# Polymer Brush-Grafted Mesoporous Silica Nanoparticles for Triggered Drug Delivery

Li Zhang, [a] Ho Pan Bei, [a] Yun Piao, [a] Yufeng Wang, [b] Mo Yang, [a] Xin Zhao*[a]

[a]    L Zhang, HP Bei, Y Piao, Dr. M Yang, Dr. X Zhao
       Department of Biomedical Engineering
       The Hong Kong Polytechnic University
       Hung Hom, Kowloon, Hong Kong, China
       E-mail: xin.zhao@polyu.edu.hk
[b]    Dr. YF Wang
       Department of Chemistry
       The University of Hong Kong
       Pokfulum Road, Hong Kong, China

**Abstract:** Mesoporous silica nanoparticles (MSNs) have been demonstrated to be one of the most promising drug delivery systems (DDSs) to transport a variety of drug/biomolecules. Functionalization of MSN surfaces with responsive polymer brushes endows them with intelligent and controllable drug delivery properties, i.e., the encapsulated drugs/biomolecules will only be released upon certain stimuli including pH, temperature variation, light irradiation, enzyme, ultrasound, or redox potential, thus maximizing their therapeutic efficiency and minimizing side effects. These polymer brushes can also increase the stability and extend the release period of the loaded cargoes. This review presents an overview of the recent research progress on stimuli-responsive controlled DDSs based on polymer brush-grafted MSNs. Utilizing the switching abilities of the grafted responsive polymer brushes, the smart DDSs show great potential in biomedical applications, especially in cancer therapy.

## 1. Introduction

Traditional methods for drug delivery through long-term frequent oral dosing or injections can obtain a certain drug concentration in blood. They, however, often suffer from several drawbacks including lack of specificity, adverse drug reactions and overdose upon administration.[1] Nanoparticle (NP) - based DDSs possess the advantages over those conventional approaches: they are able to deliver drugs on site, resulting in higher drug transport efficiency, less dosage required and reduced side effects. However, employing the NPs for drug delivery would cause problems such as insufficient circulation time and burst/unwanted drug release, reducing their treatment outcome.[1, 2] Therefore, it is of great significance to develop NPs with a controlled and sustained manner for drug release to achieve enhanced therapeutic efficacy.

To address these problems, stimuli-responsive NPs with "smart" gatekeepers, which can respond to local cell microenvironment such as pH, temperature, enzyme, redox and external triggers like light and ultrasound, are regarded as ideal tools to deliver drugs.[3, 4] Considerable studies associated with polymer-based micelles[5] or microspheres,[3] liposomes,[6] silica,[7] titanium dioxide[8] and carbon NPs[9] as stimuli-responsive drug carriers have been exploited. Among these carriers, MSNs have gained tremendous interest attributed to their remarkable features: (1) MSNs have unique pore characteristics to encapsulate various drugs, overcoming the poor water solubility and stability of drugs and also enhancing their bioavailability;[10] (2) MSNs are biocompatible and can be safely taken up by living cells through endocytosis;[11] (3) their surface active silanol groups make these NPs readily modifiable with different molecules to achieve various functions, e.g., responsive to different stimuli.

Diverse kinds of gatekeepers such as organic/inorganic NPs, linear molecules and polymer multi-layers have been used to functionalize MSNs.[12, 13] Among them, various polymers as gatekeepers are most commonly studied. Specifically, linear polymers are considered to be a powerful gatekeeper to modify MSNs thanks to their outstanding stability, drug loading capacity, simple and low-cost process. Such properties make them more advantageous compared to other polymers. For example, branched polymers and dendrimers have extremely high density of functional groups, and have been utilized popularly as surface modifier and interfacial materials.[14] However, unlike linear polymers, the chemical composition and monomer ratios for the preparation of these polymers must be precisely optimized; hence, it is relatively difficult to control the synthesis process and the complex purification for each stage may result in a low yield.[4, 15] Additionally, linear polymers are much more flexible to integrate with other polymer chains to achieve multifunctional merits, allowing for more diverse biomedical applications.[16] These stimuli-responsive linear molecules (e.g., linear polyamine, saccharide derivative and peptide sequence) can be densely end-grafted onto the surface of MSNs to form a polymer brush layer inside the pore and/or on the surface of the porous NPs to block the pore entrance, and the "close/open" mechanism can be divided into "across/parallel" or "shorten" of the liner molecules.[12] In the presence of different triggers like pH, temperature

variation and light or ultrasound irradiation, the polymer brushes will extend to open the pore entrance to release the encapsulated cargoes. On the other hand, the polymer chains would be cleaved in response to the triggers, such as enzyme and redox agents, leading to the release of loaded drugs (**Scheme 1**).[17, 18] Integrating the inherent features of different polymer chains, these stimuli-responsive polymer brush-grafted MSNs would be capable of protectively packaging therapeutic agents, achieving zero premature leakage and triggering loaded drug release from the pores under defined stimuli.[19]

This minireview paper will touch upon the synthesis and drug release mechanism of polymer brush-grafted MSNs under different stimuli for drug delivery applications. The main focus will be placed on the recent research advances in the development of novel polymer-grafted MSNs with the abilities to release therapeutic drugs in response to multifarious external or internal stimuli for controlling on-demand drug delivery.

## 2. Synthesis of polymer brush-grafted MSNs

### 2.1. Types of polymer brushes

MSNs are suitable candidates for polymer brush surface modification because of their reactivity with a wide range of polymers. A polymer brush is defined as the array of molecular chains attached to a surface in close enough proximity that they overlap each other or alter their normal gyration radius, causing a change in properties vastly different from their individual counterpart.[20] There are mainly six types of responsive polymers that can respond to pH, temperature, enzyme, light, ultrasound and redox (Table 1). Designated polymers change conformation/hydrophilicity/hydrophobicity or degrade under different stimuli (see section 3.1 for more details).

**Table 1.** List of pH, temperature, enzyme, light, ultrasound and redox sensitive polymers used as brushes to modify MSN surfaces.

| Triggers | Responsive polymers | Synthesis | References |
|---|---|---|---|
| pH | poly(l-histidine) | graft to | [7] |
| | polyaniline | graft from | [21] |
| | poly (acrylic acid) | graft to | [22] |
| Temperature | poly-N-isopropylacrylamide | graft from | [23] |
| | poly(epsilon-caprolactone) | graft to | [24] |
| | poly(ethylene glycol-lactide) | graft to | [25] |
| Enzyme | polyglutamic acid | graft from | [10] |
| | azido-GFLGR$_7$RGDS | graft to | [26] |
| Light | azobenzene/β-cyclodextrin | graft to | [27] |
| | poly-N-isopropylacrylamide | graft to | [28] |
| | gluconamide | graft to | [29] |
| | ε-poly-L-lysine | graft to | [30] |
| Ultrasound | 2-tetrahydropyranyl methacrylate/2-(2-methoxyethoxy) ethyl methacrylate | graft to | [31] |

| | pyridine disulfide hydrochloride | graft to | [32] |
|---|---|---|---|
| Redox | | | |
| | poly(ethyleneimine) | graft to | [33] |

## 2.2. Synthesis of polymer brush-grafted MSNs

Grafting polymer brushes on MSNs increase the capacity and stability of drug loading, opening up opportunities for smart release of drugs. Properties of a surface-modified MSN can be adjusted by altering polymer type and length use, which directly affects the surface area, pore volume and size, as well as the drug release profile from the NPs.[34] Brushes can be attached to the MSNs in two ways: "graft from" and "graft to". "Graft from" is the growth of monomers from the surface, forming the polymer by chain reaction, while "graft to" directly initiates attachment by reaction between the polymer brush of predetermined molecular weight end and MSN surface with flexible grafting site.[35] For example, Zhang et al.[36] developed functionalized MSNs for photothermal chemotherapy using the "graft from" approach. By reversible addition−fragmentation chain transfer (RAFT), a matrix of copolymers was first immobilized onto the MSN surface with RAFT agents, lengthened by addition reaction of monomethoxy oligo (ethylene glycol) methacrylate monomer, and quenched upon air exposure. Such "grafting from" approach results in a much denser polymer network as monomers easily diffuse to reactive sites on the surface of MSNs while the length and characteristics of individual brushes are less controllable as each polymer brush has different reaction rates.

The other approach "graft to" involves tethering of pre-formed, end-functionalized polymer chains to the MSN surface by click chemistry, which is relatively simple and highly controllable. For example, Kotsuchibashi et al.[37] synthesized polyethylene glycol (PEG) functionalized MSNs by the Stöber method and one pot click reaction. The MSNs-SS-PEG with different PEG-chain lengths were prepared by grafting same amount of MeOPEGn-SH onto the MSNs-SH via the disulfide bond linker. Grafting density of polymer brushes onto the particle using the "graft to" method would be lower compared to the "graft from" approach as steric crowding of functional groups on the previously attached polymer prevents additional grafting, so the NP is easily saturated with few polymer brushes attached. However, the "graft to" approach prevents the attachment of polymer chains to others and this allows for high controllability over the shape and length of polymers, which is essential for drug delivery and cell targeting.[38]

## 3. Stimuli-responsive drug delivery from polymer brush-grafted MSNs

These responsive polymers can be grafted onto the external surface of MSNs or inside the pores, which are normally collapsed to block the pores to encapsulate the drugs, releasing the drugs only upon stimulus that causes the brushes to extend or degrade.[17] pH, temperature, light, ultrasound sensitive polymers are normally subject to chain-shifts (conformation/hydrophilicity/hydrophobicity change) upon these stimuli whereas enzyme and redox-sensitive polymer brushes would be cleaved when exposed to corresponding triggers; these open up opportunities for different drug loading and release profiles. In this section, we will summarize the recent advances in the development of polymer brush-grafted MSNs for triggered drug release according to different stimuli.

### 3.1. pH

The use of pH as a release trigger in stimuli-responsive release systems is based on the difference of pH values between certain tissues of the body, for example, tumors tissues (pH ≈ 6.8), as well as endosomal and lysosomal cell compartments (pH ≈ 5.5) have a more acidic pH than normal tissues (pH ≈ 7.4).[39, 40] pH has become the most frequently used trigger because it is precise to control and simple to manipulate. The design of pH-triggered drug release system relies on the combination of the MSNs and the polymer brush with functional groups that can respond to pH. The polymer chains tend to interact preferentially with the water molecules, modulate their swelling properties gradually from neutral state to ionized state and then the loaded drug will depart from MSNs.[41, 42] Currently, a great number of MSN-based pH-responsive controlled release systems have been studied, especially in cancer therapy due to the significantly lower pH values in tumor tissues.[21] In one study, poly (L-histidine) (PLH) and poly (ethylene glycol) (PEG)-grafted MSNs (MSNs-PLH-PEG) with an ''on-off'' switch was designed and evaluated for tumor-specific drug release.[7] NPs with an "off" switch first accumulated in tumor site via enhanced permeability and retention (EPR) effect, then PLH accepted proton and facilitated the endocytosis of NPs by tumor cells. After being endocytosed by tumor cells, the entrapped drug escaped under the acidic endosome/lysosome. The in vivo antitumor activity of the MSNs-PLH-PEG was carried out using H22 tumor-bearing mice and the results indicated that antitumor drug sorafenib loaded MSNs-PLH-PEG exhibited good anti-proliferation and tumor growth inhibition effects. Furthermore, several research have been devoted to fabricating pH sensitive MSNs for oral chemotherapy because most of the anticancer drugs like doxorubicin (DOX) have poor oral bioavailability. Tian et al.[22] used a simple "graft to" method capping MSNs with poly (acrylic acid) (PAA) to construct a novel pH-triggered oral drug delivery system with a high drug loading capacity (785.7 mg/g) as well as excellent pH-sensitivity and good biocompatibility (**Figure 1**). In gastric environment (pH = 2.0), the PAA brushes became shrunken and formed a dense barrier on the pore outlets of PAA/MSNs, which causes closing of the pores, thus preventing the release of cargo. While in colonic environment (pH = 7.6), the cargo was released from the carrier since the pore

outlets were opened by the swollen PAA brushes. Hence, in this system, most of the DOX molecules can be protected when passing through the stomach condition and then concentrative release under colonic condition, indicating a great potential for selective treatment of colon cancer and other colon diseases.

### 3.2. Temperature

Temperature trigger is another frequently studied trigger taking advantage of the temperature difference between tissues, e.g., the tumor sites usually have a higher temperature (4 – 5°C) than the normal tissues.[23] By grafting temperature-sensitive polymers like poly-N-isopropylacrylamide (PNIPAM) and its derivatives on MSNs surface, it would be possible to control the drug release using these temperature gradients.[41, 42] These polymers exhibit a hydrophobic state at temperatures below their lower critical solution temperature (LCST), creating a diffusion barrier to hamper the drug release. At a temperature above LCST, the polymers will exhibit to a hydrophilic state, causing pore opening and drug release.[41] Ideally, thermosensitive NPs should retain their load at body temperature (~37°C) and once reached tumor site (40 - 42°C), rapid drug release occurs. However, the LCST of pure PNIPAM is 32°C, which is beyond the physiological range. To address this problem, hydrophilic monomers like acrylamide or N-isopropylmethacrylamide have been introduced into the polymer composition by copolymerization to increase the LCST of PNIPAM.[23] In addition to the widely used PNIPAM, copolymers are also used as gatekeeper for temperature controlled release.[4] A very latest report by Cho *et al.*[24] functionalized MSNs with temperature-sensitive PEG/poly(ε-caprolactone) (PEG/PCL) multiblock copolymer (MBC-MSN) as gatekeepers, allowing the release of entrapped drugs in response to heat shock stimuli. In the absence of heat shock, drugs seldom escaped from MBC-MSN as PEG/PCL blocked the pores. On the contrary, the structure of the outer shells would be opened up in the presence of heat shock, resulting in accelerated drug release. Similar results were also confirmed using cell assays, DOX@MBC-MSN showed very low cytotoxicity against A549 cells without heat shock, whereas significant cytotoxicity was observed due to the enhanced DOX release within heat-shock stimuli. These results indicated that the DOX@MBC-MSN is a promising drug delivery system to treat diseases associated with temperature changes, such as cancer and inflammatory conditions. Furthermore, MSNs functionalized with $Fe_3O_4$ core and poly[(ethylene glycol)-*co*-(L-lactide)] (PEG/PLLA) as gatekeepers were fabricated by Guo *et al.*[25] for combined chemotherapy and hyperthermia treatment of cancer. $Fe_3O_4$ is used for heat generation under an alternating magnetic field (AMF). In presence of AMF, the magnetic core exhibits hyperthermia to increase the temperature of MSNs to 45°C, causing the initially gel-like PEG/PLLA to dissolve and allowing for rapid release of DOX. The MSNs exhibited high biocompatibility and thermosensitive characteristics, as evidenced by *in vitro* tests against HeLa cells (as high as 93.7% cellular apoptosis under AMF stimuli). These results show that the DOX-$Fe_3O_4$@MSN-PEG/PLLA has good potential in responsive drug release for cancer therapy.

### 3.3. Enzyme

Owing to the excessive expression of specific enzymes at the desired biological target, the enzyme-mediated mechanism can be explored to realize drug release.[23] Advantages of the enzyme trigger lie in that it can yield rapidly as well as selective targeted drug delivery to cancer cells, leading to improved therapeutic effects.[43] For example, proteases found in the tumor microenvironment have been devoted to enzyme-mediated DDSs based on polyglutamic acid (PGA) functionalized MSNs (**Figure 2**).[10] The PGA-capped MSNs remain closed in an aqueous environment, yet they are able to deliver the cargo in the presence of pronase attributed to the hydrolysis of the peptide bonds in PGA. The accumulative cargo release amount from the prepared solids was less than 20% within 1 day in water, while in the presence of pronase, the maximum amount of cargo release could reach to 90% within 5 h. This suggested that pronase could accelerate the drug release rate and DOX-loaded NPs were able to efficiently kill more cancer cells at relatively low concentrations. In another study designed by Cheng *et al.*,[26] multifunctional peptide (azido-GFLGR$_7$RGDS) was used to modify MSNs to endow MSNs with enzyme-responsive, tumor-targeting and membrane-penetrating features, aiming at limiting the adverse effect of loaded DOX. The nanovalves involving GFLG sequences could be specifically hydrolyzed due to the overexpression of Cathepsin B enzyme in late endosomes and lysosomes of cancer cells. The DOX-loaded carrier exhibited "off-on" drug release features with a total amount of 80% of DOX release within 24 h, resulting in a higher apoptosis rate. Besides, a remarkable growth suppression of $α_vβ_3$-positive cancerous HeLa cells was observed by *in vitro* cellular experiments. In addition, other MSNs-based nanoplatforms employing gluconamide and ε-poly-L-lysine as gated materials for enzyme-driven gate-opening drug release for cancer therapy have been reported. For example, Candel *et al.*[29] synthesized enzyme responsive MSNs using amidase as biological-keys to uncap the gatekeeper polymer gluconamide through hydrolysis of amide bonds. In the absence of amidase, zero release of drugs was recorded whilst MSNs released loaded chemical therapeutic agents camptothecin completely in 25 h. Results showed that the functionalized MSNs were highly effective at suppressing proliferation of HeLa cells: within 48 h after treatment, 70% of the cells were found dead. A similar study was reported by Mondragon *et al.*[30] Proteases from bacteria *Streptomyces griseus* were instead used as stimulus and ε-poly-L-lysine as gatekeeper. In addition to *in vitro* tests of Hela cells, MCF-7 human breast adenocarcinoma cells were also tested for cell viability. Introduction of gluconamide-functionalized MSNs significantly lowered percentage of healthy cells in both sample groups upon enzyme stimulation. These results showed that studies may provide a practical strategy to design tumor-targeted and enzyme-induced DDSs for cancer therapy.

### 3.4. Light

Irradiation of the surface of functionalized MSNs with a light of characteristic wavelength is another possible strategy for controlling the release of the cargo from the NPs.[11] The advantages of using light as a trigger are that it allows a better control on the drug administration because light can be easily focalized, increasing the efficiency in pathological regions while reducing the potential side effects on the adjacent healthy tissues. Also, such light-triggered drug release strategy is a non-invasive therapy that allows special and temporal control of drug release.[23, 41] In one study, Mei *et al.*[27] obtained a reversible polymer "gate-keeper" system based on light-triggered binding and unbinding between azobenzene (Azo) and β-cyclodextrin (β-CD)-modified hollow MSNs for controlled drug release. The UV light could transform the isomerism of the Azo groups from *trans* to *cis* conformation, causing the detachment of Azo-containing amphiphilic copolymer from β-CD modified hollow MSNs, triggering the drug release. Most interestingly, Vis light irradiation could be used to stop the drug release process. This study offered a new way to solve the premature drug leakage problems in normal MSNs-based DDSs and "secondary" side effects form the overdose of drugs in the irreversible "gate-keeper" systems. Despite great progress has been made in various drug delivery systems using UV light as a stimulus, one of the main limitations of these devices is the low penetration capacity of UV light in living tissues.[41] In order to overcome this problem, DDSs capable of responding to near-infrared radiation (NIR) with higher penetration capacity, have been recently reported. Among them, the combination of photosensitizing agents with temperature responsive polymer "gate-keeper" draw much attention since the photosensitizing agents can effectively absorb NIR light energy sources and convert luminous energy into local heat, then the temperature sensitive polymer would be continuously affected by the thermal effect, giving rise to a highly controllable DOX release.[3] For example, Yang *et al.*[28] used mesoporous silica to coat gold NPs and then modified with thermally-responsive PNIPAM to construct a novel multifunctional NIR-stimulus controlled DDSs. In the presence of NIR irradiation, the cumulative release of DOX reached 78.9% within 8 h at pH 5.0, significantly higher than that without NIR irradiation (18.4%). The stepwise-triggered rapid DOX release with NIR irradiation is ascribed to the photothermal effect of gold NPs. This not only results in the shrunken state of the PNIPAM polymer shell and small hydrodynamic diameter exposing the pores of MSNs for faster release, but also triggers more DOX release from the carrier by heating. The authors have also found that the DOX-loaded carriers can be taken up by HeLa cells through endocytosis and the cell killing efficacy with addition of NIR irradiation (80.1%) was much higher than the sum of chemotherapy (14.5%) and photothermal therapy (19.4%) alone. These results demonstrated the feasibility and advantage of the novel NPs for remote-controlled drug release system.

### 3.5. Others

Apart from the aforementioned stimuli, ultrasound as a distinctive and fascinating technique has become a hotspot in recent years ascribed to their exceptional capabilities, such as non-invasiveness, non-injury and non-ionizing radiations, and the ease of regulating frequency, duty cycles and exposure time to adjust penetration depth.[23] The utilization of ultrasounds is attractive because high-frequency ultrasound can penetrate deep into the body to track and provoke drug release and increase drug accumulation with higher spatial accuracy.[44] The combination of a thermoresponsive polymer with an ultrasound-responsive monomer as a copolymer-brush grafted MSNs for ultrasound responsive drug release was studied (**Figure 3**).[31] The ultrasound-responsive character empowered the thermoresponsive polymer with the particular property of modulating its phase state by ultrasound irradiation at a selected temperature, changing its hydrophobicity and therefore the cargo could depart from the gates. Moreover, since the hybrid DDSs could be taken up by LNCaP cells, the ultrasound-responsive properties were further tested in the cytoplasm. In the presence of ultrasound, DOX-loaded MSNs showed excellent capacity to induce cell death, demonstrating that such DDSs could be stimulated by remote trigger. This is of great significance for further drug delivery and cancer therapy applications.

Additionally, the incorporation of disulfide bonds in DDSs possess promising features for intracellular delivery of drugs because the disulfide bonds can be rapidly cleaved by glutathione (GSH).[32] In view of the fact that the GSH concentrations found in extracellular (2 - 10 μM) and intracellular (2 - 10 mM), and normal and tumor tissues are discrepant,[23] this responsiveness to GSH concentration change could retain the drug while being trafficked through the plasma and release the drug once it enters the cell.[32] A novel type of stimulus-responsive disulfide cross-linkable polymer-gatekeeper (PEG-PDS) and targeting ligand (cRGDfC) decorated MSNs for tumor-targeted and controlled drug release was synthesized.[18] The addition of varying amounts of the intracellular small peptide GSH induced the cleavage of the wrapped polymer in a concentration-dependent manner, resulting in a controlled and on-demand release profile. Meanwhile, the polymer shell could be degraded under the intracellular reductive microenvironment, accelerating the drug molecules escaping from the target specific NPs and inducing cell death. In another report, Prabhakar *et al.*[33] developed a new stimuli-responsive MSNs with high drug loading capacity (120 mg/g cell-killing siRNA) using hyperbranched poly(ethyleneimine) (PEI) tethered with redox-cleavable linkers to graft onto the surface. The proposed DDSs were internalized into cancer cells efficiently and then escaped from the endosomes to the cytoplasm. Afterwards, the siRNA could be stimulated to release sustainably inside the cells owing to the intracellular reductive conditions for several days. More importantly, the efficacy of siRNA transfection was found to be comparable to Lipofectamine, which is a commonly used commercial *in vitro* transfection agent. As a result, the prepared MSN-based drug carriers offer a promising way for more efficiently and long-term delivering siRNA and, even *in vivo* gene silencing for RNA interference (RNAi) therapy.

## 3. Conclusion and Future Perspectives

In this review, we have summarized recent progress on polymer brush-grafted MSNs as smart DDSs. As shown in the aforementioned sections, these kinds of DDSs with superior advantages have become one of the most appealing candidates for drug

delivery in particular for cancer treatment. Although great achievements have been made by scientists, several challenges still remain to be conquered for further biomedical applications. For example, there are only a few reports related to the investigation of polymer brush grafted-MSNs in biological systems, involving cytotoxicity, blood compatibility, biodegradation, long-term stability, biodistribution, and excretion and clearance. Great effort is thus urgently needed to determine the biosafety of the polymer brush-grafted MSNs.

Moreover, more endeavor is required to construct dual-controlled or multi-responsive controlled MSNs-based DDSs. These stimuli should either be in an independent or in a synergistic fashion, enhancing the therapeutic effect of delivered drugs.[41] For example, due to the pH gradient and elevated temperatures of many pathological conditions, pH and temperature dual sensitive DDSs have drawn attention. This combination of internal (pH) and external (temperature) triggers was found to be able to stimulate the sensitive polymer brushes temporally and spatially, thus achieving improved therapeutic effects. Also, the existence of special enzymes in diseased tissues can be used to fabricate a dual internal stimuli-sensitive DDSs. Furthermore, the integration of external triggers like temperature and light can be remotely controlled, enlarging the switching window and improving precision and accuracy.

Last but not least, scientists should pay more attention to integrating both diagnostic and therapeutic capabilities with MSNs to develop so-called "theranostics" for more accurate therapy with fewer side effects. Theranostics enable therapy procedure to be visualized in real time through different imaging technics, thus reducing the adverse impacts of under/over-dosing for more specialized treatment efficacy. Over the coming years, it is expected that the next-generation MSNs with high versatility could reach clinical evaluation and combat devastating diseases such as cancer.

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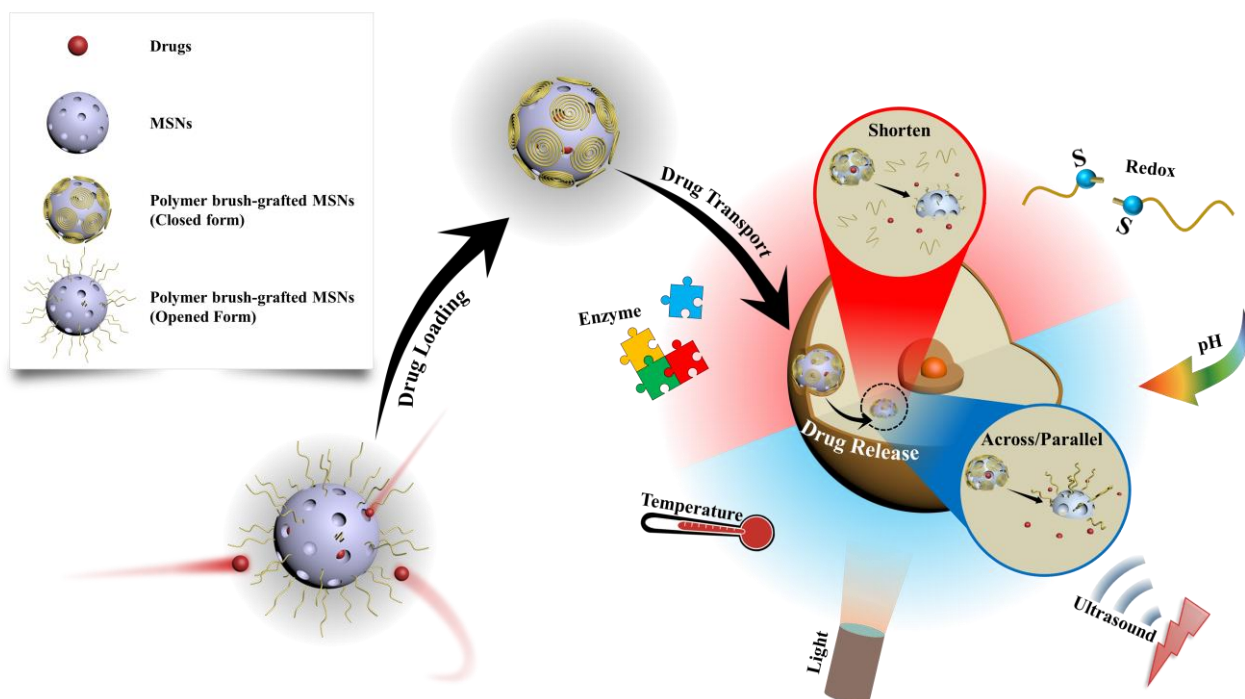[44] S. R. Sirsi, M. A. Borden, *Adv. Drug Delivery Rev.* **2014**, *72*, 3-14.

**Figure captions**

**Scheme 1.** Smart polymer brush-grafted MSNs can respond to pH, temperature, light or ultrasound ("across/parallel"), or to enzyme and redox agents ("shorten"), leading to the release of loaded drugs.

**Figure 1.** (A) Schematic illustration of fabrication of PAA capped mesoporous silica SBA-15 for pH-triggered release of DOX. (B) DOX release profiles from PAA/SBA-15 in different pH solutions. (C) DOX release profiles from mesoporous SBA-15 in different pH solutions. Insets show the photographs of supernatant liquids of DOX-loaded PAA/SBA-15 samples. (D) DOX release from PAA/SBA-15 at pH = 2.0 for 6 h and pH = 7.6 for 18 h. Image modified from [22] with permission.

**Figure 2.** (A) MSNs capped with PGA: Cargo delivery is selectively observed in the presence of lysosomal enzymes. (B) Internalization and release of rhodamine B and doxorubicin by S1 and S2 NPs, respectively, in SK-BR-3 cells (i) and cells treated with varying concentrations (from 6.25 to 100 µg/mL) of S1 or S2 NPs during 48 h, and the viability was determined using the WST-1 assay (ii). (C) Kinetics of the release of rhodamine B from solid S1 in the absence and presence of pronase. (D) Kinetics of doxorubicin release from solid S2 in the absence and presence of pronase. Image adapted from [10] with permission.

**Figure 3.** (A) Schematic illustration of the behavior in aqueous medium of dual responsive release system. (B) Release profiles of fluorescein from hybrid-MSNs in PBS solution versus time with and without ultrasound (US) exposure (b). (C) Fluorescence microscopy images of LNCaP cells incubated with rhodamine B-labeled hybrid-MSNs with fluorescein loaded after (i) and before (ii) ultrasound irradiation. Image modified from [31] with permission.
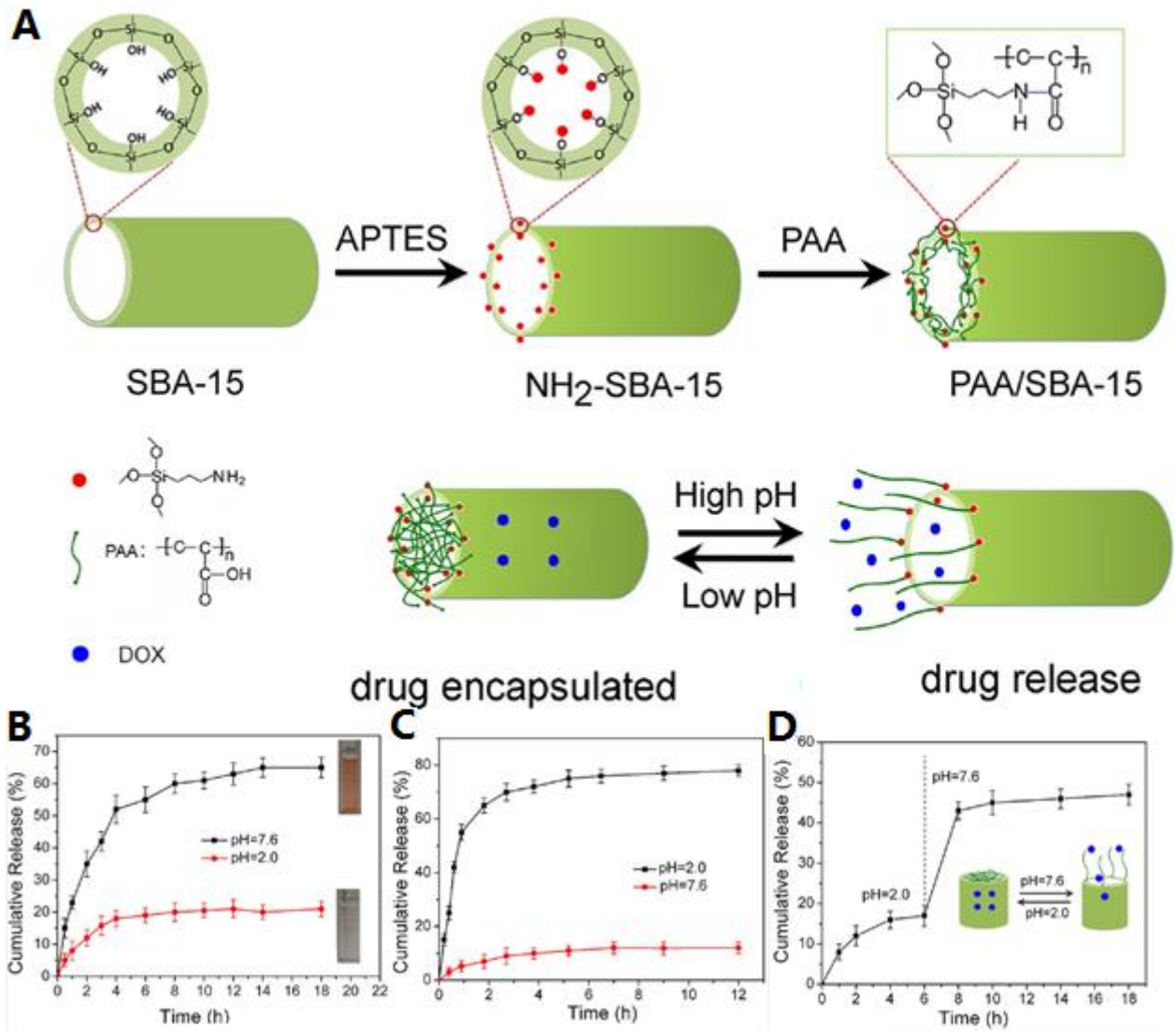


**Scheme 1**

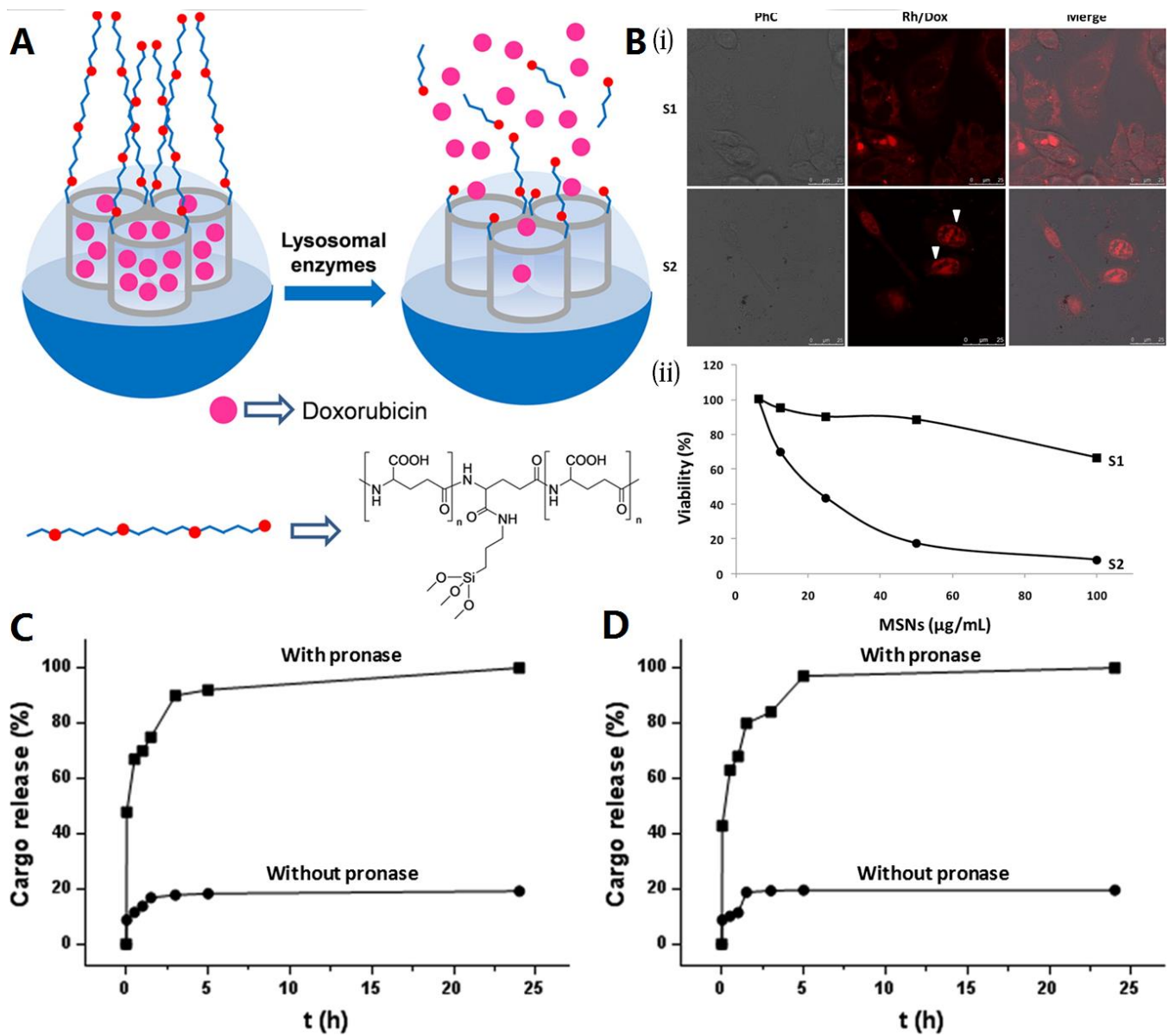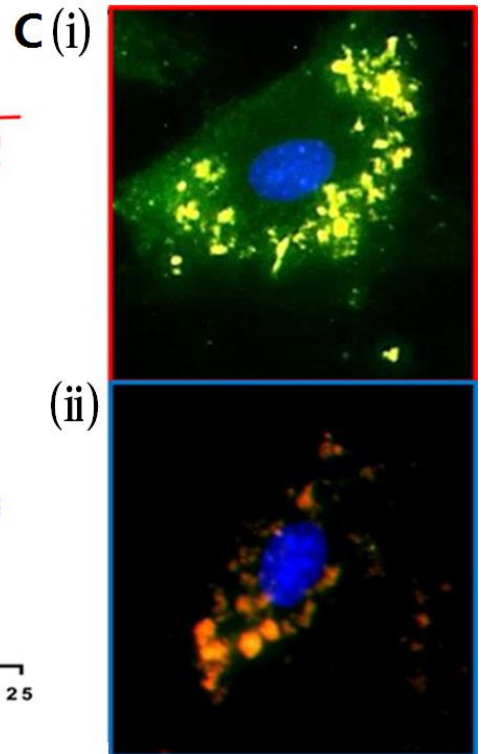**A**

SBA-15 → (APTES) → NH₂-SBA-15 → (PAA) → PAA/SBA-15

PAA: ─(C─C)ₙ─

DOX

drug encapsulated ⇌ (High pH / Low pH) drug release

**B**

**C**

**D**
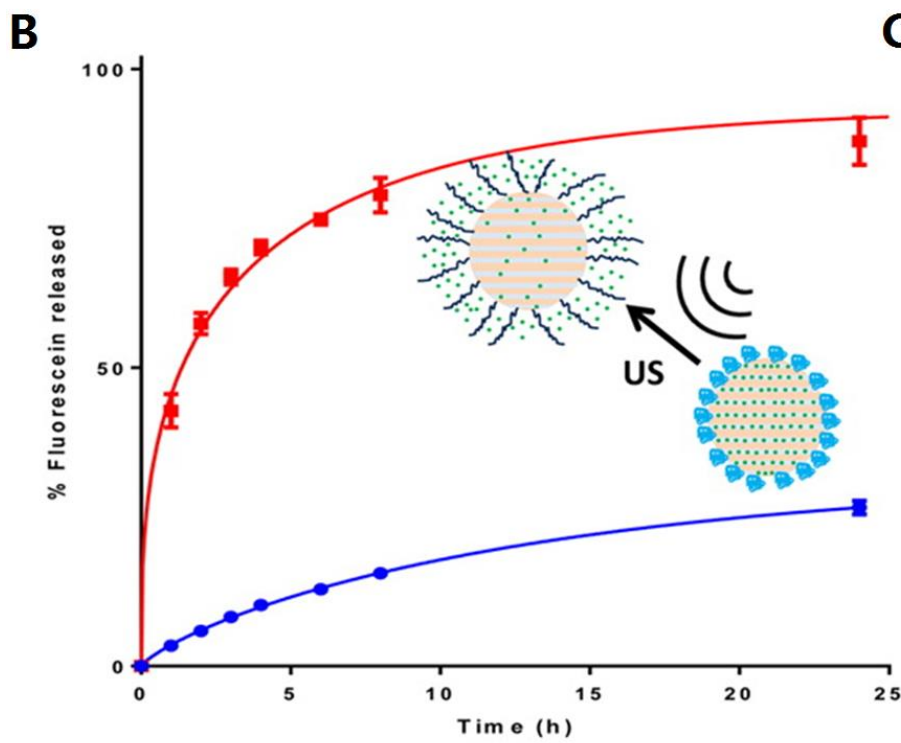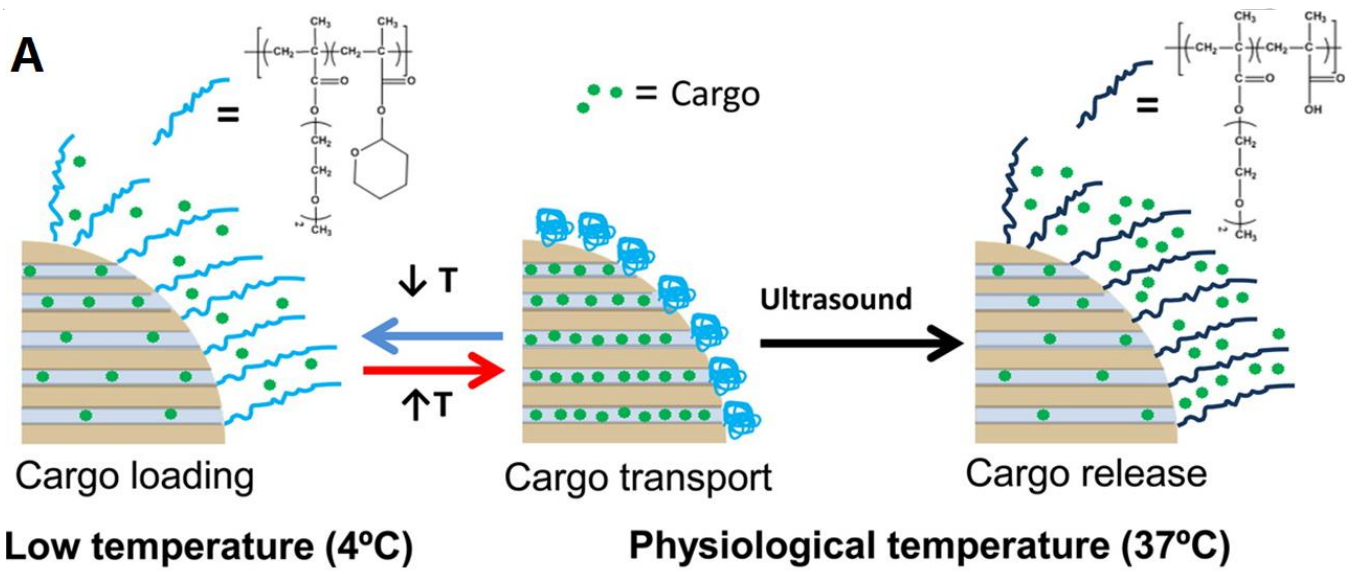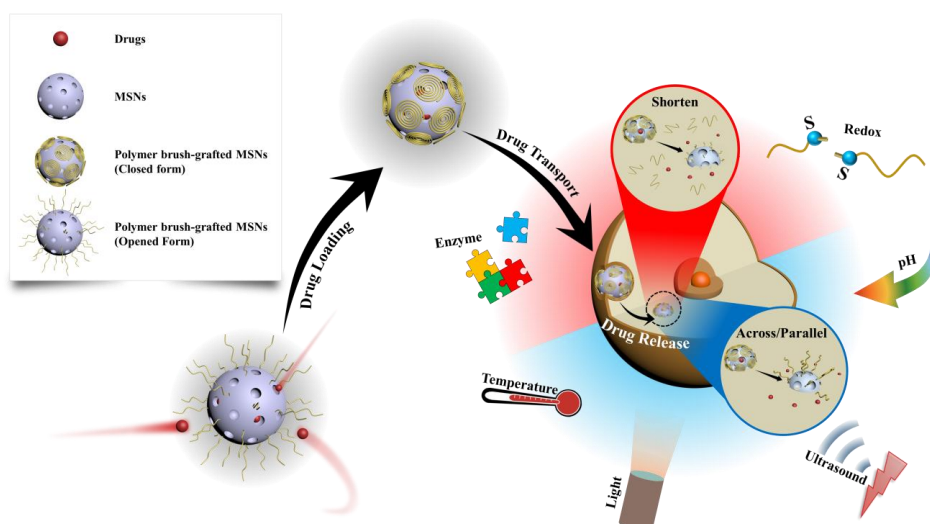
Figure 1

Figure 2

Figure 3

*Li Zhang, Ho Pan Bei,*
*Yun Piao, Yufeng Wang,*
*Mo Yang, Xin Zhao\**

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**Polymer Brush-Grafted**

**Mesoporous Silica Nanoparticles for Triggered Drug Delivery**

MSNs have been demonstrated to be one of the most promising DDSs to transport a variety of drug/biomolecules. Functionalization of MSN surfaces with responsive polymer brushes endows them with intelligent and controllable drug delivery properties. The encapsulated drugs/biomolecules will be triggered to release upon certain stimuli such as pH, temperature, light or ultrasound via "across/parallel" mechanism, or enzyme and redox agents via "shorten" mechanism.

## Entry for the Table of Contents