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Next-generation nanocarriers for colorectal cancer: passive, active, and stimuli-responsive strategies for precision therapy

Rehab Galal Abbas Mohamed, [a] Salma Mohamed Ali, [a] Iman Saad Ahmed, [a,b] Mutasem Rawas-Qalaji [a,b] and Zahid Hussain *[a,b]

Colorectal cancer (CRC) remains a major global health burden, necessitating more effective and selective therapeutic approaches. Nanocarrier-based drug delivery systems offer significant advantages by enhancing drug accumulation in tumors, reducing off-target toxicity, and overcoming resistance mechanisms. This review provides a comprehensive overview of recent advancements in nanocarriers for CRC therapy, including passive targeting *via* the enhanced permeability and retention (EPR) effect, and active targeting strategies that exploit specific tumor markers using ligands such as antibodies, peptides, and aptamers. Additionally, various stimuli-responsive systems are explored, which leverage tumor-specific cues—such as pH, redox, enzymes, light, heat, and magnetic fields—for controlled and localized drug release. Multifunctional and hybrid platforms combining multiple targeting mechanisms and therapeutic functionalities are also discussed for their potential in theranostics and personalized medicine. Unlike prior reviews, this article emphasizes emerging ligand-engineered nanosystems, multi-stimuli-responsive designs, and translational challenges, providing a forward-looking perspective on next-generation CRC nanomedicine. While preclinical studies demonstrate encouraging outcomes, clinical translation remains limited due to challenges in scalability, biocompatibility, and tumor heterogeneity. Future research should focus on the rational design of safe, smart, and modular nanocarriers, integration of machine learning tools, and personalized approaches to maximize efficacy. Overall, the evolving landscape of nanotechnology presents promising avenues for improving CRC treatment and patient prognosis.

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1. Colorectal cancer: epidemiology, pathogenesis, and clinical presentation

Colorectal cancer (CRC), also referred to as bowel cancer, is a malignant tumor originating in the colon or rectum—key components of the gastrointestinal tract.[1] It commonly arises from adenomatous or serrated polyps formed along the mucosal lining, which, over a span of 10 to 20 years, may undergo dysplastic changes and progress through the well-characterized adenoma–carcinoma sequence (Fig. 1). While polyps are generally asymptomatic, some may ulcerate, bleed, or cause rectal tenesmus and, in advanced cases, result in intestinal obstruction. Histologically, polyps are categorized as neoplastic—such as adenomatous and sessile serrated lesions—or non-neoplastic, including hyperplastic, inflammatory, or hamartomatous types.[1]

Globally, CRC poses a substantial public health challenge, ranking as the third most diagnosed cancer and the second leading cause of cancer-related mortality.[2] As of 2022, CRC accounted for approximately 1.93 million new cases and 930 000 deaths worldwide. In the United States alone, an estimated 154 270 new cases are projected for 2025, including 107 320 colon and 46 950 rectal cancers, with 52 900 deaths anticipated. Lifetime CRC risk remains significant—about 1 in 24 for men and 1 in 26 for women.[2] Although the five-year relative survival rate has improved to approximately 64%, largely due to advancements in early screening and multimodal therapies, survival drops sharply to 13–18% for metastatic disease. Of growing concern is the rising incidence of CRC in individuals under 50 years of age, increasing at an annual rate of 1–2%, despite decreasing trends in older adults.[3–7] This alarming shift is attributed to hereditary syndromes, dietary transitions, sedentary lifestyles, and gut microbiota dysregulation. By 2040, the global burden of CRC is expected to escalate by over 60% in incidence and 73% in

[a]*Department of Pharmaceutics and Pharmaceutical Technology, College of Pharmacy, University of Sharjah, Sharjah 27272, United Arab Emirates.*
E-mail: zahidh85@yahoo.com
[b]*Research Institute for Medical and Health Sciences, University of Sharjah, Sharjah 27272, United Arab Emirates*

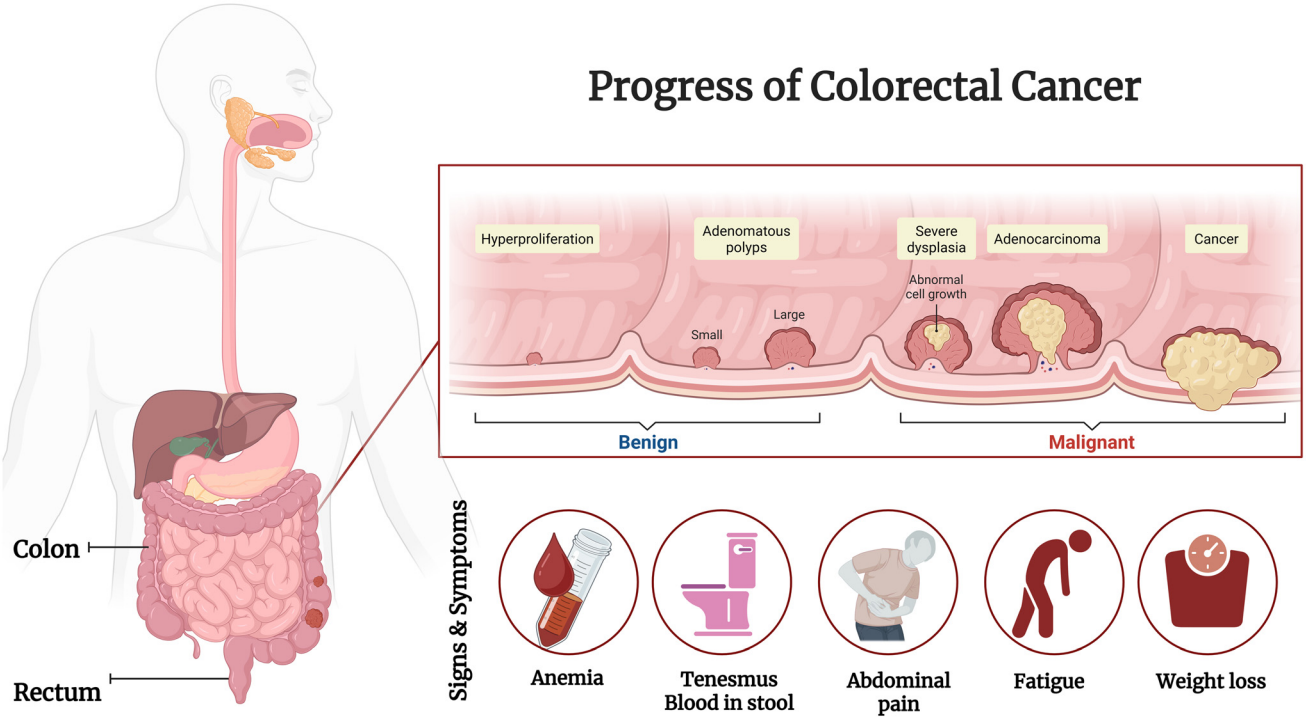

Fig. 1 Progression and clinical manifestation of CRC. The development of polyps from benign to malignant CRC. Key signs and symptoms that patient suffers include abdominal pain (bloating, nausea, and vomiting), tenesmus, presence of blood in stool or melena, general fatigue, iron-deficiency anemia and unexplained weight loss. Created with BioRender.com.

mortality, underscoring the urgency for innovative diagnostic and therapeutic interventions.

Despite these advancements, existing treatment modalities face critical limitations. Conventional chemotherapy often leads to non-specific drug biodistribution, systemic toxicity, rapid clearance, and the emergence of multidrug resistance (MDR), particularly in advanced-stage and metastatic CRC. Furthermore, tumor heterogeneity and patient-to-patient biological variability contribute to poor therapeutic outcomes. There remains a substantial unmet clinical need for precision-targeted approaches that can deliver therapeutics selectively to tumor sites while minimizing off-target effects. Additionally, barriers such as limited drug stability in the gastrointestinal tract, inefficient cellular uptake, and lack of tumor-specific stimuli-responsiveness further hinder drug delivery efficacy. These challenges necessitate the development of innovative, smart drug delivery systems—such as multifunctional nanocarriers—that can respond to the tumor microenvironment (TME), improve therapeutic index, and potentially support patient-specific treatment strategies. In this context, nanotechnology presents a transformative platform for overcoming conventional therapeutic barriers in CRC management.

CRC pathogenesis is driven by complex interactions among genetic mutations, epigenetic alterations, inflammatory processes, and gut microbiota perturbations.[1] Approximately 70% of CRCs are sporadic, arising from somatic mutations often linked to lifestyle and environmental exposures. Around 20–25% are familial in nature, lacking identifiable germline mutations but associated with a strong family history. The remaining 3–5% are hereditary, caused by inherited mutations in DNA repair genes. Notable syndromes include Lynch syndrome, involving defects in mismatch repair genes (*e.g.*, MLH1, MSH2, MSH6, PMS2), and familial adenomatous polyposis (FAP), resulting from APC gene mutations.[3–7]

CRC progression can follow distinct molecular pathways, including chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP).[8–10] CIN, implicated in ~85% of cases, is marked by stepwise mutations in APC, KRAS, and TP53. MSI involves deficient mismatch repair and generates hypermutated phenotypes, while the CIMP pathway leads to transcriptional silencing of tumor suppressor genes *via* DNA hypermethylation. An alternative serrated pathway, involving BRAF mutations and microbial dysbiosis, further complicates the molecular landscape. These insights emphasize the need for molecularly guided diagnostic and therapeutic strategies.[8–10]

Environmental and lifestyle factors significantly influence CRC risk. Diets rich in red and processed meats and low in fiber—hallmarks of Western dietary patterns—are associated with elevated CRC risk, partly by promoting chronic inflammation and disrupting gut microbial balance. Specific microbial species, such as *Fusobacterium nucleatum*, *Escherichia coli*, and *Bacteroides fragilis*, contribute to CRC by producing genotoxins, modulating immune responses, and altering host signaling pathways. Additionally, tobacco smoking exacerbates carcinogenesis by inducing molecular

abnormalities, including MSI, CIMP-high status, and BRAF mutations.[11–13]

Clinically, CRC remains silent in its early stages, which reinforces the importance of timely screening. As the disease advances, patients may present with abdominal pain, rectal bleeding, altered bowel habits, iron-deficiency anemia, unintended weight loss, and tenesmus. Tumor location influences clinical presentation—left-sided lesions often cause hematochezia and obstructive symptoms, while right-sided tumors are more likely to present with occult bleeding and anemia due to the wider luminal diameter and liquid stool content. Tumors in the proximal colon, such as the cecum, can result in significantly higher blood loss—up to fourfold greater than those located distally (approximately 9 mL day^{-1})—necessitating site-specific diagnostic vigilance.[14,15]

Collectively, these findings underscore CRC's multifaceted etiology and highlight the necessity for early detection, molecular classification, and novel treatment modalities. With the projected rise in global disease burden, there is an increasing imperative to develop and implement targeted therapies, including nanotechnology-based drug delivery systems, to improve clinical outcomes and reduce CRC-associated mortality.

2. Conventional treatments for CRC and their limitations

2.1. Chemotherapy

Chemotherapy remains a principal component of CRC treatment, particularly in advanced and metastatic stages.[16,17] These agents work by targeting rapidly dividing cells through disruption of DNA synthesis, mitosis, or other key cellular functions. Commonly employed agents include 5-fluorouracil (5-FU), which inhibits thymidylate synthase and impairs DNA repair; irinotecan, a topoisomerase I inhibitor that prevents DNA unwinding; and oxaliplatin, a platinum compound that induces DNA cross-linking and apoptosis. Oral agents such as capecitabine—an enzymatically activated prodrug of 5-FU—and trifluridine/tipiracil (TAS-102), which incorporates into DNA to disrupt its function, offer improved convenience and patient compliance.

Several combination regimens are routinely used in clinical practice. FOLFOX (5-FU, leucovorin, oxaliplatin) and CAPOX (capecitabine and oxaliplatin) are standard for stages II–IV CRC, while FOLFIRI (5-FU, leucovorin, irinotecan) is commonly used in metastatic settings. For patients with aggressive or bulky metastatic disease, the intensified FOLFOXIRI regimen may be employed. These combinations have improved response rates and progression-free survival; however, they lack tumor selectivity and are associated with significant systemic toxicities. Adverse effects such as mucositis, neutropenia, nausea, vomiting, diarrhea, hand-foot syndrome, and peripheral neuropathy frequently necessitate dose reductions or treatment discontinuation, thereby compromising therapeutic efficacy.[18]

Despite their widespread use, conventional chemotherapeutics suffer from multiple limitations. One major challenge is their non-specific mechanism of action, which leads to damage of healthy proliferating tissues such as the intestinal mucosa, bone marrow, and hair follicles. Additionally, the development of drug resistance through mechanisms like efflux pump overexpression, enhanced DNA repair, and altered drug metabolism further limits long-term efficacy. Tumor heterogeneity and variations in the TME also impede uniform drug penetration, especially in hypoxic or fibrotic regions of the tumor.[18]

Although agents like paclitaxel (PTX) and doxorubicin (DOX) have demonstrated promising anti-cancer effects in preclinical CRC models due to their microtubule-stabilizing and topoisomerase II-inhibiting properties, respectively, their clinical use in CRC remains limited due to off-target toxicity and lack of robust evidence from large-scale clinical trials.[16,17] As a result, there is an urgent need for novel delivery systems that enhance drug selectivity, improve therapeutic index, and mitigate systemic side effects.

In summary, while chemotherapy remains foundational in CRC management, its non-selective nature and associated adverse effects underscore the necessity for more precise treatment modalities. Advances in targeted drug delivery, including nanocarrier-based approaches, offer promising avenues to overcome these limitations and improve clinical outcomes for CRC patients.

2.2. Surgery

Surgical resection remains the primary and most effective curative modality for early-stage CRC, particularly when tumors are localized and amenable to complete removal with negative margins. Standard surgical approaches include partial colectomy (segmental or hemicolectomy) or total colectomy, performed *via* either open or minimally invasive laparoscopic techniques. Laparoscopic-assisted colectomy has gained favor due to its association with reduced postoperative pain, faster recovery, and fewer complications. However, it requires specialized expertise and is technically challenging in certain patient populations, such as those with obesity, previous abdominal surgeries, or advanced-stage disease with local invasion or bulky tumors.[19,20]

In cases of complicated presentations—such as acute bowel obstruction, perforation, or disseminated metastatic disease—palliative interventions like diverting colostomy or bypass procedures may be necessary to relieve symptoms and improve quality of life, though they do not offer curative intent. These procedures are especially important in elderly or high-risk patients unfit for radical resection.

For rectal cancer, surgical strategies are guided by tumor location, depth of invasion, and sphincter involvement. Total mesorectal excision is considered the gold standard for locally advanced rectal cancer, involving *en bloc* removal of the rectum along with the surrounding mesorectal fat and lymphatics to ensure oncological clearance. However, this technique is associated with significant technical complexity and risk of complications, including anastomotic leakage, pelvic

sepsis, and nerve damage. For early-stage or superficial rectal tumors, less invasive alternatives such as transanal excision (TAE) and transanal endoscopic microsurgery (TEMS) may offer comparable oncological outcomes while preserving anorectal function and reducing morbidity.[21]

In advanced rectal cancer, low anterior resection (LAR) or abdominoperineal resection (APR) may be required depending on sphincter involvement and nodal spread. These approaches aim to achieve negative circumferential resection margins (CRM) and adequate lymph node dissection, which are critical predictors of recurrence and survival. Surgical success is heavily reliant on the expertise of the multidisciplinary surgical team and the ability to manage intraoperative and postoperative complications effectively.[22]

Despite its curative potential, CRC surgery carries inherent limitations. Postoperative complications such as infections, bleeding, ileus, and anastomotic leaks can significantly prolong hospital stays and impact prognosis. Furthermore, long-term functional sequelae—such as low anterior resection syndrome (LARS), fecal incontinence, urinary dysfunction, and sexual impairment—adversely affect patients' quality of life. Neoadjuvant or adjuvant chemoradiotherapy, often used in rectal cancer, can further exacerbate these complications due to radiation-induced tissue fibrosis and vascular damage.

In conclusion, while surgical resection remains the foundation of CRC treatment, it is associated with significant perioperative and long-term challenges. Optimization of patient selection, refinement of minimally invasive techniques, and integration with adjuvant modalities are essential to maximize therapeutic benefit and minimize morbidity. Additionally, adjunctive approaches such as nanotechnology-guided imaging and intraoperative fluorescence may enhance tumor localization and margin assessment, representing an exciting frontier in surgical oncology for CRC.

2.3. Radiotherapy

Radiation therapy, which utilizes ionizing radiation to induce irreparable DNA damage and promote tumor regression, plays a more significant role in the management of rectal cancer than in colon cancer. It is especially beneficial for locally advanced rectal tumors, where it is often used as part of a multimodal treatment strategy to reduce tumor size, improve resectability, and minimize local recurrence. The main modalities include external beam radiotherapy (EBRT), which remains the standard for localized disease, and stereotactic body radiotherapy (SBRT), which delivers high-dose radiation with sub-millimeter precision to treat oligometastatic lesions—commonly in the liver or lungs.[23]

Additional radiation strategies such as brachytherapy (internal radiation) and intraoperative radiotherapy (IORT) are selectively employed based on tumor location and surgical access. These modalities can be administered as neoadjuvant therapy to downstage tumors prior to surgery, concurrently with radiosensitizing chemotherapy agents like 5-FU or capecitabine, or postoperatively to eradicate residual microscopic disease and reduce recurrence risk.[24]

Advancements in radiation delivery have led to the adoption of image-guided and conformal techniques, such as three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). These approaches enhance treatment precision by tailoring radiation dose distribution to the tumor shape, thereby maximizing tumor control while minimizing damage to adjacent normal tissues such as the bowel, bladder, and reproductive organs.[23]

Despite these advancements, radiotherapy is not devoid of complications. Acute toxicities commonly include dermatitis, proctitis, diarrhea, abdominal cramping, fatigue, and mucosal irritation. Chronic complications—such as bowel fibrosis, fecal incontinence, strictures, sexual dysfunction, and urinary disturbances—can significantly impair quality of life, particularly in younger patients. Additionally, radiation-induced vascular changes may compromise healing post-surgery and increase the risk of anastomotic leaks.

Limitations of radiotherapy also include tumor radioresistance, variability in tumor hypoxia, and the inability to distinguish tumor margins precisely in some cases, necessitating broader irradiation fields that may expose more normal tissue. Furthermore, colon cancers—especially those located proximally—are rarely treated with radiation due to anatomical constraints and increased risk of collateral damage.

In summary, radiotherapy remains a vital component of rectal cancer management, especially in locally advanced disease. Its role continues to evolve with improvements in imaging, radiation delivery, and personalized treatment planning. Ongoing research into radiosensitizers, nanotechnology-based delivery systems, and adaptive radiotherapy protocols may help overcome current limitations and further improve outcomes in CRC patients.

2.4. Immunotherapy

Immunotherapy has emerged as a transformative modality in CRC treatment, particularly in subsets characterized by microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) phenotypes. These tumors exhibit a high tumor mutational burden (TMB), leading to the generation of numerous neoantigens that render them more immunogenic and responsive to immune checkpoint blockade.[25] The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis has been a major target of immunotherapeutic intervention. Monoclonal antibodies such as nivolumab and pembrolizumab disrupt this inhibitory signaling pathway, thereby restoring T-cell-mediated cytotoxicity against tumor cells and enhancing antitumor immune responses.[25]

Additionally, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blockade with ipilimumab, particularly in combination with PD-1 inhibitors, has shown synergistic effects by enhancing T-cell priming and activation, especially in cases refractory to monotherapy. This dual blockade strategy has demonstrated durable responses and improved progression-free survival in MSI-H/dMMR CRC patients, particularly those with metastatic or treatment-refractory disease.[26]

Despite these advances, immunotherapy remains largely ineffective in microsatellite-stable (MSS) and profi-

cient mismatch repair (pMMR) CRC, which comprise the vast majority (~85%) of CRC cases. These tumors possess lower TMB, reduced neoantigen expression, and an immunosuppressive TME that hinders T-cell infiltration and activation. This immunological "cold" phenotype poses a significant barrier to checkpoint inhibitor efficacy, necessitating the development of predictive biomarkers and novel combination regimens to convert non-responsive tumors into immunologically "hot" phenotypes.[27]

Moreover, immune checkpoint inhibitors are associated with a unique spectrum of immune-related adverse events (irAEs) stemming from nonspecific immune activation. These include colitis, dermatitis, hepatitis, pneumonitis, endocrinopathies, and arthralgia, which may necessitate immunosuppressive therapy and treatment discontinuation in severe cases. The incidence and severity of irAEs vary based on the agent used, dose, treatment duration, and patient-specific immune context.

To expand the therapeutic reach of immunotherapy in CRC, current research efforts are exploring combinatorial strategies involving chemotherapy, radiotherapy, angiogenesis inhibitors, oncolytic viruses, cancer vaccines, and nanomedicine-based immunomodulators. These combinations aim to remodel the TME, enhance antigen presentation, and promote effector T-cell infiltration. Furthermore, emerging approaches such as adoptive cell therapies (*e.g.*, CAR-T, TILs), bispecific antibodies, and checkpoint inhibitors targeting novel molecules (*e.g.*, LAG-3, TIM-3) are under preclinical and clinical investigation.[27]

In conclusion, while immunotherapy offers unprecedented clinical benefit in MSI-H/dMMR CRC, its broader application remains constrained by tumor immune evasion, treatment-related toxicities, and patient heterogeneity. Personalized immune profiling, robust biomarker development, and integration with rational combination therapies are essential to unlock the full potential of immunotherapy across all CRC subtypes.

2.5. Targeted therapy

Targeted therapies have advanced CRC treatment by disrupting specific molecular pathways involved in tumor growth and progression. Anti-angiogenic agents such as bevacizumab and ramucirumab inhibit VEGF signaling, limiting tumor blood supply and enhancing chemotherapy efficacy. Ziv-aflibercept, a VEGF trap, provides broader inhibition of VEGF isoforms.[28,29]

EGFR-targeted monoclonal antibodies—cetuximab and panitumumab—are effective in KRAS/NRAS wild-type tumors by blocking MAPK and PI3K-AKT pathways. However, combining EGFR and VEGF inhibitors has shown increased toxicity without added benefit. In BRAF-mutant tumors, combined BRAF and EGFR inhibition (*e.g.*, encorafenib + cetuximab) improves survival. Similarly, HER2-positive CRC may respond to trastuzumab-based regimens, while rare fusions like NTRK and RET can be targeted with larotrectinib and selpercatinib.

Regorafenib, a multikinase inhibitor, is used in refractory metastatic CRC but has a narrow therapeutic window due to adverse events such as hepatotoxicity and hand-foot syndrome.

Despite their precision, targeted therapies are limited by resistance mutations, off-target toxicities, and high costs. Efficacy depends on accurate molecular profiling and is often improved through combination strategies with chemotherapy, immunotherapy, or nanomedicine.

2.6. Treatment by stage

The management of CRC is highly stage-specific and requires an individualized approach based on tumor location, molecular profile, patient comorbidities, and treatment goals (Table 1). In Stage 0–I disease, curative management typically involves local interventions such as endoscopic polypectomy or surgical resection. Segmental or partial colectomy is considered when high-risk histological features are present, though adjuvant therapy is generally not necessarily due to the low likelihood of recurrence.[14,30]

For Stage II colon cancer, standard treatment consists of complete surgical resection followed by a risk-adapted

Table 1 Treatment strategy in colon and rectal cancers by stages

Stage	Treatment for colon cancer	Treatment for rectal cancer
Stage 0	- Local excision or polypectomy	- Local excision or transanal resection
	- Partial colectomy (if large)	- Local excision or transanal resection
Stage I	- Partial colectomy	- Surgery (transanal resection, LAR, APR)
	- Monitor margins; possible further surgery if needed	- Additional chemo/radiation if advanced (5-FU or capecitabine)
Stage II	- Partial colectomy	- Chemoradiation (5-FU or capecitabine) + surgery
	- Neoadjuvant therapy if T4b (chemo or immunotherapy if dMMR/MSI-H)	- Surgery (LAR or APR)
Stage III	- Partial colectomy + lymph node removal	- Similar to Stage II (chemoradiation + surgery)
	- Adjuvant chemotherapy (FOLFOX or CAPEOX)	- Chemotherapy post-surgery (if needed)
Stage IV	- Surgery (if limited metastases), plus chemotherapy	- Surgery (if applicable) + chemotherapy
	- Chemotherapy: FOLFOX, CAPEOX, or alternatives	- Chemoradiation; chemotherapy (5-FU, capecitabine)
	- Targeted therapies (if indicated)	- Targeted therapies and/or immunotherapy (if indicated)
Recurrent	- Surgery (if local) + chemotherapy (if distant)	- Surgery (if local) + chemotherapy (if distant)
	- Targeted therapies or immunotherapy based on prior treatments	- Targeted therapies or immunotherapy based on prior treatments

Abbreviations: 5-FU, 5-fluorouracil; CAPEOX/XELOX, capecitabine plus oxaliplatin; FOLFOX, 5-FU, leucovorin, and oxaliplatin; FOLFIRI, 5-FU, leucovorin, and irinotecan; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; LAR, low anterior resection; APR, abdominoperineal resection; RT, radiotherapy; CT, chemotherapy.

decision on adjuvant chemotherapy. High-risk patients—those with T4 lesions, lymphovascular invasion, poor differentiation, bowel obstruction, or suboptimal lymph node sampling—may benefit from additional chemotherapy, commonly using FOLFOX or capecitabine-based regimens. In contrast, Stage II rectal cancer is usually managed with neoadjuvant chemoradiotherapy to downstage the tumor and improve resectability, followed by total mesorectal excision.[14,30]

Stage III CRC, characterized by lymph node involvement, requires a combination of surgery and adjuvant chemotherapy. Patients with colon cancer typically undergo colectomy with regional lymphadenectomy, followed by FOLFOX or CAPOX to eradicate residual microscopic disease. In rectal cancer, neoadjuvant chemoradiotherapy precedes surgery and may be followed by additional chemotherapy to enhance disease-free survival. Treatment decisions at this stage also consider the tumor's response to preoperative therapy and the patient's overall performance status.[14,30]

In Stage IV or metastatic CRC, treatment goals shift toward disease control, prolongation of survival, and symptom palliation. If metastatic lesions—commonly in the liver or lungs—are technically resectable, a curative-intent approach may include surgery combined with perioperative chemotherapy. In patients with unresectable or widespread metastases, systemic therapy becomes the cornerstone of care. Regimens such as FOLFOX, FOLFIRI, or CAPOX are selected based on the patient's tolerance, tumor biology, and molecular markers, and are often combined with targeted agents like bevacizumab or cetuximab. Molecular profiling is essential at this stage to guide therapeutic choices and optimize outcomes.[14,30]

3. Targeting strategies for CRC nanotherapy

Nanotechnology, defined as the manipulation and application of materials at the nanoscale (1–100 nm), has emerged as a transformative platform in oncology, offering novel opportunities to address the limitations of conventional therapies.[31–35] In CRC, nanocarriers hold significant potential to improve therapeutic efficacy while reducing systemic toxicity.[36] Conventional chemotherapeutics are hampered by rapid clearance, poor tumor selectivity, and dose-limiting toxicities, whereas nanoscale delivery systems improve drug pharmacokinetics, stability, and biodistribution. Many are biodegradable and exhibit low intrinsic toxicity, making them attractive candidates for clinical translation.[36,37]

As illustrated in Fig. 2, nanocarrier-based CRC therapy can be broadly categorized into three principal design strategies:

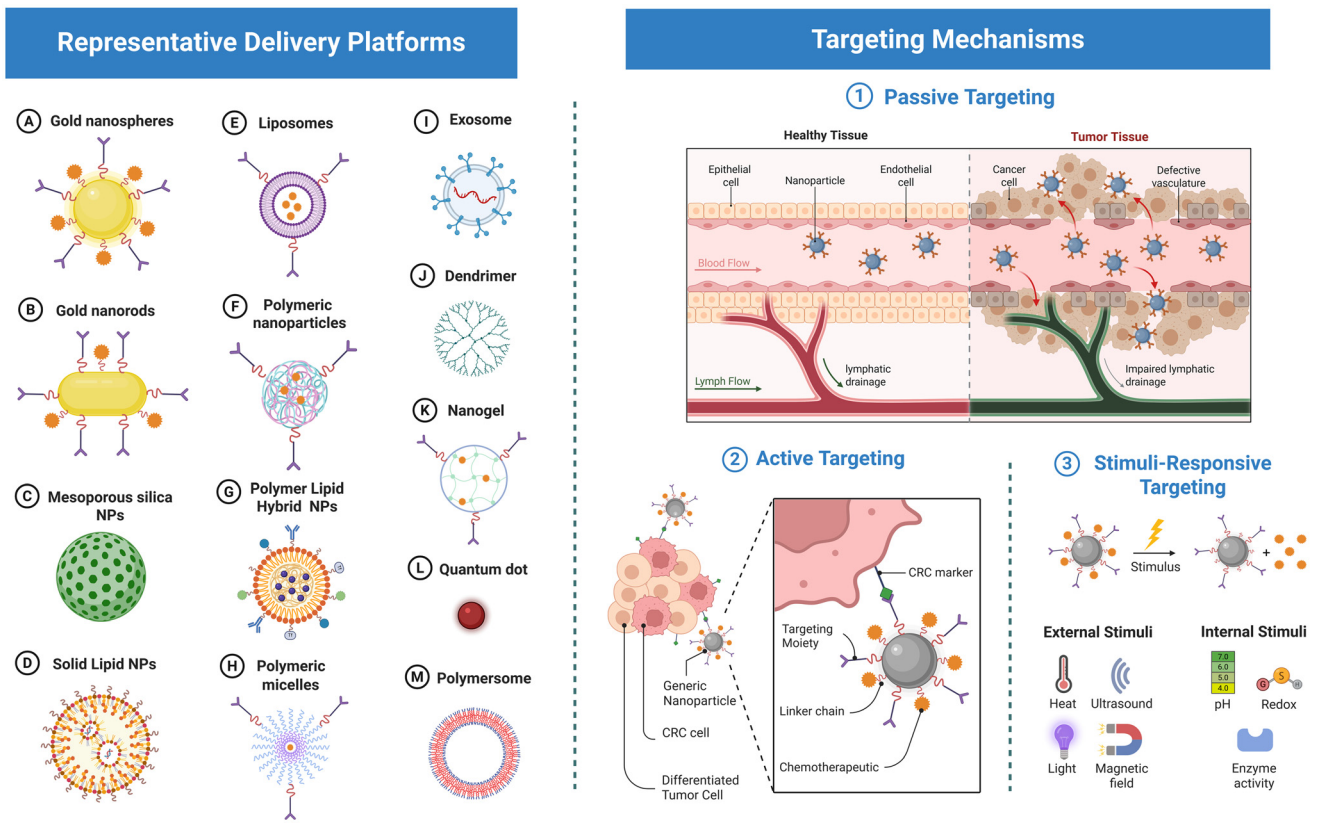

Fig. 2 Schematic overview of nanoparticle-mediated CRC therapy. (A–M) Representative delivery platforms include inorganic, lipid-based, and polymeric systems. Right panel illustrates targeting mechanisms: (1) passive targeting *via* EPR, (2) ligand-mediated active targeting, and (3) stimuli-responsive targeting triggered by endogenous (pH, redox, enzymes) or exogenous (light, heat, magnetic field, ultrasound) cues. Created with BioRender.com.

passive targeting, active targeting, and stimuli-responsive delivery. Passive targeting exploits the enhanced permeability and retention (EPR) effect, allowing nanocarriers to accumulate in tumors through leaky vasculature and impaired lymphatic drainage within the TME.[38] However, reliance on the EPR effect alone has proven inconsistent in clinical settings due to interpatient heterogeneity and variable tumor physiology. To enhance tumor selectivity, active targeting strategies have been developed in which nanocarriers are functionalized with ligands such as antibodies, aptamers, or peptides that bind receptors overexpressed on CRC cells.[39] This receptor-mediated endocytosis facilitates greater tumor uptake and intracellular drug accumulation, thereby improving therapeutic precision.

A third and increasingly important approach involves stimuli-responsive systems, or "smart" nanocarriers, which release their therapeutic payload in response to tumor-associated triggers such as acidic pH, overexpressed enzymes, oxidative stress, or exogenous stimuli (*e.g.*, heat, light, or magnetic fields). By providing spatiotemporally controlled release, these systems minimize premature drug leakage, improve tumor penetration, and reduce off-target toxicity.

Several classes of nanocarriers—including liposomes, polymeric nanoparticles (PNPs), dendrimers, solid lipid nanoparticles (SLNs), and inorganic nanoplatforms—have been developed for CRC therapy, each offering unique physicochemical attributes suited for drug encapsulation, controlled release, and tumor-specific delivery (Table 2). Despite robust preclinical advances, clinical translation remains limited. For example, a camptothecin (CPT)-based nanoformulation in combination with capecitabine and radiotherapy has entered phase Ib/II evaluation in patients with locally advanced rectal cancer.[40] Yet, no nanomedicine has received regulatory approval specifically for CRC, with barriers including large-scale manufacturing, stability concerns, and long-term safety validation.

Overall, nanotechnology is reshaping CRC treatment paradigms by enabling multimodal, tumor-specific, and stimuli-responsive strategies. While translational hurdles persist, continued innovation promises a future of more personalized, effective, and less toxic therapeutic interventions for CRC.

3.1. Passive targeting: EPR-based accumulation

Passive targeting remains a cornerstone of nanomedicine, exploiting the EPR effect to facilitate nanoparticle (NP) accumulation in tumors.[50–53] In CRC, pathological angiogenesis produces leaky vasculature, irregular perfusion, and deficient lymphatic drainage, allowing nanosized therapeutics (typically 100–250 nm) to extravasate and persist within the tumor interstitium. These abnormalities are further exacerbated by tumor-induced hypoxia, acidosis, and inflammatory mediators, which weaken endothelial junctions and basement membrane integrity.

Despite its mechanistic appeal, the EPR effect demonstrates limited reliability in human cancers, including CRC. Clinical data and meta-analyses consistently highlight its heterogeneity and patient dependence.[54,55] Variations in tumor location (colon *vs.* rectum), vascular density, stromal composition, and interstitial fluid pressure significantly influence NP accumulation. Rectal tumors often display dense fibrotic stroma and poor vascularization, reducing NPs penetration compared with more vascularized colon tumors. Moreover, vascular permeability and blood flow in human tumors are considerably lower than in murine models, where the rapid growth and immature vasculature of xenografts exaggerate EPR effects.[54,55] Even when extravasation occurs, distribution is hindered by stromal barriers such as activated fibroblasts and rigid extracellular matrix (ECM) components.

Table 2 Types of nanocarriers used in treatment of CRC along with their features and limitations

Nanocarrier	Types	Material	Features	Limitations	Ref.
Polymer-based NPs	Micelles, polymeric micelles, polymersomes, dendrimers, polymeric NPs	Natural and synthetic polymers	High drug loading capacity, biodegradability, easy to synthesize, and cost effective	Potential toxicity of polymer additives, limited stability, variability in batch quality	41 and 42
Lipid-based NPs	SLNs, liposomes, lipidic emulsion, NLCs	Phospholipids	Biodegradable, biocompatible, safer than polymeric and inorganic NPs, suitable for hydrophilic/lipophilic drugs and nucleic acids	Possibility of leakage for hydrophilic drugs, short half-life, high cost of production	43–46
		Triglyceride	Reduce toxicity of encapsulated drugs		
		Cholesterol Surfactants			
Metal and inorganic NPs	Metal NPs	Gold, zinc, silver, silica, quantum dot	Unique optical and magnetic properties, ability to deliver drugs and imaging agents	Potential toxicity, difficulties in scaling production, biocompatibility concerns	47 and 48
	Silica NPs				
Biological or biomimetic nanocarriers	Exosomes, albumin-coated NPs, red blood cells membrane camouflaged NPs	Natural biomolecules	Excellent biocompatibility, targeting capabilities, ability to cross biological barriers	Limited control over drug loading, purification challenges, potential immunogenicity	49

Nanoparticle physicochemical design also dictates passive accumulation. Parameters including size, charge, hydrophilicity, and morphology modulate systemic circulation and tumor penetration.[50–55] For example, rod-shaped NPs may marginate more effectively along endothelium, and near-neutral zeta potentials can reduce mononuclear phagocyte system (MPS) clearance, prolonging circulation. Nonetheless, these advantages are frequently offset by nonspecific uptake in the liver and spleen, as well as interpatient variability in TMEs.

To address these limitations, emerging strategies focus on transiently enhancing or normalizing tumor vasculature. Pharmacological priming with vascular disrupting agents (*e.g.*, combretastatin A4), anti-VEGF therapies (*e.g.*, bevacizumab), and physical interventions such as hyperthermia or ultrasound are under evaluation for augmenting EPR in human tumors. Complementarily, advanced imaging tools—PET, MRI, and intravital microscopy—enable real-time monitoring of NP distribution and quantification of EPR heterogeneity, potentially guiding patient stratification for EPR-based therapies. This approach aligns with the broader paradigm of personalized oncology.

In summary, while the EPR effect provides a foundational rationale for passive targeting, its variable and often modest expression in CRC underscores the need for hybrid approaches. Incorporating active targeting ligands (*e.g.*, anti-EGFR, anti-CD44, integrin-binding peptides), stimuli-responsive release systems, and companion diagnostics may help overcome EPR variability, enabling more consistent and effective nanotherapy across heterogeneous patient populations.

3.1.1. Polymeric nanocarriers (PNPs). PNPs are versatile colloidal systems engineered to achieve controlled and site-specific delivery of therapeutic agents, either by encapsulating drugs within their polymeric matrix or through surface conjugation.[56,57] Their tunable structural properties—including size, surface chemistry, and porosity—allow for high drug-loading efficiency, improved solubility of poorly water-soluble compounds, and sustained release kinetics.[58] Importantly, the shift from early non-biodegradable polymers to biodegradable and biocompatible options such as polylactic acid (PLA), chitosan, poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV), and albumin has greatly enhanced their translational potential by minimizing long-term toxicity concerns.[59]

Within this landscape, chitosan-based nanoparticles have been widely investigated due to their mucoadhesiveness, cationic nature, and ability to promote electrostatic interactions with negatively charged cancer cell membranes. Ahmad *et al.* reported cisplatin- and 5-FU-loaded chitosan NPs with mean particle sizes of 127 nm and 83 nm, respectively, achieving high entrapment efficiencies (~73% and ~95%) and sustained release over 48 h. These formulations showed superior cytotoxicity against HCT-116 cells compared to free drugs, underscoring the benefit of controlled release.[60] Building on this, derivatives such as carboxymethyl chitosan (CMCS) have been employed to improve solubility and stability. Wang *et al.* developed CMCS nanoparticles co-loaded with oxaliplatin and resveratrol (215 nm, −27.9 mV), which demonstrated enhanced colloidal stability, synergistic cytotoxicity, and significant tumor suppression in xenograft-bearing mice.[61] These findings highlight how structural modifications not only optimize physicochemical performance but also enable synergistic drug combinations that are difficult to achieve with conventional formulations.

Another important platform is polymeric micelles, which self-assemble from amphiphilic block copolymers to solubilize hydrophobic drugs. A notable example is the development of camptothecin (CPT)-loaded micelles from PEG- and oleic acid-modified chitosan derivatives. These micelles (~160 nm, −23.4 mV) remained stable under gastrointestinal conditions, displayed strong mucoadhesion, and achieved sustained CPT release. *In vitro*, they enhanced cytotoxicity in HCT116, Caco-2, and HT29 cells, while *in vivo* oral administration suppressed tumor growth with reduced systemic toxicity compared to free CPT.[62] Such designs illustrate how polymeric nanocarriers can overcome oral bioavailability barriers, a major limitation for many hydrophobic chemotherapeutics.

The versatility of PNPs also allows for the simultaneous delivery of multiple therapeutic agents, a strategy particularly relevant in CRC where multidrug resistance and redundant signaling pathways limit monotherapies. Khaledi *et al.* designed PLGA–PEG–PLGA nanoparticles co-encapsulating 5-FU and chrysin (~170 nm, −19.7 mV), which produced synergistic cytotoxicity in HT29 cells and superior tumor suppression *in vivo* compared to single-drug formulations.[63] Similarly, Xiao *et al.* developed chitosan-coated PLGA NPs for dual delivery of CPT and curcumin (~140 nm, +28 mV), achieving sequential release (CPT > CUR), long-term colloidal stability, and approximately 75% tumor suppression in xenograft models without systemic toxicity.[64] The positive surface charge in this design facilitated electrostatic binding to CRC cell membranes, enhancing internalization and apoptosis induction. Such co-delivery strategies underscore how careful tuning of release kinetics and surface charge can be leveraged to maximize therapeutic synergy while reducing adverse effects.

Other innovative systems include poly(ε-caprolactone) (PCL)-based NPs, which provide sustained drug release but suffer from limited hydrophilicity.[65] To overcome this, Ahmad *et al.* engineered aminocellulose-grafted PCL NPs (~165 nm, +25 mV) that selectively targeted CHEK2-deficient CRC cells. These nanocarriers demonstrated enhanced uptake, apoptosis induction, and ROS generation *in vitro*, while *in vivo* they significantly reduced tumor volume with minimal systemic toxicity.[66] This work highlights the potential of tailoring nanocarriers to genetic vulnerabilities in CRC, although broad applicability will depend on integrating such approaches within precision oncology frameworks supported by robust molecular diagnostics.[67]

Dendrimers represent another promising class of polymeric nanocarriers due to their highly branched architecture, monodispersity, and multivalent surface groups that permit extensive functionalization.[68,69] For instance, England *et al.* developed polyoxazoline (POx)-modified PAMAM dendrimers conju-

gated with SN-38 (~20–25 nm, near-neutral charge), which provided sustained release, potent cytotoxicity, and superior *in vivo* efficacy compared to free SN-38.[69] In SW620 xenograft mice, DEND-38 induced dose-dependent tumor regression, with some animals showing complete tumor disappearance (Fig. 3A and B). Frequent dosing (q7d) at 4–8 mg kg^{-1} achieved greater tumor suppression than less frequent regimens (q14d) (Fig. 3C). Unlike irinotecan, which caused body weight loss, DEND-38 maintained stable body weights across groups (Fig. 3D), confirming its enhanced efficacy and reduced gastrointestinal toxicity (Fig. 3).[69] PEGylated dendrimers have also been used to overcome cytotoxicity associated with cationic amine groups.[70,71] For example, PEGylated G4 PAMAM dendrimers loaded with piperlongumine (190 nm, −0.2 mV) showed enhanced tumor accumulation, improved solubility, and significantly higher anticancer activity in HCT-116 cells than the free drug.[72] These findings underscore the ability of dendrimers to balance drug-loading capacity with improved safety profiles through surface modifications, although challenges related to scalable synthesis and regulatory acceptance remain.

Taken together, polymer-based nanocarriers present a highly adaptable platform for CRC therapy, enabling oral delivery of poorly soluble drugs, co-delivery of synergistic agents, and even molecular subtype-specific targeting. Quantitative data from preclinical studies consistently demonstrate improvements in drug stability, sustained release, apoptosis induction, and tumor suppression. Yet, despite this promise, barriers to clinical translation remain substantial. Manufacturing reproducibility, long-term stability, and regulatory hurdles continue to limit widespread adoption. Moving forward, integrating polymeric nanocarriers with stimuli-responsive designs, hybrid polymer–lipid platforms, and patient-stratified treatment strategies may accelerate their translation into precision oncology. Ultimately, their structural versatility and capacity for multifunctional engineering make PNPs indispensable candidates for next-generation nanomedicine in CRC.

3.1.2. Lipid-based nanocarriers. Lipid-based nanocarriers —including liposomes, SLNs, nanostructured lipid carriers (NLCs), and lipid–polymer hybrids—have emerged as highly versatile systems for CRC therapy due to their biocompatibility, high drug-loading capacity, and ability to encapsulate both hydrophilic and hydrophobic agents.[36] These carriers improve pharmacokinetics, protect drugs from premature degradation,

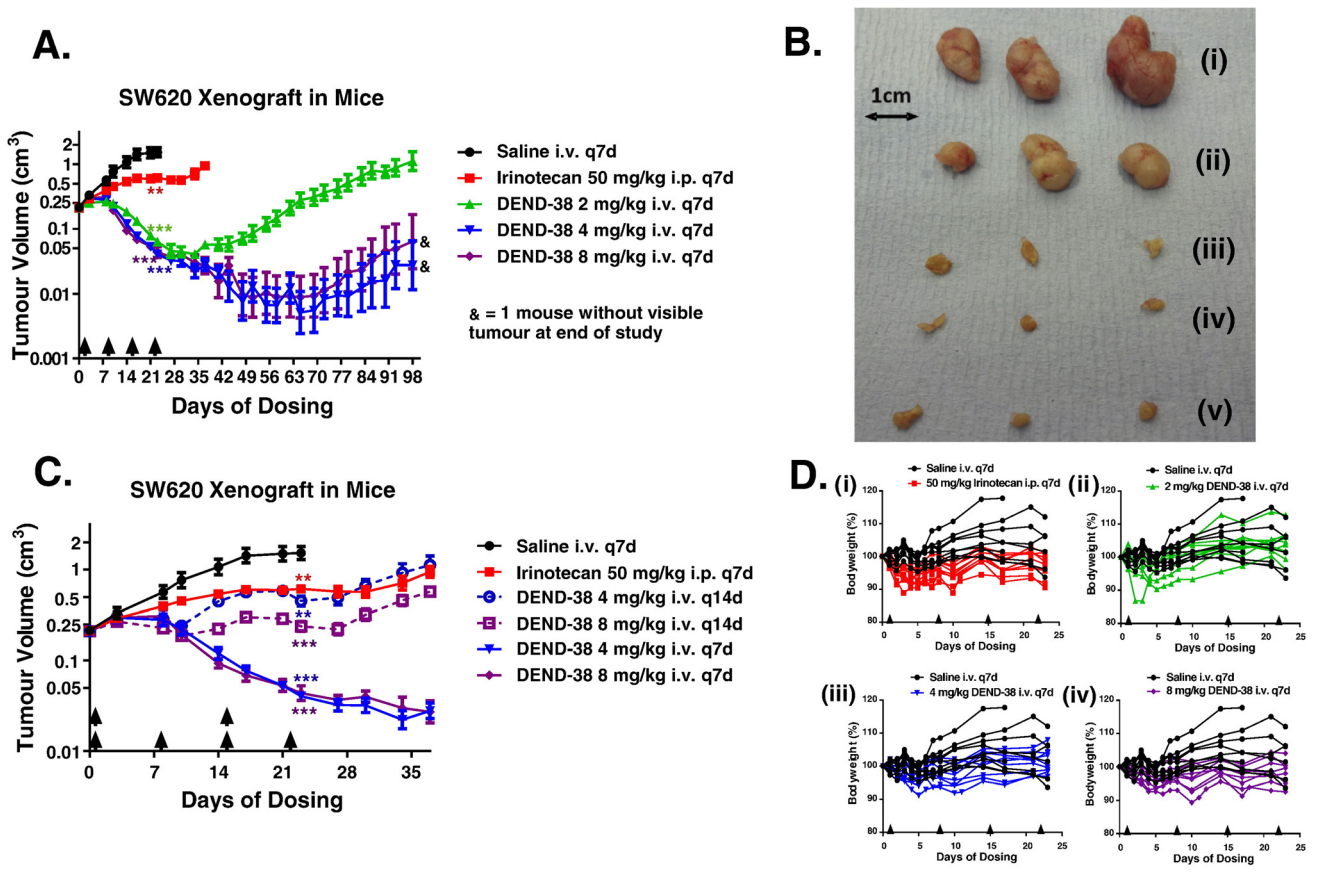

Fig. 3 (A) Dose-dependent antitumor efficacy of DEND-38 and tumor regrowth over a 72-day post-treatment period. (B) Representative tumor images 24 h after final treatment: (i) saline, (ii) irinotecan i.p., (iii–v) DEND-38 at 2, 4, and 8 mg kg^{-1}. (C) Comparison of weekly *vs.* fortnightly DEND-38 dosing (4 and 8 mg kg^{-1}). (D) Bodyweight profiles during treatment. $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* saline (day 23); & = mouse without visible tumor at study end.[69] Adopted with permission from Elsevier B.V. (Copyright © 2017).

and enable tumor-selective delivery through either passive accumulation or ligand-mediated active targeting.

Liposomes, the most extensively studied lipid-based system, are spherical vesicles composed of amphiphilic phospholipid bilayers surrounding an aqueous core. Their bilayers, which may include neutral (lecithin, cholesterol), cationic (DOTMA, DOTAP), or anionic (DPPG, DPPC) lipids, mimic natural membranes and thus confer excellent biocompatibility, biodegradability, and low immunogenicity.[73] Their self-assembly in aqueous media allows dual encapsulation: hydrophilic drugs within the aqueous core and hydrophobic drugs within the lipid bilayer. Importantly, physicochemical parameters such as particle size, zeta potential, and drug-to-lipid ratios determine stability, encapsulation efficiency, and therapeutic performance. For instance, Matbou Riahi *et al.* formulated liposomal celecoxib using thin-film hydration followed by extrusion, producing vesicles of 125 nm with a zeta potential of −23 mV, ~80% encapsulation efficiency, and spherical morphology. These liposomes displayed sustained release, inhibited tumor growth, and reduced inflammatory markers in CRC models, outperforming free celecoxib.[74]

Beyond single-drug delivery, liposomes have been adapted for co-delivery of multiple agents to combat multidrug resistance and exploit synergistic effects. Zhang *et al.* designed PEGylated liposomes encapsulating both oxaliplatin and irinotecan, prepared with hydrogenated soy phosphatidylcholine, cholesterol, and DSPE-PEG2000.[75] The vesicles (~194 nm, −3.0 mV) exhibited high dual-drug loading, spherical morphology, and strong stability. *In vitro*, they produced significantly greater cytotoxicity in CT-26 and HCT-116 cells than either free drug or their physical mixture, while *in vivo* they achieved pronounced tumor suppression with reduced systemic toxicity. Near-infrared imaging confirmed efficient tumor accumulation and prolonged retention, emphasizing the EPR-mediated targeting advantage of PEGylated liposomes (Fig. 4).[75]

PEGylation has also been used to improve circulation time and stability. Najlah *et al.* prepared PEGylated liposomes of disulfiram (DSF) *via* thin-film hydration, yielding ~145 nm vesicles with a zeta potential of −12 mV.[76] Compared to free DSF, the liposomal system exhibited enhanced cytotoxicity against HCT-116 cells, superior pharmacokinetic profiles, and stronger tumor growth inhibition in xenograft models.[76,77] Similarly, chitosan-coated flexible liposomes (C-FLs) have been developed to improve oral bioavailability and mucosal adhesion. Alshraim *et al.* prepared docetaxel-loaded C-FLs (~164 nm, +31 mV), which demonstrated improved colloidal stability, significantly enhanced cytotoxicity against HT-29 cells, and prolonged systemic circulation in rats, highlighting their promise as an oral nanocarrier for CRC therapy.[78]

SLNs represent a second generation of lipid-based carriers composed of solid lipids stabilized by surfactants, offering high payload, good stability, and controlled release.[79] PEGylated SLNs further minimize MPS clearance and prolong circulation.[80] Smith *et al.* encapsulated 5-FU into SLNs (~167 nm, −31 mV) using hot homogenization–ultrasonication. These NPs showed controlled release, enhanced cytotoxicity in HCT-116 cells, and significant tumor suppression with reduced systemic toxicity in CRC mouse models, compared to free 5-FU.[81] NLCs, which combine solid and liquid lipids, have been introduced to overcome the limited drug loading of SLNs by preventing crystallization and reducing drug expulsion during storage.[82] However, challenges remain for hydrophilic drug loading, where double emulsification or lipid–drug conjugates (LDCs) are needed, though solvent toxicity must be carefully controlled.

Overall, lipid-based nanocarriers are adaptable to diverse administration routes—including oral, injectable, pulmonary, ocular, and nasal delivery—making them clinically attractive.[83] Nevertheless, rapid clearance, stability issues, and limited targeting specificity remain obstacles. Future innovations in lipid nanotechnology—such as incorporation of active targeting ligands, integration of pH- or temperature-sensitive lipids, and design of multifunctional hybrid carriers—will be essential to overcome these barriers. Such refinements hold the potential to translate lipid-based carriers into precision nanomedicine platforms for CRC treatment.

3.1.3. Inorganic nanocarriers. Inorganic NPs, encompassing metallic, metal oxide, and ceramic-based materials such as mesoporous silica, alumina, titania, silver, and gold, represent a versatile and promising class of nanocarriers for CRC diagnosis and therapy. Their unique physicochemical features—including nanoscale dimensions, large surface area-to-volume ratios, tunable surface charge, and intrinsic optical or magnetic responsiveness—facilitate preferential tumor accumulation *via* the EPR effect, enhancing delivery efficiency and therapeutic outcomes.

Beyond structural advantages, several inorganic NPs exhibit intrinsic bioactivity. Silver nanoparticles (AgNPs), for instance, not only possess broad-spectrum antibacterial activity useful in CRC complicated by dysbiosis, but also exert direct anticancer effects by generating reactive oxygen species (ROS), inducing oxidative stress, disrupting mitochondrial function, and promoting apoptosis.[84,85] Gold nanoparticles (AuNPs) are equally attractive; Meena *et al.* engineered PEGylated AuNPs co-loaded with DOX and kaempferol. These spherical particles (~97 nm, −11 mV) showed efficient encapsulation, enhanced cellular uptake, and synergistic cytotoxicity against HCT-116 CRC cells, reflecting the advantages of dual-drug delivery.[84]

The synthesis approach strongly influences the safety and performance of inorganic NPs. While chemical reduction is widely applied, it often involves toxic solvents and harsh conditions. Green synthesis offers a sustainable alternative. Vairavel *et al.* produced stable spherical AuNPs (50–80 nm, negative charge) using *Enterococcus* sp. supernatant, which induced dose-dependent cytotoxicity in HT-29 cells through mitochondrial membrane disruption and apoptosis. Such biosynthesized NPs reduce toxicity risks while maintaining anticancer efficacy.[86]

Surface functionalization further enhances therapeutic outcomes. Alavi *et al.* developed polymeric core–shell ZnO nanoparticles doped with gadolinium (ZnO-Gd@PEGMA/OXA),

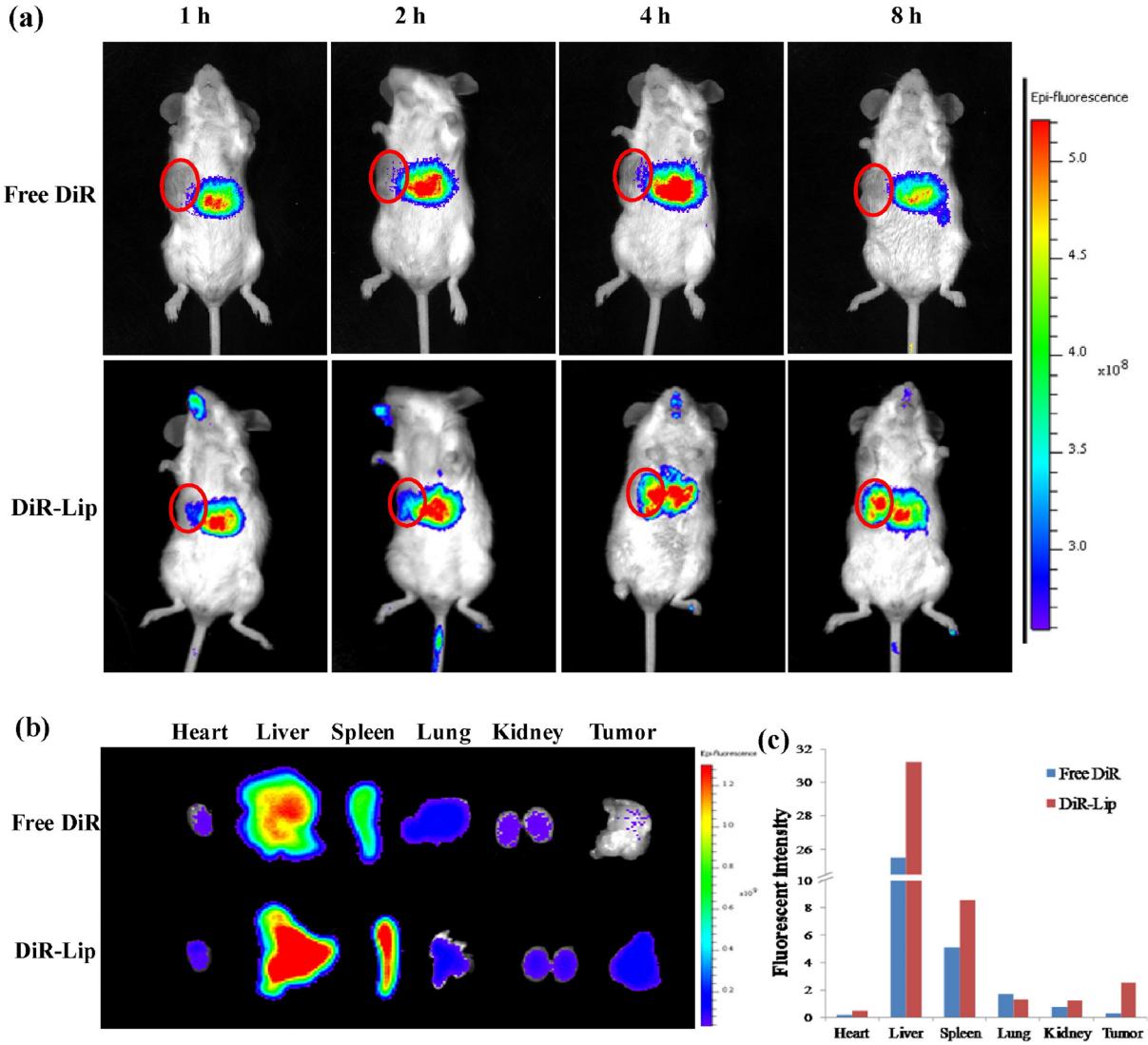

Fig. 4 Real-time NIRF imaging of CT-26 tumor-bearing mice following i.v. administration of free DiR and DiR-labeled liposomes. (a) *In vivo* fluorescence at various time points (tumors circled in red), (b) *ex vivo* organ imaging at 8 h post-injection, and (c) quantification of relative fluorescence intensity in excised organs.[75] Adopted with permission from Elsevier B.V. (Copyright © 2016).

improving oxaliplatin delivery.[87] The developed NPs (~100 nm, −9 mV) demonstrated potent *in vitro* cytotoxicity (IC_{50} = 1.9 ppm, CT-26 cells) mediated by ROS generation, while *in vivo* they significantly reduced tumor volume, increased necrosis, and lowered collagen deposition, suggesting dual anticancer and antifibrotic benefits.

Mesoporous silica nanoparticles (MSNs) are among the most studied inorganic carriers due to their high surface area, adjustable pore sizes, and chemical inertness, enabling efficient loading and controlled release of diverse therapeutics. Summerlin *et al.* synthesized colloidal MSNs (~100 nm, spherical) *via* sol–gel methods, successfully encapsulating resveratrol and achieving sustained release with superior cytotoxicity against HT-29 cells compared to free drug.[88] The evolution of MSNs has yielded advanced hybrid platforms such as silicasomes, which integrate a mesoporous silica core with a stabilizing lipid bilayer (DSPC/cholesterol/DSPE-PEG2000). Irinotecan-loaded silicasomes (~110 nm) achieved prolonged circulation ($t_{\frac{1}{2}} \approx 9.6$ h), markedly enhanced tumor accumulation (55–63 fold *vs.* free drug), and reduced systemic toxicity in orthotopic CRC models. Compared with both free irinotecan and Onivyde, silicasomes produced significantly greater tumor inhibition with lower bone marrow suppression and GI toxicity, highlighting their translational promise (Fig. 5).[89]

Other inorganic systems—including iron oxide, gold, and silver NPs—have been widely investigated as multifunctional theranostic platforms. They can be loaded with chemotherapeutics such as cisplatin, DOX, or 5-FU, while additional functionalization with pH-sensitive coatings, PEGylation, or targeting ligands further improves tumor selectivity and minimizes systemic side effects.

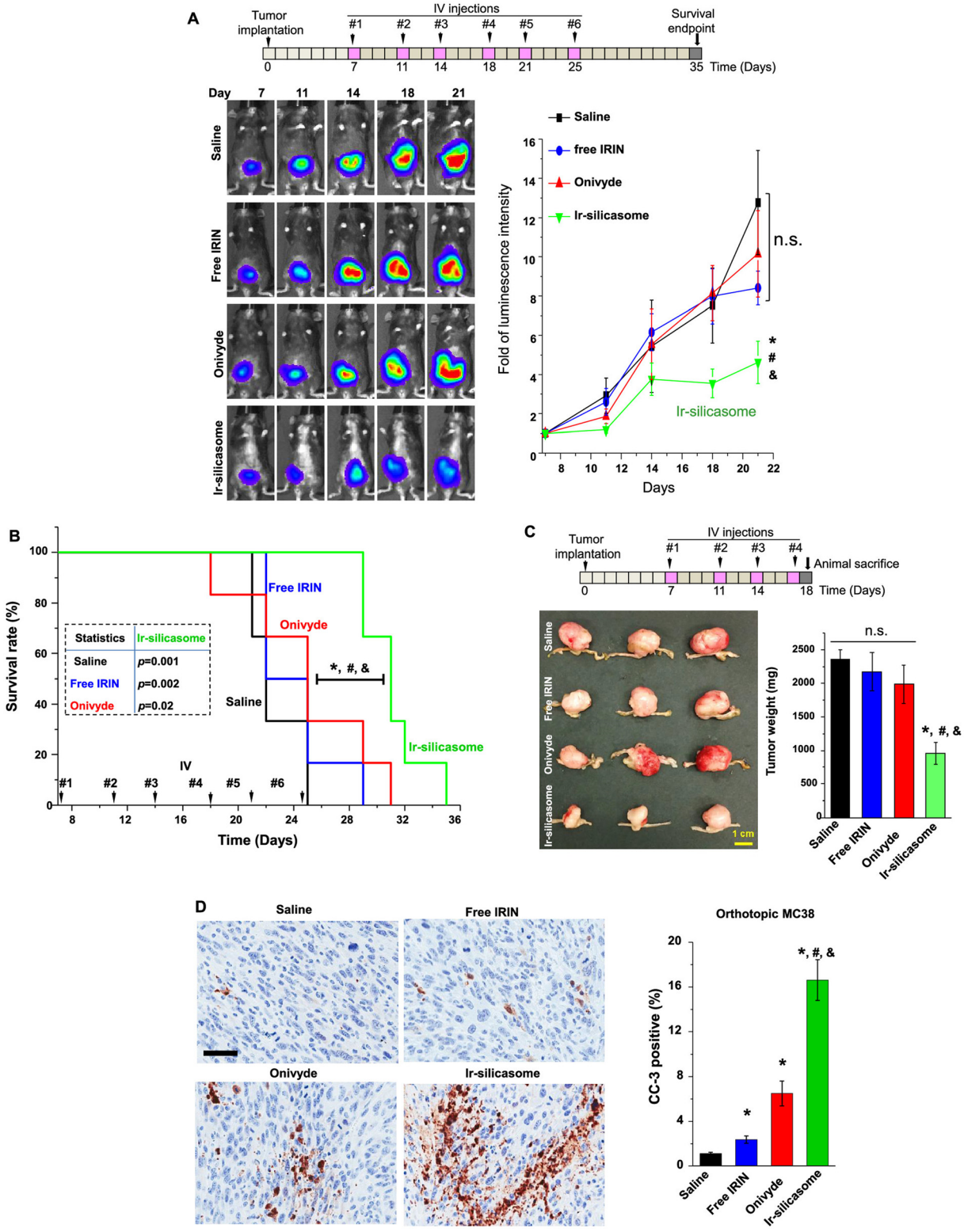

Fig. 5 Comparative efficacy of Ir-silicasome in an orthotopic MC38 CRC model. (A) Tumor progression monitored *via* IVIS imaging in mice treated with saline, free irinotecan, Onivyde, or Ir-silicasome (40 mg kg^{-1}, twice weekly, n = 6). (B) Kaplan–Meier survival analysis showing significant survival benefit for Ir-silicasome-treated mice (*p < 0.05). (C) Tumor weights measured at day 18 post-treatment (n = 3). (D) IHC analysis and quantification of cleaved caspase-3 expression in tumors, indicating apoptosis. Data expressed as mean ± SEM; *p < 0.05 *vs.* saline; #p < 0.05 *vs.* free IRIN; &p < 0.05 *vs.* Onivyde; "n.s." = not significant.[89] Adopted with permission from American Chemical Society (Copyright © 2019).

Overall, inorganic nanocarriers provide a multifaceted strategy for CRC management by combining drug delivery with diagnostic and intrinsic therapeutic functions. Advances in green synthesis, biocompatible surface coatings, and hybrid constructs such as silicasomes have substantially broadened their translational potential. Continued research is needed to optimize safety, scalability, and regulatory pathways, but their capacity to unite site-specific delivery with inherent anticancer and antibacterial properties positions inorganic NPs as powerful candidates for future precision nanomedicine in CRC.

3.1.4. Biological or biomimetic nanocarriers. Biological or biomimetic NPs—engineered from naturally derived materials such as proteins, lipoproteins, and cell membranes—have emerged as innovative nanoplatforms for CRC therapy. Their intrinsic biocompatibility, immune evasion capacity, and ability to exploit endogenous pathways for tumor targeting make them attractive alternatives to fully synthetic carriers. Among them, albumin-based NPs are particularly well studied owing to their excellent aqueous solubility, drug-binding affinity, cost-effectiveness, and safe metabolic degradation into non-toxic byproducts.[90] Human serum albumin (HSA) further offers passive tumor selectivity, as cancer cells overexpress albumin-binding proteins and exploit albumin as a nutrient source, in addition to benefiting from the EPR effect.[91]

Building on these attributes, Aljabali *et al.* formulated piceatannol (PIC)-loaded bovine serum albumin (BSA) NPs *via* desolvation, producing spherical particles (~150 nm, negative zeta potential). Compared to free PIC, these nanocarriers more effectively downregulated NF-κB (p65) and HIF-1α in CaCo-2 and HT-29 cells, inhibiting proliferation, migration, invasion, and colony formation. *In vivo*, PIC–BSA NPs reduced tumor burden and suppressed inflammation in a colitis-associated CRC model, demonstrating the dual anti-inflammatory and anticancer benefits of albumin encapsulation.[92] In a complementary approach, cetuximab (CET)-loaded egg albumin nanoparticles (CET-ANPs) were synthesized by a modified desolvation technique. These spherical particles (~170 nm, −20 mV) displayed enhanced cytotoxicity in Caco-2 cells compared to free CET, lowering IC_{50} values and inducing apoptosis, S/G_2-M phase arrest, and modulation of apoptotic proteins (upregulation of Bax and caspase-3, downregulation of Bcl-2). Such results highlight the potential of albumin nanocarriers to improve both solubility and efficacy of conventional and biological drugs.[93]

Expanding into biomimetic platforms, red blood cell (RBC) membrane-coated NPs have shown remarkable ability to evade immune clearance and prolong systemic circulation—advantages over PEGylation, which may induce accelerated blood clearance (ABC) upon repeated dosing.[94] These formulations, fabricated *via* core–shell extrusion, typically display uniform morphology (90–120 nm) and near-neutral zeta potentials, contributing to stability and stealth properties. Zhang *et al.* further demonstrated RBC membrane-coated PLGA NPs encapsulating gambogic acid (GA), which exhibited a size of ~130 nm and zeta potential of −2.1 mV. *In vitro*, they enhanced GA uptake and apoptosis in SW480 CRC cells, while *in vivo* they significantly prolonged circulation and suppressed tumor growth, confirming their potential for immune-evasive CRC therapy.[95]

Together, these findings emphasize the role of passive targeting as the foundation for biomimetic nanocarrier design. The EPR effect—mediated by tumor vasculature leakiness, poor lymphatic drainage, and heightened nutrient demand—facilitates preferential tumor accumulation. Strategies to exploit and refine this include PEGylation for extended circulation, modulation of surface charge to optimize uptake, and albumin- or membrane-coating to mimic endogenous trafficking pathways (Table 3).

However, passive targeting alone is insufficient, as tumor accumulation remains inconsistent, often subtherapeutic, and prone to off-target biodistribution. NPs size is a critical determinant: particles <10 nm are rapidly cleared renally, while those >100 nm are sequestered by the mononuclear phagocyte system (MPS) in the liver and spleen. The optimal range of 10–100 nm can still be undermined by interpatient heterogeneity in CRC vasculature and stromal barriers.[96–99] These limitations underscore the need for smarter delivery strategies. Stimuli-responsive and actively targeted biomimetic nanocarriers—engineered to release payloads in response to pH, enzyme activity, or redox gradients, or equipped with targeting ligands—are increasingly viewed as essential to achieve therapeutic precision. Nonetheless, passive targeting remains clinically relevant, especially for biomimetic and protein-based systems, where inherent EPR compatibility and prolonged circulation can be synergistically combined with advanced active or stimuli-responsive features.[100]

3.2. Active targeting: ligand-guided nanocarriers

Active targeting represents a major advancement in nanotherapeutic strategies for CRC, offering solutions to the inherent limitations of passive delivery. While passive targeting relies exclusively on the EPR effect, active targeting employs surface functionalization of NPs with ligands—often termed biovectors—that selectively recognize and bind to receptors overexpressed on CRC cells.[105] These ligands may be natural or synthetic, including monoclonal antibodies, peptides, aptamers, and carbohydrates. Upon binding, the NP–ligand complex is internalized *via* receptor-mediated endocytosis, typically through clathrin- or caveolae-dependent pathways depending on receptor type and cellular context.[31,39,52,106] This mechanism significantly enhances tumor-specific uptake and has been shown to increase NP accumulation in tumors by up to threefold compared with passive EPR-based strategies, thereby improving therapeutic efficacy and reducing systemic toxicity.[39,52,107]

In addition to enhancing tumor selectivity, active targeting also protects vulnerable therapeutic payloads. The conjugation of labile agents such as peptides or small molecules onto nanocarriers shields them from enzymatic degradation, improving drug stability and bioavailability during circulation.[108,109] The efficiency of such approaches, however, depends not only on the ligand itself but also on binding

Table 3 Summary of various nanocarriers used for passive targeting in CRC nanotherapy

Category	Type of nanocarrier	Polymer/composition	Anticancer agent(s)	Study models	Major findings	Ref.
Polymer-based	PNPs	Chitosan	Cisplatin & 5-FU	*In vitro*: HCT-116 cells	Biphasic release with initial burst release, followed by sustained release Significant increase in cytotoxicity against HCT-116 cells	60
	PNPs	*N*,*O*-Carboxymethyl chitosan (CMCS)	Co-loading of oxaliplatin + resveratrol	*In vitro*: SW480 and CT26 cells *In vivo*: tumor bearing mice	Nanoscaled dimension with smooth spherical morphology and sustained release Stronger anticancer activity *in vitro* and *in vivo* compared to free drug	61
	Core–shell PNPs	Shell: aminocellulose	LCS-1 (a SOD1 inhibitor)	*In vitro*: HCT116 cells	Blank NPs maintained 96–98% cell viability. Drug-loaded NPs displayed a 240-fold increase in selectivity and sustained release effect (90%) over 72hrs	66
	PNPs	Core: PCL PLGA-PEG-PLGA	5-FU + Chrysin	*In vitro*: HT29 cells	5-FU@Chrysin loaded NP with CI of 0.35 showed significant inhibitory growth effect compared to NPs loaded with single drug	63
	Core–shell polymeric micelles	Amphiphilic chitosan modified with PEG and oleic acid	Camptothecin (CPT)	*In vitro*: HCT116, Caco-2 and HT29 CRC cell lines *In vivo*: HCT116 xenograft mice model	Drug-loaded micelles decreased tumor development and progression after oral administration	62
	Dendrimer	PEGylated G4 PAMAM	Piperlongumine (PL)	*In vitro*: HCT-116 cells	PL@PEGylated G4 showed a sustained release after 24 h, good biocompatibility and greater induction of apoptosis compared to pure PL	72
Lipid-based	Liposomes	DSPC	5-FU + apigenin	*In vitro*: HCT-15 and HT-29 cells *In vivo*: athymic nude mice	Drugs combination exerted a synergistic effect (CI < 1) and tumor regression	101
	Lipid emulsion	Egg phosphatidylcholine & Pluronic F68	Oxaliplatin + irinotecan	*In vitro*: CT-26 and HCT-116 cells *In vivo*: BALB/c mice	Using a ratio of 1 : 1.5 of OXA/IRI, and with size of 126.9 nm and −21.1 mV surface charge, OXA showed biphasic release whereas IRI showed sustained release Co-loaded LEs showed lowest IC_{50} and highest antitumor activity *in vivo*	102
Inorganic	Zn oxide	PEGMA	Oxaliplatin	*In vitro*: CT-26 cells *In vivo*: BALB/c mice	ZnO-Gd-OXA inhibited tumor growth by inducing reactive oxygen species and inhibiting fibrosis	103
	MSN	MCM-48	Resveratrol	*In vitro*: HT-29, LS174T and RAW246 cells	Increasing solubility of Resveratrol from 54 to 106 μg mL^{-1} and faster release Greater cytotoxicity and apoptotic activity Anti-inflammatory effect with MCM-48-RES *via* inhibiting NF-κB activation	88
Biological/ biomimetic	Human serum albumin	Human serum albumin	Piperlongumine	*In vitro*: HCT-116 cells	PLNP showed an average particle size of 105 nm, a sustained drug release profile and higher anti-cancer efficacy and stability over 3 months	104
	RBCs	RBCs coated PLGA NPs	Gambogic acid (GA)	*In vitro*: SW480 cells *In vivo*: tumor bearing BALB/c mice	RBCm-GA/PLGA NPs with size of 163 nm showed sustained release, efficiently taken up by tumor cells, significantly inhibited tumor growth and prolonged survival	95

Abbreviations: 5-FU, 5-fluorouracil; CI, combination index; CMCS, *N*,*O*-carboxymethyl chitosan; CPT, camptothecin; CRC, colorectal cancer; DSPC, 1,2-distearoyl-*sn*-*glycero*-3-phosphocholine; EPR, enhanced permeability and retention; GA, gambogic acid; HSA, human serum albumin; IC_{50}, half maximal inhibitory concentration; IRI, irinotecan; LE, lipid emulsion; MSN, mesoporous silica nanoparticle; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NP, nanoparticle; OXA, oxaliplatin; PAMAM, poly(amidoamine); PCL, poly(ε-caprolactone); PEG, polyethylene glycol; PEGMA, poly(ethylene glycol) methyl ether methacrylate; PL, piperlongumine; PLGA, poly(lactic-*co*-glycolic acid); PNIPAM, poly(*N*-isopropylacrylamide); PNP, polymeric nanoparticle; RBCm, red blood cell membrane; RES, resveratrol; SOD1, superoxide dismutase 1; ZnO, zinc oxide.

Table 4 Overview of key receptors overexpressed in CRC and their corresponding ligands for active targeting

Receptors	Ligands	Ref.
EpCAM	EpCAM antibodies, peptides	112
Folate receptors (FR)	Folate, folate conjugates	113
Epidermal growth factor receptor (EGFR)	Monoclonal antibodies (*e.g.*, cetuximab), peptides	114
CD44	CD44 antibodies, peptides	115
Transferrin receptor (TfR)	Transferrin, transferrin conjugates	116 and 117
Nucleolin	Nucleolin-binding peptides/aptamers	118
Mannose receptor	Mannose, mannose conjugates	119
Hyaluronic acid receptor (HA-CD44)	Hyaluronic acid, hyaluronic acid conjugates	120
αvβ3 integrin receptor	αvβ3 integrin antibodies, peptides, RGD	121
Placenta-specific protein 1 (PLAC-1)	Flu matrix p58–66 peptide	122

affinity, conjugation chemistry (covalent *vs.* non-covalent), and the molecular profile of the TME.[110] Commonly exploited receptors in CRC include epidermal growth factor receptor (EGFR), HER2, folate receptor, and CD44, which are frequently overexpressed in malignant tissues and therefore provide accessible molecular signatures for targeted drug delivery.

Equally important are the physicochemical characteristics of the nanocarrier. Particle size, surface charge, shape, and ligand density directly influence biodistribution, receptor binding, and intracellular trafficking.[111] Nanoparticles within the 10–100 nm size range generally achieve the best compromise between tumor penetration and systemic circulation, while PEGylation remains a standard modification to reduce immunogenic clearance and prolong circulation time. The optimization of ligand density is particularly crucial; insufficient density may limit binding efficiency, whereas excessive ligand loading can induce steric hindrance or immunogenicity.

As summarized in Table 4, a diverse range of receptor–ligand combinations has been explored for CRC, underscoring the adaptability of active targeting strategies in addressing tumor heterogeneity. Collectively, these approaches represent a pivotal step toward precision nanomedicine, where the integration of tumor-specific biomarkers with engineered nanocarriers enables more efficient drug delivery, improved therapeutic indices, and reduced systemic side effects. Active targeting thus stands as a promising paradigm for advancing CRC therapy beyond the constraints of conventional delivery systems.

3.2.1. Polymeric nanocarriers. Active targeting with polymeric nanocarriers (PNPs) is typically achieved through the covalent conjugation of targeting ligands to the nanoparticle surface. Chemical coupling techniques such as carbodiimide-mediated reactions (EDC/NHS chemistry), click chemistry, and other advanced bioconjugation strategies are commonly used to achieve stable and selective ligand attachment. Among these, EDC/NHS chemistry remains the most widely applied, forming robust amide bonds between carboxyl and amino groups. Such functionalization not only enhances delivery specificity but also improves receptor-mediated uptake and therapeutic efficacy in CRC by enabling NPs to selectively recognize overexpressed receptors on tumor cells.

One of the most prominent targets in CRC is the epidermal growth factor receptor (EGFR), which is overexpressed in nearly 97% of cases.[123] In a notable study, 5-FU was encapsulated within PLGA–PEG NPs synthesized by ring-opening polymerization and surface-functionalized with anti-EGFR monoclonal antibodies.[114] PLGA was selected for its sustained release properties, while PEG conferred "stealth" behavior to reduce opsonization and clearance by the mononuclear phagocyte system (MPS). The resulting anti-EGFR-5-FU-PLGA-PEG NPs exhibited biphasic drug release, efficient receptor-mediated internalization, and potent cytotoxicity against EGFR-positive HCT116 cells (IC_{50} = 1.01 μg mL^{-1} at 48 h), outperforming both free 5-FU and non-targeted formulations.[114]

Lectin-mediated targeting has also shown promise. PLGA nanoparticles conjugated with wheat germ agglutinin (WGA)—a lectin that binds *N*-acetylglucosamine and sialic acid residues overexpressed on colon cancer cells—demonstrated enhanced endocytosis through both clathrin- and caveolae-dependent pathways.[124] Conjugation was achieved *via* EDC/NHS-mediated amide bond formation, yielding WGA-functionalized nanoparticles (WFUNP3) with superior sustained release and significantly greater anticancer activity in HT-29 and COLO-205 cells compared to free drug and non-functionalized NPs.[124]

Dendrimers, particularly poly(amidoamine) (PAMAM), represent another versatile polymeric platform for active targeting. PEGylation improves their solubility, systemic stability, and biocompatibility, while ligand conjugation enables tumor-specific recognition. Ge *et al.*[112] developed EpCAM-targeted PEGylated G4 PAMAM dendrimers for the delivery of celastrol, a hydrophobic anticancer agent. Using click chemistry, they achieved stable ligand attachment, producing ~50 nm NPs with near-neutral surface charge. *In vitro*, the targeted dendrimers enhanced uptake and induced apoptosis in SW620 CRC cells, while *in vivo* studies revealed significant tumor suppression, improved survival, and negligible systemic toxicity (Fig. 6), validating the therapeutic potential of ligand-engineered dendrimers for CRC.[112]

Polymersomes, formed through self-assembly of amphiphilic block copolymers, provide highly stable vesicular nanostructures capable of encapsulating both hydrophilic and hydrophobic therapeutics. Transferrin receptors (TfR1), upregulated in CRC due to elevated iron demand, have been lever-

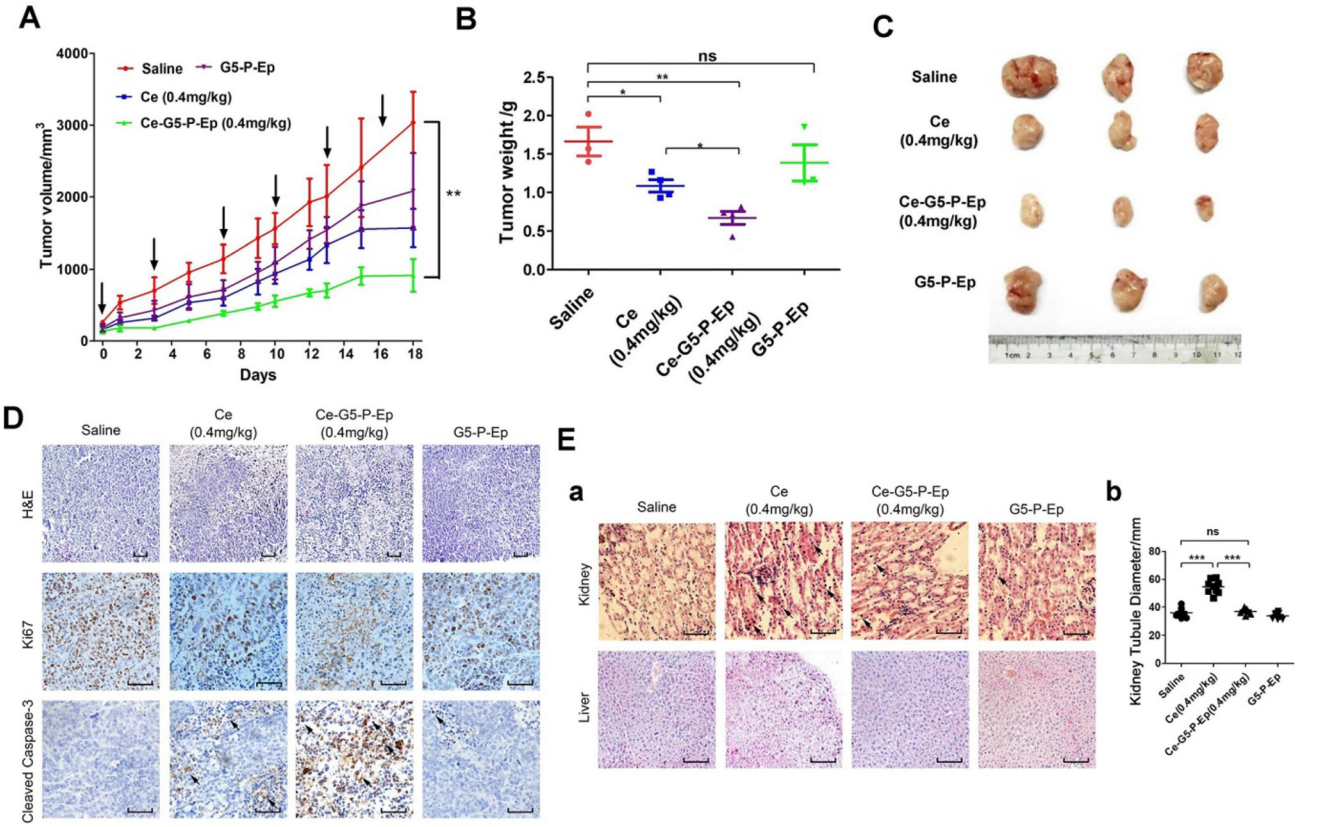

Fig. 6 *In vivo* antitumor efficacy of low-dose celastrol (0.4 mg kg^{-1}) delivered *via* multifunctional dendrimers in a SW620 xenograft mouse model. Treatment with Ce-G5-P-Ep significantly reduced tumor volume (A), weight (B), and size (C) compared to saline, free celastrol (Ce), and G5-P-Ep groups. Only three tumors from the Ce-G5-P-Ep group were collected at the endpoint due to rupture. (D) H&E, Ki-67, and cleaved caspase-3 staining showed enhanced apoptosis and reduced proliferation in Ce-G5-P-Ep group. (E) H&E staining of liver and kidney tissues (a) and quantification of kidney tubule diameter (b) indicated minimal systemic toxicity. Scale bar: 100 μm.[112] Adopted with permission from Elsevier B.V. (Copyright © 2019).

aged for targeted delivery. Wei *et al.* engineered transferrin-binding peptide (TBP)-functionalized polymersomes for DOX delivery.[116] Synthesized from maleimide-functionalized PEG-P (TMC-DTC) copolymers, TBP was covalently linked *via* maleimide–thiol chemistry at an optimized ligand density of 17.5 mol%. The resulting TBP-Ps-Dox NPs (~120 nm, slightly negative zeta potential, >90% encapsulation efficiency) demonstrated a three-fold increase in uptake and 2.5-fold higher cytotoxicity in HCT116 cells compared with non-targeted controls. *In vivo*, they prolonged circulation, enhanced tumor accumulation, and markedly inhibited tumor growth with minimal systemic toxicity (Fig. 7), underscoring their translational promise.[116]

Folate receptor (FR-α), another well-validated CRC target, has been exploited using folic acid (FA)-conjugated PEG-PCL copolymer micelles for curcumin (CUR) delivery.[125] FA was covalently linked through DCC/DMAP-mediated amide bond formation. The resulting FA/Nano-CUR micelles (30.47 nm) demonstrated potent apoptosis induction (95.27% at 48 h) *in vitro* and robust tumor suppression (77.32% inhibition by day 18) *in vivo*, with no evidence of systemic toxicity.[125] These findings confirm the value of exploiting folate metabolism in cancer cells for precise and effective nanotherapy.

Taken together, these examples highlight the breadth of ligand-functionalized polymeric nanocarriers for CRC. By combining robust conjugation chemistry with receptor-specific ligands, active targeting systems achieve superior tumor uptake, enhanced cytotoxicity, and improved therapeutic indices compared with passive systems. Whether through antibody-, lectin-, peptide-, or folate-mediated recognition, polymeric nanocarriers provide a versatile and powerful platform for precision drug delivery in CRC.

3.2.2. Lipid-based nanocarriers. Lipid-based nanocarriers are widely used in passive targeting strategies owing to their inherent biocompatibility and capacity to encapsulate both hydrophilic and hydrophobic drugs. However, their therapeutic impact is limited by rapid clearance *via* the mononuclear phagocyte system (MPS) and insufficient tumor specificity. Surface PEGylation provides partial solutions by prolonging circulation and enhancing EPR-mediated accumulation, yet cellular uptake and tumor selectivity remain suboptimal. To overcome these barriers, active targeting approaches have been developed, involving the functionalization of liposomal or lipid-based surfaces with ligands that bind to receptors overexpressed on CRC cells.[126,127] Ligand conjugation can be achieved through covalent or non-covalent strategies, with

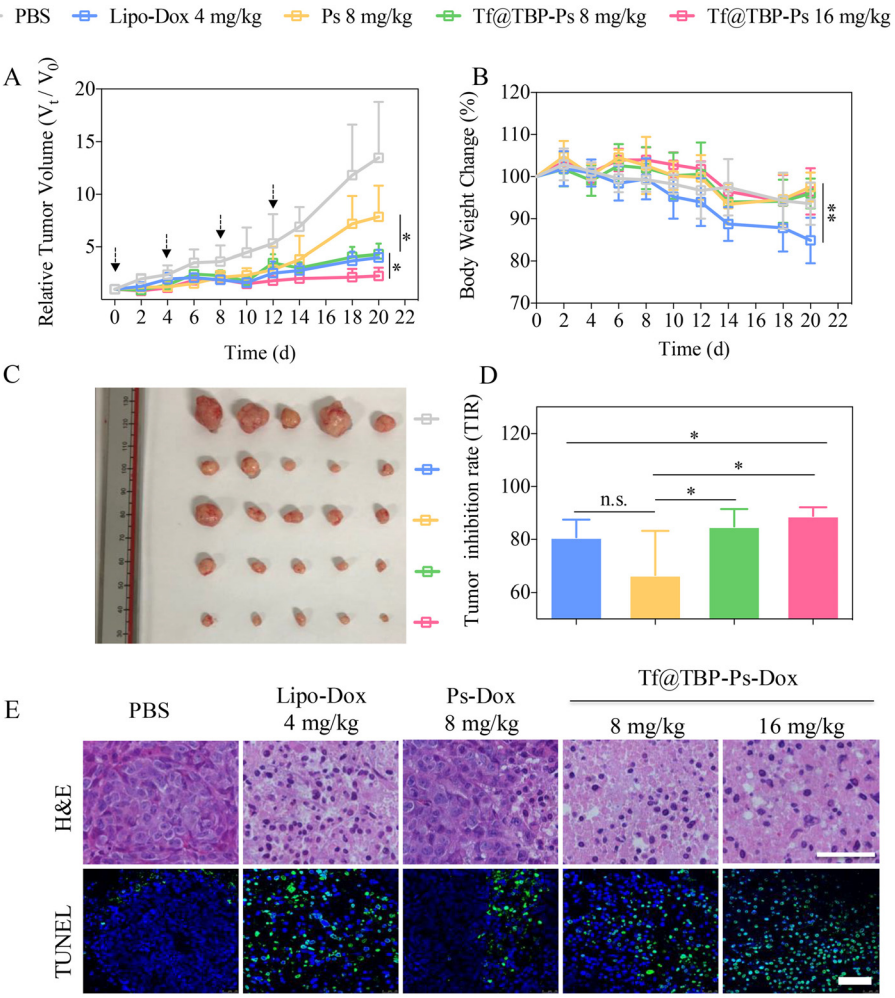

Fig. 7 *In vivo* antitumor efficacy of Tf@TBP-Ps-Dox (8 and 16 mg Dox per kg) in HCT-116 tumor-bearing nude mice (n = 5), with Ps-Dox (8 mg kg^{-1}), Lipo-Dox (4 mg kg^{-1}), and PBS as controls. Treatments were administered on days 0, 4, 8, and 12. (A) Tumor volume, (B) body weight, (C) tumor images (day 20), (D) tumor inhibition rates, and (E) H&E and TUNEL staining of tumor tissues (scale bar: 50 μm). Data shown as mean ± SD; *p < 0.05, **p < 0.01 by one-way ANOVA with Tukey's test.[116] Adopted with permission from Elsevier B.V. (Copyright © 2020).

covalent coupling often relying on hydrophobic lipid anchors such as palmitic acid or phosphatidylethanolamine (PE), which can be readily modified for ligand attachment.[128]

One example is the use of maleimide-PEG2000-DSPE as a lipid anchor for conjugating cyclic RGD (cRGD) peptides targeting αvβ3 integrins, a receptor upregulated in CRC cells. These RGD-modified liposomes were designed for the delivery of Galbanic acid (Gba), yielding nanoparticles of ~104 nm with a negative zeta potential. The system improved solubility and promoted integrin-mediated uptake in HUVEC cells. When co-administered with DOX-loaded liposomes, RGD-liposomes achieved synergistic antiproliferative effects in C26 cells and antiangiogenic activity comparable to Avastin® in CAM assays. Despite a twofold increase in tumor accumulation, off-target uptake persisted due to αvβ3 expression in normal tissues, resulting in accelerated clearance.[129–131] To mitigate this, advanced strategies such as dual-ligand targeting, selective ligand shielding, and chemical modification (*e.g.*, *N*-methylation or hydrophilic masking) are being explored to enhance tumor specificity and minimize nonspecific interactions.[132]

To improve selectivity, integrin α5β1 has emerged as a superior target, given its high expression in CRC and minimal presence in normal tissues. PEGylated liposomes functionalized with PR_b, a fibronectin-mimicking peptide, demonstrated markedly improved binding, uptake, and cytotoxicity compared with RGD-based systems, with up to 100-fold higher binding affinity (Fig. 8).[133] Dual-ligand liposomes targeting both α5β1 (PR_b) and α6β4 (AG86) integrins further enhanced selectivity, achieving up to 27-fold greater specificity and five-fold higher binding efficiency in CRC cells with balanced receptor expression.[134,135] These findings underscore the potential of receptor-specific ligands to refine liposomal targeting strategies.

Beyond conventional liposomes, cationic lipoplexes composed of DOTAP, DODAB, or DOPE have been applied for gene

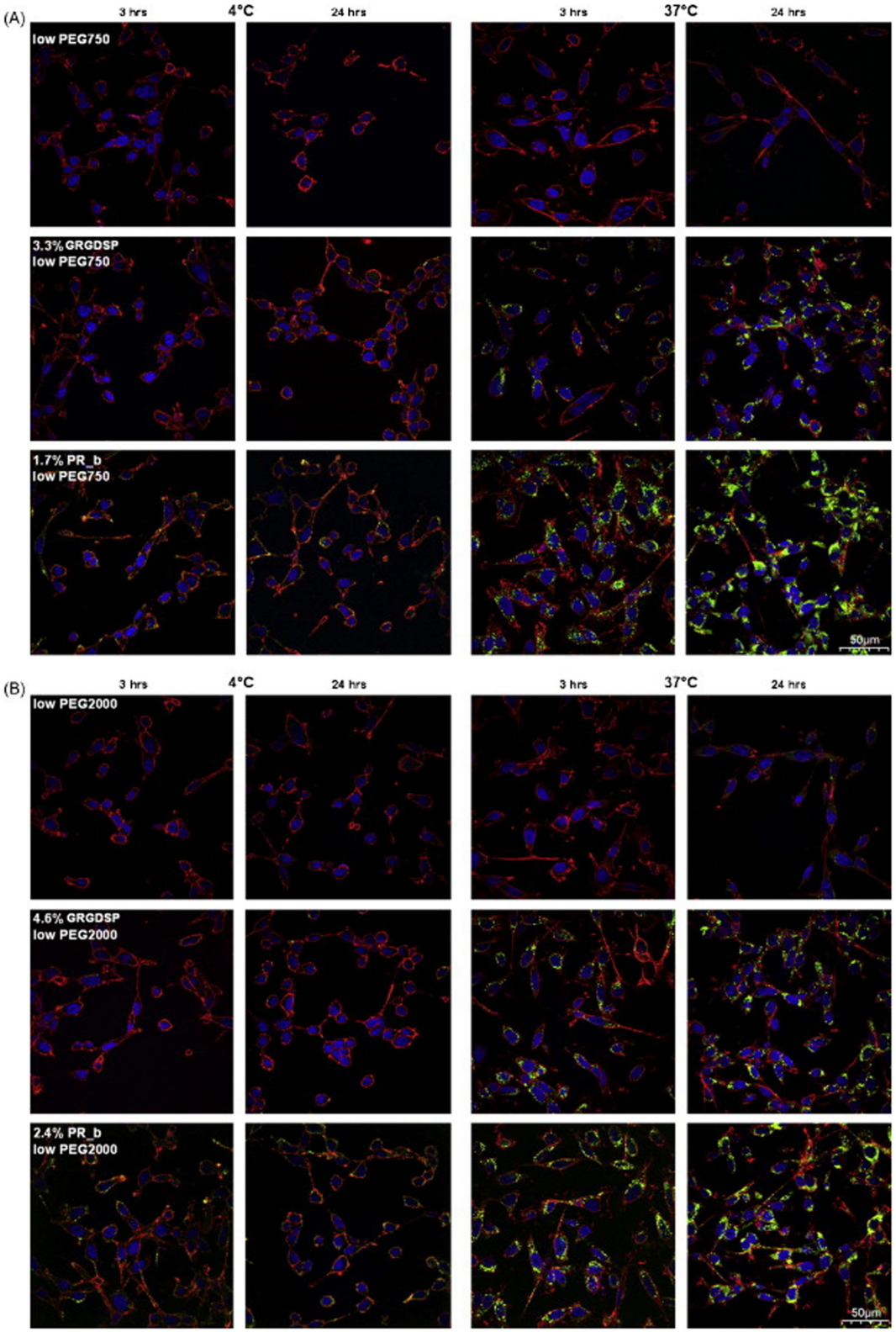

Fig. 8 Intracellular uptake of stealth liposomes in CT26.WT colon carcinoma cells. Liposomes with low PEG750 or PEG2000 were functionalized with GRGDSP or PR_b peptides and loaded with calcein (green). Confocal microscopy images (3 h and 24 h, 4 °C and 37 °C) show nucleus (blue), membrane (red), and liposomes. Orange membrane signal indicates surface binding; internal green signal indicates uptake. PR_b-liposomes exhibited superior integrin α5β1-mediated internalization; GRGDSP-liposomes showed limited uptake. Scale bar: 50 μm.[133] Adopted with permission from Elsevier B.V. (Copyright © 2008).

delivery due to their strong electrostatic interactions with nucleic acids and cellular membranes.[45] Their high positive charge enhances uptake but also causes nonspecific binding and rapid clearance. PEGylation and ligand conjugation are therefore employed to balance stability with specificity. A glucocorticoid-targeted lipoplex (D1XE-Hsp90), co-delivering ESC8 and anti-Hsp90 gene, improved tumor selectivity, prolonged survival (median ~60 *vs.* 30 days), and reduced neovascularization *in vivo*, illustrating the promise of ligand-guided gene delivery.[136]

SLNs have also been investigated as functional lipid carriers. In one study, SLNs composed of tristearin, DSPE, lipoid S75, and Tween 80 were functionalized with folic acid (FA) using EDC/Sulfo-NHS chemistry for oxaliplatin delivery. The optimized FA-SLNs (~159 nm, −28 mV) demonstrated receptor-mediated uptake, sustained release over six days, and enhanced cytotoxicity relative to free drug. Nonetheless, SLNs are constrained by limited drug-loading capacity and the risk of drug expulsion due to lipid crystallinity.[137]

NLCs address some of these shortcomings by incorporating both solid and liquid lipids, reducing crystallinity and improving encapsulation stability. A recent study coated NLCs with chitosan–folate conjugates (*via* EDC/NHS coupling) for the delivery of osthole. These folate-targeted NLCs (~179 nm, 83.5% encapsulation efficiency) displayed selective cytotoxicity against CRC cells, minimal effects on normal cells, and ancillary antioxidant and antibacterial properties.[138,139] Although further *in vivo* validation is warranted, such hybrid systems represent an important evolution in lipid nanocarrier design.

In summary, active targeting strategies have significantly enhanced the performance of lipid-based nanocarriers in CRC therapy. Through the rational selection of ligands, dual-targeting approaches, and improvements in lipid matrix design, these carriers are achieving greater tumor specificity, improved therapeutic efficacy, and reduced systemic toxicity. Continued refinement of ligand chemistry and multifunctional formulations will be essential to fully realize their clinical potential.

3.2.3. Inorganic nanocarriers. MSNs represent one of the most widely studied inorganic carriers for drug delivery, owing to their high surface area, tunable pore sizes, chemical stability, and inherent biocompatibility. Their porous structure allows efficient drug encapsulation; however, this same property can lead to premature drug leakage. To address this challenge, MSNs are often modified with polymer coatings such as chitosan and further functionalized with active targeting ligands. These modifications enhance drug retention, impart responsiveness to TME stimuli, and improve tumor selectivity.[139,140]

A representative example is the development of chitosan-coated MSNs electrostatically functionalized with the AS1411 (anti-nucleolin DNA aptamer), which specifically binds nucleolin, a protein overexpressed on many cancer cells.[118] These dual-functionalized nanocomplexes (AACS, ~130 nm) co-delivered DOX and antagomiR-21. They exhibited significantly higher uptake in nucleolin-positive cells (C26, MCF-7, and 4T1) compared to nucleolin-negative CHO cells, both *in vitro* and *in vivo*. Importantly, tumor-bearing mice treated with AACS showed a marked reduction in tumor volume ($p < 0.05$), with negligible toxicity in normal tissues. The pH-responsive degradation of chitosan under acidic TME conditions further enabled controlled drug release, demonstrating the utility of MSNs for stimuli-responsive, ligand-directed CRC therapy.[118]

To improve targeting precision, MSNs have also been engineered with dual ligands. One study functionalized silica NPs with both folic acid (FA) and hyaluronic acid (HA), targeting folate receptors and CD44/TLR4 receptors, respectively, both of which are commonly overexpressed in CRC.[119] In SW480 CRC cells, dual-ligand functionalization enhanced selectivity, with optimal receptor engagement achieved at an FA-to-surface amine (F : A) ratio of 9 and HA-to-surface amine (H : A) ratio of 0. Interestingly, excessive ligand density reduced uptake due to steric hindrance, highlighting that precise tuning of ligand ratios is critical to balance receptor affinity with cellular internalization efficiency.[119]

Quantum dots (QDs), ultrasmall semiconductor nanocrystals (<10 nm), are increasingly investigated as theranostic platforms for CRC due to their unique optical properties, large surface-to-volume ratio, and ease of surface functionalization.[141,142] Beyond imaging, QDs can be engineered for drug delivery. For example, graphene oxide (GO)-based QDs were covalently functionalized with Flu matrix p58–66 peptide, designed to target placenta-specific protein 1 (PLAC-1), a CRC-associated biomarker.[122] These functionalized QDs (+27.8 mV surface charge) achieved efficient cellular uptake and exhibited pronounced cytotoxicity in PLAC-1-positive HT-29 and HCT-116 cells. At 300 μg mL^{-1}, cell viability decreased by 54.3% and 55.1%, respectively, compared with non-functionalized QDs. Furthermore, proliferation was inhibited by 38% (HT-29) and 62% (HCT-116), with substantial PLAC-1 downregulation (52.91% and 32.89%, respectively). Despite their potent anticancer activity and diagnostic utility, clinical translation of QDs is hindered by short circulation half-life, rapid clearance, and toxicity concerns. PEGylation and alternative surface engineering approaches are being investigated to extend circulation time and improve tumor accumulation.[143]

In summary, advanced inorganic nanocarriers such as MSNs and QDs hold substantial promise for CRC nanotherapy by integrating high-capacity drug delivery with targeted and stimuli-responsive features. Ligand functionalization (aptamers, peptides, HA, FA) enhances tumor selectivity, while surface coatings mitigate premature release and improve pharmacokinetics. However, key challenges—including long-term biocompatibility, potential off-target biodistribution, and difficulties in large-scale, reproducible synthesis—remain barriers to clinical translation.[143] Addressing these limitations through optimized ligand engineering, green synthesis approaches, and hybrid formulations will be essential for realizing the full theranostic potential of inorganic nanoparticles in precision oncology.

3.2.4. Biological or biomimetic nanocarriers. Biomimetic nanocarriers are increasingly recognized as transformative platforms in CRC therapy, addressing the limitations that

hinder the clinical translation of conventional nanocarriers. Traditional systems often face instability in physiological environments, inadequate penetration across biological barriers, poor biodistribution, and limited targeting efficiency. In contrast, biomimetic strategies exploit natural materials such as cell membranes, extracellular vesicles, and macromolecules to cloak nanoparticles, thereby emulating native cellular functions. These coatings enable immune evasion, prolong systemic circulation, and improve targeting specificity, while also permitting further functionalization with ligands such as peptides, aptamers, or antibodies. By mimicking the surface markers of source cells—including erythrocytes, leukocytes, exosomes, or even bacterial and viral vectors—biomimetic nanoparticles can achieve both immune stealth and tissue-specific delivery, particularly to tumors and inflammatory sites.[144]

Albumin has emerged as one of the most widely used biomimetic carriers, valued for its long circulation half-life, intrinsic drug-binding affinity, biodegradability, and non-immunogenic nature.[90] It can be readily functionalized with targeting ligands such as folic acid, antibodies, or aptamers to achieve selective binding to receptors overexpressed in CRC. Conjugation is typically performed *via* carbodiimide-mediated coupling (EDC or DCC) or NHS-ester chemistry, which link ligands to lysine residues on albumin. For example, human serum albumin was used to coat graphene oxide nanoparticles co-loaded with 5-FU and curcumin, while folic acid conjugation conferred selectivity toward folate receptor-positive CRC cells. This system improved solubility and yielded synergistic cytotoxic and pro-apoptotic effects compared with the free drugs.[145] Similarly, folate-functionalized albumin NPs encapsulating curcumin analogs produced favorable particle sizes (~279 nm by DLS; 40–70 nm by TEM) and exhibited high tumor specificity *in vivo.*[146] AS1411 aptamer-functionalized albumin nanoparticles have further demonstrated enhanced cellular uptake, increased cytotoxicity, and superior *in vivo* efficacy with minimal systemic toxicity.[147] A related study with AS1411-decorated, docetaxel-loaded albumin nanoparticles (Apt-NPs-DTX) showed sustained drug release, significant cytotoxicity against CT26 cells at doses above 150 μg mL^{-1}, and reduced tumor volumes *in vivo* (827.19 mm^3 *vs.* 1236.61 mm^3 for non-targeted nanoparticles), highlighting the translational promise of these multifunctional systems.[148] Such albumin-based nanocarriers can be extended to other chemotherapeutics—including DOX, PTX, and gemcitabine—and are adaptable for combination therapy and theranostic applications in precision oncology.

Exosomes, naturally secreted extracellular vesicles, have also emerged as effective biomimetic delivery systems. Their innate immune-evasive properties, structural stability, and role in intercellular communication make them superior to many synthetic carriers.[149,150] For instance, HEK293-derived exosomes functionalized with AS1411 aptamer through EDC/NHS coupling enabled nucleolin-targeted DOX delivery. These DOX-Apt-Exosomes (~205.8 nm) selectively accumulated in nucleolin-positive HCT-116 cells and tumors in CT26-bearing mice, producing a 65% reduction in tumor growth compared with 33% for non-targeted exosomes. Moreover, the Apt-Exo group exhibited 100% survival, confirming reduced systemic toxicity relative to free DOX.[151] Such findings highlight the potential of exosomes as customizable, safe nanocarriers for CRC drug delivery.

DNA nanotechnology adds another dimension to biomimetic drug delivery. Programmable DNA nanostructures—including origami, aptamer-functionalized frameworks, and DNA-templated carriers—offer high structural precision, biocompatibility, and multifunctionality.[152] Guo *et al.* designed a DNA tetrahedron co-functionalized with folic acid for tumor targeting, the PL1 aptamer to block PD-1/PD-L1 immune checkpoints, and siRNA against Pcsk9 to enhance antigen presentation *via* MHC-I expression. The nanostructure (~28.6 nm, −40.89 mV) was fabricated by controlled thermal annealing and exhibited excellent stability against enzymatic degradation. It was non-cytotoxic at concentrations up to 400 nM, promoted T cell proliferation and cytokine release, and significantly inhibited tumor growth *in vivo*, accompanied by enhanced immune infiltration and minimal systemic toxicity (Fig. 9).[153] This work exemplifies how DNA nanostructures can unite immune checkpoint inhibition with gene silencing, offering a robust platform for cancer immunotherapy.

Collectively, biological and biomimetic nanocarriers—including albumin nanoparticles, exosomes, and DNA nanostructures—represent the forefront of next-generation targeted drug delivery.[154,155] Their immune compatibility, functional adaptability, and ability to integrate chemotherapy, immunotherapy, and diagnostics distinguish them from traditional carriers. Active targeting in CRC nanotherapy ultimately relies on functionalizing nanoparticles with ligands such as antibodies, peptides, aptamers, or small molecules that selectively bind to tumor-associated receptors (Table 5). These ligands enhance cellular uptake and therapeutic efficacy but typically do not radically alter systemic biodistribution. The effectiveness of active targeting depends on ligand type, binding affinity, density, and the physicochemical properties of the carrier—including size, charge, and rigidity.[156,157] Nanocarrier composition, whether polymeric, lipid-based, inorganic, or biomimetic, also dictates circulation, administration route, and release kinetics. Despite substantial progress, tumor heterogeneity, immune clearance, and the complexity of large-scale manufacturing remain key barriers. Future advances may lie in the integration of dual-ligand systems, artificial receptor engineering, and AI-guided optimization. While several biomimetic formulations are advancing toward clinical evaluation, addressing safety, reproducibility, and regulatory challenges will be essential to fully realize the potential of active targeting nanocarriers in CRC therapy.

3.3. Stimuli-responsive nanocarriers

A transformative advancement in nanomedicine is the development of stimuli-responsive ("smart") drug delivery systems. These nanocarriers are engineered from materials that remain stable and inert under normal physiological conditions, thereby preventing premature leakage of therapeutic payloads

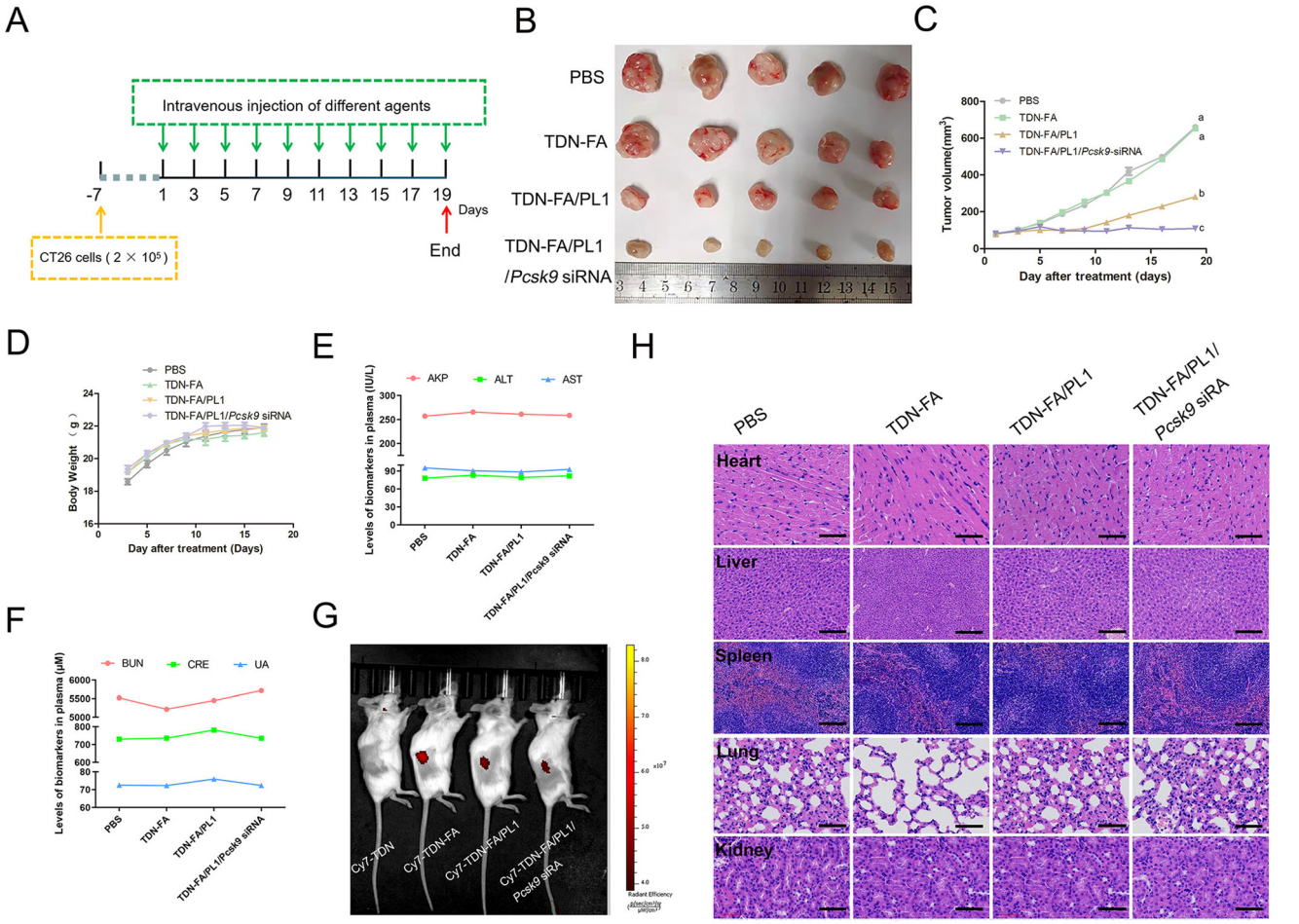

Fig. 9 *In vivo* evaluation of TDN-FA/PL1/Pcsk9 siRNA nanomedicine in CT26 colon carcinoma-bearing mice. (A) Treatment schedule: mice received PBS or nanostructures (TDN-FA, TDN-FA/PL1, TDN-FA/PL1/Pcsk9 siRNA) *via* tail vein every 2 days for 10 doses, (B–D) tumor images, tumor volume, and body weight during treatment, (E, F) liver (AKP, ALT, AST) and kidney (BUN, CRE, UA) function markers, (G) H&E staining of major organs after treatment (scale bar: 50 μm), and (H) Cy7 imaging of tumor accumulation 1 h after the third injection.[153]

during circulation.[162] Upon encountering specific endogenous or exogenous stimuli at the pathological site, however, they undergo physicochemical changes that trigger the controlled release of encapsulated drugs. This spatiotemporally precise delivery strategy significantly enhances therapeutic efficacy while reducing off-target toxicity.

Stimuli capable of inducing drug release can be broadly divided into internal (*e.g.*, pH, enzymatic activity, redox potential) and external (*e.g.*, near-infrared [NIR] light, magnetic fields, electrical impulses, or thermal energy) categories.[162] In CRC, internal stimuli are particularly advantageous for localized drug release, as they exploit pathophysiological characteristics of the TME. For example, while the healthy colon maintains a near-neutral pH (~7.2), the CRC TME is acidified (pH 6.4–6.9) due to accelerated glycolysis and lactate accumulation. pH-Sensitive nanocarriers exploit this difference by releasing their payload preferentially in the acidic tumor milieu while sparing normal tissue.[163–165]

The colon's unique microbiota also provides a powerful trigger for targeted release. Commensal and pathogenic bacteria secrete enzymes such as β-glucuronidases, proteases, and azoreductases, which can degrade specific linkers, coatings, or polymer backbones in enzyme-responsive nanocarriers. These systems enable site-specific drug activation, enhancing therapeutic precision while minimizing systemic exposure and toxicity.

Among external triggers, NIR light is particularly attractive for non-invasive and spatially controllable release. NIR-responsive carriers absorb light and convert it into localized heat, driving thermally mediated drug release or photothermal ablation. This strategy has shown promise for superficial CRC lesions accessible to optical devices. For deeper or less accessible tumors, magnetic field-responsive systems provide an alternative: superparamagnetic nanoparticles can be externally guided to the tumor site, where alternating magnetic fields induce localized hyperthermia or facilitate drug diffusion. Such approaches not only enhance intratumoral accumulation but also allow real-time imaging and tracking.

In summary, stimuli-responsive delivery systems provide a versatile and powerful strategy for CRC therapy by harnessing

Table 5 Summary of active targeting strategies in nanotherapy for CRC

Category	Type of nanocarrier	Anticancer agent(s)	Type of ligand	Study design	Major findings	Ref.
Lipid-based NPs	Liposome	Gba	RGD	*In vitro*: HUVEC endothelial cells	The co-treatment with Dox liposomes shows synergistic antiproliferative effect	129
	Liposome	5-FU	PR_b peptide	*In vitro*: CT26.WT & HCT116 cells	Optimized PR_b-targeted liposomes (high peptide content and shorter PEG) outperform GRGDSP-targeted liposomes in binding and internalization PR_b liposomes loaded with 5-FU are as cytotoxic as free 5-FU and more effective than RGD or non-targeted liposomes	133
	Lipoplexes	ESC8 and anti-Hsp90 gene	Dexamethasone	*In vitro*: CT26 & HCT15 cells *In vivo*: orthotopic colon tumor-bearing mice	GR-targeted liposomes were efficiently delivered to colon tumor cells with minimal off-target distribution, significantly reduced tumor size, proliferation and angiogenesis, and exhibiting synergistic effect of loaded drugs	136
	SLNs	Oxaliplatin	FA	*In vitro*: HT-29 cells	Sustained drug release pattern of OXA for up to 6 days	137
Polymer-based NPs	PNPs	DOX	HA	*In vivo*: Balb/c mice	Higher Dox accumulation intestines (45%) compared to free Dox (30%) shortly after administration	158
	PNPs	PTX	HA	*In vitro*: HCT116 cells *In vivo*: AOM/DSS-induced CRC mice	Utilizing rectal administration, CLSNPs showed higher accumulation selectively to tumor cells, sustained release of drug, notable increase in TUNEL-positive cells and negligible change in body weight compared to naïve NPs and free PTX	159
	PNPs	Oxaliplatin	Cetuximab mAb (single-chain variable fragment)	*In vitro*: HCT 116 cells	Significant cytotoxicity of functionalized NPs compared to undecorated NPs Induce apoptosis (99.8%)	160
	PNPs	Etoposide	Lactoferrin (LF) and melatonin	*In vitro*: HCT 116 cells *In vivo*: wister rats with CRC	ETP-CS-LF-MLT-NPs showed enhanced internalization (131%) *via* LF, prolonged circulation time, reduced tumor growth, decreased pathogenic bacteria and restored gut microbial balance with sustained inhibition of *P. mirabilis* known to exacerbate cancer progression	161
Inorganic-based MPs	Chitosan modified MSN	DOX + antagomiR (antimiR-21)	AS1411	*In vitro*: C26, MCF-7 and 4T1 cells. *In vivo*: BALB/c mice bearing C26	AACS achieved sustained release of Dox, enhanced internalization into nucleolin-expressing cancer cells and slowed tumor growth without significant weight loss *in vivo*	118
	QD made of GO	—	Flu matrix p58–66 peptide	*In vitro*: HT-29 & HCT-116 cells	Significant cellular uptake in cells expressing the antigen PLAC-1 causing reduced cell invasion and downregulated PLAC-1 expression	122
Biological/ biomimetic nanocarriers	HAS coated GO	5-FU + curcumin (CUR)	FA	*In vitro*: HT-29 & HCT-116 cells	GO-Alb-5FU-Cur-FA showed rapid (5-FU) and sustained (Cur) release, enhanced toxicity, higher internalization and inhibited cell invasion	145
	Exosomes derived from HEK293 cells	DOX	AS1411	*In vitro*: HCT-116 & HEK-293 cells. *In vivo*: BALB/c mice bearing CT26 tumor.	Functionalized exosome increased tumor cell apoptosis and inhibited tumor growth *in vivo* with minimum systemic side effects	150
	DNA nanostructure	Aptamer PL1 and Pcsk9 siRNA	FA	*In vitro*: MC38 and CT26 cells. *In vivo*: CT26 bearing mice	TDN-FA/PL1/Pcsk9-siRNA demonstrated efficient cellular uptake, especially in folate receptor-positive cells Significant accumulation in tumor and inhibited tumor growth (93%)	153

Abbreviations: 5-FU, 5-fluorouracil; Gba, Galbanic acid; AACS, aptamer–antagomiR-21-chitosan-modified mesoporous silica nanoparticles; AOM/DSS, azoxymethane/dextran sodium sulfate; APR, abdominoperineal resection; CI, combination index; CLSNPs, chitosan lipid–polymeric nanoparticles; CRC, colorectal cancer; CUR, curcumin; DOX, doxorubicin; DSC, differential scanning calorimetry; DSPE, distearoyl phosphatidylethanolamine; ETP, etoposide; ESC8, cationic lipid derivative of squalene; FA, folic acid; GA, gambogic acid; GO, graphene oxide; GR, glucocorticoid receptor; HA, hyaluronic acid; HAS, human serum albumin; HCT, human colorectal carcinoma cell line; HUVEC, human umbilical vein endothelial cells; IRI, irinotecan; LF, lactoferrin; MLT, melatonin; MSN, mesoporous silica nanoparticle; mAb, monoclonal antibody; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NP, nanoparticle; OXA, oxaliplatin; PAMAM, poly(amidoamine); Pcsk9, proprotein convertase subtilisin/kexin type 9; PEG, polyethylene glycol; PL, piperlongumine; PLAC-1, placenta-specific protein 1; PLGA, poly(lactic-*co*-glycolic acid); PNIPAM, poly(*N*-isopropylacrylamide); PNP, polymeric nanoparticle; PR_b, fibronectin-mimicking peptide; PTX, paclitaxel; QD, quantum dot; RBCm, red blood cell membrane; RES, resveratrol; SLN, solid lipid nanoparticle; SOD1, superoxide dismutase 1; TDN, tetrahedral DNA nanostructure; TfR, transferrin receptor.

endogenous features of the tumor environment or applying external triggers for precision control. These platforms offer the potential for spatially and temporally regulated release, improved therapeutic indices, and reduced systemic toxicity. In the following discussion, strategies will be organized by type of triggering stimulus rather than carrier material, in order to highlight mechanistic principles and therapeutic implications.[166]

3.3.1. pH-Responsive systems. Exploiting the acidic TME of CRC provides a powerful strategy for site-specific drug release. While systemic blood pH is tightly regulated at ~7.4, the CRC TME exhibits localized acidification (pH 6.4–6.9) resulting from enhanced glycolysis and lactate accumulation. This differential can be harnessed to engineer nanocarriers that remain stable under physiological conditions but undergo structural or chemical transformations in acidic environments, thereby releasing therapeutic payloads selectively at the tumor site.[162] To achieve this, various pH-sensitive materials—either as nanoparticle matrices or protective coatings—have been employed in CRC nanotherapy, including Eudragit S100,[167] okra gum,[168] alginate,[169] pectin,[170] and formulations incorporating pH-sensitive liposomes[171,172] or MSNs.[173]

Among these, Eudragit S100, an anionic methacrylic acid copolymer, is widely utilized for colon-targeted oral delivery, as it dissolves at pH > 7, enabling drug release specifically in the colonic environment. De Leo *et al.* developed a pH-responsive liposomal system encapsulating curcumin (CUR) using a micelle-to-vesicle transition method, followed by scalable coating with Eudragit S100.[172] The formulation (<100 nm) exhibited high encapsulation efficiency (98%), strong physicochemical stability, and preserved antioxidant activity. Controlled release studies demonstrated complete drug release within 200 min, confirming the system's potential for colonic delivery of bioactive agents.[172] In a complementary study, Wang *et al.* designed Eudragit S100-coated, pH-responsive liposomes loaded with betulinic acid. The particles (<100 nm, ~90% encapsulation efficiency) displayed sustained release, potent inhibition of CRC cell proliferation and migration, and, *in vivo*, significantly suppressed tumor growth *via* modulation of Akt/TLR and NFAT1/4 pathways. Enhanced tumor immune infiltration (increased NK, $CD3^+$, $CD8^+$ cells) further indicated a capacity for immunomodulation.[167]

To address the aggregation issues of conventional solvent-evaporation methods, Hsu *et al.* fabricated pectin/alginate microspheres coated with Eudragit S100 using a layer-by-layer polyelectrolyte approach. These pH-sensitive microspheres (PAMs) minimized release in gastric conditions (~5%) and triggered effective drug release at colonic pH (>7), thereby reducing systemic toxicity while enhancing therapeutic precision.[170] Similarly, Kassem *et al.* developed colon-targeted Eudragit® S100-coated aminated MSNs for catechin delivery.[173] Wormlike nanoparticles (<100 nm) demonstrated ~90% release at pH 7.4 compared with minimal release at acidic pH, showing selective colonic release and overcoming catechin's poor solubility and gastric instability.[173] Beyond S100, alternative Eudragit variants (L100,[174] FS[175,176]) and other enteric polymers such as HPMC, HPMCP,[177,178] and cellulose acetate phthalate (CAP)[179,180] have also been applied for colon-targeted delivery. For example, Gupta *et al.* reported enteric-coated HPMC capsules (ECHC) carrying 5-FU microsponges and calcium pectinate beads, further coated with Eudragit L100/S100. This formulation achieved ~98% drug release under colonic conditions with pectinase and demonstrated targeted colonic delivery and improved bioavailability in rabbits.[178]

Beyond oral delivery, systemically administered pH-sensitive carriers can exploit the acidic TME for selective tumor accumulation. Hodaei *et al.* designed cholesterol-free liposomes coated with cationic okra gum functionalized with trimethylammonium groups to achieve pH-responsive behavior. Co-loaded with oxaliplatin and hesperetin, these nanocarriers displayed tri-phasic release under acidic conditions (pH 5.5), with ~66% cumulative release over 24 h, and achieved ~50–60% reduction in CRC cell viability compared with free drugs.[168] Gu *et al.* further advanced the field by co-delivering docetaxel (shell) and pemetrexed (core) in pH-responsive liposomes. These formulations demonstrated strong cytotoxicity, induced immunogenic cell death, and, in murine CRC models, synergized with anti-PD-L1 immunotherapy to achieve superior tumor inhibition and reduced systemic toxicity.[171]

More sophisticated pH-sensitive designs incorporate dual-therapy approaches. A notable example is a pH-sensitive lipopolyplex delivering DOX and siRNA targeting focal adhesion kinase (FAK). The charge-convertible polymer core transitioned from neutral to cationic under acidic conditions, enabling siRNA condensation and endosomal escape. Encapsulation in PEGylated liposomes yielded nanoparticles (~170–190 nm) with high stability and TME-responsive release. Both *in vitro* and *in vivo*, the system achieved effective gene silencing, synergistic cytotoxicity, enhanced tumor accumulation, and minimal systemic toxicity.[181]

Overall, pH-responsive carriers employ functional groups such as hydrazone linkers, amine or pyridine moieties, and acid–labile bonds to undergo structural or charge transitions in acidic conditions, enabling controlled drug release. These systems address critical challenges in CRC therapy by improving tumor specificity, reducing systemic exposure, and enhancing immunomodulatory potential. Nevertheless, key translational barriers remain, including variability in patient TME acidity, optimization of biocompatible and degradable materials, and scalable manufacturing. Future research should focus on clinically translatable polymers, improved drug loading strategies, and robust *in vivo* validation to fully realize the therapeutic potential of pH-sensitive nanocarriers in precision CRC therapy.[182]

3.3.2. Enzyme-triggered delivery. Enzymes play pivotal roles in both normal physiology and cancer progression, and their dysregulated expression in the TME makes them highly attractive triggers for smart drug delivery systems. By exploiting enzymatic activity patterns unique to CRC, enzyme-responsive nanocarriers can achieve precise drug activation at tumor sites, thereby enhancing therapeutic efficacy while minimizing off-target toxicity.[162]

Proteases, particularly matrix metalloproteinases (MMPs), are key regulators of tumor invasion and metastasis. Among them, MMP-9 is prominently upregulated in CRC. To exploit this, manganese nanoparticles (MNPs) were synthesized by chemical precipitation and coated with G5 poly(amidoamine) dendrimers and a collagen IV (Col-IV) peptide—an MMP-9-specific substrate—forming Col-IV@IRI-G5MNP for irinotecan hydrochloride (IRI) delivery.[183] This multifunctional system exhibited faster but controlled drug release in the presence of MMP-9, producing significantly greater cytotoxicity in HCT116 cells than free IRI. Beyond drug delivery, Mn^{2+} release modulated tumor redox balance, increased intratumoral oxygen levels, and elevated pH, while also conferring *T*1-weighted MRI contrast. Such theranostic potential illustrates how enzyme-triggered systems can integrate therapy with real-time imaging for precision oncology.[183]

Glycosidases represent another relevant enzymatic trigger. β-Glucuronidase, overexpressed in necrotic and inflamed tumor regions, has been harnessed to activate prodrugs selectively within CRC lesions. Prijovich *et al.* designed a β-glucuronidase-activated camptothecin (CPT) prodrug, BQC-G, linked *via* a self-immolative benzyl-ether spacer.[184] In circulation, the conjugate remained inert, reducing systemic toxicity. At the tumor site, enzymatic hydrolysis released the active cytotoxin, achieving enhanced solubility, targeted activation, and potent efficacy in xenograft models.

Colonic microbiota also secrete diverse enzymes—lipases, esterases, and hydrolases—that can be exploited for localized drug release. For instance, baicalin-loaded hybrid nanoparticles comprising tripalmitin, lecithin, DSPE-PEG2000, PLGA, and chitosan were prepared *via* nanoprecipitation.[185] These nanocarriers (~184 nm, 90% entrapment efficiency) demonstrated remarkable stability in simulated gastric and intestinal fluids but achieved rapid drug release (91% at 8 h; 97% at 24 h) in rat cecal contents, confirming microbial enzyme-triggered activation. The hybrid design, combining a hydrophobic polymeric core with a lipid shell, overcame drawbacks of conventional liposomes and PNPs, improving stability and site-specific delivery.[186] Cyclodextrins (CDs) represent another microbiota-degradable platform Modified amphiphilic β-CD nanoparticles (Poly-β-CD-C6) encapsulating CPT (~135 nm, +40 mV) achieved efficient mucus penetration (~73%), prolonged colonic residence, and enhanced drug permeability (~2.7-fold across Caco-2 monolayers), alongside superior cytotoxicity in HT-29 cells, compared to free drug.[187,188]

Dual-layered formulations have been employed to further refine enzyme sensitivity. Pectin and skimmed milk powder (SMP)-coated SLNs (DL-SLNs) protected curcumin (CUR) from premature gastric degradation and enabled colonic release through pectin hydrolysis.[189] The nanoparticles exhibited high encapsulation efficiency (83.9%), long-term stability (>90 days), and enzyme-dependent release profiles—minimal at gastric pH but sustained (~92% over 72 h) in simulated colonic fluid. *In vivo*, DL-SLNs achieved enhanced colonic accumulation (9.12 μg g^{-1} at 72 h) and potent cytotoxicity (IC_{50} = 31 μM mL^{-1}).[189]

More advanced multi-responsive systems integrate enzyme and pH sensitivity. For example, MSNs loaded with veratridine were capped with casein, a substrate for MMP-7, while also incorporating hydroxyapatite.[190] Exposure to MMP-7 cleaved the casein cap, releasing the drug, whereas acidic pH simultaneously accelerated release. This dual responsiveness improved selectivity for CRC cells by enhancing intracellular uptake and sparing normal cells, highlighting the synergy of multi-stimuli designs.

Despite compelling preclinical outcomes, several barriers limit the clinical translation of enzyme-responsive carriers. Enzyme expression can vary significantly across patients and tumor regions, creating heterogeneity in therapeutic responses. Immunogenicity of enzyme-cleavable linkers, degradation by off-target enzymes, and the challenge of developing biodegradable, excretable materials also pose concerns. Future progress will depend on optimizing enzyme-specific substrates and linker chemistries, integrating multi-stimuli responsiveness, and conducting rigorous *in vivo* and toxicological evaluations. A deeper understanding of enzymatic profiles in CRC patients, combined with personalized nanomedicine approaches, will be essential to realize the full potential of enzyme-responsive nanocarriers in precision therapy.

3.3.3. Redox-sensitive nanocarriers. Tumor cells exhibit a distinct redox imbalance, characterized by elevated levels of reactive oxygen species (ROS) and abnormally high intracellular concentrations of reducing agents such as glutathione (GSH), which can reach up to 10 mM—far exceeding the micromolar concentrations found in normal tissues.[162] This biochemical disparity provides an attractive endogenous trigger for designing redox-responsive nanocarriers capable of site-specific drug release. A common strategy involves integrating redox-sensitive linkers, most notably disulfide bonds, into nanocarrier architectures. These linkages remain stable during systemic circulation but undergo cleavage in the reductive tumor milieu, releasing the therapeutic payload directly within malignant cells and thereby enhancing drug selectivity and efficacy.[191]

An innovative example is a ROS-responsive polymer–drug conjugate (P3C-Asp), created by covalently linking aspirin to a dextran backbone through a boronic ester linker highly susceptible to ROS-induced cleavage.[192] The system was synthesized using a Passerini three-component reaction to form the ROS-labile linker, followed by "click" chemistry to attach the drug–polymer conjugate. The resulting conjugates self-assembled into nanoparticles (~40 nm) that were stable under physiological conditions yet rapidly disintegrated in oxidative tumor environments, ensuring selective release of aspirin. *In vivo* studies in murine CRC models revealed preferential tumor accumulation, with 3.3-fold higher retention at 6 h post-injection and nearly sixfold by 24 h compared to free drug. Functionally, P3C-Asp nanoparticles reprogrammed the TME: reducing immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T cells, lowering prostaglandin E2 (PGE2) levels, and promoting infiltration of cytotoxic $CD8^+$ T cells and M1 macrophages. These immunomodulatory effects

converted the TME from a suppressive to a stimulatory state, leading to significant tumor inhibition without detectable systemic toxicity.[192]

Despite the promise of ROS-sensitive carriers, reliance on a single trigger may be insufficient for precise targeting, as certain physiological processes in normal tissues also involve ROS generation. To improve tumor selectivity, dual-stimuli-responsive platforms that integrate multiple tumor-specific cues—such as acidity and redox imbalance—are increasingly being developed. For instance, Chang *et al.* designed a dual pH/ROS-responsive nanoplatform (PLP-NPs) to overcome multidrug resistance (MDR) and enhance CRC therapy.[193] This system comprised a ROS-sensitive PTX prodrug (DEX-TK-PTX), pH-sensitive poly(L-histidine), and β-lapachone as a ROS generator. Following endocytosis, poly(L-histidine) enabled lysosomal escape under acidic conditions, while β-lapachone elevated intracellular ROS and depleted ATP, suppressing P-glycoprotein expression to reverse MDR. Concurrently, the high ROS levels triggered cleavage of the thioketal linker, releasing PTX for potent cytotoxicity. The nanoparticles accumulated in tumors *via* the EPR effect and exhibited robust antitumor efficacy *in vitro* and *in vivo*, outperforming single-stimuli systems. This cascade-responsive approach highlights the potential of integrating multiple TME features for precise and effective drug delivery.[193]

Overall, redox-responsive nanocarriers represent a powerful class of smart delivery systems for CRC, leveraging intrinsic redox imbalances to achieve localized release and immune reprogramming. The incorporation of dual or cascade-responsive mechanisms further enhances therapeutic precision, enabling strategies to circumvent MDR and minimize systemic toxicity. Future research should focus on refining redox trigger sensitivity, improving the biocompatibility of carrier materials, and ensuring scalability and reproducibility in synthesis, all of which will be critical for advancing these intelligent systems from preclinical promise to clinical application.

3.3.4. Light-activated systems. The pursuit of precise, minimally invasive, and highly effective cancer therapies has catalyzed growing interest in stimuli-responsive nanomedicine. Among these approaches, light-triggered systems offer unique advantages by enabling non-invasive, spatiotemporally controlled activation of therapeutic payloads. Typically harnessing NIR light, these platforms exploit photo-induced mechanisms—such as ROS generation, localized hyperthermia, or on-demand drug release—to achieve tumor-selective action. This localized activation minimizes systemic toxicity, improves intratumoral drug accumulation, and can be integrated with diagnostic imaging, thereby aligning with the principles of precision oncology.[162]

A notable example is a multifunctional nanoparticle system that combines photothermal therapy (PTT) with nitric oxide (NO) release to enhance anticancer efficacy.[194] The nanoparticles (~70 nm) achieved a drug loading efficiency of 37.1% and released NO rapidly (10.15 μM cumulative) upon 637 nm laser exposure. Concurrently, they elevated local temperatures to ~55 °C within 2 minutes, sufficient for tumor ablation. *In vitro*, the system was biocompatible under dark conditions but highly cytotoxic upon irradiation (IC_{50} = 13.78 mg L^{-1}), surpassing the efficacy of either monotherapy alone. *In vivo*, treatment resulted in a 94.9% tumor growth inhibition rate, with tumor volume reduced to 14.76% of controls, and importantly, no systemic toxicity was observed.[194]

Reduced graphene oxide (rGO) has also emerged as a potent NIR-responsive platform due to its strong optical absorbance, high photothermal conversion efficiency, and ease of functionalization. A chitosan-coated rGO nanoplatform was engineered to co-deliver DOX and IR820, a dual-function NIR dye with photothermal and photodynamic properties.[195] The system enabled real-time monitoring of intracellular distribution through Raman imaging while achieving controlled drug release. Upon 785 nm NIR irradiation, the formulation generated both hyperthermia and singlet oxygen, producing synergistic anticancer effects through combined PTT, PDT, and chemotherapy. Notably, increasing the IR820-to-DOX ratio enhanced cytotoxic efficacy, underscoring the importance of optimizing co-loading strategies.[195]

Other multifunctional nanomaterials incorporate both diagnostic and therapeutic modalities. Iron oxide (Fe_3O_4) nanoparticles coated with chitosan have been developed as dual-function agents for PDT and magnetic resonance imaging (MRI).[196] Loaded with photosensitizers, these nanoparticles induced robust ROS generation upon blue light irradiation, selectively reducing HCT116 colon cancer cell viability by 65% at 20 μg mL^{-1} ($p < 0.01$), while sparing normal HEK-293 cells. Mechanistic studies confirmed marked increases in intracellular ROS and upregulation of pro-apoptotic markers (p53, p21, caspases; 2- to 3-fold, $p < 0.05$). MRI analyses further validated their contrast-enhancing properties, highlighting their theranostic potential.[196]

Collectively, these studies underscore the promise of light-responsive nanomedicine in CRC therapy, offering localized activation, multimodal therapeutic synergy, reduced off-target toxicity, and real-time monitoring. Nevertheless, several challenges impede clinical translation. The limited penetration depth of visible and NIR light constrains applications in deep-seated CRC lesions, while long-term nanoparticle safety, risks of photothermal damage to surrounding tissues, and the scalability of complex nanoplatforms remain unresolved. Future efforts must focus on engineering advanced photosensitizers with deeper tissue penetration, integrating targeted light delivery systems (*e.g.*, fiber optics, endoscopic irradiation), and ensuring reproducibility and safety in large-scale manufacturing. With sustained interdisciplinary progress, light-triggered nanocarriers hold strong potential to advance CRC therapy toward more personalized, precise, and minimally invasive treatment paradigms.

3.3.5. Thermo-responsive nanocarriers. Thermoresponsive drug delivery systems constitute an important class of smart biomaterials engineered to exploit temperature fluctuations for site-specific and controlled release.[162] These systems are typically constructed from thermo-sensitive polymers that undergo reversible phase transitions at defined temperature

thresholds. Two principal behaviors are observed: polymers exhibiting a Lower Critical Solution Temperature (LCST), which are soluble below their critical point but undergo phase separation (*e.g.*, gelation, precipitation, or collapse) above it, and polymers with an Upper Critical Solution Temperature (UCST), which dissolve above the threshold but are less commonly applied in biomedicine due to their limited physiological relevance.[162]

In oncology, LCST-type systems are particularly attractive, as they remain stable at normal body temperature (~37 °C) and can be activated by localized hyperthermia or mild external heating (typically 40–43 °C). This transition enables precise spatial and temporal control over drug release, enhancing therapeutic concentrations at the tumor site while reducing systemic exposure. Well-studied examples include poly(*N*-isopropylacrylamide) (PNIPAM, LCST ~ 32 °C), Pluronics (polyethylene oxide–polypropylene oxide–polyethylene oxide triblock copolymers), and graft copolymers with tailored LCST values to match therapeutic requirements.[197]

Nanogels based on thermoresponsive polymers have garnered particular attention due to their favorable physicochemical properties, such as reversible sol–gel transitions, tunable swelling behavior, and enhanced cellular uptake. For instance, a chitosan-based nanogel grafted with 40% PNIPAM —identified as the optimal grafting ratio for drug encapsulation—was developed for CUR delivery.[198] This system exhibited a size reduction near its LCST, improving drug solubility, promoting cellular uptake, and significantly enhancing cytotoxicity against tumor cells in a dose-dependent manner. Such dynamic modulation of size and permeability in response to thermal stimuli demonstrates the capacity of thermoresponsive nanogels to facilitate intratumoral drug penetration while minimizing systemic toxicity.

Overall, thermoresponsive nanocarriers provide a versatile platform for improving the therapeutic index of anticancer agents. By coupling drug release with externally applied or tumor-associated hyperthermia, these systems enable controlled and localized therapy, reduce off-target effects, and can be seamlessly integrated with adjunct treatments such as hyperthermia-based sensitization or photothermal therapy. Nonetheless, further research is needed to optimize the biocompatibility, biodegradability, and kinetics of thermal transitions, while ensuring scalability and reproducibility in manufacturing. Advancing these parameters will be essential to move thermoresponsive nanocarriers from experimental proof-of-concept toward clinical translation in CRC and other solid tumors.

3.3.6. Magnetically responsive nanocarriers. Magnetic-responsive drug delivery systems (DDS) have attracted considerable interest in CRC therapy due to their ability to achieve externally guided targeting, controlled drug release, and synergy with hyperthermia-based treatments.[162] These systems primarily employ magnetic nanoparticles (MNPs)—most often iron oxide-based particles such as magnetite (Fe_3O_4)—that exhibit superparamagnetic behavior and can be precisely manipulated by external magnetic fields.[166] This property allows therapeutic carriers to be directed toward tumor sites, thereby reducing off-target toxicity and enhancing antitumor efficacy.

To improve stability, drug-loading capacity, and tumor selectivity, MNPs are frequently functionalized with biocompatible coatings or conjugated with targeting ligands. A notable example involved superparamagnetic nanoparticles (SPMNPs) functionalized with amino groups and covalently linked to monoclonal antibody 198.3 (mAb198.3), which targets FAT1, a receptor highly expressed in CRC.[199] In parallel, erythrocyte membrane-based hybrid vesicles (EMHVs) were engineered to incorporate both SPMNPs and mAb198.3. Application of a 0.1 T external magnetic field facilitated efficient tumor localization for both systems, but EMHVs achieved superior tumor suppression despite requiring ~200-fold lower antibody doses, likely due to enhanced membrane fusion and improved intracellular antibody delivery.[199]

MNPs can also be engineered for dual responsiveness by coupling magnetic targeting with redox-sensitive release. In a CT26 mouse tumor model, DOX was conjugated to chitosan–PEG-coated iron oxide nanoparticles *via* disulfide linkers.[200] Following systemic administration, the particles were guided to tumors under an external magnetic field, while the elevated glutathione (GSH) concentrations within cancer cells cleaved the disulfide bonds to trigger localized DOX release. This design minimized systemic toxicity and improved therapeutic precision, demonstrating how magnetic control and intracellular triggers can be integrated into one platform.[200]

Magnetic DDS further offer therapeutic potential through localized hyperthermia induced by alternating magnetic fields (AMF). When exposed to AMF, MNPs generate heat, inducing apoptosis and sensitizing tumor cells to chemotherapy. For example, superparamagnetic iron oxide clusters (Fe_3O_4/γ-Fe_2O_3) coated with chitosan were intratumorally injected for the delivery of 5-FU. Upon AMF exposure, the combined chemo-hyperthermia strategy produced markedly greater tumor regression compared with either treatment alone.[201]

Building on this, dual-mode systems have been designed to integrate magnetic targeting with heat-triggered drug release. In one study, liposomes encapsulating both DOX and citric acid–coated MNPs (CAMNPs) were developed.[202] The CAMNPs not only improved dispersibility but also enabled efficient incorporation into liposomal cores. When exposed to a high-frequency magnetic field (HFMF), the CAMNPs generated localized hyperthermia, destabilizing the liposomal membrane and releasing DOX in a controlled manner. This combined chemo-hyperthermic platform enhanced tumor eradication while maintaining biocompatibility, underscoring the translational promise of magnetic liposomal systems.[202]

More recently, biomimetic magnetic nanoparticles (BMNPs) —engineered to mimic natural magnetosomes—have emerged as a novel class of nanocarriers. These particles, typically 20–50 nm in size, exhibit high drug-loading capacity (*e.g.*, oxaliplatin) and stability at physiological pH, while enabling drug release under acidic tumor conditions or during hyperthermia.[203] In preclinical CRC models, BMNPs localized efficiently

to tumor tissues under magnetic guidance and significantly enhanced therapeutic efficacy without causing hematologic toxicity, positioning them as promising candidates for clinical translation.

Taken together, magnetic-responsive DDS represent a versatile and multifunctional approach to CRC management. By enabling externally guided tumor accumulation, site-specific drug release, and localized hyperthermia, these systems achieve synergistic antitumor effects while minimizing systemic side effects. Beyond drug delivery, the ability of magnetic nanoparticles to serve as contrast agents offers potential for theranostic integration. However, critical challenges remain, including improving long-term biocompatibility, refining magnetic field parameters to ensure clinical safety, and establishing scalable manufacturing processes.[204,205] Future progress will likely focus on multifunctional nanoplatforms that integrate imaging, targeting, and therapy, accelerating the translation of magnetic-responsive nanomedicine into personalized, minimally invasive treatment strategies for CRC.

4. Multifunctional and hybrid nanoplatforms

The use of single-ligand targeting in cancer nanotherapy has long been recognized as an effective means of improving drug selectivity. However, recent advances in nanotechnology have enabled the development of multifunctional DDS that integrate passive targeting, ligand-mediated recognition, and stimuli-responsive release. These next-generation nanosystems are designed to enhance tumor specificity, maximize therapeutic efficacy, and minimize systemic toxicity, representing a significant step toward personalized CRC therapy (Table 6).

One such strategy combined folate receptor-mediated targeting with pH-responsive drug release for irinotecan delivery. In this dual-targeted approach, folic acid-grafted SLNs encapsulating irinotecan were embedded in alginate microbeads and overcoated with Eudragit S100.[206] While the folate ligand enhanced receptor-mediated uptake, the Eudragit S100 coating ensured colonic release at pH > 7. Compared with ungrafted controls, folate-SLNs displayed superior cytotoxicity against COLO-205 cells, and oral administration of ^{99m}Tc-labeled folate microbeads in mice resulted in ~20% drug accumulation in colon tumors—more than double controls—alongside robust tumor growth inhibition.[206]

Another multifunctional nanoplatform employed fluorescein-labeled wheat germ agglutinin (fWGA) mounted on disulfide cross-linked, pH-sensitive alginate nanoparticles (fDTP2) for docetaxel (DTX) delivery.[207] The system exploited both acidic and reductive tumor environments, releasing 54.7% of DTX under colon-specific conditions. The nanoparticles (277.7 nm, PDI < 0.35, zeta potential −1.0 mV) demonstrated enhanced HT-29 uptake, selective cytotoxicity,

Table 6 Summary of multifunctional/hybrid nanocarriers for CRC therapy

Type of nanocarrier	Composition	Anticancer agent(s)	Target 1	Target 2	Study model	Major findings	Ref.
Liposomes	Soybean PC and cholesterol + alginate and chitosan	5-FU	AS1411	Colonic pH and colonic microflora	*In vitro*: human HT-29 cells	Sustained release and significant targetability of functionalized liposome than aptamer-free liposomes and free drug	212
LPN	PLGA core and PEG shell	Afatinib and miR-139	Targeting ligand: R peptide that targets neuropilin-1	pH-Sensitive penetrating peptide (H peptide)	*In vitro*: Caco-2 cells	Burst and higher release in acidic conditions (pH of 6.5) followed by sustained release Significant cellular uptake, induced apoptosis, inhibit cell migration and overcome resistance	213
Hybrid LPN	PLGA, DSPE-PEG2000-Mal	Irinotecan	Cetuximab	p-sensitive and NIR-triggered releases	*In vitro*: Lovo cells and MCF-7	Cet-CINPs (119 nm and −27.2 mV) effectively target, heat, release drug, generate ROS, and kill cancer cells under NIR	209
Hybrid PNPs	Al_2O_3 NPs incorporated in a matrix of sodium alginate and PVP	CUR	EPR effect	TME pH	*In vitro*: HTC 116 cells.	enhanced bioavailability of CUR and targetability in colonic cells with minimum effect on normal cells	214
Hybrid PNPs	κ-Carrageenan Sodium Alginate Graphene Oxide Iron oxide	Sunitinib	pH	External MF and NIR	*In vitro*: Caco-2 cells	CR/A@GO@Fe_3O_4@Su enabled controlled release of Sunitinib through MF and NIR irradiation, showing significant cytotoxic effects while enhancing selectivity and accumulation at the tumor site	215

Abbreviations: 5-FU, 5-fluorouracil; AS1411, anti-nucleolin aptamer; CUR, curcumin; DSPE, distearoyl phosphatidylethanolamine; EPR, enhanced permeability and retention; LPN, lipid–polymer nanoparticle; miR-139, microRNA-139; MF, magnetic field; NIR, near-infrared; NP, nanoparticle; PEG, polyethylene glycol; PEG2000-Mal, polyethylene glycol 2000-maleimide; PLGA, poly(lactic-*co*-glycolic acid); PNP, polymeric nanoparticle; PVP, polyvinylpyrrolidone; ROS, reactive oxygen species; TME, tumor microenvironment.

and reduced systemic toxicity, underscoring their promise for oral CRC chemotherapy.[207]

Multifunctionality has also been extended to co-delivery strategies. A lipid–polymer hybrid nanoparticle was developed to simultaneously deliver afatinib (a pan-HER inhibitor) and miR-139, a tumor-suppressive microRNA.[208] Coated with pH-sensitive cell-penetrating peptides and a neuropilin-1 ligand, this nanocarrier (Afa/LPN-HR) showed pH-dependent release, enhanced uptake in acidic TME, and potent inhibition of proliferation, migration, and drug resistance in CRC models. Mechanistically, it downregulated HER- and MDR-associated pathways, achieving synergistic therapeutic outcomes.[208]

Similar combinatorial approaches were demonstrated using cetuximab-modified lipid–polymer hybrid nanoparticles (Cet-CINPs) loaded with irinotecan (CPT-11).[209] These nanoparticles (~119 nm, −27.2 mV, encapsulation efficiency 43%) integrated EGFR-mediated targeting with dual pH- and NIR-responsiveness. Under NIR irradiation, localized heating (~51 °C) triggered release of ~69% CPT-11 within 72 h, enhancing cytotoxicity and ROS generation. In EGFR-overexpressing Lovo cells, viability dropped to ~20% at 40 μM CPT-11 after 48 h, far surpassing non-targeted systems.[209]

Beyond polymeric–lipid hybrids, inorganic multifunctional nanoplatforms have been designed to integrate therapy with real-time imaging. A theranostic nanosystem combined GZCIS/ZnS quantum dots (QDs) doped with gadolinium for fluorescence and MRI imaging, encapsulated within MSNs loaded with epirubicin (EPI) and sealed by gold nanoparticles as pH-sensitive gatekeepers.[210] PEGylation improved colloidal stability, while conjugation with an EpCAM-specific aptamer (SYL3C) provided active targeting. The formulation achieved 2.5-fold higher uptake in EpCAM-positive HT-29 cells than non-targeted controls, and when combined with 3 Gy radiotherapy, induced >84% apoptotic death and near-complete tumor regression *in vivo*.[210]

A related study developed hyaluronan-coated, EDTA-modified magnetic MSNs (EDTA-MMSN@HA) for cisplatin delivery.[211] HA coating facilitated CD44-mediated uptake, while EDTA improved cisplatin loading. The nanoparticles (70–100 nm) demonstrated pH-responsive drug release, enhanced *in vitro* cytotoxicity in CRC cells compared with normal cells, and favorable pharmacokinetics with improved systemic circulation and tumor retention. This system exemplifies the growing sophistication of multifunctional, receptor-targeted, and stimuli-responsive CRC therapies.[211]

Despite their potential, multifunctional and hybrid DDS face several translational challenges. The incorporation of multiple functional components increases synthetic complexity, production costs, and stability concerns, while also raising the risk of immunogenicity or off-target effects. Moreover, large-scale manufacturing under good manufacturing practice (GMP) conditions remains a significant barrier. Nevertheless, the successful integration of targeting ligands, stimuli-sensitive linkers, and imaging agents within a single nanoplatform represents a major advance toward precision medicine. By enabling simultaneous tumor-specific recognition, controlled release, and diagnostic monitoring, these systems hold promise for improving CRC treatment outcomes and advancing personalized therapeutic strategies.

5. Challenges and future perspectives

Despite substantial progress in the design and preclinical validation of nanocarrier-based systems for CRC, their clinical translation remains constrained by a series of critical challenges.[216] Tumor heterogeneity—both inter-patient and intratumoral—continues to undermine targeting efficiency. Variability in receptor expression (*e.g.*, EGFR, CD44, integrins) and inconsistencies in the TME, including pH, enzyme activity, and redox potential, often lead to suboptimal accumulation, poor tissue penetration, and unpredictable drug release in human tumors compared to controlled preclinical models.[216]

Equally significant are the manufacturing and regulatory bottlenecks. Many fabrication techniques that succeed on a laboratory scale fail to meet Good Manufacturing Practice (GMP) standards, complicating large-scale production, sterility assurance, and batch-to-batch reproducibility. Even formulations with promising therapeutic indices in animal models may falter in translation due to issues of long-term toxicity, nonspecific biodistribution, immunogenicity, and poorly characterized pharmacokinetics. These limitations highlight the gap between bench-top innovation and clinical applicability.[216,217]

Nevertheless, translation is feasible, as evidenced by several nanocarriers that have progressed to clinical trials or gained FDA approval for solid tumors, including CRC.[218–220] Notable examples include liposomal irinotecan (Onivyde®),[221] nanoparticle albumin-bound PTX (Abraxane®),[222] and SGT-53, a cationic liposomal system delivering p53 DNA.[223] These agents employ distinct strategies—ranging from passive accumulation *via* the EPR effect, to ligand-mediated receptor targeting, to nucleic acid delivery—demonstrating that with robust validation, nanocarriers can overcome translational hurdles. Table 7 summarizes representative clinical-stage and FDA-approved nanocarriers for CRC therapy, underscoring the potential of such platforms.

Looking forward, the future of CRC nanotherapy is likely to center on the design of multifunctional, biodegradable, and clinically adaptable nanoplatforms that integrate precise targeting, controlled release, and diagnostic capabilities. A transformative role is anticipated for machine learning (ML) and artificial intelligence (AI), which can accelerate rational nanocarrier design.[224,225] AI-driven models are capable of predicting optimal physicochemical parameters for drug loading and release, simulating biodistribution, and screening ligand–receptor affinities for enhanced active targeting. Importantly, ML algorithms can stratify patients based on genetic, epigenetic, and microbiome signatures, thereby tailoring nanomedicine to tumor heterogeneity—a major barrier to efficacy. By embedding predictive analytics and virtual screening into the nanomedicine pipeline, AI has the potential to streamline

Table 7 List of FDA-approved and clinical-stage nanocarriers for CRC therapy

Nanocarrier name	Nanocarrier type	Anticancer agent(s)	Targeting mechanism	Clinical status	Notes/CRC relevance
Onivyde® (MM-398)	Liposomal	Irinotecan	Passive (EPR effect)	FDA-approved for pancreatic cancer	Under investigation for metastatic CRC in combination regimens (*e.g.*, NAPOLI-1 trial)
Doxil®/Caelyx®	PEGylated liposome	DOX	Passive (long-circulating, EPR)	FDA-approved	Approved for breast, ovarian, and AIDS-related Kaposi's sarcoma; studied in CRC models
SIR-Spheres®	Resin-based microspheres	Yttrium-90	Locoregional (radioembolization)	FDA-approved for CRC liver metastases	Delivers internal radiotherapy to CRC hepatic metastases
TheraSphere®	Glass-based microspheres	Yttrium-90	Locoregional (radioembolization)	FDA-approved	Used for unresectable liver metastases from CRC
Aroplatin™ (L-NDDP)	Liposomal	Cisplatin analog	Passive (EPR effect)	Phase II (suspended)	Investigated for advanced CRC but development halted due to toxicity issues
CRLX101	Cyclodextrin–polymer NP	Camptothecin (CPT)	Passive + enhanced permeability	Phase II (completed)	Studied in combination with bevacizumab in metastatic CRC (NCT01387321)
MRX34	Liposomal miRNA mimic	miR-34a (tumor suppressor)	Passive (liposomal delivery)	Phase I (terminated)	Investigated in solid tumors including CRC; terminated due to immune-related toxicities
CALAA-01	Cyclodextrin-based NP	siRNA against RRM2	Active (transferrin receptor targeting)	Phase I (halted)	First targeted siRNA nanomedicine in clinical trials; early data included CRC patients
BIND-014	PSMA-targeted PLGA NP	Docetaxel	Active (PSMA ligand)	Phase II (discontinued)	Evaluated in solid tumors including CRC; development discontinued despite initial promise

preclinical evaluation, reduce clinical trial attrition, and expedite regulatory approval. However, this vision requires the establishment of robust, interoperable datasets, validated and explainable ML models, and close collaboration between computational scientists and experimental researchers.[224,225]

Parallel advancements are expected through combinatorial strategies, where nanocarriers are paired with immunotherapies, radiosensitizers, or gene-editing tools such as CRISPR/Cas. Such synergies may amplify antitumor immunity, overcome resistance, and enable truly personalized CRC therapies.[226–228] Yet, real-world translation demands strategic alignment among academia, industry, and regulatory bodies. Standardized guidelines for physicochemical characterization, *in vivo* performance evaluation, and toxicological assessment must be widely adopted. Furthermore, comprehensive long-term studies on biodistribution, immunogenicity, and safety are indispensable to meet regulatory expectations and ensure patient safety.[226–228]

In conclusion, the translation of CRC nanomedicine requires not only technological innovation but also interdisciplinary collaboration and regulatory harmonization. By addressing challenges of heterogeneity, scalability, and safety through advanced materials, AI-guided design, and strategic partnerships, the field can progress from promising laboratory discoveries to clinically effective, personalized nanomedicine for CRC care.

6. Conclusion

Colorectal cancer (CRC) continues to pose a formidable global health challenge, with conventional therapies constrained by poor selectivity, systemic toxicity, and acquired resistance. Nanotechnology-based targeted delivery systems represent a paradigm shift in CRC management, offering site-specific drug release, improved pharmacokinetics, and reduced off-target effects. This review has critically examined passive, active, and stimuli-responsive targeting strategies—each contributing unique advantages. While passive targeting leverages the EPR effect for tumor accumulation, active targeting utilizes ligand–receptor interactions to enhance cellular uptake. Stimuli-responsive platforms further refine delivery through spatiotemporally controlled drug release, triggered by tumor-associated cues such as acidic pH, dysregulated enzymes, redox imbalance, or external stimuli. Emerging multifunctional and hybrid systems that integrate these approaches have demonstrated superior therapeutic outcomes in preclinical CRC models, underscoring their promise for advancing precision oncology.

Despite these advances, translation into clinical success remains limited. Tumor heterogeneity, interpatient variability in TME characteristics, and inconsistent receptor expression often compromise targeting efficiency. Challenges in large-scale, GMP-compliant manufacturing, long-term safety evaluation, and regulatory approval also remain major barriers. Addressing these obstacles requires not only technological innovation but also strategic alignment between academia, industry, and regulatory authorities.

Looking forward, the future of CRC nanotherapy lies in the development of biodegradable, clinically adaptable, and multifunctional nanoplatforms capable of integrating therapeutic and diagnostic functions. Synergistic approaches combining

nanocarriers with immunotherapy, radiotherapy, and gene-editing tools such as CRISPR hold particular promise for overcoming resistance and enabling personalized treatment regimens. Furthermore, the incorporation of artificial intelligence (AI) and machine learning (ML) into nanomedicine design and patient stratification could accelerate the optimization of nanocarriers, improve predictive modeling of nanoparticle–tumor interactions, and enhance clinical trial success rates.

Collectively, addressing current limitations through interdisciplinary collaboration, technological refinement, and regulatory harmonization will be pivotal in realizing the full clinical potential of nanotechnology. With continued progress, nanomedicine holds the potential to redefine the therapeutic landscape of CRC, transforming it into a model for precision oncology and improving survival and quality of life for patients worldwide.

Conflicts of interest

The authors report no conflicts of interest in this work.

Data availability

The authors confirm that the data supporting the findings of this study is available within the article. No additional data sets were generated or analyzed.

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