Chinese Journal of Natural Medicines

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Citation: Yuqian Wang, Renqi Huang, Shufan Feng, Ran Mo, Advances in nanocarriers for targeted drug delivery and controlled drug release, Chinese Journal of Natural Medicines, 2025, 23(5), 513−528. doi: 10.1016/S1875−5364(25)60861−2.

View online: https://doi.org/10.1016/S1875−5364(25)60861−2

Chinese Journal of Natural Medicines 23 (2025) 513-528

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Advances in nanocarriers for targeted drug delivery and controlled drug release

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ARTICLE INFO

Article history:
Received 23 August 2024
Revised 13 September 2024
Accepted 24 December 2024
Available online 20 May 2025

Keywords:
Drug delivery
Nanocarrier
Tissue targeting
Controlled release
Stimuli responsiveness

ABSTRACT

Nanocarrier-based drug delivery systems (nDDSs) present significant opportunities for improving disease treatment, offering advantages in drug encapsulation, solubilization, stability enhancement, and optimized pharmacokinetics and biodistribution. nDDSs, comprising lipid, polymeric, protein, and inorganic nanovehicles, can be guided by or respond to biological cues for precise disease treatment and management. Equipping nanocarriers with tissue/cell-targeted ligands enables effective navigation in complex environments, while functionalization with stimuli-responsive moieties facilitates site-specific controlled release. These strategies enhance drug delivery efficiency, augment therapeutic efficacy, and reduce side effects. This article reviews recent strategies and ongoing advancements in nDDSs for targeted drug delivery and controlled release, examining lesion-targeted nanomedicines through surface modification with small molecules, peptides, antibodies, carbohydrates, or cell membranes, and controlled-release nanocarriers responding to endogenous signals such as pH, redox conditions, enzymes, or external triggers like light, temperature, and magnetism. The article also discusses perspectives on future developments.

1. Introduction

Nanomedicine has revolutionized the pharmaceutical industry by enhancing the biological activities and mitigating side effects of drug molecules, thus creating unprecedented opportunities for preventing and treating a wide range of major diseases [1, 2]. The first Food and Drug Administration (FDA)-approved nanomedicine, Doxil® [PEGylated liposomal doxorubicin (DOX)], received authorization in 1995 for treating specific cancer types. This formulation prolongs circulation time by evading phagocytosis by the reticuloendothelial system, improves the pharmacokinetics and biodistribution of Doxil®, and reduces its severe cardiotoxicity [3]. Notably, Doxil® achieves highly stable Doxil® [PEGylated liposomal DOX loading through an ammonium sulfate gradient approach and facilitates localized DOX release in tumors. Subsequently, the clinical validation and commercial expansion of nanotherapeutics have grown rapidly, paralleling advancements in nanotechnology, medicine, and pharmacy. Table 1 provides a representative list of nano-drug therapies in the market and under clinical investigation. Nanocarriers possess unique properties, including small size, excellent drug-loading capacity, and flexible modification potential. These characteristics provide a crucial foundation for developing nanocarrier-based drug delivery systems (nDDSs) to address therapeutic needs [4, 5]. The typical nDDSs with marketed products for clinical disease treatment include liposomes, lipid nanoparticles (LNPs), polymeric micelles, polymeric nanoparticles (NPs), protein-based NPs, inorganic NPs, and nanocrystals (Fig. 1).

Targeted drug delivery involves the directed transport of therapeutic agents to specific sites, enhancing drug administration efficacy by mitigating non-specific toxic effects associated with indiscriminate distribution in conventional delivery methods and reducing the required drug quantity [6]. CALAA-01, a polymeric NP composed of cyclodextrin-containing PEG and human transferrin (Tf), exemplifies this approach. This pioneering polymer-based nDDS for tumor-targeted small interfering ribonucleic acid (siRNA) delivery entered clinical trials for solid tumor treatment [7]. It binds to overexpressed Tf receptors on liver cancer cells, facilitating internalization through receptor-mediated endocytosis. Nanocarriers enhance drug accumulation and penetration through nanosize-derived properties or by utilizing ligand molecules, including small molecules, peptides, antibodies, and carbohydrates, to interact with specific or overexpressed cell surface receptors, thereby selectively targeting intended lesion sites [8]. Recent advancements in biomimetic targeting strategies have attracted significant attention. These approaches endow nanocarriers with homotypic or heterotypic adhesion properties of preferred cells by camouflaging nanomaterials with plasma membranes derived from cancer cells, blood cells, or stem cells, enabling specific and effective cell targeting [9]. A diverse array of nDDSs for targeted delivery of therapeutic agents has been developed and investigated to address a broad spectrum of diseases, including cancer, atherosclerosis, ischemic stroke, Alzheimer's disease (AD), Parkinson's disease (PD), peritoneal fibrosis, rheumatoid arthritis, and Type 1 diabetes (T1D) (Fig. 2).

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https://doi.org/10.1016/S1875-5364(25)60861-2

Table 1 Nanotherapeutics in clinical applications or trials.

Trade name	Drug	Indication	Formulation	Phase
DaunoXom®	Daunorubicin citrate	Acute myeloid leukemia	Liposome	Approved
AmBisome®	AmB	Fungal infection	Liposome	Approved
Myocet®	DOX	Metastatic breast cancer	Liposome	Approved
Neulasta®	Pegfilgrastim	Neutropenia	Liposome	Approved
Lipo-Dox®	DOX	Acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma	Liposome	Approved
Onivyde®	Irinotecan	Metastatic adenocarcinoma	Liposome	Approved
Amvuttra®	Vutrisiran	Polyneuropathy (damage of multiple nerves throughout the body) with hereditary transthyretin-mediated amyloidosis	LNP	Approved
Spikevax®	mRNA	COVID-19	LNP	Approved
Gardasil®	Recombinant human papillomavirus (HPV)	HPV-associated disease	Virus-like particle	Approved
Engerix-B®	Recombinant hepatitis B lipid-associated surface antigen	Hepatitis B	Vaccine	Approved
Estrasorb™	Estradiol topical	Estrogen therapy	Micelle	Approved
Genexol-PM®	PTX	Breast cancer	Micelle	Approved
Apealea®	PTX	Ovarian neoplasms	Micelle	Approved
Eligard®	Leuprolide acetate	Prostate cancer	Polymeric NP	Approved
Krystexxa®	Pegloticase	Gout	Polymeric NP	Approved
Cimzia®	Certolizumab	Crohn's disease, Rheumatoid arthritis	Polymeric NP	Approved
Nanocoll®	Albumin, Stannous	Breast cancer, Melanoma	Albumin based NP	Approved
Abraxane®	PTX	Breast cancer	Albumin based NP	Approved
Copaxone®	Glatiramer acetate	Multiple sclerosis	Polypeptide colloidal	Approved
DexFerrum®	Ferric oxyhydroxide	Iron deficiency anemia	Inorganic NP	Approved
Monofer®	Iron, Isomaltoside	Iron deficiency anemia	Inorganic NP	Approved
Injectafer®	Ferric carboxymaltose	Iron deficiency anemia	Inorganic NP	Approved
Triglide®	Fenofibrate	Dyslipidemia	Nanocrystal	Approved
Avinza®	Morphine sulfate	Severe pain	Nanocrystal	Approved
LiPlaCis	Cisplatin	Metastatic breast cancer	Liposome	Phase Ⅰ, Ⅱ
mRNA-1944	mRNA	Chikungunya virus	LNP	Phase I
Paclical	PTX	Ovarian cancer	Micelle	Phase III
BIND-014	Docetaxel	Prostate cancer	Micelle	Phase II
NK105	PTX	Breast cancer	Micelle	Phase III
ONM-100	Indocyanine green	Peritoneal carcinomatosis, Breast cancer	Micelle	Phase Ⅱ
SEL-212	Pegsiticase, Rapamycin	Gout	Polymeric NP	Phase Ⅲ
AGuIX	Gadolinium	Brain metastases	Inorganic NP	Phase I

Stimuli-responsive nanotherapies have garnered significant attention in recent years for their potential to enhance precision and efficacy in disease treatment [10]. These innovative systems employ nanocarriers that undergo physical and chemical alterations in response to environmental triggers, facilitating controlled drug release through mechanisms such as swelling, shrinking, or degradation at specific locations, in contrast to passive diffusion (Fig. 3). The applicable stimuli encompass disease-associated endogenous biochemical signals, including abnormal pH, redox conditions, and overexpressed enzymes, as well as external stimuli such as light, temperature, and magnetism. Clinical and preclinical evaluations have demonstrated improved therapeutic outcomes for stimuli-responsive anticancer nanotherapies. For example, ThermoDox, a thermosensitive liposome, has completed Phase III trials for hepatocellular carcinoma treatment [11, 12]. ThermoDox is activated by radiofrequency-generated temperatures of 39–42 °C, which induce nanopore formation within the lipid structure, enhancing membrane permeability for DOX release at the target site. These stimuli-responsive properties enable programmable drug release configurations with temporal and spatial control [13]. This review highlights emerging approaches to disease treatment utilizing nDDSs for targeted and controlled drug therapies and discusses potential future challenges and developments.

2. Tissue-targeted drug delivery

2.1. Tumor targeting

Tumor-targeted nDDSs utilize passive or active accumulation of nanocarriers in tumor tissues. Passive targeting leverages

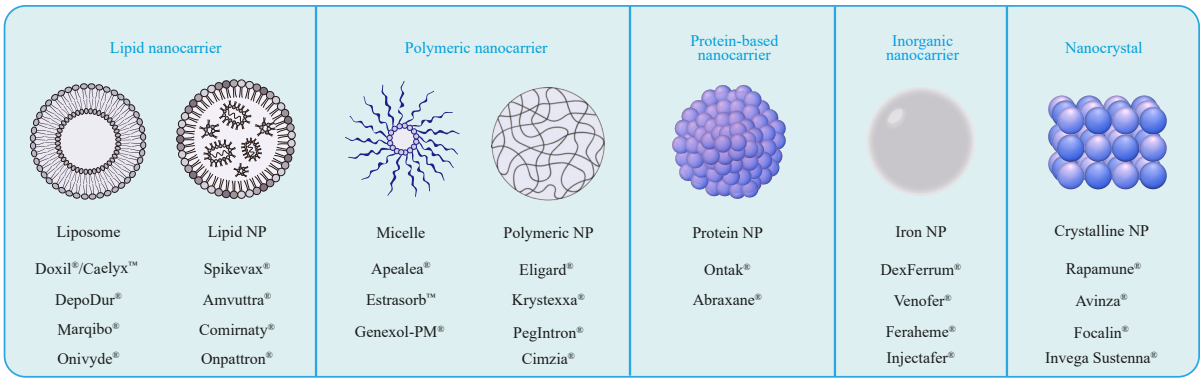

Fig. 1 Schematic of classification of representative nDDSs for clinical applications.

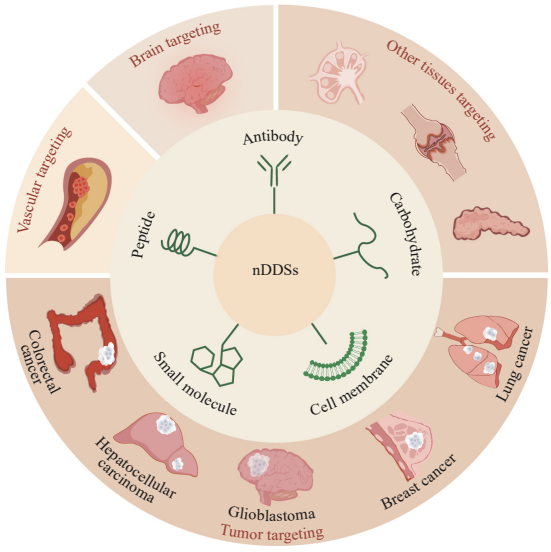

Fig. 2 Schematic of nDDSs with typical ligands of small molecules, peptides, antibodies, carbohydrates, and cell membranes for targeted transport of drug toward intended sites, such as tumor, vascular lesion (atherosclerotic plaque or thrombotic clot), brain and other tissues (lymph node, articular cavity or pancreas).

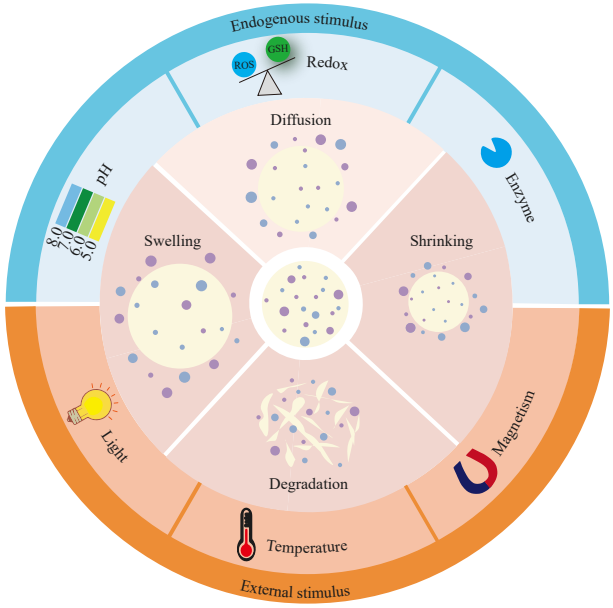

Fig. 3 Schematic of nDDSs with controlled drug release modulated by representative endogenous pathology-associated signals (pH, redox potential, enzyme, etc.) or external energy-mediated stimuli (light, temperature, magnetism, etc.). The release of drugs from nDDSs is accelerated by nanostructural changes such as swelling, shrinking, or degradation in response to these stimuli, in contrast to diffusion-based release.

the permeable vasculature and characteristic internal pressure of solid tumors for enhanced accumulation, a phenomenon known as the enhanced permeability and retention (EPR) effect [14, 15]. However, the EPR effect demonstrates significant heterogeneity, varying substantially between patients and metastases within the same individual. This variability is closely associated with the tumor's etiology, location, size, stage, and blood perfusion conditions [16]. For example, pancreatic and prostate cancers typically exhibit lower vascular density, presenting reduced EPR effects compared to hepatocellular and renal cell carcinomas. In large tumor centers, the vascular system is often fragmented due to high physical pressures and vascular dynamics, impeding the observation of the EPR effect in these regions. Active delivery of nanocarriers, employing ligand-receptor interactions, offers a potential strategy to address the limitations of targeting specific tissues beyond the EPR effect. In active targeting, nanocarriers bind to specialized bioreceptors on tumor cells through molecular recognition of surface-bound ligands, minimizing non-target cell uptake and enhancing accumulation within the tumor [17]. Various ligands have been identified to facilitate positive drug targeting, including small molecules, peptides, antibodies, and carbohydrates. Table 2 presents a compilation of nanocarrier-based active targeting therapies for various cancers (Table 2).

2.1.1. Small-molecular ligands

Small molecules such as folic acid (FA), biotin, and anisamide are increasingly utilized as targeting ligands for modifying nDDSs and enhancing tumor-targeted delivery. These ligands present several advantages, including cost-effective production, high stability, and ease of processing [18–23]. FA demonstrates elevated affinity and sensitivity for folate receptors (FRs), which are overexpressed 100- to 300-fold in various cancers compared to normal tissues [24–30]. Shi et al.[31] developed multistep targeting nanostructured lipid vectors using alendronate-polyethylene and folate-polyethylene glycol monostearate. Alendronate-mediated aggregation of its conjugates occurred in osteoblast regions surrounded by highly vascularized red marrow. FA-modified liposomes bound to FR-expressing cells, resulting in 2.4-fold higher endocytosis of liposomes and increased intracellular drug concentration compared to non-functionalized liposomes. This dual-targeting system effectively localized the site of minimal residual disease and leukemia cells, successfully reducing white blood cell counts to normal levels.

Biotin plays a crucial role in regulating metabolic reactions and chromatin remodeling [32, 33]. In addition to FA, biotin is recognized as a promising tumor-targeting small-molecular ligand, capable of targeting the sodium-dependent multivitamin transporter (SMVT) on cancer cells [34]. A study conducted by Patil

Table 2 Representative tumor-targeted nDDSs.

Type	Ligand	Targeted	Nanocarrier	Drug	Indication	Ref
Small molecule	FA	FR	NP	Cabazitaxel	Prostate cancer	25
				DOX	Nephrogenic systemic fibrosis	26
				DOX	Qsteosarcoma	27
				Methotrexate (MTX)	Breast cancer	28
	Biotin	SMVT	Liposome	PTX	Breast cancer	32
	Anisamide	Sigma receptor	NP	Ursolic acid	Melanoma	37
			Micelle	Sunitinib base	Melanoma	38
	MTX	FR	NP	Methotrexat	Lung carcinoma	20
	Fucose	Lectin receptor	NP	MTX	Breast cancer	23
Peptide	RGD	Integrin	NP	ICG	Glioblastoma	39
			Liposome	PTX	Breast cancer	58
				PTX	Melanoma	59
	IL-13	IL-13 receptor	NP	DOX	Glioblastoma	55
	G11	EGFR	NP	C6-ceramide	Human ovarian adenocarcinoma	41
	DUP1	PSMA	Micelle	PTX	Prostate tumor	43
	G12	Glypican-3	Liposome	Sorafenib, IR780	Hepatocellular carcinoma	44
	SP94	Liver tumor cell	Liposome	ICG, DOX	Hepatocellular carcinoma	47
	Angiopep-2	Low-density lipoprotein receptors	NP	siRNA	Glioblastoma	53
	Lactoferrin	Lactoferrin receptor	NP	DOX	Glioblastoma	141
Antibody	CET	EGF receptor	NP	Boronated CET	Glioma	66
				DOX	Colorectal cancer	67
			Liposome	DOX	Breast cancer	202
	HER2	HER2	NP	PTX	Ovarian cancer	68
				PTX	Breast cancer	70
	IGF-IR	IGF-IR	Nanohorn	Vincristine	Hepatocellular carcinoma	76
Carbohydrate	HA	CD44	Liposome	DOX	Breast cancer	83
			LNP	DOX, Baicalein	Breast cancer	85
			NP	PTX	Hepatocellular carcinoma	86
				Morin hydrate	Ascitic tumor	87
				ICG, DOX	Breast cancer	91
			Micelle	Curcumin	Osteosarcoma	95
			Polymersome	Granzyme B	Multiple myeloma	96
	Mannose	Mannose receptor	Liposome	Rifabutin	Tuberculosis	79
				5-Fluoracil	Hepatocellular carcinoma	82
Cell membrane	Platelet membrane	Heterotypic adhesion	Nanocrystal	DOX, Vancomycin	Breast cancer	102
				PTX	Breast cancer recurrence post-surgery	105
			Liposome	Bortezomib	Thrombus	104
				Emtansine	Breast cancer	107
				PTX	Breast cancer	108
	Immune cell membrane	Heterotypic adhesion	NP	DOX	Liver cancer	112
				PTX, Disulfiram	Lung cancer	114
			Liposome	PTX	Glioblastoma	142

et al.[35] utilized biotin-functionalized poly(L-lactide-co-glycolide) (PLGA) NPs to co-deliver paclitaxel (PTX) and a P-glycoprotein inhibitor for treating drug-resistant tumor cells. The biotin-modified PLGA NPs exhibited a 6-fold increase in PTX accumulation within tumor cells, enhanced cytotoxicity, and effectively overcame drug resistance compared to unmodified PLGA NPs.

Anisamide, a small benzamide molecule, can be attached to NP surfaces to enhance binding to the sigma-1 receptor on cancer cells [36]. Li et al. [37] developed micelles using an anisamide-decorated distearoyl phosphatidylethanolamine polyethylene glycol

(DSPE-PEG) conjugate (DSPE-PEG-AA) to improve ursolic acid accumulation in tumors *via* sigma receptor-mediated endocytosis. This strategy led to a 53% reduction in tumor growth rate following micelle treatment. In a related study, Huo et al. [38] utilized anisamide-modified micelles for targeted sunitinib delivery to tumors, achieving a two-fold increase in intratumoral sunitinib accumulation compared to oral suspension due to the micelles' enhanced targeting ability and stability. The sunitinib-loaded micelles inhibited tumor growth by suppressing tyrosine kinase activity and modulating the tumor microenvironment (TME). Additionally, when combined with a tyrosinase-associated protein vaccine, these micelles enhanced the vaccine's efficacy against advanced tumors.

2.1.2. Peptide ligands

Peptides are short chains of amino acids typically containing fewer than 50 residues and can exist in linear, branched, or cyclic forms [39–46]. Their low production cost, good stability, and ease of conjugation to nanocarrier surfaces make peptides such as arginylglycylaspartic acid (RGD), A54, interleukin-13 (IL-13), and C16Y popular choices as targeting ligands for specific receptors [47–55]. Angiogenesis, a key process in tumor development, is associated with increased expression of vascular endothelial growth factor (VEGF) receptors [56] and integrins [57] on endothelial cells. The RGD peptide, with its high affinity for the αvβ3 integrin receptor, serves as a distinctive molecular ligand for tumor targeting and is the most commonly used modified peptide for nanocarriers [58]. The fundamental sequence of the RGD peptide is Arg-Gly-Asp, with common nanomodification variants including Cys-Arg-Gly-Asp-Lys (CRGDK), cyclo RGD (cRGD) and cyclo Arg-Gly-Asp-D-Tyr-Cys (cRGDyC). Du et al. [59] developed CRGDK peptide-modified sterically-stabilized NPs containing a linoleic acid-PTX conjugate to target integrins on tumor endothelial cells. This peptide-modified liposome demonstrated a 2-fold increase in tumor accumulation in a melanoma mouse model compared to unmodified liposomes.

Phage A54 (sequence AGKGTPSLETTP) is a peptide with dual functionality: hepatocarcinoma-homingcapability and selective conjugation ability. Du et al. [60] developed PEGylated stearic acid-grafted chitosan (A54-PEG-CS-SA) micelles, employing the A54 peptide as a targeting ligand. Within 24 hours, approximately 50% of these micelles were internalized by hepatocarcinoma cells, demonstrating their specific uptake ability *in vitro*. Furthermore, the DOX-loaded al. 60 prepared a PEGylated stearic acid-grafted chitosan (A54-PEG-CS-SA) micelles exhibited significant distribution in hepatic tumor tissues, leading to enhanced tumor growth suppression and reduced potential toxicity.

The IL-13 peptide functions as an effective targeting ligand for the IL-13 receptor, which is highly expressed in various malignant tumors but minimally present or undetectable in normal tissues. Wang et al. [55] employed the IL-13 peptide as a glioma-targeting ligand to modify silica NPs for DOX delivery. Intracellular trafficking studies revealed that NPs modified with the IL-13 peptide markedly enhanced drug uptake and accumulated in the nucleus within 5 minutes, leading to improved targeting efficiency.

2.1.3. Antibody ligands

Antibodies have a long-standing history among biological ligands in precisely targeting tumor receptors [61]. NPs conjugated with antibodies can facilitate a guided drug delivery approach for specific targeting by delivering payloads to tumor tissue. Three extensively studied targets in antibody-functionalized NPs for cancer therapy are epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and prostate-specific membrane antigen (PSMA) [62–64].

The EGFR family is recognized as one of the most extensively studied receptors involved in tumor metabolism and target adaptation [65, 66]. Cetuximab (CET) selectively binds to EGFR on the surface of various cancer cells, inhibiting intracellular signal transduction pathways. This process suppresses proliferation and induces apoptosis of cancer cells, consequently reducing the production of matrix metalloproteinases (MMPs). Ye et al. [67] engineered antibody-drug conjugate (ADC)-coupled bovine serum albumin (BSA) NPs through optimized adsorption, targeting CET-valine-citrulline-DOX immunoconjugates onto BSA NPs. This nanomedicine was designed to specifically target EGFR and enhance the localized release of chemotherapeutic agents within tumor tissues while minimizing their distribution to healthy tissues.

HER2, a member of the HER family of receptor tyrosine kinases, promotes tumorigenesis and metastasis through dimerization or heterodimerization with other HER family members [68–70]. This interaction initiates autophosphorylation of tyrosine residues within the receptor's cytoplasmic domain, activating downstream signaling pathways that contribute to cancer progression. Monoclonal antibodies targeting HER2, such as Herceptin® and Perjeta®, have been employed as antibody-drug conjugates (ADCs) to deliver cytotoxic chemotherapy specifically to cancer cells [71]. Ngamcherdtrakul et al. [72] developed mesoporous silica NPs conjugated with anti-HER2 antibodies for efficient siRNA delivery. These NPs increased siRNA half-life and enhanced tumor-specific uptake by over 90%. Treatment with these NPs effectively induced apoptosis in HER2-positive breast cancer cells while sparing HER2-negative cells from programmed cell death.

PSMA, a transmembrane protein, demonstrates expression levels directly proportional to the biochemical recurrence risk of prostate cancer [73,74]. ADCs targeting PSMA or anti-PSMA antibody-conjugated NPs efficiently deliver antitumor agents to prostate tumors, followed by rapid internalization by tumor cells. Czerwińska *et al.* [75] developed a radioimmunoconjugate combining anti-PSMA antibody with NaA nano-zeolite carrier. The PSMA-positive prostate cancer C4-2 cells exhibited nearly four-fold higher sensitivity to the nanocarrier compared to PSMA-negative prostate cancer DU-145 cells, suggesting that the PSMA receptor on C4-2 cells enhanced the target selectivity and internalization of the radioimmunoconjugate. In addition to these conventional therapeutic targets, researchers have investigated other tumor-associated biomarkers as potential targets, including Tf receptors and insulin-like growth factor-I receptor (IGF-IR) [76].

2.1.4. Carbohydrate ligands

Carbohydrates, fundamental components in living organisms, serve not only as energy sources but also as a distinct class of informative biomolecules. They have been employed as targeting ligands to precisely deliver NPs to tumors due to their superior biocompatibility and unique specific recognition by selected cell surface proteins [77–82]. The most frequently utilized carbohydrate-targeting molecules, such as galactose, mannose, and hyaluronic acid (HA), can be specifically recognized by plasma membrane proteins with carbohydrate-binding structural domains, including anomeric glycoprotein receptor, mannose receptor, selectin, and hyaluronan receptor [83–85]. Cluster of differentiation 44 (CD44), a transmembrane cell surface protein, is prominently expressed in numerous cancer cells, including breast, melanoma, and liver cancers [86–89]. HA, a negatively charged naturally acidic polysaccharide, is applied as a ligand for tumor targeting due to its non-immunogenicity, excellent biocompatibility, and strong affinity to the CD44 receptors, thereby enabling active targeting of anticancer drug delivery [90–92]. Shen et al. [93] synthesized a polymer-drug conjugate, nitroimidazole-modified HA-oxalic acid-camptothecin (CPT) conjugate, which can assemble into NPs and physically encapsulate all-trans retinoic acid (ATRA) to obtain ATRA/CPT-NP. These NPs enhanced drug accumulation in breast tumors enriched with cancer stem-like cells (CSCs)

through high HA/CD44 binding interactions and adaptively released two drugs during differentiation of CSCs, demonstrating efficacy in suppressing growth, relapse, and metastasis of CSC-enriched heterogeneous breast tumors. Zheng et al. [94] synthesized TP liposome coated with HA, which facilitated the entry of TP into the tumor for improved therapeutic efficacy of breast cancer with reduced systemic toxicity. Xi et al. [95] developed micelles using amphiphilic alendronate-HA-octadecanoic acid for targeting osteosarcoma and delivering the hydrophobic anticancer drug curcumin. Curcumin-loaded alendronate-HA micelles exhibited a 3.5-fold higher targeting to bone with effective antitumor effects and inhibited the recurrence of primary malignant bone tumors compared to unfunctionalized HA micelles. Granzyme B encapsulated within HA-functionalized polymers demonstrated favorable targeting efficacy towards CD44 overexpressing multiple myeloma, promoting high aggregation of granzyme B in the bone marrow and significantly ameliorating osteoporosis in mice [96].

2.1.5. Cell membranes

Biofilm-coated NPs have emerged as promising vehicles for cancer therapy due to their inherent advantages of antigenic diversity and immune evasion capabilities on cell membrane surfaces [97–101]. Platelets, nucleated blood cells derived from megakaryocytes [102–104], vessels and aggregate at primary tumor sites through physical interactions between tumor cell integrins and platelet surface receptors. Inspired by the efficient and selective adhesion of platelet membranes to damaged blood vessels, Mei et al. [105] developed a stealth nanosystem comprising spherical PTX nanocrystals as the core, encapsulated by an outer shell of platelet membranes. This biomimetic NP system targeted surgically induced coagulation sites, effectively eliminating minimal residual tumors and mitigating conventional chemotherapy-induced toxicity.

Leukocytes are immune cells that play a vital role in defending the body against pathogens and eliminating damaged host cells [106]. These cells are classified into two primary systems: the innate immune system, which includes macrophages, neutrophils, natural killer cells, and dendritic cells, and the adaptive immune system, consisting of T and B cells [107, 108]. The inherent ability of leukocyte membranes to target inflammatory sites makes them valuable for coating NPs in tumor-targeted drug delivery. Parodi et al. [109] developed nano-porous silica particles encapsulated in leukocyte-derived cell membranes. These nanocarriers exhibited preferential binding to inflamed endothelium through the interaction of lymphocyte function-associated antigen 1 and intercellular adhesion molecule-1 on endothelial cell surfaces during inflammation. This interaction enhanced chemotherapeutic drug transport across the endothelial layer and improved tumor accumulation. In a separate study, Kang et al. [110] created nanoparticle-based drug delivery systems (nDDSs) using neutrophil membrane-coated PLGA NPs (NM-NP). The transfer of membrane-associated proteins from neutrophils to NM-NP surfaces resulted in increased cellular relevance in the 4T1 cell model under shear flow and more efficient trapping of circulating tumor cells (CTCs). NM-NP containing carfilzomib, a proteasome inhibitor, effectively depleted CTCs in blood circulation, thereby preventing the formation of pre-metastatic niches and inhibiting tumor metastasis.

Beyond the heterotypic adhesion of platelets and leukocytes to tumors, cancer cell membranes bearing tumor-specific antigens, receptors, and surface adhesion molecules exhibit homotypic binding properties. This characteristic enables NPs coated with tumor cell membranes to effectively target homologous tumors [111–113]. Mohammad et al. [114] engineered cancer cell membrane-encapsulated bio-NPs for the delivery of PTX and disulfiram. Compared to heterogeneous cell membrane-encapsulated NPs, these cancer cell membrane-coated NPs demonstrated selective recognition of source cells and facilitated a 9-fold increase in chemotherapeutic accumulation through homotypic binding mechanisms. Furthermore, researchers have explored and utilized various unconventional membrane types, including those derived from fibroblasts, bacteria, and hybrid cells, to functionalize NPs for tumor-targeted drug delivery [115–121].

2.2. Vascular targeting

Vascular aging manifests through functional and structural changes in the vasculature, characterized by lumen enlargement, increased vascular stiffness, and decreased vascular elasticity [122]. This aging process represents a significant risk factor for vascular disease and contributes substantially to the development and progression of cardiovascular and cerebrovascular disorders. Cardiovascular disease has emerged as the primary cause of non-communicable disease mortality globally [123]. Despite the availability of numerous therapeutic options for cardiovascular disease, treatment efficacy is often limited by the drug's ability to reach the target tissue. Nanoscale drug delivery systems (nDDSs) prolong the presence of drugs in the circulatory system by avoiding rapid renal excretion and facilitate exudation through the vascular system by utilizing active targeting properties, promoting effective accumulation and distribution at specific lesion sites. Inspired by the recruitment of stem cells to vascular injury sites by platelets, Tang et al. [124] developed platelet nanovesicle-fused cardiac stem cells (PNV-CSCs) for delivery to myocardial infarction injury sites. The modified cardiac stem cells expressed platelet surface markers associated with platelet adhesion at the injury site, resulting in PNV-CSCs selectively binding to collagen-coated surfaces and subendothelial clefts. PNV-CSCs, retaining the targeting and repair capabilities of the parental cell type, enhanced cardiac preservation and reduced infarct size.

Atherosclerosis is a cardiovascular disease characterized by the formation of atherosclerotic plaques, which are marked by an abnormal accumulation of lipids within the arterial wall due to endothelial cell dysfunction [125] and macrophage malfunction [126–128]. To implement a dual-cell therapeutic approach, Wu et al. [129] developed a biomimetic liposome (AP-Lipo) modified with phosphatidylserine (PtdSer) and DSPE-PEG-cRGDfK, which selectively delivered the PPARγ agonist pioglitazone to atherosclerotic lesions. al. 129 developed a biomimetic liposome (AP-Lipo) targeted activated vascular endothelial cells through the interaction between cRGDfK and αβ3 integrin and was subsequently internalized by atherosclerotic macrophages *via* the apoptotic body biomimetic “eat me” signaling of PtdSer. In a mouse model of atherosclerosis, AP-Lipo mitigated disease progression by increasing M2 macrophage polarization, thereby eliciting an anti-inflammatory response. This approach demonstrated superior efficacy compared to conventional pioglitazone treatment, which failed to significantly reduce plaque areas. Zhao et al. [130] developed a dual-targeted core-shell nanoplatform to deliver siRNA against lectin-like oxidized low-density lipoprotein receptor-1 and atorvastatin, providing sequential and selective drug access to endothelial cells and macrophages. The core-shell NPs consisted of a PLGA core encapsulating atorvastatin and complexing siRNA, a lipid bilayer for cholesterol reception, apolipoprotein A-I for macrophage targeting, and an outermost layer of HA for endothelial cell targeting. This bifunctional core-shell NP effectively delivered drugs to endothelial cells and macrophages, resulting in a 39% smaller plaque area ratio and a 63% reduction in lipid accumulation. This synergistic effect promoted atherosclerotic plaque regression by enhancing the removal of intracellular lipids and diminishing inflammation.

Cerebrovascular disease encompasses cerebral hemorrhage and ischemic stroke, with the latter accounting for over 80% of

cases [131, 132]. Intravenous thrombolysis is the primary life-saving procedure for ischemic stroke patients. The efficacy of thrombolytic therapy is time-sensitive, with treatment within a specific window effectively alleviating patients' neurological impairment. However, thrombolytics present significant challenges, including a high risk of treatment failure and intracranial hemorrhage due to non-specific distribution and off-target effects. To address these limitations, nDDSs have been developed to overcome thrombotic targeting barriers and extend the circulation time of therapeutic agents, thereby enhancing ischemic stroke treatment [133]. Xu et al. [134] presented a closed-loop delivery system of hirudin (HV/ctNG) comprising self-regulating nanogels for anticoagulant therapy, which dynamically modulated hirudin release in direct correlation with the pathological process of thrombosis. HV/ctNGs protected hirudin from plasma protein hydrolysis, and clot-targeted CR(NMe)EKA peptide ligands promoted aggregation of nanogels in the thrombus. The half-life of hirudin supplied by HV/ctNGs was greatly prolonged compared to free hirudin. HV/ctNGs preferentially accumulated in intravascular thrombus in an *in vivo* mouse model. Xu et al. [135] developed platelet membrane-camouflaged PLGA polymer NPs for the delivery of recombinant tissue-type fibrinogen activator (rt-PA) to thrombus sites. These NPs exhibited superior thrombus targeting efficiency compared to free rt-PA, increasing survival rates to 70% in a mouse model of ischemic stroke.

2.3. Brain targeting

The blood-brain barrier (BBB) serves as a biological barrier between the circulatory system and cerebral tissue, comprised of tightly joined endothelial cells in brain capillaries. This barrier effectively protects neural tissue from the infiltration of harmful substances [136, 137]. However, the BBB poses a significant obstacle in the treatment of central nervous system (CNS) disorders, as it impedes up to 95% of CNS-targeted drugs from reaching their intended site of action [138].

Glioblastoma remains a lethal CNS tumor with no effective treatment currently available [139]. A significant challenge in nanomedicine-based glioblastoma treatment is the inability of chemotherapeutic agents to traverse the BBB, impeding blood circulation and deep tumor penetration [140]. To address this issue, researchers have developed dual-targeted nanocarriers designed to enhance BBB penetration and specifically bind to the tumor site [141]. Zhou et al. [142] introduced PTX-loaded bionic chemotherapeutic nanomedicine (PTX@C-MMCL), a PTX-loaded bionic chemotherapeutic nanomedicine that combines macrophage and glioblastoma cell membranes for efficient brain tumor targeting. This innovative approach enables PTX@C-MMCL to cross the BBB *via* macrophage membranes and utilize the homotypic aggregation capacity of tumor cells through glioblastoma cell membranes. The spatiotemporal sequential delivery demonstrated effective inhibition of glioblastoma progression.

AD and PD represent the most prevalent neurodegenerative disorders worldwide. AD is characterized by memory loss and cognitive decline, stemming from irreversible neuronal damage caused by extracellular deposits of β-amyloid peptides and phosphorylated tau proteins [143]. The BBB and the requirement for specific neuronal targeting present significant challenges for nanocarriers in AD treatment. Guo et al. [144] developed a dual-ligand fusion peptide to enhance nanocarriers' capacity to target brain neurons specifically. When attached to NPs, the fusion peptide exhibited superior BBB crossing and neuronal targeting compared to monopeptide modification, significantly improving spatial learning and memory deficits in AD mouse models. PD arises from reduced dopamine levels due to dopaminergic neuron degeneration in the brain, with clinical manifestations including dyskinesia, postural instability, muscle rigidity, and resting tremors [145]. While levodopa remains the primary treatment for PD, its therapeutic efficacy is limited by poor BBB permeability. Additionally, frequent dosing is necessary to maintain high bioavailability, but prolonged levodopa administration may increase the risk of dyskinesia. Mogharbel *et al.* [146] engineered micelles composed of poly(ethylene oxide) (PEO) and poly(ε-caprolactone) (PCL) as a delivery system for the co-administration of levodopa and curcumin in PD treatment. NPs with glutathione (GSH) coating as a brain-targeting ligand enhanced bioavailability and therapeutic efficacy in neurons, facilitating the synergistic delivery of levodopa and curcumin across the BBB.

2.4. Other tissue targeting

The lymphatic system plays a crucial role in maintaining fluid homeostasis, regulating lipid metabolism, and supporting immune defense, which influences various diseases, including inflammatory and metabolic disorders, as well as cancer [147]. Developing lymph-targeted nDDSs enhances vaccination, tolerance induction, and optimization of cancer therapy. The selective delivery of NPs to lymph nodes is determined by the size, charge, and conjugated ligands of carriers. For effective lymphatic system targeting, NPs ideally range between 10 and 100 nm in diameter, as they possess optimal permeability properties and facilitate productive uptake by lymphatic vessels [148]. The shape of NPs significantly affects their interaction with antigen-presenting cells (APCs), as the contact angle influences the efficiency of NP endocytosis by macrophages and dendritic cells. Spherical NPs with smaller contact angles are more readily absorbed and effective for APC activation. The negatively charged tissue interstitium extracellular matrix substantially influences the transport of charged substances. Negatively charged NPs demonstrate enhanced stability and compatibility with biological systems, leading to more efficient accumulation in lymph nodes through interstitial water channels. Surface ligand-decorated NPs are utilized to target lymphatic-specific receptors, such as lymphatic vessel endothelial hyaluronan receptor 1, VEGF receptor 3, and peripheral node-addressing proteins, which can target lymph nodes and enhance lymphatic endothelial interactions [149]. Inspired by engineered tumor cell membranes with exogenous antigenic functions, Liu et al. [150] developed lymph-targeted NPs (R837/LNP-M-L) encapsulating imiquimod and wrapped by cancer cell membranes for conjunction with prophylactic and therapeutic cancer vaccines. R837/LNP-M-L effectively promoted co-delivery of immunogens and adjuvants to lymph nodes, inducing dendritic cell activation and cytotoxic T lymphocyte responses. These lymph-targeted NPs demonstrated inhibition of tumor growth and enhanced efficacy of anti-PD1 against stemness-derived immune-resistant melanoma.

Rheumatoid arthritis, a chronic autoimmune disorder, is characterized by abnormal vascularity and impaired lymphatic drainage in inflamed regions, exhibiting increased permeability and EPR effects analogous to tumors. Activated macrophages secrete pro-inflammatory cytokines, resulting in substantial joint and cartilage deterioration. Modifying nanocarriers with ligands to effectively target activated macrophages represents a promising approach for anti-rheumatic therapy. Chen et al. [151] engineered FR-targeted liposomes co-encapsulating methotrexate and catalase. These liposomes penetrated the synovial lumen during circulation *via* the EPR effect, followed by FR-mediated endocytosis, specifically targeting activated macrophages and releasing drugs for enhanced rheumatoid arthritis treatment.

Peritoneal fibrosis, a common complication of prolonged peritoneal dialysis, significantly hinders the continuation of dialysis in patients with end-stage renal disease. The increased expression of CXC chemokine receptor type 4 (CXCR4) on peritoneal mesothelial cells enhances their migration capability and ex-

tracellular matrix production, ultimately leading to scar tissue formation and peritoneal fibrosis. Asifullah et al. [152] developed a CXCR4 receptor-targeted liposome to deliver a combination of CXCR4 antagonist and sulfotanshinone IIA sodium to the fibrotic peritoneum. These NPs exhibited specific peritoneal targeting and notable effectiveness in reversing peritoneal fibrosis.

The pancreas plays a pivotal role in metabolic processes, converting ingested nutrients into cellular energy and regulating blood glucose through its endocrine function [153]. However, the pancreas possesses a natural blood-pancreas barrier that hinders drug delivery from blood vessels to target areas, thereby reducing drug concentration in pancreatic tissue and diminishing treatment efficacy. Zhang et al. [154] developed pancreatic tissue and compromising treatment efficacy. Zhang et al. [154] developed PD-L1 overexpressing platelets (PD-L1-platelets) to target inflamed pancreas, which protected insulin-producing β-cells from damage by inhibiting pancreatic self-reactive T-cell activity in neohyperglycemic non-obese diabetic mice. PD-L1-platelets traversed the barrier and accumulated in the pancreas due to the precise targeting of platelets to inflammatory tissues, resulting in 75% of diabetic mice maintaining normoglycemia levels after 30 days.

The primary aim of targeted nanoparticle drug delivery systems (nDDSs) is to enhance drug homing, thereby increasing payload delivery efficiency to the lesion site, reducing drug toxicity, and extending survival. To achieve this objective, researchers have developed multiple strategies to mitigate the off-target effects of existing medications. These approaches involve functionalizing nanocarrier surfaces to target various disease sites, including tumors, vasculature, brain, lymph nodes, abdomen, and pancreas. As modern biomedical science and technology progress, accurate biomarker analysis of patient lesions, based on histology and nanosensor technology, is conducted to determine personalized formulations of clinically targeted drugs [155]. Moreover, these nanomedicines can be engineered with artificial intelligence algorithms to navigate intelligently through variable disease microenvironments, enabling selective targeting and more precise agent delivery.

3. Stimuli-triggered drug release

nDDSs can be optimized to create multifunctional stimuli-responsive nanosystems that react to TME with its distinctive characteristics, including acidic pH, elevated levels of GSH and reactive oxygen species (ROS), and overexpression of specific enzymes [156]. Moreover, external and artificial stimuli can be utilized, such as various forms of irradiation, temperature fluctuations, and magnetic fields [157]. These nanocarriers maintain stability during blood circulation, enabling high drug concentration at the tumor site. Subsequently, they respond to endogenous or external triggers, releasing drugs at the target locations as required (Table 3).

3.1. Endogenous stimuli-triggered drug release

3.1.1. pH

pH variations across different *in vivo* microenvironments are commonly exploited to engineer stimuli-responsive nDDSs for regulated drug distribution [158, 159]. While normal tissues maintain a pH of approximately 7.0, extracellular tumor environments exhibit pH values between 6.0 and 7.0, with endosomal pH descending below 6.0 [160, 161]. pH-responsive delivery systems release drugs under specific pH conditions, potentially improving efficacy and reducing side effects. Moreover, co-delivery systems encapsulating multiple medications can release drugs sequentially in response to varying pH conditions, potentially enhancing synergistic effects in drug combinations [162].

pH-responsive nanocarriers are designed with chemical bonds in their structure that can be cleaved by pH changes, including ester [163], amide [164], and hydrazone bonds [165]. These chemical bonds remain stable at physiological pH but become unstable at lower pH values, leading to drug release through carrier collapse or rupture of drug-polymer conjugates. Du et al. [166] modified poly (L-lysine) on mesoporous silica NPs using benzoic imine bonds for glucose oxidase (GOx) and PTX delivery. When entrapped in endosomes, drugs were released from the mesoporous silica NPs due to hydrolysis of the benzoic imine bond and detachment of the coated poly(L-lysine), enabling the combination of starvation therapy and chemotherapy.

An alternative approach involves the utilization of amino groups within carrier materials for drug encapsulation and release [167]. When the pH falls below the acid dissociation constant, protonation of the amino group initiates drug release from the carrier [168], resulting in a proton sponge effect and endosomal escape for intracellular drug delivery [169]. Huo et al. [170] developed self-assembled NPs using methotrexate and 3-diethylaminopropyl isothiocyanate (DEAP)-conjugated hydroxyethylchitosan to deliver quercetin. In the mildly acidic TME, the designed methotrexate and DEAP protonation caused the NPs to dissolve, releasing quercetin. This process inactivated tumor-associated fibroblasts, thereby enhancing subsequent drug penetration and inhibiting tumor metastasis.

3.1.2. GSH

GSH plays a crucial role in designing stimuli-responsive nDDSs, exploiting the significant difference in GSH concentrations between extracellular and intracellular environments [171]. While GSH concentrations in blood and extracellular matrices range from 2 to 20 μmol·L^{-1}, intracellular concentrations reach 0.5–10 mol·L^{-1}, with tumor cells exhibiting levels at least four times higher [172]. This concentration gradient enables nanocarriers to maintain stability at lower extracellular GSH levels while becoming unstable at higher intracellular levels. This characteristic is essential for achieving rapid intracellular release within tumor tissue while minimizing release at off-target sites [173].

Extensive research has established the pivotal role of disulfide bonds in the structure of reduction-responsive materials [174–176]. Amphiphilic conjugates self-assemble through disulfide bonding and decompose upon entering highly reducing cytoplasm. Huo et al. [177] developed an assembly of redox-sensitive amphiphilic conjugates for the co-delivery of silibinin (SB) and PTX. The cargo was released in response to the reductive cellular microenvironment due to poly-disulfide crosslinking, enhancing the nanomedicine's permeability. Yin et al. [178] engineered a multifunctional nanoparticle (HA-PSR) with a redox-sensitive core and HA shell. The core material, designed to co-encapsulate PTX and siRNA, was fabricated using octyl-modified polyethyleneimine incorporating disulfide bonds, while thiolate HA was assembled onto the anionic shell. HA-PSR targeted CD44-overexpressing tumors through passive and active targeting mechanisms. Subsequently, gene therapeutic agents and small chemotherapeutic molecules were simultaneously released from the nanovector into cancer cells due to the cleavage of disulfide bonds by reducing agents, resulting in an enhanced synergistic antitumor effect.

3.1.3. ROS

Elevated levels of ROS, such as hydrogen peroxide (H_2O_2), hydroxyl radicals, and superoxide at tumor sites, play a crucial role in tumorigenesis and progression [179, 180]. The incorporation of responsive moieties containing elements like sulfur, boron, and tellurium into the structure of nDDSs enables ROS-responsive drug release [181–183]. Luo et al. [184] developed a prodrug-based ROS-stimulated response carrier (PPAHC) comprising chlorambucil

Table 3 Stimuli-responsive nDDSs for controlled drug release.

Stimulus	Indication	Nanocarrier	Drug	Ref
pH	Breast cancer (MCF7, 4T1 cell)	NP	DOX, Tannic acid, IR820	160
	Breast cancer (MCF7 cell)	Micelle	Mitoxantrone	164
	Breast cancer (4T1 cell)	Micelle	PTX	168
		NP	Methotrexate, Quercetin	170
	Lung cancer (LLC cell)	NP	Erlotinib, DOX	162
	Melanoma (A375 cell)	NP	Metformin, DOX	163
	Melanoma (B16F10 cell)	NP	Gambogic acid	165
	Hepatocellular carcinoma (HepG2 cell)	NP	GOx, PTX	166
	Ovarian cancer (Skvo3 cell)	Micelle	DOX, Betulinic acid	167
GSH	Breast cancer (MDA-MB-231 cell)	NP	DOX	175
		Micelle	PTX	173
	Breast cancer (4T1 cell)	NP	PTX, SB	177
	Hepatocellular carcinoma (HepG2 cell)	NP	DOX	172
		Micelle	Gambogic acid	174
	Lung cancer (A549 cell)	NP	PTX	176
		NP	PTX, siRNA	178
ROS	Cervical carcinoma (Hela cell)	Micelle	DOX	182
	Melanoma (B16F10 cell)	Nanovaccine	TRP2 peptide antigen	181
		NP	Gambogic acid, Qrotoporphyrin IX	183
	Breast cancer (MCF7 cell)	NP	Chlorambucil, Quinone methide	184
	Breast cancer (4T1 cell)	NP	LST, PTX	185
	Breast cancer (MDA-MB-231, 4T1 cell)	NP	PTX, shKIAA	186
Enzyme	Breast cancer (4T1 cell)	NP	Docetaxel, Imatinib	189
	Hepatocellular carcinoma (HepG2 cell)	Micelle	PTX, Sorafenib	188
	Ascites tumor (S180 cell)	Micelle	PTX	191
	Lung cancer (A549 cell)	NP	TRAIL, siHSP70	192
Light	Breast cancer (4T1 cell)	Liposome	ICG	198
		Liposome	IR780	202
	Breast cancer (MCF7 cell)	NP	DOX, $FeCl_3$, Tannic acid	203
Temperature	Glioma (C6 cell)	Micelle	DOX	213
	Lung cancer (Lewis malignant cell)	Liposome	VB	216
Magnetism	Breast cancer (SKBR-3 cell)	NP	DOX	219

with a self-immolation linker 4-(hydroxymethyl) phenylboronic acid for the delivery of a deoxyribonucleic acid (DNA) alkylating agent. PPAHC nanomedicines released chlorambucil in response to H_2O_2 and produced quinone methyl esters to inhibit GSH, balancing the redox system and synergistically enhancing the therapeutic efficiency of chlorambucil. Ni et al. [185] synthesized a ROS-responsive poly(D,L-lactide)-thioketal-polyethylene glycol copolymer to encapsulate micelles loaded with losartan (LST) and liposomes containing PTX. This innovative co-delivery system was designed to administer anticancer and collagen-inhibiting drugs concurrently. The NPs responded to ROS in TME, resulting in diffusive drug release from the lipid shell, while the micelles transformed from a spherical structure to smaller disc-shaped NPs, facilitating tumor penetration.

3.1.4. Enzyme

Elevated expression of multiple enzymes in tumor sites plays a crucial role in sustaining and promoting tumor proliferation, invasion, and metastasis. Frequently observed cancer-related enzymes include hyaluronidase (HAase) [186–188], MMPs [189, 190], and heparinases [191], which interact specifically with enzyme substrates to enhance drug permeability. Zhou *et al.* [192] engineered a layered modular assembly formulation (TH-s-RSC) utilizing copper-free click chemistry to modify MMP-2 sensitive peptide-conjugated tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and HA shells on cationic liposomes encapsulating siHSP70. In the acidic and enzyme-rich TME, TRAIL was released in response to extracellular molecules, while siHSP70 release was triggered by reducing conditions in the cytoplasm. TH-s-RSC ex-

tended the half-life of TRAIL and siHSP70 and demonstrated promising anticancer therapeutic efficacy. Jin et al. [193] developed the liposome (ASL-BIO-MPL), adapting its size and ligand presentation in response to stimuli, balancing effective tumor targeting and deep penetration. The polymer peptides were cleaved into shorter peptides by the highly expressed MMP-9 in TME, reducing the polymer-liposome size to release tiny micelles for tumor targeting. Residual ASL-BIO-MPL in non-target tissues was cleared using affinity hormones at appropriate doses. This two-step strategy maintained tumor targeting while demonstrating effective antitumor efficacy and tissue safety. Tang et al. [194] created a pH- and enzyme-dual-selective NP library (PGN) with a pH shift encompassing the lysosomal pH range in various cells. Imidazoquinoline (IMDQ), a potent agonist of TLR-7/8 receptor, was attached to the hydrophobic segment of PGN using the enzyme-sensitive peptide sequence Gly-Phe-Leu-Gly as the conjugating linker. PGN dissociated into polymers in the highly acidic lysosomes of M2-like tumor-associated macrophages (TAMs) while remaining intact within moderately acidic lysosomes of other cells. The conjugate was cleaved by lysosomal proteases highly expressed in M2-like TAMs, efficiently releasing IMDQ to activate TLR-like receptors 7/8 located in the endolysosomes, resulting in reprogramming M2-like TAMs to the typically characterized M1-like phenotype for potent cancer immunotherapy.

3.2. External stimuli-triggered drug release

3.2.1. Light

Light, as an external stimulus for controlled drug release, is advantageous due to its ability to induce drug release with precise spatial and temporal control [195]. In light-triggered nDDSs, drug release can be regulated by adjusting parameters such as wavelength, exposure duration, and beam diameter. Azobenzene, a common photoisomerized moiety comprising an aryl group with both cis and trans isomers, exhibits a prominent π-π transition in the ultraviolet spectrum and a weak π-π transition in the visible region. Under UV irradiation, the trans structure of azobenzene converts to cis and reverts from cis to trans under heat or visible light. Zhang et al. [196] developed nanopumps by assembling azobenzene-functionalized DNA strands on upconversion NPs (UCNP) and loading them with DOX through intercalation within the DNA helix structure. Upon near-infrared (NIR) light laser irradiation, UCNP emitted ultraviolet and visible photons, promoting continuous photoisomerization of azo molecules. The azo functioned as an activator, initiating a cyclic process of DNA hybridization and de-hybridization for controlled DOX release. This light-responsive drug release system achieved a DOX release rate of 86.7% within 30 minutes. Titanium dioxide (TiO_2) nanomaterials exhibit excellent photocatalytic properties and biocompatibility. Luo et al. [197] developed a visible light-triggered protein delivery system by coordinating hydroxyl groups onto TiO_2 NPs. Utilizing hemoglobin (Hb) as a model protein, they formed a charge transfer complex through the coordination of 3,4-dihydroxybenzoic acid (DB) with unsaturated ligand titanium ions. Hb release was triggered by visible light-induced cleavage of the coordination bond between DB and the TiO_2 surface. The released Hb maintained its structural integrity and retained its enzymatic biological activity.

Photodynamic therapy (PDT) employs light-activated photosensitizers to convert energy into oxygen, generating highly reactive singlet oxygen that induces apoptosis or necrosis [198]. Liu et al. [199] engineered a platelet film-coated self-assembled nanosystem (Van-indocyanine green (ICG)@PLT) co-loading vancomycin and ICG. This nanosensor system targeted post-operative tumor incisions, effectively accessing residual tumor cells by exploiting the interaction between p-selectin overexpressed on platelets and CD44 receptor. Under NIR laser irradiation, Van-ICG@PLT demonstrated significant cytotoxicity toward tumor cells. Moreover, the remaining Van-ICG@PLT adhered to bacteria, enhancing membrane permeability upon laser irradiation and amplifying bacterial susceptibility to vancomycin. The system utilized the complementary effects of phototherapy and platelet membrane targeting to concurrently inhibit residual tumor regeneration. Gao et al. [200] developed a regionally confined PROteolysis-TArgeting Chimeras (PROTAC) nanoplatform incorporating both ROS-activatable and hypoxia-responsive PROTAC prodrugs. PROTAC NP selectively aggregated within and deeply penetrated tumors in response to MMP-2. Photoactivity was reactivated within the acidic TME, and PROTAC was released by ROS generated through PDT. PROTAC prodrugs were revitalized in CSCs overexpressing nitroreductase under hypoxic conditions. PROTAC NP effectively degraded bromodomain containing 4 (BRD4) in both normoxic and hypoxic environments, impeding tumor progression.

Photothermal therapy (PTT) eliminates tumor cells through localized hyperthermia generated by photothermal agents activated by visible or NIR light [201–203]. Copper-based coordination NPs demonstrate high photothermal transfer efficiency, showing potential for PTT applications [204]. Zhang et al. [205] engineered ternary coordination nano-complexes comprising dopamine-modified HA, copper ions, and citric acid, which exhibited efficient photothermal conversion under NIR light. Upon entering TME, highly expressed HAase degraded the HA, releasing the copper-citric acid complex, thus achieving a synergistic effect of PTT and chemotherapy.

3.2.2. Temperature

Temperature is one of the most extensively studied stimuli for designing responsive nDDSs [206]. Hyperthermic diseased tissues and tumor sites are considered endogenous temperature stimuli, while external heat sources such as radiofrequency, temperature-controlled water bags, and microwaves can be used to increase local temperature. The thermal response of polymer materials is based on a sharp transition between the hydrophilic and hydrophobic properties of the polymer chain [207]. The phase transition occurrence depends on two main characteristics of temperature-sensitive materials: the lower critical solution temperature (LCST) and the upper critical solution temperature (UCST) [208]. Below the LCST, the material exhibits a dissolved state, while above the LCST, it becomes hydrophobic, initiating drug release from the nanocarrier [209]. Conversely, the UCST represents a change from solubility to insolubility when the material undergoes cooling [210]. Among the materials used to form temperature-sensitive micelles, poly(N-isopropylacrylamide) (PNIPAAm) and its derivatives receive the most attention due to their adjustable LCST being close to physiological conditions [211]. Akimoto *et al.* [212] reported micelles constructed from polymers based on hydrophilic PNIPAAm moieties, which formed thermo-responsive coronas on the surface, leading to particle sizes of approximately 20 nm below the LCST levels but aggregating to over 600 nm above LCST. Additionally, cellular uptake of micelles was limited at 37 °C but increased at 42 °C, likely due to enhanced hydrophobic interactions. Panja *et al.* [213] engineered a range of micelles self-assembled by polymers with hydrophobic thermo-sensitive moieties, which presented LCST varying from 30 °C to 39 °C and were loaded with DOX. Upon temperature increase above the LCST, the particle size of the micelles reduced by 57%, accompanied by a 78.57% release of DOX after 24 h. In rat subcutaneous glioma models, administration of the micelles resulted in 83.9% tumor suppression with minimal systemic toxicity. The thermo-sensitive liposome is another common temperature-sensitive nanocarrier, comprised of lipids with a specific phase transition temperature of around 42 °C or prepared by inserting temperature-sens-

itive polymers [214]. Ta et al. [215] incorporated copolymers derived from PNIPAAm into traditional thermo-sensitive liposomes loaded with DOX. While 50% of DOX was released from the traditional thermo-sensitive liposome at 43.1 °C, a relatively high thermal dose threshold risking damage to normal tissue surrounding tumor sites, the modified thermo-sensitive liposome showed 50% release of DOX at 39.6 °C, potentially reducing the thermal dose and improving safety. Zhang *et al.* [216] employed lipids of dipalmitoyl phosphatidylcholine (DPPC) and monopalmitoyl phosphatidylcholine (MPPC) to form thermo-sensitive liposomes loaded with vinorelbine bitartrate (VB). While the drug hardly released from both thermo-sensitive and non-sensitive liposomes at 37 °C, it rapidly released more than 60% of VB from thermo-sensitive liposomes compared to less than 10% from non-sensitive liposomes at 42 °C. In mouse subcutaneous lung cancer models, thermo-sensitive liposomes inhibited tumors at a rate 61.8% higher than that of non-sensitive liposomes.

3.2.3. Magnetism

Magnetic nanomaterials show promise as targeted drug delivery systems due to their capacity to facilitate localized drug release when exposed to magnetic fields [217, 218]. These magnetism-responsive systems demonstrate superior spatial focusing capabilities compared to conventional delivery platforms, addressing challenges such as physiological barrier penetration and insufficient specificity for diseased tissues. Typically, magnetically responsive nDDSs incorporate paramagnetic and superparamagnetic NPs into polymer substrates to enhance anticancer drug accumulation within tumors. In a significant study, Dorjsuren *et al.* [219] developed CET-coated liposomes encapsulating DOX and citrate-coated iron oxide magnetic NPs. This multifunctional magnetic nanoparticle system effectively promoted drug delivery to EGFR-positive cancer cells and achieved stable drug release under magnetic field stimulation, resulting in both chemotherapeutic and thermotherapeutic effects on tumor tissues.

Controlled drug release nanoplatforms leverage TME or manipulated exogenous factors to achieve precise spatiotemporal drug release, representing an efficient and promising therapeutic strategy. A recent, more compelling approach involves designing systems responsive to multiple stimuli, ensuring sequential drug release *in vivo* or exerting synergistic effects to enhance therapeutic efficacy [220]. Researchers have developed and investigated nanomaterials suitable for multiple stimulus responses, including pH/temperature, pH/redox, pH/enzyme, and bi-enzyme combinations. These nanomaterials overcome multistage, sequential, and biological barriers by employing multiple stimuli-responsive strategies, providing valuable insights into the design of hierarchically stimulated nanomedicines.

4. Conclusions and Perspectives

Advancements in nanomedicine have been propelled by the evolution of nanocarriers, which incorporate cutting-edge knowledge and technologies from medical, chemical, and engineering fields. These innovations address the constraints of traditional delivery methods in disease management. Ideal nanocarriers, distinguished by their exceptional biodegradability and biocompatibility, efficiently concentrate therapeutic agents at targeted locations through functionalization with diverse ligands. Moreover, these nanocarriers demonstrate enhanced controlled drug release due to their optimized responsive characteristics.

The progression of nano-targeting technology and innovative stimulus-responsive materials provides new insights into active homing and controlled drug delivery. The development of specifically targeted and responsive nanoplatforms through ligand-targeted activation, controlled drug release, and alterations in size or morphology optimizes the effectiveness of encapsulated small molecule drugs, nucleic acids, or other compounds in disease management and potential treatments [221, 222]. Li et al. [223] created a stimulus-responsive clustered NP system (iCluster) with an initial size of −100 nm, enabling extended circulation and enhanced extravasation through tumor vasculature fenestrations. At the tumor site, low pH-induced iCluster decomposition into −5 nm dendritic polymers, enhancing tissue permeation and cisplatin delivery into cancer cells. The iCluster significantly surpassed free cisplatin, inhibiting up to 95% of tumor growth compared to only 10% with free drugs. Kalafatovic *et al.* [224] engineered peptide micelles that underwent the morphological transition from micelles to fibers. MMP-9 catalytically hydrolyzed these micelles at the tumor site, reconfiguring them into fibrous nanostructures. The transformed nanofibers exhibited higher efficiency in sustained drug release, contributing to more effective drug concentration and therapeutic effect than free DOX. Several nanomedicines have been successfully commercialized, including Abraxane (PTX) for frontline therapy of metastatic pancreatic cancer, Vyxeos (daunorubicin and cytarabine) for acute myeloid leukemia management, and Rapamune (sirolimus) for graft rejection prevention. However, actively targeted NPs remain in clinical trials, such as trastuzumab-coupled PEGylated liposomal loaded DOX (MM-302) for $HER2^+$metastatic breast cancer treatment and docetaxel polymeric NPs targeting PSMAs (BIND-014) [225, 226]. Although MM-302 and BIND-014 demonstrated acceptable safety profiles, they failed to show satisfactory clinical results in randomized phase II trials [227, 228]. This is primarily attributed to nanomedicines' insufficient ability to overcome biological barriers, including transport to the target site, entry into target cells, and proper intracellular processing and trafficking. Before clinical application, careful consideration must be given to the ligand exposure state and the efficiency of nanocarriers' response to endogenous (variations in pH, ROS, GSH, and enzymes) or exogenous (changes in magnetic field, ultrasound, and light intensity) stimulation to achieve efficient targeting and controlled-release strategies for overcoming multilevel, sequential biological barriers and maximizing therapeutic benefit indexes.

The clinical translation of nanomedicine candidates is significantly influenced by factors such as development duration, manufacturing scalability, and associated costs (Fig. 4). The implementation of nanomedicines for clinical applications is time-consuming, primarily due to the absence of standardized protocols and effective characterization methods, which hinders research progress. Preclinical and clinical evaluations require substantial time and expertise, while regulatory uncertainties further delay approvals. To enhance yield and cost-effectiveness, optimizing and simplifying preparation processes is crucial when exploring industrial applications. Microfluidic systems have transformed nanomedicine preparation, enabling precise control of minute droplets or volumes through high-precision fluid manipulation for manageable production [229]. This technology has facilitated the integration of multiple preparation steps into a single, streamlined system, reducing fabrication time and simplifying manufacturing. Additionally, three-dimensional printing technology has markedly improved the generation of complex nano-pharmaceutical formulations, such as antigenic and antibody-conjugated nanocarriers, allowing for economical and scalable outputs [230]. Research on nDDSs often involves complex modifications to emphasize uniqueness, which presents challenges for industrial manufacturing. Further consideration should be given to easily modifiable novel additives, efficient new ligands, and simplified modification procedures. The cost of bringing nanomedicines to market is substantial, encompassing not only manufacturing expenses but also preliminary development and clinical trial costs. These high costs may impede nDDS development and limit their adoption as mainstream therapies. Most approved nanotherapies utilize traditional drug formulations to in-

crease success probability, involving lower financial risk compared to developing entirely new nanocarriers. Innovators can collaborate with government laboratories and conduct extensive clinical analyses to explore synthesis methods and cost-benefits for the clinical translation of nanomedicine.

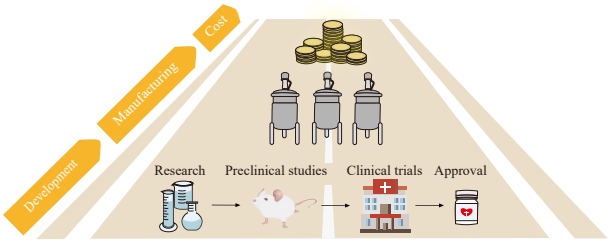

Fig. 4 Challenges in the commercialization of nanotherapeutics.

Nanopharmaceutical products have attracted significant interest due to their favorable pharmacokinetics, biodistribution, and safety profiles. nDDSs have exhibited exceptional potential in improving therapeutic efficacy while reducing adverse effects through targeted and stimulus-responsive drug release mechanisms. A strategically designed and methodical approach to addressing challenges in this field could advance nanomedicine toward delivering concrete and substantial benefits for human medicine and healthcare.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82273876), the Fok Ying-Tong Education Foundation for Young Teachers in the Higher Education Institutions of China (No. 171028), the Project of State Key Laboratory of Advanced Drug Delivery and Release Systems (No. DSQZ-ZD-200301), the Fundamental Research Fund for the Central Universities (No. 2632022YC02).

Declaration of competing interest

These authors have no conflict of interest to declare.

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