Supporting Information

Materials.

Nanopure water (18.2 MΩ; Millpore Co., USA) was used in all experiments and to prepare all buffers. Doxorubicin (Dox), Dapi, sodium hydroxide (NaOH), Tetraethylorthosilicate (TEOS), disodium hydrogen phosphate (Na_2HPO_4), were purchased from Sigma-Aldrich. Silver nitrate ($AgNO_3$), Sodium borohydride ($NaBH_4$), Poly(acrylic acid) sodium salt (35 wt%, M_W=15000), APTMOS methanol, N-cetyltrimethylammonium bromide (CTAB), Fluorescein isothiocyanate (FITC), were obtained from Alfa Aesar. All the chemicals were used as received without further purification.

The human lung adenocarcinoma cells (A549 cells) were purchased from the Cell Bank of Chinese Academy of Sciences (Shanghai).

Two oligonucleotides were designed to construct the platform: atDNA (5'-CGT ATA TCC CTA ACC CTA ACC CTA ACC CTA TAT ACG) and gcDNA (5'-GCG CCC CTA ACC CTA ACC CTA ACC CTG CGC). The sequences with underlining stand for cytosine-rich segments which could form i-motif structures under acidic condition.

Instrument.

UV-vis spectroscopy was carried out with a JASCO V-550 UV/vis spectrometer. Melting experiments were carried out on a Cary 300 UV/vis spectrophotometer equipped with a Peltier temperature control accessory. All UV/vis spectra were measured in 1.0-cm-path-length cell. Absorbance changes at 260 nm versus temperature were collected1 heating rate of 1 $^{o}C \cdot min^{-1}$. CD spectra were measured on a JASCO J-810 spectropolarimeter equipped with a temperature controlled water bath. Fluorescence measurements were carried out on Jasco-FP-6500 spectrofluorometer (Jasco International Co. LTD. Tokyo, Japan). Scanning electron microscopy (SEM) images were obtained with a Hitachi S-4800 FE-SEM. Transmission electron

microscopy (TEM) images were recorded using a FEI TECNAI G2 20 high-resolution transmission electron microscope operating at 200 kV. N_2 adsorption-desorption isotherms were recorded on a Micromeritics ASAP 2020M automated sorption analyzer. The specific surface areas were calculated from the adsorption data in the low pressure range using the BET model and pore size was determined following the BJH method.

Preparation of DNA-templated AgNCs.

DNA-AgNCs were synthesized by first cooling the solution of DNA and $AgNO_3$ to 0 ^oC and then adding $NaBH_4$ followed by vigorous shaking for 2 min. The reaction mixture was kept in the dark at 4 ^oC for 24 h before measurements. For hairpin DNA-protected silver nanocluster, ssDNA and silver nitrate were mixed at a loop base/Ag^+ ratio of 1.8, and reduced by sodium borohydride reduction at a $NaBH_4/Ag^+$ ratio of 1. All other non-hairpin DNA-protected silver nanodots were synthesized by mixing silver nitrate and ssDNA at a base/Ag^+ ratio of 2, followed by aqueous sodium borohydride solution reduction at a $NaBH_4/Ag^+$ ratio of 1. Experiments were carried out in the 20 mM phosphate buffer (pH 7).

Preparation of poly(acrylic acid)-templated AgNCs.

4.9 mg of $AgNO_3$ was added to 2 mL of 2% APTMOS methanol solution. The mixture was stirred in the dark for 2 h at 20 ^oC. After that, 41 mL of this solution was added to 40 mL of 0.12% poly(acrylic acid) (MW E 15 000) aqueous solution and incubated at 20 ^oC for 5 min. Then, $NaBH_4$ was added, followed by stirring in the dark for 24 h at 20 ^oC.

Preparation of Hollow Mesoporous Silica Microspheres (HMS).

The Fe_3O_4 spheres with a mean diameter of about 200 nm were prepared via a solvothermal method as described previously.[1] The Fe_3O_4 particles were coated with a thin silica layer generated from the hydrolysis and condensation of TEOS. Subsequently, an ordered mesoporous silica shell was coated on the Fe_3O_4@nSiO_2

surface, and the detailed procedure was described previously.[2] Fe_3O_4@nSiO_2 particles were well dispersed in a mixed solution containing CTAB (0.3 g), ethanol (60 mL), and deionized water (80 mL). Afterwards, TEOS (0.2 mL) was added dropwise to the reaction mixture under vigorous stirring and kept for 6 h at room temperature. The product was collected by magnetic separation, washed with ethanol 3 times, and dried at 60 °C in vacuum. The CTAB templates were removed by the acetone extraction. Finally, the Fe_3O_4 cores were removed using HCl solution (2 M) at 80 °C for 8 h. The final products were named hollow mesoporous sphere (HMS).

Encapsulation of DNA within HMS and constructing the DNA platform in-situ inside the HMS.

The DNA was encapsulated into HMS by a previous reported method.[3] 10 μL water solution of DNA was added into centrifuge tube with 0.3 mg HMS, then 10 μL 4 M Guanidine Hydrochloride solution and 40 μL ethanol was added. The mixture was well dispersed by vortex for 30 s and then was continuously shaken with 270 rpm at 25 ºC for 1 h. The final solution was centrifugation at 5000 rpm to separate HMS and supernatant liquid absolutely. The amount of adsorbed DNA was calculated from the differences of DNA concentration in solutions before and after adsorption process. For constructing the DNA platform in-situ inside the HMS, the HMS-DNA-AgNCs was synthesized by the method as that of DNA-AgNCs. For TEM sample preparation, the HMS-DNA-AgNPs was synthesized by increasing the $AgNO_3$ concentration to 5 times that of DNA-AgNCs.

Cell Culture.

Human lung adenocarcinoma (A549) cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% (v/v) fetal bovine serum (Gibco). The cells were kept at 37 ºC in a humidified atmosphere containing 5% CO_2 in air. The media were changed every three days, and the cells were passaged by trypsinization before confluence.

Fluorescence Imaging.

A549 cells were seeded in a 24-well plate and cultured for 24 h. The cell medium was removed, and then cells were incubated with 1.0 mL of fresh cell medium containing 10 μM of atDNA-AgNCs, 40 μg/mL FITC-HMS, 10 μM of atDNA-AgNCs-Dapi, or 75 μg/mL HMS-atDNA-AgNCs-Dapi for 3 h. Cell imaging was then carried out after washing cells with PBS. Cells were viewed and counted using an Olympus BX-51 optical system microscopy. Pictures were taken with an Olympus digital camera. Filter sets: AgNCs: Green excitation (550 nm) / Yellow emission (580 nm). Dapi: Ultraviolet excitation (350 nm)/ Blue Emission (450 nm). Lysotracker: Blue excitation (450 nm) / Green emission (550 nm).

Cytotoxicity assays.

MTT assays were used to probe cellular viability. A549 cells were seeded at a density of 5000 cells/well (90 μL total volume/well) in 96-well assay plates. After 24 h, drugs or nanoparticles at the indicated concentrations were added and cells were further incubated for 24 h. To determine toxicity, 10 μL of MTT solution (BBI) was added to each well of the microtiter plate and the plate was incubated in the CO_2 incubator for an additional 4 h. The cells then were lysed by the addition of 100 μL of DMSO. Absorbance values of formazan were determined with Bio-Rad model-680 microplate reader at 490 nm (corrected for background absorbance at 630 nm). Six replicates were done for each treatment group.

[1] H. Deng, X. L. Li, Q. Peng, X. Wang, J. P. Chen and Y. D. Li, *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 2782.

[2] Y. Deng, D. Qi, C. Deng, X. Zhang and D. Zhao, *J. Am. Chem. Soc.* **2008**, *130*, 28.

[3] X. Li, Q. R. Xie, J. X. Zhang, W. L. Xia and H. C. Gu, *Biomaterials* **2011**, *32*, 9546.

Table S1. Summary of Thermodynamic Parameters for drugs binding to DNA in 10 mM PBS buffer (pH 7.4) at 37 °C.

DNA	Drug	K_b	ΔG_{37^oC} (kJ/mol)
atDNA	Dapi	1.05×10^7	-41.667
gcDNA	Doxorubicin	7.54×10^6	-40.814

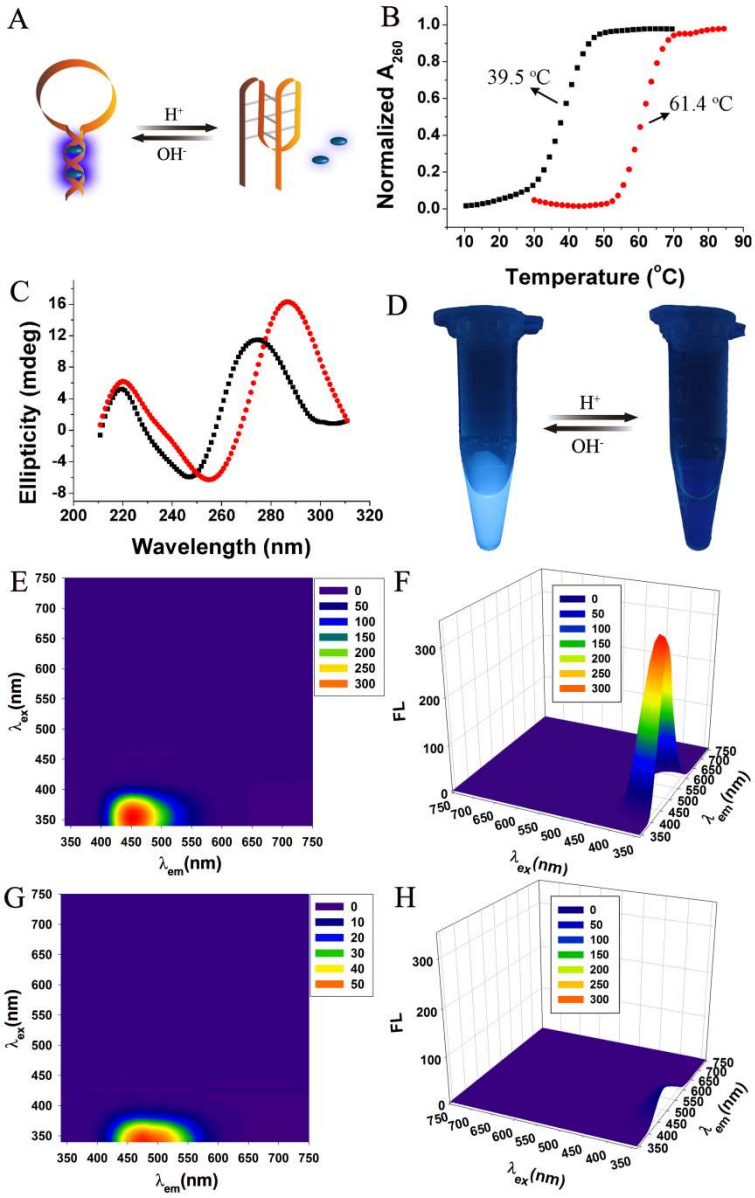

Figure S1 (A) Illustration of drug binding at the stem of hairpin structure under neutral/base condition and release under acidic condition. (B) UV melting profiles of atDNA at pH 7.4 (black line) and pH 5.0 (red line). [atDNA]= 1 μM. (C) CD spectra of atDNA at pH 7.4 (black line) or pH 5.0 (red line). [atDNA]= 2 μM (D) Photographs of atDNA-Dapi at different pH values. Fluorescence excitation-emission maps of atDNA-Dapi (E-F) at pH 7.4 and (G-H) pH 5.0. [atDNA]= 5 μM, [Dapi]=15 μM. These experiments were carried out in 10 mM PBS, 100 mM $NaNO_3$ at 37ºC.

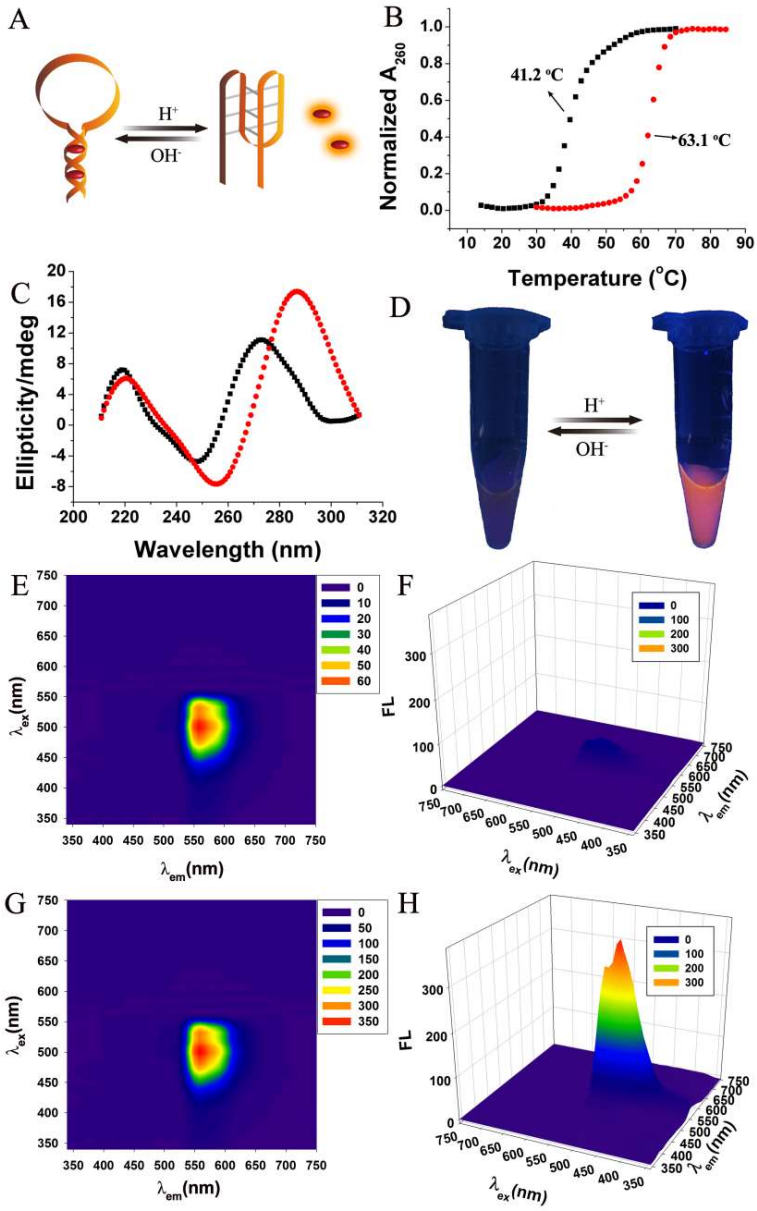

Figure S2 (A) Illustration for drug binding at the stem of hairpin structure under neutral/base condition and release under acidic condition. (B) UV melting profiles of gcDNA at pH 7.4 (black line) or pH 5.0 (red line). [gcDNA]= 1 μM. (C) CD spectra of gcDNA at pH 7.4 (black line) or pH 5.0 (red line). [gcDNA]= 2 μM. (D) Photographs of gcDNA-Dox system at pH 7.4 (left) and pH 5.0 (right). (E), (F) Fluorescence excitation-emission maps of gcDNA-Dox at pH 7.4. (G), (H) Fluorescence excitation-emission maps of gcDNA-Dox at pH 5.0. [gcDNA]= 5 μM, [Dox]=15 μM. All these experiments were carried out in 10 mM PBS, 100 mM $NaNO_3$ at 37°C.

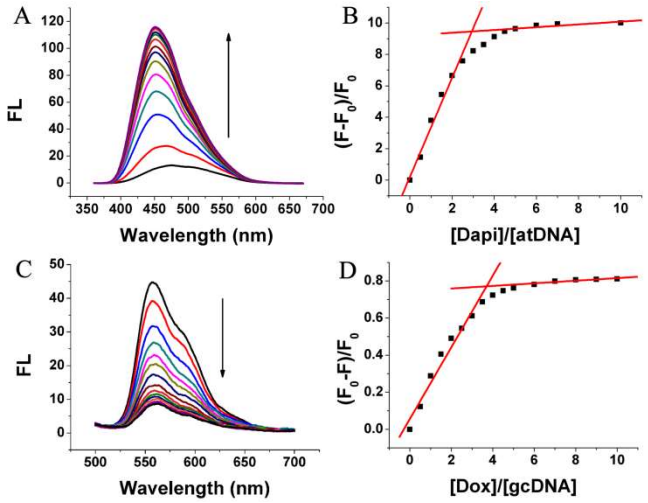

Figure S3 (A) Fluorescence titration of Dapi with atDNA. [Dapi]=5 μM. (B) The titration plot for atDNA-Dapi. Ex=354 nm, Em=475 nm. A breakpoint was observed at 3:1 ratio of [Dapi]/[atDNA]. (C) Fluorescence titration of Dox with gcDNA. [Dox]=5 μM. (D) The titration plot for Dox-gcDNA. Ex=480 nm, Em=560 nm. A breakpoint was observed at 4:1 ratio of [Dox]/[gcDNA]. All experiments were carried out in 10 mM PBS, 100 mM $NaNO_3$ (pH 7.4) at 37 ºC.

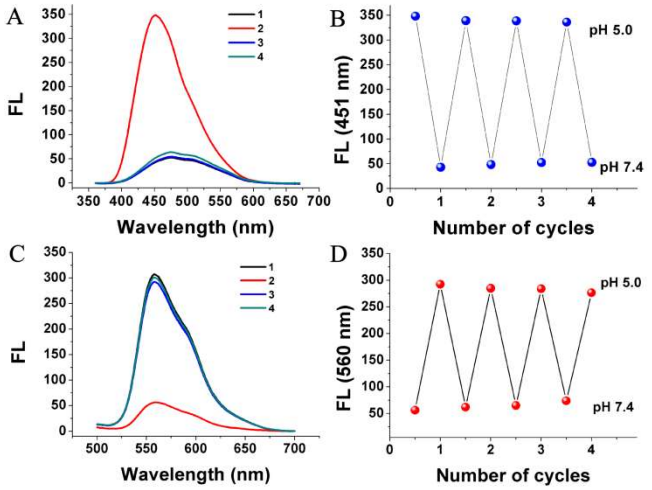

Figure S4 (A) Dapi binding and release from atDNA at different pH. 1: Dapi at pH 7.4; 2: Dapi+atDNA at pH 7.4; 3: Dapi at pH 5.0; 4: Dapi+atDNA at pH 5.0. [Dapi]=15 μM, [atDNA]=5 μM. (B) Fluoresence cycling of Dapi-atDNA at 451 nm while the pH oscillated between 7.4 and 5.0. (C) Dox binding and release from gcDNA at different pH. 1: Dox at pH 7.4; 2: Dox+gcDNA at pH 7.4; 3: Dox at pH 5.0; 4: Dox+gcDNA at pH 5.0. [Dox]=20 μM, [gcDNA]=5 μM. (D) Fluoresence cycling of Dox-gcDNA at 451 nm while the pH oscillated between 7.4 and 5.0. All experiments were carried out in 10 mM PBS, 100 mM $NaNO_3$ (pH 7.4) at 37 ºC.

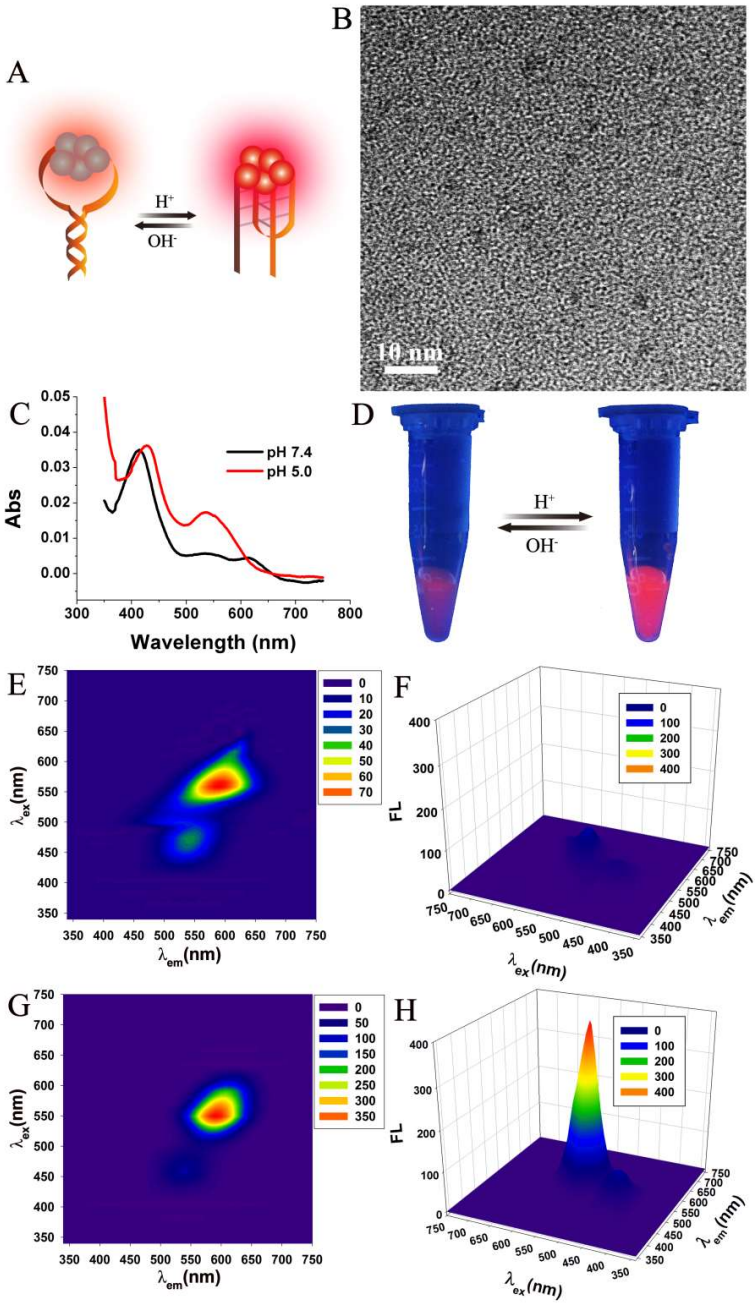

Figure S5 (A) Illustration of fluorescence change of atDNA-AgNCs at different pH. (B) TEM image of atDNA-AgNCs. (C) UV-Vis spectra of atDNA-AgNCs at different pH. (D) Photograph of atDNA-AgNCs at pH 7.4 (left) and pH 5.0 (right). Fluorescence excitation-emission maps of atDNA-AgNCs at (E-F) pH 7.4 and (G-H) pH 5.0. [atDNA-AgNCs]=5 μM.

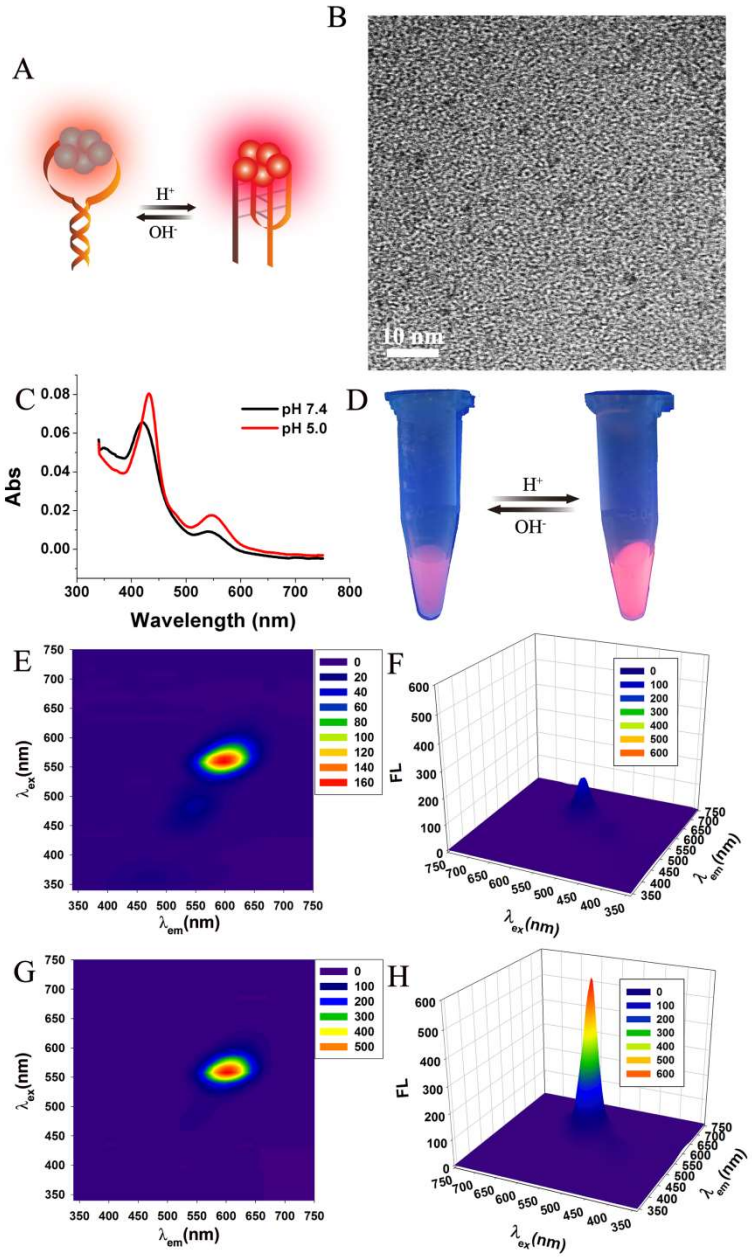

Figure S6 (A) Illustration for fluorescence changes of gcDNA-AgNCs at different pH values. (B) TEM images of gcDNA-AgNCs. (C) UV-Vis spectra of gcDNA-AgNCs at different pH values. (D) Photographs of gcDNA-AgNCs at pH 7.4 (left) and pH 5.0 (right). (E), (F) Fluorescence excitation-emission maps of gcDNA-AgNCs at pH 7.4. (G), (H) Fluorescence excitation-emission maps of gcDNA-AgNCs at pH 5.0. The experiments were carried out in 10 mM PBS, 100 mM $NaNO_3$ at 37°C. The concentration of gcDNA-AgNCs was 5 μM.

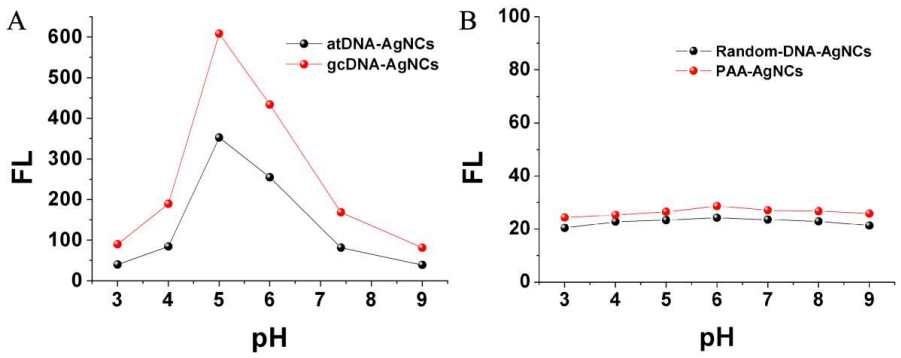

Figure S7 (A) Fluorescence intensities of atDNA-AgNCs (λex = 560 nm, λem = 600 nm) and gcDNA-AgNCs (λex = 560 nm, λem = 607). (B) Fluorescence intensities of Random-DNA-AgNCs (5'-ATG TGG AAA ATC TCT AGC AGT, λex = 560 nm, λem = 595 nm) and PAA-AgNCs (λex = 540 nm, λem = 605 nm).

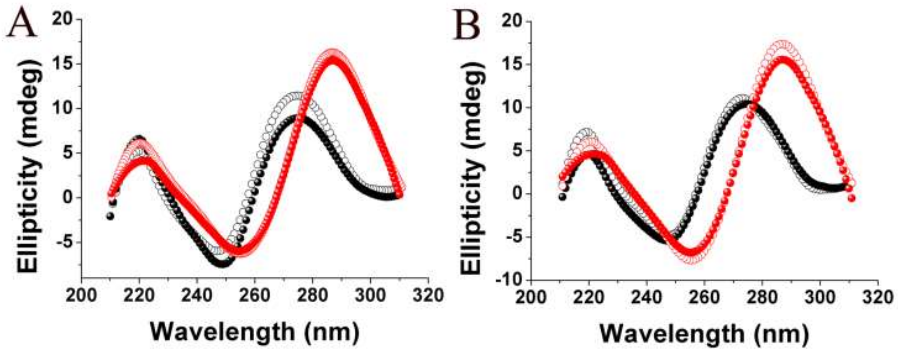

Figure S8 (A) CD spectra of atDNA-AgNCs (solid circle) compared with atDNA alone (hollow circle) at pH 7.0 (black) and pH 5.0 (red). (A) CD spectra of gcDNA-AgNCs (solid circle) compared with gcDNA alone (hollow circle) at pH 7.0 (black) and pH 5.0 (red). DNA concentration was 2 μM in strand in 10 mM PBS buffer.

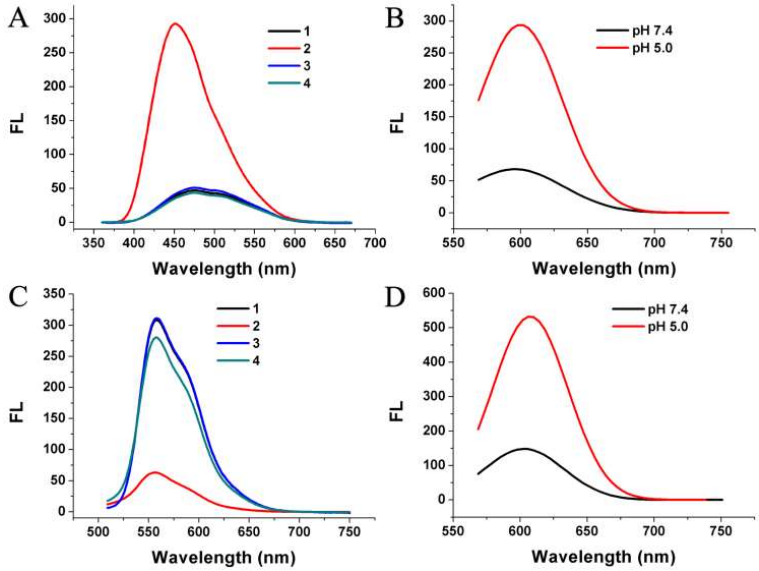

Figure S9 (A) Dapi binding and release from atDNA-AgNCs at different pH. 1: Dapi at pH 7.4; 2: Dapi+atDNA-AgNCs at pH 7.4; 3: Dapi at pH 5.0; 4: Dapi+atDNA-AgNCs at pH 5.0. [Dapi]=15 μM, [atDNA-AgNCs]=5 μM. (B) The emission spectra of atDNA-AgNCs-Dapi excited at 560 nm. (C) Dox binding and release from gcDNA at different pH. 1: Dox at pH 7.4; 2: Dox+gcDNA-AgNCs at pH 7.4; 3: Dox at pH 5.0; 4: Dox+gcDNA-AgNCs at pH 5.0. [Dox]=20 μM, [gcDNA-AgNCs]=5 μM. (D) The emission spectra of gcDNA-AgNCs-Dox excited at 560 nm.

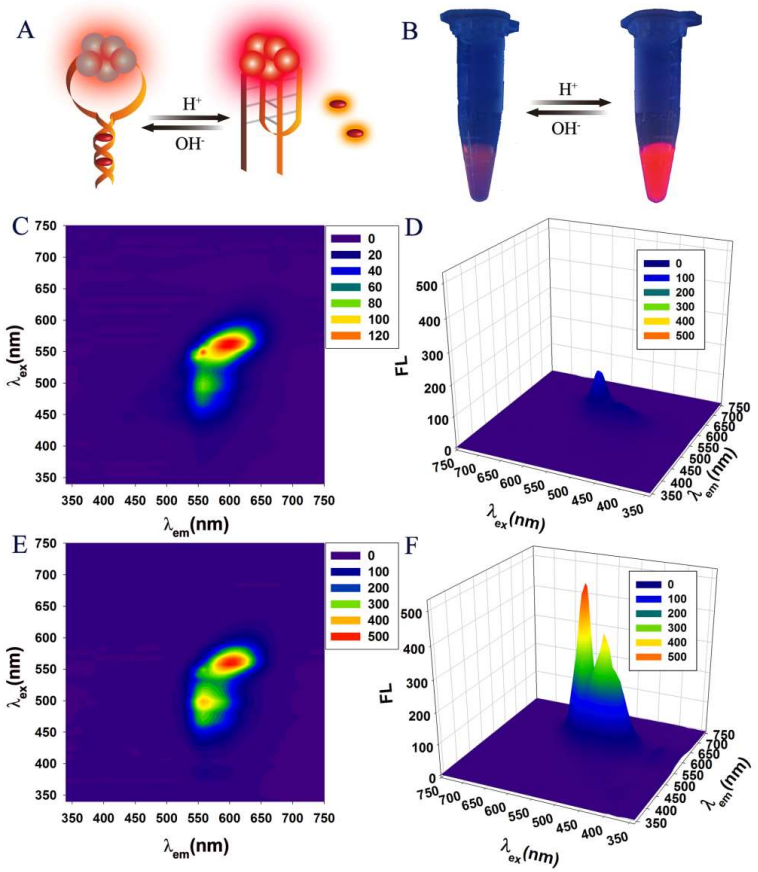

Figure S10 (A) Illustration of the integrated DNA platform with both pH-triggered drug release and fluorescence change. (B) Photograph of gcDNA-AgNCs-Dox at pH 7.4 (left) and pH 5.0 (right). (E-F) Fluorescence excitation-emission maps of gcDNA-AgNCs-Dox at pH 7.4. (G-H) Fluorescence excitation-emission maps of gcDNA-AgNCs-Dox at pH 5.0. The experiments were carried out in 10 mM PBS, 100 mM $NaNO_3$ at 37ºC. [Dox]=20 μM, [gcDNA-AgNCs]=5 μM.

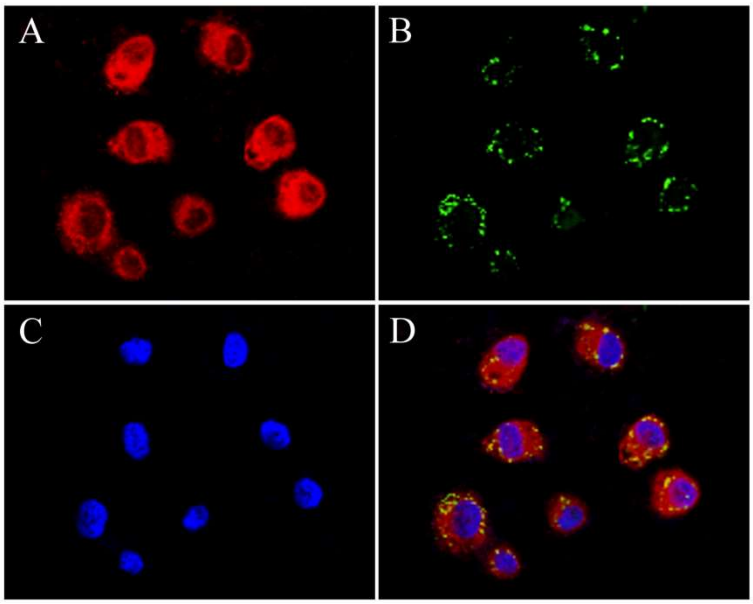

Figure S11 Fluorescence microscopy images of A549 cells after incubation with 10 μM of atDNA-AgNCs for 3 h. (A) atDNA-AgNCs, (B) Lysotracker, (C) DAPI, and (D) Merge.

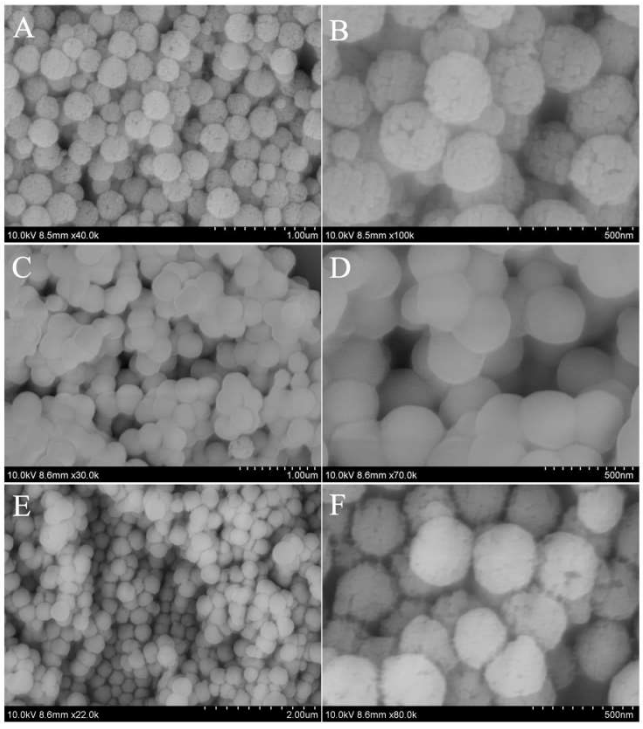

Figure S12 SEM images of (A, B) Fe_3O_4 core, (C, D) Fe_3O_4 core covered with mesporous silica layer, and (E, F) HSM nanocapsules.

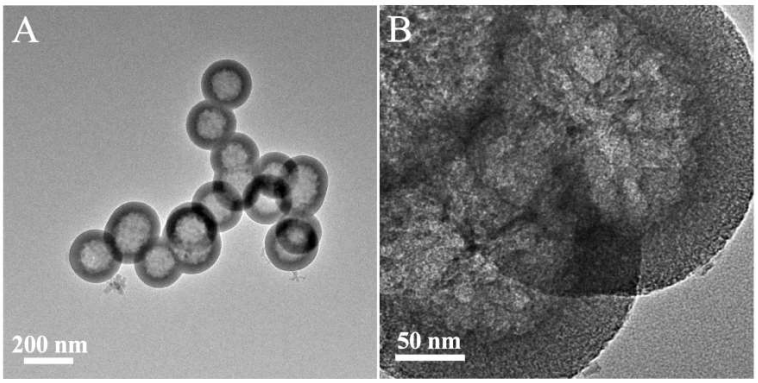

Figure S13 TEM images of HSM nanocapsules.

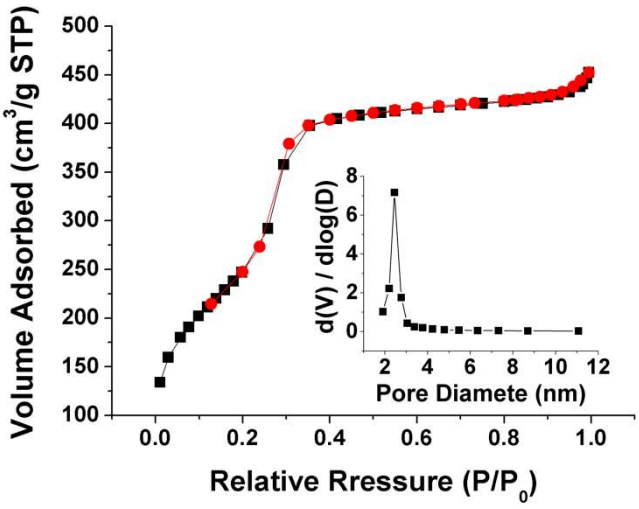

Figure S14 N_2 adsorption/desorption isothermsand the corresponding pore sized distributions (inset) for HMS.

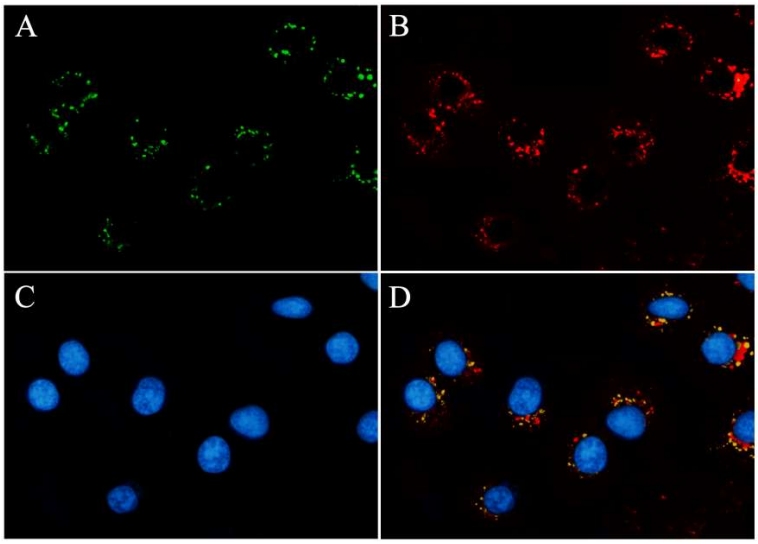

Figure S15 Fluorescence microscopy image of A549 cells after incubation with FITC-HMS (40 μg/mL) for 3 h. (A) FITC, (B) Lysotracker, (C) DAPI, and (D) Merge.

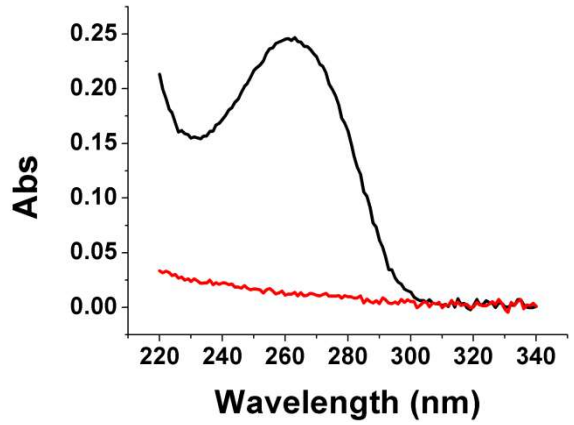

Figure S16 The absorption spectra of DNA solution before (black line) and after (red line) incubation with HMS.

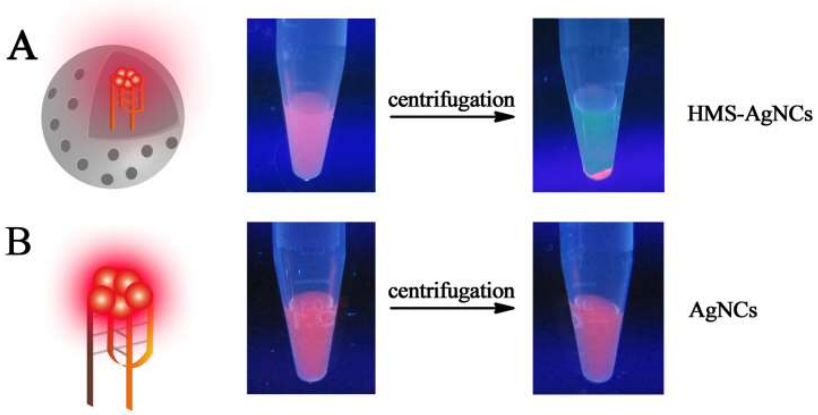

Figure S17 The photographs of (A) HMS-atDNA-AgNCs and (B) atDNA-AgNCs before and after centrifugation.

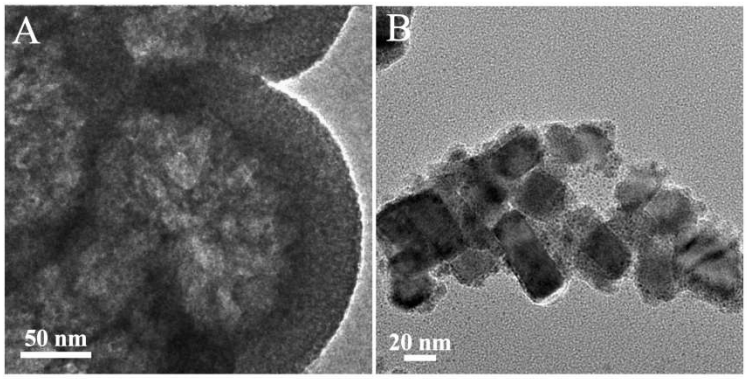

Figure S18 TEM images of AgNPs synthesis in HMS solution without DNA.

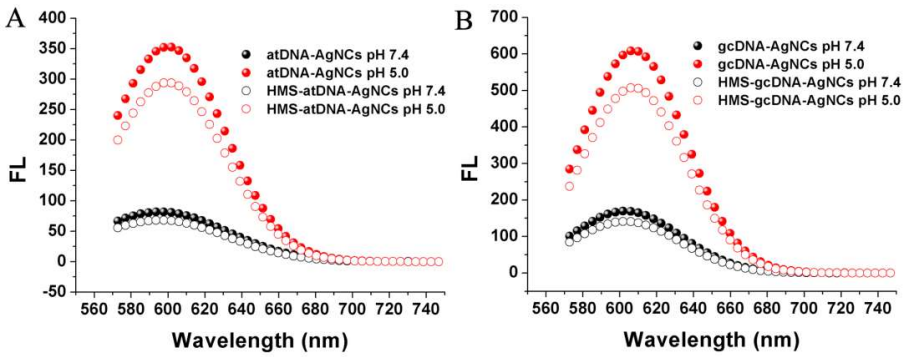

Figure S19 The fluorescence emission (λ_{ex}=560 nm) of HMS-DNA-AgNCs compared with DNA-AgNCs at pH 7.4 and 5.0.

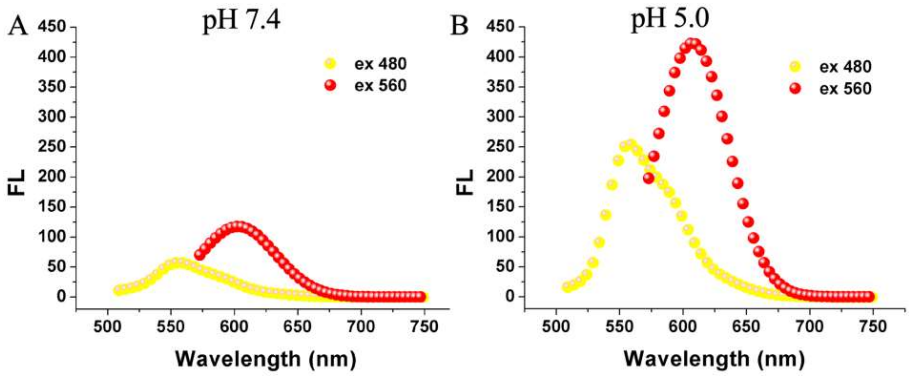

Figure S20 The fluorescence emission of HMS-gcDNA-AgNCs-Dox at (A) pH 7.4 and (B) pH 5.0.

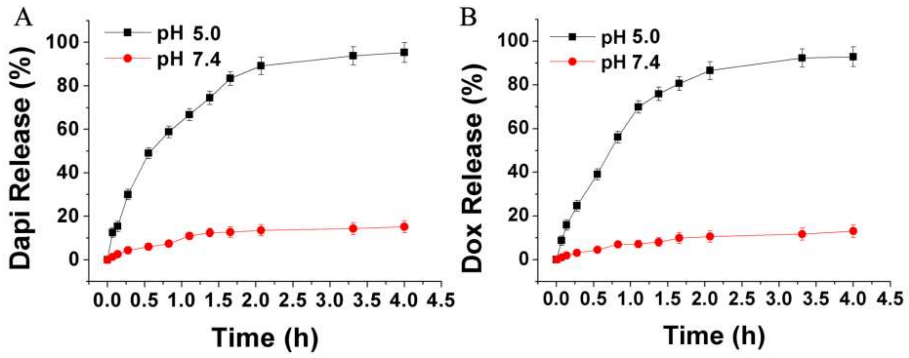

Figure S21 (A) Dapi release profiles from HMS-atDNA-AgNCs-Dapi at different pH values. (B) Dox release profiles from HMS-gcDNA-AgNCs-Dox at different pH values.

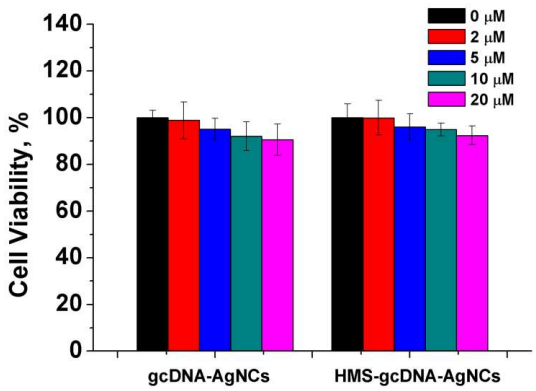

Figure S22 In vitro viability of A549 cells in the presence of gcDNA-AgNCs and HMS-gcDNA-AgNCs with various gcDNA concentrations.