Supporting Information
For

Stimuli-Responsive Functionalized Mesoporous Silica Nanoparticles for Drug Release in Response to Various Biological Stimuli

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Concentration of AuNPs-capped-MSN calculation

The TGA result presented in this paper shows 1 g of drug loaded AuNPs-Cu^{2+}-MSNs would contain 0.28 g drug, which means the amount of AuNPs-Cu^{2+}-MSNs is about 0.72 g. The inductively coupled plasma-mass spectrometry (ICP-MS) result shows 1 g AuNPs-Cu^{2+}-MSNs would contain 3.91 μg Cu^{2+}, which means 0.72 g AuNPs-Cu^{2+}-MSNs would contain 2.81 μg Cu^{2+}. Thus we can calculate that 1 g drug loaded AuNPs-Cu^{2+}-MSNs contain 0.28 g drug, about 0.72 g AuNPs-MSNs and 2.81 μg Cu^{2+}, and the ratio of MSN : drug : Cu could be calculated to be $1 : 0.39 : 3.9\times10^{-6}$.

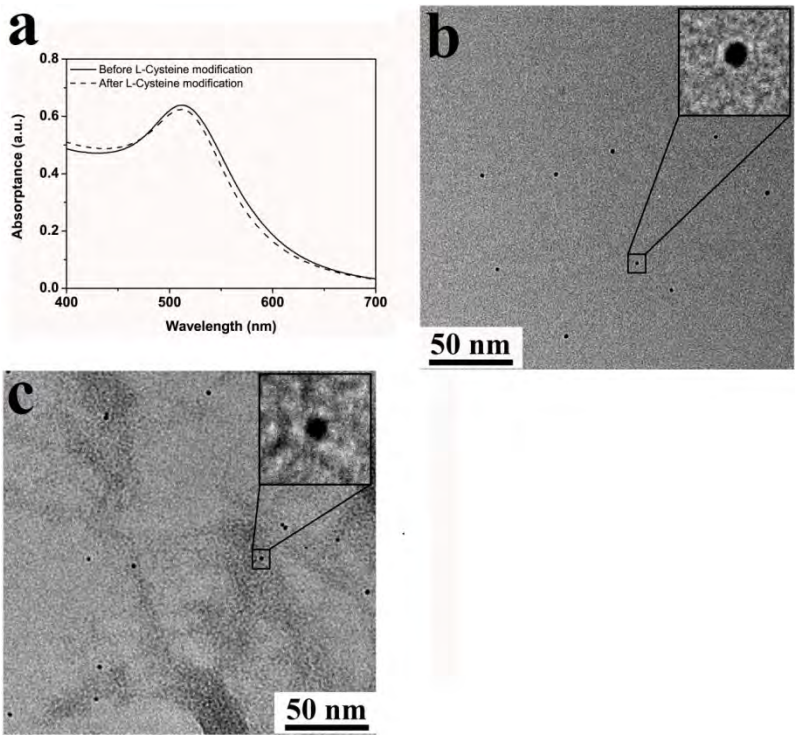

Figure S1. (a) UV-Vis spectra of AuNPs before (solid curve) and after (dash curve) L-cysteine modification. The absorption peak at about 520 nm belongs to the localized surface plasmon resonance (LSPR) for isolated AuNPs nanoparticles. (b) TEM images of AuNPs and (c) TEM images of AuNPs after L-cysteine modification. L-cysteine was presented by the dark area in (c).

Figure S1a shows a UV-vis spectrum of AuNPs before and after functionalization with L-cysteine. The only absorption band at around 512 nm in the UV-vis spectrum represents the localized surface plasmon resonance (LSPR) for isolated nanoparticles, showing the attachment of L-cysteine did not have an obvious effect on the dispersion of AuNPs in solution. Further evidence regarding the structure of these modified AuNPs was provided by transmission electron microscopy (TEM). **Figures S1b** and **S1c** show representative TEM images of the AuNPs and L-cysteine functionalized AuNPs. For both AuNPs and L-cysteine functionalized AuNPs, individually separated particles with 3 nm diameter are observed.

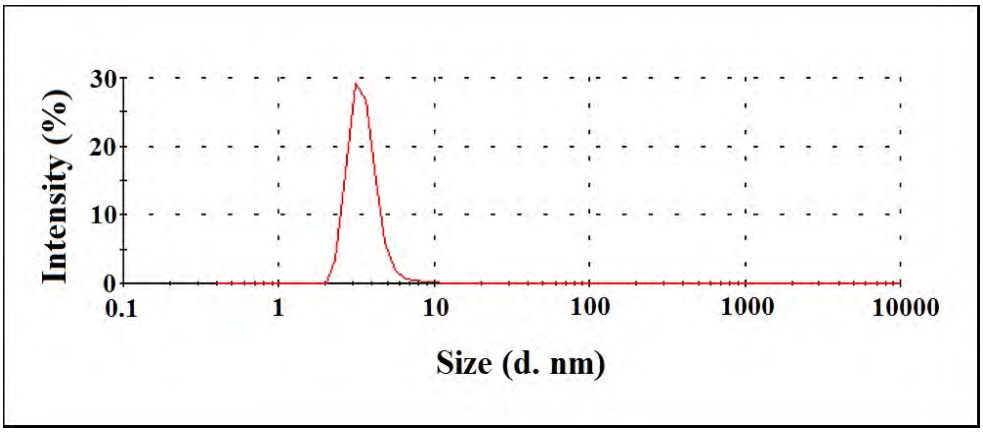

Figure S2 Size distribution of L-cysteine modified AuNPs solution under pH 7 measured by dynamic light scattering with size measured to be 4.338 (PDI=0.156)

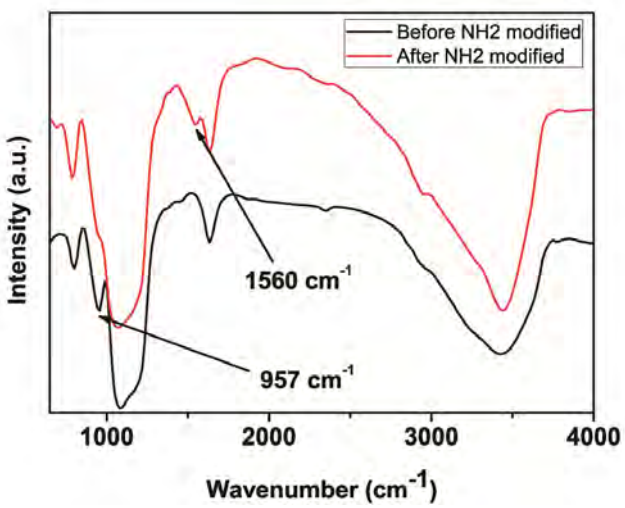

Figure S3. FT-IR spectra of MSN and 3-Aminopropyltriethoxysilane modified MSN (MSN-NH_2). Peak at 957 cm^{-1} belongs to the asymmetric vibration of Si–OH and peak at 1560 cm^{-1} belongs to in-plane bending vibration of N–H from the NH_2 groups. All samples were measured using KBr pellets. Note: The broad peaks between 3000 cm^{-1} and 4000 cm^{-1} are attributed to the –OH from water because of the wet samples.

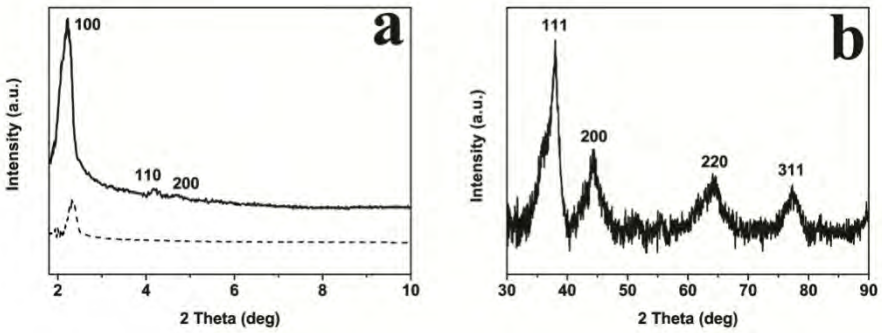

Figure S4. (a) Low angle powder X-ray diffraction patterns (XRD) of the MSN-NH_2 material before (solid line) and after (dashed line) the immobilization of AuNPs. (b) High angle powder XRD of AuNPs-capped-MSN. Peaks in (a) and (b) coincide with the characteristic peaks of MSN and AuNPs respectively.

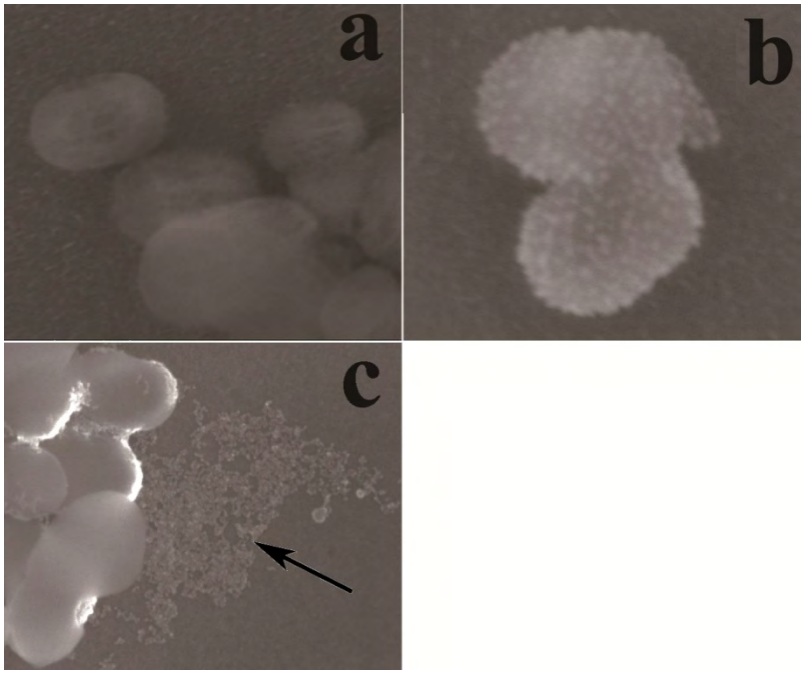

Figure S5. Scanning electron micrographs of MSN (a), AuNPs-capped-MSN under pH 5 (b) and pH 4 (c) for 20 h. Arrow indicates aggregated gold nanoparticles which are represented by white dots on the SEM images. Samples were obtained by dropping 5 μL of established solution onto glass carbon plate, and then dried for 10 h in air.

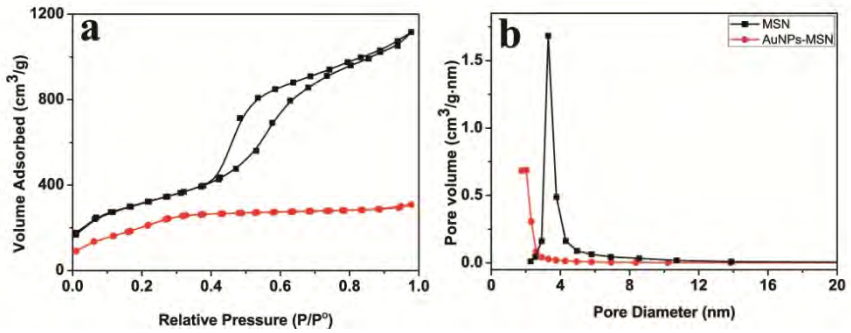

Figure S6. (a) N_2 adsorption desorption isotherms and (b) pore-size distribution of MSN and AuNPs-capped-MSN.

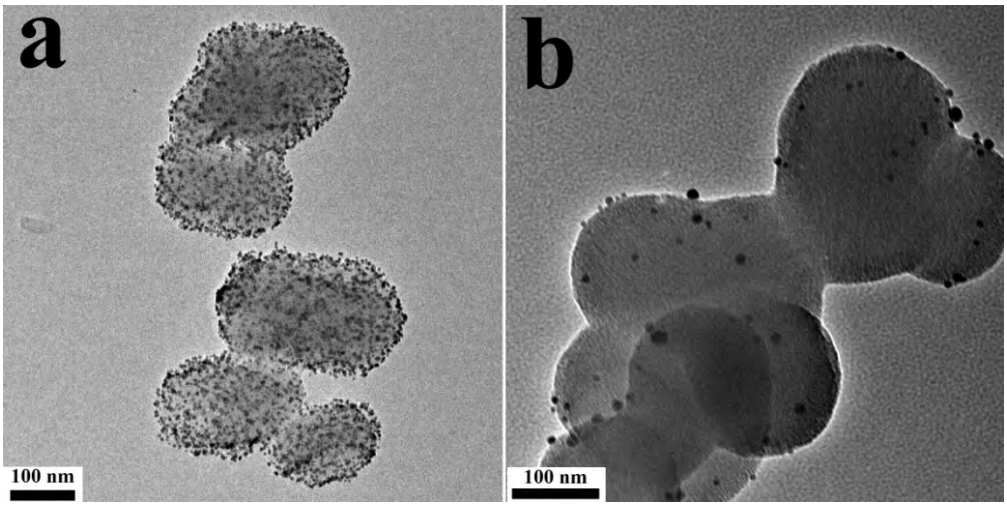

Figure S7. Transmission electron micrographs of L-cysteine functionalized AuNPs and MSN-NH_2 mixed system with (a) and without (b) Cu^{2+} after 20 h.

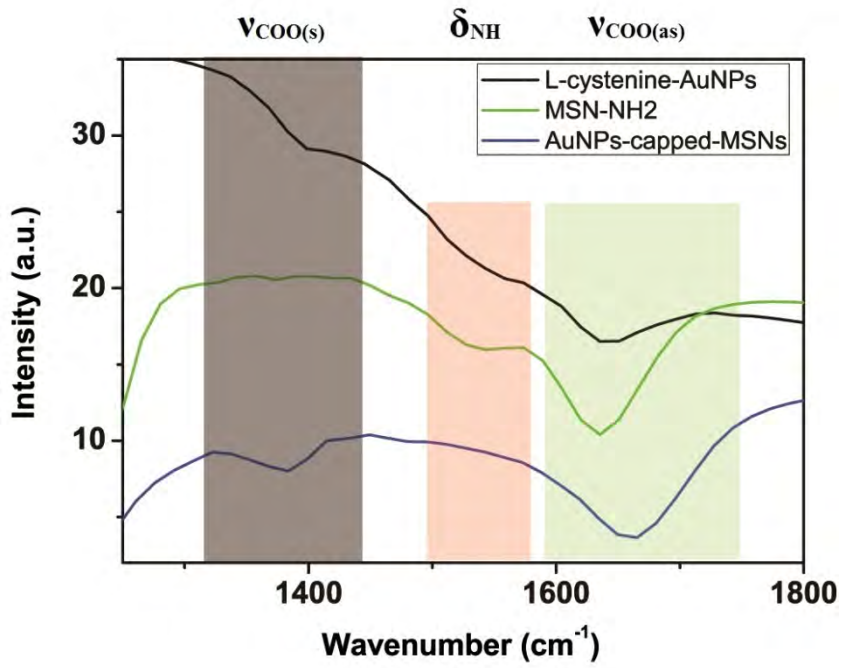

Figure S8. FT-IR spectra of L-cysteine functionalized AuNPs (L-cysteine-AuNPs, black line), 3-aminopropyltriethoxysilane modified MSN (MSN-NH_2, green line) and AuNPs-capped-MSNs with Cu^{2+} as linker (Blue line). The peaks in grey area belong to the symmetric vibration of COO^-, peaks in green area belong to the asymmetric vibration of COO^- and peaks in red area are the in-plane bending vibration of N–H from the NH_2 groups. All samples were measured using KBr pellets. Note: The peak at about 1635 cm^{-1} for MSN-NH_2 is attributed to the Si–H_2O because of the wet samples.

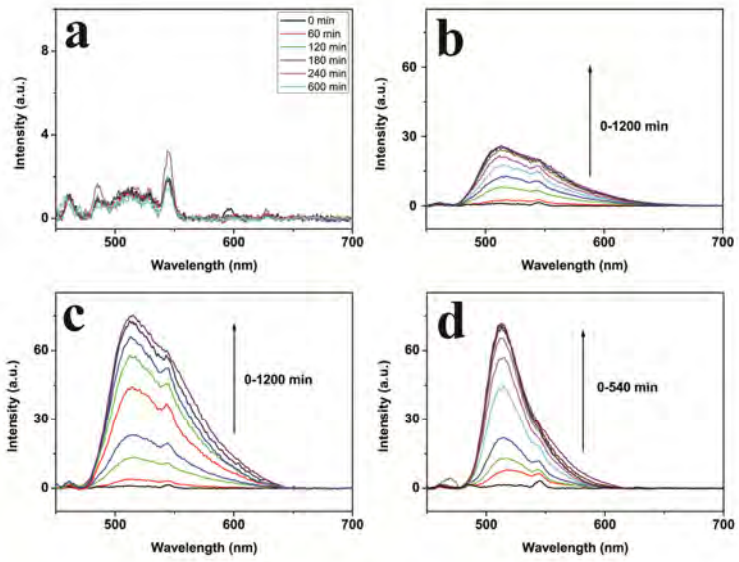

Figure S9. Fluorescence spectra of fluorescein sodium loaded AuNPs-capped-MSN at pH 5 (a), 4.5 (b) and 4 (c) with increasing of release time. (d) Fluorescence spectra of fluorescein sodium loaded MSN at pH 7 with increasing of release time. (Exc. λ = 490 nm, Em. λ = 512 nm)

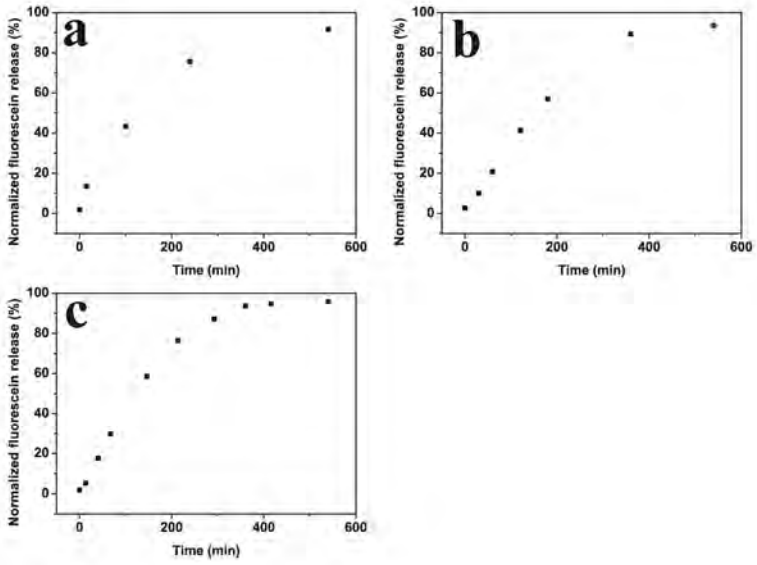

Figure S10. The percentage of the fluorescein sodium released from MSN-NH_2 versus the incubation time in PBS at at pH 4 (a), pH 5 (b) and pH 7 (c).

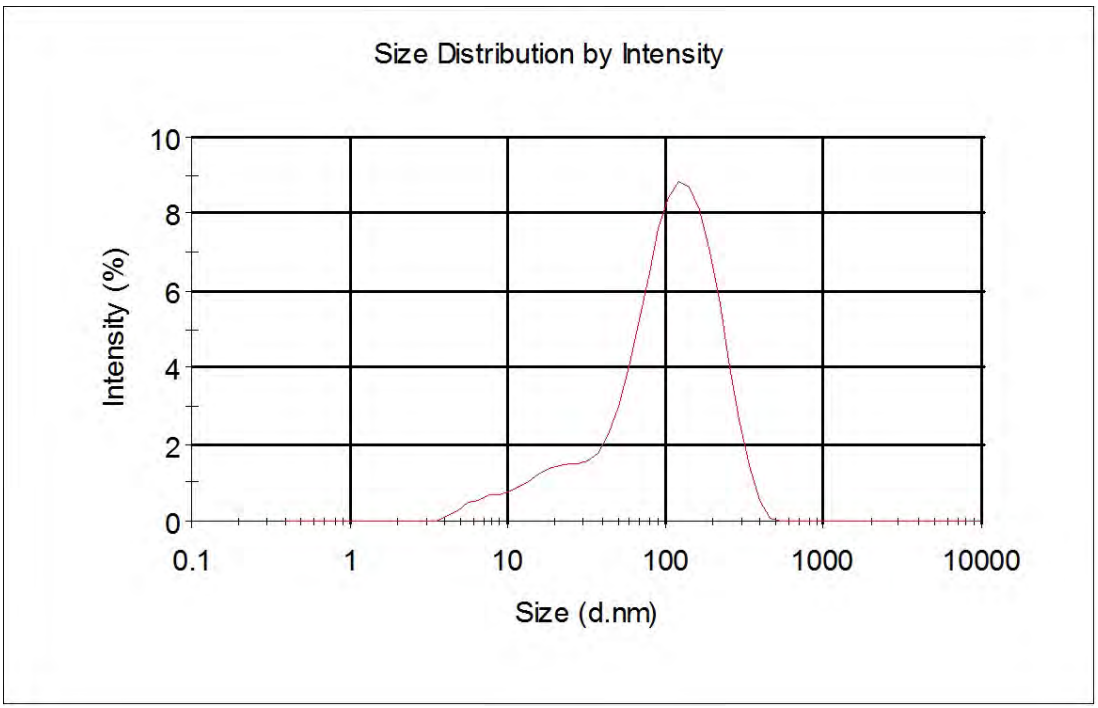

Figure S11. Size distribution of AuNPs-capped-MSN solution under pH 4 measured by dynamic light scattering.

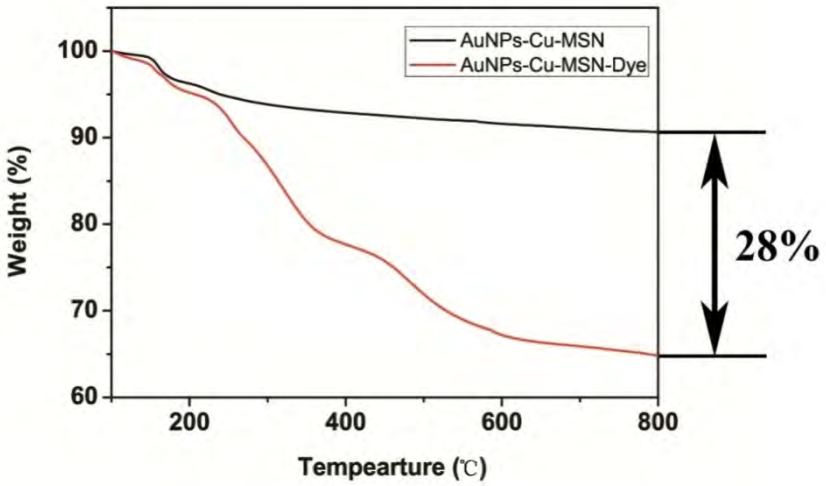

Figure S12. TGA curves of AuNPs-Cu-MSN (black curve) and fluorescein sodium loaded AuNPs-Cu-MSN (red curve). Samples were run under N_2 atmosphere.

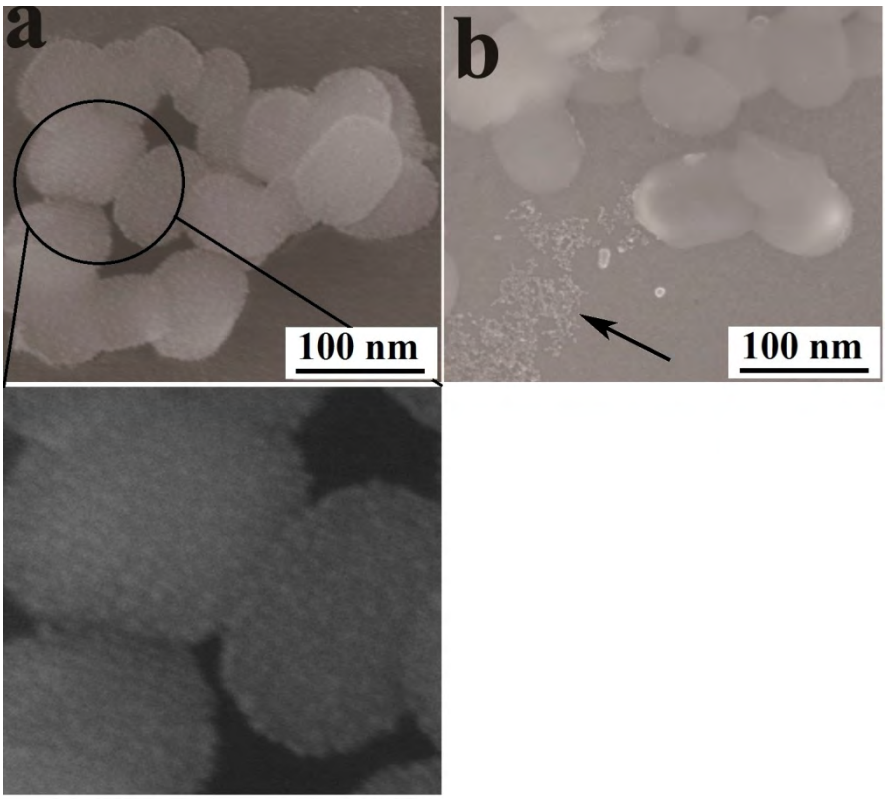

Figure S13. Scanning electron micrographs of MSN (a), AuNPs-capped-MSN before (a) and after (b) adding ATP. Arrow indicates aggregated gold nanoparticles which are represented by white dots on the SEM images. Samples were obtained by dropping 5 μL of established solution onto glass carbon plate, and then dried for 10 h in air.

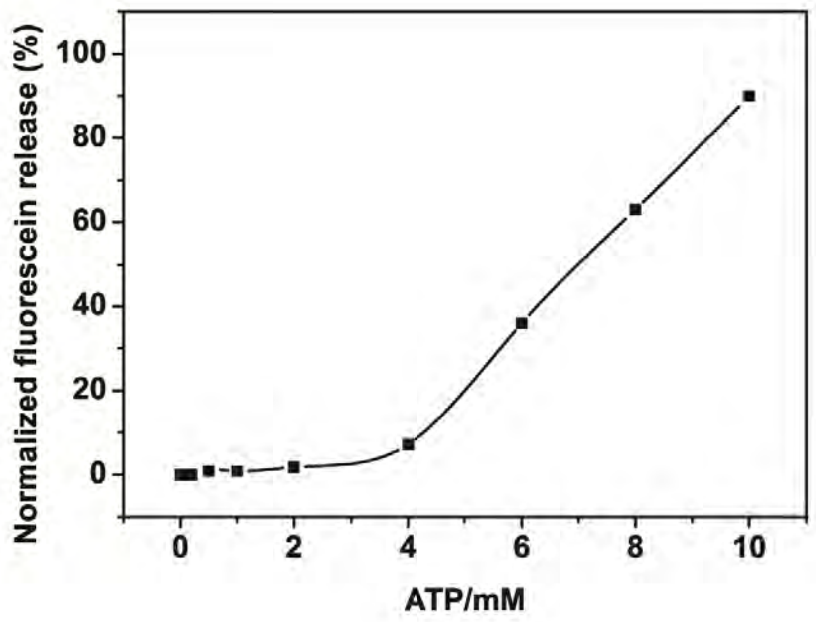

Figure S14. The percentage of the fluorescein sodium released from AuNPs-capped-MSN triggered by ATP as a function of concentration, measured after 20 h.

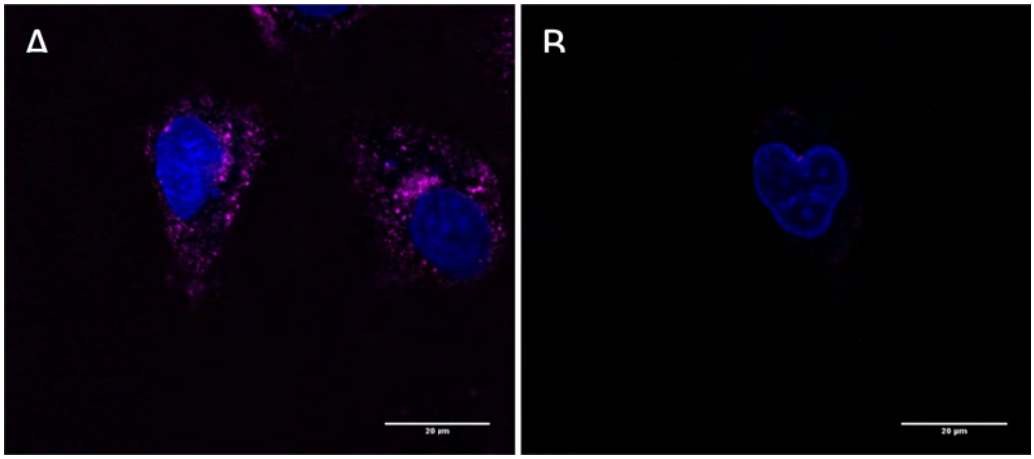

Figure S15. Chlopromazine Inhibition of human Transferrin (hTf) uptake. Cells were incubated for 2 hrs in either A.) Optimem or B.) Optimem containing 10mg/ml chlorpromazine. Cells were rinsed with PBS and then incubated with 16.7 µg/ml hTf, Alexa Fluor® 647 Conjugate for 15 minutes prior to imaging. Magenta: hTF, Blue: Hoerscht 33342 live nuclear stain.

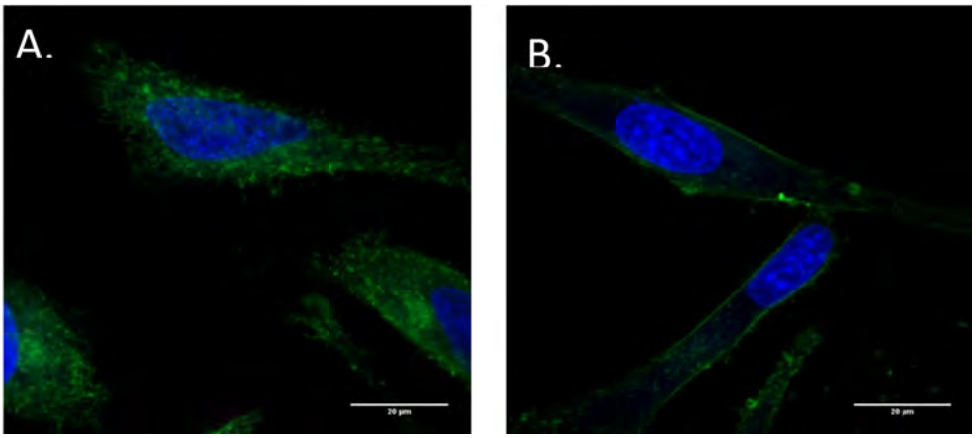

Figure S16. Genistein inhibition of Inhibition of C5-Lactosylceramide. Cells were incubated for 2 hrs in either A.) Optimem or B.) Optimem containing 200mM genistein. Cells were rinsed with PBS and then incubated with 0.81mM BODIPY® FL C5-Lactosylceramide (LacCer) for 15 minutes prior to imaging. LacCer uptake is seen as internalized vesicles (A), Inhibition (B) results in fewer internalized vesicles, and budding vesicles trapped at the membrane as indicated by arrows. Green: C5-Lactosylceramide, Blue: Hoescht 33342 live nuclear stain.

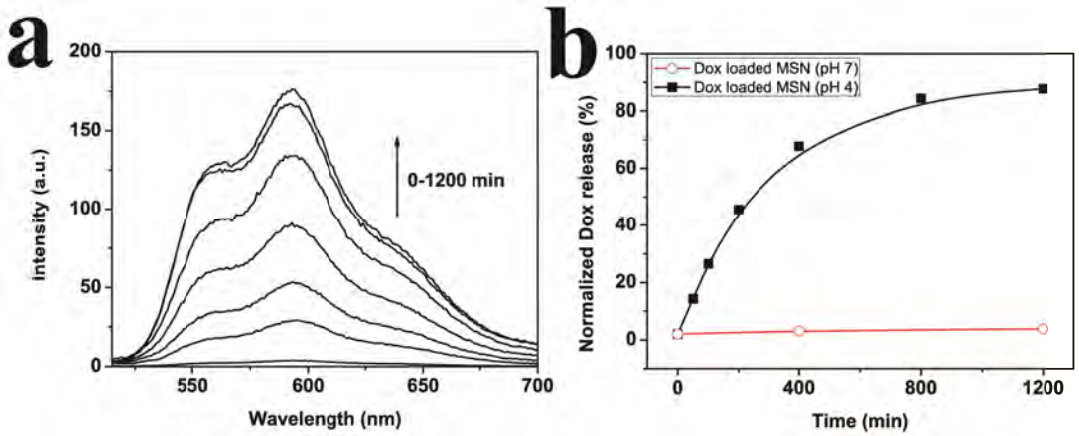

Figure S17. (a) Time-dependent fluorescence spectrum of Dox solution in PBS at pH 4. (b) The percentage of the Dox released from AuNPs-capped-MSN versus the incubation time in PBS at pH 7 (●) and pH 4 (■).

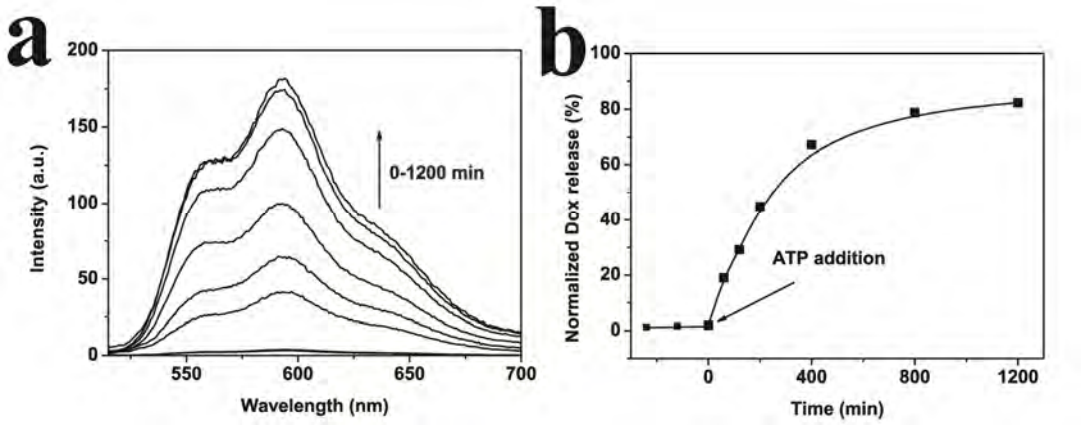

Figure S18. (a) Time-dependent fluorescence spectrum of Dox solution in PBS by adding adenosine triphosphate (ATP). (b) The percentage of the Dox released from AuNPs-capped-MSN versus the incubation time in PBS with 10 mM ATP.

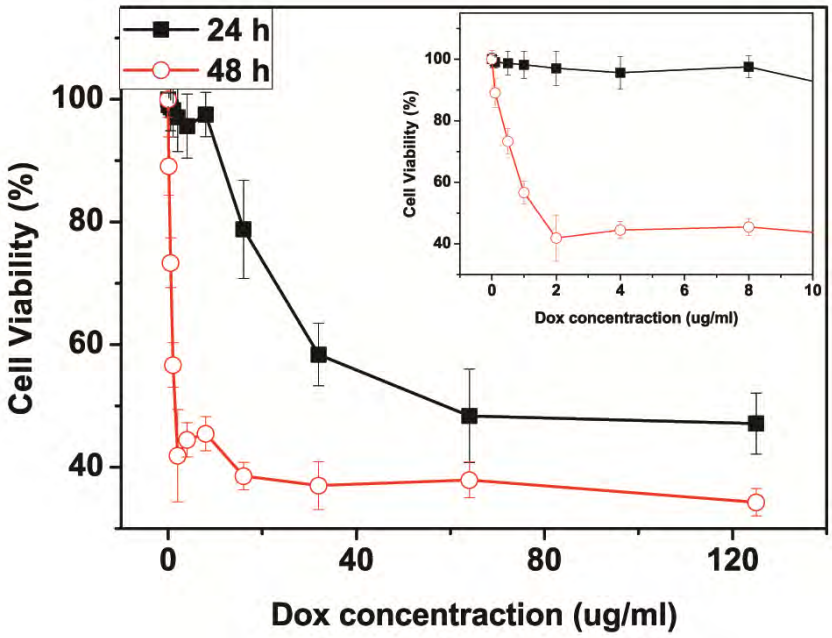

Figure S19. Viability of HeLa cells incubated with the increasing amounts of Dox loaded AuNPs-capped-MSNs with 24 h (black curve) and 48 h (red curve).

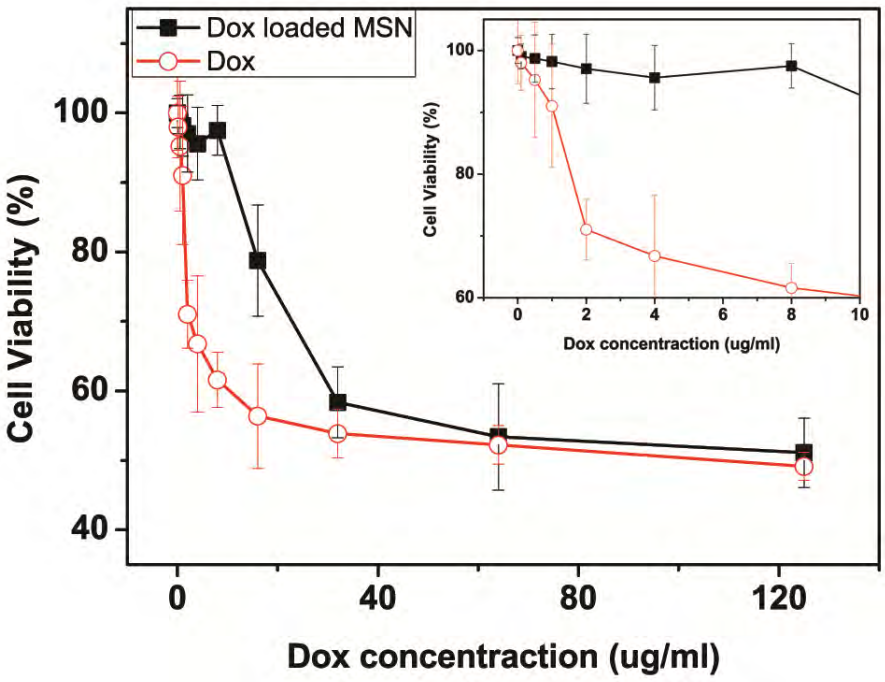

Figure 20. Viability of HeLa cells incubated with the increasing amounts of free Dox (black curve) and Dox loaded AuNPs-capped-MSNs (red curve) for 24 h.

Table S1. IR Spectral Data for the compounds and corresponding complexes (cm^{-1}).

Compound	$\nu_{COO(as)}$	$\nu_{COO(s)}$	δ_{NH}
L-cysteine Functionalized AuNPs	1639	1400	1540
MSN-NH_2	--	--	1538
AuNPs-capped-MSNs	1661	1383	--

Table S2. Concentration of Cu^{2+} at various stage of drug release. Data was obtained via inductively coupled plasma-mass spectrometry (ICP-MS).

Samples	Concentration of Cu^{2+} (ppm)
AuNPs-capped-MSN suspension (pH 7)	3.91
solution after removing of AuNPs and MSN (pH 4)[a]	0.06
solution after removing of AuNPs and MSN (pH 7, with ATP)[b]	0.02
[a, b] These process were performed by centrifuging the mixed system at 15000 r/min for 30 min, then collected the supernatant liquid (without MSN and AuNPs) carefully.	