

# Nano-Drug Delivery Systems Targeting Colorectal Cancer

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Colorectal cancer (CRC) is a usual digestive tract malignancy and the third main cause of cancer death around the world, with a high occurrence rate and mortality rate. Conventional therapies for CRC have certain side effects and restrictions. However, the exciting thing is that with the rapid development of nanotechnology, nanoparticles have gradually become more valuable drug delivery systems than traditional therapies because of their capacity to control drug release and target CRC. This also promotes the application of nano-drug targeted delivery systems in the therapy of CRC.

targeted therapy

colorectal cancer

nanoparticles

drug delivery systems

## 1. Introduction

Colorectal cancer (CRC), the third most common malignancy worldwide, forms in the colon or rectum. It is also the third most common cancer in men and the second in women separately. It is estimated that, by 2035, the number of CRC patients will reach 2.4 million and CRC will cause 1.3 million deaths worldwide <sup>[1][2]</sup>.

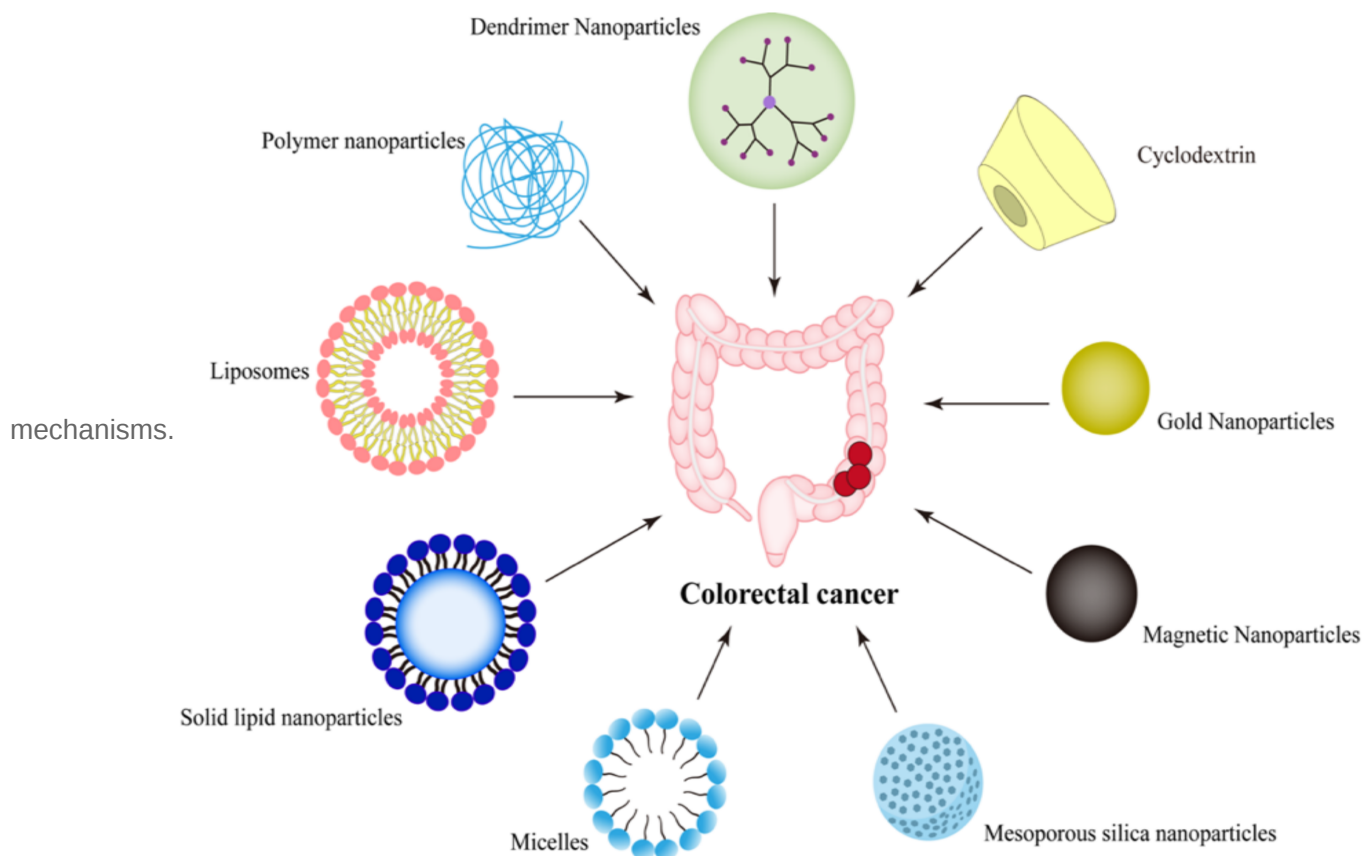
According to the histopathological features, CRC can be divided into four distinct stages, which are also the basis of European Society for Medical Oncology (ESMO) guidelines to take appropriate treatments. In stage 0 of CRC, polyps are formed in the lining of colonic mucosa. Then, in stage I, polyps deteriorate into tumors and begin to migrate into the mucosa. The surgical resection of local tumors can achieve a good therapeutic effect without additional treatment in the above periods. There are many methods of operation, such as excision of polyps on the intestinal wall, excision of intestinal segments of tumors, or standardized excision, and finally reconnecting intestinal segments for ileostomy or colostomy. In stage II, cancer can spread beyond the colon, but it will not metastasize through lymph nodes at this stage. In stage III, the cancer cells spread to the colon wall and surrounding lymph nodes, but not to nearby organs. During these periods, the patients must be treated with both radiotherapy and chemotherapy. Fluoropyrimidine or combined with other chemotherapy drug is usually used to treat CRC. In addition, microsatellite instability status can be used to determine the survival time of patients with localized tumors, and patients with high microsatellite instability will have longer survival time. However, fluorouracil-based chemotherapy is not suitable for them and may even have adverse effects <sup>[3]</sup>. In stage IV, cancer accelerates to spread to other organs of the body <sup>[4]</sup>. At this time, it is not only necessary to remove the tumor through surgery, but also to kill the tumor cells through systemic chemotherapy or the combination of chemotherapy and biological targeted therapy. The biological targeted therapy of CRC uses bevacizumab, which can combine with the vascular endothelial growth factor produced by CRC cells to block tumor angiogenesis,

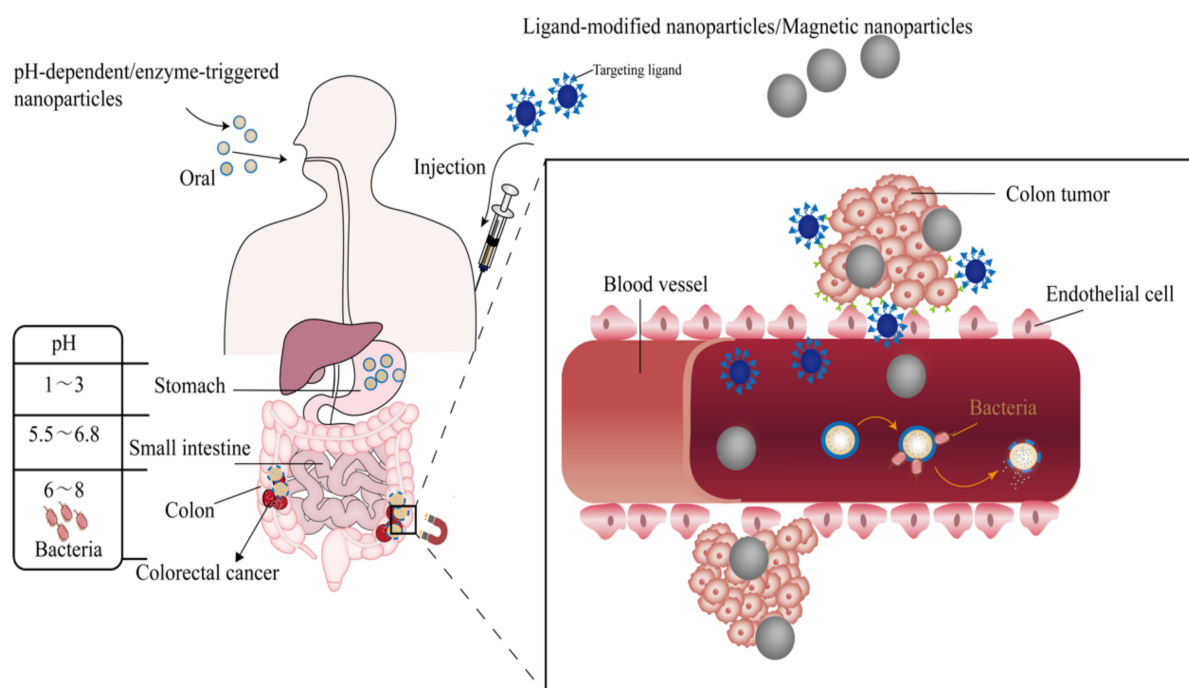
cetuximab as well as panitumumab, which can bind to epidermal growth factor receptor (EGFR) overexpressed in CRC to prevent the growth of tumor cells.

As can be seen from the above, the survival rate of CRC patients can be increased if they are diagnosed as early as possible and treated accordingly, especially before CRC metastasis. Because the first step in the development of CRC is the formation of neoplastic polyps in the colonic mucosa, which are not very dangerous. However, because the specificity of early symptoms of CRC is not obvious and it is difficult to make a differential diagnosis, CRC patients are generally diagnosed in the advanced stage or when metastasis occurs [5].

Disappointingly, traditional therapies in this stage have certain side effects and limitations. For chemotherapy, due to poor physical and chemical properties, low bioavailability, and poor tissue selectivity of chemotherapeutic drugs, patients may suffer from many serious side effects [6][7][8]. Radiotherapy can cause serious DNA damage in patients sensitive to radiation damage, leading to the further development of tumors [9]. The side effect caused by receptor inhibitors is skin irritation [10]. Immunotherapy drugs cost a lot and have many side effects [11][12]. So, it is necessary to optimize the drug delivery to a specific target and minimize the side effects [13].

It is encouraging that, with the development of nanotechnology, there are many nano-drug delivery systems targeting CRC with high-efficiency anticancer, such as lipid nanoparticles, polymer nanoparticles, and liposomes, which can realize the delivery of chemotherapeutic drugs, genes, and vaccines. Various nano-drug delivery systems targeting CRC are presented in **Figure 1**. They can significantly improve the stability of drug in vivo, reduce the systemic toxicity of drug, and overcome drug resistance. **Figure 2** shows some representative targeting



**Figure 1.** Types of nano-drug delivery systems targeting CRC.**Figure 2.** A schematic diagram of some representative targeting mechanism.

## 2. Nano-Drug Delivery Systems Targeting CRC

### 2.1. Passive Targeting Nanoparticles

It is generally believed that the anatomy and pathophysiology of solid tumors differ from that of normal tissue. For example, solid tumors have a high blood vessel density to meet the nutrition and oxygen required by tumor cells growth. Furthermore, the tumor lacks functional lymphatic vessels and the gap between tumor endothelial cells is relatively large, which can extravasate or retain macromolecular drugs. The phenomenon that makes nanoparticles accumulate in tumor cells is called the enhanced permeability and retention (EPR) effect [\[14\]](#)[\[15\]](#)[\[16\]](#).

The discovery of this phenomenon has promoted the emergence of passive targeting nanoparticles, which can target tumors through the EPR effect. In research, oxaliplatin was encapsulated into N, O-carboxymethyl chitosan nanoparticles by ionic crosslinking, and resveratrol was encapsulated into them by emulsification crosslinking. The particle size of the former was about 190.0 nm and that of the latter was about 164.2 nm. The nanoparticles enhanced the solubility, stability, and EPR effect of oxaliplatin and resveratrol, showing stronger anti-CRC activity in subcutaneous tumor-bearing mice compared to the free drug [\[17\]](#).

However, according to research findings, nanoparticles smaller than 10 nm are filtered out by the kidneys, and particles larger than 100 nm are captured by the liver, so the ideal nanoparticles should be between 10 nm and 100 nm in size, which can circulate for a long time to increase the possibility of uptake by tumors [\[18\]](#). Moreover, Anitha et al. [\[19\]](#) mentioned that the degree of vascularization in CRC is low. It can be seen that there are controversies

about the EPR effect in CRC. In recent years, scientists have gradually realized that the tumor-targeting mediated by EPR is highly heterogeneous. Hence, it is necessary to enhance the targeting ability of nanoparticles based on EPR by combining them with other targeting mechanisms [20][21].

## 2.2. Active Targeting Nanoparticles

Ligand-modified nanoparticles can actively accumulate in the tumor through a ligand–receptor binding mechanism, thus delivering the drug to the target. These nanoparticles are called active targeting nanoparticles [22]. Cancer cells overexpress some types of receptors and secrete biomolecules that can promote cell proliferation of cancer and surrounding tissues through paracrine or autocrine pathways [23]. In studies, there are two main methods to combine ligands with nanoparticles: one is to modify them chemically during the synthesis of nanoparticles, and the other is to bind ligands with polymers before the synthesis of nanoparticles [24][25]. Ligand-modified nanoparticles can accumulate in the tumor through passive targeting, and then enter tumor cells through active targeting, resulting in a more selective and enhanced therapeutic effect.

In the recent three years, the active targeting design idea of nano-drug targeted delivery systems for CRC mainly adopt the receptor–ligand binding strategy, which involved many highly expressed receptors in CRC, such as folate receptor [26], EGFR [27], CD44, epithelial cell adhesion molecule (EpCAM) [28], CD133,  $\alpha\beta3$  integrin receptor, carcinoembryonic antigen [29], nucleolin [30], mannose receptor [31], hyaluronic acid receptor [32], *N*-acetyl-d-glucosamine [33], transferrin receptor [34], checkpoint kinase 2 [35], CXCR4+ [36], lipoprotein receptor-related protein-1 [37], MUC1 [38], NRP-1 [39], *P*-selectin [40], sigma-2 receptors [41], SSTRs [42], and glucocorticoid receptor [43].

### 2.2.1. Nanoparticles Targeting EpCAM

Epithelial cell adhesion molecule (EpCAM) is a 314 amino acid and 39 kDa transmembrane glycoprotein that almost only exists on epithelial cells playing a role in adhering cells in normal cells [44][45]. As early as 1979, it has been reported as the main surface antigen of CRC [46]. Later, scholars have found that overexpression of EpCAM also existed in human adenocarcinoma cells, and it could also carry out intercellular signal transduction [47].

In many kinds of research, to make nanoparticles target CRC after systemic administration, a DNA EpCAM aptamer (SYL3C) having a strong affinity with EpCAM protein and cancer cells expressing EpCAM was modified on nanoparticles. To reduce drug toxicity and improve therapeutic effect, Ge et al. [28] synthesized biological conjugates loaded with celastrol, which could be captured by CRC overexpressed with EpCAM. EpCAM aptamer, PEG, and dendrimers constituted the conjugates. The results showed that SW620 would undergo extensive apoptosis when exposed to biological conjugates. Moreover, in the xenograft mice and zebrafish models, the biological conjugate showed low toxicity. The dendrimer used in the study is composed of biocompatible components and has an excellent multivalent effect, which can improve the safety of chemotherapeutic drugs.

In another study, the author prepared a cationic liposome to deliver miR-139-5p. The main lipids contained in it are HSPC, DOTAP, Chol, and DSPE-PEG2000-COOH. Moreover, to make the nanoparticles target CRC, the surface of it was modified with EpCAM aptamer. It is found that nanoparticles had inhibitory effects on HCT cells,

consistent with the experimental results of animal pharmacodynamics experiments. They also restrained the tumor growth of CRC mice injected subcutaneously with HCT8 [48].

In addition to the specific targets of CRC, some targets of other tumors are also expressed in CRC, which can be used as the targets of nano-drug delivery systems in the targeted therapy of CRC.

### 2.2.2. Nanoparticles Targeting Folate Receptor

The folate receptor is a cell membrane-anchored protein, which is slightly expressed or absent in normal cells, but overexpressed in various malignant tumor cells, especially in CRC [22]. Therefore, it can be used as a target. Natural polymers chitosan and chondroitin sulfate have the advantages of biocompatibility and biodegradability. Soe et al. [26] prepared self-assembled nanoparticles using these two materials to incorporate the hydrophobic drug, bortezomib, and modified the nanoparticles to actively target folate receptors.

Folate was attached to DSPE-PEG and then coupled with nanoparticles. It was found that DSPE-PEG can not only promote blood circulation, but also improve core drug loading and stability. In the pharmacodynamic experiment of animal models, researchers found that nanoparticles had a strong inhibitory effect on the transplanted tumor and were almost non-toxic to other parts outside the tumor.

### 2.2.3. Nanoparticles Targeting EGFR

The overexpression of epidermal growth factor receptor (EGFR) occurs in about one-third of epithelial malignancies. It can stimulate tumor growth, proliferation, promote angiogenesis, and promote cell invasion and metastasis. Therefore, the poor prognosis of CRC may have a great relationship with the overexpression of EGFR in CRC [49]. In order to solve this problem, targeted therapy using monoclonal antibodies to block biological pathways has been used to treat CRC.

The commonly used monoclonal antibody is cetuximab, which is used for CRC under FDA approval [50]. It can selectively target the EGFR to block signal transduction in vivo [49]. This characteristic also makes cetuximab widely used to modify nano-drug delivery systems, actively target CRC, and increase the accumulation in CRC [51].

Sankha Bhattacharya [27] formulated PLGA-PEG-coated nanoparticles to deliver anti-epidermal growth factor receptor-5-fluorouracil (5-FU), which could improve the pharmacodynamics and distribution of the drug in vivo. The Anti-EGFR mAb was bound to the polymeric nanoparticles by using m-maleimidobenzoyl-N hydroxysuccinimide ester to increase target specificity. On the other hand, polymeric nanoparticles consisting of PLGA and PEG can block opsonic action through the reticular epithelial system. These nanoparticles have great clinical value because their preparation methods are solvent emulsification and evaporation, which are simple and rapid [52].

Another attractive carrier is gold nanoparticles, which are commercially available and easily functionalized. Hallal et al. [53] found that AuNPs loaded with cetuximab had better EGFR endocytosis and could inhibit downriver signaling pathways compared with cetuximab and gold nanoparticles alone, which could inhibit cell proliferation and

accelerate cell apoptosis. This finding is of great help in solving the problem of drug resistance in the treatment of EGFR monoclonal antibodies.

Moreover, many studies found that the therapeutic effect of monoclonal antibodies could be improved by combining McAb with chemotherapeutic drugs [54][55]. Chen et al. [56] constructed a hybrid nano delivery system to deliver 5-FU, including mesoporous silica nanoparticles (MSN), a supported lipid bilayer (SLB), and cetuximab. Furthermore, the SLB-MSN was functionalized with hydrophilic PEG, which made the nanoparticles more stable, circulate longer in the blood, and more likely to accumulate in the tumor through the EPR effect. Then, to enable the nanoparticles to actively target CRC, cetuximab was coupled to the PEG terminal in SLB-MSN. The SLB-MSN has the advantages of both MSN and liposome, showing significant biocompatibility. It can also encapsulate much drug, achieve controlled release, and its stability can be greatly improved.

#### 2.2.4. Nanoparticles Targeting CD44

CD44 is a transmembrane glycoprotein that exists as an adhesion molecule on the cell surface and takes part in intercellular and cytomatrix interactions, as well as cell adhesion and migration [57]. The overexpression of CD44 in CRC cells is closely related to tumor metastasis [58][59]. Therefore, it is also a biomarker for CRC as well as a target. Hyaluronic acid (HA) is the main ligand of CD44, consisting of units of D-glucuronic acid and N-acetyl-D-glucosamine alternately. Especially, it is very popular with researchers, because of its non-toxic, excellent biocompatibility, and biodegradability [60].

Wang et al. [58] synthesized HA-decorated polydopamine nanoparticles to deliver chlorin e6 to the CRC. By coupling the HA with nanoparticles, the nanoparticles were easily internalized via endocytosis under the guidance of CD44. Moreover, chlorin e6 [61], the second-generation PS approved by FDA, and polydopamine, the photothermal agent with excellent light-thermal conversion efficiency were conjugated to promote the synergistic effect of photodynamic therapy and photothermal therapy by avoiding the toxicity induced by metal-ion. The result showed that the tumor growth was inhibited strongly in HCT-116 tumor mice, which also confirmed that the antitumor efficiency could be enhanced by combining the two treatments.

#### 2.2.5. Biomimetic Nano Delivery Systems

In addition to the ligand–receptor binding strategy, the nanoparticles can also actively target the tumor by bionic technology, which mainly uses biofilms to coat nanoparticles. This strategy can not only prevent nanoparticles from being identified by the immune system, but also make use of membrane proteins, glycoproteins, and homologous adhesion to make nanoparticles specifically accumulate in the tumor. Recently, the bionic cell membranes used in the reported nanoparticles are mainly erythrocyte membrane [62], cancer cell membrane [63], leukocyte membrane [64], and so on. Furthermore, to make the nanoparticles endowed with more properties, it is better to camouflage the nanoparticles with hybrid cell membranes.

Wang et al. [63] prepared  $\text{Zn}_{1.25}\text{Ga}_{1.5}\text{Ge}_{0.25}\text{O}_4$ :  $\text{Cr}^{3+}$ ,  $\text{Yb}^{3+}$ ,  $\text{Er}^{3+}$  persistent luminescence nanoparticles coated with mesoporous silica to deliver IR825 as well as irinotecan and encapsulated the nanoparticles with a cancer cell-



macrophage hybrid membrane. The membrane made the nanoparticles actively target the tumor, then the nanoparticles continued to glow at the tumor, which could provide an accurate position for subsequent photothermal therapy. Moreover, after the CT26 tumor-bearing mice were treated with three months of nanoparticles and laser irradiation, the relative tumor volume of mice decreased significantly.

In a study, hollow long persistence luminescence nanomaterials loaded with cisplatin were synthesized and coated with a hybrid cell membrane, which was mainly composed of a customized erythrocyte membrane that could prevent nanoparticles from being recognized by the immune system and biofilm expressing PD-1 that gave nanoparticles targeting ability. Then, this team evaluated their efficacy through in vitro anti-cancer experiments and concluded that these nanoplatforms, which played the role of immunotherapy and chemotherapy, were efficient in CT26 tumor-bearing mice [65]. These studies indicated that bionic technology may be an effective method for tumor-targeted therapy.

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## References

1. Douaiher, J.; Ravipati, A.; Grams, B.; Chowdhury, S.; Alatise, O.; Are, C. Colorectal cancer-global burden, trends, and geographical variations. *J. Surg. Oncol.* 2017, 115, 619–630.
2. Mattiuzzi, C.; Sanchis-Gomar, F.; Lippi, G. Concise update on colorectal cancer epidemiology. *Ann. Transl. Med.* 2019, 7, 609.
3. Ribic, C.M.; Sargent, D.J.; Moore, M.J.; Thibodeau, S.N.; French, A.J.; Goldberg, R.M.; Hamilton, S.R.; Laurent-Puig, P.; Gryfe, R.; Shepherd, L.E.; et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003, 349, 247–257.
4. Hashiguchi, Y.; Muro, K.; Saito, Y.; Ito, Y.; Ajioka, Y.; Hamaguchi, T.; Hasegawa, K.; Hotta, K.; Ishida, H.; Ishiguro, M.; et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int. J. Clin. Oncol.* 2020, 25, 1–42.
5. De Rosa, M.; Pace, U.; Rega, D.; Costabile, V.; Duraturo, F.; Izzo, P.; Delrio, P. Genetics, diagnosis and management of colorectal cancer (Review). *Oncol. Rep.* 2015, 34, 1087–1096.
6. Alomrani, A.; Badran, M.; Harisa, G.I.; Alshehry, M.; Alhariri, M.; Alshamsan, A.; Alkholief, M. The use of chitosan-coated flexible liposomes as a remarkable carrier to enhance the antitumor efficacy of 5-fluorouracil against colorectal cancer. *Saudi Pharm. J.* 2019, 27, 603–611.
7. Goldberg, R.M.; Tabah-Fisch, I.; Bleiberg, H.; de Gramont, A.; Tournigand, C.; Andre, T.; Rothenberg, M.L.; Green, E.; Sargent, D.J. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J. Clin. Oncol.* 2006, 24, 4085–4091.

8. Son, H.S.; Lee, W.Y.; Lee, W.S.; Yun, S.H.; Chun, H.K. Compliance and effective management of the hand-foot syndrome in colon cancer patients receiving capecitabine as adjuvant chemotherapy. *Yonsei Med. J.* 2009, 50, 796–802.
9. Joye, I.; Haustermans, K. Early and late toxicity of radiotherapy for rectal cancer. *Recent Results Cancer Res.* 2014, 203, 189–201.
10. Masago, K.; Imamichi, F.; Masuda, Y.; Ariga, N.; Fujitomi, K.; Fukumine, Y.; Hatakenaka, K.; Fujita, S.; Katakami, N. Team Management of Skin Rash Associated with Use of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors. *Asia Pac. J. Oncol. Nurs.* 2018, 5, 430–434.
11. Tang, Y.Z.; Szabados, B.; Leung, C.; Sahdev, A. Adverse effects and radiological manifestations of new immunotherapy agents. *Br. J. Radiol.* 2019, 92, 20180164.
12. Feldmann, S.M. Cancer immunotherapy in routine cost-effective cancer care? *EMBO Mol. Med.* 2018, 10, e9660.
13. Skalickova, S.; Loffelmann, M.; Gargulak, M.; Kepinska, M.; Docekalova, M.; Uhlirova, D.; Stankova, M.; Fernandez, C.; Milnerowicz, H.; Ruttkay-Nedecky, B.; et al. Zinc-Modified Nanotransporter of Doxorubicin for Targeted Prostate Cancer Delivery. *Nanomaterials* 2017, 7, 435.
14. Matsumura, Y.; Maeda, H. A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res.* 1986, 46, 6387–6392.
15. Maeda, H.; Sawa, T.; Konno, T. Mechanism of tumor-targeted delivery of macromolecular drugs, including the EPR effect in solid tumor and clinical overview of the prototype polymeric drug SMANCS. *J. Control. Release* 2001, 74, 47–61.
16. Maeda, H.; Bharate, G.Y.; Daruwalla, J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. *Eur. J. Pharm. Biopharm.* 2009, 71, 409–419.
17. Wang, Y.; Ma, J.; Qiu, T.; Tang, M.; Zhang, X.; Dong, W. In vitro and in vivo combinatorial anticancer effects of oxaliplatin- and resveratrol-loaded N,O-carboxymethyl chitosan nanoparticles against colorectal cancer. *Eur. J. Pharm. Sci.* 2021, 163, 105864.
18. Acharya, S.; Sahoo, S.K. PLGA nanoparticles containing various anticancer agents and tumour delivery by EPR effect. *Adv. Drug Deliv. Rev.* 2011, 63, 170–183.
19. Anitha, A.; Maya, S.; Sivaram, A.J.; Mony, U.; Jayakumar, R. Combinatorial nanomedicines for colon cancer therapy. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 2016, 8, 151–159.
20. Nichols, J.W.; Bae, Y.H. EPR: Evidence and fallacy. *J. Control. Release* 2014, 190, 451–464.
21. Golombek, S.K.; May, J.N.; Theek, B.; Appold, L.; Drude, N.; Kiessling, F.; Lammers, T. Tumor targeting via EPR: Strategies to enhance patient responses. *Adv. Drug Deliv. Rev.* 2018, 130, 17–



- 38.
22. Hu, Y.; He, Y.; Ji, J.; Zheng, S.; Cheng, Y. Tumor Targeted Curcumin Delivery by Folate-Modified MPEG-PCL Self-Assembly Micelles for Colorectal Cancer Therapy. *Int. J. Nanomed.* 2020, 15, 1239–1252.
23. Dabkeviciene, D.; Jonusiene, V.; Zitkute, V.; Zalyte, E.; Grigaitis, P.; Kirveliene, V.; Sasnauskiene, A. The role of interleukin-8 (CXCL8) and CXCR2 in acquired chemoresistance of human colorectal carcinoma cells HCT116. *Med. Oncol.* 2015, 32, 258.
24. Yu, D.H.; Lu, Q.; Xie, J.; Fang, C.; Chen, H.Z. Peptide-conjugated biodegradable nanoparticles as a carrier to target paclitaxel to tumor neovasculature. *Biomaterials* 2010, 31, 2278–2292.
25. Jain, A.K.; Massey, A.; Yusuf, H.; McDonald, D.M.; McCarthy, H.O.; Kett, V.L. Development of polymeric-cationic peptide composite nanoparticles, a nanoparticle-in-nanoparticle system for controlled gene delivery. *Int. J. Nanomed.* 2015, 10, 7183–7196.
26. Soe, Z.C.; Poudel, B.K.; Nguyen, H.T.; Thapa, R.K.; Ou, W.; Gautam, M.; Poudel, K.; Jin, S.G.; Jeong, J.H.; Ku, S.K.; et al. Folate-targeted nanostructured chitosan/chondroitin sulfate complex carriers for enhanced delivery of bortezomib to colorectal cancer cells. *Asian J. Pharm. Sci.* 2019, 14, 40–51.
27. Bhattacharya, S. Anti-EGFR-mAb and 5-Fluorouracil Conjugated Polymeric Nanoparticles for Colorectal Cancer. *Recent Pat. Anti-Cancer Drug Discov.* 2021, 16, 84–100.
28. Ge, P.J.; Niu, B.N.; Wu, Y.H.; Xu, W.X.; Li, M.Y.; Sun, H.S.; Zhou, H.; Zhang, X.K.; Xie, J.J. Enhanced cancer therapy of celastrol in vitro and in vivo by smart dendrimers delivery with specificity and biosafety. *Chem. Eng. J.* 2020, 383, 123228.
29. Xu, M.; Wen, Y.Y.; Liu, Y.N.; Tan, X.J.; Chen, X.; Zhu, X.F.; Wei, C.F.; Chen, L.M.; Wang, Z.; Liu, J. Hollow mesoporous ruthenium nanoparticles conjugated bispecific antibody for targeted anti-colorectal cancer response of combination therapy. *Nanoscale* 2019, 11, 9661–9678.
30. Khatami, F.; Matin, M.M.; Danesh, N.M.; Bahrami, A.R.; Abnous, K.; Taghdisi, S.M. Targeted delivery system using silica nanoparticles coated with chitosan and AS1411 for combination therapy of doxorubicin and anti-miR-21. *Carbohydr. Polym.* 2021, 266, 118111.
31. Bai, H.Z.; Wang, J.W.; Phan, C.U.; Chen, Q.; Hu, X.R.; Shao, G.Q.; Zhou, J.; Lai, L.H.; Tang, G.P. Cyclodextrin-based host-guest complexes loaded with regorafenib for colorectal cancer treatment. *Nat. Commun.* 2021, 12, 759.
32. Pan, D.C.; Krishnan, V.; Salinas, A.K.; Kim, J.; Sun, T.; Ravid, S.; Peng, K.; Wu, D.; Nurunnabi, M.; Nelson, J.A.; et al. Hyaluronic acid-doxorubicin nanoparticles for targeted treatment of colorectal cancer. *Bioeng. Transl. Med.* 2021, 6, e10166.

33. Pandey, A.N.; Rajpoot, K.; Jain, S.K. Using 5-fluorouracil-encored plga nanoparticles for the treatment of colorectal cancer: The in-vitro characterization and cytotoxicity studies. *Nanomed. J.* 2020, 7, 211–224.
34. Wei, Y.H.; Gu, X.L.; Sun, Y.P.; Meng, F.H.; Storm, G.; Zhong, Z.Y. Transferrin-binding peptide functionalized polymersomes mediate targeted doxorubicin delivery to colorectal cancer in vivo. *J. Control. Release* 2020, 319, 407–415.
35. Ahmad, A.; Ansari, M.M.; Verma, R.K.; Khan, R. Aminocellulose-Grafted Polymeric Nanoparticles for Selective Targeting of CHEK2-Deficient Colorectal Cancer. *ACS Appl. Bio. Mater.* 2021, 4, 5324–5335.
36. Serna, N.; Alamo, P.; Ramesh, P.; Vinokurova, D.; Sanchez-Garcia, L.; Unzueta, U.; Gallardo, A.; Cespedes, M.V.; Vazquez, E.; Villaverde, A.; et al. Nanostructured toxins for the selective destruction of drug-resistant human CXCR4(+) colorectal cancer stem cells. *J. Control. Release* 2020, 320, 96–104.
37. Lee, K.J.; Ko, E.J.; Park, Y.Y.; Park, S.S.; Ju, E.J.; Park, J.; Shin, S.H.; Suh, Y.A.; Hong, S.M.; Park, I.J.; et al. A novel nanoparticle-based theranostic agent targeting LRP-1 enhances the efficacy of neoadjuvant radiotherapy in colorectal cancer. *Biomaterials* 2020, 255, 120151.
38. Bagheri, E.; Abnous, K.; Farzad, S.A.; Taghdisi, S.M.; Ramezani, M.; Alibolandi, M. Targeted doxorubicin-loaded mesenchymal stem cells-derived exosomes as a versatile platform for fighting against colorectal cancer. *Life Sci.* 2020, 261, 118369.
39. Shi, Y.; Shan, S.F.; Li, C.H.; Song, X.J.; Zhang, C.X.; Chen, J.Y.; You, J.; Xiong, J.Y. Application of the Tumor Site Recognizable and Dual-Responsive Nanoparticles for Combinational Treatment of the Drug-Resistant Colorectal Cancer. *Pharm. Res.* 2020, 37, 72.
40. DuRoss, A.N.; Landry, M.R.; Thomas, C.R.; Neufeld, M.J.; Sun, C. Fucoidan-coated nanoparticles target radiation-induced P-selectin to enhance chemoradiotherapy in murine colorectal cancer. *Cancer Lett.* 2021, 500, 208–219.
41. Ramzy, L.; Metwally, A.A.; Nasr, M.; Awad, G.A.S. Novel thymoquinone lipidic core nanocapsules with anisamide-polymethacrylate shell for colon cancer cells overexpressing sigma receptors. *Sci. Rep.* 2020, 10, 10987.
42. Abdellatif, A.A.H.; Ibrahim, M.A.; Amin, M.A.; Maswadeh, H.; Alwehaibi, M.N.; Al-Harbi, S.N.; Alharbi, Z.A.; Mohammed, H.A.; Mehany, A.B.M.; Saleem, I. Cetuximab Conjugated with Octreotide and Entrapped Calcium Alginate-beads for Targeting Somatostatin Receptors. *Sci. Rep.* 2020, 10, 4736.
43. Jinka, S.; Rachamalla, H.K.; Bhattacharyya, T.; Sridharan, K.; Jaggarapu, M.; Yakati, V.; Banerjee, R. Glucocorticoid receptor-targeted liposomal delivery system for delivering small molecule ESC8 and anti-miR-Hsp90 gene construct to combat colon cancer. *Biomed. Mater.* 2021, 16, 024105.

44. Trzpis, M.; McLaughlin, P.M.; de Leij, L.M.; Harmsen, M.C. Epithelial cell adhesion molecule: More than a carcinoma marker and adhesion molecule. *Am. J. Pathol.* 2007, 171, 386–395.
45. Maetzel, D.; Denzel, S.; Mack, B.; Canis, M.; Went, P.; Benk, M.; Kieu, C.; Papior, P.; Baeuerle, P.A.; Munz, M.; et al. Nuclear signalling by tumour-associated antigen EpCAM. *Nat. Cell Biol.* 2009, 11, 162–171.
46. Herlyn, M.; Steplewski, Z.; Herlyn, D.; Koprowski, H. Colorectal carcinoma-specific antigen: Detection by means of monoclonal antibodies. *Proc. Natl. Acad. Sci. USA* 1979, 76, 1438–1442.
47. Chong, J.M.; Speicher, D.W. Determination of disulfide bond assignments and N-glycosylation sites of the human gastrointestinal carcinoma antigen GA733-2 (CO17-1A, EGP, KS1-4, KSA, and Ep-CAM). *J. Biol. Chem.* 2001, 276, 5804–5813.
48. Zhao, Y.Y.; Xu, J.J.; Le, V.M.; Gong, Q.Y.; Li, S.Y.; Gao, F.; Ni, L.; Liu, J.W.; Liang, X. EpCAM Aptamer-Functionalized Cationic Liposome-Based Nanoparticles Loaded with miR-139-5p for Targeted Therapy in Colorectal Cancer. *Mol. Pharm.* 2019, 16, 4696–4710.
49. Li, C.; Cai, G.; Song, D.; Gao, R.; Teng, P.; Zhou, L.; Ji, Q.; Sui, H.; Cai, J.; Li, Q.; et al. Development of EGFR-targeted evodiamine nanoparticles for the treatment of colorectal cancer. *Biomater Sci.* 2019, 7, 3627–3639.
50. Sabra, R.; Billa, N.; Roberts, C.J. Cetuximab-conjugated chitosan-pectinate (modified) composite nanoparticles for targeting colon cancer. *Int. J. Pharm.* 2019, 572, 118775.
51. Pedrosa, P.; Corvo, M.L.; Ferreira-Silva, M.; Martins, P.; Carneiro, M.C.; Costa, P.M.; Martins, C.; Martins, L.; Baptista, P.V.; Fernandes, A.R. Targeting Cancer Resistance via Multifunctional Gold Nanoparticles. *Int. J. Mol. Sci.* 2019, 20, 5510.
52. Rafiei, P.; Haddadi, A. Docetaxel-loaded PLGA and PLGA-PEG nanoparticles for intravenous application: Pharmacokinetics and biodistribution profile. *Int. J. Nanomed.* 2017, 12, 935–947.
53. El Hallal, R.; Lyu, N.; Wang, Y. Effect of Cetuximab-Conjugated Gold Nanoparticles on the Cytotoxicity and Phenotypic Evolution of Colorectal Cancer Cells. *Molecules* 2021, 26, 567.
54. Prewett, M.; Bassi, R.; Carrick, F.; Finnerty, B.; Ellis, L.M.; Witte, L.; Tonra, J.R.; Hicklin, D.J.; Fan, F. Cetuximab (ERBITUX (R)) enhances clinical efficacy of oxaliplatin in human colon carcinoma xenografts and reverses oxaliplatin resistance. *Clin. Cancer Res.* 2005, 11, 9048S.
55. Prewett, M.C.; Hooper, A.T.; Bassi, R.; Ellis, L.M.; Waksal, H.W.; Hicklin, D.J. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin. Cancer Res.* 2002, 8, 994–1003.
56. Chen, R.; Huang, Y.; Wang, L.; Zhou, J.; Tan, Y.; Peng, C.; Yang, P.; Peng, W.; Li, J.; Gu, Q.; et al. Cetuximab functionalization strategy for combining active targeting and antimigration capacities of

- a hybrid composite nanoplatform applied to deliver 5-fluorouracil: Toward colorectal cancer treatment. *Biomater. Sci.* 2021, 9, 2279–2294.
57. Medrano-González, P.A.; Rivera-Ramírez, O.; Montañó, L.F.; Rendón-Huerta, E.P. Proteolytic Processing of CD44 and Its Implications in Cancer. *Stem Cells Int.* 2021, 2021, 6667735.
58. Wang, X.L.; Ouyang, X.M.; Chen, J.L.; Hu, Y.; Sun, X.Y.; Yu, Z.W. Nanoparticulate photosensitizer decorated with hyaluronic acid for photodynamic/photothermal cancer targeting therapy. *Nanomedicine* 2019, 14, 151–167.
59. Lokeshwar, B.L.; Lokeshwar, V.B.; Block, N.L. Expression of CD44 in prostate cancer cells: Association with cell proliferation and invasive potential. *Anticancer Res.* 1995, 15, 1191–1198.
60. Huang, J.; Zhang, H.; Yu, Y.; Chen, Y.; Wang, D.; Zhang, G.; Zhou, G.; Liu, J.; Sun, Z.; Sun, D.; et al. Biodegradable self-assembled nanoparticles of poly (D,L-lactide-co-glycolide)/hyaluronic acid block copolymers for target delivery of docetaxel to breast cancer. *Biomaterials* 2014, 35, 550–566.
61. Gao, S.; Wang, J.; Tian, R.; Wang, G.; Zhang, L.; Li, Y.; Li, L.; Ma, Q.; Zhu, L. Construction and Evaluation of a Targeted Hyaluronic Acid Nanoparticle/Photosensitizer Complex for Cancer Photodynamic Therapy. *ACS Appl. Mater. Interfaces* 2017, 9, 32509–32519.
62. Liu, J.M.; Zhang, D.D.; Fang, G.Z.; Wang, S. Erythrocyte membrane bioinspired near-infrared persistent luminescence nanocarriers for in vivo long-circulating bioimaging and drug delivery. *Biomaterials* 2018, 165, 39–47.
63. Wang, Z.H.; Liu, J.M.; Zhao, N.; Li, C.Y.; Lv, S.W.; Hu, Y.Z.; Lv, H.; Wang, D.; Wang, S. Cancer Cell Macrophage Membrane Camouflaged Persistent Luminescent Nanoparticles for Imaging-Guided Photothermal Therapy of Colorectal Cancer. *ACS Appl. Nano Mater.* 2020, 3, 7105–7118.
64. Zhang, Q.; Dehaini, D.; Zhang, Y.; Zhou, J.; Chen, X.; Zhang, L.; Fang, R.H.; Gao, W.; Zhang, L. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. *Nat. Nanotechnol.* 2018, 13, 1182–1190.
65. Wang, Z.H.; Liu, J.M.; Yang, F.E.; Hu, Y.Z.; Lv, H.; Wang, S. Tailor-Made Cell-Based Biomimetic Nanoprobes for Fluorescence Imaging Guided Colorectal Cancer Chemo-immunotherapy. *ACS Appl. Bio Mater.* 2021, 4, 1920–1931.

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