Supporting Information for:

Photolabile Plasmonic Vesicles Assembled from Amphiphilic Gold Nanoparticles for Remote-Controlled Traceable Drug Delivery

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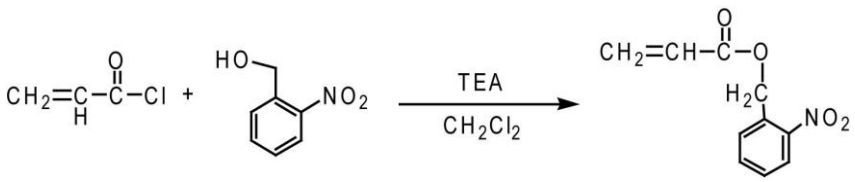
1. Synthesis of 2-nitrobenzyl acrylate (NBA). Scheme S1 shows the synthetic route of NBA. NBA was prepared following a previously reported method.[1] Briefly, 2-nitrobenzyl alcohol (3.00g) and triethylamine (TEA) (3.94 mL) were dissolved in 50 mL dichloromethane (DCM) at 0 ^{o}C, and acryloyl chloride (1.91 mL) in 10mL DCM was slowly added to it. After 12 h reaction, the mixture was filtered and the solvent evaporated. The crude mixture was purified by silica gel chromatography with 6:1 hexane/ethyl acetate.



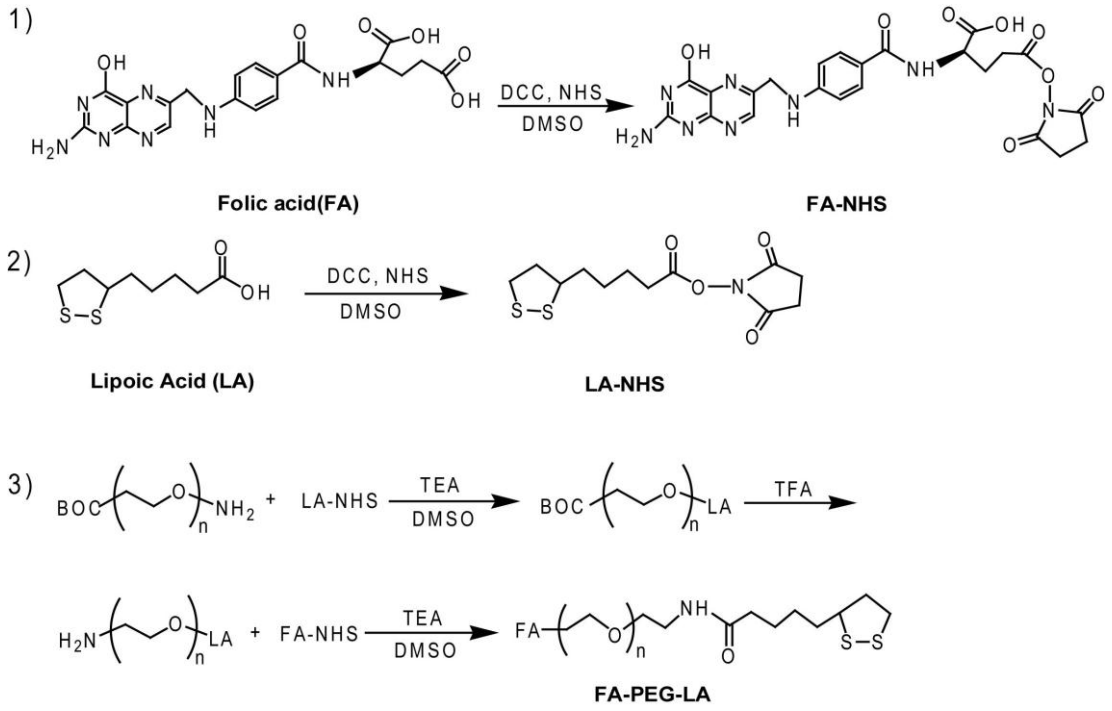
Scheme S1. Synthesis of 2-nitrobenzyl acrylate.

2. Synthesis of Lipoic Acid NHS-Ester (LA-NHS). Lipoic acid (LA, 2.00 g, 9.69 mmol) and N-hydroxysuccinimide (NHS, 1.34 g, 11.64 mmol) were dissolved in 30 mL of tetrahydrofuran (THF) at 4^{o}C in ice bath, and dicyclohexylcarbodiimide (DCC, 2.40 g, 11.64 mmol) in 5 mL of THF was slowly added to it. The solution was warmed to room temperature and stirred for 6 h. The insoluble byproduct was removed by vacuum filtration and the solvent evaporated. The crude product was redissolved in 30 mL of ethyl acetate and filtered once more by vacuum filtration. The product was recrystallized from a solution of hot ethyl acetate/hexane (1:1 v/v) as a pale-yellow solid.

3. Synthesis of H_2N-PEG-LA and MPEG-LA. To a solution of Boc-PEG-NH_2 (0.5 g) in dry dimethylsulfoxide (DMSO) (3mL) at 30^{o}C was slowly added 2.0 equiv of LA-NHS (0.065 g). The solution was stirred for 24 h at 30 ^{o}C. After the excessive DMSO was removed by evaporation, 2 mL chloroform was added to the crude product, and a clear solution was collected by filtration. A total of 0.2 mL of 90% trifluoroacetic acid (TFA) was added to the flask to deprotectBoc groups for 30 min at room temperature. The solution was precipitated using dry diethyl ether for three times, and H_2N-PEG-LA was collected by filtration and dried under vacuum at 30 ^{o}C. MPEG-LA was synthesized by the same method.

4. Synthesis of FA-PEG-LA (FA-PEG-LA). FA (0.50 g, 1.13 mM) and TEA (0.15 mL, 1.67 mmol) were dissolved in DMSO (15 mL), and DCC (0.28 g, 1.36 mmol) was slowly added to it. After the solution was stirred for 1 h at room temperature in the dark, the NHS (0.16 g, 1.36 mmol) in 1mL DMSO was added (Scheme S2). The mixture was stirred overnight in the dark at room temperature, filtered to remove the insoluble byproduct, dicyclohexylurea, and was precipitated using diethyl ether. The FA NHS-Ester (FA-NHS) was collected by filtration, washed with dry THF and dried under vacuum. FA-NHS (0.15g,

0.28mmol) and H_2N-PEG-LA (1g, 0.19 mmol) were dissolved in 6 mL DMSO and stirred for 40 h at room temperature in the dark. Chloroform was added to the reaction mixture, and a clear solution was collected by filtration. The solution was precipitated using diethyl ether, and FA-PEG-LA was collected by filtration and dried under vacuum.



Scheme S2. Synthesis of FA-PEG-LA

5. Calculation of the ratio of PEG and PNBA grafts on the nanocrystal surface.

^{1}H-NMR measurement (Figure S1) shows that the resonance of -CH_2-CH_2-O- (3.65 ppm) of PEG and that of –OCH_2- group (5.29 ppm) of PNBA has a ratio of 1:1, which leads to a molar ratio of 1:2 for ethylene glycol (EG) and NBA monomer. With the molecular weights of PEG(Mn=5 Ka) and PNBA(Mn=25 kDa, PDI=1.24), and the ratio of PEG and PNBA grafts can be calculated using Equation S1, where MW_{NBA} is the molecular weight of NBA monomer and MW_{EG} is the molecular weight of EG monomer. The result is 1:2 (PEG:PNBA).

$$Ratio\ (PEG{:}PNBA) = Ratio(EG{:}NBA)\left(\frac{MW_{PNBA}/MW_{NBA}}{MW_{PEG}/MW_{EG}}\right) \quad (Equation\ S1)$$

6. Calculation of PEG/PNBA graft density from TGA data

Given the size of a gold atom (0.017nm^3), the number of gold atom ($N_{Au\ atom}$) in 14nm Au nanoparticles can be calculated using Equation S2, where R is the radium of the gold nanoparticles. The result is 84472 gold atoms per nanoparticle and therefore the molar mass (M_{Au} nanoparticle) of the gold nanoparticle is 197 $N_{Au\ atom.}$ Combining the molar mass of the gold nanoparticle, the ratio of PEG and PNBA and the weight fraction obtained in TGA analysis, the average number of polymer grafts can be calculated by Equation S2, where W_{polymer} is the weight fraction (23.5%) of the organic part, $W_{\text{Au nanoparticle}}$ is the weight fraction of gold nanoparticle and $M_{PEG+2PNBA}$is the sum of the molar mass of one PEG and two PNBA grafts. The result is 270 grafts per nanoparticle, which include 93 PEG chains and 186 PNBA chains, and the graft density is ~0.44 chain/nm^2.

$$N_{Au\ atom} = \frac{V_{Au\ nanoparticle}}{V_{Au\ atom}} = \frac{4\pi}{3}\left(\frac{R^3}{V_{Au\ atom}}\right) \quad (Equation\ S2)$$

$$N_{\text{grafts per nanoparticle}} = \left(\frac{3W_{polymer}/M_{PEG+2PNBA}}{W_{Au\ nanoparticle}/M_{Au\ nanoparticle}}\right) \quad (Equation\ S3)$$

References

1 J. Jiang, X. Tong, D. Morris, Y. Zhao, *Macromolecules* **2006,***39*, 4633-4640.

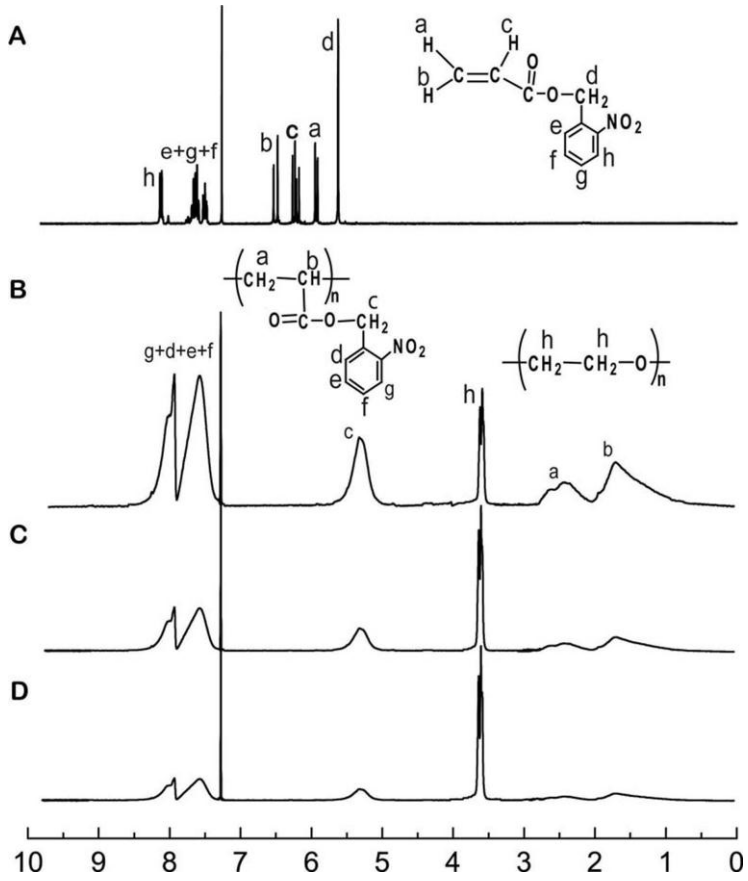


Fig. S1 (A) ^{1}H NMR (300 MHz, *δ*, ppm, $CDCl_3$) of NBA: δ 5.46 (H, s), δ 5.77 (H, d), δ 6.16 (H, t), δ6.41 (H, d), δ 7.38-7.62 (3H, m), δ 8.07 (H, d); (B) ^{1}H NMR (300 MHz, *δ*, ppm, $CDCl_3$) of Au@PEG/NBA: δ3.66 (-OCH_2CH_2-), δ1.17-1.95 (-CH_2-),δ2.14-2.72 (-C*H*-),δ5.29 (-O-CH_2-), δ7.37-8.35 (*phenyl*).AmphiphilicAu@PEG/PNBA nanoparticles with the PEG/PNBA ratioswere 1:4 (B), 1:2 (C) and 1:1 (D).

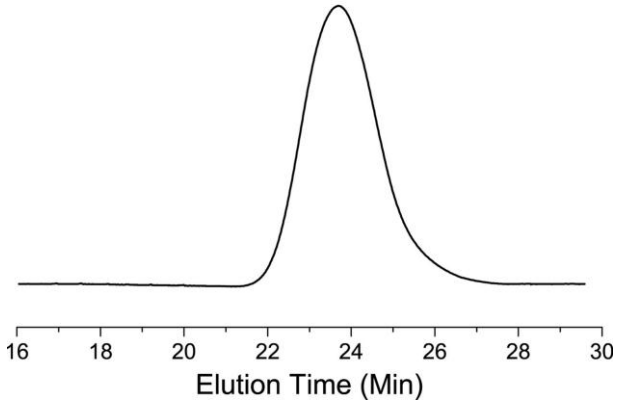


Fig. S2 GPC spectra of poly(2-nitrobenzyl acrylate) PNBA: MW=25 kDa, PDI=1.24

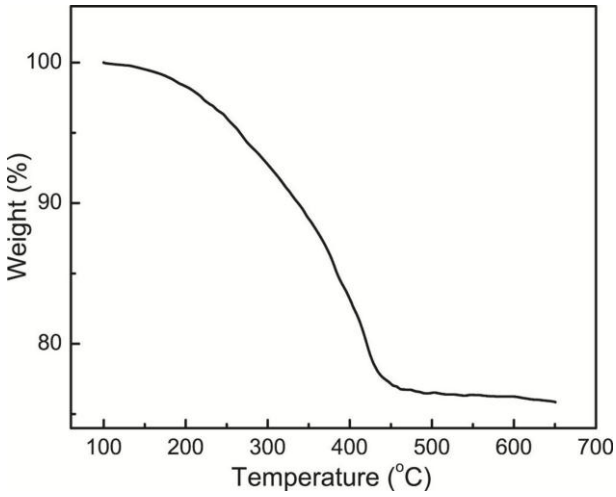


Fig. S3 TGA analysis of the gold nanoparticles grafted with mixed polymer brushes of poly(ethylene glycol) and poly(2-nitrobenzyl acrylate) (the weight fraction of the polymer brushes is 23.5%).

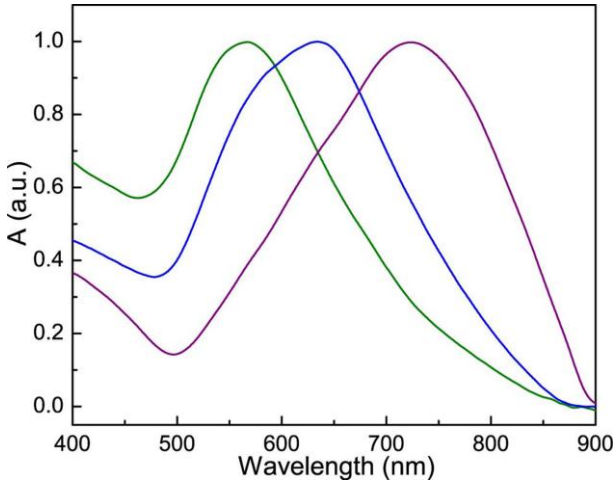


Fig. S4 UV-vis spectra of self-assembled vesicles of Au@PEG/PNBA with a PEG/PNBA ratio of 1:1 (green line), 1:2 (blue line), and 1:4 (purple line) in water

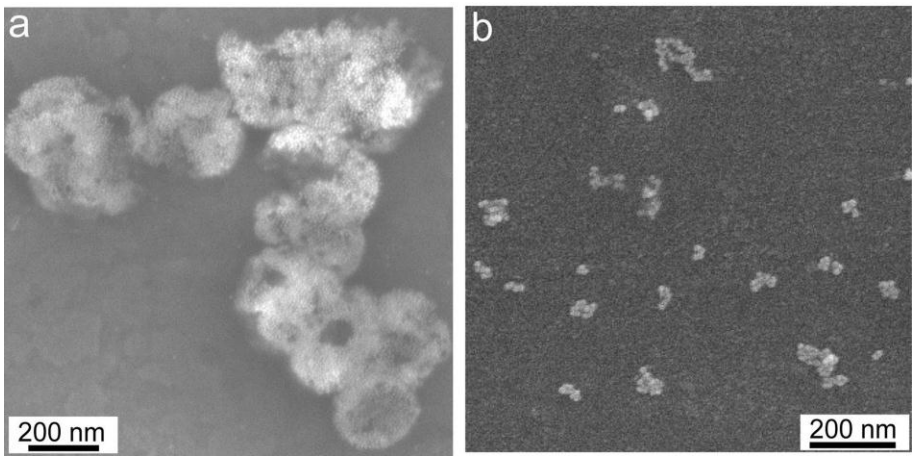


Fig. S5 Scanning electron microscopy (SEM) images of plasmonic vesicles upon photo-irradiation for 10 min (a), 15 min (b).

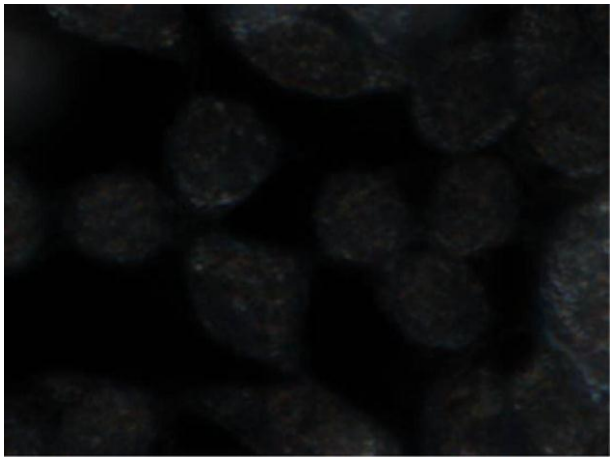


Fig. S6 Dark-field image of live MDA-MB-435 cells

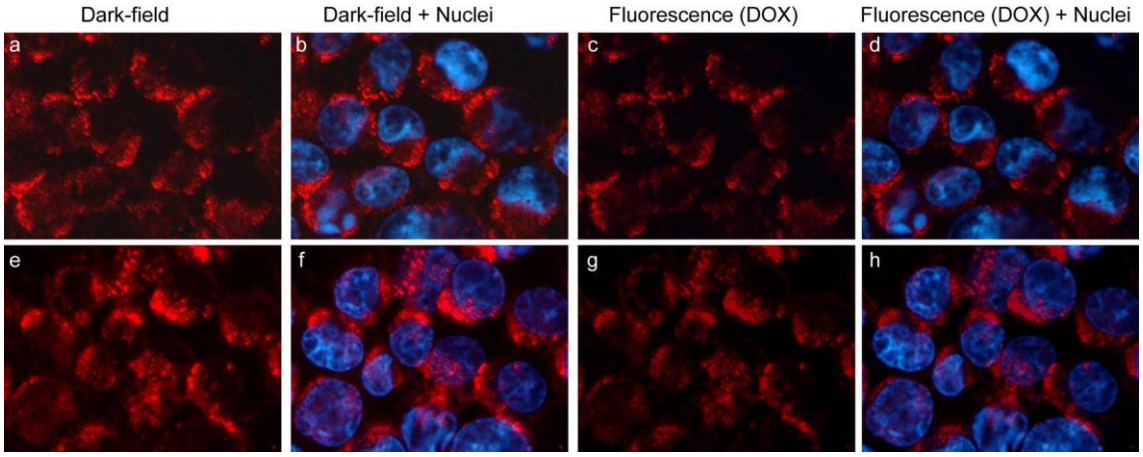


Fig. S7 Dark-field (a, e), fluorescence (c, g), and the overlaid images (b, f, d, h) of MDA-MB-435 cells incubated with folate conjugated DOX-loaded vesicles for 40 min (a-d) and 48 h (e-h) without light irradiation.

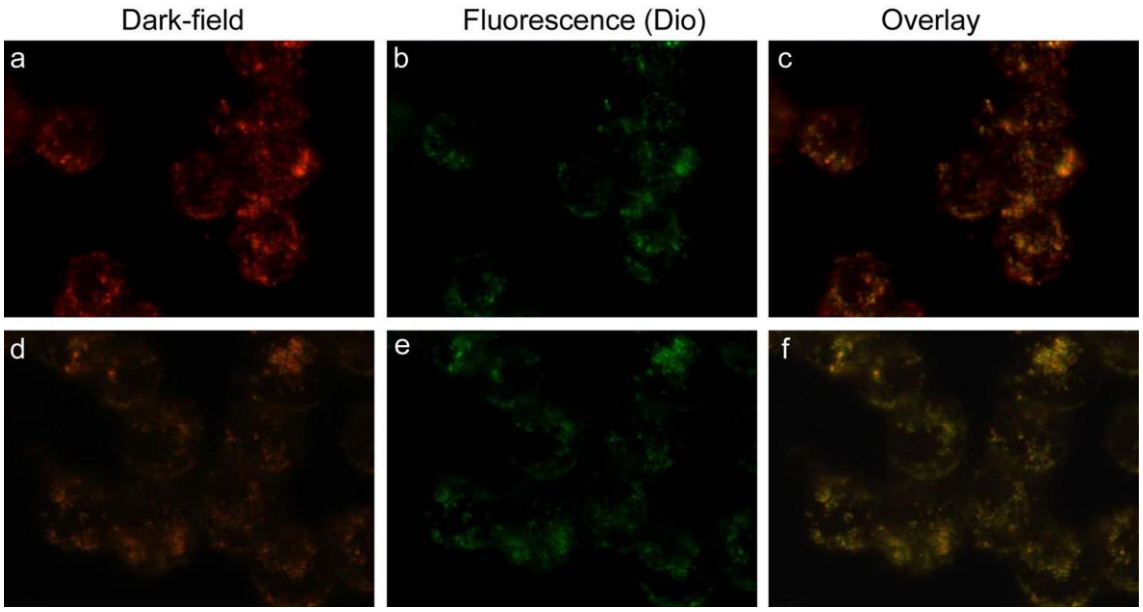


Fig. S8 The co-localization of the plasmonic vesicles and the organelle-tracking dye DiO in MDA-MB-435 cells incubated with folate-targeted vesicles for 40min without light (a-c) and with light irradiated for 15 min and post incubation for 20 min (d-f).