

Electronic Supplementary Information

Gold nanoflowers-based traceable drug delivery system for intracellular SERS imaging-guided targeted chemo-phototherapy

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Section S1. Characterization of AuNFs, AuNFs-MBA, AuNFs-MBA-RGD, AuNFs-MBA-RGD-PAA, AuNFs-MBA-RGD-PAA-DOX and PAA-SH

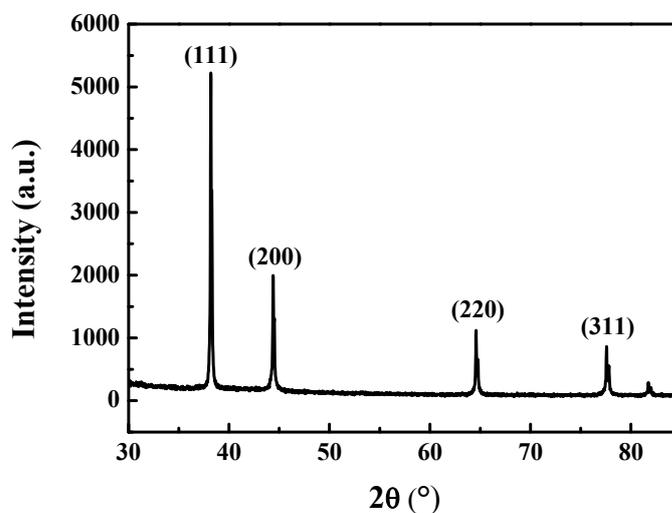


Fig. S1 XRD of AuNFs.

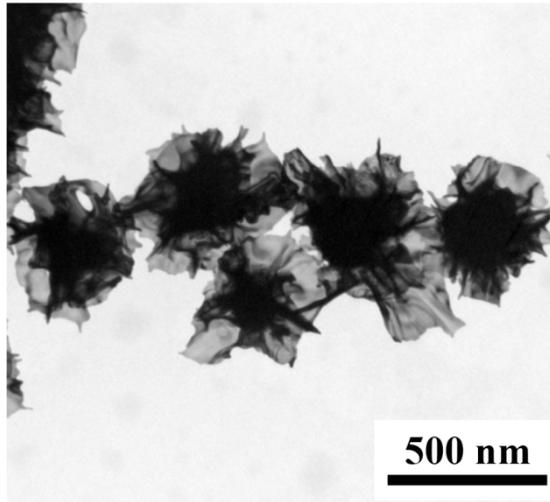


Fig. S2 TEM image of AuNFs after illumination.

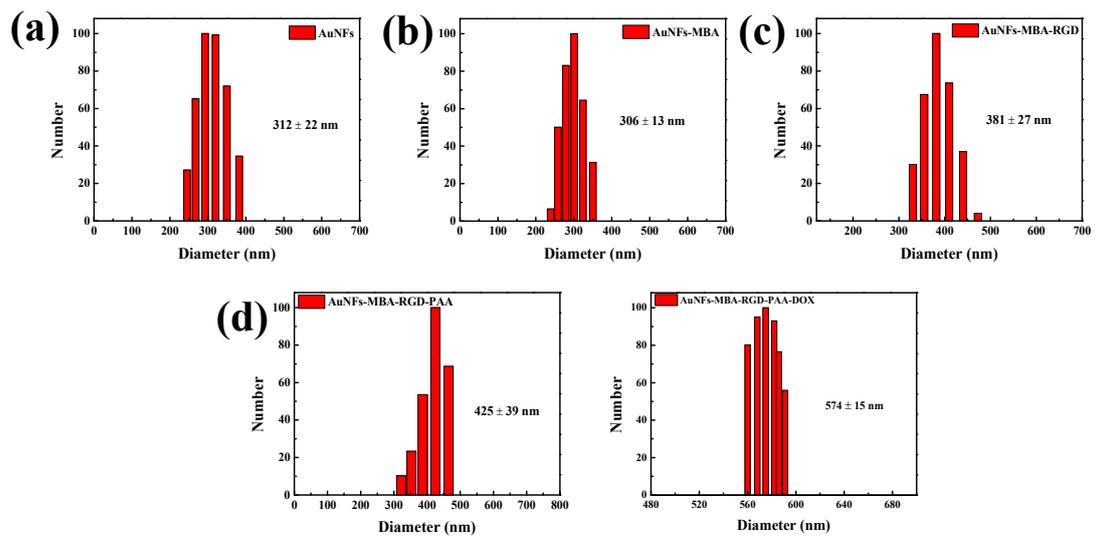


Fig. S3 DLS of AuNFs (a), AuNFs-MBA (b), AuNFs-MBA-RGD (c), AuNFs-MBA-RGD-PAA (d), AuNFs-MBA-RGD-PAA-DOX (e).

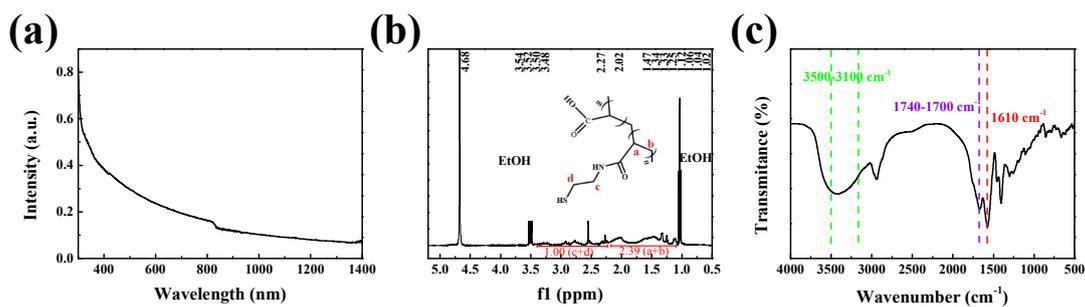


Fig. S4 Characterizations of PAA-SH, (a) UV-Vis-NIR absorption spectra, (b) NMR and (c) FT-IR.

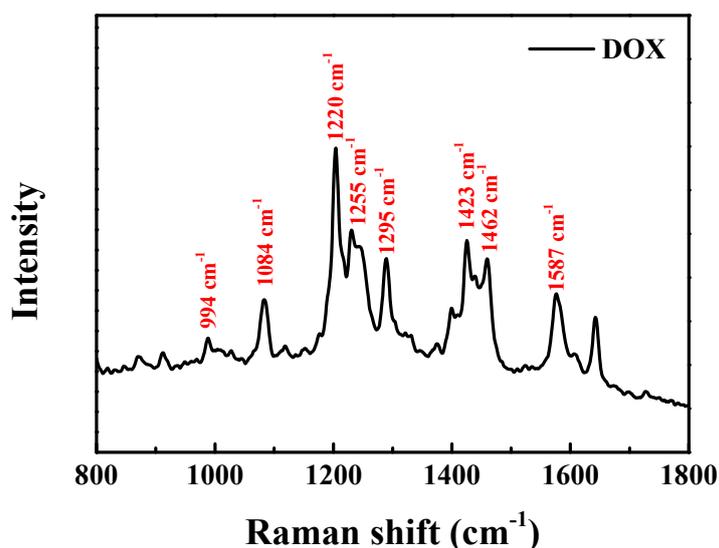


Fig. S5 Normal Raman spectra of DOX.

Section S2. Preparation and characterization of SH-PEG-COOH modified AuNF-nanocarriers and their properties of drug load and release

Firstly, different amounts of SH-PEG-COOH (0-100 mg) were dissolved respectively in 5 mL of as-prepared SERS tags solution (1.2 mM) and stirred for 20 h. For each sample, after centrifugation, different volume of PBS buffer was added to adjust the pH of the solution. Then 1 mL of 1 mg/mL DOX solution was added into 5 mL of AuNFs-MBA-RGD-PEG in the dark. The solution was stirred for 24 h and then centrifuged to remove the unloaded DOX. Finally, the

AuNFs-MBA-RGD-PEG-DOX were obtained by re-dispersing the precipitates in 5 mL of water. The drug encapsulation and release rate were calculated by the same method as mentioned in the paper.

Fig. S6a shows the amount-dependent drug encapsulation after adjusting the pH of the solution to 7.4. The drug encapsulation increased as the added SH-PEG-COOH increased from 0 to 50 mg, but the continuous increase resulted in a decrease of drug encapsulation. The drug encapsulation was up to 29.86% (calculated mass 0.2986 mg) when the fed SH-PEG-COOH was 50 mg (i.e. the finally concentration ~ 0.025 mmol). The reason may be that bits of $-\text{COO}^-$ can interact with DOX but too much SH-PEG-COOH results in crosslinking and twining.¹ Then the pH of solution was modulated to explore the influence of pH condition on drug encapsulation, and the results are shown in Fig. S6b. The alkaline environment resulted in the higher drug encapsulation at the same amount of SH-PEG-COOH modified on SERS tags. At pH 10, drug encapsulation was up to 79.66% (0.7966 mg), which was about 2.7 times of that at pH 7.4 since alkaline condition allowed the $-\text{COO}^-$ to dissociate and resulted in the solution to be negatively charged for absorbing positively charged DOX.²

The drug release property of AuNFs-MBA-RGD-PEG-DOX was studied by the method mentioned in the paper. Fig. S6c shows the drug releases (at pH 5.3) of the three AuNFs-MBA-RGD-PEG-DOX loaded DOX at pH 7.4, pH 8, and pH 10, respectively. The result indicates that the more DOX was loaded the lower release efficiency was obtained. The release efficiency of DOX at pH 5.3 was 44.66% (0.1334 mg), 21.42% (0.0857 mg) and 5.67% (0.0452 mg) for encapsulating at pH 7.4, 8 and 10, respectively, which was far less than that released from AuNFs-MBA-RGD-PAA-DOX. It may be because the electrostatic interaction at pH 10 is too strong to be protonated, and it is also possible that the structure of SH-PEG-COOH changes when the pH is too large, so that the drugs can not be released.²

References

- 1 K. Y. Lee, Y. Wang and S. Nie, *RSC Adv.*, 2015, **5**, 65651-65659.
- 2 J. Song, J. Zhou and H. Duan, *JACS*, 2012, **134**, 13458-13469.

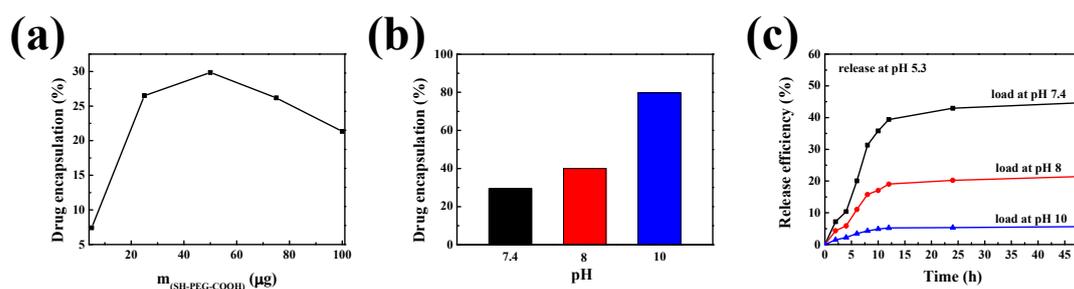


Fig. S6 (a) The dosage-dependent drug loading efficiency of SH-PEG-COOH. (b) Drug encapsulation at pH 7.4, pH 8, and pH 10, respectively. (c) The pH 5.3-drug release profiles of AuNFs-MBA-RGD-PEG-DOX loaded DOX at pH 7.4, pH 8, and pH 10, respectively.

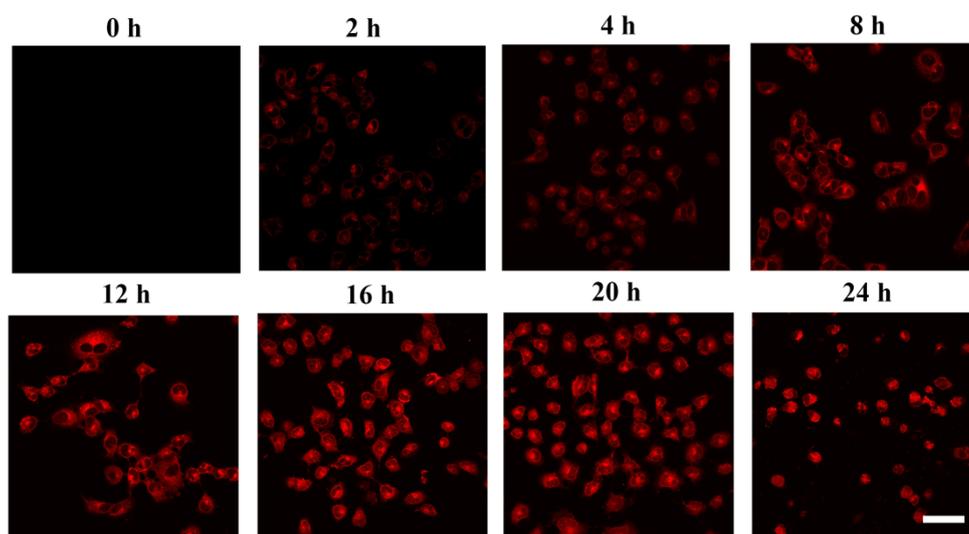


Fig. S7 Confocal fluorescence images of A549 incubated with AuNF-nanocarriers for different times. Scale bar is 50 μm .

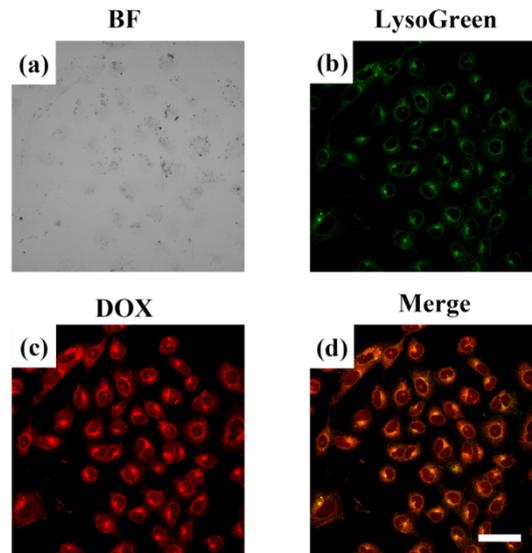


Fig. S8 Confocal images of A549 cells incubated with nanocarriers and stained by LysoGreen. (a) Bright field, (b) fluorescence image of LysoGreen (green color), (c) fluorescence image of DOX in cells (red color), and (d) merged fluorescence image of LysoGreen and DOX. Scale bar is 50 μm .

Section S3. Stability

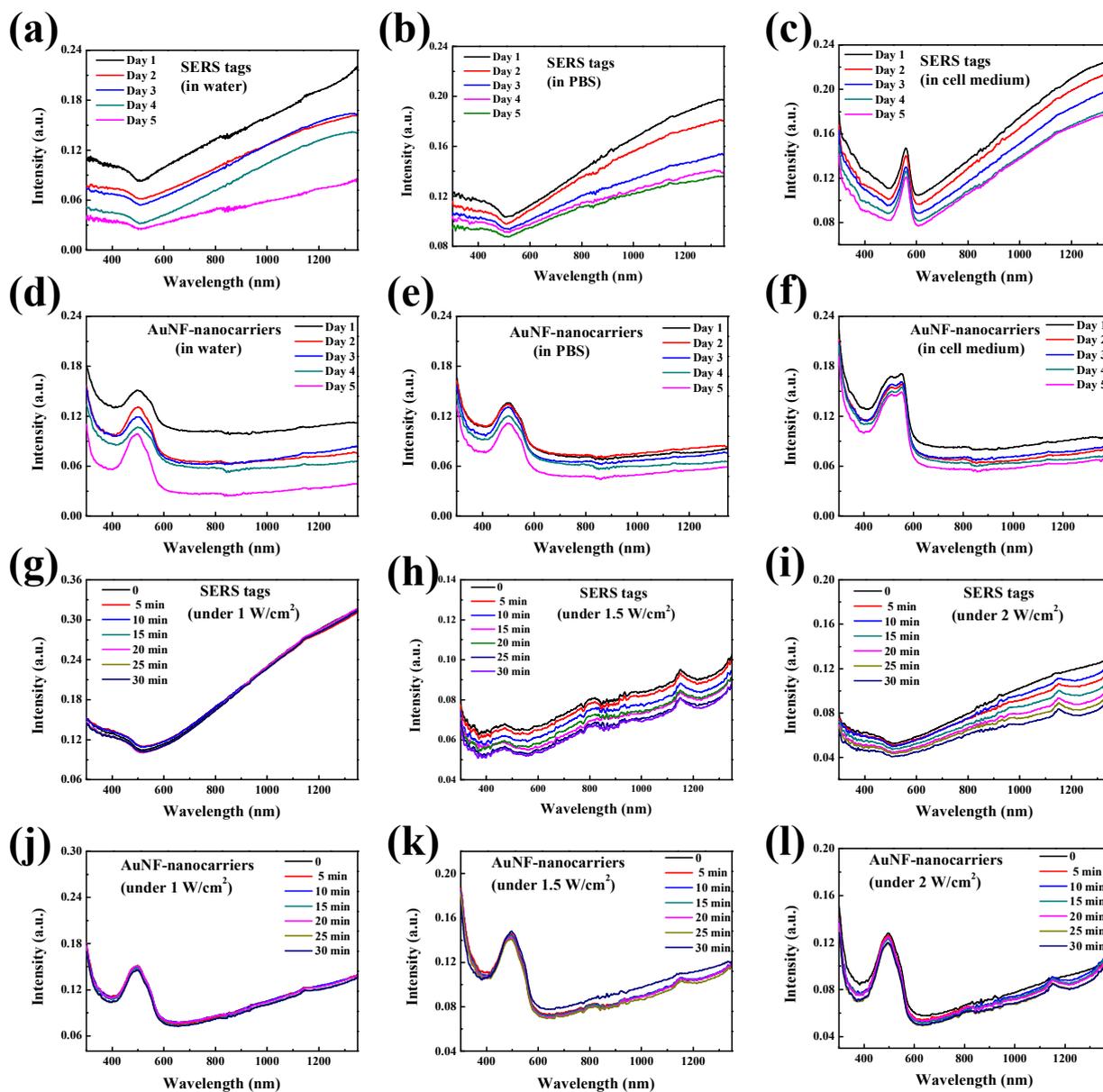


Fig. S9 Stability of AuNFs-MBA-RGD (a)-(c) and AuNFs-MBA-RGD-PAA-DOX (d)-(f) in water, PBS and cell medium, respectively. Photothermal stability of AuNFs-MBA-RGD (g)-(i) and AuNFs-MBA-RGD-PAA-DOX (j)-(l) under 1 W/cm², 1.5 W/cm², and 2 W/cm² exposure, respectively.

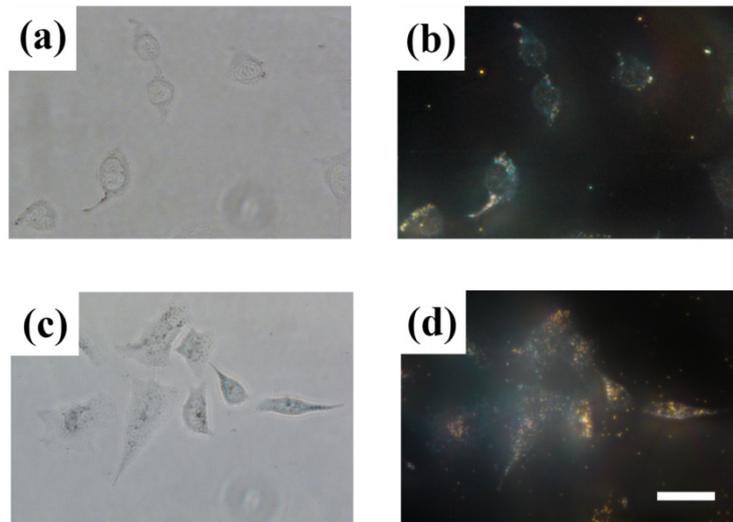


Fig. S10 Bright field microscopy image (a), dark field microscopy image (b) of A549 cells, and bright field microscopy image (c), dark field microscopy image (d) of A549 cells after incubation with AuNF-nanocarriers. Scale bar is 20 μm .