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Supporting Information for

Enhanced Cancer Cell Killing by a Targeting Gold Nanoconstruct with Doxorubicin Payload under X-ray Irradiation

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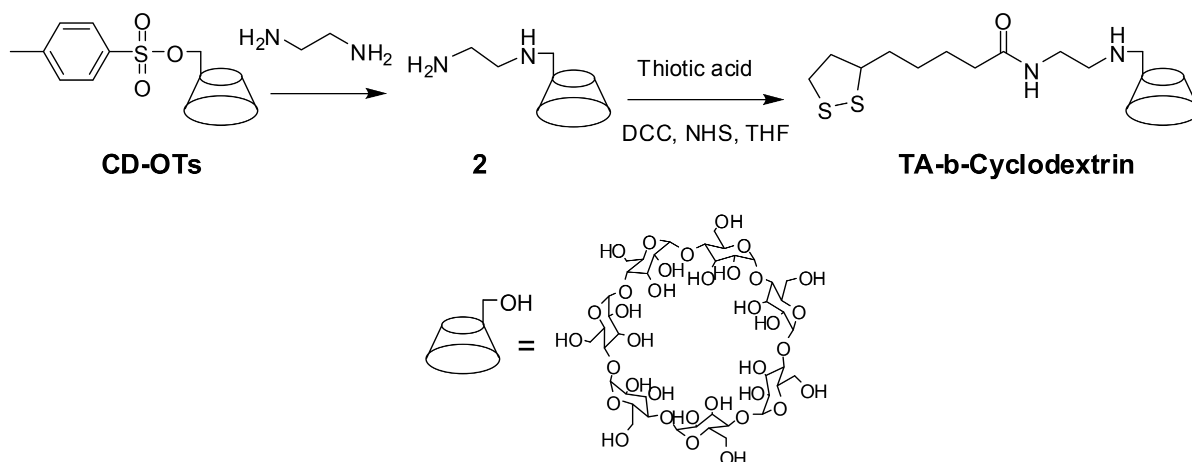
Synthesis of TA-β-Cylcodextrin (Ligand-3)



Scheme S1. Synthesis of TA-β-Cyclodextrin

β-CD-OTs[1] (1.0 g, 0.77 mmol) was dissolved in ethyl diamine (5.0 mL) by stirring at room temperature. The mixture was then stirred at 60 ^{o}C overnight. The mixture was cooled to room temperature and added to acetone (100 mL) dropwise. Lots of yellow precipitation appeared immediately. The precipitation was collected by centrifugation at 4000 rpm for 5 min and washed twice with acetone to give intermediate **2** (860 mg, 82.8%). The intermediate was used directly for next step reaction without further purification.

N,N'-Dicyclohexylcarbodiimide (DCC, 247 mg, 1.2 mmol), N-hydroxysuccinimide (NHS, 137 mg, 1.2 mmol) and TEA (279 μL, 2.0 mmol) were added to a solution of thiotic acid (206

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mg, 1.0 mmol)in THF (2 mL). The mixture was stirred for 4 h at room temperature. After removal of the precipitate by filtration, intermediate **2** (750 mg, 0.63 mmol) was added to the solution. The mixture was stirred overnight at room temperature. After the completion of the reaction, the mixture was poured into acetone (100 mL) and lots of yellow precipitation appeared. The precipitation was collected by centrifugation at 4000 rpm for 5 min and washed twice with acetone. The crude product was purified by flash chromatography to give ligand **TA-β-Cyclodextrin**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.22 – 5.53 (m, 7H), 4.84 (s, 4H), 4.47 (d, *J* = 5.4 Hz, 3H), 3.64 (s, 14H), 3.23 – 2.96 (m, 3H), 2.90 – 2.55 (m, 2H), 2.41 (s, 2H), 2.31 – 2.16 (m, 1H), 2.06 (s, 2H), 1.89 (d, *J* = 6.2 Hz, 1H), 1.73 – 1.15 (m, 6H).

Synthesis of TA-Folic Acid (Ligand-1) and TA-Secondary Ligand (Ligand-2)

TA-Folic Acid and TA-Secondary Ligand were synthesized as previously reported.[2]

References

[1] W. Tang, S.-C. Ng, *Nature Protocols* **2008**, *3*, 691-697.

[2] H. Zhou, P. Jiao, L. Yang, X. Li, B. Yan, *J. Am. Chem. Soc.* **2011**, *133*, 680-682.

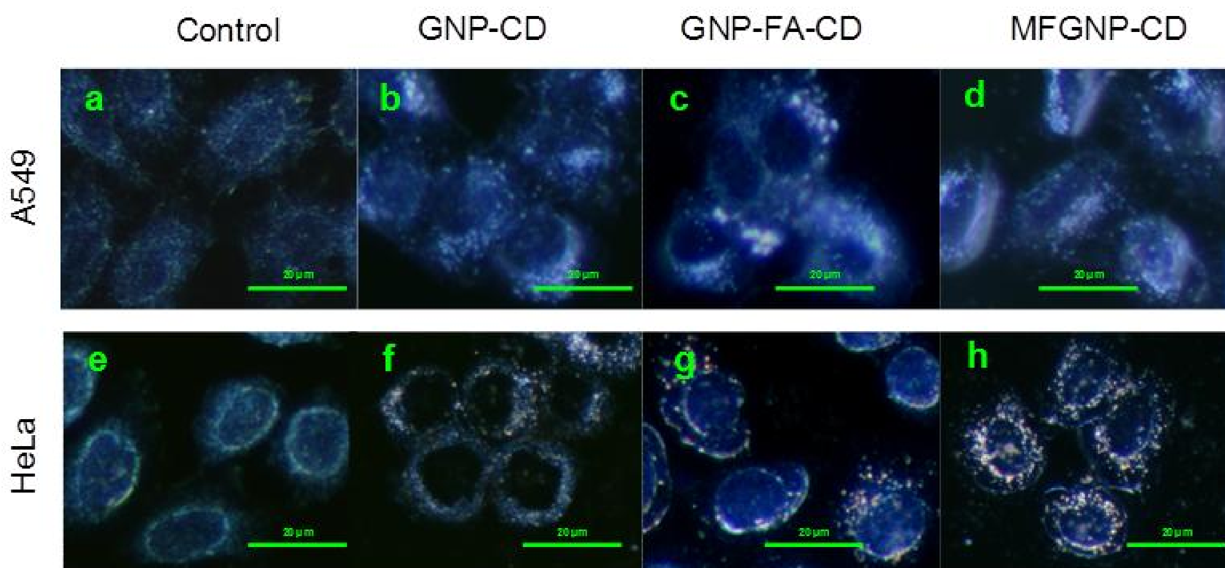

Figure S1. Dark field microscopy images of (a-d) A549 and (e-h) HeLa cells incubated with different GNPs. Yellow light scattering (f, g, h) was due to internalization of GNPs. The GNP concentration for all experiments was 50 µg/mL. The incubation time was 8 h. The scale bar is 20 µm.

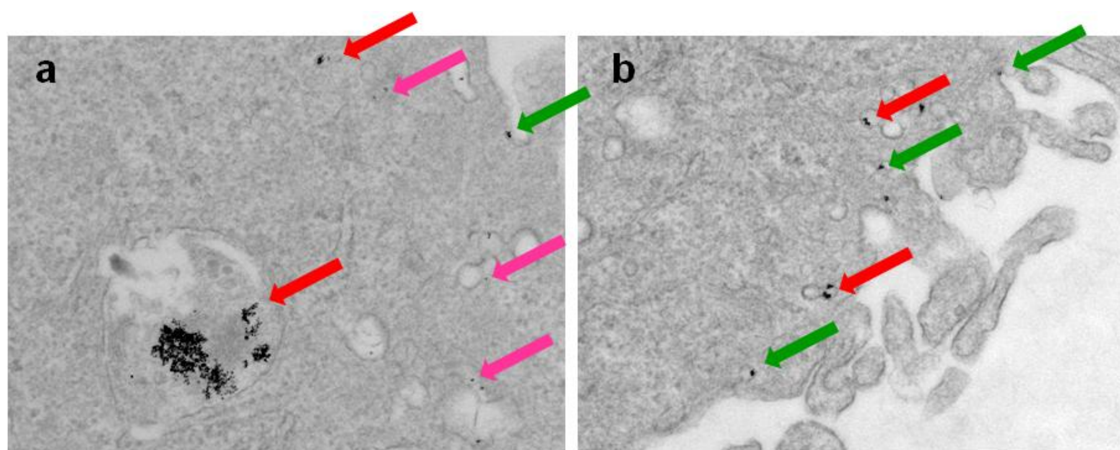

Figure S2. The internalization of MFGNP-CD in HeLa Cells. TEM in high magnification shows that GNPs enter HeLa cell through receptor mediated endocytosis (green arrow). The

internalized GNPs are localized in both endosomal-like organelles (red arrow) and cytoplasm (pink arrow). The GNP concentration for all experiments was 50 μg/mL.

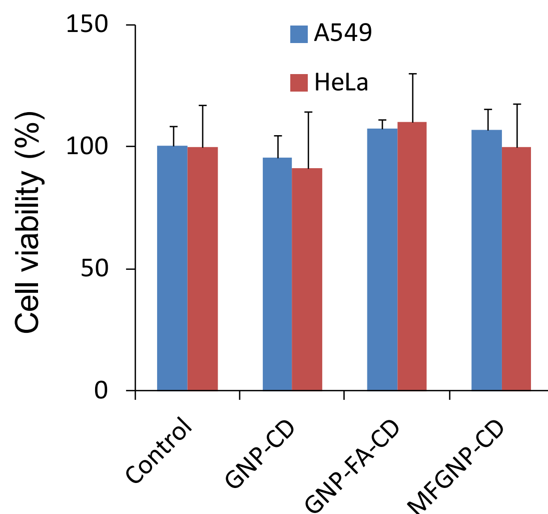

Figure S3. Cell viability of A549 and HeLa cells incubated with different GNPs. The GNP concentration for all experiments was 100 μg/mL. Cells were incubated with GNPs for 48 h. Each data point was measured in triplicate

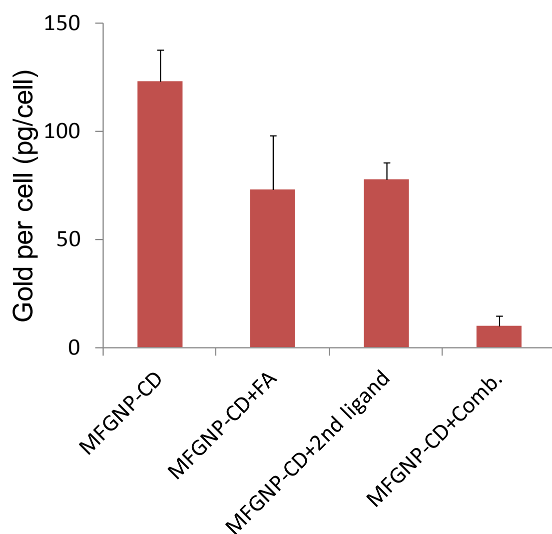

Figure S4. Quantitatively determination of the cellular uptake of GNPs in HeLa cells pretreated with TA-FA (500 μg/ml), the TA-ligand3 (500 μg/mL), or combination (250 μg/mL for each one) before adding **MFGNP-CD**. The GNP concentration for all experiments was 50 μg/mL.

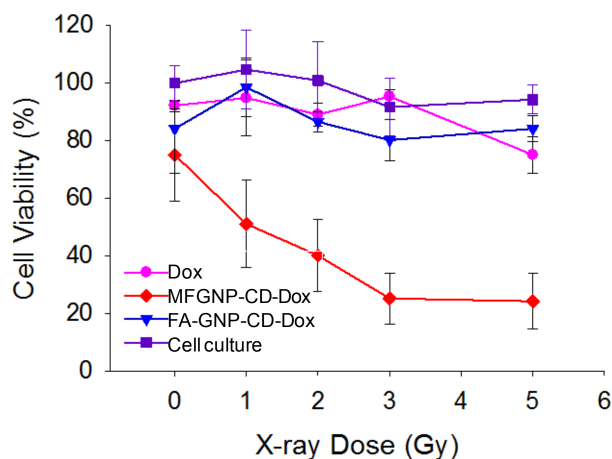

Figure S5. Cell viability of HeLa cells incubated with GNPs under different X-ray radiations. Dox and the GNP-Dox were normalized to Dox concentration as 0.1 μM. HeLa cells were incubated with Dox or GNP-Dox for 8h and extra GNPs were removed. Cells were exposed to X-ray irradiation with different doses. Cell viabilities were determined by XTT assay 48 h after X-ray exposure. The data represent the mean ± standard deviation of the results from three experiments.