International Journal of Nanomedicine Dovepress

Open Access Full Text Article REVIEW

Nanotechnology for the Diagnosis and Treatment of Liver Cancer

Yuxuan Cai[1], Weiwei Wang[1], Qinlian Jiao[1], Tangbin Hu[1], Yidan Ren[1], Xin Su[2], Zigan Li[2], Maoxiao Feng[1], Xiaoyan Liu[1], Yunshan Wang[1]

[1]Department of Clinical Laboratory, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China; [2]Department of Clinical Laboratory, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, 250033, People's Republic of China

Correspondence: Yunshan Wang, Department of Clinical Laboratory, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China, Email wangyunshansd@sdu.edu.cn

Abstract: Liver cancer has become a major global health challenge due to its high incidence, high rate of late diagnosis and limited treatment options. Although there are many clinical treatments available for liver cancer, the cure rate is still very low, and now researchers have begun to explore new aspects of liver cancer treatment, and nanotechnology has shown great potential for improving diagnostic accuracy and therapeutic efficacy and is therefore a promising treatment option. In diagnosis, nanomaterials such as gold nanoparticles, magnetic nanoparticles, and silver nanoparticles can realize highly sensitive and specific detection of liver cancer biomarkers, supporting diagnosis and real-time monitoring of the disease process. In terms of treatment, nanocarriers can realize precise targeted delivery of drugs, improve the bioavailability of liver cancer therapeutic drugs and reduce systemic toxic side effects. In addition, advanced technologies such as nanoparticle-based photothermal therapy and photodynamic therapy provide innovative solutions to overcome drug resistance and local tumor ablation. Therefore, in this paper, we will introduce nanotechnology for hepatocellular carcinoma in terms of tumor marker detection, targeted drug delivery, and synergistic PDT/CDT therapy.

Keywords: nanoparticles, tumor marker detection, drug delivery system, tumor therapy

Introduction

Liver Cancer

Liver cancer, especially hepatocellular carcinoma (HCC), is a major global health problem due to its high prevalence in many countries.[1] Liver cancer is one of the most common causes of cancer death worldwide, and is the fifth most common malignancy worldwide, with an annual case-fatality rate of about 1, indicating that most cases do not survive more than one year.[2] It is the only one of the top five deadliest cancers with an increasing incidence. Currently, the highest incidence and prevalence of primary liver cancer is in East Asia.[3] According to cancer data from GLOBOCAN 2020, liver cancer is estimated to be the second of the top five causes of cancer deaths in China in 2022,[4] although there are currently many treatments available for liver cancer, but it remains one of the most difficult cancers to treat.

Liver cancer is a malignant tumor that originates in the liver, often occurring in the context of chronic liver disease and cirrhosis.[5] Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for 70–85% of the total liver cancer burden, it usually develops in the context of advanced chronic liver disease and is mainly associated with Hepatitis B virus (HBV), Hepatitis C virus (HCV) and alcohol abuse.[6] The treatment of liver cancer is a multi-disciplinary and multi-mode treatment method, which is usually selected according to the tumor stage, the degree of underlying liver disease and the patient's performance status.[7] At present, chemotherapy, immunotherapy, hepatectomy, liver transplantation, new targeted therapy and so on are the main therapies for liver cancer.[8] However, because liver cancer is often found in the late stage, the recurrence rate after resection is high, and the rate of surgery and transplantation is low, so there are limitations.[9,10] Therefore, for liver cancer patients, new treatment is necessary.

Received: 8 August 2024
Accepted: 4 December 2024
Published: 24 December 2024

Routine Detection of Liver Cancer Biomarker

Routine Detection for Alpha-Fetoprotein (AFP)

Alpha-fetoprotein (AFP) is a plasma protein produced primarily by the liver, yolk sac, and fetus, and is often used as a clinical indicator for the specific diagnosis of primary liver cancer. AFP is an important index for early diagnosis of liver cancer, so the detection of AFP is particularly important.[11] At present, the detection methods of AFP mainly include fluorescence immunoassay, enzyme-linked immunosorbent assay, radioimmunoassay and so on. The enzyme-linked immunosorbent assay (ELISA) is to coat the solid-phase carrier with anti-AFP antibody, add the AFP in the sample to bind the antibody on the solid-phase carrier, and then add the enzyme-labeled anti-AFP antibody, formation of antibody-antigen-enzyme-labeled antibody complex, substrate color, color and the corresponding amount of AFP was positively correlated.[12] Because of its high specificity, low cost and intuitive readout, ELISA is the most suitable method for the detection of clinical biomarkers.[13]

For liver cancer, accurate early detection and diagnosis is very important. Alpha-fetoprotein (AFP) is a plasma protein mainly produced by the liver, yolk sac and fetus. It is often used as a clinical marker for the specific diagnosis of primary liver cancer. At present, AFP analysis is the main biomarker for rapid diagnosis of HCC.[14] At present, the detection of AFP is mainly based on antibody, but compared with antibody, aptamer has the characteristics of high stability, universal target, affinity and selectivity, this makes it a suitable choice for designing AFP aptamer sensing platform.[15] In recent years, more and more attention has been paid to aptamer-based biosensors. And nanomaterials are widely used in the construction of these sensors because of their unique physical chemistry properties, such as fine tuning, excellent surface-to-body ratio, and strong signal strength, the sensitivity of AFP detection and the detection ability of biomarkers are greatly improved, which provides a greater possibility for the chemical and biological detection of AFP,making nanotools a promising candidate for cancer diagnosis.[16]

Routine Testing for Other Biomarkers

Lens culinaris lectin-reactive fraction of AFP (AFP- L3) is one of the heterodimers of alpha-fetoprotein, which is mainly secreted by hepatocellular carcinoma cells, and is a specific biomarker for hepatocellular carcinoma.[17] It is important in early diagnosis, risk stratification and efficacy assessment of hepatocellular carcinoma due to its high specificity and sensitivity. Lectin Affinity Electrophoresis (LAE) method is one of the classical techniques used to detect alpha-fetoprotein heterodimers (AFP-L3).[18,19] Based on the difference in binding ability of different heterodimers to Lens culinaris lectin (LCA), AFP-L3 can bind specifically to LCA and AFP-L3 contains specific glycosylation modifications that allow it to migrate differently in electrophoresis and to form complexes with LCA, which can be isolated and quantitatively analyzed. In addition to this AFP-L3 can also be isolated using lectin affinity centrifugation columns and combined with conventional solid phase immunoassay techniques for content determination, which is a significant time saver over electrophoretic methods.[20] De-gamma-carboxyprothrombinogen [DCP] is a protein induced by vitamin K deficiency or antagonist II and has been evaluated as a serologic marker for hepatocellular carcinoma (HCC).[21] Currently, the most used clinical assay is the enzyme-linked immunosorbent assay (ELISA), which uses specific antibodies to bind DCP and detect changes in its concentration with high sensitivity and specificity. There is also a new method for the determination of decarboxylated antithrombin (DCP) activity on undiluted adsorbed plasma using glucoagglutinin, assessed by means of glucoagglutinin (SC), rather than the antigenic activity of DCP in serum. In their analysis, fully carboxylated thrombospondin was removed by adsorption of defibrinated plasma by aluminum hydroxide. Using staphylococcal coagulase, these researchers converted unabsorbed DCP to thrombin. Formation of thrombin coagulase hydrolyzes the chromogenic substrate, which is monitored by color absorption.[22]

Classic Treatment of Liver Cancer

Surgeries

Surgery is the treatment of choice for patients with liver cancer (especially hepatocellular carcinoma, HCC) to gain a chance of long-term survival. According to the patient's condition and tumor characteristics, surgical treatment is mainly divided into hepatectomy and liver transplantation. Hepatic resection is a treatment modality to remove the primary tumor and part of the surrounding liver tissue, which has a high cure rate for patients with limited hepatocellular carcinoma, but it is only applicable to patients with good liver function (eg, Child-Pugh class A) and tumors confined to the liver; however, most patients with

hepatocellular carcinoma are already in the middle to late stage when diagnosed, with multiple foci, vascular invasions, or extrahepatic metastases, which prevent them from undergoing radical surgery.[23] Even with successful surgical treatment, the 5-year recurrence rate of liver cancer is still as high as 50% to 70%.[24–26] Transplantation is a therapeutic way to replace a patient's damaged liver by transplanting a healthy donor liver. It is suitable for patients with liver cancer accompanied by severe cirrhosis or hepatic insufficiency and can treat both the tumor and the underlying liver disease at the same time. However, liver transplantation has strict selection criteria for patients, such as the size and number of tumors, whether there is vascular invasion, etc. These criteria limit the scope of liver transplantation. Moreover, patients need to use immunosuppressive drugs for a long time after liver transplantation, which may increase the risk of infection, tumor recurrence or new tumor.

Chemotherapy

The oral multi-kinase inhibitor sorafenib (sorafenib) has been recommended worldwide as a first-line treatment for advanced HCC, a recommendation also supported by the results of several trials.[27,28] Sorafenib is a multi-kinase inhibitor that promotes apoptosis, slows angiogenesis and inhibits the proliferation of tumor cells.[29] By inhibiting Raf-1 and other tyrosine kinase, sorafenib was able, these include the serine-threonine kinase RAF-1, Platelet-derived growth factor receptor beta, c-KIT, FLT-3, VEGF Receptors-2 And-3, and RET to induce cancer cell apoptosis.[30] However, with Sorafenib's long-term use, cancer cells develop resistance to the drug, making it less effective than expected. Clinically, only about 30% of patients benefit from sorafenib, and these patients typically develop significant resistance within six months.[31] In addition, the use of sorafenib in cancer patients can have adverse side effects. Symptoms include elevated serum lipase and amylase levels, hypertension, bleeding, neuropathy, leukopenia, lymphocyte, diarrhea, nausea, vomiting and dyspnea.[32,33]

Immunotherapy

Cancer cells that escape immune destruction have become a hallmark of cancer.[34] Therefore, immunotherapy has become a promising therapeutic method and is being studied for various tumors, including liver cancer, it aims to selectively target tumor cells by inducing or enhancing existing tumor Hapten responses.[35,36] Immunotherapy relies on the activity of the immune system, which is regulated by immune cells called T cells.[37] In the tumor microenvironment, T cells are fine-tuned by a set of cell-surface molecules called immune checkpoints, in addition to recognizing and presenting tumor antigens.[38,39] The checkpoint pathway is an endogenous mechanism for regulating autoimmunity, but cancer cells can use this pathway to evade immune responses. The interaction between PD-1 and its ligand programmed death ligand 1(PD-L1) (B7-H1) and PD-L2 (B7-DC) is a critical immune checkpoint and a major mechanism of immunosuppression in the tumor microenvironment.[40,41] CD8 T cells and Kupffer cells in human HCC tumor tissues expressed PD-1 and PD-L1 at high levels, respectively. PD-L1 Kupffer cells interact with PD-1 CD8 T cells, leading to effector T cell dysfunction in liver cancer.[42] The increased expression of PD-L1 in HCC is indeed associated with poor prognosis of HCC patients. Thus, the expression of inhibitory immune checkpoints may be dysregulated in the tumor microenvironment, thereby improving t cell-mediated immune responses to treat cancer through cancer immunotherapy.[43] However, immunotherapy is only effective in a subset of the population of patients with liver cancer, and many patients with liver cancer have a background of viral hepatitis (HBV or HCV infection), which may alter the effectiveness of immunotherapy. Objective remission rates (ORRs) for PD-1/PD-L1 inhibitors are also typically only around 20%, and some patients may show an initial response, but then may develop drug resistance, leading to Disease progression. The high cost of immunotherapeutic agents such as PD-1/PD-L1 inhibitors limits their availability in low- and middle-income populations.

Radiotherapy

Radiation Therapy (RT) is a method of using high-energy rays to kill liver cancer tumor cells, which mainly includes three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy (SBRT), and so on.[44] Liver tumors are sensitive to radiation therapy with moderate to high radiosensitivity, second only to bone marrow and lymphoid tissue tumors, which are very sensitive to radiation, as well as normal tissues such as bone marrow and kidneys,[45] so radiotherapy plays an increasingly important role in the treatment of hepatocellular carcinoma; however, radiotherapy has a significant effect on local control of confined tumors only, and it is mainly aimed at patients who are unsuitable for surgery or other local treatments, and Radiotherapy cannot inhibit the growth of distant

metastatic foci, so it has limited effect on liver cancer patients with extensive systemic metastases. In addition, the application of radiation therapy is limited by factors such as liver radiation tolerance, target area definition, and economic limitations, so some breakthroughs in radiation therapy are still needed.[46,47]

Status of Nanomaterials in Liver Cancer Diagnosis and Treatment

Although there are now many traditional treatments for liver cancer in the clinic, they all have certain drawbacks and limitations, resulting in poor treatment effects and poor patient survival rates. Currently in many studies the application of nanotechnology in liver cancer diagnosis and treatment has made remarkable progress. Firstly nanoparticles (eg gold nanoparticles, quantum dots, magnetic nanoparticles) can be used to detect liver cancer-specific biomarkers (eg alpha-fetoprotein AFP, AFP-L3, and aberrant thrombospondin), and these materials make early detection possible through high sensitivity and specificity. In addition, nanoparticles can enhance targeting by virtue of enhanced penetration and retention effects (ERP) or surface modification of targeting ligands to increase specificity to liver cancer tumor tissues. Nanoparticles loaded with both chemotherapeutic drugs and photothermal or photodynamic agents achieve synergistic therapeutic effects. For example, liposomal nanoparticles loaded with doxorubicin (eg, Doxil) have been approved for the treatment of a variety of cancers and are increasingly being used in liver cancer research.

Nanomaterials

Nanotechnology is an emerging and promising therapeutic tool. Nanotechnology refers to the design, characterization and application of structures, devices and systems by controlling the shape and size of nanoscale.[48] It is an emerging area of research with a variety of applications in science and technology, particularly in the development of new materials. Nanoparticles have unique properties that make them popular in materials science and biology. The field of nanotechnology has grown exponentially over the past decade, and many products containing nanoparticles are now used in applications such as food science, cosmetics and pharmaceuticals.[49] Nanoparticles (NPs) are defined as particles in the one-dimensional range of 1 to 100 nm.[50] NPs exhibits different properties depending on its size and surface function, small size and large surface area are the reasons why nanoparticles are widely used in various fields.[51] Nanoparticles are used as drug carriers and have applications in both diagnosis and treatment. Their clinical applicability depends on different parameters, such as physics and chemical property, drug loading efficiency, drug release, and most importantly, low toxicity or non-toxicity of the vehicle itself.[52]

Nanomedicine is the application of nanoscale systems with unique physical and chemical property properties to biomedicine. The unique properties of nano systems include high reactivity, small size effect, high surface volume ratio and quantum effect.[53] Nanomedicine also offers many benefits for cancer diagnosis and treatment, often due to unique material properties at the nanoscale,[54] different nanomaterials have different applications in the diagnosis and treatment of liver cancer according to their main advantages. (Table 1).

Gold Nanoparticles

Gold nanoparticles have been widely used in medicine because of their unique properties such as easy surface modification, good photothermal conversion and high x-ray absorption coefficient.[55,56] Gold nanoparticles in the treatment of the main rely on its easy surface modification and the efficacy of photothermal transformation.[57] Huang et al used anti miR-181b loaded gold nano-cage to carry out gene-photothermal therapy and achieved significant inhibition of tumor growth in SMMC-7721 tumor mice, these results indicate the potential of gold NPS as a multifunctional therapeutic agent nano-carrier for the treatment of liver cancer. Gold nanoparticles have an effective fluorescence quenching function and can be used to detect specific molecular biomarkers. DNA biosensors based on gold nanoparticles modified graphene oxide have been developed to detect cancer biomarkers, and such biosensors provide an idea for early diagnosis of cancer.[58] In addition, gold nanoparticles can be a good carrier for cancer vaccines because of their appropriate payload, low immunogenicity and biocompatibility.[59] Immunotherapy with gold nanoparticles can be used as an adjunct to surgery.[60]

Table 1 Various Types of Nanotechnology Applied to Liver Cancer Diagnosis and Treatment

Technical Direction	Types of Nanotechnology	Application Objective	Major Advantage	Sample Material or Technique
Diagnosis	Nanosensor	Monitoring of liver cancer biomarkers (AFP, AFP-L3)	Increased sensitivity and specificity, early detection	Gold nanoparticle sensors, quantum dots
	Magnetic nanoparticles	Image-guided diagnostics (MRI imaging)	Enhanced tumor localization and surveillance capabilities	Superparamagnetic iron oxide nanoparticles (SPIONs)
	Multimodal imaging nanoplatform	Enabling precision tumor Imaging	Provides a wide range of information such as CT/MRI/ photoacoustic imaging	Core-shell nanoparticles
Drug delivery	Inorganic nanoparticles	Improved tumor tissue penetration and targeting	Enhanced stability and drug loading	Polycaprolactone nanoparticles, gold nanoparticles
	Polymer nanocarriers	Enhanced targeting by ligand-specific recognition	Receptor-mediated endocytosis is efficient and accurate	Hyaluronic acid, polylactic acid-glycolic acid copolymer (PLGA)
	Liposomal nanoparticles	Targeted delivery of chemotherapy drugs	Improve drug stability and reduce toxic side effects	Doxorubicin liposome (Doxil)
Local treatment	Photodynamic nanotherapy	Killing tumor cells by generating reactive oxygen species through light energy	Precise action with few side effects	Manganese oxide nanoparticles, gold nanopillars
	Chemodynamic nanotherapy	Stimulates reactive oxygen species to destroy tumor cells	Non-invasive treatment modalities	Silicon dioxide nanoparticles, copper ion-mediated hydrogels
	Photothermal and magnetothermal Therapy	Localized heating to kill tumor cells	Ability to act on deep tumor tissue	Magnetic nanoparticles

Notes: Various types of nanotechnology for different application targets and their advantages are introduced.

Magnetic Nanoparticles

It is well known that the method of early diagnosis of liver cancer is very important. Currently, MRI is a powerful imaging modality for the diagnosis of liver cancer, but its sensitivity is still insufficient in the early detection of molecular and cellular imaging.[61,62] Magnetic nanoparticles, particularly iron oxide nanoparticles, can be used for liver imaging and cell tracking. Among them, glycosaminoglycan-targeted superparamagnetic iron oxide nanoparticles (SPIONs) can be used for MRI tracking of human hepatocellular carcinoma (HepG-2) cells due to their high uptake by the liver.[63] Several high-performance contrast agents have been developed based on SPIONs, including one called iron octapeptide oxide NPs, which is more effective than the clinically commonly used Feraheme®, it showed more significant T2 reputation.[64] The multifunctional fluorescent magnetic nanoparticle matrix, which can specifically recognize lung cancer stem cells and be used for tumor xenograft imaging, is a cancer diagnostic reagent that functions by modifying multiple fluorescent dyes and targeting ligands.[65]

Liposomal Nanoparticles (LNPs)

Liposomal nanoparticles (LNPs) are composed of lipid-like molecules capable of encapsulating hydrophilic and hydrophobic drugs, while possessing good biocompatibility, low toxicity and biodegradability. Liposomes are a promising carrier for targeted delivery, one of the most used carriers in targeted cancer therapies and have been used as drug carriers in a variety of cancer

therapies.[66,67] Doxil, the first FDA-approved liposomal chemotherapeutic nanoparticle, has achieved good anti-tumor effects in clinical practice. LNP, as a well-established and highly tunable nanocarrier, have attracted much attention in the treatment of liver cancer. Many examples have been shown that liposomes have been utilized for the treatment of HCC.[68,69] In addition to drug-carrying liposomes, LNP-based gene therapy has also progressed in recent years. Liposome-encapsulated small interfering RNA (siRNA) can effectively silence the expression of target genes in vitro.[70] It has been found that small interfering RNAs (siRNAs) delivered via LNPs targeting the Jnk2 gene are effective in reducing hepatocellular carcinoma incidence and progression.[71] In this study, siRNA molecules were encapsulated in LNPs that were optimized to ensure that they were effective in accumulating and silencing the Jnk2 gene in hepatocytes, thereby reducing the occurrence of liver cancer. More interestingly, Cao et al prepared self-treating DPPA- LNPs using the biologically inactive lipid DPPA. DPPA-LNPs exhibited significant anti-angiogenic activity in vitro and in vivo, significantly inhibited angiogenesis and tumor growth in triple-negative breast and liver cancers without the need to load any therapeutic reagents and had therapeutic efficacy superior to that of the FDA-approved sorafenib.[72] This suggests that liposomes themselves may have some tumor inhibitory effects.

Carbon-Based Nanoparticles

Carbon-based nanoparticles (ACNPs) are a class of nanomaterials with carbon as the main constituent element, which have a unique structure and excellent physicochemical properties, such as high specific surface area, good biocompatibility, chemical stability, and multifunctionality, which have led to a wide range of applications in biomedical fields. Activated carbon nanoparticles (ACNP) have spherical shape, relatively smooth surface, strong adsorption, good lymphatic tropism, high cellular uptake and excellent tumor targeting. ACNP-based drug delivery systems can reduce the concentration of drugs in the bloodstream, thereby decreasing drug toxicity, and can significantly improve the therapeutic efficacy of anticancer drugs by increasing the concentration of drugs in treatment-related tissues.[73] The nano drug delivery system using activated charcoal nanoparticles as the carrier and metformin (MET) as the drug (ACNP-MET) can selectively eliminate hepatocellular carcinoma stem cells (CSCs) and increase the effect of MET on hepatocellular carcinomas, thus achieving the goal of hepatocellular carcinoma treatment.[74]

Nanoparticles in the Diagnosis and Treatment of Liver Cancer

Detection of Biomarkers for Liver Cancer

Detection of Alpha Fetoprotein (AFP)

Noble metal nanoparticles, due to their unique optical, chemical and electrical properties, have been fully optimized and widely used in the sensitive and specific detection of AFP. In particular, gold nanoparticles have the advantages of rapid synthesis, simple synthesis, narrow size distribution, effective modification by thiols or other biological ligands, and good biocompatibility, in particular.[75,76] It has been used in a novel FELISA based on HAT-triggered fluorescence "Turn-on", in which gold nanoparticles (AuNPs) are used as carriers, the detection probe is formed by receiving a detection antibody (Ab2) and HAT labeling to form detection probes, and fluorescence-quenched Rhodamine110 bisamide derivative as substrates for the HAT. After the sandwich immune reaction, the HAT on the sandwich structure can catalyze the cleavage of the fluorescence quenched substrate to produce a strong fluorescence signal, it is used to detect ultra-low levels of alpha-fetoprotein (AFP) and Hepatitis B virus surface antigen (HBsAg), and its detection limit is much lower than that of enzyme-and fluorescein-labeled immunoassays.[77] Glucose sensors are now one of the most popular and widely used real-time detection devices. Liu et al developed a novel electrochemical E LISA strategy based on glucose detection of protein biomarkers, using AFP as a model protein and glucose amylase as a marker molecule by converting starch into glucose, it acts as a link between glucose and alpha-fetoprotein. Using AuNPs as nano-carrier, the sensitivity of detection was improved by attaching glucoamylase and signal antibody in high proportion.[78]

LSAW sensor is a new detection method for carcinoembryonic antigen, marine toxin, Okada acid and so on,[79] but its application is still not high, nanomaterials, with their high surface-to-volume ratio, ease of modification and biocompatibility, it has been used to construct the sensing membrane of the SAW sensor to improve the stability, sensitivity and specificity of the LSAW sensor for detecting tumor markers, these include gold nanoparticles (AuNPs),[80] graphene/AuNPs monolayers,[81] carbon nanotubes, SiO2/Si nanoparticles and fullerene C60. Based on molybdenum disulfide/gold nanoparticles (single-layer

Mos2/Au NPs), Wang et al developed a new kind of pseudo-finger Love-mode surface acoustic wave (LSAW) sensor, it is also used for high sensitivity and rapid detection of alpha-fetoprotein (AFP) in serum.[82]

In recent years, nano-silver has been widely used in the detection of biomarkers. A simple electrochemical immunosensor based on Ag/CeO_2 nanocomposite coated with antibody chitosan has been prepared on gold electrode, the interaction between the synthesized Ab-CS@Ag/CeO_2 nanocomposites and AFP prevented electron transfer and decreased the peak current of the voltammetric Fe $(CN)_6^{3-/4-}$ was proportional to the amount of AFP, for the sensitive diagnosis of alpha-fetoprotein (AFP) in human serum.[83] Silver (Ag) NCs is an ideal choice for optical fluorescence biosensors because of its high quantum yield, easy production and tunable fluorescence emission. Thus, a team of fluorescent aptamer sensors based on polydopamine nanospheres (PDAN)@AgNCs has been designed to detect AFP and CEA simultaneously.[84]

Detection of AFP-L3

The Lens culinaris lectin-responsive fraction of AFP (AFP- L3) is a more sensitive biomarker, which has higher sensitivity and specificity for HCC than AFP in the early stages.[85,86] Liu et al reported for the first time a potential-resolved electrochemiluminescence (ECL) immunosensor based on quantum dots (QDs), which were stabilized by dimercaptosuccinic acid due to the difference in surface microstructures. CdTe (DMSA-CdTe) quantum dots and TiO2 nanoparticle-glutathione-stabilized CdTe (TiO2- gsh -CdTe) quantum dots composites have a large difference in the ECL peak potentials, which provides a pathway for potentiometric resolution detection. The calculated AFP-L3 ratios from the prepared immunosensors had an acceptable accuracy when compared with clinical test data.[87] These results open new avenues for simple and rapid multi-component detection based on nano-ECL technology for clinical diagnosis of HCC.

Detection of De-Gamma-Carboxy Prothrombin (DCP)

Des-γ-carboxy Prothrombin (DCP), also known as PIVKA-II (Protein Induced by Vitamin K Absence or Antagonist-II), is abnormal due to deficiency of vitamin K_2 in the serum of patients with hepatocellular carcinoma (HCC) Plasminogen, another biomarker that helps in the laboratory diagnosis of primary hepatocellular carcinoma.[88,89] Its sensitivity is about 70% and specificity is about 100%.[90]

Zinc oxide nanoparticles (ZnO NPs) have shown remarkable potential in the diagnosis and treatment of various types of cancer due to their biocompatibility, biodegradability and unique physicochemical properties. In a recent study, researchers developed a screen-printed decarboxylated plasminogen (DCP) immunosensor using ZnO NPs, combining electrochemical detection techniques with immunosensors and cytosensors to develop a rapid, low-cost, and effective system for accurately evaluating DCP in the detection of hepatocellular carcinoma. This DCP immunosensor is simple, inexpensive, and reliable, allowing for the use of at-home Immediate Care Approach to screening for early-stage liver cancer becomes possible.[91]

Nanoparticle Drug Delivery

Due to its high efficacy and low side effects, and its ability to improve the biodistribution, release, activity and specificity of anticancer drugs, nano-drug delivery system has attracted great attention.[92] In recent years, hepatic targeted drug delivery systems (HTDDS) have emerged for the treatment of liver diseases. Among them, the drug delivery system for the treatment of liver cancer has also made significant progress in recent years.[93]

Passive Targeting

The first step in tumor drug delivery is the extravasation of the drug or drug carrier into the tumor.[94] Passive targeting refers to the transfer of drug-loaded particles into the body by taking advantage of the differences in vascular density and permeability between tumor tissues and normal tissues, or phagocytosis by phagocytes that recognize them as external foreign bodies, thus the passive targeting function is realized. Passive targeting typically relies on enhanced permeability and retention effects (EPR) resulting from the presence of fenestration and poor lymphatic drainage in the tissue in imperfect tumor vessels, through these spaces, nanoparticles can extravasate into extravascular spaces and accumulate in tumor tissue (Figure 1).[95,96] Traditionally, EPR-mediated tumor accumulation has been thought to be due to long-circulating nanoparticles that are fluid dynamics larger than the renal clearance threshold and can leak out of leaky tumor

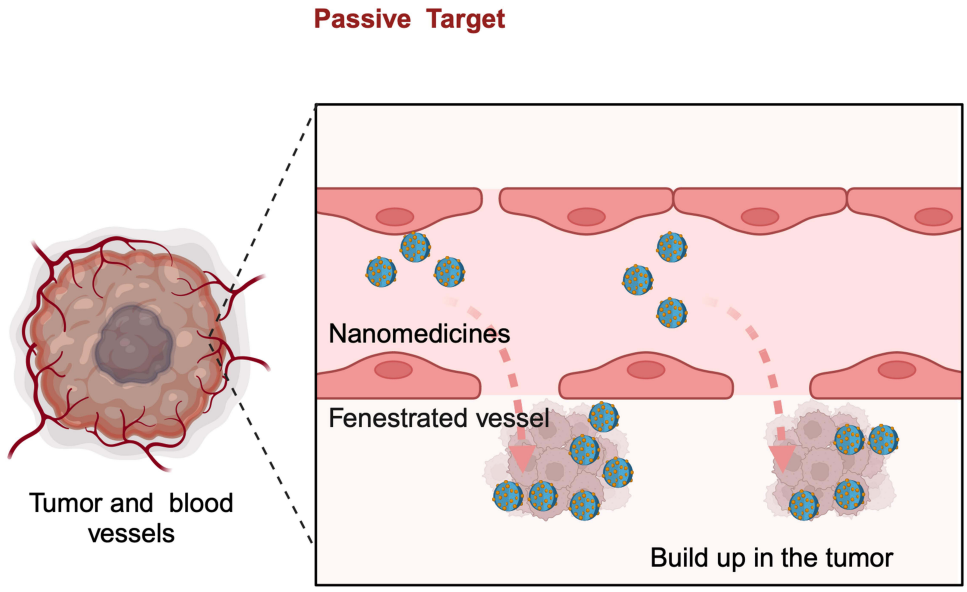

Figure 1 Passive target. Nanoparticles carry drugs through the open window of imperfect tumor blood vessels and infiltrate into the extravascular space and accumulate in tumor tissues. Created with BioRender.com.

vessels.[97] In addition, Liu et al described exploring the potential of endocytosis to target tumors as a potential additional mechanism for nanomedicine-mediated tumor targeting, especially in highly interstitial solid tumors such as ductal adenocarcinoma of the pancreas, where EPR is weak.[98]

5-FLUOROURACIL (5-FU) is one of the most important anti-tumor drugs in liver cancer, but it has many serious side effects, such as myelosuppression, gastrointestinal reaction and thrombocytopenia, and its pharmacokinetics properties are also poor, all these limits its clinical application and therapeutic effect.[99,100] So, people are actively studying ways to overcome its shortcomings, and one report has developed a new corn protein nanoparticle (ZP) to coat 5-FU, which can effectively target the liver, the relative absorption rate was highest in liver tissue. 5-FU loaded ZPs has high drug loading and stability, and its release in vitro is characterized by sustained release. And because of its passive delivery to hepatic parenchymal cells and long residence time in the circulatory system, the liver has a higher uptake effect on 5-FU-loaded ZPs.[101] The preparation of docetaxel (Doc) loaded polycaprolactone nanoparticles (DOC-NPs) by an improved nano-precipitation method has been studied. The DOC-NPs can target and deliver drugs to tumors, and because of its high cell uptake rate, EPR effect-induced passive targeting ability and penetration improvement, it has higher anti-tumor efficacy than free DOC preparation.[102]

Active Targeting

Active targeting, also known as ligand-mediated targeting, involves the use of affinity ligands on the surface of nanocarriers to efficiently and accurately enter cells via receptor-mediated endocytosis. The introduction of both hydrophilic fragments and specific ligand molecules into drug-loaded nanocarriers can prevent their uptake by macrophages, prevent their accumulation in non-target tissues or organs, and enhance drug absorption by target cells.[103] There are many ligands that can specifically recognize overexpressed receptors on the surface of living cells, and they have active targeting effects. For example, Asialoglycoprotein receptor (ASGP-R), glycyrrhizin acid receptor (GA-R), glycyrrhizin receptor (GL-R), hyaluronic acid receptor (HA-R), mannose ligand receptor (MR), folate receptor (FR), EGFR acid receptor (EGFR), etc (Figure 2).[104–108]

ASGPR is a receptor that is overexpressed on the membrane of hepatoma cells.[109,110] All ASGPRs in mammalian hepatocytes bind specifically to galactose (Gal) or its derivatives, such as n-acetyl galactosamine (GalNAc). Therefore, based on the identification of galactose receptor in the liver, galactose is linked with bioactive molecules to provide a target molecule that can reach the target liver and realize its therapeutic effect.[111,112] ASGPR has been used to modify copolymers to encapsulate cancer drugs such as sorafenib in liver cells.[113] Medina et al prepared fluorescently labeled

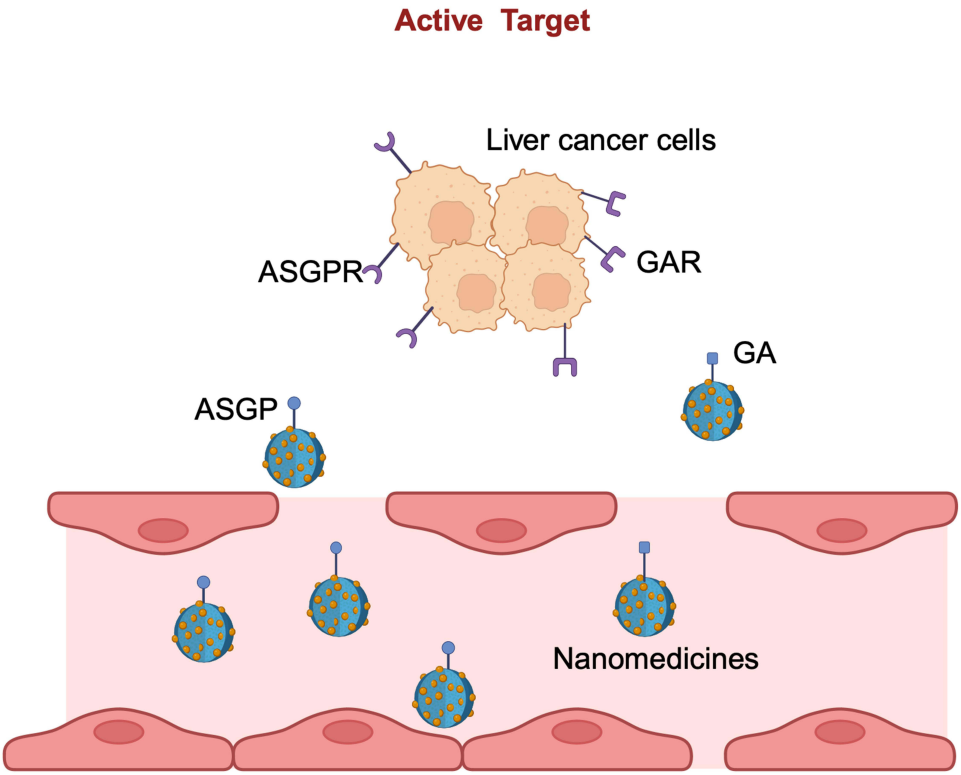

Figure 2 Active target. There are many receptors on the cell membrane of liver cancer that can bind ligands on drug-carrying nanoparticles, so that nanomedicine can enter tumor cells accurately and efficiently. Created with BioRender.com.

GalNAc-modified polyamidoamine (PAMAM-NH2, G5) dendrimers for specific delivery of chemotherapeutic drugs into liver cancer cells.[114]

Glycyrrhetinic acid (GA) is the main active component of Glycyrrhiza uralensis Fisch. Many studies have found that GA has antiviral, anti-inflammatory, anti-allergic, anti-ulcer and anti-tumor activities.[115–117] It has been reported that GA has an effective anti-tumor effect on HCC through cell cycle arrest, induction of autophagy and apoptosis, and alleviation of immunosuppression.[118,119] GA can mediate a variety of nanomaterials to target the liver, hyaluronic acid (HA): glycidyl acid-grafted hyaluronic acid (HGA) nanoparticles have been prepared by coupling HA with acylamide GA as carriers for delivery of paclitaxel (PTX) with high loading efficiency, the cytotoxicity to HepG-2 was also significant.[120] As alginate (ALG): Zhang et al constructed GA-modified and doxorubicin (DOX)-loaded alginate NPS for the treatment of liver cancer in orthotopic H22 tumor mice; its liver uptake rate was several times higher than that of non-targeted alginate NPs, and its anti-cancer effect was much better than free DOX.[121] These results indicate that GA can be used as a targeting drug in the treatment of liver cancer.

Treatment of Liver Cancer

The tumor microenvironment (TME) refers to the complex and diverse multicellular periphery of tumor origin, which is crucial for the treatment of tumors precisely because of its complex cellular environment.[122,123] Because of the rapid proliferation and metabolism of the tumor compared with normal tissues, it is characterized by hypoxia, high Glutathione, high levels of reactive oxygen species (ROS), weak acidity, overexpression of enzymes, and high levels of ATP.[124,125] Therefore, it is a good way to use nanomaterials to produce effective and precise treatments for tumors in the tumor microenvironment.

Nanomaterials as an Adjunct to Photodynamic Therapy (PDT)

The use of a single treatment strategy for cancer is often there are some deficiencies, and now the coordinated, cooperative, multi-faceted treatment strategy is more and more attention. Photodynamic therapy (PDT) is a new method

for the treatment of cancer, which has attracted much attention because of its high selectivity, non-invasive, low side-effect and non-drug resistance. PDT is a method of using photosensitizers that react with molecular oxygen after being excited by specific wavelengths of light to produce reactive oxygen species in liver cancer tumor tissues, resulting in liver cancer cell death.[126] Firstly, nanomaterials have the potential to be carriers of PDT photosensitizers because of their unique characteristics, and then PDT can produce a large amount of reactive oxygen species (ROS) in liver cancer tumor tissues under the action of photosensitizers, induces oxidative damage and ultimately cancer cell death (Figure 3).[127] A new nano-therapeutic agent (MONs@PDA-ICG) has been constructed with manganese oxide nanoflower (MONs) as the core, polydopamine (PDA) as the shell carrier, and ICG as the photosensitizer and the photothermic agent, it is used for tumor microenvironment-responsive MRI and PDT/PTT synergistic treatment of liver cancer. At the same time, hypoxia exists in the tumor microenvironment of HCC, which is a key limiting factor for PDT therapy. The MONs nucleus of this nano-therapeutic agent can produce O_2 under the acidic environment of HCC tumor, thus improve the therapeutic effect of PDT, and further increase the killing of liver cancer cells.[128]

Nanomaterials Assist Chemical Kinetics Therapy (CDT)

At present, it has become a hot spot to use nano-drug as carrier to deliver chemotherapeutic drugs to tumor site, and it also has a good delivery effect, but the drug release after delivery is still a challenge worth thinking about, at this time, the characteristics of tumor microenvironment (PH, enzyme, redox, hypoxia, etc.) can be used as a special stimulus to control the release of chemotherapeutic drugs.[129–131] Cisplatin (CP) is an important first-line chemotherapeutic agent for the treatment of liver cancer, but its clinical application is limited by intrinsic and acquired resistance and dose-limiting normal tissue toxicity.[132] To overcome the low rate of treatment in its free state, the use of nanoparticle drug delivery system has been explored to increase its efficacy. Zhang et al developed a pH-responsive controlled-release mesoporous silicon dioxide nanoparticles (MSN) formulation, in which MSN is functionalized with histidine (His)-labeled targeted peptide (B3int) via an amide bond and loaded with the anticancer drug cisplatin, Cu^{2+} was then used to seal the holes of MSNs by chelating with the His tag.[133] The resulting nanoparticles exhibit pH-responsive drug release and can effectively target tumor cells through the targeting effect of B3int. When the microenvironment of hepatoma cells is acidic, the preparation effectively releases Cu^{2+}, which can initiate chemical kinetics therapy (CDT), cytotoxic reactive oxygen species (ROS) produced by Fenton-like reactions with high concentrations of H_2O_2, which is commonly present in hepatoma cells, is lethal to hepatoma cells, while excess Glutathione (GSH) in the TME can be depleted by Cu^{2+},

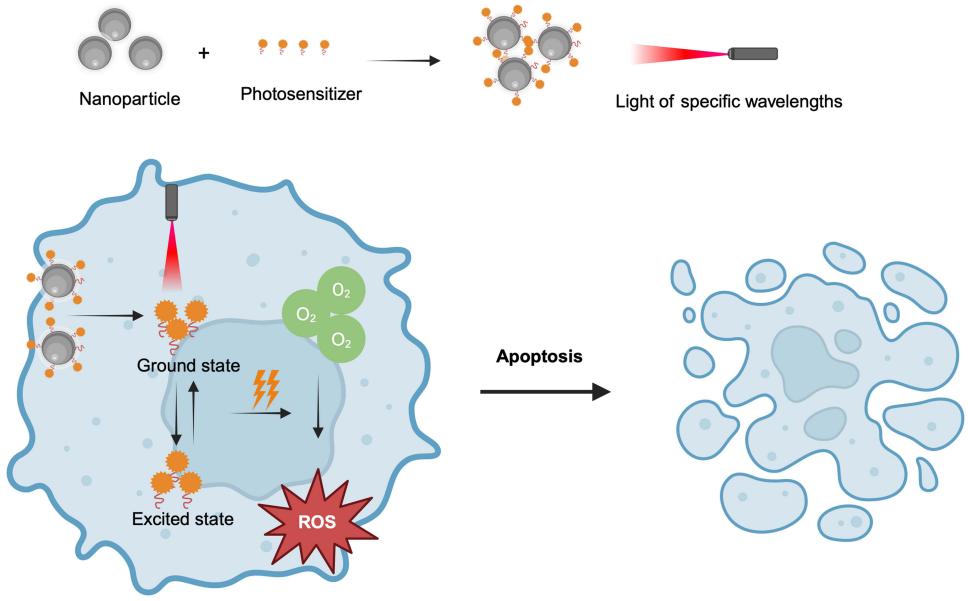

Figure 3 The role of nanomaterials in photodynamic therapy. After the nanomaterials loaded with photosensitizers enter the tumor cells, they are activated from the ground state to the excited state after being excited by light of a specific wavelength. When the nanomaterials return from the excited state to the ground state, the released energy is transferred to oxygen to produce reactive oxygen species, which leads to the apoptosis of tumor cells. Created with BioRender.com.

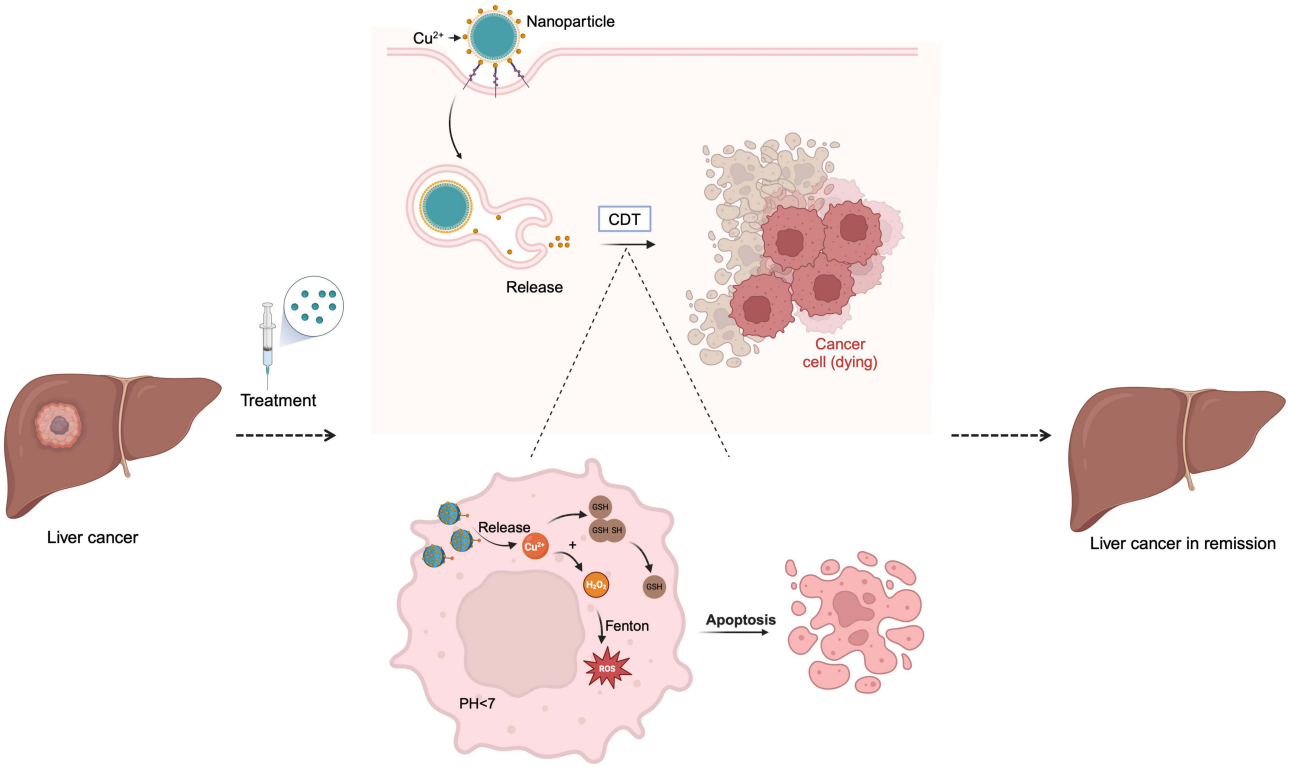

Figure 4 The role of nanomaterials in chemo dynamic therapy. Nanomedicine therapy for liver cancer can release Cu^{2+} effectively when the cell environment of liver cancer is acidic to initiate chemokinetic therapy. Cu^{2+} reacts with $H2O_2$ to produce reactive oxygen species to kill tumor cells. GSH can also be consumed by Cu^{2+}. Created with BioRender.com.

which not only can avoid chemotherapy drugs being inactivated by reducing GSH,[134] but also can retain OH free radicals, protecting CDT activity (Figure 4).[135] On this basis, Pi et al developed a natural small molecule carrier-free injection hydrogel mediated by copper ions with CDT characteristics, which can coordinate anti-tumor through apoptosis, copper degradation and anti-inflammation, and realize the regulation of TME. This program has good, targeted drug delivery and controlled release performance in the biomedical field, which further shows the new prospect of CDT in tumor therapy and potential clinical transformation ability.[136]

Challenges

In summary, although many promising advances have been made in nanotechnology-based cancer diagnostics, only a few examples have reached the clinical trial stage.[137,138] There are many challenges that need to be addressed to accelerate the translation of nanotechnology into clinical applications. First and foremost is the challenge of safety. Certain nanomaterials (eg, carbon nanotubes, quantum dots) may release toxic components in the body at certain doses or induce cytotoxicity and inflammatory responses by interacting with cell membranes and key biomolecules (eg, proteins and DNA). So, we should evaluate the possible toxicity of these nanoparticles before application, and the nature of the nanoparticles (eg, shape, size, charge, surface chemistry, targeting ligands, and composition) can affect their toxicity.[139] In addition, the biodistribution, biodegradability and pharmacokinetic properties of the nanoparticles should be considered.

The next challenge to be considered is that nanomedicines need to undergo a complex multi-step cascade in vivo to be efficacious, including injection into the blood circulation, accumulation into the tumor site, penetration into the interior of the tumor tissue, endocytosis, intracellular transport, and drug release. At the same time the monocyte-macrophage system (MPS) in vivo may quickly recognize it as a foreign body and remove it, resulting in a significant lack of accumulation and efficacy of nanomedicines in the target tissue. A series of biological barriers present in the body prevent nanoparticles from efficiently passing through each process, limiting therapeutic efficacy. Therefore, the development of nano diagnostic systems with good compatibility and efficient targeting is necessary. The third challenge is

then the large-scale production of nanomaterials. The performance of nanomaterials is highly dependent on their size, morphology and surface properties, and these parameters need to be precisely controlled; currently, most nanoparticles are produced under highly optimized conditions in the laboratory, but it may be difficult to ensure consistency with the stringent dimensional requirements of the nanoparticles and the control of their functionalization during mass production. The preparation of many nanomaterials involves complex synthesis steps (eg, template method, self-assembly, sol-gel method), and scaled-up production is prone to triggering side reactions, leading to a decrease in the purity and properties of the products. Some of the nanoparticles are prone to agglomeration and sedimentation in high concentration or large volume solutions, making it difficult to maintain dispersion. In addition, the cost-effectiveness of developing nanotechnology-based platforms must be considered.

Although nanotechnology shows great potential in the diagnosis and treatment of hepatocellular carcinoma, its clinical translation still faces challenges in terms of safety and biocompatibility, which severely limit its move from the laboratory to clinical applications.

Conclusions and Outlook

Nanotechnology shows a broad application prospect in the diagnosis and treatment of liver cancer. Its highly sensitive and specific diagnostic tools, combined with highly targeted and low-toxicity therapeutic means, provide innovative solutions to overcome the limitations of traditional diagnostic and therapeutic modes of liver cancer. Whether it is the precise detection of liver cancer biomarkers by nanoparticles, or targeted drug delivery, photothermal and photodynamic therapies using nanocarriers, these technologies have significantly improved the efficiency of early detection and therapeutic efficacy of liver cancer. However, the clinical translation of nanotechnology in liver cancer applications still faces many challenges. For example, long-term safety assessment of nanomaterials, standardization and scale-up of preparation processes, and stringent regulatory requirements are all urgent issues that need to be addressed. In addition, the rise of individualized medicine puts higher demands on the precise design of nanotechnology. Looking forward, with the further integration of biotechnology, materials science and medical engineering, nanotechnology is expected to realize a wider range of applications in liver cancer diagnosis and treatment. By strengthening basic research, optimizing the properties of nanomaterials, and promoting the integration with artificial intelligence and big data, early diagnosis, precise treatment and monitoring of treatment effects of liver cancer will take a new step forward. This will provide important support for increasing patient survival rates, improving quality of life and reducing the global liver cancer disease burden.

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Taniguchi H. Liver Cancer 2.0. *Int J Mol Sci*. 2023;24(24):17275. doi:10.3390/ijms242417275
2. Marengo A, Rosso C, Bugianesi E. Liver Cancer: connections with Obesity, Fatty Liver, and Cirrhosis. *Annu Rev Med*. 2016;67(1):103–117. doi:10.1146/annurev-med-090514-013832
3. Sun M, Gao M, Luo M, Wang T, Zhong T, Qin J. Association between air pollution and primary liver cancer in European and east Asian populations: a Mendelian randomization study. *Front Public Health*. 2023;11:1212301. doi:10.3389/fpubh.2023.1212301
4. Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J*. 2022;135(5):584–590. doi:10.1097/cm9.0000000000002108
5. Gravitz L. Liver cancer. *Nature*. 2014;516(7529):1. doi:10.1038/516S1a
6. Salazar J, Le A. The Heterogeneity of Liver Cancer Metabolism. *Adv Exp Med Biol*. 2021;1311:127–136. doi:10.1007/978-3-030-65768-0_9
7. Liu CY, Chen KF, Chen PJ. Treatment of Liver Cancer. *Cold Spring Harb Perspect Med*. 2015;5(9):a021535. doi:10.1101/cshperspect.a021535
8. Lu Q, Kou D, Lou S, et al. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. *J Hematol Oncol*. 2024;17(1):16. doi:10.1186/s13045-024-01535-8
9. Kuhlmann JB, Blum HE. Locoregional therapy for cholangiocarcinoma. *Curr Opin Gastroenterol*. 2013;29(3):324–328. doi:10.1097/MOG.0b013e32835d9dea
10. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–1022. doi:10.1002/hep.24199
11. Tzartzeva K, Obi J, Rich NE, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: a Meta-analysis. *Gastroenterology*. 2018;154(6):1706–1718.e1. doi:10.1053/j.gastro.2018.01.064

12. Hayrapetyan H, Tran T, Tellez-Corrales E, Madiraju C. Enzyme-Linked Immunosorbent Assay: types and Applications. *Methods Mol Biol*. 2023;2612:1–17. doi:10.1007/978-1-0716-2903-1_1
13. Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. *Nat Biotechnol*. 2010;28(6):595–599. doi:10.1038/nbt.1641
14. Liu L, Wang H, Xie B, Zhang B, Lin Y, Gao L. Detection of Alpha-Fetoprotein Using Aptamer-Based Sensors. *Biosensors*. 2022;12(10):780. doi:10.3390/bios12100780
15. Ngoc Huy D T, Iswanto AH, Catalan Opulencia MJ, et al. Optical and Electrochemical Aptasensors Developed for the Detection of Alpha-Fetoprotein. *Crit Rev Anal Chem*. 2024;54(4):857–871. doi:10.1080/10408347.2022.2099221
16. Zhou W, Gao X, Liu D, Chen X. Gold Nanoparticles for In Vitro Diagnostics. *Chem Rev*. 2015;115(19):10575–10636. doi:10.1021/acs.chemrev.5b00100
17. Li D, Mallory T, Satomura S. AFP-L3: a new generation of tumor marker for hepatocellular carcinoma. *Clin Chim Acta*. 2001;313(1–2):15–19. doi:10.1016/s0009-8981(01)00644-1
18. Zaninotto M, Ujka F, Lachin M, et al. Lectin-affinity electrophoresis for the detection of AFP microheterogeneities in patients with hepatocellular carcinoma. *Anticancer Res*. 1996;16(1):305–309.
19. Shimizu K, Taniichi T, Satomura S, Matsuura S, Taga H, Taketa K. Establishment of assay kits for the determination of microheterogeneities of alpha-fetoprotein using lectin-affinity electrophoresis. *Clin Chim Acta*. 1993;214(1):3–12. doi:10.1016/0009-8981(93)90297-h
20. Sun GZ, Zhao XY, Li JH, Zhao GQ, Wang SX, Kong SL. Detection of alpha-fetoprotein-L3 using agglutinin-coupled spin column to be used in diagnosis of hepatocellular carcinoma. *Zhonghua Yi Xue Za Zhi*. 2008;88(28):1986–1988.
21. Fujiyama S, Morishita T, Hashiguchi O, Sato T. Plasma abnormal prothrombin (des-gamma-carboxy prothrombin) as a marker of hepatocellular carcinoma. *Cancer*. 1988;61(8):1621–1628. doi:10.1002/1097-0142(19880415)61:8<1621::aid-cncr2820610820>3.0.co;2-c.
22. Weitz IC, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. *Hepatology*. 1993;18(4):990–997. doi:10.1002/hep.1840180434
23. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg*. 2002;235(3):373–382. doi:10.1097/00000658-200203000-00009
24. Nathan H, Schulick RD, Choti MA, Pawlik TM. Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg*. 2009;249(5):799–805. doi:10.1097/SLA.0b013e3181a38eb5
25. Shah SA, Cleary SP, Wei AC, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. *Surgery*. 2007;141(3):330–339. doi:10.1016/j.surg.2006.06.028
26. Shah SA, Greig PD, Gallinger S, et al. Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. *J Am Coll Surg*. 2006;202(2):275–283. doi:10.1016/j.jamcollsurg.2005.10.005
27. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv238–iv255. doi:10.1093/annonc/mdy308
28. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a Phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25–34. doi:10.1016/s1470-2045(08)70285-7
29. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–390. doi:10.1056/NEJMoa0708857
30. Pearson H, Marshall LV, Carceller F. Sorafenib in pediatric hepatocellular carcinoma from a clinician perspective. *Pediatr Hematol Oncol*. 2020;37(5):412–423. doi:10.1080/08880018.2020.1740844
31. Tang W, Chen Z, Zhang W, et al. The mechanisms of sorafenib resistance in hepatocellular carcinoma: theoretical basis and therapeutic aspects. *Signal Transduct Target Ther*. 2020;5(1):87. doi:10.1038/s41392-020-0187-x
32. Zhu YJ, Zheng B, Wang HY, Chen L. New knowledge of the mechanisms of sorafenib resistance in liver cancer. *Acta Pharmacol Sin*. 2017;38(5):614–622. doi:10.1038/aps.2017.5
33. Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international Phase 3 study. *Lancet*. 2023;402(10408):1133–1146. doi:10.1016/s0140-6736(23)00961-3
34. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013
35. Sprinzl MF, Galle PR. Current progress in immunotherapy of hepatocellular carcinoma. *J Hepatol*. 2017;66(3):482–484. doi:10.1016/j.jhep.2016.12.009
36. Breous E, Thimme R. Potential of immunotherapy for hepatocellular carcinoma. *J Hepatol*. 2011;54(4):830–834. doi:10.1016/j.jhep.2010.10.013
37. Xu F, Jin T, Zhu Y, Dai C. Immune checkpoint therapy in liver cancer. *J Exp Clin Cancer Res*. 2018;37(1):110. doi:10.1186/s13046-018-0777-4
38. Rotte A, Jin JY, Lemaire V. Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy. *Ann Oncol*. 2018;29(1):71–83. doi:10.1093/annonc/mdx686
39. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252–264. doi:10.1038/nrc3239
40. Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res*. 2013;19(5):1021–1034. doi:10.1158/1078-0432.Ccr-12-2063
41. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol*. 2008;8(6):467–477. doi:10.1038/nri2326
42. Wu K, Kryczek I, Chen L, Zou W, Welling TH. Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. *Cancer Res*. 2009;69(20):8067–8075. doi:10.1158/0008-5472.Can-09-0901
43. Philips GK, Atkins M. Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies. *Int Immunol*. 2015;27(1):39–46. doi:10.1093/intimm/dxu095
44. Chen W, Chiang CL, Dawson LA. Efficacy and safety of radiotherapy for primary liver cancer. *Chin Clin Oncol*. 2021;10(1):9. doi:10.21037/cco-20-89
45. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21(1):109–122. doi:10.1016/0360-3016(91)90171-y

46. Roosen J, Klaassen NJM, Westlund Gotby LEL, et al. To 1000 Gy and back again: a systematic review on dose-response evaluation in selective internal radiation therapy for primary and secondary liver cancer. *Eur J Nucl Med Mol Imaging*. 2021;48(12):3776–3790. doi:10.1007/s00259-021-05340-0
47. Brock KK. Imaging and image-guided radiation therapy in liver cancer. *Semin Radiat Oncol*. 2011;21(4):247–255. doi:10.1016/j.semradonc.2011.05.001
48. Kesharwani P, Gorain B, Low SY, et al. Nanotechnology based approaches for anti-diabetic drugs delivery. *Diabet Res Clin Pract*. 2018;136:52–77. doi:10.1016/j.diabres.2017.11.018
49. Kumar V, Kumari A, Guleria P, Yadav SK. Evaluating the toxicity of selected types of nanochemicals. *Rev Environ Contam Toxicol*. 2012;215:39–121. doi:10.1007/978-1-4614-1463-6_2
50. Gwinn MR, Vallyathan V. Nanoparticles: health effects--pros and cons. *Environ Health Perspect*. 2006;114(12):1818–1825. doi:10.1289/ehp.8871
51. Missaoui WN, Arnold RD, Cummings BS. Toxicological status of nanoparticles: what we know and what we don't know. *Chem Biol Interact*. 2018;295:1–12. doi:10.1016/j.cbi.2018.07.015
52. Puri A, Loomis K, Smith B, et al. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. *Crit Rev Ther Drug Carrier Syst*. 2009;26(6):523–580. doi:10.1615/critrevtherdrugcarriersyst.v26.i6.10
53. Wang L, Yang D, Lv JY, Yu D, Xin SJ. Application of carbon nanoparticles in lymph node dissection and parathyroid protection during thyroid cancer surgeries: a systematic review and meta-analysis. *Onco Targets Ther*. 2017;10:1247–1260. doi:10.2147/ott.S131012
54. Aghebati-Maleki A, Dolati S, Ahmadi M, et al. Nanoparticles and cancer therapy: perspectives for application of nanoparticles in the treatment of cancers. *J Cell Physiol*. 2020;235(3):1962–1972. doi:10.1002/jcp.29126
55. Alric C, Taleb J, Le Duc G, et al. Gadolinium chelate coated gold nanoparticles as contrast agents for both X-ray computed tomography and magnetic resonance imaging. *J Am Chem Soc*. 2008;130(18):5908–5915. doi:10.1021/ja078176p
56. Chen Y, Xianyu Y, Jiang X. Surface Modification of Gold Nanoparticles with Small Molecules for Biochemical Analysis. *Acc Chem Res*. 2017;50(2):310–319. doi:10.1021/acs.accounts.6b00506
57. Dhakshinamoorthy A, Navalón S, Asiri AM, Garcia H. Gold-Nanoparticle-Decorated Metal-Organic Frameworks for Anticancer Therapy. *ChemMedChem*. 2020;15(23):2236–2256. doi:10.1002/cmdc.202000562
58. Saeed AA, Sánchez JLA, O'Sullivan CK, Abbas MN. DNA biosensors based on gold nanoparticles-modified graphene oxide for the detection of breast cancer biomarkers for early diagnosis. *Bioelectrochemistry*. 2017;118:91–99. doi:10.1016/j.bioelechem.2017.07.002
59. Niikura K, Matsunaga T, Suzuki T, et al. Gold nanoparticles as a vaccine platform: influence of size and shape on immunological responses in vitro and in vivo. *ACS Nano*. 2013;7(5):3926–3938. doi:10.1021/nn3057005
60. Chen Q, Xu L, Liang C, Wang C, Peng R, Liu Z. Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy. *Nat Commun*. 2016;7(1):13193. doi:10.1038/ncomms13193
61. Ronot M, Nahon P, Rimola J. Screening of liver cancer with abbreviated MRI. *Hepatology*. 2023;78(2):670–686. doi:10.1097/hep.0000000000000339
62. Witt JS, Rosenberg SA, Bassetti MF. MRI-guided adaptive radiotherapy for liver tumours: visualising the future. *Lancet Oncol*. 2020;21(2):e74–e82. doi:10.1016/s1470-2045(20)30034-6
63. Yang RM, Fu CP, Li NN, et al. Glycosaminoglycan-targeted iron oxide nanoparticles for magnetic resonance imaging of liver carcinoma. *Mater Sci Eng C Mater Biol Appl*. 2014;45:556–563. doi:10.1016/j.msec.2014.09.038
64. Wei H, Bruns OT, Kaul MG, et al. Exceedingly small iron oxide nanoparticles as positive MRI contrast agents. *Proc Natl Acad Sci U S A*. 2017;114(9):2325–2330. doi:10.1073/pnas.1620145114
65. Zhou X, Chen L, Wang A, Ma Y, Zhang H, Zhu Y. Multifunctional fluorescent magnetic nanoparticles for lung cancer stem cells research. *Colloids Surf B Biointerfaces*. 2015;134:431–439. doi:10.1016/j.colsurfb.2015.07.030
66. Shi K, Zhao Y, Miao L, et al. Dual Functional LipoMET Mediates Envelope-type Nanoparticles to Combinational Oncogene Silencing and Tumor Growth Inhibition. *Mol Ther*. 2017;25(7):1567–1579. doi:10.1016/j.ymthe.2017.02.008
67. Hua L, Wang Z, Zhao L, et al. Hypoxia-responsive lipid-poly-(hypoxic radiosensitized polyprodrug) nanoparticles for glioma chemo- and radiotherapy. *Theranostics*. 2018;8(18):5088–5105. doi:10.7150/thno.26225
68. Wang Y, Yin Z, Gao L, Ma B, Shi J, Chen H. Lipid Nanoparticles-Based Therapy in Liver Metastasis Management: from Tumor Cell-Directed Strategy to Liver Microenvironment-Directed Strategy. *Int J Nanomed*. 2023;18:2939–2954. doi:10.2147/ijn.S402821
69. Graur F, Puia A, Mois EI, et al. Nanotechnology in the Diagnostic and Therapy of Hepatocellular Carcinoma. *Materials*. 2022;15(11):3893. doi:10.3390/ma15113893
70. El Moukhtari SH, Garbayo E, Amundarain A, et al. Lipid nanoparticles for siRNA delivery in cancer treatment. *J Control Release*. 2023;361:130–146. doi:10.1016/j.jconrel.2023.07.054
71. Woitok MM, Zoubek ME, Doleschel D, et al. Lipid-encapsulated siRNA for hepatocyte-directed treatment of advanced liver disease. *Cell Death Dis*. 2020;11(5):343. doi:10.1038/s41419-020-2571-4
72. Cao S, Zhang W, Pan H, et al. Bioactive lipid-nanoparticles with inherent self-therapeutic and anti-angiogenic properties for cancer therapy. *Acta Biomater*. 2023;157:500–510. doi:10.1016/j.actbio.2022.12.022
73. Xie J, Yong Y, Dong X, et al. Therapeutic Nanoparticles Based on Curcumin and Bamboo Charcoal Nanoparticles for Chemo-Photothermal Synergistic Treatment of Cancer and Radioprotection of Normal Cells. *ACS Appl Mater Interfaces*. 2017;9(16):14281–14291. doi:10.1021/acsami.7b02622
74. Sun L, Yao HJ, Li JC, Zhao BQ, Wang YA, Zhang YG. Activated Carbon nanoparticles Loaded with Metformin for Effective Against Hepatocellular Cancer Stem Cells. *Int J Nanomed*. 2023;18:2891–2910. doi:10.2147/ijn.S382519
75. Zhao Q, Piao J, Peng W, et al. A Metal Chelator as a Plasmonic Signal-Generation Superregulator for Ultrasensitive Colorimetric Bioassays of Disease Biomarkers. *Adv Sci*. 2018;5(7):1800295. doi:10.1002/advs.201800295
76. Rashidiani J, Kamali M, Sedighian H, Akbariqomi M, Mansouri M, Kooshki H. Ultrahigh sensitive enhanced-electrochemiluminescence detection of cancer biomarkers using silica NPs/graphene oxide: a comparative study. *Biosens Bioelectron*. 2018;102:226–233. doi:10.1016/j.bios.2017.11.011

77. Wu Y, Guo W, Peng W, et al. Enhanced Fluorescence ELISA Based on HAT Triggering Fluorescence "Turn-on" with Enzyme-Antibody Dual Labeled AuNP Probes for Ultrasensitive Detection of AFP and HBsAg. *ACS Appl Mater Interfaces*. 2017;9(11):9369–9377. doi:10.1021/acsami.6b16236
78. Liu QL, Yan XH, Yin XM, et al. Electrochemical enzyme-linked immunosorbent assay (ELISA) for α-fetoprotein based on glucose detection with multienzyme-nanoparticle amplification. *Molecules*. 2013;18(10):12675–12686. doi:10.3390/molecules181012675
79. Chang K, Pi Y, Lu W, et al. Label-free and high-sensitive detection of human breast cancer cells by aptamer-based leaky surface acoustic wave biosensor array. *Biosens Bioelectron*. 2014;60:318–324. doi:10.1016/j.bios.2014.04.027
80. Wang C, Wang C, Jin D, et al. AuNP-Amplified Surface Acoustic Wave Sensor for the Quantification of Exosomes. *ACS Sens*. 2020;5(2):362–369. doi:10.1021/acssensors.9b01869
81. Ji J, Pang Y, Li D, Wang X, Xu Y, Mu X. Single-Layered Graphene/Au-Nanoparticles-Based Love Wave Biosensor for Highly Sensitive and Specific Detection of Staphylococcus aureus Gene Sequences. *ACS Appl Mater Interfaces*. 2020;12(11):12417–12425. doi:10.1021/acsami.9b20639
82. Wang X, Ji J, Yang P, Li X, Pang Y, Lu P. A love-mode surface acoustic wave aptasensor with dummy fingers based on monolayer MoS(2)/Au NPs nanocomposites for alpha-fetoprotein detection. *Talanta*. 2022;243:123328. doi:10.1016/j.talanta.2022.123328
83. Kayani FB, Rafique S, Akram R, et al. A simple, sensitive, label-free electrochemical immunosensor based on the chitosan-coated silver/cerium oxide (CS@Ag/CeO_2) nanocomposites for the detection of alpha-fetoprotein (AFP). *Nanotechnology*. 2023;34(26):265501. doi:10.1088/1361-6528/acc8d8
84. Zhou W, Dong S. A new AgNC fluorescence regulation mechanism caused by coiled DNA and its applications in constructing molecular beacons with low background and large signal enhancement. *Chem Commun*. 2017;53(91):12290–12293. doi:10.1039/c7cc06872g
85. Malaguarnera G, Giordano M, Paladina I, Berretta M, Cappellani A, Malaguarnera M. Serum markers of hepatocellular carcinoma. *Dig Dis Sci*. 2010;55(10):2744–2755. doi:10.1007/s10620-010-1184-7
86. Bertino G, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellualar carcinoma serum markers. *Semin Oncol*. 2012;39(4):410–433. doi:10.1053/j.seminoncol.2012.05.001
87. Liu X, Jiang H, Fang Y, Zhao W, Wang N, Zang G. Quantum dots based potential-resolution dual-targets electrochemiluminescent immunosensor for subtype of tumor marker and its serological evaluation. *Anal Chem*. 2015;87(18):9163–9169. doi:10.1021/acs.analchem.5b02660
88. Liebman HA, Furie BC, Tong MJ, et al. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. *N Engl J Med*. 1984;310(22):1427–1431. doi:10.1056/nejm198405313102204
89. Yu R, Xiang X, Tan Z, Zhou Y, Wang H, Deng G. Efficacy of PIVKA-II in prediction and early detection of hepatocellular carcinoma: a nested case-control study in Chinese patients. *Sci Rep*. 2016;6(1):35050. doi:10.1038/srep35050
90. Mita Y, Aoyagi Y, Yanagi M, Suda T, Suzuki Y, Asakura H. The usefulness of determining des-gamma-carboxy prothrombin by sensitive enzyme immunoassay in the early diagnosis of patients with hepatocellular carcinoma. *Cancer*. 1998;82(9):1643–1648. doi:10.1002/(sici)1097-0142(19980501)82:9<1643::aid-cncr8>3.0.co;2-b
91. Ching CT, van Hieu N, Cheng TY, et al. Liver Cancer Detection by a Simple, Inexpensive and Effective Immunosensor with Zinc Oxide Nanoparticles. *Sensors*. 2015;15(11):29408–29418. doi:10.3390/s151129408
92. Zhang X, Zhang Q, Peng Q, et al. Hepatitis B virus preS1-derived lipopeptide functionalized liposomes for targeting of hepatic cells. *Biomaterials*. 2014;35(23):6130–6141. doi:10.1016/j.biomaterials.2014.04.037
93. Zhang X, Hlh N, Lu A, et al. Drug delivery system targeting advanced hepatocellular carcinoma: current and future. *Nanomedicine*. 2016;12(4):853–869. doi:10.1016/j.nano.2015.12.381
94. Wang CE, Stayton PS, Pun SH, Convertine AJ. Polymer nanostructures synthesized by controlled living polymerization for tumor-targeted drug delivery. *J Control Release*. 2015;219:345–354. doi:10.1016/j.jconrel.2015.08.054
95. Maeda H, Nakamura H, Fang J. The EPR effect for macromolecular drug delivery to solid tumors: improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging in vivo. *Adv Drug Deliv Rev*. 2013;65(1):71–79. doi:10.1016/j.addr.2012.10.002
96. Maeda H. Vascular permeability in cancer and infection as related to macromolecular drug delivery, with emphasis on the EPR effect for tumor-selective drug targeting. *Proc Jpn Acad Ser B Phys Biol Sci*. 2012;88(3):53–71. doi:10.2183/pjab.88.53
97. Shi Y, van der Meel R, Chen X, Lammers T. The EPR effect and beyond: strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics*. 2020;10(17):7921–7924. doi:10.7150/thno.49577
98. Liu X, Jiang J, Meng H. Transcytosis - An effective targeting strategy that is complementary to "EPR effect" for pancreatic cancer nano drug delivery. *Theranostics*. 2019;9(26):8018–8025. doi:10.7150/thno.38587
99. Vodenkova S, Buchler T, Cervena K, Veskrnova V, Vodicka P, Vymetalkova V. 5-fluorouracil and other fluoropyrimidines in colorectal cancer: past, present and future. *Pharmacol Ther*. 2020;206:107447. doi:10.1016/j.pharmthera.2019.107447
100. Sethy C, Kundu CN. 5-Fluorouracil (5-FU) resistance and the new strategy to enhance the sensitivity against cancer: implication of DNA repair inhibition. *Biomed Pharmacother*. 2021;137:111285. doi:10.1016/j.biopha.2021.111285
101. Wilson B, Ambika TV, Patel RD, Jenita JL, Priyadarshini SR. Nanoparticles based on albumin: preparation, characterization and the use for 5-flurouracil delivery. *Int J Biol Macromol*. 2012;51(5):874–878. doi:10.1016/j.ijbiomac.2012.07.014
102. Liu Q, Li R, Zhu Z, et al. Enhanced antitumor efficacy, biodistribution and penetration of docetaxel-loaded biodegradable nanoparticles. *Int J Pharm*. 2012;430(1–2):350–358. doi:10.1016/j.ijpharm.2012.04.008
103. Yan H, He L, Zhao W, et al. Poly β-cyclodextrin/TPdye nanomicelle-based two-photon nanoprobe for caspase-3 activation imaging in live cells and tissues. *Anal Chem*. 2014;86(22):11440–11450. doi:10.1021/ac503546r
104. Monestier M, Charbonnier P, Gateau C, et al. ASGPR-Mediated Uptake of Multivalent Glycoconjugates for Drug Delivery in Hepatocytes. *Chembiochem*. 2016;17(7):590–594. doi:10.1002/cbic.201600023
105. Zhang Y, Zhang X, Zeng C, et al. Targeted delivery of atorvastatin via asialoglycoprotein receptor (ASGPR). *Bioorg Med Chem*. 2019;27(11):2187–2191. doi:10.1016/j.bmc.2019.04.019
106. Oseledchyk A, Andreou C, Wall MA, Kircher MF. Folate-Targeted Surface-Enhanced Resonance Raman Scattering Nanoprobe Ratiometry for Detection of Microscopic Ovarian Cancer. *ACS Nano*. 2017;11(2):1488–1497. doi:10.1021/acsnano.6b06796
107. Lee H, Dam DH, Ha JW, Yue J, Odom TW. Enhanced Human Epidermal Growth Factor Receptor 2 Degradation in Breast Cancer Cells by Lysosome-Targeting Gold Nanoconstructs. *ACS Nano*. 2015;9(10):9859–9867. doi:10.1021/acsnano.5b05138

108. Mickler FM, Möckl L, Ruthardt N, Ogris M, Wagner E, Bräuchle C. Tuning nanoparticle uptake: live-cell imaging reveals two distinct endocytosis mechanisms mediated by natural and artificial EGFR targeting ligand. *Nano Lett*. 2012;12(7):3417–3423. doi:10.1021/nl300395q
109. Rigopoulou EI, Roggenbuck D, Smyk DS, et al. Asialoglycoprotein receptor (ASGPR) as target autoantigen in liver autoimmunity: lost and found. *Autoimmun Rev*. 2012;12(2):260–269. doi:10.1016/j.autrev.2012.04.005
110. Fallon RJ, Danaher M, Saxena A. The asialoglycoprotein receptor is associated with a tyrosine kinase in HepG2 cells. *J Biol Chem*. 1994;269 (43):26626–26629. doi:10.1016/S0021-9258(18)47064-0
111. D'Souza AA, Devarajan PV. Asialoglycoprotein receptor mediated hepatocyte targeting - strategies and applications. *J Control Release*. 2015;203:126–139. doi:10.1016/j.jconrel.2015.02.022
112. Fiume L, Di stefano G. Lactosaminated human albumin, a hepatotropic carrier of drugs. *Eur J Pharm Sci*. 2010;40(4):253–262. doi:10.1016/j.ejps.2010.04.004
113. Craparo EF, Sardo C, Serio R, et al. Galactosylated polymeric carriers for liver targeting of sorafenib. *Int J Pharm*. 2014;466(1–2):172–180. doi:10.1016/j.ijpharm.2014.02.047
114. Medina SH, Tekumalla V, Chevliakov MV, Shewach DS, Ensminger WD, El-Sayed ME. N-acetylgalactosamine-functionalized dendrimers as hepatic cancer cell-targeted carriers. *Biomaterials*. 2011;32(17):4118–4129. doi:10.1016/j.biomaterials.2010.11.068
115. Chang M, Wu M, Li H. Curcumin combined with glycyrrhetinic acid inhibits the development of hepatocellular carcinoma cells by down-regulating the PTEN/PI3K/AKT signalling pathway. *Am J Transl Res*. 2017;9(12):5567–5575.
116. Hussain H, Green IR, Shamraiz U, et al. Therapeutic potential of glycyrrhetinic acids: a patent review (2010-2017). *Expert Opin Ther Pat*. 2018;28(5):383–398. doi:10.1080/13543776.2018.1455828
117. Xu B, Wu GR, Zhang XY, et al. An Overview of Structurally Modified Glycyrrhetinic Acid Derivatives as Antitumor Agents. *Molecules*. 2017;22(6):924. doi:10.3390/molecules22060924
118. Qiu M, Wang J, Bai J, et al. Dual-Ligand-Functionalized Liposomes Based on Glycyrrhetinic Acid and cRGD for Hepatocellular Carcinoma Targeting and Therapy. *Mol Pharm*. 2023;20(4):1951–1963. doi:10.1021/acs.molpharmaceut.2c00842
119. Cai Y, Xu Y, Chan HF, Fang X, He C, Chen M. Glycyrrhetinic Acid Mediated Drug Delivery Carriers for Hepatocellular Carcinoma Therapy. *Mol Pharm*. 2016;13(3):699–709. doi:10.1021/acs.molpharmaceut.5b00677
120. Zhang L, Yao J, Zhou J, Wang T, Zhang Q. Glycyrrhetinic acid-graft-hyaluronic acid conjugate as a carrier for synergistic targeted delivery of antitumor drugs. *Int J Pharm*. 2013;441(1–2):654–664. doi:10.1016/j.ijpharm.2012.10.030
121. Zhang C, Wang W, Liu T, et al. Doxorubicin-loaded glycyrrhetinic acid-modified alginate nanoparticles for liver tumor chemotherapy. *Biomaterials*. 2012;33(7):2187–2196. doi:10.1016/j.biomaterials.2011.11.045
122. Tiwari A, Trivedi R, Lin SY. Tumor microenvironment: barrier or opportunity towards effective cancer therapy. *J Biomed Sci*. 2022;29(1):83. doi:10.1186/s12929-022-00866-3
123. Peng C, Xu Y, Wu J, Wu D, Zhou L, Xia X. TME-Related Biomimetic Strategies Against Cancer. *Int J Nanomed*. 2024;19:109–135. doi:10.2147/ijn.S441135
124. Arneth B. Tumor Microenvironment. *Medicina*. 2019;56(1):15. doi:10.3390/medicina56010015
125. Bilotta MT, Antignani A, Fitzgerald DJ. Managing the TME to improve the efficacy of cancer therapy. *Front Immunol*. 2022;13:954992. doi:10.3389/fimmu.2022.954992
126. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *CA Cancer J Clin*. 2011;61(4):250–281. doi:10.3322/caac.20114
127. Duse L, Agel MR, Pinnapireddy SR, et al. Photodynamic Therapy of Ovarian Carcinoma Cells with Curcumin-Loaded Biodegradable Polymeric Nanoparticles. *Pharmaceutics*. 2019;11(6):282. doi:10.3390/pharmaceutics11060282
128. Zhu Y, Deng M, Xu N, Xie Y, Zhang X. A Tumor Microenvironment Responsive Nanotheranostics Agent for Magnetic Resonance Imaging and Synergistic Photodynamic Therapy/Photothermal Therapy of Liver Cancer. *Front Chem*. 2021;9:650899. doi:10.3389/fchem.2021.650899
129. Li B, Shao H, Gao L, Li H, Sheng H, Zhu L. Nano-drug co-delivery system of natural active ingredients and chemotherapy drugs for cancer treatment: a review. *Drug Deliv*. 2022;29(1):2130–2161. doi:10.1080/10717544.2022.2094498
130. Tong T, Wang L, You X, Wu J. Nano and microscale delivery platforms for enhanced oral peptide/protein bioavailability. *Biomater Sci*. 2020;8 (21):5804–5823. doi:10.1039/d0bm01151g
131. Zhang Y, Wu Y, Du H, et al. Nano-Drug Delivery Systems in Oral Cancer Therapy: recent Developments and Prospective. *Pharmaceutics*. 2023;16(1):7. doi:10.3390/pharmaceutics16010007
132. Duan X, He C, Kron SJ, Lin W. Nanoparticle formulations of cisplatin for cancer therapy. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2016;8(5):776–791. doi:10.1002/wnan.1390
133. Zhang Y, Lou J, Williams GR, et al. Cu(2+)-Chelating Mesoporous Silica Nanoparticles for Synergistic Chemotherapy/Chemodynamic Therapy. *Pharmaceutics*. 2022;14(6):1200. doi:10.3390/pharmaceutics14061200
134. Marques MP, Gianolio D, Cibin G, et al. A molecular view of cisplatin's mode of action: interplay with DNA bases and acquired resistance. *Phys Chem Chem Phys*. 2015;17(7):5155–5171. doi:10.1039/c4cp05183a
135. Hao YN, Zhang WX, Gao YR, Wei YN, Shu Y, Wang JH. State-of-The-art advances of copper-based nanostructures in the enhancement of chemodynamic therapy. *J Mater Chem B*. 2021;9(2):250–266. doi:10.1039/d0tb02360d
136. Pi W, Wu L, Lu J, et al. A metal ions-mediated natural small molecules carrier-free injectable hydrogel achieving laser-mediated photo-Fenton-like anticancer therapy by synergy apoptosis/cuproptosis/anti-inflammation. *Bioact Mater*. 2023;29:98–115. doi:10.1016/j.bioactmat.2023.06.018
137. Palazzolo S, Bayda S, Hadla M, et al. The Clinical Translation of Organic Nanomaterials for Cancer Therapy: a Focus on Polymeric Nanoparticles, Micelles, Liposomes and Exosomes. *Curr Med Chem*. 2018;25(34):4224–4268. doi:10.2174/0929867324666170830113755
138. Bayda S, Hadla M, Palazzolo S, et al. Inorganic Nanoparticles for Cancer Therapy: a Transition from Lab to Clinic. *Curr Med Chem*. 2018;25 (34):4269–4303. doi:10.2174/0929867325666171229141156
139. Zhang Y, Li M, Gao X, Chen Y, Liu T. Nanotechnology in cancer diagnosis: progress, challenges and opportunities. *J Hematol Oncol*. 2019;12 (1):137. doi:10.1186/s13045-019-0833-3