery of siRNA to silence DNA repair genes, enhancing radiosensitivity. | [153] |

## Comparison of SANs and Traditional Nanomedicines

The emergence of SANs marks a profound paradigm shift in the field of nanomedicine. Compared to traditional nanocarriers, SANs not only achieve technical improvements but also represent a fundamental revolution in design philosophy and functional mechanisms. Traditional nanomedicines typically feature mature preparation processes, high structural stability, and well-defined quality control standards. However, their application remains constrained by issues such as inherent carrier toxicity, functionalization dependent on complex modifications, and limited drug loading capacity. SANs, on the other hand, demonstrate advantages such as high drug loading capacity, stimulus-responsive drug release capabilities, and flexible preparation methods. Nevertheless, their development still faces challenges, including difficulties in large-scale production, room for improvement in in vivo stability, and clinical translation remaining in its early stages. A comparison of the two is shown in Table 4.

**Table 4** Comparative Analysis of Traditional Nanomedicines and Self-Assembled Nanoparticles

| Comparison | Traditional Nanomedicines | Self-Assembled Nanoparticles (SANs) |
|---|---|---|
| **Advantages** | Established and stable preparation process | High drug loading capacity |
| | High structural stability | Stimuli-responsive release |
| | Well-defined quality control standards | Simple and diverse preparation methods |
| **Limitations** | Potential carrier toxicity | Challenges in large-scale production |
| | Functionalization often requires additional modification steps | Potential stability issues in vivo |
| | Limited drug loading capacity | Early stage of clinical translation |

Traditional nanomedicines primarily contributed by establishing the fundamental framework for tumor-targeted delivery systems. These systems encapsulate chemotherapeutic agents within carriers such as liposomes or polymeric micelles, enabling systematic targeted drug delivery. Their core value lies in leveraging nanoscale physical properties to optimize drug distribution within the body: enhancing drug accumulation in tumor tissues through increased permeability and retention effects, while simultaneously reducing systemic toxicity by minimizing drug exposure in healthy tissues. Commercially available drugs like liposomal DOX have laid the technical foundation for establishing nanomedicine delivery systems.

SANs represent a paradigm shift in nanomedicine, with their primary advantage arising from a unique, dynamic, and reversible molecular self-assembly mechanism. This mechanism allows them to respond to signals from the tumor microenvironment, such as acidic pH, overexpressed enzymes, or elevated glutathione concentrations, facilitating a transition from passive accumulation to active controlled release, thereby significantly enhancing treatment precision. Moreover, their programmability at the molecular level enables the efficient integration of multiple therapeutic modalities —including chemotherapy, PDT, immunotherapy, and gene therapy—thereby constructing synergistic therapeutic platforms where the effect of combined therapies exceeds the sum of their individual effects.

## Challenges and Future Prospects

Self-assembling nanotechnology, through the precise manipulation of intermolecular noncovalent forces such as hydrophobic interactions, electrostatic attraction, and π-π stacking, provides significant momentum for constructing structurally programmable, highly integrated nanomedicine platforms. It offers notable advantages in terms of low toxicity and multifunctional synergies, including chemotherapy, gene therapy, immunotherapy, and PDT, PTT alongside diverse preparation strategies, thereby establishing itself as a leading direction in precision cancer therapy. However, its dynamic assembly nature, which relies on weak interactions, renders it highly sensitive to environmental parameters such as temperature, pH, and ionic strength. This sensitivity poses considerable challenges in translating laboratory successes into large-scale production, as precisely replicating process conditions proves challenging, leading to significant batch-to-batch variations. While technologies like microfluidics have advanced particle size uniformity, their complex designs and high costs hinder widespread adoption. To overcome this industrial bottleneck, a multi-pronged strategy is required: First, production processes should adopt a "assembly line" model inspired by continuous flow manufacturing, ensuring each nanoparticle batch forms under identical conditions through precisely controlled micro-mixing. Second, quality control must incorporate real-time process analytical techniques for online monitoring and automatic feedback adjustment of critical parameters. Most crucially, developing simplified assembly systems—such as carrier-free prodrugs—can reduce sensitivity to process variations from the molecular design stage. The synergistic advancement of these process innovations, quality control upgrades, and molecular optimizations provides a viable pathway to systematically address the industrialization challenges of SANs. Therefore, overcoming current bottlenecks to develop advanced self-assembly strategies that combine high stability, low cost, scalability, and robust process reliability is crucial for advancing this technology from the laboratory to clinical translation and industrialization. Simultaneously, the clinical translation of SANs remains in its early stages, with large-scale, confirmatory clinical trial cases and publicly available detailed clinical data still relatively limited. Addressing bottlenecks such as large-scale production and in vivo stability, while conducting more in-depth clinical research, is essential to unlocking their true clinical potential.

## Conclusion

Multiple noncovalent interactions—including hydrophobic interactions, hydrogen bonding, π-π stacking, electrostatic forces, and van der Waals forces—play indispensable roles in the drug delivery process of self-assembling nanoparticles. These interactions synergistically drive the spontaneous formation of nanostructures, maintain their stability, and precisely regulate their biological behavior. Specifically, Hydrophobic interactions drive the encapsulation of hydrophobic drugs within the core, improving solubility while masking taste and enabling controlled release. Hydrogen bonding confers dynamic reversibility to nanostructures, enabling smart drug release responsive to stimuli like temperature and pH. π-π stacking guides ordered molecular arrangement through its directionality, constructing stable porous structures for efficient loading and targeted delivery. Electrostatic interactions mediate initial assembly and enable precise control over assembly structure and release kinetics via regulation of environmental ionic strength. Van der Waals forces, as ubiquitous stabilizing interactions, enhance

the mechanical integrity and durability of nanostructures. Compared to conventional nanoparticles, the dynamic and reversible nature of these noncovalent interactions constitutes their core advantage: they enable nanoparticles to respond to changes in the biological environment, achieving "smart" drug release. Simultaneously, their synergistic effects allow the construction of more complex, ordered multilevel structures, thereby enhancing drug loading capacity, stability, and biocompatibility. The value of these interactions manifests across diverse therapeutic processes. In cancer treatment, they jointly achieve targeted delivery and controlled release of chemotherapeutic agents. In gene therapy, electrostatic forces are pivotal for nucleic acid loading and cellular transfection. In anti-inflammatory and antioxidant applications, noncovalent-stabilized nanomicelles significantly enhance drug bioavailability and therapeutic efficacy. Through deep understanding and precise manipulation of these noncovalent interactions, coupled with innovative self-assembled materials and AI-driven prediction, we can balance the tension between dynamic flexibility and structural stability. Future research should focus on leveraging artificial intelligence to overcome the clinical challenges of SANs, paving the way for a new paradigm of intelligent, patient-specific nanomedicines.

## Abbreviations

NDDS, Nanodrug delivery system; SANs, Self-assembled Nanoparticles; PTT, Photothermal Therapy; PDT, Photodynamic Therapy; DG, Deamidated Gliadin; TA, Tannic Acid; 4-AQ, 4-Aminoquinoline; GSSF, Glycosylated Stearyl Sulfate Ferulic acid; DHA, Docosahexaenoic Acid; Doxy, Doxycycline; HAS, Human serum albumin; CPT, Camptothecin; PTX, Paclitaxel; DOX, Doxorubicin; ICG, Indocyanine Green; GBM, Glioblastoma multiforme; ICD, Immunogenic Cell Death; MPLA, Monophosphoryl lipid A; CpG ODN, CpG oligonucleotide; OLA, Olaparib; CSCs, Cancer stem cells; PBA, Phenylboronic acid; CDDP, Cisplatin; HA, Hyaluronic Acid; MPEG, Methoxy polyethylene glycol; DTX, Docetaxel; NIR, near-infrared; UA, Ursolic acid; BA, Betulinic acid; Ce6, Chlorin e6; COS, Chitosan Oligosaccharide; L-Arg, L-Arginine; BBB, Blood-brain barrier; SRF, Sorafenib; DAMPs, Damage-associated molecular patterns; LNT, Lentinan; Met, Metformin; SN38, 7-Ethyl-10-hydroxycamptothecin; TPP, Triphenylphosphine; TAM, Tamoxifen; Alb, Albumin; AC, Atorvastatin Calcium; CM, Macrophage Membrane; DC, Dendritic cell; 2-MIM, 2-Methylimidazole; SMS2, Sphingomyelin Synthase 2; ROS, Reactive oxygen species; Fru, Fructose; ATRA, All-trans retinoic acid; ASGPR, Acid glycoprotein receptor; SACs, Single-atom catalysts; PDA, Polydopamine; BCa, bladder cancer.

## Data Sharing Statement

No new data were collected, and no new ethical approval was required.

## Consent for Publication

Informed consent for publication was received from all participants.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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