Immunotherapy-based novel nanoparticles in the treatment of gastrointestinal cancer: Trends and challenges

Yi-Nan Ding, Ming Xue, Qiu-Sha Tang, Li-Jun Wang, Hui-Yan Ding, Han Li, Cheng-Cheng Gao, Wei-Ping Yu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0

P-Reviewer: Manojlovic N, Serbia; Serban ED, Romania

Received: July 21, 2022
Peer-review started: July 21, 2022
First decision: August 19, 2022
Revised: August 27, 2022
Accepted: September 15, 2022
Article in press: September 15, 2022
Published online: October 7, 2022

Abstract

Gastrointestinal cancer (GIC) is the most common cancer with a poor prognosis. Currently, surgery is the main treatment for GIC. However, the high rate of postoperative recurrence leads to a low five-year survival rate. In recent years, immunotherapy has received much attention. As the only immunotherapy drugs approved by the Food and Drug Administration (FDA), immune checkpoint blockade (ICB) drugs have great potential in cancer therapy. Nevertheless, the efficacy of ICB treatment is greatly limited by the low immunogenicity and immunosuppressive microenvironment of GIC. Therefore, the targets of immunotherapy have expanded from ICB to increasing tumor immunogenicity, increasing the recruitment and maturation of immune cells and reducing the proportion of inhibitory immune cells, such as M2-like macrophages, regulatory T cells and myeloid-derived suppressor cells. Moreover, with the development of nanotechnology, a variety of nanoparticles have been approved by the FDA for clinical therapy, so novel nanodrug delivery systems have become a research focus for anticancer therapy. In this review, we summarize recent advances in the application of immunotherapy-based nanoparticles in GICs, such as gastric cancer, hepatocellular carcinoma, colorectal cancer and pancreatic cancer, and described the existing challenges and future trends.
INTRODUCTION

Gastrointestinal cancer (GIC) has been among the most commonly diagnosed cancers in recent decades [1-5]. In recent reports, the incidence and mortality rates have gradually decreased for gastric cancer (GC), hepatocellular carcinoma (HCC) and esophageal cancer in China; in contrast, the rates for colorectal cancer (CRC) have increased[4]. Regardless of the changes in the incidence and mortality rates of GIC, the disease has greatly affected the quality of life of many individuals.

Similar to other types of cancer, GIC has several therapies available. As the most conventional means of cancer treatment, surgery, chemotherapy and radiotherapy play important roles. Although traditional therapies effectively prolong survival for patients with GIC, there are still many drawbacks that cannot be ignored[3]. Surgery, especially minimally invasive surgery and radiotherapy, can effectively shrink the tumor and even make the local tumor disappear; chemotherapy can be administered systematically to kill cancer cells[6-8]. However, these treatments cannot prevent recurrence. Moreover, for GICs, the side effects of radiotherapy and chemotherapy on the digestive system seriously affect the quality of life of patients and cannot be ignored[9-11]. To improve the therapeutic effect and reduce the occurrence of adverse reactions, clinicians often try a variety of therapeutic combinations to achieve complementary advantages[12,13].

With progress in the concept of cancer treatment and the development of diagnosis and treatment technology, various precision treatment methods, such as targeted therapy, photodynamic therapy (PDT), photothermal therapy (PTT) and immunotherapy, have emerged as new sources of hope for patients[14-19]. Some scholars believe that the characteristics of the GIC immune microenvironment are related to the high mortality of patients with GIC; therefore, treatments that target the GIC immune microenvironment are gradually being recognized[20]. As one of the therapeutic methods that targets the cancer immune microenvironment, immune checkpoint blockade (ICB) treatment has achieved great success in clinical practice, laying a good foundation for the development of cancer immunotherapy[21].

Recently, a variety of nanobased drugs (such as Eligard[22], Marqibo[23], Onivyde[24], Doxil[25], Abraxane[26], Ontak[27] and Nanotherm[28]) have been widely used in clinical practice due to several characteristics, including their low toxicity, long circulation and passive targeting ability[29,30]. However, most of the nanobased drugs mentioned above are liposomes. In addition to liposomes, there are also other types of nanoparticles that possess the same potential for clinical translation. Similar to liposomes, small extracellular vesicles and cell membrane vesicles also have lipid bilayers, and they have better biocompatibility than liposomes due to their origin[31-34]. Furthermore, due to their simple production process and high drug loading efficiency, polymersomes are also considered candidate nanoparticles for clinical translation[35-37]. There are also many kinds of novel nanoparticles, such as gold nanoparticles, manganese dioxide nanoparticles, upconversion nanoparticles (UCNPs), metal organic framework nanoparticles and mesoporous silica nanoparticles (MSNPs), which can also play important roles in different diseases or cancers through their own characteristics[38-42]. Here, among the GICs, we focus on GC, HCC, CRC and pancreatic cancer and summarize the application trends of immunotherapy-based novel nanoparticles in these cancers as well as the challenges and opportunities.
in the future.

**IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN GC**

GC remains one of the most common causes of cancer-related death globally. Although a variety of treatments have been developed, the main treatment for GC is still surgery or endoscopic resection. The probability of patients experiencing recurrence after surgery is approximately 60% [43]. Currently, the median overall survival time with fluoropyrimidine-based combination chemotherapy is less than one year. In general, the overall clinical therapeutic effect of GC is not satisfactory [44, 45]. In addition, immunotherapy for GC will become an important treatment option in the future, and nanoparticles, as highly efficient drug carriers, have played an important role in clinical practice [46-48]. Whether the combination of immunotherapy and nanoparticles can produce improved therapeutic effects is also worth examining.

Immune checkpoint inhibitors (ICIs), such as anti-programmed death receptor-1 (anti-PD-1) antibody and anti-programmed death receptor-ligand 1 (anti-PD-L1) antibody, can effectively block the PD-1/PD-L1 pathway and enhance the anticancer immune response [49]. Based on ICI treatment, Xu et al [50] prepared a novel nanoparticle named docetaxel (DOC)-PEG-PCL-monomoclonal antibody (mAb) NP, which contained DOC as the chemotherapeutic drug and conjugated PD-L1 mAb on the surface of the nanoparticle. This nanodrug delivery system (NDDS) can effectively improve drug delivery efficiency and the solubility of hydrophobic drugs such as DOC. In addition, the system can target PD-L1-positive GC cells, exhibiting clinical translation potential. Recently, scientists found that a gradually acquired heritable de novo methylation program inhibited T-cell proliferation and clonal diversity during PD-1 blockade therapy [51]. Inspired by this study, Hu et al [52] designed copolymers loaded with the epigenetic agent 5-Aza-20-deoxycytidine (DAC), and an anti-PD-1 antibody was conjugated to the surface of the nanoparticles. The nanoparticles increased the stability of DAC and improved the therapeutic effect of ICI treatment in vivo.

Due to the characteristics of the cancer immune microenvironment, T-cell infiltration in GC patients is insufficient, which limits the effect of ICB treatment in GC [53]. Guo et al [54] constructed an NDDS named HMON©IR820/Pt-NPs, which coencapsulated platinum nanoparticles (chemo-prodrugs) and IR820 (photosensitizer) into hollow mesoporous organosilica nanoparticles. IR820-mediated PDT can lead to the release of oxidative mitochondrial DNA (mitoDNA). In addition, this oxidative process can oxidize Pt(0) to cytotoxic Pt(II), which can lead to the dysfunction of nuclear DNA (nDNA). The dual damage of mitoDNA and nDNA can activate the c-GAS/stimulator of interferon genes (STING) pathway, which can directly stimulate innate immunity and increase the infiltration of CD8+ T cells, thus improving the efficacy of immunotherapy for GC.

Multiple studies have confirmed that tumor-associated macrophages (TAMs) are also involved in the composition of the tumor immune microenvironment. Moreover, M2-like macrophages can inhibit tumor immunity and promote tumor immune escape [55, 56]. Zhang et al [57]’s group designed a novel human serum albumin (HSA)-Au(III) thiosemicarbazone agent nanoparticle delivery system for chemotherapy and immunotherapy in GC. This NDDS can simultaneously directly kill GC cells and polarize TAMs into M1-like macrophages, providing a new immunotherapy strategy for clinical translation.

The majority of cancer patients are often unable to activate adequate levels of anticancer immunity, whereas therapeutic tumor vaccines can help patients proactively generate adequate anticancer immune responses against tumor-specific antigens (TSAs) and tumor-associated antigens [58]. Among the different types of tumor vaccines, dendritic cell (DC)-based tumor vaccines have been explored in clinical experiments [59, 60]. Kohnepoushi et al [61] prepared poly(lactic-co-glycolic) acid nanoparticles to protect the human gastric tumor antigen against proteolytic enzymes. In addition, nanoparticles that contain human gastric tumor antigen can facilitate DC maturation and further enhance the efficacy of DC vaccines in clinical practice.

In addition to ICB treatment and other therapies that can improve the cancer immune microenvironment, immunoadjuvants can act as a potential adjunctive therapy to stimulate anticancer immunity [62, 63]. Zhang et al [64] developed a gold nanoshell-based NDDS that can convert near-infrared (NIR) light into thermal energy, enabling PTT. Moreover, high temperature can also break thiol bonds to release gene therapy agents and oligonucleotides that contain cytosine-guanine (CpG) motifs (which are also known as immunoadjuvants). This study designed a novel NDDS combined with hyperthermia, gene therapy and immunotherapy, which exhibited encouraging anticancer efficacy against GC in vitro and in vivo (Table 1).

**IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN HCC**

Primary liver cancer is among the most commonly diagnosed cancers, most of which are HCC [65, 66]. Due to the high infection rate of hepatitis B virus, the incidence of HCC in China remains high [67].
Table 1 Overview of immunochemistry-based novel nanoparticles in the treatment of gastric cancer [PubMed Search (immunochemistry) AND (nanoparticle) AND (gastric cancer)]

| Type of nanoparticle | Treatment strategy | Drugs or active substance involved | The main involvement of immune cells | Ref. |
|----------------------|-------------------|------------------------------------|-------------------------------------|------|
| Copolymers           | ICI, chemotherapy  | DOC, PD-L1 mAb                     | T cells                             | Xu et al[50] |
| Copolymers           | ICIs, epigenetic treatment | DAC, nivolumab | PD1 CD8+ TILs | Hu et al[52] |
| Hollow mesoporous organosilica nanoparticles | Dual-damage to nDNA and miRNA activates the c-GAS/STING pathway to stimulate innate immunity | Platinum, IR820 | CD8+ T cells, DCs | Guo et al[54] |
| HSA nanoparticles    | Targeted chemotherapy and immunotherapy | Au(III) thiosemicarbazone agent | TAMs | Zhang et al[57] |
| Polymers             | DC vaccine         | Human gastric tumor antigens        | DCs | Kohnoepou et al[61] |
| Gold nanoshell       | Gene therapy, hyperthermia and immunoadjuvants therapy | HER-2 targeted siRNA, gold, CpG | DCs, T cells | Zhang et al[64] |

ICIs: Immune checkpoint inhibitors; DOC: Docetaxel; PD-L1: Programmed cell death ligand 1; mAb: Monoclonal antibody; DAC: 5-Aza-20-deoxycytidine; TILs: Tumor-infiltrating T cells; DCs: Dendritic cells; HSA: Human serum albumin; TAMs: Tumor-associated macrophages; HER-2: Human epidermal growth factor receptor-2; CpG: Cytosine–guanine.

Surgical resection of the liver is the main treatment for HCC. However, the prognosis after surgery is still poor. Recently, the development of molecular targeted therapy and immunotherapy for HCC has gained recognition in clinical studies[68]. Moreover, NDDSs can improve the efficiency of drug delivery into the tumor area and reduce side effects[69-71]. At present, a large number of studies using immunotherapy-based NDDSs have shown great potential for clinical translation.

ICB treatment has also emerged as a new option for advanced HCC[72]. However, ICB treatment alone has limited efficacy against HCC. Therefore, how to combine other kinds of therapies to improve the efficiency of ICB treatment has become a new academic topic. For example, Food and Drug Administration (FDA)-approved sorafenib-experienced patients used ipilimumab (anti-CTLA-4) combined with nivolumab (anti-PD-1) in March 2020[73]. In the last two decades, scientists have found that chemotherapeutic drugs, radiotherapy, PDT and some other treatments can induce immunogenic cell death (ICD), which can lead to the release of TSAs and increase tumor antigenicity[74]. Hence, ICD can improve the efficacy of ICB treatment by increasing tumor immunogenicity. According to the therapeutic strategies mentioned above, Xu et al[75] designed a cyclic arginine-glycine-aspartic acid peptide-modified self-assembling polymer-based NDDS. Cancer cells were damaged by PDT and chemotherapy, while induced ICD and enhanced tumor immunogenicity provided a suitable immune microenvironment for ICB treatment. Previous studies found that a lack of the p53 tumor suppressor gene leads to tumorigenesis and drug resistance[76-78]. With the development of research on the p53 tumor suppressor gene, an increasing body of evidence indicates that the p53 protein plays an important role in anticancer immunity by regulating the cancer immune microenvironment[79-81]. Furthermore, a recent study suggested that ICD induced by cytotoxic agents, such as chemotherapy drugs, may be involved in the activation of the p53 pathway[82]. Xiao et al[83] developed a novel lipid-polymer hybrid nanoparticle for mRNA delivery that can induce the expression of p53, effectively reprogramming the immune microenvironment of HCC. Moreover, combination with anti-PD-1 therapy can reverse the inhibitory immune microenvironment of HCC. To solve the problem of HCC recurrence after surgery, Li et al[84] designed a bionic NDDS consisting of MSNPs loaded with anti-PD-L1 and sorafenib and coated with platelet membranes at the surface of the MSNPs. This NDDS can target wounds and generate potent anti-HCC immunity, providing a new therapeutic idea for preventing recurrence in post-surgery HCC patients.

As we mentioned before, chemotherapy-based ICD can cause cancer cells to be more easily recognized by the immune system. However, the effect of single-drug-mediated ICD is very limited. Some studies have attempted to enhance the effect of ICD by combining two different ICD inducers to solve this problem. Yu et al[85] evaluated the potential of icaritin as an ICD inducer and utilized NDDS to deliver low doses of icaritin and doxorubicin simultaneously to the tumor area. This NDDS can reprogram the immune microenvironment and induce satisfactory anti-HCC effects. Furthermore, NDDS can lower the dose of chemotherapy to reduce the side effects.

TAMs play a major role in the immunosuppressive microenvironment of HCC[86]. Wang et al[87] screened chemokine C-C motif ligand (CCL)2 and CCL5 as two major chemokines responsible for the polarization of M2-like macrophages and designed a CCL2 and CCL5 dual-target lipid nanoparticle system. The combination of TAMs targeting lipid nanoparticles with ICB treatment achieved long-term survival in HCC mice. Similarly, as a common feature of the tumor microenvironment, hypoxia is also...
common in HCC. Hypoxia can lead to radioresistance and the formation of an immunosuppressive microenvironment, including the accumulation of TAMs and depletion of effector T cells, which are closely related to the occurrence and development of cancer[88-90]. Dai et al[91] synthesized polydopamine-nanoparticle-stabilized oxygen microcapsules that can deliver oxygen to the tumor region and rapidly increase the concentration of oxygen. In this study, oxygen microcapsules increased HCC sensitivity to radiotherapy and polarized M2-like macrophages into M1-like macrophages, consequently activating anti-HCC immunity. In addition to conventional immune cells, liver sinusoidal endothelial cells (LSECs) can also play a significant role in immunosuppressive regulation[92]. Yu et al[93] designed a simvastatin-loaded NDDS to target LSECs in HCC patients. This NDDS can reduce the capillarization of LSECs to improve the stromal microenvironment and recruit natural killer T cells to inhibit tumor progression.

Cationic lipid nanoparticles have been suggested to be suitable delivery vectors for RNA, and several messenger RNA vaccines are based on lipid nanotechnology that was approved by the FDA during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic[94-97]. Zhang et al[98] developed a total HCC-derived RNA-loaded lipid nanoparticle vaccine to target DCs and activate anticancer immunity (Figure 1 and Table 2).

**IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN CRC**

CRC is the third leading cause of cancer-related deaths globally[99]. CRC is the only cancer that can be reduced by screening. Most CRC patients can be screened by flexible sigmoidoscopy or guaiac-based fecal occult blood tests[100]. However, approximately 25% of CRC patients are at stage 4, and the 5-year survival rate is only 11%[101,102]. To improve the survival rate of advanced CRC patients, immunotherapy and nanoparticle-based drug delivery systems have become the focus of basic and clinical research for the past few years[103-105].

Similar to GC and HCC, ICB treatment is more widely used in CRC patients, but its curative effect is extremely limited, especially for mismatch repair-proficient/microsatellite instability-low CRC patients[106]. As we reported earlier, ICB treatment combined with ICD can achieve a “1 + 1 > 2” effect. A similar treatment strategy has also been applied in CRC research. For example, Yuan et al[107] utilized the ability of PDT to induce ICD and developed a photosensitive NDDS combined with ICB treatment that can enhance the response rate of anti-PD-L1 therapy in CRC. Zhu et al[108] also designed an oxaliplatin prodrug-conjugated photosensitive NDDS that can be stimulated by the NIR-II window (1000-1700 nm) for PTT, which is a proven to induce ICD. Moreover, oxaliplatin, a chemotherapy drug, is also known as an ICD inducer. This novel NDDS can induce ICD through both PTT and chemotherapy, which may provide a promising immunotherapy strategy for advanced CRC treatment. Shikonin (SK), a major active ingredient isolated from traditional Chinese medicine, has also been proven to induce ICD. Li et al[109] designed a versatile nanoparticle that can deliver knockdown siRNA for both the ICD inducer SK and PD-L1, which presents potential for CRC immunotherapy. Recently, ferroptosis was discovered as a nonapoptotic form of regulated cell death[110]. In addition, Duan et al[111]’s group proved that dihydroartemisinin (DHA), as a reactive oxygen species (ROS)-producing drug and ferroptosis inducer, can also induce ICD to potentiate anticancer immunity. Therefore, the same research group developed a Zn-pyrophosphate core-shell NDDS codeliver DHA and pyropheophorbide-iron (pyro-Fe). Glutathione and other thiol-based reductants in cancer cells can reduce Pyro-Fe to Pyro-Fe, which can catalyze the decomposition of DHA to induce ICD and ferroptosis. This novel NDDS overcame the deficiency of iron in solid tumors, enhanced the ability of DHA to induce ferroptosis and ICD, and increased the infiltration of CD8+ T cells in CRC.

In addition to actively increasing the immunogenicity of CRC, stimulating immune cells can also activate anti-CRC immunity. Immune cells can be activated by stimulating toll-like receptors (TLRs), such as DCs and macrophages. Several TLR agonists have been approved by the FDA. However, none are currently approved for CRC treatment. The major problem for TLR agonists is the small size of the drugs, which allows the drugs to spread rapidly from the administration site and cause severe systemic side effects (Figure 2)[112]. Fortunately, nanoparticle-based delivery systems can solve this problem. Bahmani et al[113] prepared a platelet membrane-coated nanoparticle loaded with the TLR7 agonist R848. This biomimetic NDDS enhanced the retention of the drug in the tumor and effectively stimulated the maturation of DCs, resulting in complete tumor eradication in a murine model of CRC.

Notably, long noncoding RNAs (lncRNAs) have recently been reported to be involved in the formation of the immunosuppressive cancer microenvironment and have become a potential immunotherapy target[114-116]. Liu et al[117] designed a bioscaffold loaded with an lncRNA-targeting biomimetic NDDS that modulated the cancer immune microenvironment against CRC recurrence after surgery. The biomimetic NDDS coated with a CRC membrane, which provides NDDS with a tumor-homing capacity and carries TSAs into the tumor area, promotes the maturation of DCs. Moreover, a plasmid-encoding short hairpin RNA against Pvtt was encapsulated inside the NDDS to enhance ICD and ameliorate granulocytic-myeloid-derived suppressor cell (G-MDSC)-mediated immunosuppression. This work provides a new perspective for NDDS-based lncRNA-targeted immunotherapy.
In recent years, as an important component of the immunosuppressive cancer microenvironment, MDSCs have also been identified as potential targets for cancer immunotherapy. Additionally, recent studies reported that MDSCs could be selectively enlarged because of the enrichment of *Fusobacterium nucleatum* (Fn) in CRC tissue, resulting in a cancer immunosuppressive microenvironment[118-121]. Dong et al.[122] proposed a phage-based antibacterial system that used the broad-spectrum antibacterial effect of silver nanoparticles (AgNPs) for antibacterial activity and then transported phage M13 into the tumor and utilized the recognition mechanism of phages to selectively kill Fn, thus preventing the recruitment of MDSCs. In addition, phages are highly immunogenic and can directly stimulate the maturation of DCs and promote the activation of M1-like macrophages, significantly enhancing the anti-CRC immune response.

Over the years, CRC vaccines have been a focus of scientific research. Zhang et al.[123] designed an in situ cancer vaccine. They reported a supramolecular assembled programmable immune activation nanomedicine (PIAN) that can produce strong and durable anticancer immunity in situ. PIAN entered the tumor area through enhanced permeability and retention (EPR) after tail vein injection and was then disassembled by the high ROS within the tumor tissue. The release of poly-[(N-2-hydroxyethyl)-aspartamide]-Pt(IV)/beta-cyclodextrin simultaneously mediated tumor cell death and antigen release. In addition, CpG/polyamidoamine (CpG/PAMAM) captured the released antigen and entered the tumor draining lymph node to stimulate DC maturation, thus activating anti-CRC-specific immunity. This excellent work provides a new idea for designing nanomedicine-based programmable *in situ* cancer vaccines for cancer immunotherapy (Table 3).

**IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN PANCREATIC CANCER**

As one of the most aggressive and fatal cancers, pancreatic cancer has been the leading cause of cancer-related deaths worldwide in the last few decades[124,125]. Most patients experience no obvious symptoms during the development of the disease. Therefore, it is difficult to diagnose the disease in the early stage, and patients often miss the optimal treatment time after they have been diagnosed with pancreatic cancer. Moreover, the majority of patients eventually relapse, even if they receive potentially radical treatment[126]. In contrast to other malignant tumors, stromal hyperplasia is the main feature of the pancreatic cancer microenvironment[127]. As a result, pancreatic cancer does not have a sufficient blood supply, so antiangiogenic drugs are not suitable for pancreatic cancer[128]. In addition, the tumor stroma of pancreatic cancer acts as a natural physical barrier between the tumor tissue and the body’s immune system, which also limits the application of immunotherapy[129,130]. Until now, most phase I and II clinical trials of immunotherapy in pancreatic cancer have failed. Interestingly, ICB treatment combined with chemotherapy and/or radiotherapy has shown encouraging clinical efficacy[131]. In recent years, with the continuous development of nanotechnology, scientists have proposed a variety of nanodelivery systems aimed at the unique pathological characteristics of pancreatic cancer. They attempted to utilize NDDSs to achieve synergistic therapy and improve the tumor microenvironment to reverse the current situation of pancreatic cancer[132].

### Table 2 Overview of Immunotherapy-based novel nanoparticles in the treatment of hepatocellular carcinoma (PubMed Search (immunotherapy) AND (nanoparticle) AND (hepatocellular carcinoma))

| Type of nanoparticle | Treatment strategy | Drugs or active substance involved | The main involvement of immune cells | Ref. |
|----------------------|--------------------|-----------------------------------|-------------------------------------|------|
| Nano-micelles        | ICD, chemotherapy, PDT | PTX, TPA/BDTO | CTLs, MDSCs, Tregs, DCs | Xu et al.[75] |
| Polymers             | p53 gene reprograms the immune microenvironment | p53 mRNA | T cells, NK cells | Xiao et al.[83] |
| MSNPs                | Anti-angiogenic drugs, ICIs | Sorafenib, PD-L1 antibody | T cells | Li et al.[84] |
| Copolymers           | ICD, chemotherapy | Icaritin, DOX | T cells, DCs | Yu et al.[85] |
| Lipid nanoparticle   | CCL2 and CCL5 dual-target | BicCCL2/5i mRNA | TAMs | Wang et al.[87] |
| Microcapsules        | Improving hypoxia | Oxygen | TAMs | Dai et al.[91] |
| Copolymers           | Mitigates LSEC capillarization | Simvastatin | NK/T cells | Yu et al.[93] |
| LNPs                 | Antigen specific vaccine | Tumor-derived RNA | T cells, DCs | Zhang et al.[98] |

ICD: Immunogenic cell death; PDT: Photodynamic therapy; CTLs: Cytotoxic T lymphocytes; PTX: Paclitaxel; MDSCs: Myeloid-derived suppressor cells; DCs: Dendritic cells; CCL2: Chemokine C-C motif ligand 2; CCL5: Chemokine C-C motif ligand 5; DOX: Doxorubicin; PD-L1: Programmed cell death ligand 1; NK cells: Natural killer cells; TAMs: Tumor-associated macrophages; Tregs: Regulatory T lymphocytes; MSNPs: Mesoporous silica nanoparticles; LSEC: Liver sinusoidal endothelial cells; LNPs: Lipid nanoparticles; NKT: Natural killer T.
Table 3 Overview of Immunotherapy-based novel nanoparticles in the treatment of colorectal cancer [PubMed Search (immunotherapy) AND (nanoparticle) AND (colorectal cancer)]

| Type of nanoparticle | Treatment strategy | Drugs or active substance involved | The main involvement of immune cells | Ref. |
|----------------------|--------------------|-----------------------------------|-------------------------------------|------|
| Copolymers           | PDT induces HIF-1α expression, leading to the upregulation of PD-L1 expression, ICIs | Photosensitizer, PD-L1 antibody | DCs, CD8+ T cells, memory T cells | Yuan et al [107] |
| Polymeric nanoparticle | PTT, chemotherapy, ICD | PROXA, donor-spacer-acceptor-spacer-donor type fluorophore | DCs, T cells, CTLs | Zhu et al [108] |
| Copolymers           | ICD, ICIs | SK, PD-L1 knockdown siRNA | DCs, TAMs, Tregs, T cells | Li et al [109] |
| Polymers             | ICD, ferroptosis | DHA | DCs, T cells | Duan et al [111] |
| Platelet membrane-coated nanoparticle | TLR7 treatment | R848 | DCs | Bahmani et al [113] |
| Liposomes with cell membrane | ICD, chemotherapy, IncRNA-targeting therapy | Oxaliplatin, shPvt1 | DCs, MDSCs, CD8+ T cells | Liu et al [117] |
| Silver nanoparticles | Anti-Fn | Phage M13 | MDSCs, DCs, TAMs | Dong et al [122] |
| Supramolecular assembled programmable immune activation nanomedicine | In-situ cancer vaccine, ICD | PPCP, C6P/PAMAM | DCs, CD8+ T cells | Zhang et al [123] |

ICIs: Immune checkpoint inhibitors; HIF-1α: Hypoxia-inducible factor 1α; PDT: Photodynamic therapy; PTT: Photothermal therapy; ICD: Immunogenic cell death; PD-L1: Programmed cell death ligand 1; PROXA: Oxaliplatin prodruk; SK: Shikonin, DHA: Dihydroartemisinin; TLR: Toll-like receptor; shPvt1: Short hair-pinned RNA against Pvt1; Fn: Fusobacterium nucleatum; LMWH-D-ε-tocopherol (LMWH) could significantly inhibit G-MDSC recruitment[141]. Therefore, Lu et al[142] designed a paclitaxel-loaded 3-aminophenylboronic acid-modified PLGA. siPD-L1*PLGA increased the infiltration of CD8+ T cells and significantly inhibited tumor growth.

As we mentioned above, the tumor stroma of pancreatic cancer limits the efficacy of immunotherapy. Wang et al[133] reported a pH-responsive clustered nanoparticle (iCluster) loaded with both siPD-L1 and transforming growth factor-β (TGF-β) receptor inhibitors (LY2157299). iCluster can deliver siPD-L1 and LY2157299 to tumor blood vessels and then release small PAMAM at acidic tumor extracellular pH (pH). Therefore, siPD-L1 can penetrate into tumor tissue as deeply as possible to activate antitumor immunity, and a TGF-β receptor inhibitor can reduce the barrier function of the tumor stroma to help more drugs penetrate into the tumor tissue, further promoting the activation of antitumor immunity. Similarly, Yu et al[134] designed a size-adjustable nanoparticle consisting of IR870 containing the thermosensitive ICB drug (BMS-202) conjugated to HSA-BMS. Under mild hyperthermia therapy, this novel nanoparticle releases the small HSA-BMS into the tumor site and relieves the immunosuppressive environment to normalize immunity. In recent years, some studies have reported that RNA interference (RNAi) has emerged as a better agent for inducing antitumor immunity than antibodies or small molecules in vivo[135]. PLGA polymers have been proven to be a potentially excellent siRNA delivery vector exhibiting low toxicity, sustained release and the EPR effect[136,137]. Jung et al[138] developed a poly(lactic-co-glycolic) acid (PLGA)-based siRNA nanoparticle named siPD-L1*PLGA. siPD-L1*PLGA increased the infiltration of CD8+ T cells and significantly inhibited tumor growth.

The poor immunogenicity and excessive immunosuppressive cancer microenvironment of pancreatic cancer result in a lack of adequate antigen-presenting cells in the tumor microenvironment. Lorkowski et al[139] reported a dual-immunostimulatory nanoparticle that was simultaneously loaded with a STING agonist and TLR4 agonist. These dual-immunostimulatory nanoparticles can be taken up by DCs in the tumor site to significantly increase the number of mature DCs and activate antitumor immunity in pancreatic cancer. Theoretically, cancer immunosuppressive cells mainly include TAMs, MDSCs and regulatory T cells (Tregs). Recent studies have shown that MDSCs are the major inhibitory immune cells in the immunosuppressive microenvironment of pancreatic cancer[140]. A previous study found that low-molecular-weight heparin-D-ε-tocopheryl (LMWH) could significantly inhibit G-MDSC recruitment[141]. Therefore, Lu et al[142] designed a paclitaxel-loaded 3-amino phenyl boronic acid-modified LMWH-based nanoparticle. This novel LMWH-based nanoparticle can inhibit the recruitment of MDSCs and weaken the immunosuppressive state.

Pyrophosis is a mode of programmed cell death[143]. Recent studies have shown that pyrophosis can induce powerful antitumor immunity[144-146]. However, pyrophosis is usually induced by chemotherapeutic drugs, which limits the applications of pyrophosis in drug-resistant tumors[147]. Ding et al[148] designed biodegradable K3ZrF7:Yb/Er UCNPs (ZrNPs) as self-therapeutic agents and pyrophosis

As we mentioned above, the tumor stroma of pancreatic cancer limits the efficacy of immunotherapy. Wang et al[133] reported a pH-responsive clustered nanoparticle (iCluster) loaded with both siPD-L1 and transforming growth factor-β (TGF-β) receptor inhibitors (LY2157299). iCluster can deliver siPD-L1 and LY2157299 to tumor blood vessels and then release small PAMAM at acidic tumor extracellular pH (pH). Therefore, siPD-L1 can penetrate into tumor tissue as deeply as possible to activate antitumor immunity, and a TGF-β receptor inhibitor can reduce the barrier function of the tumor stroma to help more drugs penetrate into the tumor tissue, further promoting the activation of antitumor immunity. Similarly, Yu et al[134] designed a size-adjustable nanoparticle consisting of IR870 containing the thermosensitive ICB drug (BMS-202) conjugated to HSA-BMS. Under mild hyperthermia therapy, this novel nanoparticle releases the small HSA-BMS into the tumor site and relieves the immunosuppressive environment to normalize immunity. In recent years, some studies have reported that RNA interference (RNAi) has emerged as a better agent for inducing antitumor immunity than antibodies or small molecules in vivo[135]. PLGA polymers have been proven to be a potentially excellent siRNA delivery vector exhibiting low toxicity, sustained release and the EPR effect[136,137]. Jung et al[138] developed a poly(lactic-co-glycolic) acid (PLGA)-based siRNA nanoparticle named siPD-L1*PLGA. siPD-L1*PLGA increased the infiltration of CD8+ T cells and significantly inhibited tumor growth.

The poor immunogenicity and excessive immunosuppressive cancer microenvironment of pancreatic cancer result in a lack of adequate antigen-presenting cells in the tumor microenvironment. Lorkowski et al[139] reported a dual-immunostimulatory nanoparticle that was simultaneously loaded with a STING agonist and TLR4 agonist. These dual-immunostimulatory nanoparticles can be taken up by DCs in the tumor site to significantly increase the number of mature DCs and activate antitumor immunity in pancreatic cancer. Theoretically, cancer immunosuppressive cells mainly include TAMs, MDSCs and regulatory T cells (Tregs). Recent studies have shown that MDSCs are the major inhibitory immune cells in the immunosuppressive microenvironment of pancreatic cancer[140]. A previous study found that low-molecular-weight heparin-D-ε-tocopheryl (LMWH) could significantly inhibit G-MDSC recruitment[141]. Therefore, Lu et al[142] designed a paclitaxel-loaded 3-amino phenyl boronic acid-modified LMWH-based nanoparticle. This novel LMWH-based nanoparticle can inhibit the recruitment of MDSCs and weaken the immunosuppressive state.

Pyrophosis is a mode of programmed cell death[143]. Recent studies have shown that pyrophosis can induce powerful antitumor immunity[144-146]. However, pyrophosis is usually induced by chemotherapeutic drugs, which limits the applications of pyrophosis in drug-resistant tumors[147]. Ding et al[148] designed biodegradable K3ZrF7:Yb/Er UCNPs (ZrNPs) as self-therapeutic agents and pyrophosis
**Figure 1 Tumor vaccine and tumor immunotherapy.** Total tumor RNA was extracted and mixed with an immune adjuvant to formulate tumor vaccine. Tumor antigen was expressed and presented or cross-presented to Th and Tc cells by antigen presenting cells in lymph node to generate specific anti-tumor response. Citation: Zhang Y, Xie F, Yin Y, Zhang Q, Jin H, Wu Y, Pang L, Li J, Gao J. Immunotherapy of Tumor RNA-Loaded Lipid Nanoparticles Against Hepatocellular Carcinoma. Int J Nanomedicine 2021; 16: 1553-1564. Copyright ©The Authors 2011. Published by Dove Medical Press. The authors have obtained the permission for figure using from the Dove Medical Press Publishing Group (Supplementary material). Ab: Antibody; Ag: Antigen; BCR: B cell receptor; TCR: T-cell receptor; MHC: Major histocompatibility complex; PRR: Pattern recognition receptors; Th1/2: T helper type 1/2; CTL: Cytotoxic T-lymphocyte; CTLA4: Cytotoxic T-lymphocyte-associated protein 4; Treg: Regulatory T cell; DC: Dendritic cell; NK: Natural killer cell; MDSC: Myeloid-derived suppressor cell; ADCC: Antibody-dependent cellular cytotoxicity; CDC: Complement-dependent cytotoxicity; SIRPα: Signal regulatory protein α; LILRB1: Leukocyte immunoglobulin like receptor B1; TIM-3: T-cell immunoglobulin and mucin domain-3; PD1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; IL-2: Interleukin-2; IFNγ: Interferon γ; KIR: Killer cell immunoglobulin-like receptor; NKG2D: Natural killer group 2 member D.

inducers for the first time. ZrNP can lead to osmotic pressure disorder and further result in an increase in ROS, the activation of caspase-1 protein, the cleavage of gasdermin, the maturation of interleukin-1β, and ultimately cytolysis. ZrNP-induced pyrophosis can lead to DC maturation and activate effector memory T cells, as well as inhibit tumor growth and metastasis.

Gemcitabine is among the most effective FDA-approved chemotherapy drugs to prolong survival in patients with pancreatic cancer. However, the immunosuppressive cancer microenvironment, especially the presence of TAMs, significantly weakens the efficacy of gemcitabine. It has even been reported that gemcitabine can induce an increase in TAMs and promote the establishment of a tumor-suppressive immune microenvironment, which further increases gemcitabine drug resistance[149]. Furthermore, gemcitabine can even induce an increase in TAMs and promote the establishment of an immunosuppressive tumor microenvironment, which further leads to gemcitabine drug resistance[150]. Thus, Wang et al.[151] developed a biomimetic nanoparticle named PC*KMCM consisting of gemcitabine-loaded PLGA nanoparticles coated with stable M2-like macrophage targeting peptides (M2pep). Pancreatic cancer cell membranes can deliver PC*KMCM to pancreatic cancer and target M2-like macrophages by M2pep to reprogram TAMs and reverse gemcitabine drug resistance. Cao et al.[152] also considered TAMs to be a therapeutic target and reported a reduction-responsive RNAi NDDS to regulate the function of TAMs and reprogram tumor lipid metabolism. On the one hand, this novel NDDS can block the activity of monoacylglycerol lipase (MGLL) by MGLL siRNA to reduce the production of free fatty acids and thus cut off the tumor’s nutrition supply. On the other hand, MGLL blockade may lead to the accumulation of 2-arachidonoylglycerol, which can be secreted into the cancer microenvironment and activate the endocannabinoid receptor-2 (CB-2), which can transform TAMs into M2-like macrophages.
Therefore, they prepared CB-2 siRNA to block CB-2 expression, preventing the transition of M2-like macrophages. The dual-RNAi NDDS developed in this research shows significant enhancement of the immunological environment in pancreatic cancer.

PTT has achieved satisfactory results in animal experiments, but it is difficult to apply widely in the clinic. The main reason is poor light penetration. It is harder to achieve the desired therapeutic effect for pancreatic cancer due to the depth of pancreatic cancer and the presence of the tumor stroma. To solve this conundrum, Wang et al. proposed magnetic resonance imaging (MRI)-guided interventional PTT (IPTT). They designed an iron oxide-based nanoparticle loaded with indocyanine green for PTT and imiquimod (IMQ) as an immunostimulant. IPTT can induce \textit{in situ} cancer vaccination, which can be amplified by IMQ. In addition, iron oxide is a widely used MRI contrast agent. A recent study reported that iron oxide can modulate the cancer microenvironment by transforming M2-like macrophages into M1-like macrophages. Overall, these novel iron oxide-based nanoparticles can improve therapeutic effects by directly killing cancer cells and activating the long-lasting immune effect by \textit{in situ} vaccination and regulation of the immune microenvironment (Table 4).

**FUTURE DIRECTIONS**

In recent years, the increased development of immunotherapy has provided hope to patients with advanced cancer. Several ICB drugs have been approved by the FDA for clinical application in cancer treatment. However, due to the immunosuppressive microenvironment, only approximately 20% of patients can benefit from ICB treatment. In addition to ICB treatment, some conventional therapies, such as chemotherapy and radiotherapy, are also closely related to the immunosuppressive tumor microenvironment. The facts we mentioned above also exist in GIC. Therefore, we believe that in addition to ICB treatment, we should focus on reversing the immunosuppressive microenvironment in the future.

Moreover, advances in nanotechnology have made drug delivery more efficient, allowing us to deliver drugs at specific times and locations based on the characteristics of the cancer and the drugs. We wondered whether the combination of nanotechnology and immunotherapy could achieve satisfactory therapeutic efficacy in GIC. Here, we summarize recent advances in immunotherapy-based novel nanoparticles in the treatment of GIC.

Since GC, HCC and CRC share similar tumor immune microenvironments, we will discuss the application of immunotherapy-based nanoparticles in these three kinds of GICs in the following paragraphs. Due to the limited monotherapy effect of ICB treatment, nanoparticles, as drug delivery vehicles, cannot significantly improve the therapeutic effect of ICB treatment. Thus, basically all ICB-based nanoparticles are combined with other therapeutic strategies. ICB treatment can reverse tumor immune escape from T cells. However, the low immunogenicity of the tumor results in insufficient T-cell infiltration in the tumor tissue. Hence, most studies have attempted to promote the therapeutic effect of ICB-based nanoparticles by inducing ICD.

ICD can increase tumor immunogenicity, but similar to ICB treatment, the immune-stimulating effect of ICD is limited. To amplify the ICD effect, some studies utilized the drug-loading capacity of nanoparticles and adopted a combination of multiple ICD inducers to enhance the immune response. Even so, we still do not recommend the combination of multiple ICD inducers to promote anticaner immunity. On the one hand, this strategy does not solve the problem of insufficient T-cell infiltration; on
the other hand, ICD inducers themselves can directly kill tumor cells. It is difficult to determine whether tumor inhibition is due to cytotoxicity or ICD-induced anticancer immunity.

Compared with ICD and ICB treatment, we believe that reprogramming the immunosuppressive tumor microenvironment by targeting inhibitory immune cells (e.g., TAMs, Tregs and MDSCs) will be a revolutionary breakthrough in cancer immunotherapy in the future. Recently, many studies have attempted to successfully reprogram the tumor immune microenvironment by polarizing M2-like macrophages into M1-like macrophages. However, few reports have designed NDDSs to target Tregs and MDSCs in the tumor microenvironment. Therefore, it is of great significance to develop NDDSs for Tregs and MDSCs. In addition, the relationship between the intestinal flora and the immunosuppressive microenvironment of CRC also deserves future attention.

TLR agonists have also emerged as a promising treatment for cancer immunotherapy. However, due to the lack of targeting of TLR agonists, free TLR agonists often lead to serious systemic side effects.

With the successful large-scale clinical application of SARS-CoV-2 mRNA vaccines, research on cancer vaccines is also imminent. Due to the high heterogeneity of cancer, RNA vaccines are the best option. However, RNA is highly unstable. Liposomes, as mature NDDSs, can prepare cancer vaccines by encapsulating RNA. In addition, to improve the vaccine effect, NDDSs can be encapsulated with immune adjuvants to promote immune activation. RNA-based cancer vaccines, as a personalized cancer treatment strategy, can effectively improve anticancer immunity.

Next, we will discuss the application of immunotherapy-based nanoparticles in pancreatic cancer. Pancreatic cancer has several characteristics that are not found in other kinds of GICs, including the following: (1) Pancreatic cancer is surrounded by a tumor stroma, resulting in a physical barrier that isolates pancreatic cancer from the surrounding immune microenvironment; (2) Due to the anatomic position of the pancreas, pancreatic cancer is located deep in the abdominal cavity and therefore is not sensitive to PDT and PTT; and (3) Unlike other GICs, pancreatic cancer lacks blood supply and can adapt to nutrient deficiency and in a long-term hypoxic state.

To pass through the physical barrier of pancreatic cancer, size-adjusted NDDSs are the best option. Due to the deep location of pancreatic cancer, PTT has limited efficacy. Inspired by a previous study, we believe that IPTT and interventional PDT can be widely applied in the treatment of pancreatic cancer.
Additionally, interventional light-mediated therapy can be extended to GC, esophageal cancer and CRC, as well as HCC.

Compared with GC, HCC and CRC, pancreatic cancer has a similar immunosuppressive microenvironment, and the immunosuppressive situation is even worse. Most of the treatment strategies mentioned in GC, HCC and CRC can also be applied in pancreatic cancer. In previous reports, immunotherapy-based nanoparticles mainly used liposomes and copolymer nanoparticles, which are chemical synthesis products. Therefore, the nanoparticles can be designed according to demand. To increase biocompatibility and deliver tumor antigens, some literature has used tumor cell membranes to prepare biomimetic NDDSs, which have also achieved good results. In addition to the abovementioned nanoparticles, we particularly recommend small extracellular vesicles (also known as exosomes) as immunotherapy-based nanoparticles. First, exosomes are naturally nanosized. Second, similar to cell membrane vesicles, exosomes derived from tumor cells can carry tumor antigens. Third, exosomes can use surface modification to achieve biological functions, such as targeting. Last, exosomes have a certain drug delivery capacity. Thus, exosomes are potential immunotherapy-based nanoparticles for GIC that have not been reported in previous studies.

CONCLUSION

GIC is a common tumor worldwide. The immune microenvironments of GC, HCC, CRC and pancreatic cancer have similarities and differences. There are still many mechanisms of immune escape in GIC that are not well understood. Therefore, we need an in-depth understanding of the characteristics of each kind of GIC to take advantage of its characteristics and design immunotherapy-based nanoparticles.

FOOTNOTES

Author contributions: Ding YN and Ding HY wrote the paper; Ding YN, Li H, Gao CC and Wang LJ carried out reference searching; Yu WP and Tang QS made review and final editing; and all authors have read and agree to the published version of the manuscript.

Supported by the National Natural Science Foundation of China, No. 82102303; and Natural Science Foundation of Jiangsu Province, China, No. BK20210231.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Yi-Nan Ding 0000-0002-1010-2874; Ming Xue 0000-0002-5178-6424; Qiu-Sha Tang 0000-0001-5701-0996; Li-Jun Wang 0000-0002-0208-0273; Hui-Yan Ding 0000-0002-5850-8080; Han Li 0000-0003-4174-8480; Cheng-Cheng Gao 0000-0002-9482-9535; Wei-Ping Yu 0000-0003-3968-3104.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 Huang F, Wang BR, Wu YQ, Wang FC, Zhang J, Wang YG. Oncolytic viruses against cancer stem cells: A promising approach for gastrointestinal cancer. World J Gastroenterol 2016; 22: 7999-8009 [PMID: 27672294 DOI: 10.3748/wjg.v22.i35.7999]
2 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7-33 [PMID: 33020204 DOI: 10.3322/caac.21708]
3 Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int J Cancer 2021 [PMID: 33818764 DOI: 10.1002/ijc.35588]
4 Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N, Chen W. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl) 2022; 135: 584-590 [PMID: 35143424 DOI: 10.1097/CM9.000000000002106]
Ding YN et al. Nanoparticles and gastrointestinal cancer

5 Neumann PA, Berlet MW, Friess H. Surgical oncology in the age of multimodality therapy for cancer of the upper and lower gastrointestinal tract. Expert Rev Anticancer Ther 2021; 21: 511-522 [PMID: 33355020 DOI: 10.1080/14737140.2021.1868991]

6 Hamed OH, Gusani NJ, Kimchi ET, Kavic SM. Minimally invasive surgery in gastrointestinal cancer: benefits, challenges, and solutions for underutilization. JSLS 2014; 18 [PMID: 25489209 DOI: 10.4293/JSLS.2014.00134]

7 Pofahl WE, Pories WJ. Current status and future directions of geriatric general surgery. J Am Geriatr Soc 2003; 51: S351-S354 [PMID: 12825667 DOI: 10.1111/j.1537-7144.2003.51347.x]

8 Ciabatti S, Cammelli S, Frakulli R, Arcelli A, Macchia G, Deodato F, Cilla S, Giacherini L, Buwenge M, Morganti AG. Radiotherapy of pancreatic cancer in older patients: A systematic review. J Geriatr Oncol 2019; 10: 534-539 [PMID: 30270196 DOI: 10.1016/j.jgerm.2018.09.007]

9 Grabenbauer GG, Holger G. Management of radiation and chemotherapy related acute toxicity in gastrointestinal cancer. Best Pract Res Clin Gastroenterol 2016; 30: 655-664 [PMID: 27644912 DOI: 10.1016/j.bpg.2016.06.001]

10 Sipavicute A, Sileika E, Burneckis A, Dulsakas A. Late gastrointestinal toxicity after radiotherapy for rectal cancer: a systematic review. Int J Colorectal Dis 2020; 35: 977-983 [PMID: 32296933 DOI: 10.1007/s00384-020-03595-x]

11 Marin JJ, Romero MR, Blazquez AG, Herrera E, Keck E, Briz O. Importance and limitations of chemotherapy among the available treatments for gastrointestinal tumours. Anticancer Agents Med Chem 2009; 9: 162-184 [PMID: 19199863 DOI: 10.2174/187152009787313828]

12 Kelly RJ. Emerging Multimodality Approaches to Treat Localized Esophageal Cancer. J Natl Comp Canc Netw 2019; 17: 1009-1014 [PMID: 31390584 DOI: 10.6004/jncn.2019.7337]

13 Metzer R, Bollschweiler E, Hölsc per AH, Warnecke-Eberz U. ERCC1: impact in multimodality treatment of upper gastrointestinal cancer. Future Oncol 2010; 6: 1735-1749 [PMID: 21422660 DOI: 10.2217/fon.10.140]

14 Tazawa H, Kagawa S, Fujiwara T. MicroRNAs as potential target gene in cancer gene therapy of gastrointestinal tumors. Expert Opin Biol Ther 2011; 11: 145-155 [PMID: 21219233 DOI: 10.1517/14712598.2011.342749]

15 Rosenbaum MW, Gonzalez RS. Targeted therapy for upper gastrointestinal tract cancer: current and future prospects. Curr Opin Oncol 2011; 23: 141-149 [PMID: 21680181 DOI: 10.1097/CCO.0b013e32834c5b9f]

16 Yano T, Wang KK. Photodynamic Therapy for Gastrointestinal Cancer. Photochem Photobiol 2020; 96: 517-523 [PMID: 31886891 DOI: 10.1111/php.13206]

17 Hao M, Kong C, Jiang C, Hou R, Zhao X, Li J, Wang Y, Gao Y, Zhang H, Yang B, Jiang J. Polydopamine-coated Au-Ag nanoparticle-guided photothermal colorectal cancer therapy through multiple cell death pathways. Acta Biomater 2019; 83: 414-424 [PMID: 30366131 DOI: 10.1016/j.actbio.2018.10.032]

18 Lee SY, Shieh MJ. Platinum(II) Drug-Loaded Gold Nanoshells for Chemo-Photothermal Therapy in Colorectal Cancer. ACS Appl Mater Interfaces 2020; 12: 4254-4264 [PMID: 31927943 DOI: 10.1021/acsami.9b11855]

19 Ding Y, Yang R, Yu W, Hu C, Zhang Z, Liu D, An Y, Wang X, He C, Liu P, Tang Q, Chen D. Chitosan oligosaccharide decorated liposomes combined with TH302 for photodynamic therapy in triple negative breast cancer. J Nanobiotechnology 2021; 19: 147 [PMID: 34011362 DOI: 10.1186/s12951-021-00891-8]

20 Zhang Y, Xu J, Zhang N, Chen M, Wang H, Zhu D. Targeting the tumour immune microenvironment for cancer therapy in human gastrointestinal malignancies. Cancer Lett 2019; 458: 123-135 [PMID: 31211212 DOI: 10.1016/j.canlet.2019.05.017]

21 He M, Yang T, Wang Y, Wang M, Chen X, Ding D, Zheng Y, Chen H. Immune Checkpoint Inhibitor-Based Strategies for Synergistic Cancer Therapy. Adv Healthc Mater 2021; 10: e2002104 [PMID: 33709564 DOI: 10.1002/adhm.202002104]

22 Sartor O. Eligard: leuprolide acetate in a novel sustained-release delivery system. Urology 2003; 61: 25-31 [PMID: 12667884 DOI: 10.1016/S0090-4295(02)02396-8]

23 FDA approves liposomal vincristine (Marqibo) for rare leukemia. Oncology (Williston Park) 2012; 26: 841 [PMID: 23013460]

24 Frampton JE. Liposomal Irinotecan: A Review in Metastatic Pancreatic Adenocarcinoma. Drugs 2020; 80: 1007-1018 [PMID: 32557396 DOI: 10.1007/s40265-020-01336-6]

25 Safra T, Muggia F, Jeffer S, Tsoa-Wei DD, Grosben S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m². Ann Oncol 2000; 11: 1029-1033 [PMID: 11038041 DOI: 10.1016/s0926-3657(166931]

26 Yardley DA. nab-Paclitaxel mechanisms of action and delivery. J Control Release 2013; 170: 365-372 [PMID: 23770008 DOI: 10.1016/j.jconrel.2013.05.041]

27 Duvic M, Talpur R. Optimizing denileukin dififtix (Ontak) therapy. Future Oncol 2008; 4: 457-469 [PMID: 18664057 DOI: 10.2217/14766964.4.4.457]

28 Rivera Gil P, Hülén D, del Mercato LL, Sasse D, Parak WJ. Nanopharmacy: Inorganic nanoscale devices as vectors and active compounds. Pharmacol Res 2010; 62: 115-125 [PMID: 20097288 DOI: 10.1016/j.phrs.2010.01.009]

29 Ding Y, Wang L, Li H, Miao F, Zhang Z, Hu C, Wu Y, Tang Q, Shao G. Application of lipid nanovesicle drug delivery system in cancer immunotherapy. J Nanobiotechnology 2022; 20: 214 [PMID: 35524277 DOI: 10.1186/s12951-022-01429-2]

30 DaunoXome approved. AIDS Patient Care STDS 1996; 10: 263 [PMID: 11361607]

31 Bost JP, Barriga H, Holme MN, Gallaud A, Maugeri M, Gupta D, Lehto T, Valadi H, Esbjörner EK, Stevens MM, El-Andaloussi S. Delivery of Oligonucleotide Therapeutics: Chemical Modifications, Lipid Nanoparticles, and Extracellular Vesicles. ACS Nano 2015; 15: 13983-14021 [PMID: 34505766 DOI: 10.1021/acsnano.150599]

32 Zou S, Wang B, Wang C, Wang Q, Zhang L. Cell membrane-coated nanoparticles: research advances. Nanomedicine (Lond) 2020; 15: 625-641 [PMID: 32098564 DOI: 10.2217/nmn-2019-0388]

33 Huang R, Cai GQ, Li J, Li XS, Liu HT, Shang XL, Zhou JD, Nie XM, Gui R. Platelet membrane-camouflaged silver metal-organic framework drug system against infections caused by methicillin-resistant Staphylococcus aureus. J Nanobiotechnology 2021; 19: 229 [PMID: 33448721 DOI: 10.1186/s12951-021-00978-2]
pulsed with tumor RNA from gastric cancer. Liu BY, Morse MA, Zhang J, Cheng N, Pan Y. Innate immunity. Nanocomposites with capability of triggering Dual-Damage of Nuclear/Mitochondrial DNA and cGAS/STING-Mediated alterations of T cell responses in the treatment of gastric cancer.

Xu S, Han Y, Ong CT, Chemotherapy of Nab-Paclitaxel, S-1, and Oxaliplatin for Gastric Cancer with Peritoneal Metastasis (NSOX Study). Nakamura M, Cheng Y, Zhao Q, Avgustinovich AV, et al. Nanoparticles in Gastric Cancer Management. 10.1186/s12951-018-0335-4

Manganese oxide nanomaterials for bacterial infection detection and therapy. J Mater Chem B 2022; 10: 1343-1358 [PMID: 35129557 DOI: 10.1039/d1tb02646a]

Connor DM, Broome AM. Gold Nanoparticles for the Delivery of Cancer Therapeutics. Adv Cancer Res 2018; 139: 163-184 [PMID: 29941104 DOI: 10.1016/bs.acr.2018.05.001]

Zhang X, Lu Y, Jia D, Qiu W, Ma X, Zhang X, Xu Z, Wen F. Acidic microenvironment responsive polymeric MOF-based nanoparticles induce immunogenic cell death for combined cancer therapy. J Nanobiotechnology 2021; 19: 455 [PMID: 34963499 DOI: 10.1186/s12951-021-01217-4]

Iranpour S, Bahrami AR, Nekooei S, Sh Saljooghi A, Matin MM. Improving anti-cancer drug delivery performance of magnetic mesoporous silica nanocarriers for more efficient colorectal cancer therapy. J Nanobiotechnology 2021; 19: 314 [PMID: 34618557 DOI: 10.1186/s12951-021-01056-3]

Smyth EC, Nilsson M, Grabsch Hl, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020; 396: 635-648 [PMID: 32261308 DOI: 10.1016/S0140-6736(20)31143-8]

Menges M, Hoeheir T. Current strategies in systemic treatment of gastric cancer and cancer of the gastroesophageal junction. J Cancer Res Clin Oncol 2009; 135: 29-38 [PMID: 18523800 DOI: 10.1007/s00432-008-0425-z]

Sasaki Y, Nishina T, Yasui H, Goto M, Muro K, Tsuji A, Koizumi W, Toh Y, Hara T, Miyata Y. Phase II trial of nanoparticle albumin-bound paclitaxel as second-line chemotherapy for unresectable or recurrent gastric cancer. Cancer Sci 2014; 105: 812-817 [PMID: 24716542 DOI: 10.1111/cas.12419]

Avgustinovich AV, Bakina OV, Afanas'ev VG, Chemerisina OV, Spirina LV, Dobrodeev AY, Buldakov M, Chyzhovnov EL. Nanoparticles in Gastric Cancer Management. Curr Pharm Des 2021; 27: 2436-2444 [PMID: 33222664 DOI: 10.2174/138161286666620120151520]

Zhao Q, Cao L, Guan L, Bie L, Wang S, Xie B, Chen X, Shen X, Cao F. Immunotherapy for gastric cancer: dilemmas and prospects. Brief Funct Genomics 2019; 18: 107-112 [PMID: 30388190 DOI: 10.1016/j.bfg.0019]

Nakamura M, Ojima T, Katsuda M, Hayata K, Kitadani J, Nakamori M, Yamaue H. Phase 1 Study of Combined Chemotherapy of Nab-Paclitaxel, S-1, and Oxaliplatin for Gastric Cancer with Peritoneal Metastasis (NSOX Study). Oncology 2021; 99: 57-61 [PMID: 32877909 DOI: 10.1159/000509598]

Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res 2020; 10: 727-742 [PMID: 32266057]

Xu S, Cui F, Huang D, Zhang D, Zhu A, Sun X, Cao Y, Ding S, Wang Y, Gao E, Zhang F. PD-L1 monoclonal antibody conjugated nanoparticles enhance drug delivery level and chemotherapy efficacy in gastric cancer cells. Int J Nanomedicine 2019; 14: 17-32 [PMID: 30587982 DOI: 10.2147/IJN.S175340]

Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell 2015; 161: 205-214 [PMID: 25866065 DOI: 10.1016/j.cell.2015.03.030]

Hu N, Li W, Hong Y, Zeng Z, Zhang J, Wu X, Zhou K, Wu F. A PD1 targeted nano-delivery system based on epigenetic alterations of T cell responses in the treatment of gastric cancer. Mol Ther Oncolytics 2022; 24: 148-159 [PMID: 35024441 DOI: 10.1016/j.omto.2021.12.006]

Kumagai S, Togashi Y, Sakai C, Kawazoe A, Kawazu M, Ueno T, Sato E, Kuwata T, Kinoshita T, Yamamoto M, Nomura S, Tsukamoto T, Mano H, Shitara K, Nishikawa H. An Oncogenic Alteration Creates a Microenvironment that Promotes Tumor Progression by Confering a Metabolic Advantage to Regulatory T Cells. Immunity 2020; 53: 187-203.e8 [PMID: 32604259 DOI: 10.1016/j.immuni.2020.06.016]

Guo W, Chen Z, Li Z, Huang H, Ren Y, Zhao B, Li G, Hu Y. Improved immunotherapy for gastric cancer by nanocomposites with capability of triggering Dual-Damage of Nuclear/mitochondrial DNA and cGAS/STING-Mediated innate immunity. Chem Eng J 2022; 443: 136428 [DOI: 10.1016/j.cej.2022.136428]

Pan Y, Yu Y, Wang X, Zhang T. Tumor-Associated Macrophages in Tumor Immunity. Front Immunol 2020; 11: 583084 [PMID: 33365025 DOI: 10.3389/fimmu.2020.583084]

Cheng N, Bai X, Shu Y, Ahmad O, Shen P. Targeting tumor-associated macrophages as an antitumor strategy. Biochem Pharmacol 2021; 183: 114354 [PMID: 33279498 DOI: 10.1016/j.bcp.2021.114354]

Zhang J, Jiang M, Li S, Zhang Z, Sun H, Yang F, Liang H. Developing a Novel Anticancer Gold(III) Agent to Integrate Chemotherapy and Immunotherapy. J Med Chem 2021; 64: 6777-6791 [PMID: 34000198 DOI: 10.1021/acs.jmedchem.1c00505]

Morse MA, Gwin WR 3rd, Mitchell DA. Vaccine Therapies for Cancer: Then and Now. Target Oncol 2021; 16: 121-152 [PMID: 33512679 DOI: 10.1007/s11153-020-00788-w]

Liu BY, Chen XH, Gu QL, Li JF, Yin HR, Zhu ZG, Lin YZ. Antitumor effects of vaccine consisting of dendritic cells pulsed with tumor RNA from gastric cancer. World J Gastroenterol 2004; 10: 630-633 [PMID: 14991927 DOI: 10.3748/wjg.v10.i5.630]
Liu R, Li S. Reducing Postoperative Recurrence of Early-Stage Hepatocellular Carcinoma by a Wound-Targeted Mechanisms. Clohessy JG, Zhang J, Pandolfi PP. Diverse genetic-driven immune landscapes dictate tumor progression through distinct Bezzi M. 10.1242/jcs.237453 Xu L. Natl Cancer Inst 2021; 13: 302-316 [PMID: 29982104 DOI: 10.1007/s10611-016-1656-8].

An Y, Yang R, Wang X, Han Y, Jia G, Hu C, Zhang Z, Liu D, Tang Q. Facile Assembly of Thermosensitive Liposomes for Active Targeting Imaging and Synergetic Chemo-/Magnetic Hyperthermia Therapy. Front Bioeng Biotechnol 2021; 9: 691091 [PMID: 34422777 DOI: 10.3389/fbioe.2021.691091].

Lee YH, Tai D, Yip C, Choo SW, Chiew V. Combinational Immunotherapy for Hepatocellular Carcinoma: Radiotherapy, Immune Checkpoint Blockade and Beyond. Front Immunol 2020; 11: 568759 [PMID: 33117354 DOI: 10.3389/fimmu.2020.568759].

Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou M-M, Ruggiero M, Gaudin G, Lencioni R, Ruggiero M, Gaudin G, Lencioni R, Hidalgo M, Fong Y. Nat Med 2012; 18: 4465-4478 [PMID: 23021730 DOI: 10.1038/nm.3119].

Xu J, Zheng Q, Cheng X, Hu S, Zhang C, Zhou X, Sun P, Wang W, Su Z, Zou T, Song Z, Xia Y, Xi G, Gao Y. Chemo-photodynamic therapy with light-triggered disassembly of theranostic nanoplatform in combination with checkpoint blockade for immunotherapy of hepatocellular carcinoma. J Nanobiotechnology 2021; 19: 355 [PMID: 34717654 DOI: 10.1186/s12951-021-01101-1].

Chang F, Sryjäinen S, Sryjäinen K. Implications of the p53 tumor-suppressor gene in clinical oncology. J Clin Oncol 1995; 13: 1007-1022 [PMID: 10200129 DOI: 10.1002/1097-0433(19950301)13:6<1007::AID-JCO9>3.0.CO;2-4].

Harris CC. Structure and function of the p53 tumor suppressor gene: clues for rational cancer therapeutic strategies. J Natl Cancer Inst 1996; 88: 1442-1455 [PMID: 8841019 DOI: 10.1093/jnci/88.20.1442].

Xu L, PirrelloKF, Chang EH. Tumor-targeted p53-gene therapy enhances the efficacy of conventional chemo/radiotherapy. J Control Release 2001; 74: 115-128 [PMID: 11489488 DOI: 10.1016/s0168-3659(01)00324-8].

Cui Y, Guo G. Immunomodulatory Function of the Tumor Suppressor p53 in Host Immune Response and the Tumor Microenvironment. Int J Mol Sci 2016; 17: 27869779 [PMID: 33939543 DOI: 10.3390/ijms17111942].

Blaghy J, Buckley MD, Vousden KH. p53, cancer and the immune response. J Cell Sci 2020; 133 [PMID: 32144194 DOI: 10.1242/jcs.237453].

Bezzi M, Seitzner N, Ishikawa T, Reschke M, Chen Y. External validation of hepatocellular carcinoma risk scores in patients with chronic hepatitis B virus infection in China. JAMA Surg 2019; 154: 209-217 [PMID: 30422241 DOI: 10.1001/jamasurg.2018.4334].

Wang DX, Yang X, Lin JZ, Bai Y, Long JY, Yang XB, Seery S, Zhao HT. Efficacy and safety of lenvatinib for patients with advanced hepatocellular carcinoma: A retrospective, real-world study conducted in China. World J Gastroenterol 2020; 26: 4465-4478 [PMID: 32874058 DOI: 10.3748/wjg.v26.i30.4465].

Lou T, Li B, Xiong P, Jin C, Chen Y. External validation of hepatocellular carcinoma risk scores in patients with chronic hepatitis B virus infection in China. J Viral Hepat 2021; 28: 1373-1380 [PMID: 32418498 DOI: 10.1111/jhj.13569].

Qing X, Xu W, Zong J, Jia X, Peng H, Zhang Y. Emerging treatment modalities for systemic therapy in hepatocellular carcinoma. Biomark Res 2021; 9: 64 [PMID: 34419152 DOI: 10.1186/s40636-021-00039-3].

Kumari P, Ghosh B, Biswas S. Nanocarriers for cancer-targeted drug delivery. J Drug Target 2016; 24: 179-191 [PMID: 26061298 DOI: 10.3109/1061186X.2015.1051049].

Jia G, Han Y, An Y, Ding Y, He C, Wang X, Tang Q. NRP-1 targeted and cargo-loaded exosomes facilitate simultaneous imaging and therapy of glioma in vitro and in vivo. Biomaterials 2018; 178: 302-316 [PMID: 29982104 DOI: 10.1016/j.biomaterials.2018.06.029].

An Y, Yang R, Wang X, Han Y, Jia G, Hu C, Zhang Z, Liu D, Tang Q. Facile Assembly of Thermosensitive Liposomes for Active Targeting Imaging and Synergetic Chemo-/Magnetic Hyperthermia Therapy. Front Bioeng Biotechnol 2021; 9: 691091 [PMID: 34422777 DOI: 10.3389/fbioe.2021.691091].

Lee YH, Tai D, Yip C, Choo SW, Chiew V. Combinational Immunotherapy for Hepatocellular Carcinoma: Radiotherapy, Immune Checkpoint Blockade and Beyond. Front Immunol 2020; 11: 568759 [PMID: 33117354 DOI: 10.3389/fimmu.2020.568759].

Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou M-M, Matillia A, Tovoli F, Knox JJ, He AR, El-Raysne BF, Acosta-Rivera M, Neely J, Shen Y, Baccan C, Cruz CMD, Hsu C. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. J Clin Oncol 2019; 37: 4012-4012 [DOI: 12.1002/jco.2019.37.13_suppl.4012].

Galluzzi L, Vitale I, Warren S, Adjiman S, Agostinis P, Martinez AB, Chan TA, Coukos G, Demaria S, Deutsch E, Draganova D, Edelson RL, Formenti SC, Fučíkova J, Gabriele L, Gaipl US, Gameiro SR, Garg AD, Golden E, Han J, Harrington KJ, Hemminki A, Hodge JW, Hossain DMS, Illidge T, Karin M, Kaufman HL, Kepp O, Kroemer G, Lasarte JJ, Loi S, Lotze MT, Manic C, Mergnhoult T, Melcher AA, Mossman KL, Prosper F, Reck forbid O, Rescigno M, Riganti C, Sestili P, Shymanskaya E, Spiek J, Stagg J, Strauss BE, Tang D, Tatsuno K, van Cool SW, Vandenabeele P, Yamazaki T, Zamarripa D, Ziyovoglu L, Cesano A, Martinola FM. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer 2020; 8 [PMID: 32209603 DOI: 10.1101/jicro.2019.00037].

Xu J, Zheng Q, Cheng X, Hu S, Zhang C, Zhou X, Sun P, Wang W, Su Z, Zou T, Song Z, Xia Y, Xi G, Gao Y. Chemo-photodynamic therapy with light-triggered disassembly of theranostic nanoplatform in combination with checkpoint blockade for immunotherapy of hepatocellular carcinoma. J Nanobiotechnology 2021; 19: 355 [PMID: 34717654 DOI: 10.1186/s12951-021-01101-1].
Nanodrug. Adv Sci (Weinh) 2022; 9: e2200477 [PMID: 35524631 DOI: 10.1002/advs.202200477]

Yu Z, Guo J, Hu M, Gao Y, Huang L. Icaritin Exacerbates Mitophagy and Synergizes with Doxorubicin to Induce Immunogenic Cell Death in Hepatocellular Carcinoma. ACS Nano 2020; 14: 4816-4828 [PMID: 32188241 DOI: 10.1021/acsnano.0c00708]

Li Z, Wu T, Zheng B, Chen L. Individualized precision treatment: Targeting TAM in HCC. Cancer Lett 2019; 485: 86-91 [PMID: 31129147 DOI: 10.1016/j.canlet.2019.05.019]

Wang Y, Tirutthani K, Li S, Hu M, Zhong G, Tang Y, Roy S, Zhang L, Tan J, Liao C, Liu R. mRNA Delivery of a Bispecific Single-Domain Antibody to Polarize Tumor-Associated Macrophages and Synergize Immunotherapy against Liver Malignancies. Adv Mater 2021; 33: e2007603 [PMID: 33945178 DOI: 10.1002/adma.202007603]

Kahakov AE, Yakimova AO. Hypoxia-Induced Cancer Cell Responses Driving Radiosensitivity of Hypoxic Tumors: Approaches to Targeting and Radiosensitizing. Cancers (Basel) 2021; 13 [PMID: 33806538 DOI: 10.3390/cancers13051102]

Manoochehrhi Khoshinani H, Afshar S, Najafi R. Hypoxia: A Double-Edged Sword in Cancer Therapy. Cancer Invest 2016; 34: 536-545 [PMID: 27824512 DOI: 10.1080/07357907.2016.1245317]

Boutillier AJ, Elsaawa SF. Macrophage Polarization States in the Tumor Microenvironment. Int J Mol Sci 2021; 22 [PMID: 34290793 DOI: 10.3390/ijms22136995]

Dai X, Ruan J, Guo Y, Sun Z, Liu J, Bao X, Zhang H, Li Q, Ye C, Wang X, Zhao CX, Zhou F, Sheng J, Chen D, Zhao P. Enhanced radiotherapy efficacy and induced anti-tumor immunity in HCC by improving hypoxia microenvironment using oxygen microcapsules. Chem Eng J 2021; 422: 130109 [DOI: 10.1016/j.cej.2021.130109]

Yang M, Zhang C. The role of liver sinusoidal endothelial cells in cancer liver metastasis. Am J Cancer Res 2021; 11: 1845-1860 [PMID: 34094657]

Yu Z, Guo J, Liu Y, Wang M, Liu Z, Gao Y, Huang L. Nano delivery of simvastatin targets liver sinusoidal endothelial cells to remodel tumor microenvironment for hepatocellular carcinoma. J Nanobiotechnology 2022; 20: 9 [PMID: 34903554 DOI: 10.1186/s12951-021-01205-x]

Kor E, Elia U, Peer D. Principles for designing an optimal mRNA lipid nanoparticle vaccine. Curr Opin Biotechnol 2022; 73: 129-136 [PMID: 34715536 DOI: 10.1016/j.cobi.2021.09.016]

Gehre MS, Brito LA, Tostanoski LH, Doppelt M, Carfi A, Barouch DH. Novel approaches for vaccine development. Cell 2021; 184: 1589-1603 [PMID: 33740454 DOI: 10.1016/j.cell.2021.02.030]

Huang H, Zhang C, Yang S, Xiao W, Zheng Q, Song X. The investigation of mRNA vaccines formulated in liposomes administered in multiple routes against SARS-CoV-2. J Control Release 2021; 335: 449-456 [PMID: 34029632 DOI: 10.1016/j.jconrel.2021.05.024]

Szelenyi J, Storm G, Ljuibimova JY, Castells M, Phillips EJ, Turjeman K, Barenholz Y, Crommelin DJA, Dobrovolskaia MA. Applying lessons learned from nanomedicines to understand rare hypersensitivity reactions to mRNA-based SARS-CoV-2 vaccines. Nat Nanotechnol 2021; 17: 337-346 [PMID: 35339599 DOI: 10.1038/s41565-022-01071-x]

Zhang Y, Xie F, Yin Y, Zhang Q, Jin H, Wu Y, Pang L, Li J, Gao J. Immunotherapy of Tumor RNA-Loaded Lipid Nanoparticles Against Hepatocellular Carcinoma. Int J Nanomedicine 2021; 16: 1553-1564 [PMID: 33658783 DOI: 10.2147/IJN.S291421]

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

Ladabaum U, Dominitz JA, Kahi C, Schoon RE. Strategies for Colorectal Cancer Screening. Gastroenterology 2020; 158: 418-432 [PMID: 31394083 DOI: 10.1053/j.gastro.2019.06.043]

Sagarik X, Vanstapel A, Verbeek S. Tumor Heterogeneity in Colorectal Cancer: What Do We Know So Far? Pathobiology 2018; 85: 72-84 [PMID: 29414818 DOI: 10.1159/000486721]

Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. Colorectal cancer statistics, 2017. CA Cancer J Clin 2017; 67: 177-193 [PMID: 28248415 DOI: 10.3332/caac.21395]

Bai J, Chen H, Bai X. Relationship between microsatellite status and immune microenvironment of colorectal cancer and its application to diagnosis and treatment. J Clin Lab Anal 2021; 35: e23810 [PMID: 33938589 DOI: 10.1002/jcla.23810]

Krasneva N, Georgieva M. Promising Therapeutic Strategies for Colorectal Cancer Treatment Based on Nanomaterials. Pharmaceutics 2022; 14 [PMID: 35745786 DOI: 10.3390/pharmaceutics14061213]

Liu H, Xu C, Meng M, Li S, Sheng S, Zhang S, Ni W, Tian H, Wang Q. Metal-organic framework-mediated multifunctional nanoparticles for combined chemo-photothermal therapy and enhanced immunotherapy against colorectal cancer. Acta Biomater 2022; 144: 132-141 [PMID: 35307591 DOI: 10.1016/j.actbio.2022.03.023]

Wangmo D, Premririt PK, Yuan C, Morris WS, Zhao X, Subramanian S. ACKR4 in Tumor Cells Regulates Dendritic Cell Migration to Tumor-Draining Lymph Nodes and T-Cell Priming. Cancers (Basel) 2021; 13 [PMID: 34638505 DOI: 10.3390/cancers13195021]

Yuan Z, Fan G, Wu H, Liu C, Zhan Y, Qiu Y, Shou C, Gao F, Zhang J, Yin P, Xu K. Photodynamic therapy synergizes with PD-L1 checkpoint blockade for immunotherapy of CRC by multifunctional nanoparticles. Mol Ther 2021; 29: 2931-2948 [PMID: 34023507 DOI: 10.1016/j.ymthe.2021.05.017]

Zhu Q, Sun F, Li T, Zhou M, Ye J, Ji A, Wang H, Ding C, Chen H, Xu Z, Yu H. Engineering Oxaliplatin Prodrug Nanoparticles for Second Near-Infrared Fluorescence Imaging-Guided Immunotherapy of Colorectal Cancer. Small 2021; 17: e2070882 [PMID: 33690984 DOI: 10.1002/snml.202070882]

Li J, Zhao M, Sun M, Wu S, Zhang H, Dai Y, Wang D. Multifunctional Nanoparticles Boost Cancer Immunotherapy Based on Modulating the Immunosuppressive Tumor Microenvironment. ACS Appl Mater Interfaces 2020; 12: 50734-50747 [PMID: 33124808 DOI: 10.1021/acsami.0c01409]

Li C, Zhang X, Yang M, Dong X. Recent Progress in Ferroptosis Inducers for Cancer Therapy. Adv Mater 2019; 31: e1904197 [PMID: 31595562 DOI: 10.1002/adma.201904197]

Duan X, Chan C, Han W, Guo N, Weichselbaum RR, Lin W. Immunostimulatory nanomedicines synergize with checkpoint blockade immunotherapy to eradicate colorectal tumors. Nat Commun 2019; 10: 1899 [PMID: 31015397 DOI: 10.1038/s41467-019-09221-x]
Ding YN et al. Nanoparticles and gastrointestinal cancer

[References]

112 Haegerbaeert RMS, Kempers M, Ceelen W, Lentacker I, Rernaut K. Nanoparticle mediated targeting of toll-like receptors to colorectal cancer. Eur J Pharm Biopharm 2022; 172: 16-30 [PMID: 35074555 DOI: 10.1016/j.ejpb.2022.01.002]

113 Bahmani B, Gong H, Luk BT, Haushalter KJ, DeTeresa E, Previti M, Zhou J, Gao W, Bui JD, Zhang L, Fang RH, Zhang J. Intratumoral immunotherapy using platelet-cloaked nanoparticles enhances antitumor immunity in solid tumors. Nat Commun 2021; 12: 1999 [PMID: 33790276 DOI: 10.1038/s41467-021-22311-z]

114 Luo Y, Yang J, Yu J, Liu X, Yu C, Hu J, Shi H, Ma X. Long Non-coding RNAs: Emerging Roles in the Immunosuppressive Tumor Microenvironment. Front Oncol 2020; 10: 48 [PMID: 32083005 DOI: 10.3389/fonc.2020.00484]

115 Huang D, Chen J, Yang L, Ouyang Q, Li J, Lao L, Zhao J, Liu J, Lu Y, Xing Y, Chen F, Su F, Yao H, Liu Q, Su S, Song E. NKILA IncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. Nat Immunol 2018; 19: 1112-1125 [PMID: 30224822 DOI: 10.1038/s41590-018-0207-y]

116 Zheng Y, Tian X, Wang T, Xia X, Cao F, Tian J, Xu P, Ma J, Xu H, Wang S. Long noncoding RNA PVT1 regulates the immnosuppression activity of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. Mol Oncol 2019; 18: 61 [PMID: 30952926 DOI: 10.1186/s12943-019-00978-2]

117 Liu F, Dai Z, Cheng Q, Xu L, Huang L, Liu Z, Li X, Wang N, Wang G, Wang L, Wang Z. LncRNA-targeting bio-scaffold mediates triple immune effects for postoperative colorectal cancer immunotherapy. Biomaterials 2022; 284: 121485 [PMID: 35367839 DOI: 10.1016/j.biomaterials.2022.121485]

118 Tlig H, Adolph TE, Gerner RR, Moschen AR. The Intestinal Microbiota in Colorectal Cancer. Cancer Cell 2018; 33: 954-964 [PMID: 29657127 DOI: 10.1016/j.ccell.2018.03.004]

119 Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 2014; 12: 661-672 [PMID: 25198138 DOI: 10.1038/nrmicro3344]

120 Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 2013; 14: 207-215 [PMID: 23954159 DOI: 10.1016/j.chom.2013.07.007]

121 Chen T, Li Q, Wu J, Wu Y, Peng W, Li H, Wang J, Tang X, Peng Y, Fu X. Fusobacterium nucleatum promotes M2 polarization of macrophages in the microenvironment of colorectal tumours via a TLR4-dependent mechanism. Cancer Immunol Immunother 2018; 67: 1635-1646 [PMID: 30121899 DOI: 10.1007/s00262-018-2233-x]

122 Dong X, Pan P, Zheng DW, Bao P, Zeng X, Zhang XZ. Bioinorganic hybrid biophotonics for modulation of intestinal microbiota to remodel tumor-immune microenvironment against colorectal cancer. Sci Adv 2020; 6: eaba1590 [PMID: 32440552 DOI: 10.1126/sciadv.abal590]

123 Zhang Y, Ma S, Liu X, Xu Y, Zhao J, Si X, Li H, Huang Z, Wang Z, Tang Z, Song W, Chen X. Supramolecular Apparatable Nanomembrane As In Situ Cancer Vaccine for Cancer Immunotherapy. Adv Mater 2021; 33: c2007293 [PMID: 33448050 DOI: 10.1002/adma.202007293]

124 GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2019; 4: 934-947 [PMID: 31648972 DOI: 10.1016/S2468-1253(19)30347-4]

125 Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol 2021; 18: 493-502 [PMID: 34002083 DOI: 10.1038/s41575-021-00457-x]

126 Zhao Z, Liu W. Pancreatic Cancer: A Review of Risk Factors, Diagnosis, and Treatment. Technol Cancer Res Treat 2020; 19: 1533033820962117 [PMID: 33357065 DOI: 10.1177/1533033820962117]

127 Nishida T, Yoshitomi H, Takano S, Kagawa S, Shimizu H, Ohtsuka M, Kato A, Furukawa K, Miyazaki M. Low Stromal Area and High Stromal Microvessel Density Predict Poor Prognosis in Pancreatic Cancer. Pancreas 2016; 45: 593-600 [PMID: 26495781 DOI: 10.1097/MPA.0000000000000499]

128 Li S, Xu HY, Wu CT, Wang QG, Jin W, Gao HL, Li H, Zhang SR, Xu JZ, Qi ZH, Ni QX, Yu XJ, Liu L. Angiogenesis in pancreatic cancer: understanding the role of lifestyle and inherited risk factors. Nat Rev Cancer 2019; 19: 479-494 [PMID: 31680205 DOI: 10.1038/s41571-018-0194-1]

129 Selvanesan BC, Meena K, Beck A, Meheus L, Lara O, Rooman I, Gravekamp C. Nicotinamide combined with gemcitabine is an immunomodulatory therapy that restrains cancerous growth in mice. J Immunother Cancer 2020; 8 [PMID: 33154149 DOI: 10.1136/jitc-2020-001250]

130 Rocha FG. Landmark Series: Immunotherapy and Targeted Therapy for Pancreatic Cancer. Ann Surg Oncol 2021; 28: 1400-1406 [PMID: 33386052 DOI: 10.1245/s10434-020-09367-9]

131 Schizas D, Charalampakis N, Kole C, Economidou P, Koustas E, Gkotsis E, Ziogas D, Psyrri A, Karamouzis MV. Immunotherapy for pancreatic cancer: 2020 update. Cancer Treat Rev 2020; 86: 102016 [PMID: 32247990 DOI: 10.1016/j.ctrv.2020.102016]

132 Jia M, Zhang D, Zhang C, Li C. Nanoparticle-based delivery systems modulate the tumor microenvironment in pancreatic cancer for enhanced therapy. J Nanobiotechnology 2021; 19: 384 [PMID: 34809634 DOI: 10.1186/s12951-021-01134-6]

133 Wang Y, Gao Z, Du X, Chen S, Zhang W, Wang J, Li H, He X, Cao J. Co-inhibition of the TGF-β pathway and the PD-L1 checkpoint by pH-responsive clustered nanoparticles for pancreatic cancer microenvironment regulation and anti-tumor immunotherapy. Biomater Sci 2020; 8: 5121-5132 [PMID: 32820750 DOI: 10.1039/d9bm00916d]

134 Yu Q, Yang J, Zhao W, Qiu Y, He J, Wan D, Li J, Wang X, He X, Liu Y, Li M, Zhang Z, He Q. Mild hyperthermia promotes immune checkpoint blockade-based immunotherapy of metastatic pancreatic cancer using size-adjustable nanoparticles. Acta Biomater 2021; 133: 244-256 [PMID: 34004605 DOI: 10.1016/j.actbio.2021.05.002]

135 Wang C, Shi X, Song H, Zhang C, Wang X, Huang P, Dong A, Zhang Y, Kong D, Wang W. Polymer-lipid hybrid nanovesicle-enabled combination of immunogenic chemotherapy and RNAi-mediated PD-L1 knockdown elicits antitumor immunity against melanoma. Biomaterials 2021; 268: 120579 [PMID: 33278683 DOI: 10.1016/j.biomaterials.2020.120579]

136 Danhier F, Ansoarena E, Silva JM, Coco R, Le Breton A, Prétat V. PLGA-based nanoparticles: an overview of biomedical applications. J Control Release 2012; 161: 505-522 [PMID: 22353619 DOI: 10.1016/j.jconrel.2012.01.043]

https://www.wjgnet.com
Coussens LM, Daldrup-Link HE. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory metabolism and repolarize macrophage for combination pancreatic cancer therapy.

Wang M, Yu P, Liu Y, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases.

Allavena P, Palmioli A, Avigni R, Sironi M, La Ferla B, Maeda A. PLGA Based Nanoparticles for the Monocyte-Mediated Anti-Tumor Drug Delivery System. J Biomed Nanotechnol 2020; 16: 212-223 [PMID: 32252882 DOI: 10.1166/jbnb.2020.2881]
