Supporting Information

A General Method for Endowing Hydrophobic Nanoparticles with Water Dispersion Abilities

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Experimental Section

Chemicals and reagents: GdCl₃, ZnCl₂, oleic acid (OA), oleylamine (OAm), and octadecylamine (OctAm), trioctylphosphine oxide (TOPO), 1-octadecene (ODE) and dimercaptosuccinic acid (DMSA) were purchased from Macklin. Sulfur powder, NaH₂PO₄, NaF, NaOH, AgNO₃, ethanol, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO) and cyclohexane were purchased from Sinopharm Chemical Reagent Co., Ltd, China. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysulfosuccinimide (NHS) were purchased from TCI. PEG2000-NH₂ and FITC-PEG2000-NH₂ was obtained from Shanghai Yare Biotech. Phosphate buffered solution (PBS), RPMI 1640, Penicillin-Streptomycin and fetal bovine serum (FBS) were obtained from Adamas Life. DAPI staining kit and calcein-AM and PI staining kit were bought from Beyotime. Deionized (DI) water was got from ELGA Centra.

Characterization: Transmission electron microscope (TEM) graph was carried out by FEI Talos F200X. X-ray diffraction (XRD) was measured by Rigaku D/MAX-2250 V. Dynamic light scattering was measured by Malvern Zetasizer Nano S. Zeta Potential was measured by Brookhaven Omni. Fourier transform infrared spectroscopy (FTIR) was measured by Bruker Thermo Fisher Nicolet 6700. Ultraviolet-visible (UV-Vis) spectrum was measured by Shimadzu UV-3600 Plus. The content of Zn, Ag, Ti and Gd was measured by inductively coupled plasma optical emission spectrometry (ICP-OES, Agilent 725). Confocal laser scanning microscopy (CLSM) was carried out on Leica TCS SP8 STED 3X. In vitro MR imaging evaluations were conducted on clinical MRI scanner (GE SIGNA Architect 3.0 T).

Synthesis of Ag-OctAm: OctAm (10 g) were mixed in a flask with three necks and heated to 180 °C under the protection of N_2 for 0.5 h. Then AgNO₃ powder (0.5 g) was poured into the flask and further reacted at 180 °C for 0.5 h. The Ag-OctAm was obtained after washed 3 times with ethanol and cyclohexane.

Synthesis of NaGdF₄-OA: GdCl₃ (1 g), 25 ml OA and 15 ml ODE were mixed in a flask with three necks and heated to 140 °C under the protection of N₂ for 1 h. Then NaF powder (1.5 g) was poured into the flask, and this mixture was heated to 290 °C for 1.5 h. The NaGdF₄-OA was obtained after washed 3 times with ethanol and cyclohexane.

Synthesis of TiO_2 -OA: Tetrabutyl titanate (1.7 g), OA (7.06 g), OAm (6.69 g) and ethanol (3.20 g) were mixed and stirred for 10 min. Ethanol (15.15 g) and DI water (0.8 g) were then added for another 5 min stirring. The mixture was then transferred to a hydrothermal synthesis reactor, and maintained at 180 °C for 18 h. The TiO₂-OA was obtained after washed 3 times with ethanol and cyclohexane.

Synthesis of ZnS-OAm: $ZnCl_2$ (2 mmol), TOPO (2.3 g) and OAm (10 mL) were mixed in a flask with three necks and heated to 170 °C under the protection of N₂ for 1 h. Then sulfur (6 mmol) solution in OAm (10 mL) was added into the flask at room temperature, and then this mixture was heated to 320 °C for 1 h. The ZnS-OAm was obtained after washed 3 times with ethanol and cyclohexane.

DMSA-based modification: DMSA (1 mmol) solution in THF (10 mL) is mixed with hydrophobic nanoparticles (about 2 mmol) solution in cyclohexane (10 mL) and stirred

for 48 hours. THF and cyclohexane were removed by rotary evaporator. Then the nanoparticles modified by DMSA were obtained after washed 3 times with ethanol.

Synthesis of ZnS-PEG: ZnS-DMSA (1 mmol) solution in DI water (10 mL), EDC (0.1 mmol) and NHS (0.3 mmol) were mixed and stirred at room temperature for 0.5 h. Then PEG2000-NH₂ (10 mg) was added to this mixture and reacted for 12 h overnight. ZnS-PEG was obtained after washed 3 times with DI water.

Synthesis of TiO_2 -FITC: TiO_2-DMSA (1 mmol) solution in DI water (10 mL), EDC (0.1 mmol) and NHS (0.3 mmol) were mixed and stirred at room temperature for 0.5 h. Then FITC-PEG2000-NH₂ (10 mg) was added to this mixture and reacted for 12 h in the dark overnight. TiO₂-FITC was obtained after washed 3 times with DI water.

The formula of solutions with different pH: The pH 7.4 solution was PBS which was bought for cell culture. The pH 5.0 solution was NaH₂PO₄ solution (10 mM) and the pH was adjusted by a small amount of NaOH.

Cell experiments: PANC-1, MG63, HUVEC and 4T1 cells were obtained from the Shanghai Institute of Cells, Chinese Academy of Sciences. All cells were maintained in media (RPMI 1640) supplemented with 10% FBS and 1% Penicillin-Streptomycin. Cells (1×10^4 cells/well) were seeded in confocal dishes and cultured for 24 h. For cytophagy, the cells were incubated with TiO₂-FITC (Ti, 50 ppm) for 4 h. After incubation, the fluorescence of TiO₂-FITC was observed by CLSM. For anticancer experiments, 4T1 cells and HUVEC cells were incubated with RPMI 1640 medium and Ag-DMSA respectively for another 24 h. After 24 h, the cells were incubated with PI (10 μ M) and calcein-AM (10 μ M) for 0.5 h. After incubation, the fluorescence was observed by CLSM.

MRI experiments: NaGdF₄-DMSA was diluted in Eppendorf tubes (2 mL volume) at various Gd concentration (0.06-0.9 mM) concentrations. T₁ map sequence: repetition time (TR) = 1000, 2000, 3000, 4000 ms; echo time (TE) = 8 ms; slice thickness = 2 mm; space = 0.5 mm; field of view (FOV) = 18; phase FOV = 0.8; freq × phase = 256 × 192; number excitations (NEX) = 2; echo train length (ETL) = 3. MR images were transferred to ADW 4.6 workstation (GE Healthcare, US). The mean T₁ values of each sample were measured by regions-of-interest (ROI) on the T₁-mapping post-processing software and the relaxation rate r1 was determined according to the linear plot of 1/T₁ versus Gd concentration.

Supplementary Figures



Figure S1. Photographs of a) NaGdF₄-OA, Ag-OctAm, ZnS-OAm, TiO₂-OA and b) NaGdF₄-DMSA, Ag-DMSA, ZnS-DMSA, TiO₂-DMSA.



Figure S2. Hydrodynamic radius of a) Ag-OctAm, b) NaGdF₄-OA, c) TiO₂-OA and d) ZnS-OAm meausred by dynamic light scattering (DLS).



Figure S3. Ultraviolet-visible (UV-Vis) spectrum of a) Ag-OctAm, b) NaGdF₄-OA, c) TiO₂-OA, d) ZnS-OAm, e) Ag-DMSA, f) NaGdF₄-DMSA, g) TiO₂-DMSA and h) ZnS-DMSA.



Figure S4. Hydrodynamic size of a) Ag-DMSA, b) NaGdF₄-DMSA, c) TiO_2 -DMSA and d) ZnS-DMSA dispersed in PBS (pH 7.4) at 1st day, 7th day and 14th day.



Figure S5. Relative release of Zn^{2+} from ZnS-DMSA under pH 5.0.



Figure S6. HUVEC and 4T1 cells viability of different concentrations of Ag-DMSA (n = 5, mean \pm SD).