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

Rusdina Bte Ladju, Zulvikar Syambani Ulhaq, Gita Vita Soraya

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 nanotheranostic modalities as a promising option to address the key challenges present in HCC management.
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 have 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 462:1:185.8 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.

**POTENTIAL OF NANOTHERANOSTICS FOR PRECISION CANCER MEDICINE**

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], lactosaccharide-based nanoparticles[44], metallic nanoparticles[45], gold nanoparticles[46], silver nanoparticles[47], dendrimer and copolymer-based nanoparticles[48], lipid-based nanomaterials[49], magnetic nanoparticles[50] iron oxide nanoparticle[51], mesoporous silica nanoparticle[52] and
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. Nanotheranostic not only provides the means for early diagnostic tools, nanomaging-therapeutic integrated medicine, targeted-therapy and tumor-specific nano-delivery agent, it also holds potential for real-time monitoring of drug response, and reduce side effects and drug toxicity in patients as shown in Figure 2.

Successful demonstration of nanotheranostics for diagnostics and targeted therapy has been shown by Roy et al. in which highly sensitive, polymer-modified gadolinium-doped iron oxide-based T contrast agents were used for successful methotrexate drug delivery. In the second application, nanotheranostics have been utilized for simultaneous imaging and cancer monitoring. An auto-fluorescent platform, constructed from a positively charged amphiphilic polymer polyethylene-imine-polylactide, was utilized to simultaneously load the antiangiogenesis agent cobretrastatins 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. 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. Nanoparticles can also be engineered to provide multimodal imaging which utilizes modified ultrasmall Ag$_2$Se 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. utilized Janus-type γ-Fe$_3$O$_4$/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 showed the use of immunotherapy-based theranostics to specifically target metastatic tissue. In said study, magnetic-responsive immunostimulatory nanoagents were added with quantum dots nanoparticle.
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 immuno-therapy.

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 effectiveness 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 nanoplatform 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-
| 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 via auto-fluorescence nanoparticles | [62]   |
|                                    | Real-time monitoring and tumor targeting via 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 nanoplatform 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.

| 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 4th 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
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 revolu-
tionized 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 nanother-
anostic 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 nanoplatfoms 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, Tsourofillos G, Garmpi A, Delleadetsima I, Kontzoglou K, Kourakis 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, Altekruse 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, Hoshiya Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018; 68: 526-549 [PMID: 28890995 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: 22332632 DOI: 10.1016/S0140-6736(11)61347-0]
9. Tang A, Hallouch O, Chunyak V, Kamaya A, Sirin 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 (Poln) 2018; 22: 141-150 [PMID: 30453585 DOI: 10.5114/co.2018.79841]
11. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 85-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
12. Mittal S, Kramer JR, Omino R, Chayanapatkul 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, Mokeel 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, Maucort-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. Baeecker 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, Kucukkuglu O, Alfinbas 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, Wang XQ, Kisseleva T, Wang-Rodriguez J, Onogeko WM. Alcohol and hepatitis virus dysregulated IncRNAs 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, Plymouth 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 Gastrointestin 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:
Ladju RB et al. Nanotheranostics for hepatocellular carcinoma

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: 2074-2083 [PMID: 19039300 DOI: 10.1002/hep.22580]

24 Hui AN, Makucchi M. Molecular basis of multistep hepatocarcinogenesis: genetic and epigenetic events. *Scand J Gastroenterol* 1999; 34: 737-742 [PMID: 10499472 DOI: 10.1080/003655299750025692]

25 Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; 31: 339-346 [PMID: 12149612 DOI: 10.1038/ng8002-339]

26 Feltelsson MA, Sun B, Satiroglu Tufan NL, Liu J, Pan J, Lian Z. Genetic mechanisms of hepatocarcinogenesis. *Oncoogene* 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, Vibeert 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/ter.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, Okhubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makucchi 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 JIG, Macias RIR, Monte MJ, Romero MR, Asensio M, Cives-Losada C, Temprano AG, Espinosa-Escudero R, Reviejo M, 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 [DOI: 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: 10.4103/0975-7466.137239]

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.0c001785]

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, Akeh M, Uji H, Kobuchi H, Sasaki T, Ozeki E, Matsuara E. A Novel 18F-Zr-labeled DDS Device Utilizing Human IgG Variant (sFv): "Lactosome" Nanoparticle-Based Theranostics for PET Imaging and Targeted Therapy. *Life (Basel)* 2021; 11 [PMID: 33670777 DOI: 10.3390/life11020158]
Fe2O3/SiO2-based nanotheranostics for dual-modal imaging and enhanced synergistic cancer therapy. 

Zhang Y, Du K, Jiang Y, etc. 2017. Biomaterials, 10.1016/j.biomaterials.2017.08.037

Nanoclusters Hybrid for Multimodal Imaging and Drug Delivery. 

10.1021/nn403617j

mesoporous silica nanoparticles. 

vivo tumor targeting and image-guided drug delivery with antibody-conjugated, radiolabeled nanoparticles for magnetic resonance cancer theranostics. 

Theranostics 2018; 8: 6322-6349 DOI: 10.7150/thno.27828

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]

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, Grumesezcu AM. Materials for Biomedical Engineering. Elsevier, 2019: 371–396

Zhang S, Yu X, Qian Y, Chen W. Multifunctional magnetic iron oxide nanoparticles: an advanced platform for cancer theranostics. 

Theranostics 2020; 10: 6278-6309 [PMID: 32483453 DOI: 10.7150/thno.42564]

Tao Y, Wang J, Xu X. Emerging and Innovative Theranostic Approaches for Mesoporous Silica Nanoparticles in Hepatocellular Carcinoma: Current Status and Advances. 

Front Bioseng Biotechnol 2020; 8: 184 [PMID: 32211399 DOI: 10.3389/fbioe.2020.00184]

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]

Mura S, Couverp. Nanotheranostics for personalized medicine. 

Adv Drug Deliv Rev 2012; 64: 1394-1416 [PMID: 22728642 DOI: 10.1016/j.addr.2012.06.006]

Sonali, Viswanath MK, Singh RP, Agrawal P, Mehata AK, Pawde DM, Narendra, Sonkar R, Mutha MS. Nanotheranostics: Emerging Strategies for Early Diagnosis and Therapy of Brain Cancer. 

Nanotheranostics 2018; 2: 70-86 [PMID: 29291164 DOI: 10.7150/thno.21638]

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]

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]

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

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]

Kundu P, Singh D, Singh A, Sahoo SK. Cancer Nanotheranostics: A Nanomedical Approach for Cancer Therapy and Diagnosis. 

Anticancer Agents Med Chem 2020; 20: 1288-1299 [PMID: 31429694 DOI: 10.2174/1871520619666190820145930]

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]

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]

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/nn304367r]

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.7b02046]

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]

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: 166-177 [PMID: 28866477 DOI: 10.1016/j.biomaterials.2017.08.077]

Du K, Lei P, Dong L, Zhang M, Gao X, Yao S, Feng J, Zhang H. In situ decorating of ultrasmall Ag2Se 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]

Zhang Y, Wan Y, Liao Y, Hu Y, Jiang T, He T, Bi W, Lin J, Gong P, Tang L, Huang P. Janus γ-Fe2O3/SiO2-based nanotheranostics for dual-modal imaging and enhanced synergistic cancer
starvation/chemodynamic therapy. Science Bulletin 2020; 65: 564-572 [DOI: 10.1016/j.scb.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]

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: 32030873]. DOI: 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]

72 Dehghani S, Hosseini M, Haghighi 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]. DOI: 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]. DOI: 10.1016/j.jconrel.2019.03.019

74 Parhi P, Sahoo SK. Trastuzumab guided nanotheranostics: A lipid based multifunctional nanof ormulation for targeted drug delivery and imaging in breast cancer therapy. J Colloidal Interface Sci 2015; 451: 198-211 [PMID: 25897856]. DOI: 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]. DOI: 10.1021/acsami.9b11060

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]. DOI: 10.1016/j.msec.2020.110786

77 Unnikrishnan BS, Sen A, Preethi GU, Joseph MM, Maya S, Shiji R, Anusree KS, Sreeleekka TT. Folic acid-appended galacto-oligolucan-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]. DOI: 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]. DOI: 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: 28012391]. DOI: 10.1016/j.ejpb.2016.12.009

80 Siňafaka PI, Okur NÇ, Karantzas ID, Okur ME, Ğündoğdu 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]. DOI: 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, Wu 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]. DOI: 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]. DOI: 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 tripleplex therapy in vitro and in vivo. J Control Release 2014; 192: 192-201 [PMID: 25034575]. DOI: 10.1016/j.jconrel.2014.06.037

84 Lv Y, Li J, Chen H, Bai Y, Zhang L. Glycyrrhetinic acid-functionalized mesoporous silica nanoparticles as hepatocellular carcinoma-targeted drug carrier. Int J Nanomedicine 2017; 12: 4361-4370 [PMID: 28652738]. DOI: 10.2147/IJN.S135626

85 Xu X, Wu C, Bao 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]

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 nanoocomplex. Biomaterials 2017; 143: 1-16 [PMID: 28755539]. DOI: 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]. DOI: 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 Nanodot 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, Kumar S, Kgd M, Momim 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, Sithichai 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: 3239-3240 [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 Vandanatin 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 doxetaxel 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 A, Ao Y. Low density lipoprotein modified silica nanoparticles loaded with doxetaxel 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, Shieue TY, Chen Y, Wang SK. Galactose Derivative-Modified Nanoparticles for Efficient siRNA Delivery to Hepatocellular Carcinoma. Biomacromolecules 2018; 19: 2330-2339 [PMID: 29808897 DOI: 10.1021/acs.biomac.8b00358]

101 Wu JW, Yang 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.S153506]

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: 28339976 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. Apamter Combined with Fluorescent Silica Nanoparticles for Detection of Hepatoma Cells. Nanoscale Res Lett 2017; 12: 96 [PMID: 28176288 DOI: 10.1186/s11671-017-1890-6]

106 Kashefi-Kheyraabadi 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/ads.202102051]
