

Supporting information

Facile Synthesis of Uniform Virus-Like Mesoporous Silica Nanoparticles for Enhanced Cellular Internalization

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EXPERIMENTAL SECTION

Chemicals

Hexadecyltrimethylammonium bromide (CTAB), decahydronaphthalene, 1-octadecene (ODE) were purchased from Sigma-Aldrich. NaOH, cyclohexane and NH_4NO_3 were obtained from Shanghai Chemical Co., Ltd. Ammonia aqueous solution (28 wt %), tetraethyl orthosilicate (TEOS), (3-Aminopropyl) triethoxysilane (APTES), triethanolamine (TEA), decahydronaphthalene (98 %) were purchased from Aladdin Industrial Inc. All chemicals were used as received without further purification.

Synthesis of solid silica nanoparticles.

Solid silica nanoparticles were prepared by a modified Stöber method. Generally, 2 mL of TEOS was added to a solution containing 40 mL of ethanol, 3 mL of deionized water and 0.8 mL of ammonia aqueous, stirring for 12 h, the products were collected by centrifuging and washed by water and ethanol for several times. Then, the samples were dried in vacuum at 45 °C for 8 h.

Synthesis of mesoporous silica nanoparticles.

The mesoporous silica nanoparticles were synthesized as the procedure reported previously. Briefly, 16 mL of (25 wt %) CTAB solution and 90 mg of triethanolamine were added to 20 mL of water and stirred gently at 60 °C for 1 h in flask, then 1.5 mL of TEOS and 1 mL of cyclohexane was added to the solution and kept at 60 °C with magnetic stirring for 24 h. The products were collected by centrifuging and washed by water and ethanol for several times, and then were dispersed in 30 mL of acetone and refluxed for 8 h to remove CTAB templates. The final products were washed with ethanol and dried in vacuum at 45 °C for 8 h.

Synthesis of the virus-like mesoporous silica nanoparticles.

The virus-like mesoporous silica nanoparticles were synthesized by an epitaxial growth approach using cationic surfactant as a template, TEOS as a silica source, NaOH as a catalyst and organic solvent such cyclohexane as the oil phase. Typically, 1.0 g of CTAB and 0.8 mL of NaOH (0.1 M) were added to 50 mL of water and

stirred gently at 60 °C for 2 h in a round bottom flask, then 20 mL of TEOS in cyclohexane (20 v/v %) was added to the solution and kept at 60 °C with stirring for 48 h. The products were collected by centrifuging and washed by water and ethanol for several times. Finally, the virus-like nanoparticles were dispersed in 50 mL of acetone and refluxed at 50 °C for 12 h to remove CTAB templates. Then, the samples were washed with ethanol and dried in vacuum at 45 °C for 8 h.

Synthesis of Fe₃O₄@virus-like mesoporous silica.

The Fe₃O₄ nanoparticles were synthesized according to the method reported previously. Briefly, FeCl₃·6H₂O (1.62 g), trisodium citrate (0.65 g), and NaAc (3.0 g) were dissolved in ethylene glycol (50 mL) with stirring. The obtained solution was transferred and sealed into a Teflon-lined autoclave (100 mL). The autoclave was heated at 180 °C for 12 h. The products were washed with deionized water and ethanol. For the preparation of Fe₃O₄@virus-like mesoporous silica, 100mg of Fe₃O₄ was dispersed in 20 mL of water by sonication. Afterward, 0.5 g of CTAB and 0.3 mL of NaOH (0.1 M) were added to the solution and stirred at 60 °C for 2 h, then 20 mL of TEOS in cyclohexane (20 v/v %) was added to the solution and kept at 60 °C in an oil bath with magnetic stirring for 48 h. The obtained products were collected by centrifuging and washed by water and ethanol for several times.

Synthesis of Ag@virus-like mesoporous silica.

Ag nanocubes were synthesized according to previous report. 100 mL of ethylene glycol (EG) was added into a 150 mL round bottomed flask and heated to 150 °C under stirring. 1.4 mL of NaSH (3.0 mM in EG) was injected into the EG solution, followed by adding 30 mL of PVP (20 mg/mL in EG). Then, 10 mL of AgNO₃ (48 mg/mL in EG) was added into above solution in dark environment. The color of solution changed from yellow to green ochre and brown within 30 min. The solution was cooled to room temperature by an ice bath. The products were isolated by precipitating the solution with acetone, followed by centrifugation, and then washed with acetone and water. Finally, the products were collected and dispersed in 10 mL

of water. The coating procedures are the same as those for Fe₃O₄@virus-like mesoporous silica except that the obtained Ag nanocubes were used as the cores.

Synthesis of Au@virus-like mesoporous silica.

Au nanorods were synthesized according to previous report. The seed solution was prepared as follows: 10 mL of 0.5 mM HAuCl₄ was added to 10 mL of 0.2 M CTAB solution. Then, 1.2 mL of 0.01 M NaBH₄ was diluted to 4 mL of water and was added to the solution under stirring. The color of the solution changed from yellow to brownish yellow. To prepare the growth solution, 3.5 g of CTAB and 0.617 g of NaOL were dissolved in 125 mL of warm water in a 500 mL flask. Then, 9.0 mL of 4 mM AgNO₃ solution was added. The solution was kept undisturbed at 30 °C for 30 min after which 125 mL of 1 mM HAuCl₄ solution was added. The solution became colorless after 90 min and 0.75 mL of HCl (37 wt. %) was added. After 15 min, 0.625 mL of 0.064 M ascorbic acid was added and stirred for 1 min. Finally, 0.2 mL of seed solution was added to the growth solution. The solution was stirred for 1 min and left undisturbed at 30°C for 24 h. The final products were isolated by centrifugation. The coating procedures are the same as those for Fe₃O₄@virus-like mesoporous silica except that the obtained Au nanorods were used as the cores.

Synthesis of Graphene Oxide (GO)@virus-like mesoporous silica.

GO was synthesized via a modified Hummers method. Briefly, in a 1 L flask, 2.5 g of graphite was mixed with 60 mL of concentrated H₂SO₄ under an ice-water bath. Then, 1.25 g of KNO₃ and 7.5 g of KMnO₄ were added into the mixture. All the operations were carried out very slowly. The solution was stirred in an ice-water bath for 3 h and at 35 °C for 2 h. Then, 60 mL of water was added. After 1.5 h, 350 mL of water was added. After another 1 h, 30 mL of H₂O₂ (30%) were added. This suspension was stirred at room temperature for 10 min. The suspension was then centrifuged and washed with 5% HCl solution and then dialyzed. The coating procedures are the same as those for Fe₃O₄@virus-like mesoporous silica except that the obtained GO nanosheets were used as the cores.

Modification and Fluorescent Labeling.

The amino groups were grafted on the three kinds of silica nanoparticles by post-synthetic modification method. Firstly, 500 mg of the silica nanoparticles was degassed on a vacuum condition at 45 °C for 24 h, and then dispersed in 40 mL of toluene by ultrasonic. Then, 200 μ L of 3-aminopropyltriethoxysilane was added, and the solution was refluxed for 8 h under the nitrogen atmosphere with continuous stirring. The products was collected by centrifuging and washed with ethanol, and water, and dried in vacuum at 60 °C. Then, 20 mg of each amino group modified silica nanoparticles was dispersed in 10 mL of ethanol, and 1.0 mg of fluorescein isothiocyanate (FITC) was added. The reaction mixture was stirred for 24 h in dark. The products were separated by centrifugation and washed with ethanol. After drying in vacuum at 45 °C, the final products were obtained.

Loading of Doxorubicin (DOX)

Doxorubicin (DOX) hydrochloride (5 mg) was dissolved in water (2.0 mL). Mesoporous silica nanoparticles (5.0 mg) were added to the solution and the suspension was stirred at room temperature for 48 h. The DOX molecules could be adsorbed in the mesopore channels. The as-prepared DOX-loaded mesoporous silica nanoparticles were collected by centrifugation. The amount of the adsorbed guests was determined from the difference between the initial amount of DOX by measuring the UV absorbance from the supernatant liquid at 480 nm quantified from a standard curve. The DOX was loaded in the virus-like mesoporous silica nanoparticles by the same procedure.

Cellular Uptake

HeLa cells were plated onto glass-bottom petri dishes at a density of 50,000 cells per dish, then cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10 % fetal bovine serum (FBS), penicillin (100 units/mL) and streptomycin (100 μ g/mL) for 24 h at 37 °C in CO₂/air (5: 95). Three types of silica nanoparticles were added at a concentration of 100 μ g/mL, respectively. After incubated for 5, 15, 30 min, 1, 2 h, respectively, the cells were washed with cold PBS for more than three times. The images were taken using a confocal laser scanning microscopy after cell nucleus

were stained by DAPI. The blue fluorescence of DAPI was observed using a 405-nm laser with the emission channel set as 425 - 475 nm. The green fluorescence (550 - 650 nm) of the FITC modified silica nanoparticles obtained above was observed by using a 488-nm laser. For HeLa cells uptake investigations, the medium was first replaced by 1.0 mL of serum-free (DMEM), and then the FITC-labeled silica nanoparticles were added before incubation at 37 °C for 30 min. Cells were washed with PBS three times and then lysed with 0.5 % (w/v) sodium dodecyl sulfate (SDS, pH 8.0). The lysate was quantified for FITC by spectrofluorimetry and protein content by the Lowry method. Uptake level was expressed as the amount of the FITC-labeled silica nanoparticles associated with 1.0 mg of cellular protein. To explore the mechanism involved in the uptake process, cells were pre-incubated with endocytic inhibitors including chlorpromazine (10 mg/mL), genistein (200 mg/mL), and amiloride (500 μM) for 30 min prior to nanoparticle application and throughout the 4-h uptake experiment at 37 °C. Results were expressed as percentage uptake of the control where cells were incubated with three types of silica nanoparticles at 37 °C for 4 h. In addition, FITC-labeled conventional and virus-like mesoporous silica nanoparticles were examined against RAW264.7 cells in both serum and serum-free conditions.

Cytotoxicity

The cytotoxicity was measured by using the Cell Counting Kit-8 (CCK-8) assay in HeLa cell. The cells were incubated and cultured with the mesoporous silica nanoparticles and virus-like mesoporous silica nanoparticles at 37 °C under 5 % CO₂ for 2 h. Then, 10 μL per well of CCK-8 in PBS solution was added to each well and incubated at 37 °C for 2 h. The quantity was determined calorimetrically by using a multi reader (TECAN, Infinite M200). The measurements were based on the absorbance values at 450 nm. The following formula was used to calculate the viability of cell growth: Viability (%) = (mean of absorbance value of treatment group/mean absorbance value of control) × 100. DOX-loaded mesoporous silica nanospheres and virus-like mesoporous silica nanoparticles were incubated with HeLa cells for 8 h. Then, cells were washed with cold PBS for more than three times to

remove the extracellular nanoparticles. In order to ensure DOX releasing, cells were incubated with fresh medium for another 6 h. Finally, 10 μL per well of CCK-8 in PBS solution was added to each well and incubated at 37 $^{\circ}\text{C}$ for 2 h. The quantity was determined calorimetrically by using a multi reader (TECAN, Infinite M200).

In vivo blood circulation experiments

Mice of 6 - 8 weeks old weighting 25 - 30 g were used for the study. Three types of silica nanoparticles (20 mg kg^{-1}) were injected via the tail vein of mice, respectively. At predetermined time points, orbital vein bleeds ($\sim 0.1 \text{ mL}$) were collected into tubes containing heparin and then incubated at 4 $^{\circ}\text{C}$. Following the collection of a full set of time points, the mice were sacrificed, plasma was separated from whole blood by centrifuging at 1000 rpm for 10 min. Silicon contents of blood samples were determined by ICP against common standards. Blood circulation half-lives ($t_{1/2}$) were obtained by first-order decay fits. The results were expressed as mean and standard deviation obtained from three mice at each time point and repeated for three times.

Biodistribution investigation

Animal model: All the animal procedures were in agreement with the guidelines of the Institutional Animal Care and Use Committee of Fudan University and performed in accordance with institutional guidelines on animal handling. U87MG mouse tumor was sheared into tissue blocks with size as $1\text{mm} \times 1\text{mm} \times 1\text{mm}$ and resuspended in sterile PBS. These tissues were implanted subcutaneously into the right arm of 5 weeks old female nude mice. All of the animal experiments were permitted by the Shanghai Science and Technology Committee.

When the tumors reached 0.4 ~ 0.6 cm in diameter (10 ~ 11 days after implant), the tumor-bearing mice were subjected to studies. Conventional and virus-like mesoporous silica nanoparticles were injected intravenously at a dose of 20 mg/kg, respectively. A quantity of 0.2 ml of saline water without silica nanoparticles was used as the control group. Mice were sacrificed 0.5, 1, 4, 12, 24, 48 and 72 h after administration. The main organs (liver, kidneys, spleen, lungs, and heart) and tumor

tissue were collected. In addition, the concentrations of Si in each tissue were measured by ICP.

Measurements and Characterization

Transmission electron microscopy (TEM), high-resolution transmission electron microscopy (HRTEM) observations were performed on JEM-2100F transmission electron microscope with an accelerating voltage of 200 kV equipped with a post-column Gatan imaging filter (GIF-Tri-dium). Scanning electron microscopy (SEM) images were taken using a Hitachi S-4800 ultrahigh resolution cold FEG with an in-lens electron optic operating at 20 kV. Nitrogen sorption isotherms were measured at 77 K with ASAP 2420 and Micromeritics Tristar 3020 analyzer (USA). Before measurements, the samples were degassed in vacuum at 180 °C for 12 h. The Brunauer-Emmett-Teller (BET) method was utilized to calculate the specific surface areas (S_{BET}) using adsorption data in a relative pressure range from 0.05 to 0.2. The pore size distribution was obtained by applying proper nonlocal density functional theory (NLDFT) methods from the adsorption branch of isotherms. Confocal laser scanning microscopy (CLSM) images were obtained in IX81, Olympus, Japan. The UV/Vis spectra were recorded on Lambda 35 PerkinElmer. The distribution of silica nanoparticles were determined by measuring silicon content in different organs by inductively coupled plasma atomic emission spectrometry (ICP) using an IRIS Advantage Duo ER/S (Thermo Fisher Scientific).

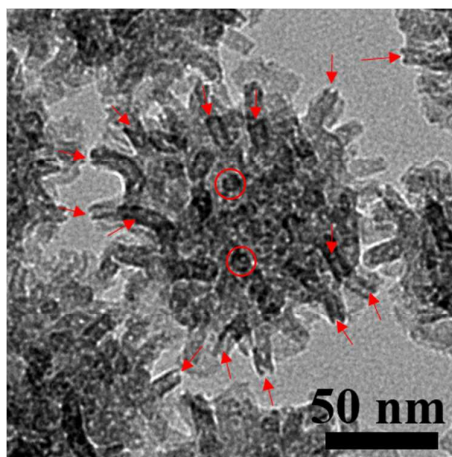


Figure S1. HR-TEM image of the virus-like mesoporous silica nanoparticles after removal of surfactants by calcination in air at 500 °C. The red arrows mark the open tubular structures, and the red circles highlight the top view of the open silica nanotubes.

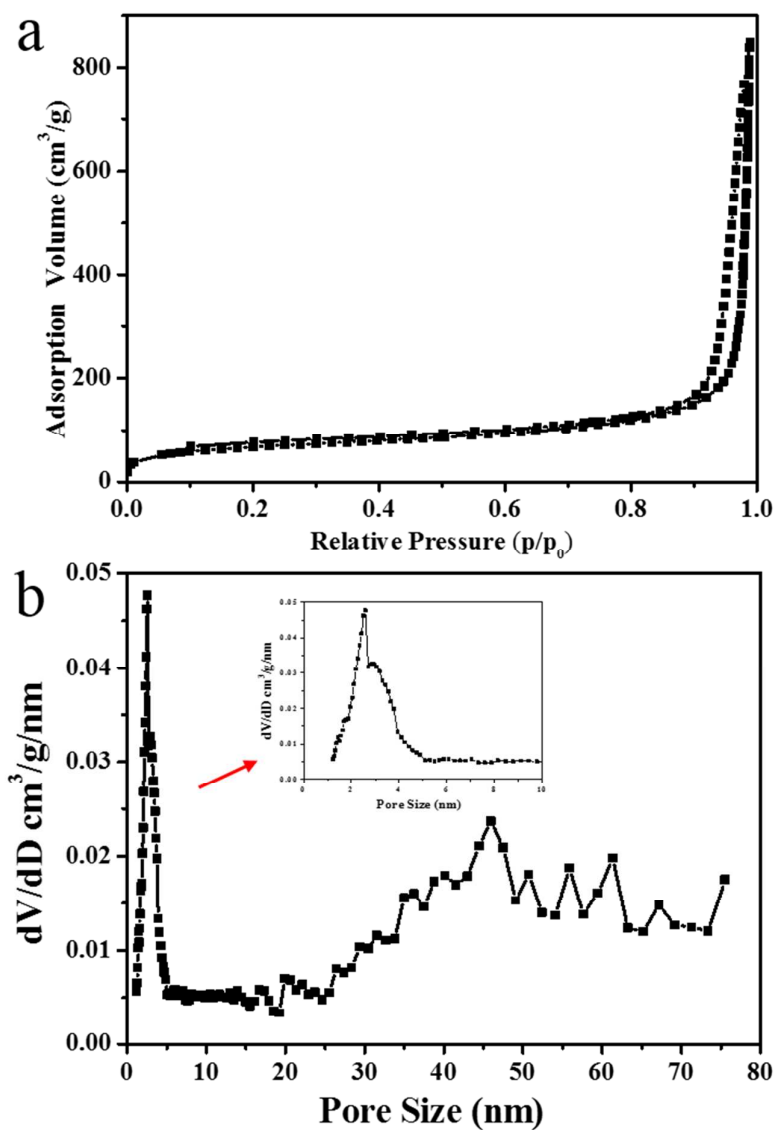


Figure S2. Nitrogen adsorption-desorption isotherms (a) and pore size distribution profile (b) of the virus-like mesoporous silica nanoparticles prepared by using surfactant CTAB as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C for 60 h. Inset in (b) is the enlarged pore size distribution in the range of 2 - 10 nm.

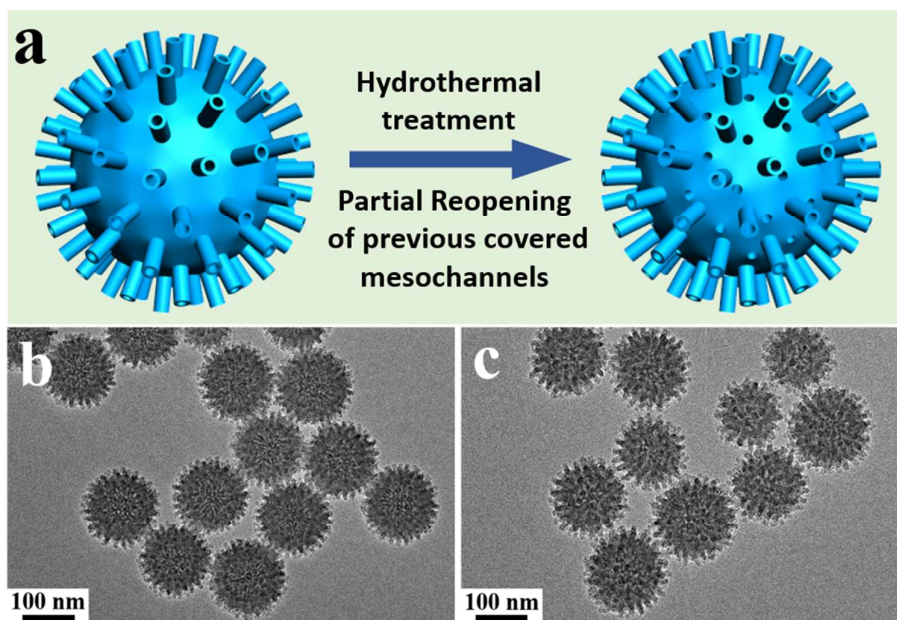


Figure S3. (a) Illustration of partial reopening of previous covered mesochannels. TEM images of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C for 48 h. (b) as-made; (c) after a hydrothermal treatment at 100 °C for 24 h. The surface area of the virus-like mesoporous silica nanoparticles increased and the morphology was well retained.

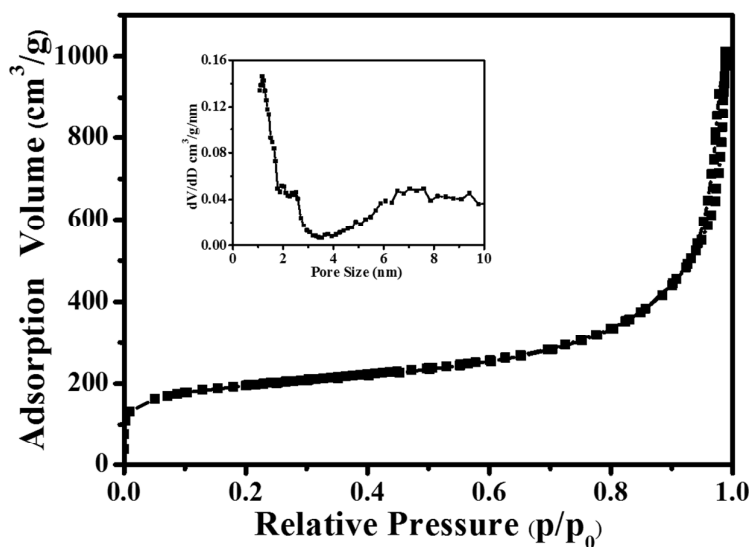


Figure S4. Nitrogen adsorption-desorption isotherms and pore size distribution profile (inset) of the virus-like mesoporous silica nanoparticles after a hydrothermal treatment at 100 °C for 24 h.

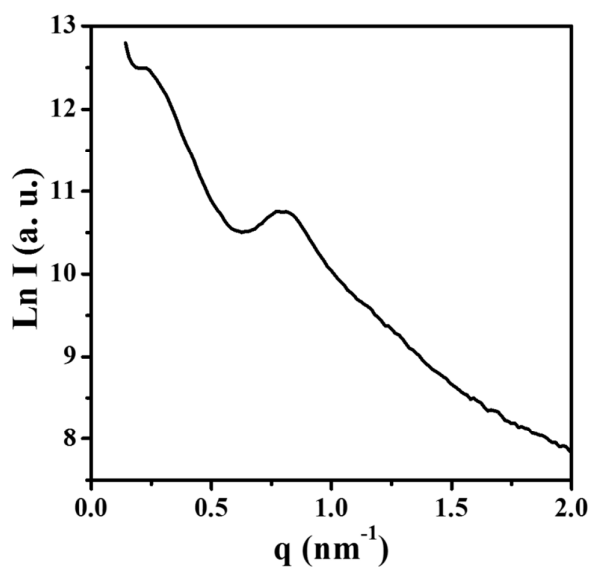


Figure S5. The small-angle X-ray scattering (SAXS) pattern of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C for 60 h. The SAXS pattern shows two scattering peaks at 0.25 and 0.81 nm⁻¹, which can be attributed to the spacings between the adjacent nanotubes and the interior mesoporous spherical core, respectively.

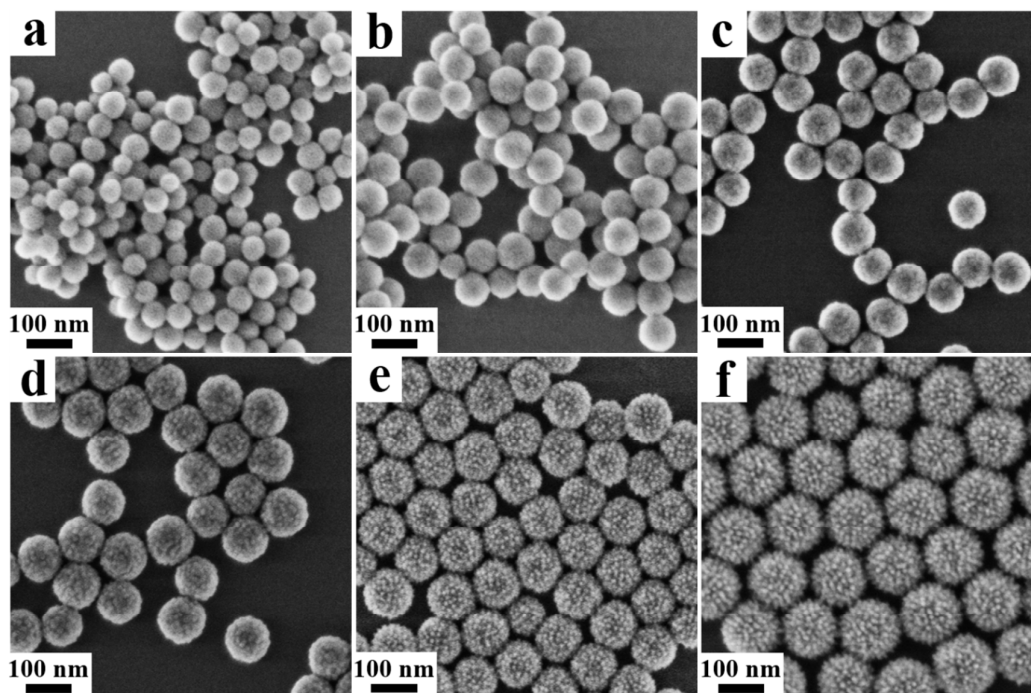


Figure S6. SEM images of the samples prepared at different reaction time: (a) 6 h; (b) 12 h; (c) 18 h; (d) 24 h; (e) 36 h; (f) 48 h, respectively, in a bi-phase (cyclohexane and water) reaction system with a low CTAB-surfactant concentration.

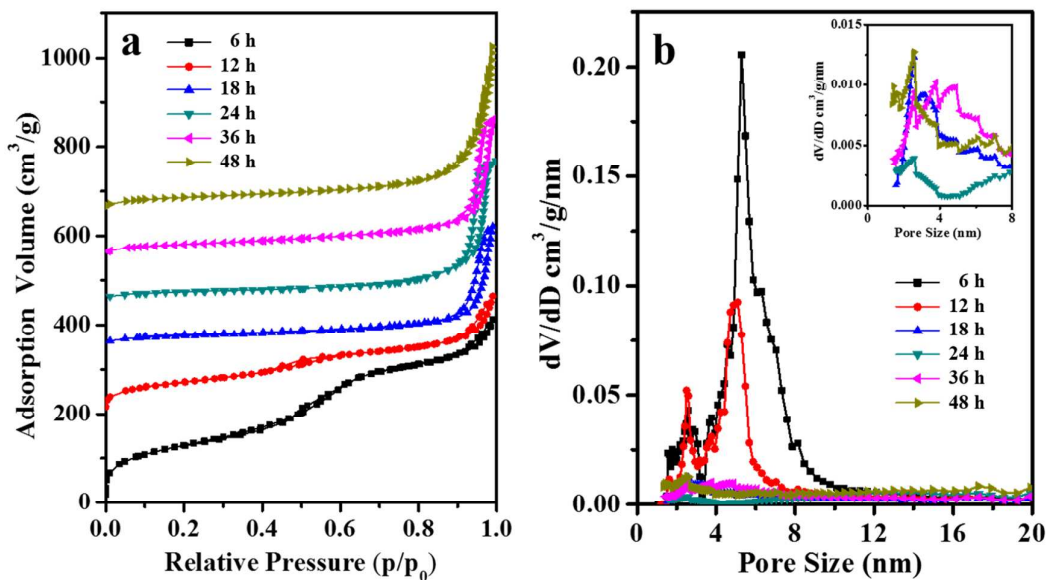


Figure S7. (a) Nitrogen adsorption-desorption isotherms and (b) pore size distribution curves of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C with different reaction time: 6; 12; 18; 24; 36; 48 h. Inset in (b) is the enlarged pore size distribution of the virus-like mesoporous silica nanoparticles with different reaction time: 18; 24; 36; and 48 h, respectively.

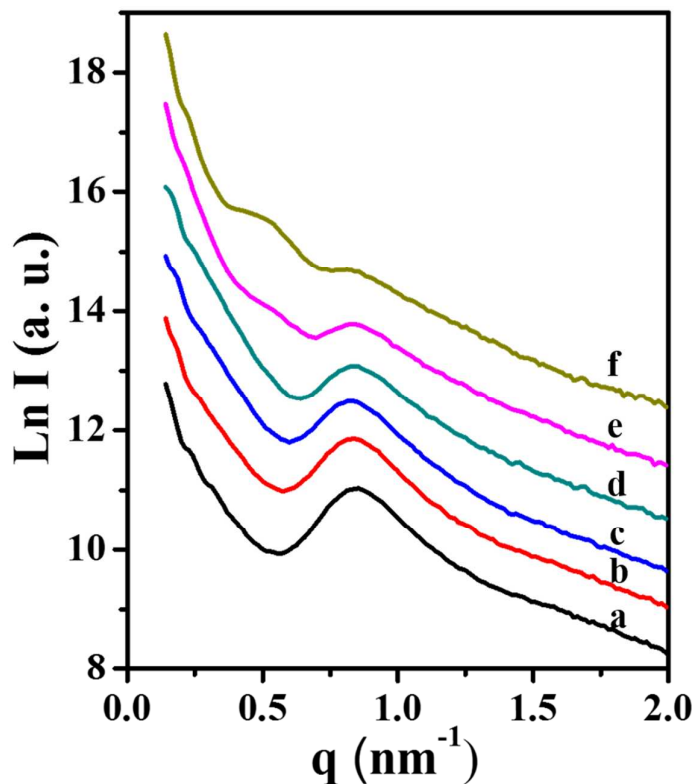


Figure S8. Small-angle X-ray scattering (SAXS) patterns of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C with different reaction time: (a) 6; (b) 12; (c) 18; (d) 24; (e) 36; (f) 48 h. The SAXS patterns show the same scattering peak at $\sim 0.87 \text{ nm}^{-1}$, indicating uniform interior mesostructures with the same cell parameter. A new scattering peak can be observed at 0.53 nm^{-1} in the SAXS pattern (e) of the virus-like mesoporous silica nanoparticles obtained after the reaction for 48 h, which is attributed to the mesoscopic distribution of the peripheral perpendicular nanotubes.

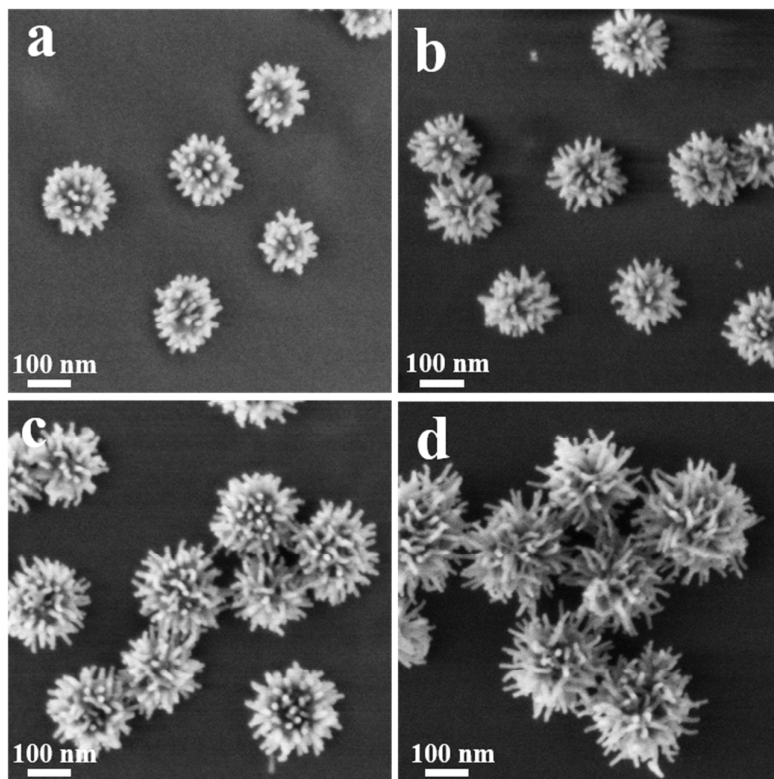


Figure S9. SEM images of the virus-like mesoporous silica nanoparticles with different length of periphery nanotubes prepared by controlling reaction time: (a) 36 h; (b) 48 h; (c) 60 h; (d) 72 h, respectively, in a bi-phase (cyclohexane and water) reaction system with a low CTAB-surfactant concentration.

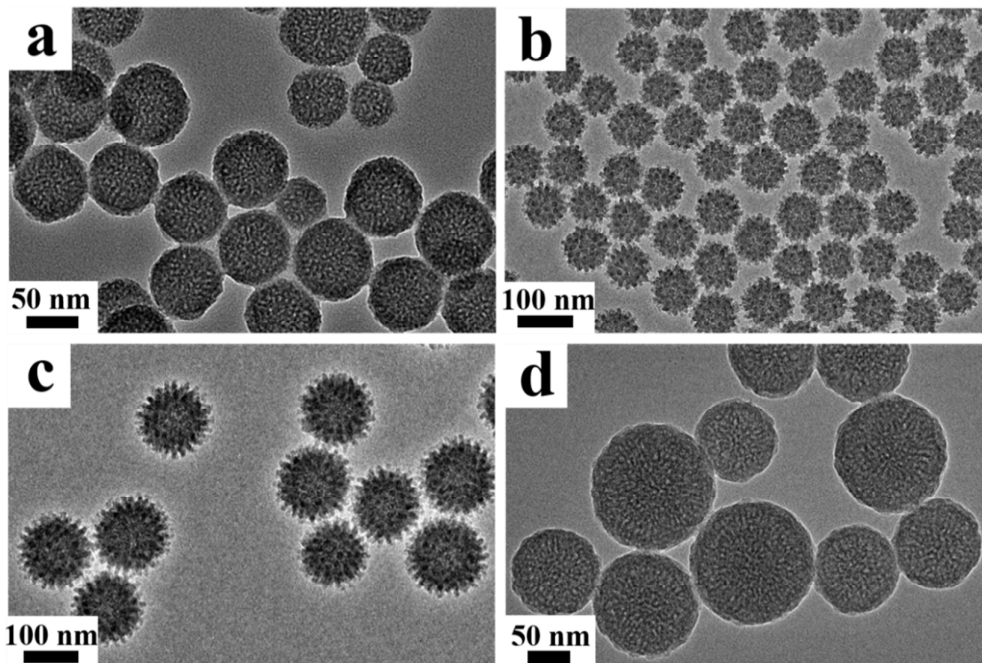


Figure S10. TEM images of the mesoporous silica nanoparticles prepared by using CTAB with different concentrations as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C for 48 h. The concentration of CTAB was set as (a) 0.25 %, (b) 1 %, (c) 2.5 % and (d) 5 %, respectively.

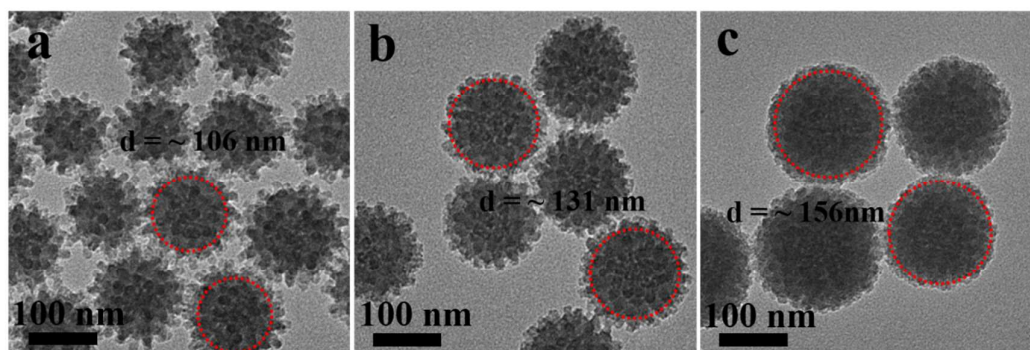


Figure S11. TEM images of the virus-like mesoporous silica nanoparticles prepared with different concentrations of CTAB: (a) 2.0 %, (b) 3.0 % and (c) 4.0 %, respectively.

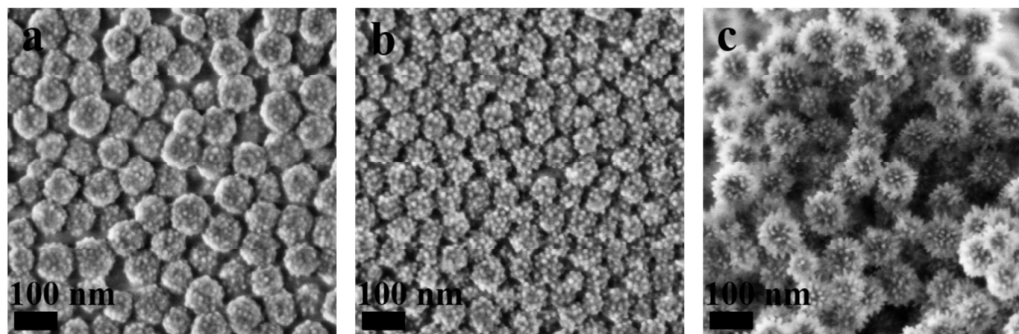


Figure S12. SEM images of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst and different oil phase: (a) octadecene; (b) decahydronaphthalene; (c) cyclohexane at 60 °C for 48 h.

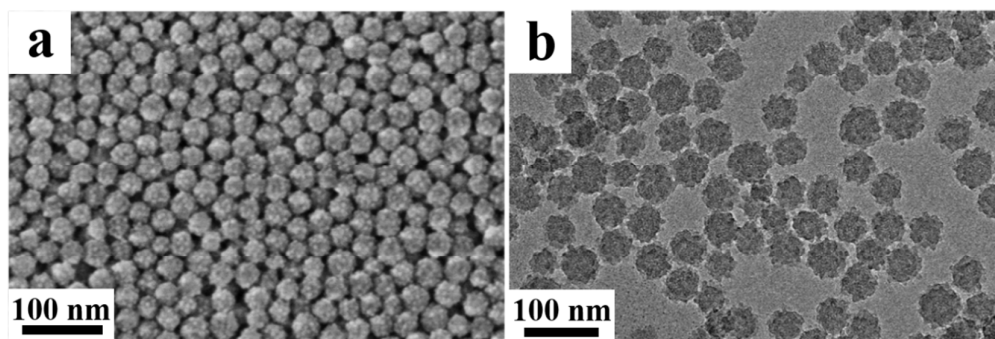


Figure S13. SEM (a) and TEM (b) images of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst in a non-oil phase system at 60 °C for 48 h, showing the similar length as those synthesized 1-octadecene system.

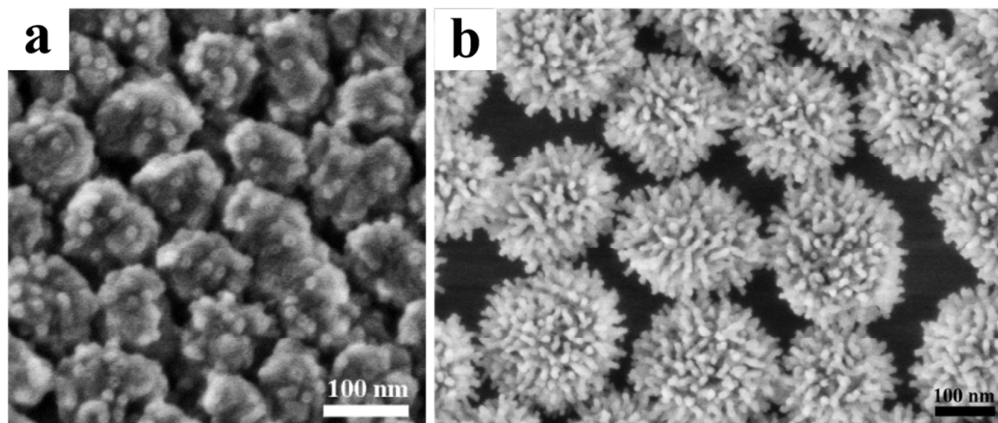


Figure S14. SEM images of the virus-like mesoporous silica nanoparticles prepared by using CTAB as a template, TEOS as a silica source, NaOH as a catalyst and cyclohexane as an oil phase at 60 °C with different reaction time: (a) 24 h and (b) 60 h. The images shows that the distinct spikes begin to form on the surface of the spherical mesoporous silica nanoparticles at 24 h, and finally the virus-like mesoporous silica nanoparticles with long nanotubes can be obtained.

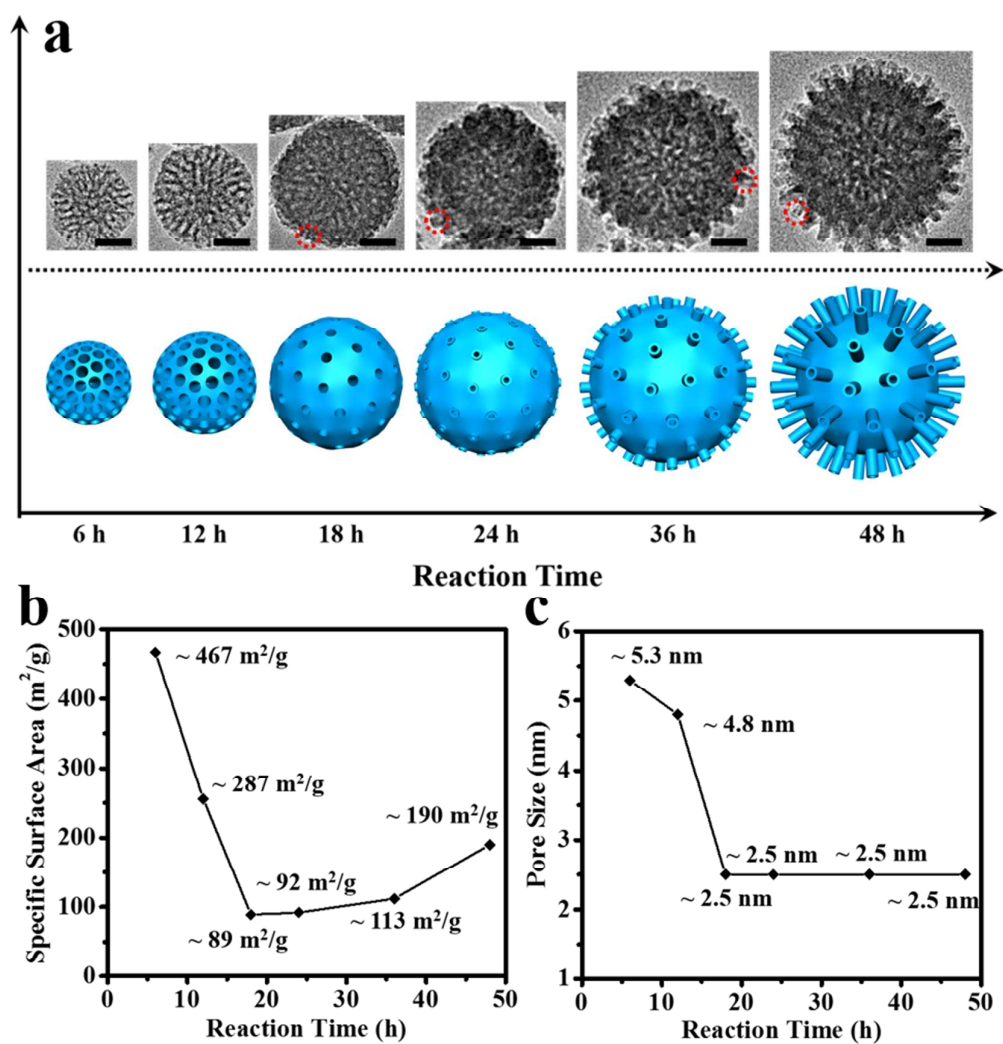


Figure S15. (a) TEM images and illustrations of the growth process for the virus-like mesoporous silica nanoparticles. (b) Surface area and (c) pore size of silica nanoparticles with different reaction time. All the scale bars are 20 nm.

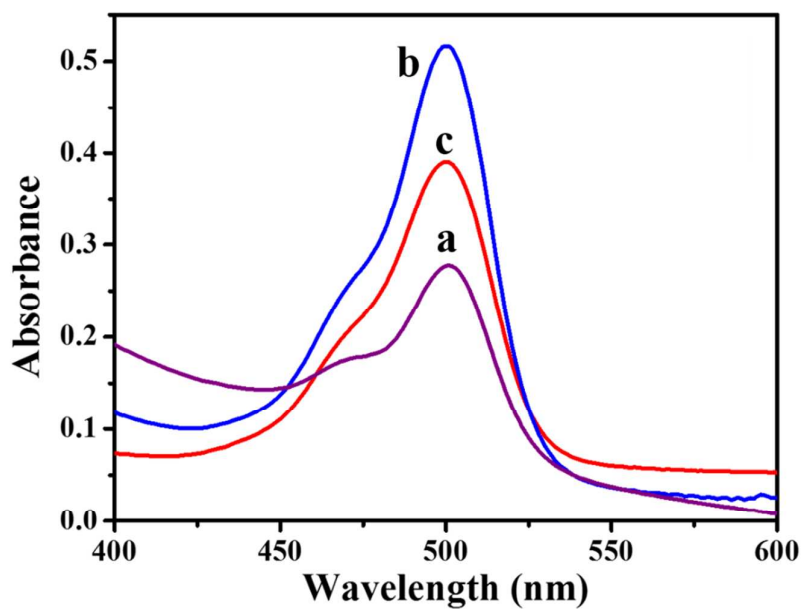


Figure S16. UV-VIS spectra of the FITC-labelled solid silica nanoparticles (a), conventional mesoporous silica nanoparticles (b) and virus-like mesoporous silica nanoparticles (c).

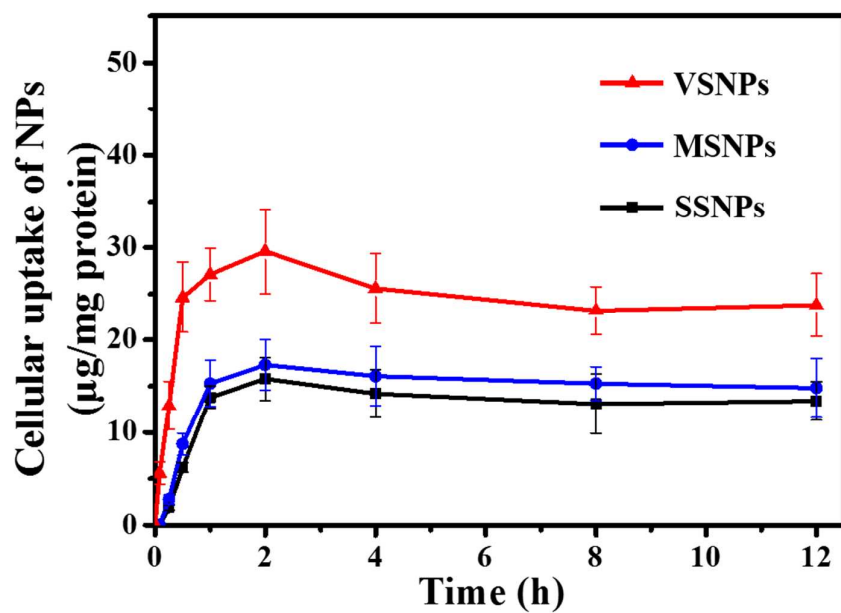


Figure S17. The relative cell uptake rates of solid silica nanoparticles (SSNNPs), conventional mesoporous silica nanoparticles (MSNNPs) and the virus-like mesoporous silica nanoparticles (VSNNPs) in HeLa cells.

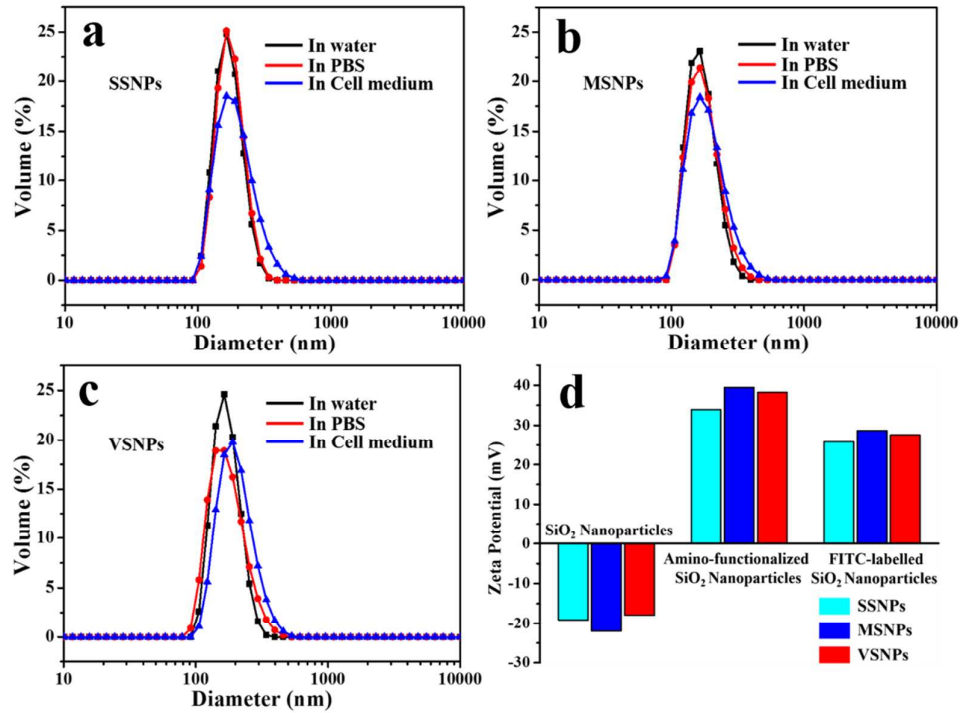


Figure S18. Size distribution and zeta potential analysis for three types of silica nanoparticles. Size distributions in water, PBS and cell media for (a) solid silica nanoparticles (SSNPs); (b) conventional mesoporous silica nanoparticles (MSNPs); (c) virus-like mesoporous silica nanoparticles (VSNNPs). Since they have similar size and good monodispersity, according to the results, the effect of size-induced and aggregation-state-induced bio-behavior can be both ignored in our test system. (d) Zeta potential analysis for the SiO₂ nanoparticles, amino-functionalized SiO₂ nanoparticles and FITC-labelled SiO₂ nanoparticles. It can be seen that there is no significant charge difference among these three samples, suggesting that the effect of zeta-potential-induced bio-behavior can be ignored in our test system.

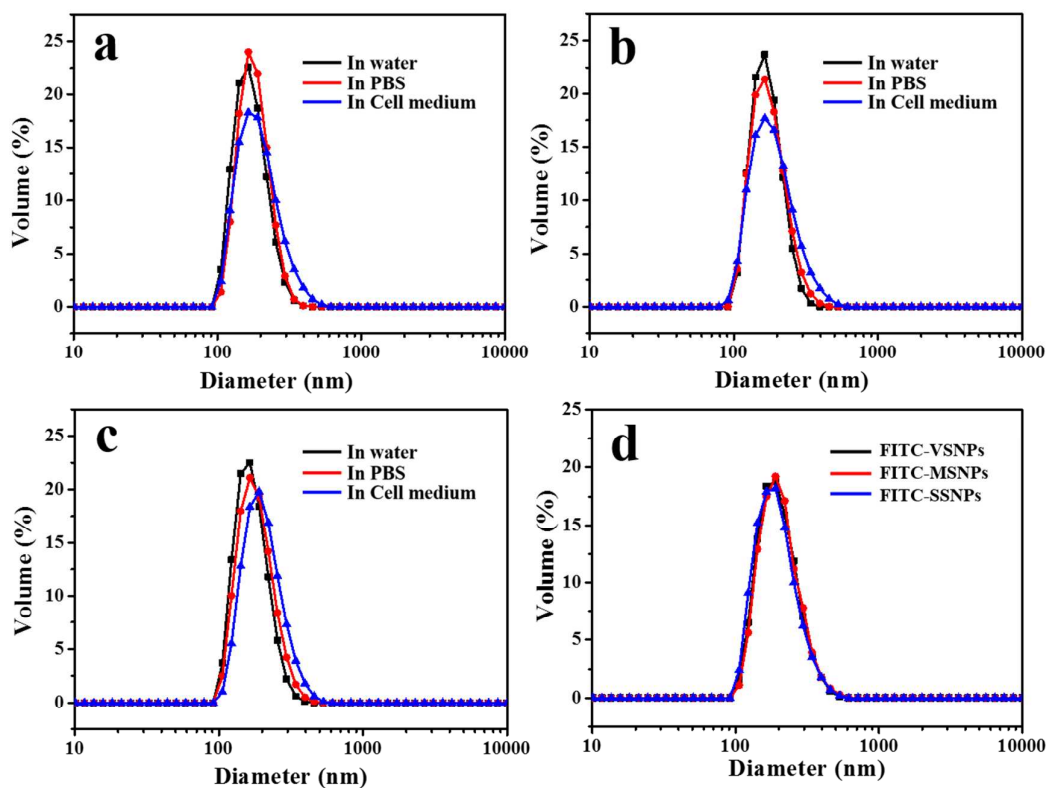


Figure S19. Size distribution analysis for three type of silica nanoparticles, which have been dispersed in water, PBS and cell culture medium for 48 h, respectively. Size distribution of (a) solid silica nanoparticles (SSNPs), (b) conventional mesoporous silica nanoparticles and (c) virus-like mesoporous silica nanoparticles (VSNPs) in water, PBS and cell medium in a course of 48 h. (d) Size distribution analysis for three types of FITC-labelled SiO₂ nanoparticles in cell culture medium.

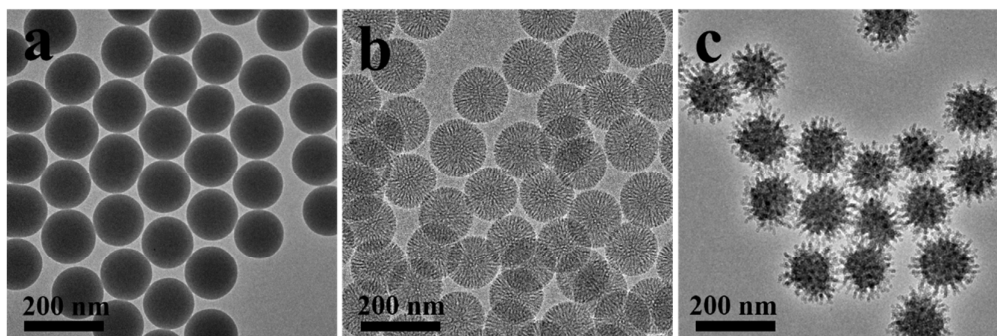


Figure S20. TEM images of the FITC functionalized particles: (a) solid silica nanoparticles, (b) conventional mesoporous silica nanoparticles, (c) virus-like mesoporous silica nanoparticles

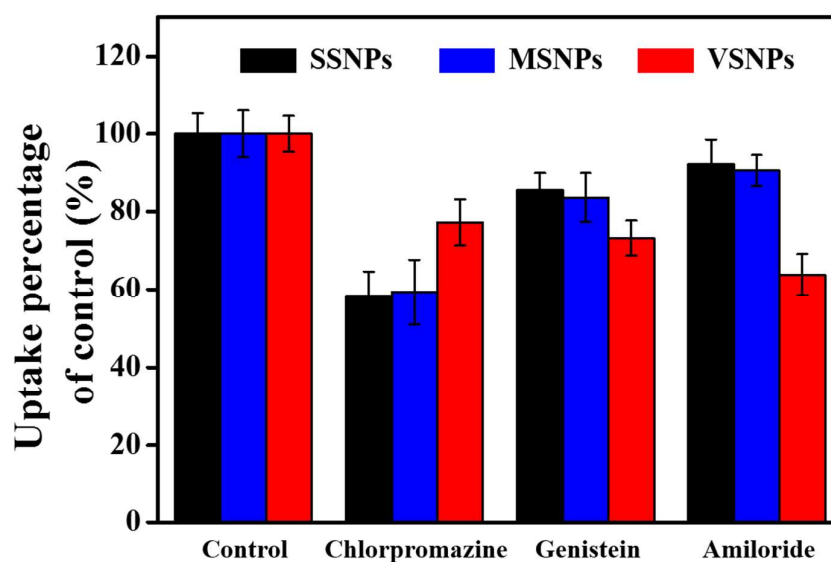


Figure S21. Probing the mechanisms of cellular internalization of three types of nanoparticles: solid silica nanoparticles (SSNPs), conventional mesoporous silica nanoparticles (MSNPS) and virus-like mesoporous silica nanoparticles (VSNPs) by using inhibitors of specific endocytic pathways. HeLa Cells were incubated with inhibitors indicated in the graph. Percent internalization was normalized to particle internalization in the absence of inhibitors.

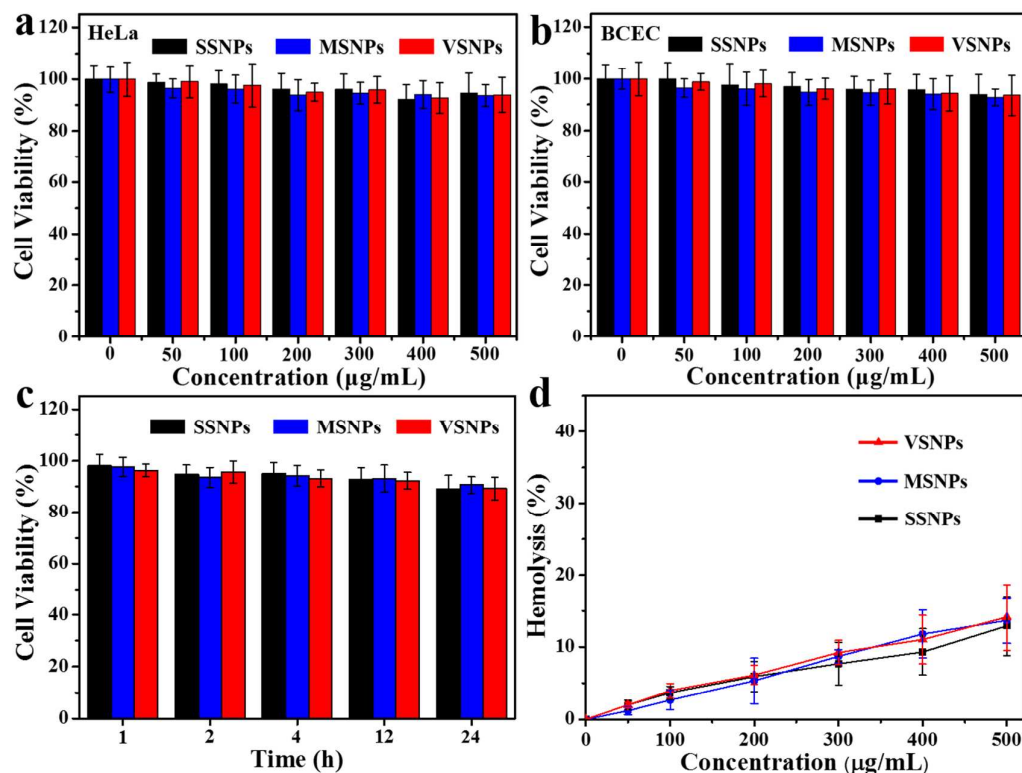


Figure S22. Cell viability assay of the solid silica nanoparticles (SSNPs), conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) in (a) HeLa cells and (b) brain capillary endothelial cells (BCEC) after incubation for 12 h. The virus-like mesoporous silica nanoparticles have a low cytotoxicity even at a concentration as high as 500 $\mu\text{g/mL}$, indicating excellent biocompatibility with both types of cells. (c) Cell viability assay of the solid silica nanoparticles (SSNPs), conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) in HeLa cells after incubation for 1, 2, 4, 12 and 24 h at a concentration as high as 500 $\mu\text{g/mL}$. (d) The hemolysis percentage of red blood cells incubated with the solid silica nanoparticles (SSNPs), conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) at different concentrations.

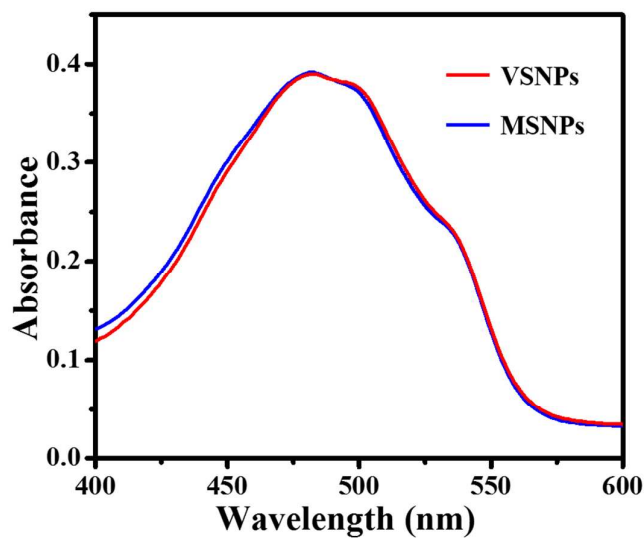


Figure S23. UV-VIS spectra of the DOX-loaded conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs).

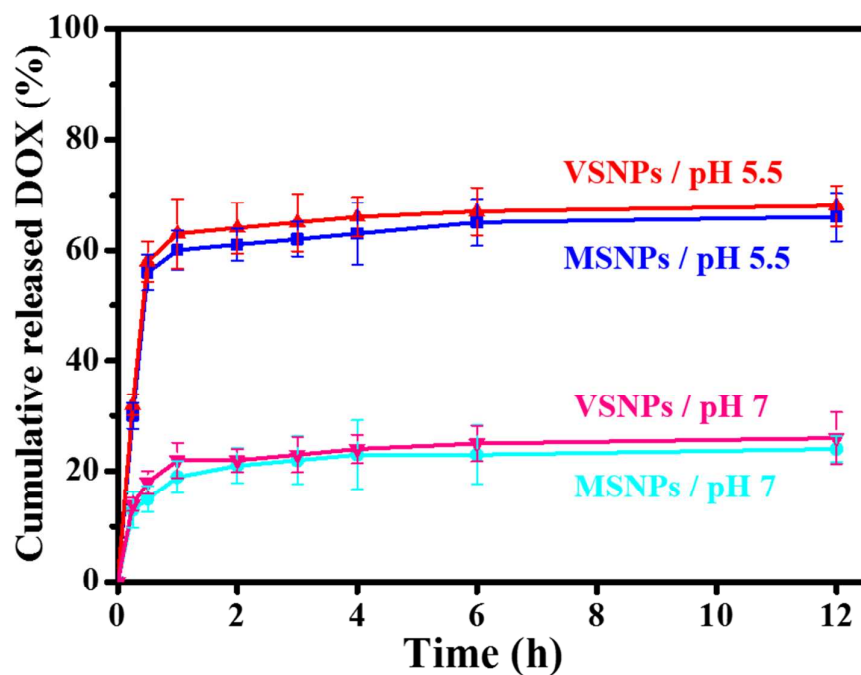


Figure S24. Release profiles of the DOX-loaded conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) in PBS under different conditions: pH 5 and pH 7.

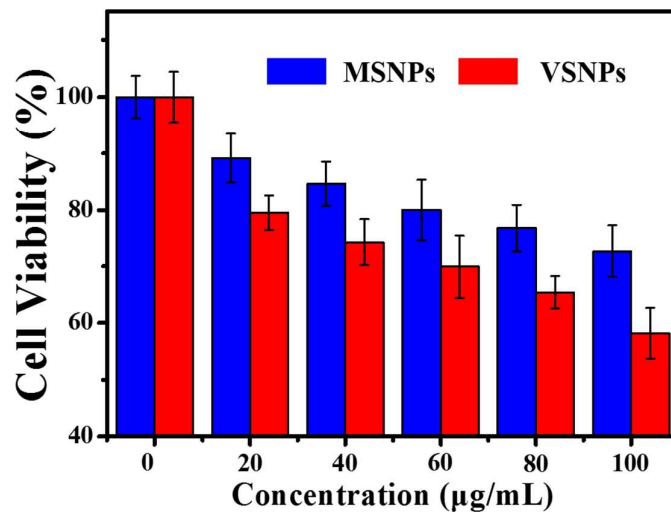


Figure S25. Cell viability assay of the DOX-loaded conventional mesoporous silica nanoparticles (MSNPs) and DOX-loaded virus-like mesoporous silica nanoparticles (VSNPs).

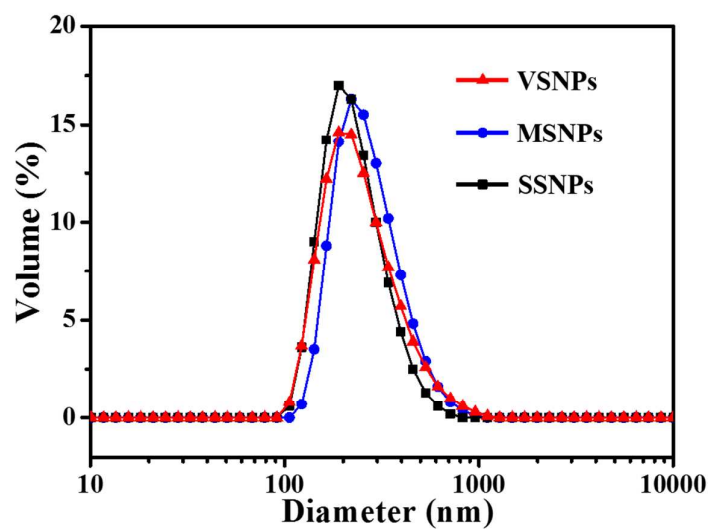


Figure S26. Size distribution analyses for three types of silica nanoparticles in serum conditions.

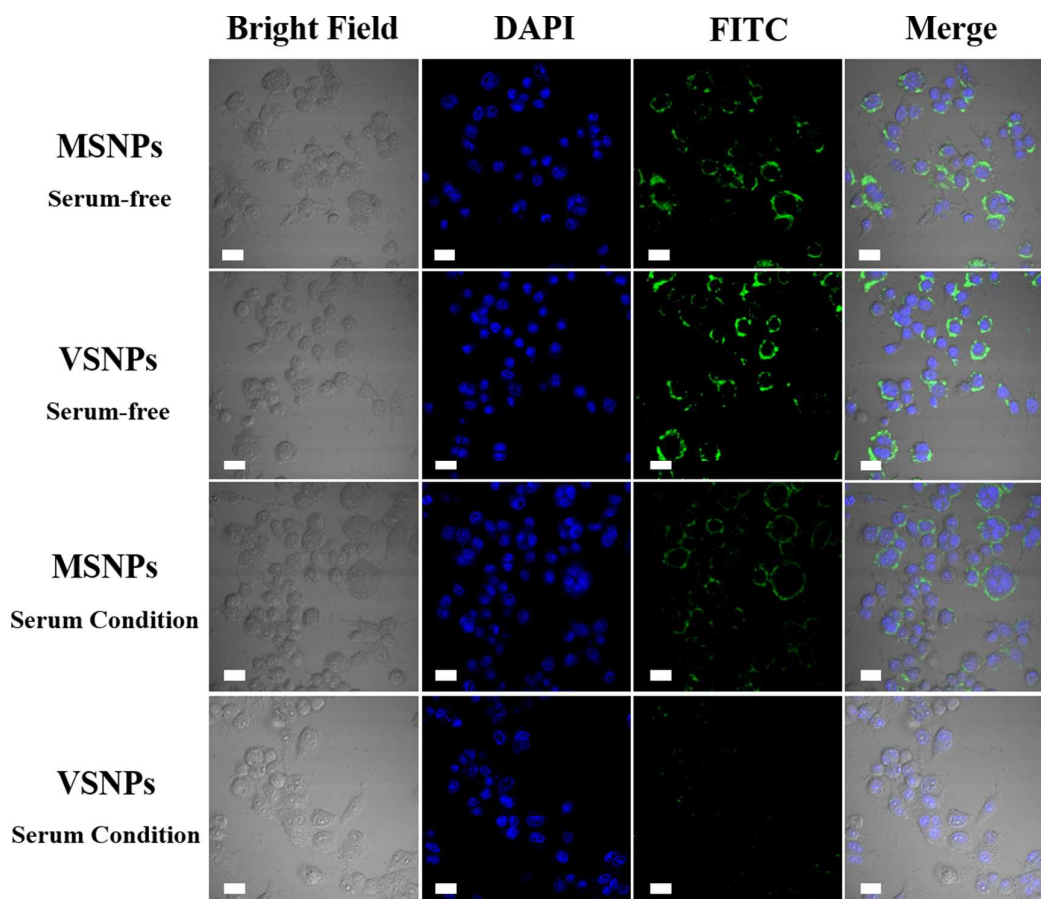


Figure S27. Confocal laser scanning microscopy (CLSM) observations of the RAW264.7 cells after incubation with conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) for 4 h in serum-free condition and serum condition, respectively. All the scale bars are 10 μm .

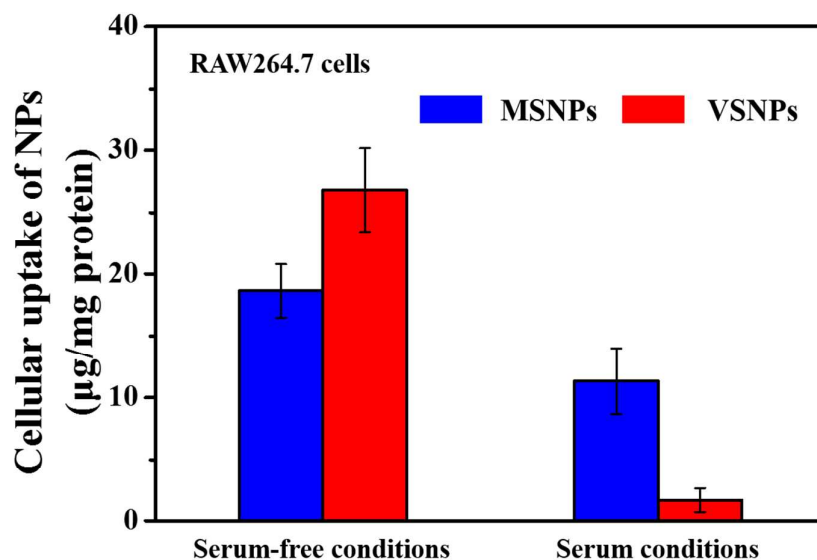


Figure S28. The relative cell uptake amounts of conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) in RAW264.7 cells for 4 h incubation in serum-free condition and serum condition, respectively.

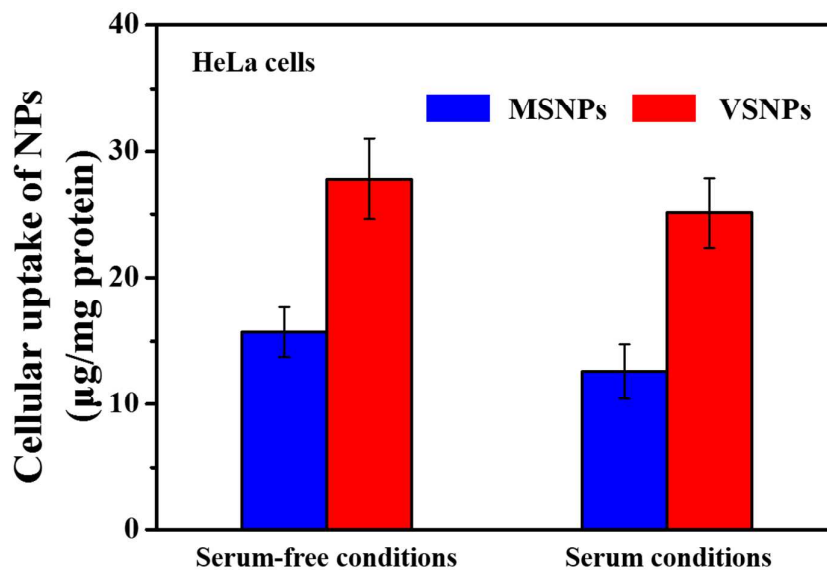


Figure S29. The relative cell uptake amounts of conventional mesoporous silica nanoparticles (MSNPs) and virus-like mesoporous silica nanoparticles (VSNPs) in HeLa cells for 4 h incubation in serum-free condition and serum condition, respectively.

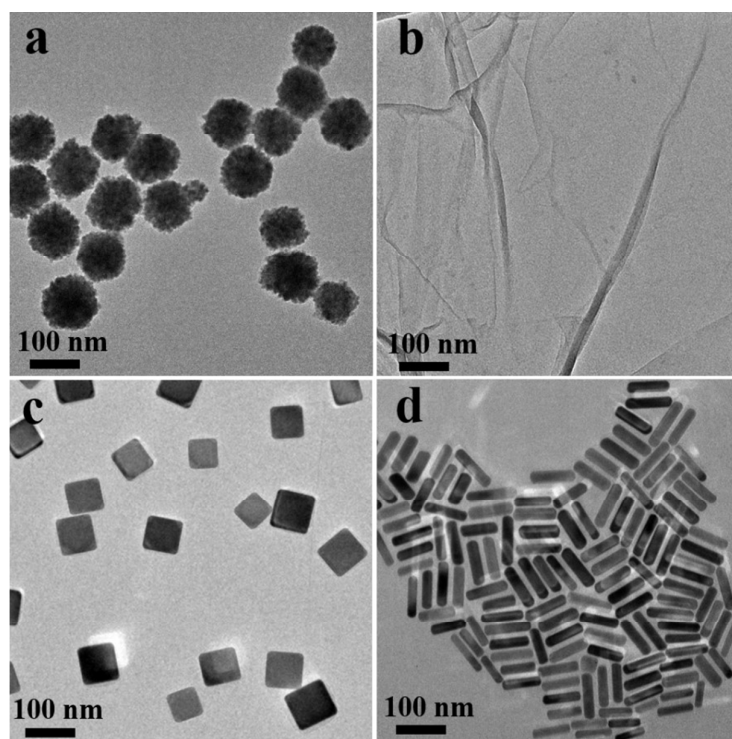


Figure S30. TEM images of (a) Fe₃O₄ nanoparticles, (b) GO nanosheets, (c) Ag nanocubes and (d) Au nanorods.