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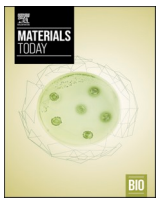

Nanomaterials in the diagnosis and treatment of gastrointestinal tumors: New clinical choices and treatment strategies

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ABSTRACT

Nanomaterials have emerged as a promising modality in the diagnosis and treatment of gastrointestinal (GI) tumors, offering significant advancements over conventional methods. In diagnostic applications, nanomaterials facilitate enhanced imaging techniques, including magnetic resonance imaging (MRI), computed tomography (CT), and fluorescence imaging, which provide improved resolution and more accurate detection of early-stage cancers. Nanoparticles (NPs), such as liposomes, dendrimers, and quantum dots, are increasingly employed for the targeted imaging of specific biomarkers associated with GI malignancies, thereby enhancing diagnostic sensitivity and specificity. Liposomes are primarily used for drug delivery due to their ability to encapsulate hydrophobic drugs, dendrimers are useful for both drug delivery and gene therapy due to their highly branched structure, and quantum dots are primarily used in imaging and diagnostics because of their fluorescent properties. We also discuss their respective advantages and limitations. In therapeutic contexts, nanomaterials play a pivotal role in the development of targeted drug delivery systems. These systems address the limitations of traditional chemotherapy by improving drug bioavailability, reducing systemic toxicity, and promoting selective accumulation at tumor sites via both passive and active targeting mechanisms. Nanomedicines, including NPs and nanocarriers, enable the precise delivery of chemotherapeutic agents, nucleic acid -based therapies, and immunomodulators directly to cancer cells, thereby optimizing therapeutic efficacy. Furthermore, nanotechnology offers the potential to modulate the tumor microenvironment (TME), a critical factor in overcoming challenges related to tumor resistance and metastasis. Despite these promising advancements, several challenges persist, including concerns regarding long-term toxicity, stability, and regulatory approval. Nonetheless, the integration of nanomaterials into clinical practice holds substantial potential for revolutionizing the management of GI cancers, paving the way for more precise, personalized, and effective therapeutic strategies.

1. Introduction

GI cancers are among the leading causes of cancer-related mortality globally, encompassing a diverse range of subtypes, including hepatocellular carcinoma (HCC), colorectal cancer (CRC), gastric cancer (GC), esophageal cancer (EC), pancreatic cancer, and cholangiocarcinoma [1,2]. These malignancies are often highly aggressive and are typically diagnosed at advanced stages, primarily due to the low rates of early detection. As a result, patients often present with locally advanced or metastatic disease at the time of diagnosis [3–5]. Consequently, the early detection and effective treatment of GI cancers remain major challenges in contemporary medicine. Despite progress in surgical interventions, chemotherapy, radiotherapy, and targeted therapies, these treatment modalities are often constrained by factors such as drug resistance, tumor heterogeneity, and the complexity of the TME [6,7]. In particular, the invasive nature and multifaceted drug resistance mechanisms of GI tumors frequently render conventional therapies inadequate, leading to significant systemic toxicity [8–10]. Therefore, novel therapeutic strategies are urgently required to improve patient survival and quality of life.

The rapid advancement of nanotechnology has recently opened up transformative opportunities for cancer treatment. The unique physicochemical properties of nanomaterials have demonstrated significant potential in drug delivery, imaging diagnostics, targeted therapy, and

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cancer immunotherapy [11,12]. Unlike traditional drug delivery systems, nanodrug carriers not only enhance the accumulation of drugs within tumor tissues but also minimize off-target toxicity in healthy tissues, thereby improving therapeutic efficacy [13,14]. Through surface modification and functionalization, nanomaterials can precisely target tumor-specific antigens, further enhancing the accuracy of treatments [15,16]. In the field of GI oncology, nanotechnology has been widely applied in targeted drug delivery systems, radiosensitization, immunotherapy, and early diagnosis [17–20]. Studies have shown that NPs can enhance drug biocompatibility and tumor penetration by delivering chemotherapeutic agents or immunomodulators directly to malignant cells, significantly improving therapeutic outcomes [21–23]. For example, in colorectal, gastric, and hepatic cancers, nanotechnology reduces the systemic toxicity of chemotherapeutic agents while increasing intratumoral drug concentrations, thereby boosting the efficacy of radiotherapy and targeted therapies [24,25].

Despite the promising potential of nanotechnology in the treatment of GI cancers, its clinical translation faces several significant challenges. Key limitations include issues related to the stability of nanodrugs, the precise control of drug release, the biocompatibility of nanocarriers, and the standardization of manufacturing processes. Additionally, the long-term toxicity and biodegradability of nanomaterials necessitate comprehensive preclinical and clinical evaluation to ensure their safety and efficacy.

In summary, nanotechnology presents transformative solutions to address the limitations of conventional therapies in the diagnosis and treatment of GI cancers, exhibiting significant clinical potential. However, to fully realize its translational impact, challenges related to carrier design, drug release regulation, standardized production, and toxicity profiling must be overcome. This review systematically synthesizes recent advances in nanomaterial-based strategies for the management of GI cancers, with a particular focus on their roles in early diagnosis, targeted drug delivery, radiosensitization, and immunotherapy. By consolidating current research, this work aims to provide both a theoretical foundation and practical guidance for the clinical translation of nanotechnology in precision oncology, while also highlighting future research directions to further advance the field.

2. TME in GI cancers and advances in immunotherapy

2.1. Complexity of the TME and immunotherapeutic progress

The TME of GI cancers, including gastric, colorectal, hepatocellular, and pancreatic carcinomas, constitutes a dynamic network that drives tumor progression and therapy resistance through complex cellular and molecular interactions (Fig. 1). In GC, tumor-associated macrophages (TAMs) polarized to the M2 phenotype secrete IL-10 and TGF-β, which suppress $CD8^+$ T cell activity and promote angiogenesis [26–28]. The TME of CRC is characterized by dense stromal fibrosis mediated by cancer-associated fibroblast (CAF) subtypes, which overexpress α-SMA and secrete extracellular matrix (ECM) proteins, such as collagen I, creating physical barriers that hinder drug penetration [29,30]. In HCC, there is an increased infiltration of myeloid-derived suppressor cells (MDSCs), particularly polymorphonuclear MDSCs (PMN-MDSCs), which

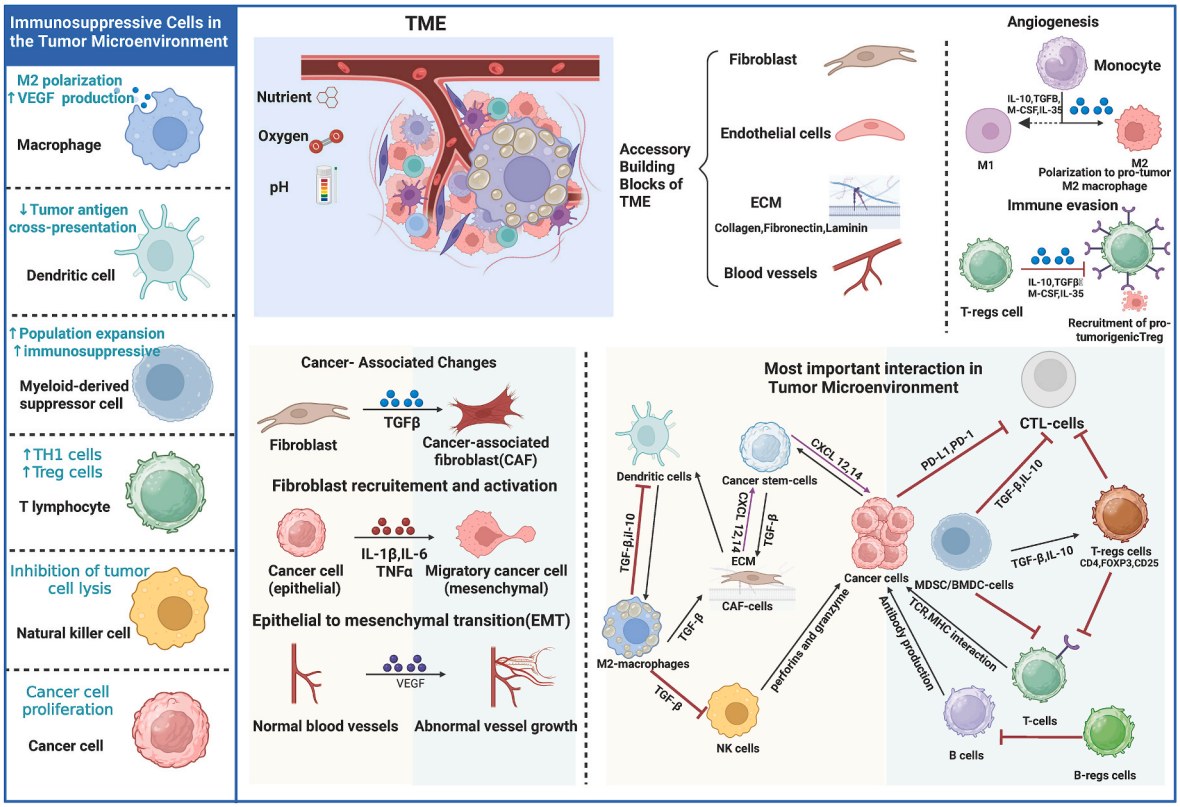

Fig. 1. The molecular mechanisms and interactions within the tumor microenvironment (TME).
The TME is defined by a wide variety of cell types, including heterogeneous cancer cells and a spectrum of immune cells such as T and B lymphocytes, tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), neutrophils, and eosinophils. Furthermore, the TME comprises stromal cells like cancer-associated fibroblasts (CAFs), pericytes, and mesenchymal stromal cells. It also encompasses the blood and lymphatic vasculature, along with tissue-specific cells such as neurons and adipocytes. These cellular components communicate through the release of extracellular matrix (ECM) components, growth factors, cytokines, and extracellular vesicles (EVs), facilitating intercellular communication within the TME and beyond, thereby promoting tumor progression. Due to the significant roles these cell types play in tumor development and therapeutic responses, numerous nanoparticle-based (NP-based) therapies targeting the TME have emerged in recent years. *Created with BioRender.com.*

inhibit natural killer (NK) cell cytotoxicity through arginase-1-mediated depletion of L-arginine [31,32]. Pancreatic ductal adenocarcinoma (PDAC) further exemplifies TME complexity, with hypoxic niches (oxygen concentration <1 %) activating HIF-1α, which in turn upregulates VEGF and CXCR4, promoting metastatic spread to the liver and lungs [33,34] (Fig. 1).

ECM remodeling in GI cancers is primarily mediated by matrix metalloproteinases (MMPs) and lysyl oxidases (LOXs). For example, the overexpression of MMP-9 in CRC degrades basement membranes, facilitating local invasion [35], while LOXL2 in PDAC crosslinks collagen fibers, thereby stiffening the stromal matrix and impairing gemcitabine delivery [36]. Extracellular vesicles (EVs) derived from GI tumors exhibit dual roles: exosomes derived from HCC carry PD-L1, which directly binds to PD-1^{+} T cells, inducing T cell exhaustion [37], whereas GC-derived EVs transport Wnt5a to CAFs, stimulating the secretion of CXCL12 and recruiting immunosuppressive regulatory T cells (Tregs) [38]. Acidosis (pH 6.5–6.8) within the TME exacerbates immune evasion. In esophageal squamous cell carcinoma (ESCC), low extracellular pH upregulates lactate dehydrogenase A (LDHA), resulting in increased lactate production, which inhibits interferon-gamma (IFN-γ) production by cytotoxic T lymphocytes (CTLs) [39] (Fig. 1).

Recent advancements in immunotherapy have made significant strides in addressing the TME-driven challenges in GI cancers (Fig. 2). Immune checkpoint inhibitors (ICIs), such as pembrolizumab (anti-PD-1), have emerged as first-line therapies for microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic CRC, achieving objective response rates of approximately 40 % by reactivating tumor-infiltrating lymphocytes (TILs) [40]. In HCC, the combination of tremelimumab (anti-CTLA-4) and durvalumab (anti-PD-L1) demonstrated a 24 % improvement in overall survival in the Phase III HIMALAYA trial, attributed to the dual blockade of T cell exhaustion pathways [41]. However, chimeric antigen receptor T-cell (CAR-T) therapies

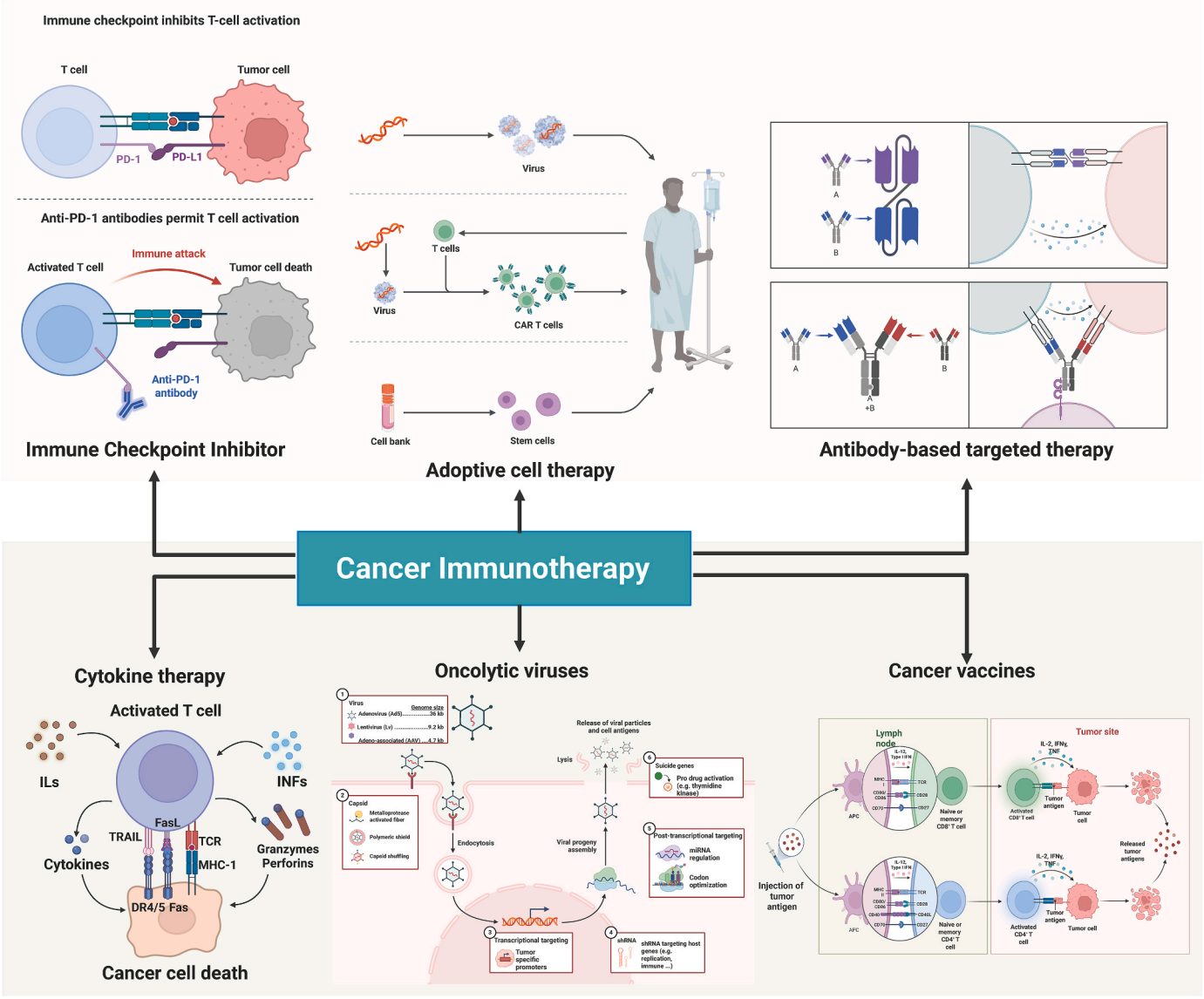

Fig. 2. Categories of cancer immunotherapy treatments.
Presently, clinical oncology employs several immunotherapeutic modalities such as immune checkpoint inhibitors, adoptive cell transfer, monoclonal antibody-based therapies, cancer vaccines, oncolytic virotherapy, and cytokine-based treatments. Key molecules involved include PD-1 (programmed cell death protein 1), TIM-3 (T cell immunoglobulin and mucin-domain containing-3), and CTLA-4 (cytotoxic T lymphocyte-associated protein 4). Essential cytokines and ligands are interleukins (ILs), interferons (IFNs), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), death receptors 4/5 (DR4/5), and Fas ligand (FasL). Important components in the immune response include the T cell receptor (TCR), major histocompatibility complex class I (MHC-I), dendritic cells (DC), and cytotoxic T lymphocytes (CTL). *Created with BioRender.com.*

targeting GI-specific antigens, such as HER2 in GC and carcinoembryonic antigen (CEA) in CRC, face challenges including on-target/off-tumor toxicity and CAF-mediated T cell exclusion. For instance, Claudin18.2-targeted CAR-T cells caused severe mucosal toxicity in GC patients due to off-target binding to normal gastric epithelium, underscoring the need for more tumor-selective targeting strategies [42,43].

Cancer vaccines are being re-engineered to counteract the immunosuppressive effects of the TME. In PDAC, mRNA lipid nanoparticles (LNPs) encoding the mutant KRASˆG12D, combined with TLR7/8 agonists, elicited neoantigen-specific T cell responses in 30 % of patients in a Phase I trial. However, the efficacy of this approach was limited by persistent infiltration of Tregs [44]. Personalized neoantigen vaccines synthesized from surgically resected CRC tumors induced $CD8^+$ T cell responses against mutant APC and TP53 epitopes, yet failed to control disease progression in microsatellite-stable (MSS) subtypes, primarily due to TGF-β-mediated T cell dysfunction [45]. These challenges highlight the need for combining vaccines with agents that modulate the TME. For example, in HCC, adenoviral vector-based vaccines co-expressing GPC3 and IL-12, when combined with lenvatinib (which normalizes tumor vasculature), resulted in a threefold increase in $CD8^+$ TILs, thereby enhancing T cell infiltration [46] (Fig. 2).

2.2. Nanomaterial-based strategies for TME targeting

Nanomaterials provide precise tools to overcome TME barriers through both active and passive targeting mechanisms [47] (Fig. 3A and B). **Active targeting** involves the functionalization of nanoparticles (NPs) with specific ligands, such as antibodies, peptides, or aptamers, that recognize and bind to overexpressed receptors on cancer cells or associated stromal components. This strategy is highly specific and aims to target molecular markers that are present on the surface of tumor cells or the tumor microenvironment (TME). For example, EGFR antibody-conjugated NPs selectively deliver chemotherapeutics like gemcitabine to EGFR-positive pancreatic cancer cells, resulting in a threefold increase in intratumoral drug accumulation compared to untargeted systems. Similarly, hyaluronic acid (HA)-modified liposomes exploit the overexpression of CD44 receptors on cancer-associated fibroblasts (CAFs) to deliver siRNA, silencing CAF-derived TGF-β and collagen I, thereby disrupting stromal barriers and enhancing nanoparticle penetration into the tumorNPs [48] (Fig. 3A).

Passive targeting capitalizes on the unique physiological features of tumors, including leaky vasculature and impaired lymphatic drainage, which collectively contribute to a phenomenon known as the enhanced permeability and retention (EPR) effect. Tumor blood vessels are often structurally abnormal, with irregularly sized gaps between endothelial cells, allowing NPs, typically ranging from 50 to 200 nm in size, to passively accumulate in tumor tissues. This is further facilitated by the poor lymphatic drainage in tumors, which prevents the efficient removal of NPs, thus promoting their retention within the tumor siteNPs [49] (Fig. 3B). For example, albumin-bound paclitaxel nanoparticles exploit the EPR effect to enhance drug retention in hypovascular gastric tumors. This strategy ensures that a higher concentration of the drug is delivered directly to the tumor, minimizing exposure to healthy tissues and reducing systemic toxicity. In clinical applications, this approach has been shown to reduce systemic toxicity by approximately 40 % while simultaneously improving the antitumor efficacy, thus enhancing both the therapeutic window and the safety profile of chemotherapeutic

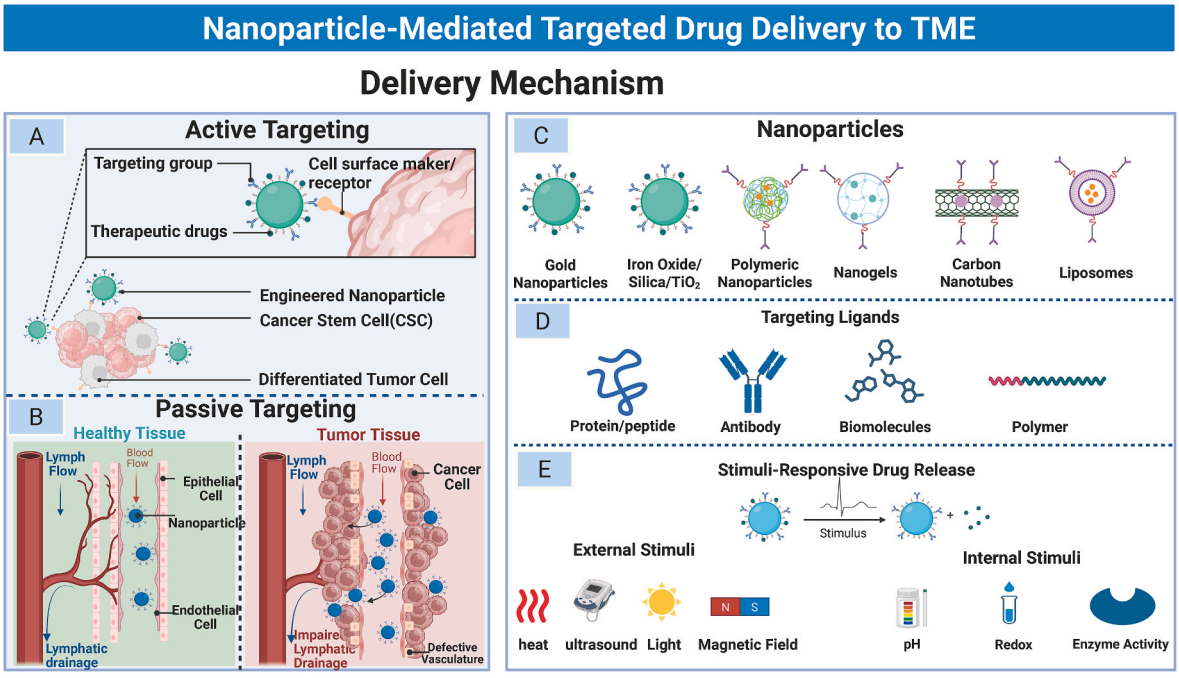

Fig. 3. Nanomedicine Approaches for Targeting the Tumor Microenvironment (TME).
A) Active Targeting: Following nanoparticle (NP) extravasation into the desired tissue, surface ligands enable active targeting by binding to specific receptors on target cells or tissues. This "active targeting" mechanism boosts NP accumulation and cellular uptake via receptor-mediated endocytosis, particularly benefiting drugs that require intracellular action and cannot easily cross the cell membrane. B) Passive Targeting: Beyond active targeting, NPs can also accumulate passively through the leaky vasculature characteristic of solid tumors and inflamed tissues, exploiting the Enhanced Permeability and Retention (EPR) effect. This passive targeting facilitates drug release into the extracellular matrix (ECM) and diffusion throughout the tissue, enhancing therapeutic outcomes. C) Various NP classes, each with multiple subclasses, present unique advantages and limitations regarding cargo delivery and patient response. D) Tailoring NP surface properties—such as material composition, structure, targeting ligands, and responsiveness—through intelligent design can optimize them for specific applications. E) Stimuli-responsive nanocarriers exhibit significant potential in tumor drug delivery, precision imaging, and theranostics. These advanced carriers can accumulate in tumors, specifically target cancer cells, and adapt their functions based on both external and internal stimuli, thus improving their efficacy in diverse therapeutic and diagnostic contexts. *Created with BioRender.com.*

agents. Moreover, the EPR effect is not only beneficial for drug delivery but also aids in the targeting of imaging agents, thereby improving the diagnostic capabilities for cancer detection and monitoring.

In summary, active targeting is based on molecular recognition and receptor-ligand interactions for precise drug delivery to specific tumor markers, while passive targeting relies on the intrinsic properties of the tumor vasculature and microenvironment to enhance the accumulation and retention of nanoparticles in tumor tissues. Both strategies offer distinct advantages and can be complementary in improving the specificity and efficacy of nanoparticle-based therapies.

Stimuli-responsive nanocarriers enhance spatiotemporal control by releasing therapeutic payloads in response to specific biochemical or physical cues within the TME. For example, pH-sensitive polymeric micelles, such as poly(ethylene glycol)-b-poly(β-amino ester), undergo structural rearrangement in the acidic TME (pH 6.5–6.8), selectively releasing doxorubicin within tumors while remaining stable in systemic circulation at physiological pH (7.4) [50,51]. Similarly, redox-responsive disulfide-bonded NPs degrade rapidly in the high glutathione (GSH) environment of HCC, facilitating the release of platinum (IV) prodrugs that induce DNA crosslinking [52] (Fig. 3E).

Innovative multifunctional systems integrate both targeting and stimuli-responsive properties. An exemplary approach involves gold nanorods functionalized with TGF-β inhibitors and coated with near-infrared (NIR) light-absorbing materials. Upon NIR irradiation, these nanorods generate localized hyperthermia (45–50 °C), enabling the ablation of CAFs, while simultaneously releasing TGF-β inhibitors to block SMAD2/3 signaling [53]. This dual-action strategy results in a 70 % reduction in α-SMA^{+} CAF density and a fourfold increase in CD8^{+} T cell infiltration in CRC models. Consequently, this approach reverses immunosuppression and enhances the efficacy of PD-1 blockade [54] (Fig. 3D and E).

Emerging platforms are increasingly integrating real-time imaging

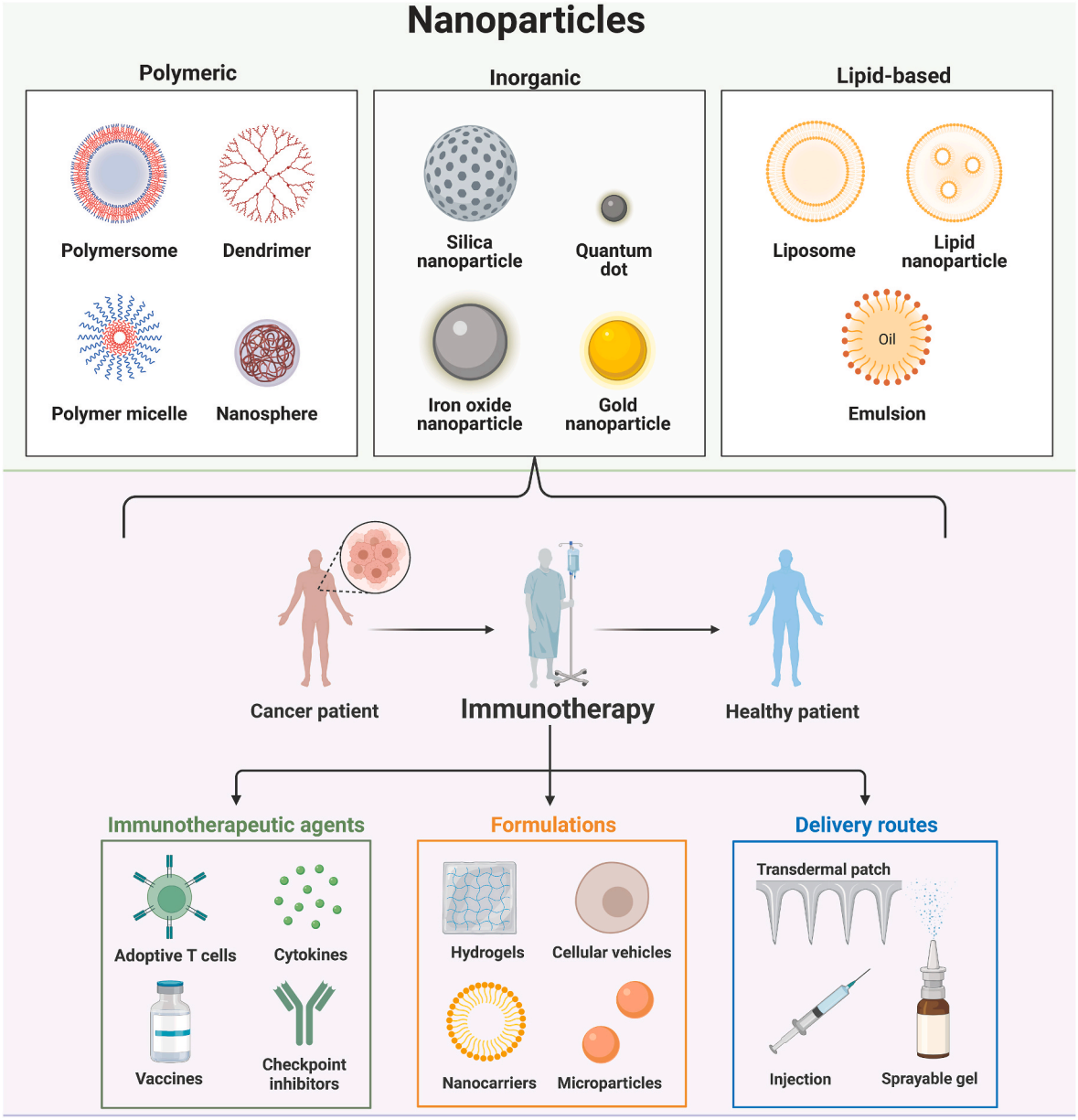

Fig. 4. Various categories of nanotechnology-driven cancer immunotherapies.
These innovative cancer vaccines leveraging nanotechnology can be divided into several groups: nanovaccines derived from tumor lysates, peptide-based nanovaccines, nanovaccines targeting tumor-specific antigens, viral vector-based nanovaccines, and mRNA nanovaccines. Abbreviations: TLS refers to tumor lysate, and TLR stands for Toll-like receptor. *Created with BioRender.com.*

with therapeutic modalities. An example of this approach is manganese-doped mesoporous silica NPs (Mn-MSNs), which encapsulate chemotherapeutic agents and release paramagnetic Mn^{2+} ions in response to the acidic TME. This release enables MRI-guided monitoring of drug release and tumor response [55]. Such theranostic systems illustrate the potential of nanomaterials to bridge the gap between diagnostics and therapy in GI oncology.

2.3. Nanotechnology-driven immunotherapy innovations

Nanoplatforms have significantly advanced cancer immunotherapy by enhancing the precision of antigen delivery and modulating immune activation kinetics, thereby overcoming the limitations of conventional therapeutic approaches (Fig. 4). Tumor lysate tumor lysates (TLS)-based nanovaccines encapsulate whole TLS, which are rich in neoantigens and damage-associated molecular patterns (DAMPs), along with Toll-like receptor (TLR) agonists, such as CpG oligonucleotides. For instance, polylactic-co-glycolic acid (PLGA) NPs loaded with TLS and CpG-ODN activate dendritic cells (DCs) through TLR9 signaling, resulting in a fivefold increase in MHC-I/II presentation and the stimulation of tumor-specific $CD4^+$ and $CD8^+$ T cell responses in metastatic CRC models [56] (Fig. 4).

mRNA nanovaccines utilize LNPs to protect and deliver mRNA encoding tumor-associated antigens into DCs. Upon translation, the mutant KRAS protein is processed and presented via MHC-I, triggering $CD8^+$ T cell responses that reduce tumor burden by 60 % in syngeneic mouse models. Recent advancements include the incorporation of nucleoside-modified mRNA, such as pseudouridine, which helps evade innate immune recognition, thereby prolonging antigen expression and enhancing the durability of the vaccine (Fig. 4).

Combinatorial nanotherapies synergistically combine immunomodulation with cytotoxic therapies. pH-sensitive mesoporous silica NPs co-loaded with CTLA-4 inhibitors and oxaliplatin serve as an illustrative example of this approach [57]. In the acidic TME, these NPs release oxaliplatin to induce immunogenic cell death (ICD), thereby promoting the surface exposure of calreticulin and the release of ATP, which facilitate the recruitment of DCs. Simultaneously, the NPs block CTLA-4, alleviating Treg-mediated immunosuppression [58]. This dual action converts immunologically "cold" gastric tumors into "hot" microenvironments, increasing the intratumoral $CD8^+$/Treg ratio from 1:3 to 8:1 and enhancing anti-PD-1 response rates by 40 % (Fig. 4).

Future directions in cancer therapy are focused on the development of multifunctional theranostic nanosystems. For example, photoacoustic imaging-guided nanovaccines, which integrate indocyanine green (ICG) with tumor antigens, enable real-time visualization of DC migration to lymph nodes while simultaneously stimulating TLR4-mediated DC maturation [14]. In patients with microsatellite stable CRC (MSS CRC), personalized neoantigen vaccine therapy has shown promising therapeutic prospects. Studies have demonstrated that over 50 % of vaccinated patients developed neoantigen-specific anti-tumor immune responses, and the progression-free survival of these patients was significantly extended to 19 months [59] (Fig. 4). Furthermore, virus-like nanoparticles (VLPs) designed to mimic oncolytic viruses are being engineered to deliver interleukin-12 (IL-12) and granulocyte-macrophage colony-stimulating factor (GM-CSF) directly to tumors. This approach activates NK cells and reprograms M2-like TAMs into an M1 phenotype, resulting in a 75 % reduction in liver metastasis in preclinical HCC models [60]. By dismantling stromal barriers, reprogramming immunosuppressive cells, and amplifying antigen-specific immune responses, nanomaterials are redefining therapeutic paradigms for GI cancers, offering potential for durable remission even in advanced stages.

3. Application of nanomaterials in the diagnosis of GI tumors

From a clinical perspective, endoscopy remains essential for the diagnosis of GI tract lesions, providing direct visualization and enabling tissue sampling. Despite its significant utility, endoscopy is an invasive procedure that requires skilled operators and may cause discomfort to patients. Alternative imaging modalities, including CT, MRI, and positron emission tomography (PET), are widely used in the diagnostic evaluation of GI cancers [61]. These non-invasive techniques are crucial for assessing tumor size, location, and metastasis. However, they have notable limitations, including low sensitivity for detecting small or early-stage lesions, difficulties in distinguishing benign from malignant tissues, and the nephrotoxicity risks associated with contrast agents, particularly in patients with renal impairment.

Biomarkers serve as an essential diagnostic tool in GI oncology. With advancements in molecular biology, a variety of biomarkers, including circulating tumor DNA (ctDNA), microRNAs, and protein profiles, have been identified [62–66]. These biomarkers can indicate the presence of cancer, even in asymptomatic individuals or during the early stages of the disease, when conventional imaging may be insufficient. Recent studies have confirmed the efficacy of ctDNA and serum proteins in detecting advanced GI cancers, although their role in the early detection of tumors remains under investigation.

Nanotechnology is transforming the landscape of GI cancer diagnostics. NPs offer several advantages over traditional diagnostic approaches, including enhanced imaging capabilities, improved tumor targeting, and reduced invasiveness. For example, NPs can be specifically engineered to function as contrast agents for CT or MRI, thereby enhancing the specificity and accuracy of tumor detection relative to conventional contrast agents. Given the rapid advancements in nanotechnology, the development of non-invasive, cost-effective diagnostic techniques holds significant promise for the early detection of GI cancers.

3.1. Nanotechnology-based biomarkers

Nanotechnology has revolutionized the detection of molecular biomarkers in GI cancers, offering ultrasensitive and multiplexed analysis, particularly in early-stage disease. Recent advancements in nanobiosensor design have shown significant versatility in targeting a wide range of biomarkers, such as miRNAs, proteins, and ctDNA, which are pivotal for diagnosing GI tumors. Table 1 illustrates examples of nanotechnology-based biomarkers for GI cancers. For instance, Zhang et al. engineered a dual-target-responsive fluorescent nanomachine capable of simultaneously detecting miR-5585-5p and PLS3 mRNA in GC without the need for RNA extraction or enzymatic amplification, demonstrating high diagnostic accuracy for early-stage GC (EGC) [67]. In a similar approach, Luan et al. developed a primer exchange reaction (PER)-based platform for multiplexed profiling of GC-related miRNAs in serum, offering robust clinical utility in distinguishing cancer patients from healthy controls [68]. These approaches exemplify a shift towards minimally invasive, amplification-free detection systems that preserve biomarker integrity while reducing procedural complexity.

Electrochemical and optical nanosensors are key technologies enabling ultra-low detection limits. For example, Shahbazi-Derakhshi et al. developed a nanocomposite-based electrochemical biosensor for detecting miRNA-21 in GC cell lines, achieving a detection limit of 2.94 fM across a broad linear range (10 fM–100 nM) [77]. Surface-enhanced Raman scattering (SERS) platforms also highlight this trend. Huang et al. created a microfluidic SERS chip capable of detecting CEA and VEGF at sub-pg/mL levels in early GC, with results strongly correlating to ELISA data [69]. Moreover, integrating machine learning with SERS analysis, as demonstrated by Liu et al., significantly enhanced diagnostic specificity, achieving an area under the curve (AUC) of 0.96 when classifying tumor-derived small extracellular vesicles (sEVs) from blood, saliva, and tissue samples [70]. These multimodal platforms combine nanotechnology with artificial intelligence (AI) to address the heterogeneity of GI tumors, offering enhanced diagnostic capabilities.

Further innovations in nanomaterial engineering have enabled

Table 1
Nanotechnology-based biomarkers in GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Fluorescent Nanomachine	GC	Tumor Cell Imaging and Serum Diagnosis	Dual-target responsive amplification system detecting miR-5585-5p and PLS3 mRNA	[67]
Isothermal Nucleic Acid Primer Exchange Reaction (PER)	GC	Serum Biomarker Detection	Quantification of miRNA biomarkers using bioinformatics-selected miRNA panels	[68]
Gold Nanosheets (GNS)	GC	Protein Biomarker Detection (CEA, VEGF)	Surface-Enhanced Raman Scattering (SERS) microfluidic chip for simultaneous detection of multiple biomarkers	[69]
Gold Nanocone Array	GC	Non-invasive GC Detection	SERS triggered by gold nanocone array and machine learning algorithm to analyze spectral features	[70]
PtS2-coated Optical Fiber	GC	IL10 and IL1β Detection	SPR sensor with combined tapered and U-shaped structures for increased sensitivity	[71]
GeP Nanosheets	GC	miR-378c Detection	SPR biosensor with atomic-level defect engineering and in-situ growth of AuNPs for enhanced sensitivity	[72]
DNA Cascade Reaction-Triggered IEV Nanocapsule (DCR-IEVN)	HCC	Ultra-sensitive and Specific Detection of tEV Subpopulations	One-pot, one-step flow cytometry to encapsulate tEV subpopulations into larger particles	[73]
Gold nanoparticles	CRC	Preoperative detection of lymph node metastasis (LNM)	SERS combined with CEA levels; SVM model for urine nucleoside detection	[74]
Hydrogel with nucleic acid amplification	GC	Detection of exosomal miRNA from metastatic GC	Rolling circle amplification within hydrogel targeting miRNA-21 and miRNA-99a; portable fluorometer for onsite detection	[75]
2D Nitrogen-Doped Carbon Nanosheets (CNS)	EC	Breath Biomarker Screening	Solid-phase Microextraction (SPME) fiber coating with MOF (ZIF-8) for enhanced gas chromatography-mass spectrometry (GC-MS) detection	[76]

unprecedented spatial and temporal resolution in biomarker detection. Li et al. optimized a PtS2-modified fiber-optic surface plasmon resonance (SPR) sensor for the picomolar-level detection of IL-10 and IL-1β in GC serum, utilizing two-dimensional (2D) materials to enhance surface plasmonic fields [71]. Similarly, Zhou et al. used defect-engineered GeP nanosheets coupled with gold nanoparticles (AuNPs) to construct an SPR biosensor for stage-specific monitoring of miR-378c during GC progression [72]. These developments underscore the critical role of nanoscale surface modifications in enhancing both the sensitivity and biomarker-binding affinity of diagnostic sensors.

The clinical application of nanotechnology extends beyond diagnostics into therapeutic monitoring. For example, DCR-IEVN, a nano-enabled platform, achieves 96.7 % accuracy in differentiating HCC from cirrhosis through exosome subpopulation analysis, illustrating the potential for dynamic disease surveillance [73]. Additionally, the integration of SERS-based urinary nucleoside profiling with CEA levels, as demonstrated by Wang et al., enhanced the preoperative prediction of CRC lymph node metastasis with 91 % accuracy [74]. This shift towards liquid biopsy-compatible nanosystems is addressing the growing need for real-time, noninvasive biomarker tracking in GI oncology.

Despite these promising advancements, significant challenges remain, particularly regarding standardization, large-scale clinical validation, and cost-effectiveness. Emerging solutions include paper-based nanodevices like the NACH system, which detects miRNA-21 and miRNA-99a at femtomolar (fM) concentrations, suitable for use in resource-limited settings [75], and breath-based diagnostics utilizing MOF-derived carbon nanosheets for early EC screening [76]. Future research should focus on integrating multi-omics data, enabling longitudinal biomarker profiling, and harmonizing nanotechnology with existing clinical workflows to facilitate personalized management of GI malignancies.

3.2. *Imaging diagnosis*

Nanotechnology has transformed GI cancer imaging by enabling multimodal, high-resolution tumor visualization that integrates diagnostic and therapeutic functions. Leveraging the unique physicochemical properties of nanomaterials, recent advancements have overcome traditional limitations of spatial resolution, tissue penetration, and target specificity in cancer imaging. Examples of nanotechnology-based imaging for GI tumors are summarized in Table 2.

AuNPs have emerged as versatile contrast agents for CT imaging. Lai et al. developed charged AuNPs that selectively aggregate in small HCC, improving tumor delineation in orthotopic sHCC mouse models. This system demonstrated high geometric and dosimetric accuracy in AI-processed CT images (using 3D U-Net/Trans-U-Net models) while maintaining low cytotoxicity, both in vitro and in vivo [78]. Beyond CT, multifunctional nanocomposites, such as the hollow mesoporous silica nanoparticle (HMSN)-Cy7.5-FA system developed by Yang et al., enable dual-modal MRI/fluorescence imaging in metastatic cancer models. The folate receptor-targeted probe enhances tumor monitoring and biocompatibility, highlighting the potential of hybrid nanomaterials for multi-parametric imaging [79].

Nanotechnology also integrates real-time imaging with localized therapeutic interventions. For instance, Lu et al. pioneered personalized magnetic hyperthermia therapy (MHT) using patient-specific 3D tumor

Table 2
Nanotechnology-based imaging in GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Gold Nanoparticles (Au-NP)	sHCC	Contrast agent for CT imaging, enhanced imaging with AI	Improved CT imaging, AI-driven auto image processing, low toxicity	[78]
Hollow Mesoporous Silica Nanoparticles (HMSN)	Cancer (general)	MRI/Fluorescence imaging for tumor monitoring	Tumor-specific targeting, pH-responsive MRI contrast enhancement	[79]
Gold Nanorods (AuNRs)	HCC	Drug delivery system, enhanced fluorescence imaging	Enhanced fluorescence and drug penetration, increased apoptosis with NIR laser	[80]
Gold Nanocone Arrays (AuNCs)	GC	Non-invasive diagnostic tool (SERS for sEV analysis)	Surface-enhanced Raman spectroscopy (SERS) for exosome detection	[70]
Nanoparticle-Enhanced Chemotherapy (nab-paclitaxel)	Gastrointestinal Cancer (Late-stage)	Chemotherapy enhancement, Side effect reduction	Reduced platinum use in chemotherapy, improved drug efficacy, clinical response evaluation	[81]
Curcumin Nanoparticles (NCur)	Colorectal Cancer (CaCo-2, HT-29)	Drug delivery, Cytotoxicity in cancer cells	Induction of apoptosis and DNA damage in cancer cells, enhanced cell uptake	[82]

models (generated via Mimics/COMSOL simulations). This approach optimized the distribution of magnetic nanoparticles (MNPs), ensuring uniform intratumoral heating (>42 °C) under MRI guidance, effectively balancing efficacy and safety in GI malignancies [83]. Similarly, Salmonella-mimicking gold nanorods (SM-AuNRs) loaded with doxorubicin combined dual fluorescence imaging with photothermal therapy (PTT). In CRC models, SM-AuNRs showed enhanced tumor penetration and NIR-triggered drug release, increasing apoptosis rates by 2.3-fold compared to conventional chemotherapy [80].

The integration of nanotechnology with artificial intelligence (AI) has revolutionized molecular image interpretation. For example, surface-enhanced Raman scattering (SERS) platforms, when combined with machine learning algorithms, can decode the biochemical signatures of cancer-derived sEVs. In one study, SERS fingerprinting achieved 90 % accuracy in classifying GI tumor sEVs, revealing distinct metabolic pathways in tissue, blood, and saliva samples [70]. These tools not only enhance diagnostic precision but also offer valuable insights into tumor heterogeneity and the underlying mechanisms of tumor progression.

In clinical settings, nanotechnology is enhancing the assessment of therapeutic responses. Feng et al. incorporated nanopaclitaxel into oxaliplatin/S-1 (SOX) neoadjuvant regimens for advanced GC. The nano-enhanced regimen improved treatment response rates and reduced systemic toxicity, demonstrating the potential of nanocarriers to optimize chemoradiotherapy outcomes [81]. Additionally, Alduais et al. developed selenium-curcumin nanocomposites (NCur-SeNP-Fu) that induced DNA damage in CRC cells (CaCo-2 IC50: 10.35 mg/L). Ultrastructural imaging and comet assays confirmed apoptotic effects, suggesting their dual role as therapeutic agents and imaging-guided cytotoxicity monitors [82].

4. Nanomaterials based treatment in GI tumors

4.1. Radiotherapy for the treatment of GI tumors

The integration of nanotechnology into radiotherapy (RT) has introduced innovative strategies to overcome the limitations of conventional radiation treatment for GI cancers, including radioresistance, tumor hypoxia, and off-target toxicity. By leveraging the unique physicochemical properties of nanomaterials, researchers are developing novel approaches to enhance radiation energy deposition, modulate tumor biology, and promote synergistic multimodal therapies. Nanotechnology-based radiotherapy strategies for GI tumors are summarized in Table 3.

Recent advances in high atomic number (Z) nanomaterials have shown significant potential to enhance localized radiation effects. For instance, Zhou et al. developed a covalent organic framework (COF) nanozyme (TADI-COF-Fc) co-loaded with iodine and ferrocene. This platform enhances RT efficacy through three mechanisms: (1) iodine's photoelectric effect for increased X-ray absorption, (2) water radiolysis-induced hydroxyl radical (•OH) generation, and (3) ferrocene-mediated disruption of redox homeostasis in esophageal cancer (EC) models. This tripartite strategy reduced the required radiation dose and minimized damage to healthy tissues [84]. Similarly, in pancreatic cancer models, intratumoral synthesis of AuNPs overcame stromal barriers caused by desmoplasia, improving tumor growth inhibition by 2.3-fold and extending median survival from 102 to 235 days. AuNPs acted as radiation sensitizers, concentrating energy deposition within the tumor, thus enhancing the treatment of fibrotic GI malignancies [85].

Beyond enhancing physical energy deposition, nanotechnology is also targeting the biological drivers of radioresistance. One example is the use of bismuth sulfide nanoflowers (Bi@PP) to deliver miR-339-5p, a microRNA that inhibits USP8-mediated DNA repair in ESCC cancer stem cells (CSCs). This system suppressed CSC stemness and amplified radiation-induced DNA damage, leading to synergistic tumor regression. These nanomaterials serve as both carriers and radiosensitizers, addressing CSC-mediated recurrence, a major cause of RT failure [88]. These strategies directly address the root cause of RT failure—CSC-mediated recurrence—by integrating molecular targeting with nanomaterial-enhanced radiation.

Hypoxia in the TME is another significant challenge to RT efficacy. To overcome this, a hypoxia-responsive nanosystem was developed, co-loaded with tirapazamine (TPZ) and redox modulators (KP372-1/MK-2206). This system activates TPZ under hypoxic conditions and suppresses Akt-driven resistance, reducing the required radiation dose by 40 % in CRC models. These strategies demonstrate how nanomaterials can transform RT-resistant tumor niches into therapeutic vulnerabilities [86].

Emerging nanozymes further enhance radiation therapy by combining enzymatic catalysis with RT. For example, ultrasmall Bi2Sn2O7 nanozymes exhibit ultrasound (US)-enhanced peroxidase, oxidase, and catalase-like activities. Under US irradiation, these nanozymes disrupt mitochondrial function and generate reactive oxygen species (ROS), inducing PANoptosis, a coordinated cell death pathway involving apoptosis, necroptosis, and pyroptosis. In GC models, this approach led to a 78 % suppression of primary tumors and a 65 % reduction in metastatic burden, outperforming conventional radiotherapy alone [87].

Despite these advancements, challenges remain in optimizing nanomaterial biodistribution, ensuring long-term biosafety, and scaling clinical applications. Future research should focus on developing imaging-guided nanotheranostics for real-time dose modulation, incorporating immune checkpoint inhibitors (ICIs) to enhance radiation-induced ICD, and validating multi-omics biomarkers to predict treatment responses. By bridging material innovation with tumor biology, nanotechnology has the potential to transform radiotherapy into a precise, personalized treatment modality for GI oncology.

4.2. Phototherapy for the treatment of GI tumors

Phototherapy, which includes photodynamic therapy (PDT) and PTT, has emerged as a minimally invasive and spatially precise approach for the treatment of GI cancers [89,90]. The integration of

Table 3
Nanotechnology-based radiotherapy for the treatment of GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Iodine and Ferrocene-loaded Covalent Organic Framework (TADI-COF-Fc)	ESCC	Enhance radiation therapy for esophageal cancer	Iodine atoms increase X-ray absorption, promote water radiolysis, and produce ROS; ferrocene surface modification disrupts redox homeostasis via lipid peroxides and antioxidant depletion	[84]
Gold Nanoparticles (GNPs)	PC	Enhance radiotherapy efficacy	Gold nanoparticles are synthesized in situ from gold ions, targeting cancer cell nuclei, increasing radiosensitivity, and improving tumor suppression in combination with radiation	[85]
Polymer Vesicles Loaded with TPZ, KP372-1, and MK-2206	Various Digestive Tract Cancers	Hypoxia-targeted radiosensitization	Oxygen consumption and hypoxia normalization using NAD(P)H quinone oxidoreductase 1, combined with TPZ activation and MK-2206 inhibition, enhance radiosensitivity in hypoxic tumors	[86]
Bi2Sn2O7 Nanomaterials with Ultrasound-amplified Multienzyme Activity	Various Digestive Tract Tumors	Induce PANoptosis and improve radiotherapy sensitivity	Bi2Sn2O7 triggers PANoptosis via mitochondrial dysfunction and ROS accumulation; ultrasound enhances therapeutic effects and inhibits lung metastasis	[87]

nanotechnology has significantly enhanced the efficacy of these therapies by facilitating tumor-targeted delivery, enabling multifunctional synergy, and providing real-time imaging guidance. Recent advancements underscore the versatility of nanoplatforms in addressing key challenges, such as limitations in light penetration, tumor hypoxia, and immunosuppressive TMEs. Nanotechnology-based based phototherapy for the treatment of GI tumors were showed in Table 4 and Fig. 5.

A key innovation in cancer treatment lies in the design of photosensitizer (PS)-loaded nanocarriers with tumor-specific targeting. Ren et al. developed fluorescent carbon dots (GCDs) conjugated with chlorin e6 (Ce6) and cisplatin prodrugs for EGFR-targeted PDT and chemotherapy in GC. This system demonstrated 95 % ROS generation under laser irradiation and exhibited selective cytotoxicity toward EGFR-overexpressing tumors, highlighting the potential of dual-modal therapy guided by molecular imaging [91]. Similarly, Simela et al. developed ZnPcS4-AuNP antibody conjugates for CRC-specific PDT, where PEGylated AuNPs enhanced PS stability and tumor penetration. This approach resulted in a 3.2-fold increase in the ablation of 3D multicellular spheroids compared to free PS [92]. These studies exemplify how surface engineering of nanomaterials can enhance both specificity and therapeutic payload delivery.

To overcome tumor hypoxia—a critical barrier to PDT efficacy—researchers have developed oxygen-economizing and self-oxygenating nanosystems. Liu et al. engineered BSA-MnO2 nanozymes (BMIOC) that catalytically decompose endogenous hydrogen peroxide (H2O2) to generate oxygen, alleviating hypoxia in EC while delivering IR820 for real-time imaging and enhanced PDT. This strategy achieved 80 % tumor suppression in vivo by combining catalase-like activity with light-triggered ROS generation [93]. Similarly, Xie et al. fabricated TiO2-coated carbon nanotubes (MCNTs) that induce apoptosis in CRC via AKT pathway inhibition under NIR light. Hypoxia mitigation was further confirmed by downregulation of HIF-1α expression [94]. These strategies underscore the dual role of nanomaterials as both oxygen modulators and phototherapeutic agents.

The combination of PTT with immunotherapy is opening new possibilities for systemic tumor control. Li et al. engineered a dual-targeting nanoassembly (GOx@FeNPs) functionalized with cRGD and anisamide for CRC-specific delivery. Upon NIR irradiation, this platform mediated localized hyperthermia ($\Delta T > 25\ ^{\circ}C$) and ferroptosis, while the αPD-L1 checkpoint blockade alleviated immunosuppression. This approach resulted in over 90 % tumor inhibition and robust abscopal effects in metastatic models [95]. In a similar vein, Chen et al. developed M1NV NPs co-loaded with ICG and M1 macrophage-polarizing agents, which reshaped the HCC microenvironment by converting M2-like TAMs into antitumor M1 phenotypes. Single-cell RNA sequencing revealed a 3.5-fold increase in cytotoxic T-cell infiltration following PTT/PDT treatment, demonstrating the potential of phototherapy-induced immune modulation [96].

Nanomaterials also address challenges related to light delivery and tissue penetration. Viral spike-mimetic gold nanoviroids (AuNVs) utilize macropinocytosis for enhanced tumor penetration in CRC, outperforming conventional AuNPs and gold nanostars (AuNSs) in drug accumulation. This led to a 5.8-fold increase in mitoxantrone delivery and improved PTT efficacy under NIR-II irradiation [97]. In pancreatic ductal adenocarcinoma (PDAC)—a stroma-rich, phototherapy-resistant malignancy—Qu et al. developed midkine-targeted semiconductor polymer nanoparticles that generate ROS upon light activation, inducing ICD and synergizing with PD-1 blockade to extend survival by 150 % in orthotopic models [98]. These advancements highlight the critical importance of tailoring the geometry and surface chemistry of nanomaterials to overcome tumor-specific biophysical barriers.

Emerging theranostic nanosystems that integrate real-time imaging with adaptive therapy are also gaining traction. Bian et al. developed AuHQ nanoparticles that self-assemble in pancreatic tumors upon cleavage by cathepsin E, enabling fluorescence-photoacoustic dual imaging and NIR-triggered PTT. When combined with IDO1 inhibitors, this platform achieved 85 % primary tumor regression and a 70 % reduction in liver metastases, demonstrating the potential of image-guided combinatorial regimens [99]. Similarly, Xu et al. engineered LR-S-CD/CpG@LNP nanobiotics for CRC and liver metastases treatment. These nanobiotics induced ICD via PDT while modulating gut microbiota to favor Lactobacillus enrichment, suppressing tumor growth and metastatic niche formation through a dual mechanism [100].

Despite these advancements, challenges remain in optimizing light

Table 4
Nanotechnology-based phototherapy for the treatment of GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Green Carbon Dots (GCDs) loaded with Ce6 and Pt-EGF	Tumors with EGFR (e.g., Colon Cancer)	Enhanced PDT and chemotherapy	Ce6 produces ROS under laser irradiation to induce apoptosis; Pt(IV) prodrug activated by GSH in the tumor microenvironment; EGF for targeted therapy	[91]
PEGylated Gold Nanoparticles (AuNPs) conjugated with ZnPcS4	CRC	PDT and enhanced therapeutic effect in 3D tumor spheroids	Laser-induced ZnPcS4 photosensitization; improved delivery with anti-GCC antibody; enhanced therapeutic effect in 3D MCTS model	[92]
Carbon Manganese Nanocage Enzyme (BSA-MnO2)	Esophageal Cancer	Real-time imaging, photothermal therapy (PTT), photodynamic therapy (PDT)	Catalyzing H2O2 to oxygen to alleviate hypoxia, enhancing PDT and PTT, tumor-specific targeting through acid-activated features	[93]
TiO2-coated Multiwalled Carbon Nanotubes (MCNTs)	CRC	Near-infrared (NIR) laser-induced apoptosis and cell cycle modulation	TiO2 coating enhances NIR-induced apoptosis and inhibits cell cycle proteins (CCNA1, CCND1); suppression of the AKT pathway	[94]
GOx@FeNPs Nanoparticles	CRC	Photothermal therapy (PTT) and immune response enhancement	Combines PTT, Fenton reaction, and immune activation via αPD-L1 to induce tumor cell death and enhance antitumor immune response	[95]
Mesoporous Polydopamine (MPDA) + Indocyanine Green (ICG) Nanoplatform (M1NV)	HCC	Photothermal therapy (PTT), immunotherapy, tumor regression	Inducing M2 TAM polarization to M1, increasing cytotoxic T-cell infiltration, single-cell RNA sequencing for immune modulation	[96]
Gold Nanoparticles with Viral-like Spikes (AuNV)	Colorectal Cancer	Enhanced tumor penetration, chemo-photothermal therapy	AuNVs penetrate via phagocytosis, induce drug accumulation and deep tumor penetration; enhanced by NIR-II laser	[97]
Tumor-specific Midkine Nanobody (Nb) + Semiconductor Polymer Nanoparticles (NP)	PDAC	Photodynamic therapy (PDT), immunotherapy, tumor imaging	Targeting tumor microenvironment (TME) with Nb, generation of reactive oxygen species (ROS) under light, immune activation via PDT	[98]
Liposomes loaded with IR780 and EN4	Various Cancers, including CRC	Combined PTT and cancer stem cell inhibition	IR780 mediates PTT, while EN4 inhibits c-Myc, reducing cancer stem cells; enhanced photoacoustic (PA) imaging for real-time monitoring	[99]
LR-S-CD/CpG@LNP Nanobacterial Platform	Colorectal Cancer + Liver Metastasis	Photodynamic therapy (PDT), immune modulation	Inducing immunogenic cell death (ICD), promoting dendritic cell maturation, enhancing T-cell infiltration, modulating gut microbiota	[100]

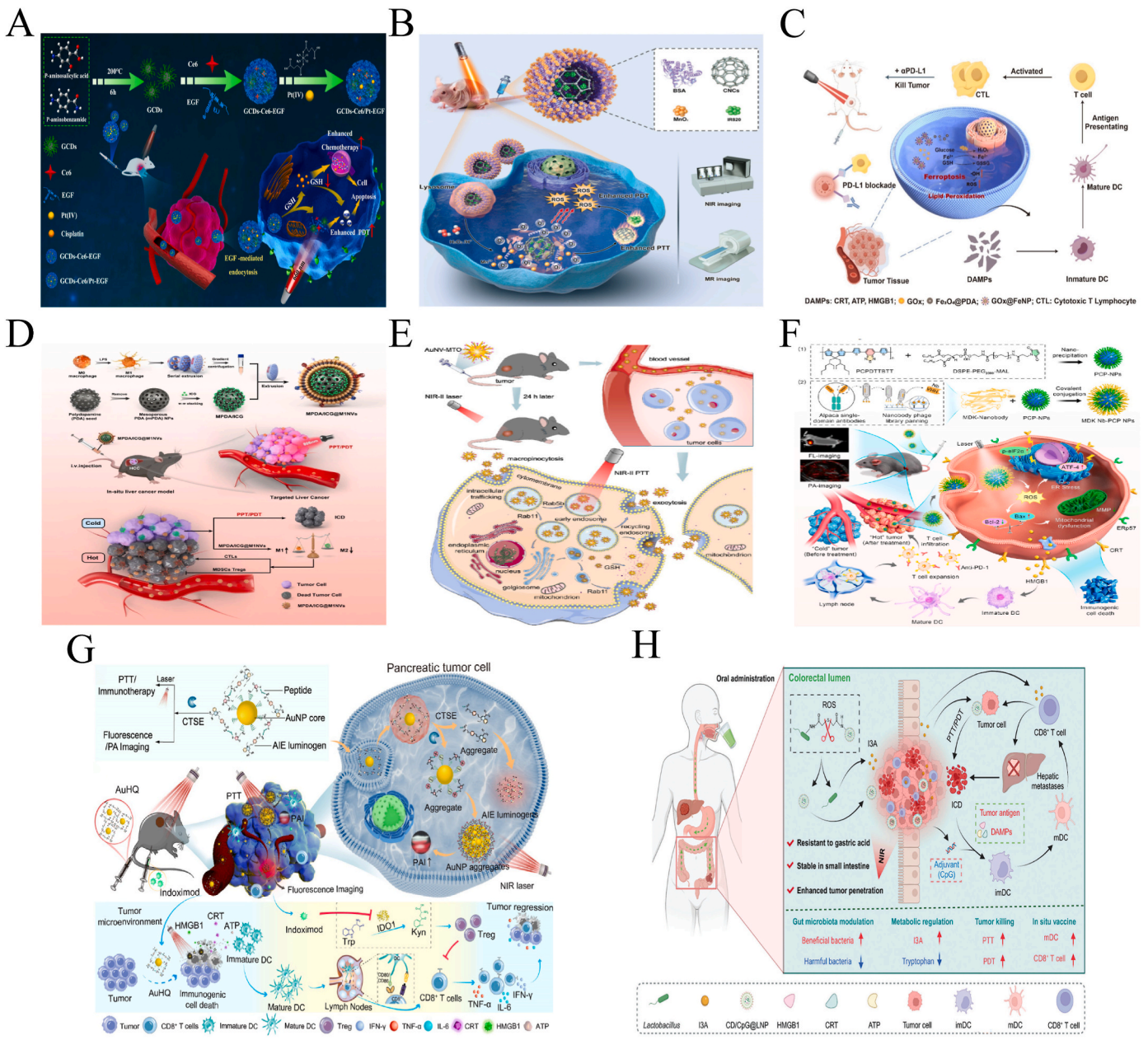

Fig. 5. Nanotechnology-based phototherapy for the treatment of GI tumors.
A. Schematic illustration of the synthesis, and working mechanism of the all-in-one theranostic nanoplatform, GCDs-Ce6/Pt-EGF, for enhanced chemo/photodynamic cancer therapy. Reproduced with permission [91]. Copyright 2022, Elsevier. B. Schematic illustration to show the synergistical action mechanism of the nanosystem in tumor therapy. Reproduced with permission [93]. Copyright 2020, Royal Society of Chemistry. C. Schematic illustration of GOx@FeNPs-mediated PTT synergizing with ferroptosis by inducing ICD to improve colorectal cancer immunotherapy. Reproduced with permission [95]. Copyright 2024, BMC. D. Schematic illustration of the mechanism exploration of synergistic photoimmunotherapy strategy based on a novel exosome-like nanosystem for remodeling the immune microenvironment of HCC. Reproduced with permission [96]. Copyright 2024, Springer. E. Schematic illustration of the interactions between virus-like AuNV-MTO particles and cancer cells. Reproduced with permission [97]. Copyright © 2024, American Chemical Society. F. Schematic diagram of precise photodynamic therapy for pdac based on mdk nb-pcp nps-induced icdcombined with immune checkpoint blockades. Reproduced with permission [98]. Copyright © 2024, American Chemical Society. G. Scheme of Pancreatic Cancer-specific AuNP-based Phototheranostic Modulator (AuHQ). Reproduced with permission [99]. Copyright © 2024, American Chemical Society. H. Schematic illustration of oral LR-S-CD/CpG@LNPs to achieve tumor accumulation, in situ vaccination, and activation of systemic antitumor immune responses against CRC. Reproduced with permission [100]. Copyright © 2025 Wiley-VCH GmbH.

dosimetry, minimizing off-target thermal damage, and standardizing nanomaterial biocompatibility. Future research should focus on developing NIR-II/III-responsive agents for better tissue penetration, utilizing AI-driven algorithms for precise phototherapy dosing, and conducting clinical trials to validate the efficacy of multimodal nanoplatforms. By integrating photochemistry, immunology, and materials science, nanotechnology is set to revolutionize phototherapy, positioning it as a cornerstone of precision oncology for GI malignancies.

4.3. *Immunotherapy for the treatment of GI tumors*

The integration of nanotechnology into cancer immunotherapy has significantly advanced the treatment of GI malignancies by addressing key challenges such as immune evasion, immunosuppressive microenvironments, and systemic toxicity. Nanomaterials function as precision tools to enhance ICB, reprogram tumor-associated immune cells, and facilitate multimodal therapeutic synergies, thereby offering new

prospects for the treatment of refractory and metastatic GI cancers. Nanotechnology-based based immunotherapy for the treatment of GI tumors were listed in Table 5 and Fig. 8.

A fundamental aspect of nano-immunotherapy is enhancing immune checkpoint blockade (ICB) efficacy through targeted delivery and modulation of the TME. Li et al. engineered PLGA-PEG nanoparticles (NpsNPs) encapsulating circRHBDD1 siRNA to silence PD-L1 in GC. This approach achieved 70 % tumor suppression when combined with anti-PD-1 therapy, effectively countering circRNA-mediated immune escape and showcasing the potential of RNA interference (RNAi) nanotechnology in enhancing ICB efficacy [101]. Similarly, Yang et al. developed pH/protease-responsive PROTAC nanocarriers (PSRN) that degrade cyclin-dependent kinases (CDK4/6) in CRC, thereby boosting tumor immunogenicity and improving the response to PD-1 blockade. Dual degradation of CDK4/6 and PD-L1 reprogrammed the TME, leading to a 3.5-fold increase in cytotoxic T lymphocyte (CTL) infiltration [102]. Nanomedicine strategies further exploit a variety of nano-formulations—including liposomes, polymeric micelles, and VLPs—to encapsulate immunomodulators or block immune checkpoints (Fig. 6). For instance, AuNPs functionalized with PD-1 antibodies enhance T cell activation through sustained release in tumor-draining lymph nodes, while mesoporous silica NPs co-delivering CTLA-4-targeting siRNA and chemotherapy agents enable dual checkpoint inhibition (Fig. 7).

Reprogramming immunosuppressive myeloid cells, particularly TAMs, is a critical strategy in cancer immunotherapy. Yan et al. developed zoledronate-mineralized NpsNPs (Nano-IFNγ/Zole) to deliver IFNγ to TAMs, inhibiting Rab protein prenylation and activating transcription factor EB (TFEB), which induced M2-to-M1 macrophage polarization. This metabolic reprogramming reduced CRC recurrence by 60 % in murine models, highlighting the synergistic potential of nanotherapy and macrophage-directed immunomodulation [103]. Similarly, Xu et al. developed selenium-based NpsNPs (PAP-SeNP) that polarize M2-like TAMs via TLR4 and NF-κB signaling, enhancing anti-HCC immunity and increasing the M1/M2 ratio by 2.8-fold [110]. These nanosystems exemplify how precise targeting of myeloid checkpoints can transform "cold" tumors into immunologically active sites.

Nanomaterials are also effective in inducing ICD to prime adaptive immunity. Fang et al. engineered calcium carbonate NpsNPs (DECP) co-loaded with doxorubicin and evolocumab, which triggered ICD in HCC while depleting Tregs and expanding $CD8^+$ T cell populations. This dual mechanism elevated the intratumoral $CD8^+$/Treg ratio from 1.2 to 4.5, enhancing PD-1 blockade efficacy and suppressing metastasis [104]. Similarly, Wang et al. utilized cGAS-STING agonists delivered via MIT/NAP co-loaded nanocarriers to activate DCs, boosting the effectiveness of PD-1 antibody therapy in HCC. The combination therapy extended median survival from 35 to 65 days, emphasizing the importance of innate immune pathway activation to overcome resistance to ICB [105].

Emerging platforms are increasingly integrating nanomaterial intelligence with multimodal therapeutic interactions. Huai et al. developed MMP-2 and GSH-responsive liposomes (ENP919@5-FU) for PDAC treatment. This formulation depletes CAFs while releasing 5-fluorouracil (5-FU), effectively reversing TME immunosuppression. This approach resulted in a 75 % reduction in α-SMA^+ stromal density and a 4-fold increase in $CD8^+$ T cell infiltration, demonstrating the potential of nanotechnology to overcome physical and biochemical barriers to immune activation [106]. For HCC, Li et al. developed macrophage membrane-camouflaged nanodrugs (MFMP) that co-deliver MAT2A inhibitors and anti-PD-L1 antibodies. This combination achieved 90 % primary tumor regression and durable immune memory by targeting CSCs and Tregs [107].

At the forefront of nano-immunotherapy, biomimetic designs and spatiotemporal control mechanisms are playing a pivotal role. Da et al. engineered platelet membrane-coated mesoporous silica NpsNPs (aPD-1-PLTM-HMSNs@Sora) to evade immune clearance and selectively target HCC. This system enhanced sorafenib delivery while blocking PD-1, leading to a 2.2-fold increase in tumor-specific T cell activation compared to free drugs. The nanocarrier system also demonstrated excellent biocompatibility and no significant organ toxicity in vivo, making it a promising drug delivery system [108]. Similarly, Shen et al. designed cholesterol-degrading catalytic hydrogels (DA-COD-OD-HCS) that synergize with microwave ablation and ICB to induce ferroptosis and stimulate anti-HCC immunity, effectively suppressing distant metastases without off-target toxicity [109].

Despite these advancements, challenges remain in optimizing the pharmacokinetics of nanomaterials, scaling up production, and translating combinatorial therapeutic regimens into clinical practice. Future research should focus on developing universal nanovaccines targeting neoantigens, real-time imaging-guided dosing of immunotherapies, and AI-driven nanoplatform design for personalized immune modulation. By integrating immunology, materials science, and systems biology, nanotechnology is set to redefine precision immuno-oncology, especially for gastrointestinal cancers.

4.4. Nucleic acid (NA) delivery for treating GI tumors

The targeted delivery of NAs via nanotechnology has emerged as a transformative strategy for modulating oncogenic pathways in GI cancers. By overcoming biological barriers such as enzymatic degradation, limited cellular uptake, and off-target effects, nanocarriers facilitate the

Table 5
Nanotechnology-based immunotherapy for the treatment of GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
PLGA-PEG Nanoparticles (si-circRHBDD1)	GC	Immune modulation, cancer immunotherapy	CircRHBDD1 upregulation of PD-L1 expression, impeding $CD8^+$ T-cell infiltration, and reprogramming T-cell mediated immune response	[101]
PSRN (Polymer-based PROTAC Conjugated Nanoparticles)	CRC	Immune checkpoint blockade enhancement, protein degradation	pH-sensitive and enzyme-sensitive cleavage, enhancement of PD-L1 expression, immune checkpoint blockade through CDK4/6 degradation	[102]
Nano-IFNγ/Zole (Bisphosphonate Minimized Nanoparticles)	Colon Cancer	Immune modulation, metabolic reprogramming of TAMs	Targeting TAM metabolic reprogramming via IFNγ, activation of JAK/STAT1 signaling pathway, remodeling TIME to reduce tumor recurrence	[103]
CaCO3 Nanoparticles	HCC	Inducing ICD, immune modulation	Neutralizes tumor acidity, induces ICD, enhances MHC-I expression, increases mature DCs, $CD8^+$ T-cells, and NK cells	[104]
AEAA-PEG-PLGA Nanocarriers	HCC	Co-delivery of drugs, immune modulation	Activates cGAS-STING pathway, reshapes immunosuppressive TME, enhances anti-PD-1 antibody efficacy	[105]
Liposomal Nanovesicles	PDAC	Drug delivery, immune modulation	Dual response to MMP-2 and GSH, enhances tumor uptake, sustained release of 5-FU and NLG919, synergistic anti-tumor effect	[106]
Hollow Mesoporous Manganese Dioxide (MnO2) Nanoparticles	HCC	Immune checkpoint blockade, immune activation	Releases FIDAS-5 to reverse immune suppression, activates STING pathway, enhances HCC antigenicity, induces immunogenic cell death	[107]
Hollow Mesoporous Silica Nanoparticles (HMSNs)	HCC	Targeted drug delivery, immune activation	Co-delivery of aPD-1 and Sorafenib, activates toxic T-cells, increases Sorafenib release	[108]
Cholesterol-targeted Hydrogel (DA-COD-OD-HCS)	HCC	Enhanced chemotherapy, immune checkpoint inhibition	Releases cholesterol oxidase (COD), induces ferroptosis, enhances anti-tumor immune response, combined with PD-L1 inhibition	[109]

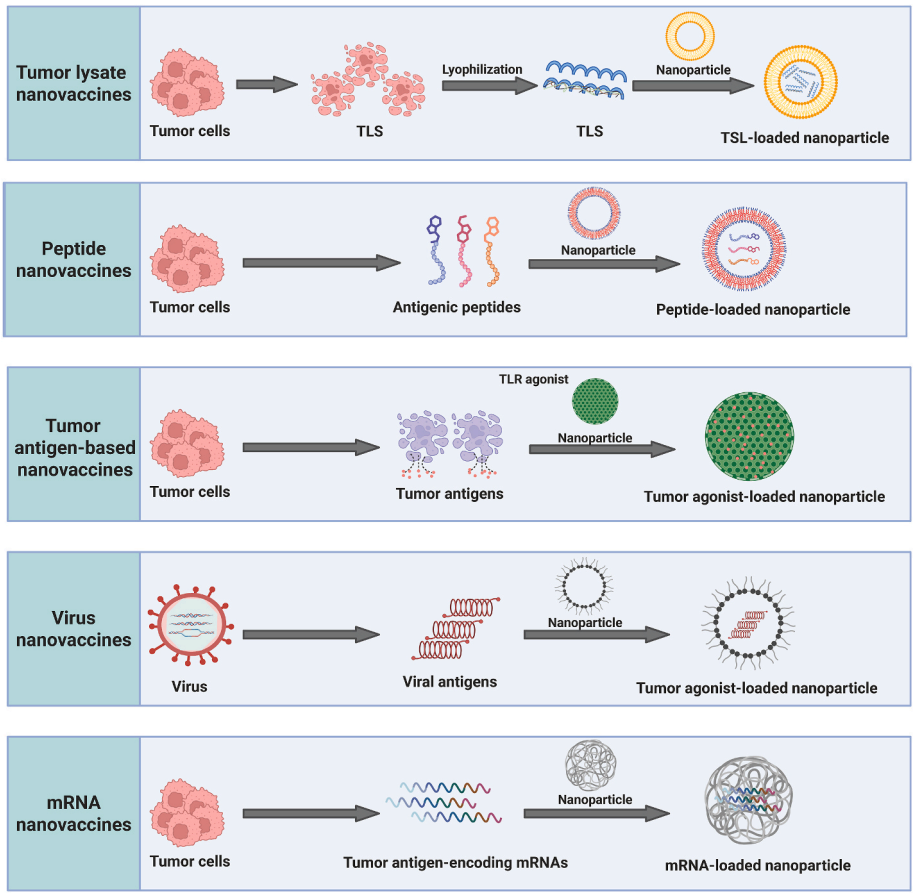

Fig. 6. Nanomedicine strategies have been harnessed to boost the effectiveness of cancer immunotherapy.
Nanoparticles, known for their high molecular encapsulation capabilities, extended bloodstream presence, and exceptional targeting properties, serve as a versatile platform to trigger systemic antitumor responses and enhance the efficacy of traditional immunotherapeutic approaches. Diverse nanoformulations, including mesoporous silica nanoparticles, liposomes, micelles, polymeric nanoparticles, gold nanoparticles, and virus-like nanoparticles, have been engineered and applied in cancer immunotherapy. Key elements include PD-1 (programmed cell death-1), CAR (chimeric antigen receptor), IL-2 (interleukin-2), and IL-12 (interleukin-12). *Created with BioRender.com. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)*

precise regulation of tumor-suppressive genes, silencing of oncogenes, and modulation of the immune response. This approach offers unprecedented opportunities for advancing precision oncology. Nanomaterials based NA delivery for treating GI tumors were shown in Table 6 and Fig. 9.

Recent advancements in polymeric nanomaterials highlight their potential for co-delivering NAs alongside complementary therapeutic modalities. Chen et al. engineered a cationic polythiophene derivative (PT2) conjugated with folate for targeted delivery of siRNA in HCC. The PT2-siRNA@PEG-FA nanocomplex achieved 80 % knockdown of NUDT1 gene expression and generated cytotoxic singlet oxygen and hydroxyl radicals under ultrasound irradiation. This strategy synergized RNAi with sonodynamic therapy, resulting in 90 % tumor growth inhibition in vivo, with selective accumulation at the tumor site and minimal toxicity to healthy organs [111]. Similarly, Wu et al. developed polyethyleneimine-based nanoparticles (PEI/NPs@M) encapsulating pcDNA-ACYP2 plasmids, which restored ACYP2 expression in HCC. This approach inhibited telomerase activity and the KCNN4/ERK signaling pathway, reducing metastatic burden by 70 % in murine models while maintaining biocompatibility [112]. These studies exemplify how polymer-based systems can integrate gene therapy with multifunctional payloads to address the complexities of tumor heterogeneity.

Lipid-based and endogenous vesicle systems are also crucial for enhancing the stability and biodistribution of NAs. For instance, sphingomyelin nanosystems (ANK-SNs) were developed for delivering ankylosing spondylitis peptide (ANK) in CRC. ANK-SNs suppressed Th17-mediated IL-17 secretion and fibroblast-derived TSLP, achieving 50 % greater inhibition of pro-tumor cytokines at one-tenth the dose of free ANK. This demonstrates the ability of LNPs to improve therapeutic efficacy while minimizing systemic toxicity [113]. Additionally, Zhang et al. explored tumor-derived exosomes as natural carriers for NAs, demonstrating that circSTAU2—a circular RNA downregulated in GC—functions as a sponge for miR-589, upregulating CAPZA1 and inhibiting GC proliferation and metastasis. The identification of MBNL1 as a regulator of circSTAU2 biogenesis provides valuable insights into endogenous RNA trafficking [114].

Magnetic nanomaterials are increasingly used for spatially controlled NA delivery, enhancing therapeutic specificity. Tang et al. designed ferrimagnetic vortex-domain iron oxide nanorings (FVIO) that combine sorafenib-induced ferroptosis with magnetothermal therapy (MHT) in HCC. FVIO-mediated hyperthermia (42–45 °C) led to a threefold increase in ROS accumulation and inhibited GPX4, enhancing sorafenib's ferroptotic efficacy and achieving 85 % tumor suppression with minimal off-target effects [115]. In addition, the weight of the treated experimental animals remained stable without significant fluctuations. Through histological examination, researchers confirmed that this treatment method did not produce significant toxic reactions to major organs. This approach highlights the potential of physical stimulus-responsive nanomaterials to enhance NA-based therapies through precise spatiotemporal control.

Despite these advancements, challenges remain in optimizing endosomal escape, minimizing immunogenicity, and scaling up Good

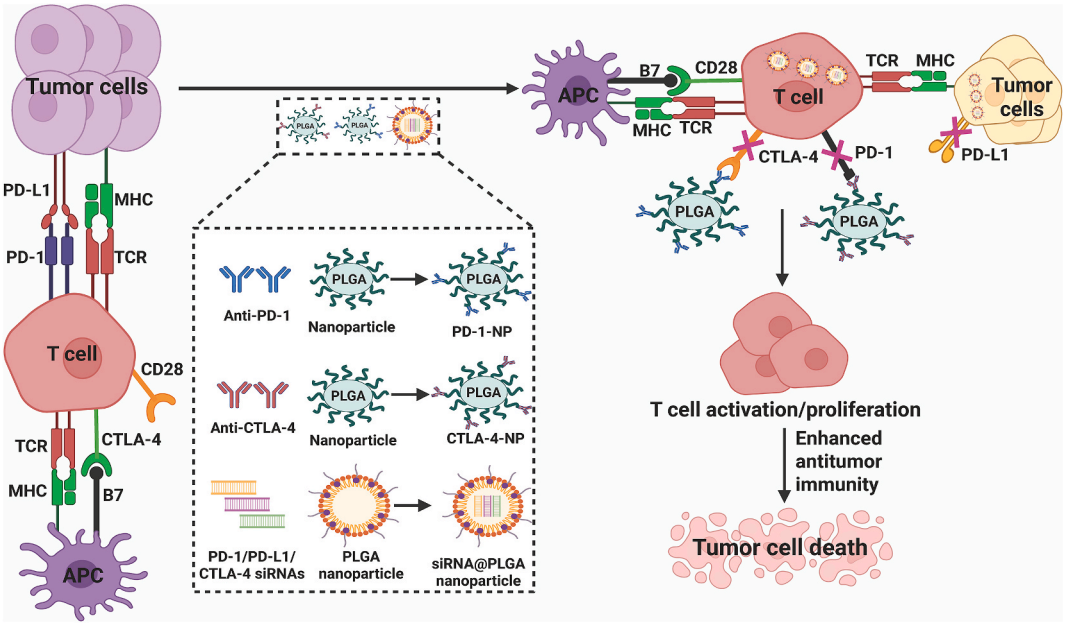

Fig. 7. Nanotechnology-based modulation of immune checkpoints enhances T cell-driven antitumor immunity.
Nanoparticles encapsulating anti-CTLA-4 or anti-PD-1 antibodies, along with siRNAs targeting PD-1, PD-L1, or CTLA-4, can potentiate T cell immune responses by inhibiting immune checkpoint pathways, leading to the destruction of cancer cells. Acronyms: PD-1 (programmed cell death-1), CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), PD-L1 (programmed cell death-ligand 1), PLGA (poly(lactic-co-glycolic-acid)), PD-1-NP (anti-PD-1 antibody-loaded nanoparticle), CTLA-4-NP (anti-CTLA-4 antibody-loaded nanoparticle), APC (antigen-presenting cell), MHC (major histocompatibility complex), TCR (T cell receptor). *Created with BioRender.com.*

Manufacturing Practice (GMP)-compliant production. Future research should focus on developing biomimetic nanocarriers that replicate viral transduction mechanisms, delivering CRISPR-Cas9 ribonucleoproteins for multiplexed gene editing, and employing AI-driven nanoparticle design to predict in vivo performance. By integrating nucleic acid chemistry, materials science, and systems biology, nanotechnology can fully realize the potential of gene-centric therapies for gastrointestinal malignancies.

4.5. Nanosystems for drug delivery to GI tumors

The development of nanoscale drug delivery systems (NDDS) has significantly advanced the treatment of GI cancers by overcoming key challenges, including poor drug solubility, non-specific biodistribution, and TME-mediated resistance. Recent innovations in nanomaterial engineering have facilitated precise spatiotemporal control over drug release, improved tumor targeting, and enabled synergistic multimodal therapies, thereby advancing the field of personalized oncology. Nanosystems for drug delivery to GI tumors were displayed in Table 7 and Fig. 10.

4.5.1. Targeted delivery and tumor homing strategies

Ligand-mediated active targeting is a cornerstone in the design of NDDS. Wei et al. engineered galactosamine (Gal)-decorated mesoporous silica nanoparticles (Gal-PDA-MSN) to target the asialoglycoprotein receptor (ASGPR) in HCC. This system achieved an 85 % higher drug accumulation in HepG2 tumors compared to non-targeted controls, with excellent biocompatibility and no significant organ toxicity within therapeutic doses [116]. Similarly, Zhou et al. developed folate receptor-targeted erythrocyte membrane-coated nanoparticles (CMD-BHQ3-PTL/DOX$^{@}$RBCM), demonstrating a 3.2-fold increase in tumor penetration in metastatic CRC models by combining hypoxia-responsive drug release and immune evasion [117]. In another approach, He et al. designed HCC-homing nanoparticles (Cel/Zein$^{@}$-HANPs) coated with hyaluronic acid (HA), targeting CD44-overexpressing CSCs. This system resulted in a 60 % reduction in tumor recurrence in murine models [122].

4.5.2. Stimuli-responsive and adaptive release systems

Smart NDDS responsive to TME cues, such as pH, redox conditions, and enzymatic activity, have significantly enhanced therapeutic specificity. Guo et al. developed ATP/pH-dual responsive ZIF-90 nanoparticles (HCPT$^{@}$ZIF-90-PEG-FA) for colon cancer treatment, achieving 90 % drug release in acidic lysosomes while maintaining minimal leakage in circulation [118]. Wu et al. engineered GLUT1/CD71-targeted liposomes that release NF-κB inhibitors and siRNA upon activation by MMPs. This system reversed stromal fibrosis and enhanced drug penetration fourfold in orthotopic PDAC models [123]. These systems exemplify how intelligent nanomaterials can decode the complexities of the TME to optimize therapeutic windows.

4.5.3. Overcoming multidrug resistance (MDR)

Nanotechnology has introduced innovative solutions to overcome chemoresistance, such as co-delivery systems and epigenetic modulation. Gao et al. developed cell membrane-camouflaged PLGA nanoparticles (PMPNs) co-loaded with doxorubicin and curcumin. These nanoparticles bypassed P-glycoprotein-mediated efflux in resistant EC, restoring drug sensitivity by 75 % [120]. Wang et al. pioneered the use of PROTAC-based nanoparticles to degrade STAT3 in HCC CSCs via the ubiquitin-proteasome pathway, reducing tumor initiation by 90 % while activating antitumor immunity [124]. In addition, unmodified liposomes mainly accumulate in non targeted organs such as the liver, lungs, and kidneys, while liposomes modified with cRGD and TK significantly increase tumor targeting and have no significant toxicity in normal liver cells, without affecting STAT3 expression levels. These approaches underscore the potential of NDDS to reset molecular mechanisms driving resistance.

4.5.4. Multimodal synergistic therapies

Combining chemotherapy with immunotherapy, radiotherapy, or physical ablation is a transformative approach in cancer treatment. Yu et al. engineered rapamycin/OX40L co-loaded, folate-targeted

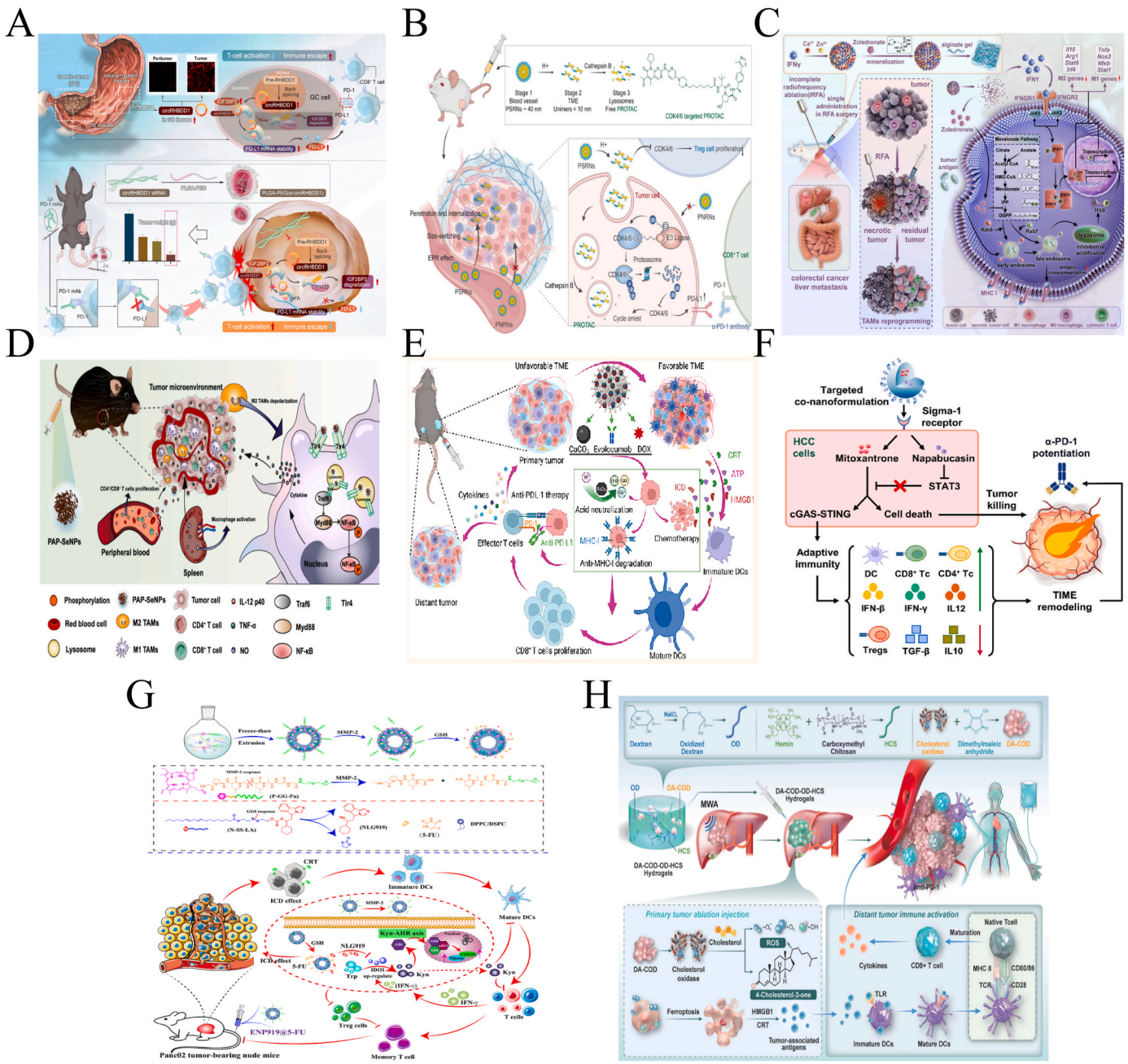

Fig. 8. Nanotechnology-based immunotherapy for the treatment of GI tumors.
A. Schematic diagram of circRHBDD1 in promoting immune escape through the IGF2BP2/PD-L1 axis and serving as a nanotherapeutic target in GC. Reproduced with permission [101]. Copyright 2024, BMC. B. The schematic illustration of the sequential responsive process of PSRNs after intravenous administration. The proposed behavior of protein-degradation and immunoregulation post PSRNs and ICBs combination therapy in the tumor-bearing mice. Reproduced with permission [102]. Copyright 2024, Springer Nature. C. Scheme of establishment and application of Nano-IFNγ/Zole for remodeling the suppressive TIME induced by iRFA. Reproduced with permission [103]. Copyright 2025, Theranostics. D. Schematic illustration of PAP-SeNPs mobilizing immunity to inhibit tumor progression via Tlr4/Myd88/NF-κB axis in the H22 tumor model of mice. Reproduced with permission [110]. Copyright 2024, Elsevier. E. Schematic diagram of multiple immunomodulatory strategies basedon targeted regulation of proproteinconvertase subtilisin/kexin type 9 andimmune homeostasis against hepatocellular carcinoma. Reproduced with permission [104]. Copyright 2024, Royal Society of Chemistry. F. Nano co-delivery of mitoxantrone and napabucasin deactivates STAT3 and reinforces cGAS-STING activation for promoting the outcome of anti-PD-1 antibody to HCC. Reproduced with permission [105]. Copyright 2025, Elsevier. G. Schematic illustration of the MMP-2-sheddable and GSH-responsive nanovesicle for circulating tumor chemoimmunotherapy amplification. The mechanism of ENP919@5-FU mediated chemo-immunotherapy to treat PDAC by remodeling tumor microenvironment. Reproduced with permission [106]. Copyright 2024, BMC. H. Schematic diagram illustrating how the cholesterol-targeted catalytic hydrogel enhances MWA treatment and boosts antitumor immunity and the preparation of a cholesterol-targeted catalytic hydrogel for locoregional treatment of HCC. Reproduced with permission [109]. Copyright © 2025 Wiley-VCH GmbH.

liposomes (FA@R/O Lps), inducing ICD in CRC while promoting dendritic cell maturation. This approach achieved 80 % tumor regression compared to 45 % with free drugs [121]. In HCC, Sun et al. developed ultrasound-triggered lenvatinib nanoparticles (Len-RNP), synchronizing antiangiogenic effects with $CD8^+$ T cell activation, leading to a 60 % cure rate in treated mice via abscopal immune responses [125]. These platforms exemplify how NDDS can effectively orchestrate cross-talk between cytotoxic and immunomodulatory pathways.

Table 6
Nanotechnology-based nucleic acid delivery for treating GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Cationic Poly(thiophene) Derivative (PT2)	HCC	Gene therapy (siRNA delivery), Synergistic Sonodynamic Therapy (SDT)	PT2 generates ROS (1O2 and O2•-) under ultrasound (US) irradiation; si-NUDT1 inhibits tumor cell proliferation and increases ROS, enhancing SDT therapy	[111]
Polyetherimide Nanoparticles (PEI/NP)	HCC	Gene therapy, Tumor targeting	siRNA (pcDNA-ACYP2) encapsulated in PEI/NP; ACYP2 silencing inhibits HCC cell proliferation and metastasis by regulating TERT activity and KCNN4/ERK pathway	[112]
Ceramide Nanoliposomes (ANK-SNs)	Inflammatory response in tumors	Modulation of immune response	ANK-SNs inhibit T-helper 2 (Th2) and Th17 inflammation, reduce tumor-promoting cytokine release, and offer reduced toxicity	[113]
Exosome-encapsulated CircSTAU2	GC	Gene silencing, Tumor progression inhibition	CircSTAU2 overexpression suppresses GC cell proliferation, invasion, and migration by modulating miR-589/CAPZA1 axis through exosome delivery	[114]
Iron Oxide Nanorings (FVIO)	HCC	Enhanced ferroptosis, Synergistic chemotherapy	FVIO promotes iron uptake, increases ROS levels and lipid peroxidation (LPO), further activating ferroptosis and inhibiting tumor growth	[115]

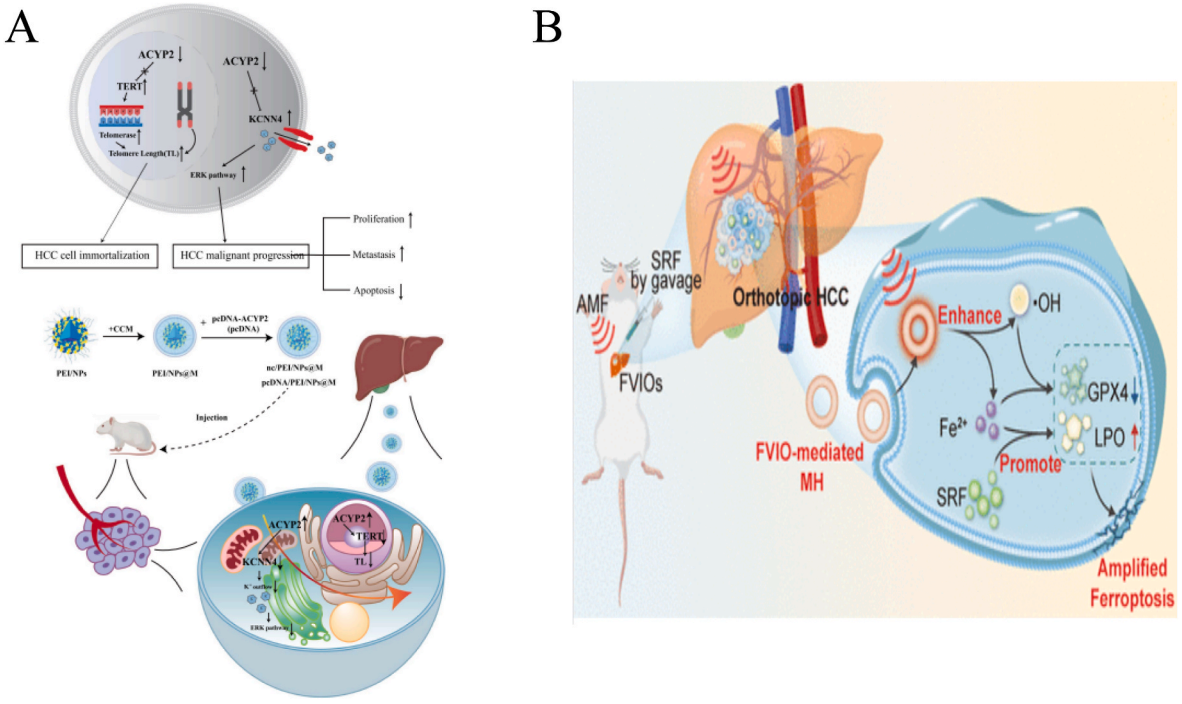

Fig. 9. Nanotechnology-based nucleic acid delivery for treating GI tumors.
A. Schematic diagram of ACYP2 functions as an innovative nano-therapeutic target to impede the progression of hepatocellular carcinoma by inhibiting the activity of TERT and the KCNN4/ERK pathway. Reproduced with permission [112]. Copyright 2024, BMC. B. Schematic diagram of intracellular magnetic hyperthermia sensitizes sorafenib to orthotopic hepatocellular carcinoma via amplified ferroptosis. Reproduced with permission [115]. Copyright © 2024, American Chemical Society.

Table 7
Nanosystems for drug delivery to GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Mesoporous Silica Nanoparticles (MSN)	HepG2	Drug delivery, pH-sensitive release	Galactose modification for targeting, pH-sensitive drug release	[116]
Biomimetic Nanoparticles (CMD-BHQ3-PTL/DOX@RBCM)	General Cancer Models	Targeted delivery of chemotherapeutics (PTL, DOX)	Tumor metastasis inhibition via Hippo/YAP1/SOX9 pathway regulation	[117]
ZIF-90-based nanoparticles (HCPT@ZIF-90-PEG-FA)	Colon Cancer	Drug delivery (10-hydroxycamptothecin - HCPT)	pH-sensitive and ATP-triggered drug release, enhanced drug cytotoxicity and tumor eradication	[118]
Ferritin Nanocage (for Cisplatin, CDDP)	ESCC	Drug encapsulation, controlled release	Prevention of drug inactivation, improved platinum delivery to tumor cells	[119]
PLGA-based Nanoparticles (PMPNs)	ESCC	Co-delivery of DOX and Curcumin (Cur)	Cell membrane coating for targeting, resistance overcoming, inhibition of tumor growth	[120]
Folic acid-modified nanoliposomes (FA@R/O Lps)	CRC	Drug delivery (Rapamycin and Oxaliplatin - Rapa/OXP)	Targeted tumor delivery, immune modulation, enhanced efficacy	[121]

4.5.5. Clinical translation and future perspectives

Despite significant preclinical advancements, challenges remain in scaling GMP-compliant production, addressing long-term nanotoxicity, and validating targeting efficacy in human clinical trials. Potential solutions include optimizing NDDS using patient-derived organoids and employing AI-driven nanoparticle design. For example, Bartkowski et al.

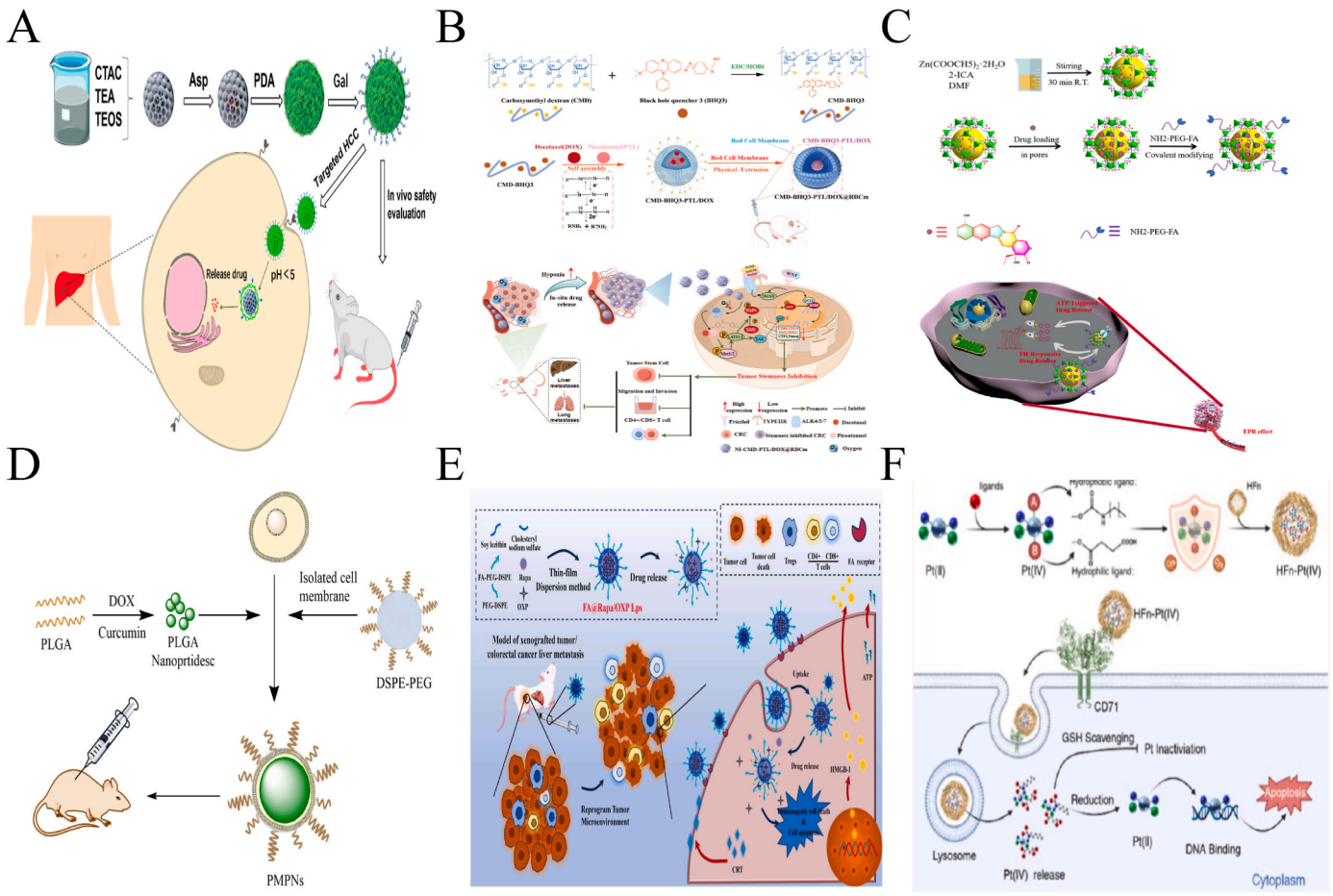

Fig. 10. Nanosystems for drug delivery to GI tumors.
A. Preparation of mesoporous silica nanoparticles loaded with aspirin for targeted therapy of liver cancer. Reproduced with permission [116]. Copyright 2024, MDPI. B. Synthesis of CMD-BHQ3-PTL/DOX@RBCM and mechanism of cancer treatment by targeting cancer stemness. Reproduced with permission [117]. Copyright © 2025 Wiley-VCH GmbH. C. Schematic illustration of ZIF-90 as a drug delivery system. Reproduced with permission [118]. Copyright 2024, Royal Society of Chemistry. D. Illustration of the preparation of PMPNs and in vivo therapy. Reproduced with permission [120]. Copyright 2021, Frontiers Media S.A. E. Augmenting immunogenic cell death by folate-conjugated nano-liposome codelivery rapamycin and oxaliplatin for colorectal cancer immunotherapy. Reproduced with permission [121]. Copyright 2024, Elsevier. F. Schematic illustration of structure-guided design of ferritin–platinumprodrugs for targeted therapy of esophagealsquamous cell carcinoma. Reproduced with permission [119]. Copyright © 2024, American Chemical Society.

developed carbon nano-onions (CNOs) targeting $CD44^{+}$ PDAC cells, achieving 50 % greater gemcitabine delivery to tumors compared to healthy tissues [126]. Shanmugam et al. developed HA-grafted mesoporous silica nanoparticles (MSN-PG-HA) for targeting CSCs, which have entered phase I clinical trials and shown preliminary safety in GI malignancies [127].

The next frontier in cancer treatment lies in the development of universal NDDS platforms that can be adapted to distinct molecular tumor subtypes and the dynamic evolution of the TME. By integrating nanotechnology, systems biology, and clinical insights, the field is poised to deliver transformative therapies for GI cancers with unparalleled precision.

4.6. *Chemotherapy for the treatment of GI tumors*

Chemotherapy remains a cornerstone in the management of GI cancers; however, its clinical efficacy is often limited by several factors, including systemic toxicity, the development of drug resistance, and the immunosuppressive TME. Traditional chemotherapy drugs affect both cancerous and healthy cells, leading to off-target effects and significant adverse reactions. Additionally, the TME can hinder the effectiveness of chemotherapy by promoting drug resistance and impeding drug penetration. Recent advancements in nanotechnology and drug delivery systems aim to address these limitations by enabling tumor-targeted delivery, controlled and adaptive drug release, and multimodal therapeutic approaches. Nanomaterials can enhance drug accumulation at the tumor site, reduce systemic exposure, and bypass mechanisms of drug resistance, thereby improving treatment efficacy while minimizing side effects. These innovations mark a significant shift toward precision oncology, providing more personalized and effective treatment strategies for GI cancers. Nanotechnology-based chemotherapy for treating GI tumors is summarized in Table 8 and Fig. 11.

Advances in tumor-targeted nanocarriers have enabled precise drug delivery while actively remodeling the TME. Park et al. developed oxaliplatin-loaded nanomicelles (OPt/LDC-NM) as part of an oral metronomic CAPOX regimen for CRC, which synergized with anti-PD-1 therapy to achieve a 91 % complete response rate. Mechanistically, this platform activated the cGAS-STING pathway, induced ICD, and reversed immunosuppression within the TME, underscoring the therapeutic power of nanomedicine–immunotherapy combinations [128]. Similarly, Yang et al. introduced a programmable nanoreshaper ($DAS^{@}P/H/pp$) that disrupts the extracellular matrix via pH-triggered charge reversal and hyaluronidase release. This strategy enhanced NK cell infiltration by 3.5-fold and significantly boosted cytotoxicity in GC models [129].

Stimuli-responsive nanosystems have enhanced chemotherapeutic precision by leveraging tumor-specific biochemical cues. Ma et al.

Table 8
Nanotechnology-based chemotherapy for the treatment of GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Nano-micelles (OPt/LDC-NM)	CRC (CT26)	Oral chemotherapeutic delivery (CAPOX)	Activates cGAS STING pathway, induces immunogenic cell death, modulates immune cells in tumor microenvironment	[128]
Programmable nanoremodeler (DAS@P/H/pp)	Cancer (general)	Tumor microenvironment remodeling, NK cell recruitment	Acid-triggered charge reversal and HAase release to degrade extracellular matrix, enhancing NK cell recruitment	[129]
Recombinant drug delivery system (POACa)	CRC (SW-480)	Tumor-specific activation of 5-FU	pH and thymidine phosphorylase-dependent activation, enhanced chemotherapy sensitivity, reduced off-target toxicity	[130]
Nanoparticles (DATCPT)	PC	Enhanced drug delivery and chemotherapy	pH-responsive release, improved drug uptake, and tumor growth inhibition	[131]
Polymeric nanoparticles (DOX + PLB)	HCC	Chemotherapy sensitization and STAT3 inhibition	PLB-mediated STAT3 inhibition enhances DOX efficacy, overcoming drug resistance in HCC	[132]
pH-GSH-H2O2-GGT-sensitive nano-prodrug (PBA-COS-ss-DOX/γ-PGA)	HCC (HepG2)	Targeted chemotherapy (DOX) with oxidative stress amplification	GSH-activated release of DOX via disulfide bond cleavage, PBA-COS-mediated cellular uptake, GGT-targeted delivery	[133]
Fungal-triggered in situ chemotherapy drug generator (SC@CS@5-FC)	CRC (in situ model)	Targeted chemotherapy delivery via oral prodrug (5-FC)	Tumor-targeting via yeast (SC) chemotaxis, HAase-triggered drug release, conversion of 5-FC to toxic 5-FU by SC's CD	[134]
Bacterial membrane-based nanovaccine (F.nuclearum membrane + CpG)	CRC	Immunotherapy via enhanced antigen delivery	CpG oligonucleotide integrated into bacterial membrane, improved dendritic cell delivery, immune activation	[135]
Supramolecular nanoparticles (DAS@CD-OxPt(IV))	CRC (CT26)	Dual chemotherapy (OxPt(IV) + DAS)	pH-triggered assembly, DNA damage via p53 inhibition, sustained drug release, enhanced immune response	[136]

designed a 5′-deoxy-5-fluorocytidine (DFCR)-based nanoactivator (POACa) for CRC, which is selectively activated by the acidic TME and thymidine phosphorylase. Through hydrogen peroxide-induced oxidative stress, calcium overload, and localized 5-FU release, the system achieved 80 % tumor suppression with a low combination index (0.11) and minimal off-target toxicity [130]. In pancreatic cancer, DATCPT nanoparticles enabled pH-triggered camptothecin release, reducing tumor volume to 18.38 % of controls, validating the efficacy of pH-responsive delivery in acidic environments [131]. These systems exemplify how material intelligence can synchronize drug release with tumor pathophysiology, thereby maximizing therapeutic efficacy while minimizing damage to healthy tissues.

Overcoming MDR remains a key focus of nanotherapeutics. Cao et al. co-delivered doxorubicin and plumbagin (PLB) using functionalized PLGA nanoparticles, which jointly inhibited STAT3 signaling in doxorubicin-resistant HCC. The co-delivery system achieved a 70 % reduction in tumor volume with no detectable systemic toxicity [132]. Likewise, Cui et al. developed a multi-stimuli-responsive prodrug (PBA-COS-ss-DOX/γ-PGA) activated by pH, glutathione (GSH), and γ-glutamyl transpeptidase (GGT) in HCC. The system triggered caspase-3-mediated apoptosis and oxidative stress, achieving 85 % tumor inhibition while minimizing organ toxicity compared to traditional DOX formulations [133]. PBA-COS-ss-DOX/γ - PGA nano formulations have significantly reduced organ toxicity and good biocompatibility compared to traditional DOX, effectively reducing damage to the heart, liver, spleen, and kidneys, providing a safer treatment option for HCC.

Emerging platforms are redefining chemotherapy by integrating immune modulation and microbiome engineering. Qin et al. constructed a fungal-based nanodrug generator (SC@CS@5-FC) that enzymatically converts 5-fluorocytosine into cytotoxic 5-FU within the TME, extending survival by 2.3-fold in orthotopic CRC models [134]. In another innovation, Chen et al. developed a biomimetic nanovaccine using cholesterol-modified CpG oligonucleotides embedded in *Fusobacterium nucleatum* membranes. This system co-delivered antigens and adjuvants to dendritic cells, reduced CRC metastasis by 60 %, and preserved gut microbiota integrity [135]. These innovations highlight the transformative potential of nanotechnology to extend the therapeutic boundaries of traditional chemotherapy.

Despite promising preclinical outcomes, challenges remain in large-scale production, long-term safety validation, and efficacy across patient populations. Ye et al. addressed these barriers by designing redox/pH-dual responsive supramolecular nanoparticles (DAS@CD-OxPt(IV)), which demonstrated prolonged circulation (>12 h) and 90 % suppression of lung metastases in preclinical models [136]. Looking forward, the integration of AI-guided nanocarrier design, real-time imaging for precision delivery, and clinical validation of combination regimens will be essential. By uniting chemopharmacology, immunology, and systems nanotechnology, personalized treatments for gastrointestinal malignancies are becoming increasingly attainable—offering new hope for patients with advanced or treatment-resistant cancers.

4.7. Combined-therapy for the treatment of GI tumors

The complexity and heterogeneity of GI tumors require therapeutic strategies that integrate multiple modalities to overcome challenges such as drug resistance, immunosuppression, and metastatic spread. Recent advances in nanotechnology and biomaterial engineering have facilitated the rational design of combination therapies that synergize chemotherapy, radiotherapy, immunotherapy, and physical ablation, thereby enhancing therapeutic efficacy while minimizing systemic toxicity. These multimodal approaches capitalize on the unique properties of nanomaterials to spatially and temporally coordinate therapeutic actions, effectively addressing the multifaceted nature of GI malignancies. Nanotechnology-based combined-therapy for treating GI tumors were shown in Table 9 and Fig. 12.

Recent innovations in cancer therapy focus on developing TME-responsive nanosystems that combine chemotherapy with PDT or oxidative stress treatments. Shi et al. engineered hypoxia-sensitive nanoparticles (NpsNPs) co-loaded with the TOPK inhibitor OTS964 and the photosensitizer Ce6. These nanoparticles selectively accumulated in esophageal squamous cell carcinoma (ESCC) tumors, releasing OTS964 under hypoxic conditions to inhibit tumor cell proliferation while generating cytotoxic singlet oxygen upon laser-activated PDT. This dual approach resulted in 85 % tumor suppression and a 70 % reduction in hepatic metastasis in preclinical models. Furthermore, the platform enabled real-time fluorescence imaging to guide precision treatment [137]. Similarly, Li et al. developed calcium peroxide-based nanoparticles (LDCNSO) modified with lecithin/DSPE-PEG for transarterial embolization (TAE) in liver cancer. Upon ultrasound-triggered "sonic explosion," LDCNSO released reactive oxygen species (ROS) and calcium ions, inducing oxidative stress and mitochondrial apoptosis. This strategy achieved a 65 % reduction in tumor volume in rabbit orthotopic models, demonstrating the potential of combining physical interventions with oxidative stress-driven nanotherapy. Importantly, LDCNSO showed no significant toxicity to normal cells and did not accumulate in major organs, indicating its selective toxicity to tumor cells under ultrasound stimulation [138]. Moreover, LDCNSO does not accumulate significantly in major organs and has no significant toxicity to normal cells, but exhibits selective toxicity to tumor cells under

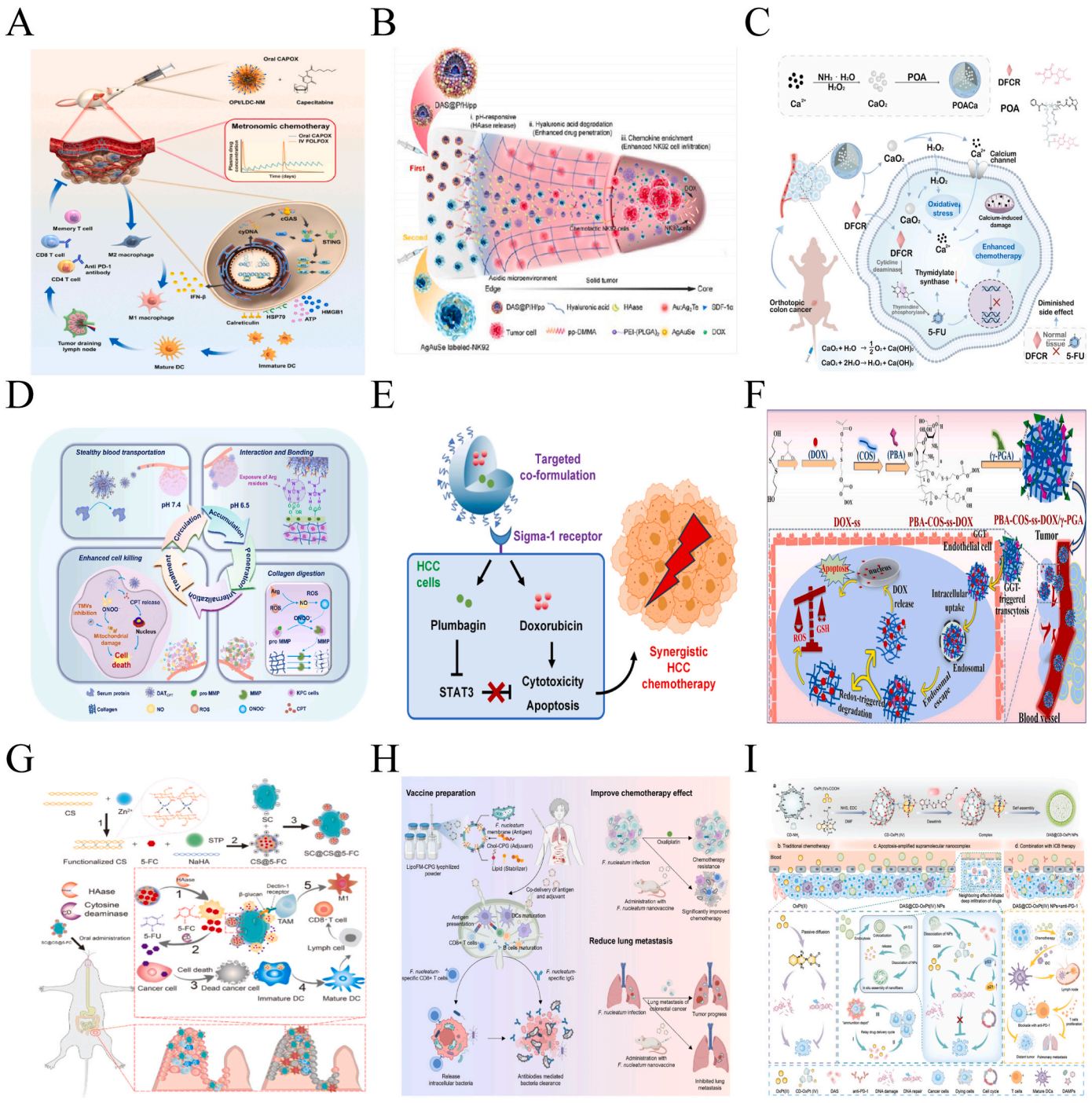

Fig. 11. Nanotechnology-based chemotherapy for the treatment of GI tumors.
A. The mechanism of action of oral CAPOX and αPD-1 in the LMCC microenvironment. Reproduced with permission [128]. Copyright 2024, Elsevier. B. Schematic illustration of programmed remodeling of the tumor milieu to enhance nk cellimmunotherapy combined with chemotherapy for pancreatic cancer. Reproduced with permission [129]. Copyright © 2024, American Chemical Society. C. The Schematic illustration of the functioning procedure of POACa. Reproduced with permission [130]. Copyright 2024, Elsevier. D. Schematic illustration of the in vivotransport of DATCPT during anticancer drug delivery. This includes stealthy blood transport, interaction and bonding at tumor site, collagendigestion, subsequent deep tumor penetration and enhanced cell killing. Reproduced with permission [131]. Copyright © 2025, American Chemical Society. E. Nano co-delivery of doxorubicin and plumbagin for synergistic HCC chemotherapy. Reproduced with permission [132]. Copyright 2024, Elsevier. F. Schematic illustration of synthetic assembly and cascade transcytosis and transcellular transport of PBA-COS-ss-DOX/γ-PGA. Reproduced with permission [133]. Copyright 2024, Elsevier. G. Schematic illustration of the preparationprocess of the in situ chemotherapeutic generator sc@cs@5-fc and the treatmentof colorectal cancer by oral SC@CS@5-FC. Reproduced with permission [134]. Copyright © 2024, American Chemical Society. H. The schematic illustrates how the nanovaccine induces robust anti-F. nucleatum immune responses that significantly improve the efficiency of chemotherapy and reduce the cancer metastasis in F. nucleatum-infected CRC. Reproduced with permission [135]. Copyright 2024,Science China Press. I. Schematic illustration of neighboring effect-initiated supramolecular nanocomplex with sequential infiltration as irreversible apoptosis inducer for synergetic chemo-immunotherapy. Reproduced with permission [136]. Copyright © 2024 Wiley-VCH GmbH.

Table 9
Nanotechnology-based combined-therapy for the treatment of GI tumors.

Nanomaterial Type	Cancer Type	Main Function	Main Mechanism	Reference
Hypoxia-sensitive nanoparticles (OTS964 + Photodynamic agent)	ESCC	Imaging-guided therapy (Chemo + Photodynamic Therapy)	Selective drug delivery to ESCC tumor, inhibition of TOPK, apoptosis induction, suppression of liver metastasis and recurrence	[137]
Ca2+-loaded LDCNSO nanoparticles (with TAE)	HCC	Drug delivery (Oxidative stress + Chemotherapy)	Ultrasound-induced cavitation to release radicals, oxidative stress, and apoptosis induction	[138]
Chitosan-based nanoparticles (LCH + MCH) with herbal extract	CRC	Drug delivery (Polyphenol encapsulation)	Controlled release of polyphenols in gastrointestinal pH, improved bioavailability, and tumor inhibition	[139]
HA-modified liposomes (HA-Lip-ICT)	HCC	Drug delivery (Chemotherapy + Targeted therapy)	HA-CD44 receptor interaction for enhanced drug delivery, pH-dependent release, and improved tumor targeting	[140]
Arsenic–ferrosoferric oxide nanoparticles (AFCNC)	ESCC	Combined therapy (Chemotherapy + Radiotherapy)	Enhanced ROS generation, YAP inhibition, and tumor growth suppression, increased chemotherapy and radiotherapy sensitivity	[141]
Bioactive Black Phosphorus (BP)	PDAC	Immunomodulation and tumor suppression	BP induces tumor-associated gene downregulation, CAF suppression, and survival extension in PDAC animal models	[142]

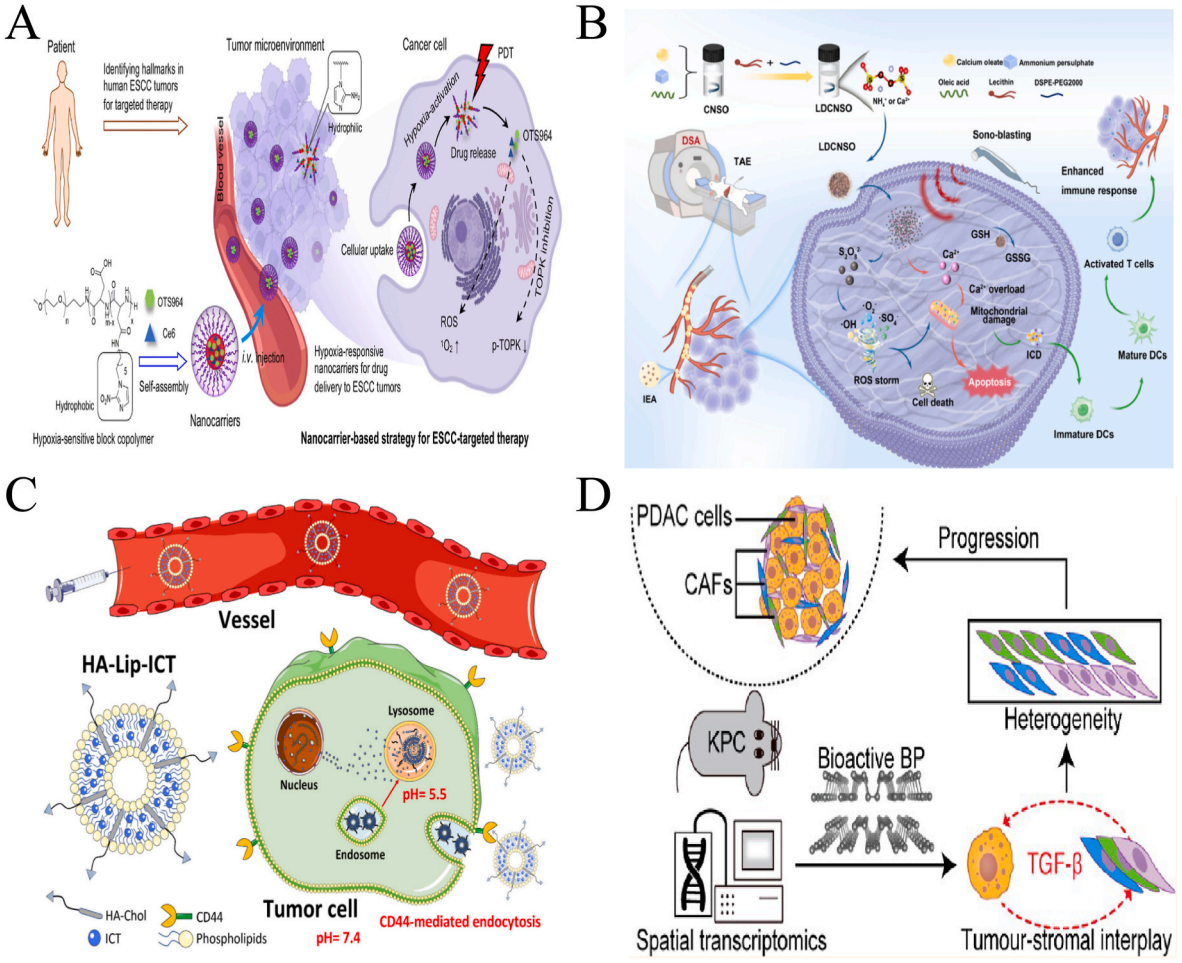

Fig. 12. Nanotechnology-based combined-therapy for the treatment of GI tumors.
A. Schematic illustration of developing OTS964 and Ce6-loaded OTS964/Ce6@NPs for targeting the hallmarks of ECSS toward tumor photodynamic therapy and TOPK inhibition. Reproduced with permission [137]. Copyright © 2023, American Chemical Society. B. Schematic illustration of the synthesis of ldcnso and the underlying therapeutic mechanism of ldcnso. Reproduced with permission [138]. Copyright © 2024, American Chemical Society. C. Schematic overview of the hyaluronic acid-modified liposomes loaded with icaritin (HA-Lip-ICT) and its proposed anti-tumor mechanism. Reproduced with permission [140]. Copyright 2024, Frontiers Media S.A. D. Schematic illustration of effect of bioactive black phosphorusnanomaterials on cancer-associatedfibroblast heterogeneity in pancreatic cancer. Reproduced with permission [142]. Copyright © 2024, American Chemical Society.

ultrasound stimulation.

Natural product-based nanotherapies are emerging as promising strategies to enhance biocompatibility and reduce off-target effects. Siles-Sánchez et al. encapsulated yarrow extracts, rich in chlorogenic acid and dicaffeoylquinic acids, into chitosan nanoparticles using ionotropic gelation and spray-drying techniques. The spray-dried particles achieved a 90 % encapsulation efficiency and demonstrated sustained release under gastrointestinal pH conditions, effectively inhibiting colon adenocarcinoma proliferation through synergistic antioxidant and pro-apoptotic effects. This study highlights the potential of phytochemical-nanomaterial hybrids to bridge traditional medicine with modern oncology [139]. In parallel, Sun et al. developed HA-modified icaritin

liposomes (HA-Lip-ICT) for HCC. The HA coating enhanced tumor targeting by improving cellular uptake by 3.2-fold compared to non-targeted liposomes. In vivo, HA-Lip-ICT reduced tumor burden by 75 % through dual inhibition of the STAT3 and VEGF pathways, demonstrating the value of ligand-directed delivery in natural compound-based therapies [140].

For aggressive and therapy-resistant tumors, multimodal nanoplatforms that integrate chemotherapy, radiotherapy, and molecular targeting have shown exceptional promise. Zhou et al. designed a GSH-responsive arsenide nanohybrid (AFCNC) co-delivering arsenic trioxide and the YAP inhibitor verteporfin. In ESCC models, AFCNC disrupted redox homeostasis to enhance ROS generation while inhibiting YAP/TAZ oncogenic signaling. Combined with cisplatin-based radiotherapy, this strategy achieved a 90 % reduction in tumor growth and a 60 % decrease in metastasis, highlighting the synergy between DNA damage and pathway inhibition [141]. Similarly, bioactive black phosphorus (BP) nanosheets in pancreatic ductal adenocarcinoma (PDAC) models downregulated tumor-associated genes, including KRAS and TGF-β, while depleting CAFs. Administered at 1.5 mg/kg twice weekly to transgenic KPC mice, BP extended median survival by 150 % compared to controls, demonstrating its dual role as both a chemosensitizer and a stromal disruptor [142].

Despite these advancements, several challenges persist in optimizing the pharmacokinetics of nanomaterials, scaling up manufacturing processes, and ensuring long-term safety. Future research efforts should prioritize AI-guided nanocarrier design, the use of patient-derived organoid platforms for personalized therapy testing, and clinical trials that evaluate combinatorial therapeutic regimens. By integrating nanotechnology, systems biology, and clinical insights, the field is poised to deliver transformative combination therapies that address the multidimensional complexity of GI cancers, ultimately enhancing patient survival and quality of life.

5. Discussion and prospects

In recent years, nanomaterials have made significant advancements in the diagnosis and treatment of GI cancers. The continuous evolution of nanotechnology has highlighted its immense potential in cancer therapy, owing to the unique properties of nanomaterials. Specifically, in the treatment of GI malignancies such as HCC, CRC, GC, and EC, nanotechnology has found extensive applications in targeted drug delivery, radiosensitization, immunotherapy, and early diagnosis. First, NPs, when used as drug carriers, enable precise tumor targeting through surface modification and functionalization, significantly enhancing the localized concentration of drugs within tumors. Nanocarriers not only improve the solubility and stability of drugs but also mitigate systemic toxicity by limiting drug distribution to healthy tissues [143,144]. For example, studies on CRC have demonstrated that NP-based drug delivery systems enhance the permeability of the intestinal epithelium and provide tumor-specific targeting, thereby improving therapeutic outcomes [18,145]. Additionally, nanotechnology has made substantial progress in augmenting the efficacy of radiotherapy. NPs enhance radiation sensitivity by facilitating the accumulation of radio-enhancing agents in tumor cells, optimizing the therapeutic response [146–148].

Second, nanomaterials play a critical role in cancer immunotherapy. By designing immunomodulatory nanomaterials, researchers can effectively activate the host immune system to recognize and eradicate tumor cells [144,149,150]. For instance, NPs that deliver tumor antigens or immune-activating factors have been shown to enhance antigen-specific immune responses and promote antitumor immunity [151,152]. Furthermore, studies suggest that nanotechnology holds significant promise in immunotherapy for HCC and pancreatic cancer [153–155].

Despite the significant advancements in nanomaterial research, the clinical translation of these technologies in GI oncology encounters several critical challenges. One major limitation is stability, as the interactions between NPs and biological systems remain incompletely understood, potentially leading to premature drug release or degradation. Controlled drug release presents another obstacle; ideal nanocarriers must release their payloads precisely at tumor sites while remaining inert in healthy tissues. Achieving the balance between precise spatiotemporal control and therapeutic efficacy demands innovative engineering solutions. Furthermore, biocompatibility and biodegradability are pressing concerns. While many nanomaterials exhibit short-term safety, their long-term accumulation in organs such as the liver and kidneys could lead to toxicity. Consequently, the design of biodegradable nanomaterials with non-toxic byproducts is imperative.

Additionally, the scalability and standardization of manufacturing processes present substantial barriers to clinical adoption. Successful laboratory-scale developments must be translated into reproducible, cost-effective production methods, which require the establishment of rigorous quality control frameworks. Furthermore, challenges related to regulatory approval and large-scale manufacturing need to be addressed to bring these technologies into routine clinical use.

To better assess the feasibility and overcome these challenges, successful cases of nanomaterial applications, such as the use of personalized nanomedicines in neoantigen-based immunotherapies, provide valuable insights. For instance, certain Phase I clinical trials have demonstrated promising results in patients with MSS CRC, highlighting the potential for targeting specific neoantigens to enhance immune responses. However, the application of such platforms requires addressing both the challenges of long-term stability and targeting specificity to ensure consistent clinical outcomes.

Future research should prioritize strategies focused on functionalization and multitargeting to enhance tumor specificity. This may include leveraging the EPR effect or receptor-mediated targeting. Multitargeting approaches, which address tumor heterogeneity and drug resistance, are increasingly recognized as critical priorities. For instance, NPs functionalized with ligands targeting dual receptors, such as EGFR and HER2, can improve tumor selectivity while minimizing off-target effects. Additionally, the development of nanomaterials with tunable degradation rates that align with drug release kinetics is crucial for optimizing therapeutic outcomes. Both natural polymers, such as polylactic acid, and synthetic polymers, such as polyamino acids, show promise due to their biocompatibility and controlled degradation properties. To minimize immunogenicity, surface modifications with polyethylene glycol (PEG) or lipid bilayers can effectively evade immune clearance and prolong the circulation time of the nanomaterials.

Integrating nanotechnology with conventional treatments such as chemotherapy, radiotherapy, and immunotherapy offers a promising approach to overcoming therapeutic resistance. For instance, NPs co-loaded with chemotherapeutic agents and immune checkpoint inhibitors (ICIs), such as anti-PD-1, can synergistically enhance tumor cell killing while simultaneously activating the immune response. Radiosensitizing NPs, when combined with localized radiation, increase tumor-specific DNA damage while minimizing harm to surrounding healthy tissues. Additionally, nanomaterials can serve as carriers for tumor-associated antigens, cytokines, or immune adjuvants, thereby priming DCs and amplifying cytotoxic T cell responses. For example, LNPs encapsulating neoantigens and TLR agonists have demonstrated efficacy in preclinical models of pancreatic cancer.

Nanotechnology presents transformative solutions to overcome the limitations of conventional therapies in the treatment of GI cancers. By advancing strategies such as functionalization, biodegradability, and combination therapies, researchers can unlock the full potential of nanomaterials for precision oncology. However, critical challenges related to stability, manufacturing, and toxicity must be addressed to facilitate successful clinical translation. Future research should prioritize interdisciplinary collaboration to optimize the design of nanomaterials, overcome current barriers, and expedite their integration into clinical practice.

6. Conclusion

This review highlights the applications of nanomaterials in the diagnosis and treatment of GI tumors, synthesizing the latest research advancements in this area. Nanotechnology holds significant promise in targeted drug delivery, radiosensitivity enhancement, cancer immunotherapy, and early diagnosis. Notably, surface modifications and functionalization of nanodrug carriers enhance therapeutic efficacy while minimizing off-target effects in healthy tissues. Moreover, nanotechnology introduces innovative strategies for improving radiotherapy and immunotherapy, thereby substantially enhancing treatment precision and therapeutic outcomes.

Despite the promising potential of nanomaterials in GI cancer therapy, several challenges persist, including issues related to carrier stability, controlled drug release, biodegradability, and manufacturing scalability. Consequently, future research should focus on optimizing nanomaterial design, enhancing biocompatibility, standardizing production protocols, and refining toxicity profiling. With ongoing advancements in nanotechnology and its integration with multimodal therapeutic strategies, nanomaterials are poised to play an increasingly pivotal role in the precision medicine of GI cancers.

CRediT authorship contribution statement

Liping Chen: Writing – original draft. **Qingqing Li:** Writing – review & editing, Writing – original draft.

Ethics approval and consent to participate

None.

Consent for publication

None.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbrivation

Gastrointestinal GI
magnetic resonance imaging MRI
computed tomography CT
hepatocellular carcinoma HCC
colorectal cancer CRC
gastric cancer GC
esophageal cancer EC
tumor microenvironment TME
tumor-associated macrophages TAMs
cancer-associated fibroblasts CAFs
extracellular matrix ECM
myeloid-derived suppressor cells MDSCs
polymorphonuclear MDSCs PMN-MDSCs
natural killer NK
pancreatic ductal adenocarcinoma PDAC
lysyl oxidases LOXs
extracellular vesicles EVs
regulatory T cells Tregs
esophageal squamous cell carcinoma ESCC
lactate dehydrogenase A LDHA
interferon-gamma IFN-γ;
cytotoxic T lymphocytes CTLs
immune checkpoint inhibitors ICIs
microsatellite instability-high MSI-H;
mismatch repair-deficient dMMR
tumor-infiltrating lymphocytes TILs
chimeric antigen receptor T-cell CAR-T;
Carcinoembryonic antigen CEA
lipid nanoparticles LNPs
microsatellite-stable MSS
enhanced permeability and retention EPR
near-infrared NIR
tumor lysates TLS
damage-associated molecular patterns DAMPs
Toll-like receptor TLR
polylactic-co-glycolic acid PLGA
dendritic cells DCs
immunogenic cell death ICD
indocyanine green ICG
interleukin-12 IL-12
granulocyte-macrophage colony-stimulating factor GM-CSF
positron emission tomography PET
circulating tumor DNA ctDNA
nanoparticles NPs
early-stage gastric cancer EGC
vascular endothelial growth factor VEGF
small extracellular vesicles sEVs
area under the curve AUC
surface plasmon resonance SPR
two-dimensional 2D
gold nanoparticles AuNPs
femtomolar fM
small hepatocellular carcinoma sHCC
magnetic hyperthermia therapy MHT
magnetic nanoparticles MNPs
Salmonella-mimicking gold nanorods SM-AuNRs
artificial intelligence AI
surface-enhanced Raman scattering SERS
oxaliplatin/S-1 SOX
tumor regression grading TRG
radiotherapy RT
covalent organic framework COF
cancer stem cells CSCs
tirapazamine, TPZ
NADPH Quinone Dehydrogenase 1 NQO1
reactive oxygen species ROS
photodynamic therapy PDT
photothermal therapy PTT
chlorin e6 Ce6
gold nanoviroids AuNVs
gold nanostars AuNSs
immune checkpoint blockade ICB
RNA interference RNAi
cytotoxic T lymphocyte CTL;
virus-like nanoparticles VLPs
transcription factor EB TFEB
matrix metalloproteinase-2 MMP-2
5-fluorouracil 5-FU
methionine adenosyltransferase 2A MAT2A

nucleic acids NAs
ultrasound US;
magnetothermal therapy MHT
nanoscale drug delivery systems NDDS
asialoglycoprotein receptor ASGPR
hyaluronic acid HA
hydroxycamptothecin HCPT
lenvatinib NPs Len-RNP
Good Manufacturing Practice, GMP
carbon nano-onions CNOs
multidrug resistance MDR
plumbagin PLB
γ-glutamyl transpeptidase GGT
5-fluorocytosine, 5-FC
transarterial embolization TAE
HA-modified icaritin liposomes HA-Lip-ICT
black phosphorus BP
polyethylene glycol PEG
HA-grafted mesoporous silica nanoparticles MSN-PG-HA
manganese-doped mesoporous silica NPs Mn-MSNs

Data availability

No data was used for the research described in the article.

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