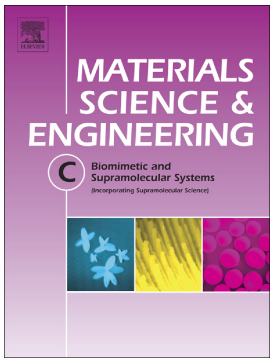

Functionalized mesoporous silica nanoparticles and biomedical applications

Thai Thanh Hoang Thi, Van Du Cao, Thi Nhu Quynh Nguyen, Duc Thuan Hoang, Van Cuong Ngo, Dai Hai Nguyen

PII: S0928-4931(17)34346-1
DOI: https://doi.org/10.1016/j.msec.2019.01.129
Reference: MSC 9387

To appear in: *Materials Science & Engineering C*

Received date: 4 November 2017
Revised date: 12 December 2018
Accepted date: 29 January 2019

Please cite this article as: T.T.H. Thi, V.D. Cao, T.N.Q. Nguyen, et al., Functionalized mesoporous silica nanoparticles and biomedical applications, Materials Science & Engineering C, https://doi.org/10.1016/j.msec.2019.01.129

Functionalized Mesoporous Silica Nanoparticles and Biomedical Applications

Thai Thanh Hoang Thi[1], Van Du Cao[2], Thi Nhu Quynh Nguyen[2], Duc Thuan Hoang[2], Van Cuong Ngo[2], Dai Hai Nguyen[3,4]*

[1]*Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City 700000*

[2]*Faculty of Pharmacy, Lac Hong University, Buu Long Ward, Bien Hoa City, Dong Nai Province 810000, Vietnam.*

[3]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi 100000, Vietnam.*

[4]*Institute of Applied Materials Science, Vietnam Academy of Science and Technology 01 TL29, District 12, Ho Chi Minh City 700000, Vietnam.*

***Corresponding author**: nguyendaihai@iams.vast.vn

Abstract:

Since the first report in early 1990s, mesoporous silica nanoparticles (MSNs) have progressively attracted the attention of scientists due to their potential applications in physic, energy storage, imaging, and especially in biomedical engineering. Owning the unique physiochemical properties, such as highly porosity, large surface area and pore volume, functionalizable, tunable pore and particle sizes and biocompatibility, and high loading cavity, MSNs offer efficient encapsulation and then controlled release, and in some cases, intracellular delivery of bioactive molecules for biomedical applications. During the last decade, functionalized MSNs that show respond upon the surrounding stimulus changes, such as temperature, pH, redox, light, ultrasound, magnetic or electric fields, enzyme, redox, ROS, glucose, and ATP, or their combinations, have continuously revolutionized their potential applications in biomedical engineering. Therefore, this review focuses on discussion the recent fabrication of functionalized MSNs and their potential applications in drug delivery, therapeutic treatments, diagnostic imaging, and biocatalyst. In addition, some potential clinical applications and challenges will also be discussed.

Keywords: MSN; Nanocarriers; Nanoparticles; Stimuli-responsive delivery system; Controlled release; Diagnostic imaging; Catalyst; Theranostic applications; Drug delivery.

1. Introduction

Over the past decades, the development of nanotechnology has provided powerful tools to create nanostructure materials that can be used in biomedical applications, such as drug delivery, disease diagnostic, medical imaging, and tissue regeneration. Functionalized nanomaterials, such as polymeric liposomes, dendrimers and self-assembly nanoparticles, or inorganic gold nanoparticles, ferric oxide nanoparticles, carbon nanotubes, and mesoporous silica nanoparticles (MSNs), have been fabricated and characterized, and their potential biomedical applications have incredible progresses. Among these systems, MSNs offer many outstanding advantages, such as large pore volume (up to 2.5 cm^3/g), high surface area (>1000 m^2/g), tailorable pore diameter (1.3-50 nm), functionalizable, biodegradable, high chemical and biological stability as well as good biocompatibility [1-5]. MSNs are the versatile materials comprised of porous structures with hundreds of atomic level arranged mesopores that were first reported by Japanese scientists in 1990 [2], and concurrently by American scientists at the Mobil Research and Development Corporation in 1992, named MCM-41 [3, 4]. Years later, MSNs with larger pores, named SBA-15 were synthesized [6, 7]. Scientists have paid a significant attention to synthesize, characterize, and control the structure of MPNs in order to understand their properties and target their potential applications [8-11].

Several years after discovered, the first potential application of MSNs in control the delivery of therapeutic molecules has been reported [12]. MCM-41 based MSNs showed the ability to load and control the release of Ibuprofen (IBU), an anti-inflammatory and analgesic drug, for more than 3 days. This finding has revolutionized the potential applications of MSNs in biomedical engineering and nanomedicine that significantly increased the attention of scientists. The porous structure of MSNs can be used to load a huge amount of bioactive therapeutic molecules for subsequently controlled release while the high surface area can be easily functionalized to improve their performances. There is a variety of strategy to modify the surface of MSNs with functional groups and ligands to improve their physicochemical properties, such as sensitivity to temperature, pH, light, magnetic and electric fields, redox agents, and ultrasound (US), glucose, and enzyme, site-targeted ability, improving biocompatibility), biodegradability, and excretion, and ability to control the release of loaded bioactive molecules). Nowadays, MSNs have been used in a variety of biomedical applications, including drug delivery, therapeutic treatments, diagnostic imaging, and biocatalyst. In addition, functionalized MSNs can be combined with other agents, such as quantum dots, fluorescent agents, magnetic nanoparticles, and nanocrystals to broaden their ultimate applications.

This review will discuss the recent progress in fabrication of smart functionalized MSNs that are sensitive with the stimulus changes in surrounding environment, such as temperature, pH, redox, light, US, magnetic or electric fields, enzyme, glucose, and ATP, or their combinations. The strategy to

fabricate and functionalize MSNs, their potential applications in biomedical engineering, such as drug delivery, therapeutic treatments, diagnostic imaging, and biocatalyst, and their potential clinical challenges will also be discussed.

2. Fabrication of MSNs and Functionalization

In general, MSNs can be synthesized via 4 different methods, including template-directed method [3, 4, 13], sol-gel method [14], microwave assisted technique [15], and chemical etching technique [16], which have been discussed in the literature [17, 18]. For example, in template-directed method, known as the cheapest method to prepare ordered MSNs, nano-size structured micellar templates were first prepared followed by adding of the silica precursor, such as tetraethyl orthosilicate, for reacting and depositing on the surface of these templates. The constructs were then treated with calcination process to remove micellar templates for obtaining MSNs [19] (Fig. 1). The original porous structured MSNs offer the ability to effectively encapsulate large amounts of bioactive molecules and protect them from degradation before releasing. However, physical trapped bioactive molecules in the MSN carriers could result in the uncontrollable release behaviors with initial burst. In addition, the remaining silanol functional groups in MSNs could inhibit the bioactivity of proteases [20, 21] or cause hemolysis by interacting with phospholipid layers on the membranes of red blood cells [22]. However, these silanol functional groups can be easily modified with other functional ligands to improve the properties and expand the potential applications of MSPs in biomedical engineering.

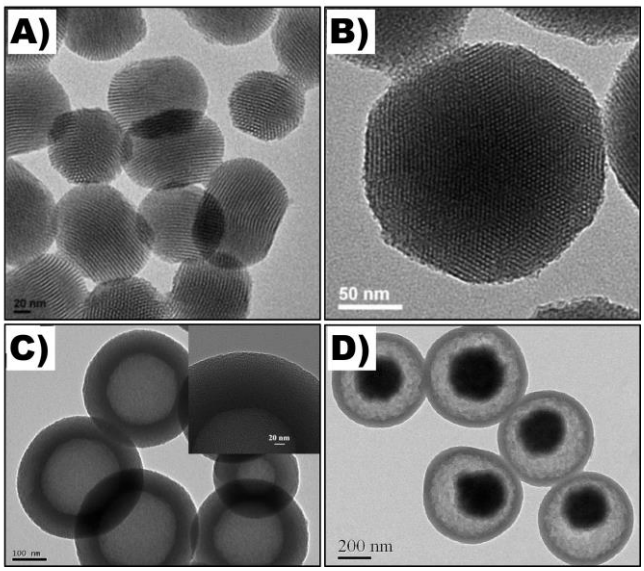

Fig. 1. TEM images of some bare (A, B), hollow (C) and magnetic NP core (D) MSNs. Reproduced with permission from [23], [24], [5], and [25] for (A), (B), (C) and (D), respectively.

Several strategies have been used to functionalize ligands onto the surface of MSNs for providing the sustained and/or controled delivery of bioactive molecules, increasing the cytocompatibility,

improving targeted activity, and controlling the biological responses. This section discusses recently progresses in functionalization the surface of MSNs to improve their performances. It focusses on modified ligands that response to the vibration of surrounding stimuli, such as temperature, pH, light, magnetic and electric fields, US, redox agents, glucose, and enzyme, as well as specific cell targeting receptors for improving biocompatibility, biodegradability, excretion, and ability to control and localize the release of loaded bioactive molecules to minimize the systemic cytotoxicity effect. Fig. 2 shows the potential strategies that can be used to functionalize MSNs [26].

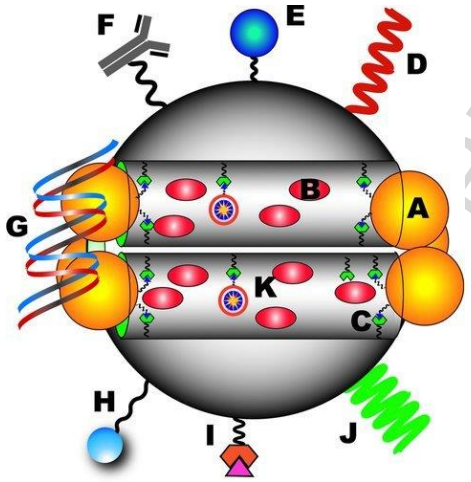

Fig. 2: Strategies can be used to functionalize MSNs: A) functionalized gatekeepers; B) interaction of loaded molecules with MSNs in the interior of the pores to increase the retention time; C) stimuli-responsive linkers for chemically conjugation gatekeepers to MSNs; D) functionalized polymer for stabilizing, such as PEG; E) functionalized bioimaging agents, such as magnetic nanoparticles, quantum dots, or fluorophores; F) targeting ligands to target specific cell receptors; G) complexation with plasmid DNA; H) additional functionalized ligands, such as for improving cell-penetrating; I) functionalized diagnostic labels. J) stimuli-responsive functionalized polymers. K) functionalized groups that could modify the metabolism of cells. Reproduced with permission from [26].

2.1. Functionalized MSNs for temperature response

Temperature is one of the most popular and easiest stimulus for practically control that has been used to trigger the response of MSN delivery systems in biomedical application. Original MSNs are inorganic materials and do not response to the vibration of temperature. Therefore, temperature-sensitive polymeric ligands were conjugated to the surface to regulate the property of functionalized MSNs, such as swelling, hydrophobicity, and ionic affinity, with changing temperature. Temperature-sensitive MSNs delivery systems are inactive at the physiological temperature (37 ^{o}C) for circulation in the body but become active at higher temperature at tumor targeted sites, especially in combination with hyperthermia therapy due to the conformation change of the conjugated polymeric ligands. This strategy can provide localized, controlled and sustained delivery systems that prevent systemic cytotoxicity.

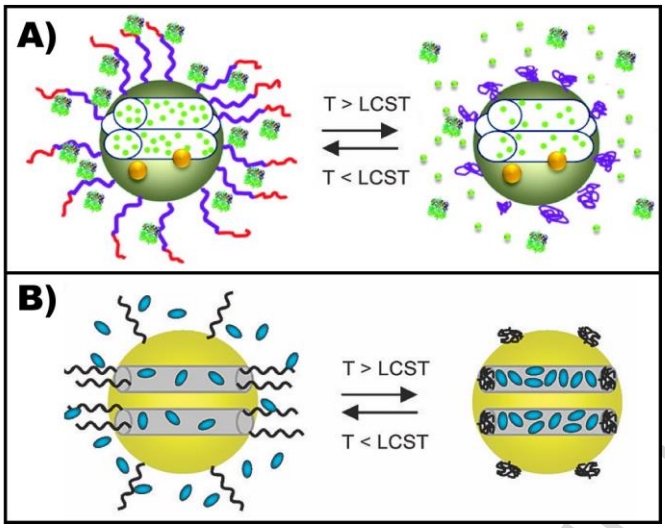

Fig. 3. Functionalized MNSs for temperature-trigger the payload release. (A) functionalized polymers act as "gatekeeper" to prevent the release but collapse to expose the pores for releasing the payloads. Reproduced with permission from [33]; (B) the collapsing functionalized polymers acts as "gatekeeper" to prevent the release. Reproduced with permission from [27]

Poly(N-isopropylacrylamide) (PNIPAM) is one of the most popular well-known temperature-sensitive polymer that has been conjugated to improve the thermo-responsive properties of MSNs [27-38]. PNIPAM was separately synthesized before conjugating to the MSNs [27] (check [35]) or directly prepared by copolymerization of N-isopropylacrylamide monomers (NIPAM) with modified methacrylate [28-33] or vinyl [36] groups on the surface of MSNs. For example, pyridine disulfide PNIPAM (PNIPAM-S-S-Pyr) can be synthesized via atom transfer radical polymerization (ATRP) before conjugating to the surface of thiolated MSNs using thiol-disulfide exchange reaction [27]. ATRP initiator can also be conjugated to MSNs before initiating the ATRP of NIPAM to directly synthesize PNIPAM from the surface of MSNs [34, 39]. PNIPAM is water soluble at temperatures below its lower critical solution temperature (LCST) of 32-34 ^{o}C but exhibit a coil-to-globule transition at higher LCST due to the increase in hydrophobicity. This temperature change behavior of PNIPAM can be used to control the delivery of bioactive molecules from the pores of MSNs using two opposite strategies. In the first strategy, bioactive molecules can be loaded in the pores of MSNs, which are blocked by a layer of "gatekeeper" soluble conjugated PNIPAM at lower LCST. At temperate higher LCST, however, the soluble PNIPAM exhibits a conformational change to form collapsed globules and expose the pores to surround environment for bioactive molecules release (Fig. 3A) [29-31, 34, 35]. This strategy can be achieved in large pore size MSNs and short conjugated polymer chain length. In contrast, the collapsed globules of PNIPAM at temperature higher than LCST in the second strategy can be used as "gatekeeper" to trap the loaded payloads in the pores of MSNs to provide sustained release with minimal initial burst (Fig. 3B) [27, 28]. This strategy can be achieved in small pores MSNs and long conjugated polymer.

Oder molecules, including poly(ε-caprolactine) (PCL) and short peptides, were also reported as temperature-sensitive moieties for conjugation on the surface of MSNs, which acted as a "gatekeeper" [40-42]. EDC chemistry [40, 41] or "click" reaction [42] have been used to conjugated these molecules to the surface of MSNs. When PCL-conjugated MSNs were treated to heat shock at the melting point of PCL (45 ^{o}C), the PCL loosen its structure on the outer shells of MSNs and loaded active molecules can release [40]. Similar behavior was also observed when hyperthermia condition was applied to peptide-conjugated MSNs [41, 42]. In addition, physical coating of temperature-sensitive liposomes [43] or polymer [35] layers could also be used to modify the surface of MSNs. For example, liposomes comprised of lipid bilayer coated on the outer surface of doxorubicin (DOX)-loaded MSNs via sonification process could improve the hemocompatibility of MSNs and prevented the release loaded molecules from the pores at physiological temperature for long term circulation but increased permeability and allowed the release of the payload when temperature was increased to higher melting point of liposomes [43].

2.2. Functionalized MSNs for light response

Light has been widely used in fabrication of nanomaterials and control the release of bioactive molecules [44-46] because it offers many advantage, such as ease of control, extremely high spatially and temporally precision, remote, and a broad range of wavelength and intensity. Many light-sensitive moieties, such as derivatives of ortho-nitrobenzyl (ONB), derivatives of coumarin, thymine, derives of azobenzene (Azo), spiropyran. These moieties exhibit structural changes up on exposing to a wide range of wavelength light that can be used to regulate the property of conjugated ligands in the surface of MSNs. This section will discuss in more details of these strategies.

ONB has been report as photolabile moiety introduced to polymeric hydrogel to control the release of RNA molecules from the hydrogel via UV light application [44, 45]. ONB was also used as a photolabile moiety to control the release of payloads form MSNs. Bioactive molecules can be loaded into the pores of MSNs, and the ONB-contained capping pieces were covalently [47, 48] or electrostatically [49] conjugated to the surface of MSNs to prevent the release of the payload. When these systems were exposed to UV light, the photo-degradation of ONB group lead to the release of capping pieces and subsequently the payload (Fig. 4A). For example, ethyl dimethyl ammonium bromide positive block was conjugated to AuNP via ONB linkage that could ionically interact with negative charged MSNs to block the leaded DOX in the pores of MSNs to prevent the release [49]. Upon the exposure to UV light (365 nm), the ONB group was photo-degraded and the AuNP and loaded DOX was released inside human cells. DOX can also be loaded to ONB-carbamate functionalized MSNs for UV triggered release [50]. Under UV light application, the degradation of

ONB-carbamate groups led to the formation of positively charged propylammonium moieties on the surface nanoparticle, which change the surface charge of MSNs and accelerate the release of DOX.

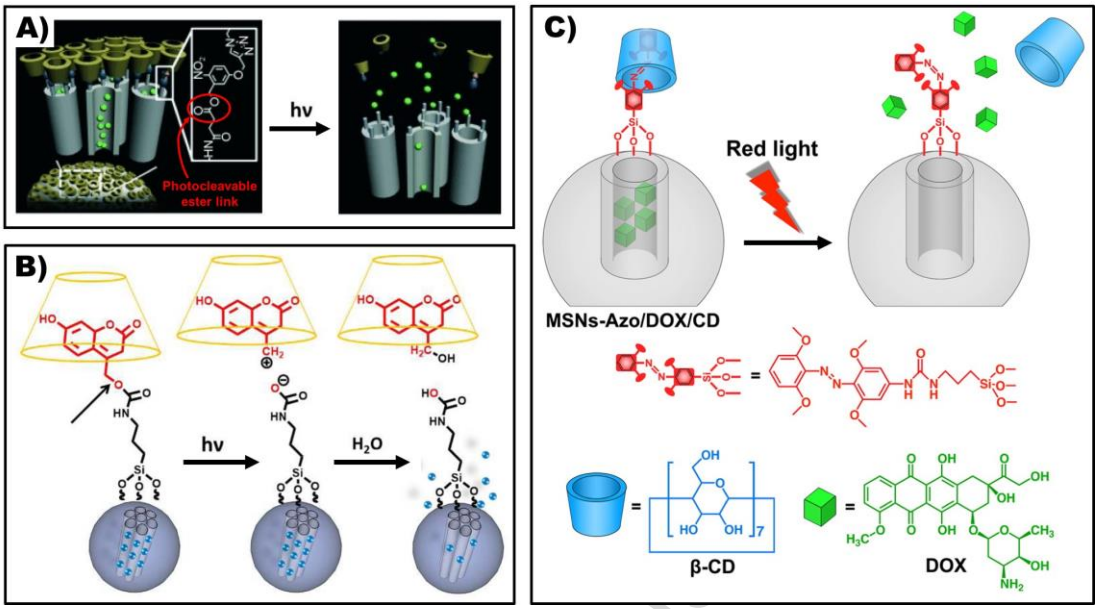

Fig. 4. Functionalized MSNs for light-trigger payload release. (A, B) CD "gatekeeper" was covalently linked to the surface of MSNs via ONB-based (A) or coumarin-based (B) photocleavable moiety to trap (left) and activate (right) the controlled release of payloads under UV light application. Reproduced with permission from [47] for (A) and [51] for (B). (C) Azo-derivative functionalized MSNs capped with CD via Azo/CD host-guest interaction for red light-triggered payload release. Reproduced with permission from [52].

Similar to ONB, coumarin-derived molecules can also be degraded upon exposed to UV light (~400 nm) or NIR (~800 nm). Coumarin was conjugated to the surface of MSNs via urethane linkage followed by loading the payload and capping with CD (gatekeeper" to prevent the diffusion [51]. No released payload was detected after 2.5 h in the absence of UV light (376 nm), while more than 40% and 70% of payload was released after 2.5 and 7.5 h switching to UV, respectively (Fig. 4B). Hydrophobic polymer containing long-alkyl-modified coumarin pendent groups synthesized via RAFT followed by grafting folic acid (FA) was coated on the surface of DOX-loaded octadecyl-functionalized hollow MSNs (H-MSNs) via hydrophobic interaction, that served as hydrophobic barrier to prevent the pre-mature release of loaded DOX ("closed" state) [53]. Upon application of femtosecond pulse NIR (800 nm), the polymer became hydrophilic due to the degradation of coumarin pendant groups, and detached from the surface of MSNs ("opened" state) that allow DOX release from pores to surrounding media. Coumarin and ONB can also be combined in one system for two independent wavelength light-triggered sequential release of two different bioactive molecules [54]. Cationic poly(2-(N,N-dimethylaminoethyl)methacrylate) (PDMAEMA) was functionalized to surface of MSNs through coumarin linker and the system was then loaded with ONB-modified DOX and short-hairpin RNA (shRNA) for photo trigger release. The release of the shRNA and DOX from the

MSNs was independently regulated by 405 and 365 nm light irradiations due to selectively degradation of coumarin and ONB, respectively [54]. Coumarin derivatives also exhibit the dimerization at 365 nm ("closed" state) and its reversible photo-cleavage at 254 nm ("opened" state) that has been used for capping and regulating the released of payloads when functionalized to the MSNs [55-58]. Similarly, photocontrol the monomer-dimer transformation was also observed in thymine derivatives [59]. Exposure thymine-functionalized MSNs to 365 nm light could prevented the diffusion of the payload ("closed" state) due to the cyclobutane dimerization of thymine while switching to 240 nm light allowed the release of the entrapped guest molecules due to the photocleavage of cyclobutane dimer to return mono-thymine.

The photo-sensitivity of ONB and most coumarin based moieties is irreversible due to the photo-degradation of ONB or coumarin groups. The bioactive molecules have to be loaded into MSNs prior to capping with ONB- or coumarin-containing pieces and one the systems are exposed to UV light, they cannot be reused. In contrast, Azo-derived molecules offer the ability of reversible photo-isomerization from trans to cis forms and vice versa upon exposure to UV light (~360 nm) and blue light (~450 nm), respectively, that has been widely used in fabricating of photo-responsive nanomaterial approaches. When the Azo derivatives were conjugated to the pore surface of MSNs, their trans-cis transformation can act as dynamic wagging motion pump for controlling the release of loaded bioactive molecules [60]. By continuous exposing to light (413 nm), the constant transformation between trans and cis photo-isomerization of N=N bond in Azo group create dynamic wagging motion that pushed the loaded camptothecin (CPT), an anticancer drug, out of MSNs, which showed significantly effect in inhibition cancer cell growth while no effect was observed in dark condition. The trans-isomer of Azo derivatives has rod-like and apolar shape that can form hos-guest interaction with both α- and β-cyclodextrin (CD), which is not achieved in cis-isomer in Azo molecules due to its bigger size. Azo derivatives functionalized MSNs have been used to load of bioactive molecules followed by capping with CD derivatives to prevent the diffusion of loaded bioactive molecules from MSN pores [52, 61, 62]. CD can be also functionalized to MSNs followed by loading of drug molecules and then capping with Azo-containing polymers for the same purpose [63]. When light (365 nm or 625 nm) was exposure to these MSNs, the trans to cis transformation lead to the breakage of Azo-CD interaction for release of capping molecules and subsequent release of loaded bioactive molecules (Fig. 4C). For example, when Azo-containing amphiphilic copolymer comprised of 6-(4-(phenyldiazenyl)phenoxy)hexyl methacrylate (PHM) and poly(ethylene glycol) methyl ether methacrylate (PEGMEM) ((PPHM-co-PEGMEM or PPP) was synthesized by radical copolymerization and used to cap CD-functionalized H-MSNs loaded with Ibuprofen (IBU), less than 10% loaded IBU was release after 4 days under visible light condition [63]. In contrast, when the samples were exposed to UV light (365 nm), 80 wt% of IBU was released after 4 days.

The interaction between CD and Azo-derived molecules in the form of stalks from the surface of MSNs was also reported as precise method for light-trigger release of bioactive molecules from MSNs [64-66]. When naphthalene-1,3-disulfonic acid-Azo stalk crosses the center of CD ring and conjugate to the outer surface of MSNs or Au cored MSNs (Au@MSNs), the CD-Azo stalks act as doors to control the release of the loaded curcumin [64] or DOX [65]. The trans-isomer interacts with CD that create a distance between CD ring and the surface of MSNs for loading bioactive molecules in to the pores. By exposing the MSNs to UV light (365 nm), the trans-to-cis transformation lead to the breakage of CD-Azo interaction and moving of CD ring toward to the surface of MSNs, due to the hindrance of naphthalene-1,3-disulfonic acid at the other end of Azo group, that prevents the diffusion of loaded molecules ("closed" state). By irradiation NIR (808 nm) to Au@MSNs, the release of the pay load was significantly increased due to the opening of pore gate cause by Azo cis-to-trans transformation, which lead to the moving way of CD form the surface of MSNs due to the interaction with trans Azo [65]. In these systems, the length of stalks from MSN surface to N=N bond in Azo group play a critical role in loading the payloads, which have to smaller stalk length. The cis-isomer of Azo is not stable and may relax back, in dark, to the trans-isomer, and therefore the cis-Azo "closed" state may not be an ideal for long term storage or controlled release from MSNs. To overcome this limitation, Azo-centralized stalks containing adamantine (Ad) at one end crosses the center of CD to conjugate to surface of MSNs have been fabricated to fabricate trans-Azo "closed" system [66]. Bioactive can be loaded into the pores of these system in organic solvent (ethanol) or in cis-Azo "opened" state under UV light (377 nm) followed by capping via solvent exchange to water or relaxation of cis-to-trans Azo to prevent the diffusion of the payload. Upon the application of UV light (377 nm), trans-to-cis transition push the CD ring toward the far Ad-contained end of stalk and the system changed to "opened" state for release the payload. The length of stalk can be controlled for loading molecules with specific size and these system is only suitable for small pore MSNs [66].

Beside CD, other molecules also can be used for interaction with trans-Azo to cap the load payload. Cucurbit(8)uril (CB(8)) is a macrocyclic host molecule that can simultaneously interact with two guest molecules inside its cavity to for a stable heteroternary complex. CB(8) was reported to interact with trans-Azo functionalized H-MSNs and viologen functionalized ferrite oxide (MV-Fe_3O_4) to trap the loaded molecules inside the pore of MSNs ("closed" state) [67]. Upon the application of UV light (350 nm), the trans-to-cis transformation break the CB(8)-Azo interaction and the system become "opened" state for release of the payload. The trans-cis transformation of Azo groups when modified into DNA (DNA) can also regulate the "opened" and "closed" states of DNA-tagged MSNs [68]. Trans-Azo in Azo-DNA promote the hybridization of Azo-DNA and DNA-MSNs and subsequently cap the pores to create the "closed" state while the UV-induced (300-380 nm) cis-Azo dehybridized the interaction between DNAs to return "opened" state for release the payload.

Spiropyran is a hydrophobic photochromatic molecule that can transform to hydrophilic positive charged merocyanine upon exposure to UV light (250-380 nm) due to the breaking the C-O linkage but transfer back to the original spiropyran-form under visible light. Spiropyran has been coupled to the surface of MSNs for light-triggered the released of loaded bioactive molecules [69, 70]. Payload can be loaded in the pores of positive charged merocyanine-form functionalized MSNs followed by adding of negatively charged poly(amidoamine) dendrimers for capping to prevent the release ("closed" state) [69]. When the system was exposed to visible light, the transformation from positive charged merocyanine to neutral spiropyran could uncap the negatively charged dendrimers and allow the prelease of payload ("opened" state). However, the merocyanine-form is not stable without UV exposure and slowly converts to spiropyran-form and therefore the payload may be undesirable leaking from the system. To overcome this issue, spiropyran-form has been used as a "gatekeeper" in the "closed" state for storing and circulation and the payload release was controlled using UV light (365 nm) [70]. The surface of MSNs was functionalized with hydrophobic molecules, perfluorodecyltriethoxysilane, and spiropyran before loading the bioactive molecules. The hydrophobicity of spiropyran form and perfluorodecyl provides a thin layer hydrophobic barrier to prevent the release of the payload from MSNs. Under UV light (365 nm) exposure, spiropyran was converted to the hydrophilic merocyanine-form, which broke the hydrophobic layer and wetted the surface of MSNs for the release of loaded molecules.

Au nanoparticles (AuNPs) have large optical adsorption coefficients in the near-infrared region and offer efficient photothermal energy conversion that allow them to efficiently convert the absorbed radiation into hyperthermia [71]. The hyperthermia from AuNPs has been used for NIR-triggered control the release of payload from MSNs [39, 71-73]. The AuNPs were used as "gatekeeper" to prevent the release of loaded Chlorin e6 (Ce6) from MSNs due the absorbing of AuNPs onto the surface of MSNs via electrostatic interaction [72]. The system can be turn to "opened" state for Ce6 release under NIR (660 nm) irradiation due to the hyperthermia effect from AuNPs, which break the electrostatic interaction. AuNPs were also employed as central cores of MSNs (AuNP@MSNs) to provide the hyperthermia effect under NIR to trigger the transformation of "gatekeeper" molecules for activation the release of payloads [39, 71]. For example, the release of DOX loaded in AuNR@MSN functionalized with temperature-sensitive aliphatic poly(urethane-amine) (PUA) was significantly accelerated under NIR irradiation (808 nm) due to the shrinkage of the PUA polymer chains caused by increasing temperature [71]. In addition, other strategies have also been used for light-trigger the release of payloads from MSNs via hyperthermia effect under NIR irradiation. For example, single wall CNT and GO nanosheets has been placed in the core [74] or wrapped on the surface [75] of MSNs, respectively, to provide hyperthermia effect under NIR irradiation to control the release of loaded DOX for cancer treatment.

Many other strategies have also been reported for capping the pores of MSNs to trap the payloads, which subsequently were exposed to light for triggering the release. (Ru(bpy)2(PPh3))Cl (bpy = bipyridine, PPh3 = triphenylphosphine) was conjugated to thiolated MSNs to trap the payloads followed by irradiation with visible light (455 nm) to trigger the release of capping species and loaded molecules [76]. Functionalization of 6,8-dihydroxy-1,3-pyrenedisulfonic acid disodium salt (DHDS, a photoacid inducer) and an aniline-derived molecule to the surface of MSNs offered the capacity of photo-regulated interaction with CD [77]. The interaction of CD with uncharged aniline group prevented the diffusion of payloads under visible light. However, this interaction was detached under UV light (408 nm) exposure due to the protonation of aniline by H+ generated from DHDS that led to the uncapping of CD and releasing of payloads.

2.3. Functionalized MSNs for magnetic field response

Magnetic field is highly available and offers fast and precise methods to manipulate the response of magnetic materials. Superparamagnetic ferric oxide nanoparticles (M-Fe-NPs), including Fe3O4 and γ-Fe2O3, are the most popular sources of magnetic that have been widely used in biomedical applications such as in vivo magnetic resonance imaging, magnetic-mediated hyperthermia for delivery of therapeutic agents and cancer treatment [25, 31, 33, 78-91]. These M-Fe-NPs can be functionalized into the core of MSNs to create magnetic MSNs (M-MSNs) [82-86, 92-94] or used to cap on the surface of MSNs [95] for improving their performance in controlling the release of bioactive molecules, controlling site-targeting and MRI [82, 83, 86].

Hyperthermia is an important property of M-Fe-NPs under the external magnetic field (EMF). The hyperthermia of M-Fe-NPs has been used to solely regulate the release of the payload [84-87] or trigger the detaching of capping pieces for regulating the release of bioactive molecules [31, 88-91]. For example, model dye molecules loaded in amino functionalized M-MSNs caped with CB(6) nanovalves could not release from the systems in the absence of EMF for more than 4h but exhibited a storm release after 1 min under the application of a single pulse of EMF due to the inducing of hyperthermic effects under oscillating EMF (Fig. 5) [88]. M-Fe-NPs were also used to cap the surface of MSNs to prevent the premature diffusion of bioactive molecules [81, 95]. MSNs were functionalized with single-stranded DNA followed by loading the payloads and capping with complementary sequence DNA-conjugated M-Fe-NPs [81]. The hybridization of both DNA strands completely seals the pores of MSNs to prevent the diffusion of the payload. Upon application to EMF, the increase of temperature caused by hyperthermia effect melted double-stranded DNA that broke the barrier and allow the release of the payloads. The assembly and disassembly of the double-stranded DNA is reversible that offer the “on-off” release mechanism [81].

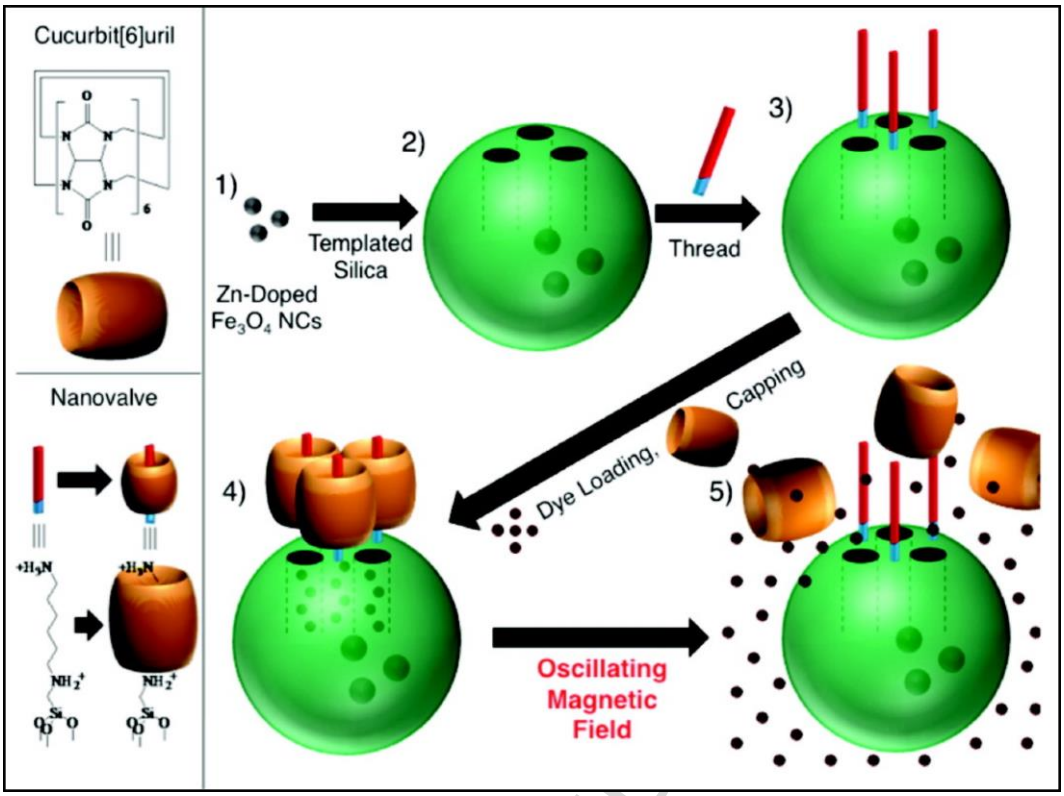

Fig. 5. Fabrication and release mechanism of payload from functionalized MSNs with magnetic response: (1) magnetic NPs; (2) MSNs with magnetic NPs in the core; (3) amino stalks attached to the surface of MSN; (4) loading of drug followed by capping with CB(6) via host-guest interaction; (5) applying of oscillating EMF to induce hyperthermia effect for release the capping pieces and loaded drug. Reproduced with permission from [88].

In addition, other form of magnetic moiety, including carbon-encapsulated ferric magnetic colloidal nanoparticles [96], Gd ions [73, 97, 98], and MnOx [99-101] can also offer magnetic property to MNSs and provide hyperthermia effect [96] or ability to control the biodistribution of MSNs [97] using EMF. The magnetic-responsive moieties can also be co-functionalized with other stimuli-sensitive moieties such as temperature [31, 90, 91, 102] or light [89] to enhance the performance of the MSNS systems. For example, when PNIPAM was functionalized to M-MSNs, the EMF can induce the hyperthermia effect to trigger the response of PNIPAM for control the release of the payloads [31, 90, 91, 102]. The synergistic effect in trigger the release of loaded DOX from M-MSNs capped with graphene when the system was exposure to both bot light and EMF was also observed [89].

2.4. Functionalized MSNs respond to ultrasound

Ultrasound (US) that has been widely used in imaging diagnosis is weakly absorbed by water and tissue and therefore is a promising stimulus to regulate the response of MSNs to improve their performance in delivery of bioactive molecules and imaging. US can induce the hyperthermia and cavitation effect in functionalized MSNs to trigger the response of co-functionalized ligands and/or delivery of loaded payloads. Porous structure of MSNs offers ultrasound imaging capability that can

be used as a theranostic tool to guide the delivery of insulin-like growth factor (IGF), a model pro-survival agent, to prevents stem cell death [98]. Functionalized MSNs was reported to effectively trigger the hydrophobic drug release and significant cytoclasis [103], and improve the contrast of US imaging. The release of hydrophobic pyrene model drug co-encapsulated with liquid perfluorohexane (PFH) in the pores of Au-doped H-MSNs and capped with PEG was remarkable increased upon exposure the system under the US irradiation due to the hyperthermia effect and subsequently cavitation of PFP. These effects significantly induced the cytoclasis and improved the contrast of ultrasound imaging both in vitro and in vivo [103]. The encapsulation of PFH bubble generator was also enhanced the resolution of US image to facilitate the focusing of therapeutic spot in the targeted tumor tissue [25, 99].

Hydrophobic floured alkyl or alkyl have been functionalized to the surface of MSNs to provide the dried pores for entrapping air to form US responsive bubbles upon high-intensity focused ultrasound (HIFU) exposure that can be used for effective cancer cell killing in synergistic combination US [104-106]. For example, when hydrophobic octyl functionalized MSNs were suspension in Pluronic F127 solution, the MSNs with air filled pores could be formed that are stable in buffer and serum but the air bubbles were released by HIFU exposure to improve the contrast of US imaging and designing sensor platforms [106]. In a reverse approach, entrapping drug loaded MSNs in gas bubbles could help to increase the circulation, prevent systemic cytotoxicity, and enhance the targeted deposition of MSNs by US destruction the bubbles to release the MSNs at tumor site [107].

The hyperthermia effect from MSNs under US irradiation was reported to induce the degradation of linkages between MSNs and capping molecules [108]. PEG was use to partially cap the topotecan (TOP)-loaded amino functionalized MSNs via 4,4′-azobis(4-cyanovaleric acid) (ABCVA) thermal degradable linkers to prevent the premature diffusion of encapsulated drugs and modulate the surface charged of MSNs. ABCVA is decomposed to create 2 free radicals at 70 ^{o}C or upon exposure to US irradiation due to the localized hyperthermia effect that initiate the cleavage of linkages between MSNs and PEG and subsequently the departure of PEG for TOP release and exposing the amino group to increase the positive surface charge of MSNs for improving the cell internalization [108]. The cavitation effect of MSNs under HIFU was reported to initiate the release of loaded DOX in polydopamine (PDA)-coat MSNs with a unique DOX-releasing pulsatile fashion by switching the on/off HIFU status [109].

Hydrophobic poly(2-tetrahydropyranyl methacrylate) (PTHPMA) is US-degradable polymer that can be hydrolysis to form hydrophilic poly(methacrylic acid) (PMA) and tetrahydropyranol under the application of US. These hydrophobic and hydrophilic change under US application was inherited to regulate the surface property of PTHPMA functionalized MSNs for controlling the payloads [110]

[111]. Random copolymer poly(2-(2-methoxyethoxy) ethyl methacrylate)-co-PTHPMA (p(MEO_2MA-co-THPMA)) was functionalized to the surface of MSNs via EDC chemistry for US-induced the release of loaded DOX [110]. The stretching morphology of polymer at low temperature (4 °C, lower LCST) allows loading of DOX to the pores of MSNs while the collapse of polymer at 37 °C close the pore entrances to prevent premature DOX release. Upon US irradiation, the hydrolysis of PTHPMA increase the hydrophilicity of polymer due to the formation of –COOH groups led to the formation of coil-like structure to open the gates for DOX release (Fig. 6) [110]. Similar behavior was also achieved when PTHPMA-co-poly(amino ethyl methacrylate) (P(THPMA-co-AEMA)) was EDC chemistry grafted to the surface of MSNs followed by loading and releasing 5-flurouracil (5-FU) [111].

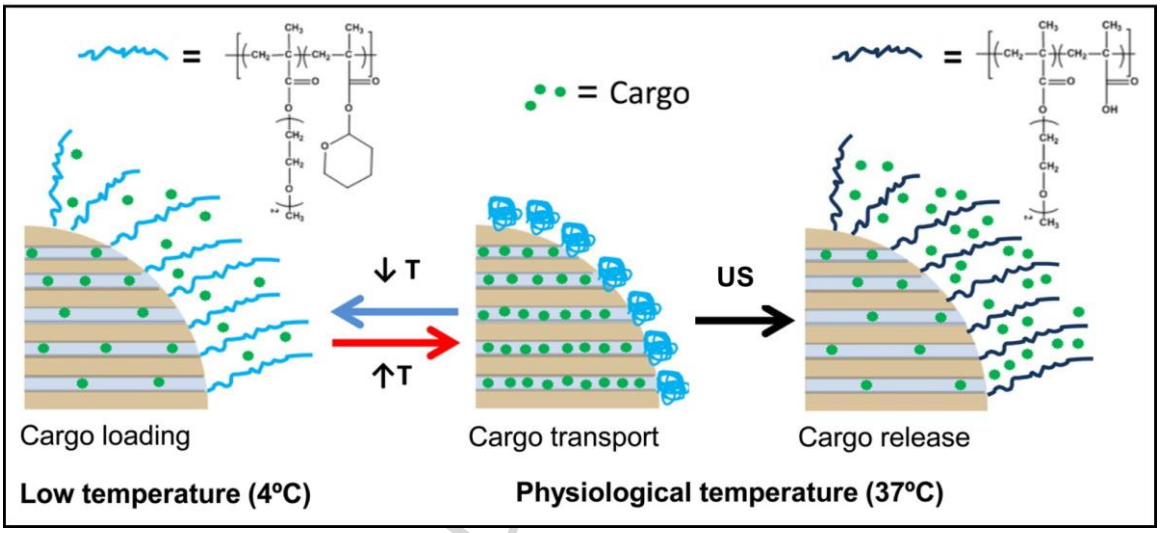

Fig. 6. Schematic showing the release of payloads from p(MEO_2MA-co-THPMA) functionalized MSNs in response to temperature and US. Reproduced with permission from [110].

2.5. Functionalized MSNs for electric field response

Electric field is highly available and has been widely use in our basic daily life as well as medical equipment to improve health condition. Electric field has also been used to tailor the release behavior of encapsulated biomolecules from MSNs [112-115]. Bipolar 4-(3-cyanophenyl)butylene molecules have been functionalized into the inner surface of pores of MSNs and served as nanoimpellers under application of external electric field to control the release of loaded IBU [112]. Regulating the frequency of external electric field could modulate the swinging rate of the bipolar molecules, and subsequently the release rate of loaded IBU could be tailored. Implying the similar concept, copolymers comprised of N-isopropylacrylamide and 4-nitrophenyl methacrylate (PNIPAM-co-PNPMA) were directly synthesized on the surface of MSNs to provide responsive property under the change of two stimuli, temperature and electric field [114]. The copolymer acted as protecting layer to prevent the release of the payload and the release of loaded IBU was accelerated upon increasing the

frequency of applied field or lowering the temperature due to the response of PNPMA and PNIPAM respectively.

Static electric field is also able to trigger the release of bioactive molecules from hybrid MSNs/hydrogel system [113]. The hybrid MSNs/hydrogel system was coated on the surface of titanium plate using electrodeposition method and chitosan solution containing IBU-loaded MSNS. Less than 30% drug released from the system in the absence of static electric field while almost 100% IBU released after 3h trigger under cathodic voltage (-5.0 V) [113]. On other approach, static electric field was used in combination with light to trigger the release of two different model drug molecules from MSNs [115]. Calcein loaded MSNs were capped with CD via ONB-based photocleavable linkage followed by loading of p-coumaric acid in the CD ring and capping with ferrocene through the host-guest interaction (Fig. 7). The host-guest interaction between ferrocene capped agent and CD is disassociation under applying of electric field (+1.5V) for departing of ferrocene and release of p-coumaric acid. Further applying of the system to UV could trigger the release of calcein due to the degradation of ONB-linkage and uncapping of CD from surface of MSNs. Although not many MSNs system that provides the ability of electric-controlled payload release has been reported, electric field has a great potential in controlling drug release form MSNs.

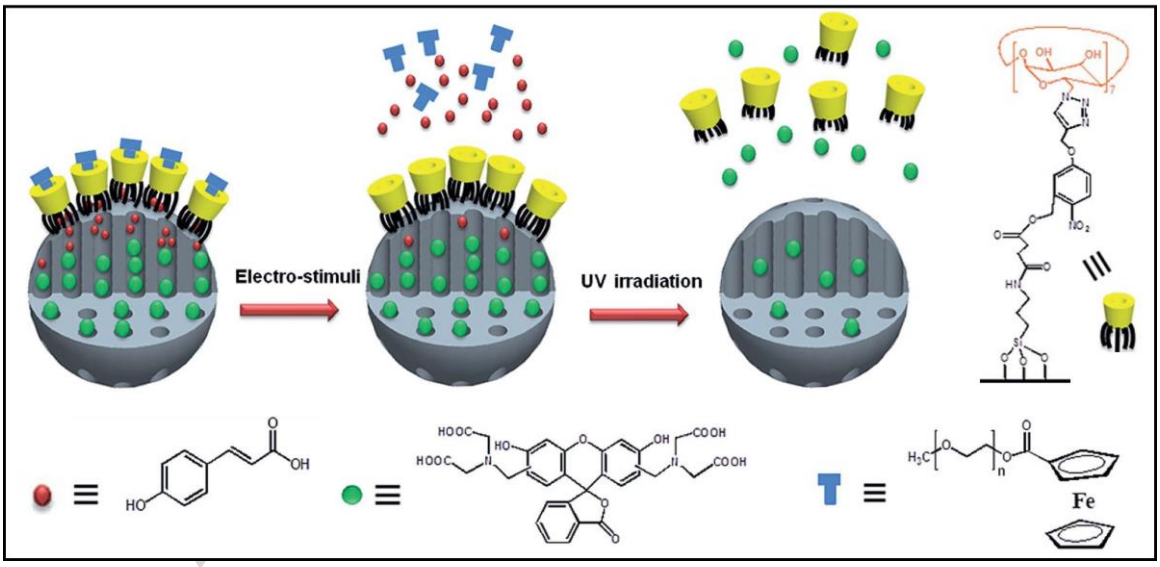

Fig. 7. Schematic showing the release of payloads from MSNs in response to electric and UV light. The capped ferrocene agents depart under applying of electric field for first payload release and UV can trigger the release of second payload. Reproduced with permission from [115].

2.6. Functionalized MSNs for pH response

pH is one of the key factor of biological fluid, blood stream and healthy tissues, which is normally 7.4, and is subjected to change under certain conditions, such as inflammation and tumor sites (pH~6.8). pH is also found much lower in some cytosols (pH 6.5-5.5) and lysosomes (pH 5.5-

4.5). Therefore, using pH to harness the behavior and performance of functionalized MSNs has been widely investigated. Although the bared MSNs have ability to accelerate the release of loaded molecules, such as DOX, at low pH due to the weakening the electrostatic interaction, the triggering effectiveness is rather weak and slow [5, 100, 116-119]. In addition, the loaded molecules can unexpected diffuse out of the MSNs that may cause systemic toxicity. In order to prevent premature diffusion and provide more powerful and robust triggering, many different strategies have been established to functionalize the MSNs.

Functionalization molecules containing the carboxylic acid (COOH) or amine groups to the surface of MSNs is one of the simplest strategies to introduce pH-responsive moieties to MSNs. COOH-contained ligands, including short molecules or polymers, were covalently functionalized [31, 120-122] or physically coated [123] on the surface of MSNs to provide electrostatic interaction with cationic bioactive molecules [120], or act as capping pieces [31, 121-123] to prevent the premature diffusion of loading bioactive molecules. At physiological pH, the functionalized MSNs encapsulated with payloads are stable for long term circulation without systemic cytotoxicity. Upon the reduction of pH, for example in the tumor surrounding area or in the cytoplasm, the system is activated due to the collapse of COOH-contained ligands, which led to the opening of pores for releasing the payloads. On the opposite strategies, amine-containing ligands were conjugated to MSNs to induce electrostatic interaction with anionic bioactive molecules [124] or act as gatekeeper layers [92, 102, 119, 125-128] to trap the payloads in the pores. A wide range of molecules can be employed as amine-contained ligands, including small molecule 3-aminopropyl triethoxysilane [124], poly(3-(3-methacrylamidopropyl-(dimethyl)-ammonio) propane-1-sulfonate)-grafted polydopamine (PDA) [119], poly(2-(dimethylamino)ethyl acrylate) [125], poly(2-(pentamethyleneimino)ethyl methacrylate) [126] polylysine-grafted polyethylenimine copolymers [127]. Conjugated amine-contained ligands could also be used for conjugation or interaction with the capping pieces, such as CD [129], polyCD [130], CB(7) [131], negatively charged AuNP core BSA shield (AuNP@BSA) NPs [132], and mixture of cysteine modified AuNP (AuNP-Cys) and Cu^{2+} [133] or Fe^{2+} [134]. Similar to COOH-contained ligands, these systems and loaded molecules are stable at physiological pH for circulation or deposition to the targeted sites with minimal systemic cytotoxicity and the loaded bioactive molecules could be released at reduced pH environment due to the protonation of amine groups and/or departure of capping pieces. For example, poly(2-vinylpyridine) (PVP) is hydrophobic and water insoluble at physiological pH 7.4 that collapsed on the surface of MSNs to prevent the diffusion of loaded payloads after conjugation [128]. When the system was exposure to pH 5.0, the PVP is protonated and then becomes hydrophilic and water soluble, which lead to the exposure of MSNs pores to surrounding environment for payload release (Fig. 8A).

Acid-labile functional groups that are stable at neutral pH but degraded at acidic pH of tumor tissues or cytoplasm have been widely used as pH responsive moieties to control the performance of MNSs. These moieties include acetal linker [135-137], amide linker [138, 139], boronate linkage [140-143], Schiff base linkage [142, 144], hydrazone bond [145-147] and cis-aconitic acid derivatives [148, 149] were functionalized as linkers between MSNs and capping pieces [135, 136, 138-143, 148, 149] or bioactive molecules [137, 144, 146, 147]. At physiological pH, bioactive molecules loaded or conjugated in these systems are stable for long term circulation and/or deposition to the targeted sites with minimal systemic cytotoxicity. Upon exposure to acidic pH, the degradation of these acid-labile linkers led to the detaching of capping pieces and releasing of encapsulated or tethered bioactive molecules (Fig. 8B). For example, DOX was loaded in boronic acid functionalized H-MSNs followed by capping with 3-(3,4-dihydroxyphenyl) propionic acid functionalized CD via boronic acid-catechol ester bonds (boronate linkages), and subsequently host-guest conjugated with Ad coupled PEG via Schiff base linkage (Fig. 8B) [142]. The system is stable for circulation under physiological pH 7.4 with minimal initial DOX release after 1h of incubation. When the system was exposed to pH 6.8, the release of DOX slightly increased because only the Schiff base bond between the PEG and Ad were cleaved. In contrast, storm DOX release was observed at pH 5.0 due to the degradation of boronate linkages and subsequently detaching of CD capping pieces [142]. In the other example, DOX was conjugated to MSNs via hydrazone bond acid-labile linker and could not be released at physiological pH 7.4 [146]. However, when the system was exposed to pH 5.5, storm release of DOX was observed due to the degradation of hydrazone linker (Fig. 8C). Similar release behavior was also observed when TAMRA dye, a model drug, was conjugated to MSNs via acetal linker [136].

In addition, mineral, oxide and salt of metal can be used to functionalize to MSNs to improve their pH-response property due to the dissolution of metal at low pH [101, 150-153]. The functionalization can be done during the fabrication of MSNs [150, 151] or used as a capping process after loading of the payload [101, 152, 153]. Lipids and lipid conjugated polymers were also reported to form a pH-responsive capping layer to protect the diffusion of the loaded biomolecules for long term circulation under physiological pH 7.4 [154]. Upon exposure under pH 5.0, storm increase of payload was observed due to the disruption of the lipid membrane.

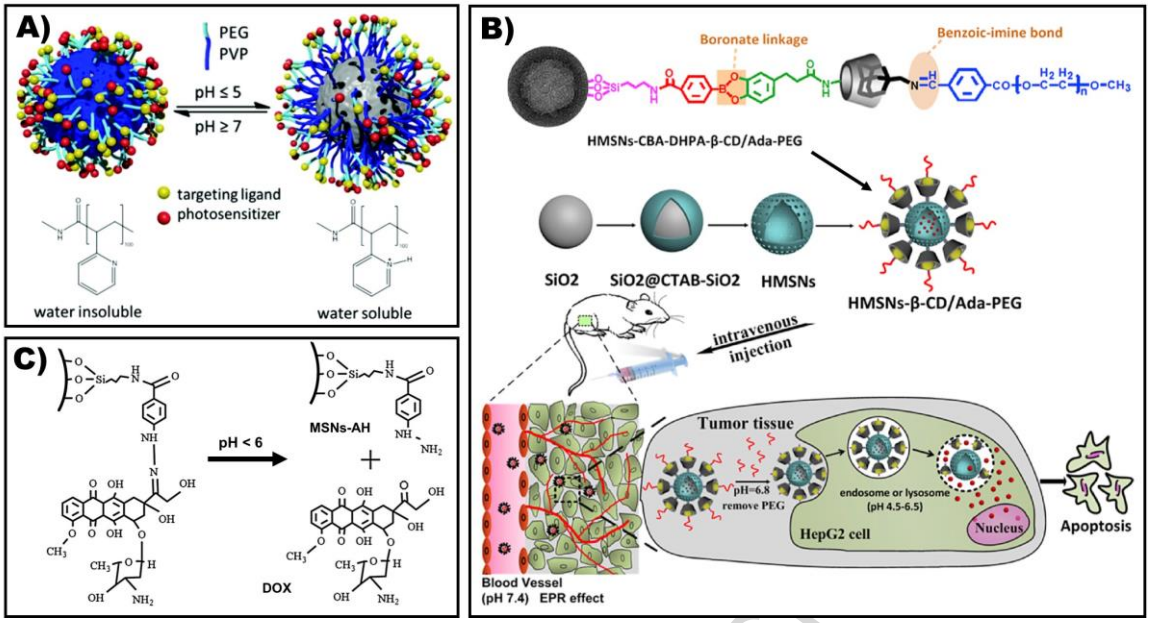

Fig. 8. (A) Schematic showing the concept of the pH-responsive delivery system. The pores can be reversibly opened and closed through changes in the water solubility of the functionalized polymer. Reproduced with permission from [128]. (B) Structure of cascade pH-responsive H-MSNs (HMSNs)-based drug delivery system (top) and schematic illustration of drug delivery process from HMSNs-β-CD/Ada-PEG system in response to pH under tumor microenvironment in vivo (bottom). Reproduced with permission from [142]. (C) Schematic illustration the degradation of the hydrazone bond under acidic condition. Reproduced with permission from [146].

2.7. Functionalized MSNs for Redox agent response

Redox molecules such as glutathione (GSH), dithiothreitol (DTT), and tris(2-carboxyethyl)phosphine possess the ability to degrade the disulfide bond (-S-S-) into two thiol groups in aqueous media. Especially, GSH concentration in cancer cells is significantly higher (approximately 3-fold) compared to normal healthy cells or even more than 100-fold in blood stream [155-157]. In addition, the majority of synthesized MSNs served as nanocarriers for cancer therapy. Therefore, functionalization ligands into the MSNs via redox-degradable disulfide bonds has been used for intracellularly delivery of chemo-payloads to enhance the bioactivity and minimize the systemic cytotoxicity.

Many strategies have been developed to functionalize the MSNs with disulfide bonds for redox-control delivery. In one of the simplest approach, bis-(N-3(triethoxysilyl)propyl 3-carboxamide-4-hydroxy phenyl) disulfide has been used to deposit on the surface of DOX-loaded MSNs to serve as a redox-responsive gatekeeper [155]. Minimal DOX release was detected from the system at pH 6.5 without the presence of GSH while storm DOX release was found after adding GSH to the release media [155]. Typical routes for ligands functionalization onto the surface of MSNs via disulfide bonds include: (1) modification surface of MSNs with thiol groups [24, 156-158] or with pyridine (Pyr) via

disulfide bond [130, 159, 160] followed by capping through disulfide exchange or host-guest interaction with Pyr [130]; (2) functionalization the surface of MSNs with –COOH [1, 23, 127, 131, 161-164] or primary amino [90, 157, 165-171] groups via disulfide bond followed by conjugation of capping pieces; (3) chemically [172] or physically [173] coating disulfide bond containing polymer to the surface of MSNs to serve as gatekeepers. Different chemistries have been used to conjugated capping pieces to -COOH or amino groups on the surface of MSNs, including host-guest interaction between CD and Ad [1, 23] or Pyr [130] or between primary amine and CB(7) [131], EDC conjugation chemistry [23, 127, 157, 161, 162, 165], silane direct deposit [136] and click reaction [171]. In these systems, the loaded biomolecules are stabilized and trapped inside the functionalized MSNs for circulation and can be released under redox intracellularly environment to improve the bioactivity and reduce the systemic cytotoxicity (Fig. 9). In addition, functionalized disulfide containing mesoporous organosilica to serve as an outer redox-degradable layer of MSNs for chemo-therapeutic delivery was also reported to improve loading capacity and delivery efficiency [174].

Some examples of functionalized MSNs for redox-trigger bioactive molecules delivery will be discussed in detail. For example, mPEG-SS-Pyr has been used to capped the dye-loaded MSNs to prevent premature release [156]. Less than 10% of dye could release from MSNs after 24h in the absence of reduction agents while storm release of dye has been observed in the presence of GSH with ~55% dye released within the first 5h. DOX was loaded into the pores of the MSN-SS-Pyr followed by capping with polyCD via host-guest interaction between CD and Pyr to prevent the DOX diffusion (Fig. 9A) and the release of DOX could be control either trigger the pH or adding of GSH [130]. The disassociation of CD-Pyr interaction due to the protonation of Pyr at acidic pH and/or the degradation of disulfide bond under the presence of GSH led to the storm release of DOX (Fig. 9A). In another example, DOX could be loaded in the C18 alkyl disulfide conjugated MSNs (MNS-SS-C18) followed by capping with Pluronic P123 via hydrophobic interaction between C18 and propylene glycol block in P123 to prevent the diffusion of DOX (Fig. 9B) [158]. DOX was trapped in the pores of MSNS and slowly released overtime in the absence of redox agents but abruptly increase in release rate was observed with the presence of GSH due to the degradation of disulfide bond and subsequently detaching of C18-P123 from surface of MSNs. Thiolated transferrin (Tf) protein has been used to cap the surface of DOX-loaded thiolated MSNs to prevent DOX initial burst release [24]. In the absence of redox agents, less than 20% DOX released from the system after 24h. However, storm DOX release was observed in the presence of GSH with over 55% DOX released after 5h due to the detaching of Tf (Fig. 9C).

Beside disulfide bond, other moieties were also reported to be triggered by redox agents. Bis-(N-3(triethoxysilyl)propyl carbamate) diselenide was reported to conjugate to the surface of DOX

loaded in Fe_3O_4@MSNs for preventing DOX diffusion [175]. Similar to disulfide bond, the diselenide bond is also degraded under high concentration of redox agent, GSH. DOX could not diffuse out of the system in the absence of a redox agent, but exhibited a storm release when GSH was added. The release of DOX also can be regulated by changing the GSH concentration [175]. The linkages between Au and thiol (Au-S) [176, 177] or silver and thiol (Ag-S) [178], or organic Pt^{4+} [83] were also reported to be degraded under redox environment. For example, AuNP was used to cap DOX-loaded thiolated MSNs to prevent DOX diffusion. Minimal amount released DOX was detected in the absence of a redox agent while DOX storm release was achieved in media containing GSH [177].

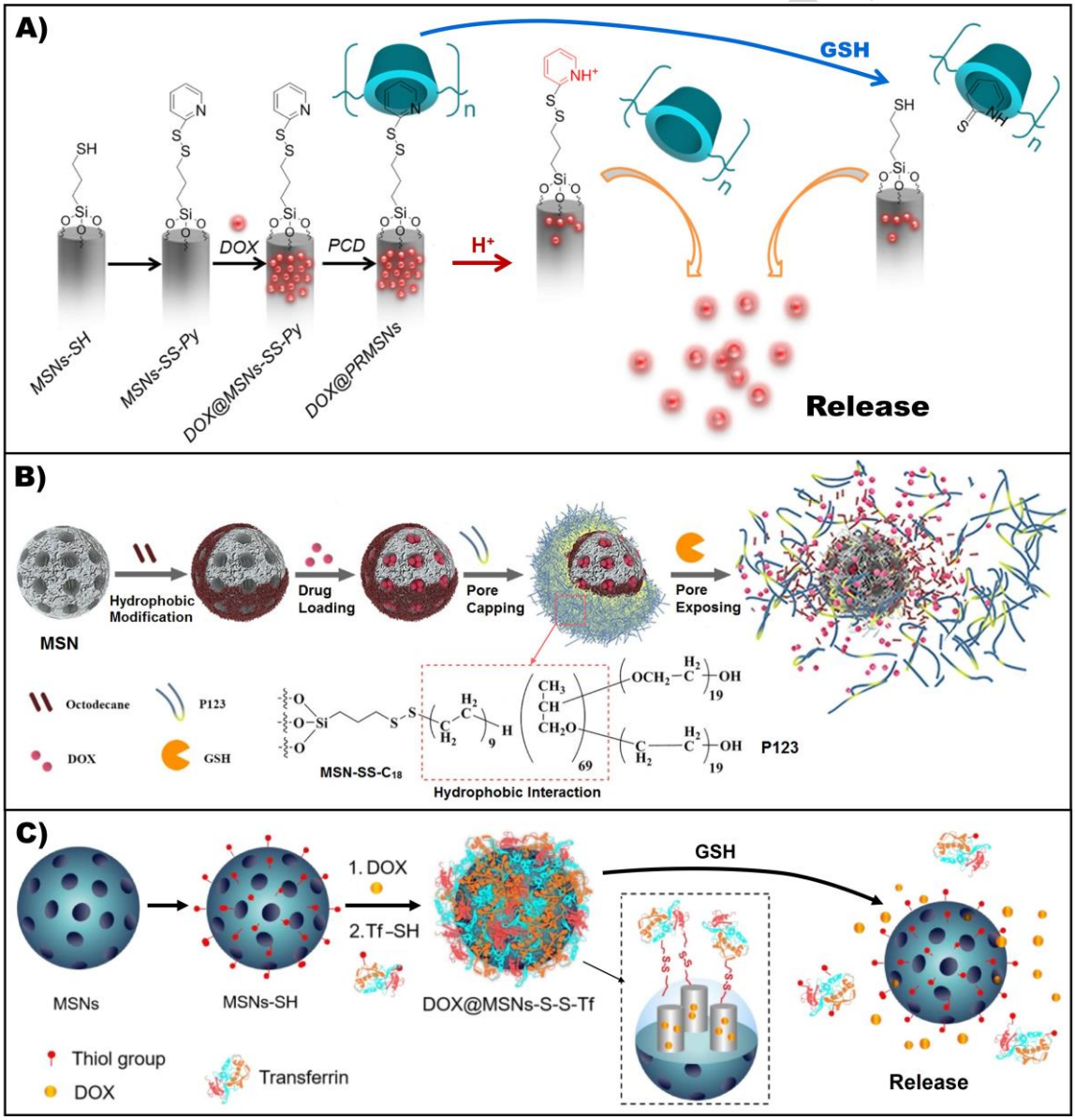

Fig. 9. (A) Schematic showing the fabrication of MSN-SS-Pyr capped with polyCD via host-guest interaction and pH- and/or redox-triggered DOX release. Reproduced with permission from [130]. (B) Schematic showing the fabrication of DOX loaded MNS-SS-C18 capped with Pluronic P123 and redox-triggered DOX release. Reproduced with permission from [158]. (C) Schematic showing the capping of Tf onto DOX loaded MSNs via disulfide bond and the redox-triggered DOX release. Reproduced with permission from [24].

2.8. Functionalized MSNs for ROS response

Reactive oxygen species (ROS), such as H_2O_2, generation is part of metabolic reactions that occurred at a higher degree in relation with certain diseases, for example Alzheimer and heart failure, and in the process of aging and inflammation. Therefore, ROS is can be used as a signal to regulate the release of therapeutic to prevent these diseases. Cyclic ester linkages between arylboronic acid derivatives and adjacent diol molecules stable in the normal bio fluid but can be degraded in the presence of ROS, such as H_2O_2 [179-182]. Bioactive molecules were loaded into phenylboronic acid conjugated MSNs followed by capping with adjacent diol molecules, including human IgG [179] and β-D-glucose-AuNPs [180] to prevent the diffusion of the payload. In the presence of H_2O_2 in the local microenviroment, the phenylborate ester bonds were degraded to form phenol groups and, therefore, the capped molecules detached from the surface of MSNs, which subsequently led to the increasing in release rate of the payloads [179, 180]. For example, β-D-glucose-AuNPs have been used to cap metal chelator clioquinol (CQ)-loaded phenylboronic acid functonalized MSNs for H_2O_2-controlled delivery of the metal chelator CQ under Alzheimer disease microenvironment [180]. It was reported that the aggregation of amyloid beta (Aβ) is strongly effected by metal ions and create neurotoxicity and formation of ROS in Alzheimer disease. Therefore, the ROS pieces, such as H_2O_2, in the Alzheimer disease brain microenvironment could control the release of metal chelator CQ to reduce the aggregation of Aβ, and therefore, reduce the Aβ aggregation-related neurotoxicity (Fig. 10).

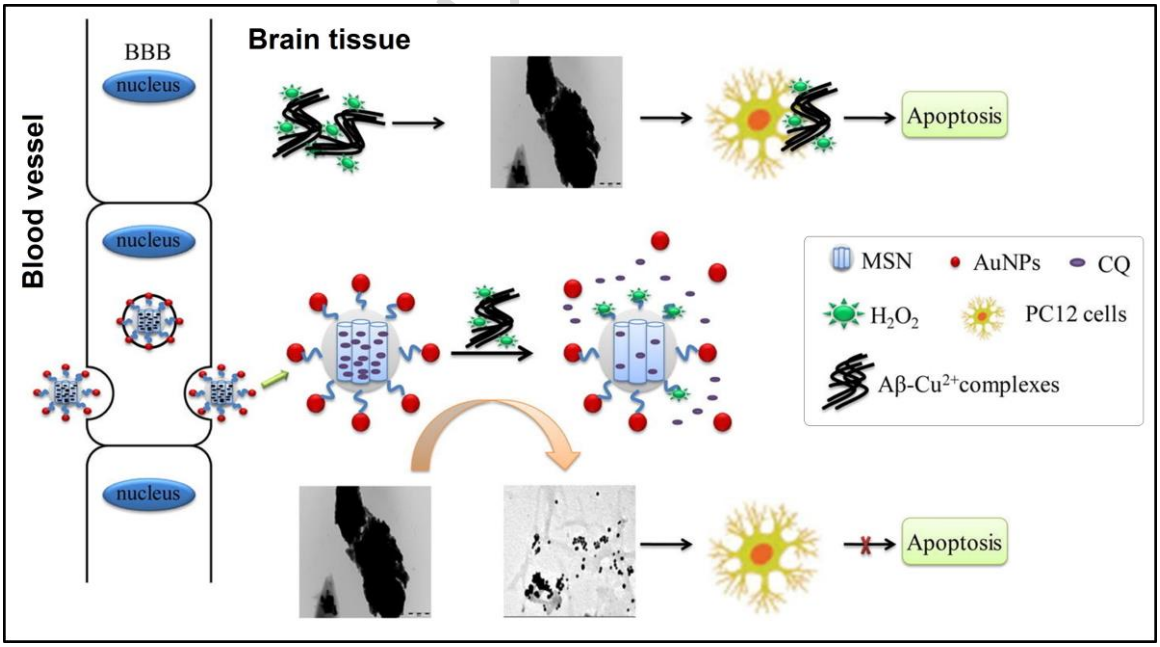

Fig. 10. ROS-controlled payload release from functionalized MSNs. Nanocarriers comprised of β-D-glucose-AuNPs capped on surface of MSNs via phenylborate ester bond passes blood-brain barrier (BBB), and the degradation of phenylborate ester bond under ROS rich microenvironment in Alzheimer disease led to the release of metal chelator CQ. The released CQ prevents the aggregation of Aβ, and therefore, reduces the Aβ aggregation-related apoptosis

of PC12 cells. Reproduced with permission from [180].

Other forms of phenylborate ester bonds for ROS responsive was also reported. Arylboronate pinacol ester containing molecules were conjugated to MSNs followed by loading bioactive molecules and capping with CD via host-guest interaction between arylboronate pinacol ester bonds with CD [181, 182]. The degradation of arylboronate ester bonds under the presence of H_2O_2 lead to the departure of capped CD and then payloads were released. In addition, AgNPs was also reported to response to the presence of H_2O_2 due to the dissolution. Payloads were trapped inside the MSNs capped with citrate-functionalized AgNPs and exhibited only less than 10% release over 72h in the absence of H_2O_2 [183]. However, in the presence of H_2O_2 approximately 60% of the payloaded was release at the same course. H_2O_2 was also reported to oxidize the phenols groups in the PDA to quinone which resulted in loosening of the coated PDA layer and increasing the release rate of loaded DOX from MSNs [109].

2.9. Functionalized MSNs for enzyme response

Enzymes are the most important macromolecular biological catalysts in living body that involve in thousands biochemical reaction type and cell metabolism processes to sustain life [184]. Different enzymes could be found to have a high expression in specific cell types, and therefore the enzymes can be used as unique signals to regulate the intracellular delivery of bioactive molecules, especially the toxic chemotherapeutic in cancer therapy. Many different ligands have been functionalized to the surface of MSNs to fabricate enzyme-induced intracellular controlled delivery of the payloads due to the advantages of enzyme-trigger delivery systems such as mild intracellular condition, highly selectivity, and low side effects. For example, oligo DNA containing telomere repeat complementary sequences CCCTAA was used to wrap on the surface of MSNs to prevent the diffusion and protect the loaded fluorescein or DOX during circulation. However, under the presence of telomerase enzyme in cell cytoplasm, fluorescein or DOX were storm released for imaging [185] or chemotherapy [186].

Cancer cells and tumor tissues were reported to show highly expression of many different enzymes, such as matrix metalloproteinase 2 (MMP-2) [82, 171, 187, 188], Cathepsin B [189], and hyaluronidase (HAase) [164-166, 188]. Using these enzymes to regulate the intracellular release of chemothepareutic at local tumor area for cancer treatment can reduce the amount of drug, enhance the treatment effect and minimize the systemic cytotoxicity. Gelatin or peptides containing PLGVR or PVGLIG sequences were reported to be degraded under exposure to the MMP-2 and have been used to cap on the surface of MSNs to prevent the premature diffusion of loaded molecules [82, 171, 187, 188]. Under the presence of MMP-2, especially at the tumor sites, the degradation of these peptides led to the storm release of the payloads. For example, to protect and prevent the diffusion of loaded

DOX, increase the circulation time, and enhance the tumor deposition of the MSN-based nanocarries, the DOX-loaded MSNs were capped with CD via disulfide bond, followed by conjugation of peptide containing cancer cell targeting RGD and MMP-2 cleavable PLGVR sequence, and subsequently conjugation of anionic poly(aspartic acid) (PASP) (Fig. 11A) [171]. The anionic PASP layer stabilize the system during circulation under physiological conditions by avoiding nonspecific uptake. The abundant presentation of MMP-2 at the tumor site could target PLGVR sequence for removing PASP layer and subsequently exposing cancer cell targeting RGD peptide for internalization. In the presence of high GSH concentration in endosomes and lysosomes, the disulfide bonds were cleaved and the CD capping pieces were removed for storm DOX release to enhance the chemotherapeutic effect and minimize the systemic cytotoxicity to healthy cells (Fig. 11A) [171]. Using a similar concept, HA [164-166, 188] or peptide containing GFLG sequence [189] were functionalized on the surface of DOX-loaded MSNs for preventing DOX premature diffusion and controlling DOX intercellular release from MSNs in response to HAase and cathepsin B enzymes, respectively, which are normally overexpressed in endosomes and lysosomes of cancer cells.

Specific colonic enzyme has been also reported to trigger the release of 5-FU chemotherapeutic from functionalized MSNs [190]. 5-FU-loaded MSNs were coated with guar gum to prevent the diffusion of drug under all pH condition of stomach (1.2), intestine (7.4) and colon (6.8). When the carriers arrive colon, the colonic enzymes secreted from colonic microflora could degrade the gum guar layer for 5-FU site specific delivery (Fig. 11B). No released 5-FU was found at all pH without the presence of colonic enzymes while storm release of 5-FU was observed when the enzyme was introduced into release media. This system offers the ability to protect the pH-sensitive biomolecules for targeting colonic region to treat colonic diseases via orally administration. In addition, other functionalized molecules such as cytosine-phosphodiester-guanine oligodeoxynucleotide (CpG ODN) [191], Ag-stabilized triplex DNA formed by complex a double-strand DNA NF-kB p50 transcription factor (TF) and a Ag-single strand DNA [192], and po(lylysine-dopamine) [193] were also reported to be degraded/disassociated under the presence of deoxyribonuclease I, TF and pepsin, respectively, for control the release of the payloads.

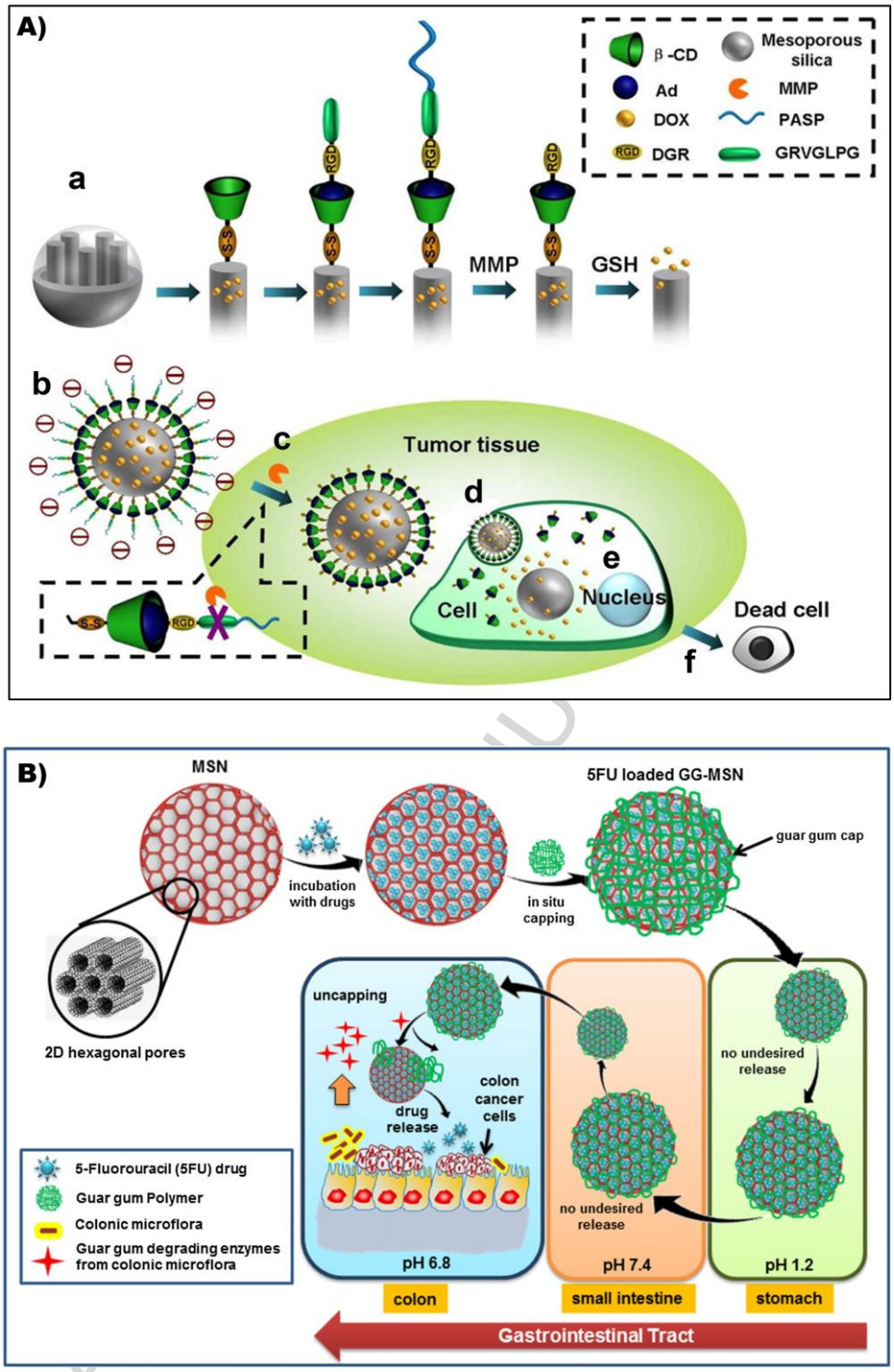

Fig. 11. Schematic illustration of the functionalization MSN-based platforms and their enzyme-controlled payloads release. (A) nanocarriers comprised of DOX-loaded MSNs capped with CD via disulfide bond, conjugated RGD-contained peptide and MMP-2 cleavable PLGVR sequence, and anionic PASP and tumor-trigger delivery: (a) functionalization protocol; (b) nanocarriers under physiological condition; (c) MMP-trigger PASP removal; (d) RGD-mediated cell uptake; (e) redox-trigger DOX intercellular delivery; (f) apoptosis of tumor cells. Reproduced with permission from [171]. (B) Schematic diagram depicting the concept of guar gum capped MSN-based nanocarriers for colon specific drug delivery triggered by colonic enzymes. Reproduced with permission from [190].

2.10. Functionalized MSNs for glucose response

Glucose is an essential component that circulates in the blood of animals as blood sugar. Blood sugar is extremely high in diabetic patient and therefore can be used as an important signal to control the release of insulin, a protein drug for diabetic treatment, or other therapeutic molecules. Phenylboronic acid (PBA) derivatives can interact with specific molecules possessing 1,2- or 1,3-diol moieties to form a reversible covalent boronate bond that can be separated in the presence of glucose due to the competition [140, 194, 195]. 4-carboxy-PBA has been functionalized onto the surface of amino MSNs via EDC chemistry followed by loading the bioactive molecules and capping with gluconic acid modified insulin (G-Ins) [194] or sodium alginate (Fig. 12A) [195] to fabricate glucose-response nanocarriers. The payloads were completely trapped in the pores of MSNs and could not diffuse out in the absence of glucose but exhibited a burst/storm release when glucose was added to media and competed with gluconic acid [194] or alginate [195] to interact with PBA, which removed the capping pieces for the payload release (Fig. 12A). The self-regulated insulin release from PBA functionalized MSNs could be a promising approach for self-controlling blood glucose in diabetes therapy [195]. In addition, glucose can also compete with mannose functionalized on surface of MNSs to interact with capped Concanavalin A for control the release of payloads [196].

Enzyme glucose oxidase (GOx) is widely used for the determination of free glucose in body fluids that can catalyze the oxidation of glucose in the presence of oxygen to form H_2O_2 and gluconic acid [197]. GOx has been functionalized to MNS to fabricate glucose-responsive nanocarriers for controlling the delivery of bioactive molecules [182, 198-200]. To fabricate the nanocarriers, MSNs were functionalized with pinacol phenylboronate followed by loading of insulin and GOx and capping with CD via host-guest interaction between pinacol phenylboronate and CD [182]. Littler amount of insulin was released from the system in PBS but the release rate was abruptly increased after adding glucose to release media due to the degradation of pinacol phenylboronate ester bonds and detaching of CD caps. The pinacol phenylboronate ester bonds was converted to quinone derivative caused by the generated H_2O_2 when GOx converted glucose to gluconic acid. GOx was also used to cap glucosamine functionalized MSN via inhibitor-enzyme interaction for glucose-triggered delivery bioactive molecules [198]. No payload diffusion in the absence of glucose was observed while storm release was achieved when glucose was added to the release media due to the competitive combination of glucose with GOx (Fig. 12B). In another approach, CD-modified GOx (CD-GOx) was used to cap the insulin loaded MSNs functionalized with benzimidazol via host-guest interaction between CD-benzimidazole for glucose-trigger insulin release [199]. In the presence of glucose, GOx could oxidize glucose to form gluconic acid that lead to localized decrease pH and disassociation of CD-benzimidazole interaction, due to the ionization of benzimidazole, to promote the insulin release (Fig.

12C) [199]. In addition, glucose-triggering localized decrease pH to dissolve the ZnO capping pieces for insulin release form MSNs was also reported [200].

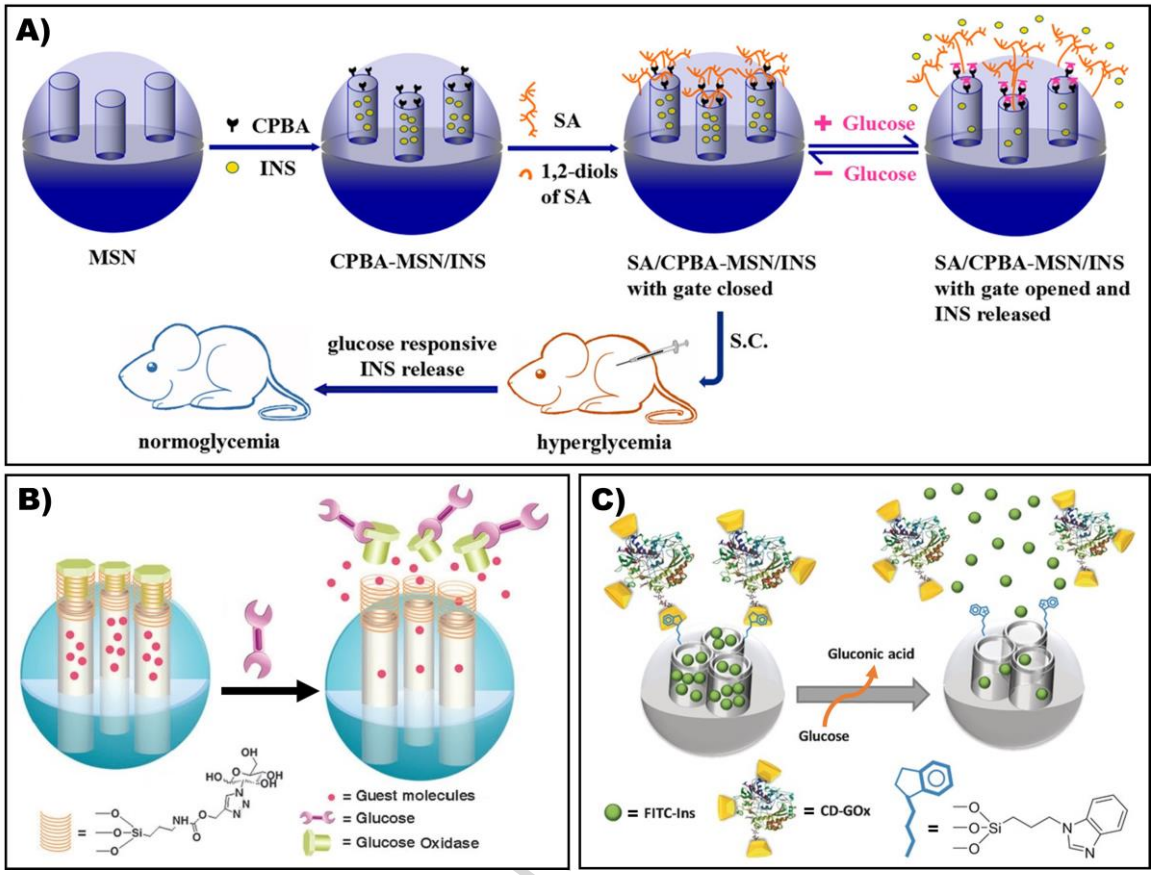

Fig. 12. Schematic illustration of the glucose-triggered payload release from functionalized MSNs nanocarriers composed of: (A) PBA functionalized MSNs capped with alginate via boronate ester bond, which is separated in the presence of glucose, reproduced with permission from [195]; (B) glucosamine functionalized MSNs capped with GOx due to the competitive interaction of glucose with GOx, reproduced with permission from [198]; (C) benzimidazol functionalized MSNs capped with CD-GOx via host-guest interaction between CD-benzimidazole, Reproduced with permission from [199].

2.11. Functionalized MSNs for ATP response

Adenosine-5′-triphosphate (ATP) is a multifunctional nucleotide that involves in a wide range of biological processes in living cells, such as muscle contraction, nerve impulse propagation, cells functioning, synthesis and degradation of biomolecules, and membrane transport [201]. The expression of ATP increases in certain cells or biological processes, especially in the neural stem cells and cancer cells [202], and therefore ATP can be used as a signal to control the delivery of biomolecules from MNS-based nanocaariers. ATP-aptamer possesses the unique characteristic and chemical structure to bind with ATP molecules that have been used for ATP-controlling the release of bioactive molecules from MSNs. Adenosine has been functionalized to the surface of MSNs for capping with ATP-aptamer functionalized on the surface of AuNPs to completely prevent the diffusion of the payloads in the absence of ATP [203]. When APT was introduced into the release media, the

storm payload release has been achieved due to the competitive binding of free ATP with ATP-aptamer conjugated on AuNPs followed by detaching of capped AuNPs (Fig. 13A). ATP-aptamer was also functionalized on to the surface of MSNs via 8 extended bases that can form duplex structure with the first 8 bases of aptamer for acting as gatekeeper to close the pore for completely block the diffusion of payloads [204]. In the presence of ATP, the duplex structure transformed to form hairpin structure and open the pore for payload release. ATP-aptamer has also been reported to form sandwich-type DNA structure with two different single strand DNAs [205] or graphene quantum dots (GQD) [206] to serve as capping pieces to prevent premature diffusion of payloads while allow the release in the presence of ATP competitive binding with free ATP.

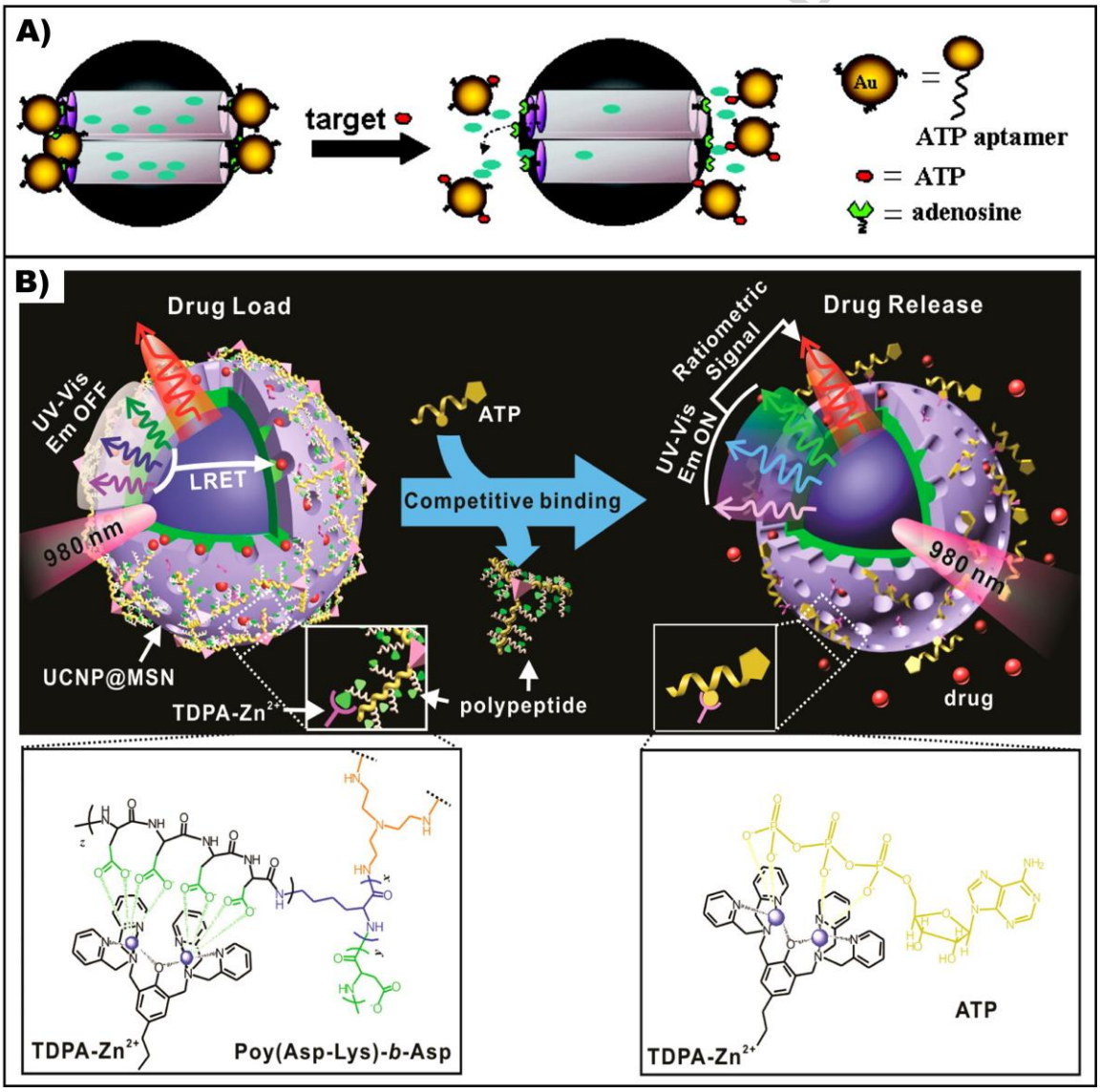

Fig. 13. (A) Shematic showing the ATP-aptamer functionalized AuNPs capped on the surface of denosine functionalized MSNs via denosine-ATP-aptamer binding to prevent the release of loaded fluorescein (left) and the release of payload was selectively triggered in the presence of ATP via competitive interaction with ATP-aptamer followed by detaching of capped AuNPs (right). Reproduced with permission from [203] with reorganizing. (B) Schematic representation of the real-time monitoring of ATP-responsive drug release from polypeptide wrapped TDPA-Zn^{2+}-UCNP@MSNs. Small molecule drugs (red) were entrapped within the

mesopores of the silica shell on the hybrid NPs and the branched polypeptide capped the pores through a multivalent interaction between the oligo-aspartate side chain in the polypeptide and the TDPA-Zn^{2+} complex on the surface of NPs. The UV-Vis emission from the multicolor UCNP under 980 nm excitation was quenched because of the luminescence resonance energy transfer (LRET) between the loaded drugs and the UCNPs. Addition of ATP led to a competitive interaction of ATP to the TDPA-Zn^{2+} complex due to the high binding affinity of ATP to the metallic complex, which resulted in exposing the pore on MSNs surface for drug release. The drug release was accompanied with an enhancement in the UV-Vis emission of UCNP, which allows for real-time monitoring of the drug release. Reproduced with permission from [202].

ATP can bind metal divalent ions, such as Cu^{2+} and Zn^{2+}, with high affinity, and therefore, metal divalent ion complexes can be used as capping pieces for ATP-trigger the payload release in the presence of ATP [133, 202]. Cysteine decorated AuNPs were used to cap the surface of amino MSNs via Cu^{2+} bridges for completely trap the payload in the absence of ATP. By introducing ATP to the media, higher binding affinity of Cu^{2+} and with ATP led to the departure of AuNPs for payload release [133]. In a similar concept, zinc-dipicolylamine analog (TDPA-Zn^{2+}) was grafted on the surface of multicolor upconversion nanoparticles (UCNPs) coated with mesoporous silica core-shell structure (UCNP@MSN) and complexed with poly(Asp-Lys)-b-Asp peptide via multivalent interactions between Asp and Zn^{2+} to protect the payload and prevent the light emission of UCNPs [202]. In the presence of ATP, the formation of higher binding affinity ATP-Zn^{2+} complex led to the disassociation of Asp-Zn^{2+} interaction and subsequently departure of capping peptide for payload release and light emission of UCNPs (Fig. 13B).

2.12. Functionalized MSNs for cell targeting

Systemic delivery of toxic biomolecules, especially chemotherapeutics, from MSN-based nanocarriers may cause undesired cytotoxic to the healthy cells. To minimize these systemic cytotoxic effect, MSNs can be functionalized with specific cell targeting ligands to localize the nanocarriers at the designated cells/tissues due to the targeting to cell specific receptors. TAT-peptide that contains YGRKKRRQRRR sequence can bind with cancer cells available importin α and β receptors and subsequently target the cell nuclear pore complexes for entering their nuclei [207] (Fig. 14A), and therefore it has been used to conjugated to MNSs for targeting cancer cells to deliver chemotherapeutic [207, 208] or harvesting cell DNA [55]. For example, DOX-loaded TAT-functionalized MSNs significantly increased both intracellular and intranuclear DOX concentrations in multidrug resistant MCF-7/ADR cancer cells at much more effectively level than free DOX or non-functionalized MSNs [208]. Similarly, CREKA [209], SP94 [210] and KALA [211] peptides has also been reported to significantly increase cancer cell internalization ability of MSNs when functionalized on their surface.

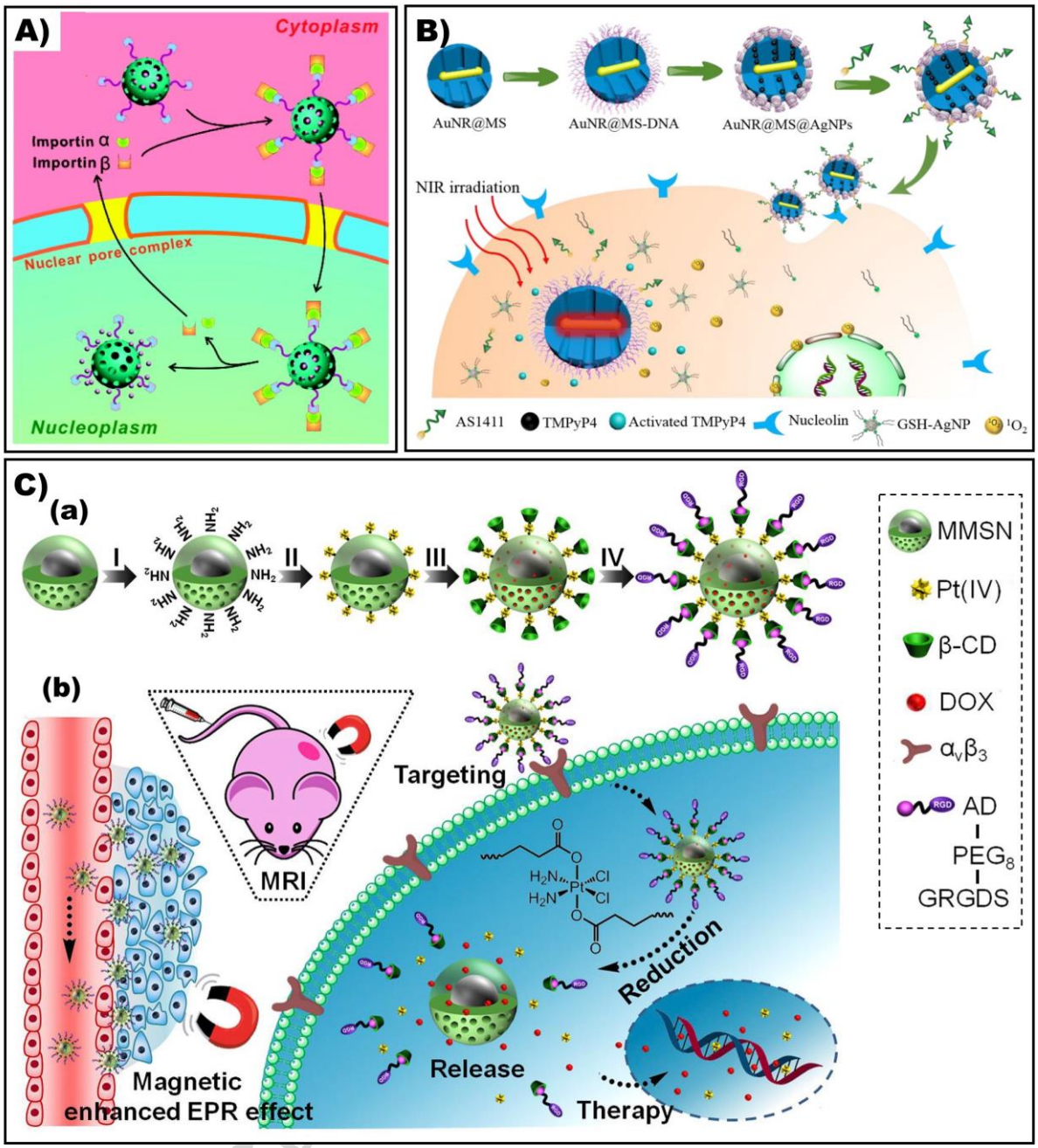

Fig. 14. (A) Schematic showing the transportation of DOX loaded MSNs functionalized with TAT across the nuclear membrane via importin α and β receptors targeting. Reproduced with permission from [207]. (B) Schematic showing steps to fabricate the AgNPs gated AuNP@MSNs functionalized with AS141-aptamer and its nucleolin-mediated cell internalization followed by redox-triggered the payload release; NIR could also be used to induce the hyperthermia effect. Reproduced with permission from [178]. (C) Schematic showing the design and proposed mechanism of the multifunctional M-MSNs (MMSNs) for tumor-targeted MRI and precise therapy: (a) The functionalization protocol of the MMSN. (b) The precise treatment strategy by using multifunctional MMSNs: the external magnetic field enhanced EPR effect to increase the deposition of nanocarriers at tumor sites while the RGD-peptide induced the targeting effect to facilitate the receptor-mediated cell internalization, then the platinum(IV) prodrug was reduced by the redox agents that induced the removal of gatekeeper and triggered the intracellular drug release for precise therapy. Reproduced with permission from [83].

AS141-aptamer containing TTG GTG GTG GTG GTT GTG GTG GTG GTG G sequence possesses highly and specificity recognition capability with nucleolin on the surface of cancer cells, and have been widely used for tumor cell targeting to deliver chemotherapeutics [75, 178, 206]. For example, by decorating AS141-aptamer on the surface of drug loaded core@shell AuNP@MSNs functionalized with DNA and capped with AgNPs, the formed nanocarriers could provide cancer cells targeting, and redox and light responsive ability [178]. AS141-aptamer facilitated the cancer cell internalization while high concentration of redox agent in cytoplasm provided redox-triggered drug release and AuNRs offered photothermal effect under NIR light to enhance the therapeutic effect of the system (Fig. 14B).

Cancer cells possess different type of receptors in their surface, which may be used for targeted delivery of nanocarriers. Folate receptor alpha is highly expressing in a wide range of gynecological cancers that has been used for tumor targeting using Folic acid (FA) containing ligands [212]. FA was reported to functionalize directly on the surface of MSNs or capping pieces to enhance FA receptor-mediated endocytosis in cancer cells for targeting delivery of chemotherapeutics and preventing systemic cytotoxicity to healthy cells [23, 92, 107, 117, 121, 127-130, 175, 213-215]. Similarly, CD44 receptor-mediated endocytosis has been reported to enhance the targeting delivery of MNS-based nanocarriers functionalized with HA to cancer cells [157, 163-166, 173, 188, 216]. MSNs were also functionalized with lactobionic acid (LA), which contains a galactose group and targets to asialoglycoprotein receptor (ASGPR) overexpressed in most cancer cells, to enhance cellular endocytosis in targeted cancer cells [130, 138, 170, 217]. Other ligands that target their receptors overexpressed on the surface of cancer cells, such as RGD containing peptides target integrin receptors [83, 160, 171, 189, 218], Tf peptide targets Tf receptor (TfR1 or CD71) [24, 159, 219], and phenylboronic acid targets sialic acid residues [143, 187], have been shown to significantly enhance the cancer cells targeted delivery of functionalized MSN-based nanocarriers. For example, when the M-MSNs was loaded with DOX followed by chemically capping with CD via Pt^{4+} bridge and then functionalization with RGD containing peptide to fabricated nanocarriers (Fig. 14C), the presentation of nanocarriers in cytoplasm of cancer cells is 2.6-fold more than that in the normal cells after 8 h of culture due to the targeting effect of conjugated RDG [83].

2.13. Functionalized MSNs for multiple signals response

Most of the biosignals that regulate the response of functionalized MSNs present in the tissue microenvironment. For example, cancer tissues have low pH and cancer cells are rich of redox agents, enzyme, and targeting receptors. In addition, the external signals, such as temperature, electric and magnetic fields, and light are readiness and easy to control. Therefore, functionalization the MSNs with multiple ligands could enhance the synergetic effect in controlled delivery of therapeutic while

minimize the systemic cytotoxicity of toxic biomolecules. A wide range of combination ligands among of temperature, pH, magnetic and electric fields, glucose, enzyme, ATP and targeting has been reported.

Functionalized MSNs that response to more than 1 signal can inherit the advantages of all conjugated ligands, which offer more available tool to regulate the performance of MSNs. Ligands that response to pH have been combined with those response to redox agents to enhance the synergetic effect in localized control the delivery of therapeutic molecules [48, 90, 116, 130, 131, 136, 162, 220]. Due to the different of pH and redox concentration at cancer sites and/or in cancer cells, these signals could trigger the release of encapsulated biomolecules from the MSNs nanocarriers (Fig. 9A). pH-responsive ligands were also be co-functionalized with ligands response to temperature [90, 102, 122, 123], magnetic [31, 94, 97, 102] or light [101, 116, 118, 125, 134, 146-149, 221-224] or ATP [133] or glucose [140, 196, 200] or enzyme [148, 225] or US and ROS [109] to enhance the delivery efficiency and therapeutic effect. For example, to prepare nanocarriers response to pH and then enzyme with tracking ability via fluorescence imaging, quantum dot (QD)-doped MSNS were functionalized with zwitterionic oppositely charged functional groups (-COO^- and -$HN^+(Me)_2$) and then coated with PCL via freeze-vacuum-thaw cycles method [148]. The -COO^- group in zwitterionic layer was conjugated to MSNs via a pH cleavable amide group, which can be degraded and create a primary amine group when the pH is less than 6.8. The functionalized nanocarriers are stable for prolonged circulation time in neutral physiological conditions but convert to positive charged at low pH tumor site to facilitate the cellular uptake and consequently enhance the tumor accumulation. The presentation of unique enzyme (esterase) in the cancer cells could trigger the intercellular release of loaded chemotherapeutic (DOX) to inhibit cell growth and enhance cell apoptosis (Fig. 15). The incorporated QD also provided a useful tool to effectively track preloaded drugs and label target cells. This strategy not only provide better therapeutic effects in cancer treatment but also reduce the undesired systemic cytotoxicity [148]. In addition, ligands response to redox agents was also combined with those response to light [176, 177], or US [172], or temperature and magnetic [90] were also reported.

Functionalization the MSNs to target the specific destination cells is important strategy to minimize the systemic cytotoxicity effect. The MSNs can be functionalized with a cancer cell targeted ligand and a redox sensitive moiety to targeted delivery of chemotherapeutics to specific redox rich microenvironment in the cancer cells but not the healthy one [23, 24, 157, 159, 160, 170, 173, 213]. The ligands that response to pH [127, 130, 218] or enzyme [164-166, 171] or light [178] or magnetic field [83, 163, 175] were added to improve the delivery efficiency and/or the synergetic effect. For example, when the M-MSNs was loaded with DOX followed by chemically capping with CD via Pt^{4+} bridge and then functionalization with RGD containing peptide to fabricate nanocarriers, the

presentation of nanocarriers in cytoplasm of cancer cells is 2.6-fold more than that in the normal cells after 8 h of culture due to the targeting effect of conjugated RDG [83]. In addition, the accumulation of these nanocarriers at the cancer site could be enhanced by using an EMF while the highly concentration of redox agent in cytoplasm of cancer cell could facilitate the release of DOX by disassociating Pt^{4+} bridge and converting into Pt^{2+} prodrug form, which significant enhance the therapeutic effect of chemotherapeutics with minimal side effects (Fig. 14C). The magnetic property also allowed these nanocarriers serving as promising contrast agents for tumor-targeted MRI [83]. In addition, the cell targeted ligands can also be used in combination with an additional ligand responses to enzyme [187-189], light [55, 75, 219] and US [107, 211] to improve the therapeutically effect.

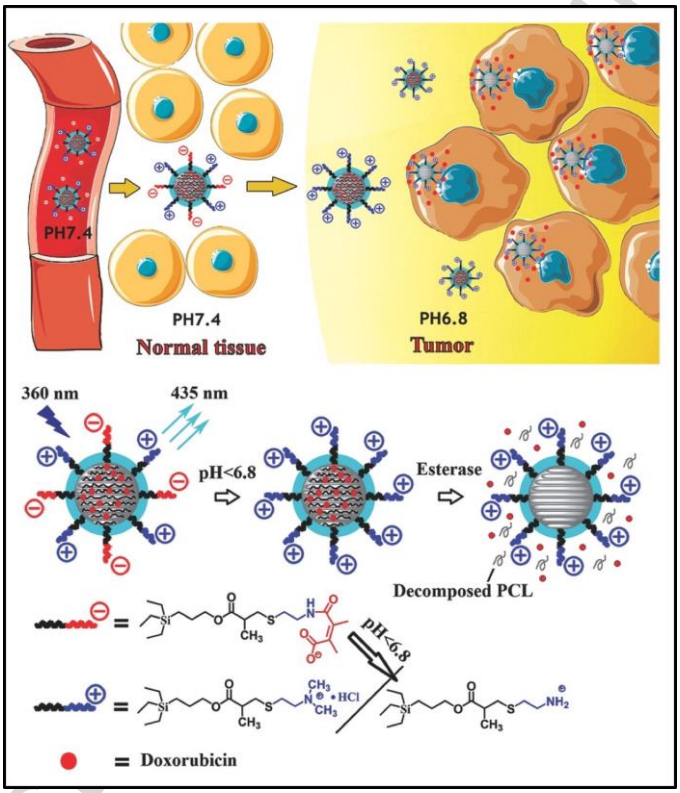

Fig. 15. Schematic showing the nanocarriers composed of DOX loaded QD-doped MSNs functionalized with zwitterionic oppositely charged functional groups ($-COO^-$ and $-HN^+(Me)_2$) and coated with PCL. The zwitterionic group is stable for prolonged circulation in neutral physiological conditions but converts to positively charged amine group at the tumor site (pH<6.8) to facilitate the internalization. In tumor cells, the enzymatic degradation of capped PCL activates the DOX release to induce the apoptosis. The incorporated QD provides tracking tool to effectively track the carriers and/or targeted cells. Reproduced with permission from [148].

Many other combinations have been also reported to provide flexible tools for regulating the release of bioactive molecules. These functionalized systems have been discussed in previous individual section. They are the combination of magnetic fields with enzyme [82, 93], or US [25] [99] or light [89], or temperature [91], or combination of temperature and US [111] or light [39], or

combination of light and electric field [115], or combination of glucose and ROS [182].

3. Potential biomedical application of MSNs

MSNs possess highly porous structure for efficient encapsulation bioactive molecules, ability to be functionalized with different highly reactive groups for ligand conjugation to improve the performance, small side for cell internalization and intracellular delivery of bioactive molecules, that offer a wide range of potential application in biomedical engineering (**Table 1**). This section will focus on the potential application of MSNs as nanocarriers for drug delivery, agents for diagnosis imaging and biocatalyst.

3.1. MSN-based nanocarriers for delivery of bioactive molecules

MSNs offer many advantages to become a novel class of nanocarriers for drug delivery due to their unique properties, such as porous structure for high loading capacity, chemical stability, and surface functionality for stabilizing, biocompatibility, controlled release with or without stimuli regulation, and specific cell targeting. MSNs have shown their ability to encapsulate and control the release of a wide range of bioactive molecules, such as anticancer drugs, DNA, siRNA, growth factor and enzyme, for different application including cancer and diabetic treatment, imaging and biosensor (**Table 1**). MSNs have been functionalized with different ligands to prevent the premature diffusion of loaded bioactive molecules in their pore and then the external signals can be used to trigger the properties of ligands for controlling the release of payloads.

3.1.1. Control anticancer therapeutics release for cancer chemotherapies

The release of different anticancer drugs, such as DOX [65, 130-132, 146-149, 226-230], camptothecin (CPT) [60, 61, 70, 125, 202, 231], 5-Fu [111, 190, 232, 233], Erlotinib [92], Methotrexate (MTX) [102, 209], tanshinone IIA (TAN) [107], topotecan (TOP) [108], etoposide (ETO) [129], irinotecan [154], cisplatin [214], and banoxantrone (AQ4N) [101], and other anticancer therapeutics, such as RNA molecules [54, 127, 167, 174, 210, 211, 217, 234-236], from MSN-based nanocarriers have been investigated. Although the MSNs offer high drug loading capacity, the native MSNs could not provide the sustain and/or control delivery of these anticancer drugs due to the diffusion of payloads and might exhibit undesired systemic cytotoxicity to the healthy tissues. Therefore, difference approaches were discovered to minimize the initial burst release of encapsulated drugs. By functionalizing the MSNs with different ligands, for example ligands response to temperature, light, electrical and magnetic fields, pH, enzyme, ROS or targeting ligands as discussed in previous sections, the released of anticancer drugs can be triggered and or targeted to specific cell types.

Ligands response to temperature [39-41] , light [39, 60, 61, 70, 233, 237], US [111], and magnetic [88] [89] and electric fields [113, 114] have been functionalized to the surface of MSNs to offer more facilitated tool over control the release of loaded drugs. These ligands could protect the encapsulated drug in MSNs for circulation in biological fluid before being activated for control drug release. For example, nanocarriers comprised of Dox-loaded M-MSNc capped with graphene quantum dots (GQD) exhibited hyperthermia effect under magnetic field or light (808 nm) and subsequently accelerated the DOX release rate and synergistic effect of chemotherapy and magnetic hyperthermia therapy in inhibiting the cancer cell growth [89]. In another example, little amount of DOX (~5%) could release from CD-capped DOX-loaded azo-derivatives functionalized MSNs after 6h in the absence of light while ~40% loaded DOX was released at the same period of time in the presence of red light irradiation (625 nm) [52]. The abruptly DOX release was attributed to the departure of CD caused by cis-to-trans transformation of azo group under light exposure as described in Fig. 4C. These functionalized MSN-based nanocarriers loaded with anticancer drugs have been investigated to suppress the tumor growth in vivo and showed significant higher efficacy compared to anticancer drug only [54, 73, 238]. Combination of ligands response to multiple stimuli could enhance the synergistic antitumor efficiency effect of the treatment compared to individual monotherapies [74, 237]. For example, DOX intercellular release from nanocarriers comprised of DOX-loaded PEG-modified MSNs coated with carbon nanotube (CNT) could be triggered under irradiation of NIR light, which resulted in significant increase in cancer cell killing effect in vitro [74]. After the nanocarriers were intravenous injected into tumor bearing mice, a remarkable synergistic antitumor effect was achieved in group with NIR light irradiation compared to monotherapies.

Although functionalized ligands response to temperature, light, US, and magnetic and electric fields could be used to regulate and/or enhance the drug release behavior, the release is not selective that may cause the undesired cytotoxic to healthy tissues. Selected cancer cells/tissue delivery of anticancer drugs from nanocarriers could provide more precise control and enhance the therapeutic effect as well as decrease the dose of chemotherapeutics. Tumor sites/cells possess highly expression of chemical and/or biological signals, such as low pH, high concentration of redox agents, enzyme and ATP, and availability of specific receptor. Therefore, functionalized ligands response to these signals could offer precise site/cell specific delivery of toxic chemotherapeutic to minimize the systemic cytotoxicity. Individual signal include pH [100, 119, 126, 132, 139, 141-143, 145-147, 150-153, 224, 239], redox agents [1, 155, 158, 161, 168, 170, 174], enzyme [186-190, 192], and ATP [202, 206] or their combination with others [24, 48, 82, 83, 92, 97, 109, 116, 123, 125, 127, 130, 131, 148, 162-166, 171, 172, 175, 218, 220, 223, 225] could trigger the release of anticancer drugs from functionalized MSNs either in vitro or in vivo to inhibit the growth of cancer cells or tumors. For example, the release of DOX loaded in nanocarriers comprised Pyr functionalized MSNs via disulfide

bond and then capped with polyCD via host-guest interaction between CD and Pyr (Fig. 9A) could be triggered by either low pH or high concentration of GSH in cancer cells adding of GSH [130]. In another example, nanocarriers comprised of enzyme MMP-2 responsive PLGVR containing peptide functionalized M-MSNs loaded with DOX only exhibit cytotoxicity to MMP-2 expressing HT-1080 cells while retain nontoxicity to negative MMP-2 expressing NIH/3T3 cells [82]. In addition, the external magnetic field could be used to enhance the accumulate of nanocarriers at the tumor site, which significantly increase the ability to suppress the tumor growth compared to non-magnetic or no-nanocarriers treatment groups. The magnetic property also offers the ability for tumor diagnosis via non-invasive MRI technique.

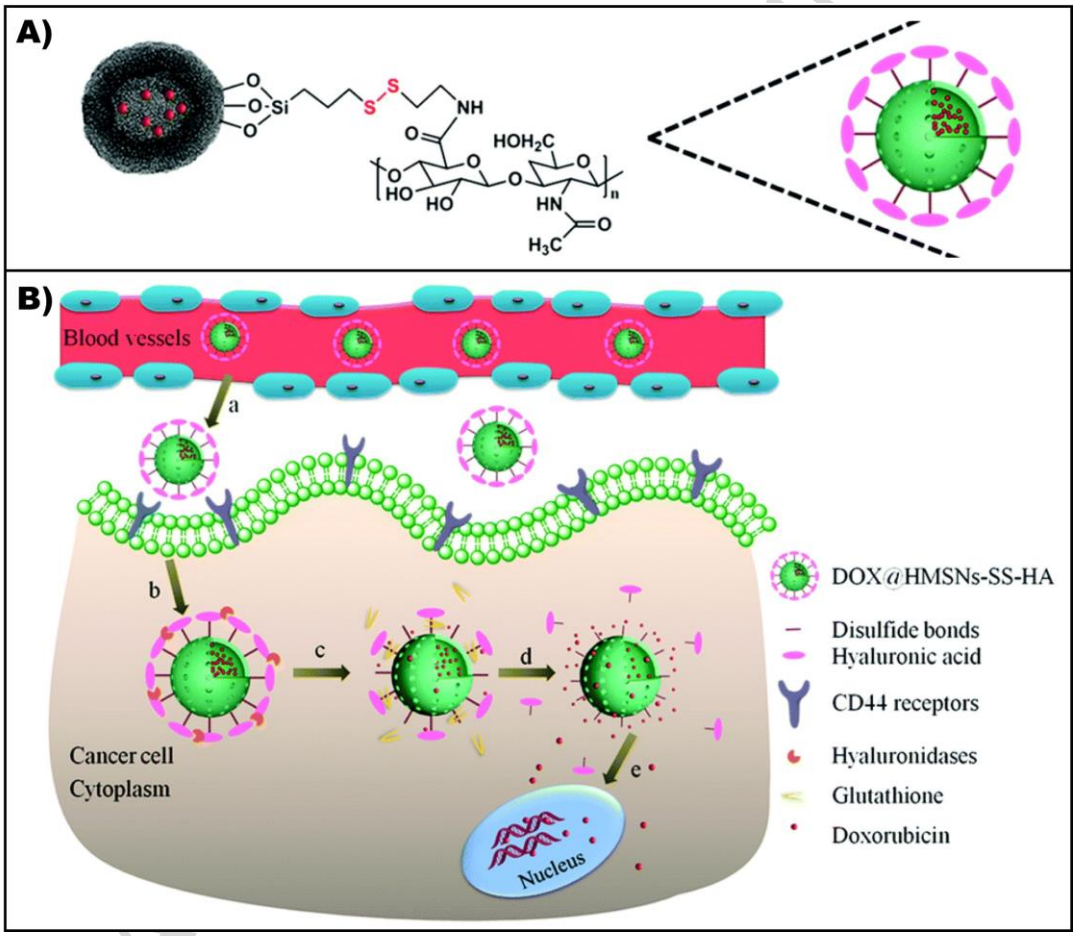

Fig. 16. (A) Schematic showing structure of the HA conjugated DOX loaded H-MSNs via disulfide bond. (B) The mechanism of enzyme and redox dual responsive drug release based on the structural change of DOX@HMSNs-SS-HA. (a) Specific binding to the CD44-receptors on 4T1 cells; (b) CD44-mediated endocytosis of DOX@HMSNs-SS-HA; (c) the degradation of HA by HAase accompanied with release of some DOX; (d) further release of DOX triggered by GSH in the cytoplasm; (e) released DOX entering into the nucleus and its therapeutic effects. Reproduced with permission from [165].

Cancer cells possess highly expression of certain receptors, such as importin α and β receptors for TAT-peptide [207, 208], FA receptor for FA [127-130], CD44 receptor for HA [163-166],

asialoglycoprotein receptor for LA [130, 138, 170, 217], integrin receptors for RGD-contained peptide [83, 160, 171, 189, 218], and Tf receptor for Tf peptide [24, 159, 219]. When the MSNs are functionalized with these molecules, the cancer cells targeting effect can increase the internalization ability of the nanocarriers for improving the localized and controlled chemotherapeutic delivery (Fig. 14), which is important in controlling the growth of multidrug resistant tumor [54, 154, 174, 234, 240] . For example, the nanocarriers comprised HA conjugated DOX loaded H-MSNs via disulfide bond could target the CD44 receptor over-expressed in 4T1 cells and enhanced the nanocarriers deposition at tumor cells, where the redox agents and HAase enzyme could trigger the localized released of DOX for inducing the cancer cell epoptosis (Fig. 16) [165]. When the nanocarriers were intravenously injected into 4T1 tumour-bearing mice, the majority of nanocarriers were deposited at tumor site and the tumor growth was completely suppressed for 14 d while the tumors significantly developed in the non-functionalized nanocarriers or DOX solution groups with approximately 6-fold increase in volume [165].

Other anticancer therapeutics, such as siRNA [127, 167, 210, 211, 217, 234, 235] and shRNA [54, 174, 236], have been delivered via functionalized MSN-based nanocarriers. B-cell lymphoma 2 (Bcl-2)-targeted siRNA was co-delivered with DOX into multidrug resistant A2780/AD human ovarian cancer cells [234] and MDA-MB-231 breast cancer cells [127] using MSN-based nanocarrieers, which showed significantly enhanced efficacy of chemotherapy due to the silencing Bcl-2 message RNA and significantly suppressing the nonpump resistance, and therefore, substantially enhance the anticancer action of DOX. Similarly, P-glycoprotein (P-gp) short-hairpin RNA (shRNA) was co-delivered with DOX from MSN-based nanocarriers for enhancement the DOX activity in multidrug resistance cancer cells in cancer treatment [54, 174]. P-gp protein is overexpressed in various human multidrug resistance cancer cells that regulate the transportation of anticancer drugs out of cell across cellular membranes, and therefore, silencing the expression of P-gp protein could enhance the retention of anticancer drugs in the cancer cells and enhance the therapeutic effect [54]. When DOX and cationic poly(2-(N,N-dimethylaminoethyl) methacrylate) for shRNA interaction were functionalized to MSNs via OBN and coumarin ester derivative linkages, respectively, the nanocarriers can be used to deliver both DOX and P-gp shRNA for via independent light irradiation to enhance the DOX activity for treatment of multidrug resistance cancer [54]. The intercellular release of the shRNA and DOX was independently regulated by 405 and 365 nm light irradiations due to selectively cleaved coumarin and o-nitrobenzyl ester, respectively, which enhanced drug localization and retention, and finally provide the synergistic effect to significantly improve the chemotherapeutic effects both in vitro and in vivo. The release sequence of shRNA and DOX for optimizing the synergistic effect was reported to provide the provided the most effect for inhibition the tumor growth in multidrug resistance HepG2/ADR tumor bearing mice over the course of 24d [54]. Using similar concept, others siRNA or

shRNA, such as short hairpin RNA tumor necrosis factor receptor-associated factor-3 (shRNA-TRAF3) [236], vascular endothelial growth factor (VEGF) targeted siRNA (siVEGF) [211, 217], AllStars Hs Cell Death Control siRNA [167] and cyclin-specific siRNA [210] have also been delivered via MSN-based nanocarriers and demonstrated the potential in suppressing the growth of cancer cells.

US-guided high intensity focused ultrasound (HIFU) surgical therapy via functionalized MSNS have also been reported to show the potential in cancer therapy [25, 103, 105]. Air [105] or liquid perfluorohexane (PFH) [25, 103] were trapped in functionalized MSNs before delivery to cancer cells followed by applying low-energy US or HIFU to generate bubble via cavitation and/or hyperthermia effects to suppress the growth of cancer cells in vitro and tumors in vivo. For example, when the nanocarriers fabricated from M-MSNs loaded with liquid PFH were injected into BALB/c female nude mice bearing MDA-MB-231 breast cancer, followed by applying the a.c. EME, the ultrasound signals are greatly improved and the tumors were completely ablated after 4 days while tumors were significantly increased in control saline treated group [25].

3.1.2. Disease treatment

MSN-based nanocarriers have been reported to have potential in treatment of Alzheimer's disease [179, 180] or heart failure [64, 181]. It was reported that the Alzheimer's disease could be promoted by metal ions via accelerating the Aβ aggregation and formation of ROS, which could be blocked through metal chelators [180]. As discussed in previous section, nanocarriers composed of metal chelator clioquinol (CQ)-loaded phenylboronic acid functonalized MSNs capped with β-D-glucose-AuNPs exhibited the H_2O_2-controlled delivery of the metal chelator CQ under Alzheimer disease microenvironment. The released CQ prevented the aggregation of Aβ, and therefore, reduce the Aβ aggregation-related apoptosis of PC12 cells in Alzheimer's disease (Fig. 10) [180]. In another approach, localized delivery of curcumin [64] or captopril [181] from MSN-based nanocarriers could improve the heartbeat rate and cardiac output in zebrafish experiencing acute transgenic KillerRed (SqKR15)-based ROS-triggered heart failure model. In addition, functionalized MSNs response to glucose have shown the potential in control blood glucose level in diabetic animal models [182, 195, 200].

3.1.3. Wound healing and tissue Regeneration

Although rare but the potential application of MSN-based nanocarriers have been shown in wound healing and tissue regeneration [241, 242] . The injured sites normally content an elevated concentration of ROS, which may cause cellular senescence, fibrotic scarring, and inflammation. ROS-

reponsive functionalized MSN-based nanocarriers were reported to promote wound healing process [241]. Ultrasmall ceria nanocrystals were doped on the surface of amino functionalized MSNs to provide a highly versatile ROS-scavenging tissue adhesive nanocomposite. The ceria nanocrystals in the system not only offered strong tissue adhesion strength, but also significantly accelerated the wound healing process with much improved skin appendage morphogenesis and limited scar formation [241]. Positively charged functionalized MSN-based nanocarriers have been reported to deliver hepatocyte nuclear factor 3β plasmid DNA (pHNF3β) for significantly improving the differentiation of induced pluripotent stem cells into hepatocyte-like cells with mature functions within 2 weeks in vitro [243]. Increasing the delivery frequency of pHNF3β even further improved the degree of differentiation. PEI functionalized MSNs nanocarriers loaded with growth factors were also reported to direct the differentiation of mouse embryonic stem cells (mESCs) into hepatocyte-like cells (iHeps) in vitro and in vivo [242]. The system showed significantly improvement in differentiation toward iHeps in vitro with mature functions while induced the regeneration of damaged hepatic tissues after four weeks transplantation into liver-injured mice.

3.2. Imaging and diagnostic therapy

Monitoring the localized and targeted delivery of chemotherapeutic is important in order to minimize the systemic cytotoxicity. Different ligands and molecules, such as Chlorin e6 [72], FITC [130], hoechst [132], carbon dot [164, 168], ^{64}Cu [176], fluorescein [185], multicolor upconversion nanoparticle [202] and N,N-phenylenebis(salicylideneimine)dicarboxylic acid (Salphdc) [121], have been functionalized to MSNs to fabricate nanocarriers which not only can deliver the chemotherapeutic but also offer the ability to monitor the biodistribution of nanocarriers. For example, nanocarriers fabricated from DOX loaded ^{64}Cu-labeled MSNs gated with AuNPs could not only offer the NIR-triggered DOX release and the synergistic effect of photothermal therapy in cancer therapy but also provide biotools, PET imaging, to detect the existence of clinically relevant spontaneous lung tumors in a urethane-induced lung cancer mouse model [176].

Magnetic NPs were functionalized into MSNs to provide magnetically properties for either regulating the release of payloads or serving as MRI agents [95, 101]. The most popular magnetic NPs is Fe_3O_4 and Fe_2O_3 that were widely used to decorate MSNs for serving as MRI-sensitive probes [25, 82, 83, 86, 95, 102, 244]. By incorporating the magnetic NPs, the functionalized MSN-based nanocarriers can be used as non-invasive MRI agents for the real-time diagnosis the tumor treatment process of living animals. For example, by doping Fe_2O_3 NPs to MSNs, they exhibited excellent longitudinal (R1) and transverse relaxivities (R2) with R2/R1 ratio close to 1, which have potential as a magnetic contrast agent [244]. When the Fe_3O_4 NPs were incorporated to the core of MSNs, they not

only enhanced the accumulation nanocarriers in the cancer site under EMF but also increased the contrast in MR imaging in vivo [83]. In addition, magnetic NPs were also co-incorporated with PFH into MSNs to enhance both MRI and US signals as well as anti-cancer effect [25, 99]. For example, when PFH was loaded into M-MSNs to form nanocarriers, the magnetic hyperthermia effect could lead to vaporization of the loaded PFH, which generated PFH gas bubbles and significantly improve the ultrasound signals [25]. These effects also showed highly efficient anticancer effects by completely suppressing the tumor growth after 4d of treatment.

Gadolinium (Gd) [73, 97, 98, 163, 215, 245-247] and MnOx [99-101] are also important magnetic sources for functionalization into the core or on the surface of MSNs. Paradigmatic Gd doped MSNs were reported as highly efficient MRI contrast agents with highly potential for disease diagnosis [246, 247]. Fluorosilane or polyfluorosiloxane could also be co-functionalized with Gd to MSNs to serve as ^{19}F MRI-sensitive and ^{1}H MRI-sensitive probes, respectively, to fabricate nanocarriers that provides dual detection of ^{1}H and ^{19}F MRI signals [245]. Non-metal perfluoro-15-crown-5-ether (PFCE) was functionalized to MSNs for serving as MRI agents for targeting theranostic cancer treatment [248].

To enhance the US signal, PFH and hydrophobic alkyl were functionalized onto MSNs for increasing bubble cavitation effect [103, 104, 106, 172]. Perfluorodecyl functionalized MSNs were reported to exhibit a significant and strong contrast intensity with approximately 6-fold increase in the duration of enhancing compared to lipid microbubble systems [104]. Co-functionalization of US-hyperthermia agent AuNPs and PFH onto MSNs could lead to significant thermal accumulation effects and PFH bubble cavitations for enhancing signal of ultrasound imaging and HIFU anti-tumor efficacy [103]. In addition, functionalization of active ^{64}Cu nuclear reactor onto MSNs could have potential to be used as nanocarriers for localized therapeutic delivery and PET imaging and maybe in radiotherapy [209].

3.3. Biocatalyst

MSNs possess high surface area and absorption capacity, excellent mechanical stability, with uniform pore distribution, and functionalizable surface that are suitable for acting as biocatalyst, especially encapsulation and protection enzymes against proteolysis and attenuate immunological response for intercellular bioanalysis. Nanosystem comprised of luciferin loaded in the pores MSNs functionalized with AuNPs as capping pieces via disulfide bond, and conjugated with PEGylated luciferase has been for self-catalyst luminescence for evaluating tumor development [249]. In the presence of intracellular ATP and redox, the released luciferase catalyzed the oxidation luciferin that emitted luminescence. The nanosystem provides a unique platform for evaluating tumor development,

monitoring the response to treatments and measuring the therapeutic efficacy. In another approach, a nanosystem fabricated by in situ forming of AuNPs on surface of amino MSNs could serve as a robust nanoreactor with enzyme-mimetic catalytic property for cascade reaction through self-activated process, in which the nanosystem mimicked GOx to catalytically oxidize glucose in the presence of O_2 to produce gluconic acid and H_2O_2. This design can be used to fabricate artificial enzymes with versatile functionalities and reactivities that can be beneficial for a wide range of applications including biocatalysis, bioassays, nano-biomedicine and nanotechnology [250]. H-MSNs loaded with horseradish peroxidase (HRP) acted as an intracellular catalyst for the oxidation of the prodrug indole-3-acetic acid to produce free radical toxic moieties for inhabitation the growth of cancer cells [251].

Table 1: Summary of potential biomedical application of MSN-based nanosystems referenced in this article.

Anticancer drug delivery for cancer treatment and imaging		
Application	***Drug or signal***	***Reference***
In vitro delivery	DOX	[1, 23, 24, 38-40, 48, 53, 62, 65, 71, 75, 109, 110, 116-119, 126-128, 131-133, 139, 141, 143, 145, 147, 149, 151-153, 158, 160, 162, 166, 169, 171, 173, 177, 188, 189, 192, 207, 208, 218, 220, 224-227, 229, 230, 239]
	DOX + RNA	[127, 161, 234]
	5-FU	[111, 190, 232, 233]
	Camptothecin (CPT)	[60, 61, 70, 125]
	6-MP	[157]
	Erlotinib	[92]
	Gemcitabine	[132]
	Imatinib mesylate	[35]
	Methotrexate (MTX)	[156]
	PTX	[49]
	Tanshinone IIA	[107]
	$TMPyP_4$	[178]
	Topotecan	[108]
In vitro delivery + cell imaging	DOX	[130, 146, 148, 164, 168, 172, 176, 206, 219]
	DOX+ CPT	[202]
	Etoposide	[129]
	MTX	[209]
	-	[104, 106, 137, 185]
In vitro delivery + MRI	DOX	[31, 41, 88, 89, 100, 155, 175, 223, 247, 248]
	CPT	[95]
	MTX	[102]
	-	[98, 244-246]
Treatment cancer in vivo	DOX	[74, 121, 123, 134, 142, 150, 159, 165, 170, 186, 187, 213, 228, 237, 238]
	DOX + RNA	[54, 174]
	AQ4N	[101]
	Ce6	[72]
	Cisplatin	[214]
	Irinotecan	[154]
	RGD-hylin a1	[120]
	siVEGF	[211]

	US	[103, 105]
Treatment cancer in vivo + MRI	DOX	[73, 82, 83, 97, 163, 215]
	HSV-TK/GCV gene	[86]
	US	[25, 99]
Delivery other drugs		
Application	***Drug***	***Reference***
In vitro delivery system	siRNA	[127, 167, 210, 217, 234-236]
	IBU	[28, 30, 63, 122, 152, 183]
	Enrofloxacin	[85]
	Naproxen	[56, 58]
	p53 gene	[161]
	Protein drug	[222]
	Quercetin	[29]
	SO and UA	[138]
	Vitamin E	[124]
	IGF	[98]
Disease treatment		
Disease	***Drug***	***Reference***
Alzheimer's	CQ	[179, 180]
Heart failure	Curcumin	[64]
	Captopril	[181]
Diebetic	Insulin	[182, 195, 200]
Tissue regeneration and wound healing		
Growth factor delivered from MSNs induced the differentiation of mouse embryonic stem cells into hepatocyte-like cells		[242]
Hepatocyte nuclear factor 3β plasmid DNA delivered from MSNs improved the differentiation of induced pluripotent stem cells into hepatocyte-like cells		[243]
Ce2+ encapsulated MSNS significantly accelerated the wound healing process with much improved skin appendage morphogenesis and limited scar formation on SD rats		[241]
Other applications		
Biosensor		[59, 93, 252]
Biocatalyst		[249-251]
Anti-bacteria		[253-255]

3.4. Other applications

Beside those potential biomedical applications discussed in previous section, functionalized MSNs have also been used as nanocarriers for other application, such as biosensor [59, 93], bioassay [252] and anti-bacteria [253-255]. For example, Fe-based M-MMSs doped with Ni nanosystem has demonstrated the highly selective recognition of His-tagged enzymes via the conjugation between the His-tag and Ni ions. been used as a convenient and high throughput detection of histidine-tagged enzymes [93]. This nanosystem provide offer a potential for separation and immobilization of a broad range of polyhistidine-tagged proteins. MSNs functionalized with phenyltrimethyl groups could entrap thymolphthalein, a pH-indicator, for selectively detecting prostate specific antigen (PSA) that provide an alternative approach for detecting important biomarkers in complex biological samples at low cost

and timely fashion [252]. AuNPs functionalized MSNs with antibiotic-loaded nanovehicles exhibited a synergistic antibacterial effect that showed potential in the treatment of drug-resistant infections [255].

4. Conclusion and future perspective

MSNs have been widely studied to find the potential in biomedical applications thank to their unique properties, such as controllable pore and particle sizes, high surface area and pore volume, functionalizable surface, excellent stability and biocompatibility, and absorption/loading capacity. This article provided an overview in fabrication of functionalized MSN and strategies to regulate the response of MSN-based nanocarriers for potential application as drug delivery systems, chemotherapeutics, therapeutics for disease treatment, imaging contrast agents, biocatalysts and biosensors. The highly functionalizable property of MNSs allow conjugation different types of ligands on their surface to tailor their performance. A huge progress has been achieved since MSNs were reported as drug delivery system for the first time in 2001. By functionalization ligands that sensitive to external stimuli, such as temperature, magnetic and electric fields, light and US, or internal tissue/cell available signals, such as pH, redox agents, enzyme, ATP, ROS and molecular targeted receptors, to the MSNs, they can be used as nanoplatforms for controlled, localized, and targeted delivery of various chemotherapeutics, proteins, enzyme and RNA. They can also be used as intracellular biocaltalysis, biosensors to detect important biomarkers, and imaging contrast agents to improve the US and MRI signals in diagnostic therapies.

Functionalized MNS-based platforms that response multiple stimulus signals not only provide the ability to control the delivery of bioactive molecules but also offer a precise localized and targeted tissue/cells which help to enhance the therapeutic efficiency and minimize the side systemic cytotoxicity to the healthy tissues/cells. These systems also offer the ability to delivery multiple bioactive molecules for enhancing the synergistic effect to improve the therapeutic efficacy. The H-MSNs can offer a significantly higher internal cavity for further increasing loading capacity. For example, the combination of targeting functionalization and intracellular co-delivery of anticancer drugs and siRNA from MNSs can enhance the cancer cells targeting, localization and drug retention for synergistic effect in cancer treatment. In addition, external stimuli signals can also be used to enhance the therapeutic effect, including hyperthermia from light and US, magnetically targeting or imaging guidance.

Although MSN-bases platforms offer many advantages, their low degradation rate may increase their accumulation in the body/tissue. Their modification with other form of silica-based mesoporous NPs, which was named mesoporous organosilica NPs containing disulfide bond on its structure [256,

257], may offer multiple steps controlled delivery platforms in redox rich cancer cell environment to enhance the therapeutic effect and biodegradability of the platforms [174]. The MSN-based platforms were mainly investigated for controlled delivery of therapeutic molecules, especially anticancer drugs, for cancer therapy while limited number of study focused on other disease and tissue regeneration. The functionalized MSN-based have been reported to offer high loading capacity and protection ability to a wide range of bioactive molecules as well as ability of localized and controlled intracellular delivery, and therefore, the beneficial effect of these advantages in regulating the tissue regeneration process at cellular level need to be investigated. In addition, the synthesis of functionalized MSN-based requires multiple steps with complicated chemical reactions that limited industrial scale fabrication and raised a concert about the potential aggregation of functionalized MSNs as well as. Finally, further laboratory designs, pre-clinical and clinical trial explorations, including synthesis and structure optimization, systematic biosafety evaluations, and in vivo theranostic performances, should be focused to enable the successful biomedical applications of these smarted nanosystems.

Acknowledgement

This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.03-2018.46.

References

[1] T.T. Nguyen Thi, *et al.*, Hierarchical self-assembly of heparin-PEG end-capped porous silica as a redox sensitive nanocarrier for doxorubicin delivery, Mater Sci Eng C Mater Biol Appl, 70 (2017) 947-954.
[2] T. Yanagisawa, *et al.*, The Preparation of Alkyltriinethylaininonium–Kaneinite Complexes and Their Conversion to Microporous Materials, Bulletin of the Chemical Society of Japan, 63 (1990) 988-992.
[3] Kresge, C.T., *et al.*, Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism, Nature, 359 (1992) 710-712.
[4] J.S. Beck, *et al.*, A new family of mesoporous molecular sieves prepared with liquid crystal templates, Journal of the American Chemical Society, 114 (1992) 10834-10843.
[5] H. Xu, *et al.*, A facile route for rapid synthesis of hollow mesoporous silica nanoparticles as pH-responsive delivery carrier, Journal of colloid and interface science, 451 (2015) 101-107.
[6] A. Katiyar, *et al.*, Synthesis of ordered large pore SBA-15 spherical particles for adsorption of biomolecules, J Chromatogr A, 1122 (2006) 13-20.
[7] D. Zhao, *et al.*, Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 angstrom pores, Science, 279 (1998) 548-552.
[8] S. Inagaki, *et al.*, An ordered mesoporous organosilica hybrid material with a crystal-like wall structure, Nature, 416 (2002) 304-307.
[9] S. Che, *et al.*, Synthesis and characterization of chiral mesoporous silica, Nature, 429 (2004) 281-284.
[10] C.Y. Lai, *et al.*, A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules, J Am Chem Soc, 125 (2003) 4451-4459.

[11] D.R. Radu, *et al.*, Fine-tuning the degree of organic functionalization of mesoporous silica nanosphere materials via an interfacially designed co-condensation method, Chem Commun (Camb), DOI 10.1039/b412618a(2005) 1264-1266.
[12] M. Vallet-Regi, *et al.*, A New Property of MCM-41: Drug Delivery System, Chemistry of Materials, 13 (2001) 308-311.
[13] Q. Cai, *et al.*, The preparation of highly ordered MCM-41 with extremely low surfactant concentration, Microporous and Mesoporous Materials, 32 (1999) 1-15.
[14] A.B.D. Nandiyanto, *et al.*, Synthesis of spherical mesoporous silica nanoparticles with nanometer-size controllable pores and outer diameters, Microporous and Mesoporous Materials, 120 (2009) 447-453.
[15] T. Sánchez, *et al.*, Ultrasounds and microwave-assisted synthesis of mesoporous hectorites, Microporous and Mesoporous Materials, 171 (2013) 24-34.
[16] H. Zhang, *et al.*, Synthesis of hollow ellipsoidal silica nanostructures using a wet-chemical etching approach, Journal of colloid and interface science, 375 (2012) 106-111.
[17] P. Zhao, *et al.*, Synthesis and Drug Delivery Applications for Mesoporous Silica Nanoparticles J Med Biotechnol 1(2017) 1-8.
[18] S. Kumar, *et al.*, Synthesis Methods of Mesoporous Silica Materials, Materials Today: Proceedings, 4 (2017) 350-357.
[19] B.G. Trewyn, *et al.*, Biocompatible mesoporous silica nanoparticles with different morphologies for animal cell membrane penetration, Chemical Engineering Journal, 137 (2008) 23-29.
[20] S.M. Sieburth, *et al.*, Silanediols: A New Class of Potent Protease Inhibitors, Angew Chem Int Ed Engl, 37 (1998) 812-814.
[21] S. Singh, *et al.*, Serine protease inhibition by a silanediol peptidomimetic, Organic letters, 14 (2012) 4422-4425.
[22] H. Kettiger, *et al.*, Interactions between silica nanoparticles and phospholipid membranes, Biochimica et biophysica acta, 1858 (2016) 2163-2170.
[23] Q. Zhang, *et al.*, Multifunctional Mesoporous Silica Nanoparticles for Cancer-Targeted and Controlled Drug Delivery, Advanced Functional Materials, 22 (2012) 5144-5156.
[24] X. Chen, *et al.*, Transferrin gated mesoporous silica nanoparticles for redox-responsive and targeted drug delivery, Colloids and surfaces. B, Biointerfaces, 152 (2017) 77-84.
[25] Z. Teng, *et al.*, A magnetic droplet vaporization approach using perfluorohexane-encapsulated magnetic mesoporous particles for ultrasound imaging and tumor ablation, Biomaterials, 134 (2017) 43-50.
[26] J.L. Vivero-Escoto, *et al.*, Mesoporous silica nanoparticles for intracellular controlled drug delivery, Small, 6 (2010) 1952-1967.
[27] Y.-Z. You, *et al.*, Temperature-Controlled Uptake and Release in PNIPAM-Modified Porous Silica Nanoparticles, Chemistry of Materials, 20 (2008) 3354-3359.
[28] S.A. Jadhav, *et al.*, Poly(NIPAM- co -MPS)-grafted multimodal porous silica nanoparticles as reverse thermoresponsive drug delivery system, Asian Journal of Pharmaceutical Sciences, 12 (2017) 279-284.
[29] E. Ugazio, *et al.*, Thermoresponsive mesoporous silica nanoparticles as a carrier for skin delivery of quercetin, Int J Pharm, 511 (2016) 446-454.
[30] V. Brunella, *et al.*, Hybrid drug carriers with temperature-controlled on–off release: A simple and reliable synthesis of PNIPAM-functionalized mesoporous silica nanoparticles, Reactive and Functional Polymers, 98 (2016) 31-37.
[31] Z.F. Tian, *et al.*, Magnetic mesoporous silica nanoparticles coated with thermo-responsive copolymer for potential chemo- and magnetic hyperthermia therapy, Microporous and Mesoporous Materials, 256 (2018) 1-9.
[32] J.H. Chang, *et al.*, PNIPAm grafted amino-functionalized mesoporous silica for thermo-responsive chromium elimination, Applied Surface Science, 424 (2017) 115-121.
[33] A. Baeza, *et al.*, Magnetically triggered multidrug release by hybrid mesoporous silica nanoparticles, Chemistry of Materials, 24 (2012) 517-524.

[34] E. Yu, *et al.*, Improved controlled release of protein from expanded-pore mesoporous silica nanoparticles modified with co-functionalized poly(n-isopropylacrylamide) and poly(ethylene glycol) (PNIPAM-PEG), Colloids and surfaces. B, Biointerfaces, 149 (2017) 297-300.
[35] C. Amgoth, *et al.*, Thermosensitive block copolymer [(PNIPAM)-b-(Glycine)] thin film as protective layer for drug loaded mesoporous silica nanoparticles, Materials Research Express, 4 (2017) 105306.
[36] S. Nagappan, *et al.*, Synthesis and functionalisation of mesoporous materials for transparent coatings and organic dye adsorption, New Journal of Chemistry, 42 (2018) 10254-10262.
[37] Y. Liu, *et al.*, A novel dual temperature responsive mesoporous imprinted polymer for Cd(II) adsorption and temperature switchable controlled separation and regeneration, Chemical Engineering Journal, 328 (2017) 11-24.
[38] F. Yu, *et al.*, Temperature-sensitive copolymer-coated fluorescent mesoporous silica nanoparticles as a reactive oxygen species activated drug delivery system, Int J Pharm, 536 (2018) 11-20.
[39] J.P. Yang, *et al.*, Spatially Confined Fabrication of Core-Shell Gold Nanocages@Mesoporous Silica for Near-Infrared Controlled Photothermal Drug Release, Chemistry of Materials, 25 (2013) 3030-3037.
[40] I.-H. Cho, *et al.*, Heat shock responsive drug delivery system based on mesoporous silica nanoparticles coated with temperature sensitive gatekeeper, Microporous and Mesoporous Materials, 253 (2017) 96-101.
[41] Y. Xu, *et al.*, A smart magnetic nanosystem with controllable drug release and hyperthermia for potential cancer therapy, Rsc Advances, 5 (2015) 99875-99883.
[42] C. de la Torre, *et al.*, Temperature-controlled release by changes in the secondary structure of peptides anchored onto mesoporous silica supports, Chem Commun (Camb), 50 (2014) 3184-3186.
[43] Q. Zhang, *et al.*, Thermo-responsive mesoporous silica/lipid bilayer hybrid nanoparticles for doxorubicin on-demand delivery and reduced premature release, Colloids and surfaces. B, Biointerfaces, 160 (2017) 527-534.
[44] Huynh, C.T., *et al.*, Cytocompatible Catalyst-Free Photodegradable Hydrogels for Light-Mediated RNA Release To Induce hMSC Osteogenesis, ACS Biomaterials Science & Engineering, DOI (2017).
[45] C.T. Huynh, *et al.*, Light-triggered RNA release and induction of hMSC osteogenesis via photodegradable, dual-crosslinked hydrogels, Nanomedicine (Lond), 11 (2016) 1535-1550.
[46] S.S. Agasti, *et al.*, Photoregulated release of caged anticancer drugs from gold nanoparticles, J Am Chem Soc, 131 (2009) 5728-5729.
[47] C. Park, *et al.*, Photoresponsive cyclodextrin-covered nanocontainers and their sol-gel transition induced by molecular recognition, Angew Chem Int Ed Engl, 48 (2009) 1275-1278.
[48] Y. Zhang, *et al.*, Polymer-Coated Hollow Mesoporous Silica Nanoparticles for Triple-Responsive Drug Delivery, ACS Appl Mater Interfaces, 7 (2015) 18179-18187.
[49] J.L. Vivero-Escoto, *et al.*, Photoinduced intracellular controlled release drug delivery in human cells by gold-capped mesoporous silica nanosphere, J Am Chem Soc, 131 (2009) 3462-3463.
[50] N.Z. Knezevic, *et al.*, Light- and pH-responsive release of doxorubicin from a mesoporous silica-based nanocarrier, Chemistry, 17 (2011) 3338-3342.
[51] T.M. Guardado-Alvarez, *et al.*, Activation of snap-top capped mesoporous silica nanocontainers using two near-infrared photons, J Am Chem Soc, 135 (2013) 14000-14003.
[52] D. Wang, *et al.*, Red-Light-Responsive Supramolecular Valves for Photocontrolled Drug Release from Mesoporous Nanoparticles, Langmuir, 32 (2016) 632-636.
[53] W.D. Ji, *et al.*, Coumarin-containing photo-responsive nanocomposites for NIR light-triggered controlled drug release via a two-photon process, Journal of Materials Chemistry B, 1 (2013) 5942-5949.
[54] M. Wu, *et al.*, Photoresponsive Nanovehicle for Two Independent Wavelength Light-Triggered Sequential Release of P-gp shRNA and Doxorubicin To Optimize and Enhance Synergistic Therapy of Multidrug-Resistant Cancer, ACS Appl Mater Interfaces, 10 (2018) 19416-19427.

[55] Y. Zhang, *et al.*, In Situ and Timed Extraction of Cellular Peptides from Live HeLa Cells by Photo-Switchable Mesoporous Silica Nanocarriers, Analytical chemistry, 88 (2016) 8380-8384.
[56] E. Beňová, *et al.*, A drug delivery system based on switchable photo-controlled p-coumaric acid derivatives anchored on mesoporous silica, Journal of Materials Chemistry B, 5 (2017) 817-825.
[57] F. Wang, *et al.*, Reversible crosslinking terpolymer shell-based mesoporous silica nanoparticles as on-off nanocarriers for pyrene-releasing application, Journal of the Taiwan Institute of Chemical Engineers, DOI 10.1016/j.jtice.2018.06.013(2018).
[58] V. Zeleňák, *et al.*, Photo-switchable nanoporous silica supports for controlled drug delivery, New Journal of Chemistry, 42 (2018) 13263-13271.
[59] D. He, *et al.*, A light-responsive reversible molecule-gated system using thymine-modified mesoporous silica nanoparticles, Langmuir, 28 (2012) 4003-4008.
[60] J. Lu, *et al.*, Light-activated nanoimpeller-controlled drug release in cancer cells, Small, 4 (2008) 421-426.
[61] J. Croissant, *et al.*, Two-photon-triggered drug delivery via fluorescent nanovalves, Small, 10 (2014) 1752-1755.
[62] G.F. Luo, *et al.*, An indicator-guided photo-controlled drug delivery system based on mesoporous silica/gold nanocomposites, Nano Research, 8 (2015) 1893-1905.
[63] X. Mei, *et al.*, Light-triggered reversible assemblies of azobenzene-containing amphiphilic copolymer with beta-cyclodextrin-modified hollow mesoporous silica nanoparticles for controlled drug release, Chem Commun (Camb), 48 (2012) 10010-10012.
[64] H. Yan, *et al.*, Functional mesoporous silica nanoparticles for photothermal-controlled drug delivery in vivo, Angew Chem Int Ed Engl, 51 (2012) 8373-8377.
[65] M. Li, *et al.*, NIR-triggered drug release from switchable rotaxane-functionalized silica-covered Au nanorods, Chem Commun (Camb), 50 (2014) 9745-9748.
[66] D. Tarn, *et al.*, A reversible light-operated nanovalve on mesoporous silica nanoparticles, Nanoscale, 6 (2014) 3335-3343.
[67] C. Hu, *et al.*, Hollow mesoporous raspberry-like colloids with removable caps as photoresponsive nanocontainers, Nanoscale, 8 (2016) 7840-7844.
[68] Q. Yuan, *et al.*, Photon-manipulated drug release from a mesoporous nanocontainer controlled by azobenzene-modified nucleic acid, ACS Nano, 6 (2012) 6337-6344.
[69] E. Aznar, *et al.*, Photochemical and Chemical Two-Channel Control of Functional Nanogated Hybrid Architectures, Advanced Materials, 19 (2007) 2228-2231.
[70] L. Chen, *et al.*, A light-responsive release platform by controlling the wetting behavior of hydrophobic surface, ACS Nano, 8 (2014) 744-751.
[71] Z. Song, *et al.*, Mesoporous silica-coated gold nanorods with a thermally responsive polymeric cap for near-infrared-activated drug delivery, Journal of Materials Science, 53 (2018) 7165-7179.
[72] Q. Sun, *et al.*, A photoresponsive and rod-shape nanocarrier: Single wavelength of light triggered photothermal and photodynamic therapy based on AuNRs-capped & Ce6-doped mesoporous silica nanorods, Biomaterials, 122 (2017) 188-200.
[73] Y.L. Dai, *et al.*, 808 nm near-infrared light controlled dual-drug release and cancer therapy in vivo by upconversion mesoporous silica nanostructures, Journal of Materials Chemistry B, 5 (2017) 2086-2095.
[74] J.J. Liu, *et al.*, Mesoporous Silica Coated Single-Walled Carbon Nanotubes as a Multifunctional Light-Responsive Platform for Cancer Combination Therapy, Advanced Functional Materials, 25 (2015) 384-392.
[75] Y. Tang, *et al.*, An aptamer-targeting photoresponsive drug delivery system using "off-on" graphene oxide wrapped mesoporous silica nanoparticles, Nanoscale, 7 (2015) 6304-6310.
[76] N.Z. Knezevic, *et al.*, Functionalized mesoporous silica nanoparticle-based visible light responsive controlled release delivery system, Chem Commun (Camb), 47 (2011) 2817-2819.
[77] T.M. Guardado-Alvarez, *et al.*, Nanovalve activation by surface-attached photoacids, Chem Commun (Camb), 50 (2014) 8388-8390.

[78] H.D. Nguyen, *et al.*, Magnetic properties of Cr doped Fe3O4 porous nanoparticles prepared through a co-precipitation method using surfactant, Advances in Natural Sciences: Nanoscience and Nanotechnology, 5 (2014) 035017.
[79] T.N. Le Thi, *et al.*, Development of new magnetic nanoparticles: Oligochitosan obtained by γ-rays and –coated Fe 3 O 4 nanoparticles, Applied Surface Science, 422 (2017) 863-868.
[80] D.Q. Hoang, *et al.*, Functionalization of Fe3O4 nanoparticles with biodegradable chitosan-grafted-mPEG for paclitaxel delivery, Green Processing and Synthesis, 5 (2016) 459-466.
[81] E. Ruiz-Hernandez, *et al.*, Smart drug delivery through DNA/magnetic nanoparticle gates, ACS Nano, 5 (2011) 1259-1266.
[82] E. Li, *et al.*, Multifunctional Magnetic Mesoporous Silica Nanoagents for in vivo Enzyme-Responsive Drug Delivery and MR Imaging, Nanotheranostics, 2 (2018) 233-242.
[83] W.H. Chen, *et al.*, Rational design of multifunctional magnetic mesoporous silica nanoparticle for tumor-targeted magnetic resonance imaging and precise therapy, Biomaterials, 76 (2016) 87-101.
[84] C. Tao, *et al.*, Magnetic mesoporous silica nanoparticles for potential delivery of chemotherapeutic drugs and hyperthermia, Dalton Trans, 43 (2014) 15482-15490.
[85] F. Liu, *et al.*, One-step synthesis of magnetic hollow mesoporous silica (MHMS) nanospheres for drug delivery nanosystems via electrostatic self-assembly templated approach, Chem Commun (Camb), 51 (2015) 2357-2360.
[86] Z. Wang, *et al.*, Shape-controlled magnetic mesoporous silica nanoparticles for magnetically-mediated suicide gene therapy of hepatocellular carcinoma, Biomaterials, 154 (2018) 147-157.
[87] D. Shao, *et al.*, The shape effect of magnetic mesoporous silica nanoparticles on endocytosis, biocompatibility and biodistribution, Acta biomaterialia, 49 (2017) 531-540.
[88] C.R. Thomas, *et al.*, Noninvasive remote-controlled release of drug molecules in vitro using magnetic actuation of mechanized nanoparticles, J Am Chem Soc, 132 (2010) 10623-10625.
[89] X. Yao, *et al.*, Graphene Quantum Dots-Capped Magnetic Mesoporous Silica Nanoparticles as a Multifunctional Platform for Controlled Drug Delivery, Magnetic Hyperthermia, and Photothermal Therapy, Small, 13 (2017).
[90] M. Hegazy, *et al.*, Construction of polymer coated core-shell magnetic mesoporous silica nanoparticles with triple responsive drug delivery, Polymer Chemistry, 8 (2017) 5852-5864.
[91] R.C.S. Azevedo, *et al.*, Combining mesoporous silica–magnetite and thermally-sensitive polymers for applications in hyperthermia, Journal of Sol-Gel Science and Technology, 72 (2014) 208-218.
[92] N. Avedian, *et al.*, pH-sensitive biocompatible mesoporous magnetic nanoparticles labeled with folic acid as an efficient carrier for controlled anticancer drug delivery, Journal of Drug Delivery Science and Technology, 44 (2018) 323-332.
[93] J. Lee, *et al.*, High throughput detection and selective enrichment of histidine-tagged enzymes with Ni-doped magnetic mesoporous silica, J. Mater. Chem. B, 1 (2013) 610-616.
[94] A. Pourjavadi, *et al.*, Chitosan based supramolecular polypseudorotaxane as a pH-responsive polymer and their hybridization with mesoporous silica-coated magnetic graphene oxide for triggered anticancer drug delivery, Polymer, 76 (2015) 52-61.
[95] P.J. Chen, *et al.*, Multifunctional magnetically removable nanogated lids of Fe3O4-capped mesoporous silica nanoparticles for intracellular controlled release and MR imaging, Journal of Materials Chemistry, 21 (2011) 2535-2543.
[96] X. Yu, *et al.*, Preparation of magnetic mesoporous silica nanoparticles as a multifunctional platform for potential drug delivery and hyperthermia, Sci Technol Adv Mater, 17 (2016) 229-238.
[97] Y. Chen, *et al.*, Multifunctional envelope-type mesoporous silica nanoparticles for pH-responsive drug delivery and magnetic resonance imaging, Biomaterials, 60 (2015) 111-120.
[98] P.J. Kempen, *et al.*, Theranostic mesoporous silica nanoparticles biodegrade after pro-survival drug delivery and ultrasound/magnetic resonance imaging of stem cells, Theranostics, 5 (2015) 631-642.
[99] Y. Chen, *et al.*, Multifunctional mesoporous composite nanocapsules for highly efficient MRI-guided high-intensity focused ultrasound cancer surgery, Angew Chem Int Ed Engl, 50 (2011) 12505-12509.

[100] H. Gao, *et al.*, (99m)Tc-conjugated manganese-based mesoporous silica nanoparticles for SPECT, pH-responsive MRI and anti-cancer drug delivery, Nanoscale, 8 (2016) 19573-19580.
[101] D. Zhang, *et al.*, pH / Hypoxia Programmable Triggered Cancer Photo-Chemotherapy Based on Semiconducting Polymer dot hybridized Mesoporous Silica Framework, Chemical Science, DOI 10.1039/c8sc02408a(2018).
[102] M. Farshbaf, *et al.*, pH- and thermo-sensitive MTX-loaded magnetic nanocomposites: synthesis, characterization, and in vitro studies on A549 lung cancer cell and MR imaging, Drug development and industrial pharmacy, 44 (2018) 452-462.
[103] X. Wang, *et al.*, Au-nanoparticle coated mesoporous silica nanocapsule-based multifunctional platform for ultrasound mediated imaging, cytoclasis and tumor ablation, Biomaterials, 34 (2013) 2057-2068.
[104] Q. Jin, *et al.*, Superhydrophobic mesoporous silica nanoparticles as ultrasound contrast agents, 2016 IEEE International Ultrasonics Symposium (IUS), IEEE, Tours, France, 2016, pp. 1-4.
[105] Y. Zhao, *et al.*, Effective cancer cell killing by hydrophobic nanovoid-enhanced cavitation under safe low-energy ultrasound, Chem Asian J, 9 (2014) 790-796.
[106] A. Yildirim, *et al.*, Stable Encapsulation of Air in Mesoporous Silica Nanoparticles: Fluorocarbon-Free Nanoscale Ultrasound Contrast Agents, Adv Healthc Mater, 5 (2016) 1290-1298.
[107] Y. Lv, *et al.*, Ultrasound-Triggered Destruction of Folate-Functionalized Mesoporous Silica Nanoparticle-Loaded Microbubble for Targeted Tumor Therapy, Adv Healthc Mater, 6 (2017).
[108] J.L. Paris, *et al.*, Mesoporous silica nanoparticles engineered for ultrasound-induced uptake by cancer cells, Nanoscale, 10 (2018) 6402-6408.
[109] X. Li, *et al.*, pH and Ultrasound Dual-Responsive Polydopamine-Coated Mesoporous Silica Nanoparticles for Controlled Drug Delivery, Langmuir, DOI 10.1021/acs.langmuir.8b01091(2018).
[110] J.L. Paris, *et al.*, Polymer-Grafted Mesoporous Silica Nanoparticles as Ultrasound-Responsive Drug Carriers, ACS Nano, 9 (2015) 11023-11033.
[111] T.S. Anirudhan, *et al.*, Temperature and ultrasound sensitive gatekeepers for the controlled release of chemotherapeutic drugs from mesoporous silica nanoparticles, Journal of Materials Chemistry B, 6 (2018) 428-439.
[112] Y. Zhu, *et al.*, Dipolar molecules as impellers achieving electric-field-stimulated release, J Am Chem Soc, 132 (2010) 1450-1451.
[113] P.K. Zhao, *et al.*, A study of chitosan hydrogel with embedded mesoporous silica nanoparticles loaded by ibuprofen as a dual stimuli-responsive drug release system for surface coating of titanium implants, Colloids and Surfaces B-Biointerfaces, 123 (2014) 657-663.
[114] F. Li, *et al.*, Dual-responsive drug delivery system with real time tunable release behavior, Microporous and Mesoporous Materials, 200 (2014) 46-51.
[115] L. Tan, *et al.*, The dual-stimulated release of size-selected cargos from cyclodextrin-covered mesoporous silica nanoparticles, Rsc Advances, 5 (2015) 10393-10399.
[116] J. Wen, *et al.*, Construction of A Triple-Stimuli-Responsive System Based on Cerium Oxide Coated Mesoporous Silica Nanoparticles, Sci Rep, 6 (2016) 38931.
[117] H. Geng, *et al.*, Shape-Controlled Hollow Mesoporous Silica Nanoparticles with Multifunctional Capping for In Vitro Cancer Treatment, Chemistry, 23 (2017) 10878-10885.
[118] X. Yao, *et al.*, Mesoporous Silica Nanoparticles Capped with Graphene Quantum Dots for Potential Chemo-Photothermal Synergistic Cancer Therapy, Langmuir, 33 (2017) 591-599.
[119] F. Ji, *et al.*, Engineering Polyzwitterion and Polydopamine Decorated Doxorubicin-Loaded Mesoporous Silica Nanoparticles as a pH-Sensitive Drug Delivery, Polymers, 10 (2018) 326.
[120] J. Cao, *et al.*, A pH-dependent Antibacterial Peptide Release Nano-system Blocks Tumor Growth in vivo without Toxicity, Sci Rep, 7 (2017) 11242.
[121] L. Dai, *et al.*, Dendrimerlike mesoporous silica nanoparticles as pH-responsive nanocontainers for targeted drug delivery and bioimaging, ACS Appl Mater Interfaces, 7 (2015) 7357-7372.
[122] X.Q. Jin, *et al.*, Dual (pH- and temperature-) stimuli responsive nanocarrier with bimodal mesoporous silica nanoparticles core and copolymer shell for controlled ibuprofen-releasing: Fractal feature and diffusion mechanism, Microporous and Mesoporous Materials, 254 (2017) 77-85.

[123] Y. Chen, *et al.*, In vivo distribution and antitumor activity of doxorubicin-loaded N-isopropylacrylamide-co-methacrylic acid coated mesoporous silica nanoparticles and safety evaluation, Eur J Pharm Biopharm, 85 (2013) 406-412.
[124] Z. Mai, *et al.*, Novel functional mesoporous silica nanoparticles loaded with Vitamin E acetate as smart platforms for pH responsive delivery with high bioactivity, Journal of colloid and interface science, 508 (2017) 184-195.
[125] Y. Tian, *et al.*, Light- and pH-activated intracellular drug release from polymeric mesoporous silica nanoparticles, Colloids and surfaces. B, Biointerfaces, 134 (2015) 147-155.
[126] T. Chen, *et al.*, Intelligent Drug Delivery System Based on Mesoporous Silica Nanoparticles Coated with an Ultra-pH-Sensitive Gatekeeper and Poly(ethylene glycol), ACS Macro Letters, 5 (2015) 55-58.
[127] X.J. Zhou, *et al.*, Dual-Responsive Mesoporous Silica Nanoparticles Mediated Codelivery of Doxorubicin and Bcl-2 SiRNA for Targeted Treatment of Breast Cancer, Journal of Physical Chemistry C, 120 (2016) 22375-22387.
[128] S. Niedermayer, *et al.*, Multifunctional polymer-capped mesoporous silica nanoparticles for pH-responsive targeted drug delivery, Nanoscale, 7 (2015) 7953-7964.
[129] M.P. Shirani, *et al.*, Ingenious pH-sensitive etoposide loaded folic acid decorated mesoporous silica-carbon dot with carboxymethyl-βcyclodextrin gatekeeper for targeted drug delivery and imaging, Materials Science and Engineering: C, 92 (2018) 892-901.
[130] J. Liu, *et al.*, Supramolecular Modular Approach toward Conveniently Constructing and Multifunctioning a pH/Redox Dual-Responsive Drug Delivery Nanoplatform for Improved Cancer Chemotherapy, ACS Appl Mater Interfaces, 10 (2018) 26473-26484.
[131] Q.L. Li, *et al.*, pH and Glutathione Dual-Responsive Dynamic Cross-Linked Supramolecular Network on Mesoporous Silica Nanoparticles for Controlled Anticancer Drug Release, ACS Appl Mater Interfaces, 7 (2015) 28656-28664.
[132] J.G. Croissant, *et al.*, Protein-gold clusters-capped mesoporous silica nanoparticles for high drug loading, autonomous gemcitabine/doxorubicin co-delivery, and in-vivo tumor imaging, J Control Release, 229 (2016) 183-191.
[133] X. Chen, *et al.*, Stimuli-responsive functionalized mesoporous silica nanoparticles for drug release in response to various biological stimuli, Biomater. Sci., 2 (2014) 121-130.
[134] R.H. Jin, *et al.*, Core-Satellite Mesoporous Silica-Gold Nanotheranostics for Biological Stimuli Triggered Multimodal Cancer Therapy, Advanced Functional Materials, 28 (2018) 1801961.
[135] R. Liu, *et al.*, pH-responsive nanogated ensemble based on gold-capped mesoporous silica through an acid-labile acetal linker, J Am Chem Soc, 132 (2010) 1500-1501.
[136] H.Y. Chiu, *et al.*, Clickable Multifunctional Large-Pore Mesoporous Silica Nanoparticles as Nanocarriers, Chemistry of Materials, 30 (2018) 644-654.
[137] R.C.H. Wong, *et al.*, pH-Responsive Dimeric Zinc(II) Phthalocyanine in Mesoporous Silica Nanoparticles as an Activatable Nanophotosensitizing System for Photodynamic Therapy, ACS Appl Mater Interfaces, 9 (2017) 23487-23496.
[138] R. Zhao, *et al.*, Simultaneous inhibition of growth and metastasis of hepatocellular carcinoma by co-delivery of ursolic acid and sorafenib using lactobionic acid modified and pH-sensitive chitosan-conjugated mesoporous silica nanocomplex, Biomaterials, 143 (2017) 1-16.
[139] G.F. Luo, *et al.*, Charge-reversal plug gate nanovalves on peptide-functionalized mesoporous silica nanoparticles for targeted drug delivery, Journal of Materials Chemistry B, 1 (2013) 5723-5732.
[140] L. Tan, *et al.*, Glucose- and pH-responsive nanogated ensemble based on polymeric network capped mesoporous silica, ACS Appl Mater Interfaces, 7 (2015) 6310-6316.
[141] X. Chen, *et al.*, Mesoporous silica nanoparticles capped with fluorescence-conjugated cyclodextrin for pH-activated controlled drug delivery and imaging, Microporous and Mesoporous Materials, 217 (2015) 46-53.
[142] J. Liu, *et al.*, Hollow mesoporous silica nanoparticles facilitated drug delivery via cascade pH stimuli in tumor microenvironment for tumor therapy, Biomaterials, 83 (2016) 51-65.

[143] Y. Zhang, *et al.*, "Three-in-One" Multifunctional Gatekeeper Gated Mesoporous Silica Nanoparticles for Intracellular pH-Activated Targeted Cancer Therapy, ACS Applied Bio Materials, DOI 10.1021/acsabm.8b00050(2018).
[144] Z. Tian, *et al.*, Aldehyde-functionalized dendritic mesoporous silica nanoparticles as potential nanocarriers for pH-responsive protein drug delivery, Mater Sci Eng C Mater Biol Appl, 71 (2017) 452-459.
[145] U.V. Vo, *et al.*, Effective pH-responsive Hydrazine-Modified Silica for Doxorubicin Delivery, Asian Journal of Medicine and Health, 4 (2017) 1-7.
[146] T. Yan, *et al.*, pH-Sensitive mesoporous silica nanoparticles for chemo-photodynamic combination therapy, Colloids and surfaces. B, Biointerfaces, 161 (2018) 442-448.
[147] R.C.H. Wong, *et al.*, Encapsulating pH-Responsive Doxorubicin-Phthalocyanine Conjugates in Mesoporous Silica Nanoparticles for Combined Photodynamic Therapy and Controlled Chemotherapy, Chemistry, 23 (2017) 16505-16515.
[148] Z. Liu, *et al.*, Carbon-Quantum-Dots-Loaded Mesoporous Silica Nanocarriers with pH-Switchable Zwitterionic Surface and Enzyme-Responsive Pore-Cap for Targeted Imaging and Drug Delivery to Tumor, Adv Healthc Mater, 5 (2016) 1401-1407.
[149] X.M. Yao, *et al.*, Dual pH-responsive mesoporous silica nanoparticles for efficient combination of chemotherapy and photodynamic therapy, Journal of Materials Chemistry B, 3 (2015) 4707-4714.
[150] X. Hao, *et al.*, Hybrid Mesoporous Silica-Based Drug Carrier Nanostructures with Improved Degradability by Hydroxyapatite, ACS Nano, 9 (2015) 9614-9625.
[151] Y. He, *et al.*, Synthesis of pH-Responsive Biodegradable Mesoporous Silica-Calcium Phosphate Hybrid Nanoparticles as a High Potential Drug Carrier, ACS Appl Mater Interfaces, 9 (2017) 44402-44409.
[152] F. Muhammad, *et al.*, pH-Triggered controlled drug release from mesoporous silica nanoparticles via intracelluar dissolution of ZnO nanolids, J Am Chem Soc, 133 (2011) 8778-8781.
[153] J. Zhang, *et al.*, Multifunctional Mesoporous Silica Nanoparticles Based on Charge-Reversal Plug-Gate Nanovalves and Acid-Decomposable ZnO Quantum Dots for Intracellular Drug Delivery, ACS Appl Mater Interfaces, 7 (2015) 26666-26673.
[154] X. Zhang, *et al.*, Biofunctionalized polymer-lipid supported mesoporous silica nanoparticles for release of chemotherapeutics in multidrug resistant cancer cells, Biomaterials, 35 (2014) 3650-3665.
[155] C. Yang, *et al.*, Fe3O4@mSiO2 core–shell nanocomposite capped with disulfide gatekeepers for enzyme-sensitive controlled release of anti-cancer drugs, Journal of Materials Chemistry B, 3 (2015) 1010-1019.
[156] Y. Cui, *et al.*, Mesoporous silica nanoparticles capped with disulfide-linked PEG gatekeepers for glutathione-mediated controlled release, ACS Appl Mater Interfaces, 4 (2012) 3177-3183.
[157] Q. Zhao, *et al.*, Hyaluronic acid oligosaccharide modified redox-responsive mesoporous silica nanoparticles for targeted drug delivery, ACS Appl Mater Interfaces, 6 (2014) 20290-20299.
[158] L. Sha, *et al.*, Hydrophobic interaction mediated coating of pluronics on mesoporous silica nanoparticle with stimuli responsiveness for cancer therapy, Nanotechnology, 29 (2018) 345101.
[159] Y. Tian, *et al.*, Redox stimuli-responsive hollow mesoporous silica nanocarriers for targeted drug delivery in cancer therapy, Nanoscale Horizons, 1 (2016) 480-487.
[160] D. Xiao, *et al.*, A redox-responsive mesoporous silica nanoparticle capped with amphiphilic peptides by self-assembly for cancer targeting drug delivery, Nanoscale, 7 (2015) 10071-10077.
[161] J.T. Lin, *et al.*, Redox-responsive nanocarriers for drug and gene co-delivery based on chitosan derivatives modified mesoporous silica nanoparticles, Colloids and surfaces. B, Biointerfaces, 155 (2017) 41-50.
[162] J. Jiao, *et al.*, Redox and pH dual-responsive PEG and chitosan-conjugated hollow mesoporous silica for controlled drug release, Mater Sci Eng C Mater Biol Appl, 67 (2016) 26-33.
[163] L. Chen, *et al.*, Multifunctional Redox-Responsive Mesoporous Silica Nanoparticles for Efficient Targeting Drug Delivery and Magnetic Resonance Imaging, ACS Appl Mater Interfaces, 8 (2016) 33829-33841.

[164] Q. Zhao, *et al.*, Hyaluronic acid and carbon dots-gated hollow mesoporous silica for redox and enzyme-triggered targeted drug delivery and bioimaging, Mater Sci Eng C Mater Biol Appl, 78 (2017) 475-484.
[165] L. Huang, *et al.*, A dual-responsive, hyaluronic acid targeted drug delivery system based on hollow mesoporous silica nanoparticles for cancer therapy, Journal of Materials Chemistry B, 6 (2018) 4618-4629.
[166] Q. Zhao, *et al.*, Dual-stimuli responsive hyaluronic acid-conjugated mesoporous silica for targeted delivery to CD44-overexpressing cancer cells, Acta biomaterialia, 23 (2015) 147-156.
[167] N. Prabhakar, *et al.*, Stimuli-responsive hybrid nanocarriers developed by controllable integration of hyperbranched PEI with mesoporous silica nanoparticles for sustained intracellular siRNA delivery, Int J Nanomedicine, 11 (2016) 6591-6608.
[168] J. Jiao, *et al.*, Fluorescent carbon dot modified mesoporous silica nanocarriers for redox-responsive controlled drug delivery and bioimaging, Journal of colloid and interface science, 483 (2016) 343-352.
[169] H. Kim, *et al.*, Glutathione-induced intracellular release of guests from mesoporous silica nanocontainers with cyclodextrin gatekeepers, Adv Mater, 22 (2010) 4280-4283.
[170] L. Dai, *et al.*, Redox-responsive nanocarrier based on heparin end-capped mesoporous silica nanoparticles for targeted tumor therapy in vitro and in vivo, Langmuir, 30 (2014) 7867-7877.
[171] J. Zhang, *et al.*, Multifunctional envelope-type mesoporous silica nanoparticles for tumor-triggered targeting drug delivery, J Am Chem Soc, 135 (2013) 5068-5073.
[172] L. Qiao, *et al.*, Laccase-mediated formation of mesoporous silica nanoparticle based redox stimuli-responsive hybrid nanogels as a multifunctional nanotheranostic agent, Nanoscale, 8 (2016) 17241-17249.
[173] L. Palanikumar, *et al.*, Hyaluronic Acid-Modified Polymeric Gatekeepers on Biodegradable Mesoporous Silica Nanoparticles for Targeted Cancer Therapy, ACS Biomaterials Science & Engineering, 7 (2018).
[174] L. Sun, *et al.*, Core-shell hierarchical mesostructured silica nanoparticles for gene/chemo-synergetic stepwise therapy of multidrug-resistant cancer, Biomaterials, 133 (2017) 219-228.
[175] N. An, *et al.*, Gated magnetic mesoporous silica nanoparticles for intracellular enzyme-triggered drug delivery, Mater Sci Eng C Mater Biol Appl, 69 (2016) 292-300.
[176] B. Cheng, *et al.*, Gold Nanosphere Gated Mesoporous Silica Nanoparticle Responsive to Near-Infrared Light and Redox Potential as a Theranostic Platform for Cancer Therapy, Journal of biomedical nanotechnology, 12 (2016) 435-449.
[177] Y. Yang, *et al.*, Gold nanoparticle-gated mesoporous silica as redox-triggered drug delivery for chemo-photothermal synergistic therapy, Journal of colloid and interface science, 508 (2017) 323-331.
[178] Z. Zhang, *et al.*, Silver nanoparticle gated, mesoporous silica coated gold nanorods (AuNR@MS@AgNPs): low premature release and multifunctional cancer theranostic platform, ACS Appl Mater Interfaces, 7 (2015) 6211-6219.
[179] J. Geng, *et al.*, Mesoporous silica nanoparticle-based H2O2 responsive controlled-release system used for Alzheimer's disease treatment, Adv Healthc Mater, 1 (2012) 332-336.
[180] L. Yang, *et al.*, Gold nanoparticle-capped mesoporous silica-based H2O2-responsive controlled release system for Alzheimer's disease treatment, Acta biomaterialia, 46 (2016) 177-190.
[181] S.Y. Tan, *et al.*, Responsive mesoporous silica nanoparticles for sensing of hydrogen peroxide and simultaneous treatment toward heart failure, Nanoscale, 9 (2017) 2253-2261.
[182] B. Xu, *et al.*, H2O2-Responsive mesoporous silica nanoparticles integrated with microneedle patches for the glucose-monitored transdermal delivery of insulin, Journal of Materials Chemistry B, 5 (2017) 8200-8208.
[183] F. Muhammad, *et al.*, Synthesis of oxidant prone nanosilver to develop H2O2 responsive drug delivery system, Langmuir, 31 (2015) 514-521.
[184] J.M. Berg, *et al.*, Biochemistry, 5th edition, New York: W H Freeman2002.
[185] R. Qian, *et al.*, Switchable fluorescent imaging of intracellular telomerase activity using telomerase-responsive mesoporous silica nanoparticle, J Am Chem Soc, 135 (2013) 13282-13285.

[186] P. Srivastava, *et al.*, Telomerase Responsive Delivery of Doxorubicin from Mesoporous Silica Nanoparticles in Multiple Malignancies: Therapeutic Efficacies against Experimental Aggressive Murine Lymphoma, Bioconjug Chem, 29 (2018) 2107-2119.
[187] J. Liu, *et al.*, Enzyme responsive mesoporous silica nanoparticles for targeted tumor therapy in vitro and in vivo, Nanoscale, 7 (2015) 3614-3626.
[188] Y. Zhang, *et al.*, Mesoporous silica nanoparticle-based intelligent drug delivery system for bienzyme-responsive tumour targeting and controlled release, R Soc Open Sci, 5 (2018) 170986.
[189] Y.J. Cheng, *et al.*, Enzyme-induced and tumor-targeted drug delivery system based on multifunctional mesoporous silica nanoparticles, ACS Appl Mater Interfaces, 7 (2015) 9078-9087.
[190] B. Kumar, *et al.*, Mesoporous silica nanoparticle based enzyme responsive system for colon specific drug delivery through guar gum capping, Colloids and surfaces. B, Biointerfaces, 150 (2017) 352-361.
[191] Y. Zhu, *et al.*, Cytosine-phosphodiester-guanine oligodeoxynucleotide (CpG ODN)-capped hollow mesoporous silica particles for enzyme-triggered drug delivery, Dalton Trans, 40 (2011) 10203-10208.
[192] X. Yang, *et al.*, Synthesis of Hollow Mesoporous Silica Nanorods with Controllable Aspect Ratios for Intracellular Triggered Drug Release in Cancer Cells, ACS Appl Mater Interfaces, 8 (2016) 20558-20569.
[193] C. Hu, *et al.*, A Facile Strategy to Prepare an Enzyme-Responsive Mussel Mimetic Coating for Drug Delivery Based on Mesoporous Silica Nanoparticles, Langmuir, 33 (2017) 5511-5518.
[194] Y. Zhao, *et al.*, Mesoporous silica nanoparticle-based double drug delivery system for glucose-responsive controlled release of insulin and cyclic AMP, J Am Chem Soc, 131 (2009) 8398-8400.
[195] L. Hou, *et al.*, Self-Regulated Carboxyphenylboronic Acid-Modified Mesoporous Silica Nanoparticles with "Touch Switch" Releasing Property for Insulin Delivery, ACS Appl Mater Interfaces, 10 (2018) 21927-21938.
[196] S. Wu, *et al.*, Glucose- and pH-responsive controlled release of cargo from protein-gated carbohydrate-functionalized mesoporous silica nanocontainers, Angew Chem Int Ed Engl, 52 (2013) 5580-5584.
[197] C.M. Wong, *et al.*, Glucose oxidase: natural occurrence, function, properties and industrial applications, Appl Microbiol Biotechnol, 78 (2008) 927-938.
[198] M. Chen, *et al.*, A glucose-responsive controlled release system using glucose oxidase-gated mesoporous silica nanocontainers, Chem Commun (Camb), 48 (2012) 9522-9524.
[199] M. Oroval, *et al.*, Self-Regulated Glucose-Sensitive Neoglycoenzyme-Capped Mesoporous Silica Nanoparticles for Insulin Delivery, Chemistry, 23 (2017) 1353-1360.
[200] B. Xu, *et al.*, Microneedles Integrated with ZnO Quantum-Dot-Capped Mesoporous Bioactive Glasses for Glucose-Mediated Insulin Delivery, Acs Biomaterials Science & Engineering, 4 (2018) 2473-2483.
[201] Y. Zhou, *et al.*, Intracellular ATP levels are a pivotal determinant of chemoresistance in colon cancer cells, Cancer Res, 72 (2012) 304-314.
[202] J. Lai, *et al.*, Real-Time Monitoring of ATP-Responsive Drug Release Using Mesoporous-Silica-Coated Multicolor Upconversion Nanoparticles, ACS Nano, 9 (2015) 5234-5245.
[203] C.L. Zhu, *et al.*, Bioresponsive controlled release using mesoporous silica nanoparticles capped with aptamer-based molecular gate, J Am Chem Soc, 133 (2011) 1278-1281.
[204] V.C. Ozalp, *et al.*, Aptamer-based switchable nanovalves for stimuli-responsive drug delivery, Chemistry, 17 (2011) 9893-9896.
[205] X. He, *et al.*, ATP-responsive controlled release system using aptamer-functionalized mesoporous silica nanoparticles, Langmuir, 28 (2012) 12909-12915.
[206] F.F. Zheng, *et al.*, Aptamer/Graphene Quantum Dots Nanocomposite Capped Fluorescent Mesoporous Silica Nanoparticles for Intracellular Drug Delivery and Real-Time Monitoring of Drug Release, Analytical chemistry, 87 (2015) 11739-11745.
[207] L. Pan, *et al.*, Nuclear-targeted drug delivery of TAT peptide-conjugated monodisperse mesoporous silica nanoparticles, J Am Chem Soc, 134 (2012) 5722-5725.

[208] L. Pan, *et al.*, Overcoming multidrug resistance of cancer cells by direct intranuclear drug delivery using TAT-conjugated mesoporous silica nanoparticles, Biomaterials, 34 (2013) 2719-2730.
[209] L.B.D. Freitas, *et al.*, Multifunctional mesoporous silica nanoparticles for cancer-targeted, controlled drug delivery and imaging, Microporous and Mesoporous Materials, 242 (2017) 271-283.
[210] C.E. Ashley, *et al.*, Delivery of small interfering RNA by peptide-targeted mesoporous silica nanoparticle-supported lipid bilayers, Acs Nano, 6 (2012) 2174-2188.
[211] Y. Chen, *et al.*, Highly effective inhibition of lung cancer growth and metastasis by systemic delivery of siRNA via multimodal mesoporous silica-based nanocarrier, Biomaterials, 35 (2014) 10058-10069.
[212] K. Siwowska, *et al.*, Folate Receptor-Positive Gynecological Cancer Cells: In Vitro and In Vivo Characterization, Pharmaceuticals (Basel), 10 (2017)
[213] Q. Zhang, *et al.*, Biocompatible, Uniform, and Redispersible Mesoporous Silica Nanoparticles for Cancer- Targeted Drug Delivery In Vivo, Advanced Functional Materials, 24 (2014) 2450-2461.
[214] X.S.B.J. Liu, *et al.*, A dual responsive targeted drug delivery system based on smart polymer coated mesoporous silica for laryngeal carcinoma treatment, New Journal of Chemistry, 38 (2014) 4830-4836.
[215] Q. Sun, *et al.*, Theranostic Nanoplatform: Triple-Modal Imaging-Guided Synergistic Cancer Therapy Based on Liposome-Conjugated Mesoporous Silica Nanoparticles, ACS Appl Mater Interfaces, 10 (2018) 1963-1975.
[216] V. Nairi, *et al.*, Mesoporous silica nanoparticles functionalized with hyaluronic acid. Effect of the biopolymer chain length on cell internalization, Colloids and surfaces. B, Biointerfaces, 168 (2018) 50-59.
[217] G. Zheng, *et al.*, Co-delivery of sorafenib and siVEGF based on mesoporous silica nanoparticles for ASGPR mediated targeted HCC therapy, Eur J Pharm Sci, 111 (2018) 492-502.
[218] D. Xiao, *et al.*, A dual-responsive mesoporous silica nanoparticle for tumor-triggered targeting drug delivery, Small, 10 (2014) 591-598.
[219] M. Martínez-Carmona, *et al.*, Mesoporous silica nanoparticles grafted with a light-responsive protein shell for highly cytotoxic antitumoral therapy, Journal of Materials Chemistry B, 3 (2015) 5746-5752.
[220] R. Jin, *et al.*, Multiple-Responsive Mesoporous Silica Nanoparticles for Highly Accurate Drugs Delivery to Tumor Cells, ACS omega, 3 (2018) 4306-4315.
[221] W. Wang, *et al.*, A selective release system based on dual-drug-loaded mesoporous silica for nanoparticle-assisted combination therapy, Chemistry, 20 (2014) 7796-7802.
[222] J. Zhao, *et al.*, AND logic-like pH- and light-dual controlled drug delivery by surface modified mesoporous silica nanoparticles, Mater Sci Eng C Mater Biol Appl, 73 (2017) 1-7.
[223] M.S. Moorthy, *et al.*, Design of core-shell magnetic mesoporous silica hybrids for pH and UV light stimuli-responsive cargo release, RSC Advances, 6 (2016) 29106-29115.
[224] G. Wang, *et al.*, Visible Light and pH Responsive Polymer-Coated Mesoporous Silica Nanohybrids for Controlled Release, Macromolecular bioscience, 16 (2016) 990-994.
[225] A. Hakeem, *et al.*, Dual stimuli-responsive nano-vehicles for controlled drug delivery: mesoporous silica nanoparticles end-capped with natural chitosan, Chem Commun (Camb), 50 (2014) 13268-13271.
[226] S. Khatoon, *et al.*, Hypoxia-Responsive Mesoporous Nanoparticles for Doxorubicin Delivery, Polymers, 10 (2018) 390.
[227] J.L. Paris, *et al.*, Vectorization of ultrasound-responsive nanoparticles in placental mesenchymal stem cells for cancer therapy, Nanoscale, 9 (2017) 5528-5537.
[228] C. Xu, *et al.*, Bacteria-like mesoporous silica-coated gold nanorods for positron emission tomography and photoacoustic imaging-guided chemo-photothermal combined therapy, Biomaterials, 165 (2018) 56-65.
[229] A. Llopis-Lorente, *et al.*, Au-Mesoporous silica nanoparticles gated with disulfide-linked oligo(ethylene glycol) chains for tunable cargo delivery mediated by an integrated enzymatic control unit, Journal of Materials Chemistry B, 5 (2017) 6734-6739.

[230] X. Chen, *et al.*, Light-Induced Hydrogel Based on Tumor-Targeting Mesoporous Silica Nanoparticles as a Theranostic Platform for Sustained Cancer Treatment, ACS Appl Mater Interfaces, 8 (2016) 15857-15863.
[231] J. Lu, *et al.*, Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs, Small, 3 (2007) 1341-1346.
[232] T.V. Tran, *et al.*, Supramolecular chemistry at interfaces: host-guest interactions for attaching PEG and 5-fluorouracil to the surface of porous nanosilica, Green Processing and Synthesis, 5 (2016) 521-528.
[233] B.K. Poudel, *et al.*, In situ fabrication of mesoporous silica-coated silver-gold hollow nanoshell for remotely controllable chemo-photothermal therapy via phase-change molecule as gatekeepers, Int J Pharm, 548 (2018) 92-103.
[234] A.M. Chen, *et al.*, Co-delivery of doxorubicin and Bcl-2 siRNA by mesoporous silica nanoparticles enhances the efficacy of chemotherapy in multidrug-resistant cancer cells, Small, 5 (2009) 2673-2677.
[235] X. Li, *et al.*, The packaging of siRNA within the mesoporous structure of silica nanoparticles, Biomaterials, 32 (2011) 9546-9556.
[236] J. Zhang, *et al.*, Large-pore mesoporous silica nanospheres as vehicles for delivering TRAF3-shRNA plasmids to Kupffer cells, Biochem Biophys Res Commun, 469 (2016) 196-202.
[237] L. Hai, *et al.*, DNA-Functionalized Hollow Mesoporous Silica Nanoparticles with Dual Cargo Loading for Near-Infrared-Responsive Synergistic Chemo-Photothermal Treatment of Cancer Cells, ACS Applied Nano Materials, 1 (2018) 3486-3497.
[238] H. Meng, *et al.*, Use of size and a copolymer design feature to improve the biodistribution and the enhanced permeability and retention effect of doxorubicin-loaded mesoporous silica nanoparticles in a murine xenograft tumor model, ACS Nano, 5 (2011) 4131-4144.
[239] M. Martinez-Carmona, *et al.*, Lectin-conjugated pH-responsive mesoporous silica nanoparticles for targeted bone cancer treatment, Acta biomaterialia, 65 (2018) 393-404.
[240] D.H. Nguyen, *et al.*, Targeted doxorubicin nanotherapy strongly suppressing growth of multidrug resistant tumor in mice, Int J Pharm, 495 (2015) 329-335.
[241] H. Wu, *et al.*, Ceria nanocrystals decorated mesoporous silica nanoparticle based ROS-scavenging tissue adhesive for highly efficient regenerative wound healing, Biomaterials, 151 (2018) 66-77.
[242] M. Wang, *et al.*, Sustained Delivery Growth Factors with Polyethyleneimine-Modified Nanoparticles Promote Embryonic Stem Cells Differentiation and Liver Regeneration, Adv Sci (Weinh), 3 (2016) 1500393.
[243] W. Chen, *et al.*, Nonviral cell labeling and differentiation agent for induced pluripotent stem cells based on mesoporous silica nanoparticles, ACS Nano, 7 (2013) 8423-8440.
[244] S. Gandhi, *et al.*, Superparamagnetic nanosystems based on iron oxide nanoparticles & mesoporous silica: synthesis & evaluation of their magnetic, relaxometric and biocompatability properties, Journal of Materials Chemistry, 21 (2011) 15698-15707.
[245] M. Bouchoucha, *et al.*, Fluorinated Mesoporous Silica Nanoparticles for Binuclear Probes in (1)H and (19)F Magnetic Resonance Imaging, Langmuir, 33 (2017) 10531-10542.
[246] K.M.L. Taylor, *et al.*, Mesoporous silica nanospheres as highly efficient MRI contrast agents, J Am Chem Soc, 130 (2008) 2154-2155.
[247] G. Zhang, *et al.*, Hydroxylated Mesoporous Nanosilica Coated by Polyethylenimine Coupled with Gadolinium and Folic Acid: A Tumor-Targeted T(1) Magnetic Resonance Contrast Agent and Drug Delivery System, ACS Appl Mater Interfaces, 7 (2015) 14192-14200.
[248] T. Nakamura, *et al.*, Mesoporous silica nanoparticles for (19)F magnetic resonance imaging, fluorescence imaging, and drug delivery, Chem Sci, 6 (2015) 1986-1990.
[249] X. Sun, *et al.*, Luciferase and luciferin co-immobilized mesoporous silica nanoparticle materials for intracellular biocatalysis, J Am Chem Soc, 133 (2011) 18554-18557.
[250] Y. Lin, *et al.*, Mesoporous silica-encapsulated gold nanoparticles as artificial enzymes for self-activated cascade catalysis, Biomaterials, 34 (2013) 2600-2610.

[251] F.P. Chang, *et al.*, Enzyme encapsulated hollow silica nanospheres for intracellular biocatalysis, ACS Appl Mater Interfaces, 6 (2014) 6883-6890.
[252] F. Shao, *et al.*, Enzyme-Free Immunosorbent Assay of Prostate Specific Antigen Amplified by Releasing pH Indicator Molecules Entrapped in Mesoporous Silica Nanoparticles, Analytical chemistry, 90 (2018) 8673-8679.
[253] Z.M. Chang, *et al.*, Janus silver mesoporous silica nanobullets with synergistic antibacterial functions, Colloids and surfaces. B, Biointerfaces, 157 (2017) 199-206.
[254] F. Wu, *et al.*, Mesoporous Silica Nanoparticles-Encapsulated Agarose and Heparin as Anticoagulant and Resisting Bacterial Adhesion Coating for Biomedical Silicone, Langmuir, 33 (2017) 5245-5252.
[255] Y. Wang, *et al.*, Antibiotic-loaded, silver core-embedded mesoporous silica nanovehicles as a synergistic antibacterial agent for the treatment of drug-resistant infections, Biomaterials, 101 (2016) 207-216.
[256] P. Huang, *et al.*, Metalloporphyrin-Encapsulated Biodegradable Nanosystems for Highly Efficient Magnetic Resonance Imaging-Guided Sonodynamic Cancer Therapy, J Am Chem Soc, 139 (2017) 1275-1284.
[257] P. Huang, *et al.*, Molecularly organic/inorganic hybrid hollow mesoporous organosilica nanocapsules with tumor-specific biodegradability and enhanced chemotherapeutic functionality, Biomaterials, 125 (2017) 23-37.

Highlights

- Discuss the fabrication of mesoporous silica nanoparticles (MSNs) and their functionaliza tion.
- Discuss the performance of functionalized MSNs in response to stimuli signals
- Discuss the ability of functionalized MSNs to serve as nanocarriers for therapeutic deliver y, imaging agents and biocatalyst.
- Discuss the potential applications of these functionalized MSNs in biomedical engineerin g, and their challenge and future perspectives.