Intracellular GSH-activated Galactoside Photosensitizers for Targeted Photodynamic Therapy and Chemotherapy

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Synthesis of BOC-OEA

2-Aminoethanol (2.04 mL, 34 mmol) was dissolved in 1 M NaOH solution (100 mL) and the mixture was stirred for 24 h. A separate solution of di-tert-butyl dicarbonate (8.89 g, 40.8 mmol) in 1, 4-dioxane (50 mL) was added to the above mixed solution. The solution was further stirred for 48 hours. The reaction was quenched with water and the solution was extracted with ethyl acetate (3 × 75 mL). The organic layer was washed with brine (75 mL) and dried over MgSO₄, filtered, and concentrated in vacuo to yield the tert-buty1-2-hydroxyethyl carbamate (BOC-OEA) (4.06 g, 74%) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.51 (s, 1H), 3.96 (s, 1H), 3.34-3.23 (m, 2H), 2.97-2.85 (m, 2H), 1.12 (s, 9H).

Synthesis of disulfide-modified carboxyl terminal porphyrin (TPP-S-S-COOH)

TPP-S-S-COOH was synthesized via esterification by coupling TPPC6-OH with 3, 3′-dithiodipropionic acid. Typically, TPPC6-OH (1.34 g, 2 mmol), 3, 3′-dithiodipropionic acid (0.84 g, 4 mmol) and DMAP (0.246 g, 2 mmol ) were dissolved in 50 mL anhydrous DMF under N₂ atmosphere, cooled to 0 °C in an ice-water bath, and then DCC (0.82 g, 4 mmol) in 5 mL DMF was added dropwise into above solution, and the solution was stirred at room temperature overnight. Then the reaction mixture was filtered to remove dicyclohexylurea and washed with DCM and water, dried with MgSO₄. After DCM was removed by evaporation, the crude product was purified on a silica gel column with petroleum ether/ethyl acetate (3:2 v/v) as the eluent. The second band gave TPP-S-S-COOH. Yield: 1.61 g (87.1 %).

Scheme. S1 Synthetic route of TPPC6-S-S-COOH
Synthesis of TPP-S-S-PEG

The amphiphilic photosensitizer TPP-S-S-PEG was synthesized via esterification by coupling TPP-S-S-COOH with PEG \((M_n = 1,000)\). Typically, TPP-S-S-COOH (100 mg, 0.111 mmol), PEG (1.11 g, 1.11 mmol) and DMAP (0.183 g, 0.15 mmol) were dissolved in 15 mL anhydrous DCM under argon atmosphere, cooled to 0 °C in an ice-water bath, and then DCC (0.309 g, 1.5 mmol) in 5 mL DCM was added dropwise into above solution, and the solution was stirred at room temperature overnight. Then the reaction mixture was filtered to remove dicyclohexylurea and washed with DCM and water, dried with MgSO\(_4\). After DCM was removed by evaporation, the crude product was purified on a silica gel column with petroleum ether/ethyl acetate (1:2 v/v) as the eluent. Yield: 84.3 mg (40 %).

Scheme. S2 Synthetic route of TPPC6-S-S-PEG

Fig. S1. \(^1\)H NMR spectrum of tert-butyl-2-hydroxyethyl carbamate (BOC-EOA)
**Fig. S2.** $^1$H NMR spectrum of 2-((tert-butoxycarbonyl)amino) ethoxy-$\beta$-D-galactopyranose ($\beta$-D-GalPA-BOC)

**Fig. S3.** $^1$H NMR spectrum of 2-((tert-butoxycarbonyl)amino) ethoxy-$\beta$-D-galactose ($\beta$-D-Gal-BOC)
**Fig. S4.** $^1$H NMR spectrum of disulfide-modified carboxyl terminal porphyrin (TPP-S-S-COOH)

**Fig. S5.** $^1$H NMR spectrum of TPP-S-S-PEG
Critical micelle concentration (CMC) of TPP-S-S-Gal micelles

Pyrene was used as a fluorescent probe to determine the critical micelle concentration (CMC) of TPP-S-S-Gal micelles. 5 mL of pyrene solution in acetone was added into a series of volumetric flasks ensuring that the final pyrene concentration was $6.0 \times 10^{-7}$ mol L$^{-1}$. Acetone was evaporated and a predetermined amount of TPP-S-S-Gal solutions was added into the volumetric flasks, which were adjusted by adding deionized water to get different concentration solutions. The fluorescence spectrum was obtained using an F-4500 fluorescence spectrometer at an excitation wavelength of 335 nm. Emission wavelength values at 372 nm and 383 nm were monitored and recorded. The CMC was estimated as the cross-point when extrapolating the intensity ratio $I_{372}/I_{383}$ at low and high concentration regions.

![Graph](image)

**Fig. S6.** Plots of $I_3/I_1$ vs copolymer concentration for block copolymer in deionized water with different concentrations (from 0.00025 to 0.1 mg mL$^{-1}$)
Fig. S7. CLSM images of A549 cells incubated with TPP-S-S-PEG micelles and TPP-S-S-Gal micelles for 24 h (a) TPP-S-S-PEG micelles; (b) TPP-S-S-Gal micelles. (scale bar: 20 μm)