


## ADVANCED REVIEW

# Understanding the mechanisms of silica nanoparticles for nanomedicine

Ziyuan Li<sup>1,2</sup> | Yingwen Mu<sup>1,2</sup> | Cheng Peng<sup>1,3</sup> | Martin F. Lavin<sup>4</sup> |  
Hua Shao<sup>1,2</sup> | Zhongjun Du<sup>1,2</sup> 

<sup>1</sup>School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan, China

<sup>2</sup>Shandong Academy of Occupational Health and Occupational Medicine, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, China

<sup>3</sup>Queensland Alliance for Environmental Health Sciences (QAEHS), The University of Queensland, Brisbane, Queensland, Australia

<sup>4</sup>University of Queensland Centre for Clinical Research (UQCCR), The University of Queensland, Brisbane, Queensland, Australia

## Correspondence

Hua Shao, Cheng Peng, and Zhongjun Du, Department of Toxicology, Shandong Academy of Occupational Health and Occupational Medicine, Shandong First Medical University & Shandong Academy of Medical Sciences, No. 18877, Jingshi Road, Jinan, Shandong 250062, China. Email: chinashaohua5888@163.com (H. S.), c.peng@uq.edu.au (C. P.), and duzj1981@163.com (Z. D.)

## Funding information

the Tsung Cho-Chang Educational Foundation, Grant/Award Number: UQ-019171; Key Research and Development Plan of Shandong Province, Grant/Award Numbers: 2017GSF18186, 2018GSF118018; Medical and Health Technology Development Plan Project of Shandong Province, Grant/Award Number: 2016WS0540; National Natural Science Foundation of China, Grant/Award Numbers: 81602893, 81872575; Natural Science Foundation of Shandong Province, Grant/Award Numbers: ZR2015YL049, ZR2018MH036; The Innovation Project of Shandong Academy of Medical Science

## Abstract

As a consequence of recent progression in biomedicine and nanotechnology, nanomedicine has emerged rapidly as a new discipline with extensive application of nanomaterials in biology, medicine, and pharmacology. Among the various nanomaterials, silica nanoparticles (SNPs) are particularly promising in nanomedicine applications due to their large specific surface area, adjustable pore size, facile surface modification, and excellent biocompatibility. This paper reviews the synthesis of SNPs and their recent usage in drug delivery, biomedical imaging, photodynamic and photothermal therapy, and other applications. In addition, the possible adverse effects of SNPs in nanomedicine applications are reviewed from reported *in vitro* and *in vivo* studies. Finally, the potential opportunities and challenges for the future use of SNPs are discussed.

This article is categorized under:

Nanotechnology Approaches to Biology > Nanoscale Systems in Biology  
Therapeutic Approaches and Drug Discovery > Emerging Technologies

## KEYWORDS

biocompatibility, nanomedicine, silica nanoparticles

## 1 | INTRODUCTION

Nanomedicine is the application of the principles and methods of nanoscience and technology to medicine, aimed at developing more sensitive and rapid medical methods and understanding the processes and mechanisms of life activities at the

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *WIREs Nanomedicine and Nanobiotechnology* published by Wiley Periodicals LLC.

more micro or nano level (Albanese, Tang, & Chan, 2012; Bregoli et al., 2016; Emerich, 2005; Lloyd-Parry, Downing, Aleisaei, Jones, & Coward, 2018). Worldwide it is evident that there is increasing emphasis on biomedical applications of a wide range of nanomaterials including silica nanoparticles (SNPs), superparamagnetic iron oxide nanoparticles, gold nanoparticles, and graphene and metal organic frameworks (Cheng, Deng, Lin, Cai, & Zink, 2019; Darweesh, Ayoub, & Nazzal, 2019; Rive et al., 2019; Yan et al., 2019; Zhong, Kankala, Wang, & Chen, 2019). Among nanomaterials, SNPs have great developmental potential and have become a research hotspot for their great developmental potential.

SNPs are inorganic engineered materials ranging in size from 1 to 100 nm. They have unique characteristics including large specific surface area, easy synthesis and amplification, facile surface modification, and robust delivery systems (Pasqua, Cundari, Ceresa, & Cavaletti, 2009; Patel et al., 2008; Qian & Bogner, 2012; Yamamoto & Kuroda, 2018; Yazdimamaghani, Barber, Hadipour Moghaddam, & Ghandehari, 2018). Compared to silicon nanoparticles (also known as silicon quantum dots), SNPs have gained more research attention on medicine applications (Joo et al., 2015; O'Farrell, Houlton, & Horrocks, 2006; Santos, Makila, Airaksinen, Bimbo, & Hirvonen, 2014). SNPs have been widely used in the field of nanomedicine and pharmacy, in particular in drug delivery system. Mesoporous silica nanoparticles (MSNs) have the ability to load a wide variety of fluorescent molecules while protecting dye molecules from harsh environmental conditions, thereby enhancing light stability and concentrating light signals with better resolution for diagnostic and monitoring purposes (Gimenez et al., 2015; Yang, Feng, & Liu, 2016). While SNPs are widely used, their safety has been of great concern for human health (Chen, Chen, & Shi, 2013). The main safety issue for the use of SNPs is their direct cytotoxicity, immune toxicity, and genotoxicity that affected particle size, potential aggregation, long-term bioaccumulation, and hemolytic activity (Feng et al., 2019; Hadipour Moghaddam, Mohammadpour, & Ghandehari, 2019; Janssen et al., 2018; Paris, Baeza, & Vallet-Regi, 2019). Furthermore, published data showed some inconsistencies between *in vitro* and *in vivo* studies (Murugadoss et al., 2017). To address this and other issues, this review provides a comprehensive overview of SNPs in nanomedicine. First, we briefly introduce the current preparation processes for SNPs followed by a focus on the functions and applications of SNPs in different fields of nanomedicine. For the safety concerns of SNPs, we review the data from nanotoxicology studies both *in vivo* and *in vitro*. Finally, we attempt to identify and summarize the opportunities and challenges for SNPs in other nanomedical applications. For other recent reviews (Jeelani, Mulay, Venkat, & Ramalingam, 2019; Narayan, Nayak, Raichur, & Garg, 2018; Wu, Mou, & Lin, 2013), we critically synthesize the current knowledge widely involved and review the opposing viewpoints from the perspective of *in vitro* and *in vivo* toxicology. At last, we give possible viewpoints in facing the potential unfavorable effects of the nanomaterials.

## 2 | SYNTHESIS OF SNPs

### 2.1 | Synthetic processes

#### 2.1.1 | Stöber method

The Stöber method is one of the sol-gel methods, which was proposed by Stöber, Fink, and Bohn (1968). It has been widely used in the synthesis of SNPs since it can form monodisperse solid particles without a template (Lieberman, Mendez, Trogler, & Kummel, 2014). The experimental method involves combining tetraethyl orthosilicate (TEOS) or other silicates with water, alcohol, and ammonia in a mixture to form a large number of silicic acid molecules. The silicic acid molecule is dehydrated or dealcoholized to form a Si-O-Si condensate. After the concentration reaches supersaturation, the primary SNPs rapidly aggregate to form primary silica particles which are further grown into more stable silica particles. Soluble silicic acid molecules or condensates continue to react and control the growth on its surface, and finally become SNPs (Blaaderen, Geest, & Vrij, 1992; Green et al., 2003).

Solid and mesoporous SNPs can be prepared by the Stöber method. SNPs are characterized by high uniformity and purity, excellent crystal shape, and optical transparency. However, the expensive raw materials required in the preparation process are expensive, time-consuming and have the potential to cause environmental pollution. Therefore, more extensive studies with more economical raw materials and efficient production are required for the development of the Stöber method.

#### 2.1.2 | Microemulsion method

Microemulsion is an isotropic, surfactant stable, and thermodynamically stable system composed of two incompatible liquids, and is considered as a synthetic "nanoreactor" (Wolf & Feldmann, 2016). Reactants usually form a

microemulsion as an aqueous phase and then contact with another reactant to form nanoparticles (NPs) (Boutonnet, Kizling, Stenius, & Maire, 1982). The particle shape of the NPs prepared by this method is narrow, and different particle sizes can be obtained by changing the different parameters of the microemulsion system.

SNPs with a particle size below 100 nm can be prepared by the microemulsion method. The experimental device is simple and easy to operate and the particle size distribution and shape of the SNPs can be controlled by changing the experimental conditions. The method could be improved if a higher purity of SNPs could be obtained by removing the organic components produced during the synthesis process (Aubert et al., 2010).

### 2.1.3 | Gas phase method

The gas phase method generally uses silicon tetrachloride (tetrachlorosilane) as a raw material, and hydrolyzes silicon tetrachloride gas with hydrogen and oxygen at a high temperature to obtain a fumed silica, and uses a sol atomizer to obtain a polydisperse or monodisperse liquid (Lu et al., 1999). The droplets are further heat-treated to obtain the desired NPs with a low density and unique mesoporous structure. The advantages of preparing SNPs by the gas phase method are high purity, high dispersion, and less hydroxyl groups on the surface. However, the disadvantages are expensive raw materials, high energy consumption, complex technology, and specialized equipment (Buesser & Pratsinis, 2012). Because of their excellent reinforcing properties, the NPs produced by this method are mainly used to enhance the rubber properties (Cohen-Addad, Roby, & Sauviat, 1985).

### 2.1.4 | Precipitation method

The precipitation method involves different chemical components in the solution state and subsequently adding the precursor precipitant to the mixed solution to form the precipitate (Nele, Vidal, Bhering, Carlos Pinto, & Salim, 1999). The precipitate is then dried or calcined into SNPs. The production process involves simple steps and less consumption of energy, but impurities and aggregation can readily occur. Therefore, an organic dispersion is required in the silicate solution, which may lead to good dispersion of the SNPs.

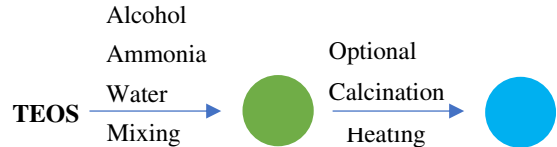
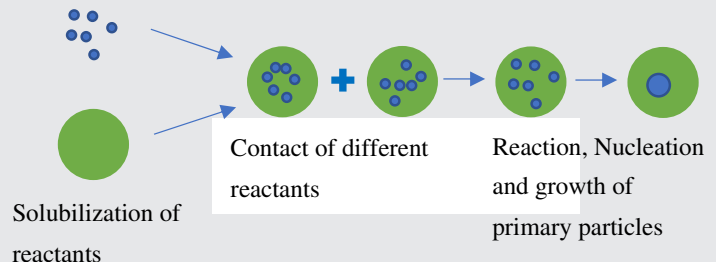
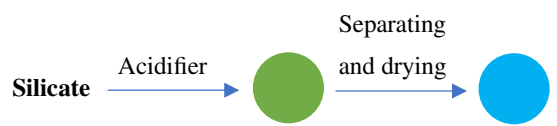
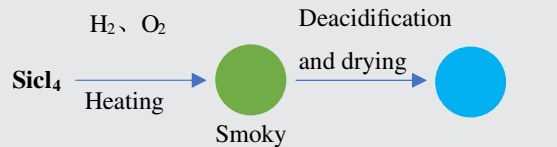
Comparison of the synthesis processes is listed in Table 1.

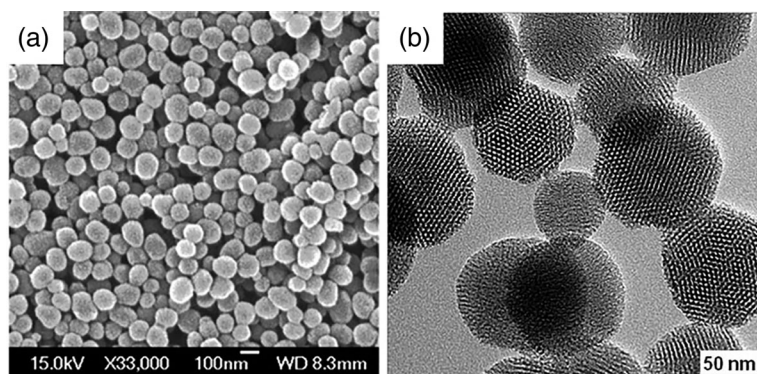
## 2.2 | Mesoporous silica nanoparticles

MSNs are widely used in nanomedicine because of their high porosity and biocompatibility, easy surface modification, and self-adjuvancity (Nguyen, Choi, & Kim, 2019). Methods for preparing MSNs with good dispersion properties used in medicine include fast self-assembly, soft and hard templating, a modified Stöber method, dissolving reconstruction, and modified gas phase method (Wu et al., 2013). The most commonly used method is the Stöber method (L. Chen, Zhou, & He, 2019). As an example, Grün, Lauer, and Unger (1997) used an improved Stöber synthesis to prepare sub-micron MCM-41 particles. Subsequent to that, 100 nm MCM-41 SNPs were obtained by using a diluted surfactant solution (Cai et al., 2001). MSNs less than 50 nm were obtained by adding a hydrochloric acid solution to the previous cetyl trimethylammonium chloride and a triblock copolymer as cationic and nonionic surfactants to the typical Stöber method (Li, Barnes, Bosoy, Stoddart, & Zink, 2012; Suzuki, Ikari, & Imai, 2004). Among the various MSNs, MCM-41 particles are widely studied in nanomedicine (Figure 1). MCM-41 particles are synthesized by using TEOS or sodium metasilicate as a silica precursor, the surfactant cetyltrimethylammonium bromide (CTAB) as a liquid crystal template and an alkali as the catalyst (Li et al., 2012; Tang, Li, & Chen, 2012).

These reaction parameters can be freely adjusted to produce stable and monodisperse MSNs with various shapes, pore structures, and particle sizes. The shape of MSNs can be directly controlled by changing the morphology of the CTAB template (Slowing, Trewyn, Giri, & Lin, 2007). Rod-shaped CTAB micelles can be obtained by carefully selecting the reagent composition ratio of the CTAB, water, and pH of the solution (using ammonia or sodium hydroxide) (Slowing, Vivero-Escoto, Trewyn, & Lin, 2010; Yu, Greish, McGill, Ray, & Ghandehari, 2012). Similarly, doping a photosensitizing molecule chlorin e6 (Ce6) into MSNs during the sol-gel process shows that the morphology of the mesoporous silica changes from spherical to rod-shaped (Yang, Gong, Qian, et al., 2015). The rod-shaped particles are shown in Figure 2a,b. Previous studies have reported 12-corner SNPs (Sun et al., 2017). The CTAB micelle size and size

**TABLE 1** Comparison of the four synthesis processes

Synthetic processes	Schematic diagram	Characteristic
Stöber method	<p style="text-align: center;"><b>Schematic diagram</b></p> 	Particle uniformity; high purity; good optical transparency
Microemulsion method		Particle size below 100 nm; simple operation; homogeneous inorganic compound powder
Gas phase method		High porosity; low thermal conductivity; high cost
Precipitation method		Solid particles; large particle size; suitable for industrial production

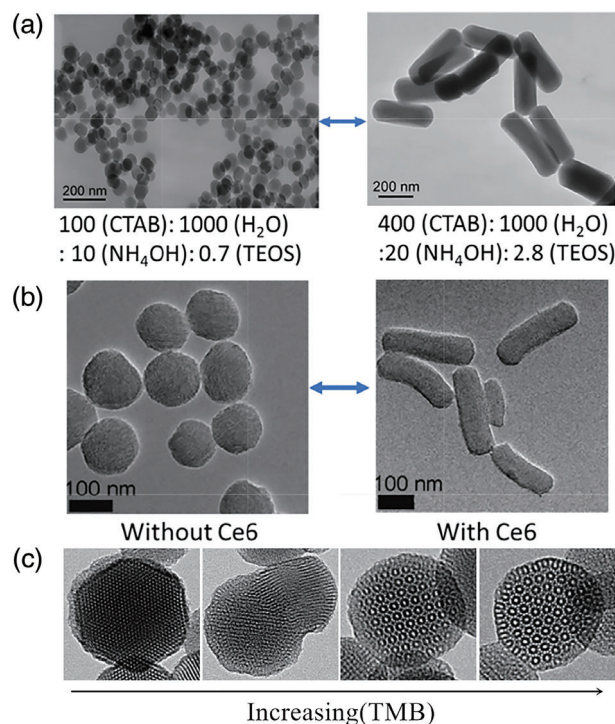
**FIGURE 1** (a) SEM image of MCM-41 mesoporous silica nanoparticles; (b) TEM image of MCM-41 (Reprinted with permission from Li et al. (2012). Copyright 2012 Royal Society of Chemistry)

distribution were systematically altered by adjusting the concentration of the micelle pore expander, mesitylene (TMB). The Transmission Electron Microscope (TEM) image shows that as the TMB concentration increases, the MSN structure changes from a hexagon to a multichamber to a cube, and finally becomes a 12-corner symmetrical structure (Figure 2c).

### 2.3 | Core-shell SNPs

Another research group developed a technology that is most commonly used for the synthesis of core-shell SNPs (Yang, Lind, & Troglor, 2008). They first coated polystyrene templates with poly-L-lysine and then performed a polycondensation reaction with hydrolyzed tetramethyl orthosilicate. After calcination, the hollow nanoshells had a 6–10 nm thick

**FIGURE 2** TEM images: (a) molar reagent ratio, (b) the dopant to silica networks, (c) TEM images of MSNs prepared from TEOS/AEAPTMS with 12, 29, 47, and 116 mM mesitylene (TMB), using a constant ammonium hydroxide concentration (13.8 mM) and stirring rate (650 rpm) (Reprinted with permission from Huang, Teng, Chen, Tang, and He (2010). Copyright 2010 Springer; Sun et al. (2017). Copyright 2017. Nature Publishing Group; Yang, Gong, Qian, et al. (2015). Copyright 2015 Elsevier)



shell and the diameter of the NPs isotropically decreased 10–20%. The core could be composed of metals for templating, which produces core-shell SNPs (Vivero-Escoto, Huxford-Phillips, & Lin, 2012). Wang, Tang, Zhao, Wan, and Chen (2014) prepared the magnetite–silica core–shell nanoparticles (Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>NPs) by direct oxidation from silicon powder. This technology provides a new opportunity for the preparation of core shell NPs for biomedical applications. Herein, Reis et al. (2019) develop a new polymeric coating for the gold–core SNPs by combining different ratios (25/75, 50/50, and 75/25) of two materials, poly-2-ethyl-2-oxazoline and  $\beta$ -cyclodextrin ( $\beta$ -CD). This improved the biological properties of the gold–core silica shell NPs and provided new ideas for cancer treatment.

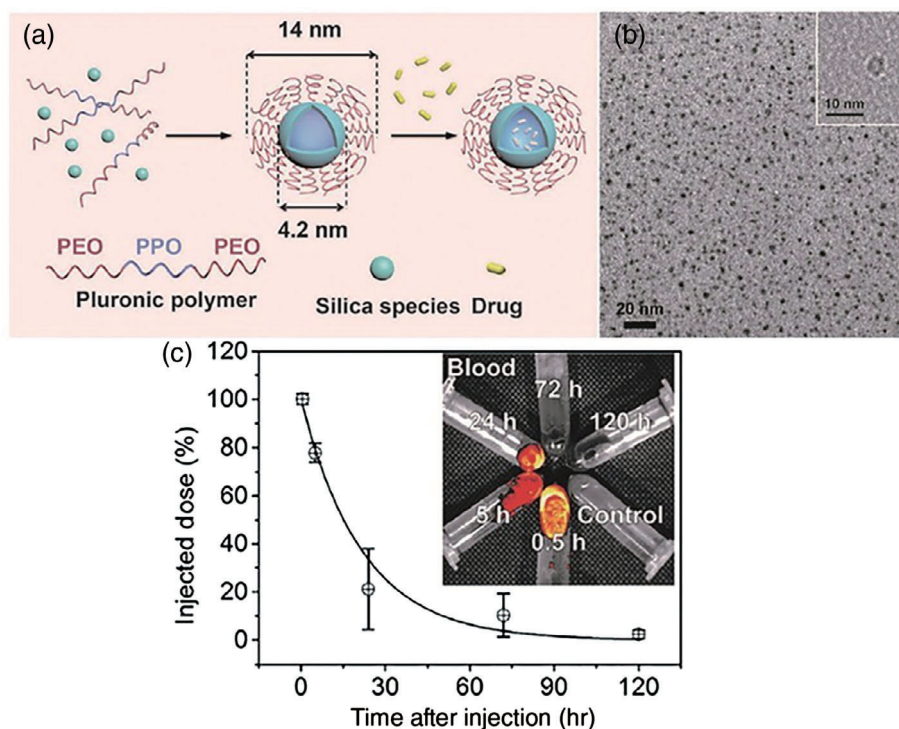
### 3 | NANOMEDICINE APPLICATIONS

#### 3.1 | Drug delivery

Since 2001 when MSNs were first proposed as potential drug delivery systems (Vallet-Regi, Rámila, del Real, & Pérez-Pariente, 2001), different SNPs have been widely used in drug delivery (Vallet-Regi & Tamasoi, 2018). Table 2 summarizes several SNPs-based drug delivery systems, including instant drug delivery systems, sustained drug delivery systems, stimulus response control drug delivery systems, and targeted drug delivery systems. Additional studies successfully synthesized a controlled release system composed of MSNs with covalently bound dipalmitoyl moieties supporting phosphorylated lipids. The system could release a model molecule, fluorescein from the pores of lipid bilayer coated MSNs (LB-MSNs) via a chemically triggered disulfide reduction (Roggers, Lin, & Trewyn, 2012). The system indicated that LB-MSNs could potentially be used to design a drug delivery system capable for controlled release. In 2013, this group further developed a drug delivery system for photosensitive cooperative treatment of cancer with cytotoxic cadmium sulfide nanoparticles and camptothecin (Knezevic & Lin, 2013). The system was further optimized by Zhao et al. (2016) who reported the Cy-5.5-labeled silica cross-linked PEO132-PPO50-PEO132 (F108) micelles with 14 nm ultra-small fluid dynamic particle size. These micelles provide a stronger drug diffusion barrier from the polymer core across the silica cross-linking layer, exhibiting a half-life in the blood circulation for up to 19 hr. This lead to efficient accumulation through the well-known enhanced permeability and retention effect in subcutaneously transplanted tumor models (Niu, Li, & Shi, 2017) described in Figure 3. Li, Zhang, Sheng, and Sun (2017) proposed SNPs with a thyroid stimulating hormone receptor targeting specific targets for thyroid cancer. Doxorubicin (DOX) nanoparticles can be triggered by an acid to release the drug payload for cancer treatment. Hadipour Moghaddam, Yazdimaghani, and

**TABLE 2** Comparison of the SNPs-based drug delivery systems

Drug delivery systems	Type	Characteristic	Model drug	References
Immediate drug delivery systems (IDDSs)		Improving dissolution rate of hydrophobic drugs	Telmisartan (TEL), prednisolone, etc.	Zhang et al. (2012), Sen Karaman et al. (2018)
Sustained drug delivery systems (SDDSs)	Unmodified; modified	Providing long-term drug release	Felodipine, nonsteroidal anti-inflammatory, etc.	Zhang et al. (2012), Ahmadi, Dehghannejad, Hashemikia, Ghasemnejad, and Tabebordbar (2014)
Stimuli-responsive controlled drug delivery systems (CDDSs)	<i>Endogenous:</i> pH, redox, enzyme, glucose, H <sub>2</sub> O <sub>2</sub> , ATP <i>Exogenous:</i> Thermo, light, magnetic, ultrasound, electro	Effective control of drug release	$\beta$ -Cyclodextrin, dexamethasone, etc.	Meng et al. (2010), Giri, Trewyn, Stellmaker, and Lin (2005), Deng et al. (2011)
Targeted drug delivery systems (TDDSs)		Targeted delivery of drugs, less dosage, tumor drug	Doxorubicin, camptothecin, TNF- $\alpha$ protein, etc.	Ashley et al. (2011), Porta et al. (2013)

**FIGURE 3** Schematic illustration (a) and TEM images of silica cross-linked F108 micelles (b). Blood-circulation time of silica cross-linked F108 micelles determined by ICP-OES (c) (Reprinted with permission from Niu et al. (2017). Copyright 2017 Royal Society of Chemistry; Zhao et al. (2016). Copyright 2016 Wiley)

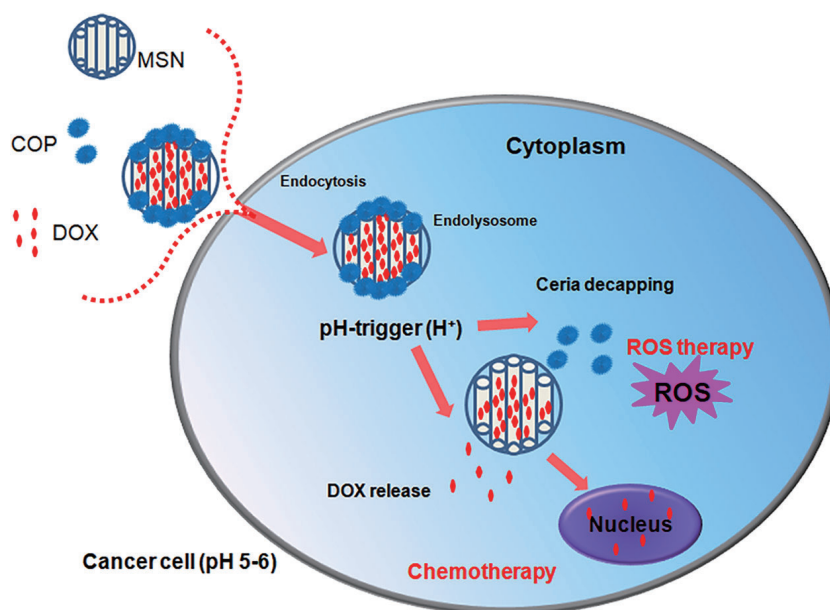
Ghandehari (2018) prepared glutathione (GSH)-sensitive hollow mesoporous NPs (HMSiO<sub>2</sub> NPs) using a selective etching strategy based on structural differences. These particles were compared with non-GSH-sensitive TEOS HMSiO<sub>2</sub> in terms of synthesis methods, characterization, DOX release curves, and in vitro cytotoxicity to MCF-7 breast cancer cells. These results showed that HMSiO<sub>2</sub> NPs had the advantages of high load capacity and controlled degradation at 100  $\mu$ g/ml concentration and the particles can hold 9  $\mu$ g/ml of DOX and effectively kill cancer cells. Juthani et al. (2020) functionalized ultrasmall fluorescent core-shell SNPs, referred to as Cornell prime dots (C'dots), with v integrin-binding (cRGDY), or nontargeting (cRADY) peptides, and PET labels (<sup>124</sup>I, <sup>89</sup>Zr) and investigated the utility of dual-modality

cRGD-C' dots for enhancing accumulation, distribution, and retention (ADR) in a genetically engineered mouse model of glioblastoma (mGBM). As a result, there was an improvement in brain tumor drug delivery and penetration, and an enhancement of ADR were achieved. Singh et al. (2019) prepared MSNs decorated with cerium oxide nanoparticles (COP@MSNs) using a pH-triggered response mechanism to control drug release and intracellular drug delivery. They blocked the mesopores of the carboxyl-functionalized MSNs with aminated COP. These pores were opened under acidic conditions to release the loaded drug and to establish a pH responsive drug delivery system (Figure 4). With the unique properties of SNPs and trigger response mechanisms (pH sensitive, light sensitive, magnetically sensitive, etc.), SNPs play a potential role in the treatment of diseases, especially in the treatment of tumors.

### 3.2 | Biomedical imaging

Compared to traditional materials, SNPs exhibit enhanced images in biomedical imaging characteristics (Cho, Glaus, Chen, Welch, & Xia, 2010; Choi & Frangioni, 2010). In recent years, studies on the application of SNPs to imaging techniques have been reported (Vivero-Escoto et al., 2012). These studies indicated that SNPs are powerful in making contrast agents of the chemical stability under various physiological conditions, high sensitivity and selectivity for the target, and good image contrast. In addition, having a long delay, SNPs have sufficient circulation time in blood. Tumor imaging is an important part of biomedical imaging. Another study found that nanoparticles administered by intravenous injection gave a strong fluorescence in tumors and magnetic resonance imaging (MRI) and computed tomography (CT) signals were enhanced (Yang, Gong, Liu, et al., 2015). Wu et al. (2008) were first to report the use of MSNs for bimodal imaging in animal models. Chen et al. (2014) combined copper-64 and 800 CW onto MSNs, and successfully imaged tumor blood vessels in vivo using positron emission tomography (PET) imaging and near-infrared imaging techniques using a multimode approach. The results showed that both in vivo PET and fluorescence imaging resolutions are significantly improved with this combination. In addition, fluorescently labeled mesoporous silica nanoparticles are also used as an endoscopic contrast agent for the diagnosis of precancerous lesions of the colon.

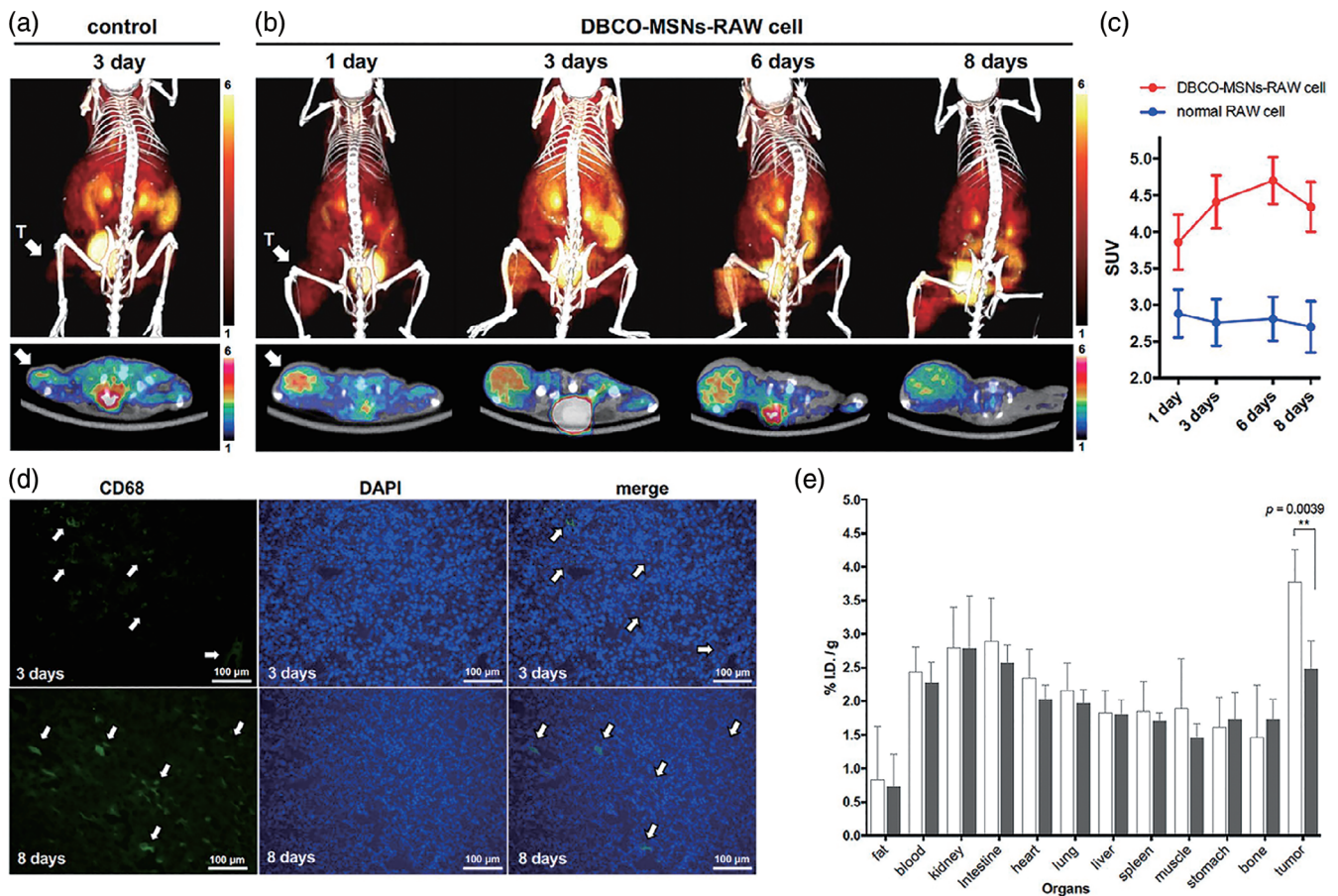
Khatik et al. (2019) reported MRI for tissue-specific T1/T2 double contrast. They developed a fancy kind of magnus nano-bullets (Mn-DTPA-F-MSNs) distinguished by a magnetic ( $\text{Fe}_3\text{O}_4$ -NPs) head combined with mesoporous silica ( $\text{SiO}_2$ ) that persisted in the body. Subsequently, they modified the mesoporous  $\text{SiO}_2$  group and finally loaded them with  $\text{Mn}^{2+}$ . The results show that the magnus nano-bomb enhances the T1-weighted MRI effect of redox reaction in GSH in vitro and in vivo. Jeong et al. (2019) designed a PET imaging protocol that promoted an in vivo strain-promoted alkyne azide cycloaddition (SPAAC) covalent labeling reaction in macrophages in vivo to track macrophages by using azadibenzocyclooctyne-tethered PEGylated mesoporous silica nanoparticles (DBCO-MSNs) with the short half-life F-18-labeled azide-radiotracer. This imaging scheme forms  $^{18}\text{F}$ -labeled azadibenzocycloocta-triazolic MSNs ( $^{18}\text{F}$ -DBCOT-



**FIGURE 4** Schematic illustration shows the intracellular ROS therapy and chemotherapy of DOX-loaded COP@MSNs system triggered by pH in cancer cells (Reprinted with permission from Singh et al. (2019). Copyright 2019 ACS Publications)

MSNs), in RAW 264.7 cells by an orthogonal SPAAC reaction of DBCO-MSNs with [ $^{18}\text{F}$ ] fluoropentaethylene glycolic azide ([ $^{18}\text{F}$ ]2). Thus, the macrophages successfully migrated to the tumor site. Finally, the results of tissue radioactivity distribution were consistent with those of PET imaging (Figure 5). Besides, a new cup-shaped SNP was found to be useful for ultrasonic imaging (F. Chen, Ma, et al., 2017). The novel cup-shaped SNP also called an exosome-like silica nanoparticles (ELS) was prepared by emulsion templating. They compared ELS with other SNPs and found that ELS strengthened particle echogenicity as well as improved the cell labeling efficiency. It also increased the *in vitro* and *in vivo* echogenicity of stem cells, providing clues to the use of further application of SNPs in ultrasound imaging. In addition, their team reported an ultrasound-capable biodegradable SNPs that showed no cytotoxicity at the 250  $\mu\text{g}/\text{ml}$  concentration required for labeling, and cleared from cells in approximately 3 weeks (Kempen et al., 2015).

Table 3 shows the difference among optical imaging, MRI, PET, CT, and ultrasound imaging. These five bioimaging technologies based on SNPs have both advantages and disadvantages. For example, the image resolution of a simple and fast optical imaging is low and CT imaging with high spatial resolution may have a radiation risk. However, the combination of multimodal imaging techniques may improve individual imaging techniques. A study showed that mesoporous silica-based triple-modal nanoprobe could be successfully applied to long-term imaging of tumor draining sentinel lymph nodes (Huang et al., 2012). The imaging results of different modalities are consistent and complementary because of the high stability and robustness of nanoprobe. In addition, biocompatibility is an important condition for the application of SNPs-based developers in nanomedicine in any imaging technologies. Park et al. (2010) not only



**FIGURE 5** Macrophage cell tracking PET imaging via bioorthogonal  $^{18}\text{F}$ -labeling in a tumor model. (a,b) Three-dimensional reconstruction (upper) and transverse section (lower) combined PET-CT images of  $^{18}\text{F}$ -labeled azide ([ $^{18}\text{F}$ ]2; 11.1 MBq) in U87 MG tumor-bearing mice treated with only normal RAW 264.7 cells ( $2 \times 10^6$  cells) 3 days earlier (control study; a) or in mice treated with DBCO-MSNs-RAW cells ( $2 \times 10^6$  cells; 0.1 ng Si/cell) 1, 3, 6, or 8 days earlier (cell tracking study; b), recorded 1 hr after injection of [ $^{18}\text{F}$ ]2. T = tumor, and (c) standardized uptake values (SUVs) in tumor area. (d) Immunofluorescence analysis of RAW264.7 cells in tumor tissue obtained from U87 MG tumor-bearing mice treated with DBCO-MSNs-RAW cells 3 and 8 days earlier. (e) Biodistribution of [ $^{18}\text{F}$ ]2 in U87MG tumor-bearing mice treated with DBCO-MSNs-RAW cells (cell tracking; white bar) or only RAW 264.7 cells 3 days earlier (control; gray bar), measured 1 hr after injection (Reprinted with permission from Jeong et al. (2019). Copyright 2019 Elsevier)



**TABLE 3** Comparison of the different bioimaging technology

Bio-imaging	Imaging medium	Advantages	Disadvantages	Contrast medium (SNPs)	References
Optical imaging	Fluorescence	High sensitivity, multicolor imaging, simple operation, low cost	Low spatial resolution, poor tissue penetration	Fluorescent dye-conjugated MSNs, CDs@MSNs, etc.	Heidegger et al. (2016), Fu et al. (2015)
Magnetic resonance imaging (MRI)	Magnetic field (radio waves)	High spatial resolution, no tissue penetrating limit, harmless	High cost, low sensitivity, long imaging time, hard calculating	Fe <sub>3</sub> O <sub>4</sub> @MSNs, HMnO@MSNs, MSN-DTTA-Gd, etc.	Kim et al. (2008), Kim et al. (2011), Taylor et al. (2008)
Positron emission tomography (PET)	γ-ray	High sensitivity, quantitative, no tissue penetrating limit, whole-body-scanning	Radiation risk, low spatial resolution	DBCO-PEG-MSNs, <sup>89</sup> Zr-MSNs, etc.	Lee, Kim, Jeong, et al. (2013), F. Chen, Goel, et al. (2015)
Computed tomography (CT)	X-ray	High spatial resolution, no tissue penetrating limit	Radiation risk, unquantifiable analysis	Au@MSNs, FePt@MSN, etc.	Song et al. (2015), F. Chen, Ma, et al. (2017)
Ultrasound imaging	Ultrasonic waves	Real-time, low cost	Multiple influencing factors, low resolution	MSN-PFH, ELS, etc.	Wang et al. (2012), F. Chen, Ma, et al. (2017)

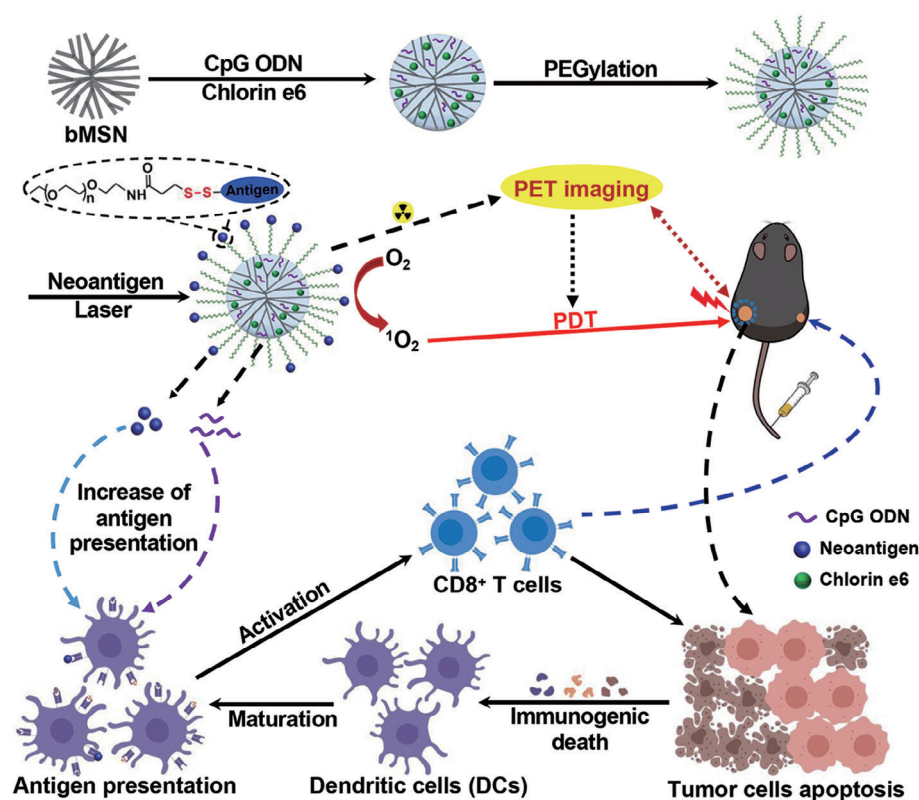
successfully used MRI and optical imaging to identify mesenchymal stem cells (MSCs) labeled with multimodal imaging nanoprobes, but also proved the biocompatibility of nanoprobes.

### 3.3 | Photodynamic therapy

Photodynamic therapy (PDT) is an effective, noninvasive treatment for local tumors that are accessible to light sources. PDT activates light-sensitive molecules (photosensitizers) by lasers of a specific wavelength and then produces cytotoxic reactive oxygen species (ROS), which ultimately leads to vascular closure and tumor cell death (Abrahamse & Hamblin, 2016; Lucky, Soo, & Zhang, 2015; Wang, Tao, Cheng, & Liu, 2011). PDT usually requires synergy with other biomedical methods to achieve optimal results. To achieve this, W. H. Chen, Luo, et al. (2017) constructed a multifunctional nanoplatfrom (TPZ@MCMSN-Gd<sup>3+</sup>) used in in vivo studies to demonstrate that under the guidance of near-infrared fluorescence/MRI, TPZ@MCMSN-Gd<sup>3+</sup> exhibited preferential aggregation at the tumor site through the synergistic action of PDT and bio-induced chemotherapy, leading to significant inhibition of tumor progression. Yang et al. (2017) adsorbed the photosensitizer chloramphenicol e6 (Ce6) and the antitumor drug (DOX) on magnetic mesoporous silica nanoparticles (M-MSNs) and showed nanocomposites could enhance the ability of MRI and CT imaging to allow for real-time imaging to guide the combination of PDT and chemotherapy to achieve a highly effective synergistic anti-tumor effects in vivo. Tumor-bearing Balb/c mice were used as an animal model for PDT and chemotherapy, and achieved synergistic anti-tumor effects in vivo. Hu et al. (2018) developed a new self-contained oxygen PDT platform-zeolite-catalase-MB nanocapsule (ZCM nanocapsule) that accurately implanted ZCM nanocapsules into the tumor area under real-time ultrasound imaging guidance and near-infrared laser irradiation, resulting in complete killing of local pancreatic cancer (PC) cells. In addition, Zhang et al. (2016) reported that combined synergistic treatment can effectively evade drug resistance. However, the use of PDT to treat disseminated, metastatic cancer remains challenging. Xu, Nam, Hong, Xu, and Moon (2019) developed a multifunctional nanomaterial system using a combination of PDT and individualized cancer immunotherapy, which provides new hope for the resolution of systemic disseminated and metastatic tumors (Figure 6).

### 3.4 | Photothermal therapy

Photothermal therapy (PTT), a method which uses light-absorbing nanomaterials to convert radiation into heat for tumor ablation, is an ideal adjuvant therapy in the treatment of tumors because of its controllability, simplicity and



**FIGURE 6** Schematic illustration of fabrication of bMSN (CpG/Ce6)-neoantigen and mechanism of bMSN (CpG/Ce6)-neoantigen nano-vaccines for PDT-enhanced cancer immunotherapy (Reprinted with permission from Xu et al. (2019). Copyright 2019 ACS Publications)

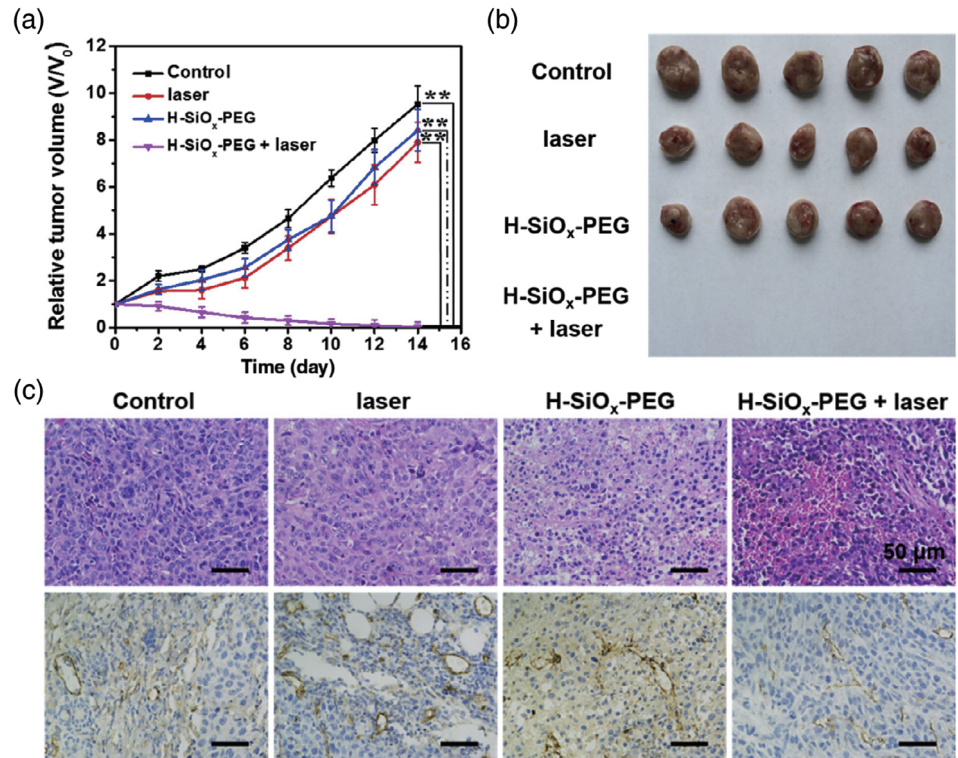
non-invasiveness (Menon et al., 2013; Wang et al., 2020). Yu, Yang, Chen, and Li (2017) reported that synthetic non-stoichiometric hollow silica nanoparticles (H-SiO<sub>x</sub> NPs) produce high photothermal conversion efficiency under 1,064 nm laser irradiation, which is highly effective for cancer treatment in vivo (Figure 7). Wang et al. (2019) prepared a multifunctional Janus structure of gold triangle-mesoporous silica nanoparticles (NPs) as a multifunctional platform to deliver a hypoxia-activated prodrug (TPZ) for topical PTT. In this method coupling of folate-linked polyethylene glycol provides the Janus nanoplatform with targeting and minimal operational characteristics for the treatment of liver cancer. *in vitro* and *in vivo* experiments demonstrated that combined radiation sensitivity and photothermal anti-tumor effects of the Janus nanoplatform, provide an effective and safe strategy for the treatment of liver cancer (Zhu et al., 2017).

However, PTT is ineffective for the ablation of certain tumor cells and can cause damage to healthy tissues (Li, Mivechi, & Weitzel, 1995), which may be due to an intracellular “autophagy” mechanism (White, 2015). In order to resolve this problem, T. Chen, Cen, et al. (2019) investigated bismuth crystal-embedded silica (Bi@SiO<sub>2</sub>) nanoparticles, loaded with an autophagy inhibitor (chloroquine, CQ). They demonstrated that CQ molecules are transported intracellularly using SNPs, which significantly attenuated the degradation of autolysosomes by lysosomes in tumor cells, thereby inducing an inhibition of autophagy and resistance to PTT. These studies compensated for the shortcomings of PTT, and the combined effects achieved under milder near-infrared radiation conditions have greatly improved both *in vitro* and *in vivo* anti-tumor effects.

### 3.5 | Others applications

In addition to the main applications outlined above, SNPs also play an effective role in anti-bacterial infection, wound healing, and the promotion of bone regeneration (Jia et al., 2019; Nethi, Das, Patra, & Mukherjee, 2019; Zhao et al., 2019). In the application of anti-bacterial infection, SNPs can combine the characteristics of large surface area/pore volume, adjustable pore size and capacity for controlling release, and better control for the loading and release of antibacterial agents, to improve the effect of anti-bacterial infections (Fernandez-Moure, Evangelopoulos, Colvill, Van Eps, & Tasciotti, 2017). Gonzalez et al. (2018) treated bacterial infections with nanocarriers containing antibiotics that could penetrate bacterial walls. They combined polycationic dendrimers with levofloxacin-loaded MSNs to trigger

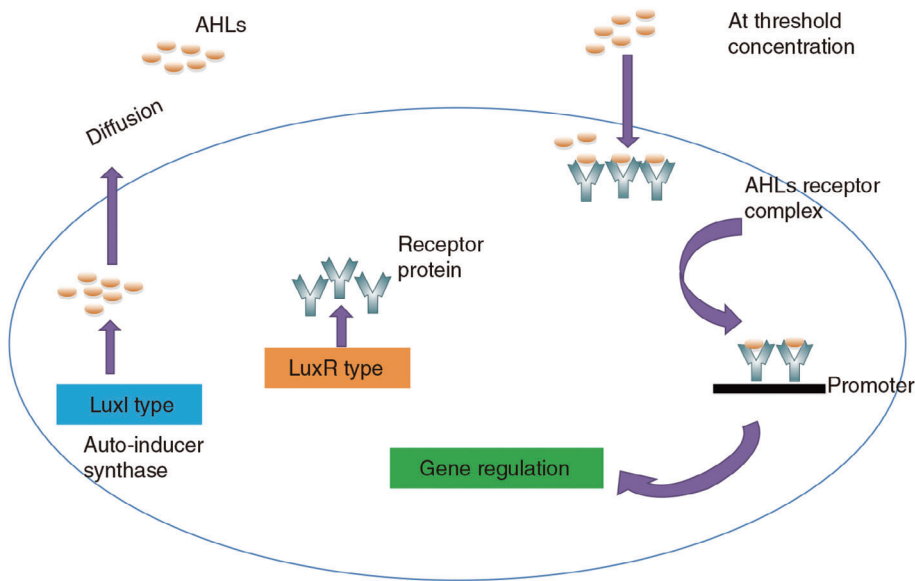
**FIGURE 7** (a) Tumor growth curves of mice with different treatments. (b) Representative photographs of tumors obtained from mice at day 14 after different treatments. (c) H&E staining (top row) and CD31 staining (bottom row) of tumor slices at day 2 in mice of each group after treatment (Reprinted with permission from Yu et al. (2017). Copyright 2017 Elsevier)



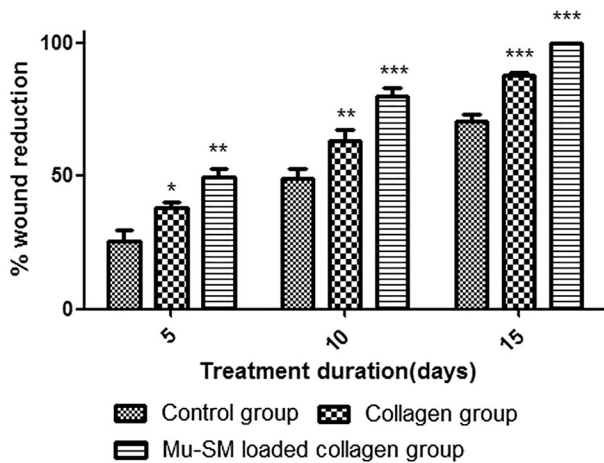
effective antibacterial action against Gram-negative bacterial biofilms. When SNPs loaded antimicrobial peptides such as Il-37 (Izquierdo-Barba et al., 2009), non-steroidal anti-inflammatory drugs (Scavo et al., 2015), and antibiotics (Perelman, Pacholski, Li, VanNieuwenhze, & Sailor, 2008), were placed in the center of a bacteria-containing AGAR gel, neither Gram-positive *Staphylococcus aureus* nor Gram-negative *Escherichia coli* showed obvious signs of bacterial growth. In another study, the quorum quenching potential of metal and metal oxide NPs were employed using targeted QS regulated virulence of Gram-negative bacteria (Hayat et al., 2019). Figure 8 is a schematic diagram of quorum sensing in Gram-negative bacteria. Miller (2015) prepared functionalized SNPs carrying the quenching molecule ( $\beta$ -CD) and the results showed that the functionalized SNPs of cyclodextrin could persist in the bacterial cell environment and quenched the extracellular bacterial communication molecules, finally achieving the antibacterial effect.

In relation to local application for wound healing, Quignard, Coradin, Powell, and Jugdaohsingh (2017) reported the effect of SNPs on proliferation and migration of human skin fibroblasts (CCD-25SK). The authors found that SNPs were absorbed by fibroblasts and dissolved inside the cells, releasing silicic acid, which ultimately promotes wound healing (Nethi et al., 2019). Perumal, Ramadass, and Madhan (2014) combined three materials, collagen, mupirocin, and sol-gel treated silica microspheres in a coordinated way to establish a wound healing material as a scaffold. The results showed that Wistar rats with biomedical composite had a shorter time to complete wound epithelialization than the control group (Figure 9). Furthermore, the composite exhibits good water absorption, sustained drug availability, and antibacterial activity. Therefore, SNPs biomedical composite may be a promising strategy for wound healing in the future.

In addition, SNPs plays an important role in bone regeneration. Beck Jr. et al. (2012) found that SNPs mediated an inhibitory effect on osteoclasts and a stimulating effect on osteoblasts in vitro. SNPs significantly increased bone mineral density in mice. Weitzmann et al. (2015) also reported that the 50 nm SNPs could regulate the differentiation of osteoblasts and inhibit the differentiation of osteoclasts. In vivo models of mice, bone density, bone volume, and biochemical markers of bone formation were significantly increased. These results indicate that SNPs have certain biological activity on bone regeneration. In recent studies, Jia et al. (2019) synthesized mesoporous silica coated magnetic ( $\text{Fe}_3\text{O}_4$ ) nanoparticles (M-MSNs) and found that they had the ability to promote osteogenic differentiation and bone regeneration with bone marrow MSCs in a rat distraction osteogenesis (DO) model. Mora-Raimundo, Lozano, Manzano, and Vallet-Regi (2019) developed a system based on MSNs coated with poly(ethylenimine). This system was capable of transporting SOST siRNA and osteogenic peptide into the cell, and SOST siRNA silenced the osteoporosis related gene SOST (SOST gene inhibits Wnt signaling pathway and reduces osteoblastic differentiation), so as to



**FIGURE 8** Quorum sensing in Gram-negative bacteria. LuxI protein produces a signaling molecule termed as acyl homoserine lactones (AHL). With increasing the population density, an increase in the concentration of AHL is also observed. When it reaches to a certain threshold level, AHLs enter the cell and subsequently bind to LuxR-type proteins to activate the expression of target genes (Reprinted with permission from Hayat et al. (2019). Copyright 2019 Future Science Group)



**FIGURE 9** Percentage wound contraction for control (untreated wound), collagen and Mu-SM collagen treatment. Significant difference in the efficacy was observed throughout the treatment duration for both collagen and Mu-SM loaded collagen compared to the untreated group (Reprinted with permission from Perumal et al. (2014). Copyright 2014 Elsevier)

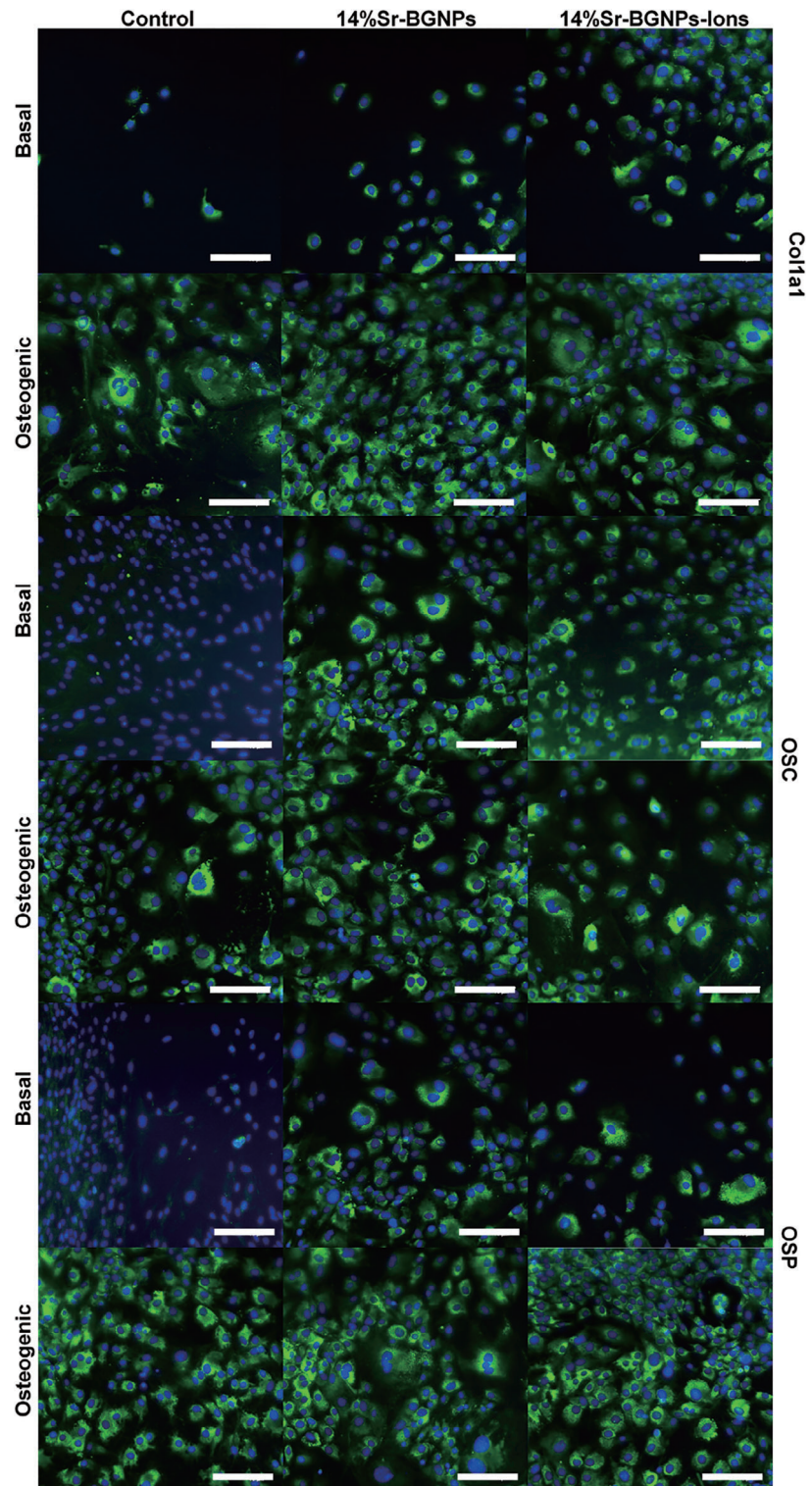
promote bone formation. Another group of researchers, prepared SNPs ( $90 \pm 10$  nm) and added calcium and strontium to produce monodispersed strontium containing bioactive glass nanoparticles (Sr-BGNPs) by using the modified Stöber method (Naruphontjirakul, Porter, & Jones, 2018). They investigated the osteogenic response of a murine pre-osteoblast cell line, MC3T3-E1, for nanoparticles. Immunohistochemistry staining of Col1a1, osteocalcin (OSC) and osteopontin (OSP) showed that these proteins were expressed in the MC3T3-E1 cells following 3 weeks of culture. At the same time, the expressions of late osteogenic differentiation markers, OSC and OSP, in the 14% Sr-BGNPs group were significantly higher than those of 0% Sr-BGNPs group (Figure 10). These data suggest that Sr-BGNPs may be beneficial to bone regeneration and used as an inorganic drug for bone regeneration. Therefore, the effect of SNPs on bone regeneration may be applied clinically in the future.

#### 4 | BIOCOMPATIBILITY

Due to SNPs properties consisting of a large specific surface area, easy surface modification and good biocompatibility facilitate the application and the study for further research of SNPs (Johnston et al., 2000; Ravi Kumar et al., 2004). On the other hand, there are concerns about the inconsistent data reported on SNPs for both in vivo and in vitro studies as well as safety issues (Murugadoss et al., 2017). In addition, a large number of toxicological studies have shown that the toxicity of SNPs is related to their concentration, particle size, surface properties, cell type, and other factors (Kim, Joachim, Choi, & Kim, 2015). Prior to application in nanomedicine, the mechanisms associated with toxicity of SNPs need to be understood in greater detail, and steps need to be taken to minimize health risk.

## 4.1 | Toxicological studies—in vitro

SNPs may cause cytotoxic effects in some cell lines through different mechanisms, including apoptosis, autophagy, pyroptosis, oxidative stress, and inflammatory responses. Among these, ROS-mediated effects are considered to be an important mechanism for SNPs cell damage (Murugadoss et al., 2017). MCM-41 particles showed active oxides in cells, causing oxidative stress and damage (Fritsch-Decker, Marquardt, Stoeger, Diabate, & Weiss, 2018; Kusaczuk, Kretowski, Naumowicz, Stypulkowska, & Cechowska-Pasko, 2018; Petrick, Rosenblat, Paland, & Aviram, 2016). SNPs



**FIGURE 10** Fluorescence image, DAPI (blue), Col1a1, OSC, and OSP staining (all green) of MC3T3-E1 cells exposure to 14% Sr-BGNPs and their ionic release products (Sr-BGNP concentration at 250  $\mu\text{g}/\text{ml}$ ) in basal and osteogenic conditions (3-week culture period). Scale bar 150  $\mu\text{m}$  (Reprinted with permission from Naruphontjirakul et al. (2018). Copyright 2018 Elsevier)

cause cytotoxicity without increasing ROS levels (Frohlich et al., 2009; Thomassen et al., 2011). In addition, Tao et al. (2008) and Huang et al. (2010) found that SNPs can inhibit cellular respiration, proliferation, and apoptosis. Some studies found that there are other ways in which SNPs can cause cytotoxicity. For instance, SNPs can induce autophagy by damaging the structure of lysosomes, increasing membrane permeability, downregulating the expression of lysosomal proteases and cathepsin B, thus damaging the function of lysosomes (Wang et al., 2017). Although the exact mechanism of autophagy is not clear, SNPs-induced autophagy is very evident. Recently, SNPs of different sizes were tested for their toxicity in different cells. These studies found SNPs can induce the pyroptosis in primary microglia, macrophages J774A.1 and N9 cells (Du et al., 2019). Cell death through the toxicity of SNP remains to be fully illustrated.

SNPs can cause other adverse effects such as genotoxicity, immunotoxicity, and neurotoxicity. Among these, immunity and genotoxicity are the focus of attention (Chen et al., 2018; Yazdimamaghani, Moos, Dobrovolskaia, & Ghandehari, 2019). At high cytotoxic doses, SNPs can induce the formation of micronuclei (Guichard et al., 2016). These toxicities are consistent in different cell lines and with different SNPs (Gonzalez et al., 2010; Maser et al., 2015). Recent studies have found that SNPs can induce genotoxicity in human tumor cell lines (lung, kidney, skin, and gastrointestinal system), which is related to the induction of oxidative stress (Duan et al., 2013; Guichard et al., 2015; Tarantini et al., 2015). The amplitude of this effect is negatively correlated with the size of the NPs. However, in a study by Guichard et al. (2016), Py-SNPs (20 nm) induced a significant increase in DNA strand breakage at 100  $\mu\text{g}/\text{cm}^2$  (24 hr) and c-SNPs (15 nm) showed a similar effect at 50 or 100  $\mu\text{g}/\text{cm}^2$ . However, none of these SNPs raised ROS levels so the mechanism of the DNA damage by SNPs needs further research (Magdolenova et al., 2014).

The toxic effects of SNPs on the immune system have been inadequately addressed. The properties of SNPs on the cellular uptake by immune cells and the subsequent immune responses need further research. After exposure to NPs, macrophages, dendritic cells, and T-lymphocytes produce biological responses mediated by inflammatory signaling pathways, ROS, and so on (Chen et al., 2018). Di Cristo et al. (2016) found that Py-SNPs (~14 nm) induced an increase in tumor necrosis factor- $\alpha$ , interleukin (IL)-6 and IL-1 $\beta$  in RAW.264.7 macrophages. Other results show that with a decrease in particle size, the cytotoxicity of SNPs to Langerhans cells becomes stronger (Nabeshi et al., 2010). It has been found that negatively charged SNPs exert the strongest immunotoxicity *in vivo* for lymphocytes. They inhibit the proliferation of lymphocytes, inhibit the killing activity of NK cells, and reduce the production of pro-inflammatory cytokines and nitric oxide (Kim et al., 2014).

## 4.2 | Toxicological studies—in vivo

*In vivo* studies usually involve toxicity studies using animals in which SNPs are administered primarily by inhalation, orally, topically and intravenously. SNPs may be distributed to different parts of the body depending on the route of exposure such as lung, liver, spleen, skin, kidney, and brain tissue (He et al., 2008; Huang et al., 2011; Lu, Liong, Li, Zink, & Tamanai, 2010). At the same time, NPs have two pathways of excretion from the body. One way is through the kidneys, being filtered out by the urine and the other is through the liver by secreting bile through the feces (Lee et al., 2014).

Some studies showed that SNPs could accumulate in the liver and spleen (He et al., 2008; Linden, 2018; Shao et al., 2017). Liu et al. (2011), using fluorescence and ultrastructural localization techniques, observed that a single intravenous injection of SNPs was distributed to the liver and spleen of animals. The high-dose (1,280 mg/kg) showed significant degeneration, lymphocytic infiltration, and necrosis. Intraperitoneal injections showed an increase in liver and spleen weight, spleen lymphocyte proliferation as determined by cellular markers (CD3+, CD45+, CD4+, and CD8+), macrophage infiltration, spleen red pulp expansion, and white pulp atrophy (Lee, Kim, Lee, et al., 2013). The smaller the size of the NPs that enters the body through oral or intravenous injection, the easier it is to pass through the kidneys and then excreted in the urine. During this process, SNPs may cause kidney damage, and a significant increase in creatinine levels in the blood, tubular atrophy, necrosis, and renal fibrosis (X. Chen, Zhouhua, et al., 2015; Hao, Li, & Tang, 2014; Li et al., 2015; Shamsi, Ahmed, & Bano, 2017). In other studies, the size of the NPs directly affects the extent of damage to the lung tissue (Handa et al., 2017). Huang et al. (2011) found that PEG-modified MSNs accumulated in lung tissue, affecting blood circulation time, and up-regulating the levels of alveolar macrophages. Another study showed that propylamine-modified MSNs causes lung inflammation, an increase in neutrophils, and may even lead to macrophage cell death (van Rijt et al., 2016).

These results indicated the potential toxicity of SNPs, while other studies have failed to find toxic effects of NPs administration. For example, no toxicity was observed in chronic oral intake and skin exposure studies (Murugadoss

et al., 2017). Yun et al. (2015) found that SNPs (12 nm) did not cause abnormal changes in blood biochemical and hematological parameters for acute and subchronic exposed rats. Several studies have also found that different types of SNPs are distributed to different organs but no abnormal symptoms were observed (Heidegger et al., 2016; Huang et al., 2011; Lee et al., 2010). Ryu et al. (2014) exposed rats to L-arginine coated SNPs (20 nm) for 90 days (6 hr exposure/day) through skin contact at different doses, but no changes in the skin were found. The results were supported by Shim et al. (2014) who performed toxicological studies of effects on the blood–brain barrier at different times after exposing SNPs via oral and dermal. After 28 and 90 days of oral administration of SNPs and after 90 days of percutaneous administration, no significant brain deposition and toxic effects were observed.

To confirm the unfavorable effects of SNPs, more comprehensive and systematic research needs to be conducted. The role of the physicochemical properties of SNPs *in vitro* and *in vivo* also needs further studies. The long-term toxicity and the effect of continuous exposure to health, especially the co-exposure problems of SNPs and chemical composition need to be addressed. It is also necessary to establish the nanotoxicology related standard about toxicity detection method and practical application. Investigating and producing biodegradable nanoparticles materials is another way to reduce the potential toxicity (Li & Liu, 2017; Su & Kang, 2020).

## 5 | CONCLUSION

Nanomedicine has developed rapidly as a consequence of progresses of science and technologies in multiple and varied research approaches. Due to the large specific surface area, easy synthesis and amplification, easy surface modification, and good biocompatibility, SNPs have been a research hotspot in the field of nanomaterials and nanomedicine. In the field of drug delivery, MSNs utilize their own mesoporous structure and porosity advantages to achieve drug delivery possibilities by adjusting the pore size and modifying the surface. Moreover, compared to conventional SNPs, the more advanced SNPs that are now being developed have the advantage of versatility for simultaneous bioimaging and drug delivery. The use of bio-imaging to monitor the drug delivery in real time can improve medical treatments. In addition, SNPs have relevant applications to several research fields such as PTT, PDT, antibacterial infection, wound healing, and bone regeneration.

While SNPs are widely used, their biosafety issues are of concerned. Both *in vitro* and *in vivo* studies showed that SNPs may cause cytotoxicity, hepatosplenic toxicity, genotoxicity, and immunotoxicity. However, in many toxicity studies, the results are inconsistent and the direction of the research is not clear cut. Given the use of SNPs in medical applications, we need to document the biocompatibility and toxicokinetic data in greater detail. Therefore, in order to succeed in the clinical application of SNPs more research is required to develop and standardize the procedures, more comprehensive and detailed research support is needed, and precisely defined the regulatory requirements. At the same time, it is expected that the application of SNPs in nanomedicine will bring more health benefits to human beings in the future.

## ACKNOWLEDGMENTS

This research was funded by National Natural Science Foundation of China (grant nos. 81602893, 81872575); Natural Science Foundation of Shandong Province (grant nos. ZR2015YL049, ZR2018MH036); Medical and Health Technology Development Plan Project of Shandong Province (grant no. 2016WS0540); Key Research and Development Plan of Shandong Province (grant nos. 2017GSF18186, 2018GSF118018); and The Innovation Project of Shandong Academy of Medical Science, and the Tsung Cho-Chang Educational Foundation (grant no. UQ-019171).

## CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

## AUTHOR CONTRIBUTIONS

**Ziyuan Li:** Data curation; methodology; writing-original draft. **Yingwen Mu:** Data curation; writing-original draft. **Cheng Peng:** Funding acquisition; methodology; writing-original draft; writing-review and editing. **Martin Lavin:** Formal analysis; methodology; writing-review and editing. **Hua Shao:** Data curation; funding acquisition; methodology; writing-review and editing. **Zhongjun Du:** Data curation; funding acquisition; methodology; resources; writing-original draft; writing-review and editing.

## ORCID

Zhongjun Du  <https://orcid.org/0000-0001-7422-6035>

## RELATED WIRES ARTICLE

[Mesoporous silica nanoparticles for tissue-engineering applications](#)

## REFERENCES

- Abrahamse, H., & Hamblin, M. R. (2016). New photosensitizers for photodynamic therapy. *The Biochemical Journal*, 473(4), 347–364. <https://doi.org/10.1042/bj20150942>
- Ahmadi, E., Dehghannejad, N., Hashemikia, S., Ghasemnejad, M., & Tabebordbar, H. (2014). Synthesis and surface modification of mesoporous silica nanoparticles and its application as carriers for sustained drug delivery. *Drug Delivery*, 21(3), 164–172. <https://doi.org/10.3109/10717544.2013.838715>
- Albanese, A., Tang, P. S., & Chan, W. C. (2012). The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annual Review of Biomedical Engineering*, 14, 1–16. <https://doi.org/10.1146/annurev-bioeng-071811-150124>
- Ashley, C. E., Carnes, E. C., Phillips, G. K., Padilla, D., Durfee, P. N., Brown, P. A., ... Brinker, C. J. (2011). The targeted delivery of multicomponent cargos to cancer cells by nanoporous particle-supported lipid bilayers. *Nature Materials*, 10(5), 389–397. <https://doi.org/10.1038/nmat2992>
- Aubert, T., Grasset, F., Mornet, S., Duguet, E., Cador, O., Cordier, S., ... Haneda, H. (2010). Functional silica nanoparticles synthesized by water-in-oil microemulsion processes. *Journal of Colloid and Interface Science*, 341(2), 201–208. <https://doi.org/10.1016/j.jcis.2009.09.064>
- Beck, G. R., Jr., Ha, S. W., Camalier, C. E., Yamaguchi, M., Li, Y., Lee, J. K., & Weitzmann, M. N. (2012). Bioactive silica-based nanoparticles stimulate bone-forming osteoblasts, suppress bone-resorbing osteoclasts, and enhance bone mineral density in vivo. *Nanomedicine*, 8(6), 793–803. <https://doi.org/10.1016/j.nano.2011.11.003>
- Blaaderen, A. V., Geest, J. V., & Vrij, A. (1992). Monodisperse colloidal silica spheres from tetraalkoxysilanes: Particle formation and growth mechanism. *Journal of Colloid & Interface Science*, 154(2), 481–501.
- Boutonnet, M., Kizling, J., Stenius, P., & Maire, G. (1982). The preparation of monodisperse colloidal metal particles from microemulsions. *Colloids and Surfaces*, 5(3), 209–225. [https://doi.org/10.1016/0166-6622\(82\)80079-6](https://doi.org/10.1016/0166-6622(82)80079-6)
- Bregoli, L., Movia, D., Gavigan-Imedio, J. D., Lysaght, J., Reynolds, J., & Prina-Mello, A. (2016). Nanomedicine applied to translational oncology: A future perspective on cancer treatment. *Nanomedicine*, 12(1), 81–103. <https://doi.org/10.1016/j.nano.2015.08.006>
- Buesser, B., & Pratsinis, S. E. (2012). Design of nanomaterial synthesis by aerosol processes. *Annual Review of Chemical and Biomolecular Engineering*, 3, 103–127. <https://doi.org/10.1146/annurev-chembioeng-062011-080930>
- Cai, Q., Luo, Z.-S., Pang, W.-Q., Fan, Y.-W., Chen, X.-H., & Cui, F.-Z. (2001). Dilute solution routes to various controllable morphologies of MCM-41 silica with a basic medium. *Chemistry of Materials*, 13(2), 258–263. <https://doi.org/10.1021/cm990661z>
- Chen, F., Goel, S., Valdovinos, H. F., Luo, H., Hernandez, R., Barnhart, T. E., & Cai, W. (2015). In vivo integrity and biological fate of chelator-free zirconium-89-labeled mesoporous silica nanoparticles. *ACS Nano*, 9(8), 7950–7959. <https://doi.org/10.1021/acsnano.5b00526>
- Chen, F., Ma, M., Wang, J., Wang, F., Chern, S. X., Zhao, E. R., ... Jokerst, J. V. (2017). Exosome-like silica nanoparticles: A novel ultrasound contrast agent for stem cell imaging. *Nanoscale*, 9(1), 402–411. <https://doi.org/10.1039/c6nr08177k>
- Chen, F., Nayak, T. R., Goel, S., Valdovinos, H. F., Hong, H., Theuer, C. P., ... Cai, W. (2014). In vivo tumor vasculature targeted PET/NIRF imaging with TRC105(Fab)-conjugated, dual-labeled mesoporous silica nanoparticles. *Molecular Pharmaceutics*, 11(11), 4007–4014. <https://doi.org/10.1021/mp500306k>
- Chen, L., Liu, J., Zhang, Y., Zhang, G., Kang, Y., Chen, A., ... Shao, L. (2018). The toxicity of silica nanoparticles to the immune system. *Nanomedicine (London, England)*, 13(15), 1939–1962. <https://doi.org/10.2217/nnm-2018-0076>
- Chen, L., Zhou, X., & He, C. (2019). Mesoporous silica nanoparticles for tissue-engineering applications. *WIREs Nanomedicine and Nanobiotechnology*, 11(6), e1573. <https://doi.org/10.1002/wnan.1573>
- Chen, T., Cen, D., Ren, Z., Wang, Y., Cai, X., Huang, J., ... Han, G. (2019). Bismuth embedded silica nanoparticles loaded with autophagy suppressant to promote photothermal therapy. *Biomaterials*, 221, 119419. <https://doi.org/10.1016/j.biomaterials.2019.119419>
- Chen, W. H., Luo, G. F., Qiu, W. X., Lei, Q., Liu, L. H., Wang, S. B., & Zhang, X. Z. (2017). Mesoporous silica-based versatile theranostic nanopatform constructed by layer-by-layer assembly for excellent photodynamic/chemo therapy. *Biomaterials*, 117, 54–65. <https://doi.org/10.1016/j.biomaterials.2016.11.057>
- Chen, X., Zhouhua, W., Jie, Z., Xinlu, F., Jinqiang, L., Yuwen, Q., & Zhiying, H. (2015). Renal interstitial fibrosis induced by high-dose mesoporous silica nanoparticles via the NF-kappaB signaling pathway. *International Journal of Nanomedicine*, 10, 1–22. <https://doi.org/10.2147/ijn.S73538>
- Chen, Y., Chen, H., & Shi, J. (2013). In vivo bio-safety evaluations and diagnostic/therapeutic applications of chemically designed mesoporous silica nanoparticles. *Advanced Materials*, 25(23), 3144–3176. <https://doi.org/10.1002/adma.201205292>
- Cheng, C. A., Deng, T., Lin, F. C., Cai, Y., & Zink, J. I. (2019). Supramolecular nanomachines as stimuli-responsive gatekeepers on mesoporous silica nanoparticles for antibiotic and cancer drug delivery. *Theranostics*, 9(11), 3341–3364. <https://doi.org/10.7150/thno.34576>
- Cho, E. C., Glaus, C., Chen, J., Welch, M. J., & Xia, Y. (2010). Inorganic nanoparticle-based contrast agents for molecular imaging. *Trends in Molecular Medicine*, 16(12), 561–573. <https://doi.org/10.1016/j.molmed.2010.09.004>



- Choi, H. S., & Frangioni, J. V. (2010). Nanoparticles for biomedical imaging: Fundamentals of clinical translation. *Molecular Imaging*, 9(6), 291–310.
- Cohen-Addad, J. P., Roby, C., & Sauviat, M. (1985). Characterization of chain binding to filler in silicone-silica systems. *Polymer*, 26(8), 1231–1233. [https://doi.org/10.1016/0032-3861\(85\)90258-7](https://doi.org/10.1016/0032-3861(85)90258-7)
- Darweesh, R. S., Ayoub, N. M., & Nazzal, S. (2019). Gold nanoparticles and angiogenesis: Molecular mechanisms and biomedical applications. *International Journal of Nanomedicine*, 14, 7643–7663. <https://doi.org/10.2147/ijn.S223941>
- Deng, Z., Zhen, Z., Hu, X., Wu, S., Xu, Z., & Chu, P. K. (2011). Hollow chitosan-silica nanospheres as pH-sensitive targeted delivery carriers in breast cancer therapy. *Biomaterials*, 32(21), 4976–4986. <https://doi.org/10.1016/j.biomaterials.2011.03.050>
- Di Cristo, L., Movia, D., Bianchi, M. G., Allegri, M., Mohamed, B. M., Bell, A. P., ... Bergamaschi, E. (2016). Proinflammatory effects of pyrogenic and precipitated amorphous silica nanoparticles in innate immunity cells. *Toxicological Sciences*, 150(1), 40–53. <https://doi.org/10.1093/toxsci/kfv258>
- Du, Q., Ge, D., Mirshafiee, V., Chen, C., Li, M., Xue, C., ... Sun, B. (2019). Assessment of neurotoxicity induced by different-sized Stober silica nanoparticles: Induction of pyroptosis in microglia. *Nanoscale*, 11(27), 12965–12972. <https://doi.org/10.1039/c9nr03756j>
- Duan, J., Yu, Y., Li, Y., Yu, Y., Li, Y., Zhou, X., ... Sun, Z. (2013). Toxic effect of silica nanoparticles on endothelial cells through DNA damage response via Chk1-dependent G2/M checkpoint. *PLoS One*, 8(4), e62087. <https://doi.org/10.1371/journal.pone.0062087>
- Emerich, D. F. (2005). Nanomedicine – Prospective therapeutic and diagnostic applications. *Expert Opinion on Biological Therapy*, 5(1), 1–5. <https://doi.org/10.1517/14712598.5.1.1>
- Feng, L., Yang, X., Liang, S., Xu, Q., Miller, M. R., Duan, J., & Sun, Z. (2019). Silica nanoparticles trigger the vascular endothelial dysfunction and prethrombotic state via miR-451 directly regulating the IL6R signaling pathway. *Particle and Fibre Toxicology*, 16(1), 16. <https://doi.org/10.1186/s12989-019-0300-x>
- Fernandez-Moure, J. S., Evangelopoulos, M., Colvill, K., Van Eps, J. L., & Tasciotti, E. (2017). Nanoantibiotics: A new paradigm for the treatment of surgical infection. *Nanomedicine (London, England)*, 12(11), 1319–1334. <https://doi.org/10.2217/nnm-2017-0401>
- Fritsch-Decker, S., Marquardt, C., Stoeger, T., Diabate, S., & Weiss, C. (2018). Revisiting the stress paradigm for silica nanoparticles: Decoupling of the anti-oxidative defense, pro-inflammatory response and cytotoxicity. *Archives of Toxicology*, 92(7), 2163–2174. <https://doi.org/10.1007/s00204-018-2223-y>
- Frohlich, E., Samberger, C., Kueznik, T., Absenger, M., Roblegg, E., Zimmer, A., & Pieber, T. R. (2009). Cytotoxicity of nanoparticles independent from oxidative stress. *The Journal of Toxicological Sciences*, 34(4), 363–375. <https://doi.org/10.2131/jts.34.363>
- Fu, C., Qiang, L., Liang, Q., Chen, X., Li, L., Liu, H., ... Meng, X. (2015). Facile synthesis of a highly luminescent carbon dot@silica nanorattle for in vivo bioimaging. *RSC Advances*, 5(57), 46158–46162. <https://doi.org/10.1039/C5RA04311E>
- Gimenez, C., de la Torre, C., Gorbe, M., Aznar, E., Sancenon, F., Murguia, J. R., ... Amoros, P. (2015). Gated mesoporous silica nanoparticles for the controlled delivery of drugs in cancer cells. *Langmuir*, 31(12), 3753–3762. <https://doi.org/10.1021/acs.langmuir.5b00139>
- Giri, S., Trewyn, B. G., Stellmaker, M. P., & Lin, V. S. (2005). Stimuli-responsive controlled-release delivery system based on mesoporous silica nanorods capped with magnetic nanoparticles. *Angewandte Chemie (International Edition in English)*, 44(32), 5038–5044. <https://doi.org/10.1002/anie.200501819>
- Gonzalez, B., Colilla, M., Diez, J., Pedraza, D., Guembe, M., Izquierdo-Barba, I., & Vallet-Regi, M. (2018). Mesoporous silica nanoparticles decorated with polycationic dendrimers for infection treatment. *Acta Biomaterialia*, 68, 261–271. <https://doi.org/10.1016/j.actbio.2017.12.041>
- Gonzalez, L., Thomassen, L. C., Plas, G., Rabolli, V., Napierska, D., Decordier, I., ... Kirsch-Volders, M. (2010). Exploring the aneugenic and clastogenic potential in the nanosize range: A549 human lung carcinoma cells and amorphous monodisperse silica nanoparticles as models. *Nanotoxicology*, 4, 382–395. <https://doi.org/10.3109/17435390.2010.501913>
- Green, D. L., Lin, J. S., Lam, Y.-F., Hu, M. Z. C., Schaefer, D. W., & Harris, M. T. (2003). Size, volume fraction, and nucleation of Stober silica nanoparticles. *Journal of Colloid and Interface Science*, 266(2), 346–358. [https://doi.org/10.1016/s0021-9797\(03\)00610-6](https://doi.org/10.1016/s0021-9797(03)00610-6)
- Grün, M., Lauer, I., & Unger, K. K. (1997). The synthesis of micrometer- and submicrometer-size spheres of ordered mesoporous oxide MCM-41. *Advanced Materials*, 9(3), 254–257. <https://doi.org/10.1002/adma.19970090317>
- Guichard, Y., Fontana, C., Chavinier, E., Terzetti, F., Gate, L., Binet, S., & Darne, C. (2016). Cytotoxic and genotoxic evaluation of different synthetic amorphous silica nanomaterials in the V79 cell line. *Toxicology and Industrial Health*, 32(9), 1639–1650. <https://doi.org/10.1177/0748233715572562>
- Guichard, Y., Maire, M. A., Sebillaud, S., Fontana, C., Langlais, C., Micillino, J. C., ... Gate, L. (2015). Genotoxicity of synthetic amorphous silica nanoparticles in rats following short-term exposure. Part 2: Intratracheal instillation and intravenous injection. *Environmental and Molecular Mutagenesis*, 56(2), 228–244. <https://doi.org/10.1002/em.21928>
- Hadipour Moghaddam, S. P., Mohammadpour, R., & Ghandehari, H. (2019). In vitro and in vivo evaluation of degradation, toxicity, bio-distribution, and clearance of silica nanoparticles as a function of size, porosity, density, and composition. *Journal of Controlled Release*, 311–312, 1–15. <https://doi.org/10.1016/j.jconrel.2019.08.028>
- Hadipour Moghaddam, S. P., Yazdimamaghani, M., & Ghandehari, H. (2018). Glutathione-sensitive hollow mesoporous silica nanoparticles for controlled drug delivery. *Journal of Controlled Release*, 282, 62–75. <https://doi.org/10.1016/j.jconrel.2018.04.032>
- Handa, T., Hirai, T., Izumi, N., Eto, S. I., Tsunoda, S. I., Nagano, K., ... Tsutsumi, Y. (2017). Identifying a size-specific hazard of silica nanoparticles after intravenous administration and its relationship to the other hazards that have negative correlations with the particle size in mice. *Nanotechnology*, 28(13), 135101. <https://doi.org/10.1088/1361-6528/aa5d7c>

- Hao, N., Li, L., & Tang, F. (2014). Shape-mediated biological effects of mesoporous silica nanoparticles. *Journal of Biomedical Nanotechnology*, 10(10), 2508–2538. <https://doi.org/10.1166/jbn.2014.1940>
- Hayat, S., Muzammil, S., Shabana, Aslam, B., Siddique, M. H., Saqalein, M., & Nisar, M. A. (2019). Quorum quenching: Role of nanoparticles as signal jammers in Gram-negative bacteria. *Future Microbiology*, 14, 61–72. <https://doi.org/10.2217/fmb-2018-0257>
- He, X., Nie, H., Wang, K., Tan, W., Wu, X., & Zhang, P. (2008). In vivo study of biodistribution and urinary excretion of surface-modified silica nanoparticles. *Analytical Chemistry*, 80(24), 9597–9603. <https://doi.org/10.1021/ac801882g>
- Heidegger, S., Gossl, D., Schmidt, A., Niedermayer, S., Argyo, C., Endres, S., ... Bourquin, C. (2016). Immune response to functionalized mesoporous silica nanoparticles for targeted drug delivery. *Nanoscale*, 8(2), 938–948. <https://doi.org/10.1039/c5nr06122a>
- Hu, D., Chen, Z., Sheng, Z., Gao, D., Yan, F., Ma, T., ... Hong, M. (2018). A catalase-loaded hierarchical zeolite as an implantable nanocapsule for ultrasound-guided oxygen self-sufficient photodynamic therapy against pancreatic cancer. *Nanoscale*, 10(36), 17283–17292. <https://doi.org/10.1039/c8nr05548c>
- Huang, X., Li, L., Liu, T., Hao, N., Liu, H., Chen, D., & Tang, F. (2011). The shape effect of mesoporous silica nanoparticles on biodistribution, clearance, and biocompatibility in vivo. *ACS Nano*, 5(7), 5390–5399. <https://doi.org/10.1021/nn200365a>
- Huang, X., Teng, X., Chen, D., Tang, F., & He, J. (2010). The effect of the shape of mesoporous silica nanoparticles on cellular uptake and cell function. *Biomaterials*, 31(3), 438–448. <https://doi.org/10.1016/j.biomaterials.2009.09.060>
- Huang, X., Zhang, F., Lee, S., Swierczewska, M., Kiesewetter, D. O., Lang, L., ... Chen, X. (2012). Long-term multimodal imaging of tumor draining sentinel lymph nodes using mesoporous silica-based nanoprobe. *Biomaterials*, 33(17), 4370–4378. <https://doi.org/10.1016/j.biomaterials.2012.02.060>
- Izquierdo-Barba, I., Vallet-Regi, M., Kupferschmidt, N., Terasaki, O., Schmidtchen, A., & Malmsten, M. (2009). Incorporation of antimicrobial compounds in mesoporous silica film monolith. *Biomaterials*, 30(29), 5729–5736. <https://doi.org/10.1016/j.biomaterials.2009.07.003>
- Janssen, H. C., Warwas, D. P., Dahlhaus, D., Meissner, J., Taptimthong, P., Kietzmann, M., ... Angrisani, N. (2018). In vitro and in vivo accumulation of magnetic nanoporous silica nanoparticles on implant materials with different magnetic properties. *Journal of Nanobiotechnology*, 16(1), 96. <https://doi.org/10.1186/s12951-018-0422-6>
- Jeelani, P. G., Mulay, P., Venkat, R., & Ramalingam, C. (2019). Multifaceted application of silica nanoparticles. A review. *Silicon*. <https://doi.org/10.1007/s12633-019-00229-y>
- Jeong, H. J., Yoo, R. J., Kim, J. K., Kim, M. H., Park, S. H., Kim, H., ... Kim, D. W. (2019). Macrophage cell tracking PET imaging using mesoporous silica nanoparticles via in vivo bioorthogonal F-18 labeling. *Biomaterials*, 199, 32–39. <https://doi.org/10.1016/j.biomaterials.2019.01.043>
- Jia, Y., Zhang, P., Sun, Y., Kang, Q., Xu, J., Zhang, C., & Chai, Y. (2019). Regeneration of large bone defects using mesoporous silica coated magnetic nanoparticles during distraction osteogenesis. *Nanomedicine*, 21, 102040. <https://doi.org/10.1016/j.nano.2019.102040>
- Johnston, C. J., Driscoll, K. E., Finkelstein, J. N., Baggs, R., O'Reilly, M. A., Carter, J., ... Oberdorster, G. (2000). Pulmonary chemokine and mutagenic responses in rats after subchronic inhalation of amorphous and crystalline silica. *Toxicological Sciences*, 56(2), 405–413. <https://doi.org/10.1093/toxsci/56.2.405>
- Joo, J., Liu, X., Kotamraju, V. R., Ruoslahti, E., Nam, Y., & Sailor, M. J. (2015). Gated luminescence imaging of silicon nanoparticles. *ACS Nano*, 9(6), 6233–6241. <https://doi.org/10.1021/acs.nano.5b01594>
- Juthani, R., Madajewski, B., Yoo, B., Zhang, L., Chen, P. M., Chen, F., ... Brennan, C. W. (2020). Ultrasmall core-shell silica nanoparticles for precision drug delivery in a high-grade malignant brain tumor model. *Clinical Cancer Research*, 26(1), 147–158. <https://doi.org/10.1158/1078-0432.Ccr-19-1834>
- Kempen, P. J., Greasley, S., Parker, K. A., Campbell, J. L., Chang, H. Y., Jones, J. R., ... Jokerst, J. V. (2015). Theranostic mesoporous silica nanoparticles biodegrade after pro-survival drug delivery and ultrasound/magnetic resonance imaging of stem cells. *Theranostics*, 5(6), 631–642. <https://doi.org/10.7150/thno.11389>
- Khatik, R., Wang, Z., Li, F., Zhi, D., Kiran, S., Dwivedi, P., ... Yang, Q. (2019). “Magnus nano-bullets” as T1/T2 based dual-modal for in vitro and in vivo MRI visualization. *Nanomedicine*, 15(1), 264–273. <https://doi.org/10.1016/j.nano.2018.10.005>
- Kim, I. Y., Joachim, E., Choi, H., & Kim, K. (2015). Toxicity of silica nanoparticles depends on size, dose, and cell type. *Nanomedicine*, 11(6), 1407–1416. <https://doi.org/10.1016/j.nano.2015.03.004>
- Kim, J., Kim, H. S., Lee, N., Kim, T., Kim, H., Yu, T., ... Hyeon, T. (2008). Multifunctional uniform nanoparticles composed of a magnetite nanocrystal core and a mesoporous silica shell for magnetic resonance and fluorescence imaging and for drug delivery. *Angewandte Chemie (International Edition in English)*, 47(44), 8438–8441. <https://doi.org/10.1002/anie.200802469>
- Kim, J. H., Kim, C. S., Ignacio, R. M., Kim, D. H., Sajo, M. E., Maeng, E. H., ... Kim, S. K. (2014). Immunotoxicity of silicon dioxide nanoparticles with different sizes and electrostatic charge. *International Journal of Nanomedicine*, 9(Suppl. 2), 183–193. <https://doi.org/10.2147/ijn.S57934>
- Kim, T., Momin, E., Choi, J., Yuan, K., Zaidi, H., Kim, J., ... Gilad, A. A. (2011). Mesoporous silica-coated hollow manganese oxide nanoparticles as positive T1 contrast agents for labeling and MRI tracking of adipose-derived mesenchymal stem cells. *Journal of the American Chemical Society*, 133(9), 2955–2961. <https://doi.org/10.1021/ja1084095>
- Knezevic, N. Z., & Lin, V. S. (2013). A magnetic mesoporous silica nanoparticle-based drug delivery system for photosensitive cooperative treatment of cancer with a mesopore-capping agent and mesopore-loaded drug. *Nanoscale*, 5(4), 1544–1551. <https://doi.org/10.1039/c2nr33417h>

- Kusaczuk, M., Kretowski, R., Naumowicz, M., Stypulkowska, A., & Cechowska-Pasko, M. (2018). Silica nanoparticle-induced oxidative stress and mitochondrial damage is followed by activation of intrinsic apoptosis pathway in glioblastoma cells. *International Journal of Nanomedicine*, 13, 2279–2294. <https://doi.org/10.2147/ijn.S158393>
- Lee, J. A., Kim, M. K., Paek, H. J., Kim, Y. R., Kim, M. K., Lee, J. K., ... Choi, S. J. (2014). Tissue distribution and excretion kinetics of orally administered silica nanoparticles in rats. *International Journal of Nanomedicine*, 9(Suppl 2), 251–260. <https://doi.org/10.2147/ijn.S57939>
- Lee, J. E., Lee, N., Kim, H., Kim, J., Choi, S. H., Kim, J. H., ... Hyeon, T. (2010). Uniform mesoporous dye-doped silica nanoparticles decorated with multiple magnetite nanocrystals for simultaneous enhanced magnetic resonance imaging, fluorescence imaging, and drug delivery. *Journal of the American Chemical Society*, 132(2), 552–557. <https://doi.org/10.1021/ja905793q>
- Lee, S., Kim, M. S., Lee, D., Kwon, T. K., Khang, D., Yun, H. S., & Kim, S. H. (2013). The comparative immunotoxicity of mesoporous silica nanoparticles and colloidal silica nanoparticles in mice. *International Journal of Nanomedicine*, 8, 147–158. <https://doi.org/10.2147/ijn.S39534>
- Lee, S. B., Kim, H. L., Jeong, H. J., Lim, S. T., Sohn, M. H., & Kim, D. W. (2013). Mesoporous silica nanoparticle pretargeting for PET imaging based on a rapid bioorthogonal reaction in a living body. *Angewandte Chemie (International Edition in English)*, 52(40), 10549–10552. <https://doi.org/10.1002/anie.201304026>
- Li, G. C., Mivechi, N. F., & Weitzel, G. (1995). Heat shock proteins, thermotolerance, and their relevance to clinical hyperthermia. *International Journal of Hyperthermia*, 11(4), 459–488. <https://doi.org/10.3109/02656739509022483>
- Li, L., & Liu, H. (2017). Biodegradable inorganic nanoparticles: An opportunity for improved cancer therapy? *Nanomedicine (London, England)*, 12(9), 959–961. <https://doi.org/10.2217/nnm-2017-0057>
- Li, L., Liu, T., Fu, C., Tan, L., Meng, X., & Liu, H. (2015). Biodistribution, excretion, and toxicity of mesoporous silica nanoparticles after oral administration depend on their shape. *Nanomedicine*, 11(8), 1915–1924. <https://doi.org/10.1016/j.nano.2015.07.004>
- Li, S., Zhang, D., Sheng, S., & Sun, H. (2017). Targeting thyroid cancer with acid-triggered release of doxorubicin from silicon dioxide nanoparticles. *International Journal of Nanomedicine*, 12, 5993–6003. <https://doi.org/10.2147/ijn.S137335>
- Li, Z., Barnes, J. C., Bosoy, A., Stoddart, J. F., & Zink, J. I. (2012). Mesoporous silica nanoparticles in biomedical applications. *Chemical Society Reviews*, 41(7), 2590–2605. <https://doi.org/10.1039/C1CS15246G>
- Lieberman, A., Mendez, N., Trogler, W. C., & Kummel, A. C. (2014). Synthesis and surface functionalization of silica nanoparticles for nanomedicine. *Surface Science Reports*, 69(2–3), 132–158. <https://doi.org/10.1016/j.surfrep.2014.07.001>
- Linden, M. (2018). Biodistribution and excretion of intravenously injected mesoporous silica nanoparticles: Implications for drug delivery efficiency and safety. *Enzyme*, 43, 155–180. <https://doi.org/10.1016/bs.enz.2018.07.007>
- Liu, T., Li, L., Teng, X., Huang, X., Liu, H., Chen, D., ... Tang, F. (2011). Single and repeated dose toxicity of mesoporous hollow silica nanoparticles in intravenously exposed mice. *Biomaterials*, 32(6), 1657–1668. <https://doi.org/10.1016/j.biomaterials.2010.10.035>
- Lloyd-Parry, O., Downing, C., Aleisaei, E., Jones, C., & Coward, K. (2018). Nanomedicine applications in women's health: State of the art. *International Journal of Nanomedicine*, 13, 1963–1983. <https://doi.org/10.2147/ijn.S97572>
- Lu, J., Liang, M., Li, Z., Zink, J. I., & Tamanoi, F. (2010). Biocompatibility, biodistribution, and drug-delivery efficiency of mesoporous silica nanoparticles for cancer therapy in animals. *Small*, 6(16), 1794–1805. <https://doi.org/10.1002/smll.201000538>
- Lu, Y., Fan, H., Stump, A., Ward, T. L., Rieker, T., & Brinker, C. J. (1999). Aerosol-assisted self-assembly of mesostructured spherical nanoparticles. *Nature*, 398(6724), 223–226. <https://doi.org/10.1038/18410>
- Lucky, S. S., Soo, K. C., & Zhang, Y. (2015). Nanoparticles in photodynamic therapy. *Chemical Reviews*, 115(4), 1990–2042. <https://doi.org/10.1021/cr5004198>
- Magdolenova, Z., Collins, A., Kumar, A., Dhawan, A., Stone, V., & Dusinska, M. (2014). Mechanisms of genotoxicity. A review of in vitro and in vivo studies with engineered nanoparticles. *Nanotoxicology*, 8(3), 233–278. <https://doi.org/10.3109/17435390.2013.773464>
- Maser, E., Schulz, M., Sauer, U. G., Wiemann, M., Ma-Hock, L., Wohlleben, W., ... Landsiedel, R. (2015). In vitro and in vivo genotoxicity investigations of differently sized amorphous SiO<sub>2</sub> nanomaterials. *Mutation Research, Genetic Toxicology and Environmental Mutagenesis*, 794, 57–74. <https://doi.org/10.1016/j.mrgentox.2015.10.005>
- Meng, H., Xue, M., Xia, T., Zhao, Y. L., Tamanoi, F., Stoddart, J. F., ... Nel, A. E. (2010). Autonomous in vitro anticancer drug release from mesoporous silica nanoparticles by pH-sensitive nanovalves. *Journal of the American Chemical Society*, 132(36), 12690–12697. <https://doi.org/10.1021/ja104501a>
- Menon, J. U., Jadeja, P., Tambe, P., Vu, K., Yuan, B., & Nguyen, K. T. (2013). Nanomaterials for photo-based diagnostic and therapeutic applications. *Theranostics*, 3(3), 152–166. <https://doi.org/10.7150/thno.5327>
- Miller, K. P. (2015). *Bacterial communication and its role as a target for nanoparticle-based antimicrobial therapy*, University of South Carolina – Columbia. <https://scholarcommons.sc.edu/etd/3188>
- Mora-Raimundo, P., Lozano, D., Manzano, M., & Vallet-Regi, M. (2019). Nanoparticles to knockdown osteoporosis-related gene and promote osteogenic marker expression for osteoporosis treatment. *ACS Nano*, 13(5), 5451–5464. <https://doi.org/10.1021/acsnano.9b00241>
- Murugadoss, S., Lison, D., Godderis, L., Van Den Brule, S., Mast, J., Brassinne, F., ... Hoet, P. H. (2017). Toxicology of silica nanoparticles: An update. *Archives of Toxicology*, 91(9), 2967–3010. <https://doi.org/10.1007/s00204-017-1993-y>
- Nabeshi, H., Yoshikawa, T., Matsuyama, K., Nakazato, Y., Arimori, A., Isobe, M., ... Tsutsumi, Y. (2010). Size-dependent cytotoxic effects of amorphous silica nanoparticles on Langerhans cells. *Pharmazie*, 65(3), 199–201.
- Narayan, R., Nayak, U. Y., Raichur, A. M., & Garg, S. (2018). Mesoporous silica nanoparticles: A comprehensive review on synthesis and recent advances. *Pharmaceutics*, 10(3), 118. <https://doi.org/10.3390/pharmaceutics10030118>

- Naruphontjirakul, P., Porter, A. E., & Jones, J. R. (2018). In vitro osteogenesis by intracellular uptake of strontium containing bioactive glass nanoparticles. *Acta Biomaterialia*, 66, 67–80. <https://doi.org/10.1016/j.actbio.2017.11.008>
- Nele, M., Vidal, A., Bhering, D. L., Carlos Pinto, J., & Salim, V. M. M. (1999). Preparation of high loading silica supported nickel catalyst: Simultaneous analysis of the precipitation and aging steps. *Applied Catalysis A: General*, 178(2), 177–189. [https://doi.org/10.1016/S0926-860X\(98\)00285-3](https://doi.org/10.1016/S0926-860X(98)00285-3)
- Nethi, S. K., Das, S., Patra, C. R., & Mukherjee, S. (2019). Recent advances in inorganic nanomaterials for wound-healing applications. *Bio-materials Science*, 7(7), 2652–2674. <https://doi.org/10.1039/c9bm00423h>
- Nguyen, T. L., Choi, Y., & Kim, J. (2019). Mesoporous silica as a versatile platform for cancer immunotherapy. *Advanced Materials*, 31(34), e1803953. <https://doi.org/10.1002/adma.201803953>
- Niu, D., Li, Y., & Shi, J. (2017). Silica/organosilica cross-linked block copolymer micelles: A versatile theranostic platform. *Chemical Society Reviews*, 46(3), 569–585. <https://doi.org/10.1039/c6cs00495d>
- O'Farrell, N., Houlton, A., & Horrocks, B. R. (2006). Silicon nanoparticles: Applications in cell biology and medicine. *International Journal of Nanomedicine*, 1(4), 451–472. <https://doi.org/10.2147/nano.2006.1.4.451>
- Paris, J. L., Baeza, A., & Vallet-Regi, M. (2019). Overcoming the stability, toxicity, and biodegradation challenges of tumor stimuli-responsive inorganic nanoparticles for delivery of cancer therapeutics. *Expert Opinion on Drug Delivery*, 16(10), 1095–1112. <https://doi.org/10.1080/17425247.2019.1662786>
- Park, K. S., Tae, J., Choi, B., Kim, Y. S., Moon, C., Kim, S. H., ... Kim, S. (2010). Characterization, in vitro cytotoxicity assessment, and in vivo visualization of multimodal, RITC-labeled, silica-coated magnetic nanoparticles for labeling human cord blood-derived mesenchymal stem cells. *Nanomedicine*, 6(2), 263–276. <https://doi.org/10.1016/j.nano.2009.07.005>
- Pasqua, L., Cundari, S., Ceresa, C., & Cavalletti, G. (2009). Recent development, applications, and perspectives of mesoporous silica particles in medicine and biotechnology. *Current Medicinal Chemistry*, 16(23), 3054–3063. <https://doi.org/10.2174/092986709788803079>
- Patel, K., Angelos, S., Dichtel, W. R., Coskun, A., Yang, Y. W., Zink, J. I., & Stoddart, J. F. (2008). Enzyme-responsive snap-top covered silica nanocontainers. *Journal of the American Chemical Society*, 130(8), 2382–2383. <https://doi.org/10.1021/ja0772086>
- Perelman, L. A., Pacholski, C., Li, Y. Y., VanNieuwenhze, M. S., & Sailor, M. J. (2008). pH-triggered release of vancomycin from protein-capped porous silicon films. *Nanomedicine (London, England)*, 3(1), 31–43. <https://doi.org/10.2217/17435889.3.1.31>
- Perumal, S., Ramadass, S., & Madhan, B. (2014). Sol-gel processed mupirocin silica microspheres loaded collagen scaffold: A synergistic biocomposite for wound healing. *European Journal of Pharmaceutical Sciences*, 52, 26–33. <https://doi.org/10.1016/j.ejps.2013.10.006>
- Petrick, L., Rosenblat, M., Paland, N., & Aviram, M. (2016). Silicon dioxide nanoparticles increase macrophage atherogenicity: Stimulation of cellular cytotoxicity, oxidative stress, and triglycerides accumulation. *Environmental Toxicology*, 31(6), 713–723. <https://doi.org/10.1002/tox.22084>
- Porta, F., Lamers, G. E., Morrhayim, J., Chatzopoulou, A., Schaaf, M., den Dulk, H., ... Kros, A. (2013). Folic acid-modified mesoporous silica nanoparticles for cellular and nuclear targeted drug delivery. *Advanced Healthcare Materials*, 2(2), 281–286. <https://doi.org/10.1002/adhm.201200176>
- Qian, K. K., & Bogner, R. H. (2012). Application of mesoporous silicon dioxide and silicate in oral amorphous drug delivery systems. *Journal of Pharmaceutical Sciences*, 101(2), 444–463. <https://doi.org/10.1002/jps.22779>
- Quignard, S., Coradin, T., Powell, J. J., & Jugdaohsingh, R. (2017). Silica nanoparticles as sources of silicic acid favoring wound healing in vitro. *Colloids and Surfaces. B, Biointerfaces*, 155, 530–537. <https://doi.org/10.1016/j.colsurfb.2017.04.049>
- Ravi Kumar, M. N., Sameti, M., Mohapatra, S. S., Kong, X., Lockey, R. F., Bakowsky, U., ... Lehr, C. M. (2004). Cationic silica nanoparticles as gene carriers: Synthesis, characterization and transfection efficiency in vitro and in vivo. *Journal of Nanoscience and Nanotechnology*, 4(7), 876–881. <https://doi.org/10.1166/jnn.2004.120>
- Reis, C. A., Rodrigues, C. F., Moreira, A. F., Jacinto, T. A., Ferreira, P., & Correia, I. J. (2019). Development of gold-core silica shell nanospheres coated with poly-2-ethyl-oxazoline and beta-cyclodextrin aimed for cancer therapy. *Materials Science & Engineering. C, Materials for Biological Applications*, 98, 960–968. <https://doi.org/10.1016/j.msec.2019.01.068>
- Rive, C., Reina, G., Wagle, P., Treossi, E., Palermo, V., Bianco, A., ... Schumacher, B. (2019). Improved biocompatibility of amino-functionalized graphene oxide in *Caenorhabditis elegans*. *Small*, 15(45), e1902699. <https://doi.org/10.1002/sml.201902699>
- Roggers, R. A., Lin, V. S., & Trewyn, B. G. (2012). Chemically reducible lipid bilayer coated mesoporous silica nanoparticles demonstrating controlled release and HeLa and normal mouse liver cell biocompatibility and cellular internalization. *Molecular Pharmaceutics*, 9(9), 2770–2777. <https://doi.org/10.1021/mp200613y>
- Ryu, H. J., Seong, N. W., So, B. J., Seo, H. S., Kim, J. H., Hong, J. S., ... Son, S. W. (2014). Evaluation of silica nanoparticle toxicity after topical exposure for 90 days. *International Journal of Nanomedicine*, 9(Suppl 2), 127–136. <https://doi.org/10.2147/ijn.S57929>
- Santos, H. A., Makila, E., Airaksinen, A. J., Bimbo, L. M., & Hirvonen, J. (2014). Porous silicon nanoparticles for nanomedicine: Preparation and biomedical applications. *Nanomedicine (London, England)*, 9(4), 535–554. <https://doi.org/10.2217/nnm.13.223>
- Scavo, M. P., Gentile, E., Wolfram, J., Gu, J., Barone, M., Evangelopoulos, M., ... Shen, H. (2015). Multistage vector delivery of sulindac and silymarin for prevention of colon cancer. *Colloids and Surfaces. B, Biointerfaces*, 136, 694–703. <https://doi.org/10.1016/j.colsurfb.2015.10.005>
- Sen Karaman, D., Patrignani, G., Rosqvist, E., Smatt, J. H., Orłowska, A., Mustafa, R., ... Rosenholm, J. M. (2018). Mesoporous silica nanoparticles facilitating the dissolution of poorly soluble drugs in orodispersible films. *European Journal of Pharmaceutical Sciences*, 122, 152–159. <https://doi.org/10.1016/j.ejps.2018.06.027>

- Shamsi, A., Ahmed, A., & Bano, B. (2017). Structural transition of kidney cystatin induced by silicon dioxide nanoparticles: An implication for renal diseases. *International Journal of Biological Macromolecules*, 94(Pt B), 754–761. <https://doi.org/10.1016/j.ijbiomac.2016.10.019>
- Shao, D., Lu, M. M., Zhao, Y. W., Zhang, F., Tan, Y. F., Zheng, X., ... Chen, L. (2017). The shape effect of magnetic mesoporous silica nanoparticles on endocytosis, biocompatibility and biodistribution. *Acta Biomaterialia*, 49, 531–540. <https://doi.org/10.1016/j.actbio.2016.11.007>
- Shim, K. H., Jeong, K. H., Bae, S. O., Kang, M. O., Maeng, E. H., Choi, C. S., ... An, S. S. (2014). Assessment of ZnO and SiO<sub>2</sub> nanoparticle permeability through and toxicity to the blood-brain barrier using Evans blue and TEM. *International Journal of Nanomedicine*, 9(Suppl. 2), 225–233. <https://doi.org/10.2147/ijn.S58205>
- Singh, R. K., Patel, K. D., Mahapatra, C., Parthiban, S. P., Kim, T. H., & Kim, H. W. (2019). Combinatory cancer therapeutics with nanoceria-capped mesoporous silica nanocarriers through pH-triggered drug release and redox activity. *ACS Applied Materials & Interfaces*, 11(1), 288–299. <https://doi.org/10.1021/acsami.8b17958>
- Slowing, I. I., Trewyn, B. G., Giri, S., & Lin, V. S.-Y. (2007). Mesoporous silica nanoparticles for drug delivery and biosensing applications. *Journal of Materials Chemistry*, 17(8), 1225–1236. <https://doi.org/10.1002/adfm.200601191>
- Slowing, I. I., Vivero-Escoto, J. L., Trewyn, B. G., & Lin, V. S. Y. (2010). Mesoporous silica nanoparticles: Structural design and applications. *Journal of Materials Chemistry*, 20(37), 7924–7937. <https://doi.org/10.1039/C0JM00554A>
- Song, J. T., Yang, X. Q., Zhang, X. S., Yan, D. M., Wang, Z. Y., & Zhao, Y. D. (2015). Facile synthesis of gold nanospheres modified by positively charged mesoporous silica, loaded with near-infrared fluorescent dye, for in vivo X-ray computed tomography and fluorescence dual mode imaging. *ACS Applied Materials & Interfaces*, 7(31), 17287–17297. <https://doi.org/10.1021/acsami.5b04359>
- Stöber, W., Fink, A., & Bohn, E. (1968). Controlled growth of monodisperse silica spheres in the micron size range. *Journal of Colloid and Interface Science*, 26(1), 62–69. [https://doi.org/10.1016/0021-9797\(68\)90272-5](https://doi.org/10.1016/0021-9797(68)90272-5)
- Su, S., & Kang, P. M. (2020). Systemic review of biodegradable nanomaterials in nanomedicine. *Nanomaterials (Basel)*, 10(4), 656. <https://doi.org/10.3390/nano10040656>
- Sun, Y., Ma, K., Kao, T., Spoth, K. A., Sai, H., Zhang, D., ... Wiesner, U. (2017). Formation pathways of mesoporous silica nanoparticles with dodecagonal tiling. *Nature Communications*, 8(1), 252. <https://doi.org/10.1038/s41467-017-00351-8>
- Suzuki, K., Ikari, K., & Imai, H. (2004). Synthesis of silica nanoparticles having a well-ordered mesostructure using a double surfactant system. *Journal of the American Chemical Society*, 126(2), 462–463. <https://doi.org/10.1021/ja038250d>
- Tang, F., Li, L., & Chen, D. (2012). Mesoporous silica nanoparticles: Synthesis, biocompatibility and drug delivery. *Advanced Materials*, 24(12), 1504–1534. <https://doi.org/10.1002/adma.201104763>
- Tao, Z., Morrow, M. P., Asefa, T., Sharma, K. K., Duncan, C., Anan, A., ... Souid, A. K. (2008). Mesoporous silica nanoparticles inhibit cellular respiration. *Nano Letters*, 8(5), 1517–1526. <https://doi.org/10.1021/nl080250u>
- Tarantini, A., Huet, S., Jarry, G., Lancelleur, R., Poul, M., Tavares, A., ... Fessard, V. (2015). Genotoxicity of synthetic amorphous silica nanoparticles in rats following short-term exposure. Part 1: Oral route. *Environmental and Molecular Mutagenesis*, 56(2), 218–227. <https://doi.org/10.1002/em.21935>
- Taylor, K. M., Kim, J. S., Rieter, W. J., An, H., Lin, W., & Lin, W. (2008). Mesoporous silica nanospheres as highly efficient MRI contrast agents. *Journal of the American Chemical Society*, 130(7), 2154–2155. <https://doi.org/10.1021/ja710193c>
- Thomassen, L. C., Rabolli, V., Masschaele, K., Alberto, G., Tomatis, M., Ghiazza, M., ... Fubini, B. (2011). Model system to study the influence of aggregation on the hemolytic potential of silica nanoparticles. *Chemical Research in Toxicology*, 24(11), 1869–1875. <https://doi.org/10.1021/tx2002178>
- Vallet-Regi, M., Rámila, A., del Real, R. P., & Pérez-Pariente, J. (2001). A new property of MCM-41: Drug delivery system. *Chemistry of Materials*, 13(2), 308–311. <https://doi.org/10.1021/cm0011559>
- Vallet-Regi, M., & Tamanoi, F. (2018). Chapter one – Overview of studies regarding mesoporous silica nanomaterials and their biomedical application. In F. Tamanoi (Ed.), *The Enzymes* (Vol. 43, pp. 1–10). Cambridge, MA: Elsevier. <https://doi.org/10.1016/bs.enz.2018.07.001>
- van Rijt, S. H., Bolukbas, D. A., Argyo, C., Wipplinger, K., Naureen, M., Datz, S., ... Stoeger, T. (2016). Applicability of avidin protein coated mesoporous silica nanoparticles as drug carriers in the lung. *Nanoscale*, 8(15), 8058–8069. <https://doi.org/10.1039/c5nr04119h>
- Vivero-Escoto, J. L., Huxford-Phillips, R. C., & Lin, W. (2012). Silica-based nanoprobe for biomedical imaging and theranostic applications. *Chemical Society Reviews*, 41(7), 2673–2685. <https://doi.org/10.1039/c2cs15229k>
- Wang, C., Tao, H., Cheng, L., & Liu, Z. (2011). Near-infrared light induced in vivo photodynamic therapy of cancer based on upconversion nanoparticles. *Biomaterials*, 32(26), 6145–6154. <https://doi.org/10.1016/j.biomaterials.2011.05.007>
- Wang, J., Wu, X., Shen, P., Wang, J., Shen, Y., Shen, Y., ... Deng, J. (2020). Applications of inorganic nanomaterials in photothermal therapy based on combinational cancer treatment. *International Journal of Nanomedicine*, 15, 1903–1914. <https://doi.org/10.2147/IJN.S239751>
- Wang, J., Yu, Y., Lu, K., Yang, M., Li, Y., Zhou, X., & Sun, Z. (2017). Silica nanoparticles induce autophagy dysfunction via lysosomal impairment and inhibition of autophagosome degradation in hepatocytes. *International Journal of Nanomedicine*, 12, 809–825. <https://doi.org/10.2147/ijn.S123596>
- Wang, S., Tang, J., Zhao, H., Wan, J., & Chen, K. (2014). Synthesis of magnetite-silica core-shell nanoparticles via direct silicon oxidation. *Journal of Colloid and Interface Science*, 432, 43–46. <https://doi.org/10.1016/j.jcis.2014.06.062>
- Wang, X., Chen, H., Chen, Y., Ma, M., Zhang, K., Li, F., ... Shi, J. (2012). Perfluorohexane-encapsulated mesoporous silica nanocapsules as enhancement agents for highly efficient high intensity focused ultrasound (HIFU). *Advanced Materials*, 24(6), 785–791. <https://doi.org/10.1002/adma.201104033>

- Wang, Z., Chang, Z. M., Shao, D., Zhang, F., Chen, F., Li, L., ... Dong, W. F. (2019). Janus gold triangle-mesoporous silica nanoplatfoms for hypoxia-activated radio-chemo-photothermal therapy of liver cancer. *ACS Applied Materials & Interfaces*, *11*(38), 34755–34765. <https://doi.org/10.1021/acsami.9b12879>
- Weitzmann, M. N., Ha, S. W., Vikulina, T., Roser-Page, S., Lee, J. K., & Beck, G. R., Jr. (2015). Bioactive silica nanoparticles reverse age-associated bone loss in mice. *Nanomedicine*, *11*(4), 959–967. <https://doi.org/10.1016/j.nano.2015.01.013>
- White, E. (2015). The role for autophagy in cancer. *The Journal of Clinical Investigation*, *125*(1), 42–46. <https://doi.org/10.1172/jci73941>
- Wolf, S., & Feldmann, C. (2016). Microemulsions: Options to expand the synthesis of inorganic nanoparticles. *Angewandte Chemie (International Edition in English)*, *55*(51), 15728–15752. <https://doi.org/10.1002/anie.201604263>
- Wu, S. H., Lin, Y. S., Hung, Y., Chou, Y. H., Hsu, Y. H., Chang, C., & Mou, C. Y. (2008). Multifunctional mesoporous silica nanoparticles for intracellular labeling and animal magnetic resonance imaging studies. *ChemBiochem*, *9*(1), 53–57. <https://doi.org/10.1002/cbic.200700509>
- Wu, S.-H., Mou, C.-Y., & Lin, H.-P. (2013). Synthesis of mesoporous silica nanoparticles. *Chemical Society Reviews*, *42*(9), 3862–3875. <https://doi.org/10.1039/C3CS35405A>
- Xu, C., Nam, J., Hong, H., Xu, Y., & Moon, J. J. (2019). Positron emission tomography-guided photodynamic therapy with biodegradable mesoporous silica nanoparticles for personalized cancer immunotherapy. *ACS Nano*, *13*(10), 12148–12161. <https://doi.org/10.1021/acsnano.9b06691>
- Yamamoto, E., & Kuroda, K. (2018). Preparation and controllability of mesoporous silica nanoparticles. *Enzyme*, *44*, 1–10. <https://doi.org/10.1016/bs.enz.2018.09.001>
- Yan, L., Luo, L., Amirshaghghi, A., Miller, J., Meng, C., You, T., ... Cheng, Z. (2019). Dextran-benzoporphyrin derivative (BPD) coated superparamagnetic Iron oxide nanoparticle (SPION) micelles for T2-weighted magnetic resonance imaging and photodynamic therapy. *Bioconjugate Chemistry*, *30*(11), 2974–2981. <https://doi.org/10.1021/acs.bioconjchem.9b00676>
- Yang, G., Gong, H., Liu, T., Sun, X., Cheng, L., & Liu, Z. (2015). Two-dimensional magnetic WS<sub>2</sub>@Fe<sub>3</sub>O<sub>4</sub> nanocomposite with mesoporous silica coating for drug delivery and imaging-guided therapy of cancer. *Biomaterials*, *60*, 62–71. <https://doi.org/10.1016/j.biomaterials.2015.04.053>
- Yang, G., Gong, H., Qian, X., Tan, P., Li, Z., Liu, T., ... Liu, Z. (2015). Mesoporous silica nanorods intrinsically doped with photosensitizers as a multifunctional drug carrier for combination therapy of cancer. *Nano Research*, *8*(3), 751–764. <https://doi.org/10.1007/s12274-014-0558-0>
- Yang, H., Chen, Y., Chen, Z., Geng, Y., Xie, X., Shen, X., ... Liu, Y. (2017). Chemo-photodynamic combined gene therapy and dual-modal cancer imaging achieved by pH-responsive alginate/chitosan multilayer-modified magnetic mesoporous silica nanocomposites. *Biomaterials Science*, *5*(5), 1001–1013. <https://doi.org/10.1039/c7bm00043j>
- Yang, J., Lind, J. U., & Trogler, W. C. (2008). Synthesis of hollow silica and titania nanospheres. *Chemistry of Materials*, *20*(9), 2875–2877. <https://doi.org/10.1021/cm703264y>
- Yang, K., Feng, L., & Liu, Z. (2016). Stimuli responsive drug delivery systems based on nano-graphene for cancer therapy. *Advanced Drug Delivery Reviews*, *105*(Pt B), 228–241. <https://doi.org/10.1016/j.addr.2016.05.015>
- Yazdimamaghani, M., Barber, Z. B., Hadipour Moghaddam, S. P., & Ghandehari, H. (2018). Influence of silica nanoparticle density and flow conditions on sedimentation, cell uptake, and cytotoxicity. *Molecular Pharmaceutics*, *15*(6), 2372–2383. <https://doi.org/10.1021/acs.molpharmaceut.8b00213>
- Yazdimamaghani, M., Moos, P. J., Dobrovolskaia, M. A., & Ghandehari, H. (2019). Genotoxicity of amorphous silica nanoparticles: Status and prospects. *Nanomedicine*, *16*, 106–125. <https://doi.org/10.1016/j.nano.2018.11.013>
- Yu, T., Greish, K., McGill, L. D., Ray, A., & Ghandehari, H. (2012). Influence of geometry, porosity, and surface characteristics of silica nanoparticles on acute toxicity: Their vasculature effect and tolerance threshold. *ACS Nano*, *6*(3), 2289–2301. <https://doi.org/10.1021/nn2043803>
- Yu, X., Yang, K., Chen, X., & Li, W. (2017). Black hollow silicon oxide nanoparticles as highly efficient photothermal agents in the second near-infrared window for in vivo cancer therapy. *Biomaterials*, *143*, 120–129. <https://doi.org/10.1016/j.biomaterials.2017.07.037>
- Yun, J. W., Kim, S. H., You, J. R., Kim, W. H., Jang, J. J., Min, S. K., ... Che, J. H. (2015). Comparative toxicity of silicon dioxide, silver and iron oxide nanoparticles after repeated oral administration to rats. *Journal of Applied Toxicology*, *35*(6), 681–693. <https://doi.org/10.1002/jat.3125>
- Zhang, W., Shen, J., Su, H., Mu, G., Sun, J. H., Tan, C. P., ... Mao, Z. W. (2016). Co-delivery of cisplatin prodrug and chlorin e6 by mesoporous silica nanoparticles for chemo-photodynamic combination therapy to combat drug resistance. *ACS Applied Materials & Interfaces*, *8*(21), 13332–13340. <https://doi.org/10.1021/acsami.6b03881>
- Zhang, Y., Wang, J., Bai, X., Jiang, T., Zhang, Q., & Wang, S. (2012). Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. *Molecular Pharmaceutics*, *9*(3), 505–513. <https://doi.org/10.1021/mp200287c>
- Zhao, G., Chen, Y., He, Y., Chen, F., Gong, Y., Chen, S., ... Wang, J. (2019). Succinylated casein-coated peptide-mesoporous silica nanoparticles as an antibiotic against intestinal bacterial infection. *Biomaterials Science*, *7*(6), 2440–2451. <https://doi.org/10.1039/c9bm00003h>
- Zhao, L., Yuan, W., Ang, C. Y., Qu, Q., Dai, Y., Gao, Y., ... Zhao, Y. (2016). Silica-polymer hybrid with self-assembled PEG corona excreted rapidly via a hepatobiliary route. *Advanced Functional Materials*, *26*(18), 3036–3047. <https://doi.org/10.1002/adfm.201505155>
- Zhong, J., Kankala, R. K., Wang, S. B., & Chen, A. Z. (2019). Recent advances in polymeric nanocomposites of metal-organic frameworks (MOFs). *Polymers (Basel)*, *11*(10), 1627. <https://doi.org/10.3390/polym11101627>

Zhu, H., Chen, Y., Yan, F. J., Chen, J., Tao, X. F., Ling, J., ... Mao, Z. W. (2017). Polysarcosine brush stabilized gold nanorods for in vivo near-infrared photothermal tumor therapy. *Acta Biomaterialia*, 50, 534–545. <https://doi.org/10.1016/j.actbio.2016.12.050>

**How to cite this article:** Li Z, Mu Y, Peng C, Lavin MF, Shao H, Du Z. Understanding the mechanisms of silica nanoparticles for nanomedicine. *WIREs Nanomed Nanobiotechnol*. 2021;13:e1658. <https://doi.org/10.1002/wnan.1658>