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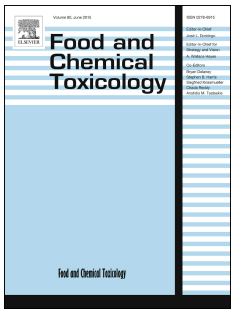

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Nanoengineered silica: properties, applications and toxicity

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Abstract

Silica nanoparticles are widely used for biomedical purposes, but also in cosmetic products, food, the car industry, paints, etc. Considering their mega production, one should not ignore their potential hazardous effects on humans, flora and fauna. Human exposure to nanosilica can occur unintentionally in daily life and in industrial settings. Here, we review the common methods of silica nanoparticle production and its applications in biomedical investigations and nanotoxicology. The use of silica nanoparticles in biomedicine is discussed in terms of drug delivery, their responsiveness to different stimuli, theranostic applications and their uses in the food and cosmetic industries. Advantages and limitations of silica nanoparticles are presented and the effects of these nanoparticles are discussed in relation to their route of entry and impact on biochemical and epigenetic processes in human and animal cells.

1. Introduction

A considerable number of consumer products and biomedical tools contain nanoparticles (NPs)(Lucia Foglia et al., 2011). “The Nanodatabase” is an inventory of commercially available products that contain engineered nanoparticles on the European consumer market. Most products fall into the category of health and fitness (close to 2000), and about one sixth of all products fall into the category of home and garden. More than 700 are personal care products and about 400 are used in clothing. The most abundant nanomaterial employed for these purposes is silver, mainly due to its well-known antibacterial activity, followed by titanium and silicon (http://nanodb.dk/en/). Silicon is one of the most abundant elements on Earth and crystalline silica in the form of quartz is the most abundant mineral in the Earth’s crust. Silicon is recognized as an essential nutrient, but detrimental health effects manly associated with dust inhalation have also been reported (Heinemann et al., 2013).

The properties and cytotoxic effects of silica nanoparticles (SiNPs) have not been fully defined (Mebert et al., 2013), but those with high specific surface areas are generally more cytotoxic (Oberdörster et al., 2005; Yu et al., 2009). The cytotoxic effects of SiNPs also depend on their size, charge and concentration (Gonzalez et al., 2014; Santo-Orihuela et al., 2016). The rapid growth of nanotechnological applications and the associated concern about human and environmental exposure are the main driving forces for nanotoxicological investigations (Oberdörster et al., 2007).

SiNPs with favourable properties, such as biocompatibility and biodegradability, have been exploited in the pharmaceutical industry (Echazu et al., 2016), mainly to disperse poorly water-soluble therapeutic agents in aqueous media (Castillo et al., 2017). Size, shape and surface functionalization (Mamaeva et al., 2013), as well as modifications needed for active targeting or

stimulus-responsive drug release, were described in more detail elsewhere (Martínez-Carmona et al., 2015; Baeza et al., 2015).

SiNPs have been also employed as fillers because they can promote cell adhesion and proliferation. Their biodegradability, high mechanical strength and ability to stimulate tissue repair have been exploited (Lima and Mano, 2015; Pina et al., 2015; Song et al., 2015). In addition, colloidal silica has long been considered a safe additive to food and pharmaceutical formulations.

This review provides an overview of SiNP synthesis methods, and their applications in cosmetics, the food industry and biomedical research. Potential exposure risks associated to SiNPs via different routes (e.g. dermal, oral, intranasal) are also discussed. Finally, the epigenetic changes caused by SiNPs are highlighted.

2. Silica Nanoparticles

2.1 Synthesis of Silica Nanoparticles

A well-known method to produces non-porous SiNPs is the so-called “Aerosil” method. Particles are produced at high temperatures (around 1000 and 2500˚C) by flame hydrolysis from $SiCl_4$ (siliciumtetrachloride)(Sepeur, 2008). Other industrial methods to produce amorphous silica are precipitation and gelification. Details of industrial synthetic methods are provided in “Reference Document on Best Available Techniques for the Manufacture of Large Volume Inorganic Chemicals–Solids and Others industry” (EUROPEAN COMMISSION, 2007).

Colloidal SiNPs can be synthesized by sol-gel processes based on the Stöber method. In 1968, Stöber *et al*., reported a system of chemical reactions whereby hydrolysis of alkyl silicates and subsequent condensation of silicic acid in alcohol solutions, using ammonia as a catalyst, resulted in the controlled growth of spherical SiNPs of uniform size (50 to 2000 nm

diameter)(Stöber et al., 1968). During the process, Si-OR and Si-OH containing species condensate into siloxane compounds by forming siloxane bonds (Si-O-Si). Condensation takes place by either alcohol or, more often, water elimination (**Figure 1**)(Levy and Zayat, 2015). Some of the advantages of sol-gel methods are that the synthesis is straightforward, scalable and controllable. Particle size, distribution and morphology can be controlled by changing the reaction parameters (L. P. Singh et al., 2014).

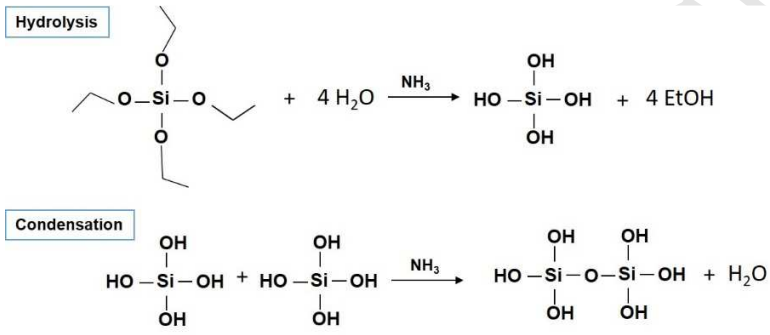

Figure 1. Schematic representation of possible hydrolysis and condensation steps of the Stöber method reactions.

The microemulsion method is widely used for nanoparticle preparation (Tan et al., 2011). Porous SiNPs (**Figure 2**) can be prepared in water-in-oil (W/O) microemulsions. The alkyl silicate molecules solubilized in the oil phase of microemulsions diffuse to the surfactant layer and penetrate into the water pool, where the hydrolysis reaction takes place (Yamauchi et al., 1989). The advantage of this method – compared to the one-phase reaction – is that the reaction is more easily controlled (Sepeur, 2008). The use of organic solvents and surfactants in the microemulsion methods is a disadvantage because of high costs, need for purification and nanoparticle recovery for large-scale synthesis (Wang et al., 2011). Mesoporous SiNPs (MSNs) with variable pore sizes are generally synthesized in the presence of a supramolecular assembled surfactant that acts as a structure-directing template. Spherical SiNPs with regular pores,

consisting of unidimensional, hexagonally shaped cavities, can be obtained by adding a cationic surfactant to the reaction mixture. These nanoparticles have large surface areas and adjustable pore sizes (Y. Wang et al., 2015), which makes them promising drug nanocarriers. The effect of pH in the reaction mixture, the characteristics of surfactants or copolymers as well as the concentration and source of silica have been reviewed by Wu *et al*. (Wu et al., 2013). In their study, the synthesis of hollow SiNPs (HSNs) with a large cavity using hard (i.e. polymer beads, inorganic nanoparticles) and soft (i.e. micelles, vesicles) templates was also proposed. Zhao *et al*. synthesized NPs using amphiphilic triblock copolymers to direct the organization of polymerizing silica species (Zhao et al., 1998). SiNPs with different morphologies prepared by the procedures described in this section are summarized in **Figure 2 (A-E)**. Among the complex particles are core-shell nanoparticles with a silica core or silica shell (**Fig 2F**)(Ghosh Chaudhuri and Paria, 2012), york/shell (**Fig 2G**) hybrid structures consisting of a movable core inside a hollow shell of the same or different material (Purbia and Paria, 2015) and Janus (**Fig 2H**) nanoparticles with heterogeneous surfaces (Schick et al., 2014).

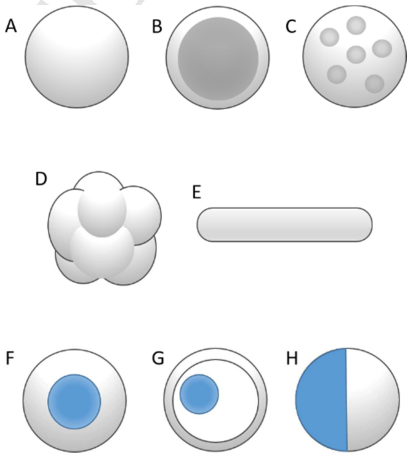

Figure 2. Schematic representation of (A) non-porous, (B) hollow, (C) mesoporous, (D) amorphous, (C) rod, (E) core-shell, (F) yolk/shell and (G) Janus SiNPs.

3. Applications of nanosilica in the food industry

SiNPs have been used in processed food production and food storage. Amorphous silica has been employed as anticaking agent, antifoaming agent or flow aid in powdered food. Silicon dioxide is listed as food additive in the European Union under code E551. The United States Food and Drug Administration classifies silicon dioxide and amorphous silica as anticaking agents. Silica is used as clarifying/fining agent in the juice, oil and brewery sectors, or as flavor/aroma carrier (Barahona et al., 2016). The daily intake of silica from food is estimated to be 9.4 mg/kg, of which 1.8 mg/kg is within the nano-size range. In food products containing synthetic amorphous silica, up to 43 % of the total content was shown to be nano-sized (van der Zande et al., 2014). Powdered products like milk powder, instant soups and spices may contain SiNPs. The concentration of these particles was found to be in the range of <0.1–1.0 mg/g of product, with particle sizes ranging from 50–200 nm. Many of these products are powdered sauces and seasoning mixtures, instant noodles, pancakes and cake mixtures, coffee creamers and vitamins (Dekkers et al., 2011).

There are many potential applications for nano-additives: they may be used to modify food properties such as taste, sensation, color, texture, consistency or shelf life, to fortify basic foods with nutrients and vitamins, to enhance bioavailability, to indicate food quality and freshness or to ensure traceability (Winkler et al., 2016). Silica particles may also reach food products indirectly, for example from packaging. The effect of 4 nm and 5 nm NPs as nano-fillers in a main pullulan coating on bioriented polypropylene was evaluated for its oxygen and carbon dioxide barrier properties, as well as its frictional, optical and wettability properties, in relation to the pullulan ratio (colloidal silica ratios of 1:0.15 and 1:0.45). An improvement in the barrier

properties against O_2 and CO_2 was observed, with the best performance by particles with the highest surface area (O_2TR and CO_2TR around 30 mL m^{-2} 24 h^{-1} and 80 mL m^{-2} 24 h^{-1} at 23 ˚C under dry conditions), compared to the pristine pullulan-coated BOPP (O_2TR and CO_2TR around 480 mL m^{-2} 24 h^{-1} and CO_2TR 1245 mL m^{-2} 24 h^{-1})(Cozzolino et al., 2016). Hybrid antifouling and antimicrobial coatings were obtained using a fluoropolymer and cationic SiNPs on stainless steel. Such hybrid structures reduce problems related to microbial cross-contamination in food processing (e.g. *Listeria monocytogenes*)(K. Huang et al., 2016).

4. Application of nanosilica in cosmetics

In 1986, liposomes were first incorporated in cosmetics by the Christian Dior company. After that, many cosmetic manufacturers followed by incorporating nanotechnology into their formulations (Wu, 2012). Nanoscale versions of ingredients are used in cosmetics to provide better UV protection, deeper skin penetration, long-lasting effects, increased color and finish quality (Sepeur, 2008). Nano forms of silica are used in leave-on and rinse-off cosmetic products for hair, skin, lips, face and nails. According to the Scientific Committee on Consumer Safety (SCCS) analysis, data available for amorphous silica are inadequate and insufficient to draw any firm conclusion either for or against the safety of these synthetic materials. SCCS identified and listed the highest concentration in each product category, 38.0 % in temporary hair styling, 7.5 % in lipstick, 7.0 % in toothpaste, 3.8 % in eyeliner, 2.5 % in eye shadow and 0.1 % in products with antiperspirant activity, among others.(SCCS and Hoet, 2016)**.** An increase in silica particles in cosmetic products is anticipated. For example, UV filters in sunscreen formulations are enhanced by the presence of bismuth titanates BixTiyOz in MSNs, which combines UV shielding properties with the suppression of photocatalytic activity (Zaccariello et al., 2017). The encapsulation of organic sunscreen into particles can reduce its phototoxicity and degradation. In

a recent study, physical encapsulation of ethylhexyl salicylate in HSNs and covalent incorporation of salicylate and curcuminoid was carried out. It was found that the best way to reduce leaking and photodegradation of these organic compounds was covalent attachment, in particular with bridged sunscreen monomers (Tolbert et al., 2016).

5. Applications of nanosilica for biomedical purposes

Silica is a promising material for drug delivery and imaging systems. **Figure 3** summarizes some examples of SiNPs as drug carriers, with or without imaging functions, targeting abilities or responsiveness to different stimuli. Nanosilica materials are also promising in other medical applications, such as vaccination adjuvants (Mody et al., 2013), gene delivery and sensors, which will not be covered in the present work.

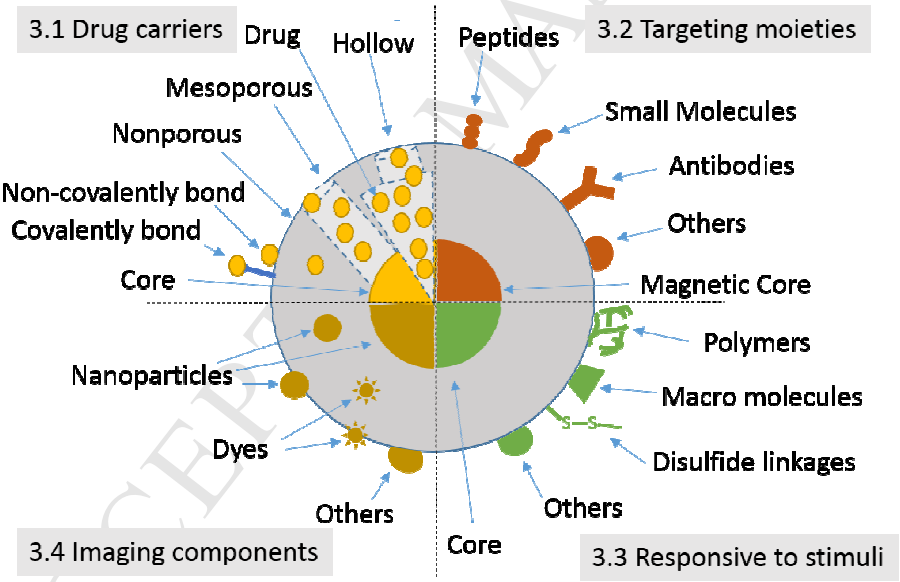

Figure 3. Schematic representation of silica nanoparticles (SiNPs). 3.1 Types of SiNPs for delivering biologically active agents and drugs. 3.2 Targeting moieties on the surface of SiNPs or magnetic composites. 3.3 SiNPs responding to stimuli e.g. pH, glutathione, magnetic field, light and temperature. 3.4 SiNPs for optical, magnetic resonance and other bioimaging applications.

5.1. Drug Carriers

SiNPs have been studied as drug delivery systems for improved solubility (biological, chemical and physical), clearance, controlled and targeted drug release. MSNs were found to enhance the solubility of resveratrol by ~95 % and increase its *in vitro* release (Summerlin et al., 2016). Silica-coated flexible liposomes were shown to significantly enhance oral absorption of the poorly water-soluble curcumin, with 2.35-fold higher bioavailability compared to curcumin suspension (Li et al., 2012). Surface functionalization is a common strategy to enhance the loading of SiNPs. Bare and organosilane (amino, thiol and sulfonate) grafted non-porous SiNPs showed different loading capacities of gentamicin sulfate and sodium rifamycin, suggesting that the main sorption driving forces are attractive electrostatic and hydrophobic interactions, respectively (Mebert et al., 2016). Similarly, the loading capacity of mitoxantrone varied with differently functionalized MSNs. The highest loading was achieved with thiol-modified particles (18 % w/w), followed by mixed thiol/amino- and amino-functionalized MSNs (Wani et al., 2012). Greater antibacterial activity and gentamicin loading capacity was achieved with particles of size bigger than 100 nm (Alvarez et al., 2014). Surface morphologies, such as roughness and pore size, are other aspects by which SiNPs can be improved as drug delivery systems. Differences in adsorption and release of hydrophobic molecules was achieved by controlling the surface roughness of mesoporous hollow silica nanospheres, which lead to an unusual hydrophobicity (Ahmad Nor et al., 2015). A higher loading of quercetin was reported in particles with pore sizes 3.5 and 5.0 nm (Ugazio et al., 2016).

5.2. Targeted delivery with SiNPs

Targeted silica and silica-based nanoparticles have attracted much attention, particularly in cancer treatment and diagnosis. Different targeting strategies have been applied and reviewed (Yang and Yu, 2016). SiNPs have been functionalized with small molecules, such as folic acid

(FA). Folate receptors are overexpressed in several human cancers and FA-conjugated NPs are promising drug delivery systems for receptor-mediated endocytosis. FA-MSNs were highly internalized in A549 and IGROV-1 cancer cells, but much less in differentiated SH-SY5Y human neuroblastoma cells and rat embryonic dorsal root ganglia sensory neurons (Ceresa et al., 2013). Doxorubicin and siRNA against B-cell lymphoma 2 (Bcl-2) co-delivery was achieved with polyethyleneimine (PEI)-FA-coated HMSNs (Ma et al., 2013). A significantly higher uptake rate at the tumor site of was observed with FA-MSNs compared non-targeted MSNs in *ex vivo* bioimaging of intravenously-injected BALB/c mice bearing 4T1-tumors (Sarkar et al., 2016). Hyaluronic acid (HA) receptors are also overexpressed in a variety of carcinomas (Lokeshwar et al., 2014). SiNPs conjugated or capped with this polymer have also been developed for targeted delivery. MSNs coated with poly-(L-lysine) and HA showed an enhanced effect when used in photodynamic therapy against HCT 116 colorectal cancer cells overexpressing the CD44 receptor. This effect was reduced by pre-incubating the cells with excess HA, indicating the involvement of active endocytosis (Gary-Bobo et al., 2012). Moreover, once internalized, HA-SiNPs can be transported out of the cells. This allows the HA-capped particles to penetrate deeper inside the tumors, presumably through receptor (CD44) mediated transcytosis. Doxorubicin-loaded particles showed a 10-fold increase in cytotoxicity (IC50=1.3 mM) in ovarian cancer spheroids in comparison to the free drug (El-Dakdouki et al., 2013). The selective targeting of individual leukemia cells was achieved with anti-EGFR antibodies (Durfee et al., 2016). An average 3-fold enhancement in tumor accumulation was achieved with anti-CD105 antibody-conjugated particles compared to non-targeted MSNs. Tumor vasculature-targeting MSNs loaded with doxorubicin were investigated for theranostic applications. MSNs conjugated with near-infrared dye (ZW800) and 64Cu-chelator (1,4,7-

triazacyclononane-triacetic acid) were used for tumor dual-modality imaging with positron emission tomography (PET)/near-infrared fluorescence (NIRF)(F. Chen et al., 2014).

5.3. Stimuli responsive SiNPs

Modified silica and silica-based nanoparticles responding to pH, redox and external stimuli have been extensively studied in efforts to alter pharmacokinetics and biodistribution profiles of drugs. The use of MSNs and MSN-based materials in cancer therapy was recently reviewed by Mekaru *et al*. (Mekaru et al., 2015). pH-responsive materials are attractive for cancer therapy because the tumor core is usually more acid than circulating blood due to lactic acid accumulation. pH-responsive materials, e.g. chitosan, a cationic biopolymer, were widely used for biomedical applications. These constructs were reported as non-immunogenic and biodegradable (Nilsen-Nygaard et al., 2015). Chitosan-poly (methacrylic acid)-capped MSNs loaded with doxorubicin showed pH-dependent drug release after 24 h at 37˚C. Seventy % of the loaded drug was released at pH 5.5 (endosomes), 34 % at pH 6.8 (tumor extracellular milieu), while only 18 % of the drug was released at pH 7.4 (blood circulation). Doxorubicin as a positively-charged molecule is retained by electrostatic interactions with the negatively-charged polymer proportionally to the pH of the medium (Tang et al., 2011). A pH-responsive material set to improve tuberculosis treatment was achieved by covalently binding isoniazid to MSNs via a hydrazone bond to form a nanoparticle-based prodrug system. The pH-sensitive bond was cleaved in the acidified endolysosomal compartment. While no differences were found *in vitro* between these NPs and free drug administration in macrophages, it was found *in vivo* that the particles killed 2-4 times more *Mycobacterium tuberculosis* in the lungs, liver and spleen than the equivalent dose of free drug in BALB/c mice (female, 8 weeks) (Hwang et al., 2015).

Glutathione (GSH) is a powerful reducing agent due to its sulfhydryl group, and is elevated in many tumors (Gamcsik et al., 2012). Tan *et al*. studied the influence of chain length (3, 5 or 7 carbon atoms), terminal group (cyclohexyl, adamantly or n-butyl) and density of disulfide-appended functional ligands on doxorubicin loading capacity and release kinetics. The group found that intermediate chain length, ligand grafting and cyclohexyl terminal group were suitable for complexation with β-CD for drug incorporation and retention in mesopores. It was proposed that a higher number of ligands on the surface could lower loading capacity by blocking mesopores (Tan et al., 2014). In a study by Maggini *et al*., redox-responsive breakable mesoporous SiNPs containing disulfide bridges directly inserted in their frameworks were synthesized. The disintegration ability of these NPs was confirmed in glioma C6 cells (Maggini et al., 2016). Dual pH- and redox-responsive particles were achieved by grafting hollow mesoporous SiNPs (HMSNs) with chitosan via cleavable disulfide bonds. At pH 7.4, the chitosan chains are collapsed, forming a shell layer that covers the surface of the particle. The cationic polymer can be protonated in acidic conditions, making the polymer layers swell and open the mesoporous channels, thus releasing the loaded doxorubicin. In addition, in the presence of GSH, the disulfide bonds are reduced to thiol groups, which induced the separation of the polymer chains from the particle, allowing the fast release of the drug from the cavities of these NPs (Jiao et al., 2016b). External stimuli can also be used to trigger drug release. A thermoresponsive delivery system able to release quercetin when in contact with skin was constructed by free radical copolymerization of N-isopropylacrylamide and 3-(methacryloxypropyl)trimethoxysilane inside the mesopores (Ugazio et al., 2016). Near-infrared light-responsive DNA-hybrid-gated nanocarriers have been synthesized. Photothermal effects

caused denaturation of DNA and drug (doxorubicin and curcumin) release from DNA and mesopores (Yuanxin Zhang et al., 2015).

Table 1. Application of silica nanoparticles (SiNPs) in cancer treatment.

Type of SiNPs	Characteristics	Drugs	Reference
Hollow mesoporous SiNPs	Targeted, grafted with epidermal growth factor	5-fluorouracil	(Chen et al., 2015) (She et al., 2015)
Hollow mesoporous SiNPs	Targeted, adamantanamine was grafted onto the orifices and lactobionic acid-grafted-β-cyclodextrin was immobilized on the surface	Doxorubicin	(Luo et al., 2014)
Hollow mesoporous SiNPs	Targeted and co-delivery, folic acid-coated and polyethyleneimine-conjugated	Doxorubicin and siRNA	(Ma et al., 2013)

Hollow mesoporous SiNPs	pH and redox dual-responsive, responsive nanovalve stalk/β-cyclodextrins	Doxorubicin (rhodamine 6G)	(Zhu and Wang, 2016)
Hollow mesoporous SiNPs	Redox and pH dual-responsive, chitosan grafted	doxorubicin	(Jiao et al., 2016b)
Hollow mesoporous SiNPs	Dual-stimuli polymer shell responsive to redox/temperature, copolymer of two oligo(ethylene glycol) macromonomers cross-linked by the disulfide linker N,N′-bis(acryloyl)cystamine	Doxorubicin	(Jiao et al., 2013)
Hollow mesoporous SiNPs	pH, reduction and light triple-responsive, modified with poly(2-(diethylamino)ethyl) methacrylate	Doxorubicin	(Yuanyuan Zhang et al., 2015)
Hollow SiNPs	Glutathione-responsive	Doxorubicin	(D. Wang et al.,

			2014)
Hollow mesoporous SiNPs	Pd nanosheet-covered, combining chemotherapy with photothermal therapy	Doxorubicin	(Fang et al., 2012)
Hollow mesoporous SiNPs	Polymeric prodrug coated, combined photothermal therapy and chemotherapy	Doxorubicin near-infrared absorbing dye	(Y. Zhang et al., 2016)
Hollow mesoporous SiNPs	Internal radiation source to achieve deep-seated tumor therapy without using external light source	Photosensitizer (chlorin e6) and oxophilic zirconium-89 radionuclide	(Kamkaew et al., 2016)
Mesoporous SiNPs	Enhanced saturated solubility	Resveratrol	(Summerlin et al., 2016)
Mesoporous SiNPs	Redox-responsive, self-destructive behavior, disulfide-doped	Temozolomide	(Maggini et al., 2016)
Mesoporous SiNPs	Bone-targeted, zoledronic acid	Doxorubicin	(Sun et al., 2016)

Mesoporous SiNPs	Controlled delivery, polyglutamic acid capped	Doxorubicin (rhodamine B)	(Tukappa et al., 2016)
Mesoporous SiNPs	pH-sensitive polymer (Poly4-vinylpyridine)	methotrexate	(Abbaszad Rafi et al., 2016)
Mesoporous SiNPs	pH-responsive, APTES modified	Doxorubicin	(Y. Wang et al., 2016)
Mesoporous SiNPs	pH-sensitive dual-targeting, polydopamine-coated and functionalized with Asn-Gly-Arg	Doxorubicin	(Hu et al., 2016)
Mesoporous SiNPs	pH-sensitive, polydopamine-coated	Doxorubicin	(Zheng et al., 2014)
Mesoporous SiNPs	Co-delivery	Cisplatin prodrug and chlorin e6	(W. Zhang et al., 2016)
Mesoporous SiNPs	Co-delivery, PEGylated lipid bilayer	Xitinib and celastrol	(Choi et al., 2016)
Mesoporous SiNPs	Redox-responsive and targeted, immobilized cytochrome c and tailored S1411 aptamer	Doxorubicin	(Zhang et al., 2014)

Mesoporous SiNPs	Redox-responsive, heparin and lactobionic acid	Doxorubicin	(Dai et al., 2014)
Mesoporous SiNPs	Co-delivery, polyethylenimine-polyethylene glycol functionalized	Epirubicin and siRNA	(Mohammad Yahya Hanafi-Bojd et al., 2016)
Mesoporous SiNPs	Co-delivery, covalently-attached PEG	Doxorubicin and siRNA	(Meng et al., 2013)
Mesoporous SiNPs	pH-sensitive and targeted, doubly modified with TAT peptide and acid-cleavable polyethylene glycol, shell constituted by galactose-modified poly(allylamine hydrochloride)-citraconic anhydride	Doxorubicin	(Han et al., 2016)
Mesoporous SiNPs	Nuclear-targeted, conjugated TAT peptide	Doxorubicin	(Pan et al., 2013, 2012)
Mesoporous SiNPs	Combined delivery	Temozolomide and anti-	(Bertucci et al., 2015)

		miR221 PNA	
Mesoporous SiNPs	Targeted co-delivery, capped with PAA-CS covalently conjugated cRGD peptide	Topotecan and quercetin	(Murugan et al., 2016)
Mesoporous SiNPs	pH-responsive, guanidine-functionalized, PEGylated	Curcumin	(Ma'mani et al., 2014)
Mesoporous SiNPs	Co-delivery, coated Cu1.8S nanoparticles modified with aptamer-modified GC-rich DNA-helix, NIR-responsive DNA-hybrid-gated nanocarrier	Doxorubicin and curcumin	(Yuanxin Zhang et al., 2015)
Mesoporous SiNPs	----	Mitoxantrone doxorubicin and methotrexate	(Haoquan Zheng et al., 2015)
Mesoporous SiNPs	Co-delivery, amino group-modified	Methotrexate and	(N. Song et al., 2016)

		mitoxantrone	
Mesoporous SiNPs	pH-responsive, targeted, coordination polymer coated (zinc and 1,4-bis (imidazol-1-ylmethyl) benzene)	Topotecan	(Xing et al., 2012)
Mesoporous SiNPs	pH-responsive, nanogated highly acid-labile benzoic-imine linker, polypseudorotaxane-capped	Doxorubicin	(Gao et al., 2011)
Mesoporous SiNPs	pH-responsive, alginate/chitosan multilayers coating	Doxorubicin	(Feng et al., 2014)
Mesoporous SiNPs	pH-responsive, polymer shell chitosan/poly (methacrylic acid)	Doxorubicin	(Tang et al., 2011)
Mesoporous SiNPs	Reduction-responsive, poly(acrylic acid)	Doxorubicin	(H. Li et al., 2013)
Mesoporous SiNPs	Ultrasound-responsive, polymer grafted (poly(2-	Doxorubicin	(Paris et al., 2015)

	(2-methoxyethoxy)ethyl methacrylate))		
Mesoporous SiNPs	Stimuli-responsive, bis-aminated poly(glycerol methacrylate)s and cucurbit[7]uril	Doxorubicin	(Q.-L. Li et al., 2014)
Mesoporous SiNPs	Co-delivery, controlled and targeted, avidin molecules	Cisplatin and proteasome inhibitor bortezomib	(van Rijt et al., 2015)
Mesoporous SiNPs	Carboxyl-functionalized	Cisplatin	(Gu et al., 2013)
Mesoporous SiNPs	Carboxyl-functionalized	Doxorubicin	(Xie et al., 2014)
Mesoporous SiNPs	Controlled release, carboxylate	Cisplatin	(Lin et al., 2012)
Mesoporous SiNPs	Targeted, covalently conjugated 6-mercaptopurine	Cisplatin	(Lv et al., 2016)
Mesoporous SiNPs	Targeted, desthiobiotin and vitamin H	Doxorubicin	(L.-L. Li et al., 2013)
Mesoporous SiNPs	------	Paclitaxel	(Fu et al., 2016; Jia et al., 2012)
Mesoporous SiNPs	Co-delivery	Paclitaxel and	(Jia et al., 2015)

		tetrandrine	
Mesoporous SiNPs	Co-delivery, lipid-coated	Gemcitabine and paclitaxel	(Meng et al., 2015)
Mesoporous SiNPs	Targeted and responsive to hyaluronidase, functionalized with biotin-modified hyaluronic acid	Doxorubicin	(M. Zhang et al., 2016)
Mesoporous SiNPs	Targeted, hyaluronic acid-modified	Doxorubicin	(M. Yu et al., 2013)
Mesoporous SiNPs	Stimuli responsive, hyaluronic acid conjugated	Doxorubicin	(Q. Zhao et al., 2015)
Mesoporous SiNPs	Active targeting, endolysosomal escape and multilevel drug release, multifunctional hyaluronic acid derivatives modified sulfhydryl and amino-cofunctionalized	Doxorubicin	(Yang et al., 2016)
Mesoporous SiNPs	FITC-labeled,	Paclitaxel	(Yuan et al., 2013)

	covalently linked with paclitaxel		
Mesoporous SiNPs	Co-delivery, gold cluster bovine serum albumin nanogates	Gemcitabine and doxorubicin	(Croissant et al., 2016)
Mesoporous SiNPs	pH-sensitive, modified dextrin coat	Doxorubicin	(Abbaszad Rafi et al., 2016)
Mesoporous SiNPs	pH and glutathione stimuli-responsive, CB-EDA-PGOHMA grafted	Doxorubicin	(Li et al., 2015)
Mesoporous SiNPs	Nuclear-targeted, folic acid and dexamethasone	Doxorubicin	(Xiong et al., 2015)
Mesoporous SiNPs	Conjugated doxorubicin and folic acid	Doxorubicin	(Fan et al., 2011)
Mesoporous SiNPs	Targeted, folic acid	Doxorubicin	(Guo et al., 2012)
Mesoporous SiNPs	Targeted, folic acid	Quercetin	(Sarkar et al., 2016)
Mesoporous SiNPs	Targeted, folic acid and gelatin layer PEG	Doxorubicin	(Zou et al., 2015)
Mesoporous SiNPs	Targeted and pH-responsive, folic acid	Curcumin	(J. Wang et al., 2016)
Mesoporous SiNPs	pH-responsive, gelatin	Doxorubicin	(Zou et al., 2013)

	capped		
Mesoporous SiNPs	Mitochondria targeted, triphenoylphosphonium	Doxorubicin	(Qu et al., 2015)
Mesoporous SiNPs	Bioresponsive, zwitterionic, gatekeeper composed of carboxylic groups and quaternary amine groups	Doxorubicin	(Khatoon et al., 2016)
Mesoporous silica platform	Temperature- and NIR-responsive, conjugated to CuS nanoparticles with complementary DNA sequences	Doxorubicin	(Lei Zhang et al., 2015)
Mesoporous SiNPs	Redox-responsive, poly(ethylene glycol)-capped	Doxorubicin (safranin O)	(Giménez et al., 2015)
Mesoporous SiNPs	Stimuli-responsive, hybrid lipid-capped (polymer d-α-tocopherol polyethylene glycol 1000 succinate)	Doxorubicin	(Han et al., 2015)
Mesoporous SiNPs	Esterase- and pH-	Doxorubicin	(Fernando et al.,

	responsive, poly(β-amino ester)-capped		2015)
Mesoporous SiNPs	Targeted, HB5 aptamer-functionalized silica, carbon nanoparticles chemo-photothermal therapeutic platform	Doxorubicin	(K. Wang et al., 2015)
Mesoporous SiNPs	Targeted and glutathione-responsive, Poly(γ-glutamic acid) coated mercaptopropyl-functionalized core, doxorubicin covalently conjugated	Doxorubicin	(Du et al., 2015)
Mesoporous SiNPs	pH-sensitive, poly(L-glutamic acid) grafted	Doxorubicin	(Zheng et al., 2013)
Mesoporous SiNPs	Functionalized with phosphonate, polyethylene glycol and polyethylenimine-polyethylene glycol	Epirubicin	(Hanafi-Bojd et al., 2015)
Mesoporous SiNPs	Targeted, membrane-	Doxorubicin	(Cheng et al., 2015)

	penetrating and enzyme-induced drug delivery, α-cyclodextrin modified by multifunctional peptide (azido-GFLGR7RGDS)		
Mesoporous SiNPs	Stimuli-responsive, cellulose-conjugated	Doxorubicin	(Hakeem et al., 2016)
Mesoporous SiNPs	pH-responsive, hyaluronic acid lipid membrane	Doxorubicin	(Z. Wang et al., 2016)
Mesoporous SiNPs	Ca^{2+}-dependent release, gold nanoparticles coated with α-synuclein	Doxorubicin (rhodamine 6G)	(Lee et al., 2014)
SiNPs	Organically-modified (3-aminopropyl-trimethoxysilane)	Curcumin	(S. P. Singh et al., 2014)
SiNPs	Targeted, hyaluronic acid	Curcumin	(Singh et al., 2015)
SiNPs	Thermoresponsive, poly(N-isopropylacrylamide-co-acrylamide)	Doxorubicin	(A. Li et al., 2014)

SiNPs	Targeted, hyaluronan-coated containing a highly fluorescent core	Doxorubicin	(El-Dakdouki et al., 2013)
SiNPs	Targeted, folate-functionalized	Curcumin	(de Oliveira et al., 2016)
SiNPs	Co-delivery, corona covered	Doxorubicin and meloxicam	(Shahabi et al., 2015)
SiNPs	Combined treatment, graphene shell, serum protein-modified and photothermal therapy	Doxorubicin	(Yuwei Liu et al., 2015)
SiNPs	Functionalized with [3-(2-aminoethyl amino)propyl]trimethoxysilane covalently bonding rose bengal or anthraquinone-2-carboxylic acid, photodynamic therapy	Rose bengal or anthraquinone-2-carboxylic acid	(de Souza Oliveira et al., 2016)
Nonporous SiNPs	External shell containing primary	Cisplatin-based Pt(IV)	(Ravera et al., 2016)

	amino groups (3-aminopropyl and *N*-(6-aminohexyl)aminomethylene)	complexes	
Nonporous SiNPs	Stimuli-responsive, camptothecin and doxorubicin covalently encapsulated	Camptothecin or doxorubicin	(Z. Xu et al., 2015)
Mesoporous silica shell	Targeted and pH-sensitive, Fe_3O_4 nanoparticles core wrapped with chitosan	Doxorubicin	(Wu et al., 2017)
Silica shell	Co-delivery, transferrin-conjugated magnetic silica PLGA nanoparticles	Doxorubicin and paclitaxel	(Cui et al., 2013)
Silica shell	Sensitive to magnetic field and pH, Fe_3O_4 core coated with mPEG-poly(L-Asparagine)	Doxorubicin	(S. Yu et al., 2013)
Silica shell	Co-delivery and targeted, magnetic Fe_3O_4/Fe cores	ABT-888 and temozolomid	(Muñoz-Gámez et al., 2015)

		e	
Mesoporous silica matrix	Fe_3O_4 nanoparticles combining chemotherapy and hyperthermia	Doxorubicin	(Tao and Zhu, 2014)
Mesoporous silica shell	Co-delivery and targeted, magnetic Fe_3O_4 core and modified with PEI-FA	VEGF shRNA and doxorubicin	(Li et al., 2016)
Silica shell	Controlled release and targeted, magnetite nanoparticle and acrylamidopropyl modified	Methotrexate	(Farjadian et al., 2016)
Silica shell	Gold core, photothermal	Methotrexate	(Huo et al., 2015)
Silica shell	Temperature and pH dual-responsive, poly(N-isopropylacrylamide) co-acrylic acid hydrogel core	Doxorubicin	(Hu et al., 2013)
Mesoporous silica shell	Targeted and	Doxorubicin	(Y. Wang et al.,

	photothermal, graphitic carbon core and conjugated SP13 peptide		2014)
Silica shell	pH-responsive, calcium carbonate core	Doxorubicin	(Y. Zhao et al., 2015)
Mesoporous silica shell	Oleic acid-stabilized hydrophobic Bi_2S_3 chemotherapeutic and X-ray therapy	Doxorubicin	(Ma et al., 2015)
Mesoporous silica shell	Photothermal therapy, copper selenide nanoparticles ($Cu_{2-x}Se$) core and PEG modification	Doxorubicin	(Liu et al., 2014)
Silica shell	Photothermal therapy under near-infrared laser irradiation, C60 fullerene-silica nanoparticle system surface-decorated with hyaluronan	Doxorubicin (indocyanine green)	(Hai Wang et al., 2016)

Table 2. Application of silica nanoparticles (SiNPs) in other treatments.

Type of NP	Characteristics	Drug	Application	Reference
Mesoporous SiNPs	Thermoresponsive copolymer-grafted copolymerization of 3-(methacryloxypropyl)trimethoxysilane and Nisopropylacrylamide	Quercetin	Skin	(Ugazio et al., 2016)
Mesoporous SiNPs	3-aminopropyltriethoxysilane modified	Antioxidant molecules (caffeic acid or rutin)	Diminish the impact of oxidative stress induced after transfection into cells	(Ebabe Elle et al., 2016)
Mesoporous SiNPs	Aminopropyl functionalized	Quercetin	Topical nanocarriers	(Sapino et al., 2015)
Mesoporous SiNPs	----	Zinc oxide nanoparticles	Antifungal	(Mitra et al., 2015)
Mesoporous SiNPs	Immobilized with silver–indole-3	Silver–indole-3	Antibacterial	(Kuthati et al., 2015)

	acetic acid hydrazide	acetic acid		
Mesoporous SiNPs	Polystyrene sulfonate and poly (allylamine hydrochloride)	Gentamicin		(Tamanna et al., 2015)
Mesoporous SiNPs	-----	Phytochemicals (curcumin and chrysin)	Nose-to-brain delivery	(Lungare et al., 2016)
Mesoporous SiNPs	Coated with polyethyleneimine	Plasmid DNA (fluorescein isothiocyanate)	Gene therapy	(X. Zhang et al., 2016)
Mesoporous SiNPs	[Poly (methacrylic acid-co-vinyl triethoxylsilane)] coated	Insulin	Diabetes (oral delivery of protein and peptide drugs)	(Guha et al., 2016)
Mesoporous SiNPs	Fluorescent doped 3-aminopropyl	PTEN-inhibitor bisperoxov	Stimulating axonal regeneration	(Kim et al., 2016)

	triethoxysilane modified	anadium (rhodamine B isothiocyanate)		
Mesoporous SiNPs	PEGylated	Puerarin	Treatment of cardiovascular diseases	(Liu et al., 2016)
Mesoporous SiNPs	Fluorescent	5-azacytidine (fluorescein isothiocyanate isomer I)	Heart disease	(J. Cheng et al., 2016)
Mesoporous SiNPs	----	Tetracycline	Periodontitis and dental bone infections	(Koneru et al., 2015)
Mesoporous SiNPs	Stimulus-responsive, coated with poly(ethylene imine)-poly(ethylene glycol)	Isoniazid	Tuberculosis	(Hwang et al., 2015)

Mesoporous SiNPs	ε-poly-L-lysine capped	Histidine kinase autophosphorylation inhibitors (rhodamine)	Broadening antibacterial spectrum	(Velikova et al., 2016)
SiNPs	Coated with the hydroxypropyl methylcellulose phthalate	Insulin		(Zhao et al., 2013)
SiNPs	APTES-grafted	Quercetin	Antioxidative and anti-inflammatory activities	(Lee et al., 2016)
SiNPs	CTAB surface-modified or PEGylated	Quercetin	Against Cu(II)-induced oxidative stress in neurodegeneration	(Nday et al., 2015)
Silica-coated	Silica-coated flexible liposomes	Curcumin	Enhanced oral bioavailability	(Li et al., 2012)
Mesoporous silica shell	γ-Fe2O3 nanoparticle core	Tolbutamide or	Diabetes and cancers	(Sinha et al., 2014)

	functionalized with phenylboronic acid	camptothecin		
Silica shell	Silver-containing nanorattles	Silver	Implant infections	(Priebe et al., 2016)
Silica-coated	Iron oxide nanoparticles	Mycophenolic acid	Immunosuppressant	(Hwang et al., 2016)
Mesoporous silica shell	Magnetic nanoparticles (Fe_3O_4) and PEG-modified	Cytosine-guanine containing oligodeoxynucleotides	Immunotherapy	(Hengrui Zheng et al., 2015)
Silica-coated	Magnetic nanoparticles	Streptokinase and tissue plasminogen activator	Thrombolytic therapy	(Tadayon et al., 2015)

5.4. SiNPs for bioimaging

High-sensitivity detection can allow for less invasive diagnostic approaches. Such systems could speed up treatment decision-making (Giljohann and Mirkin, 2009). Although SiNPs do not possess imaging properties themselves, they can trap imaging agents and be functionalized. Silica-based nanoparticles have been studied in Optical Imaging (OI), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), single-photon emission computed

tomography (SPECT) and computed tomography (CT), among others. Lim *et al*. summarized the pros and cons of nanomaterials used for bioimaging and therapeutics, highlighting the applications of silica-based hybrid nanocarriers as theranostic systems (Lim et al., 2016).

Non-covalently bound organic dyes, such as rhodamine and fluorescein, are usually obtained by dissolving the fluorophores in the synthesis medium. Auger *et al.* performed a comparative study of different hydrophilic and organic dyes encapsulations, namely Propyl Asrtra Blue Iodide (PABI), 4,4',4'',4'''-(porphine-5,10,15,20-tetrayl)tetrakis(benzoic acid) (PPC), IR 806, Nile Blue A perchlorate, 1,1',3,3,3',3'-Hexamethylindotricarbocyanine iodide (HITC), Cardiogreen, Rhodamine B and Fluorescein, into SiNPs by the microemulsion synthesis method. Fluorescein and rhodamine B were successfully encapsulated by dissolving in the aqueous phase at a concentration of 0.1 M follow by hydrolysis of TEOS initiated by the addition of aqueous ammonia to the reaction mixture (Auger et al., 2011). Covalent binding of the dye can significantly reduce fluorophore leaking. Dyes with groups such as succinimidyl esters or isothiocyanates are available commercially and can react with amine groups. Thus, covalent bonding can be achieved by pre-conjugating the dye molecule, e.g. fluorescein isothiocyanate (FITC) with APTES or APTMS. N-1-(3-timethoxy-silylilpropyl)-N-fluoresceyl thiourea (FITC-APTMS) can be obtained by stirring FITC and APTMS in an ethanoic solution in the dark for 24 h. This compound is then added to the particle synthesis medium to obtain fluorescent SiNPs. In the same way, maleimides can react with the thiol groups thiol silanes such as (3-mercaptopropyl)triethoxysilane (Schulz and McDonagh, 2012; Yao et al., 2006). Organic dyes have advantages, such as low cost and commercial availability, and disadvantages, such as short Stokes shift, poor photochemical stability, susceptibility to photobleaching and decomposition under repeated excitation, among others (Auger et al., 2011). Silica was used as

capsule to synthesis Up-conversion bioimaging systems. PdTPBP was used as a sensitizer and perylene, or BPEA, as acceptor. These NPs were conjugated with antibodies or peptides to selectively target breast and colon cancer cells, respectively. These particles showed cancer-specific and differential-color imaging at a single wavelength excitation *in vitro* and *in vivo* (Kwon et al., 2016). Multicolor (Vis-NIR) mesoporous silica nanospheres were synthesized by linking lanthanide complexes using 2-(5-bromothiophen)imidazo[4,5-f][1,10]phenanthroline. These nanomaterials show visible (Eu, Tb, Sm) and NIR (Sm, Nd, Yb) luminescence (Ying Liu et al., 2015). Silica encapsulation of aqueous cadmium sulfide (CdS) quantum dots (QDs) efficiently quenched their toxicity. The viability of human umbilical vein endothelial cells (HUVECs) was 10 % and 60 % after 24 h exposure to QDs or silica-coated QDs at the concentration of 1 mg/mL, respectively. Similarly, cell viabilities were 3 % (QDs) and 40 % (silica coated-QDs) in glioma cells (Gl-1 cells)(Veeranarayanan et al., 2012). Superhydrophobic MSNs were designed as ultrasound contrast agent. A bubble precursor was loaded in the mesopores, and under acoustic pressure was converted to the interfacial bubbles on the hydrophobic surface (Q. Jin et al., 2017). Silica-based multifunctional heterostructures that exhibited near-infrared (NIR) absorption and luminescence in the visible region were obtained by coating QDs with silica and then with gold speckles. A 16 nm thick silica shell showed the most suitable geometry to preserve QD emission in the visible region and to generate NIR absorption from metal (Fanizza et al., 2016). Magnetic resonance imaging (MRI) is another field where the incorporation of silica showed advantages. Silica-coated iron oxide nanoparticles (Fe_3O_4@SiO_2 NPs) showed enhanced stability in human mesenchymal stem cells (hMSCs). Also, these NPs labelled hMSCs more efficiently and appeared to be solely distributed in the

cytoplasm during cell proliferation, a promising feature for *in vivo* stem cell tracking (Tian et al., 2014).

Table 3. Application of silica nanoparticles (SiNPs) in diagnosis

Type of NP	Characteristic	Label type	Application	Reference
Mesoporous silica nanocomposite	Gold nanoparticles co-doped with Gd_2O_3	Optical and magnetic resonance	Cancer diagnosis	(H. Wang et al., 2016)
Mesoporous SiNPs	Rhodamine 6G and fluorescein	Fluorescence	detection of liver cancer cells	(Tao et al., 2016)
Mesoporous SiNPs	Conjugated with DOTA-N-hydroxysuccinimide-ester and ^{111}In labeled	Radiolabeling	Tracking of Glioblastoma	(S.-H. Cheng et al., 2016)
Mesoporous SiNPs	PEG, TRITC and Gd_2O_3	Fluorescence and magnetic resonance imaging	Bladder cancer	(Wu et al., 2014)
SiNPs	Indocyanine green and technetium-99m, and polyamidoamine-	Near-infrared fluorescence and radioactive	Imaging of HER2-expressing tumors	(Yamaguchi et al., 2016)

	based functionalized			
SiNPs	Streptavidin-conjugated and fluorescein isothiocyanate (FITC)-doped	Fluorescence	Hepatoma	(Hu et al., 2017)
Multifunctional silica-based nanocapsules	PdTPBP was used as sensitizer and perylene or BPEA as acceptor	Up-conversion	Target breast or colon cancer cells	(Kwon et al., 2016)
SiNPs	Gadolinium-conjugated fluorescent dye-conjugated and surface-modified polyamine and polycarboxyl functional groups	Magnetic resonance imaging and fluorescence	Cancer cell imaging and biodistribution	(An et al., 2015)
Silica	Hollow ultrathin iron (III)–doped	Ultrasound	Nonpalpable tumors	(Ward et al., 2016)
Mesoporous silica	Near-infrared dye ZW800, labeled with T(1) contrast	Near-infrared optical, magnetic resonance and	Sentinel lymph nodes	(Huang et al., 2012)

	agent Gd(3+) and radionuclide (64)Cu	positron emission tomography imaging		
Silica coated	Gadolinium (Gd)-based nanoparticles functionalized with 3-Aminopropyltriethoxysilane (APTES).	Magnetic resonance imaging	Tumor imaging	(Laranjeira et al., 2017)
Silica coated	$Gd_2(CO_3)_3$:Tb	Optical and magnetic resonance	Contrast agent	(Wu et al., 2012)
Silica coated	Gold nanorods	Photoacoustic imaging	Optimizing stem cell therapy	(Jokerst et al., 2012)

5.5 SiNPs as theranostics

Theranostics provide imaging and therapeutic functions in one system (Xie et al., 2010). Some of them have targeting and stimulus-responsive moieties, and several examples have been presented in the previous sections.

Mesoporous SiNPs integrating magnetic resonance imaging and a therapeutic pro-apoptotic peptide, KLA (HGGKLAKLAKKLAKLAK), were showed to induce mitochondrial swelling and apoptosis. In the study, a lipid bilayer was attached onto the surface of the MSNs

and doped with a paramagnetic lanthanide ion, Gadolinium (Gd) (Y. Jin et al., 2017). In another work, two drugs, i.e. hydrophobic camptothecin (CPT) and doxorubicin (DOX), were loaded into the pores of MSNs and CdS quantum dots. In these particles, the fluorescence of both CdS and DOX was quenched. In acidic conditions (pH 5), the drugs were released and the fluorescence of both agents was recovered. The potency of these NPs carrying both drugs was shown to be greater than that of single drug-loaded NPs (Muhammad et al., 2014).

Table 4. Nanoparticles (NPs) as cancer theranostics.

Type of NP	Characteristics	Drug	Reference
Fe_3O_4@mSiO_2-FA-CuS-PEG nanocomposite	Magnetic resonance imaging and targeted chemo-photothermal therapy	Doxorubicin	(Gao et al., 2016)
Organically-modified SiNPs loaded with doxorubicin and cyanine dye	Near-infrared fluorescence and chemotherapy with adjuvant hyperthermia for image guided cancer therapy	Doxorubicin	(Nagesetti and McGoron, 2016)
Silica-coated hollow carbon nanospheres encapsulating IONPs cluster	Ultrasound imaging and photothermal ablation under magnetically and MR imaging guided therapy	---	(Y.-K. Huang et al., 2016)
Zn-ferrite nanoparticles coated with SiO_2 layer	Magnetic resonance imaging and hyperthermia treatment	---	(Starsich et al., 2016)

Wormlike mesoporous silica nanocarriers decorated with iron oxide nanoparticles and functionalized gold nanoparticles	Magnetic resonance imaging, computed tomography, targeted, folic acid	Doxorubicin	(Tseng et al., 2016)
Mesoporous-silica-coated Gd_2O_3:Eu/SiNPs	Diagnosis and therapy	Doxorubicin	(W. Song et al., 2016)
Fluorescent carbon dot modified mesoporous silica	Responsive drug release and real-time imaging, cancer treatment	Doxorubicin	(Jiao et al., 2016a)
Multifunctional platform composed of graphene quantum dots and magnetic mesoporous SiNPs	Controlled drug delivery, magnetic hyperthermia, and photothermal therapy	Doxorubicin	(Yao et al., 2016)
Fe_3O_4@m-SiO_2@YPO_4:Tb^{3+} particles surface modified with β-cyclodextrin and folic acid	Fluorescent, magnetically guided delivery	5-fluorouracil	(Sahu and Mohapatra, 2013)
Benzonitrile-functionalized mesoporous SiNPs grafted with ruthenium(II) dipyridophenazine	Luminescent	Ruthenium(II) complex and paclitaxel	(Frasconi et al., 2013)

Gold nanorods coated with mesoporous silica shell capped with thermoresponsive polymer	X-ray CT, near-infrared responsive	Doxorubicin	(Baek et al., 2016)
GdOF:Ln cores mesoporous silica shells	Up-conversion luminescent, magnetic resonance imaging, computed tomography, photodynamic therapy and photothermal therapy	Doxorubicin	(Lv et al., 2015)
Mesoporous silica-encased gold nanorod	Photosensitizer-doped for two-photon-activated photodynamic therapy and two-photon luminescence	---	(N.-T. Chen et al., 2014)
Mesoporous SiNPs	Magnetic resonance imaging - Gadolinium (Gd)	Pro-apoptotic peptide, KLA (HGGKLA KLAKKLA KLAK)	(Y. Jin et al., 2017)
Mesoporous SiNPs capped by gadolinium-based bovine serum albumin complex (BSA-Gd) and hyaluronic acid	Magnetic resonance imaging, redox-sensitive and targeted	Doxorubicin	(Chen et al., 2016)

Hydrophobic ZnSe:Mn/ZnS core, folate-conjugated hybrid silica nanocapsules	Fluorescent quantum dots	Paclitaxel	(Zhao et al., 2017)
UCNPs@mSiO2@Fe3O4-PEG	Dual modal up-conversion luminescence and magnetic resonance imaging	Doxorubicin	(Bei Liu et al., 2015)
Fe_3O_4 core mesoporous silica shell	Magnetic resonance imaging, transferrin (Tf)- and a near-infrared fluorescent dye (Cy 7)-modified, near-infrared fluorescence	Paclitaxel	(Jiao et al., 2015)
Mesoporous SiNPs	Quantum dots and fluorescent doxorubicin	Camptothecin and doxorubicin	(Muhammad et al., 2014)
Magnetic mesoporous SiNPs	pH-responsive, alginate/chitosan polyelectrolyte multilayers, bifunctional Fe3O4-Au core nanoparticles, magnetic resonance and computed tomography imaging	Photosensitizer chlorin e6 and doxorubicin	(Yang et al., 2017a)
Mesoporous SiNPs with a lipid bilayer attached onto the	Magnetic resonance imaging, Gadolinium	KLA (HGGKLA	(Y. Jin et al., 2017)

surface		KLAKKLAKLAK)	
Core–shell-satellite NaGdF4:Yb,Er,Mn,Co@mSiO2-CuS	Up-conversion luminescence, computer tomography, magnetic resonance imaging and photodynamic therapy	Photosensitizer (ZnPc) and doxorubicin	(Wang et al., 2017)
Au core mesoporous SiNPs, indocyanine green loaded	Near-infrared response photothermal therapy platform and NIR/computer tomography	---	(Zeng et al., 2016)
Core-shell silica-PEG	Fluorescence emission, photoacoustic, near-infrared optical imaging and photothermal properties, doped with triethoxysilane-derivatized cyanine 5.5 (Cy5.5) and cyanine 7 (Cy7) dyes	---	(Prodi et al., 2016)
Mesoporous SiNPs	Luminescence	Doxorubicin	(Chen et al., 2013)

6. Toxicity

6.1 Dermal exposure

The human skin is a barrier composed of highly organized and heterogeneous layers: the dermis, epidermis and hypodermis. It has been shown that small nanoparticles can penetrate human skin.

Transcutaneously applied 40 nm nanoparticles were able to penetrate human skin and enter epidermal CD1a+ cells *in vitro*, while 750 and 1500 nm particles did not (Vogt et al., 2006). An important interindividual variability of particle penetration and uptake was found, and immune status as well as donor age seem to play a role (Vogt et al., 2006). Dermal administration of SiNPs did not cause skin damage or toxicity in internal organs of Sprague Dawley rats (6 weeks old) treated with 20 nm particles at 500, 1000, and 2000 mg/kg for 90 days (Ryu et al., 2014). 3D *in vitro* models are gaining much interest for bridging the gap between *in vitro* and *in vivo* studies in nanotoxicology. "Spheroid" models with different cell types are commonly used in nanotoxicological investigations. For example, a 3D reconstructed skin micronucleus (RSMN) was used to test BASF Levasil® SiNPs (16 and 85 nm). The dose-response effects were then compared to that of a 2D micronucleus assay using monocultured human B cells (TK6). Dose was normalized in terms of NPs mass to the number of cells. Acetone was found to be a suitable vehicle for the study (Wills et al., 2016). Finally, Nafisi *et al*., summarized 10 parameters to be evaluated to assess NPs percutaneous penetration, emphasizing the lack of information in long-term *in vivo* studies (Nafisi et al., 2015).

6.2 Oral exposure

Orally-administered SiNPs can be absorbed from the gastrointestinal tract and dissolved silica can be carried away in the blood. Dissolved nano-silica did not show significant toxicity (Dekkers et al., 2011). Silicon dioxide (E551) does not release dissolved silica in acidic conditions, but could do so in alkaline environments (Fruijtier-Pölloth, 2016). An *in vitro* study carried out with 5 mg/ml 27 nm SiNPs showed 0.11 ± 0.04 % solubility in simulated gastric fluid (0.2 % NaCl, 0.32 % pepsin, pH 1.5) and no dissolution in phosphate buffered saline (PBS, pH 7.4). Particles were transported by M cells in an *in vitro* model of human intestinal follicle-

associated epithelium (FAE) 3D culture system (Lee et al., 2017). *In vitro* studies using the averted gut sac method combined with an inductively coupled plasma optical emission spectrometer, 65, 322, and 1140 nm silica particles, and carboxyl- or amine-modified 70 and 72 nm SiNPs suggested that SiNPs are absorbed through the intestine. The absorption of carboxyl and amine NPs from the mucosal side to the serosal side was greater after incubation for 45 min (Yoshida et al., 2014). Size and surface modification affected mucopermeability in a study with porcine jejunal mucus. SiNPs of different size (10, 50, 100 and 200 nm) and surface coating (aminated, carboxylated, methyl-PEG1000ylated, and methyl-PEG2000ylated) were tested. Smaller particles (10 and 50 nm) showed higher transport compared to larger ones (100 and 200 nm). Higher transport through mucus was found with the anionic NPs. The cationic particles seemed to interact with the mucus, making it more viscous and less capable of swelling (Bhattacharjee et al., n.d.). To evaluate interactions between particles and food components, a 500 mg/kg single dose of food-grade SiNPs was orally-administrated to Sprague Dawley rats (male, 5 weeks). Particles were dispersed either in water or in 1 % (w/v) solutions of albumin or glucose. Most particles seemed to be directly eliminated in feces. A time-dependent increase in the plasma concentration of SiNPs was observed in the presence of albumin or glucose. The total Si levels were elevated in the kidneys, liver, lungs, and spleen of the animals (Lee et al., 2017). Histopathological examination revealed no abnormalities in any tissues (liver, kidney, large intestine, brain, lungs, spleen, heart, stomach and small intestine) after orally exposing BALB/c mice (female, 6 weeks) for 28 days at a daily dose of 2.5 mg. Furthermore, no significant changes were found in the plasma levels of ALT (marker of liver function), BUN (sensitive indicator of kidney damage) and counts of total monocytes, granulocytes, or platelets. Based on these results, in which the selected dose was around 10 times the safety limit of silica for

consumption by adults set by the United Kingdom Food Standards Agency's Expert Group on Vitamins and Minerals (700 mg silica/day), it seems that these NPs are safe to use in food production (Yoshida et al., 2014). However, it was reported that SiNPs may interfere with oral tolerance, which may be a possible cause for food allergy. Oral tolerance implicates the recognition of orally-ingested non-self-antigens to avoid excessive immune responses. Oral tolerance to ovalbumin (OVA) was induced in immunized BALB/c mice (males, 8 weeks). Five days prior immunization, animals were orally administrated 0.1, 1, or 10 mg of 39 nm particle suspension on a daily basis. Mice were euthanized three weeks after immunization. Results showed a dose-dependent increase in the level of OVA-specific IgG in OVA-tolerized mice and induced proliferation of OVA-immunized splenocytes in response to OVA. There was also an increased expression of OVA-specific IgG1, IgE, and IgG2a, indicative of TH1 and TH2 responses (Toda and Yoshino, 2016).

6.3 Intranasal exposure

The effects of occupational exposure to crystalline silica dust was investigated in the context of silicosis, chronic bronchitis, chronic obstructive pulmonary disease and lung cancer (Merget et al., 2002). A study carried out with 29.7 nm SiNPs in male F344 rats (8–10 weeks old) showed that these particles have the potential to translocate from the lung to different organs via the circulatory and lymphatic systems following inhalation. Rats were exposed for 4-6 h to aerosolized NPs at concentrations ranging between 3.5 mg/m^3 to 34.0 mg/m^3. The animals were sacrificed at 24 h or 7 days post-exposure. Lungs, lung lymph nodes, liver, kidneys and spleen were harvested (Guttenberg et al., 2016). The method of NPs administration seems to influence

body distribution. A single dose of core-shell particles containing a paramagnetic core of Fe_3O_4 was administrated via intravenous injection (100 μg in 250 μL) or intratracheal instillation (100 μg in 50 μL) in BALB/c OlaHsd mice (6 weeks old). The study showed that intravenously-administrated NPs mainly accumulated in the liver and were retained there for over 84 days, while for the same period of time, intratracheal instillation resulted in almost complete particle clearance from the lungs, along with NP distribution to the spleen and kidneys (Smulders et al., 2016)**.**

SiNPs can also affect the immune system. For example, 5 mg/kg SiNPs administrated via the intranasal route in male C57BL/6J mice (7 weeks old) affected the anti-microbial defense mechanisms of the host. Increased susceptibility to lethal *Pseudomonas aeruginosa* was observed in mice pre-treated with NPs (Delaval et al., 2015). Follow-up of these studies are warranted considering the importance of the immune system and its role in peripheral and central organs.

7. Epigenetics

Epigenetic processes involve changes in gene expression without alterations in the DNA sequence (Reamonbuettner et al., 2008). These changes include DNA methylation, histone tail modification as well as non-coding RNA (ncRNA)-mediated events (Stoccoro et al., 2013). Epigenetic changes can be stable and/or changed in response to environmental stimuli and thus have important pathological roles in response to engineered nanomaterials, including SiNPs. SiO_2 are present in the air, and as such can be inhaled and potentially cause cardiopulmonary damage (Chen et al., 2008). Remarkably, few studies have examined epigenetic changes in response to SiNPs. For instance, it was demonstrated that there is an altered microRNA (miRNA) profile in the lungs upon intratracheal installation of both nano-sized SiO_2 as well as

micro-sized SiO_2 that causes silicosis. miRNAs are a large group of non-coding RNAs (ncRNAs) that down-regulate protein expression by triggering translational repression and/or mRNA degradation (Keene, 2007). Because aberrant expression of miRNA is implicated in many diseases, considerable efforts are being made to establish miRNA signatures as biomarkers of environmental exposures. Even at relatively low nano-sized SiO_2 concentrations (6.25 mg/ml), numerous miRNA being up-or down-regulated are reported (Yang et al., 2010). For example, pulmonary miR212, miR-18a and miR-208 were higher in response to SiO_2 than in unexposed rats. These miRNAs are involved in lung development and in pathways related to immune responses, signaling cascades and growth factor responses (*e.g.* TGF-β and connective tissue growth factor [CTFG]). In this same study, there were corresponding differences in target genes/proteins including programmed cell death protein 4 (PDCD4) and LIN28B, targets of miR-208 and miR212, respectively (Yang et al., 2017b). As these two proteins have been implicated in inflammatory responses (Iliopoulos et al., 2009; Lee et al., 2013), it may be that dysregulation of miRNA facilitates pulmonary inflammation, thereby contributing to lung damage from inhaled nano-sized SiO_2.

The ability of SiNPs to cause changes in miRNA may also be useful as a biomarker of exposure. nSP70 are SiNPs with a diameter of 70nm that are capable of inducing liver damage. The expression of liver-specific/enriched miRNA miR-122, miR-192 and miR-194 were evaluated after exposure to nSP70. along with SiNPs with diameters of 300 nm (nSP300) and 1000 nm (mSP1000). Serum levels of miR-122 and miR-192 as well as the liver proteins alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly higher in mice exposed to sNP70 compared to controls, nSP300 or mSP1000 (Nagano et al., 2013). In fact, the sensitivity of miR-122 was at least as good as those of the traditional markers ALT and AST

(Nagano et al., 2013). Given that an increase in circulating miR-122 represents an important new biomarker of liver damage from multiple types of injury (Laterza et al., 2013; Leelahavanichkul et al., 2015; Roderburg et al., 2015), it may be that miR-122 in combination with increased miR-192 represents an early and selective marker of acute exposure to SiNPs.

In addition to changes in miRNA, there is emerging evidence that SiO_2 can also affect methylation patterns in numerous cell types. One consequence of these (methylation and miRNA) epigenetic alterations is increased cell death. A recent *in vitro* study used the human bronchial epithelial cells BEAS-2B to evaluate DNA methylation in response to SiNPs. Not only did SiNPs cause apoptotic cell death, these particles also resulted in hypermethylation of apoptosis-related genes *cAMP responsive element binding protein 3 like-1* (*CREB3L1)* and *Bcl-2* as a consequence of alterations in the PI3K/AKT signaling pathway (Zou et al., 2016). It was speculated that decreased expression (due to hypermethylation) of these apoptotic regulators contributed to apoptosis in response to SiNPs. SiNPs also induced apoptosis in male germ (spermatogonia) cells (GC-2 cells). While the implications for male fertility are unclear, these studies highlight the emerging importance of epigenetic alterations caused by SiNPs and the consequences for cell survival. Overall, these results showed a decrease in the expression of miR-98 (B. Xu et al., 2015). It was confirmed that this decrease was responsible for the increase in caspase-3 expression, a key executioner caspase in the apoptotic cascade (B. Xu et al., 2015).

Aside from inhalation, occupational exposure to SiNPs can also result in unwanted effects in skin cells. Nano-sized SiO_2 particles may cause both direct DNA damage or epigenetic changes that are associated with increased cytotoxicity (Gong et al., 2010; Yang et al., 2010). In the human epidermal keratinocyte cell line HaCaT, exposure to 15 nm SiO_2 particles caused global DNA hypomethylation that was accompanied by a decrease in the expression of the DNA

methyltransferases (DNMT) 1 and DNMT3a (Gong et al., 2010). There was also a decrease in the expression of methyl-CpG binding protein 2 (MBD2), a protein that binds to methylated DNA to suppress transcription from a methylated gene (Gong et al., 2010). The expression of PARP-1 (poly(ADP-ribose) polymerases-1), a gene involved in DNA repair, was decreased in response to SiO_2 and was associated with alterations in methylation (Gong et al., 2012). It remains to be seen whether this global hypomethylation results in corresponding changes in gene/protein expression.

These studies highlight the emerging importance of epigenetics towards the toxicological profile of SiNPs. Overall, there is support for the view that epigenetic changes occur in response to nano-sized silica. However, there are still many unanswered questions. For example, why is there a different methylation profile in lung versus skin cells? Is this due to cell-specific differences? Are long non-coding RNA (LncRNA) affected by SiNPs? Future research is needed to fully understand how epigenetic alterations from SiNPs exposure affect biological and pathological processes and ultimately, human health.

8. Conclusions and perspectives

SiNPs of different shapes and sizes are present in products used in day-to-day life. Even though there are studies supporting their safety, these are insufficient and in some cases, controversial. Factors such as size and surface modifications have been shown to be important when assessing toxicity. Better understanding the interaction between human biology and nanoparticles of different surface composition and size will allow us to use these nanoparticles as better drug delivery nanocarriers.

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9. References

Abbaszad Rafi, A., Mahkam, M., Davaran, S., Hamishehkar, H., 2016. A Smart pH-responsive Nano-Carrier as a Drug Delivery System: A hybrid system comprised of mesoporous nanosilica MCM-41 (as a nano-container) & a pH-sensitive polymer (as smart reversible gatekeepers): Preparation, characterization and in vitro release studies of an anti-cancer drug. Eur. J. Pharm. Sci. 93, 64–73. doi:10.1016/j.ejps.2016.08.005

Ahmad Nor, Y., Niu, Y., Karmakar, S., Zhou, L., Xu, C., Zhang, J., Zhang, H., Yu, M., Mahony, D., Mitter, N., Cooper, M.A., Yu, C., 2015. Shaping Nanoparticles with Hydrophilic Compositions and Hydrophobic Properties as Nanocarriers for Antibiotic Delivery. ACS Cent. Sci. 1, 328–334. doi:10.1021/acscentsci.5b00199

Alvarez, G.S., Helary, C., Mebert, A.M., Wang, X., Coradin, T., Desimone, M.F., 2014. Antibiotic-loaded silica nanoparticle-collagen composite hydrogels with prolonged antimicrobial activity for wound infection prevention. J. Mater. Chem. B 2, 4660–4670. doi:10.1039/C4TB00327F

An, S.S., Kim, J., Kim, B.-T.K., Wang, T., Seo, S.-W., Lee, H., Sung, D., Yi, D.K., 2015. Silica nanoparticle-based dual imaging colloidal hybrids: cancer cell imaging and biodistribution. Int. J. Nanomedicine 215. doi:10.2147/IJN.S88311

Auger, A., Samuel, J., Poncelet, O., Raccurt, O., 2011. A comparative study of non-covalent encapsulation methods for organic dyes into silica nanoparticles. Nanoscale Res. Lett. 6, 328–328. doi:10.1186/1556-276X-6-328

Baek, S., Singh, R.K., Kim, T.-H., Seo, J., Shin, U.S., Chrzanowski, W., Kim, H.-W., 2016. Triple Hit with Drug Carriers: pH- and Temperature-Responsive Theranostics for Multimodal Chemo- and

Photothermal Therapy and Diagnostic Applications. ACS Appl. Mater. Interfaces 8, 8967–8979. doi:10.1021/acsami.6b00963

Baeza, A., Colilla, M., Vallet-Regí, M., 2015. Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery. Expert Opin. Drug Deliv. 12, 319–337. doi:10.1517/17425247.2014.953051

Barahona, F., Ojea-Jimenez, I., Geiss, O., Gilliland, D., Barrero-Moreno, J., 2016. Multimethod approach for the detection and characterisation of food-grade synthetic amorphous silica nanoparticles. J. Chromatogr. A 1432, 92–100. doi:10.1016/j.chroma.2015.12.058

Bertucci, A., Prasetyanto, E.A., Septiadi, D., Manicardi, A., Brognara, E., Gambari, R., Corradini, R., De Cola, L., 2015. Combined Delivery of Temozolomide and Anti-miR221 PNA Using Mesoporous Silica Nanoparticles Induces Apoptosis in Resistant Glioma Cells. Small 11, 5687–5695. doi:10.1002/smll.201500540

Bhattacharjee, S., Mahon, E., Harrison, S.M., McGetrick, J., Muniyappa, M., Carrington, S.D., Brayden, D.J., n.d. Nanoparticle passage through porcine jejunal mucus: Microfluidics and rheology. Nanomedicine Nanotechnol. Biol. Med. doi:10.1016/j.nano.2016.11.017

Castillo, R.R., Colilla, M., Vallet-Regí, M., 2017. Advances in mesoporous silica-based nanocarriers for co-delivery and combination therapy against cancer. Expert Opin. Drug Deliv. 14, 229–243. doi:10.1080/17425247.2016.1211637

Ceresa, C., Nicolini, G., Rigolio, R., Bossi, M., Pasqua, L. and Cavaletti, G., 2013. Functionalized Mesoporous Silica Nanoparticles: A Possible Strategy to Target Cancer Cells Reducing Peripheral Nervous System Uptake. Curr. Med. Chem. 20, 2589–2600. doi:10.2174/0929867311320200007

Chen, F., Hong, H., Shi, S., Goel, S., Valdovinos, H.F., Hernandez, R., Theuer, C.P., Barnhart, T.E., Cai, W., 2014. Engineering of Hollow Mesoporous Silica Nanoparticles for Remarkably Enhanced Tumor Active Targeting Efficacy. Sci. Rep. 4, 5080.

Cheng, J., Ding, Q., Wang, J., Deng, L., Yang, L., Tao, L., Lei, H., Lu, S., 2016. 5-Azacytidine delivered by mesoporous silica nanoparticles regulates the differentiation of P19 cells into cardiomyocytes. Nanoscale 8, 2011–2021. doi:10.1039/C5NR08560H

Cheng, S.-H., Yu, D., Tsai, H.-M., Morshed, R.A., Kanojia, D., Lo, L.-W., Leoni, L., Govind, Y., Zhang, L., Aboody, K.S., Lesniak, M.S., Chen, C.-T., Balyasnikova, I.V., 2016. Dynamic In Vivo SPECT Imaging of Neural Stem Cells Functionalized with Radiolabeled Nanoparticles for Tracking of Glioblastoma. J. Nucl. Med. 57, 279–284.

Cheng, Y.-J., Luo, G.-F., Zhu, J.-Y., Xu, X.-D., Zeng, X., Cheng, D.-B., Li, Y.-M., Wu, Y., Zhang, X.-Z., Zhuo, R.-X., He, F., 2015. Enzyme-Induced and Tumor-Targeted Drug Delivery System Based on Multifunctional Mesoporous Silica Nanoparticles. ACS Appl. Mater. Interfaces 7, 9078–9087. doi:10.1021/acsami.5b00752

Chen, H., Zhen, Z., Tang, W., Todd, T., Chuang, Y.-J., Wang, L., Pan, Z., Xie, J., 2013. Label-Free Luminescent Mesoporous Silica Nanoparticles for Imaging and Drug Delivery. Theranostics 3, 650–657. doi:10.7150/thno.6668

Chen, L., She, X., Wang, T., He, L., Shigdar, S., Duan, W., Kong, L., 2015. Overcoming acquired drug resistance in colorectal cancer cells by targeted delivery of 5-FU with EGF grafted hollow mesoporous silica nanoparticles. Nanoscale 7, 14080–14092. doi:10.1039/C5NR03527A

Chen, L., Zhou, X., Nie, W., Zhang, Q., Wang, W., Zhang, Y., He, C., 2016. Multifunctional Redox-Responsive Mesoporous Silica Nanoparticles for Efficient Targeting Drug Delivery and Magnetic Resonance Imaging. ACS Appl. Mater. Interfaces 8, 33829–33841. doi:10.1021/acsami.6b11802

Chen, N.-T., Tang, K.-C., Chung, M.-F., Cheng, S.-H., Huang, C.-M., Chu, C.-H., Chou, P.-T., Souris, J.S., Chen, C.-T., Mou, C.-Y., Lo, L.-W., 2014. Enhanced Plasmonic Resonance Energy Transfer in Mesoporous Silica-Encased Gold Nanorod for Two-Photon-Activated Photodynamic Therapy. Theranostics 4, 798–807. doi:10.7150/thno.8934

Chen, Z., Meng, H., Xing, G., Yuan, H., Zhao, F., Liu, R., Chang, X., Gao, X., Wang, T., Jia, G., Ye, C., Chai, Z., Zhao, Y., 2008. Age-Related Differences in Pulmonary and Cardiovascular Responses

to SiO_2 Nanoparticle Inhalation: Nanotoxicity Has Susceptible Population. Environ. Sci. Technol. 42, 8985–8992. doi:10.1021/es800975u

Choi, J.Y., Ramasamy, T., Kim, S.Y., Kim, J., Ku, S.K., Youn, Y.S., Kim, J.-R., Jeong, J.-H., Choi, H.-G., Yong, C.S., Kim, J.O., 2016. PEGylated lipid bilayer-supported mesoporous silica nanoparticle composite for synergistic co-delivery of axitinib and celastrol in multi-targeted cancer therapy. Acta Biomater. 39, 94–105. doi:10.1016/j.actbio.2016.05.012

Cozzolino, C.A., Castelli, G., Trabattoni, S., Farris, S., 2016. Influence of colloidal silica nanoparticles on pullulan-coated BOPP film. Food Packag. Shelf Life 8, 50–55. doi:10.1016/j.fpsl.2016.03.003

Croissant, J.G., Zhang, D., Alsaiari, S., Lu, J., Deng, L., Tamanoi, F., AlMalik, A.M., Zink, J.I., Khashab, N.M., 2016. Protein-gold clusters-capped mesoporous silica nanoparticles for high drug loading, autonomous gemcitabine/doxorubicin co-delivery, and in-vivo tumor imaging. J. Controlled Release 229, 183–191. doi:10.1016/j.jconrel.2016.03.030

Cui, Y., Xu, Q., Chow, P.K.-H., Wang, D., Wang, C.-H., 2013. Transferrin-conjugated magnetic silica PLGA nanoparticles loaded with doxorubicin and paclitaxel for brain glioma treatment. Biomaterials 34, 8511–8520. doi:10.1016/j.biomaterials.2013.07.075

Dai, L., Li, J., Zhang, B., Liu, J., Luo, Z., Cai, K., 2014. Redox-Responsive Nanocarrier Based on Heparin End-Capped Mesoporous Silica Nanoparticles for Targeted Tumor Therapy in Vitro and in Vivo. Langmuir 30, 7867–7877. doi:10.1021/la501924p

Dekkers, S., Krystek, P., Peters, R.J.B., Lankveld, D.P.K., Bokkers, B.G.H., van Hoeven-Arentzen, P.H., Bouwmeester, H., Oomen, A.G., 2011. Presence and risks of nanosilica in food products. Nanotoxicology 5, 393–405. doi:10.3109/17435390.2010.519836

Delaval, M., Boland, S., Solhonne, B., Nicola, M.-A., Mornet, S., Baeza-Squiban, A., Sallenave, J.-M., Garcia-Verdugo, I., 2015. Acute exposure to silica nanoparticles enhances mortality and increases lung permeability in a mouse model of Pseudomonas aeruginosa pneumonia. Part. Fibre Toxicol. 12. doi:10.1186/s12989-014-0078-9

de Oliveira, L.F., Bouchmella, K., Gonçalves, K. de A., Bettini, J., Kobarg, J., Cardoso, M.B., 2016. Functionalized Silica Nanoparticles As an Alternative Platform for Targeted Drug-Delivery of Water Insoluble Drugs. Langmuir 32, 3217–3225. doi:10.1021/acs.langmuir.6b00214

de Souza Oliveira, R.C., Corrêa, R.J., Teixeira, R.S.P., Queiroz, D.D., da Silva Souza, R., Garden, S.J., de Lucas, N.C., Pereira, M.D., Bello Forero, J.S., Romani, E.C., Ribeiro, E.S., 2016. Silica nanoparticles doped with anthraquinone for lung cancer phototherapy. J. Photochem. Photobiol. B 165, 1–9. doi:10.1016/j.jphotobiol.2016.10.008

Durfee, P.N., Lin, Y.-S., Dunphy, D.R., Muñiz, A.J., Butler, K.S., Humphrey, K.R., Lokke, A.J., Agola, J.O., Chou, S.S., Chen, I.-M., Wharton, W., Townson, J.L., Willman, C.L., Brinker, C.J., 2016. Mesoporous Silica Nanoparticle-Supported Lipid Bilayers (Protocells) for Active Targeting and Delivery to Individual Leukemia Cells. ACS Nano 10, 8325–8345. doi:10.1021/acsnano.6b02819

Du, X., Xiong, L., Dai, S., Qiao, S.Z., 2015. γ-PGA-Coated Mesoporous Silica Nanoparticles with Covalently Attached Prodrugs for Enhanced Cellular Uptake and Intracellular GSH-Responsive Release. Adv. Healthc. Mater. 4, 771–781. doi:10.1002/adhm.201400726

Ebabe Elle, R., Rahmani, S., Lauret, C., Morena, M., Bidel, L.P.R., Boulahtouf, A., Balaguer, P., Cristol, J.-P., Durand, J.-O., Charnay, C., Badia, E., 2016. Functionalized Mesoporous Silica Nanoparticle with Antioxidants as a New Carrier That Generates Lower Oxidative Stress Impact on Cells. Mol. Pharm. 13, 2647–2660. doi:10.1021/acs.molpharmaceut.6b00190

Echazu, M.I.A., Tuttolomondo, M.V., Foglia, M.L., Mebert, A.M., Alvarez, G.S., Desimone, M.F., 2016. Advances in collagen, chitosan and silica biomaterials for oral tissue regeneration: from basics to clinical trials. J. Mater. Chem. B 4, 6913–6929. doi:10.1039/C6TB02108E

El-Dakdouki, M.H., Pure, E., Huang, X., 2013. Development of drug loaded nanoparticles for tumor targeting. Part 2: Enhancement of tumor penetration through receptor mediated transcytosis in 3D tumor models. Nanoscale 5, 3904–3911. doi:10.1039/C3NR90022C

EUROPEAN COMMISSION, 2007. Reference Document on Best Available Techniques for the Manufacture of Large Volume Inorganic Chemicals–Solids and Others industry. Chapter 5:

Synthetic Amorphous Silica., in: Reference Document on Best Available Techniques for the Manufacture of Large Volume Inorganic Chemicals–Solids and Others Industry. pp. 255–294.

Fan, J., Fang, G., Wang, X., Zeng, F., Xiang, Y., Wu, S., 2011. Targeted anticancer prodrug with mesoporous silica nanoparticles as vehicles. Nanotechnology 22, 455102.

Fang, W., Tang, S., Liu, P., Fang, X., Gong, J., Zheng, N., 2012. Pd Nanosheet-Covered Hollow Mesoporous Silica Nanoparticles as a Platform for the Chemo-Photothermal Treatment of Cancer Cells. Small 8, 3816–3822. doi:10.1002/smll.201200962

Fanizza, E., Urso, C., Iacobazzi, R.M., Depalo, N., Corricelli, M., Panniello, A., Agostiano, A., Denora, N., Laquintana, V., Striccoli, M., Curri, M.L., 2016. Fabrication of photoactive heterostructures based on quantum dots decorated with Au nanoparticles. Sci. Technol. Adv. Mater. 17, 98–108. doi:10.1080/14686996.2016.1153939

Farjadian, F., Ghasemi, S., Mohammadi-Samani, S., 2016. Hydroxyl-modified magnetite nanoparticles as novel carrier for delivery of methotrexate. Int. J. Pharm. 504, 110–116. doi:10.1016/j.ijpharm.2016.03.022

Feng, W., Nie, W., He, C., Zhou, X., Chen, L., Qiu, K., Wang, W., Yin, Z., 2014. Effect of pH-Responsive Alginate/Chitosan Multilayers Coating on Delivery Efficiency, Cellular Uptake and Biodistribution of Mesoporous Silica Nanoparticles Based Nanocarriers. ACS Appl. Mater. Interfaces 6, 8447–8460. doi:10.1021/am501337s

Fernando, I.R., Ferris, D.P., Frasconi, M., Malin, D., Strekalova, E., Yilmaz, M.D., Ambrogio, M.W., Algaradah, M.M., Hong, M.P., Chen, X., Nassar, M.S., Botros, Y.Y., Cryns, V.L., Stoddart, J.F., 2015. Esterase- and pH-responsive poly([small beta]-amino ester)-capped mesoporous silica nanoparticles for drug delivery. Nanoscale 7, 7178–7183. doi:10.1039/C4NR07443B

Frasconi, M., Liu, Z., Lei, J., Wu, Y., Strekalova, E., Malin, D., Ambrogio, M.W., Chen, X., Botros, Y.Y., Cryns, V.L., Sauvage, J.-P., Stoddart, J.F., 2013. Photoexpulsion of Surface-Grafted Ruthenium Complexes and Subsequent Release of Cytotoxic Cargos to Cancer Cells from Mesoporous Silica Nanoparticles. J. Am. Chem. Soc. 135, 11603–11613. doi:10.1021/ja405058y

Fruijtier-Pölloth, C., 2016. The safety of nanostructured synthetic amorphous silica (SAS) as a food additive (E 551). Arch. Toxicol. 90, 2885–2916. doi:10.1007/s00204-016-1850-4

Fu, Q., Hargrove, D., Lu, X., 2016. Improving paclitaxel pharmacokinetics by using tumor-specific mesoporous silica nanoparticles with intraperitoneal delivery. Nanomedicine Nanotechnol. Biol. Med. 12, 1951–1959. doi:10.1016/j.nano.2016.04.013

Gamcsik, M.P., Kasibhatla, M.S., Teeter, S.D., Colvin, O.M., 2012. Glutathione Levels in Human Tumors. Biomark. Biochem. Indic. Expo. Response Susceptibility Chem. 17, 671–691. doi:10.3109/1354750X.2012.715672

Gao, Y., Ma, R., An, Y., Shi, L., 2011. Nanogated vessel based on polypseudorotaxane-capped mesoporous silica via a highly acid-labile benzoic-imine linker. Symp. Innov. Polym. Control. Deliv. Conf. Abstr. First Symp. Innov. Polym. Control. Deliv. 152, Supplement 1, e81–e82. doi:10.1016/j.jconrel.2011.08.137

Gao, Z., Liu, X., Deng, G., Zhou, F., Zhang, L., Wang, Q., Lu, J., 2016. Fe3O4@mSiO2-FA-CuS-PEG nanocomposites for magnetic resonance imaging and targeted chemo-photothermal synergistic therapy of cancer cells. Dalton Trans. 45, 13456–13465. doi:10.1039/C6DT01714B

Gary-Bobo, M., Brevet, D., Benkirane-Jessel, N., Raehm, L., Maillard, P., Garcia, M., Durand, J.-O., 2012. Hyaluronic acid-functionalized mesoporous silica nanoparticles for efficient photodynamic therapy of cancer cells. Photodiagnosis Photodyn. Ther. 9, 256–260. doi:10.1016/j.pdpdt.2011.12.010

Ghosh Chaudhuri, R., Paria, S., 2012. Core/Shell Nanoparticles: Classes, Properties, Synthesis Mechanisms, Characterization, and Applications. Chem. Rev. 112, 2373–2433. doi:10.1021/cr100449n

Giljohann, D.A., Mirkin, C.A., 2009. Drivers of biodiagnostic development. Nature 462, 461–464. doi:10.1038/nature08605

Giménez, C., de la Torre, C., Gorbe, M., Aznar, E., Sancenón, F., Murguía, J.R., Martínez-Máñez, R., Marcos, M.D., Amorós, P., 2015. Gated Mesoporous Silica Nanoparticles for the Controlled Delivery of Drugs in Cancer Cells. Langmuir 31, 3753–3762. doi:10.1021/acs.langmuir.5b00139

Gong, C., Tao, G., Yang, L., Liu, J., Liu, Q., Li, W., Zhuang, Z., 2012. Methylation of PARP-1 promoter involved in the regulation of nano-SiO2-induced decrease of PARP-1 mRNA expression. Toxicol. Lett. 209, 264–269. doi:10.1016/j.toxlet.2012.01.007

Gong, C., Tao, G., Yang, L., Liu, J., Liu, Q., Zhuang, Z., 2010. SiO2 nanoparticles induce global genomic hypomethylation in HaCaT cells. Biochem. Biophys. Res. Commun. 397, 397–400. doi:10.1016/j.bbrc.2010.05.076

Gonzalez, C.G., Álvarez, G.S., Camporotondi, D.E., Foglia, M.L., Aimé, C., Diaz, L.E., Coradin, T., Desimone, M.F., 2014. Preliminary Evaluation of Median Lethal Concentrations of Stöber Silica Particles with Various Sizes and Surface Functionalities Towards Fibroblast Cells. Silicon. doi:10.1007/s12633-014-9203-5

Guha, A., Biswas, N., Bhattacharjee, K., Sahoo, N., Kuotsu, K., 2016. pH responsive cylindrical MSN for oral delivery of insulin- Design, Fabrication and Evaluation. Drug Deliv. 1–30. doi:10.1080/10717544.2016.1209796

Gu, J., Liu, J., Li, Y., Zhao, W., Shi, J., 2013. One-Pot Synthesis of Mesoporous Silica Nanocarriers with Tunable Particle Sizes and Pendent Carboxylic Groups for Cisplatin Delivery. Langmuir 29, 403–410. doi:10.1021/la3036264

Guo, R., Li, L.-L., Zhao, W.-H., Chen, Y.-X., Wang, X.-Z., Fang, C.-J., Feng, W., Zhang, T.-L., Ma, X., Lu, M., Peng, S.-Q., Yan, C.-H., 2012. The intracellular controlled release from bioresponsive mesoporous silica with folate as both targeting and capping agent. Nanoscale 4, 3577–3583. doi:10.1039/C2NR30425B

Guttenberg, M., Bezerra, L., Neu-Baker, N.M., del Pilar Sosa Idelchik, M., Elder, A., Oberdörster, G., Brenner, S.A., 2016. Biodistribution of inhaled metal oxide nanoparticles mimicking

occupational exposure: a preliminary investigation using enhanced darkfield microscopy. J. Biophotonics 9, 987–993. doi:10.1002/jbio.201600125

Hakeem, A., Zahid, F., Duan, R., Asif, M., Zhang, T., Zhang, Z., Cheng, Y., Lou, X., Xia, F., 2016. Cellulose conjugated FITC-labelled mesoporous silica nanoparticles: intracellular accumulation and stimuli responsive doxorubicin release. Nanoscale 8, 5089–5097. doi:10.1039/C5NR08753H

Hanafi-Bojd, M.Y., Jaafari, M.R., Ramezanian, N., Xue, M., Amin, M., Shahtahmassebi, N., Malaekeh-Nikouei, B., 2015. Surface functionalized mesoporous silica nanoparticles as an effective carrier for epirubicin delivery to cancer cells. Eur. J. Pharm. Biopharm. 89, 248–258. doi:10.1016/j.ejpb.2014.12.009

Han, L., Tang, C., Yin, C., 2016. pH-Responsive Core–Shell Structured Nanoparticles for Triple-Stage Targeted Delivery of Doxorubicin to Tumors. ACS Appl. Mater. Interfaces 8, 23498–23508. doi:10.1021/acsami.6b07173

Han, N., Zhao, Q., Wan, L., Wang, Y., Gao, Y., Wang, P., Wang, Z., Zhang, J., Jiang, T., Wang, S., 2015. Hybrid Lipid-Capped Mesoporous Silica for Stimuli-Responsive Drug Release and Overcoming Multidrug Resistance. ACS Appl. Mater. Interfaces 7, 3342–3351. doi:10.1021/am5082793

Heinemann, S., Coradin, T., Desimone, M.F., 2013. Bio-inspired silica-collagen materials: Applications and perspectives in the medical field. Biomater. Sci. 1, 688–702. doi:10.1039/c3bm00014a

Huang, K., Chen, J., Nugen, S.R., Goddard, J.M., 2016. Hybrid Antifouling and Antimicrobial Coatings Prepared by Electroless Co-Deposition of Fluoropolymer and Cationic Silica Nanoparticles on Stainless Steel: Efficacy against Listeria monocytogenes. ACS Appl. Mater. Interfaces 8, 15926–15936. doi:10.1021/acsami.6b04187

Huang, X., Zhang, F., Lee, S., Swierczewska, M., Kiesewetter, D.O., Lang, L., Zhang, G., Zhu, L., Gao, H., Choi, H.S., Niu, G., Chen, X., 2012. Long-term multimodal imaging of tumor draining sentinel lymph nodes using mesoporous silica-based nanoprobes. Biomaterials 33, 4370–4378. doi:10.1016/j.biomaterials.2012.02.060

Huang, Y.-K., Su, C.-H., Chen, J.-J., Chang, C.-T., Tsai, Y.-H., Syu, S.-F., Tseng, T.-T., Yeh, C.-S., 2016. Fabrication of Silica-Coated Hollow Carbon Nanospheres Encapsulating Fe3O4 Cluster for Magnetical and MR Imaging Guided NIR Light Triggering Hyperthermia and Ultrasound Imaging. ACS Appl. Mater. Interfaces 8, 14470–14480. doi:10.1021/acsami.6b04759

Hu, J., Zhang, X., Wen, Z., Tan, Y., Huang, N., Cheng, S., Zheng, H., Cheng, Y., 2016. Asn-Gly-Arg-modified polydopamine-coated nanoparticles for dual-targeting therapy of brain glioma in rats. Oncotarget Adv. Online Publ. Page 5.

Huo, X., Dai, C., Tian, D., Li, S., Li, X., 2015. Au@SiO2 core–shell structure involved with methotrexate: Fabrication, biodegradation process and bioassay explore. Int. J. Pharm. 496, 965–975. doi:10.1016/j.ijpharm.2015.10.052

Hu, X., Hao, X., Wu, Y., Zhang, J., Zhang, X., Wang, P.C., Zou, G., Liang, X.-J., 2013. Multifunctional hybrid silica nanoparticles for controlled doxorubicin loading and release with thermal and pH dual response. J. Mater. Chem. B 1, 1109–1118. doi:10.1039/C2TB00223J

Hu, Z., Tan, J., Lai, Z., Zheng, R., Zhong, J., Wang, Y., Li, X., Yang, N., Li, J., Yang, W., Huang, Y., Zhao, Y., Lu, X., 2017. Aptamer Combined with Fluorescent Silica Nanoparticles for Detection of Hepatoma Cells. Nanoscale Res. Lett. 12. doi:10.1186/s11671-017-1890-6

Hwang, A.A., Lee, B.-Y., Clemens, D.L., Dillon, B.J., Zink, J.I., Horwitz, M.A., 2015. pH-Responsive Isoniazid-Loaded Nanoparticles Markedly Improve Tuberculosis Treatment in Mice. Small 11, 5066–5078. doi:10.1002/smll.201500937

Hwang, J., Lee, E., Kim, J., Seo, Y., Lee, K.H., Hong, J.W., Gilad, A.A., Park, H., Choi, J., 2016. Effective delivery of immunosuppressive drug molecules by silica coated iron oxide nanoparticles. Colloids Surf. B Biointerfaces 142, 290–296. doi:10.1016/j.colsurfb.2016.01.040

Iliopoulos, D., Hirsch, H.A., Struhl, K., 2009. An Epigenetic Switch Involving NF-κB, Lin28, Let-7 MicroRNA, and IL6 Links Inflammation to Cell Transformation. Cell 139, 693–706. doi:10.1016/j.cell.2009.10.014

Jia, L., Li, Z., Shen, J., Zheng, D., Tian, X., Guo, H., Chang, P., 2015. Multifunctional mesoporous silica nanoparticles mediated co-delivery of paclitaxel and tetrandrine for overcoming multidrug resistance. Int. J. Pharm. 489, 318–330. doi:10.1016/j.ijpharm.2015.05.010

Jia, L., Shen, J., Li, Z., Zhang, D., Zhang, Q., Duan, C., Liu, G., Zheng, D., Liu, Y., Tian, X., 2012. Successfully tailoring the pore size of mesoporous silica nanoparticles: Exploitation of delivery systems for poorly water-soluble drugs. Int. J. Pharm. 439, 81–91. doi:10.1016/j.ijpharm.2012.10.011

Jiao, J., Liu, C., Li, X., Liu, J., Di, D., Zhang, Y., Zhao, Q., Wang, S., 2016a. Fluorescent carbon dot modified mesoporous silica nanocarriers for redox-responsive controlled drug delivery and bioimaging. J. Colloid Interface Sci. 483, 343–352. doi:10.1016/j.jcis.2016.08.033

Jiao, J., Li, X., Zhang, S., Liu, J., Di, D., Zhang, Y., Zhao, Q., Wang, S., 2016b. Redox and pH dual-responsive PEG and chitosan-conjugated hollow mesoporous silica for controlled drug release. Mater. Sci. Eng. C 67, 26–33. doi:10.1016/j.msec.2016.04.091

Jiao, Y., Sun, Y., Chang, B., Lu, D., Yang, W., 2013. Redox- and Temperature-Controlled Drug Release from Hollow Mesoporous Silica Nanoparticles. Chem. – Eur. J. 19, 15410–15420. doi:10.1002/chem.201301060

Jiao, Y., Sun, Y., Tang, X., Ren, Q., Yang, W., 2015. Tumor-Targeting Multifunctional Rattle-Type Theranostic Nanoparticles for MRI/NIRF Bimodal Imaging and Delivery of Hydrophobic Drugs. Small 11, 1962–1974. doi:10.1002/smll.201402297

Jin, Q., Lin, C.-Y., Kang, S.-T., Chang, Y.-C., Zheng, H., Yang, C.-M., Yeh, C.-K., 2017. Superhydrophobic silica nanoparticles as ultrasound contrast agents. Ultrason. Sonochem. 36, 262–269. doi:10.1016/j.ultsonch.2016.12.001

Jin, Y., Zhang, N., Li, C., Pu, K., Ding, C., Zhu, Y., 2017. Nanosystem composed with MSNs, gadolinium, liposome and cytotoxic peptides for tumor theranostics. Colloids Surf. B Biointerfaces 151, 240–248. doi:10.1016/j.colsurfb.2016.12.024

Jokerst, J.V., Thangaraj, M., Kempen, P.J., Sinclair, R., Gambhir, S.S., 2012. Photoacoustic Imaging of Mesenchymal Stem Cells in Living Mice *via* Silica-Coated Gold Nanorods. ACS Nano 6, 5920–5930. doi:10.1021/nn302042y

Kamkaew, A., Cheng, L., Goel, S., Valdovinos, H.F., Barnhart, T.E., Liu, Z., Cai, W., 2016. Cerenkov Radiation Induced Photodynamic Therapy Using Chlorin e6-Loaded Hollow Mesoporous Silica Nanoparticles. ACS Appl. Mater. Interfaces 8, 26630–26637. doi:10.1021/acsami.6b10255

Keene, J.D., 2007. RNA regulons: coordination of post-transcriptional events. Nat. Rev. Genet. 8, 533–543. doi:10.1038/nrg2111

Khatoon, S., Han, H.S., Lee, M., Lee, H., Jung, D.-W., Thambi, T., Ikram, M., Kang, Y.M., Yi, G.-R., Park, J.H., 2016. Zwitterionic mesoporous nanoparticles with a bioresponsive gatekeeper for cancer therapy. Zwitterionic Mater. 40, 282–292. doi:10.1016/j.actbio.2016.04.011

Kim, M.S., El-Fiqi, A., Kim, J.-W., Ahn, H.-S., Kim, H., Son, Y.-J., Kim, H.-W., Hyun, J.K., 2016. Nanotherapeutics of PTEN Inhibitor with Mesoporous Silica Nanocarrier Effective for Axonal Outgrowth of Adult Neurons. ACS Appl. Mater. Interfaces 8, 18741–18753. doi:10.1021/acsami.6b06889

Koneru, B., Shi, Y., Wang, Y.-C., Chavala, H.S., Miller, L.M., Holbert, B., Conson, M., Ni, A., Di Pasqua, J.A., 2015. Tetracycline-Containing MCM-41 Mesoporous Silica Nanoparticles for the Treatment of Escherichia coli. Molecules 20. doi:10.3390/molecules201119650

Kuthati, Y., Kankala, R.K., Lin, S.-X., Weng, C.-F., Lee, C.-H., 2015. pH-Triggered Controllable Release of Silver–Indole-3 Acetic Acid Complexes from Mesoporous Silica Nanoparticles (IBN-4) for Effectively Killing Malignant Bacteria. Mol. Pharm. 12, 2289–2304. doi:10.1021/mp500836w

Kwon, O.S., Song, H.S., Conde, J., Kim, H., Artzi, N., Kim, J.-H., 2016. Dual-Color Emissive Upconversion Nanocapsules for Differential Cancer Bioimaging In Vivo. ACS Nano 10, 1512–1521. doi:10.1021/acsnano.5b07075

Laranjeira, M., Shirosaki, Y., Yoshimatsu Yasutomi, S., Miyazaki, T., Monteiro, F.J., 2017. Enhanced biosafety of silica coated gadolinium based nanoparticles. J. Mater. Sci. Mater. Med. 28. doi:10.1007/s10856-017-5855-1

Laterza, O.F., Scott, M.G., Garrett-Engele, P.W., Korenblat, K.M., Lockwood, C.M., 2013. Circulating miR-122 as a potential biomarker of liver disease. Biomark. Med. 7, 205–210. doi:10.2217/bmm.12.107

Lee, D., Hong, J.W., Park, C., Lee, H., Lee, J.E., Hyeon, T., Paik, S.R., 2014. Ca2+-Dependent Intracellular Drug Delivery System Developed with "Raspberry-Type" Particles-on-a-Particle Comprising Mesoporous Silica Core and α-Synuclein-Coated Gold Nanoparticles. ACS Nano 8, 8887–8895. doi:10.1021/nn5034955

Lee, G.H., Lee, S.J., Jeong, S.W., Kim, H.-C., Park, G.Y., Lee, S.G., Choi, J.H., 2016. Antioxidative and antiinflammatory activities of quercetin-loaded silica nanoparticles. Colloids Surf. B Biointerfaces 143, 511–517. doi:10.1016/j.colsurfb.2016.03.060

Lee, J.-A., Kim, M.-K., Song, J.H., Jo, M.-R., Yu, J., Kim, K.-M., Kim, Y.-R., Oh, J.-M., Choi, S.-J., 2017. Biokinetics of food additive silica nanoparticles and their interactions with food components. Colloids Surf. B Biointerfaces 150, 384–392. doi:10.1016/j.colsurfb.2016.11.001

Leelahavanichkul, A., Somparn, P., Panich, T., Chancharoenthana, W., Wongphom, J., Pisitkun, T., Hirankarn, N., Eiam-Ong, S., 2015. Serum miRNA-122 in acute liver injury induced by kidney injury and sepsis in CD-1 mouse models: miRNA-122 in ALF induced by AKI. Hepatol. Res. 45, 1341–1352. doi:10.1111/hepr.12501

Lee, W.-M., Paik, J.-S., Cho, W.-K., Oh, E.-H., Lee, S.-B., Yang, S.-W., 2013. Rapamycin Enhances TNF-α-Induced Secretion of IL-6 and IL-8 through Suppressing PDCD4 Degradation in Orbital Fibroblasts. Curr. Eye Res. 38, 699–706. doi:10.3109/02713683.2012.750368

Levy, D., Zayat, M. (Eds.), 2015. The Sol-Gel handbook: synthesis, characterization, and applications. Wiley-VCH, Weinheim.

Li, A., Zhang, J., Xu, Y., Liu, J., Feng, S., 2014. Thermoresponsive Copolymer/SiO2 Nanoparticles with Dual Functions of Thermally Controlled Drug Release and Simultaneous Carrier Decomposition. Chem. – Eur. J. 20, 12945–12953. doi:10.1002/chem.201402836

Li, C., Zhang, Y., Su, T., Feng, L., Long, Y., Chen, Z., 2012. Silica-coated flexible liposomes as a nanohybrid delivery system for enhanced oral bioavailability of curcumin. Int. J. Nanomedicine 7, 5995–6002. doi:10.2147/IJN.S38043

Li, H., Zhang, J.Z., Tang, Q., Du, M., Hu, J., Yang, D., 2013. Reduction-responsive drug delivery based on mesoporous silica nanoparticle core with crosslinked poly(acrylic acid) shell. Mater. Sci. Eng. C 33, 3426–3431. doi:10.1016/j.msec.2013.04.033

Li, L.-L., Xie, M., Wang, J., Li, X., Wang, C., Yuan, Q., Pang, D.-W., Lu, Y., Tan, W., 2013. A vitamin-responsive mesoporous nanocarrier with DNA aptamer-mediated cell targeting. Chem. Commun. 49, 5823–5825. doi:10.1039/C3CC41072B

Lima, A.C., Mano, J.F., 2015. Micro-/nano-structured superhydrophobic surfaces in the biomedical field: part I: basic concepts and biomimetic approaches. Nanomed. 10, 103–119. doi:10.2217/nnm.14.174

Lim, W.Q., Phua, S.Z.F., Xu, H.V., Sreejith, S., Zhao, Y., 2016. Recent advances in multifunctional silica-based hybrid nanocarriers for bioimaging and cancer therapy. Nanoscale 8, 12510–12519. doi:10.1039/C5NR07853A

Lin, C.-H., Cheng, S.-H., Liao, W.-N., Wei, P.-R., Sung, P.-J., Weng, C.-F., Lee, C.-H., 2012. Mesoporous silica nanoparticles for the improved anticancer efficacy of cis-platin. Int. J. Pharm. 429, 138–147. doi:10.1016/j.ijpharm.2012.03.026

Li, Q.-L., Sun, Y., Sun, Y.-L., Wen, J., Zhou, Y., Bing, Q.-M., Isaacs, L.D., Jin, Y., Gao, H., Yang, Y.-W., 2014. Mesoporous Silica Nanoparticles Coated by Layer-by-Layer Self-assembly Using Cucurbit[7]uril for in Vitro and in Vivo Anticancer Drug Release. Chem. Mater. 26, 6418–6431. doi:10.1021/cm503304p

Li, Q.-L., Xu, S.-H., Zhou, H., Wang, X., Dong, B., Gao, H., Tang, J., Yang, Y.-W., 2015. pH and Glutathione Dual-Responsive Dynamic Cross-Linked Supramolecular Network on Mesoporous Silica Nanoparticles for Controlled Anticancer Drug Release. ACS Appl. Mater. Interfaces 7, 28656–28664. doi:10.1021/acsami.5b10534

Li, T., Shen, X., Geng, Y., Chen, Z., Li, L., Li, S., Yang, H., Wu, C., Zeng, H., Liu, Y., 2016. Folate-Functionalized Magnetic-Mesoporous Silica Nanoparticles for Drug/Gene Codelivery To Potentiate the Antitumor Efficacy. ACS Appl. Mater. Interfaces 8, 13748–13758. doi:10.1021/acsami.6b02963

Liu, B., Li, C., Ma, P. ’an, Chen, Y., Zhang, Y., Hou, Z., Huang, S., Lin, J., 2015. Multifunctional NaYF4:Yb, Er@mSiO2@Fe3O4-PEG nanoparticles for UCL/MR bioimaging and magnetically targeted drug delivery. Nanoscale 7, 1839–1848. doi:10.1039/C4NR05342G

Liu, X., Ding, Y., Zhao, B., Liu, Y., Luo, S., Wu, J., Li, J., Xiang, D., 2016. In vitro and in vivo evaluation of puerarin-loaded PEGylated mesoporous silica nanoparticles. Drug Dev. Ind. Pharm. 42, 2031–2037. doi:10.1080/03639045.2016.1190742

Liu, X., Wang, Q., Li, C., Zou, R., Li, B., Song, G., Xu, K., Zheng, Y., Hu, J., 2014. Cu2-xSe@mSiO2-PEG core-shell nanoparticles: a low-toxic and efficient difunctional nanoplatform for chemo-photothermal therapy under near infrared light radiation with a safe power density. Nanoscale 6, 4361–4370. doi:10.1039/C3NR06160D

Liu, Y., Bai, J., Jia, X., Jiang, X., Guo, Z., 2015. Fabrication of Multifunctional SiO2@GN-Serum Composites for Chemo-Photothermal Synergistic Therapy. ACS Appl. Mater. Interfaces 7, 112–121. doi:10.1021/am507658v

Liu, Y., Sun, L., Liu, J., Peng, Y.-X., Ge, X., Shi, L., Huang, W., 2015. Multicolor (Vis-NIR) mesoporous silica nanospheres linked with lanthanide complexes using 2-(5-bromothiophen)imidazo[4,5-f][1,10]phenanthroline for in vitro bioimaging. Dalton Trans. 44, 237–246. doi:10.1039/C4DT02444C

Lokeshwar, V.B., Mirza, S., Jordan, A., 2014. Targeting Hyaluronic Acid Family for Cancer Chemoprevention and Therapy. Adv. Cancer Res. 123, 35–65. doi:10.1016/B978-0-12-800092-2.00002-2

Lucia Foglia, M., Solange Alvarez, G., Nicolas Catalano, P., Mathilde Mebert, A., Eduardo Diaz, L., Coradin, T., Federico Desimone, M., 2011. Recent Patents on the Synthesis and Application of Silica Nanoparticles for Drug Delivery. Recent Pat. Biotechnol. 5, 54–61. doi:10.2174/187220811795655887

Lungare, S., Hallam, K., Badhan, R.K.S., 2016. Phytochemical-loaded mesoporous silica nanoparticles for nose-to-brain olfactory drug delivery. Int. J. Pharm. 513, 280–293. doi:10.1016/j.ijpharm.2016.09.042

Luo, Z., Hu, Y., Cai, K., Ding, X., Zhang, Q., Li, M., Ma, X., Zhang, B., Zeng, Y., Li, P., Li, J., Liu, J., Zhao, Y., 2014. Intracellular redox-activated anticancer drug delivery by functionalized hollow mesoporous silica nanoreservoirs with tumor specificity. Biomaterials 35, 7951–7962. doi:10.1016/j.biomaterials.2014.05.058

Lv, R., Yang, P., He, F., Gai, S., Li, C., Dai, Y., Yang, G., Lin, J., 2015. A Yolk-like Multifunctional Platform for Multimodal Imaging and Synergistic Therapy Triggered by a Single Near-Infrared Light. ACS Nano 9, 1630–1647. doi:10.1021/nn5063613

Lv, X., Zhao, M., Wang, Y., Hu, X., Wu, J., Jiang, X., Li, S., Cui, C., Peng, S., 2016. Loading cisplatin onto 6-mercaptopurine covalently modified MSNS: a nanomedicine strategy to improve the outcome of cisplatin therapy. Drug Des. Devel. Ther. Volume 10, 3933–3946. doi:10.2147/DDDT.S116286

Maggini, L., Cabrera, I., Ruiz-Carretero, A., Prasetyanto, E.A., Robinet, E., De Cola, L., 2016. Breakable mesoporous silica nanoparticles for targeted drug delivery. Nanoscale 8, 7240–7247. doi:10.1039/C5NR09112H

Mamaeva, V., Sahlgren, C., Lindén, M., 2013. Mesoporous silica nanoparticles in medicine—Recent advances. Adv. Drug Deliv. Rev. 65, 689–702. doi:10.1016/j.addr.2012.07.018

Ma'mani, L., Nikzad, S., Kheiri-manjili, H., al-Musawi, S., Saeedi, M., Askarlou, S., Foroumadi, A., Shafiee, A., 2014. Curcumin-loaded guanidine functionalized PEGylated I3ad mesoporous silica nanoparticles KIT-6: Practical strategy for the breast cancer therapy. Eur. J. Med. Chem. 83, 646–654. doi:10.1016/j.ejmech.2014.06.069

Ma, M., Huang, Y., Chen, H., Jia, X., Wang, S., Wang, Z., Shi, J., 2015. Bi2S3-embedded mesoporous silica nanoparticles for efficient drug delivery and interstitial radiotherapy sensitization. Biomaterials 37, 447–455. doi:10.1016/j.biomaterials.2014.10.001

Martínez-Carmona, M., Colilla, M., Vallet-Regí, M., 2015. Smart Mesoporous Nanomaterials for Antitumor Therapy. Nanomaterials 5, 1906–1937. doi:10.3390/nano5041906

Ma, X., Zhao, Y., Ng, K.W., Zhao, Y., 2013. Integrated Hollow Mesoporous Silica Nanoparticles for Target Drug/siRNA Co-Delivery. Chem. – Eur. J. 19, 15593–15603. doi:10.1002/chem.201302736

Mebert, A.M., Aime, C., Alvarez, G.S., Shi, Y., Flor, S.A., Lucangioli, S.E., Desimone, M.F., Coradin, T., 2016. Silica core-shell particles for the dual delivery of gentamicin and rifamycin antibiotics. J. Mater. Chem. B 4, 3135–3144. doi:10.1039/C6TB00281A

Mebert, A.M., Camporotondi, D.E., Foglia, M.L., Alvarez, G.S., Orihuela, P.L.S., Diaz, L.E., Desimone, M.F., 2013. Controlling the interaction between cells and silica nanoparticles. J. Biomater. Tissue Eng. 3, 108–121. doi:10.1166/jbt.2013.1069

Mekaru, H., Lu, J., Tamanoi, F., 2015. Development of mesoporous silica-based nanoparticles with controlled release capability for cancer therapy. Multifunct. Nanodevices Nanobots Bioimaging Cancer Diagn. Stem Cell Ther. Regen. Med. 95, 40–49. doi:10.1016/j.addr.2015.09.009

Meng, H., Mai, W.X., Zhang, H., Xue, M., Xia, T., Lin, S., Wang, X., Zhao, Y., Ji, Z., Zink, J.I., Nel, A.E., 2013. Codelivery of an Optimal Drug/siRNA Combination Using Mesoporous Silica Nanoparticles To Overcome Drug Resistance in Breast Cancer in Vitro and in Vivo. ACS Nano 7, 994–1005. doi:10.1021/nn3044066

Meng, H., Wang, M., Liu, H., Liu, X., Situ, A., Wu, B., Ji, Z., Chang, C.H., Nel, A.E., 2015. Use of a Lipid-Coated Mesoporous Silica Nanoparticle Platform for Synergistic Gemcitabine and Paclitaxel Delivery to Human Pancreatic Cancer in Mice. ACS Nano 9, 3540–3557. doi:10.1021/acsnano.5b00510

Merget, R., Bauer, T., Küpper, H., Philippou, S., Bauer, H., Breitstadt, R., Bruening, T., 2002. Health hazards due to the inhalation of amorphous silica. Arch. Toxicol. 75, 625–634. doi:10.1007/s002040100266

Mitra, S., Patra, P., Pradhan, S., Debnath, N., Dey, K.K., Sarkar, S., Chattopadhyay, D., Goswami, A., 2015. Microwave synthesis of ZnO@mSiO2 for detailed antifungal mode of action study: Understanding the insights into oxidative stress. J. Colloid Interface Sci. 444, 97–108. doi:10.1016/j.jcis.2014.12.041

Mody, K.T., Popat, A., Mahony, D., Cavallaro, A.S., Yu, C., Mitter, N., 2013. Mesoporous silica nanoparticles as antigen carriers and adjuvants for vaccine delivery. Nanoscale 5, 5167–5179. doi:10.1039/C3NR00357D

Mohammad Yahya Hanafi-Bojd, Mahmoud Reza Jaafari, Navid Ramezanian, Khalil Abnous and Bizhan Malaekeh-Nikouei, 2016. Co-delivery of Epirubicin and siRNA Using Functionalized Mesoporous Silica Nanoparticles Enhances In vitro and In vivo Drug Efficacy. Curr. Drug Deliv. 13, 1–7. doi:10.2174/1567201813666151231094056

Muhammad, F., Guo, M., Wang, A., Zhao, J., Qi, W., Guo, Y., Zhu, G., 2014. Responsive delivery of drug cocktail via mesoporous silica nanolamps. J. Colloid Interface Sci. 434, 1–8. doi:10.1016/j.jcis.2014.07.024

Muñoz-Gámez, J.A., López Viota, J., Barrientos, A., Carazo, Á., Sanjuán-Nuñez, L., Quiles-Perez, R., Muñoz-de-Rueda, P., Delgado, Á., Ruiz-Extremera, Á., Salmerón, J., 2015. Synergistic cytotoxicity of the poly (ADP-ribose) polymerase inhibitor ABT-888 and temozolomide in dual-drug targeted magnetic nanoparticles. Liver Int. 35, 1430–1441. doi:10.1111/liv.12586

Murugan, C., Rayappan, K., Thangam, R., Bhanumathi, R., Shanthi, K., Vivek, R., Thirumurugan, R., Bhattacharyya, A., Sivasubramanian, S., Gunasekaran, P., Kannan, S., 2016. Combinatorial nanocarrier based drug delivery approach for amalgamation of anti-tumor agents in bresat cancer cells: an improved nanomedicine strategies. Sci. Rep. 6, 34053.

Nafisi, S., Schäfer-Korting, M., Maibach, H.I., 2015. Perspectives on percutaneous penetration: Silica nanoparticles. Nanotoxicology 9, 643–657. doi:10.3109/17435390.2014.958115

Nagano, T., Higashisaka, K., Kunieda, A., Iwahara, Y., Tanaka, K., Nagano, K., Abe, Y., Kamada, H., Tsunoda, S., Nabeshi, H., Yoshikawa, T., Yoshioka, Y., Tsutsumi, Y., 2013. Liver-specific microRNAs as biomarkers of nanomaterial-induced liver damage. Nanotechnology 24, 405102. doi:10.1088/0957-4484/24/40/405102

Nagesetti, A., McGoron, A.J., 2016. Multifunctional organically modified silica nanoparticles for chemotherapy, adjuvant hyperthermia and near infrared imaging. Colloids Surf. B Biointerfaces 147, 492–500. doi:10.1016/j.colsurfb.2016.07.048

Nday, C.M., Halevas, E., Jackson, G.E., Salifoglou, A., 2015. Quercetin encapsulation in modified silica nanoparticles: potential use against Cu(II)-induced oxidative stress in neurodegeneration. J. Inorg. Biochem. 145, 51–64. doi:10.1016/j.jinorgbio.2015.01.001

Nilsen-Nygaard, J., Strand, P.S., Vårum, M.K., Draget, I.K., Nordgård, T.C., 2015. Chitosan: Gels and Interfacial Properties. Polymers 7. doi:10.3390/polym7030552

Oberdörster, G., Oberdörster, E., Oberdörster, J., 2005. Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles. Environ. Health Perspect. 113, 823–839. doi:10.1289/ehp.7339

Oberdörster, G., Stone, V., Donaldson, K., 2007. Toxicology of nanoparticles: A historical perspective. Nanotoxicology 1, 2–25. doi:10.1080/17435390701314761

Pan, L., He, Q., Liu, J., Chen, Y., Ma, M., Zhang, L., Shi, J., 2012. Nuclear-Targeted Drug Delivery of TAT Peptide-Conjugated Monodisperse Mesoporous Silica Nanoparticles. J. Am. Chem. Soc. 134, 5722–5725. doi:10.1021/ja211035w

Pan, L., Liu, J., He, Q., Wang, L., Shi, J., 2013. Overcoming multidrug resistance of cancer cells by direct intranuclear drug delivery using TAT-conjugated mesoporous silica nanoparticles. Biomaterials 34, 2719–2730. doi:10.1016/j.biomaterials.2012.12.040

Paris, J.L., Cabañas, M.V., Manzano, M., Vallet-Regí, M., 2015. Polymer-Grafted Mesoporous Silica Nanoparticles as Ultrasound-Responsive Drug Carriers. ACS Nano 9, 11023–11033. doi:10.1021/acsnano.5b04378

Pina, S., Oliveira, J.M., Reis, R.L., 2015. Natural-Based Nanocomposites for Bone Tissue Engineering and Regenerative Medicine: A Review. Adv. Mater. 27, 1143–1169. doi:10.1002/adma.201403354

Priebe, M., Widmer, J., Löwa, N.S., Abram, S.-L., Mottas, I., Woischnig, A.-K., Brunetto, P.S., Khanna, N., Bourquin, C., Fromm, K.M., 2016. Antimicrobial silver-filled silica nanorattles with low immunotoxicity in dendritic cells. Nanomedicine Nanotechnol. Biol. Med. doi:10.1016/j.nano.2016.08.002

Prodi, L., Biffi, S., Petrizza, L., Garrovo, C., Rampazzo, E., Andolfi, L., Giustetto, P., Nikolov, I., Kurdi, G., Danailov, M., Zauli, G., Secchiero, P., 2016. Multimodal near-infrared-emitting PluS Silica nanoparticles with fluorescent, photoacoustic, and photothermal capabilities. Int. J. Nanomedicine Volume 11, 4865–4874. doi:10.2147/IJN.S107479

Purbia, R., Paria, S., 2015. Yolk/shell nanoparticles: classifications, synthesis, properties, and applications. Nanoscale 7, 19789–19873. doi:10.1039/C5NR04729C

Qu, Q., Ma, X., Zhao, Y., 2015. Targeted delivery of doxorubicin to mitochondria using mesoporous silica nanoparticle nanocarriers. Nanoscale 7, 16677–16686. doi:10.1039/C5NR05139H

Ravera, M., Gabano, E., Zanellato, I., Perin, E., Arrais, A., Osella, D., 2016. Functionalized nonporous silica nanoparticles as carriers for Pt(iv) anticancer prodrugs. Dalton Trans. doi:10.1039/C6DT03133A

Reamonbuettner, S., Mutschler, V., Borlak, J., 2008. The next innovation cycle in toxicogenomics: Environmental epigenetics. Mutat. Res. Mutat. Res. 659, 158–165. doi:10.1016/j.mrrev.2008.01.003

Roderburg, C., Benz, F., Vargas Cardenas, D., Koch, A., Janssen, J., Vucur, M., Gautheron, J., Schneider, A.T., Koppe, C., Kreggenwinkel, K., Zimmermann, H.W., Luedde, M., Trautwein, C., Tacke, F., Luedde, T., 2015. Elevated miR-122 serum levels are an independent marker of liver injury in inflammatory diseases. Liver Int. 35, 1172–1184. doi:10.1111/liv.12627

Ryu, H.J., Seong, N., So, B.J., Seo, H., Kim, J., Hong, J.-S., Park, M., Kim, M.-S., Kim, Y.-R., Cho, K.-B., Seo, M.Y., Kim, M.-K., Maeng, E.H., Son, S.W., 2014. Evaluation of silica nanoparticle toxicity after topical exposure for 90 days. Int. J. Nanomedicine 9, 127–136. doi:10.2147/IJN.S57929

Sahu, S., Mohapatra, S., 2013. Multifunctional magnetic fluorescent hybrid nanoparticles as carriers for the hydrophobic anticancer drug 5-fluorouracil. Dalton Trans. 42, 2224–2231. doi:10.1039/C2DT31812A

Santo-Orihuela, P., Foglia, M., Targovnik, A., Miranda, M., Desimone, M., 2016. Nanotoxicological Effects of SiO_2 Nanoparticles on Spodoptera frugiperda Sf9 Cells. Curr. Pharm. Biotechnol. 17, 465–470. doi:10.2174/1389201017051603031656O4

Sapino, S., Ugazio, E., Gastaldi, L., Miletto, I., Berlier, G., Zonari, D., Oliaro-Bosso, S., 2015. Mesoporous silica as topical nanocarriers for quercetin: characterization and in vitro studies. Eur. J. Pharm. Biopharm. 89, 116–125. doi:10.1016/j.ejpb.2014.11.022

Sarkar, A., Ghosh, S., Chowdhury, S., Pandey, B., Sil, P.C., 2016. Targeted delivery of quercetin loaded mesoporous silica nanoparticles to the breast cancer cells. Biochim. Biophys. Acta BBA - Gen. Subj. 1860, 2065–2075. doi:10.1016/j.bbagen.2016.07.001

SCCS, Hoet, P.H.M., 2016. Opinion of the Scientific Committee on Consumer Safety (SCCS) – Revision of the opinion on the safety of the use of Silica, Hydrated Silica, and Silica Surface Modified with

Alkyl Silylates (nano form) in cosmetic products. Regul. Toxicol. Pharmacol. 74, 79–80. doi:10.1016/j.yrtph.2015.11.005

Schick, I., Lorenz, S., Gehrig, D., Tenzer, S., Storck, W., Fischer, K., Strand, D., Laquai, F., Tremel, W., 2014. Inorganic Janus particles for biomedical applications. Beilstein J. Nanotechnol. 5, 2346–2362. doi:10.3762/bjnano.5.244

Schulz, A., McDonagh, C., 2012. Intracellular sensing and cell diagnostics using fluorescent silica nanoparticles. Soft Matter 8, 2579–2585. doi:10.1039/C2SM06862A

Sepeur, S., 2008. Nanotechnology: Technical Basics and Applications, American coatings literature. Vincentz Network.

Shahabi, S., Treccani, L., Dringen, R., Rezwan, K., 2015. Utilizing the protein corona around silica nanoparticles for dual drug loading and release. Nanoscale 7, 16251–16265. doi:10.1039/C5NR04726A

She, X., Chen, L., Velleman, L., Li, C., Zhu, H., He, C., Wang, T., Shigdar, S., Duan, W., Kong, L., 2015. Fabrication of high specificity hollow mesoporous silica nanoparticles assisted by Eudragit for targeted drug delivery. J. Colloid Interface Sci. 445, 151–160. doi:10.1016/j.jcis.2014.12.053

Singh, L.P., Bhattacharyya, S.K., Kumar, R., Mishra, G., Sharma, U., Singh, G., Ahalawat, S., 2014. Sol-Gel processing of silica nanoparticles and their applications. Adv. Colloid Interface Sci. 214, 17–37. doi:10.1016/j.cis.2014.10.007

Singh, S.P., Sharma, M., Gupta, P.K., 2015. Cytotoxicity of curcumin silica nanoparticle complexes conjugated with hyaluronic acid on colon cancer cells. Int. J. Biol. Macromol. 74, 162–170. doi:10.1016/j.ijbiomac.2014.11.037

Singh, S.P., Sharma, M., Gupta, P.K., 2014. Enhancement of phototoxicity of curcumin in human oral cancer cells using silica nanoparticles as delivery vehicle. Lasers Med. Sci. 29, 645–652. doi:10.1007/s10103-013-1357-7

Sinha, A., Chakraborty, A., Jana, N.R., 2014. Dextran-Gated, Multifunctional Mesoporous Nanoparticle for Glucose-Responsive and Targeted Drug Delivery. ACS Appl. Mater. Interfaces 6, 22183–22191. doi:10.1021/am505848p

Smulders, S., Ketkar-Atre, A., Luyts, K., Vriens, H., De Sousa Nobre, S., Rivard, C., Van Landuyt, K., Baken, S., Smolders, E., Golanski, L., Ghosh, M., Vanoirbeek, J., Himmelreich, U., Hoet, P.H., 2016. Body distribution of SiO2–Fe3O4 core-shell nanoparticles after intravenous injection and intratracheal instillation. Nanotoxicology 10, 567–574. doi:10.3109/17435390.2015.1100761

Song, F., Li, X., Wang, Q., Liao, L., Zhang, C., 2015. Nanocomposite Hydrogels and Their Applications in Drug Delivery and Tissue Engineering. J. Biomed. Nanotechnol. 11, 40–52. doi:10.1166/jbn.2015.1962

Song, N., Zhao, M., Wang, Y., Hu, X., Wu, J., Jiang, X., Li, S., Cui, C., Peng, S., 2016. Nanomedical strategy to prolong survival period, heighten cure rate, and lower systemic toxicity of S180 mice treated with MTX/MIT. Drug Des. Devel. Ther. 10, 2701–2711. doi:10.2147/DDDT.S113804

Song, W., Di, W., Qin, W., 2016. Synthesis of mesoporous-silica-coated Gd2O3:Eu@silica particles as cell imaging and drug delivery agents. Dalton Trans. 45, 7443–7449. doi:10.1039/C5DT04908C

Starsich, F.H.L., Sotiriou, G.A., Wurnig, M.C., Eberhardt, C., Hirt, A.M., Boss, A., Pratsinis, S.E., 2016. Silica-Coated Nonstoichiometric Nano Zn-Ferrites for Magnetic Resonance Imaging and Hyperthermia Treatment. Adv. Healthc. Mater. n/a–n/a. doi:10.1002/adhm.201600725

Stöber, W., Fink, A., Bohn, E., 1968. Controlled growth of monodisperse silica spheres in the micron size range. J. Colloid Interface Sci. 26, 62–69. doi:10.1016/0021-9797(68)90272-5

Stoccoro, A., Karlsson, H.L., Coppedè, F., Migliore, L., 2013. Epigenetic effects of nano-sized materials. Toxicology 313, 3–14. doi:10.1016/j.tox.2012.12.002

Summerlin, N., Qu, Z., Pujara, N., Sheng, Y., Jambhrunkar, S., McGuckin, M., Popat, A., 2016. Colloidal mesoporous silica nanoparticles enhance the biological activity of resveratrol. Colloids Surf. B Biointerfaces 144, 1–7. doi:10.1016/j.colsurfb.2016.03.076

Sun, W., Han, Y., Li, Z., Ge, K., Zhang, J., 2016. Bone-Targeted Mesoporous Silica Nanocarrier Anchored by Zoledronate for Cancer Bone Metastasis. Langmuir 32, 9237–9244. doi:10.1021/acs.langmuir.6b02228

Tadayon, A., Jamshidi, R., Esmaeili, A., 2015. Delivery of tissue plasminogen activator and streptokinase magnetic nanoparticles to target vascular diseases. Int. J. Pharm. 495, 428–438. doi:10.1016/j.ijpharm.2015.09.008

Tamanna, T., Bulitta, J.B., Yu, A., 2015. Controlling antibiotic release from mesoporous silica nano drug carriers via self-assembled polyelectrolyte coating. J. Mater. Sci. Mater. Med. 26, 117. doi:10.1007/s10856-015-5444-0

Tang, H., Guo, J., Sun, Y., Chang, B., Ren, Q., Yang, W., 2011. Facile synthesis of pH sensitive polymer-coated mesoporous silica nanoparticles and their application in drug delivery. Int. J. Pharm. 421, 388–396. doi:10.1016/j.ijpharm.2011.10.013

Tan, S.Y., Ang, C.Y., Li, P., Yap, Q.M., Zhao, Y., 2014. Drug Encapsulation and Release by Mesoporous Silica Nanoparticles: The Effect of Surface Functional Groups. Chem. – Eur. J. 20, 11276–11282. doi:10.1002/chem.201403551

Tan, T.T.Y., Liu, S., Zhang, Y., Han, M.-Y., Selvan, S.T., 2011. 5.14 - Microemulsion Preparative Methods (Overview) A2 - Andrews, David L., in: Scholes, G.D., Wiederrecht, G.P. (Eds.), Comprehensive Nanoscience and Technology. Academic Press, Amsterdam, pp. 399–441.

Tao, C., Zhu, Y., 2014. Magnetic mesoporous silica nanoparticles for potential delivery of chemotherapeutic drugs and hyperthermia. Dalton Trans. 43, 15482–15490. doi:10.1039/C4DT01984A

Tao, L., Song, C., Huo, C., Sun, Y., Zhang, C., Li, X., Yu, S., Sun, M., Jin, B., Zhang, Z., Yang, K., 2016. Anti-CD155 and anti-CD112 monoclonal antibodies conjugated to a fluorescent mesoporous silica nanosensor encapsulating rhodamine 6G and fluorescein for sensitive detection of liver cancer cells. Analyst 141, 4933–4940. doi:10.1039/C5AN01908G

Tian, F., Chen, G., Yi, P., Zhang, J., Li, A., Zhang, J., Zheng, L., Deng, Z., Shi, Q., Peng, R., Wang, Q., 2014. Fates of Fe3O4 and Fe3O4@SiO2 nanoparticles in human mesenchymal stem cells assessed by synchrotron radiation-based techniques. Biomaterials 35, 6412–6421. doi:10.1016/j.biomaterials.2014.04.052

Toda, T., Yoshino, S., 2016. Amorphous nanosilica particles block induction of oral tolerance in mice. J. Immunotoxicol. 13, 723–728. doi:10.3109/1547691X.2016.1171266

Tolbert, S.H., McFadden, P.D., Loy, D.A., 2016. New Hybrid Organic/Inorganic Polysilsesquioxane–Silica Particles as Sunscreens. ACS Appl. Mater. Interfaces 8, 3160–3174. doi:10.1021/acsami.5b10472

Tseng, Y.-J., Chou, S.-W., Shyue, J.-J., Lin, S.-Y., Hsiao, J.-K., Chou, P.-T., 2016. A Versatile Theranostic Delivery Platform Integrating Magnetic Resonance Imaging/Computed Tomography, pH/cis-Diol Controlled Release, and Targeted Therapy. ACS Nano 10, 5809–5822. doi:10.1021/acsnano.5b08130

Tukappa, A., Ultimo, A., de la Torre, C., Pardo, T., Sancenón, F., Martínez-Máñez, R., 2016. Polyglutamic Acid-Gated Mesoporous Silica Nanoparticles for Enzyme-Controlled Drug Delivery. Langmuir 32, 8507–8515. doi:10.1021/acs.langmuir.6b01715

Ugazio, E., Gastaldi, L., Brunella, V., Scalarone, D., Jadhav, S.A., Oliaro-Bosso, S., Zonari, D., Berlier, G., Miletto, I., Sapino, S., 2016. Thermoresponsive mesoporous silica nanoparticles as a carrier for skin delivery of quercetin. Int. J. Pharm. 511, 446–454. doi:10.1016/j.ijpharm.2016.07.024

van der Zande, M., Vandebriel, R.J., Groot, M.J., Kramer, E., Herrera Rivera, Z.E., Rasmussen, K., Ossenkoppele, J.S., Tromp, P., Gremmer, E.R., Peters, R.J., Hendriksen, P.J., Marvin, H.J., Hoogenboom, R.L., Peijnenburg, A.A., Bouwmeester, H., 2014. Sub-chronic toxicity study in rats orally exposed to nanostructured silica. Part. Fibre Toxicol. 11, 8. doi:10.1186/1743-8977-11-8

van Rijt, S.H., Bölükbas, D.A., Argyo, C., Datz, S., Lindner, M., Eickelberg, O., Königshoff, M., Bein, T., Meiners, S., 2015. Protease-Mediated Release of Chemotherapeutics from Mesoporous Silica

Nanoparticles to ex Vivo Human and Mouse Lung Tumors. ACS Nano 9, 2377–2389. doi:10.1021/nn5070343

Veeranarayanan, S., Poulose, A.C., Mohamed, M.S., Nagaoka, Y., Iwai, S., Nakagame, Y., Kashiwada, S., Yoshida, Y., Maekawa, T., Kumar, D.S., 2012. Synthesis and application of luminescent single CdS quantum dot encapsulated silica nanoparticles directed for precision optical bioimaging. Int. J. Nanomedicine 7, 3769–3786. doi:10.2147/IJN.S31310

Velikova, N., Mas, N., Miguel-Romero, L., Aguado, L.P., Stolte, E., Zaccaria, E., Cao, R., Taverne, N., Murguía, J.R., Martinez-Manez, R., Marina, A., Wells, J., 2016. Broadening the antibacterial spectrum of histidine kinase autophosphorylation inhibitors via the use of ε-poly-L-lysine capped mesoporous silica-based nanoparticles. Nanomedicine Nanotechnol. Biol. Med. doi:10.1016/j.nano.2016.09.011

Vogt, A., Combadiere, B., Hadam, S., Stieler, K.M., Lademann, J., Schaefer, H., Autran, B., Sterry, W., Blume-Peytavi, U., 2006. 40 nm, but not 750 or 1,500 nm, Nanoparticles Enter Epidermal CD1a+ Cells after Transcutaneous Application on Human Skin. J. Invest. Dermatol. 126, 1316–1322. doi:10.1038/sj.jid.5700226

Wang, D., Xu, Z., Chen, Z., Liu, X., Hou, C., Zhang, X., Zhang, H., 2014. Fabrication of Single-Hole Glutathione-Responsive Degradable Hollow Silica Nanoparticles for Drug Delivery. ACS Appl. Mater. Interfaces 6, 12600–12608. doi:10.1021/am502585x

Wang, H., Agarwal, P., Zhao, S., Yu, J., Lu, X., He, X., 2016. Combined cancer therapy with hyaluronan-decorated fullerene-silica multifunctional nanoparticles to target cancer stem-like cells. Biomaterials 97, 62–73. doi:10.1016/j.biomaterials.2016.04.030

Wang, H., Zhang, S., Tian, X., Liu, C., Zhang, L., Hu, W., Shao, Y., Li, L., 2016. High sensitivity of gold nanoparticles co-doped with Gd2O3 mesoporous silica nanocomposite to nasopharyngeal carcinoma cells. Sci. Rep. 6, 34367.

Wang, J., Sugawara-Narutaki, A., Fukao, M., Yokoi, T., Shimojima, A., Okubo, T., 2011. Two-Phase Synthesis of Monodisperse Silica Nanospheres with Amines or Ammonia Catalyst and Their Controlled Self-Assembly. ACS Appl. Mater. Interfaces 3, 1538–1544. doi:10.1021/am200104m

Wang, J., Wang, Y., Liu, Q., Yang, L., Zhu, R., Yu, C., Wang, S., 2016. Rational Design of Multifunctional Dendritic Mesoporous Silica Nanoparticles to Load Curcumin and Enhance Efficacy for Breast Cancer Therapy. ACS Appl. Mater. Interfaces 8, 26511–26523. doi:10.1021/acsami.6b08400

Wang, K., Yao, H., Meng, Y., Wang, Y., Yan, X., Huang, R., 2015. Specific aptamer-conjugated mesoporous silica–carbon nanoparticles for HER2-targeted chemo-photothermal combined therapy. Acta Biomater. 16, 196–205. doi:10.1016/j.actbio.2015.01.002

Wang, Y., Sun, Y., Wang, J., Yang, Y., Li, Y., Yuan, Y., Liu, C., 2016. Charge-Reversal APTES-Modified Mesoporous Silica Nanoparticles with High Drug Loading and Release Controllability. ACS Appl. Mater. Interfaces 8, 17166–17175. doi:10.1021/acsami.6b05370

Wang, Y., Wang, K., Zhang, R., Liu, X., Yan, X., Wang, J., Wagner, E., Huang, R., 2014. Synthesis of Core–Shell Graphitic Carbon@Silica Nanospheres with Dual-Ordered Mesopores for Cancer-Targeted Photothermochemotherapy. ACS Nano 8, 7870–7879. doi:10.1021/nn5027214

Wang, Y., Yang, G., Wang, Y., Zhao, Y., Jiang, H., Han, Y., Yang, P., 2017. Multiple imaging and excellent anticancer efficiency of an upconverting nanocarrier mediated by single near infrared light. Nanoscale 9, 4759–4769. doi:10.1039/C6NR09030C

Wang, Y., Zhao, Q., Han, N., Bai, L., Li, J., Liu, J., Che, E., Hu, L., Zhang, Q., Jiang, T., Wang, S., 2015. Mesoporous silica nanoparticles in drug delivery and biomedical applications. Nanomedicine Nanotechnol. Biol. Med. 11, 313–327. doi:10.1016/j.nano.2014.09.014

Wang, Z., Tian, Y., Zhang, H., Qin, Y., Li, D., Gan, L., Wu, F., 2016. Using hyaluronic acid-functionalized pH stimuli-responsive mesoporous silica nanoparticles for targeted delivery to CD44-overexpressing cancer cells. Int. J. Nanomedicine Volume 11, 6485–6497. doi:10.2147/IJN.S117184

Wani, A., Muthuswamy, E., Savithra, G.H.L., Mao, G., Brock, S., Oupický, D., 2012. Surface Functionalization of Mesoporous Silica Nanoparticles Controls Loading and Release Behavior of Mitoxantrone. Pharm. Res. 29, 2407–2418. doi:10.1007/s11095-012-0766-9

Ward, E.P., Wang, J., Mendez, N., Yang, J., Barback, C., Wang-Rodriguez, J., Trogler, W., Kummel, A.C., Blair, S., 2016. Utilization of iron (III)-doped nanoshells for in vivo marking of nonpalpable tumors using a VX2 rabbit model. Am. J. Surg. 212, 1140–1146. doi:10.1016/j.amjsurg.2016.09.013

Wills, J.W., Hondow, N., Thomas, A.D., Chapman, K.E., Fish, D., Maffeis, T.G., Penny, M.W., Brown, R.A., Jenkins, G.J.S., Brown, A.P., White, P.A., Doak, S.H., 2016. Genetic toxicity assessment of engineered nanoparticles using a 3D in vitro skin model (EpiDerm^{TM}). Part. Fibre Toxicol. 13, 50. doi:10.1186/s12989-016-0161-5

Winkler, H.C., Suter, M., Naegeli, H., 2016. Critical review of the safety assessment of nano-structured silica additives in food. J. Nanobiotechnology 14, 44. doi:10.1186/s12951-016-0189-6

Wu, J., Jiang, W., Shen, Y., Jiang, W., Tian, R., 2017. Synthesis and characterization of mesoporous magnetic nanocomposites wrapped with chitosan gatekeepers for pH-sensitive controlled release of doxorubicin. Mater. Sci. Eng. C 70, Part 1, 132–140. doi:10.1016/j.msec.2016.08.054

Wu, S.-H., Mou, C.-Y., Lin, H.-P., 2013. Synthesis of mesoporous silica nanoparticles. Chem. Soc. Rev. 42, 3862–3875. doi:10.1039/C3CS35405A

Wu, X., 2012. Nanotechnology in Cosmetics: A Review. Cosmet. Toilet. 6, 266–272.

Wu, Y., Shi, M., Zhao, L., Feng, W., Li, F., Huang, C., 2014. Visible-light-excited and europium-emissive nanoparticles for highly-luminescent bioimaging in vivo. Biomaterials 35, 5830–5839. doi:10.1016/j.biomaterials.2014.03.080

Wu, Y., Xu, X., Tang, Q., Li, Y., 2012. A new type of silica-coated $Gd_2(CO_3)_3$:Tb nanoparticle as a bifunctional agent for magnetic resonance imaging and fluorescent imaging. Nanotechnology 23, 205103. doi:10.1088/0957-4484/23/20/205103

Xie, J., Lee, S., Chen, X., 2010. Nanoparticle-based theranostic agents. Dev. Theranostic Agents Co-Deliv. Ther. Imaging Agents 62, 1064–1079. doi:10.1016/j.addr.2010.07.009

Xie, M., Xu, Y., Shen, H., Shen, S., Ge, Y., Xie, J., 2014. Negative-charge-functionalized mesoporous silica nanoparticles as drug vehicles targeting hepatocellular carcinoma. Int. J. Pharm. 474, 223–231. doi:10.1016/j.ijpharm.2014.08.027

Xing, L., Zheng, H., Cao, Y., Che, S., 2012. Coordination Polymer Coated Mesoporous Silica Nanoparticles for pH-Responsive Drug Release. Adv. Mater. 24, 6433–6437. doi:10.1002/adma.201201742

Xiong, L., Du, X., Kleitz, F., Qiao, S.Z., 2015. Cancer-Cell-Specific Nuclear-Targeted Drug Delivery by Dual-Ligand-Modified Mesoporous Silica Nanoparticles. Small 11, 5919–5926. doi:10.1002/smll.201501056

Xu, B., Mao, Z., Ji, X., Yao, M., Chen, M., Zhang, X., Hang, B., Liu, Y., Tang, W., Tang, Q., Xia, Y., 2015. miR-98 and its host gene Huwe1 target Caspase-3 in Silica nanoparticles-treated male germ cells. Sci. Rep. 5. doi:10.1038/srep12938

Xu, Z., Liu, S., Kang, Y., Wang, M., 2015. Glutathione- and pH-responsive nonporous silica prodrug nanoparticles for controlled release and cancer therapy. Nanoscale 7, 5859–5868. doi:10.1039/C5NR00297D

Yamaguchi, H., Tsuchimochi, M., Hayama, K., Kawase, T., Tsubokawa, N., 2016. Dual-Labeled Near-Infrared/99mTc Imaging Probes Using PAMAM-Coated Silica Nanoparticles for the Imaging of HER2-Expressing Cancer Cells. Int. J. Mol. Sci. 17. doi:10.3390/ijms17071086

Yamauchi, H., Ishikawa, T., Kondo, S., 1989. Surface characterization of ultramicro spherical particles of silica prepared by w/o microemulsion method. Int. Symp. Adsorpt. 37, 71–80. doi:10.1016/0166-6622(89)80107-6

Yang, D., Wang, T., Su, Z., Xue, L., Mo, R., Zhang, C., 2016. Reversing Cancer Multidrug Resistance in Xenograft Models via Orchestrating Multiple Actions of Functional Mesoporous Silica Nanoparticles. ACS Appl. Mater. Interfaces 8, 22431–22441. doi:10.1021/acsami.6b04885

Yang, H., Chen, Y., Chen, Z., Geng, Y., Xie, X., Shen, X., Li, T., Li, S., Wu, C., Liu, Y., 2017a. Chemo-photodynamic combined gene therapy and dual-modal cancer imaging achieved by pH-responsive alginate/chitosan multilayer-modified magnetic mesoporous silica nanocomposites. Biomater Sci. doi:10.1039/C7BM00043J

Yang, H., Zhang, Y., Li, W., Lao, C., Li, M., Zheng, Y., 2017b. Altered microRNA expression profiles in lung damage induced by nanosized SiO_2. Bioengineered 8, 45–54. doi:10.1080/21655979.2016.1227578

Yang, X., Liu, J., He, H., Zhou, L., Gong, C., Wang, X., Yang, L., Yuan, J., Huang, H., He, L., Zhang, B., Zhuang, Z., 2010. SiO2 nanoparticles induce cytotoxicity and protein expression alteration in HaCaT cells. Part. Fibre Toxicol. 7, 1. doi:10.1186/1743-8977-7-1

Yang, Y., Yu, C., 2016. Advances in silica based nanoparticles for targeted cancer therapy. Nanomedicine Nanotechnol. Biol. Med. 12, 317–332. doi:10.1016/j.nano.2015.10.018

Yao, G., Wang, L., Wu, Y., Smith, J., Xu, J., Zhao, W., Lee, E., Tan, W., 2006. FloDots: luminescent nanoparticles. Anal. Bioanal. Chem. 385, 518–524. doi:10.1007/s00216-006-0452-z

Yao, X., Niu, X., Ma, K., Huang, P., Grothe, J., Kaskel, S., Zhu, Y., 2016. Graphene Quantum Dots-Capped Magnetic Mesoporous Silica Nanoparticles as a Multifunctional Platform for Controlled Drug Delivery, Magnetic Hyperthermia, and Photothermal Therapy. Small n/a–n/a. doi:10.1002/smll.201602225

Yoshida, T., Yoshioka, Y., Takahashi, H., Misato, K., Mori, T., Hirai, T., Nagano, K., Abe, Y., Mukai, Y., Kamada, H., Tsunoda, S., Nabeshi, H., Yoshikawa, T., Higashisaka, K., Tsutsumi, Y., 2014. Intestinal absorption and biological effects of orally administered amorphous silica particles. Nanoscale Res. Lett. 9, 532. doi:10.1186/1556-276X-9-532

Yuan, L., Chen, W., Hu, J., Zhang, J.Z., Yang, D., 2013. Mechanistic Study of the Covalent Loading of Paclitaxel via Disulfide Linkers for Controlled Drug Release. Langmuir 29, 734–743. doi:10.1021/la304324r

Yu, K.O., Grabinski, C.M., Schrand, A.M., Murdock, R.C., Wang, W., Gu, B., Schlager, J.J., Hussain, S.M., 2009. Toxicity of amorphous silica nanoparticles in mouse keratinocytes. J. Nanoparticle Res. 11, 15–24. doi:10.1007/s11051-008-9417-9

Yu, M., Jambhrunkar, S., Thorn, P., Chen, J., Gu, W., Yu, C., 2013. Hyaluronic acid modified mesoporous silica nanoparticles for targeted drug delivery to CD44-overexpressing cancer cells. Nanoscale 5, 178–183. doi:10.1039/C2NR32145A

Yu, S., Wu, G., Gu, X., Wang, J., Wang, Y., Gao, H., Ma, J., 2013. Magnetic and pH-sensitive nanoparticles for antitumor drug delivery. Colloids Surf. B Biointerfaces 103, 15–22. doi:10.1016/j.colsurfb.2012.10.041

Zaccariello, G., Back, M., Zanello, M., Canton, P., Cattaruzza, E., Riello, P., Alimonti, A., Benedetti, A., 2017. Formation and Controlled Growth of Bismuth Titanate Phases into Mesoporous Silica Nanoparticles: An Efficient Self-Sealing Nanosystem for UV Filtering in Cosmetic Formulation. ACS Appl. Mater. Interfaces 9, 1913–1921. doi:10.1021/acsami.6b13252

Zeng, C., Shang, W., Liang, X., Liang, X., Chen, Q., Chi, C., Du, Y., Fang, C., Tian, J., 2016. Cancer Diagnosis and Imaging-Guided Photothermal Therapy Using a Dual-Modality Nanoparticle. ACS Appl. Mater. Interfaces 8, 29232–29241. doi:10.1021/acsami.6b06883

Zhang, B., Luo, Z., Liu, J., Ding, X., Li, J., Cai, K., 2014. Cytochrome c end-capped mesoporous silica nanoparticles as redox-responsive drug delivery vehicles for liver tumor-targeted triplex therapy in vitro and in vivo. J. Controlled Release 192, 192–201. doi:10.1016/j.jconrel.2014.06.037

Zhang, L., Li, Y., Jin, Z., Yu, J.C., Chan, K.M., 2015. An NIR-triggered and thermally responsive drug delivery platform through DNA/copper sulfide gates. Nanoscale 7, 12614–12624. doi:10.1039/C5NR02767E

Zhang, M., Xu, C., Wen, L., Han, M.K., Xiao, B., Zhou, J., Zhang, Y., Zhang, Z., Viennois, E., Merlin, D., 2016. A hyaluronidase responsive nanoparticle-based drug delivery system for targeting colon cancer cells. Cancer Res. doi:10.1158/0008-5472.CAN-16-1681

Zhang, W., Shen, J., Su, H., Mu, G., Sun, J.-H., Tan, C.-P., Liang, X.-J., Ji, L.-N., 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 Appl. Mater. Interfaces 8, 13332–13340. doi:10.1021/acsami.6b03881

Zhang, X., Zhang, J., Quan, G., Yang, P., Pan, X., Wu, C., 2016. The Serum-Resistant Transfection Evaluation and Long-Term Stability of Gene Delivery Dry Powder Based on Mesoporous Silica Nanoparticles and Polyethyleneimine by Freezing-Drying. AAPS PharmSciTech 1–8. doi:10.1208/s12249-016-0617-9

Zhang, Y., Ang, C.Y., Li, M., Tan, S.Y., Qu, Q., Luo, Z., Zhao, Y., 2015. Polymer-Coated Hollow Mesoporous Silica Nanoparticles for Triple-Responsive Drug Delivery. ACS Appl. Mater. Interfaces 7, 18179–18187. doi:10.1021/acsami.5b05893

Zhang, Y., Ang, C.Y., Li, M., Tan, S.Y., Qu, Q., Zhao, Y., 2016. Polymeric Prodrug Grafted Hollow Mesoporous Silica Nanoparticles Encapsulating Near-Infrared Absorbing Dye for Potent Combined Photothermal-Chemotherapy. ACS Appl. Mater. Interfaces 8, 6869–6879. doi:10.1021/acsami.6b00376

Zhang, Y., Hou, Z., Ge, Y., Deng, K., Liu, B., Li, X., Li, Q., Cheng, Z., Ma, P., Li, C., Lin, J., 2015. DNA-Hybrid-Gated Photothermal Mesoporous Silica Nanoparticles for NIR-Responsive and Aptamer-Targeted Drug Delivery. ACS Appl. Mater. Interfaces 7, 20696–20706. doi:10.1021/acsami.5b05522

Zhao, D., Feng, J., Huo, Q., Melosh, N., Fredrickson, G.H., Chmelka, B.F., Stucky, G.D., 1998. Triblock Copolymer Syntheses of Mesoporous Silica with Periodic 50 to 300 Angstrom Pores. Science 279, 548. doi:10.1126/science.279.5350.548

Zhao, Q., Liu, J., Zhu, W., Sun, C., Di, D., Zhang, Y., Wang, P., Wang, Z., Wang, S., 2015. Dual-stimuli responsive hyaluronic acid-conjugated mesoporous silica for targeted delivery to CD44-overexpressing cancer cells. Acta Biomater. 23, 147–156. doi:10.1016/j.actbio.2015.05.010

Zhao, T., Liu, X., Li, Y., Zhang, M., He, J., Zhang, X., Liu, H., Wang, X., Gu, H., 2017. Fluorescence and drug loading properties of ZnSe:Mn/ZnS-Paclitaxel/SiO2 nanocapsules templated by F127 micelles. J. Colloid Interface Sci. 490, 436–443. doi:10.1016/j.jcis.2016.11.079

Zhao, X., Shan, C., Zu, Y., Zhang, Y., Wang, W., Wang, K., Sui, X., Li, R., 2013. Preparation, characterization, and evaluation in vivo of Ins-SiO2-HP55 (insulin-loaded silica coating HP55) for oral delivery of insulin. Position Pap. Comment. More Eff. Adv. Drug Deliv. Syst. 454, 278–284. doi:10.1016/j.ijpharm.2013.06.051

Zhao, Y., Luo, Z., Li, M., Qu, Q., Ma, X., Yu, S.-H., Zhao, Y., 2015. A Preloaded Amorphous Calcium Carbonate/Doxorubicin@Silica Nanoreactor for pH-Responsive Delivery of an Anticancer Drug. Angew. Chem. Int. Ed. 54, 919–922. doi:10.1002/anie.201408510

Zheng, H., Tai, C.-W., Su, J., Zou, X., Gao, F., 2015. Ultra-small mesoporous silica nanoparticles as efficient carriers for pH responsive releases of anti-cancer drugs. Dalton Trans. 44, 20186–20192. doi:10.1039/C5DT03700J

Zheng, H., Wen, S., Zhang, Y., Sun, Z., 2015. Organosilane and Polyethylene Glycol Functionalized Magnetic Mesoporous Silica Nanoparticles as Carriers for CpG Immunotherapy In Vitro and In Vivo. PLoS ONE 10, e0140265. doi:10.1371/journal.pone.0140265

Zheng, J., Tian, X., Sun, Y., Lu, D., Yang, W., 2013. pH-sensitive poly(glutamic acid) grafted mesoporous silica nanoparticles for drug delivery. Int. J. Pharm. 450, 296–303. doi:10.1016/j.ijpharm.2013.04.014

Zheng, Q., Lin, T., Wu, H., Guo, L., Ye, P., Hao, Y., Guo, Q., Jiang, J., Fu, F., Chen, G., 2014. Mussel-inspired polydopamine coated mesoporous silica nanoparticles as pH-sensitive nanocarriers for controlled release. Int. J. Pharm. 463, 22–26. doi:10.1016/j.ijpharm.2013.12.045

Zhu, X., Wang, C.-Q., 2016. pH and redox-operated nanovalve for size-selective cargo delivery on hollow mesoporous silica spheres. J. Colloid Interface Sci. 480, 39–48. doi:10.1016/j.jcis.2016.06.043

Zou, Y., Li, Q., Jiang, L., Guo, C., Li, Y., Yu, Y., Li, Y., Duan, J., Sun, Z., 2016. DNA Hypermethylation of CREB3L1 and Bcl-2 Associated with the Mitochondrial-Mediated Apoptosis via PI3K/Akt Pathway in Human BEAS-2B Cells Exposure to Silica Nanoparticles. PLOS ONE 11, e0158475. doi:10.1371/journal.pone.0158475

Zou, Z., He, D., He, X., Wang, K., Yang, X., Qing, Z., Zhou, Q., 2013. Natural Gelatin Capped Mesoporous Silica Nanoparticles for Intracellular Acid-Triggered Drug Delivery. Langmuir 29, 12804–12810. doi:10.1021/la4022646

Zou, Z., He, X., He, D., Wang, K., Qing, Z., Yang, X., Wen, L., Xiong, J., Li, L., Cai, L., 2015. Programmed packaging of mesoporous silica nanocarriers for matrix metalloprotease 2-triggered tumor targeting and release. Biomaterials 58, 35–45. doi:10.1016/j.biomaterials.2015.04.034