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## Nanotheranostics: A powerful next-generation solution to tackle hepatocellular carcinoma

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### Abstract

Hepatocellular carcinoma (HCC) is an epidemic burden and remains highly prevalent worldwide. The significant mortality rates of HCC are largely due to the tendency of late diagnosis and the multifaceted, complex nature of treatment. Meanwhile, current therapeutic modalities such as liver resection and transplantation are only effective for resolving early-stage HCC. Hence, alternative approaches are required to improve detection and enhance the efficacy of current treatment options. Nanotheranostic platforms, which utilize biocompatible nanoparticles to perform both diagnostics and targeted delivery, has been considered a potential approach for cancer management in the past few decades. Advancement of nanomaterials and biomedical engineering techniques has led to rapid expansion of the nanotheranostics field, allowing for more sensitive and specific diagnosis, real-time monitoring of drug delivery, and enhanced treatment efficacies across various malignancies. The focus of this review is on the applications of nanotheranostics for HCC. The review first explores the current epidemiology and the commonly encountered obstacles in HCC diagnosis and treatment. It then presents the current technological and functional advancements in nanotheranostic technology for cancer in general, and then specifically explores the use of nanotheranostic modalities as a promising option to address the key challenges present in HCC management.



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**Core Tip:** Hepatocellular carcinoma (HCC) is a global epidemic burden. The high mortality rate is mostly due to late diagnosis and complexity of treatment. Nanotheranostics is a potential approach for HCC management. We herein discuss the challenges of HCC management, the advancement of nanotheranostics in cancer, and the potential role of nanotheranostics to address the current challenges in HCC management.

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## INTRODUCTION

### *Epidemic burden and risk factors of hepatocellular carcinoma*

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and remains the second leading cause of cancer-related deaths worldwide[1,2]. It accounts for around 90% of all primary liver cancer cases worldwide[3], and is an epidemic burden in both developing and developed countries[4]. Whilst certain endemic areas such as East Asia has shown a decreasing trend, regions such as Europe, Africa, and the United States display increasing trends in HCC incidence rate with substantial morbidity and mortality[5,6]. Concerningly, cases have doubled in Europe and America as a result of lifestyle factors such as alcohol abuse, smoking, obesity, and metabolic diseases[7-10]. Variations among age and gender are also interesting epidemiologic features of HCC. Men have a higher prevalence of HCC than women with a ratio of 462.4:185.8 new cases per year in developing countries[11]. Respectively, the risk of HCC significantly increases among those who are older than 40 years of age[12].

The risk factors and etiologies of HCC vary depending on geographic region and lifestyle. Hepatitis B and C infections are major etiological factors that significantly contribute to HCC globally[13-15], accounting for 44% and 21% of HCC cases respectively[16], with the highest number of hepatitis B cases occurring in Asia. Other possible risk factors include the increasing number of nonalcoholic fatty liver disease (NAFLD)[17], alcohol addiction[18,19], and aflatoxin consumption[20]. In Western, Central, and Eastern Europe and North America, a majority of HCC cases were attributed to NAFLD/non-alcoholic steatohepatitis, obesity, and excessive alcohol consumption. In contrast, most HCC cases in Asia and Africa were attributed to hepatitis B virus infection[21,22]. The viral and metabolic etiologies described above not only contributes to HCC occurrence, but also implicates a high risk of de novo recurrence, leading to the development of incurable and advanced stage disease that is resistant towards therapeutic efforts such as complete tumor resection or ablation[6].

### *Pathological complexity of HCC*

Due to the multifactorial nature of HCC, several cellular phenomena can be observed, including hypoxia, inflammation, oxidative stress, and tumor microenvironment. Indeed, the molecular mechanism of liver carcinogenesis involves multiple endogenous and exogenous genetic alterations[23]. Hepatocarcinogenesis is a deliberate and complex multistep process associated with somatic genomic alterations, leading to the production of cellular intermediates that progress into hepatocellular carcinoma[24]. The development of HCC involves a combination of continuous inflammatory damage, necrosis, and fibrotic deposition. The pre-neoplastic stage is a long process that typically requires 10 to 30 years of time. During this stage, phenotypically altered hepatocytes are formed as a result of either DNA methylation alterations, pathogenic agent's reaction, and point mutation or loss of heterozygosity, which occur in part

through epigenetic mechanisms that lead to the development of dysplastic hepatocytes in foci and nodules. Aberrant and dysplastic hepatocytes are related to the accumulation of permanent structural alteration and changes in genes and chromosomes[25]. Alterations in the malignant phenotype are often distinct, suggesting heterogeneity at the genomic level[25,26].

### **Challenges in HCC diagnosis**

Early diagnosis is a major challenge in HCC management, and in most cases, the lack of early diagnostic modalities lead to less than optimal treatment outcomes. In developed countries, 30%-60% of HCC cases can be diagnosed early, enabling higher success rates of curative treatment. Contrastingly, HCC cases in developing countries are mostly diagnosed in late stages, leading to substantially lower likelihood of curative treatment[27]. Diagnosis of HCC is in fact, an important and critical phase that relates directly to the survival and prognosis of the patients.

### **Complexity of HCC treatment**

Treatment of HCC itself is also complex and multifaceted, and outcome depends on the time of diagnosis and the presence of additional comorbidities. Prompt diagnosis of HCC is correlated with better outcomes of curative therapies. This is demonstrated by studies that show higher efficacy of local radiofrequency ablation and surgical intervention (liver transplantation and liver resection) in the very early and early-stage HCC as compared to later stages[8,28]. However, most HCC patients are excluded from definitive surgical resection due to late diagnosis. In such cases, liver transplantation can be the best treatment for HCC with a low risk of recurrence, though it is suggested as a second line treatment due to the disparity between limited liver donor resources and the increasing number of patients[29,30]. Based on international guidelines, late stage HCC patients (intermediate and advanced) may receive palliative treatment such as chemoembolization and systemic therapy, while terminal patients can only receive supportive care[27,28,31].

Issues such as tumor recurrence and drug resistance are also major obstacles that frequently complicate HCC management[32,33]. The 5-year recurrence probability of HCC is around 62% after liver ablation[34] and 80% after liver resection[35]. Palliative treatment often have unexpected and poor outcomes related with high refractoriness to systemic therapy that lead to development of multidrug resistance[36-38].

### **Need for a novel approach in HCC management**

The challenges associated with both diagnosis and treatment of HCC has resulted in the high mortality rates across the globe, and calls upon innovative approaches that can improve the prognosis of HCC patients. In the following sections, we describe the rapid advances and implementation of theranostic-based nanomedicine and nanoparticles (nanotheranostic) as a promising option (Figure 1) for the improvement of HCC patient outcomes and quality of life.

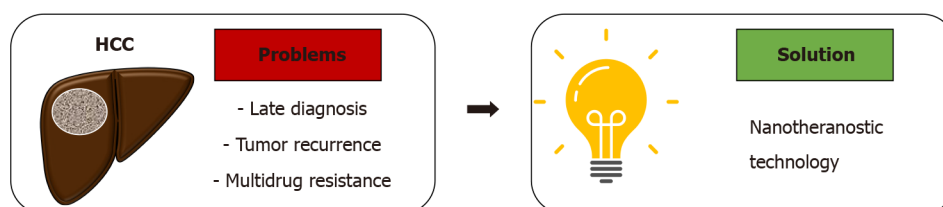
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## **POTENTIAL OF NANOTHERANOSTICS FOR PRECISION CANCER MEDICINE**

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Nanotheranostic modalities present a promising solution to the diagnostic and therapeutic challenges encountered in HCC management, through the use of biocompatible nanoparticles that simultaneously performs both diagnostic and therapeutic functions. This approach potentially provides a more personalized and targeted approach to cancer therapy, wherein the nanoparticles can be designed to detect specific biomarkers of the target malignant region, allow real-time monitoring or visualisation of the target, and finally deliver therapeutic modalities in a more precise manner. In recent years, the nanosensor and nanomedicine technologies have experienced major development, and have paved the way for promising means of nanotheranostics implementation in cancer management.

Nanotheranostic is a real-time combination of novel therapeutic and modern diagnostic tool or imaging into a single agent linked and integrated by nanoparticles [39,40]. Nanoparticles are the key components of the nanotheranostic agent[41] which include aptamer[42], DNA nanostructure[43], lactosome-based nanoparticles[44], metallic nanoparticles[45], gold nanoparticle[46], silver nanoparticle[47], dendrimer and copolymer-based nanoparticles[48], lipid-based nanomaterials[49], magnetic nanoparticles[50] iron oxide nanoparticle[51], mesoporous silica nanoparticle[52] and



**Figure 1** Hepatocellular carcinoma current problems and solution. HCC: Hepatocellular carcinoma.

quantum dots nanoparticle[53].

Nanotheranostic is an ideal choice for cancer treatment in the era of personalized medicine due to its potential to overcome the diagnostic and therapeutic challenges described prior[54]. Nanotheranostic not only provides the means for early diagnostic tools[55], nanoimaging-therapeutic integrated medicine[56], targeted-therapy[57] and tumor-specific nano-delivery agent[58], it also holds potential for real-time monitoring of drug response, and reduce side effects and drug toxicity in patients[59,60] as shown in Figure 2.

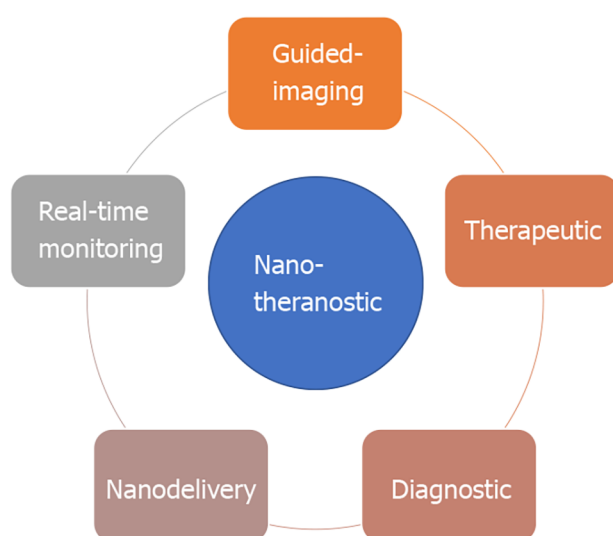
Successful demonstration of nanotheranostics for diagnostics and targeted therapy has been shown by Roy *et al*[61] in which highly sensitive, polymer-modified gadolinium-doped iron oxide-based  $T_1$  contrast agents were used for successful methotrexate drug delivery. In the second application, nanotheranostics have been utilized for simultaneous imaging and cancer monitoring[62]. An auto-fluorescent platform, constructed from a positively charged amphiphilic polymer polyethyl-eneimine-poly(lactide), was utilized to simultaneously load the antiangiogenesis agent cobtreastatin together with near-infrared (NIR) dye IR825 and heat-shock protein inhibitors. Altogether, the mechanism represents self-monitoring nanotheranostics, which in a mouse model demonstrated inhibitive properties in the tumour site through anti-angiogenesis and gene silencing enhanced photothermal therapy, while allowing real-time fluorescence monitoring.

The final and most widely developed application of nanotheranostics is for simultaneous imaging and targeted therapy, which has been shown to substantially increase the overall efficacy of therapies[63-65]. Theranostic platform choice has expanded rapidly in the past decade, and typically combines imaging modalities such as magnetic resonance imaging (MRI), NIR fluorescence, photoacoustic (PA) or ultrasound imaging, with therapeutic modalities such as chemotherapeutic agents, x-rays, hyperthermia, or free radicals.

Depending on the desired diagnostic and therapeutic modality, the nanoparticle of choice may be composed of metals, polymers, carbons and lipids. Each choice provides its own unique characteristics and physicochemical interactions, and also require different fabrication and functionalization procedures. As an example, successful magnetic-based imaging in a nanotheranostic platform is achievable using iron oxide, which is also desired due to its low toxicity and chemical stability. But many platforms prefer the use of multi-functional semiconducting polymers with hydrophobic properties, which simultaneously allow imaging through easy interactions with aromatic chemotherapeutic agents[66]. Nanoparticles can also be engineered to provide multimodal imaging[67] which utilizes modified ultrasmall  $Ag_2Se$  nanodots to allow upconversion luminescence, downshifting luminescence, computed tomography and PA imaging techniques.

An increasingly common approach in cancer theranostics is the use of multimodal therapy. To illustrate, the study by Zhang *et al*[68] utilized Janus-type  $\gamma-Fe_2O_3/SiO_2$  nanoparticles to combine the glucose oxidase-mediated cancer starvation strategy with hydroxyl radicals as chemodynamic therapy. Interestingly, nanoparticles can also be designed to become responsive towards environmental stimuli in drug-resistant tumours, meaning that it can be developed specifically towards the pathological profile of the tumor microenvironment as well as the organ-specific tissues and compartments, which contribute to the overall specificity of the drug delivery. For highly complex pathologies such as HCC with drug resistance, this provides a myriad of options for exploration, and becomes an interesting approach for future implementation of HCC-specific nanotheranostics.

Finally, it is also worth noting that metastasis remains a major issue in cancers such as HCC where diagnosis tends to be late. An interesting strategy[69] showed the use of immunotherapy-based theranostics to specifically target metastatic tissue. In said study, magnetic-responsive immunostimulatory nanoagents were added with



**Figure 2** Applications of cancer nanotheranostic.

superparamagnetic iron oxide nanoparticles and cytosine-phosphate-guanine oligodeoxynucleotides. These engineered components allow for PA and MRI in addition to acting as a therapeutic agent for photothermally triggered immunotherapy.

To illustrate these advancements, we present the current modalities of cancer nanotheranostics in Table 1. In general, cancer nanotheranostics has been used for simultaneous diagnostics and therapeutic[70], real-time monitoring of malignancies [71], guided-imaging[72,73], drug-delivery[74] and multimodal-targeted therapy[75-79].

## TACKLING HCC WITH NANOTHERANOSTICS

The nanotheranostic platform is a promising approach that is urgently needed to overcome the limitations of conventional therapy and diagnosis for more efficient HCC management. Figure 3 illustrates the multimodality of the nanotheranostic platform, which utilizes multipurpose nanoparticles for targeted nano-delivery, continuously controlled release of anticancer agents, guided imaging and early detection, for superior effectivity of transport[80]. Management of HCC requires powerful theranostic-based nanoparticles for early diagnostics and therapeutics with higher sensitivity and specificity, and to surpass the limitation of tissue penetration [81]. Previous studies have demonstrated the promising potential of silica-based nanomaterial as a potent nanotheranostic platform of HCC targeted-therapy nano-delivery[82-86]. In addition, many advances in HCC-specific nanotheranostics platforms are illustrated in Table 2, which demonstrates the multifunctional role of nanotheranostics as a detector to identify the HCC cell and tumor inhibitor by suppressing proliferation, migration and invasion of HCC[87,88].

One of the most remarkable advancements of the nanotheranostic platform is imaging and nano-delivery integration as an innovative resolution for early HCC diagnosis and *in situ* drug release. *In vivo* and *ex vivo* investigations have observed specific nanopatform activation by the tumor, with minimized toxicity towards non-target cells[89]. Integration of multifunctional nanoparticles with MRI may provide novel perspectives in tumor imaging technology to enhance HCC management and treatment strategy. High precision quantification and sensitivity of nanoimaging technology is needed for tissue penetration issue in early diagnosis of HCC[90].

Aptamer-based nanotheranostic is also a potential tool for HCC management due to its unique characteristics. This oligonucleotide nanomedicine has high specificity and affinity towards various types of target molecules[91]. In HCC clinical application, aptamer-based nanotheranostic development targeting the epithelial cell adhesion molecule demonstrated an improvement of MRI application and drug-delivery with high efficiency of doxorubicin released specifically towards cancer cells[92].

Improvement of therapeutic success is urgently needed for patients with unresectable and advanced HCC. The combination between nanomedicine as a nano-



**Table 1 Cancer nanotheranostics**

Applications	Principle	Ref.
Diagnostic and therapeutic	Stimuli responsive nanoparticle and targeted drug delivery	[61]
	Activatable nanotheranostic systems diagnosis and therapy of peritoneal metastasis	[70]
Real-time monitoring and therapeutic	Self-monitoring and triple-collaborative therapy <i>via</i> auto-fluorescence nanoparticles	[62]
	Real-time monitoring and tumor targeting <i>via</i> dual-fluorescent hydroxyapatite-doxorubicin	[71]
Guided-imaging and nanodelivery	Nanoparticle conjugated with antibody for tumor targeting and guided drug delivery	[63]
	A protein-stabilized multifunctional nanoplatfor for multimodal imaging and drug-delivery	[64]
Guided-imaging and therapeutic	Dual-targeting nanotheranostic with chemosensitizing agent for MDR chemotherapy	[65]
	Multifunctional nanocarrier for fluorescence imaging guided chemo-photothermal	[66]
	Dual-modal imaging and synergistic cancer starvation/chemodynamic therapy	[68]
	Tetra-modal imaging guided photothermal therapy	[67]
	Bimodal imaging guided photothermal-triggered immunotherapy	[69]
	Hierarchical tumor acidity-responsive magnetic nanobomb photodynamic therapy	[73]
	Lipid based nanoparticles nanodelivery-anticancer drug and nanoimaging	[74]
	The self-assembly nanoparticles with guided imaging and chemotherapeutic drugs	[76]
	Biocompatible nanoparticles as targeted-nanodelivery of chemotherapeutic agent	[77]
	Dual-modality mapping guided photothermal ablation for metastatic cancer	[78]
	Magnetic nanoparticle-doxorubicin for enhancing nanoimaging and targeted therapy	[79]

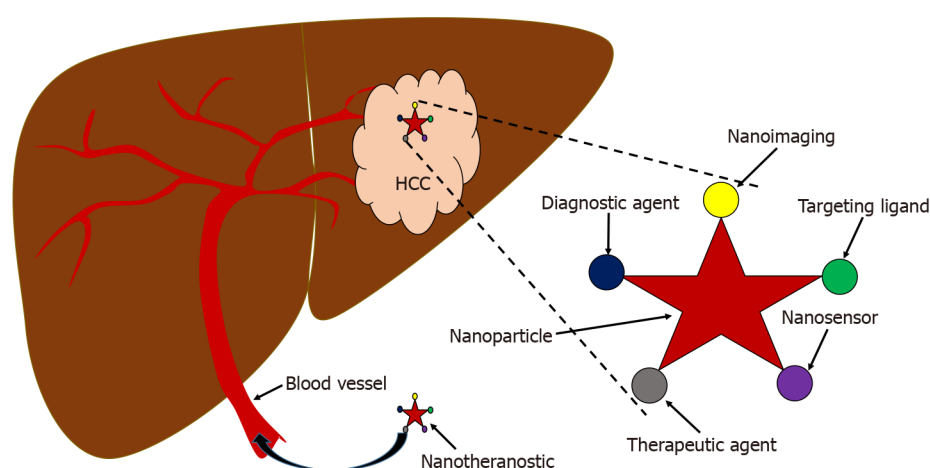
MDR: Multidrug resistance.

**Table 2 Nanotheranostic development against hepatocellular carcinoma**

Applications	Principle	Ref.
Diagnostic and therapeutic	Conventional SELEX	[87]
	CE-SELEX	[88]
	Magnetic nanoparticle-aptamer	[92]
Enhancing therapeutic	Inducing tumor regression using siRNA-nanoparticle construction	[100]
	Enhancing the anticancer efficacy using siRNA-nanoparticle construction	[101]
	Enhancing chemotherapy using microRNA 375-nanoparticle construction	[102]
	Synergistic antitumor effect of microRNA 375-nanoparticle construction	[103]
Diagnostic and guided-imaging	'Activatable' aptamer-based fluorescence probe	[104]
	Streptavidin-fluorescent silica nanoparticles combination	[105]
	Aptamer- based electrochemical biosensors	[106]
Gene editing	Next-generation CRISPR/Cas technology	[107]

HCC: Hepatocellular carcinoma; SELEX: Systematic Evolution of Ligands by Exponential Enrichment.

delivery system with cancer immunotherapy holds great potential for enhancing the nanotherapeutic outcome for this population. A promising targeted-nano-delivery immunotherapy for advanced HCC that is currently undergoing clinical trial is the 4<sup>th</sup> generation chimeric antigen receptor (CAR) T cells targeting glypican-3 (GPC3) (ClinicalTrials.gov Identifier: NCT03884751)[93]. This study showed promising phase I results in regard to antitumor activity and safety profile of CAR-GPC3 T-cell immunotherapy. The antitumor activity is positively associated with tumor response with no grade 3/4 neurotoxicity effect in any patients[94]. Several studies have also been done



**Figure 3 Multimodality of the nanotheranostic platform.** HCC: Hepatocellular carcinoma.

to achieve said goal by conjugating anticancer drugs with nanoparticles, rendering the treatment safer with more effective systemic administration due to the platform's capability of controlling and postponing drug release. In the *in vivo* mouse model, tumor specific uptake of the controlled drug release for several weeks was observed, with minimal toxicity[95].

Molecular-targeted nano-therapies have also been constructed for nano-delivery using a modular design of polymeric nanoparticles for selective accumulation of drug pay load within tumor lesions. In *in vivo* mouse models, the intravenous drug injection was more effective for tumor inhibition than oral administration. This has revolutionized anticancer therapy by enhancing the efficacy and potency of therapeutics through inhibition of the angiogenesis pathway, tumor growth, tube formation and metastasis[96]. Targeted drug delivery using mesoporous silica nanoparticle is also promising. Nanoconstruction of silica nanorattle encapsulated docetaxel exhibited low toxicity with high antitumor activity, making it a prospective candidate for nano-delivery system[97]. Moreover, modified silica nanoparticles targeting low density lipoprotein and loaded with two anticancer drugs for liver cancer chemotherapy showed increased delivery efficiency based on *in vitro* and *in vivo* analysis[98].

In addition to anticancer drug nano-delivery for HCC treatment, the nanotheranostic platform is also suitable for targeted nano-delivery of small interfering RNA based therapeutics. This can be used as gene therapy to knock down a specific gene [99-101], and micro RNA for enhancing chemotherapy efficiency[102] to overcome multi-drug resistance in HCC[103].

## FUTURE PERSPECTIVES

HCC is an extremely complex and heterogeneous disease with diverse molecular profiles, aetiology and subtypes. Since conventional approaches still fail to overcome limitations in HCC management, nanotheranostic is a promising alternative to overcome the problems. Rapid development in nanotechnology has added a tremendous value on cancer therapy. The future of cancer nanomedicine lies on multimodal nanoplatforms that combine targeting ligands, imaging agents, diagnostic agents and therapeutic components into one unit of functionalized nanoparticles. Thus, multifunctionality is a powerful and unique advantage of nanotheranostic over traditional methods, and evidence has shown its capacity to work efficiently and noninvasively *in vivo* without systemic toxicity. Development of nanotheranostic in the right direction requires improvement of platforms so that it can be optimized simultaneously for proficient performance as the best clinical outcome in HCC.

## CONCLUSION

In summary, nanotheranostic is an emerging and promising approach for HCC diagnosis/imaging and therapy in the future. Nanotheranostic is a powerful, unique, and multifunctional tool that yields positive impact both in the basic research and

clinical application of HCC. We predict that in a near future nanotheranostic platform will continue to exponentially grow and progressively implemented in the development of novel and efficacious diagnostic and therapeutic agents towards cancers, including HCC. Further expansion would be needed to assist clinical translation of the promising preclinical studies in HCC.

## REFERENCES

- 1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: [30207593](#) DOI: [10.3322/caac.21492](#)]
- 2 **Kulik L**, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. *Gastroenterology* 2019; **156**: 477-491.e1 [PMID: [30367835](#) DOI: [10.1053/j.gastro.2018.08.065](#)]
- 3 **Llovet JM**, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, Gores G. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2016; **2**: 16018 [PMID: [27158749](#) DOI: [10.1038/nrdp.2016.18](#)]
- 4 **Dimitroulis D**, Damaskos C, Valsami S, Davakis S, Garmpis N, Spartalis E, Athanasiou A, Moris D, Sakellariou S, Kykalos S, Tsourouflis G, Garmpi A, Delladetsima I, Kontzoglou K, Kouraklis G. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. *World J Gastroenterol* 2017; **23**: 5282-5294 [PMID: [28839428](#) DOI: [10.3748/wjg.v23.i29.5282](#)]
- 5 **Petrick JL**, Kelly SP, Altekruze SF, McGlynn KA, Rosenberg PS. Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030. *J Clin Oncol* 2016; **34**: 1787-1794 [PMID: [27044939](#) DOI: [10.1200/JCO.2015.64.7412](#)]
- 6 **Fujiwara N**, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol* 2018; **68**: 526-549 [PMID: [28989095](#) DOI: [10.1016/j.jhep.2017.09.016](#)]
- 7 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: [21296855](#) DOI: [10.3322/caac.20107](#)]
- 8 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: [22353262](#) DOI: [10.1016/S0140-6736\(11\)61347-0](#)]
- 9 **Tang A**, Hallouch O, Chernyak V, Kamaya A, Sirlin CB. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. *Abdom Radiol (NY)* 2018; **43**: 13-25 [PMID: [28647765](#) DOI: [10.1007/s00261-017-1209-1](#)]
- 10 **Rawla P**, Sunkara T, Muralidharan P, Raj JP. Update in global trends and aetiology of hepatocellular carcinoma. *Contemp Oncol (Pozn)* 2018; **22**: 141-150 [PMID: [30455585](#) DOI: [10.5114/wo.2018.78941](#)]
- 11 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: [25651787](#) DOI: [10.3322/caac.21262](#)]
- 12 **Mittal S**, Kramer JR, Omino R, Chayanupatkul M, Richardson PA, El-Serag HB, Kanwal F. Role of Age and Race in the Risk of Hepatocellular Carcinoma in Veterans With Hepatitis B Virus Infection. *Clin Gastroenterol Hepatol* 2018; **16**: 252-259 [PMID: [28870660](#) DOI: [10.1016/j.cgh.2017.08.042](#)]
- 13 **Hemming AW**, Berumen J, Mekeel K. Hepatitis B and Hepatocellular Carcinoma. *Clin Liver Dis* 2016; **20**: 703-720 [PMID: [27742009](#) DOI: [10.1016/j.cld.2016.06.007](#)]
- 14 **Goto K**, Roca Suarez AA, Wrensch F, Baumert TF, Lupberger J. Hepatitis C Virus and Hepatocellular Carcinoma: When the Host Loses Its Grip. *Int J Mol Sci* 2020; **21** [PMID: [32357520](#) DOI: [10.3390/ijms21093057](#)]
- 15 **de Martel C**, Maucourt-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. *Hepatology* 2015; **62**: 1190-1200 [PMID: [26146815](#) DOI: [10.1002/hep.27969](#)]
- 16 **Baecker A**, Liu X, La Vecchia C, Zhang ZF. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. *Eur J Cancer Prev* 2018; **27**: 205-212 [PMID: [29489473](#) DOI: [10.1097/CEJ.0000000000000428](#)]
- 17 **Seyda Seydel G**, Kucukoglu O, Altinbasv A, Demir OO, Yilmaz S, Akkiz H, Otan E, Sowa JP, Canbay A. Economic growth leads to increase of obesity and associated hepatocellular carcinoma in developing countries. *Ann Hepatol* 2016; **15**: 662-672 [PMID: [27493104](#) DOI: [10.5604/16652681.1212316](#)]
- 18 **Zheng H**, Li P, Kwok JG, Korrapati A, Li WT, Qu Y, Wang XQ, Kisseleva T, Wang-Rodriguez J, Ongkeko WM. Alcohol and hepatitis virus-dysregulated lncRNAs as potential biomarkers for hepatocellular carcinoma. *Oncotarget* 2018; **9**: 224-235 [PMID: [29416609](#) DOI: [10.18632/oncotarget.22921](#)]
- 19 **Yang JD**, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589-604 [PMID: [31439937](#) DOI: [10.1038/s41575-019-0186-y](#)]
- 20 **Kew MC**. Aflatoxins as a cause of hepatocellular carcinoma. *J Gastrointest Liver Dis* 2013; **22**: 305-310 [PMID: [24078988](#)]
- 21 **André F**. Hepatitis B epidemiology in Asia, the Middle East and Africa. *Vaccine* 2000; **18** Suppl 1:

- S20-2 [PMID: 10683538 DOI: 10.1016/s0264-410x(99)00456-9]
- 22 **Ghouri YA**, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. *J Carcinog* 2017; **16**: 1 [PMID: 28694740 DOI: 10.4103/jcar.JCar\_9\_16]
  - 23 **Aravalli RN**, Steer CJ, Cressman EN. Molecular mechanisms of hepatocellular carcinoma. *Hepatology* 2008; **48**: 2047-2063 [PMID: 19003900 DOI: 10.1002/hep.22580]
  - 24 **Hui AM**, Makuuchi M. Molecular basis of multistep hepatocarcinogenesis: genetic and epigenetic events. *Scand J Gastroenterol* 1999; **34**: 737-742 [PMID: 10499472 DOI: 10.1080/003655299750025642]
  - 25 **Thorgeirsson SS**, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; **31**: 339-346 [PMID: 12149612 DOI: 10.1038/ng0802-339]
  - 26 **Feitelson MA**, Sun B, Satiroglu Tufan NL, Liu J, Pan J, Lian Z. Genetic mechanisms of hepatocarcinogenesis. *Oncogene* 2002; **21**: 2593-2604 [PMID: 11971194 DOI: 10.1038/sj.onc.1205434]
  - 27 **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
  - 28 **de Lope CR**, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. *J Hepatol* 2012; **56** Suppl 1: S75-S87 [PMID: 22300468 DOI: 10.1016/S0168-8278(12)60009-9]
  - 29 **Vitale A**, Peck-Radosavljevic M, Giannini EG, Vibert E, Sieghart W, Van Poucke S, Pawlik TM. Personalized treatment of patients with very early hepatocellular carcinoma. *J Hepatol* 2017; **66**: 412-423 [PMID: 27677712 DOI: 10.1016/j.jhep.2016.09.012]
  - 30 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]
  - 31 **Forner A**, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010; **30**: 61-74 [PMID: 20175034 DOI: 10.1055/s-0030-1247133]
  - 32 **Daher S**, Massarwa M, Benson AA, Khoury T. Current and Future Treatment of Hepatocellular Carcinoma: An Updated Comprehensive Review. *J Clin Transl Hepatol* 2018; **6**: 69-78 [PMID: 29607307 DOI: 10.14218/JCTH.2017.00031]
  - 33 **Guo J**, Li L, Guo B, Liu D, Shi J, Wu C, Chen J, Zhang X, Wu J. Mechanisms of resistance to chemotherapy and radiotherapy in hepatocellular carcinoma. *Transl Cancer Res* 2018; **7**: 765-781 [DOI: 10.21037/tcr.2018.05.20]
  - 34 **Facciorusso A**, Del Prete V, Antonino M, Crucinio N, Neve V, Di Leo A, Carr BI, Barone M. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. *Dig Liver Dis* 2014; **46**: 1014-1019 [PMID: 25085684 DOI: 10.1016/j.dld.2014.07.012]
  - 35 **Imamura H**, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003; **38**: 200-207 [PMID: 12547409 DOI: 10.1016/s0168-8278(02)00360-4]
  - 36 **Tang W**, Chen Z, Zhang W, Cheng Y, Zhang B, Wu F, Wang Q, Wang S, Rong D, Reiter FP, De Toni EN, Wang X. The mechanisms of sorafenib resistance in hepatocellular carcinoma: theoretical basis and therapeutic aspects. *Signal Transduct Target Ther* 2020; **5**: 87 [PMID: 32532960 DOI: 10.1038/s41392-020-0187-x]
  - 37 **Marin JGG**, Macias RIR, Monte MJ, Romero MR, Asensio M, Sanchez-Martin A, Cives-Losada C, Temprano AG, Espinosa-Escudero R, Reviejo M, Bohorquez LH, Briz O. Molecular Bases of Drug Resistance in Hepatocellular Carcinoma. *Cancers (Basel)* 2020; **12** [PMID: 32585893 DOI: 10.3390/cancers12061663]
  - 38 **Duan B**, Huang C, Bai J, Zhang YL, Wang X, Yang J, Li J. Multidrug Resistance in Hepatocellular Carcinoma. In: Tirnitz-Parker JEE. Hepatocellular Carcinoma. Brisbane (AU): Codon Publications, 2019
  - 39 **Muthu MS**, Leong DT, Mei L, Feng SS. Nanotheranostics - application and further development of nanomedicine strategies for advanced theranostics. *Theranostics* 2014; **4**: 660-677 [PMID: 24723986 DOI: 10.7150/thno.8698]
  - 40 **Jeelani S**, Reddy RC, Maheswaran T, Asokan GS, Dany A, Anand B. Theranostics: A treasured tailor for tomorrow. *J Pharm Bioallied Sci* 2014; **6**: S6-S8 [PMID: 25210387 DOI: 10.4103/0975-7406.137249]
  - 41 **Madanayake NH**, Rienzie R, Adassooriya NM. Nanoparticles in Nanotheranostics Applications. In: Rai M, Jamil B. Nanotheranostics: Applications and Limitations. Cham: Springer International Publishing, 2019: 19-40
  - 42 **Ravichandran G**, Rengan AK. Aptamer-Mediated Nanotheranostics for Cancer Treatment: A Review. *ACS Appl Nano Mater* 2020; **3**: 9542-9559 [DOI: 10.1021/acsanm.0c01785]
  - 43 **Nicolson F**, Ali A, Kircher MF, Pal S. DNA Nanostructures and DNA-Functionalized Nanoparticles for Cancer Theranostics. *Adv Sci (Weinh)* 2020; **7**: 2001669 [PMID: 33304747 DOI: 10.1002/advs.202001669]
  - 44 **Lim MSH**, Ohtsuki T, Takenaka F, Kobayashi K, Akehi M, Uji H, Kobuchi H, Sasaki T, Ozeki E, Matsuura E. A Novel <sup>89</sup>Zr-labeled DDS Device Utilizing Human IgG Variant (scFv): "Lactosome" Nanoparticle-Based Theranostics for PET Imaging and Targeted Therapy. *Life (Basel)* 2021; **11** [PMID: 33670777 DOI: 10.3390/life11020158]



- 45 **Silva CO**, Pinho JO, Lopes JM, Almeida AJ, Gaspar MM, Reis C. Current Trends in Cancer Nanotheranostics: Metallic, Polymeric, and Lipid-Based Systems. *Pharmaceutics* 2019; **11** [PMID: 30625999 DOI: 10.3390/pharmaceutics11010022]
- 46 **Gao Q**, Zhang J, Gao J, Zhang Z, Zhu H, Wang D. Gold Nanoparticles in Cancer Theranostics. *Front Bioeng Biotechnol* 2021; **9**: 647905 [PMID: 33928072 DOI: 10.3389/fbioe.2021.647905]
- 47 **Zhang P**, Hu C, Ran W, Meng J, Yin Q, Li Y. Recent Progress in Light-Triggered Nanotheranostics for Cancer Treatment. *Theranostics* 2016; **6**: 948-968 [PMID: 27217830 DOI: 10.7150/thno.15217]
- 48 **Ray S**, Li Z, Hsu CH, Hwang LP, Lin YC, Chou PT, Lin YY. Dendrimer- and copolymer-based nanoparticles for magnetic resonance cancer theranostics. *Theranostics* 2018; **8**: 6322-6349 [PMID: 30613300 DOI: 10.7150/thno.27828]
- 49 **Tang WL**, Tang WH, Li SD. Cancer theranostic applications of lipid-based nanoparticles. *Drug Discov Today* 2018; **23**: 1159-1166 [PMID: 29660478 DOI: 10.1016/j.drudis.2018.04.007]
- 50 **Carvalho de Jesus P da C**, Pellosi DS, Tedesco AC. Chapter 12 - Magnetic nanoparticles: applications in biomedical processes as synergic drug-delivery systems. In: Holban A-M, Grumezescu AM. *Materials for Biomedical Engineering*. Elsevier, 2019: 371-396
- 51 **Zhao S**, Yu X, Qian Y, Chen W, Shen J. Multifunctional magnetic iron oxide nanoparticles: an advanced platform for cancer theranostics. *Theranostics* 2020; **10**: 6278-6309 [PMID: 32483453 DOI: 10.7150/thno.42564]
- 52 **Tao Y**, Wang J, Xu X. Emerging and Innovative Theranostic Approaches for Mesoporous Silica Nanoparticles in Hepatocellular Carcinoma: Current Status and Advances. *Front Bioeng Biotechnol* 2020; **8**: 184 [PMID: 32211399 DOI: 10.3389/fbioe.2020.00184]
- 53 **Chen H**, Liu Z, Wei B, Huang J, You X, Zhang J, Yuan Z, Tang Z, Guo Z, Wu J. Redox responsive nanoparticle encapsulating black phosphorus quantum dots for cancer theranostics. *Bioact Mater* 2021; **6**: 655-665 [PMID: 33005829 DOI: 10.1016/j.bioactmat.2020.08.034]
- 54 **Mura S**, Couvreur P. Nanotheranostics for personalized medicine. *Adv Drug Deliv Rev* 2012; **64**: 1394-1416 [PMID: 22728642 DOI: 10.1016/j.addr.2012.06.006]
- 55 **Sonali**, Viswanadh MK, Singh RP, Agrawal P, Mehata AK, Pawde DM, Narendra, Sonkar R, Muthu MS. Nanotheranostics: Emerging Strategies for Early Diagnosis and Therapy of Brain Cancer. *Nanotheranostics* 2018; **2**: 70-86 [PMID: 29291164 DOI: 10.7150/ntno.21638]
- 56 **Sivasubramanian M**, Chuang YC, Chen NT, Lo LW. Seeing Better and Going Deeper in Cancer Nanotheranostics. *Int J Mol Sci* 2019; **20** [PMID: 31315232 DOI: 10.3390/ijms20143490]
- 57 **Zhang P**, Chen H, Liu J, Liu G. Genetically Engineered Plasma Membrane Nanovesicles for Cancer-Targeted Nanotheranostics. *Methods Mol Biol* 2019; **2054**: 283-294 [PMID: 31482462 DOI: 10.1007/978-1-4939-9769-5\_18]
- 58 **Mendes LP**, Lima EM, Torchilin VP. Chapter 9 - Targeted Nanotheranostics for Selective Drug Delivery in Cancer. In: Conde J. *Handbook of Nanomaterials for Cancer Theranostics*. Elsevier, 2018: 245-277
- 59 **Fan Z**, Fu PP, Yu H, Ray PC. Theranostic nanomedicine for cancer detection and treatment. *J Food Drug Anal* 2014; **22**: 3-17 [PMID: 24673900 DOI: 10.1016/j.jfda.2014.01.001]
- 60 **Kundu P**, Singh D, Singh A, Sahoo SK. Cancer Nanotheranostics: A Nanomedicinal Approach for Cancer Therapy and Diagnosis. *Anticancer Agents Med Chem* 2020; **20**: 1288-1299 [PMID: 31429694 DOI: 10.2174/1871520619666190820145930]
- 61 **Roy E**, Patra S, Madhuri R, Sharma PK. Stimuli-responsive poly(N-isopropyl acrylamide)-co-tyrosine@gadolinium: Iron oxide nanoparticle-based nanotheranostic for cancer diagnosis and treatment. *Colloids Surf B Biointerfaces* 2016; **142**: 248-258 [PMID: 26962761 DOI: 10.1016/j.colsurfb.2016.02.053]
- 62 **Shao L**, Li Q, Zhao C, Lu J, Li X, Chen L, Deng X, Ge G, Wu Y. Auto-fluorescent polymer nanotheranostics for self-monitoring of cancer therapy via triple-collaborative strategy. *Biomaterials* 2019; **194**: 105-116 [PMID: 30590240 DOI: 10.1016/j.biomaterials.2018.12.021]
- 63 **Chen F**, Hong H, Zhang Y, Valdovinos HF, Shi S, Kwon GS, Theuer CP, Barnhart TE, Cai W. In vivo tumor targeting and image-guided drug delivery with antibody-conjugated, radiolabeled mesoporous silica nanoparticles. *ACS Nano* 2013; **7**: 9027-9039 [PMID: 24083623 DOI: 10.1021/nn403617j]
- 64 **Han L**, Xia JM, Hai X, Shu Y, Chen XW, Wang JH. Protein-Stabilized Gadolinium Oxide-Gold Nanoclusters Hybrid for Multimodal Imaging and Drug Delivery. *ACS Appl Mater Interfaces* 2017; **9**: 6941-6949 [PMID: 28177224 DOI: 10.1021/acsami.7b00246]
- 65 **Yang C**, Pang X, Chen W, Wang X, Lin G, Chu C, Zhang X, Deng X, Chen X, Liu G. Environmentally responsive dual-targeting nanotheranostics for overcoming cancer multidrug resistance. *Science Bulletin* 2019; **64**: 705-714 [DOI: 10.1016/j.scib.2019.04.019]
- 66 **Jiang Y**, Cui D, Fang Y, Zhen X, Upputuri PK, Pramanik M, Ding D, Pu K. Amphiphilic semiconducting polymer as multifunctional nanocarrier for fluorescence/photoacoustic imaging guided chemo-photothermal therapy. *Biomaterials* 2017; **145**: 168-177 [PMID: 28866477 DOI: 10.1016/j.biomaterials.2017.08.037]
- 67 **Du K**, Lei P, Dong L, Zhang M, Gao X, Yao S, Feng J, Zhang H. In situ decorating of ultrasmall Ag<sub>2</sub>Se on upconversion nanoparticles as novel nanotheranostic agent for multimodal imaging-guided cancer photothermal therapy. *Appl Mater Today* 2020; **18**: 100497 [DOI: 10.1016/j.apmt.2019.100497]
- 68 **Zhang Y**, Wan Y, Liao Y, Hu Y, Jiang T, He T, Bi W, Lin J, Gong P, Tang L, Huang P. Janus  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>/SiO<sub>2</sub>-based nanotheranostics for dual-modal imaging and enhanced synergistic cancer

- starvation/chemodynamic therapy. *Science Bulletin* 2020; **65**: 564-572 [DOI: [10.1016/j.scib.2019.12.024](https://doi.org/10.1016/j.scib.2019.12.024)]
- 69 **Guo Y**, Ran Y, Wang Z, Cheng J, Cao Y, Yang C, Liu F, Ran H. Magnetic-responsive and targeted cancer nanotheranostics by PA/MR bimodal imaging-guided photothermally triggered immunotherapy. *Biomaterials* 2019; **219**: 119370. [DOI: [10.1016/j.biomaterials.2019.119370](https://doi.org/10.1016/j.biomaterials.2019.119370)]
  - 70 **Ling S**, Yang X, Li C, Zhang Y, Yang H, Chen G, Wang Q. Tumor Microenvironment-Activated NIR-II Nanotheranostic System for Precise Diagnosis and Treatment of Peritoneal Metastasis. *Angew Chem Int Ed Engl* 2020; **59**: 7219-7223 [PMID: [32030871](https://pubmed.ncbi.nlm.nih.gov/32030871/)] DOI: [10.1002/anie.202000947](https://doi.org/10.1002/anie.202000947)]
  - 71 **Kang Y**, Sun W, Fan J, Wei Z, Wang S, Li M, Zhang Z, Xie Y, Du J, Peng X. Ratiometric real-time monitoring of hydroxyapatite–doxorubicin nanotheranostic agents for on-demand tumor targeted chemotherapy. *Mater Chem Front* 2018; **2**: 1791-1798 [DOI: [10.1039/C8QM00215K](https://doi.org/10.1039/C8QM00215K)]
  - 72 **Dehghani S**, Hosseini M, Haghgoo S, Changizi V, Akbari Javar H, Khoobi M, Riahi Alam N. Multifunctional MIL-Cur@FC as a theranostic agent for magnetic resonance imaging and targeting drug delivery: *in vitro* and *in vivo* study. *J Drug Target* 2020; **28**: 668-680 [PMID: [31886726](https://pubmed.ncbi.nlm.nih.gov/31886726/)] DOI: [10.1080/1061186X.2019.1710839](https://doi.org/10.1080/1061186X.2019.1710839)]
  - 73 **Yang HY**, Jang MS, Li Y, Fu Y, Wu TP, Lee JH, Lee DS. Hierarchical tumor acidity-responsive self-assembled magnetic nanotheranostics for bimodal bioimaging and photodynamic therapy. *J Control Release* 2019; **301**: 157-165 [PMID: [30905667](https://pubmed.ncbi.nlm.nih.gov/30905667/)] DOI: [10.1016/j.jconrel.2019.03.019](https://doi.org/10.1016/j.jconrel.2019.03.019)]
  - 74 **Parhi P**, Sahoo SK. Trastuzumab guided nanotheranostics: A lipid based multifunctional nanoformulation for targeted drug delivery and imaging in breast cancer therapy. *J Colloid Interface Sci* 2015; **451**: 198-211 [PMID: [25897856](https://pubmed.ncbi.nlm.nih.gov/25897856/)] DOI: [10.1016/j.jcis.2015.03.049](https://doi.org/10.1016/j.jcis.2015.03.049)]
  - 75 **Dai Y**, Wang B, Sun Z, Cheng J, Zhao H, Wu K, Sun P, Shen Q, Li M, Fan Q. Multifunctional Theranostic Liposomes Loaded with a Hypoxia-Activated Prodrug for Cascade-Activated Tumor Selective Combination Therapy. *ACS Appl Mater Interfaces* 2019; **11**: 39410-39423 [PMID: [31578854](https://pubmed.ncbi.nlm.nih.gov/31578854/)] DOI: [10.1021/acsami.9b11080](https://doi.org/10.1021/acsami.9b11080)]
  - 76 **Tang J**, Zheng F, Zhao J. Self-assembled multifunctional nanotheranostics loading GEM for targeted lung cancer therapy. *Mater Sci Eng C Mater Biol Appl* 2020; **112**: 110786 [PMID: [32409023](https://pubmed.ncbi.nlm.nih.gov/32409023/)] DOI: [10.1016/j.msec.2020.110786](https://doi.org/10.1016/j.msec.2020.110786)]
  - 77 **Unnikrishnan BS**, Sen A, Preethi GU, Joseph MM, Maya S, Shiji R, Anusree KS, Sreelekha TT. Folic acid-appended galactoxyloglucan-capped iron oxide nanoparticles as a biocompatible nanotheranostic agent for tumor-targeted delivery of doxorubicin. *Int J Biol Macromol* 2021; **168**: 130-142 [PMID: [33278441](https://pubmed.ncbi.nlm.nih.gov/33278441/)] DOI: [10.1016/j.ijbiomac.2020.11.205](https://doi.org/10.1016/j.ijbiomac.2020.11.205)]
  - 78 **Wang S**, Zhang Q, Luo XF, Li J, He H, Yang F, Di Y, Jin C, Jiang XG, Shen S, Fu de L. Magnetic graphene-based nanotheranostic agent for dual-modality mapping guided photothermal therapy in regional lymph nodal metastasis of pancreatic cancer. *Biomaterials* 2014; **35**: 9473-9483 [PMID: [25175596](https://pubmed.ncbi.nlm.nih.gov/25175596/)] DOI: [10.1016/j.biomaterials.2014.07.064](https://doi.org/10.1016/j.biomaterials.2014.07.064)]
  - 79 **Mosafer J**, Abnous K, Tafaghodi M, Mokhtarzadeh A, Ramezani M. In vitro and in vivo evaluation of anti-nucleolin-targeted magnetic PLGA nanoparticles loaded with doxorubicin as a theranostic agent for enhanced targeted cancer imaging and therapy. *Eur J Pharm Biopharm* 2017; **113**: 60-74 [PMID: [28012991](https://pubmed.ncbi.nlm.nih.gov/28012991/)] DOI: [10.1016/j.ejpb.2016.12.009](https://doi.org/10.1016/j.ejpb.2016.12.009)]
  - 80 **Siafaka PI**, Okur NÜ, Karantas ID, Okur ME, Gündoğdu EA. Current update on nanoplatforms as therapeutic and diagnostic tools: A review for the materials used as nanotheranostics and imaging modalities. *Asian J Pharm Sci* 2021; **16**: 24-46 [PMID: [33613728](https://pubmed.ncbi.nlm.nih.gov/33613728/)] DOI: [10.1016/j.ajps.2020.03.003](https://doi.org/10.1016/j.ajps.2020.03.003)]
  - 81 **Xiang D**, Zheng C, Zhou SF, Qiao S, Tran PH, Pu C, Li Y, Kong L, Kouzani AZ, Lin J, Liu K, Li L, Shigdar S, Duan W. Superior Performance of Aptamer in Tumor Penetration over Antibody: Implication of Aptamer-Based Theranostics in Solid Tumors. *Theranostics* 2015; **5**: 1083-1097 [PMID: [26199647](https://pubmed.ncbi.nlm.nih.gov/26199647/)] DOI: [10.7150/thno.11711](https://doi.org/10.7150/thno.11711)]
  - 82 **Wang JK**, Zhou YY, Guo SJ, Wang YY, Nie CJ, Wang HL, Wang JL, Zhao Y, Li XY, Chen XJ. Cetuximab conjugated and doxorubicin loaded silica nanoparticles for tumor-targeting and tumor microenvironment responsive binary drug delivery of liver cancer therapy. *Mater Sci Eng C Mater Biol Appl* 2017; **76**: 944-950 [PMID: [28482611](https://pubmed.ncbi.nlm.nih.gov/28482611/)] DOI: [10.1016/j.msec.2017.03.131](https://doi.org/10.1016/j.msec.2017.03.131)]
  - 83 **Zhang B**, Luo Z, Liu J, Ding X, Li J, Cai K. Cytochrome c end-capped mesoporous silica nanoparticles as redox-responsive drug delivery vehicles for liver tumor-targeted triplex therapy in vitro and in vivo. *J Control Release* 2014; **192**: 192-201 [PMID: [25034575](https://pubmed.ncbi.nlm.nih.gov/25034575/)] DOI: [10.1016/j.jconrel.2014.06.037](https://doi.org/10.1016/j.jconrel.2014.06.037)]
  - 84 **Lv Y**, Li J, Chen H, Bai Y, Zhang L. Glycyrhethinic acid-functionalized mesoporous silica nanoparticles as hepatocellular carcinoma-targeted drug carrier. *Int J Nanomedicine* 2017; **12**: 4361-4370 [PMID: [28652738](https://pubmed.ncbi.nlm.nih.gov/28652738/)] DOI: [10.2147/IJN.S135626](https://doi.org/10.2147/IJN.S135626)]
  - 85 **Xu X**, Wu C, Bai A, Liu X, Lv H, Liu Y. Folate-Functionalized Mesoporous Silica Nanoparticles as a Liver Tumor-Targeted Drug Delivery System to Improve the Antitumor Effect of Paclitaxel. *J Nanomater* 2017; **2017**: e2069685 [DOI: [10.1155/2017/2069685](https://doi.org/10.1155/2017/2069685)]
  - 86 **Zhao R**, Li T, Zheng G, Jiang K, Fan L, Shao J. Simultaneous inhibition of growth and metastasis of hepatocellular carcinoma by co-delivery of ursolic acid and sorafenib using lactobionic acid modified and pH-sensitive chitosan-conjugated mesoporous silica nanocomplex. *Biomaterials* 2017; **143**: 1-16 [PMID: [28755539](https://pubmed.ncbi.nlm.nih.gov/28755539/)] DOI: [10.1016/j.biomaterials.2017.07.030](https://doi.org/10.1016/j.biomaterials.2017.07.030)]
  - 87 **Lee YJ**, Lee SW. Regression of hepatocarcinoma cells using RNA aptamer specific to alpha-fetoprotein. *Biochem Biophys Res Commun* 2012; **417**: 521-527 [PMID: [22166203](https://pubmed.ncbi.nlm.nih.gov/22166203/)] DOI: [10.1016/j.bbrc.2011.11.153](https://doi.org/10.1016/j.bbrc.2011.11.153)]
  - 88 **Dong L**, Tan Q, Ye W, Liu D, Chen H, Hu H, Wen D, Liu Y, Cao Y, Kang J, Fan J, Guo W, Wu W.

- Screening and Identifying a Novel ssDNA Aptamer against Alpha-fetoprotein Using CE-SELEX. *Sci Rep* 2015; **5**: 15552 [PMID: 26497223 DOI: 10.1038/srep15552]
- 89 **Lei Y**, Tang J, Shi H, Ye X, He X, Xu F, Yan L, Qiao Z, Wang K. Nature-Inspired Smart DNA Nanoductor for Activatable In Vivo Cancer Imaging and In Situ Drug Release Based on Recognition-Triggered Assembly of Split Aptamer. *Anal Chem* 2016; **88**: 11699-11706 [PMID: 27807977 DOI: 10.1021/acs.analchem.6b03283]
  - 90 **Malla RR**, Kumari S, Kgg D, Momin S, Nagaraju GP. Nanotheranostics: Their role in hepatocellular carcinoma. *Crit Rev Oncol Hematol* 2020; **151**: 102968 [PMID: 32416345 DOI: 10.1016/j.critrevonc.2020.102968]
  - 91 **Ladju RB**, Pascut D, Massi MN, Tiribelli C, Sukowati CHC. Aptamer: A potential oligonucleotide nanomedicine in the diagnosis and treatment of hepatocellular carcinoma. *Oncotarget* 2018; **9**: 2951-2961 [PMID: 29416827 DOI: 10.18632/oncotarget.23359]
  - 92 **Pilapong C**, Sitthichai S, Thongtem S, Thongtem T. Smart magnetic nanoparticle-aptamer probe for targeted imaging and treatment of hepatocellular carcinoma. *Int J Pharm* 2014; **473**: 469-474 [PMID: 25089503 DOI: 10.1016/j.ijpharm.2014.07.036]
  - 93 **Carsgen Therapeutics, Ltd.** A Phase I Clinical Study of Chimeric Antigen Receptor T Cells Targeting Glypican-3 (CAR-GPC3 T Cells) in Patients With Advanced Hepatocellular Carcinoma. [accessed 2021 Mar 18]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://clinicaltrials.gov/ct2/show/NCT03884751>
  - 94 **Shi D**, Shi Y, Kaseb AO, Qi X, Zhang Y, Chi J, Lu Q, Gao H, Jiang H, Wang H, Yuan D, Ma H, Li Z, Zhai B. Chimeric Antigen Receptor-Glypican-3 T-Cell Therapy for Advanced Hepatocellular Carcinoma: Results of Phase I Trials. *Clin Cancer Res* 2020; **26**: 3979-3989 [PMID: 32371538 DOI: 10.1158/1078-0432.CCR-19-3259]
  - 95 **Xu L**, Xu S, Wang H, Zhang J, Chen Z, Pan L, Wang J, Wei X, Xie H, Zhou L, Zheng S, Xu X. Enhancing the Efficacy and Safety of Doxorubicin against Hepatocellular Carcinoma through a Modular Assembly Approach: The Combination of Polymeric Prodrug Design, Nanoparticle Encapsulation, and Cancer Cell-Specific Drug Targeting. *ACS Appl Mater Interfaces* 2018; **10**: 3229-3240 [PMID: 29313660 DOI: 10.1021/acsami.7b14496]
  - 96 **Wang J**, Wang H, Li J, Liu Z, Xie H, Wei X, Lu D, Zhuang R, Xu X, Zheng S. iRGD-Decorated Polymeric Nanoparticles for the Efficient Delivery of Vandetanib to Hepatocellular Carcinoma: Preparation and in Vitro and in Vivo Evaluation. *ACS Appl Mater Interfaces* 2016; **8**: 19228-19237 [PMID: 27381493 DOI: 10.1021/acsami.6b03166]
  - 97 **Li L**, Tang F, Liu H, Liu T, Hao N, Chen D, Teng X, He J. In vivo delivery of silica nanorattle encapsulated docetaxel for liver cancer therapy with low toxicity and high efficacy. *ACS Nano* 2010; **4**: 6874-6882 [PMID: 20973487 DOI: 10.1021/nn100918a]
  - 98 **Ao M**, Xiao X, Ao Y. Low density lipoprotein modified silica nanoparticles loaded with docetaxel and thalidomide for effective chemotherapy of liver cancer. *Braz J Med Biol Res* 2018; **51**: 1-10 [PMID: 29513882 DOI: 10.1590/1414-431X20176650]
  - 99 **Varshosaz J**, Farzan M. Nanoparticles for targeted delivery of therapeutics and small interfering RNAs in hepatocellular carcinoma. *World J Gastroenterol* 2015; **21**: 12022-12041 [PMID: 26576089 DOI: 10.3748/wjg.v21.i42.12022]
  - 100 **Huang KW**, Lai YT, Chern GJ, Huang SF, Tsai CL, Sung YC, Chiang CC, Hwang PB, Ho TL, Huang RL, Shiue TY, Chen Y, Wang SK. Galactose Derivative-Modified Nanoparticles for Efficient siRNA Delivery to Hepatocellular Carcinoma. *Biomacromolecules* 2018; **19**: 2330-2339 [PMID: 29808997 DOI: 10.1021/acs.biomac.8b00358]
  - 101 **Wu JY**, Wang ZX, Zhang G, Lu X, Qiang GH, Hu W, Ji AL, Wu JH, Jiang CP. Targeted co-delivery of Beclin 1 siRNA and FTY720 to hepatocellular carcinoma by calcium phosphate nanoparticles for enhanced anticancer efficacy. *Int J Nanomedicine* 2018; **13**: 1265-1280 [PMID: 29551896 DOI: 10.2147/IJN.S156328]
  - 102 **Zhao P**, Li M, Wang Y, Chen Y, He C, Zhang X, Yang T, Lu Y, You J, Lee RJ, Xiang G. Enhancing anti-tumor efficiency in hepatocellular carcinoma through the autophagy inhibition by miR-375/sorafenib in lipid-coated calcium carbonate nanoparticles. *Acta Biomater* 2018; **72**: 248-255 [PMID: 29555460 DOI: 10.1016/j.actbio.2018.03.022]
  - 103 **Xue H**, Yu Z, Liu Y, Yuan W, Yang T, You J, He X, Lee RJ, Li L, Xu C. Delivery of miR-375 and doxorubicin hydrochloride by lipid-coated hollow mesoporous silica nanoparticles to overcome multiple drug resistance in hepatocellular carcinoma. *Int J Nanomedicine* 2017; **12**: 5271-5287 [PMID: 28769563 DOI: 10.2147/IJN.S135306]
  - 104 **Lai Z**, Tan J, Wan R, Zhang Z, Hu Z, Li J, Yang W, Wang Y, Jiang Y, He J, Yang N, Lu X, Zhao Y. An 'activatable' aptamer-based fluorescence probe for the detection of HepG2 cells. *Oncol Rep* 2017; **37**: 2688-2694 [PMID: 28339076 DOI: 10.3892/or.2017.5527]
  - 105 **Hu Z**, Tan J, Lai Z, Zheng R, Zhong J, Wang Y, Li X, Yang N, Li J, Yang W, Huang Y, Zhao Y, Lu X. Aptamer Combined with Fluorescent Silica Nanoparticles for Detection of Hepatoma Cells. *Nanoscale Res Lett* 2017; **12**: 96 [PMID: 28176286 DOI: 10.1186/s11671-017-1890-6]
  - 106 **Kashefi-Kheyrabadi L**, Mehrgardi MA, Wiechec E, Turner AP, Tiwari A. Ultrasensitive detection of human liver hepatocellular carcinoma cells using a label-free aptasensor. *Anal Chem* 2014; **86**: 4956-4960 [PMID: 24754473 DOI: 10.1021/ac500375p]
  - 107 **Kong H**, Ju E, Yi K, Xu W, Lao YH, Cheng D, Zhang Q, Tao Y, Li M, Ding J. Advanced Nanotheranostics of CRISPR/Cas for Viral Hepatitis and Hepatocellular Carcinoma. *Adv Sci (Weinh)* 2021; e2102051 [PMID: 34665528 DOI: 10.1002/adv.202102051]



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