Supporting Information

Redox/photo dual-responsive, self-targeted, and photosensitizer-laden bismuth sulfide nanourchins for combination therapy in cancer

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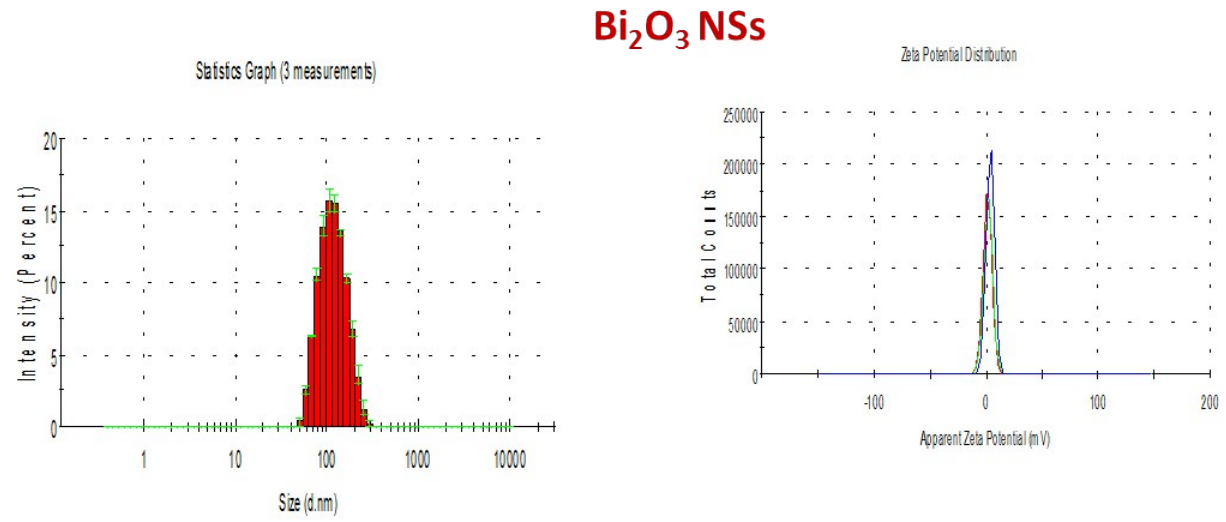

Sample	Particle size (nm)	Poly-dispersity index (PDI)	Zeta Potential (mV)
Bi_2O_3 NPs	109.4 ± 0.86	0.117 ± 0.01	2.29 ± 1.24
Bi_2S_3 NPs	150.9 ± 3.61	0.103 ± 0.06	-33.7 ± 0.40

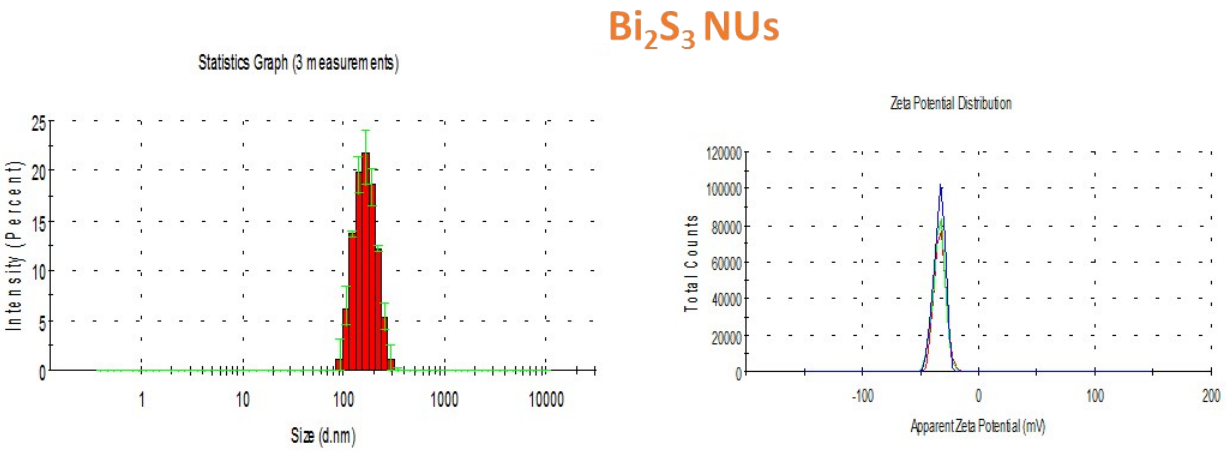

Figure S1. DLS characterization of Bi_2O_3 NSs and Bi_2S_3 NUs.

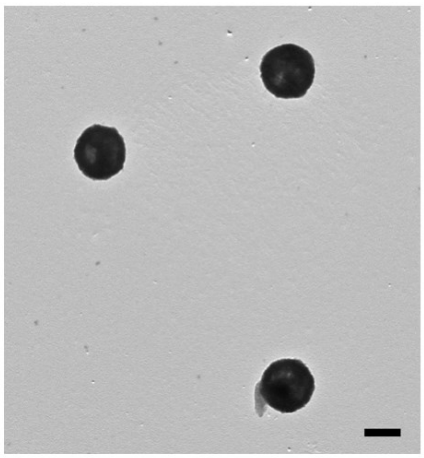

Figure S2. TEM image of Bi_2O_3 NSs, Scale bar: 100 nm.

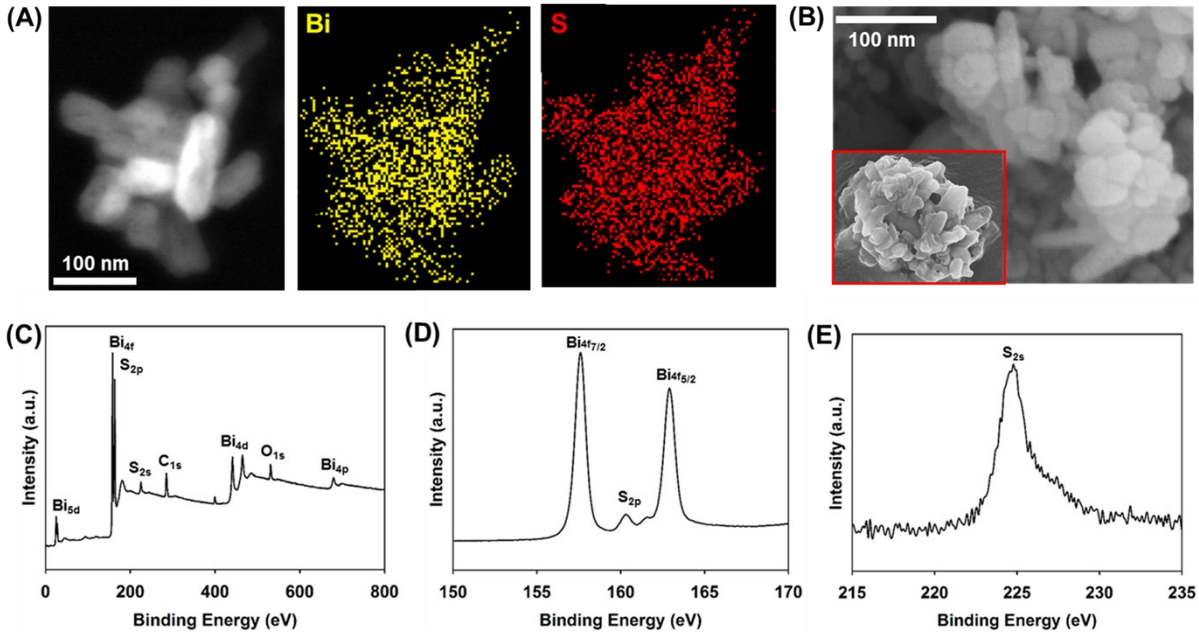

Figure S3. (A) TEM-EDS mapping, (B) SEM imaging, and (C, D, and E) XPS analysis of Bi_2S_3 NUs.

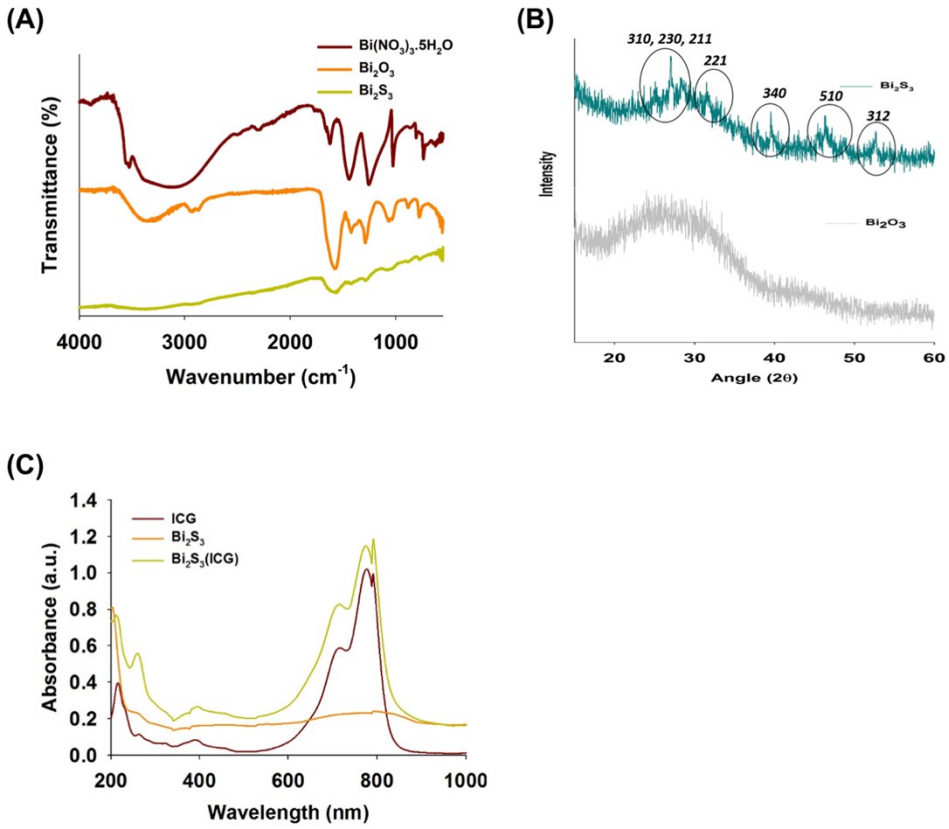

Figure S4. (A) FTIR spectras of $Bi(NO_3)_3.5H_2O$, Bi_2O_3 NSs and Bi_2S_3 NUs. (B) XRD spectras of Bi_2O_3 NSs and Bi_2S_3 NUs. (C) UV/Vis spectral analysis of ICG, Bi_2S_3 and Bi_2S_3(ICG) NUs.

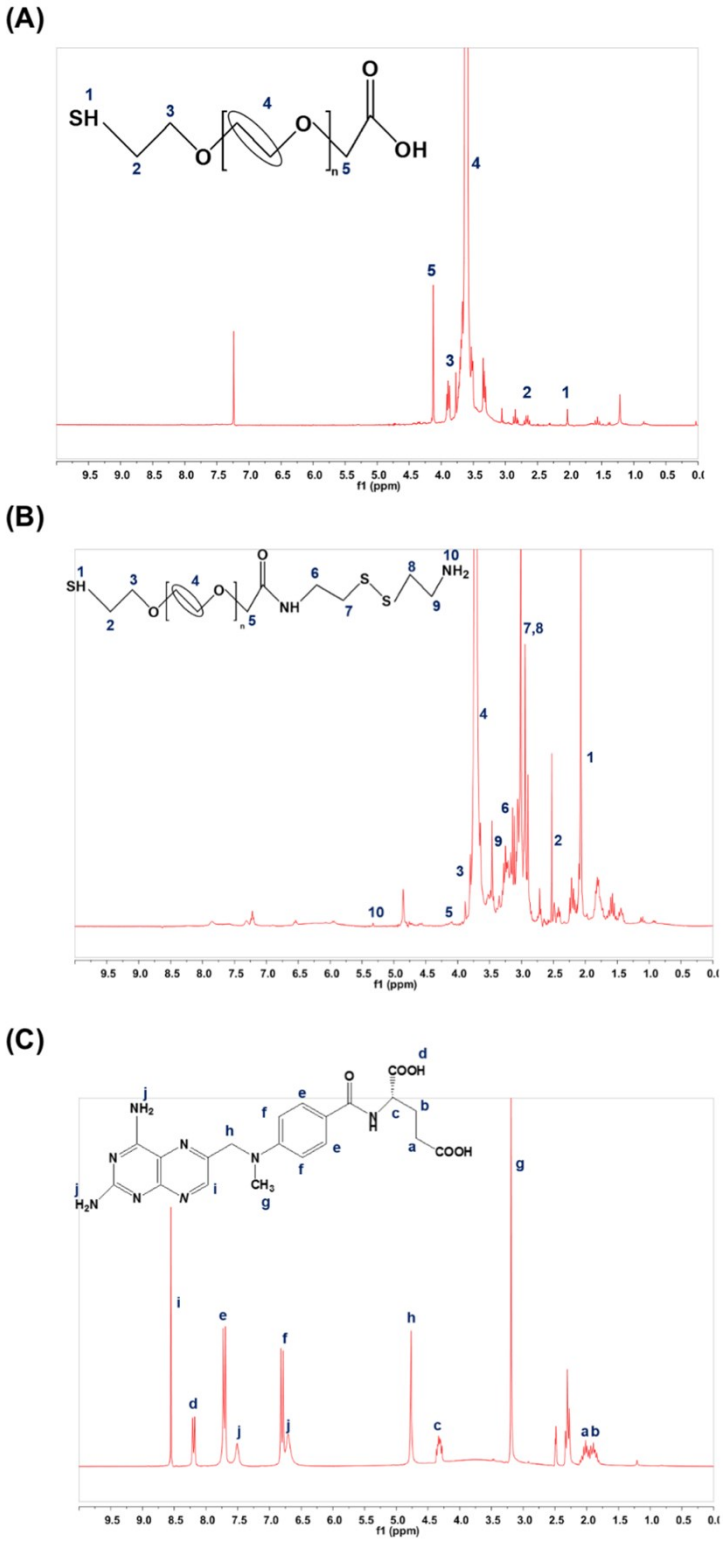

Figure S5. ^{1}H NMR spectra of SH-PEG$_{5k}$-COOH (A) with its characteristic peaks and SH-PEG$_{5k}$-S-S-NH$_2$ (B) after the reaction with cystamine with preserved peaks of SH-PEG$_{5k}$-COOH and added peaks of cystamine. ^{1}H NMR spectra of MTX (C) with its characteristic peaks and SH-PEG$_{5k}$-S-S-MTX.

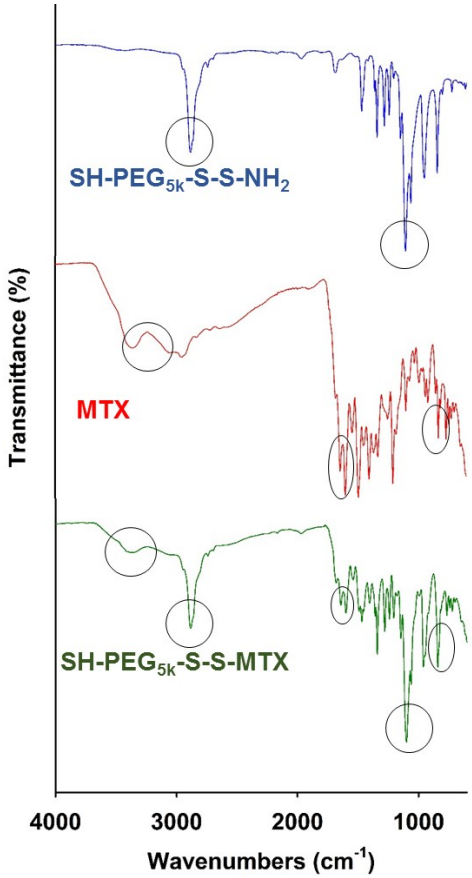

Figure S6. FTIR spectra of SH-PEG$_{5k}$-S-S-NH$_2$, MTX, and SH-PEG$_{5k}$-S-S-MTX.

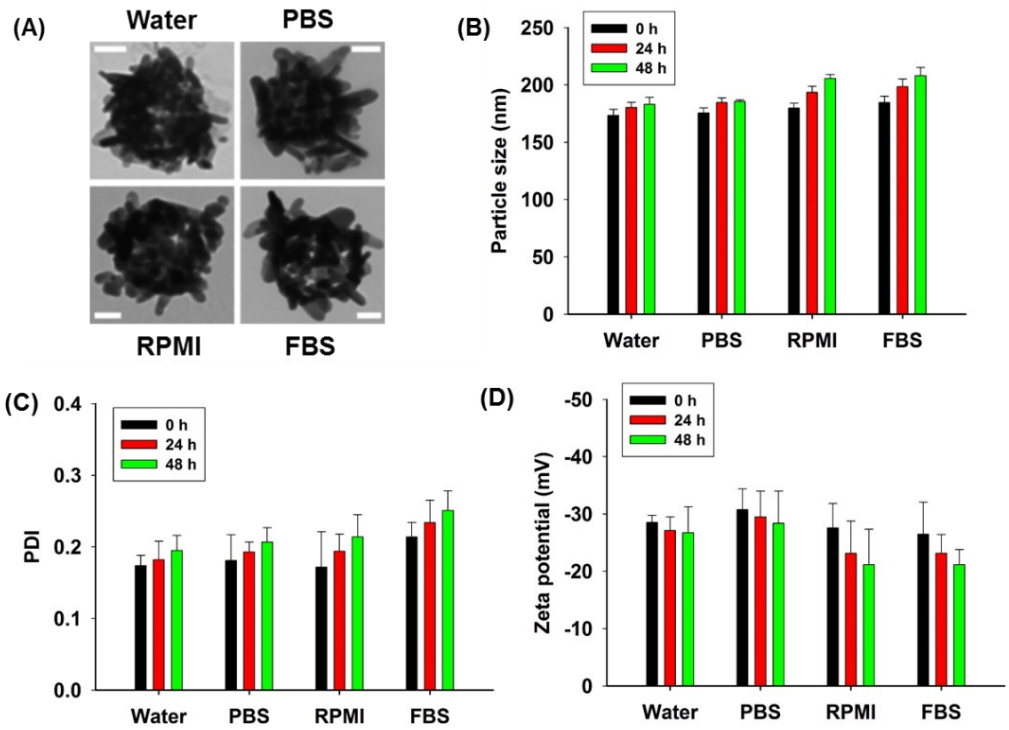

Figure S7. Stability evaluations from TEM imaging (A) and DLS characterization (B, C, and D) of Bi_2S_3(ICG)-PEG-S-S-MTX NUs in different media (water, PBS, RPMI, and FBS) up to 48 h (Scale bar: 50 nm).

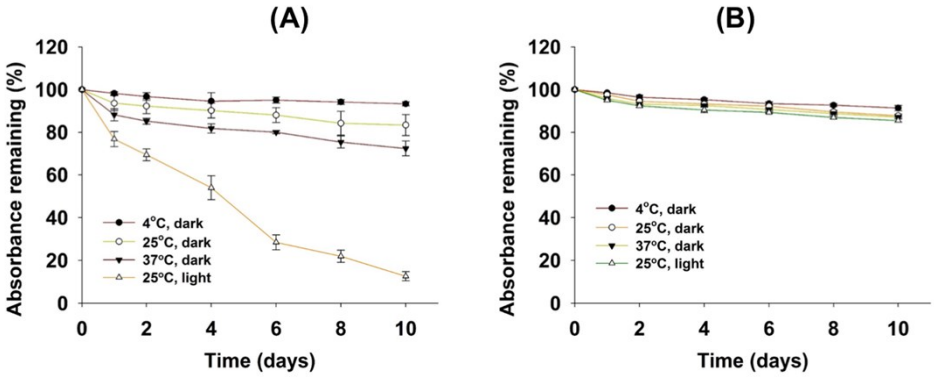

Figure S8. Assessment of stability of ICG and ICG in Bi_2S_3(ICG)-S-S-MTX at different conditions (dark (4ºC, 25ºC and 37ºC) and light (25ºC).

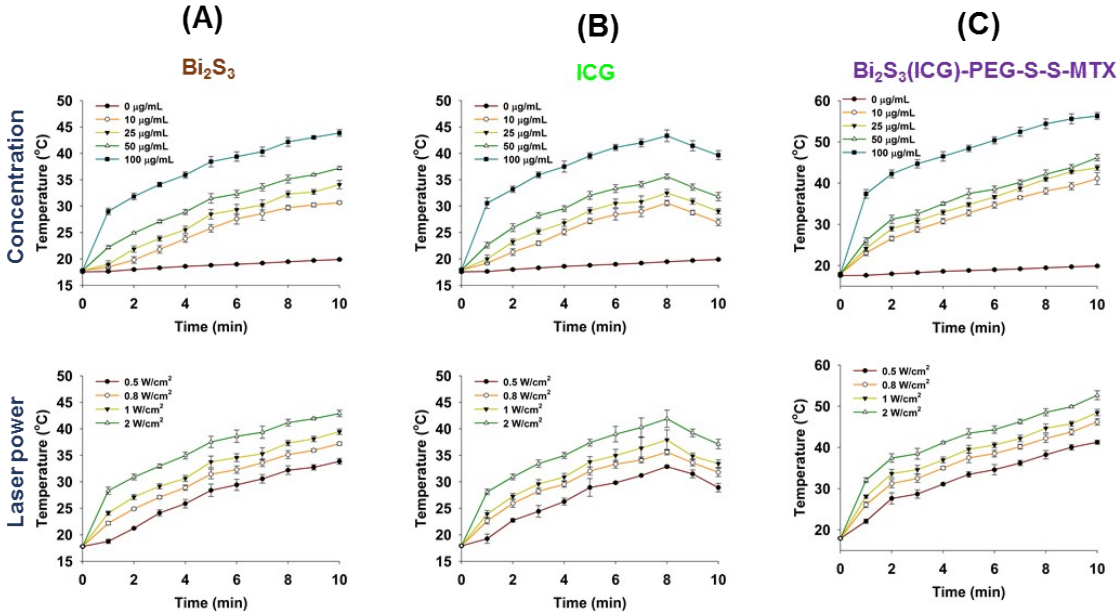

Figure S9. Assessment of photothermal performance of Bi_2S_3 (A), ICG (B), and Bi_2S_3 (ICG)-S-S-MTX (C) at different concentrations (0, 10 ,25, 50, and 100 µg/mL) with 0.8 W/cm^2 and at concentration of 50 µg/mL with different power intensities (0.5, 0.8, 1, and 2 W/cm^2) of NIR laser (808 nm) up to 10 min. Concentration mentioned in Bi_2S_3(ICG)-S-S-MTX is of Bi_2S_3, and the ratio of concentration of Bi_2S_3:ICG was 1:8.

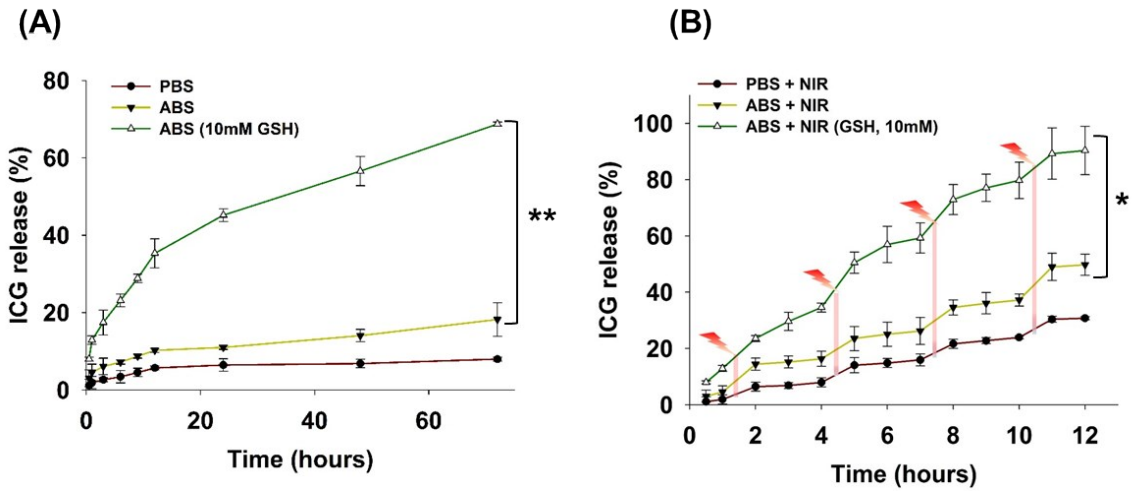

Figure S10. *In vitro* release profile of ICG in PBS, ABS (with and without 10 mM GSH) and with NIR irradiation (808 nm, 0.8 W/cm^2, 10 min), (*p<.05; **p<.01; ***p<.001).

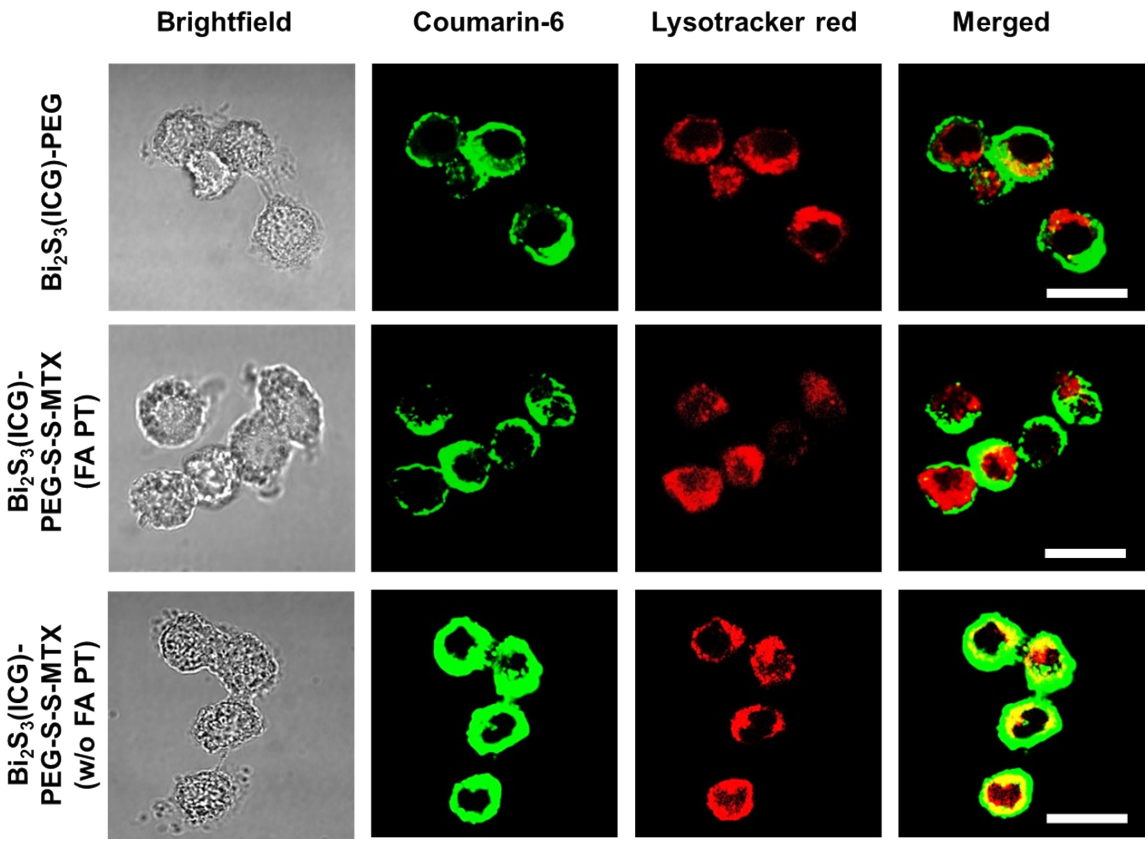

Figure S11. Confocal images of HCT116 cells and A549 cells after incubation with Bi_2S_3(ICG)-PEG and Bi_2S_3(ICG)-PEG-S-S-MTX NUs (3 μg/mL, 60 min), and with and without FA PT, Scale bar: 20 μm. Coumarin-6 was used to stain the nanoparticles, and lysotracker red was used to stain the lysosome; FA PT, folic acid pretreatment.

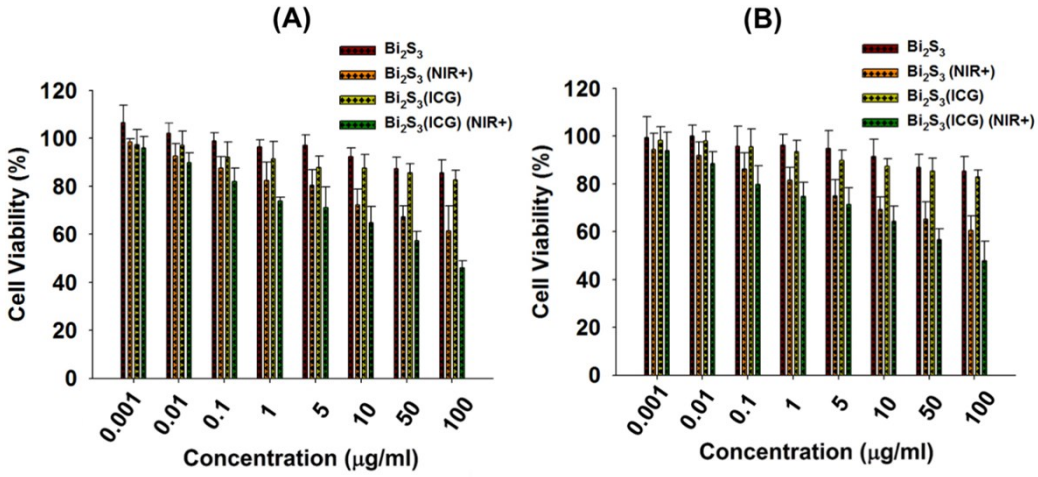

Figure S12. *In vitro* cell cytotoxicity profiles of Bi_2S_3 and Bi_2S_3(ICG) in (A) HCT-116 and (B) A549 cells with or without NIR irradiation (808 nm, 0.8 W/cm^2, 5 min) after 24 h.

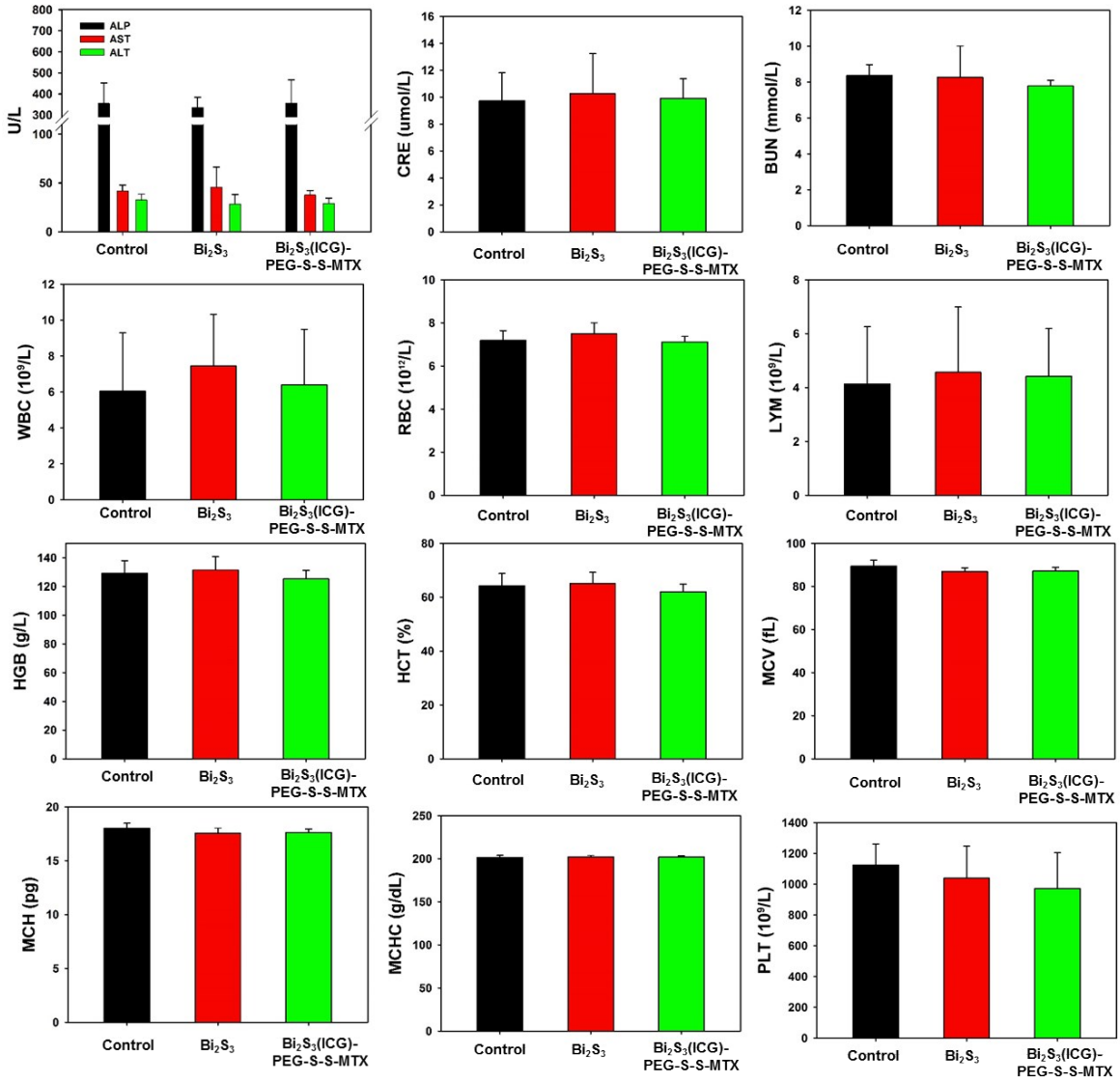

Figure S13. Blood biochemistry and complete blood panel analysis of mice after receiving i.v. injection with saline**,** Bi_2S_3, and Bi_2S_3(ICG)-PEG-S-S-MTX based on the weight of a mouse (15 mg of Bi kg^{-1}) for 15 days. The examined parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (CREA), white blood cell (WBC) counts, red blood cell (RBC) counts, lymphocyte (LYM), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelets (PLT).

Table S1. Histopathological-histomorphometrical analysis of principal organs taken from xenograft athymic nude mice

Groups	Heart	Liver	Spleen	Lung	Kidney
Group 1	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)
Treatment					
Group 2	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)
Group 3	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)
Group 4	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)
Group 5	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)
Group 6	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)

Values were numbers of abnormal fields/total observed fields (Six histological fields in each group)

Group 1 = Control;
Group 2 = Bi_2S_3(ICG)-PEG;
Group 3 = MTX;
Group 4 = Bi_2S_3(ICG)-PEG-S-S-MTX;
Group 5 = Bi_2S_3(ICG)-PEG (NIR+);
Group 6 = Bi_2S_3(ICG)-PEG-S-S-MTX (NIR+)

Bi_2S_3 = Bismuth sulfide; ICG = Indocyanine green; MTX = Methotrexate; NIR+ = Near-in fra red irradiation; PEG = Polyethylene glycol; S-S = Disulfide bond