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Nanoformulation-based drug delivery systems for the treatment of gastric cancer: recent developments and future prospects

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Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide. Despite significant efforts and recent advances in GC treatment, therapeutic efficacy remains suboptimal. In recent years, emerging nanomaterials have demonstrated considerable potential for cancer therapy, primarily due to their ability to function as drug carriers that enable targeted and precise delivery of therapeutic agents to tumour tissues. This not only increases therapeutic efficacy but also reduces side effects. Herein, we present a comprehensive review of the major types of nanoformulations, including liposomes, albumin-based nanoparticles (NPs), polymer-based NPs, inorganic NPs, and cell-derived nanomaterials. We also examine recently reported nanoformulations for various GC treatment strategies, such as chemotherapy, radiotherapy, immunotherapy, gene therapy, phototherapy, and combined therapy. We highlight the design concepts and principles underlying these nanoformulations employed in GC treatment. Additionally, we discuss the challenges associated with nanoformulation-based treatments for GC as well as future prospects in this rapidly evolving field.

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1. Introduction

According to the latest estimates released by GLOBOCAN in 2020, gastric cancer (GC) is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide.[1] Despite a global decline in the incidence rates of GC, a population-based modelling study predicts a 62% increase in the number of new GC cases, projecting 1.77 million cases by 2040.[2] Hence, the future global treatment burden of GC remains substantial. GC is a highly heterogeneous disease encompassing various histological and molecular subtypes. The World Health Organization (WHO) has classified GC into several histopathological subtypes, including tubular, papillary, mucinous and others.[3] The Cancer Genome Atlas (TCGA) proposed four molecular subtypes of GC: Epstein–Barr virus-positive (EBV+), microsatellite instability (MSI), genomically stable, and chromosomal instability (CIN).[4] However, despite these classifications, the clinical utility of these histological and molecular subtypes for guiding GC treatment decisions remains limited. Several risk factors are associated with GC, including *Helicobacter pylori* infection, excess body fat, cigarette smoking, high-salt diets, and processed meats.[5] Notably, nearly 90% of GC cases are attributed to *Helicobacter pylori* infection.[6,7] Eradicating this infection has been shown to reduce both the incidence and mortality associated with GC.[8,9]

Owing to the lack of specific symptoms in patients with early-stage GC and the limited implementation of invasive endoscopic screening, approximately 80% of patients are diagnosed in a locally advanced or metastatic stage.[10–12] For these GC patients, the treatment strategy is comprehensive treatment with surgery as the main way. Chemotherapy, radiotherapy, targeted therapy and immune therapy, which are aimed at improving long-term survival and lowering the risk of recurrence of GC, have become important adjuvant therapies for GC. However, these adjuvant therapies have several drawbacks that limit their effectiveness in the treatment of GC. For example, chemotherapy is a nonspecific approach that can kill both tumour cells and normal cells, which may cause severe side effects, including bone marrow suppression, gastrointestinal reactions, and hair loss.[13] In addition, while chemotherapeutic drugs are typically effective for GC patients during the initial phase of treatment, they inevitably develop drug resistance in the later stage, ultimately leading to treatment failure.[14] Most gastric adenocarcinoma patients are not sensitive to radiotherapy and

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have limited benefits from it.[15] In the last decade, immune checkpoint inhibitors (ICIs) have emerged as an exciting treatment strategy across a spectrum of malignancies. However, only a small number of GC patients have a durable response to ICI treatment, and the efficacy of ICIs is very limited.[16,17] Anti-human epidermal growth factor receptor 2 (HER2) antibody (pertuzumab and trastuzumab-emtansine) treatment is the most commonly used targeted therapy for HER2-positive GC, which accounts for 17–20% of all cases of GC.[4,18] However, it has not been effective at improving survival in HER2-positive GC patients.[19,20] Therefore, poor targeting, low therapeutic efficacy, and serious side effects are currently the main obstacles in adjuvant therapies for GC in clinical practice, and new therapies and strategies are urgently needed.

In recent years, researchers have focused on the field of nanoformulations to address the aforementioned issues. Typically, nanoformulations involve the use of nanomaterials with external dimensions ranging from 1 nanometre to several hundred nanometres.[21,22] Typical nanoformulations include liposomes, albumin-based nanoparticles (NPs), polymer-based NPs and inorganic NPs, while novel nanoformulations also include biomimetic reconstituted high-density lipoproteins (rHDLs), exosomes and hybrid NPs.[21,22] Compared with traditional formulations, nanoformulations have the following advantages in tumour treatment. (1) Because of the leaky vasculature and poor lymphatic drainage of tumour tissue, nanoformulations can selectively accumulate in tumour tissue through enhanced permeability and retention (EPR) effects, thus improving the anticancer efficacy and decreasing adverse effects.[23,24] (2) Nanoformulations can improve the solubility of poorly soluble drugs and protect drugs from degradation to increase their stability. (3) The biological properties of nanoformulations can be improved by chemical or biological modifications, allowing them to escape clearance by the mononuclear phagocyte system (MPS) and the reticuloendothelial system (RES) or achieve precise active targeting to a specific organ or cell type.[22,25] In this review, we present commonly used nanoformulation-based delivery systems. Moreover, we extensively review different nanoformulation-mediated strategies for GC therapy, including chemotherapy, radiotherapy, immunotherapy, gene therapy, phototherapy, and combined therapy (Fig. 1). In addition, we discuss the challenges and limitations of these nanoformulations in clinical translation.

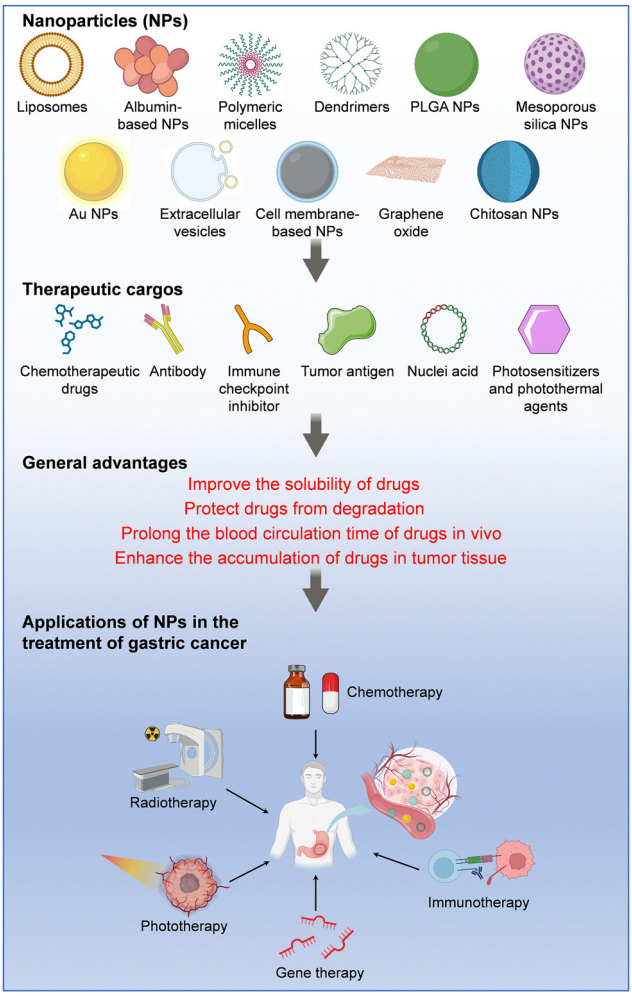

Fig. 1 Nanoformulation-based drug delivery systems for various gastric cancer treatment strategies.

2. Major modalities of nanoformulation-based drug delivery systems

Currently, a wide range of nanoformulations are used to treat GC, mainly including liposomes, albumin-based NPs, polymer-based NPs, inorganic NPs, and cell-derived nanomaterials. Each nanoformulation has unique properties and has been applied to different treatment approaches, ultimately improving the efficacy of GC treatment and reducing side effects.

2.1. Liposomes

Liposomes are spherical structures composed of a phospholipid bilayer membrane surrounding an aqueous core that is capable of carrying and delivering both hydrophilic and hydrophobic drugs.[26] The liposomal drug delivery system effectively increases the solubility of hydrophobic drugs, thereby increasing their therapeutic efficacy. Moreover, since the cell membrane also consists of a phospholipid bilayer, liposomes have high biocompatibility and low toxicity. To prevent rapid clearance by the RES, liposomes are usually modified with poly(ethylene glycol) (PEG).[27] At present, some liposome-formulated anticancer drugs, including liposomal paclitaxel (PTX) (Lipusu®),[28] liposomal irinotecan (Onivyde®)[29] and liposomal doxorubicin (DOX) (Myocet® and Caelyx®),[30] have already been approved for clinical use or in clinical trials. Although the *in vivo* biodistribution of liposomes has improved, further modifications are needed to increase their therapeutic efficacy. Current research focuses on two main types of liposomes: ligand-targeted liposomes and stimuli-responsive liposomes. Ligand-targeted liposomes have been developed by modifying their lipid layer with selective ligands

to target specific receptors on tumour cells.[31,32] Stimuli-responsive liposomes have been designed to release encapsulated drugs in response to external stimuli, such as light, temperature, pH, enzyme, *etc.*, enabling on-demand drug release.[33,34] These versatile liposomes have vital research value and clinical potential as drug delivery systems for the treatment of GC.

2.2. Albumin-based NPs

Human serum albumin (HSA) is the most abundant plasma protein.[35] As an endogenous nanocarrier from the human body, albumin has superior biocompatibility, excellent biodegradability, low immunogenicity, and low cytotoxicity. The hydrophobic region of albumin can bind hydrophobic drugs, increasing their solubility in plasma.[35] The molecular weight of albumin is greater than the renal threshold, so its circulation time is long, which facilitates its accumulation in tumour tissue.[35] HSA-based NPs exploit a dual-receptor mechanism involving the 60 kDa glycoprotein (gp60) and secreted protein acidic and rich in cysteine (SPARC) for tumour cell targeting.[36] Circulating NPs first bind gp60 receptors overexpressed on vascular endothelial cells, which mediates their transendothelial transport into the tumour interstitium. Within the tumour microenvironment (TME), NPs subsequently bind SPARC, which is abundantly expressed in this compartment. This SPARC interaction facilitates the receptor-mediated endocytosis of the NPs into tumour cells. This receptor-specific uptake pathway enables NPs to bypass drug efflux mechanisms, promoting significant intracellular accumulation. For example, albumin-formulated PTX demonstrated a 4.2-fold higher delivery efficiency compared to Cremophor EL-formulated PTX.[37] Furthermore, HSA possesses abundant functional groups, including sulfhydryl groups, amino groups, and carboxyl groups, which facilitate surface functionalization for active targeting.[35] At present, albumin-formulated PTX (Abraxane®), which improves the solubility of PTX and reduces the toxicity compared to solvent-based PTX, has been approved for clinical use in the treatment of various tumours.[38,39] Owing to the inherent properties and modifiability of albumin, an increasing number of albumin-formulated drugs are expected to receive approval for clinical applications in the future.

2.3. Polymer-based NPs

2.3.1. Polymeric micelles. Micelles, which have hydrophilic shells and hydrophobic cores, are formed by the self-assembly of amphiphilic block copolymers in aqueous media.[40] The hydrophilic shell enhances the stability of micelles while protecting the drugs from the external environment, and the hydrophobic core holds the micelle together and encapsulates insoluble drugs. Diblock copolymers (A–B) or triblock copolymers (A–B–A) with hydrophilic (A) and hydrophobic (B) segments are most commonly used for preparing polymeric micelle formulations.[40] These block copolymers exhibit highly complex and interdependent interactions. The structure and length of each block, the molecular weight of the polymer, and the quantity of the drug loaded contribute to the tuneable properties of the micelles.[41] At present, several polymeric micelle formulations have received approval for clinical use in the treatment of cancer, such as polymeric micelle-formulated leuprolide (Eligard®),[42] polymeric micelle-formulated pegaspargase (Oncaspar®),[42] and polymeric micelle-formulated PTX (Genexol-PM®, Nanoxel®, and Paclical®).[43–45] In future research, a more profound understanding of the interactions between blocks, along with a rational design approach for block polymers, such as surface modifications of micelles to achieve active targeted delivery and environmentally responsive release, will further increase their utility as drug carriers.

2.3.2. Dendrimers. Dendrimers are polymers with well-defined three-dimensional (3D) branched structures that have a central core, a dendritic skeleton made up of repeated branching units, and numerous functional groups on the surface, such as sulfydryl groups, amino groups, and carboxyl groups.[46] Owing to this unique structure, dendrimers exhibit excellent hydrophilicity and are less than 20 nm in size.[47] This characteristic endows them with an exceptional ability to traverse biological barriers, including mucosal membranes and endothelial layers. In addition, the presence of multiple functional groups on the surface of dendrimers offers unique advantages.[46,48] These functional groups increase the drug loading capacity by allowing drugs to be not only physically encapsulated within the inner cavity of dendrimers but also chemically bound to the functional groups. Moreover, ligands can be conjugated to the surfaces of these functional groups, thereby imparting active targeting capabilities and facilitating effective drug accumulation at tumour sites. To date, however, no dendrimer-based nanoformulations have received approval for clinical application. One of the primary reasons for this is the potential long-term toxicity to organs, which is caused mainly by factors such as the cationic charge density on their surface and the number of terminal primary amines.[46,49] There is no doubt that more efforts are needed to make dendrimers applicable in clinical practice in the near future.

2.3.3. Poly(lactic-*co*-glycolic acid) (PLGA) NPs. PLGA NPs are among the most versatile nanosized drug delivery systems because of their biocompatibility and biodegradable properties. PLGA can be degraded into lactic acid and glycolic acid, which are endogenous and easily metabolized by the body *via* the Krebs cycle.[50] Because of the minimal systemic toxicity of PLGA as a drug delivery carrier, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved its use in injectable formulations for clinical applications.[51] Hydrophilic or hydrophobic antitumour drugs can be encapsulated in the internal space or adsorbed on the surface of PLGA NPs. To prevent PLGA NPs from being recognized and eliminated from the bloodstream by the RES, their surfaces are typically modified with PEG, which has been demonstrated to increase their blood circulation half-life by several orders of magnitude.[27,52] In addition, PLGA is a favoured substance for the fabrication of NPs because its size can be controlled, and it can be chemically modified to endow it with passive and active tumour-targeting capabilities.[53,54] However, several critical issues associated with PLGA NPs must be addressed, such as the high initial burst release rate of the drug.[55] Moreover, the biological roles of PLGA with its

degradation products *in vivo* remain unclear. While some studies have reported their tumour-promoting effects within the TME, others have indicated their potential to inhibit tumour growth.[56,57] Future in-depth investigations into PLGA are required to resolve these conflicting observations.

2.4. Inorganic NPs

2.4.1. Gold NPs. Owing to their excellent photothermal conversion capabilities, inertness, nontoxicity, ease of synthesis, and ability to modify size and shape, as well as surface functionalization with ligands, gold NPs have emerged as a prominent class of inorganic NPs in drug delivery systems.[58] Gold NPs are extensively utilized in photothermal therapy (PTT) because of their ability to convert absorbed light from the visible-near-infrared (VIS-NIR) region into heat through a nonradiative process.[58] In addition, gold NPs possess a high atomic number and electron density. When subjected to electromagnetic radiation, they can effectively absorb X-ray energy and interact with radiation, positioning them as promising radiosensitizers for patients with tumours.[59] However, the production cost of gold NPs constrains their market growth. Moreover, similar to most other NPs, the observations of gold NPs to date have relied primarily on *in vitro* studies and animal model data. A more systematic evaluation is essential for assessing the safety and efficacy of gold NPs within the context of reconstructing actual tumour occurrence scenarios.

2.4.2. Mesoporous silica NPs. Mesoporous silicon NPs (MSNs) are inorganic NPs with pore sizes ranging from 2 to 50 nm that are characterized by a high specific surface area, adjustable particle size and morphology, high mechanical/thermal stability, rapid release kinetics, and easy surface functionalization.[60,61] The large surface area and high pore volume of MSNs provide a high loading capacity for anticancer drugs. Especially, for hydrophobic drugs, the MSN drug delivery system effectively increases their solubility in plasma. In recent years, gated MSNs have garnered significant attention because of the incorporation of molecular gates onto their external surface, often referred to as gatekeepers or nanovalves.[62,63] These gates effectively obstruct the transport of drugs from the pores to the exterior environment. Upon exposure to specific stimuli—chemical, biochemical, or physical—the molecular gate is disrupted, thereby facilitating pore opening for drug release. This mechanism enables the targeted and on-demand release of therapeutic agents. Despite the significant potential of MSNs as drug delivery systems in the realm of biomedicine, the advancement of their clinical translation remains notably sluggish. In the future, long-term toxicological evaluations of MSNs using clinically relevant models are urgently needed.

2.4.3. Graphene oxide (GO) NPs. GO is a two-dimensional (2D) NP derived from the oxidation of graphite.[64] It possesses abundant oxygen-containing functional groups, including carboxyl, epoxy, and hydroxyl groups located on its basal plane and edges, which allows for further surface functionalization aimed at active targeting.[65] Its amphiphilic structure facilitates the efficient loading and delivery of both hydrophobic and hydrophilic therapeutic agents. To prevent rapid clearance by the RES, GO is often modified with PEG. Additionally, GO demonstrates excellent photothermal conversion capabilities under NIR irradiation,[66] positioning it as a potent agent for phototherapy against GC. Current research efforts are focused on optimizing biocompatibility and minimizing off-target toxicity to facilitate clinical translation. Despite its promising potential, therapies based on GO NPs remain largely in experimental stages; thus, further *in vivo* validation is essential to address long-term biosafety and pharmacokinetic challenges.

2.4.4. Chitosan NPs. Chitosan NPs (ChNPs) are cationic, biodegradable carriers derived from chitin, composed of repeating glucosamine and *N*-acetylglucosamine units.[67] These particles form stable nanostructures through ionic gelation, self-assembly, or covalent cross-linking, leveraging their polycationic nature to encapsulate diverse therapeutic payloads (*e.g.*, hydrophobic drugs, proteins, and nucleic acids) *via* electrostatic interactions.[67] ChNPs enhance drug solubility, protect biologics from degradation, and enable controlled release through pH-dependent diffusion, swelling, or enzymatic degradation—particularly advantageous in the acidic TME.[68] To augment specificity and evade RES clearance, they are functionalized with PEG or ligands for active targeting of receptors overexpressed in cancers. Despite promising preclinical outcomes in drug delivery and cancer therapy, clinical translation faces challenges such as batch-to-batch variability, limited solubility at physiological pH, and hemocompatibility concerns during systemic delivery.[69] Future innovation focuses on stimuli-responsive systems and ligand engineering to overcome multidrug resistance and optimize tumour-specific delivery.

2.5. Cell-derived materials

2.5.1. Extracellular vesicles. Extracellular vesicles (EVs) are naturally released particles from nearly all types of cells.[70] According to the definition of the International Society for Extracellular Vesicles, EVs include exosomes, microvesicles, microparticles, apoptotic bodies, and other nonreplicating EV subgroups.[71] Studies have shown that EVs are important mediators of intercellular communication and can deliver various bioactive substances, such as nucleic acids, proteins, lipids, and metabolites, to target cells in the body, playing crucial roles in physiological and pathological processes.[72] Structurally, EVs are composed of a lipid bilayer, which has been exploited as a "natural" NP to carry anticancer drugs.[73] In recent years, engineering strategies have been adopted to further improve EVs for use as effective carriers of antitumour drugs. For example, direct modification of EVs with targeted molecules enables them to specifically target tumour cells,[74] or genetic engineering techniques can be used on the originating cells to endow the surface of their secreted EVs with functional ligands.[75] Several critical issues remain to be addressed, such as the need for improved technologies for isolation, purification, and large-scale production; challenges related to long-term storage; and the abnormal accumulation of EVs in the liver. Emerging research focused on addressing these challenges has

generated considerable optimism regarding the potential application of EVs as drug delivery carriers in tumour therapy.[76]

2.5.2. Cell membrane-based NPs. Cell membrane-based NPs (CMBNPs) are core–shell nanostructures formed by coating a layer of natural cell membrane on the surface of NPs, which retain the physicochemical properties of the NPs while also having the functionality of source cell membranes.[77] These biomimetic systems exhibit high biocompatibility and low immunogenicity, evading immune clearance by mimicking autologous cells.[77] CMBNPs can be classified according to the type of source cells used in their construction, including white blood cells, red blood cells, cancer cells, and platelets (subcellular). The various types of cell membranes can impart specific biological functions to CMBNPs. White blood cell membranes confer inflammation tropism through receptors (*e.g.*, LFA-1 and CXCR1/CXCR2) that enable chemotaxis towards inflammatory cytokines released by tumours, facilitating extravasation through inflamed endothelium and accumulating to tumour sites.[77,78] Moreover, subtypes like macrophages can directly bind adhesion molecules on tumour cells to target metastases.[77,78] Red blood cell membranes maximize systemic circulation duration *via* CD47-mediated ''don't-eat-me'' signaling to phagocytes, minimizing RES clearance to potentiate passive tumour accumulation through the EPR effect.[77,78] Cancer cell membranes enable homotypic targeting by retaining cancer cell-specific adhesion molecules (*e.g.*, EpCAM and N-cadherin), promoting preferential uptake by homologous tumour cells.[78,79] Platelet membranes target circulating tumour cells *via* P-selectin/CD44 interactions, enabling metastasis suppression *via* localized therapeutic delivery.[77,78] Recent years have witnessed an increasing focus on the research of hybrid CMBNPs and engineered CMBNPs. Hybrid CMBNPs are designed by fusing membranes derived from two distinct cell types onto NP cores.[80,81] This biomimetic approach synergistically integrates the functionalities of the source cells. Additional engineering strategies for CMBNPs include lipid insertion, membrane fusion, genetic modification, and metabolic engineering.[82,83] Both hybrid CMBNPs and engineered CMBNPs aim to enhance tumour targeting and therapeutic efficacy further.

In conclusion, the aforementioned different nanomaterials share certain commonalities while also exhibiting distinct properties (Table 1). When selecting such materials as drug carriers for tumour treatment, their biocompatibility, biodegradability, toxicity, immunogenicity, surface modifiability, drug loading capacity, and ability to traverse biological barriers must be comprehensively evaluated. Furthermore, a thorough understanding of the biological characteristics and microenvironment of tumours is crucial for the appropriate selection and rational design of nanomaterials. Additionally, while this review categorizes nanomaterials into distinct groups, combination strategies that involve different materials are also being explored. Notably, there is an increasing body of research on hybrid materials that leverage the advantages of individual NPs while simultaneously addressing their limitations.[84,85]

3. Application of nanoformulations in the treatment of GC

The diverse nanoformulation platforms described above form a versatile toolkit for developing advanced therapeutic strategies against GC. Building upon this foundation, the following section examines the application of these nanocarriers across the spectrum of GC treatment modalities. We critically review recent studies demonstrating how the intrinsic attributes and engineered features of specific nanoformulations (*e.g.*, liposomes, polymeric NPs, inorganic NPs, and cell-derived materials) are leveraged to enhance therapeutic efficacy and address the limitations of conventional chemotherapy, radiotherapy, immunotherapy, gene therapy, phototherapy, and combined therapy for GC. Particular emphasis is placed on the rational design principles enabling targeted delivery, controlled release, and overcoming biological barriers within the gastric context.

3.1. Chemotherapy

Chemotherapeutic drugs are cytotoxic drugs that can kill cancer cells to prevent further growth and improve the patient survival rate or quality of life. The chemotherapeutic drugs that are active against GC include fluoropyrimidines (5-fluorouracil, capecitabine, S-1, and trifluridine-tipiracil), platinum-based drugs (cisplatin and oxaliplatin), taxanes (PTX and docetaxel), topoisomerase inhibitors (irinotecan) and anthracyclines (epirubicin).[10,16] Currently, chemotherapy remains the mainstay of treatment for advanced GC because it significantly improves the survival of GC patients. However, extensive chemotherapeutic drug resistance and severe side effects occur in GC patients.[86,87] The emergence of chemotherapeutic-related nanoformulations is expected to further increase their anticancer efficacy and decrease their toxicity.

Encouragingly, several nanoformulations of chemotherapeutic drugs related to GC, as mentioned above, have been approved for clinical use or are currently undergoing clinical trials (Table 2). Owing to its low solubility, PTX is typically formulated in a 50 : 50 mixture of Cremophor EL and dehydrated ethanol, a combination commonly referred to as Taxol.[88,89] However, Cremophor EL is associated with nonlinear pharmacokinetics and serious side effects, such as hypersensitivity, neurotoxicity, and nephrotoxicity.[90,91] As a result, prolonged infusion times and pretreatments are needed.[88,89] NP delivery systems are promising vehicles for drug delivery because they can improve aqueous solubility, reduce side effects, increase permeability, and prolong the circulation half-life of PTX.[88,89] At present, a number of PTX nanoformulations have been approved for cancer treatment, such as HSA (Abraxane®),[92] liposomes (Lipusu®),[28] polymeric micelles (Genexol-PM®, Nanoxel®, and Paclical®),[43–45] and emulsion (Liporaxel®).[93] The common advantage of the above-mentioned PTX nanoformulations is that they completely avoid the use of Cremophor EL and ethanol and improve the solubility of PTX. Although the above-mentioned PTX nanoformulations with improved therapeutic safety have been applied in the clinic, their clinical therapeutic efficacy for GC is not superior

Table 1 Comparison of different NPs

Types of NPs	Size range	Common components	Preparation methods	Advantages	Disadvantages
Liposome	50–300 nm	Phospholipids and cholesterol	Thin-film hydration, extrusion, microfluidics	High biocompatibility and biodegradability, simultaneously encapsulating hydrophilic/hydrophobic drugs, easy functionalization and surface modification	Quick and rapid removal of the body, poor storage stability, high costs
Albumin-based NPs	100–300 nm	Human serum albumin	Desolvation, nab™ technology	Natural biocompatibility, non-toxicity, good biodegradability, low immunogenicity	Low drug loading capacity
Polymer-based NPs					
Polymeric micelles	10–100 nm	Amphiphilic block copolymers	Self-assembly in aqueous/organic solvents	High drug loading capacity (hydrophobic drugs), reducing the uptake by macrophages, prolonging the blood circulation time	Complex synthetic process, polymer residues may cause toxicity, instability *in vivo*
Dendrimers	1–15 nm	Synthetic polymers (*e.g.*, PAMAM: polyamidoamine) with terminal targeting ligands (*e.g.*, folate)	Stepwise synthesis (divergent/convergent approaches) with iterative functionalization	Precisely controllable nanostructures, good capability to traverse biological barriers, easy functionalization and surface modification	Complicated synthetic procedures, potential long-term toxicity to organs
PLGA NPs	50–500 nm	Poly(lactic-*co*-glycolic acid)	Emulsion-solvent evaporation (oil-in-water emulsion)	High biocompatibility and biodegradability, sustained-release properties (ranging from several days to several weeks)	High initial burst release rate of the drug
Inorganic NPs					
Gold NPs	1–100 nm	Gold core with citrate/thiol stabilizers	Chemical reduction (*e.g.*, citrate-based Turkevich method); biosynthesis using plant extracts	High photothermal conversion capabilities, easy to modify in size and shape, easy functionalization and surface modification	Prolonged retention may lead to organ toxicity, solubility limitations, high costs
Mesoporous silica NPs	50–300 nm	Silica framework templated by surfactants (*e.g.*, CTAB: cetyltrimethylammonium bromide); organosilane modifiers for functionalization	Sol–gel synthesis with surfactant templates	High specific surface area, high drug loading capacity, easy functionalization and surface modification, good chemical stability	Poor biodegradability, short-half life
Graphene oxide NPs	50–500 nm	Graphene oxide sheets	Hummers' method–ultrasonic exfoliation–chemical reduction	High drug loading capacity, high photothermal conversion capabilities	Potential toxicity, complex purification, poor biodegradability
Chitosan NPs	80–300 nm	Chitosan	Ionic gelation–emulsion crosslinking–spray drying	Good biodegradability, low toxicity	Poor solubility at physiological pH, batch-to-batch variability
Cell-derived materials					
Extracellular vesicles	50–200 nm	Lipid bilayers with membrane proteins, endogenous nucleic acids (*e.g.*, miRNA)	Ultracentrifugation of cell supernatants, tangential flow filtration for scalable isolation	High biocompatibility, low immunogenicity, ability to cross biological barriers, wide range of sources	Difficulty in large-scale production, not easy to store for a long time
Cell membrane-based NPs	Size dictated by core NPs, membrane adds 5–10 nm shells	Synthetic core + natural membrane	Extrusion, sonication, microfluidic electroporation	Prolonging the blood circulation time, evading clearance from the immune system, intrinsic targeting capability	The processes of membrane extraction and coating are complex, poor stability of membrane proteins, difficult to scale-up manufacturing

NPs: nanoparticles.

Table 2 Currently approved nanoformulations of chemotherapeutic drugs for gastric cancer in clinical use or trials

Commercial name	Nanodelivery system	Composition	Status	Size (nm)	Common dose/ MTD (mg m^{-2})	Route of administration
Abraxane®	Albumin-based NPs	PTX and albumin	Off-label GC use	130	260/300	i.v.
Lipusu®	Liposome	PTX, lecithin and cholesterol	GC clinical use	400	175/no data	i.v.
Genexol-PM®	Polymeric micelles	PTX and mPEG-PDLLA	Phase II GC trials (NCT02261415)	25	260/390	i.v.
Onivyde®	Liposome	Irinotecan HCl	Phase II GC trials (NCT02559791)	110	70/120	i.v.
EndoTAG®-1	Cationic liposomal	PTX, DOTAP/DOPC	Phase II/III GC trials (NCT01546987)	180–220	22/24 (weekly)	i.v.
Cynviloq™	Polymeric micelles	PTX and mPEG-PDLLA	Off-label GC use	20–50	300/340	i.v.
Gem-Lipo	PEGylated liposome	Gemcitabine	Phase II GC trials (UMIN000036549)	100–120	1000/1200	i.v.

PTX: paclitaxel; NPs: nanoparticles; MTD: maximum authorized dose; i.v.: intravenous; mPEG-PDLLA: monomethoxy-poly(ethylene glycol)-*block*-poly(D,L-lactide); GC: gastric cancer; HCl: hydrochloride; DOTAP: 1,2-diO-oleoyl-3-trimethylammonium-propane; DOPC: 1,2-diO-oleoyl-*sn*-glycero-3-phosphocholine.

to that of Taxol.[93,94] This is a result of many complicated factors, such as the poor affinity between nanocarriers and PTX resulting in a low drug loading rate and poor drug loading stability, the utilization of only passive targeted drug delivery strategies leading to the inefficient accumulation of PTX in tumour tissues, and the PTX nanoformulations failing to solve the problem of drug resistance. Therefore, researchers have devoted significant efforts to the rational design of more efficient and intelligent nanoformulations for chemotherapeutic drugs.

To overcome these limitations, alternative approaches are needed to improve drug delivery efficiency. While the encapsulation of drugs into nanocarriers *via* noncovalent interactions is relatively straightforward, such approaches may result in premature drug release during blood circulation, thereby undermining the effective delivery of drugs to tumour sites.[95] In contrast, the covalent bonding of drugs to nanocarriers, coupled with drug release triggered by the TME, can effectively address this issue. For this purpose, Shi *et al.*[96] developed arginine–glycine–aspartic acid (RGD)-decorated PEG-PTX-conjugated micelles (RGD@Micelles) for targeted GC therapy. Hydrophilic PEG and the hydrophobic drug PTX can be stably conjugated *via* disulfide linkages, which can be cleaved *via* reduction by glutathione (GSH). Because the GSH concentration in cancer cells is much greater than that in normal cells, the RGD@Micelles can release PTX efficiently in response to intracellular GSH after GC cell uptake. *In vivo* experiments using a mouse xenograft model of GC indicated that RGD@Micelles could be efficiently delivered to the tumour site and exhibited high anticancer efficacy and low toxicity.

It has been gradually recognized that passively targeted drug delivery strategies based on the EPR effect have several limitations, as the EPR effect cannot significantly improve clinical therapeutic efficacy.[97] For this reason, actively targeted drug delivery, which is based on specific recognition and binding between ligands decorated on nanocarriers and receptors overexpressed on the surface of cancer cells, has received considerable attention and can effectively increase the concentration of chemotherapeutic drugs at the tumour site, greatly decreasing their toxicity and increasing anticancer efficacy.[98] Yang *et al.*[99] constructed a dual-targeting core–shell hybrid NP system for the delivery of SN38 (a nuclear enzyme topoisomerase I inhibitor) to HER2- and CD44-overexpressing GCs. The core of the NP is made of PLGA encapsulating SN38, while the shell is decorated with an anti-HER2 peptide and hyaluronic acid (HA) to specifically target HER2 and CD44, respectively. *In vivo* biodistribution experiments revealed that the targeting capacity of dual-targeting hybrid NPs was obviously greater than that of PLGA NPs and HA-hybrid NPs, resulting in increased accumulation of SN38 within the HGC27 tumour-bearing nude mouse model. In addition to the above-mentioned study, NPs also have been surface-functionalized with molecules targeting CA199,[100] CD320,[101] and nucleolin[102] for actively targeted GC therapy.

Drug resistance is a major challenge in tumour therapy, as tumour cells develop various mechanisms to counteract the cytotoxic effects of chemotherapeutic drugs, hindering their ability to kill tumour cells effectively. The molecular and cellular mechanisms of drug resistance to chemotherapy are complex and include increased drug efflux, reduced drug uptake, altered deoxyribonucleic acid (DNA) damage repair, and the inhibition of autophagy and apoptosis pathways.[103] NP delivery systems can be used to target key factors involved in drug resistance mechanisms, thereby addressing the challenges of drug resistance. Aberrant activation of the PI3K/AKT pathway, which promotes the proliferation of cancer cells and inhibits apoptosis, thereby contributing to drug resistance, has been reported in GC.[104] Therefore, inhibition of the PI3K/AKT pathway could be a promising strategy to reverse drug resistance in GC. Cai *et al.*[54] developed PLGA NPs loaded with docetaxel and the PI3K inhibitor LY294002 for GC treatment. *In vivo* experiments revealed that the PLGA NP-based drug delivery system increased the cellular uptake of docetaxel and LY294002. More importantly, compared with the docetaxel group and the LY294002 group, the PLGA (docetaxel+ LY294002) group had the highest tumour inhibitory efficacy. In addition to the abnormal activation of signalling pathways, increased drug efflux is a significant contributor to drug resistance. As a member of the adenosine triphosphate (ATP)-binding cassette transporter family, P-glycoprotein (P-gp) plays a crucial role in efficiently pumping chemotherapeutic drugs out of cells.[105] This process leads to reduced intracellular concentrations of these drugs and diminishes their therapeutic efficacy. The overexpression of P-gp in GC[106] has been reported, and the inhibition of P-gp could be a promising strategy to combat drug resistance. XMD8-92 is a kinase inhibitor with anticancer activity that has been proven to effectively downregulate P-gp expression.[107,108] Hence, Yang *et al.*[109] developed a drug delivery system that simultaneously carries DOX, XMD8-92, and superparamagnetic iron oxide NPs

(SPIOs) for GC imaging and chemotherapy. This drug delivery system uses biotin-modified PEG-blocked-poly(L-leucine) (biotin-PEG-*b*-Leu) micelles as the basic nanoframework (Fig. 2a). Biotin can actively target GC, while poly(L-leucine) can respond to the acidic TME to release drugs. With SPIOs incorporated, the DXS@NPs system is suitable for magnetic resonance (MR) imaging. Furthermore, XMD8-92 downregulates P-gp expression, leading to increased retention of DOX within tumour cells (Fig. 2b). *In vivo* studies on drug-resistant tumour-bearing mice confirmed that this nanoformulation had a significantly greater anticancer effect than did free DOX.

3.2. Radiotherapy

Radiotherapy uses ionizing radiation to induce cytotoxic damage in proliferating cells, which plays an important role in the treatment of primary and metastatic solid tumours and the inhibition of locoregional recurrence.[110] However, most GC patients are insensitive to radiotherapy. The underlying mechanisms are complex and are associated with alterations in DNA repair processes, cellular energetics, growth signalling pathways, inflammation, angiogenesis and hypoxia.[15,111] Consequently, there is a significant need to incorporate radiosensitizers, such as chemotherapeutic drugs and high-atomic-number elements, to enhance the cytotoxic effects of radiotherapy on GC cells. In particular, a number of radiosensitizers have been engineered into nanoplatforms to enhance the therapeutic effect of radiotherapy and reduce systemic side effects by taking advantage of the ability of NPs to selectively accumulate in tumour tissue.

Chemotherapeutic drugs, such as PTX and DOX, are commonly used as radiosensitizers in clinical practice and can enhance the therapeutic effect of radiotherapy by arresting cancer cells in the most radiation-sensitive phases of the cell cycle and eliminating radioresistant cells in late S phase.[112] A previous study reported that DOX can exhibit radioenhancement efficacy in GC.[113] However, the nonspecific distribution and systemic side effects of DOX limit its use as a radiosensitizer in combination with radiotherapy. To solve this problem, Cui *et al.*[114] synthesized novel NPs consisting of a gelatinase-cleavage peptide with PEG and a poly(ε-caprolactone) (PCL)-based structure for the delivery of DOX to GC tissues. Because gelatinase is highly expressed in GC, once the NPs accumulate in GC tissues through passive targeting, the gelatinase-cleavage peptides are degraded by gelatinases, resulting in the release of DOX. *In vivo* experiments revealed that the radioenhancement efficacy of DOX-NPs was greater than that of DOX without increasing the risk of systemic side effects.

High-atomic-number elements, such as gold (Au, $Z = 79$) and silver (Ag, $Z = 47$), can effectively absorb X-ray energy and then emit various secondary electrons.[58,115] These secondary electrons not only damage DNA directly but also react with water to increase the production of reactive oxygen species (ROS) to cause DNA damage.[58,115] Because of these unique properties of high-atomic-number elements, they have been widely used as radiosensitizers during radiotherapy in studies of tumour treatment. Zhang *et al.*[116] designed chitosan-modified gold NPs (CS-GNPs) to evaluate their potential to increase the sensitivity of GC cells to radiotherapy. The chitosan coating on the surface of the gold NPs increased their biocompatibility and reduced allergic reactions and immune rejection. *In vitro* experiments showed that the survival fraction of GC cells incubated with CS-GNPs was obviously lower than that of those incubated with irradiation alone. Huang *et al.*[117] reported a simple ''one-pot'' synthesis of Ag microspheres from silver nitrate ($AgNO_3$) with hydrazine monohydrate ($N_2H_4{\cdot}H_2O$) as a reducer in the presence of bovine serum albumin. Individual Ag microspheres are composed of many nanoscale Ag assemblies. *In vitro* cell assays revealed that, compared with radiotherapy alone, Ag microspheres could increase radiation-induced cytotoxicity in GC cells. Future research stemming from the two aforementioned studies should concentrate on modifying NPs to endow them with active tumour-targeting capabilities. Additionally, it is essential to utilize reliable preclinical tumour models, such as patient-derived xenograft (PDX), to assess their radioenhancement efficacy in deep-seated tumours *in vivo*.

Owing to the high oxygen consumption of cancer cells, the TME is hypoxic, which can further lead to radioresistance by increasing free radical scavenging and changing patterns of gene expression.[118] Pyrogallol (PG) is a trihydroxybenzene compound that promotes the production of ROS, making it a promising radiosensitizer to overcome hypoxia-induced radioresistance.[119] On the basis of this mechanism, Wang *et al.*[120] constructed PG-loaded mesoporous organosilica NPs (MON@PG) to increase GC radiotherapy sensitivity. MONs have an ample surface area, low toxicity and decent biocompatibility. More specifically, they can achieve biodegradation in a GSH-containing environment. Since GC cells and their microenvironment are rich in GSH, MON@PG can achieve tumour-specific drug release. In xenograft GC models, the MON@PG plus radiotherapy group exhibited significantly improved tumour growth inhibition compared with the group receiving radiotherapy alone, suggesting that MON@PG may have potential as a radiosensitizer in GC radiotherapy.

3.3. Immunotherapy

Cancer immunotherapy is a method that activates or enhances the natural mechanisms of the immune system to attack cancer cells.[121] Four principal strategies are used in cancer immunotherapy: ICIs, adoptive immunotherapy, tumour vaccines, and nonspecific immunomodulators. Although immunotherapy is a promising cancer treatment method, the clinical application of immunotherapy still faces several challenges related to efficacy and safety. For example, with regard to efficacy, many solid tumours are characterized by immune suppression and evade immune attack through multiple resistance mechanisms, resulting in a lower response rate to ICIs;[122] with regard to safety, an excessive immune response may induce cytokine release syndrome and vascular leak syndrome.[123] Nanoformulations have been widely used in cancer immunotherapy research because they can increase the accumulation of immunomodulators in tumours or lymphoid organs, enable more effective targeting of

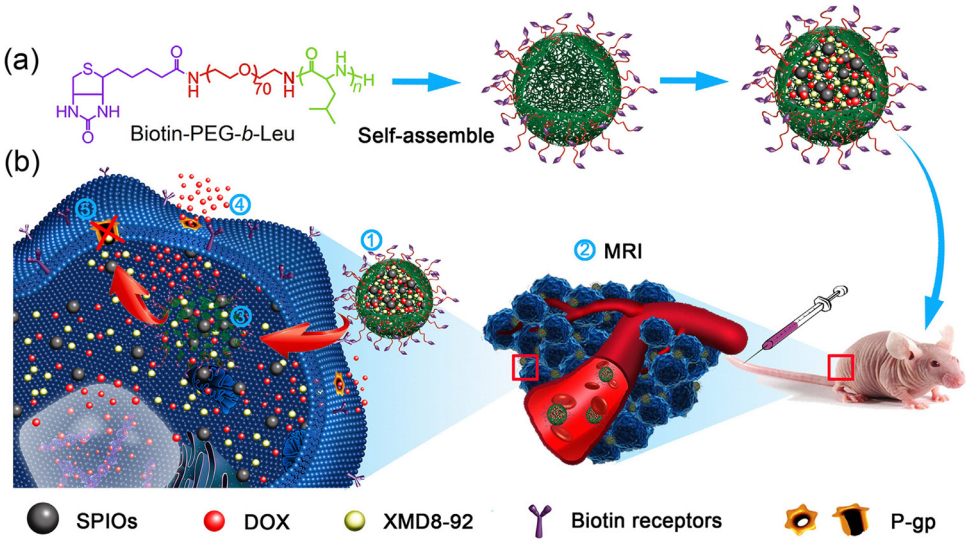

Fig. 2 Schematic representation of the DXS@NP theranostic platform. (a) The construction of DXS@NPs, which simultaneously carries DOX, XMD8-92, and SPIOs. (b) The DXS@NPs are utilized for GC MR imaging and chemotherapy in drug-resistant GC within xenograft models. Reproduced with permission from ref. 109. Copyright 2019, Science China Press.

the desired tumour and/or immune cells, and reduce off-target adverse effects.[124]

ICIs have been the most extensively studied class of immunotherapy to date. The two most common checkpoint inhibition strategies are PD-1/PD-L1 blockade and CTLA4 inhibition.[125] ICIs can induce a longer lasting antitumour response in only a few subsets of advanced GC patients, and the efficacy of single-agent therapy is limited.[17] The potential mechanisms of resistance to ICI in GC include various factors, such as insufficient infiltration of T cells into the TME, abnormalities in critical signalling pathways, and the presence of inhibitory factors in the TME.[126] To improve the efficacy of ICIs in GC, researchers have carried out a series of related studies using NPs as efficient drug delivery carriers. Li *et al.*[127] compared the differential profiles of circular RNAs (circRNAs) between paired GC tissues and adjacent non-cancerous gastric tissues and discovered remarkably high expression levels of circRHBDD1 in GC tissues. Furthermore, they found that circRHBDD1 inhibited the ubiquitination and degradation of IGF2BP2 by competing with TRIM25. The elevated levels of IGF2BP2 enhanced the stability of PD-L1 mRNA through m^{6}A modification, thereby facilitating immune escape in GC (Fig. 3a). Consequently, the authors developed PLGA–PEG (si-circRHBDD1)

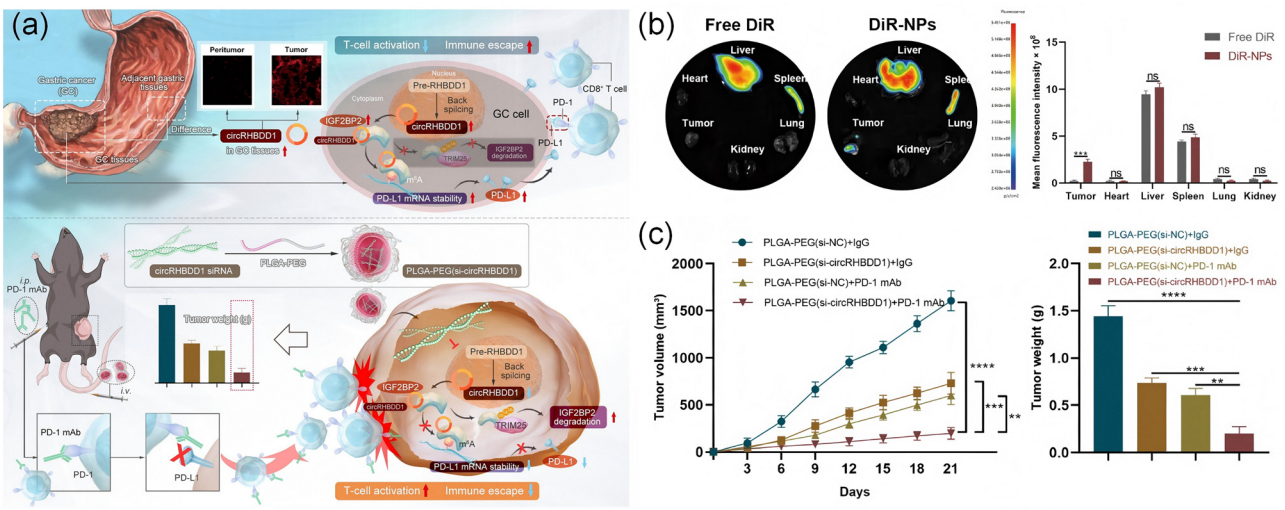

Fig. 3 Schematic representation of the mechanisms by which circRHBDD1 promotes immune escape in GC, along with the combined therapeutic platform utilizing PLGA-PEG (si-circRHBDD1) NPs and anti-PD-1. (a) The high expression levels of circRHBDD1 in GC promote immune escape through the IGF2BP2/PD-L1 axis and utilize circRHBDD1 as a nanotherapeutic target in GC. (b) The *in vitro* fluorescence imaging of tumours and major organs following the injection of DiR NPs or free DiR demonstrated the superior tumour-targeting capability of the DiR NPs. (c) The combination therapy utilizing PLGA-PEG (si-circRHBDD1) NPs alongside anti-PD-1 significantly inhibited tumour growth in xenograft GC models.[127] Copyright 2024, Springer Nature.

NPs – composed of a PLGA core encapsulating siRNA and a PEGylated stealth shell for prolonged circulation and enhanced tumour accumulation *via* the EPR effect – to augment the therapeutic effect of PD-1 inhibitors in GC. Upon cellular internalization, these NPs release si-circRHBDD1, which degrades circRHBDD1, thereby restoring TRIM25-mediated ubiquitination of IGF2BP2. This leads to reduced PD-L1 expression and subsequent reversal of T-cell exhaustion. Utilizing a C57BL/6 GC model, they first evaluated the tumour-targeting capability of these NPs. *In vitro* fluorescence imaging of tumours and major organs following administration of DiR NPs or free DiR confirmed the superior tumour-targeting ability of the DiR NPs (Fig. 3b). Furthermore, combination therapy employing PLGA-PEG (si-circRHBDD1) NPs alongside anti-PD-1 significantly suppressed tumour growth compared to anti-PD-1 monotherapy (Fig. 3c).

The anti-PDL1 effect of αPDL1 could be improved by blocking the TGF-β1 signalling pathway, which converts the tumour immune microenvironment from the "immune-excluded phenotype" to the "immune-inflamed phenotype".[128,129] Wu *et al.*[130] developed TGF-β1 small interfering ribonucleic acid (siRNA)-loaded NPs in which αPDL1 was linked to PEG and PCL, after which the resulting TGF-β1 siRNA was encapsulated in αPDL1-PEG-PCL (siTGF-β1-αPDL1-PEG-PCL). αPDL1 can not only actively target PDL1-overexpressing GC cells to deliver TGF-β1 siRNA but also promote the immune checkpoint blockade to enhance the antitumour effect of ICI therapy. The results indicated that the siTGF-β1-αPDL1-PEG-PCL NPs efficiently reduced the amount of TGF-β1 mRNA in MFC cells and converted the immune microenvironment of MFC tumour-engrafted mice.

A hypoxic microenvironment can cause tumours to develop resistance to ICIs by inhibiting antitumour immune effector cells and promoting immune escape.[131] TH-302 (evofosfamide), a hypoxia-activated prodrug, can be bioreduced to produce cytotoxic metabolites under hypoxic conditions.[132] Previous studies have shown that the agent TH-302 can reduce the hypoxic area of cancer and increase sensitivity to ICIs.[133,134] To enhance the bioavailability and tumour-targeting capability of TH-302, Wang *et al.*[135] designed monomethoxy-PEG-PLGA-encapsulated TH-302 NPs (TH-302 NPs) (Fig. 4a). Utilizing a GC xenograft tumour model, a small-animal live imaging system revealed significantly enhanced tumour accumulation of DiR-labelled NPs compared to free DiR, demonstrating superior tumour-targeting efficacy conferred by nanoencapsulation (Fig. 4b). *In vivo* experiments further confirmed that combining TH-302 NPs with αPD1 significantly reduced the hypoxic area of tumour tissues (Fig. 4c) and markedly improved immunotherapeutic efficacy *versus* αPD1 monotherapy (Fig. 4d). Mechanistically, this combination therapy synergistically: (1) depleted hypoxia-induced immunosuppressive cells *via* TH-302-derived cytotoxic metabolites and (2) reversed PD-L1 upregulation by destabilizing HIF-1α. Consequently, it markedly increases $CD8^+$ T cell infiltration and elevates levels of TNF-α, IFN-γ, and granzyme B within tumour tissues (Fig. 4a).

Personalized therapeutic tumour vaccines are designed to amplify tumour-specific T-cell responses to kill cancer cells through active immunization.[136] To prevent the rapid *in vivo* clearance of vaccines and increase their bioavailability, nanodrug delivery systems have played important roles.[137] Liu *et al.*[138] generated a personalized neoantigen nanovaccine for adjuvant GC immunotherapy. The selected neoantigen peptide was conjugated to the amphiphilic lipids 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[hydroxysuccinimidyl(polyethyleneglycol)] (DSPE-PEG2000-NHS) to synthesize the NPs. This nanovaccine triggered superior protective efficacy against tumour recurrence and promoted longer survival than free neoantigens did in mouse forestomach carcinoma (MFC) tumour-bearing mice. Even more exciting was that they conducted a phase I clinical trial to evaluate the efficacy of this nanovaccine in GC patients, with results

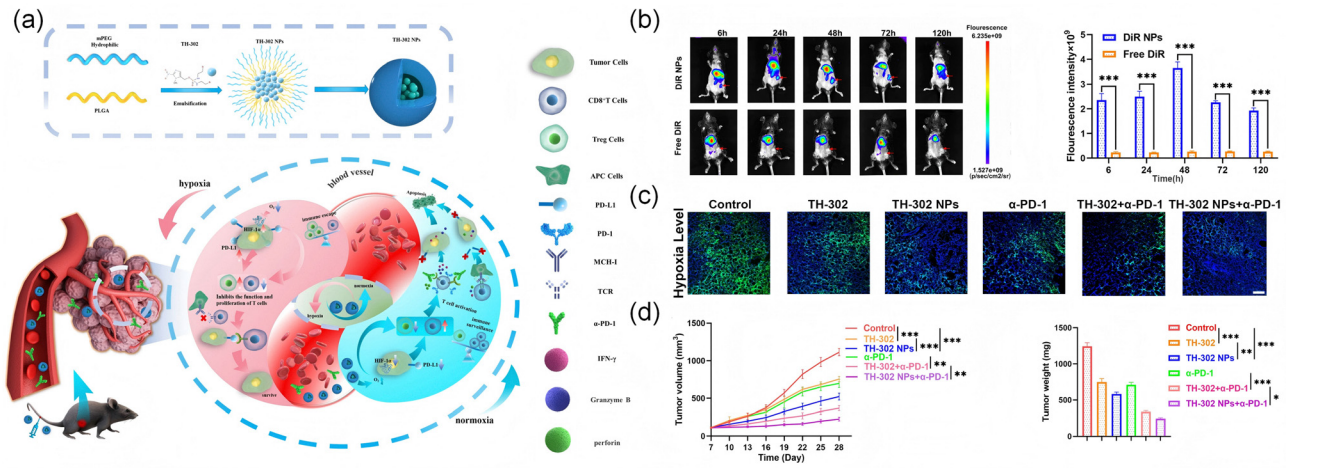

Fig. 4 Schematic representation of the mechanisms by which TH-302 NPs and α-PD-1 alleviate the hypoxic tumour microenvironment, along with the combined therapeutic platform utilizing TH-302 NPs and α-PD-1. (a) Mechanisms of antitumour synergistic immunotherapy mediated by TH-302 NPs and α-PD-1 by alleviating the hypoxic tumour microenvironment. (b) Real-time imaging using a small-animal live imaging system demonstrated the superior tumour-targeting capability of DiR NPs in a GC xenograft tumour model. (c) Pimonidazole staining confirmed that the combination of TH-302 NPs with α-PD-1 significantly reduced the hypoxic areas within tumour tissues. (d) The combined therapy utilizing TH-302 NPs alongside α-PD-1 significantly inhibited tumour growth in xenograft GC models.[135] Copyright 2023, Springer Nature.

showing that the immune response remained evident one year after vaccination, and the one- and two-year disease-free survival rates were significantly higher than those previously reported.

3.4. Gene therapy

Cancer gene therapy is an alternative treatment method that introduces therapeutic genes into cancer cells to cause cell death or slow the growth of the cancer.[139] Gene therapy for GC strategically targets oncogene suppression (STAT3, BCL2, KRAS, and Gil1),[140–142] angiogenesis/metastasis inhibition (VEGFA),[143] tumour suppressor restoration (miR-21 and miR-532-3P),[141,144] and cancer stem cell elimination (CD44).[145] Gene therapy has become a promising approach for cancer treatment in recent decades. However, the administration of unmodified naked nucleic acids faces obstacles because they are easily degraded by ribonucleases, are not easily taken up by cancer cells, and are unable to target tumour sites, which limits their efficacy in systemic delivery.[146] Hence, various nucleic acid delivery strategies, especially NPs, have been explored.[147,148] NPs provide a protective environment for nucleic acids, increasing their *in vivo* stability and enabling their selective accumulation in tumour tissue.[147,148] Additionally, NPs can be functionalized with targeted ligands to improve their cellular uptake, thereby increasing the overall efficacy of gene therapy.[149]

siRNAs are produced from cytoplasmic double-stranded RNA, which is cleaved into 21–23 base pair fragments by an endonuclease called double-stranded RNA-specific endoribonuclease (DICER).[150,151] Following their formation, siRNAs are loaded into the RNA-induced silencing complex, where they bind to target mRNAs, triggering sequence-specific cleavage and subsequent degradation of the target mRNAs and thereby ultimately silencing or downregulating the expression of the target gene.[150,151] Gastric cancer stem cells (CSCs) are closely linked with the initiation, growth, recurrence, and metastasis of GC;[152] hence, effective targeting of CSCs is considered a promising therapeutic strategy. Previous studies have indicated that high expression of the transcription factor glioma-associated oncogene homolog 1 (Gli1) plays a central role in maintaining and regulating CSC stemness in a variety of tumours.[153,154] Therefore, Yao H *et al.*[155] suggested that blocking Gli1 with siRNA to eliminate gastric CSCs is an ideal treatment strategy for GC. Furthermore, they developed di-stearoyl-phosphatidyl-ethanolamine-hyaluronic-acid (DSPE-HA) single-point conjugate-modified cationic liposomes to deliver Gli1 siRNA. This DSPE-HA single-point conjugate served two purposes. First, it can make the entire NP negatively charged, thereby increasing its biocompatibility; second, HA can specifically target CD44-overexpressing GC. *In vitro* and *in vivo* experiments revealed that Gli1-targeting siRNA NPs are selectively accumulated in GC tissues, which significantly decreased Gli1 protein expression and effectively prevented GC recurrence.

B-cell lymphoma 2 (Bcl2) is an oncogene involved in cancer development that inhibits cell death.[156] Thus, directly targeting the apoptotic mechanism with a Bcl2 inhibitor could be a promising therapeutic approach. In this context, Kumar R *et al.*[157] envisioned a novel synergistic treatment strategy involving Bcl2 gene silencing *via* the codelivery of the Bcl2 inhibitor navitoclax (NAVI) and Bcl2 siRNA to induce the death of GC cells. Furthermore, they developed a mucoadhesive nanocarrier composed of β-glucan and docosahexaenoic acid to deliver NAVI and siRNA, enabling effective targeted therapy for GC *via* oral administration. The *in vivo* results confirmed that the mucoadhesive nanocarrier could protect NAVI and siRNA from the harsh stomach environment, achieving a stomach retention time of at least 5 h. Furthermore, the mucoadhesive delivery system downregulated Bcl2 expression and induced apoptosis in GC cells. Notably, Kumar R *et al.* developed an emerging mucoadhesive nanocarrier with great potential for the oral delivery of both small and large molecules. Compared with conventional treatments, mucosal adhesion can increase therapeutic efficacy while minimizing side effects.

MicroRNAs (miRNAs) are small, endogenous, single-stranded, non-protein coding RNA molecules 19 to 24 nucleotides in length that can inhibit protein translation through binding to the 3′ untranslated regions (UTRs) of target mRNAs and causing their degradation.[158] Chen Z *et al.*[159] reported that miR-532-3p can bind to the 3′-UTR of RAB3IP, increasing the rate of apoptosis in human GC cells. On the basis of these findings, they further constructed VB12-conjugated and miR-532-3p-loaded PLGA-PEG NPs (miR-532-3p@PLGA-PEG-VB12 NPs) to fight the progression of CD320-overexpressing GC cells.[160] Through VB12 receptor (CD320)-mediated endocytosis, the ability of the miR-532-3p@PLGA-PEG-VB12 NPs to target GC was enhanced. *In vitro* and *in vivo* experiments revealed that the NPs markedly inhibited the proliferation of GC cells. In addition, some previous studies reported that increased miR-34a levels in cancer cells can induce cell apoptosis and inhibit cell metastasis and that miR-34a is usually downregulated in most GC.[161] Therefore, restoring and increasing intracellular miR-34a expression is an advantageous strategy for the treatment of GC. Furthermore, some studies have reported that sialylated carbohydrate antigens are overexpressed in various types of tumour cells, and phenylboronic acid (PBA) has been recognized for its selective recognition and high affinity for sialic acid (SA).[162] On the basis of the above research results, Song Z *et al.*[163] designed a PBA-functionalized amine-terminated polyamidoamine dendrimer to deliver miR-34a (PPP/miR-34a) to SA-positive GC. Compared with that of nontargeted NPs, the *in vivo* biodistribution of PPP/miR-34a in xenograft cancer models showed significantly greater accumulation and a stronger inhibitory effect on tumour growth.

3.5. Phototherapy

Phototherapy, namely, phototriggered therapeutic modalities, has gained significant attention as an effective approach for cancer treatment. This is attributed to its advantages of noninvasiveness, high spatiotemporal precision, remarkable efficiency, and favourable biosafety profile.[164,165] Phototherapy mainly consists of photodynamic therapy (PDT) and PTT. Photosensitizers and photothermal agents are the cores of PDT and PTT, respectively. A photosensitizer produces massive amounts of ROS under NIR irradiation to induce local cancer

cell apoptosis, necrosis, or autophagy.[166] The photothermal agents generate heat upon NIR light irradiation to cause local hyperthermia and thereby induce irreversible cancer cell death.[167] However, the majority of photosensitizers and photothermal agents exhibit high hydrophobicity, instability, and low delivery efficiency, which significantly restrict their therapeutic efficacy in systemic administration. NPs can serve as ideal carriers to mitigate these challenges because of their unique properties.

As a promising photosensitizer, Al(III) phthalocyanine chloride tetrasulfonic acid (AlPcS4) exhibits superior PDT effects in various cancer cell lines.[168,169] However, Xin *et al.*[170] reported that the antigrowth effect of AlPcS4 on GC was limited because AlPcS4 penetrates poorly into GC cells and that HSA has a high binding affinity for AlPcS4. Hence, they synthesized a series of NPs, including gold nanorods (AuNRs), a cationic liposome (Clip), and Pluronic® F127 nanomicelles, to improve the limited antitumour effects of AlPcS4-PDT on GC cells to varying degrees. Clip exhibited the highest drug delivery efficiency for AlPcS4, attributed to enhanced intracellular bioavailability and reduced binding affinity to serum proteins. Positively charged AuNRs exhibited the most effective antigrowth properties because of their multifaceted capabilities. These compounds not only facilitated the delivery of AlPcS4 and reduced its binding affinity to serum proteins but also increased the generation of singlet oxygen and exerted a pronounced photothermal effect, which together contributed to the direct induction of cell death.

In addition to the high binding affinity of HSA to the photosensitizers mentioned above, the hypoxic and antioxidant-rich TME can severely impair the efficacy of PDT.[171,172] The hypoxia caused by the rapid proliferation of tumour cells limits the production of ROS; moreover, overexpressed reductive substances tend to eliminate ROS, thereby protecting tumour cells. Blocking mitochondrial glutaminase (GLS) is an effective means to reduce oxygen consumption and prevent the generation of intracellular reductive substances.[173,174] Hence, Li *et al.*[175] constructed a PDT system named IRCB@M, in which a photosensitizer (IR-780) and a GLS inhibitor (CB-839) were self-assembled and then encapsulated by GC cell membranes for homologous targeting (Fig. 5a). The *in vivo* results indicated that the antitumour effect was significantly enhanced with the introduction of CB-839 compared to PDT alone. Mechanistically, CB-839 inhibits the glutamine (Gln) metabolic pathway, resulting in a reduction of cellular oxygen consumption through oxidative phosphorylation (OXPHOS) and decreasing the production of reductive substances such as nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione (GSH) (Fig. 5b). This inhibition further amplifies the efficacy of PDT.

As prominent photothermal materials, semiconductor copper sulfide (CuS) NPs have been widely utilized for cancer PTT.[176,177] To integrate imaging tags into well-designed CuS NPs to realize the imaging-guided PTT of cancers and further increase the accuracy of real-time detection and treatment, Shi *et al.*[178] designed T-MAN, a multifunctional CuS-based nanoplatform comprising (1) oleylamine (OA)-coated Gd/CuS nanodisks for photothermal conversion and MR imaging, (2) a DSPE-PEG layer for stability, (3) a cRGD ligand for tumour targeting *via* integrin $\alpha_v\beta_3$ binding, and (4) an matrix metalloprotease-2 (MMP-2)-cleavable peptide substrate ((QSY21)-GGPLG VRGK(Cy5.5)-SH) (Fig. 6a). Under NIR irradiation, T-MAN exhibited high photothermal efficiency, enabling effective tumour cell ablation. The incorporated $Gd3^+$ conferred MR imaging capability with high spatial resolution, while the QSY21 quencher suppressed Cy5.5 fluorescence until MMP-2-mediated peptide cleavage. Notably, cRGD not only targeted $\alpha_v\beta_3$—overexpressed on GC cells—but also facilitated MMP-2 activation, promoting substrate cleavage. Following intravenous administration, T-MAN accumulated in GC tissues *via* $\alpha_v\beta_3$-mediated delivery. Therefore, extracellular and cell surface MMP-2 cleaved the peptide, restoring Cy5.5 fluorescence. This fluorescence/MR bimodal imaging guided precise NIR irradiation, ensuring accurate tumour delineation and therapy (Fig. 6b). Additionally, indocyanine green (ICG) can serve as a photothermal agent under near-infrared 808 nm laser irradiation.[179,180] Furthermore, it functions as a fluorescent substance that is visible in the NIR region and can be utilized for the identification of an anatomical structure, tissue vascularization and sentinel nodes.[181,182] Shao *et al.*[183] synthesized novel ICG-loaded, ROS-responsive, RGD-modified NPs for simultaneous NIR imaging and PTT of GC. These NPs consisted of four parts: carboxymethyl chitosan (CMCh) served as a hydrophilic shell to make the NPs water soluble; benzeneboronic acid pinacol ester (BAPE) formed a hydrophobic end and hydrolysed in the presence of excessive ROS at the tumour site to release ICG; RGD peptides were modified on the surface of the NPs to specifically bind to integrins overexpressed in the GC; and ICG was used as a dual-functional dye to achieve NIR imaging and PTT. *In vivo* studies showed that, compared with nontargeted NPs, these NPs can more accurately display the tumour location and margin in SGC7901 tumour-bearing mice through NIR imaging and have a stronger tumour-inhibitory effect upon NIR light irradiation.

3.6. Combined therapy

Owing to intratumoral heterogeneity, dynamic adaptive resistance mechanisms, and the complex TME that impedes drug biodistribution, a single therapeutic modality often fails to achieve optimal therapeutic outcomes in cancer treatment.[184] In contrast to monotherapy, cancer combination therapy seeks to coordinate multimodal interventions aimed at concurrently disrupting malignant cell populations and TME components.[185,186] This approach offers several advantages: it can overcome drug resistance induced by heterogeneity through multimechanism synergy, reduce drug dosage and minimize toxic side effects *via* collaborative synergy, and provide multifaceted inhibition of tumour growth and metastasis.[185,186] Nanocarriers further enhance combination therapy by facilitating the spatiotemporal codelivery of synergistic agents, overcoming biological barriers *via* size- and ligand-mediated tumour targeting, and minimizing systemic toxicity *via* pharmacokinetic optimization while preserving therapeutic efficacy.

Although PTT is an effective strategy for cancer treatment, it cannot completely eradicate cancer cells on its own because of

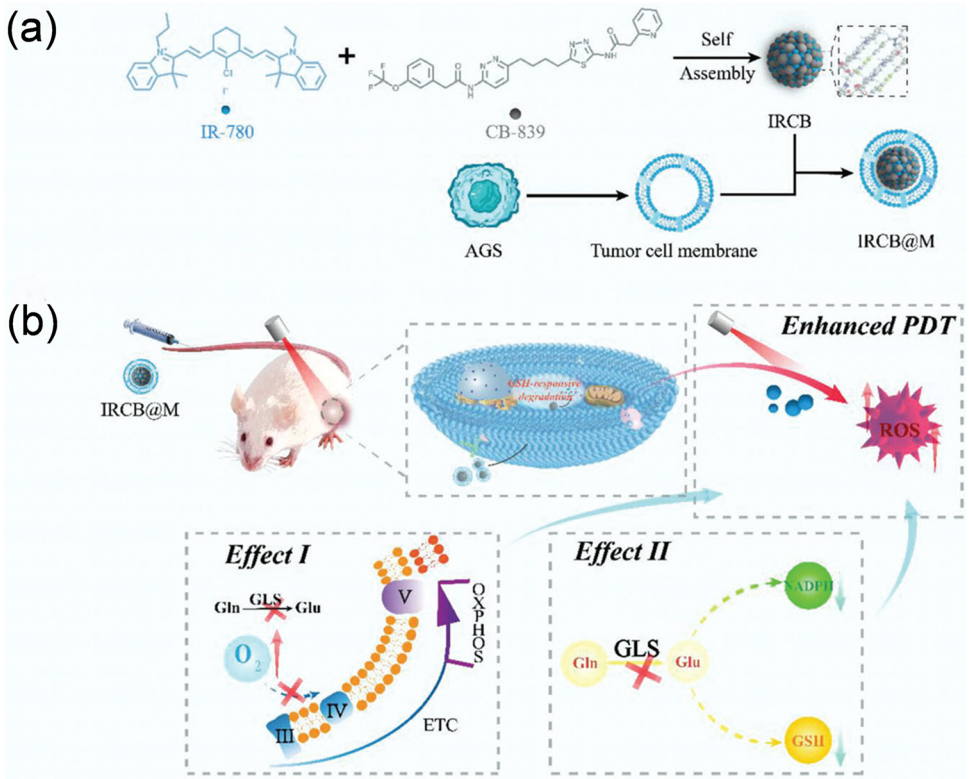

Fig. 5 Schematic representation of the IRCB@M therapeutic platform and its mechanisms of enhancing PDT through dual effects. (a) The preparation of IRCB@M, which dual-loads the photosensitizer IR-780 and the GLS inhibitor CB-839. (b) The IRCB@M enhances the efficacy of PDT by reducing oxygen consumption and inhibiting the synthesis of reductive substances. Reproduced with permission from ref. 175. Copyright 2023, Wiley-VCH GmbH.

its uneven heat distribution and the hypoxic microenvironment present within tumours.[187,188] The survival of cancer cells following PTT may contribute to local recurrence and distant metastasis. Therefore, a combinational approach that integrates PTT with other therapeutic modalities may represent the optimal strategy for maximizing control over cancer progression. Xia *et al.*[75] integrated PTT with chemotherapy for the treatment of GC. They initially employed genetic engineering techniques to modify EVs derived from normal human embryonic kidney (HEK-293) cells by displaying cadherin 17 (CDH17)-specific nanobodies (E8) on their surface, enabling active targeting to CDH17-overexpressing GCs. They subsequently dual-loaded the photothermal agent ICG along with the chemotherapeutic drug dinitroazetidine derivative RRx-001 into engineered EVs (I/R@E8-EVs) (Fig. 7a). *In vivo* results indicated that the CDH17 nanobody-engineered EVs could increase the ability of EVs to target CDH17-overexpressing GC (Fig. 7b). Compared with the RRx-001@E8-EVs and ICG@E8-EVs plus NIR groups, the I/R@E8-EVs plus NIR group presented more potent tumour growth inhibition and prolonged survival, exhibiting synergistic antitumour activities, in GC PDX models (Fig. 7c). Mechanistically, RRx-001 can block the CD47-signal regulatory protein α (SIRPα) pathway, thereby enhancing the phagocytosis of macrophages towards cancer cells and subsequently suppressing tumour growth. ICG-induced PTT not only induces tumour apoptosis, necrosis, and immunogenic cell death (ICD), but also promotes the polarization of macrophages from the M2 to M1 phenotype (Fig. 7a).

Drug resistance presents a significant challenge to the efficacy of chemotherapy for the treatment of GC in clinical practice, as it severely impacts treatment outcomes.[189] For example, PTX is recommended as a first-line treatment for GC patients.[16] However, prolonged administration of PTX can readily lead to the development of drug resistance because of the overexpression of P-gp, which facilitates the efflux of intracellular PTX from GC cells, thereby reducing its concentration within these cells and diminishing its therapeutic effectiveness.[190–192] In recent years, combining PTX with phototherapy has emerged as a promising strategy to combat PTX resistance. Guo *et al.*[193] developed a drug delivery system that incorporated PTX onto PEG-modified and oxidized sodium alginate (OSA)-functionalized graphene oxide (GO) nanosheets, referred to as PTX@GO PEG-OSA. The amido linkage between GO-PEG and OSA enables pH-sensitive drug release, resulting in a faster degradation rate in acidic TME. *In vitro* and *in vivo* experimental results indicated that the combination of PTX@GO PEG-OSA with NIR irradiation induced synergistic effects through chemotherapy/PTT/PDT, demonstrating superior antitumour efficacy compared with single-modality chemotherapy or phototherapy alone. More interestingly, the *in vitro* results demonstrated that the addition of PDT had a

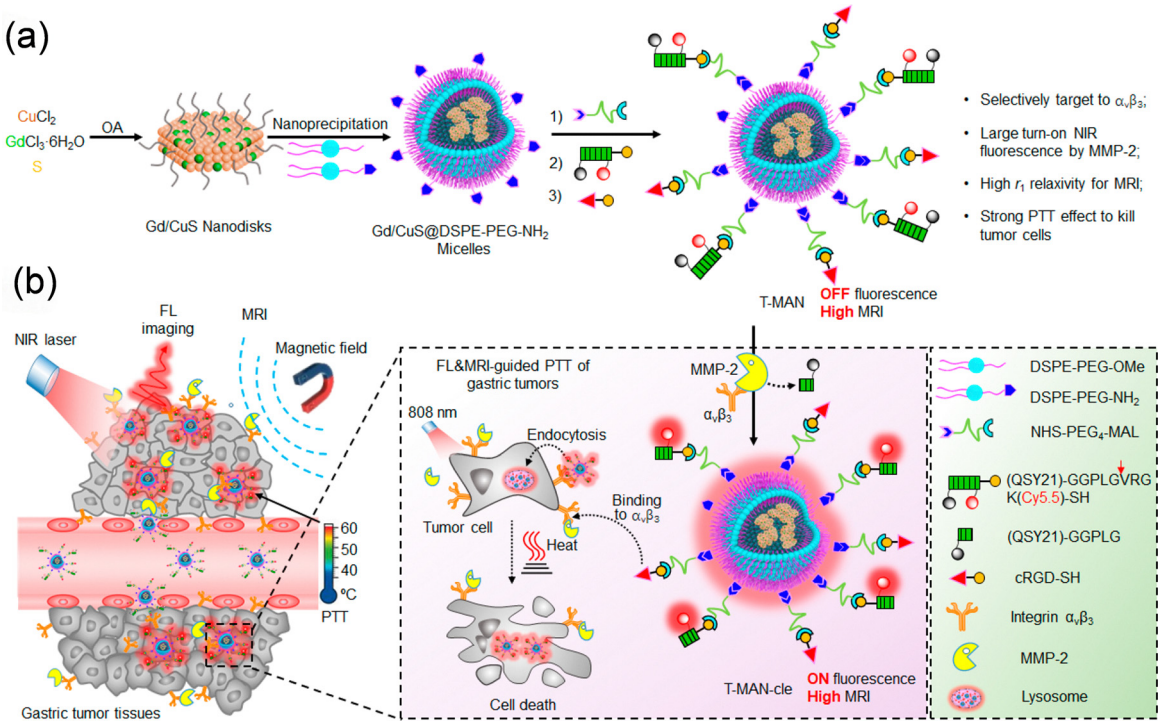

Fig. 6 Schematic representation of the T-MAN theranostic platform. (a) An illustration depicting the structure and synthesis of T-MAN. (b) Schematic representation of the mechanism by which T-MAN facilitates fluorescence/MR imaging-guided PTT for GC *in vivo*.[178] Copyright 2019, American Chemical Society.

superadditive effect on the therapeutic efficiency in the PTX@GO PEG-OSA groups. Mechanistically, Guo *et al.* discovered that PTX@GO-PEG-OSA could generate excessive ROS under NIR irradiation, which would attack mitochondrial respiratory chain complex enzymes. This action leads to reduced availability of ATP for P-gp functions, effectively inhibiting the efflux pump activity of P-gp and ultimately reversing drug resistance in GC.

4. Challenges and prospects

As one of the most prevalent malignant tumours worldwide, GC is treated primarily through surgery, chemotherapy, targeted therapy, immunotherapy, and other comprehensive approaches. Despite significant advances in treatment modalities, the prognosis for GC patients remains poor due to the poor targeting capabilities and affinity of traditional drugs,

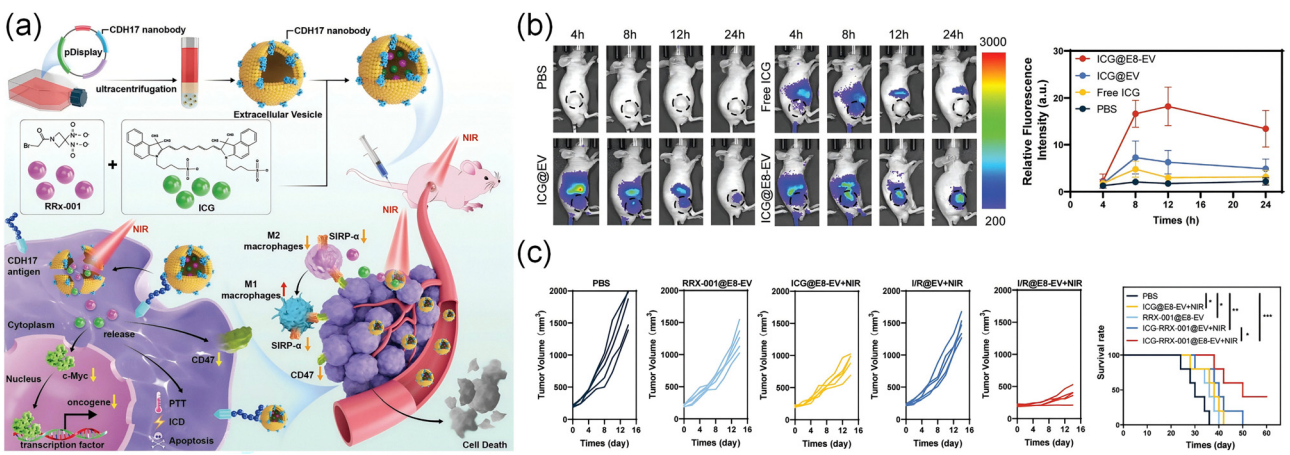

Fig. 7 Schematic representation of the synergistic antitumour mechanisms of I/R@E8-EVs through PTT and chemotherapy, along with the I/R@E8-EV therapeutic platform. (a) The I/R@E8-EVs simultaneously incorporates the photothermal agent ICG and the chemotherapeutic drug RRx-001 for GC theragnostic and induces polarization of tumour associated macrophages. (b) Real-time imaging using a small-animal live imaging system demonstrated that the CDH17 nanobody-engineered EVs could increase the ability of EVs to target CDH17-overexpressing GC. (c) The I/R@E8-EVs demonstrates synergistic antitumour mechanisms through PTT and chemotherapy in GC PDX models. Reproduced with permission from ref. 75. Copyright 2022, Wiley-VCH GmbH.

which often lead to low therapeutic efficacy and severe side effects. In recent decades, nanoformulations have been explored as drug carriers to address these challenges, representing a promising strategy for enhancing current treatments and improving patient prognosis in GC. In this review, we summarized novel nanoformulations developed for the treatment of GC in recent years that have demonstrated substantial improvements in efficacy and safety in studies conducted with animal models (Table 3). However, alongside the advantages offered by nanoformulations, their translation into clinical applications presents several challenges. After all, it is essential to consider clinical translation as the ultimate goal when developing nanoformulations for therapeutic use.

Poor delivery efficiency and safety concerns present significant challenges for the clinical translation of nanoformulations. Wilhelm *et al.*[194] conducted a survey of the literature over the past decade and reported that only 0.7% of administered nanoformulations were successfully delivered to solid tumours. Furthermore, the data indicate that the approval rate of emerging nanodrugs is less than 10%, primarily because of safety issues encountered during preclinical and clinical studies.[42] Therefore, the design of nanoformulations serves as a cornerstone for nanotechnology, with aspirations to achieve efficient and safe drug delivery *in vivo*. From administration to arrival at tumour sites, NPs face various sequential obstacles, including clearance by the MPS and RES, protein opsonization, endothelial extravasation *via* the EPR effect, the impediment of tumour penetration by a dense extracellular matrix and elevated interstitial pressure, cellular internalization, escape from endosomal and lysosomal compartments, and the action of drug efflux pumps.[195,196] Particularly, in the context of GC, when designing nanoformulations for oral administration, it is essential to thoroughly consider the unique characteristics of the gastric environment. For example, gastric acid and pepsin can degrade drugs, thereby affecting their stability; the mucus barrier present in the stomach may hinder drug penetration; and continuous peristalsis can result in an excessively short residence time for drugs within this organ. If these obstacles are not comprehensively and systematically addressed in NP design, the ultimate antitumour efficacy will be significantly diminished. For a long time, nano-bio interaction studies have been conducted independently, which is time-consuming and inefficient. Machine learning (ML) is facilitating substantial advances across numerous fields, including drug discovery and materials science. In the context of developing nanoformulations, we can integrate previous individual studies on

Table 3 Summary of representative drug delivery systems for GC treatment

Drugs	Delivery carrier	Targeted ligand/receptor	*In vitro* models	*In vivo* model	Advantages	Ref.
PTX	Nanostructured micelles	RGD/$\alpha_v\beta_3$	SGC7901; SGC7901/ADR cells and NIH 3T3 cells	CDX	Targeting	96
SN38	PLGA NPs	Anti-HER2/HER2; HA/CD44	HGC27	CDX	Targeting	99
Doc and LY294002	PLGA NPs	—	MKN45	CDX	Stability	54
Dox, XMD8-92, and SPIOs	PEG-*b*-Leu micelles	Biotin/biotin receptor	SGC7901; SGC7901/VCR cells	CDX	Targeting; release	109
Dox	PEG-Pep-PCL NPs	—	BGC823	CDX	Stability	114
PG	MONs	—	MFC; MKN45	MFC cell-engrafted mice	Release	120
si-circRHBDD1	PLGA-PEG NPs	—	MKN28	CDX	Stability	127
siTGF-β1	PEG-PCL NPs	Anti-PDL1/PDL1	MFC; MKN45	MFC cell-engrafted mice	Targeting; stability	130
TH-302	PLGA-PEG NPs	—	MKN45; MKN28	CDX	Stability	135
Glil siRNA	Cationic liposomes	HA/CD44	AGS	CDX	Targeting; stability	155
Navitoclax and Bcl2 siRNA	β-glucan and docosahexaenoic acid	—	AGS	NMNNU-induced animal GC model	Targeting	157
MiR-532-3p	PLGA-PEG NPs	VB12/CD320	BGC823	CDX	Targeting; stability	160
MiR-34a	Nanostructured dendrimers	PBA/SA	BGC823	CDX	Targeting; stability	163
IR-780 and CB-839	GC cell membranes	—	AGS	CDX	Targeting	175
Gd/CuS	DSPE-PEG_{2000} micelles	RGD/$\alpha_v\beta_3$	MKN45	CDX	Targeting	178
ICG	CMCh-BAPE NPs	RGD/$\alpha_v\beta_3$	SGC7901	CDX	Targeting; release	183
ICG and RRx-001	EVs	Anti-CDH17/CDH17	MKN45; IM95; AGS; TMK1	CDX; PDX	Targeting	75
PTX	GO-based nanosheets	—	HGC27/PTX	CDX	Release	193

GC: gastric cancer; PTX: paclitaxel; NPs: nanoparticles; RGD: arginine-glycine-aspartic acid; CDX: cell-derived xenograft; PLGA: poly(lactic-*co*-glycolic acid); HER2: human epidermal growth factor receptor; HA: hyaluronic acid; DOX: doxorubicin; SPIOs: superparamagnetic iron oxide NPs; PEG-*b*-Leu: poly(ethylene glycol)-blocked-poly(L-leucine); Doc: docetaxel; PEG-Pep-PCL: poly(ethylene glycol)-peptide- poly(ε-caprolactone); PG: pyrogallol; MONs: mesoporous organosilica nanoparticles; ICIs: immune checkpoint inhibitors; PBA: phenylboronic acid; SA: sialic acid; DSPE: 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine; ICG: indocyanine green; CMCh-BAPE: carboxymethyl chitosan- benzeneboronic acid pinacol ester; EVs: extracellular vesicles; PDX: patient-derived xenograft; GO: graphene oxide.

nano-bio interactions to establish a searchable database in which data-driven ML algorithms can be employed to predict optimal nanoformulations for targeting and delivery to specific tumours.[197]

The absence of reliable preclinical research models that can accurately simulate actual cancer remains a significant barrier to the clinical translation of NPs. Generally, the experimental models employed for NPs in tumour research can be categorized into three types on the basis of their dimensionality: *in vitro* 2D cell models, *in vitro* 3D cell spheroid models, and *in vivo* cell-derived xenograft models. However, none of these models can closely recapitulate the genotypic, phenotypic, histological and malignant features of actual cancers, which accounts for the general failure of NPs in clinical trials. A classic example is the EPR effect, which is widely accepted as one of the universal pathophysiological features of solid tumours and serves as a fundamental principle for designing and developing tumour-targeting delivery systems for anticancer nanodrugs. Nevertheless, notable differences exist between animal tumour models and human tumours in terms of the EPR effect, as evidenced by the very low delivery efficiency of NPs into human tumour tissue compared with that in animal tumour models.[198] Fortunately, recent advancements in preclinical tumour modelling have opened new avenues for evaluating NP functionality. For example, patient-derived organoid (PDO) and PDX models represent promising developments. PDOs are miniature, 3D, self-organized tissue culture models derived from primary patient tumour stem cells, which have potential as powerful tools for assessing the uptake, toxicity, efficacy, and underlying mechanisms associated with NPs.[199,200] However, PDOs also have limitations: as *in vitro* models, they cannot accurately predict therapeutic responses to nanodrugs following systemic intravenous administration and subsequent delivery to tumour sites *in vivo*. The PDX model is established by transplanting patient tumour fragments from surgical resections or biopsies into critically immunodeficient mice.[201] This model has gained popularity for evaluating the antitumour effects of nanoformulations because it effectively mimics the complex, multistep processes involved in the *in vivo* delivery of these nanoformulations.[202] However, PDX models also face certain challenges, particularly in terms of unsuitability for immunotherapy research on tumours. In this context, the emerging humanized mouse model serves as a valuable supplement to the PDX model.[203] Looking ahead, PDO and PDX models can be jointly utilized to facilitate the clinical translation of nanoformulations.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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