Cancer Biol Med 2016. doi: 10.20892/j.issn.2095-3941.2016.0065

REVIEW

OPEN ACCESS

Nanomaterials incorporated ultrasound contrast agents for cancer theranostics

Lei Fu[1], Heng-Te Ke[2]

[1]Center of Systems Medicine, Chinese Academy of Medical Sciences, Suzhou Institute of Systems Medicine, Suzhou 215123, China; [2]College of Pharmaceutical Sciences, Soochow University, Suzhou 215123, China

ABSTRACT Nanotechnology provides various nanomaterials with tremendous functionalities for cancer diagnostics and therapeutics. Recently, theranostics has been developed as an alternative strategy for efficient cancer treatment through combination of imaging diagnosis and therapeutic interventions under the guidance of diagnostic results. Ultrasound (US) imaging shows unique advantages with excellent features of real-time imaging, low cost, high safety and portability, making US contrast agents (UCAs) an ideal platform for construction of cancer theranostic agents. This review focuses on the development of nanomaterials incorporated multifunctional UCAs serving as theranostic agents for cancer diagnostics and therapeutics, via conjugation of superparamagnetic iron oxide nanoparticles (SPIOs), CuS nanoparticles, DNA, siRNA, gold nanoparticles (GNPs), gold nanorods (GNRs), gold nanoshell (GNS), graphene oxides (GOs), polypyrrole (PPy) nanocapsules, Prussian blue (PB) nanoparticles and so on to different types of UCAs. The cancer treatment could be more effectively and accurately carried out under the guidance and monitoring with the help of the achieved theranostic agents. Furthermore, nanomaterials incorporated theranostic agents based on UCAs can be designed and constructed by demand for personalized and accurate treatment of cancer, demonstrating their great potential to address the challenges of cancer heterogeneity and adaptation, which can provide alternative strategies for cancer diagnosis and therapeutics.

KEYWORDS Cancer; theranostics; ultrasound contrast agents; nanomaterials; nanomedicine

Introduction

Nanotechnology is a multidisciplinary research field involving physics, chemistry, biology, engineering, material science and clinical medicine, providing a variety of nanoscale materials with extraordinary features for diagnostics and therapeutics of cancer[1-6]. In the recent years, a unique cancer treatment strategy, theranostics, has been developed by combination of imaging diagnosis and imaging guided therapeutic interventions to enable accurate detection and personalized treatment of cancer with high efficacy[7-12]. Theranostics can deliver both diagnostic and imaging-guided therapeutic functions simultaneously, which can address the challenges of cancer heterogeneity and adaptation[13,14]. Therefore, nanomaterials with excellent nature of easy functionalization and significant biocompatibility as well as their optical, electronic, magnetic and structural properties, are ideal candidates as theranostic nanomedicine for cancer diagnosis and therapy. Furthermore, the combination of various imaging modalities could make it possible to carry out cancer therapy under the guidance of multi-modal contrast imaging, achieving visualized and personalized treatment of cancer[15,16].

There are several medical imaging methods for clinical cancer diagnosis, including X-ray computed tomography (CT), ultrasound (US) imaging, magnetic resonance imaging (MRI), positron emission computed tomography (PET) and so on. Among all the diagnostic imaging techniques, US has its unique advantage due to its features of real-time, low cost, and high safety[17], making it the ideal candidate for imaging guided cancer therapy. With the use of ultrasound contrast agents (UCAs), the resolution and sensitivity of clinical US imaging have made great improvements[18-20]. Typical UCAs are microbubbles (MBs) that composed of an inner gaseous core with a thin shell coating. The shell materials including proteins[21], saccharides[22], surfactants[23], polymers[24] and lipids[25] are used to form a protective layer outside the inner gas cores like air, nitrogen, sulfur hexafluoride (SF_6) and perfluorocarbons (PFCs)[26-28].

Two or more biomedical imaging techniques are usually

Correspondence to: Heng-Te Ke
E-mail: htke@suda.edu.cn
Received July 30, 2016; accepted September 13, 2016.
Available at www.cancerbiomed.org

applied together in clinic to reach more reliable diagnostic results, since each imaging modality has its specific advantages as well as limitations. Therefore, in the recent years, the idea of using multimodal imaging modalities in combination has attracted the attention of researchers[29]. US could display real-time images, nevertheless, its spatial and anatomical resolution is relatively poor compared to other imaging methods. The disadvantages of US might be overcomed by the integration of other imaging modalities with excellent spatial and anatomical resolution. Therefore, multimodal imaging agents composed of UCAs incorporated with other imaging probes could provide more detailed and accurate diagnostic results for better guidance of cancer treatment. Furthermore, by integration of proper nanomaterials with therapeutic functionalities, theranostic agents based on UCAs could be constructed for cancer treatment.

In this review, we will focus on the latest development on nanomaterials incorporated multifunctional UCAs serving as theranostic agents for multimodal imaging and cancer therapy, via combination of different types of UCAs and nanomaterials including superparamagnetic iron oxide nanoparticles (SPIOs), CuS nanoparticles, DNA, gold nanoparticles (GNPs), gold nanorods (GNRs), gold nanoshell (GNS), graphene oxides (GOs), Prussian blue (PB) nanoparticles, and polypyrrole (PPy) nanocapsules, etc. (**Figure 1**). This review will provide a comprehensive design and fabrication of nanomaterials incorporated UCAs for cancer theranostics.

Theranostic agents based on protein UCAs

Feinstein et al.[30] reported in 1984 that the albumin in the blood improved the stability of hand-made MB UCAs and sonication produced more stable MBs with controlled size. It resulted in the first commercial UCA, Albunex[31] (Molecular Biosystems), which consisted of air-filled albumin MBs ranging from 1 to 15 μm with more than 95% being smaller than 10 μm. Albumin-based UCAs are widely used in clinical diagnosis and research field.

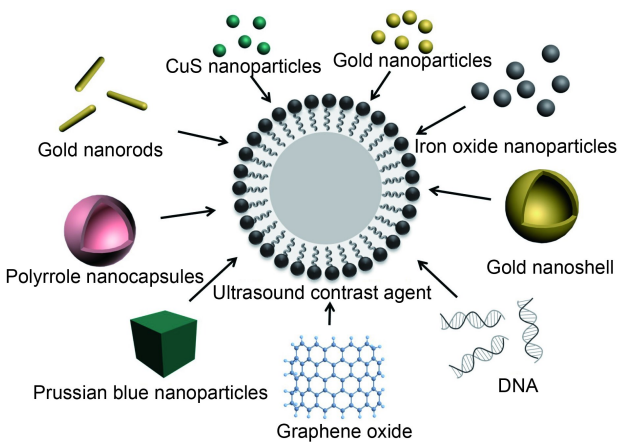

Figure 1 Various functional nanomaterials can be incorporated into UCAs.

Gold nanomaterials exhibit good biocompatibility as well as magnificent optical and electronic properties, making them possible to be used in biological and medical applications[32]. GNRs have well-defined shapes and their longitudinal plasmon resonances (LPRs) can be finely tuned as a function of aspect ratio to the near infrared (NIR) region, a spectral window which permits photons to penetrate biological tissues with relatively high transmittivity[33]. Recently, Wang and co-workers[34] developed GNRs loaded albumin microbubbles (AuMBs) for combined US and photoacoustic imaging and photothermal therapy. AuMBs were fabricated by sonication of the solution containing 2.67 nM GNRs, 2% human serum albumin, 0.04% (w/v) avidin and filling with PFC (C_3F_8) gas, then modified via biotin-avidin technique to result in antimouse VEGFR2 targeted AuMBs. *In vivo* ultrasonography revealed that the targeted AuMBs could identify the angiogenesis region in the tumor and extend the retention time for longer US imaging. The GNRs could induce photoacoustic imaging and thermal therapy under NIR irradiation, demonstrating the combined diagnostic and therapeutic properties of AuMBs.

Theranostic agents based on lipid/surfactant UCAs

Lipids[25,35] and surfactants[23] are extensively used as shell materials to fabricate MBs UCAs due to their capabilities to lower the surface tension and stabilize MBs via forming a coating layer[19]. Amphiphilic molecules can self-assemble into a monolayer shell at the interface between the gas core and surrounding aqueous medium to form gas-filled MBs. When the MBs are exposed to US, they start to cavitate. The microstreams and shock waves generated during cavitation may lead to a local release of drugs loaded on the MBs. At the same time, temporary perforate cell membranes (sonoporation) may occur to result in the intracellular delivery of the released drugs. Furthermore, the microjets and shock waves could also permeabilize blood vessels, allowing the release of high molecular weight drugs and nanoparticles[36-39]. Therefore, MBs with anticancer drugs or functional nanomaterials payload could serve as efficient US

triggered delivery system for imaging guided cancer treatment.

SPIOs are widely applied T2-weighted MRI contrast agents, which can provide a safe and strong negative contrast enhancement of the target lesion in MRI due to their high susceptibility and biocompatibility[40-43]. Fan's group developed multi-functional phospholipid coated C_3F_8 encapsulated MBs loaded with therapeutic agent (doxorubicin, DOX) and MRI contrast agents SPIOs via adapted thin-film hydration method[44]. The blood-brain barrier (BBB) can be reversibly opened without damaging the neurons by US MB cavitation within the cerebral microvasculature for delivery of therapeutic compounds to the brain[45]. Thus, the *in vivo* experiments proved that the DOX-SPIO-MBs could temporarily open the BBB and perform drug delivery to the brain due to cavitation upon the focused US exposure. Besides, they can carry out dual modal MRI/US contrast imaging diagnosis, and magnetic targeting to achieve enhanced drug delivery for imaging guided tumor treatment. Based on this study, they further fabricated a therapeutic SPIO-DOX (SD) complex that can be conjugated to MBs (SD-MB). The SD-MB could targeted release SD complexes through BBB under focused US exposure to allow dual modal brain imaging and drug delivery for chemotherapy[46]. Moreover, their group also incorporated SPIOs into drug-embedded acoustic droplets to allow both magnetism-assisted targeting and MRI guided US-triggered acoustic droplet vaporization, which is a mechanical and chemical theranostic strategy for tumor treatment[47]. The developed theranostic agents may provide a novel strategy for future imaging guided therapy of brain tumors.

MB UCAs have been developed as image-guided promising vehicles of genes for targeted delivery. Sonoporation is an effective method of promoting extravasation of large macromolecules, such as plasmid DNA, to improve delivery to tissue beyond the vasculature[48-50]. Branched polyethylenimine (PEI) was modified with polyethylene glycol (PEG) and thiol. The resulted PEI-PEG was then covalently attached to maleimide groups on lipid MB UCAs. Polyplex-MBs was prepared by loading DNA to achieve increased circulation in the bloodstream and decreased non specific adhesion. A luciferase bioluminescence reporter plasmid DNA was coupled to the PEI-MBs, and site-specific delivery was fulfilled using US applied over the tumor area following bolus injection of the DNA/PEI-MBs, showing over 10-fold higher bioluminescence from the tumor region compared to the untreated[51]. It suggested that the PEI-MB UCAs would offer improved control of DNA loading for US-guided tissue transfection and gene therapy of cancer[52].

siRNA-loaded nanobubbles (siRNA-NBs) were also developed via hetero-assembling strategy by Shuai's group using siRNA-complexed polymeric micelles and gas-cored lipid nanobubbles. Sufficient tumor accumulation of the nanoscale siRNA-NBs can be achieved via the EPR effect, allowing efficient delivery of siRNA micelles into cancer cells with the help of US exposure for imaging guided gene therapy[53]. It indicates that US sensitive micro/nanobubble UCAs with DNA/siRNA payloads could act as potential theranostic platform for US-trigged and guided gene therapy.

CuS nanoparticles could penetrate into the tumor interstitium for efficient ablation of tumor cells due to their NIR absorption and small size[54-56]. Furthermore, the NIR absorption of CuS nanoparticles is derived from d-d transition of Cu^{2+} ions, which is not affected by the solvent or the surrounding environment[54]. Therefore, using surfactant MB ST68[57-60] as a template, CuS nanoparticles loaded MBs (CuS-ST68 MBs) was constructed by depositing photothermal conducting CuS nanoparticles onto the outer surface of gas-filled MBs, which consisted of inert C_3F_8 gas and a monolayer shell of surfactant mixtures of Span 60 and Tween 80. *In vitro* and *in vivo* ultrasonography proved the contrast-enhancement capability of CuS-ST68 MBs. Besides, targeted CuS nanoparticles delivery using US-targeted MB destruction (UTMD)[36,38,61,62] to destroy tumor cells by the photothermal effect could be fulfilled by CuS-ST68 MBs as well (**Figure 2**)[63].

Theranostic agents based on polymeric UCAs

Polymeric microcapsules, typically composed of poly lactic acid (PLA) with outstanding biocompatibility and biodegradability, could serve as UCAs with good US contrast-enhanced capabilities and other advantages: they have good mechanical strength to be stable; they can load either hydrophilic or hydrophobic species or both during the double emulsion fabrication procedure to become functionalized; they are surface-charged and have functional groups on the surface so that they could be easily modified to acquire more utilities such as site-targeted capability[24,64,65].

By constructing echogenic PLA microcapsules employing the water-in-oil-in-water (W/O/W) double emulsion method[24,64,65], GNR-loaded PLA microcapsules have been developed for combined US contrast imaging and photothermal therapy via electrostatic adsorption of GNRs on the microcapsule surfaces under the help of polyelectrolytes[66]. GNS was introduced to substitute GNRs to achieve higher payload of gold nanomaterials on

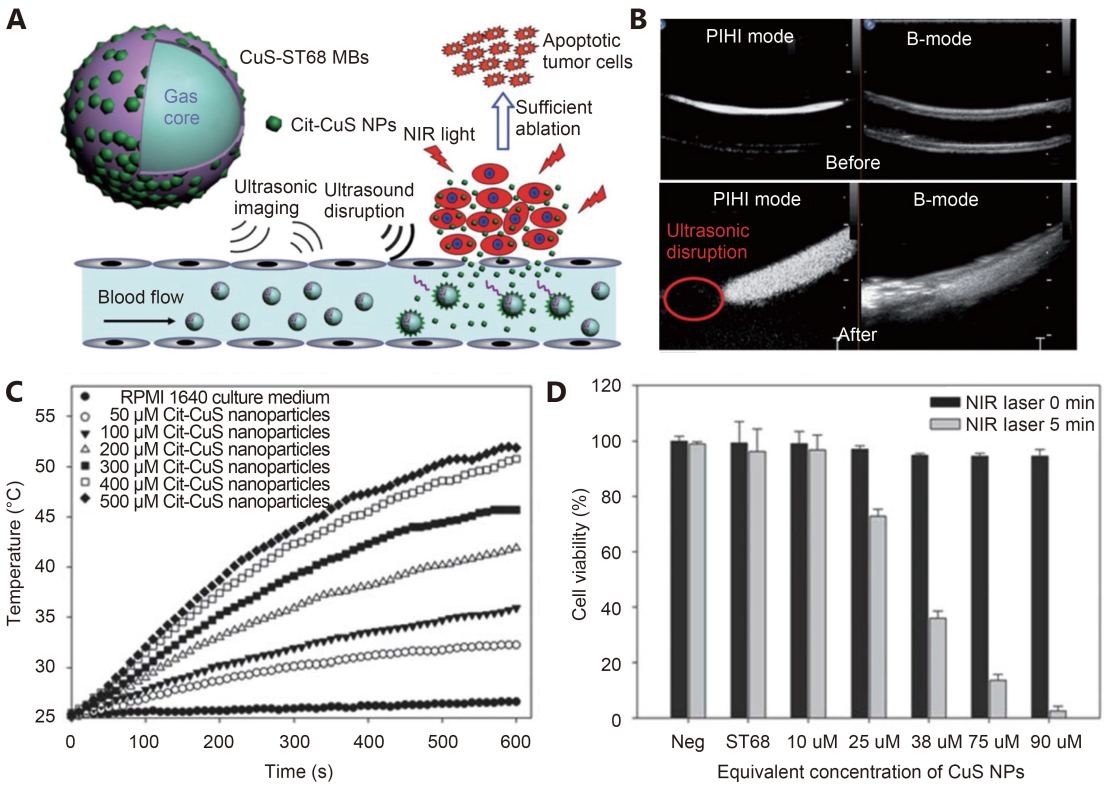

Figure 2 (A) Schematic illustration of combined ultrasonic imaging and enhanced photothermal therapy with CuS-ST68 MBs through UTMD. (B) *In vitro* US contrast-enhanced images in a latex tube before and after CuS-ST68 MBs injection in PIHI contrast mode and B-mode. The CuS-ST68 MBs could be disrupted to lose imaging capability (red circled area) through UTMD upon enhanced US, showing the potential of targeted delivery of CuS NPs to tumor. (C) Concentration-dependent photothermal temperature elevation upon exposure to NIR light (808 nm, 2 W). (D) HeLa cell viability after treatment with different concentrations of CuS-ST68 MBs with or without NIR laser irradiation. Reproduced with permission from Ref. 63. Copyright 2013 Royal Society of Chemistry.

microcapsules. GNS has a spherical dielectric core particle and a thin nanoscale gold shell around with highly tunable plasmon resonance, which determines the absorbing and scattering properties of the composite particles. By controlling the thickness of the gold shell and the diameter of the core, the plasmon resonance and the resulting optical absorption of GNSs can be tuned to the region of NIR, where the absorption of human tissues is minimal and penetration is optimal[67]. The strong optical absorption of nanoshell can rapidly increase the local temperature under the NIR irradiation[68]. Therefore, a novel multifunctional theranostic agent based on gold nanoshelled microcapsules (GNS-MCs) was designed and prepared by the electrostatic adsorption of GNPs on the PLA microcapsule surfaces as seeds, and the formation of GNS by surface seeding method (**Figure 3 A-C**)[69]. The microcapsules can cross pulmonary capillaries and show systemic enhancement. When irradiated with NIR radiation, GNS-MCs could raise the local temperature so that cancer cells were killed with surroundings remains unharmed.

Using BT474 breast cancer xenografted models, GNS-MCs were able to serve as an US enhancer to guide the intratumoral injection and ensure their uniform distribution. *In vivo* studies showed the intratumoral temperature could be heated up to nearly 70 °C for 8 min when treated with GNS-MCs injection with NIR laser irradiation, resulting in the gradual tumor volume decrease with 6 out of 7 mice cured at 17 days after treatment. It demonstrated that US imaging-guided photothermal therapy with theranostic GNS-MCs would be a promising technique for *in situ* treatment of breast cancer (**Figure 3 D and E**)[70].

Although US imaging could display the real-time images with higher contrast under the help of UCAs, the resolution of the US images is relatively poor compared to other imaging methods, and the imaging process can be easily interfered by bone- and gas-filled structures like the brain

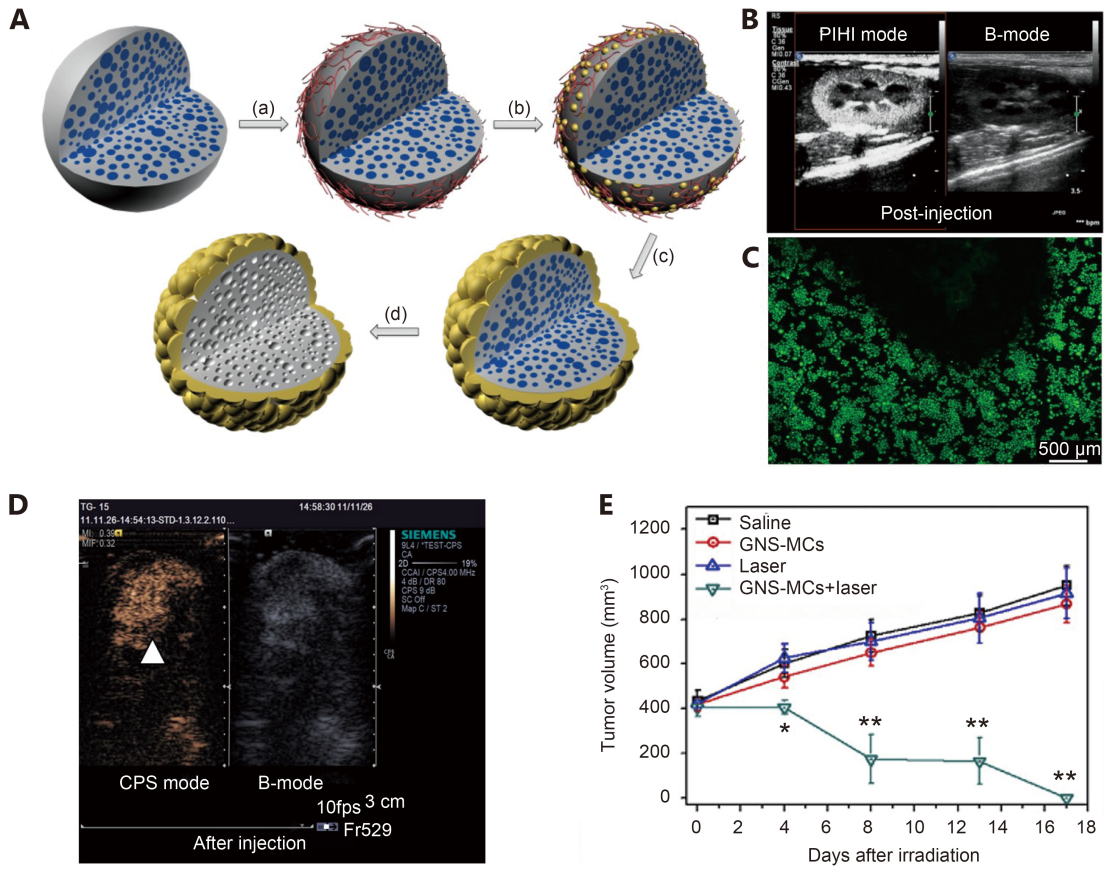

Figure 3 (A) Schematic diagram of the fabrication process of gold nanoshelled microcapsules (GNS-MCs). a: electrostatic adsorption of positive charged poly allylamine hydrochloride (PAH) onto microcapsules generated by double-emulsion method; b: deposition of GNPs onto PAH-coated microcapsules; c: formation of GNSs by the surface-seeding method; d: lyophilization to sublimate the encapsulated water in the inner aqueous phase of the microcapsules to produce small hollow spaces. (B) *In vivo* ultrasonograms in the rabbit right kidney showed US enhancement after administration of GNS-MCs. (C) Fluorescent microscopic images of HeLa cells with both agent and laser treatment stained by calcein AM indicated the photothermal cytotoxicity of GNS-MCs. (D) CPS contrast and B-mode images of the tumor after injection of GNS-MCs. (E) Quantitative measurement of tumor volumes after different treatments of each group demonstrated the excellent anti-tumor efficacy of GNS-MCs under the NIR light irradiation. Reproduced with permission from Ref. 63. Copyright 2013 Royal Society of Chemistry.

and stomach. The drawbacks of US happen to be the merits of CT with excellent spatial resolution based on density. Therefore, it might be a great combination of US and CT for better diagnostics to guide and monitor the cancer therapy. GNPs with large atomic number (z=79), high X-ray absorption coefficient (5.16 cm^2/g at 100 keV), and especially the great biocompatibility and non-toxicity[71-73], could be the ideal candidates for contrast-enhanced CT imaging[74-77]. On the other hand, GOs exhibit superior optical absorption in the NIR region and photothermal conversion, large surface area and lower cost compared with noble metal nanoparticles, making GOs an appealing candidate for photothermal ablation of cancer[78]. Thus, theranostic microcapsules were successfully fabricated by introducing GNPs into PLA microcapsules with depositing GO onto the surface via electrostatic layer-by-layer self-assembly technique. The obtained microcapsules could serve as a contrast agent to simultaneously enhance US and CT imaging greatly both *in vitro* and *in vivo*. As an effective photothermal enhancer, the NIR laser light ablated the tumor completely within 9 days in the presence of the microcapsules and the tumor growth inhibition rate was 83.8% (**Figure 4**)[78].

SPIOs could also be integrated into polymer UCAs for MRI contrast enhancement. Using PLA/PLGA or Pluronic F127 based UCAs as an encapsulation vehicle, SPIOs were loaded by emulsion methods[79], with other functional

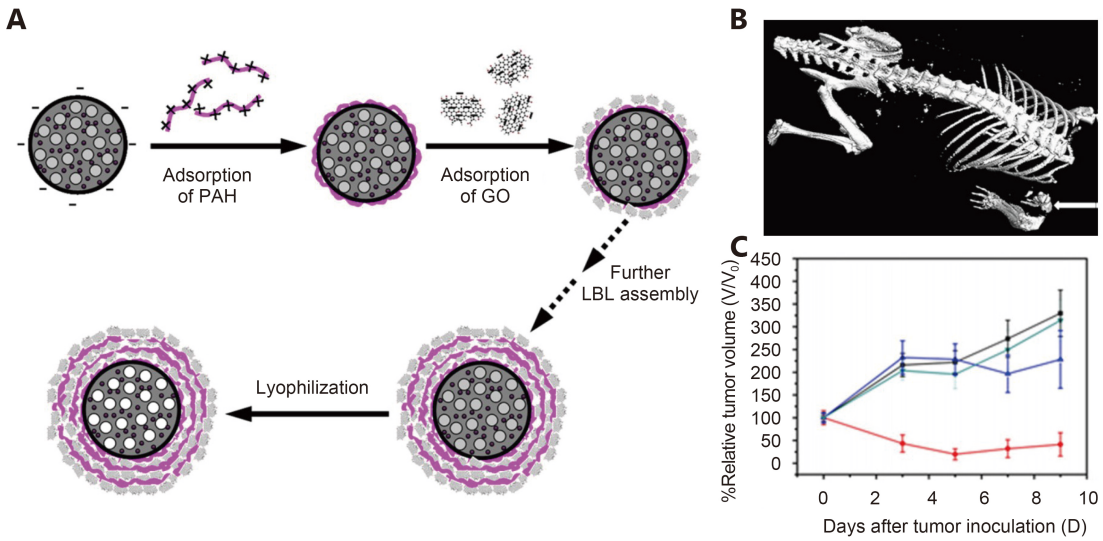

Figure 4 (A) Schematic illustration of the fabrication process of microcapsule of Au@PLA-$(PAH/GO)_n$ by layer-by-layer (LBL) technique. (B) *In vivo* X-ray CT imaging of mice after intramuscular injection of Au@PLA-$(PAH/GO)_2$ microcapsules (the white arrow points to the microcapsule-injected region). (C) Quantitative measurement of tumor volume in mice after different treatments [■saline (black), ●agent+laser (red), ▼saline+laser (green), ▲agent (blue)]. Reproduced with permission from Ref. 63. Copyright 2013 Royal Society of Chemistry.

materials like DOX[80], Carmustine (bis-chloroethylnitrosourea, BCNU)[81] and GOs[82]. Huang et al.[81] designed and prepared SPIO-stabilized and BCNU-loaded nanobubbles based on the thermosensitive polymer F127 and polyacrylic acid (PAA). Both US and MRI contrast enhanced imaging were achieved with the help of the multifunctional contrast agents. Moreover, under the external magnetic targeting, higher US and MR signals could be displayed compared to the same site without magnetic targeting. The tumor growth profile of different treatment revealed that, the tumors exhibited half the growth rate of the control group with injection of BCNU loaded nanobubbles and high intensity focused ultrasound (HIFU) exposure, showing the significant tumor inhibition. The multifunctional system for dual-modal US/MRI imaging guided HIFU therapy and US triggered drug delivery would provide a potential alternative solution for efficient and imaging-guided cancer treatment[82].

PPy materials have received great attention in bioelectronics and biomedical application due to their inherent features, including high conductivity, outstanding stability and good biocompatibility[83-85]. PPy NPs have been demonstrated as an attractive and photothermal agent with high photothermal conversion efficiency for tumor ablation owing to the strong NIR absorption spectrum[86]. Therefore, a photothermal UCA of PPy hollow microspheres (PPyHMs) was first time constructed from the PPy polymer via a facile oil-in-water (O/W) microemulsion method. PPyHMs could generate US contrast consistently with the echo signals for no less than 5 min, and completely ablate the tumor in the presence of NIR laser light[87].

Theranostic agents based on liquid PFC UCAs

PFCs with unique properties such as high oxygen solubility, low surface tension, hydrophobicity and lipophobicity, inertness and absence of metabolism, safety and biocompatibility, have been developed for various medical purposes[88,89]. Because of their high difference of density with air and their poor solubility in water, liquid PFCs such as perfluorooctyl bromide (PFOB) have been encapsulated in the biodegradable and biocompatible polymeric shells to prepare nano-scale UCAs with great stability and echogenicity[90,91]. Unlike blood-pool MB based UCAs, nano-sized UCAs are advantageous for tumor imaging mainly due to their unique size range that promotes a high tissue extravasation rate, resulting in an increased number of agents passing through the vessels feeding the tumor to achieve satisfactory imaging[92,93].

As mentioned above, gold nanomaterials could serve as CT contrast agent due to their high X-ray absorption coefficient. GNS is widely used as "light-activated nanoscopic heater" to

significantly enhance the efficiency of photothermal therapy[94,95]. Therefore, gold nanoshelled PFOB nanocapsule UCAs were developed for US/CT imaging guided photothermal ablation of tumors. It's the first report of GNS serving as the dual-functional nanomaterials for both CT contrast imaging and photothermal tumor ablation[96]. Gold nanoshelled PFOB nanocapsules (PGsP NCs) were constructed by the same gold seeding method[69] on the PFOB nanocapsules generated via an adapted oil-in-water emulsion solvent evaporation process[90], with surface PEG modification to increase anti-fouling capabilities for long circulation time. *In vivo* US/CT contrast imaging was successfully carried out through intravenous injection of PGsP NCs. Using human glioblastoma tumor-bearing nude mice as xenograft models, the local temperature of tumors could be heated up to about 60 ℃ with the irradiation of 808 nm NIR laser, and the temperature lasted more than 7 min during the whole 10 min exposure, ensuring the effective thermal ablation of tumors. On 16th day after treatment, the tumor shrunk 67.6% in tumor size with 5 out of 8 mice cured. Compared with control group, the tumor growth was inhibited by 96.7%, suggesting great treatment effect of PGsP NCs induced photothermal tumor ablation[96].

By incorporation of SPIOs into the gold nanoshelled PFOB nanocapsules, a novel theranostic nano-UCA, PGS-SP NCs were obtained for dual-modal US/MRI contrast imaging guided photothermal therapy[97]. PGS-SP NCs could be not only used for the guidance under US contrast imaging, but also applicable via intravenous administration to targetly accumulate in the tumor sites for MRI guidance due to the EPR effect. The abnormalities in the tumor tissue lead to higher permeability of tumor vessels to the nanocapsules compared with normal vessels, and the impaired clearance of the nanocapsules from the interstitial space of the tumor could result in targeted accumulation on tumor sites (due to longer retention enhanced by PEGylation)[6]. The targeted accumulated nanocapsules can display the tumor areas to guide the NIR laser irradiation for photothermal ablation of tumors without damaging the surrounding healthy tissues. The tumor growth was inhibited by 82.2% by two times of intravenous injection of PGS-SP NCs with NIR laser irradiation, suggesting that sufficient accumulation of PGS-SP NCs could trigger the great photothermal effect locally for effective photothermal tumor ablation (**Figure 5**).

Niu et al.[98] developed SPIOs and PFOB co-loaded organic/inorganic hybrid vesicles via facile self-assembly/sol-gel approach for dual-modality US/MR imaging and guided HIFU ablation. With the help of the theranostic agent, the focused US can be precisely located on the VX2 tumor tissue in the liver of rabbits under MRI guidance for enhanced HIFU therapeutic efficacy. Using PPy as loading materials as well as photothermal absorbers, PFOB encapsulated PPy nanocapsules were obtained. Owing to the encapsulated liquid PFOB and strong NIR absorption of PPy polymeric shell, the resulted PPy nanocapsules showed great promise in US imaging guided photothermal ablation of xenografted tumors without inducing any significant side effect[99].

Apart from various organic polymers as protective shells outside the liquid PFC cores, inorganic nanomaterials could also be utilized to form hollow nanostructures with PFC in the inner cavities. Shi's group constructed a nanometer-sized inorganic enhancement agent (MSNC-PFH) for HIFU treatment of cancer, which consists of mesoporous silica nanocapsules (MSNCs) as the shell and encapsulated temperature-sensitive perfluorohexane (PFH) as bubble generator[100]. With exposure to HIFU, PFH bubbles could be generated and released through the mesopore channels of MSNCs for contrast enhanced US imaging, owing to the HIFU-induced local temperature rise. Moreover, HIFU therapeutic efficacy can be significantly enhanced by the generated PFH bubble, which can offer a unique superiority in localized tumor necrosis and drug delivery.

PB is a conventional dye used for hundreds of years. PB nanoparticles have been developed recently for catalysts, contrast agents, drug carriers, photoacoustic tomography and photothermal therapy[101]. Jia et al.[101] fabricated phase transition hydrophobic liquid PFC perfluoropentane (PFP) encapsulated hollow PB nanocubes (HPB-PFP) for cancer theranostics. The PB shell could induce excellent photothermal effect under NIR laser irradiation, resulting in not only superior photothermal therapeutics but also PFP gasfication and bubble formation for enhanced US contrast imaging. *In vivo* tumor imaging demonstrated significant signal enhancement could be observed with HPB-PFP injection and laser exposure. The enhanced US images could be utilized for better diagnosis and guidance of photothermal tumor ablation, making HPB-PFP a potential theranostic nanomedicine for cancer treatment[101].

Summary and perspectives

Numerous functional nanomaterials including SPIOs, CuS nanoparticles, GNPs/GNRs/GNS, DNA, siRNA, GO, PPy nanocapsules and PB nanoparticles have been incorporated to different types of UCAs to obtain additional functionalities for cancer diagnosis and therapeutics. The differences among UCAs for preparation of theranostic agents are shown in **Table 1**. Protein-based UCAs were the first commercial

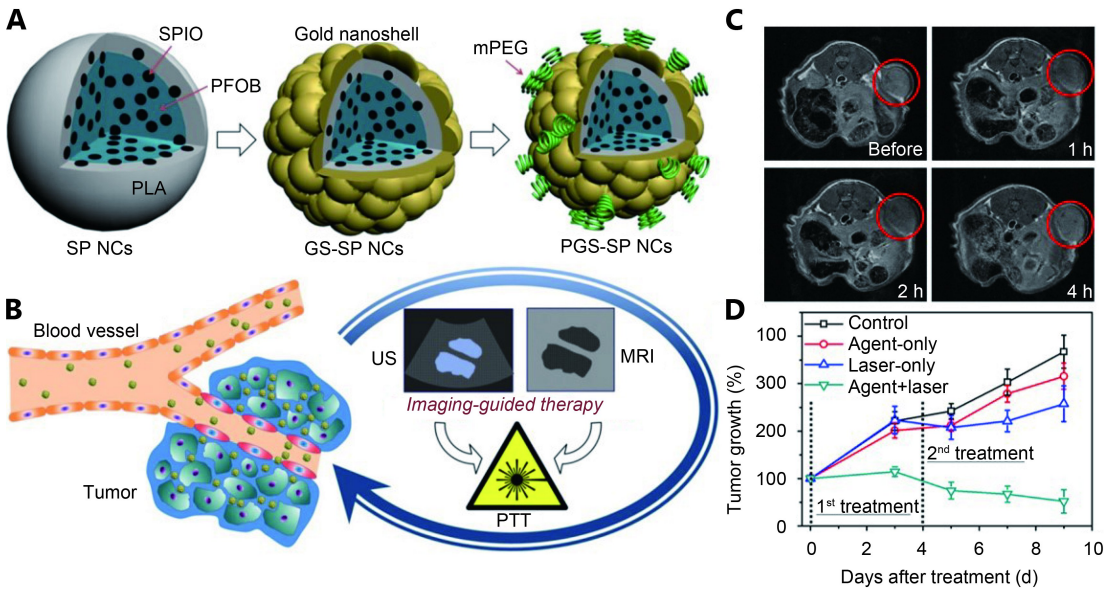

Figure 5 (A) Schematic illustration of the fabrication procedure of PGS-SP NCs. (B) The bimodal US/MRI guided tumor photothermal therapy (PTT) process using PGS-SP NCs. (C) T2-weighted MR images of the tumors at different time points after intravenous injection of the agent for visualization of tumor areas to guide the following photothermal ablation (tumors are highlighted in the red circles). (D) Therapeutic effectiveness expressed as tumor growth rate in each group after treatment in nude mice xenograft models. Reproduced with permission from Ref. 97. Copyright 2014 Ivyspring International Publisher.

Table 1 The comparison among different types of UCAs for the construction of theranostic agents

Types	Stability	Echogenicity	Biocompatibility	Functional modification	Other features	Incorporated nanomaterials
Protein UCAs	Poor	Fair	Good	Poor	-	GNRs[34]
Lipid/surfactant UCAs	Fair	Good	Good	Fair	UTMD	SPIOs[44-47], DNA[51,52], SiRNA[53], CuS[63]
Polymeric UCAs	Good	Fair	Fair	Good	HIFU	GNRs[66], GNS[69,70], GNPs[78], GOs[78,82], SPIOs[81,82], PPy[87]
Liquid PFC UCAs	Fair	Poor	Fair	Fair	Enhanced permeability	GNS[96,97], SPIOs[97,98], PPy[99], Silica[100], PB[101]

products available in the market due to the great biocompatibility. However, the relatively poor stability limits their functional modification, with rare reports in the construction of theranostic agents. Lipid/Surfactant-based UCAs are extensively studied for contrast enhanced imaging and UTMD drug delivery due to the excellent echogenicity and their similarity to conventional drug carriers such as liposomes or micelles. Nevertheless, the nanomaterials could not be easily incorporated into lipid/surfactant UCAs owing to the instability of their soft shells. On the contrary, polymeric UCAs with tremendous stability and easy functional decoration capability were able to load various nanomaterials to prepare multifunctional theranostic agents. Although exhibiting mediocre echogenicity, polymeric UCAs could facilitate HIFU therapy, providing potential alternative functionalities for theranostic agents. Unlike the other three types of blood-pool MB UCAs, liquid PFC encapsulated UCAs with nanomaterial payloads could be generated in nano-scale sizes, leading to enhanced vessel permeability to improve tumor targeting and retention for efficient tumor imaging and therapy. With proper optimization and rational design, the well-constructed nanomaterials incorporated nano-UCAs based on liquid PFC might have great potential for clinical application of cancer theranostics.

The cancer treatment could be more effectively and accurately carried out under the guidance and monitoring via

multimodal imaging with the achieved multifunctional UCAs. In the cancer theranostic procedure, multimodal imaging guidance could display dynamic complementary information about the tumors for planning, targeting, monitoring, controlling and assessing treatment response for the therapeutic treatment, which helps alter the treatment strategy accordingly with personalization and high efficacy. Notably, all the procedures in the whole cancer treatment based on theranostic UCAs could be noninvasive or minimally invasive to avoid unnecessary risks. Moreover, the nanomaterial-loaded UCAs could be designed and developed by demand for personalized treatment of cancer, which makes nanomaterials incorporated multifunctional UCAs involved treatment strategy a potential alternative methodology for noninvasive cancer theranostics.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Grant No. 81501585), the Natural Science Foundation of Jiangsu Province of China (Grant No. BK20150348), the Natural Science Foundation of the Jiangsu Higher Education Institutions of China (Grant No. 15KJB310019), and China Postdoctoral Science Foundation (Grant No. 2015M570475 and 2016T90496).

Conflict of interest statement

No potential conflicts of interest are disclosed.

References

1. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005; 5: 161-71.
2. Wang X, Yang L, Chen ZG, Shin DM. Application of nanotechnology in cancer therapy and imaging. CA Cancer J Clin. 2008; 58: 97-110.
3. Cuenca AG, Jiang H, Hochwald SN, Delano M, Cance WG, Grobmyer SR. Emerging implications of nanotechnology on cancer diagnostics and therapeutics. Cancer. 2006; 107: 459-66.
4. Nie S, Xing Y, Kim GJ, Simons JW. Nanotechnology applications in cancer. Annu Rev Biomed Eng. 2007; 9: 257-88.
5. Farokhzad OC, Langer R. Nanomedicine: developing smarter therapeutic and diagnostic modalities. Adv Drug Deliv Rev. 2006; 58: 1456-9.
6. Barreto JA, O'Malley W, Kubeil M, Graham B, Stephan H, Spiccia L. Nanomaterials: applications in cancer imaging and therapy. Adv Mater. 2011; 23: H18-40.
7. Warner S. Diagnostics plus therapy = theranostics. Scientist. 2004; 18: 38-9.
8. Lammers T, Kiessling F, Hennink WE, Storm G. Nanotheranostics and image-guided drug delivery: current concepts and future directions. Mol Pharm. 2010; 7: 1899-912.
9. Sun D. Nanotheranostics: integration of imaging and targeted drug delivery. Mol Pharm. 2010; 7: 1879.
10. Mura S, Couvreur P. Nanotheranostics for personalized medicine. Adv Drug Deliv Rev. 2012; 64: 1394-416.
11. Chen XY, Gambhlr SS, Cheon J. Theranostic nanomedicine. Acc Chem Res. 2011; 44: 841.
12. Mikhaylov G, Mikac U, Magaeva AA, Itin VI, Naiden EP, Psakhye I, et al. Ferri-liposomes as an MRI-visible drug-delivery system for targeting tumours and their microenvironment. Nat Nanotechnol. 2011; 6: 594-602.
13. Sumer B, Gao JM. Theranostic nanomedicine for cancer. Nanomedicine (Lond). 2008; 3: 137-40.
14. Melancon MP, Zhou M, Li C. Cancer Theranostics with near-infrared light-activatable multimodal nanoparticles. Acc Chem Res. 2011; 44: 947-56.
15. Xie J, Lee S, Chen XY. Nanoparticle-based theranostic agents. Adv Drug Deliver Rev. 2010; 62: 1064-79.
16. Cho NH, Cheong TC, Min JH, Wu JH, Lee SJ, Kim D, et al. A multifunctional core-shell nanoparticle for dendritic cell-based cancer immunotherapy. Nat Nanotechnol. 2011; 6: 675-82.
17. Liu Z, Kiessling F, Gätjens J. Advanced nanomaterials in multimodal imaging: design, functionalization, and biomedical applications. J Nanomater. 2010; 2010: 894303.
18. Cosgrove D. Ultrasound contrast agents: An overview. Eur J Radiol. 2006; 60: 324-30.
19. Xing ZW, Ke HT, Wang JR, Zhao B, Yue XL, Dai ZF, et al. Novel ultrasound contrast agent based on microbubbles generated from surfactant mixtures of Span 60 and polyoxyethylene 40 stearate. Acta Biomater. 2010; 6: 3542-9.
20. Xing ZW, Wang JR, Ke HT, Zhao B, Yue XL, Dai ZF, et al. The fabrication of novel nanobubble ultrasound contrast agent for potential tumor imaging. Nanotechnology. 2010; 21: 145607.
21. Barnhart J, Levene H, Villapando E, Maniquis J, Fernandez J, Rice S, et al. Characteristics of Albunex: air-filled albumin microspheres for echocardiography contrast enhancement. Invest Radiol. 1990; 25 Suppl 1: S162-4.
22. Smith MD, Elion JL, McClure RR, Kwan OL, DeMaria AN. Left heart opacification with peripheral venous injection of a new saccharide echo contrast agent in dogs. J Am Coll Cardiol. 1989; 13: 1622-8.
23. Singhal S, Moser CC, Wheatley MA. Surfactant-stabilized microbubbles as ultrasound contrast agents: stability study of Span 60 and Tween 80 mixtures using a Langmuir trough. Langmuir. 1993; 9: 2426-9.
24. El-Sherif DM, Wheatley MA. Development of a novel method for synthesis of a polymeric ultrasound contrast agent. J Biomed Mater Res A. 2003; 66: 347-55.
25. Hasik MJ, Kim DH, Howle LE, Needham D, Prush DP. Evaluation of synthetic phospholipid ultrasound contrast agents. Ultrasonics. 2002; 40(9): 973-82.

26. Arthur Kort IK. Microbubble formation: *In vitro* and *in vivo* observation. J Clin Ultrasound. 1982; 10: 117-20.
27. Blomley MJK, Cooke JC, Unger EC, Monaghan MJ, Cosgrove DO. Science, medicine, and the future-Microbubble contrast agents: a new era in ultrasound. Br Med J. 2001; 322: 1222-5.
28. Raisinghani A, DeMaria AN. Physical principles of microbubble ultrasound contrast agents. Am J Cardiol. 2002; 90: 3J-7J.
29. Louie AY. Multimodality imaging probes: design and challenges. Chem Rev. 2010; 110: 3146-95.
30. Feinstein SB, Ten Cate FJ, Zwehl W, Ong K, Maurer G, Tei C, et al. Two-dimensional contrast echocardiography. I. *In vitro* development and quantitative analysis of echo contrast agents. J Am Coll Cardiol. 1984; 3: 14-20.
31. Walker R, Wiencek JG, Aronson S, Zaroff J, Glock D, Thisted R, et al. The influence of intravenous Albunex injections on pulmonary arterial pressure, gas exchange, and left ventricular peak intensity. J Am Soc Echocardiogr. 1992; 5: 463-70.
32. Lim YT, Park OO, Jung HT. Gold nanolayer-encapsulated silica particles synthesized by surface seeding and shell growing method: near infrared responsive materials. J Colloid Interf Sci. 2003; 263: 449-53.
33. Tong L, Wei QS, Wei A, Cheng JX. Gold Nanorods as contrast agents for biological imaging: optical properties, surface conjugation and photothermal effects. Photochem Photobiol. 2009; 85: 21-32.
34. Wang YH, Liao AH, Chen JH, Chris Wang CR, Li PC. Photoacoustic/ultrasound dual-modality contrast agent and its application to thermotherapy. J Biomed Opt. 2012; 17: 0450011.
35. Klibanov AL. Targeted delivery of gas-filled microspheres, contrast agents for ultrasound imaging. Adv Drug Deliver Rev. 1999; 37: 139-57.
36. Lindner JR. Microbubbles in medical imaging: current applications and future directions. Nat Rev Drug Discov. 2004; 3: 527-32.
37. Lentacker I, De Smedt SC, Sanders NN. Drug loaded microbubble design for ultrasound triggered delivery. Soft Matter. 2009; 5: 2161-70.
38. Hernot S, Klibanov AL. Microbubbles in ultrasound-triggered drug and gene delivery. Adv Drug Deliver Rev. 2008; 60: 1153-66.
39. Pitt WG, Husseini GA, Staples BJ. Ultrasonic drug delivery--a general review. Expert Opin Drug Deliv. 2004; 1: 37-56.
40. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, et al. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chem Rev. 2008; 108: 2064-110.
41. Yoo D, Lee JH, Shin TH, Cheon J. Theranostic Magnetic Nanoparticles. Accounts Chem Res. 2011; 44: 863-74.
42. Lee JH, Huh YM, Jun YW, Seo JW, Jang JT, Song HT, et al. Artificially engineered magnetic nanoparticles for ultra-sensitive molecular imaging. Nat Med. 2007; 13: 95-9.
43. Ghosh D, Lee Y, Thomas S, Kohli AG, Yun DS, Belcher AM, et al. M13-templated magnetic nanoparticles for targeted *in vivo* imaging of prostate cancer. Nat Nanotechnol. 2012; 7: 677-82.
44. Fan CH, Ting CY, Lin HJ, Wang CH, Liu HL, Yen TC, et al. SPIO-conjugated, doxorubicin-loaded microbubbles for concurrent MRI and focused-ultrasound enhanced brain-tumor drug delivery. Biomaterials. 2013; 34: 3706-15.
45. Unger EC, Porter T, Culp W, Labell R, Matsunaga T, Zutshi R. Therapeutic applications of lipid-coated microbubbles. Adv Drug Deliv Rev. 2004; 56: 1291-314.
46. Fan CH, Cheng YH, Ting CY, Ho YJ, Hsu PH, Liu HL, et al. Ultrasound/magnetic targeting with SPIO-DOX-microbubble complex for image-guided drug delivery in brain tumors. Theranostics. 2016; 6: 1542-56.
47. Wang CH, Kang ST, Yeh CK. Superparamagnetic iron oxide and drug complex-embedded acoustic droplets for ultrasound targeted theranosis. Biomaterials. 2013; 34: 1852-61.
48. Deckers R, Moonen CT. Ultrasound triggered, image guided, local drug delivery. J Control Release. 2010; 148: 25-33.
49. Bohmer MR, Chlon CH, Raju BI, Chin CT, Shevchenko T, Klibanov AL. Focused ultrasound and microbubbles for enhanced extravasation. J Control Release. 2010; 148: 18-24.
50. Klibanov AL, Shevchenko TI, Raju BI, Seip R, Chin CT. Ultrasound-triggered release of materials entrapped in microbubble-liposome constructs: a tool for targeted drug delivery. J Control Release. 2010; 148: 13-7.
51. Sirsi SR, Hernandez SL, Zielinski L, Blomback H, Koubaa A, Synder M, et al. Polyplex-microbubble hybrids for ultrasound-guided plasmid DNA delivery to solid tumors. J Control Release. 2012; 157: 224-34.
52. Jin Q, Wang Z, Yan F, Deng Z, Ni F, Wu J, et al. A novel cationic microbubble coated with stearic acid-modified polyethylenimine to enhance DNA loading and gene delivery by ultrasound. PLoS One. 2013; 8: e76544.
53. Yin T, Wang P, Li J, Zheng R, Zheng B, Cheng D, et al. Ultrasound-sensitive siRNA-loaded nanobubbles formed by hetero-assembly of polymeric micelles and liposomes and their therapeutic effect in gliomas. Biomaterials. 2013; 34: 4532-43.
54. Li Y, Lu W, Huang Q, Huang M, Li C, Chen W. Copper sulfide nanoparticles for photothermal ablation of tumor cells. Nanomedicine (Lond). 2010; 5: 1161-71.
55. Zhang G, Yang Z, Lu W, Zhang R, Huang Q, Tian M, et al. Influence of anchoring ligands and particle size on the colloidal stability and *in vivo* biodistribution of polyethylene glycol-coated gold nanoparticles in tumor-xenografted mice. Biomaterials. 2009; 30: 1928-36.
56. Burns AA, Vider J, Ow H, Herz E, Penate-Medina O, Baumgart M, et al. Fluorescent silica nanoparticles with efficient urinary excretion for nanomedicine. Nano Lett. 2009; 9: 442-8.
57. Wheatley MA, Singhal S. Structural Studies on Stabilized Microbubbles - Development of a Novel Contrast Agent for Diagnostic Ultrasound. React Polym. 1995; 25: 157-66.
58. Wang W, Moser CC, Wheatley MA. Langmuir trough study of surfactant mixtures used in the production of a new ultrasound contrast agent consisting of stabilized microbubbles. J Phys Chem. 1996; 100: 13815-21.

59. Basude R, Duckworth JW, Wheatley MA. Influence of environmental conditions on a new surfactant-based contrast agent: ST68. Ultrasound Med Bio. 2000; 26: 621-8.
60. Wheatley MA, Forsberg F, Dube N, Patel M, Oeffinger BE. Surfactant-stabilized contrast agent on the nanoscale for diagnostic ultrasound imaging. Ultrasound Med Bio. 2006; 32: 83-93.
61. Price RJ, Skyba DM, Kaul S, Skalak TC. Delivery of colloidal, particles and red blood cells to tissue through microvessel ruptures created by targeted microbubble destruction with ultrasound. Circulation. 1998; 98: 1264-7.
62. Bekeredjian R, Chen SY, Frenkel PA, Grayburn PA, Shohet RV. Ultrasound-targeted microbubble destruction can repeatedly direct highly specific plasmid expression to the heart. Circulation. 2003; 108: 1022-6.
63. Zha Z, Wang S, Zhang S, Qu E, Ke H, Wang J, et al. Targeted delivery of CuS nanoparticles through ultrasound image-guided microbubble destruction for efficient photothermal therapy. Nanoscale. 2013; 5: 3216-9.
64. Cui WJ, Bei JZ, Wang SG, Zhi G, Zhao YY, Zhou XS, et al. Preparation and evaluation of poly(L-lactide-co-glycolide) (PLGA) microbubbles as a contrast agent for myocardial contrast echocardiography. J Biomed Mater Res B. 2005; 73: 171-8.
65. El-Sherif DM, Lathia JD, Le NT, Wheatley MA. Ultrasound degradation of novel polymer contrast agents. J Biomed Mater Res A. 2004; 68:71-8.
66. Ke H, Wang J, Dai Z, Jin Y, Qu E, Xing Z, et al. Bifunctional gold nanorod-loaded polymeric microcapsules for both contrast-enhanced ultrasound imaging and photothermal therapy. J Mater Chem. 2011; 21: 5561-4.
67. Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, et al. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. P Natl Acad Sci USA. 2003; 100: 13549-54.
68. Yang J, Lee J, Kang J, Oh SJ, Ko HJ, Son JH, et al. Smart drug-loaded polymer gold nanoshells for systemic and localized therapy of human epithelial cancer. Adv Mater. 2009; 21: 4339-42.
69. Ke H, Wang J, Dai Z, Jin Y, Qu E, Xing Z, et al. Gold-nanoshelled microcapsules: a theranostic agent for ultrasound contrast imaging and photothermal therapy. Angew Chem Int Ed. 2011; 50: 3017-21.
70. Wang S, Dai Z, Ke H, Qu E, Qi X, Zhang K, et al. Contrast ultrasound-guided photothermal therapy using gold nanoshelled microcapsules in breast cancer. Eur J Radiol. 2014; 83: 117-22.
71. Connor EE, Mwamuka J, Gole A, Murphy CJ, Wyatt MD. Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity. Small. 2005; 1: 325-7.
72. Shukla R, Bansal V, Chaudhary M, Basu A, Bhonde RR, Sastry M. Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: A microscopic overview. Langmuir. 2005; 21: 10644-54.
73. Hayat MA. Colloidal gold: principles, methods, and applications. San Diego: Academic Press. 1989.
74. Geso M. Gold nanoparticles: a new X-ray contrast agent. Br J Radiol. 2007; 80: 64-5.
75. Popovtzer R, Agrawal A, Kotov NA, Popovtzer A, Balter J, Carey TE, et al. Targeted gold nanoparticles enable molecular CT imaging of cancer. Nano Lett. 2008; 8: 4593-6.
76. Kim D, Park S, Lee JH, Jeong YY, Jon S. Antibiofouling polymer-coated gold nanoparticles as a contrast agent for *in vivo* x-ray computed tomography imaging. J Am Chem Soc. 2007; 129: 7661-5.
77. Alric C, Taleb J, Le Duc G, Mandon C, Billotey C, Le Meur-Herland A, et al. Gadolinium chelate coated gold nanoparticles as contrast agents for both X-ray computed tomography and magnetic resonance imaging. J Am Chem Soc. 2008; 130: 5908-15.
78. Jin Y, Wang J, Ke H, Wang S, Dai Z. Graphene oxide modified PLA microcapsules containing gold nanoparticles for ultrasonic/CT bimodal imaging guided photothermal tumor therapy. Biomaterials. 2013; 34: 4794-802.
79. Sun Y, Zheng Y, Ran H, Zhou Y, Shen H, Chen Y, et al. Superparamagnetic PLGA-iron oxide microcapsules for dual-modality US/MR imaging and high intensity focused US breast cancer ablation. Biomaterials. 2012; 33: 5854-64.
80. Niu C, Wang Z, Lu G, Krupka TM, Sun Y, You Y, et al. Doxorubicin loaded superparamagnetic PLGA-iron oxide multifunctional microbubbles for dual-mode US/MR imaging and therapy of metastasis in lymph nodes. Biomaterials. 2013; 34: 2307-17.
81. Huang HY, Hu SH, Hung SY, Chiang CS, Liu HL, Chiu TL, et al. SPIO nanoparticle-stabilized PAA-F127 thermosensitive nanobubbles with MR/US dual-modality imaging and HIFU-triggered drug release for magnetically guided *in vivo* tumor therapy. J Control Release. 2013; 172: 118-27.
82. Li XD, Liang XL, Yue XL, Wang JR, Li CH, Deng ZJ, et al. Imaging guided photothermal therapy using iron oxide loaded poly(lactic acid) microcapsules coated with graphene oxide. J Mater Chem B. 2014; 2: 217-23.
83. Jang J, Yoon H. Multigram-scale fabrication of monodisperse conducting polymer and magnetic carbon nanoparticles. Small. 2005; 1: 1195-9.
84. Hong JY, Yoon H, Jang J. Kinetic study of the formation of polypyrrole nanoparticles in water-soluble polymer/metal cation systems: a light-scattering analysis. Small. 2010; 6: 679-86.
85. Oh WK, Yoon H, Jang J. Size control of magnetic carbon nanoparticles for drug delivery. Biomaterials. 2010; 31:1342-8.
86. Zha Z, Yue X, Ren Q, Dai Z. Uniform polypyrrole nanoparticles with high photothermal conversion efficiency for photothermal ablation of cancer cells. Adv Mater. 2013; 25:777-82.
87. Zha Z, Wang J, Qu E, Zhang S, Jin Y, Wang S, et al. Polypyrrole hollow microspheres as echogenic photothermal agent for ultrasound imaging guided tumor ablation. Sci Rep. 2013; 3: 2360.
88. Tran TD, Caruthers SD, Hughes M, Marsh JN, Cyrus T, Winter PM, et al. Clinical applications of perfluorocarbon nanoparticles for molecular imaging and targeted therapeutics. Int J Nanomedicine. 2007; 2: 515-26.

89. Diaz-Lopez R, Tsapis N, Fattal E. Liquid perfluorocarbons as contrast agents for ultrasonography and (19)F-MRI. Pharm Res. 2010; 27: 1-16.
90. Pisani E, Tsapis N, Galaz B, Santin M, Berti R, Taulier N, et al. Perfluorooctyl bromide polymeric capsules as dual contrast agents for ultrasonography and magnetic resonance imaging. Adv Funct Mater. 2008; 18: 2963-71.
91. Pisani E, Tsapis N, Paris J, Nicolas V, Cattel L, Fattal E. Polymeric nano/microcapsules of liquid perfluorocarbons for ultrasonic imaging: physical characterization. Langmuir. 2006; 22: 4397-402.
92. Lanza GM, Wallace KD, Fischer SE, Christy DH, Scott MJ, Trousil RL, et al. High-frequency ultrasonic detection of thrombi with a targeted contrast system. Ultrasound Med Biol. 1997; 23: 863-70.
93. Kwon S, Wheatley MA. Development and characterization of PLA nanodispersion as a potential ultrasound contrast agent for cancer site imaging. Bioengineering Conference, 2005 Proceedings of the IEEE 31st Annual Northeast.
94. Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, et al. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. Proc Natl Acad Sci USA. 2003; 100: 13549-54.
95. Loo C, Lowery A, Halas NJ, West J, Drezek R. Immunotargeted nanoshells for integrated cancer imaging and therapy. Nano Letters. 2005; 5: 709-11.
96. Ke H, Yue X, Wang J, Xing S, Zhang Q, Dai Z, et al. Gold nanoshelled liquid perfluorocarbon nanocapsules for combined dual modal ultrasound/CT imaging and photothermal therapy of cancer. Small. 2014; 10: 1220-7.
97. Ke H, Wang J, Tong S, Jin Y, Wang S, Qu E, et al. Gold nanoshelled liquid perfluorocarbon magnetic nanocapsules: a nanotheranostic platform for bimodal ultrasound/magnetic resonance imaging guided photothermal tumor ablation. Theranostics. 2014; 4: 12-23.
98. Niu D, Wang X, Li Y, Zheng Y, Li F, Chen H, et al. Facile synthesis of magnetite/perfluorocarbon co-loaded organic/inorganic hybrid vesicles for dual-modality ultrasound/magnetic resonance imaging and imaging-guided high-intensity focused ultrasound ablation. Adv Mater. 2013; 25: 2686-92.
99. Zha Z, Wang J, Zhang S, Wang S, Qu E, Zhang Y, et al. Engineering of perfluorooctylbromide polypyrrole nano-/microcapsules for simultaneous contrast enhanced ultrasound imaging and photothermal treatment of cancer. Biomaterials. 2014; 35: 287-93.
100. Wang X, Chen H, Chen Y, Ma M, Zhang K, Li F, et al. Perfluorohexane-encapsulated mesoporous ailica nanocapsules as enhancement agents for highly efficient high intensity focused ultrasound (HIFU). Adv Mater. 2012; 24: 785-91.
101. Jia X, Cai X, Chen Y, Wang S, Xu H, Zhang K, et al. Perfluoropentane-encapsulated hollow mesoporous prussian blue nanocubes for activated ultrasound imaging and photothermal therapy of cancer. ACS Appl Mater Interfaces. 2015; 7: 4579-88.

Cite this article as: Fu L, Ke H. Nanomaterials incorporated ultrasound contrast agents for cancer theranostics. Cancer Biol Med. 2016; 13: 313-24. doi: 10.20892/j.issn.2095-3941.2016.0065