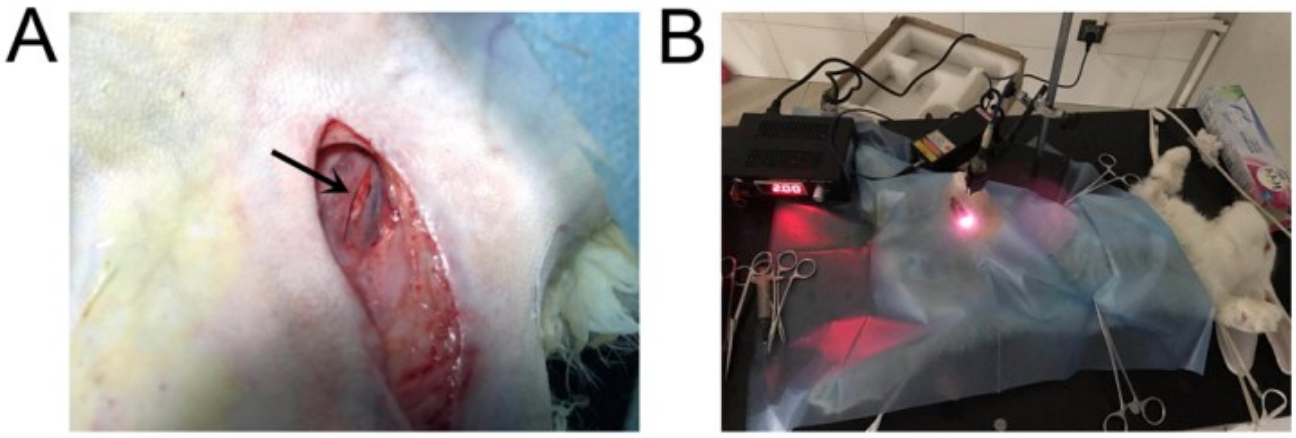
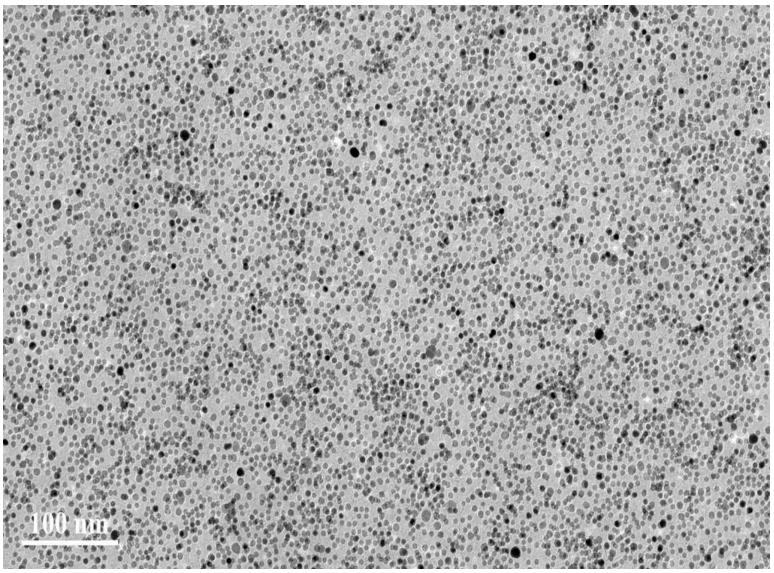
Electronic Supplementary Material (ESI) for Biomaterials Science.

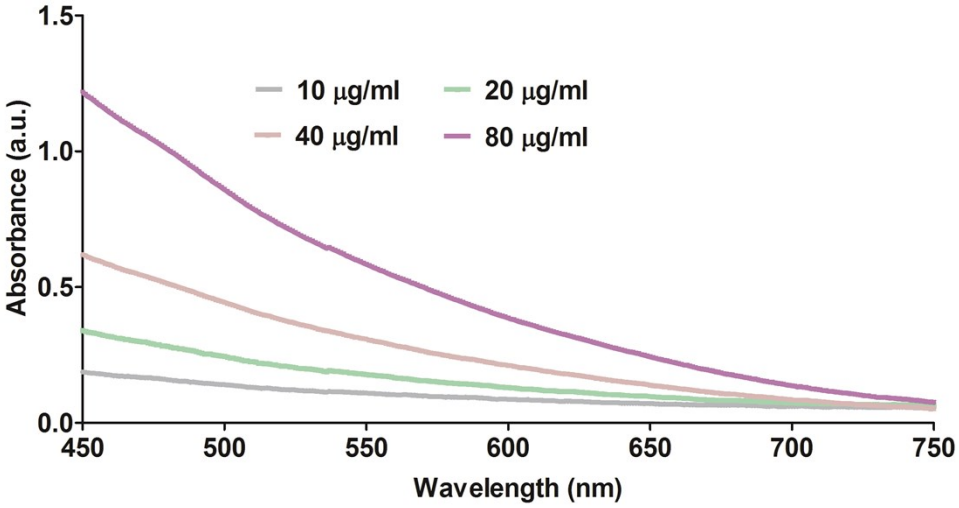
Electronic Supplementary Information



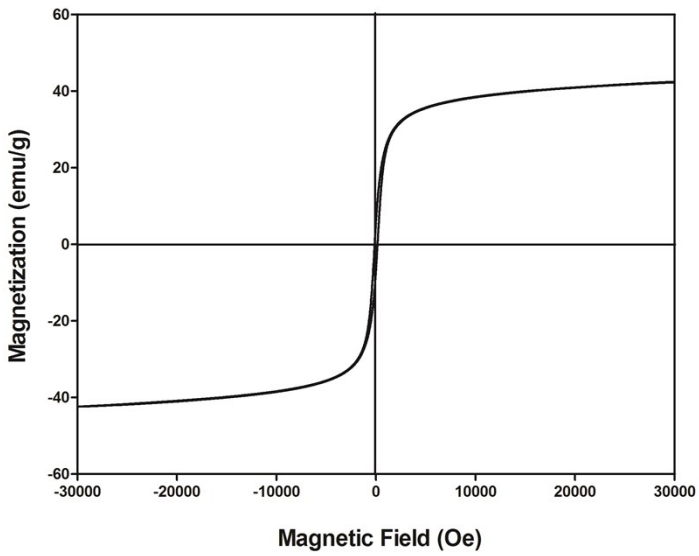
Supplementary Figure 1. (A) The right femoral plaque of the rabbit was surgically exposed and **(B)** irradiated by a near-infrared laser for 15 min. Black arrow indicates the right femoral plaque.



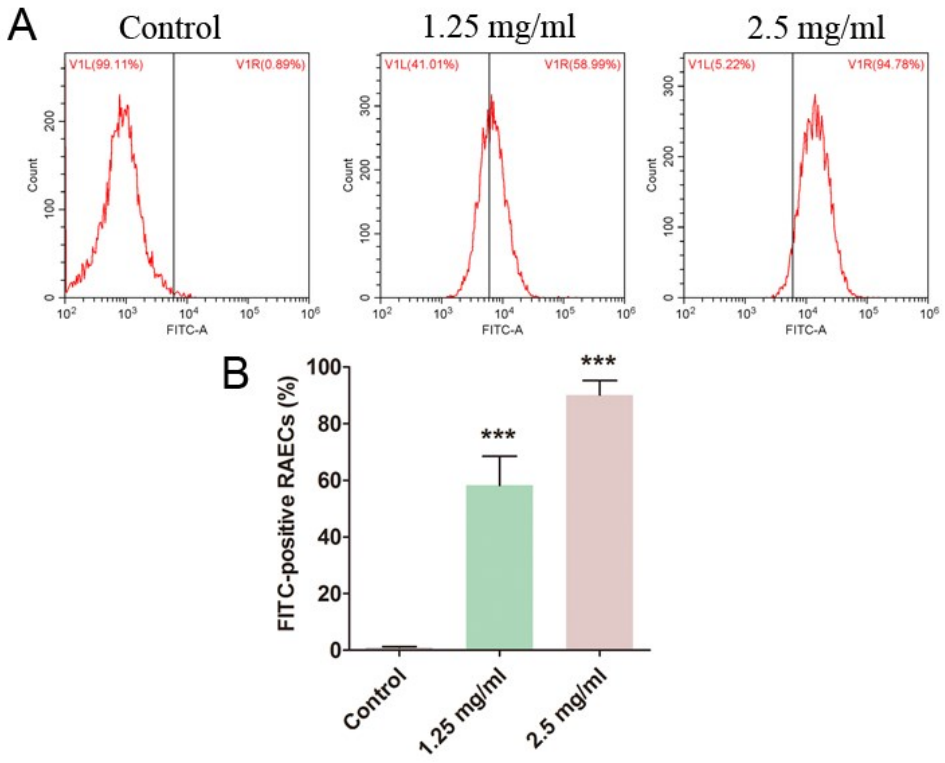
Supplementary Figure 2. Transmission electron microscopy image of 3 nm $MnFe_2O_4$.



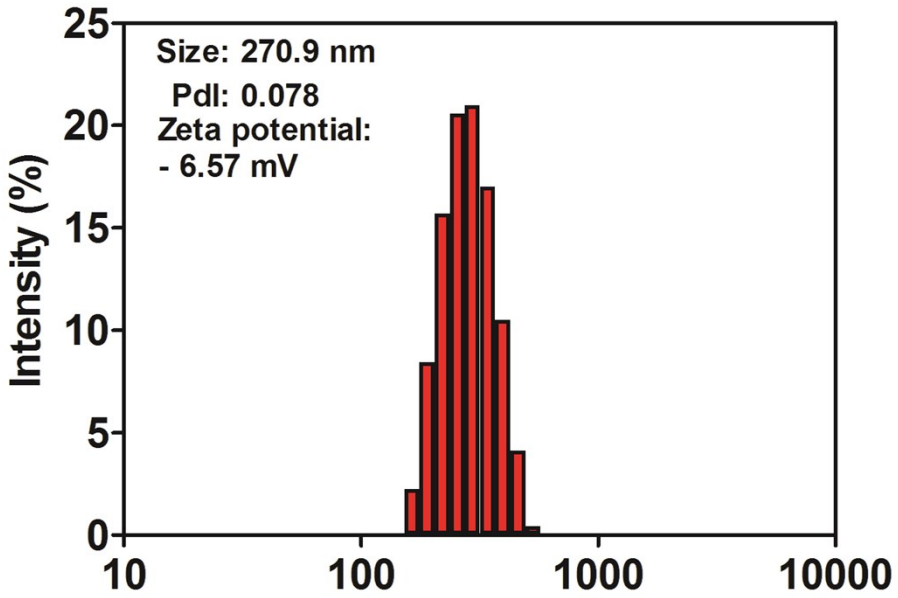
Supplementary Figure 3. Visible absorbance spectra of 3 nm $MnFe_2O_4$ at elevated concentrations.



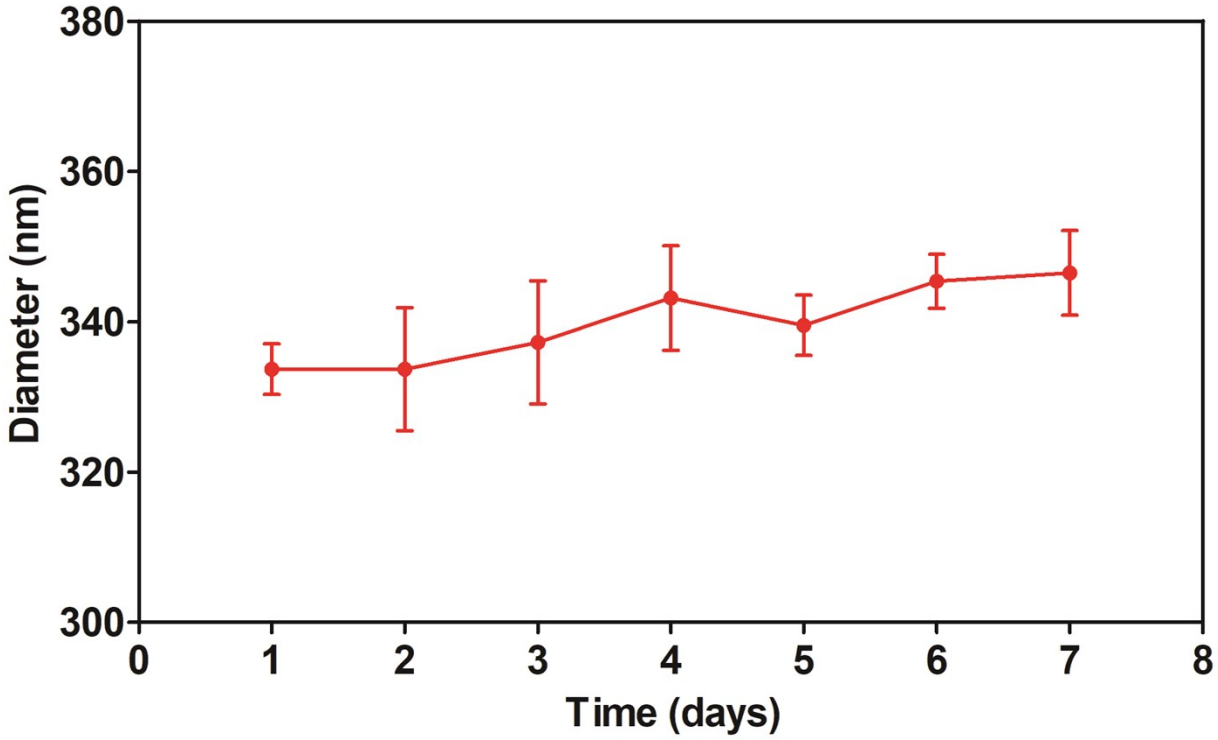
Supplementary Figure 4. Magnetization hysteresis loops of 3 nm $MnFe_2O_4$ at 300 K ranging from −30 kOe to +30 kOe.



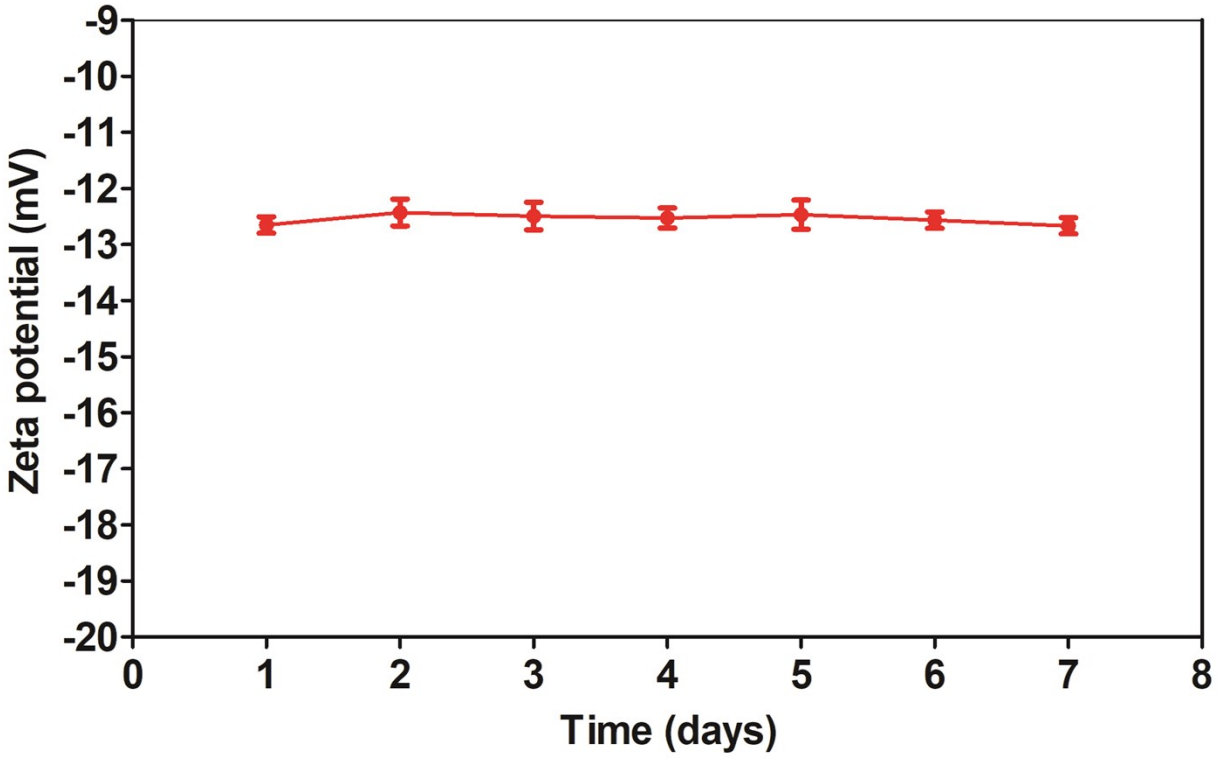
Supplementary Figure 5. Cell-targeting behavior of ramucirumab. After incubating rabbit aortic endothelial cells (RAECs) with FITC-labeled ramucirumabfor 3 h, the cells were harvested and analyzed using flow cytometry. **(A)** Representative cytograms and **(B)** quantification of FITC-positive RAECs (n = 3). *** $p < 0.001$ *vs*. control.



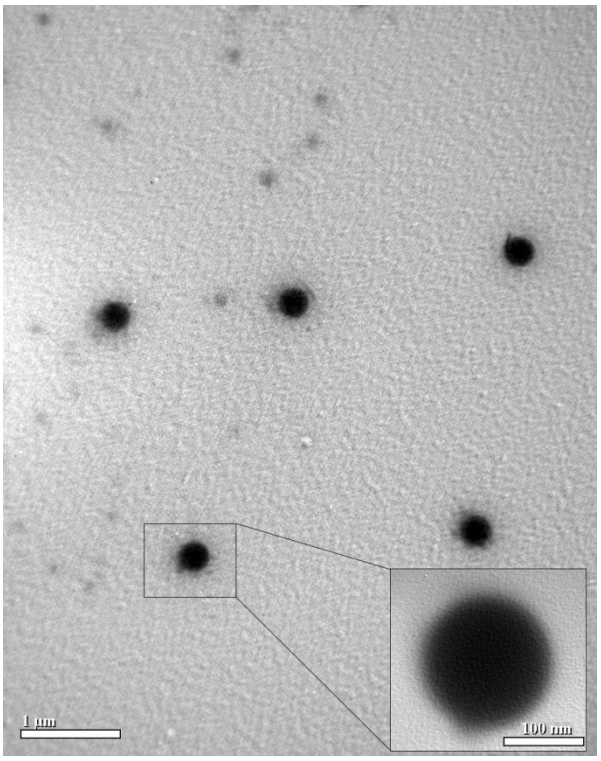
Supplementary Figure 6. The size distribution and zeta potential of PFH@PLGA/$MnFe_2O_4$ nanoparticles determined by dynamic light scattering.



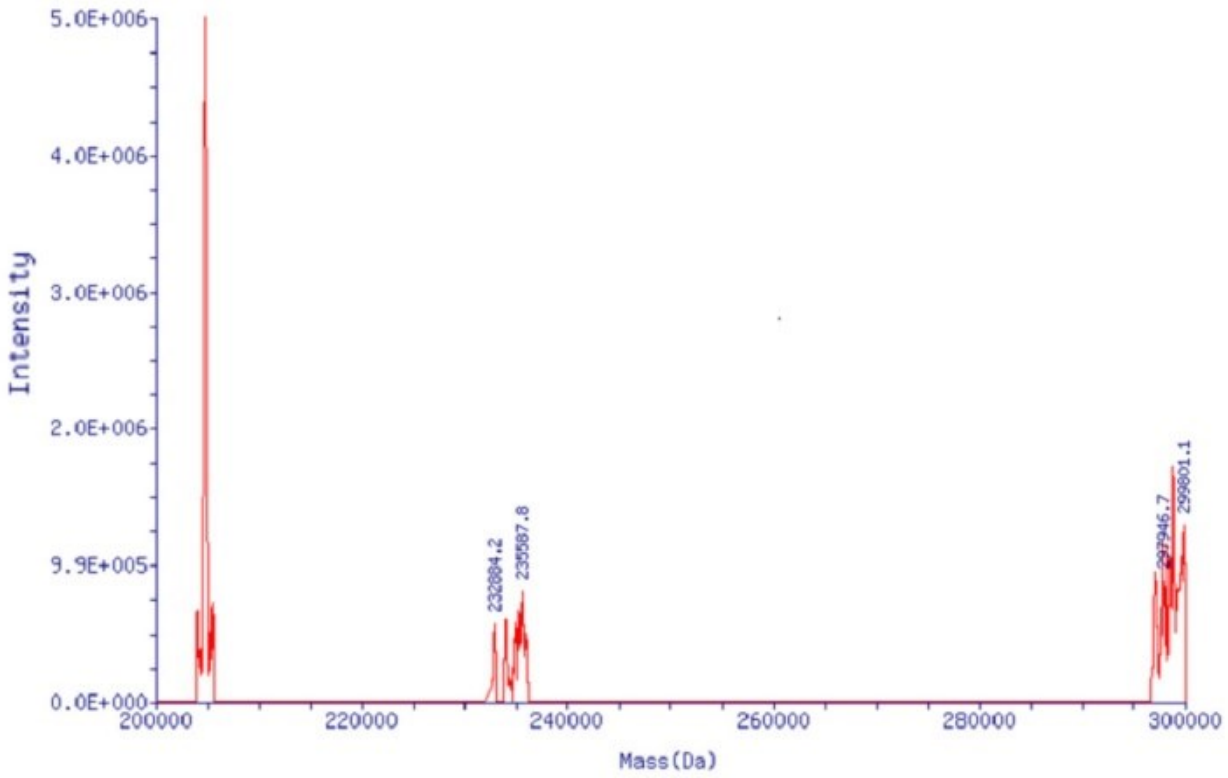
Supplementary Figure 7. The size distribution of PFH@PLGA/$MnFe_2O_4$-Ram nanoparticles within 7 days.



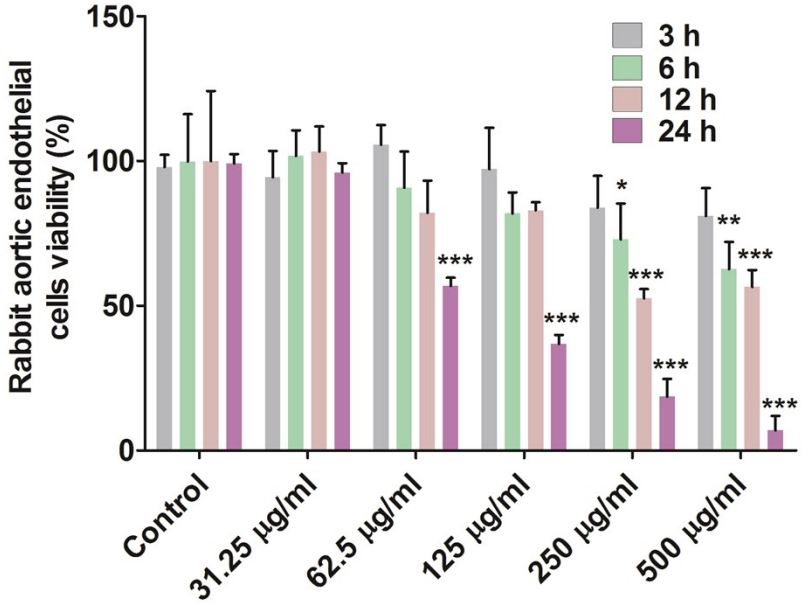
Supplementary Figure 8. The zeta potential of PFH@PLGA/$MnFe_2O_4$-Ram nanoparticles over 7 days.



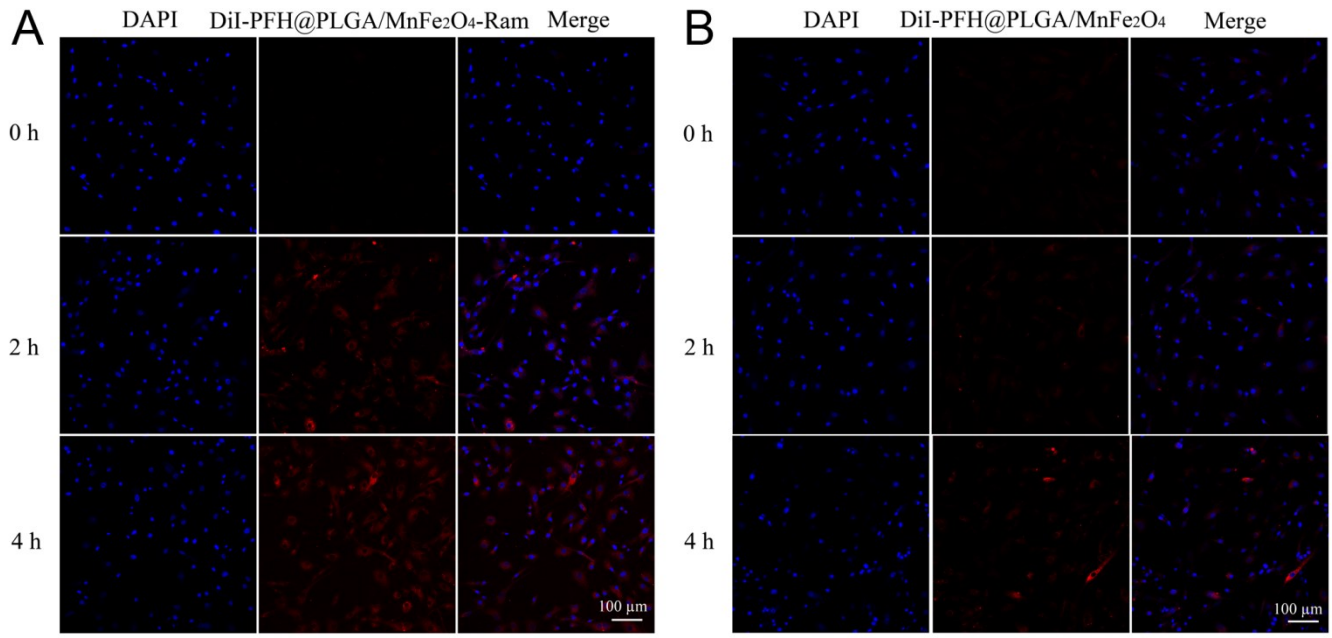
Supplementary Figure 9. Transmission electron microscopy image of PFH@PLGA-Ram nanoparticles.



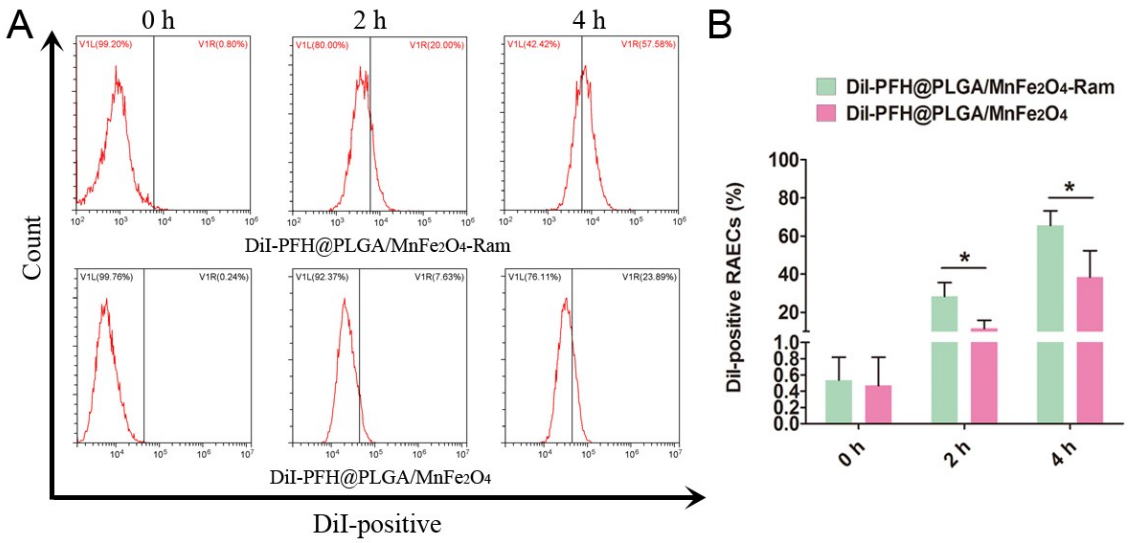
Supplementary Figure 10. Mass spectrum of PLGA-PEG-ramucirumab. $PLGA_{25,000}$-PEG_{5000}-COOH (50 mg) was used to fabricate NPs via the double emulsion method. Ramucirumab (average 130,000 Da MW) was conjugated to the surface of NPs using the carbodiimide method. Then, the NPs were dissolved by DMSO and identified by mass spectroscopy.



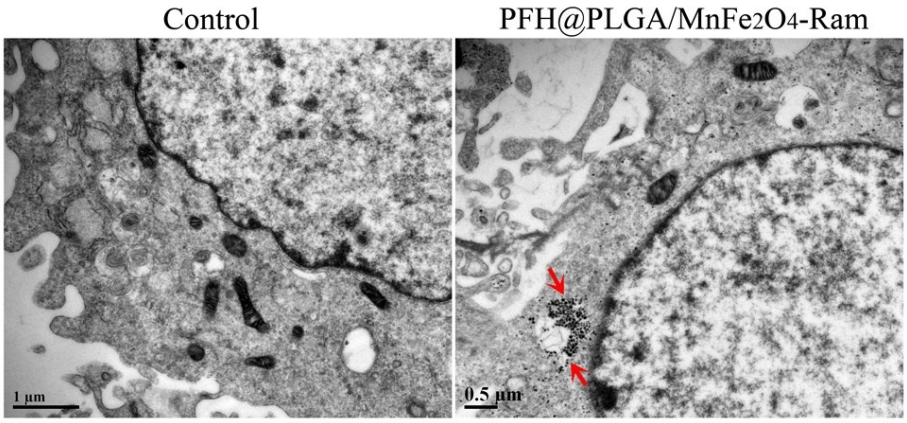
Supplementary Figure 11. Cell viability of RAECs treated with different concentrations (31.25, 62.5, 125, 250, and 500 μg/mL) of PFH@PLGA/$MnFe_2O_4$-Ram nanoparticles (NPs) for 3, 6, 12, and 24 h detected using the CCK-8 assay (n = 5). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* control.



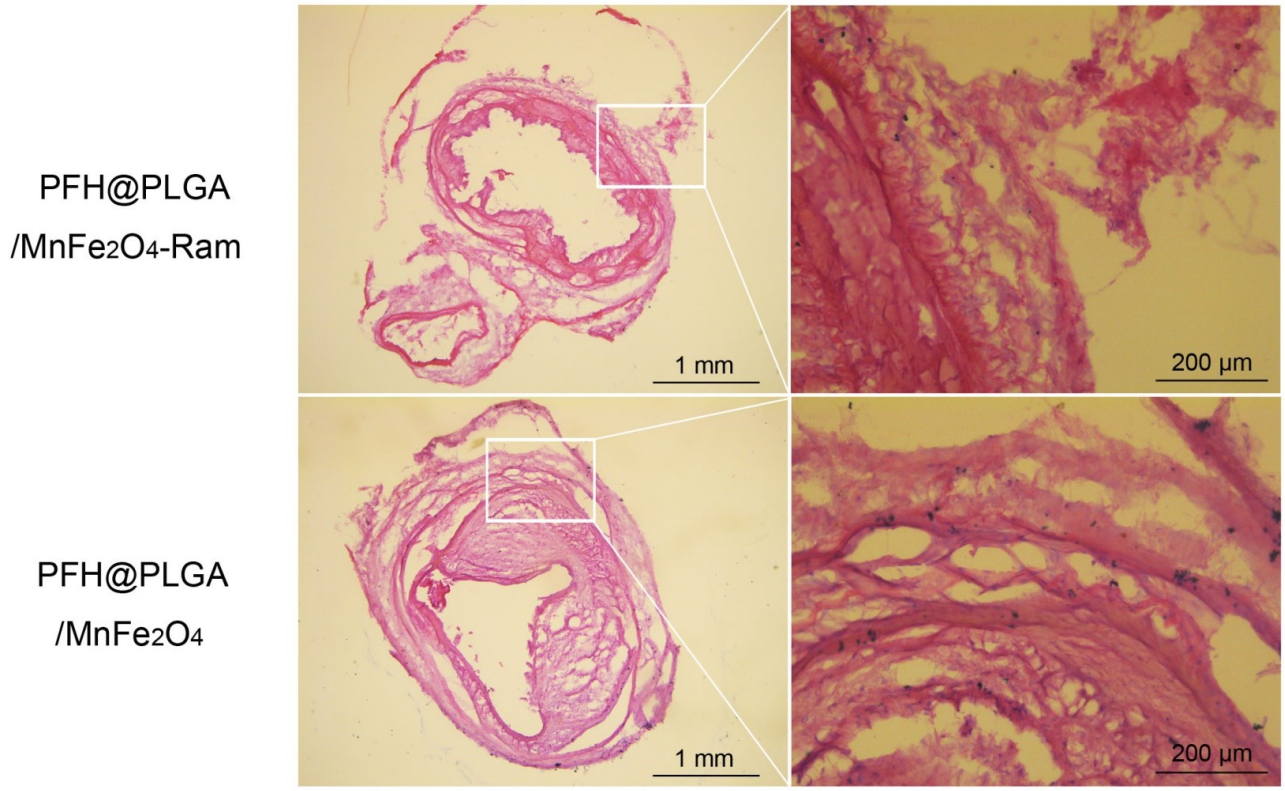
Supplementary Figure 12. Cellular uptake of DiI-labeled **(A)** PFH@PLGA/$MnFe_2O_4$-Ram NPs and **(B)** PFH@PLGA/$MnFe_2O_4$ NPs in RAECs observed using confocal microscopy after 0, 2, and 4 h of incubation.



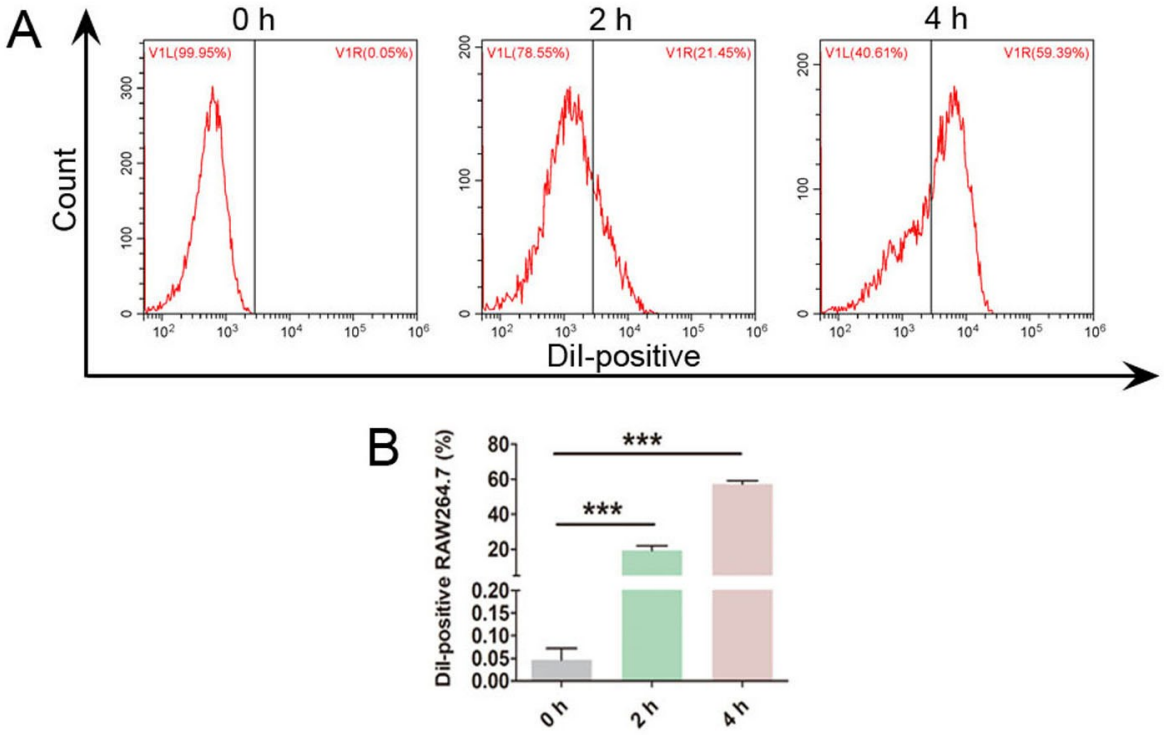
Supplementary Figure 13. Flow cytometry analysis of DiI-labeled PFH@PLGA/ $MnFe_2O_4$-Ram NPs and PFH@PLGA/$MnFe_2O_4$ NPs in RAECs. (A) Representative cytograms and **(B)** quantification of DiI-positive RAECs (n = 3). * $p < 0.05$.



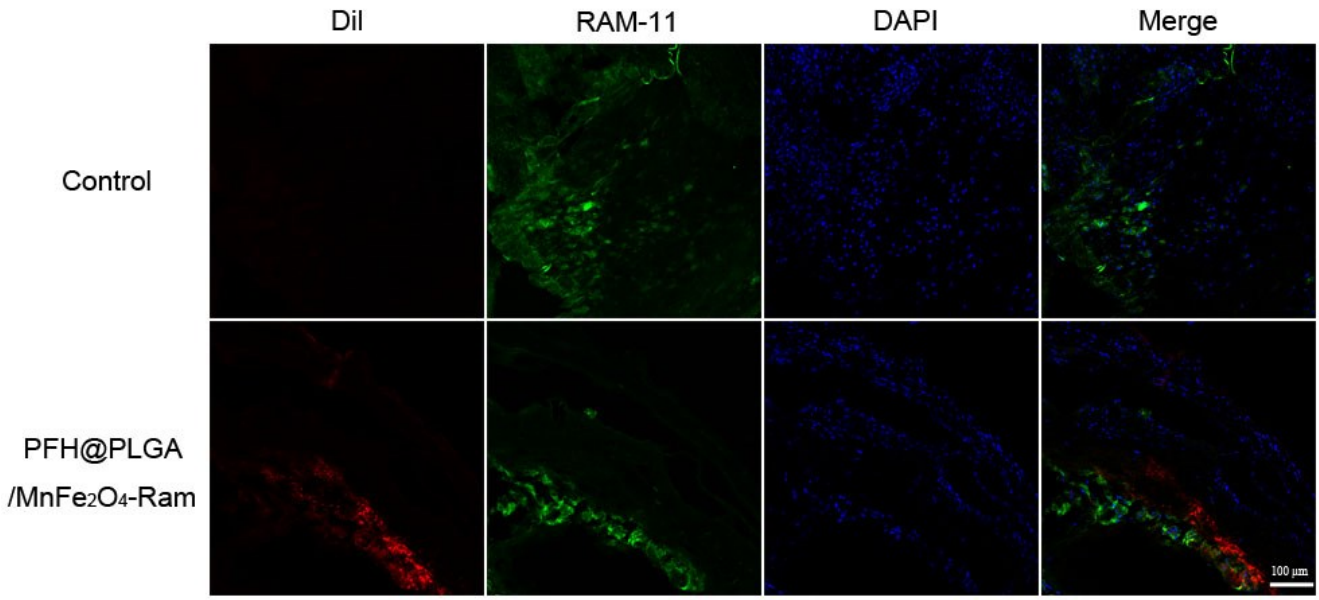
Supplementary Figure 14. Transmission electron microscopy of RAECs incubated with PFH@PLGA/$MnFe_2O_4$-Ram NPs. After incubation of RAECs with PFH@PLGA/$MnFe_2O_4$-Ram NPs for 4 h, NPs accumulated in the RAECs were observed. Red arrows indicate PFH@ PLGA/$MnFe_2O_4$-Ram NPs accumulated in the cytosol of RAECs.



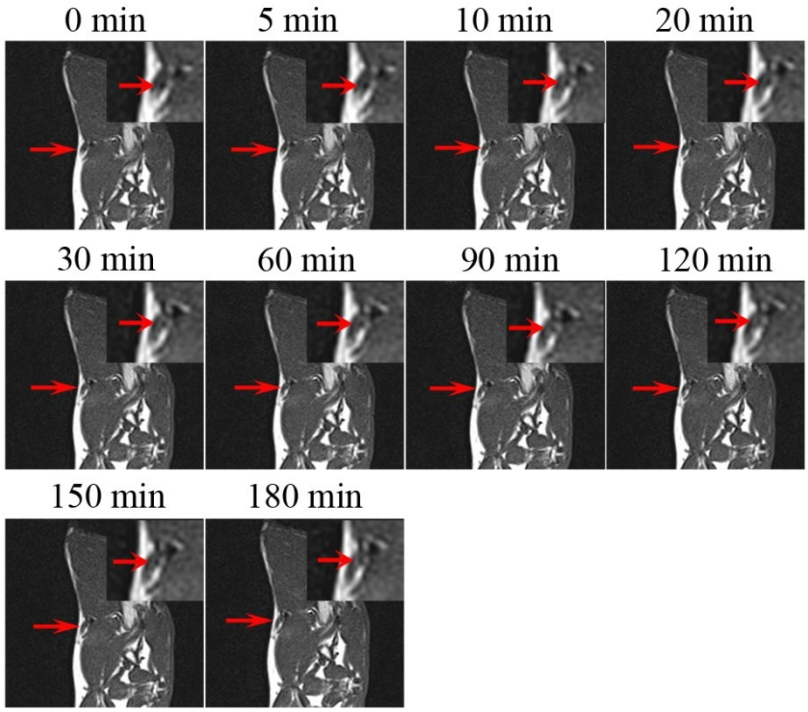
Supplementary Figure 15. Hematoxylin and eosin staining of the indicated groups.



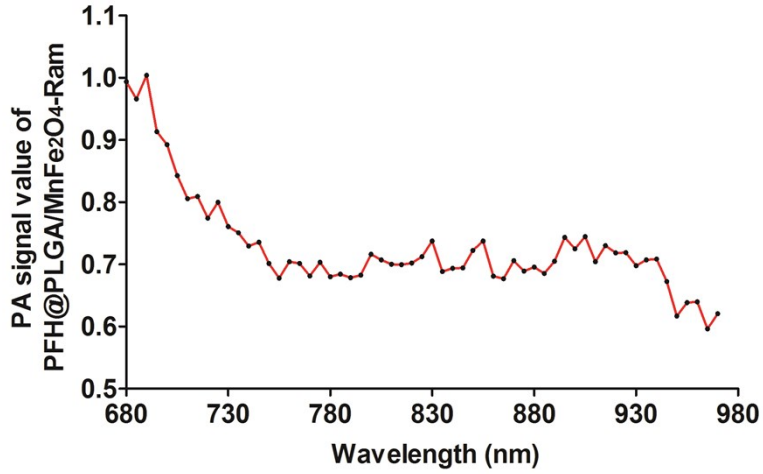
Supplementary Figure 16. Flow cytometry analysis of DiI-labeled PFH@PLGA/$MnFe_2O_4$-Ram NPs in RAW264.7 macrophages. (A) Representative cytograms and **(B)** quantification of DiI-positive macrophages (n = 3). *** $p < 0.001$.



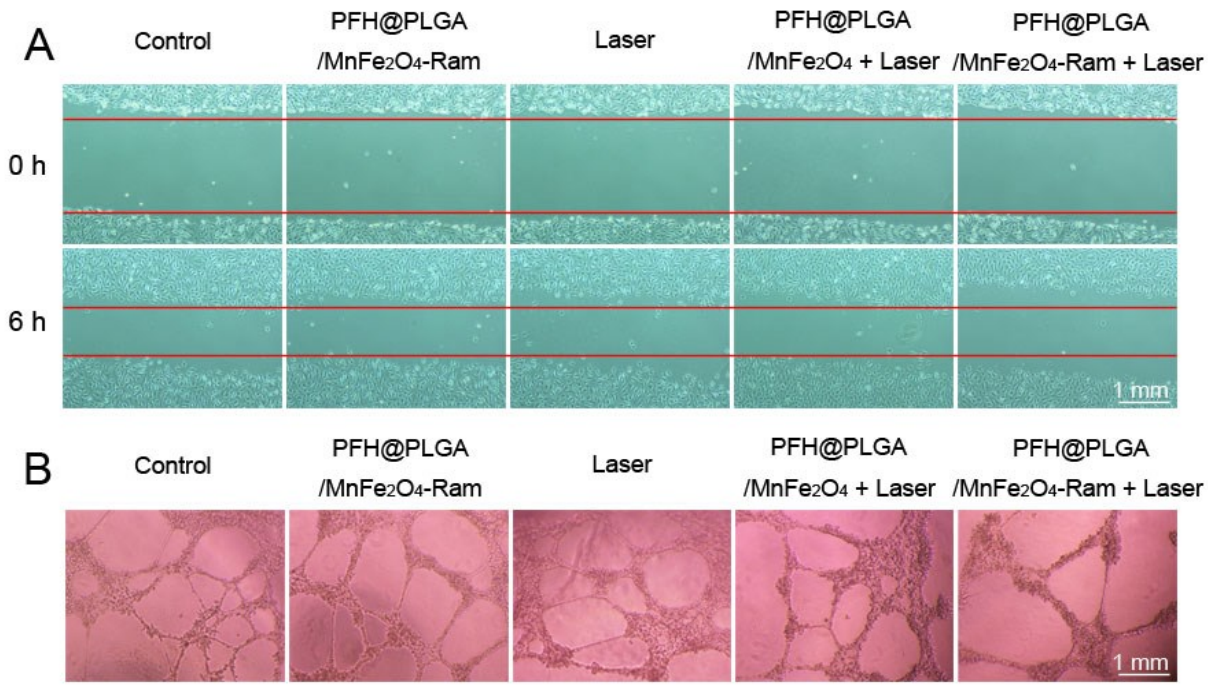
Supplementary Figure 17. At 90 min after intravenous injection of DiI-labeled PFH@PLGA/MnFe2O4-Ram NPs, the plaque-bearing rabbit was sacrificed and the RAM-11-positive macrophages were colocalized with the DiI-labeled PFH@PLGA/$MnFe_2O_4$-Ram NPs, as assessed by immunofluorescence.



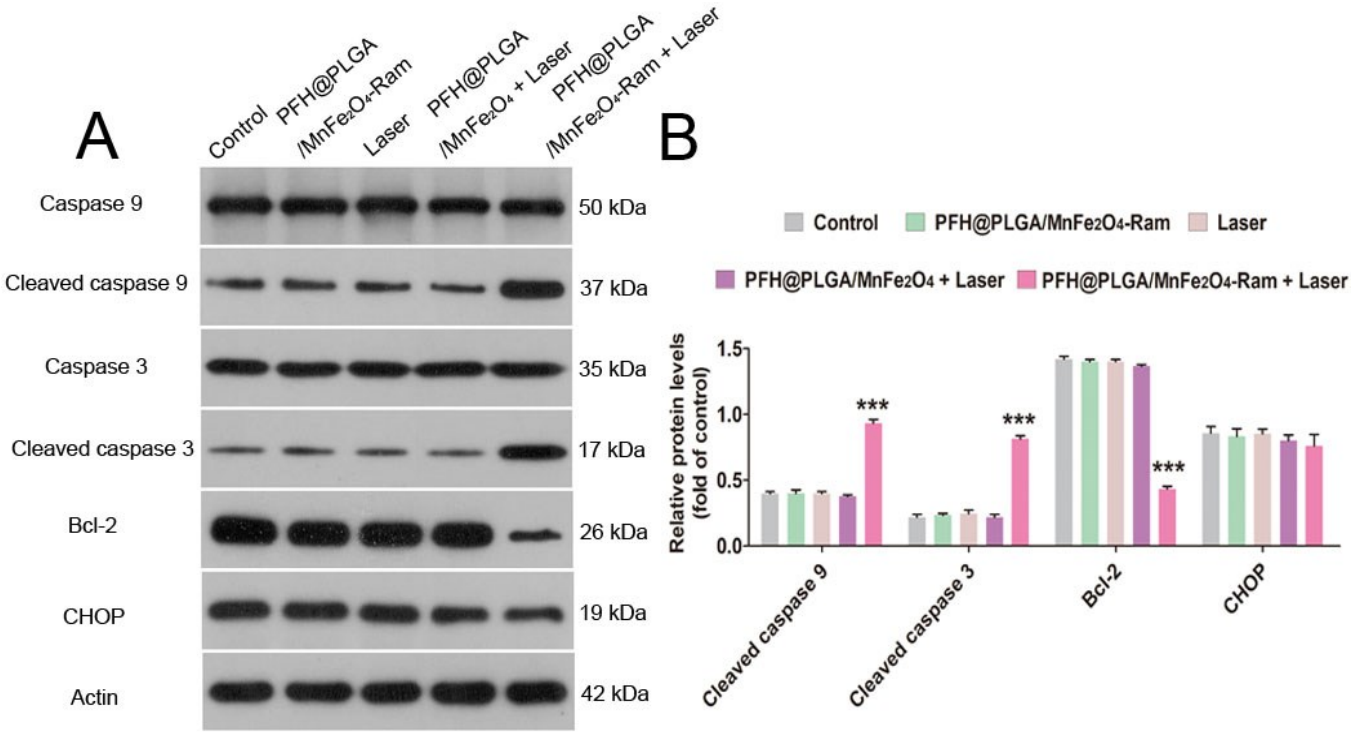
Supplementary Figure 18. ***In vivo*** **magnetic resonance imaging.** T1 images of rabbit femoral plaque after injection of PFH@PLGA/$MnFe_2O_4$ NPs recorded at different time points. Red arrow in each image indicates the femoral plaque.



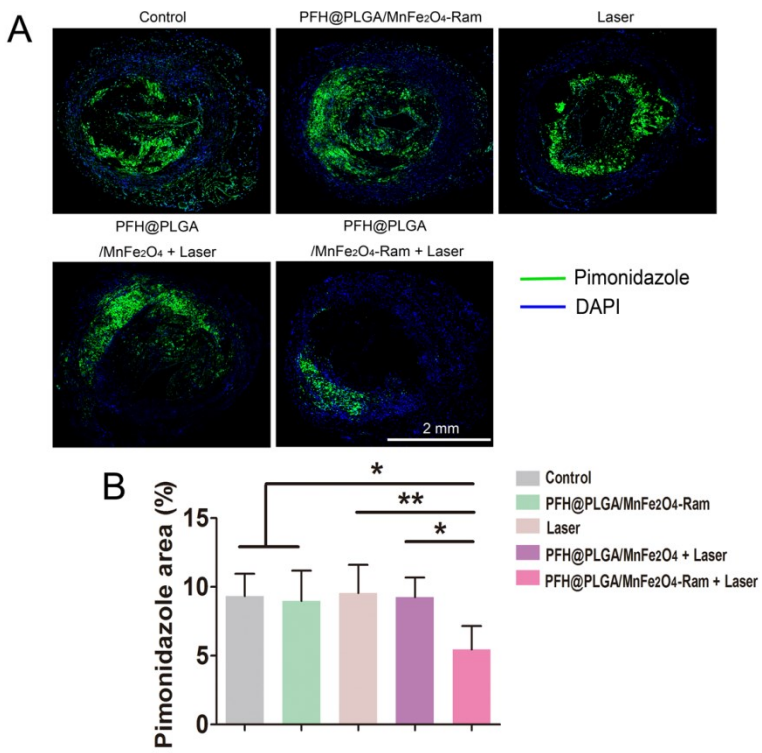
Supplementary Figure 19. Photoacoustic intensity of the PFH@PLGA/$MnFe_2O_4$-Ram NPs under full-spectrum scanning (680–970 nm).



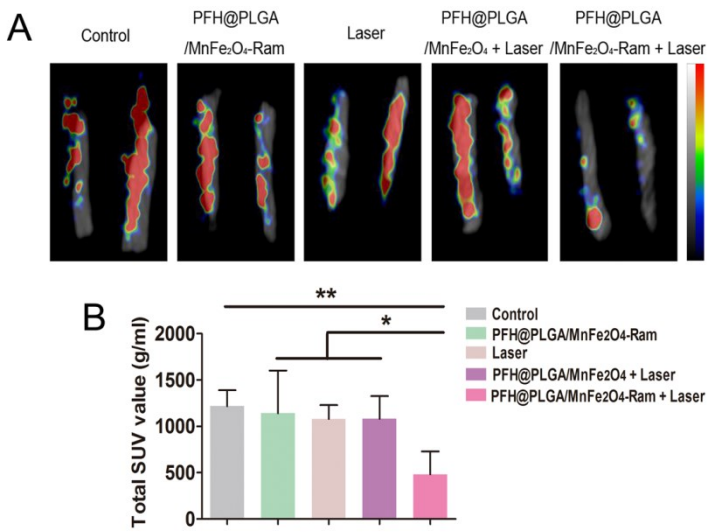
Supplementary Figure 20. PFH@PLGA/$MnFe_2O_4$-Ram NP-mediated PTT inhibited migration and tube formation of RAECs. Representative images of RAEC **(A)** migration 6 h after scratching and **(B)** tube formation.



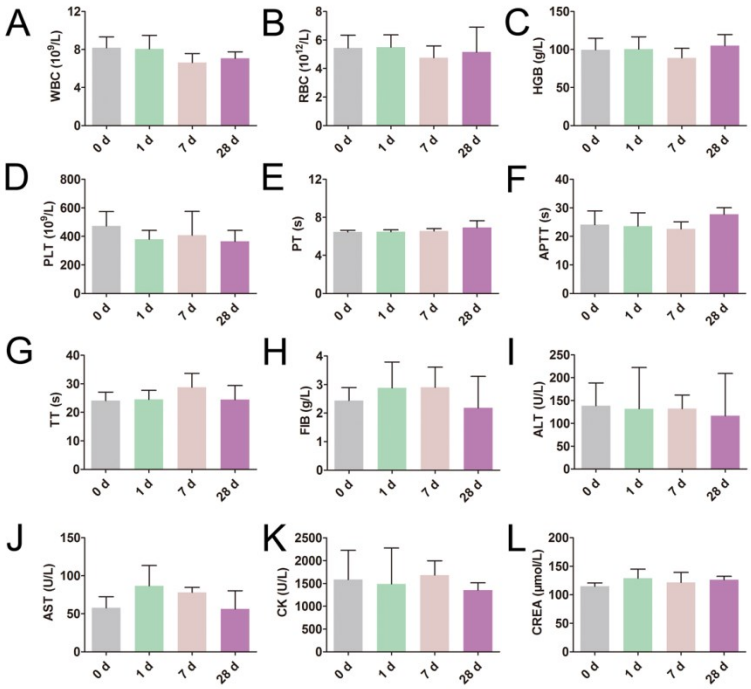
Supplementary Figure 21. PFH@PLGA/$MnFe_2O_4$-Ram NP-mediated PTT induces RAEC apoptosis. RAECs were treated with PFH@PLGA/$MnFe_2O_4$-Ram NP-mediated PTT and lysed at 6 h post treatment. **(A)** Representative western blot of RAECs probed with antibodies against the indicated proteins. **(B)** Protein expression relative to that of actin was quantified by densitometry (n = 3). *** $p < 0.001$ vs. control.



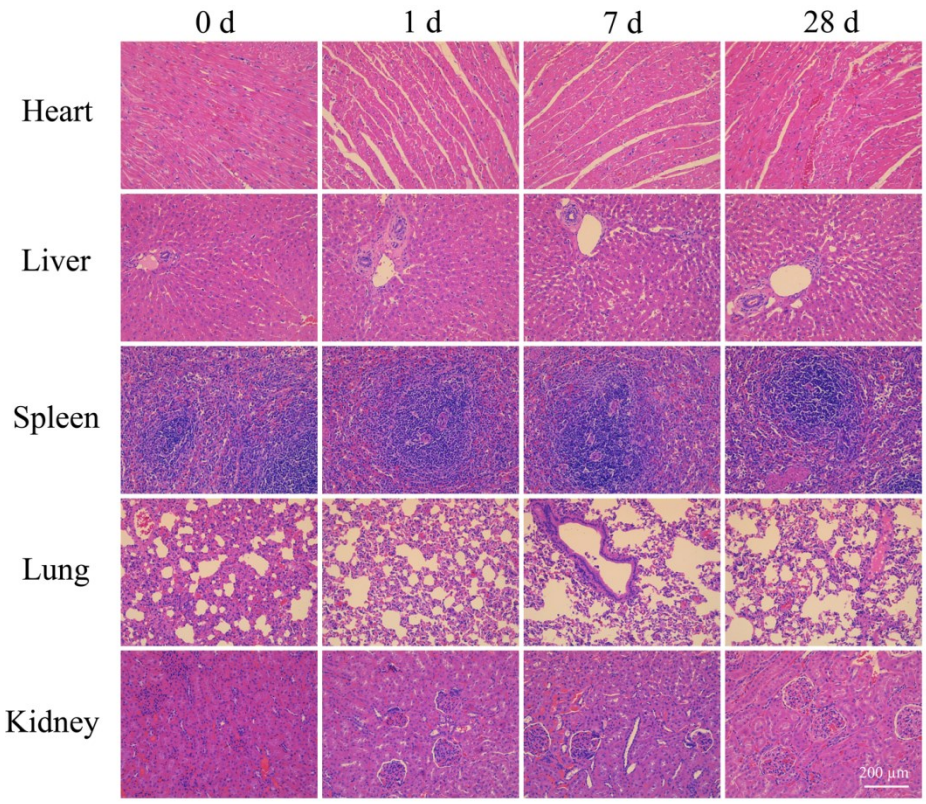
Supplementary Figure 22. PFH@PLGA/$MnFe_2O_4$-Ram NP-mediated photothermal therapy decreases hypoxia in the rabbit femoral advanced plaque on day 3 after treatment. (A) Representative sections and **(B)** quantification of hypoxic area in plaques from different groups (n = 5). * $p < 0.05$, ** $p < 0.01$.



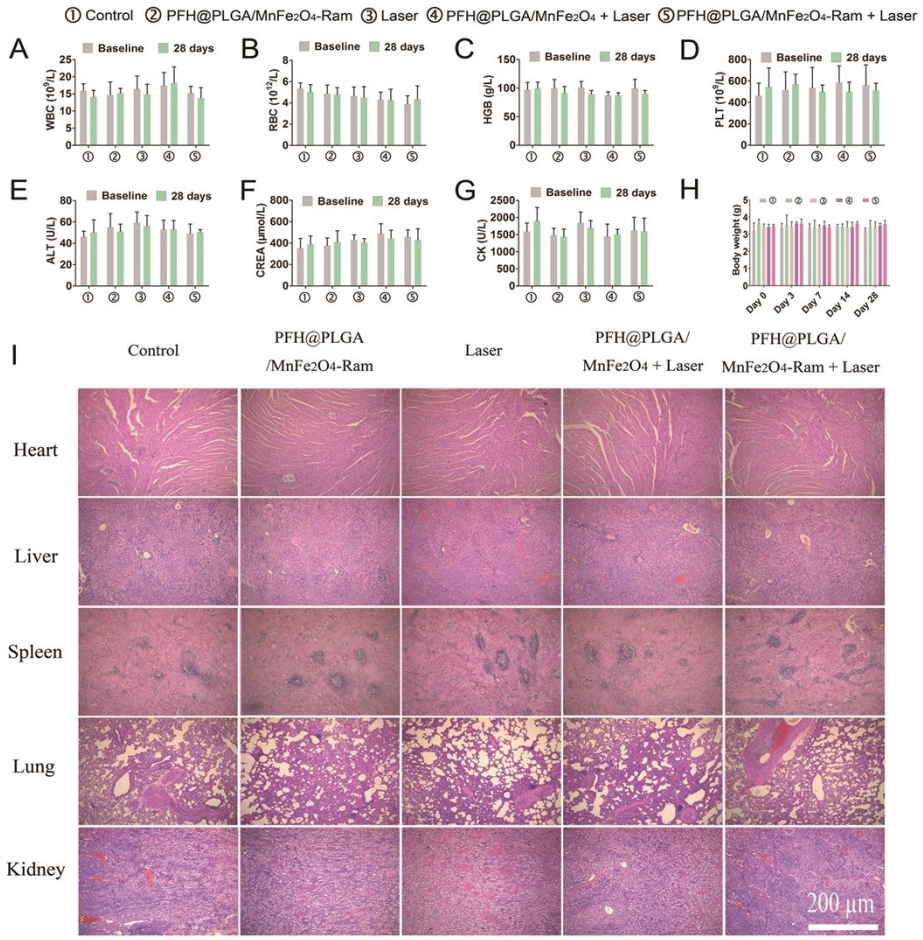
Supplementary Figure 23. PFH@PLGA/$MnFe_2O_4$-Ram NP-mediated photothermal therapy attenuates vessel inflammation in the rabbit femoral advanced plaque on day 28 after treatment. (A) Representative 3D fused ^{18}F-FDG-positron emission tomography/computed tomography images of the rabbit femoral artery. **(B)** Quantification of the total standardized uptake value (SUV) in the indicated groups (n = 4). * $p < 0.05$, ** $p < 0.01$.



Supplementary Figure 24. (A–L) Blood analysis of healthy rabbits after 0, 1, 7, and 28 days of intravenous exposure to PFH@PLGA/$MnFe_2O_4$-Ram NPs (n = 5).



Supplementary Figure 25. Histopathological images of healthy rabbit organs after 0, 1, 7, and 28 days of intravenous exposure to PFH@PLGA/$MnFe_2O_4$-Ram NPs.



Supplementary Figure 26. In vivo biocompatibility evaluation. (A–G) Blood analysis of plaque-bearing rabbits at baseline and day 28 following treatment in the indicated groups (n = 6). **(H)** Time-dependent body weight changes in plaque-bearing rabbits in the indicated groups (n = 5). **(I)** Representative hematoxylin and eosin staining of plaque-bearing rabbit organs (heart, liver, spleen, lung, and kidney) excised on day 28 after treatment in the indicated groups.