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Janus metallic mesoporous silica nanoparticles: Unique structures for cancer theranostics

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Abstract

Janus metallic mesoporous silica nanoparticles (JMMSNs) possess biphasic geometries of distinct compositions or anisotropic structures that provide unique optical, magnetic, thermal, and electric properties for combined diagnosis and therapy in a potentially synergistic and stimuli-responsive manner. Here, we review the recent progress in the rational design and development of JMMSNs for cancer theranostics. We first introduce magnetic JMMSNs as a multifunctional platform to perform magnetic field-mediated circulating tumor cell isolation and detection, cancer-targeting, magnetic resonance imaging, and hyperthermia therapy. We then detail plasmonic JMMSNs for surface-enhanced Raman scattering-based detection, computed tomography, photoacoustic imaging, and photo- and radio-responsive therapies. Finally, we highlight upconversion JMMSNs for photoactivation-based drug release and therapy, computed tomography, and magnetic resonance imaging. Overall, we summarize the advantages of JMMSNs that make them promising for cancer theranostic applications.

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Introduction

Cancer is the leading cause of morbidity and mortality worldwide and is enormously costly to both patients and society at large [1]. There is a growing interest in applying nanotechnology against cancer by combining therapeutics and diagnostics, which has been termed 'theranostics' [2]. These nanomedicines can modulate the biodistribution and tumor accumulation of systemically administered probes or drugs, thereby offering new avenues for the development of cancer theranostics that display improved efficacy and safety [3]. Among several nanomedicines, mesoporous silica nanoparticles (MSNs) have been extensively used for cancer theranostics because of their attractive features such as large surface area, tunable porous structure, easy surface functionalization, and inherent biocompatibility [4–8]. Given the optical, magnetic, thermal, and electric properties of metallic nanomaterials, hybrid platforms comprising metallic cores and mesoporous silica shells have driven progress in cancer theranostics, including biomarker sensing, drug delivery, molecular imaging, and combined therapy [9–11]. However, several drawbacks are connected with core–shell metallic mesoporous silica nanoparticles (MMSNs), including considerable interference in each metal-based property, and limited stimuli-responsive drug release, which limit their broad applications. The intrinsic limitation of symmetrical structures has prompted the development and application of sophisticated structures with more versatile and orthogonal functions for effective cancer theranostics.

Janus particles, defined by Casagrande and de Gennes after the double-faced Roman mythology god, possess hierarchical structures combining fascinating properties of different parts [12,13]. Although Janus particles combine individual components, their fingerprint physical properties and surface chemistry remain relatively unperturbed, in contrast with core–shell symmetrical structures [14]. In the past few decades, Janus

particles with well-controlled structures have demonstrated great performance in biosensing, bioimaging, and drug delivery [14,15]. Compared to core–shell MMSNs, the signal and functional interference between different metallic materials in imaging and therapy is diminished in Janus structures, thus facilitating cancer detection, multimodal imaging, and combined treatment in an accurate and synergistic way. On the other hand, Janus metallic mesoporous silica nanoparticles (JMMSNs) provide multiple regions for both diagnostic and therapeutic agent loading and exhibit spatiotemporal release in response to separate stimuli. Therefore, JMMSNs hold great potential in constructing multifunctional platforms for more versatile and flexible cancer theranostics (Figure 1). In the current review, recent progress on how the Janus structure of MMSNs facilitates cancer theranostics, including isolation and detection, targeting, imaging, drug delivery, and physical therapy, is summarized. In particular, magnetic, plasmonic, and upconversion JMMSNs with different unique advantages in cancer theranostics are categorized separately. Following this, the comparative performance of JMMSNs and conventional core–shell compartments is discussed in detail. Finally, the challenges and perspectives of JMMSNs toward cancer theranostics are presented.

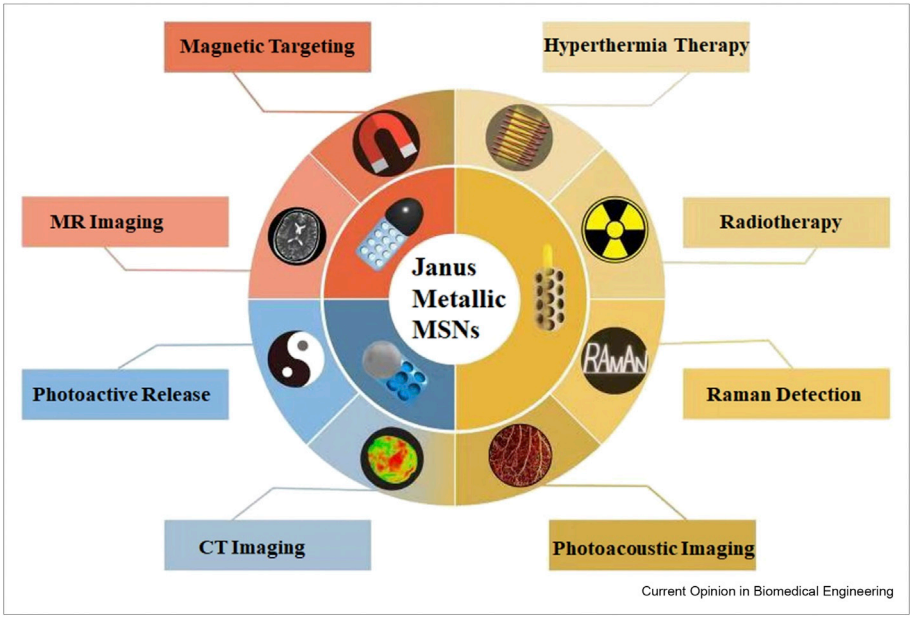
Janus magnetic MSNs for cancer theranostics

Magnetic nanoparticles have generated great interest in the field of cancer theranostics because of their intrinsic magnetic properties that enable them not only to be used as contrast agents in magnetic resonance imaging (MRI), but also as a therapeutic carrier in conjunction with hyperthermia [16]. Specifically, these magnetic nanoparticles have been used as magnetic field-mediated biomarkers, for cell isolation and detection, and for cancer-targeted delivery of both diagnostic and therapeutic agents [17]. In the following sections, some of the latest and most significant reports on the impact of Janus magnetic MSNs with specific magnetic properties on cancer theranostics are summarized.

Magnetic field-based cell isolation and detection

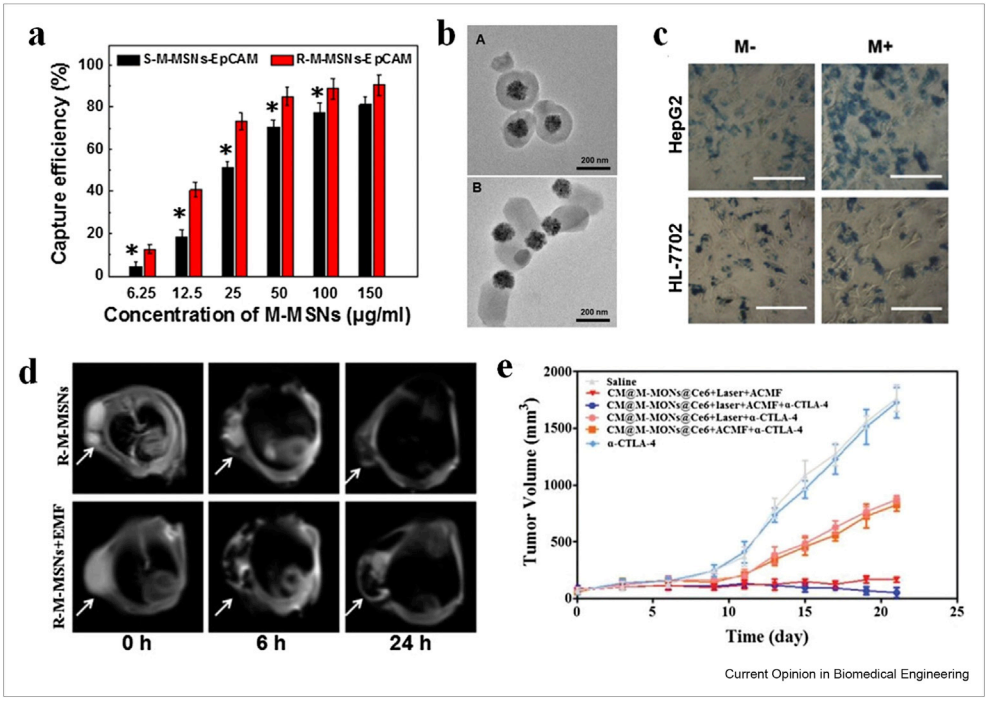
Given their strong magnetic response behavior with less mesoporous silica interfering, Janus magnetic MSNs have been used for magnetic field-based cell isolation and detection in body fluids or samples from cancer patients [18]. Chang et al. reported that anti–EpCAM-functionalized Janus magnetic mesoporous silica nanoparticles exhibited faster enrichment for magnetic isolation and stronger fluorescence detection of circulating tumor cells (CTCs) with the aid of the EpCAM antibody than their core–shell compartments (Figure 2a) [18]. Janus magnetic MSNs (89.6%) exhibited a significantly higher capture efficiency than that of core–shell magnetic MSNs (79.7%) for MCF-7 cells. The better performance of such JMMSNs on the immunomagnetic detection of CTCs in both spiked cells and real clinical blood samples might open new avenues to the rational design of asymmetrical sensors with less magnetic property interference for sensitive and efficient CTC isolation and detection.

Figure 1



Graphical illustrations of eight well-known applications of Janus MMSNs in cancer theranostics. Upper-left: Magnetic JMMSNs. Right: Plasmonic JMMSNs. Bottom-left: Upconversion JMMSNs.

Figure 2



Janus magnetic MSNs have been used for magnetic field-mediated CTC detection, magnetic targeting, MR imaging, and hyperthermia therapy. **(a)** The efficiency of capturing breast cancer cells with different core–shell magnetic MSN or Janus magnetic MSN concentrations. Reproduced from Ref. [18] with permission from American Chemical Society (2018). **(b)** Transmission electron microscopy (TEM) images of (A) sphere-like core–shell magnetic MSNs (200 nm) and (B) rod-like Janus magnetic MSNs (250 × 100 nm). Reproduced from Ref. [20] with permission from Elsevier (2017). **(c)** Uptake of Janus magnetic MSNs with or without EMF exposure on HepG2 or HL-7702 cells. Reproduced from Ref. [22] with permission from Elsevier (2016). **(d)** T_2-weighted images of HepG2 tumor-bearing mice 6 and 24 h after intravenous injection with Janus magnetic MSNs with and without EMF exposure. Reproduced from Ref. [23] with permission from Elsevier (2018). **(e)** The synergistic antitumor effects of Janus magnetic MSN-mediated PDT and magnetic hyperthermia in combination with anti-CTLA4 checkpoint blockade. Reproduced from Ref. [25] with permission from Wiley (2019).

Magnetic field-targeted drug delivery

Nanoparticle morphology is known to influence cellular uptake, endocytosis mechanisms, intercellular transportation, biodistribution, and biocompatibility [19]. Shao et al. systematically revealed that rod-like Janus magnetic MSNs were capable of higher intracellular internalization and tumor accumulation than sphere-like magnetic MSNs via different endocytic pathways, which would give rise to a new generation of JMMSNs with improved sensitivity and efficiency in cancer theranostics (Figure 2b) [20]. 'Magnetic targeting,' a concept proposed in 2010, would yield deeper tumor tissue penetration, a major barrier in cancer theranostics, under an external magnetic field (EMF) [21]. For example, the cellular uptake and tumor accumulation of doxorubicin (DOX)-loaded Janus magnetic MSNs was significantly enhanced on exposure to an EMF, resulting in remarkable tumor suppression and significantly reduced systematic toxicity [22]. Given their higher saturation magnetization values of 58.7 versus 46.9 emu/g, Janus magnetic MSNs also possessed higher drug-loading efficiency, faster drug-release behavior, and enhanced gene delivery with the aid of the EMF than their core–shell counterparts (Figure 2c) [23]. Together, these findings demonstrate the potential of magnetic JMMSNs as efficient and safe carriers for small molecule, gene, and protein delivery in magnetic targeting-based cancer theranostics.

Magnetic-mediated cancer theranostics

In addition to magnetic targeting, magnetic JMMSNs have some inherent advantages for cancer theranostics because of their asymmetric structure and distinct properties that permit specific MR imaging and magnetic hyperthermia [23–28]. Such multifunctional platforms could realize MRI-guided therapy as well as allowing real-time monitoring of drug distribution and therapeutic outcomes. Shao et al. demonstrated the enhanced magnetic targeting effect and the tumor accumulation behavior of magnetic JMMSNs, which was suitable for better MRI in cancer theranostics [23]. The transverse relaxivity (r2) values of Janus magnetic

MSNs (109.1 $mM^{-1}s^{-1}$) were higher than that of core–shell magnetic MSNs (70.0 $mM^{-1}s^{-1}$). The performance of EMF-enhanced gene therapy and magnetic hyperthermia was further explored with long-term monitoring via MRI, achieving the inhibition of MRI-guided combined cancer therapy (Figure 2d). This group used the same carrier to co-deliver the antitumor drug DOX and the anti-inflammatory drug berberine, achieving the inhibition of chemotherapy-triggered cancer repopulation by blocking the Caspase-3-iPLA2-COX-2 axis [24]. They also developed magnetic JMMSNs for MRI and multiple therapies, including photodynamic therapy (PDT), magnetic hyperthermia, and immunotherapy [25]. These biodegradable nanoplatforms exhibited redox/pH-triggered photosensitizer (PS) release accompanied by matrix degradation, resulting in the combination of MRI, PDT, and magnetic hyperthermia *in vitro* and *in vivo*. Synergistic immunogenic cell death boosted tumor-specific immune responses, facilitating the efficient and safe eradication of primary and deeply metastatic tumors (10 times lower in the number of pulmonary metastatic nodules) with the aid of an anti–CTLA-4 antibody (Figure 2e). In another study, Zhang et al. reported JMMSNs conjugated with glucose oxidase for cancer theranostics [26]. This multifunctional platform not only realized dual photoacoustic/T2 MR imaging but also achieved synergistic cancer starvation/chemodynamic therapy in breast cancer models. Thus, magnetic JMMSNs can form a versatile and feasible platform for magnetic-guided cancer theranostics.

Janus plasmonic MSNs for cancer theranostics

The development of plasmonic materials has presented new opportunities in biomedicine [29]. These metallic nanoparticles exhibit intense collective plasmonic resonance and extremely low quantum yield for detection or imaging, while the absorbed photon energy can be converted into heat with high efficiency upon optical illumination [30]. To improve the manipulation of their plasmonic properties and colloid stability, the integration of plasmonic nanoparticles and mesoporous silica has been achieved for cancer theranostics, specifically in optical-responsive drug release and monitoring. In such a scenario, MMSNs composed of plasmonic materials (e.g., gold, silver, etc.) have been widely used as contrast agents for detection and diagnosis, such as surface-enhanced Raman scattering (SERS), computed tomography (CT), and photoacoustic (PA) imaging. However, their intrinsic surface plasmon resonance (SPR) and high radiation absorption properties allow for the combination of photothermal and radiotherapy with chemo- and immunotherapy. In the following section, some of the latest and most significant reports on the impact of Janus plasmonic MSNs on cancer theranostics are summarized.

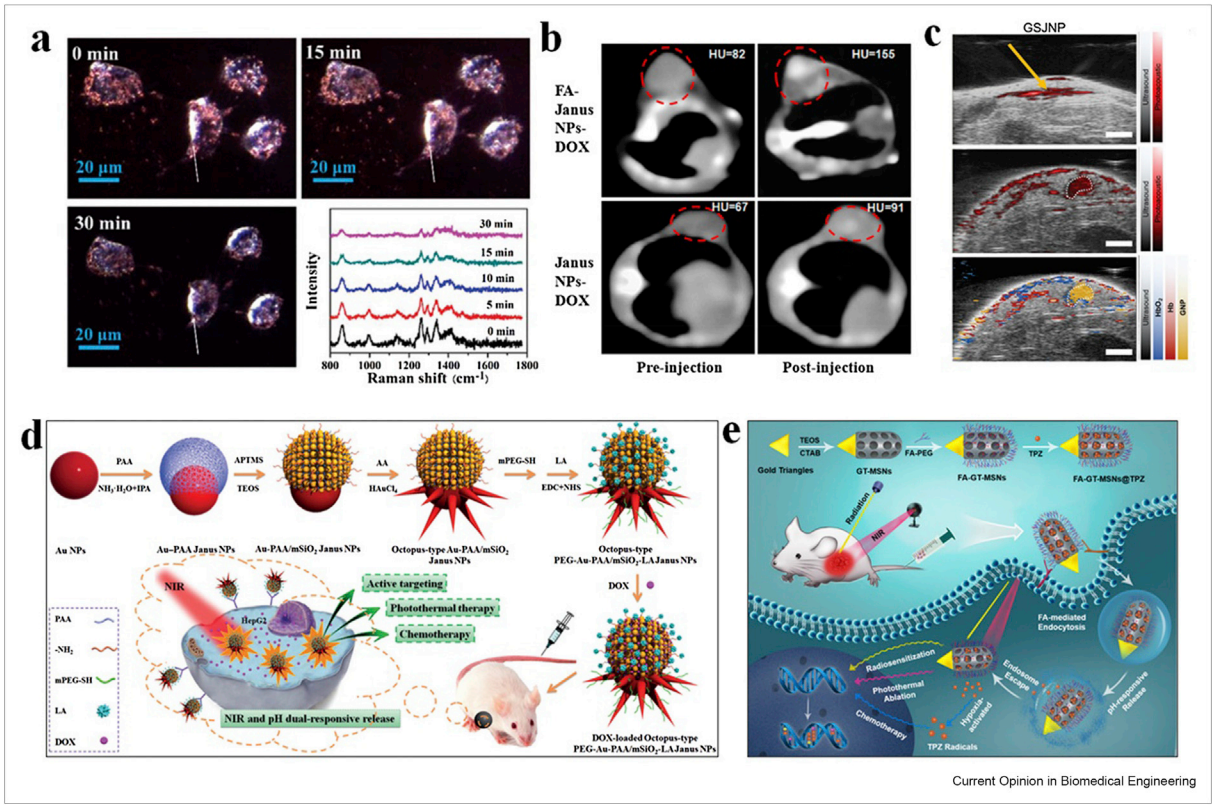
SERS-based detecting

Plasmonic nanoparticles with tailored surface functionalization are widely used as sensors for label-free detection via surface-enhanced Raman spectroscopy (SERS) [31]. Although silica coating can improve the stability of nanosensors in the environment to avoid aggregation, the SPR property can be compromised and results in lower sensitivity during SERS detection [32,33]. To meet these challenges, Shao et al. developed Janus silver-mesoporous silica nanoparticles with high SPR activity for pH-responsive antitumor drug delivery and simultaneous SERS imaging of drug release [32]. pH-responsive DOX release was monitored via SERS, which might enable targeted detection and traceable drug delivery. Similarly, Cao et al. designed sophisticated Janus gold-mesoporous silica nanoparticles for the codelivery of DOX and 7-hydroxycoumarin-3-carboxylate (CMR) and tracked drug release via both fluorescence resonance energy transfer (FRET) and SERS [33]. In this system, the change in the CMR fluorescence signal and the decrease in 6 MP indicated by SERS were used to monitor the dual-drug release within cancer cells in real time (Figure 3a). Together, these studies highlight the appeal of Janus plasmonic MSNs in monitoring responsive drug release via SERS.

CT and PA imaging

Given the intrinsic radiation absorption and SPR properties, Janus plasmonic MSNs permit CT and PA imaging in cancer diagnosis [34,35]. Wang et al. developed Janus gold MSNs with less interfering SPR properties and liver cancer-targeting effects [34]. Such Janus MSNs exhibited higher drug loading content than core–shell compartment (17.2% vs. 49.5%), resulting in lower combination index radiochemotherapy was (0.63 vs 0.81). In addition to achieving chemoradiotherapy, CT imaging revealed that DOX-loaded Janus gold MSNs could selectively accumulate at the tumor site, indicating the feasibility of using this nanoplatform as a folic acid-targeted CT imaging agent for liver cancer diagnosis (Figure 3b). In another case, Park et al. reported another Janus gold MSN as a contrast agent for PA imaging [35]. The interactions between the exposed gold surfaces generated plasmon-coupled nanoparticles with high PA intensity in the near-infrared region, resulting in better lymph node imaging performance than their core–shell structures via *in situ* aggregation (Figure 3c). Furthermore, the heterogeneous structure of Janus gold MSNs also enabled FRET imaging functions, which have been introduced before. Together, Janus plasmonic MSNs are attractive for a broad range of

Figure 3



Janus plasmonic MSNs have been used for surface-enhanced Raman scattering-based detection, computed tomography, and photoacoustic imaging, as well as photo- and radio-responsive therapies. **(a)** Dark-field microscopy (DFM) images and SERS spectra showing real-time monitoring of drug release from Janus gold MSNs in HeLa cells. Reproduced from Ref. [33] with permission from The Royal Society of Chemistry (2016). (b) CT images of SMMC-7721 tumor-bearing nude mice at 24 h post-injection with Janus gold MSNs. Reproduced from Ref. [34] with permission from American Chemical Society (2017). **(c)** Combined ultrasound and photoacoustic images (λ = 700 nm, scale bar = 2 mm) of mice injected with Janus gold MSNs. Reproduced from Ref. [35] with permission from The Royal Society of Chemistry (2018). **(d)** Graphical illustration of Janus gold MSNs with pH and NIR light dual-stimuli-responsive properties for actively targeted and chemo-photothermal cancer therapy. Reproduced from Ref. [38] with permission from Wiley (2015). **(e)** Graphical illustration of Janus gold MSNs with tumor targeting, pH-responsive drug release, hypoxia-activated chemotherapy, and radiosensitive and photothermal activities for combined cancer therapy. Reproduced from Ref. [39] with permission from American Chemical Society (2019).

applications in multiple molecular imaging and further cancer theranostics.

Photo- and radio-responsive therapies

Phototherapy, including photothermal therapy (PTT) and PDT, uses photoconversion agents or PSs to generate heat or singlet oxygen (SO), respectively, to kill cancer cells under laser irradiation [36]. Many Janus plasmonic MSNs have been fabricated for various photo-based cancer therapies [37–43]. Along these lines, Zhang et al. designed octopus-like Janus gold MSNs for synergistic chemo-photothermal cancer therapy [37]. Such multifunctional nanoplatforms not only exhibit high DOX loading but also achieve pH and NIR dual-responsive release properties (Figure 3d). After chemo-photothermal treatment, tumor growth was almost stopped, indicating effective synergistic efficacy. Wang et al. developed ICG-loaded Janus silver MSNs for combined cancer chemo-phototherapy under NIR irradiation [38]. Specifically, silver ions released from Janus silver MSNs that were triggered by light-induced efficient chemotherapy to supplement PTT. Janus silver MSNs@ICG + NIR irradiation group displayed stronger tumor inhibition rates (88.9%) than that of MSNs@ICG + NIR irradiation group (54.7%). Given that gold nanomaterials have emerged as efficient radiosensitizers, the same group has demonstrated that Janus gold MSNs also exhibit strong sensitivity to radiotherapy [34]. These Janus nanoplatforms have better performance in the combination of chemotherapy- and radiotherapy-mediated synergistic antitumor effects with reduced systematic toxicity than core–shell gold MSNs. These authors further used Janus gold MSNs to deliver a hypoxia-activated prodrug for extrinsic radiosensitization, local PTT, and hypoxia-specific chemotherapy [39]. In this context, hypoxia-specific chemotherapy supplemented the ineffectiveness of radio-photothermal therapy in hypoxic tumor tissues,

resulting in remarkable tumor growth inhibition without systematic toxicity (Figure 3e). Collectively, Janus plasmonic MSNs can serve as a versatile nanoplatform that enables integration of multiple light-guided theranostic modalities involving phototherapy, radiotherapy, and chemotherapy, along with PA and CT imaging.

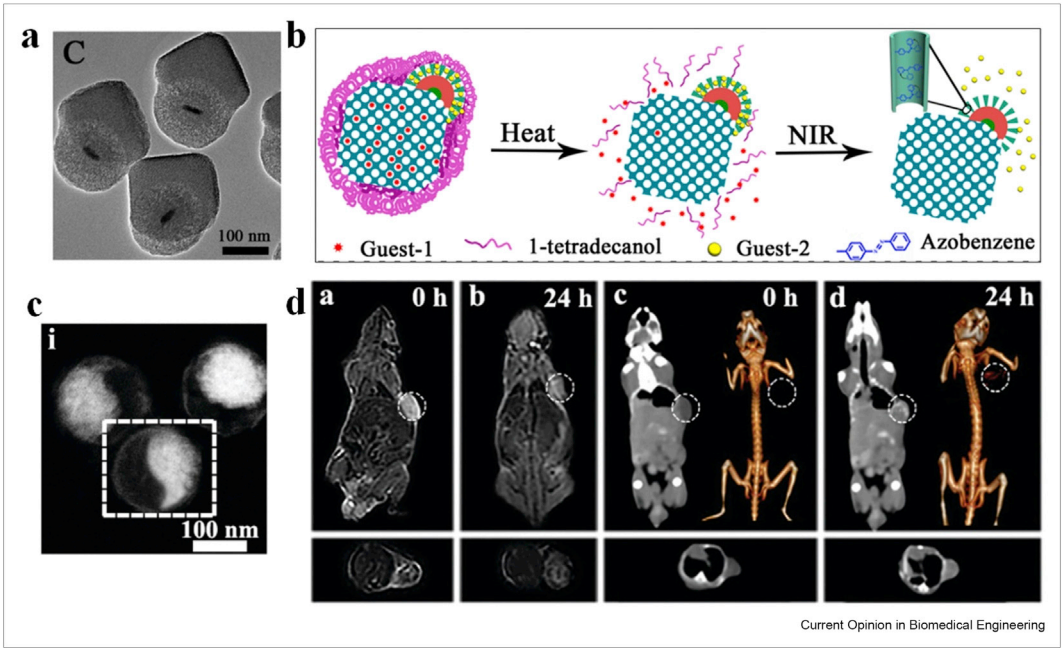
Janus upconversion MSNs for cancer theranostics

Upconversion materials have received considerable attention because of their unique features in efficiently converting near-infrared light (NIR) to ultraviolet or visible light via an upconversion process [44]. Given their unique advantages, including low background autofluorescence, deep photon penetration, minimal photodamage, and high sensitivity, upconversion materials have been used as versatile transducers for luminescence imaging and detection, especially for multiple molecular imaging (e.g. CT, MRI) after doping with functional rare-earth ions [45]. The clever combination of upconversion nanoparticles and mesoporous silica not only improved the chemical stability and reduced cytotoxicity but also achieved efficient cancer theranostics, including multimodal cancer imaging, photoactivation-based chemotherapy, and PDT, along with combined therapy. In the following section, some recent and significant reports on the impact of Janus upconversion MSNs on cancer theranostics are summarized.

Photoactivation-based drug release

Upconversion material-mediated photoactivation encompasses an umbrella of techniques, such as photo-triggered release, PDT, and photoisomerization [46]. Conventional core–shell upconversion MSNs have homogeneous inner cavities that can only load drug molecules with similar properties and release drugs in response to a single stimulus. To achieve multiple-triggered-responsive drug release, Li et al. reported Janus upconversion MSNs containing silica-coated upconversion nanospheres and periodic mesoporous organosilica nanotubes [47]. With the assistance of the unique optical properties of the upconversion nanocores and the thermal–sensitive properties of phase-change molecules, the Janus nanoplatform realized heat- and NIR light-bimodal triggered dual drug release separately and efficient cancer cell killing efficiency, demonstrating the advantages of co-loading hydrophobic/hydrophilic drugs and independent release of each drug from separate domains (Figure 4a and b). Janus upconversion MSNs realize significantly higher efficiency for tumor killing (more than 50%) compared to that of the single-triggered drugs delivery system (~25%). The same group further fabricated

Figure 4



Janus upconversion MSNs have been used for photoactivation-based drug release and therapy, along with multimode imaging. **(a)** Transmission electron microscopy (TEM) images of Janus upconversion MSNs. **(b)** Schematic presentation of heat and NIR dual-controlled drug release systems using Janus upconversion MSNs. Reproduced from Ref. [47] with permission from American Chemical Society (2014). **(c)** High angle annular dark field scanning transmission electron microscopy (HAADF-STEM) image of Janus upconversion MSNs. **(d)** T_2-weighted MRI and CT images of mice after tail vein injection of Janus upconversion MSNs. Reproduced from Ref. [49] with permission from The Royal Society of Chemistry (2019).

another Janus upconversion MSN with single-hole structures for co-delivery of BSA and DOX [48]. The release of these dual-sized guests can be well controlled independently by heat and NIR light, allowing for more opportunities in multidrug delivery and combined therapy of cancer.

Multimode theranostics

Based on the unique photoactivation-mediated drug release, Janus upconversion MSNs have been further used for multiple molecular imaging and combined therapy [49,50]. Chen et al. developed Janus upconversion MSNs with discrete hydrophilic exterior surfaces that exhibited hierarchical pores and a hydrophobic interior cavity [49]. Co-loading hydroxycamptothecin and DOX at a fixed molar ratio in discrete compartments and the release of each drug from independent channels reduced the undesirable adverse effects of different chemotherapeutic drugs. This multifunctional platform not only permitted luminescence, CT, and MR imaging but also exhibited efficient and safe multimodal imaging-guided synergic cancer therapy (Figure 4c and d). The tumor inhibition ratios of the HCPT/DOX-loaded Janus upconversion MSNs were reached to 98.0% and 97% in the two patient-derived xenograft models. In another study, Zhou et al. reported biodegradable Ce6-loaded Janus upconversion MSNs for improved cancer PDT [50]. On the one hand, redox- and pH-responsive released Ce6 could be activated via NIR to produce ROS. On the other hand, the silica matrix could be degraded to consume GSH to enhance PDT, together achieving safe and efficient cancer PDT. Thus, Janus upconversion MSNs can also be considered as a promising platform for photoactivatable cancer theranostics.

Conclusion and future perspective

Like most other scientific advances that have revolutionized medicine over the past decades, cancer theranostics must also mature before its full impact can be realized. Although Janus MMSNs have shown their superiority over core–shell structure and drawn ever-increasing interest and translational potential in cancer theranostics, several obstacles have yet to be surmounted for broader applications and clinical translation. The first issue lies in the biocompatibility of Janus MMSNs in cancer theranostics. Although most Janus MMSNs show excellent performance on cancer theranostics, weak colloidal stability, low biodegradability, and toxicity of these nanostructures hinder the prospect for further clinical translation. Thus, the introduction of organosilica precursors with stimuli-sensitive linkers into the MSN framework will improve biodegradability and eventual clearance from the body. Systematic investigation of the biodistribution, biocompatibility, and biosafety profiles of Janus MMSNs needs to be further evaluated to accelerate clinical translation. Another challenge relates to more extensive validation, ideally pursued in multiple laboratories. The exploration of Janus MMSNs in cancer theranostics is still in its infancy, as many of these studies are proof-of-concept studies that have been performed on only one single diagnostic and one therapeutic mode. A well-designed combination of multimodal imaging and combined therapy may demonstrate the unique advantages of Janus MMSNs to justify their high developmental costs. For example, an integration of these cancer theranostics with immunotherapy in a space-, time-, and dosage-dependent manner will excite the field of nanomedicine. Through the rational integration of a wide range of features that offer multiple functions to one Janus nanoplatform, these unique magic bullets approximate the versatile magic bullets in sensing, multimodal imaging or combined therapy in cancer theranostics. We expect that Janus MMSNs will shed light on efficient and safe theranostics and that the true goal of cancer management — dramatic improvement in patient survival — will become a reality in the foreseeable future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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