Supplementary materials

Metformin-based nanoreactor via alleviating hypoxia and reducing ATP for cancer synergistic therapy

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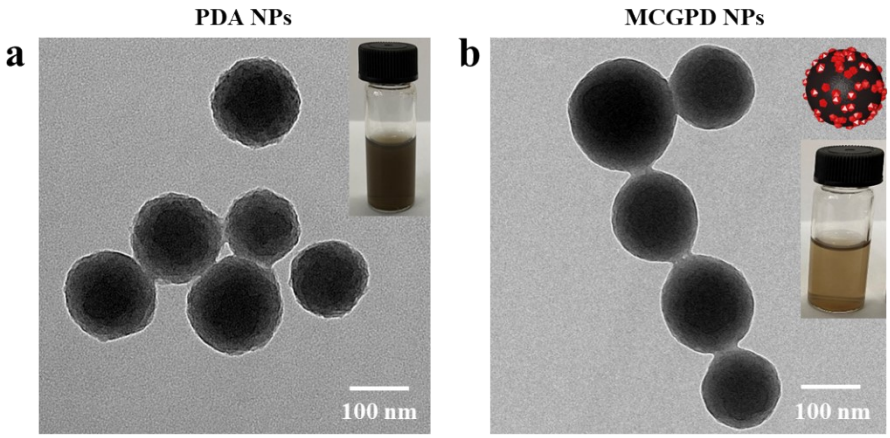

Figure S1. TEM image of (a) PDA NPs and (b) MCGPD NPs.

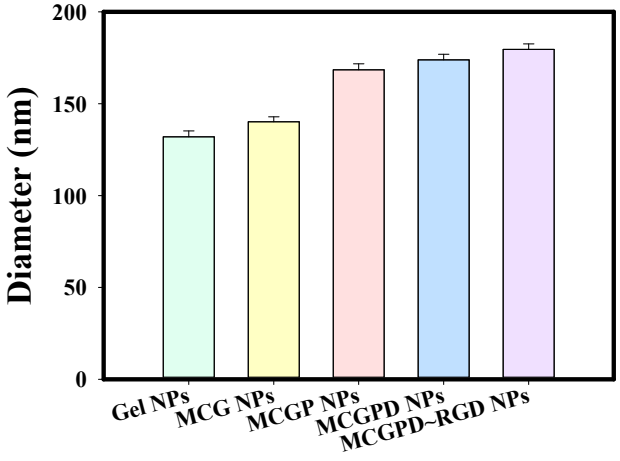

Figure S2. Dynamic light scattering (DLS) of Gel NPs, MCG NPs, MCGP NPs, MCGPD NPs, and MCGPD~RGD NPs.

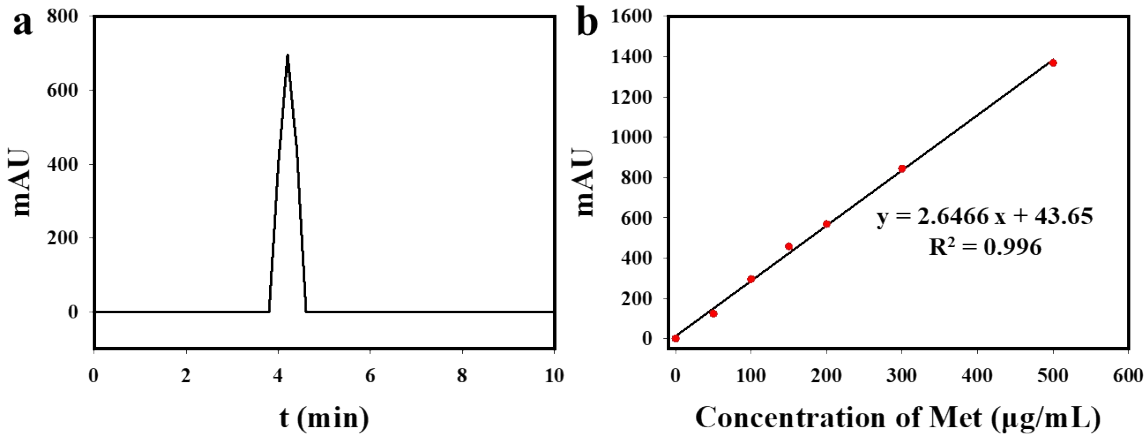

Figure S3. High performance liquid chromatography (HPLC) spectrogram of metformin. (b) The standard curve of Met based on HPLC.

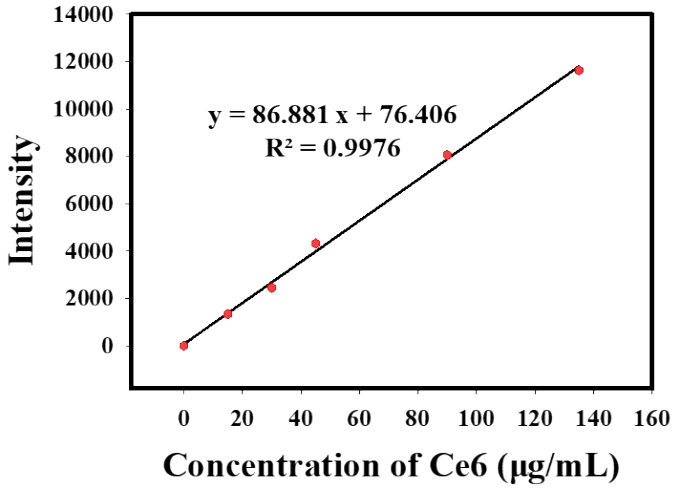

Figure S4. The standard curve of Ce6 based on fluorescence spectroscopy.

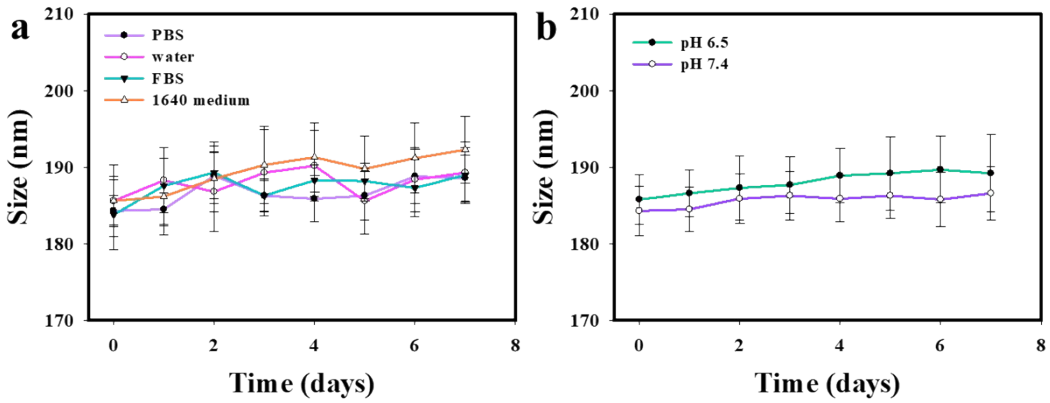

Figure S5. (a)The size change after MCGPD~RGD NPs soaking in PBS, water, FBS, and 1640 medium during 7 days. (b) Stability of MCGPD~RGD NPs in PBS with different pH values.

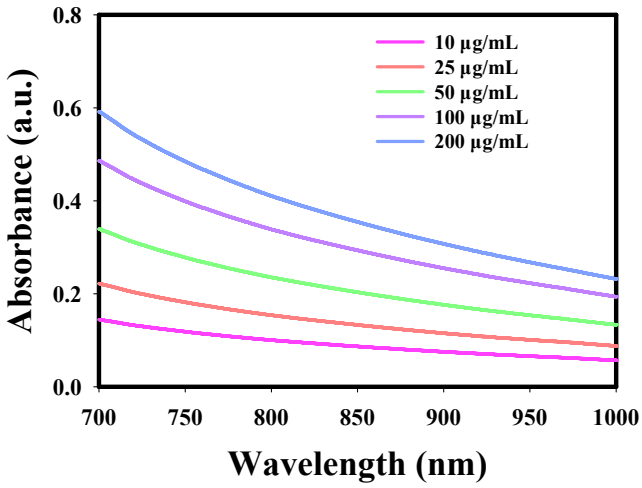

Figure S6. UV-vis-NIR absorption spectra of aqueous suspensions of dispersed MCGPD~RGD at varied concentrations (10, 25, 50, 100, or 200 µg mL^{-1}).

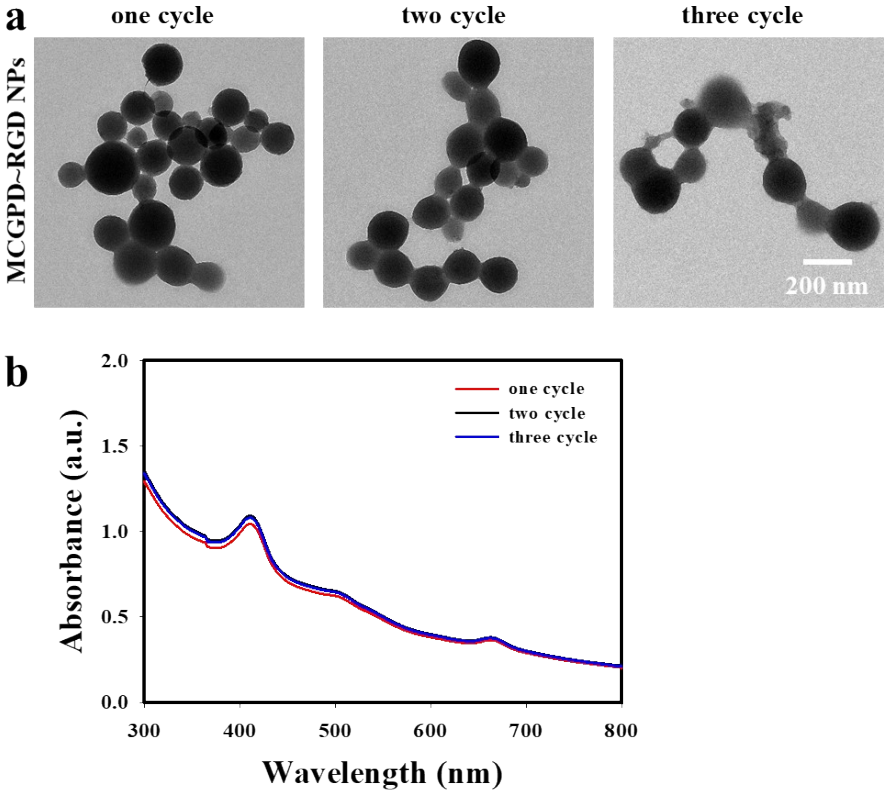

Figure S7. TEM images and UV-vis absorption spectra of MCGPD~RGD NPs after three cycles of laser irradiation.

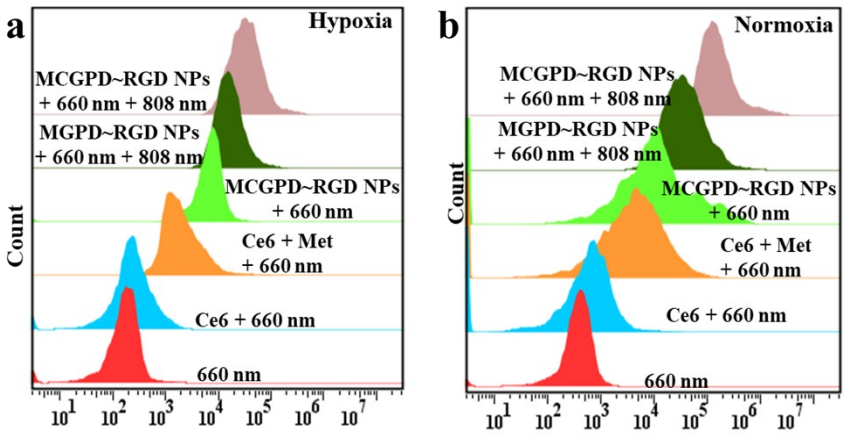

Figure S8. Flow cytometric analysis on the intracellular ROS levels after different treatments under hypoxia (a) or normoxia (b) condition.

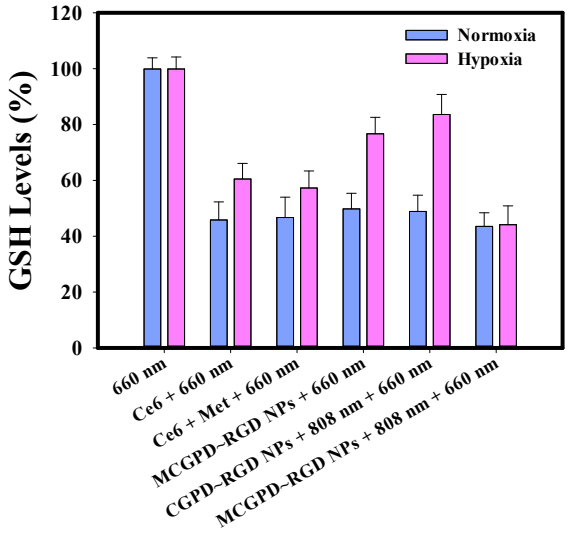

Figure S9. GSH level in MCF-7 cells after different treatment under normoxia or hypoxia.

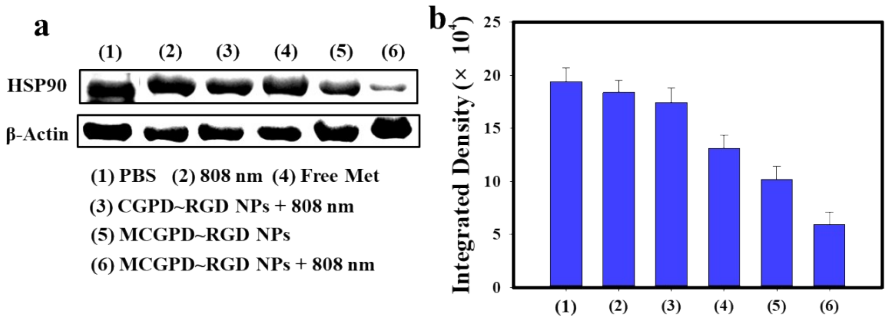

Figure S10. Western blot analysis of HSP90 (a) and corresponding semi-quantitative analysis (b) in MCF-7 cells after different treatment.

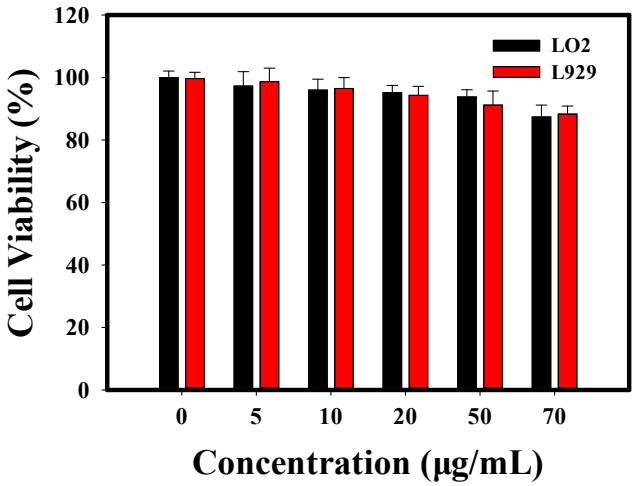

Figure S11. Cell viability of normal cells (LO2 cells and L929 cells) after treatment with different concentrations of MCGPD~RGD with 808 nm and 660 nm irradiation.

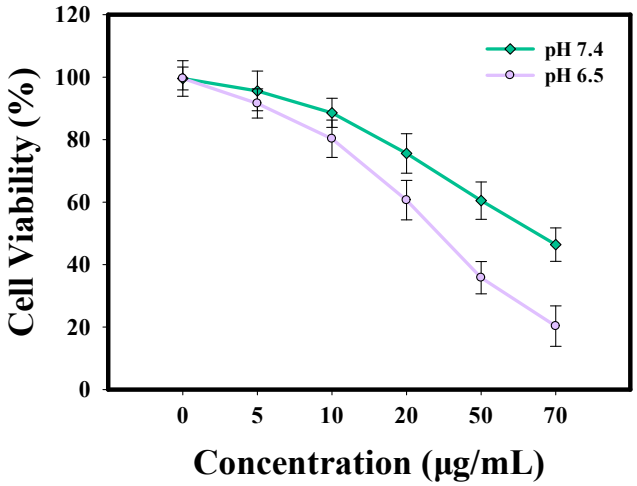

Figure S12. Cell viability of MCF-7 cells after treatment at various concentrations of MCGPD~RGD in acidic (pH = 6.5) or physiological conditions (pH = 7.4) culture medium with 808 nm and 660 nm irradiation.

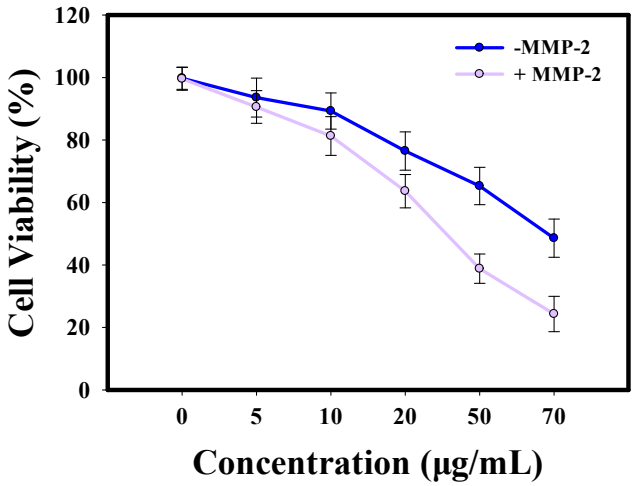

Figure S13. Cell viability of MCF-7 cells after treatment at various concentrations of MCGPD~RGD with or without addition MMP-2 in acidic (pH = 6.5) culture medium addition with 808 nm and 660 nm irradiation.

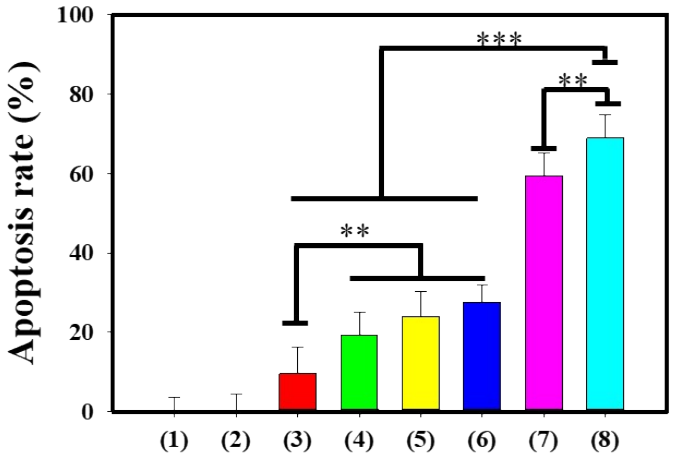

Figure S14. Apoptosis rate of MCF-7 cells after incubation with (1) PBS, (2) PBS + 660 nm + 808 nm, (3) MCGPD~RGD NPs (pH 7.4), (4) MCGPD~RGD NPs (pH 6.5), (5) MCGPD~RGD NPs + pH 6.5 + MMP-2, (6) MCGPD~RGD NPs + pH 6.5 + MMP-2 + 660 nm, (7) MCGPD~RGD NPs + pH 6.5 + MMP-2 + 808 nm, or (8) MCGPD~RGD NPs + pH 6.5 + MMP-2 + 808 nm + 660 nm for 24 h.

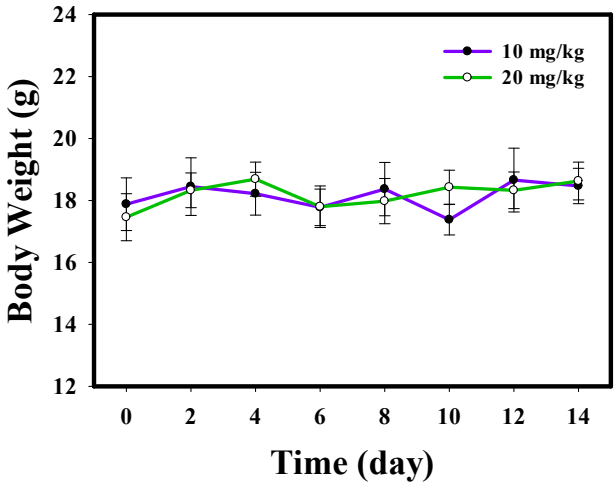

Figure S15. Body weight variation of nude mice after intravenous injection of MCGPD~RGD NPs (10 or 20 mg kg^{-1}) during the whole treatment period.

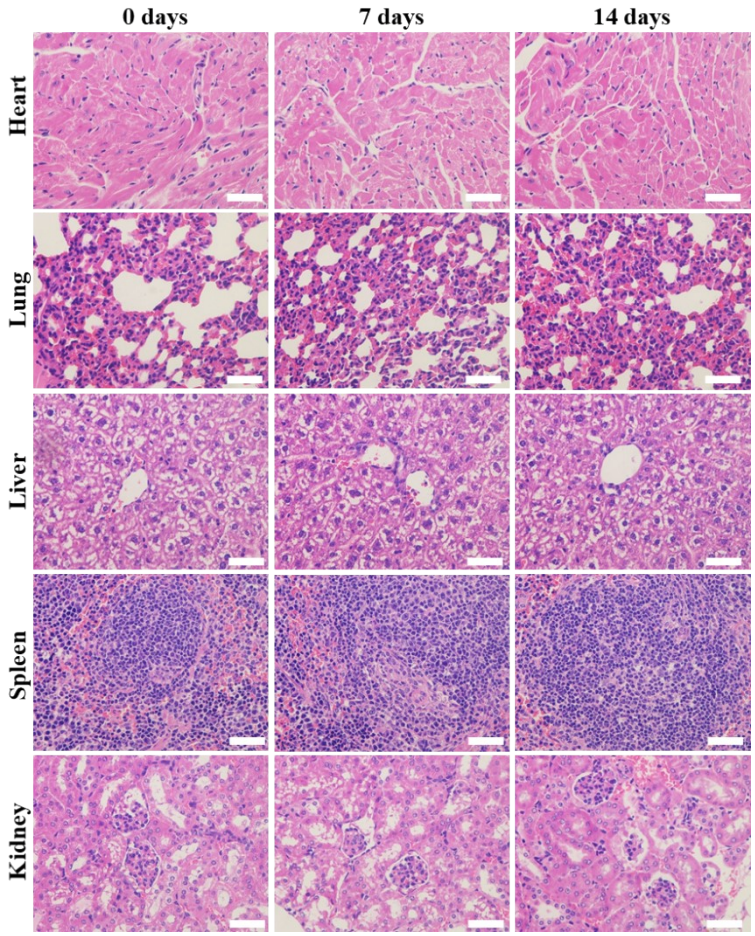

Figure S16. H&E staining analysis of the major organs (heart, liver, spleen, lung, and kidney) of the mice after intravenous injection with MCGPD~RGD NPs (20 mg kg^{-1}) for 0, 7, or 14 days. Scale bars: 100 μm.

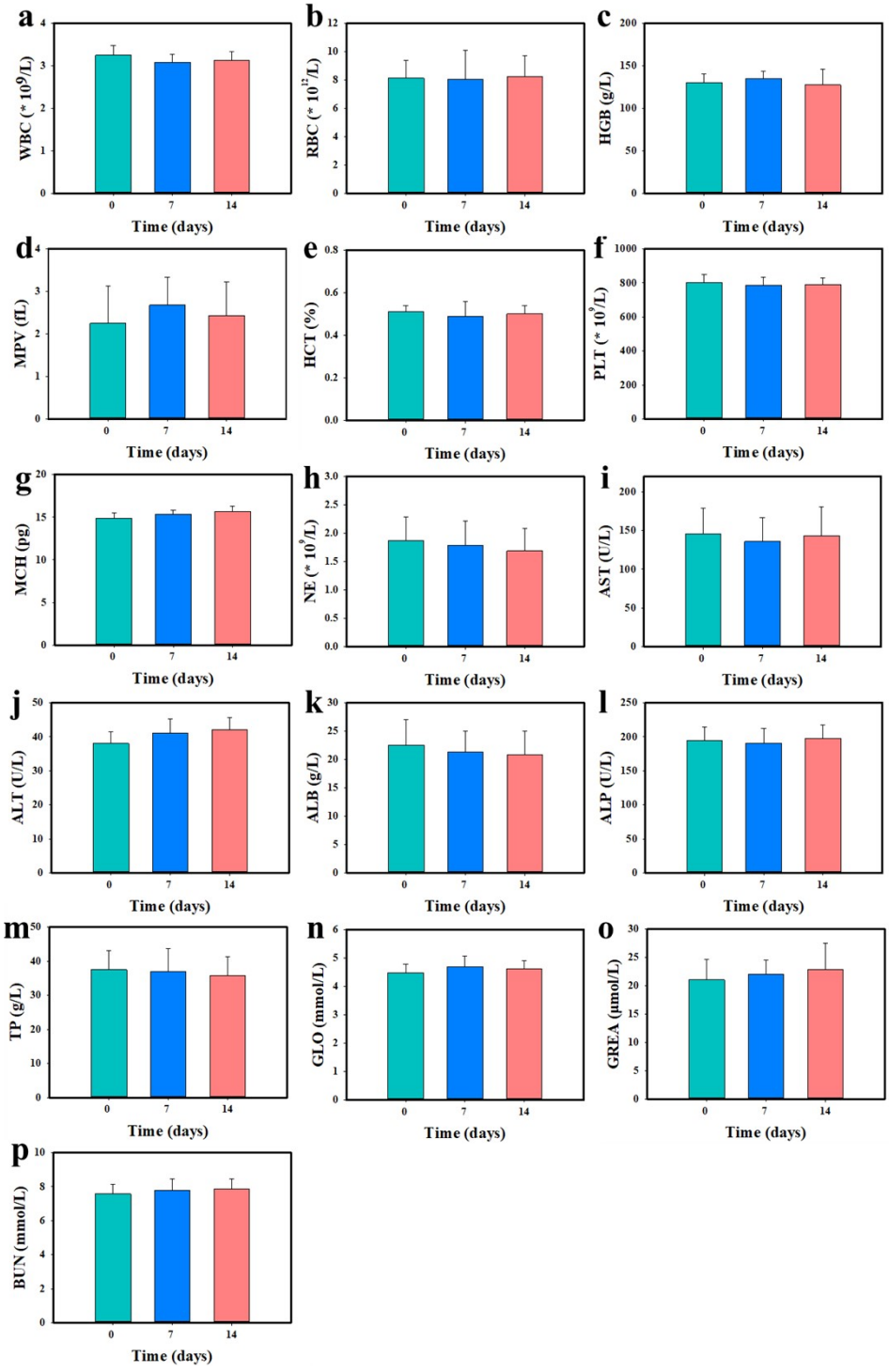

Figure S17. Routine blood parameters and biochemical indexes examination of the mice after intravenous injection with MCGPD~RGD NPs (20 mg kg^{-1}) for 0, 7, or 14 days. (a) WBC, white blood cells count; (b) RBC, red blood cell count; (c) HGB, hemoglobin; (d) MPV, mean platelet volume; (e) HCT, hematocrit; (f) PLT, platelet

count; (g) MCH, mean corpuscular hemoglobin; (h) NE, neutrophil count; (i) AST, aspartate aminotransferase; (j) ALT, alanine aminotransferase; (k) ALB, albumin; (l) ALP, alkaline phosphatase; (m) TP, total protein; (n) GLO, globulin; (o) CREA, creatinine; (p) BUN, blood urea nitrogen.

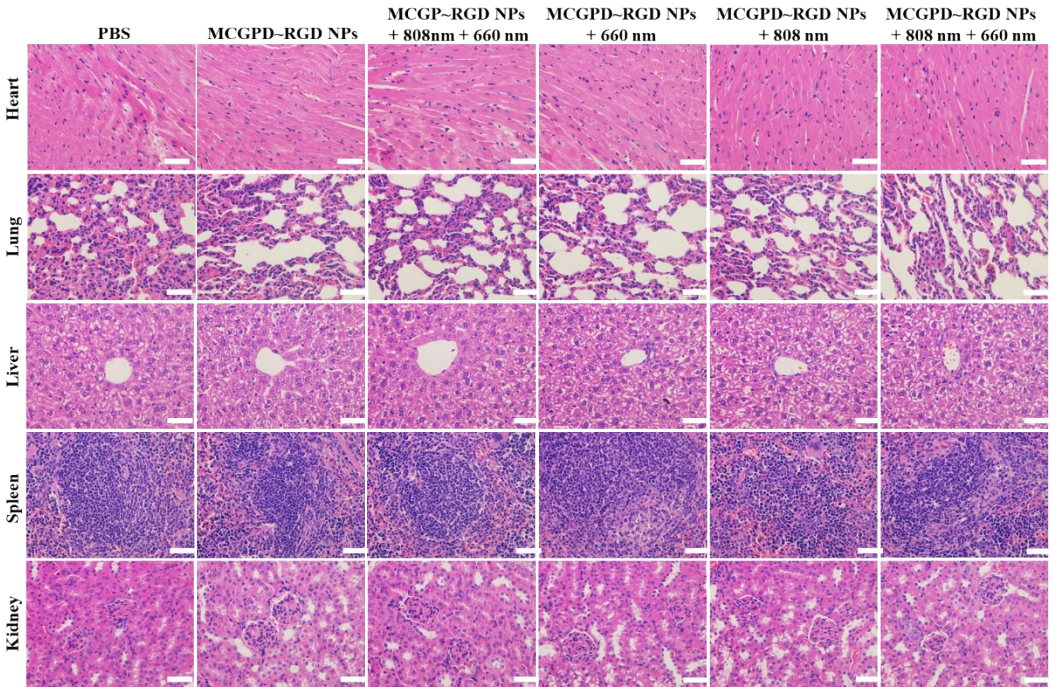

Figure S18. H&E staining analysis of the sacrificed heart, liver, spleen, lung, and kidney after treatment with PBS, MCGPD~RGD NPs, MCGP~RGD NPs + 808 nm + 660 nm, MCGPD~RGD NPs + 660 nm, MCGPD~RGD NPs + 808 nm, or MCGPD~RGD NPs + 808 nm + 660 nm on the 14th day. Scale bar: 100 μm.