ADVANCED MATERIALS

Supporting Information

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SupraCells: Living Mammalian Cells Protected within Functional Modular Nanoparticle-Based Exoskeletons

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Supplementary Materials for

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Wei Zhu[a,b,*,‡], Jimin Guo[b,‡], Shahrouz Amini[c], Yi Ju[d], Jacob Ongudi Agola[b], Andreas Zimpel[e], Jin Shang[f], Achraf Noureddine[b], Frank Caruso[d], Stefan Wuttke[e], Jonas G. Croissant[b,*], C. Jeffrey Brinker[b,*]

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Section S1. General information

Reagents. All chemicals and reagents were used as received. Zinc nitrate hexahydrate, 2-methylimidazole, zirconium(IV) chloride, terephthalic acid, 2-aminoterephthalic acid, dimethylformamide (DMF), trimesic acid, iron(III) chloride hexahydrate, tetraethyl orthosilicate (TEOS), (3-aminopropyl)triethoxysilane (APTES), ammonium hydroxide, ammonium nitrate, hexadecyltrimethylammonium bromide (CTAB), cyclohexane, tannic acid, benzene-1,4-diboronic acid, ethylenediaminetetraacetic acid, rhodamine B isothiocyanate mixed isomers, fluorescein isothiocyanate, iron(III) acetylacetonate ($Fe(acac)_3$), copper(II) nitrate, 7,7,8,8-tetracyanoquinododimethane (TCNQ), benzyl alcohol, methanol, Ham's F-12K (Kaighn's) medium, Iscove's modified Dulbecco's media (IMDM), formaldehyde solution (36.5-38% in H_2O), dimethyl sulfoxide (DMSO), doxorubicin (DOX), silver nanoparticles, Congo red, 5,10,15,20-tetrakis(4-sulfona-tophenyl)-21H,23H-porphine manganese (III) chloride, and gentamicin were purchased from Sigma-Aldrich. 2-(*N*-(7-nitrobenz-2-oxa-1,3-dia zol-4-yl)Amino)-2-deoxyglucose (2-NBDG), Alexa Fluor™ 633 NHS ester (succinimidyl ester) were purchased from Thermo Fisher Scientific. Heat-inactivated fetal bovine serum (FBS), 10X phosphate-buffered saline (PBS), 1X trypsin-EDTA solution, and penicillin-streptomycin (PS) were purchased from Gibco (Logan, UT). Dulbecco's modification of Eagle's medium (DMEM) was obtained from Corning Cellgro (Manassas, VA). Absolute (200 proof) ethanol was obtained from Pharmco-Aaper (Brookfield, CT). CellTiter-Glo 2.0 Assay was purchased from Promega (Madison, WI). Hoechst 33342 were obtained from Thermo Fisher Scientific (Rockford, IL). 1X phosphate-buffered saline (PBS), Alexa Fluor 488 phalloidin and rhodamine phalloidin were purchased from Life Technologies (Eugene, OR). Milli-Q water with a resistivity of 18.2 MΩ cm was obtained from an inline Millipore RiOs/Origin water purification system.

Characterization. Scanning electron microscopy (SEM) analyses and energy-dispersive X-ray spectroscopy (EDS) elemental mappings were performed on a Hitachi SU-8010 field-emission scanning electron microscope at 15.0 kV. Transmission electron microscopy (TEM) and high-resolution TEM (HRTEM) imaging were carried out using a Hitachi model H-7650 transmission electron microscope at 200 kV. Wide-angle powder X-ray diffraction (PXRD) patterns were acquired on a Rigaku D/MAX-RB (12 kW) diffractometer with monochromatized Cu Kα

radiation (λ = 0.15418 nm), operating at 40 KV and 120 mA. The UV-Vis absorption spectra were recorded using a Perkin-Elmer UV/vis Lambda 35 spectrometer. The fluorescence emission measurements were carried out using a fluorescence spectrometer (Perkin-Elmer LS55). To characterize the mechanical properties of the samples, a Triboindenter TI950 (Bruker-Hysitron) equipped with a standard 2D transducer and Berkovich tip were used. Three-color images were acquired using a Zeiss LSM510 META (Carl Zeiss MicroImaging, Inc.; Thornwood, NY, USA) operated in channel mode of the LSM510 software.

Section S2. Nanoparticles synthesis

ZIF-8 NPs synthesis. ZIF-8 NPs were synthesized following previously reported methods with minor modification.[1] First, 2.27 g 2-methylimidazole was dissolved in 8.0 g Milli-Q water, and then 0.117 g $Zn(NO_3)_2$•$6H_2O$ dissolved in 0.8 g Milli-Q water was added under fast stirring (6000 rpm). The operation was performed at room temperature. After stirring for 15 min, the particles were collected by centrifuging, and then washed with ethanol several times. The synthesized ZIF-8 NPs were stored in EtOH before use.

MIL-100(Fe) NPs synthesis. MIL-100(Fe) NPs were synthesized following previously reported methods with no modification.[2] Briefly, 2.43 g iron(III) chloride hexahydrate (9.0 mmol) and 0.84 g trimesic acid (4.0 mmol) in 30 ml H_2O were mixed in a Teflon tube, sealed, and placed in the microwave reactor (Microwave, Synthos, *Anton Paar*). The temperature of the mixed solution was fast increased to 130 °C under solvothermal conditions (P = 2.5 bar) within 30 seconds, and then kept at 130 °C for 4 minutes and 30 seconds, and finally cooled down again to room temperature. The synthesized NPs were centrifuged down and then washed twice with EtOH. The dispersed NPs were allowed to sediment overnight, and then the supernatant of the sedimented suspension was filtrated (filter discs grade: 391, *Sartorius Stedim Biotech*) three times to finally yield the required MIL-100(Fe) NPs. The synthesized MIL-100(Fe) NPs were stored in EtOH before use.

UiO-66/UiO66-NH_2 NPs synthesis. UiO-66 NPs were synthesized following previously reported methods with no modification.[3] Briefly, 25.78 mg $ZrCl_4$ (0.11 mmol) and 13.29 mg 1,4-benzenedicarboxylic acid (0.08 mmol) were dissolved in 10 mL of DMF solution. Then 1.441 g

acetic acid (0.024 M) was added into the above solution. The mixed solution was placed in an oven (120 °C) for 24 h. After the reaction mixture was cooled to room temperature, the resulted NPs were subsequently washed with DMF and methanol via centrifugation redispersion cycles. The synthesized UiO-66 NPs were stored in EtOH before use. For the synthesis of UiO66-NH_2, the same protocol was used except the replacing the organic ligand 1,4-benzenedicarboxylic acid to 2-amino terephthalic acid.

MET-3 (Fe) NPs Synthesis. MET-3 (Fe) NPs were synthesized following previously reported methods with no modification.[4] Briefly, 1.22 g $Cu(NO_3)_2 \cdot 3H_2O$ (5.24 mmol) and 0.58 g trimesic acid (2.76 mmol) were first dissolved in 5 g DMSO solution to form the precursor solution. Then 0.2 mL of the precursor solution was dropped into 10 mL methanol solution under stirring in 1 min. After the stirring was continued for 20 min, the precipitate was collected by centrifugation and washed several times with methanol. The synthesized HKUST-1 NPs were stored in MeOH before use.

Mesoporous silica NPs ($mSiO_2$) synthesis. MSN NPs were synthesized following previously reported methods in our group with no modification.[5] Briefly, 0.29 g of CTAB (0.79 mmol) was dissolved in 150 mL of 0.51 M ammonium hydroxide solution in a 250 mL beaker, sealed with parafilm (Neenah, WI), and placed in a mineral oil bath at 50 °C. After continuously stirring for 1 h, 3 mL of 0.88 M TEOS solution in EtOH and 1.5 µL APTES were combined and added immediately to the mixed solution. After another 1 h of continuous stirring, the particle solution was stored at 50 °C for another 18 h under static conditions. Next, the solution was passed through a 1.0 µm Acrodisc 25 mm syringe filter (PALL Life Sciences, Ann Arbor, MI) followed by a hydrothermal treatment at 70 °C for 24 h. To remove the CTAB, the synthesized $mSiO_2$ NPs were transferred to 75 mM ammonium nitrate solution in ethanol, and placed in an oil bath at 60 °C for 1 h with reflux and stirring. The $mSiO_2$ NPs were then washed in 95% ethanol and transferred to 12 mM HCl ethanolic solution and heated at 60 °C for 2 h with reflux and stirring. Finally, $mSiO_2$ NPs were washed in 95% ethanol, then 99.5% ethanol, and stored in 99.5% ethanol before use.

Fe_3O_4 NPs synthesis. Bare Fe_3O_4 NPs were synthesized following the reported methods with no

modification.[6] Briefly, 0.687 g of $Fe(acac)_3$ (1.94 mmol) was dissolved in 9 mL of benzyl alcohol. The mixed solution was heated to 170 °C with reflux and stirring at 1500 rpm for 24 h. After the reaction was cooled down to room temperature, 35 mL EtOH was added into the mixed, and then centrifuged at 20000 rpm for 10 min. The supernatant was discarded, and the resulted precipitate was washed with EtOH twice to yield to the required Fe_3O_4 NPs. The synthesized Fe_3O_4 NPs were stored in EtOH before use.

Section S3. Cell culture

Cell culture was performed using standard procedures (atcc.org). For adherent cells, HeLa (CCL-2) and A549 (CCL-185) were obtained from American Type Culture Collection (ATCC) and maintained in DMEM and F-12K media containing 10% FBS at 37 °C and 5% CO_2, respectively. Cells were passaged at approximately 80% confluency. For coating purposes, living adherent cells (HeLa and A549) were removed from plate bottom using Trypsin-EDTA (0.25%) and then suspended in culture media. For suspension cells, HL-60 (CCL240) was obtained from American Type Culture Collection (ATCC) and maintained in IMDM media containing 10% FBS at 37^{o}C and 5% CO_2. The media of HL-60 cell were changed every 3 days. For phagocytosis purposes, HL-60 cells were differentiated into neutrophil-like cells by addition of 1.3% DMSO to the culture medium for 10 days.[7]

Section S4. SupraCell construction

Synthesis of SupraCells with ZIF-8 NPs coating. Two million living mammalian cells were rinsed with 1X PBS, and then suspended in 500 μL of 400 μg/mL ZIF-8 NPs in 1X PBS solution. After 10 s vortex, 500 μL of 32 μg/mL tannic acid in 1X PBS solution were added with 30 s vigorous mixing. Then, the living mammalian cells with ZIF-8 NP coatings (SupraCell-ZIF-8) were then rinsed with 1X PBS twice, and stored in culture media.

Synthesis of SupraCells with MIL-100(Fe) NPs coating. Two million living cells were rinsed with 1X PBS and then suspended in 500 μL of 200 μg/mL MIL-100(Fe) NPs in 1X PBS solution. After 10s vortex and 1min incubation, 500 μL of 32μg/mL tannic acid in 1X PBS solution were added with 60 s vigorous mixing. Then, the living mammalian cells with MIL-100(Fe) NP

coatings {SupraCell-MIL-100(Fe)} were then rinsed with 1X PBS twice, and stored in culture media.

Synthesis of SupraCells with MET-3-Fe NPs coating. Two million living mammalian cells were rinsed with 1X PBS, and then suspended in 500 μL of 400 μg/mL MET-3-Fe NPs in 1X PBS solution. After 10 s vortex, 500 μL of 32 μg/mL tannic acid in 1X PBS solution were added with 30 s vigorous mixing. Then, the living mammalian cells with MET-3-Fe NP coatings (SupraCell-MET-3-Fe) were then rinsed with 1X PBS twice, and stored in culture media.

Synthesis of SupraCells with $mSiO_2$ NPs coating. Protocol A): for amine-functionalized $mSiO_2$ NPs, before coating, the synthesized NPs were incubated in a tannic acid solution (0.4 mg/mL in 0.5X PBS) for 3 h and then washed with DI water twice. For living mammalian cells coating, Two million living cells were rinsed with 1X PBS and then suspended in 500 μL of 100 μg/mL MSNs in 1X PBS solution. After 10 s vortex and 1 min incubation, 500 μL of 12 μM benzene-1,4-diboronic acid in 1X PBS solution were added with 60 s vigorous mixing. Then, the living mammalian cells with $mSiO_2$ NP coatings (SupraCell- $mSiO_2$) were then rinsed with 1X PBS twice, and stored in culture media.

Protocol B): for thiol-functionalized $mSiO_2$ NPs, the synthesized NPs were washed with DI water twice. For living mammalian cells coating, Two million living cells were rinsed with 1X PBS and then suspended in 500 μL of 100 μg/mL MSNs in 1X PBS solution. After 10 s vortex and 1 min incubation, 500 μL of 50 μg/mL 4-arm-PEG5K-SH and 50 μM H_2O_2 in 1X PBS solution were added with 60 s vigorous mixing. Then, the living mammalian cells with $mSiO_2$ NP coatings (SupraCell-$mSiO_2$) were then rinsed with 1X PBS twice, and stored in culture media.

Synthesis of SupraCells with Fe_3O_4 NPs coating. Before coating, the bare Fe_3O_4 NPs were incubated in a tannic acid solution (0.4 mg/mL in 0.5X PBS) for several hours and then washed with DI water twice. For living mammalian cells coating, two million living cells were rinsed with 1X PBS and then suspended in 500 μL of 100 μg/mL Fe_3O_4 NPs in 1X PBS solution. After 10s vortex and 1 min incubation, 500 μL of 12 μM benzene-1,4-diboronic acid in 1X PBS solution were added with 60 s vigorous mixing. Then, the living mammalian cells with Fe_3O_4 NP

coatings (SupraCell- Fe_3O_4) were then rinsed with 1X PBS twice, and stored in culture media.

Section S5. Cell viability test

Cell viability of the constructed SupraCells was assessed by CellTiter-Glo 2.0 Assay. Briefly, SupraCell samples were first diluted to the concentration of 50,000 cells/mL, and then 100 μL of the SupraCell samples were added into 96-well plate (White Opaque). After that, 100 μL of CellTiter-Glo 2.0 Reagent was dispensed into each well. The luminescence was recorded 10 minutes after addition of CellTiter-Glo 2.0 Reagent by a BioTek microplate reader. The Cell viability was calculated as a percentage of non-coated mammalian cells.

Section S6. SupraCell shell controlled disassembly or dissociation

SupraCell-ZIF-8 or SupraCell-MIL-100(Fe) were rinsed with 1X PBS, and then suspended in 20 mM EDTA-PBS solution (pH 5.0) for different times (maximum time: 30 min) to allow the controlled disassembly of MOF NP exoskeleton. Then, the cells were rinsed with 1X PBS twice and stored in culture media.

Section S7. Cell culture and proliferation test

Native HeLa cells and SupraCell-ZIF-8 were rinsed with 1x PBS and then incubated with culture media in eppendorf microtubes for 24 h. Under this condition, only few cells attach to the microtube wall and most of cells remain in suspension state. After 2 h or 24 h incubation, SupraCell-ZIF-8 was rinsed with 1x PBS, and then suspended in EDTA-PBS solution to remove the shell. After that, the cells were rinsed with 1x PBS twice and stored in culture media.

For imaging, native HeLa cells and SupraCell-ZIF-8 (stored 2 h or 24 h, followed by disassembly of the exoskeleton) maintained at the density of 100,000 cells/mL were seeded on glass substrates and then cultured at 37 °C and 5% CO_2. The cell samples were imaged using the Leica DMI3000 B inverted microscope.

For the cell proliferation test, native HeLa cells and SupraCell-ZIF-8 (stored 24 h followed by disassembly of the exoskeleton) were assessed by CellTiter-Glo 2.0 Assay. Briefly, 100 μL of cell samples at the density of 100,000 cells/mL were seeded in 96-well plates and then cultured at 37 °C and 5% CO_2. After that, 100 μL of CellTiter-Glo 2.0 Reagent was dispensed into each well. The luminescence was recorded 10 minutes after addition of CellTiter-Glo 2.0 Reagent by a

BioTek microplate reader. The cell proliferation was calculated as a percentage of initial cell samples.

Section S8. SupraCell mechanical characterization

To characterize the mechanical properties of the samples, a Triboindenter TI950 (Bruker-Hysitron) equipped with a standard 2D transducer and Berkovich tip was used. The tip was calibrated using a standard Fused Quartz sample for the required contact depth. To remove the surface roughness effects, the extracted curves with contact depths less than 50 nm have not been used for our data analysis. A rigid glass plate (E ~60 GPa) was used as the substrate for our indentation studies. The extracted stiffness and elastic modulus of the samples have been calculated according to the theory developed by Oliver-Pharr,[8] and using the unloading section of the curves.

Section S9. SupraCell Permeability test

The SupraCell permeability test was performed on SupraCell-MIL-100(Fe) toward a fluorescent glucose sugar of 2-NBDG and a nucleic acid (nuclear) staining dye of Hoechst 33342. Briefly, the native HeLa cells and supra-HeLa cells with MIL-100(Fe) coating were incubated with sugar of 2-NBDG (200 μM) and nuclear staining dye of Hoechst 33342 (3.2 μM) in cell culture media under cell culture condition for 1 h. After incubation, the cell samples were imaged using the Leica DMI3000 B inverted microscope.

Section S10. SupraCell Cytoprotection test

Cytoprotection test to DOX. The cytoprotection test was performed on SupraCell-MIL-100(Fe). Briefly, the native HeLa cells and SupraCell-MIL-100(Fe) were seeded on a 96-well plate at the density of 200,000 cells/mL. Then different concentrations of DOX (0.01, 0.1, 1.0, 10, 20, and 50 μg/ML) were added to the cell culture media under cell culture conditions. After incubation for 2 h, the viability of the cells or SupraCells was measured by CellTiter-Glo 2.0 Assay.

Cytoprotection test to Ag NPs. The cytoprotection test was performed on SupraCell-MIL-100(Fe). Briefly, the native HeLa cells and SupraCell-MIL-100(Fe) were seeded on a 96-well

plate at a density of 200,000 cells/mL. Then, various solutions of different concentrations of Ag NPs (0, 4, 8, and 12 μg/ML) were added to the cell culture media under cell culture conditions. After incubation for 4 h, the viability of the cells or SupraCells was measured by CellTiter-Glo 2.0 Assay.

Section S11. Phagocytosis assay

Phagocytosis studies of GFP-expressing salmonella typhimurium bacteria were performed in 10% FBS with DMSO free IMDM medium which was preheated to 37^{o}C. Bacteria solutions were added to differentiated HL-60 cells and supra-HL-60-MIL-100(Fe) in a 100:1 bacteria/cells ratio, and then incubated for 1 h at 37 °C under rotation. Subsequently, both of the cells were rinsed with 1X PBS twice. Then the cells were incubated with 50 μg/mL gentamicin under cell culture condition for 30min to remove extracellular bacteria. After that, the cells were fixed in 3.7% formaldehyde in 1X PBS at room temperature for 10 min, rinsed with PBS, and then cellular filamentous actin network and nuclei were stained by rhodamine phalloidin and hoechst 33342, respectively. After staining, the cell samples were imaged using the Leica DMI3000 B inverted microscope.

Section S12. SupraCell tolerance at harsh conditions

Tolerance to pH. Native HeLa cells and Supra-HeLa cell-MIL-100(Fe) were rinsed with saline solution (154 mM NaCl), and then suspended in saline solution at the density of 1,000,000 cells/mL. 20 μL of cell saline solution was added on the 96-well plate, and then 80 μL of different pH solutions with the same ion strength were dispensed into the well. The final pH value was adjusted to 4, 5, 6, 7.4, 8, 9, 10, or 11. The plate was then placed in an incubator at 37^{o}C and 5% CO_2 for 1 h. After 1 h incubation, the viability of the cells was measured by the CellTiter-Glo 2.0 Assay.

Tolerance of ion strength. Native HeLa cells and Supra-HeLa cell-MIL-100(Fe) were rinsed with 1X PBS and then incubated in 0.25X PBS, 0. 5X PBS, 0.75X PBS, 1X PBS, 2X PBS, 3X PBS, 4X PBS, 5X PBS for 1 h, respectively. After 1 h incubation, the viability of the cells was measured by the CellTiter-Glo 2.0 Assay. For imaging purposes, the cell samples were fixed in 3.7% formaldehyde in the related PBS solution at room temperature for 10 min, rinsed with PBS,

and then the cellular filamentous actin network and nuclei were stained with fluorescent probes of Alexa Fluor 488 phalloidin and Hoechst 33342, respectively. After staining, the cell samples were imaged using the Leica DMI3000 B inverted microscope and Leica TCS SP8 confocal laser scanning microscope. The cell counting was processed by Image Pro-Plus software.

Tolerance toward ROS. The ROS tolerance test was performed on Supra-HeLa cell-MIL-100(Fe) toward H_2O_2. Briefly, the native HeLa cells and Supra-HeLa cell-MIL-100(Fe) were rinsed with 1X PBS, and then suspended again in 1X PBS. Then, the cell samples were seeded on the 96-well plate at the density of 20,000 cells/well, and then incubated with different concentration of H_2O_2 (0, 2, 4, 6, and 8 mM) in 1X PBS solution at room temperature. After 1 h incubation, the viability of the cells was measured by the CellTiter-Glo 2.0 Assay.

Tolerance toward UV exposure. Native HeLa cells and Supra-HeLa cell-MIL-100(Fe) {or Supra-HeLa cell-MIL-100(Fe) with Congo red dye loading} were rinsed with 1X PBS, and then suspended again in 1X PBS. The cells were seeded on the UV transparent 96-well plate at the density of 200,000 cells/mL. The plate was placed in a home-made dark chamber equipped with compact UV Lamps (4 W lamps, Entela UL3101). The distance between the plate and the UV lamp was adjusted to be 5 cm.[9] After UV irradiation for 2 h (254 and 308 nm, respectively), the viability of the cells was measured by the CellTiter-Glo 2.0 Assay and LIVE/DEAD® Cell Imaging Kit.

Section S13. SupraCell-Modular nanoparticle superassembly

Amine-functionalized $mSiO_2$ NPs with Fluorescein isothiocyanate, Rhodamine B isothiocyanate, and Alexa Fluor™ 633 NHS Ester (Succinimidyl Ester) labeling were used for modular nanoparticle superassembly. Before coating, all the NPs were in a tannic acid solution (0.4 mg/mL in 0.5X PBS) for several hours and then washed with DI water twice. For SupraCell construction, Two million living cells were rinsed with 1X PBS and then suspended in 500 μL of 100 μg/mL mixed $mSiO_2$ (~1:1:1 ratio) in 1X PBS solution. After 10 s vortex and 1 min incubation, 500 μL of 12 μM benzene-1,4-diboronic acid in 1X PBS solution were added with 60 s vigorous mixing. Then, the living mammalian cells simultaneously coated with three kinds of $mSiO_2$ were then rinsed with 1X PBS twice, and stored in culture media.

Section S14. SupraCell-Magnetic manipulation

Magnetic SupraCells were oriented and displaced in the application of an external magnetic field produced by a neodymium magnet. The bright field images were taken by Leica DMI3000 B inverted microscope to evaluate the magnetic manipulation.

Section S15. SupraCell-In situ NO sensing

Supra-Raw 264.7-UiO-66-NH_2 was rinsed with 1X PBS and suspended cell culture media. The cells were seeded on the black 96-well plate at the density of 6,000,000 cells/mL. LPS solution was added to Supra-Raw 264.7@ UiO-66-NH_2 with a final concentration of 20 μg/mL. After that, Supra-Raw 264.7@UiO-66-NH_2 with or without LPS was incubated at 37 °C and 5% CO_2. The presence of NO was determined through fluorescence signals measured by a BioTek microplate reader with excitation at 370 nm and emission at 440 nm. All fluorescence measurements were performed at room temperature.

Section S16. SupraCell Conductivity measurement

Supra-Hela cell-MET-3 (Fe) was deposited on conductive indium tin oxide coated glass slides. For electrical measurements, Keithley 6487 picoammeter/voltage source was retro-fitted inside of FEI Quanta 3D FEG Dual Beam (SEM/FIB) (FEI, Hillsboro, OR, USA) to control and measure the current and voltage between the probe and substrate (Fig. S36). Probe tips are polycrystalline tungsten wire electrochemically etched to an end radius of curvature of less than 250 nm.

Section S17. Figures

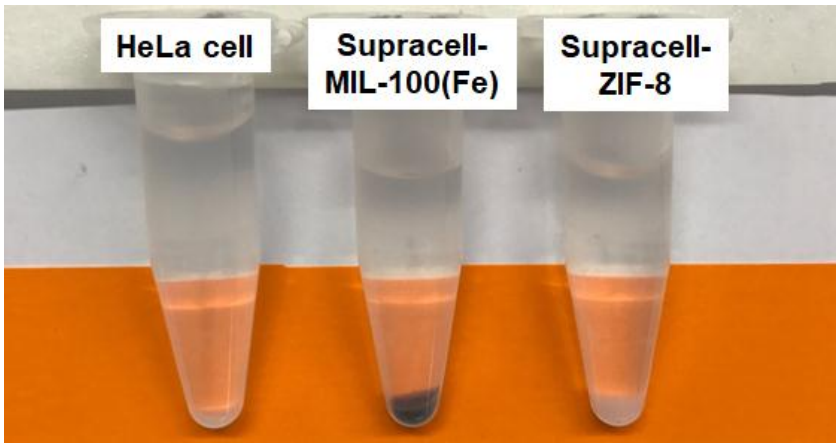


Fig. S1. Optical image of the pellets of HeLa cells, Supra-HeLa cell-MIL-100 (Fe), and Supra-HeLa cell-ZIF-8.

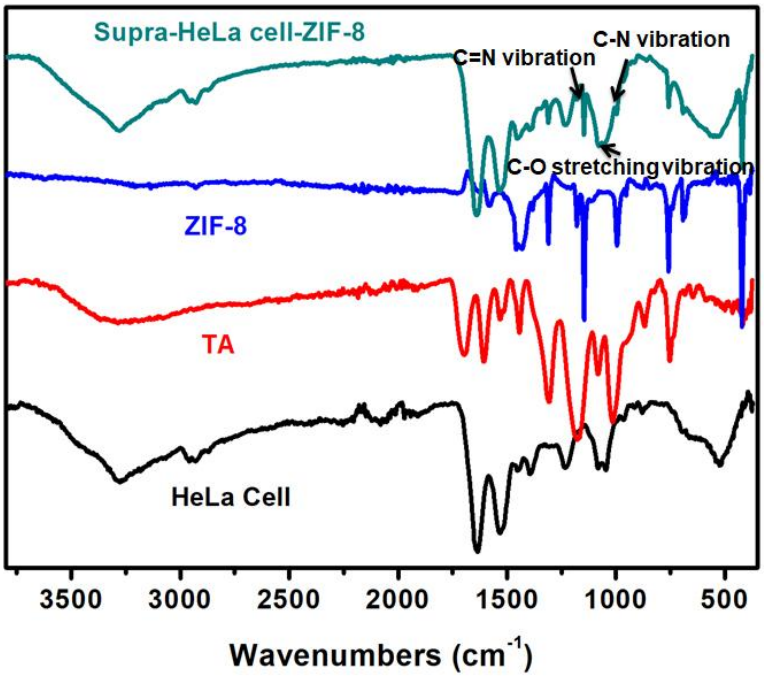


Fig. S2. Fourier transform infrared spectrophotometry (FT-IR) of native HeLa cells, tannic acid, ZIF-8 NPs, and Supra-HeLa cell-ZIF-8.

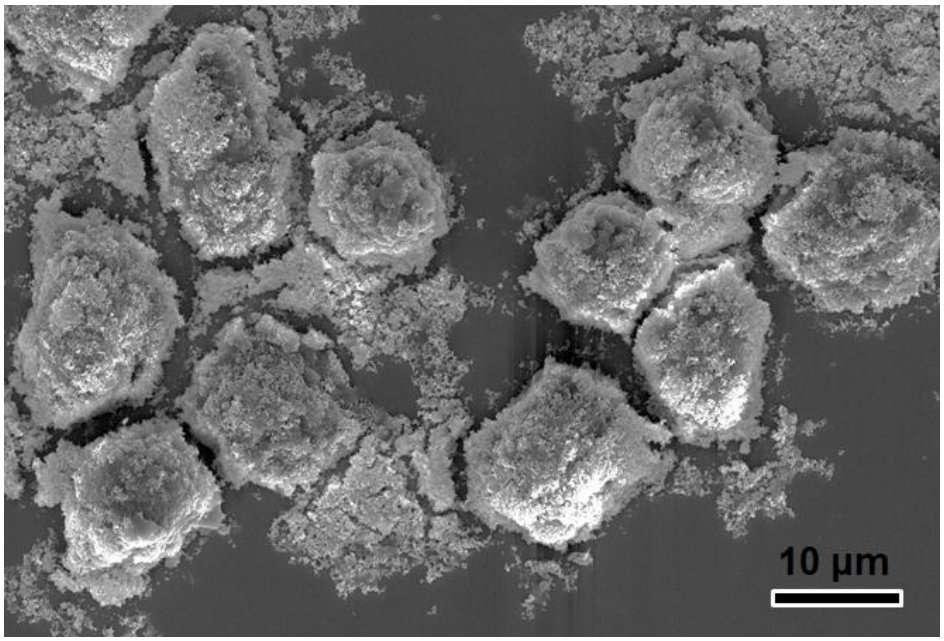


Fig. S3. SEM image of a Supra-HeLa cell-ZIF-8.

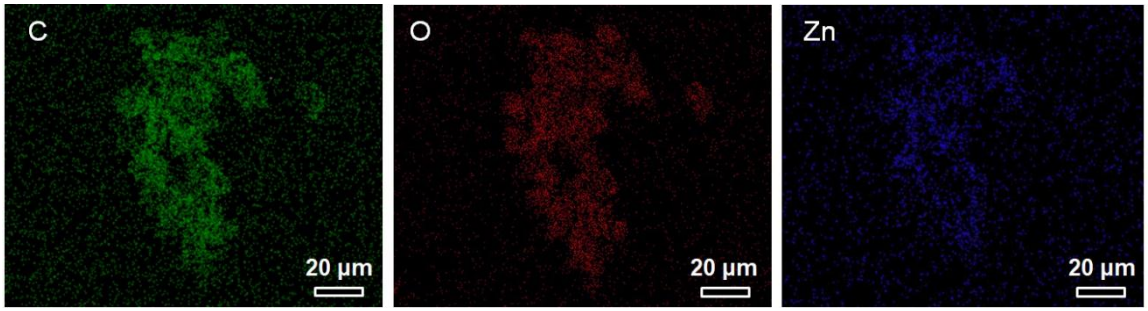


Fig S4. EDS carbon, oxygen, and zinc elemental mappings of the Supra-HeLa cell-ZIF-8.

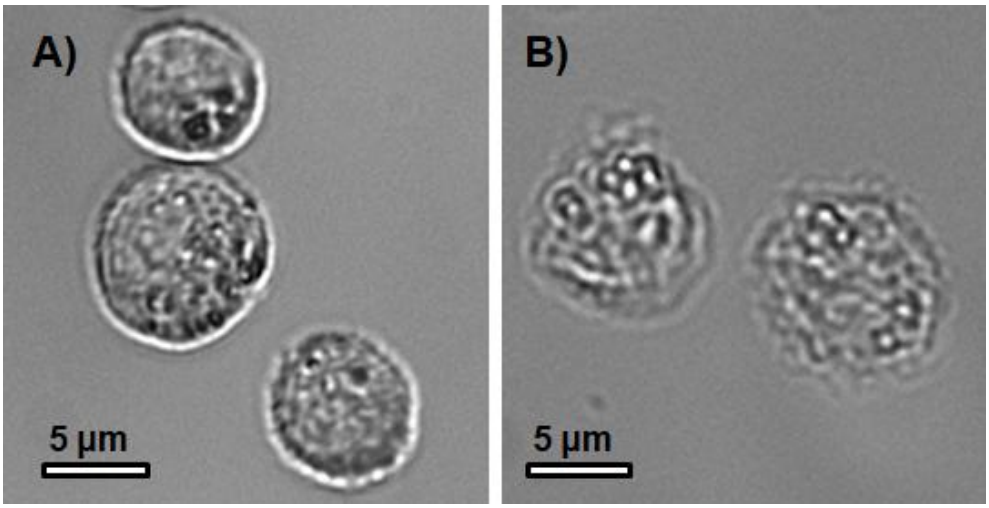


Fig. S5. Bright field images of A549 cell (A) and Supra-A549 Cell-ZIF-8 (B).

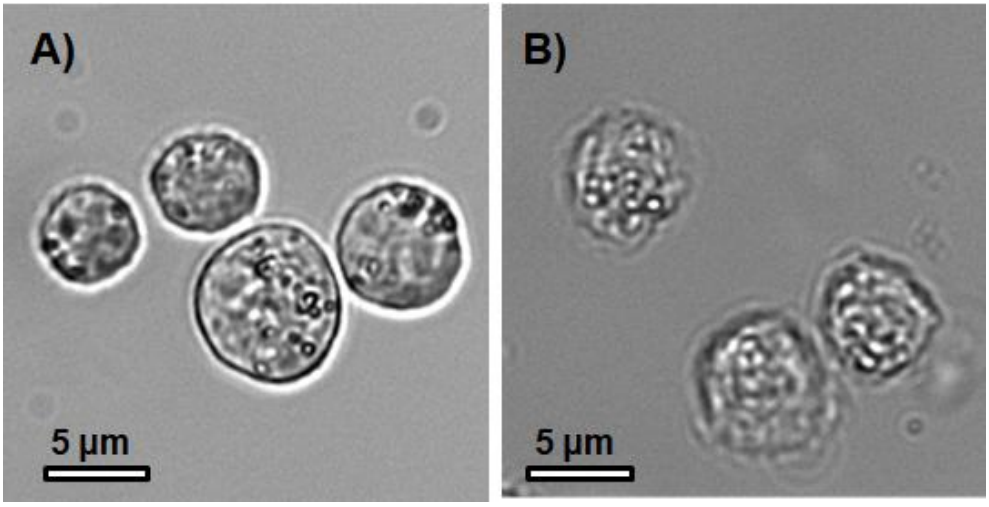


Fig. S6. Bright field images of HL-60 cell (A) and Supra-HL-600 cell-ZIF-8 (B).

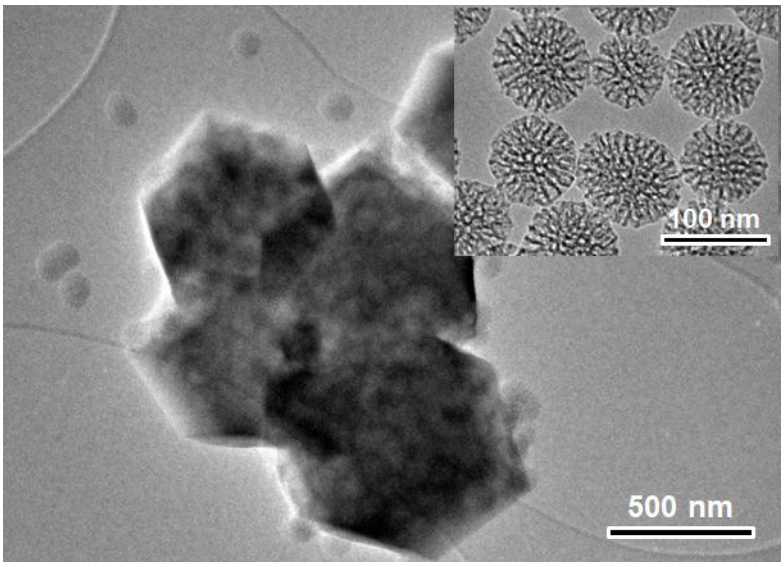


Fig. S7. TEM image of the NP of MSN@ZIF-8; insert is the TEM image of MSN.

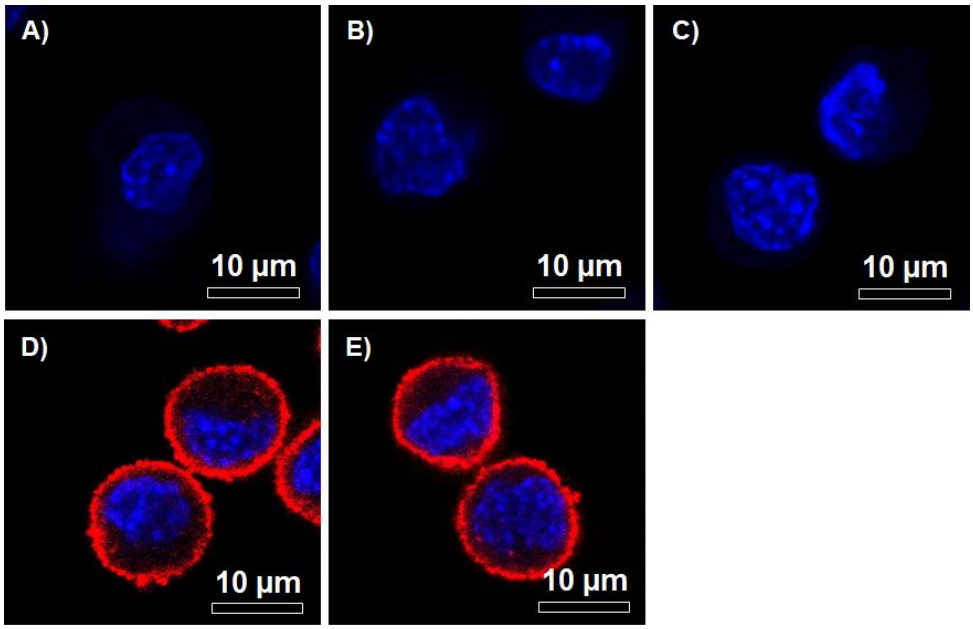


Fig. S8. Fluorescence images of HeLa cell after the coating of different concentrations of Alexa Fluor 647-labeled MSN@ZIF-8 NPs: 10 (A), 20 (B), 60 (C), 100 (D), and 160 (E) µg/mL, where the concentration of TA is a constant of 16 µg/mL. The formed SupraCells have been washed for three times before imaging.

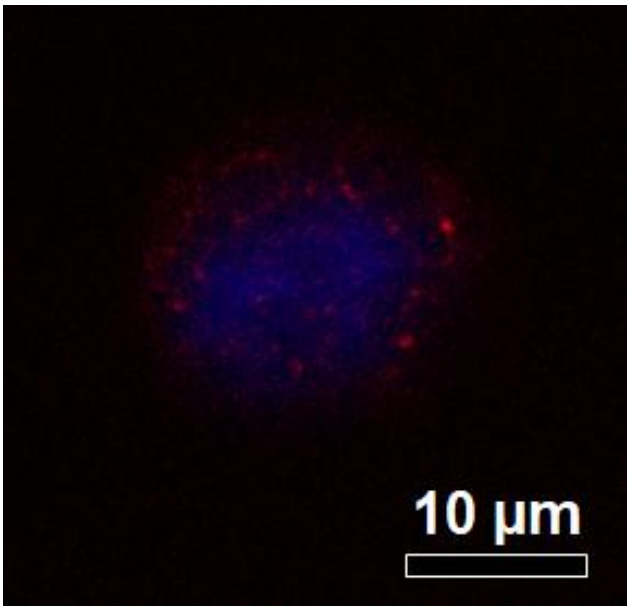


Fig. S9. Fluorescence images of HeLa cell after the coating of Alexa Fluor 647-labeled MSN@ZIF-8 NPs at the concentration of 10 µg/mL, and tannic acid of 16 µg/mL. The formed SupraCells have not been washed before imaging.

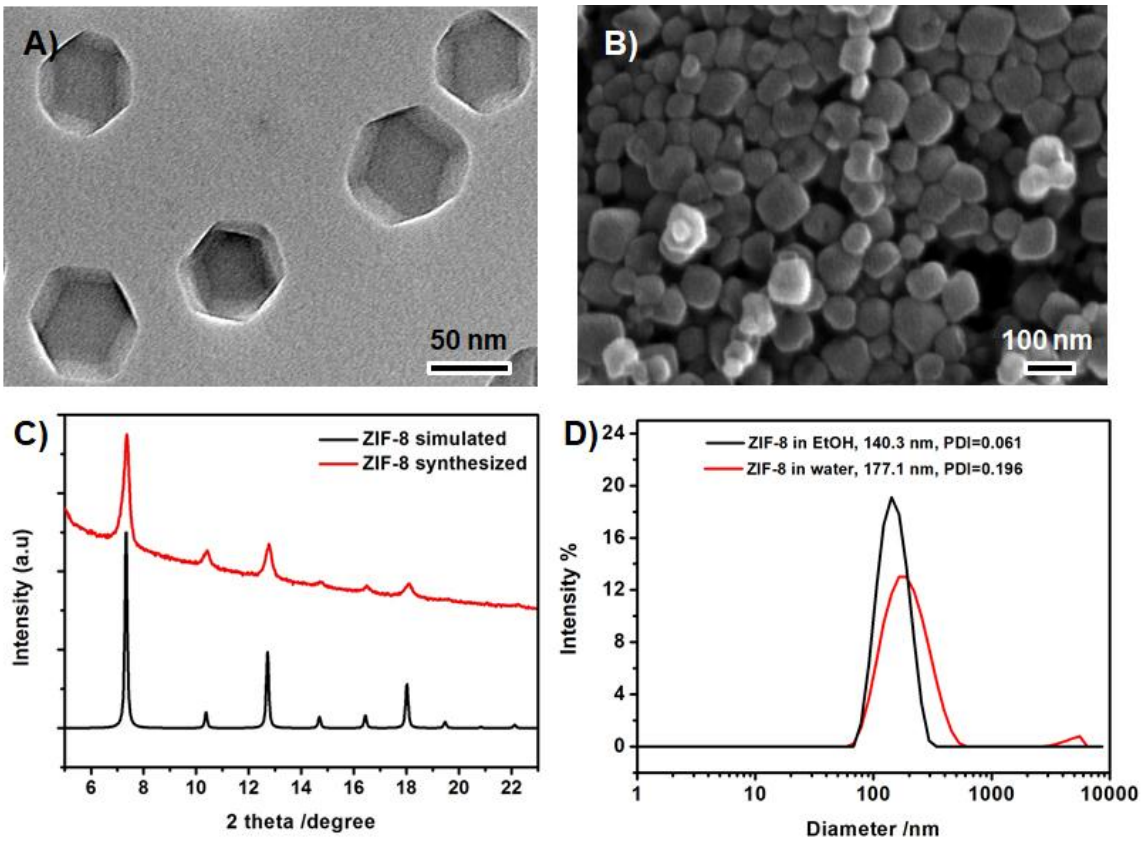


Fig. S10. TEM (A) and SEM image (B) of ZIF-8 NPs. (C) Wide PXRD patterns of the simulated ZIF-8, and as-synthesized ZIF-8. (D) DLS data of the as-synthesized ZIF-8 NPs in water or EtOH.

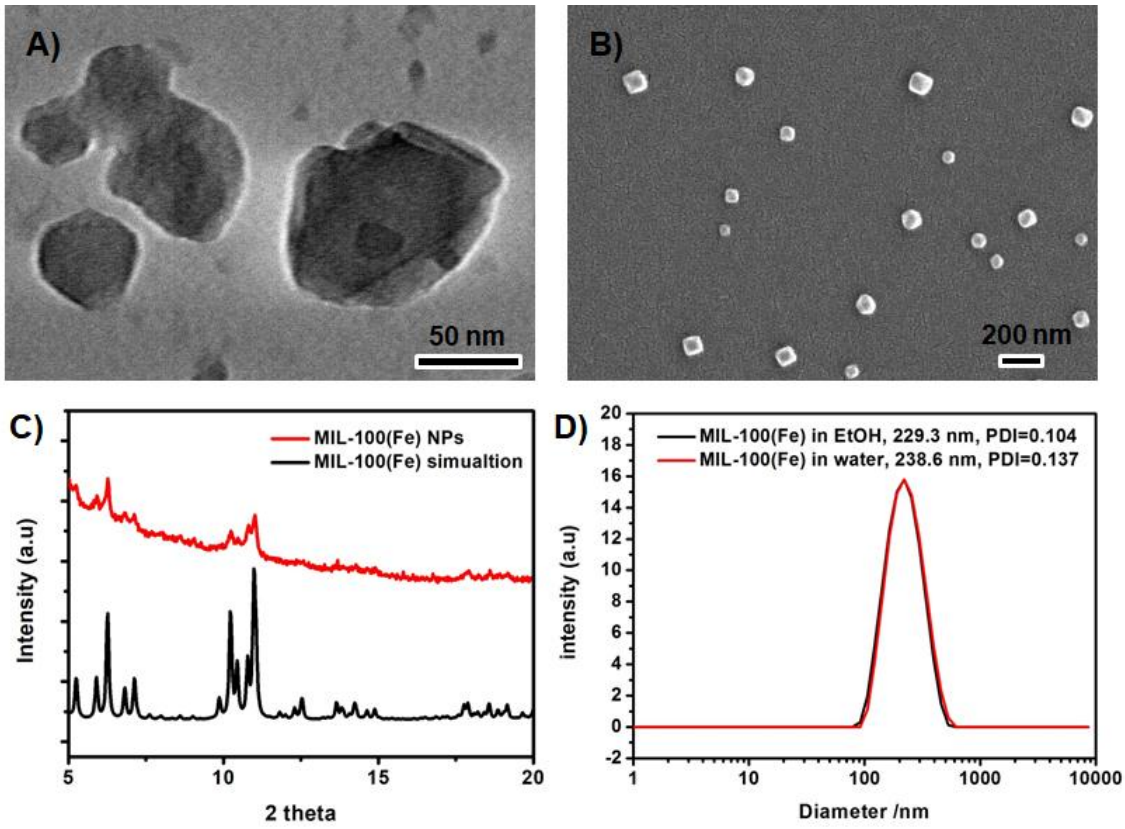


Fig. S11. TEM (A) and SEM image (B) of MIL-100(Fe) NPs. (C) Wide PXRD patterns of the simulated MIL-100(Fe), and as-synthesized MIL-100(Fe). (D) DLS data of the as-synthesized MIL-100(Fe) NPs in water or EtOH.

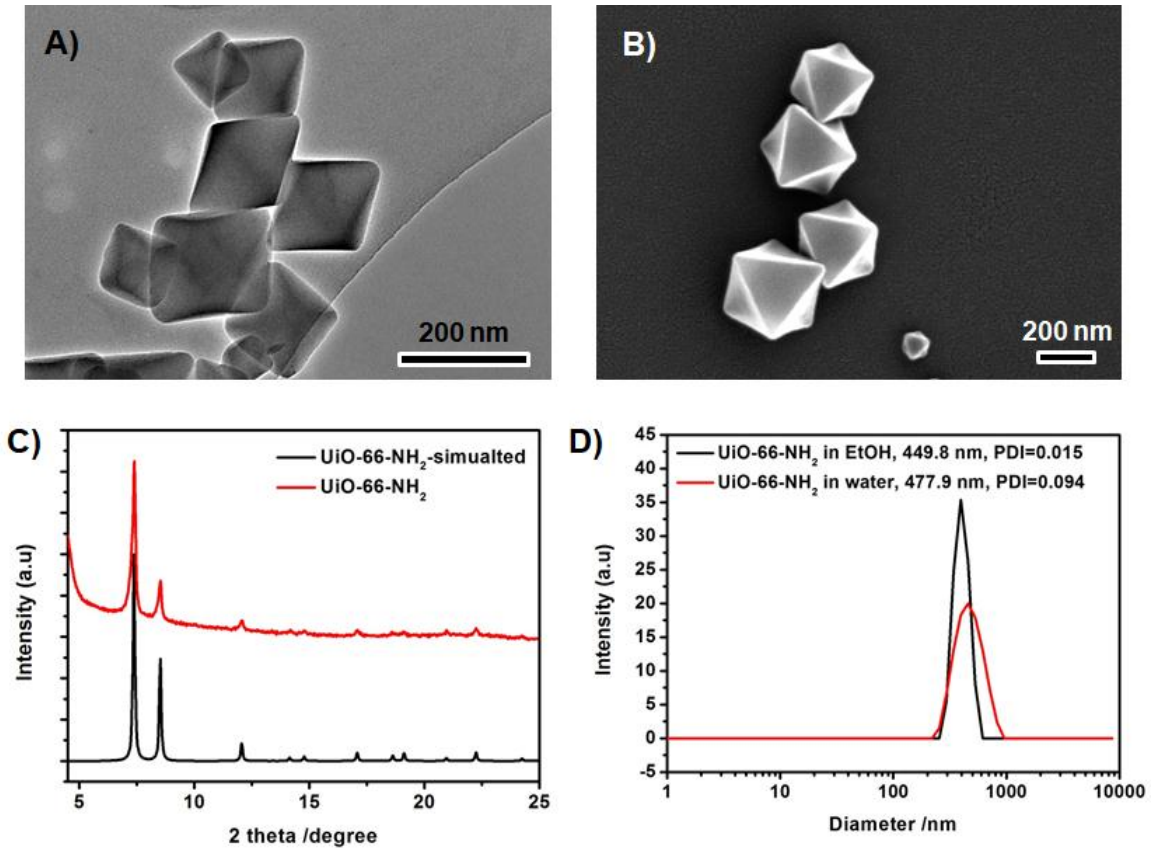


Fig. S12. TEM (A) and SEM (B) image of UiO66-NH_2 MOF NPs. (C) Wide PXRD patterns of the simulated UiO66-NH_2, and as-synthesized UiO66-NH_2. (D) DLS data of the as-synthesized UiO66-NH_2 in water or EtOH.

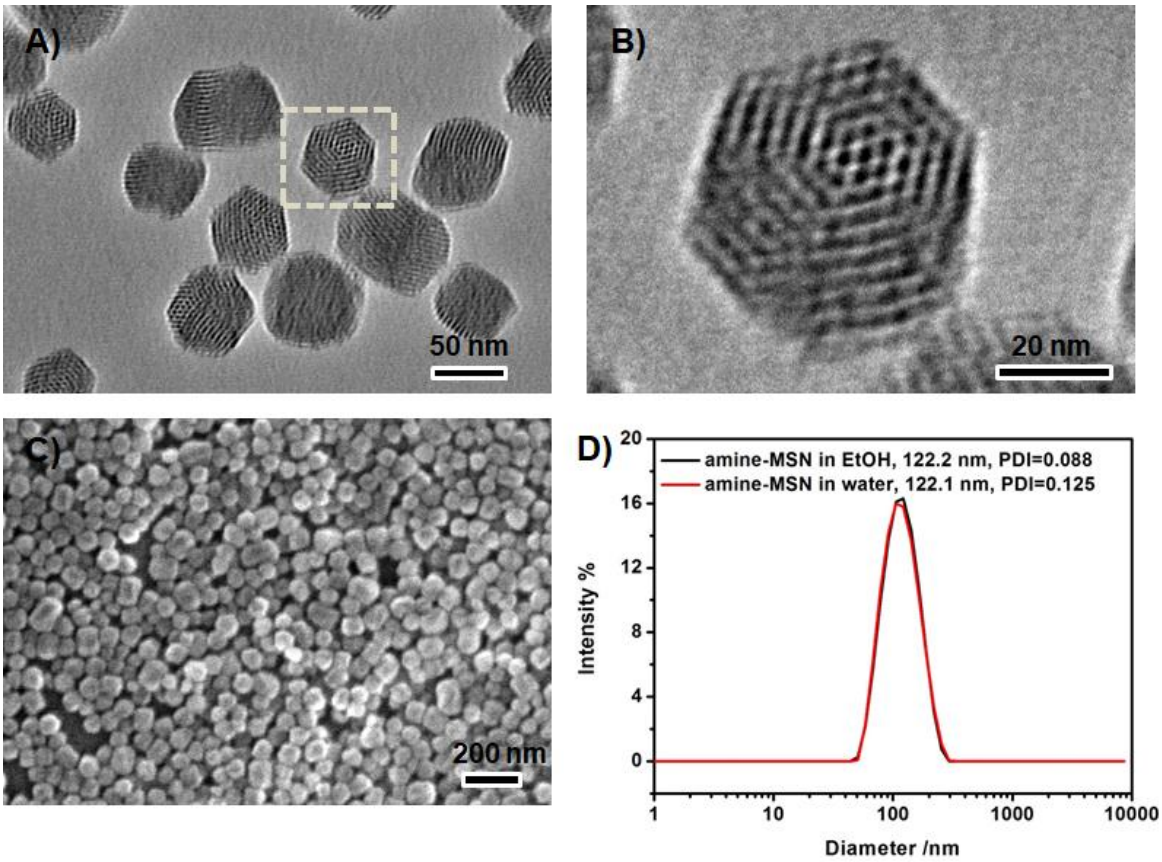


Fig. S13. TEM (A-B) and SEM (C) images of amine-functionalized mesoporous silica NPs; DLS data of amine-functionalized mesoporous silica NPs in water or EtOH.

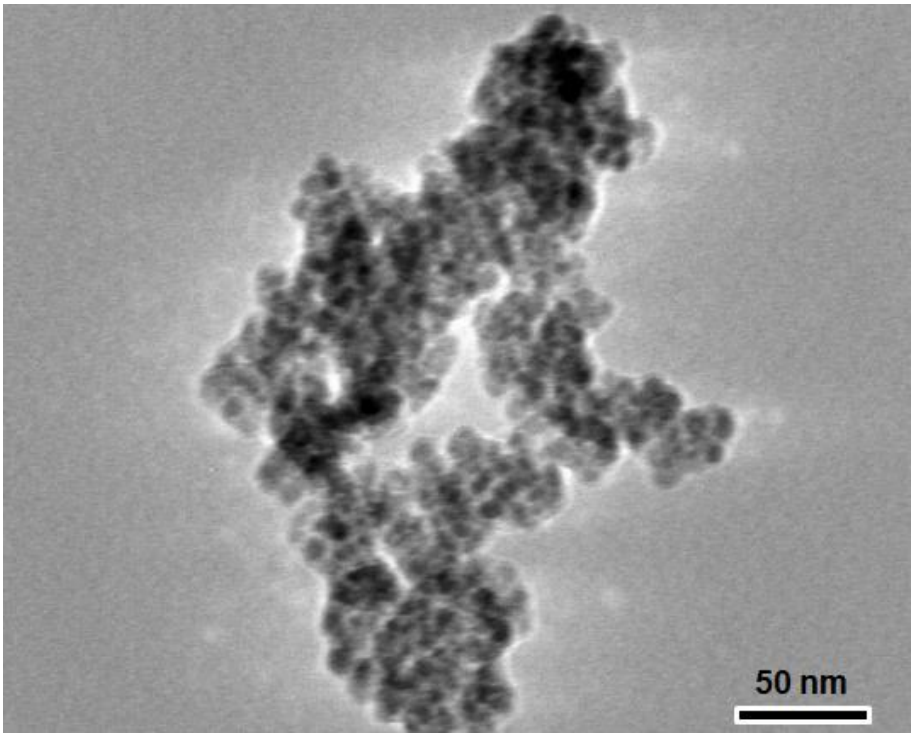
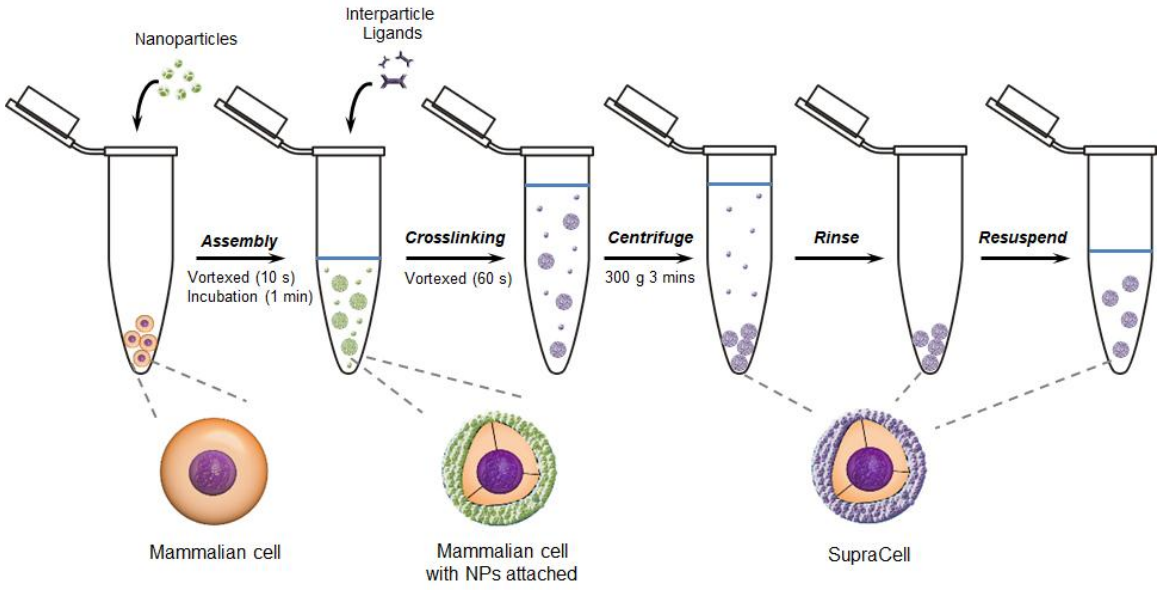


Fig. S14. TEM image of Fe_3O_4 NPs



Scheme S1. Schematic illustration of the fabrication of SupraCells.

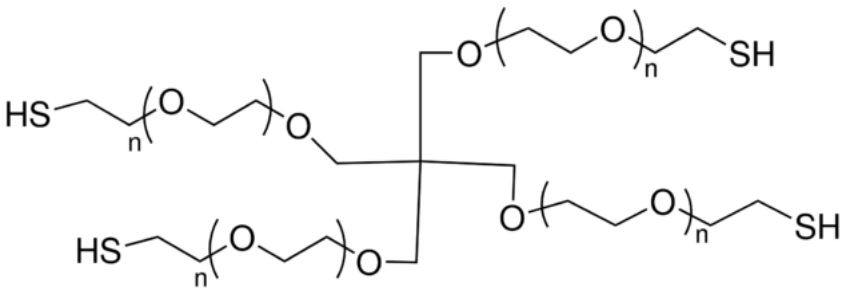


Fig. S15. The molecular structure of 4-arm-PEG5K-SH.

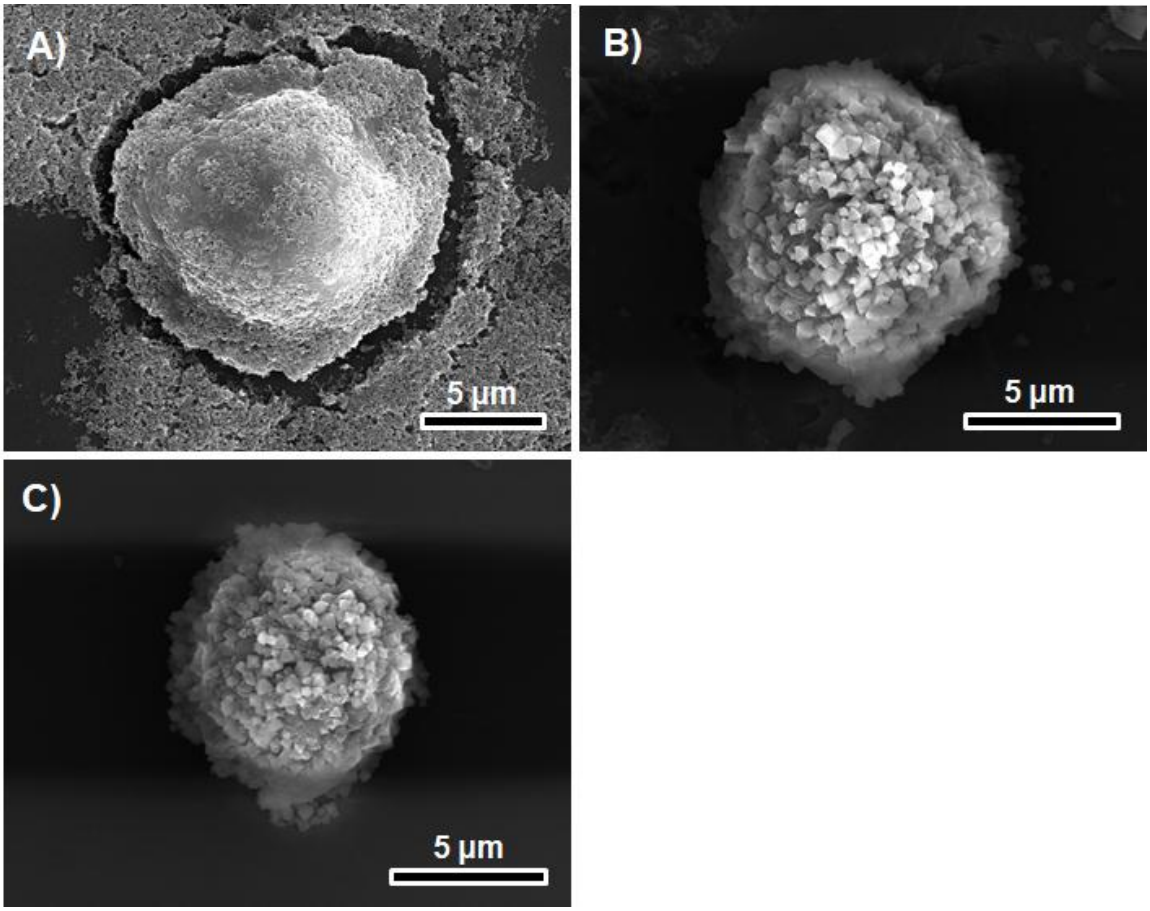


Fig. S16. SEM images of the Supra-HeLa cell-MIL-100 (Fe) (A), Supra- Raw 264.7 cell-UiO-66-NH_2 (B), and Supra-HeLa cell-MET-3(Fe) (C).

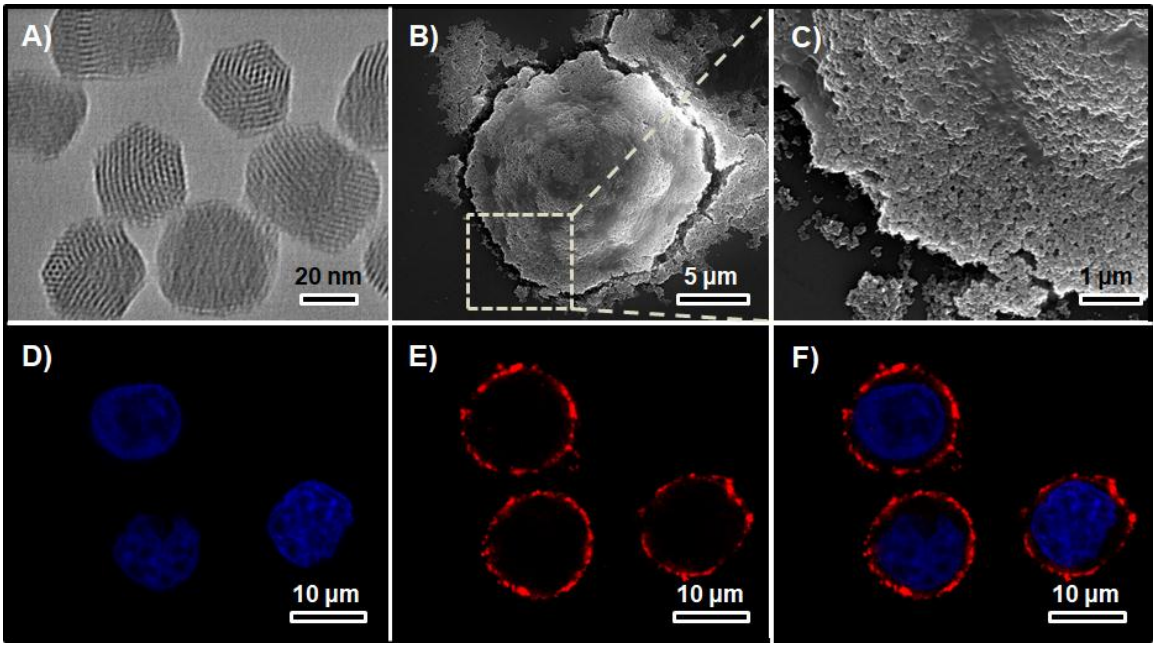


Fig. S17. (A) TEM image tannic-modified mesoporous silica NPs. (B-C) SEM image of Supra-HeLa cell-$mSiO_2$. (D-F) Fluorescence image of Supra-HeLa cell-$mSiO_2$: nucleus, $mSiO_2$ exoskeleton, combined image (from left to right).

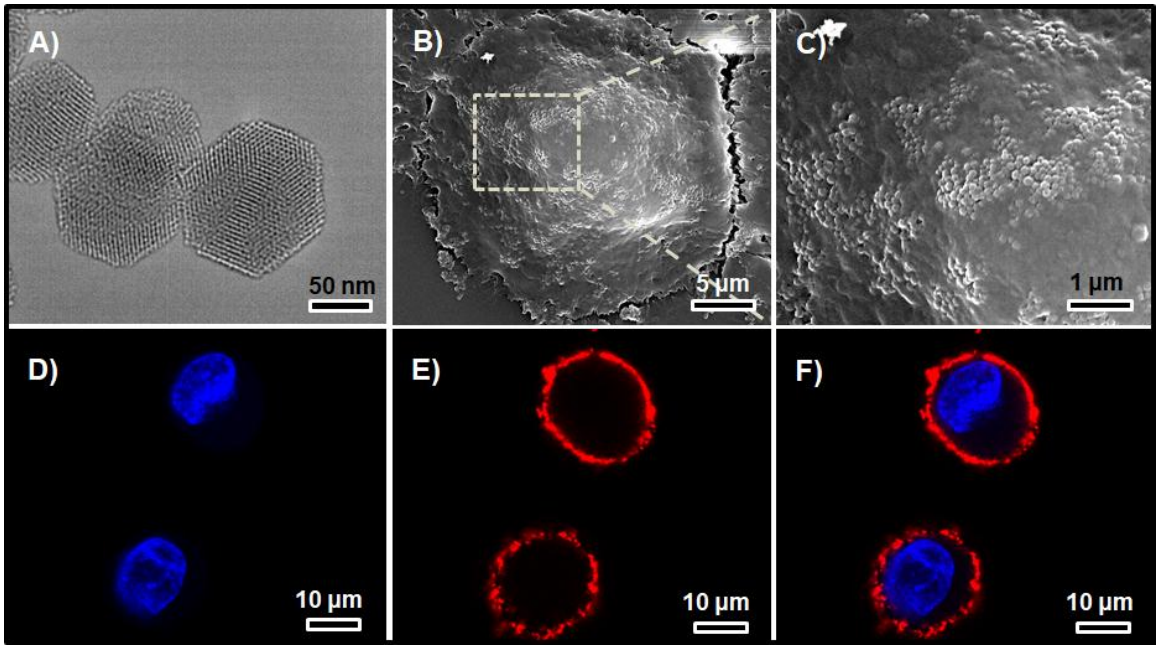


Fig. S18. (A) TEM image thiol-modified mesoporous silica NPs. (B) SEM image of Supra-HeLa cell-$mSiO_2$. (D-F) Fluorescence image of Supra-HeLa cell-$mSiO_2$: nucleus, $mSiO_2$ exoskeleton, combined image (from left to right).

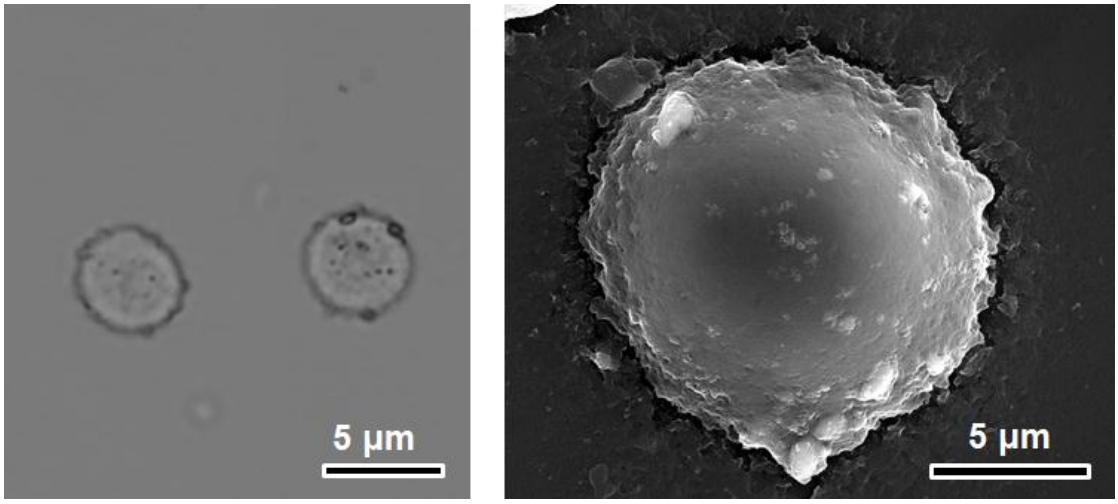


Fig. S19. Optical (left) and SEM image (right) of magnetic Supra-HeLa cell-Fe_3O_4.

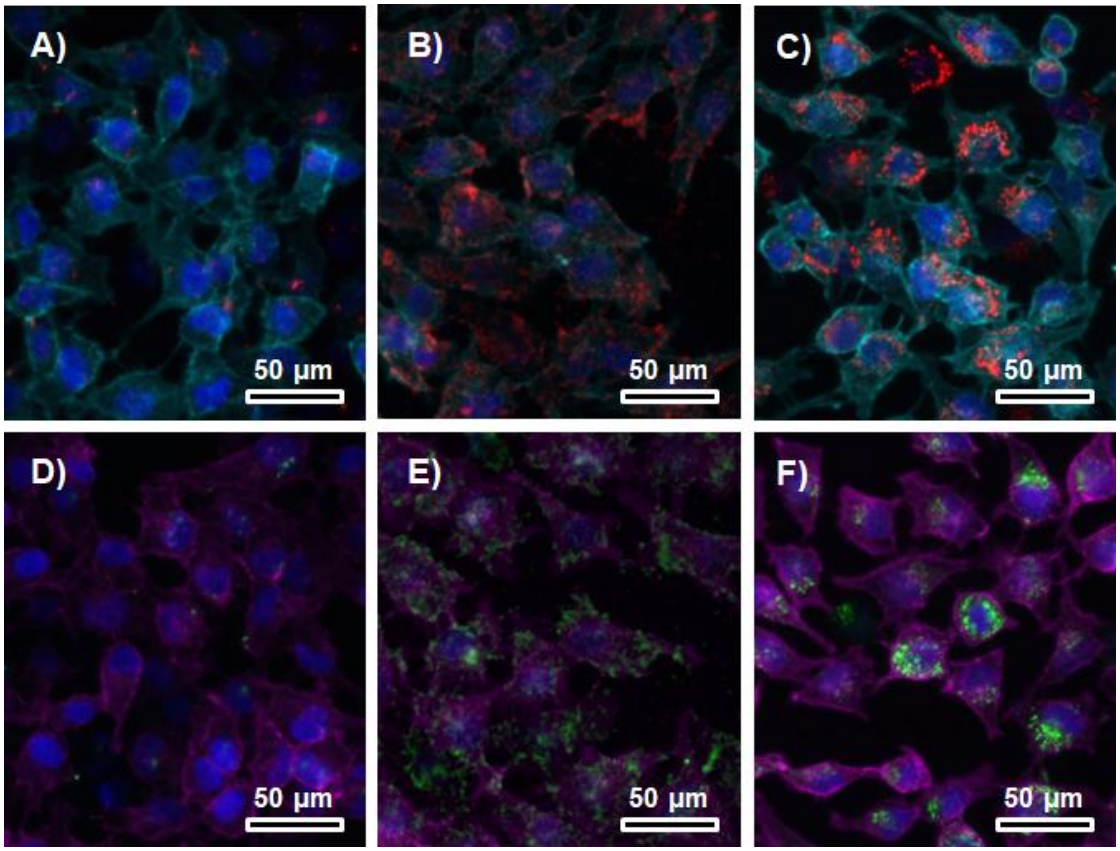


Fig. S20. Fluorescence microscopy images of $mSiO_2$ (red) (A-C) and UiO-66-NH_2 (green) (D-F) NPs internalized by HeLa cells at different time intervals of 5 min (A and D), 1 h (B and E), and 6 h (C and F).

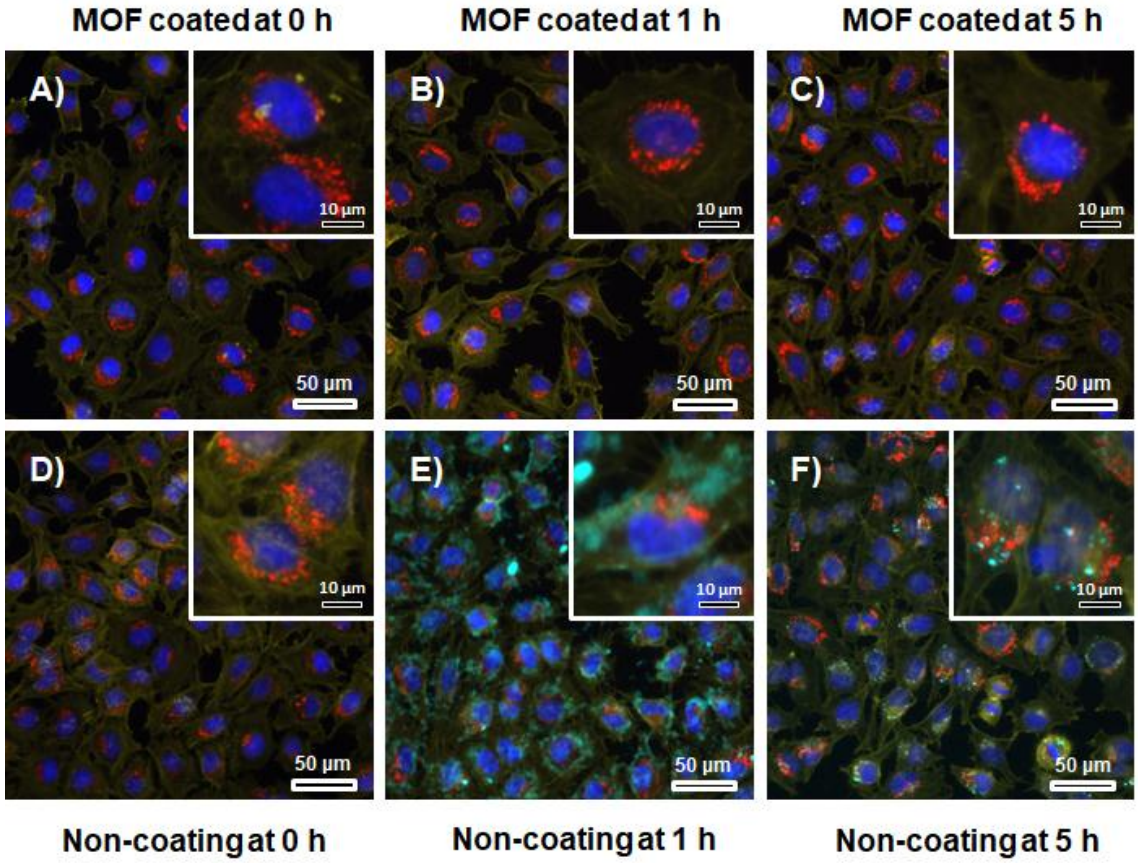


Fig. S21. Fluorescence microscopy images of $mSiO_2$ (cyan) internalized by HeLa cells with or without ZIF-8 NP-based exoskeletons at different time intervals of 0 h (A,D), 1 h (B,E), and 5 h (C,F). At the time of 0 h, the HeLa cells were pre-incubated with $mSiO_2$ (red) for 5 h.

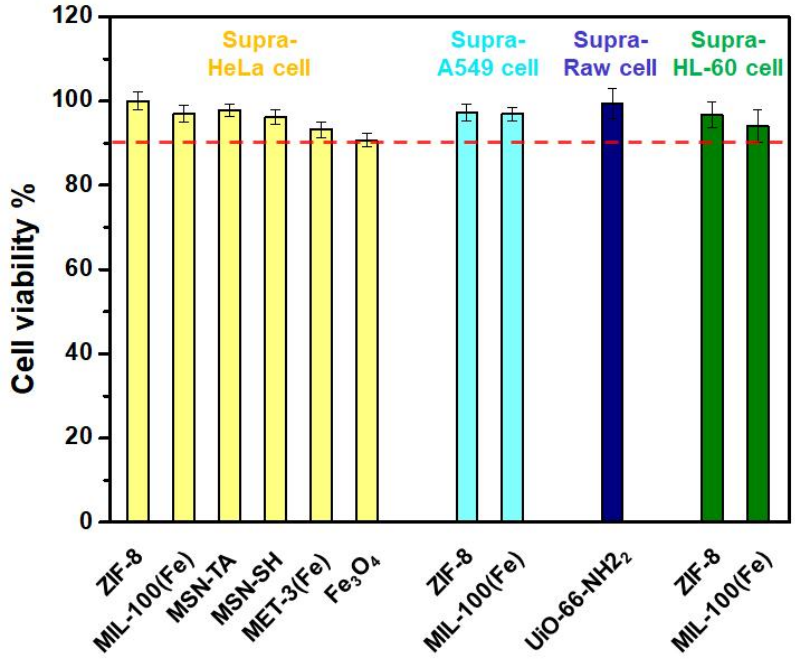


Fig. S22. Cell viability of various SupraCells after NPs coating.

HeLa Cell

ZIF-8 (μg mL^{-1})	0	10	20	50	100	200
mean	100	99.6	99.9	99.1	99.2	98.7
SD	1.7	1.8	3.1	2.8	3.6	2.3
MIL-100 (Fe) (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.8	99.1	99.0	99.5	99.0
SD	2.0	2.2	1.3	2.6	1.9	2.4
UiO-66-NH_2 (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.6	98.2	100.0	99.0	99.9
SD	2.2	2.4	3.5	0.7	2.1	1.6
$mSiO_2$ (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.3	99.4	100.0	99.5	99.9
SD	0.9	2.2	1.3	1.5	1.9	2.3
Fe_3O_4 (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.9	98.5	99.5	98.2	98.4
SD	1.8	1.0	4.2	3.3	2.7	3.2

A549 Cell

ZIF-8 (μg mL^{-1})	0	10	20	50	100	200
mean	100	99.3	99.0	99.1	99.4	99.4
SD	1.8	1.8	3.2	1.9	2.7	3.4
MIL-100 (Fe) (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.7	99.8	99.1	99.1	99.0
SD	1.0	2.3	2.3	2.6	3.0	2.4
UiO-66-NH_2 (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.2	100	99.1	99.1	98.8
SD	2.4	2.7	3.8	1.9	2.4	1.8
$mSiO_2$ (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	99.8	99.2	99.1	99.5	98.2
SD	1.8	1.1	2.1	1.3	2.8	3.3
Fe_3O_4 (μg mL^{-1})	**0**	**10**	**20**	**50**	**100**	**200**
mean	100	98.9	99.1	99.0	99.5	98.7
SD	1.9	3.1	2.3	2.4	2.8	3.3

Table S1. Cytotoxicity profiles of various NPs against HeLa (left) and A549 Cells (right).

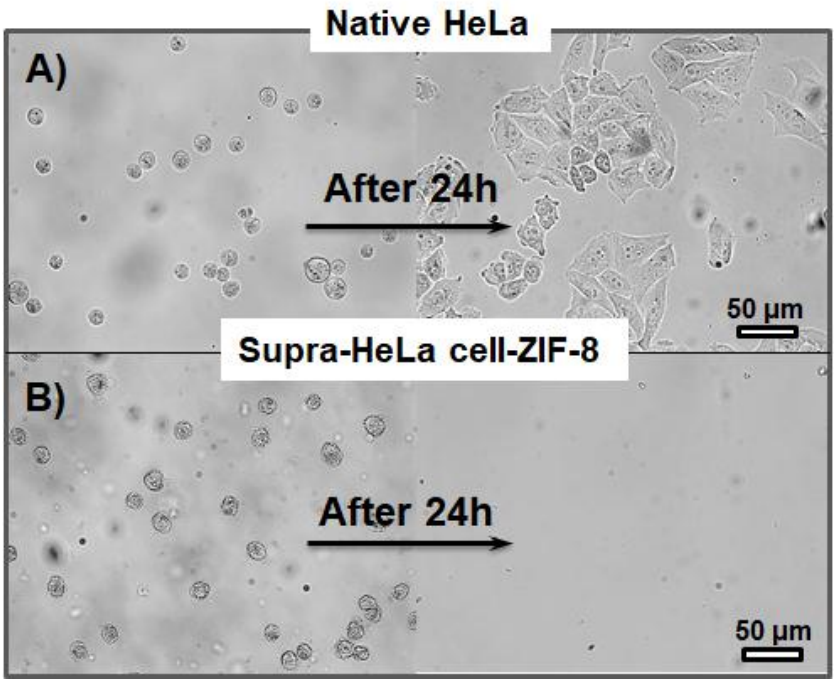


Fig. S23. Optical microscopy images of native HeLa cells (A) and Supra-HeLa cell-ZIF-8 (B) in culture flasks after cell seeding and 24 h culture.

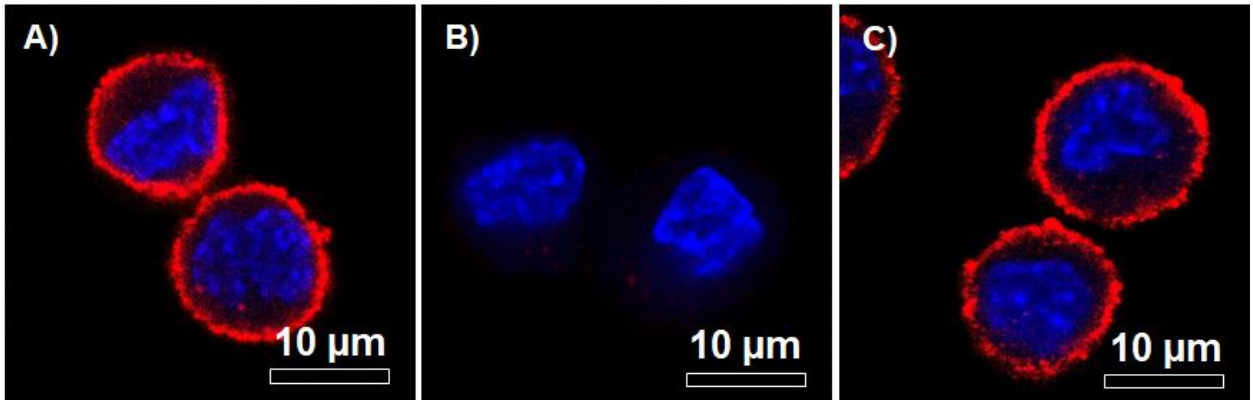


Fig. S24. Fluorescent images of Supra-HeLa cell-Alexa Fluor 647-labeled MSN@ZIF-8 after the treatment of high concentration of EDTA (20 mM, pH 5.0) for 0 min (A), 30 min (B), and low concentration of EDTA (1 mM, pH 7.4) for 30 min.

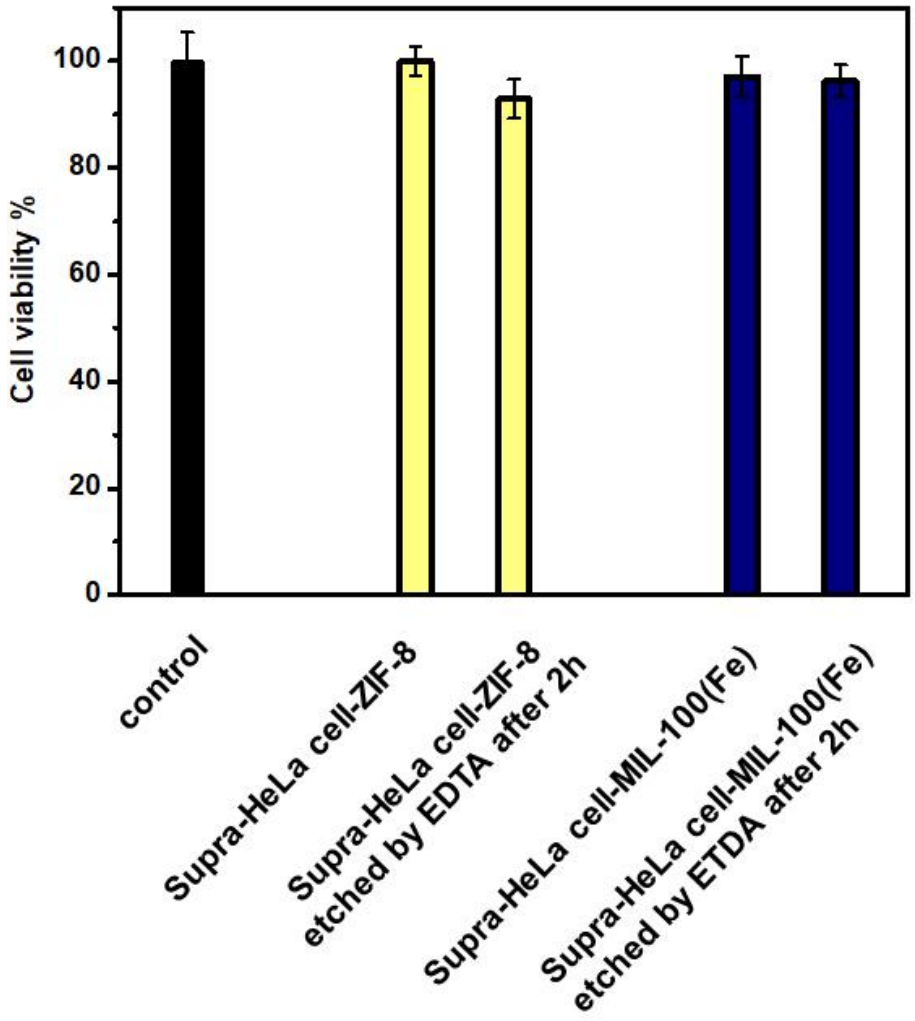


Fig. S25. Cell viability of Supra-HeLa cell-ZIF-8/MIL-100(Fe) after the treatment of EDTA for 30 min to remove the MOF shell.

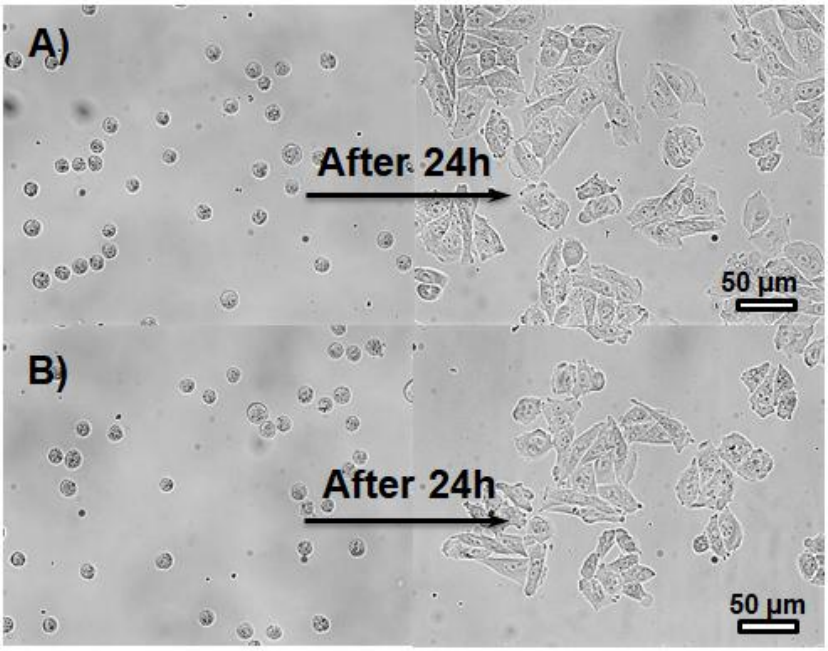


Fig. S26. Supra-HeLa cell-ZIF-8 attachment and proliferation after the removal of ZIF-8 shell at the encapsulation time of 2 h (A) and 24 h (B).

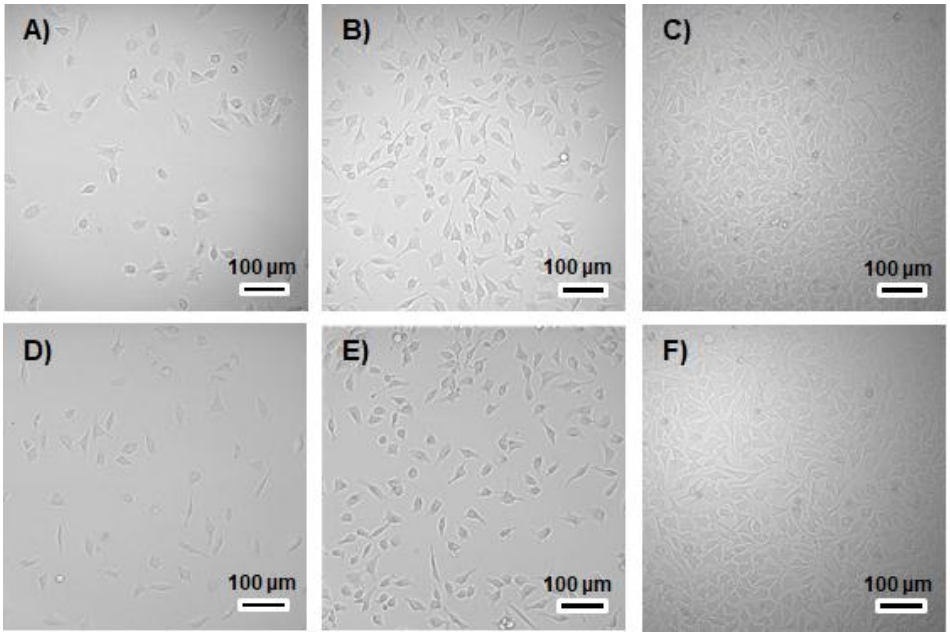


Fig. S27. The proliferation of native HeLa cell (A-C) and Supra-HeLa cell-ZIF-8 after shell removal after the encapsulation for 24 h (D-F) at different time intervals: 6 h, 24 h, and 72 h.

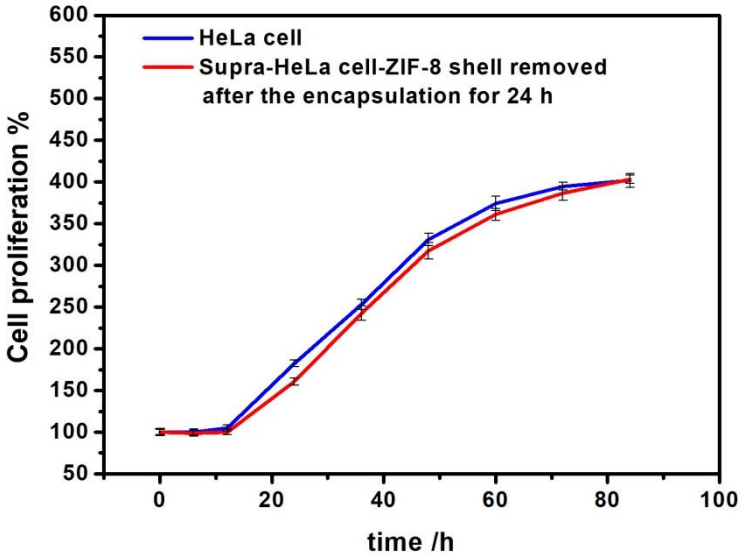


Fig. S28. The cell proliferation rate of native HeLa cell and Supra-HeLa cell-ZIF-8 after shell removal after the encapsulation for 24 h.

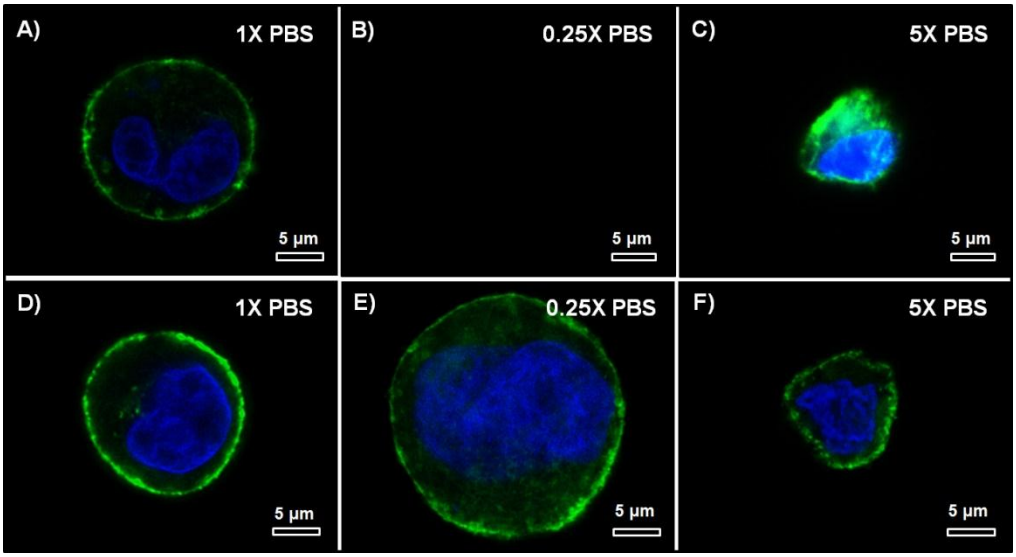


Fig. S29. Confocal image of HeLa cell (A-C) and Supra-HeLa cell-MIL-100(Fe) (D-F) in different PBS solutions: 1X, 0.25X, and 5X, respectively. Clearly, at the hypotonic condition of 0.25X PBS, compared to SupraCells, the control cells rapidly swell and then lyse after the same incubation period (1 h), resulting in nothing to be imaged. On the contrary, the control cells shrink to a greater extent than Supracells under the same hypertonic conditions (5X PBS), indicating the protective effect from the formed exoskeleton.

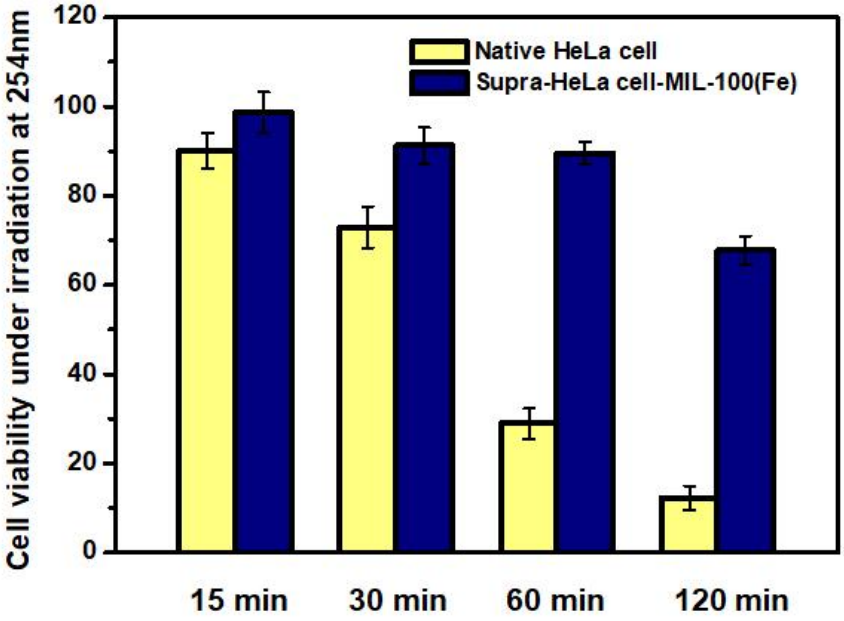


Fig. S30. Cell viability of native HeLa cell and Supra-HeLa cell-MIL-100(Fe) under UV irradiation (254 nm, 4W) for different incubation times.

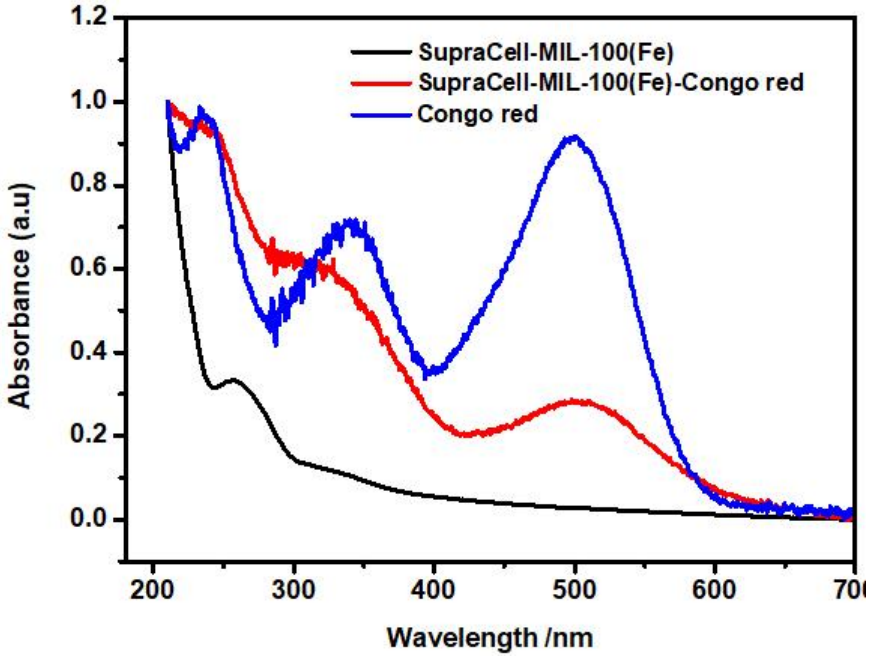


Fig. S31. UV-Vis spectra of Congo red and SupraCell-MIL-100(Fe) based on HeLa cells with or without Congo red dye loading in PBS (1X) solution.

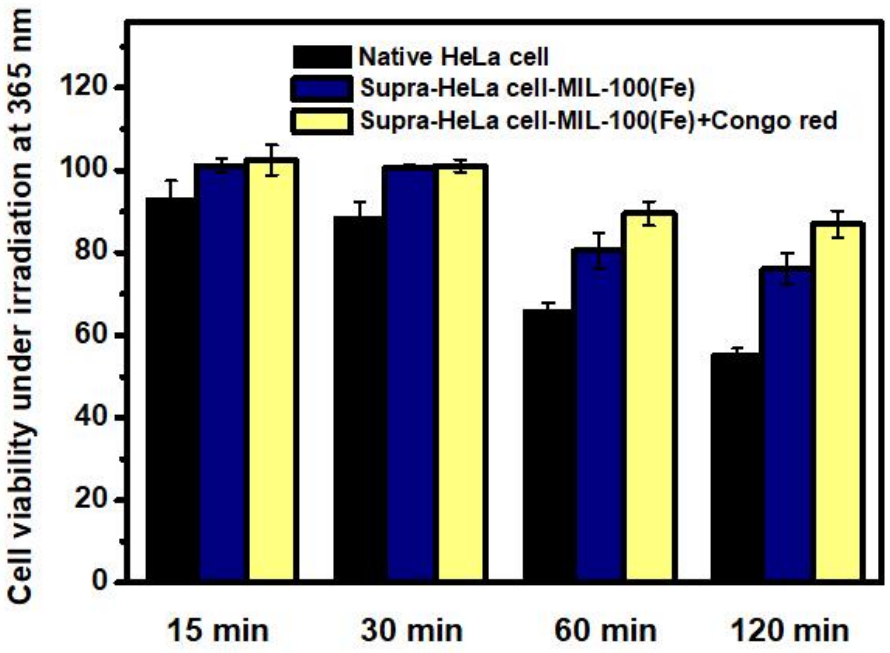


Fig. S32. Cell viability of native HeLa cell and Supra-HeLa cell-MIL-100(Fe) under UV irradiation (365 nm, 4W) for different incubation times.

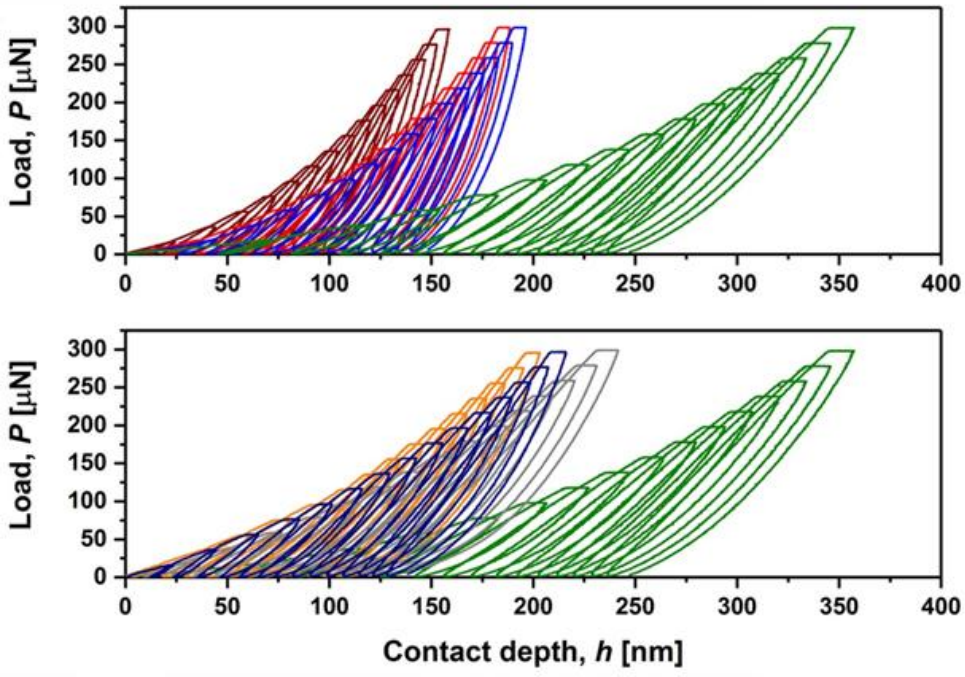


Fig. S33. Loading-unloading curves for native HeLa cells and Supra-HeLa cell-ZIF-8 and Supra-HeLa cell MIL-100(Fe) with different coating thicknesses.

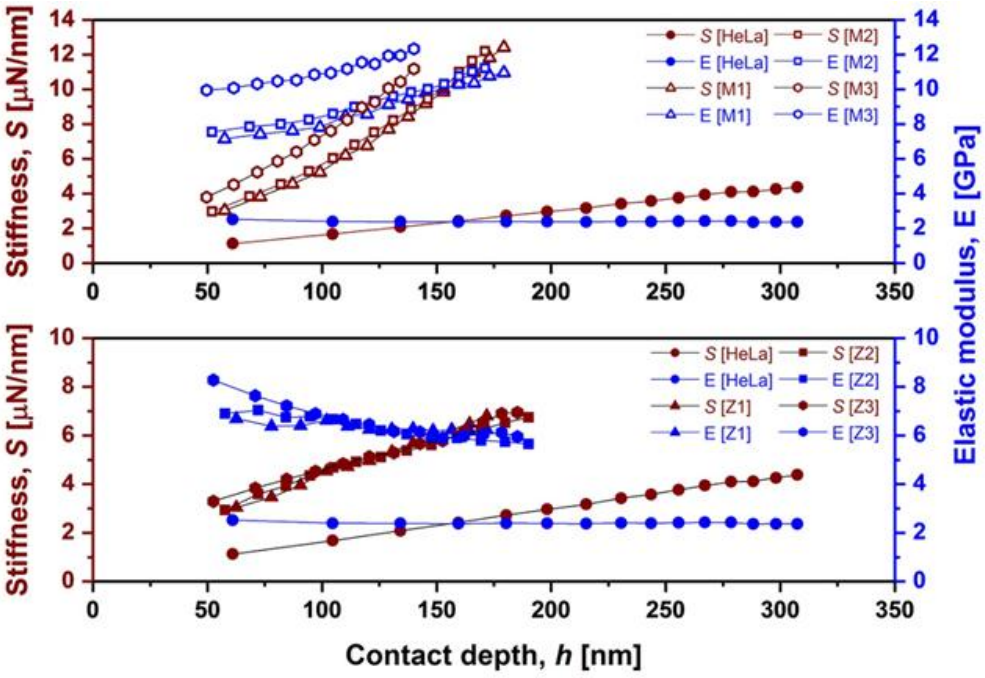


Fig. S34. Stiffness/elastic modulus versus contact depths for Supra-HeLa cell-ZIF-8 and Supra-HeLa cell-MIL-100(Fe) with different coating cycles (Z1-Z3 or M1-M3 means the coating cycles of 1 to 3).

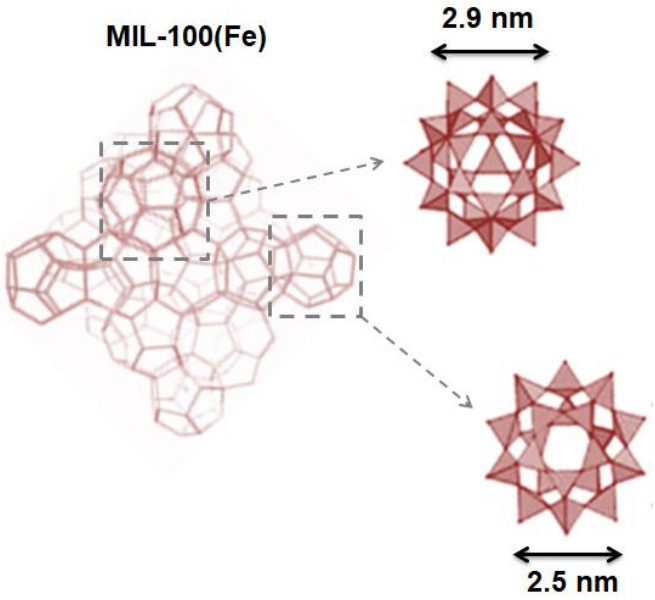


Fig. S35. Schematic illustration of the two mesocages in MIL-100(Fe)

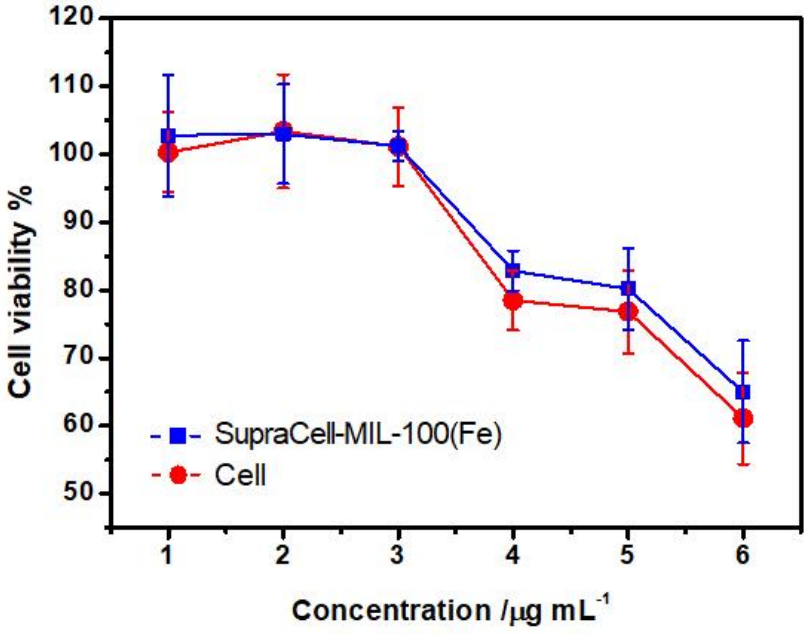


Fig. S36. Size-selective permeability studies of SupraCell-MIL-100(Fe) involving drug (DOX) permeation based on cell viability study.

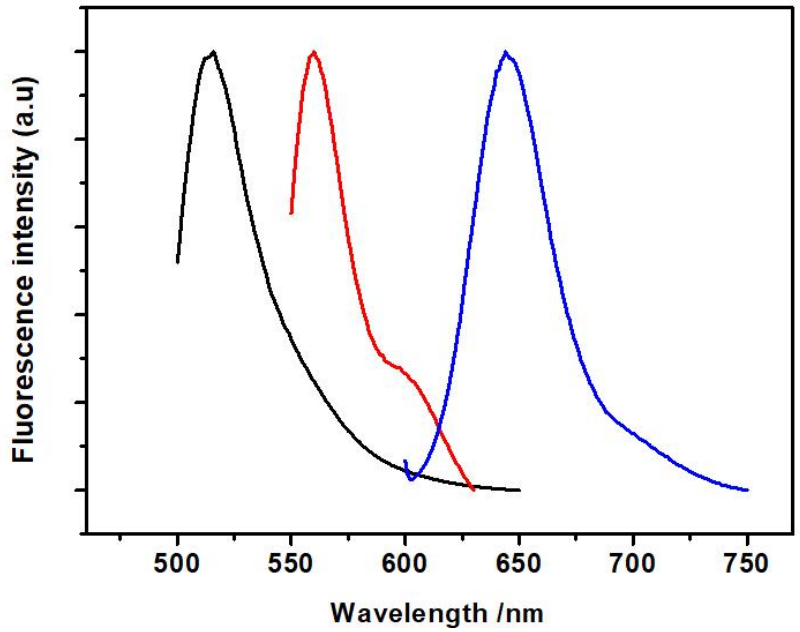


Fig. S37. Fluorescent emission spectra of mesoporous silica NPs functionalized with different fluorescent dyes.

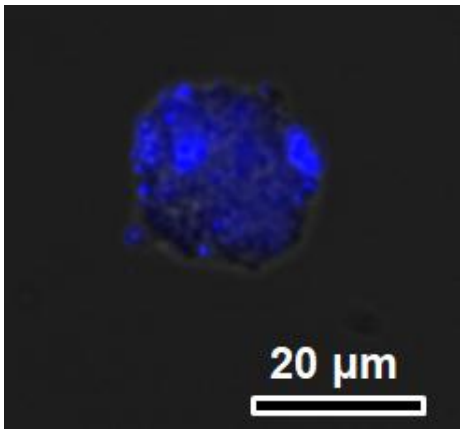


Fig. S38. Fluorescence and DIC image of SupraCell-UiO66-NH_2 based on Raw 264.7 cells for intracellular NO sensing.

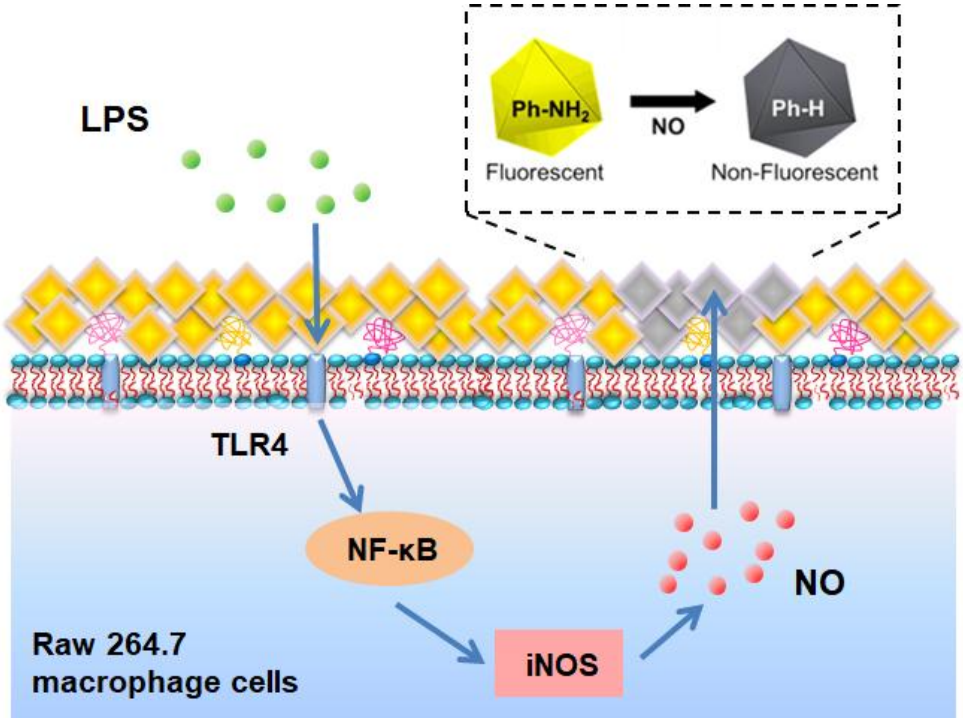


Fig. S39. Schematic illustration of NO activation pathway. Lipopolysaccharide (LPS) cross the MOF layer and bind with the toll-like receptor 4 (TLR4) on Raw 264.7 macrophage cells. Activation of TLR4 by LPS leads to the NF-κB activation and induced the expression of inducible nitric oxide synthase (iNOS), and then release NO. Released NO quenches the fluorescence of the UiO-66-NH_2 MOF NPs.

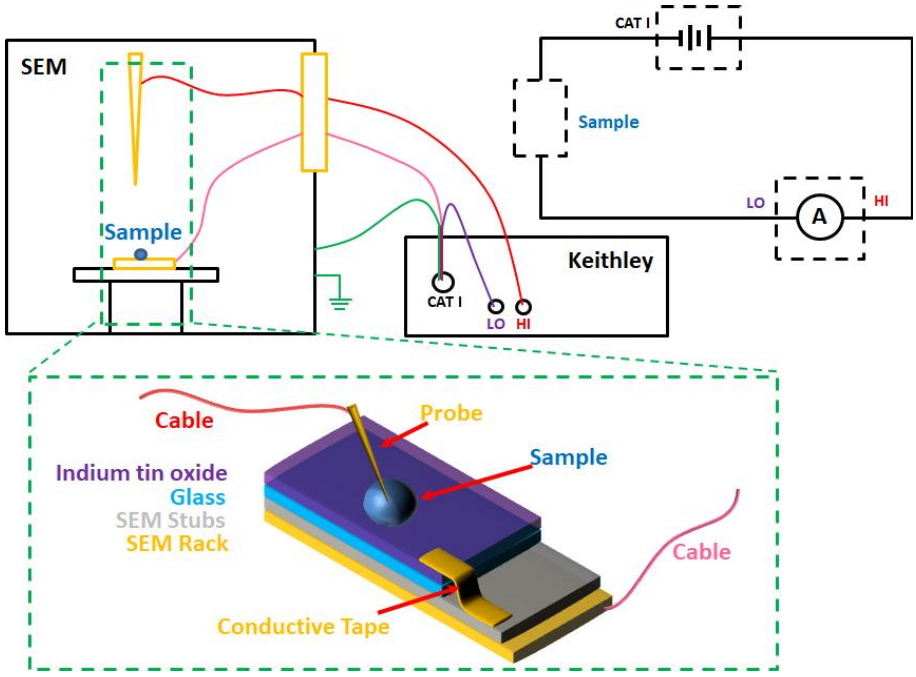


Fig. S40. Schematic illustration of in-situ SEM electrical characterization.

Movie S1.

Bright-field microscopy images of magnetically-actuated SupraCell-Fe_3O_4

Section S18. Supplementary references

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