

Supplementary Figures

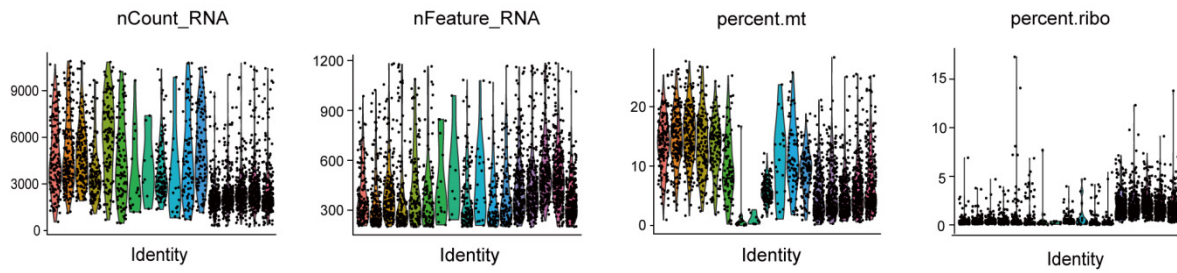


Figure S1. Cell quality control images.

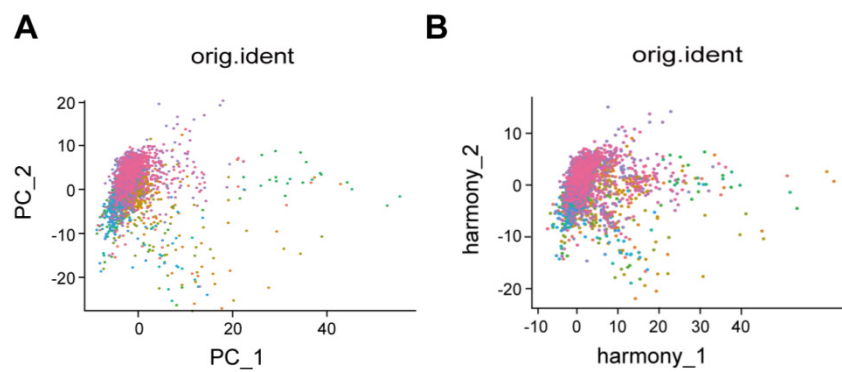


Figure S2. (A) Principal component analysis plot. (B) Harmony analysis plot.

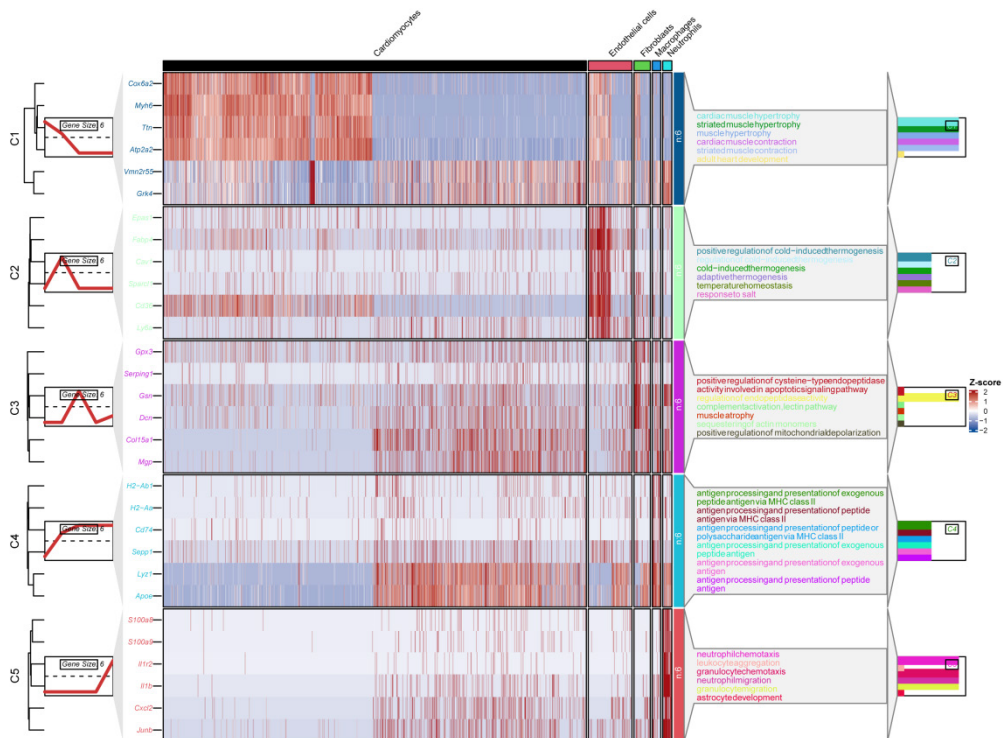


Figure S3. Heatmap of cluster differential enrichment analysis.

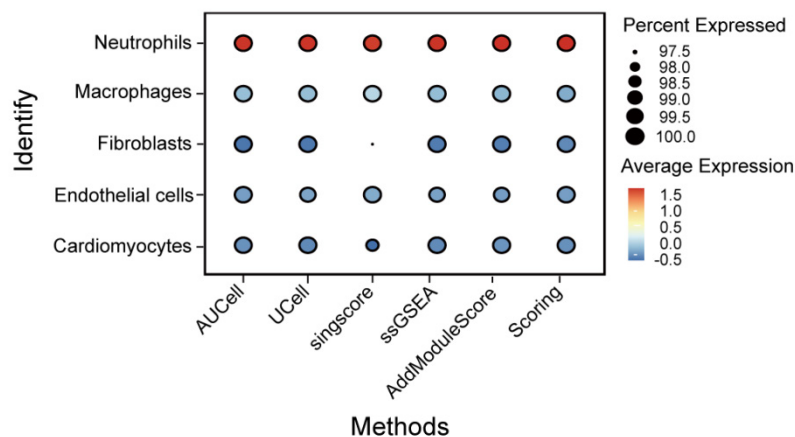


Figure S4. Expression of pyroptosis genes in different cell clusters evaluated by multiple algorithms.

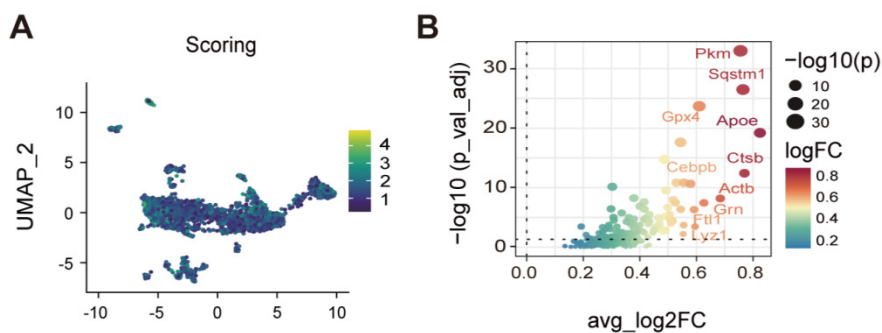


Figure S5. (A) UMAP visualization of single-cell data colored by scoring. (B) Volcano plot of differentially expressed genes.

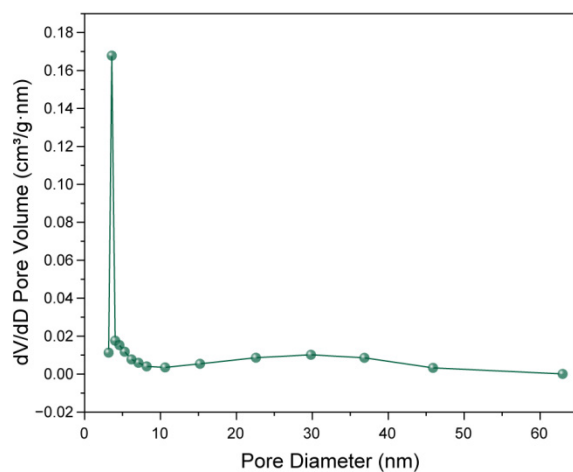


Figure S6. Pore size distribution of the HMPB.

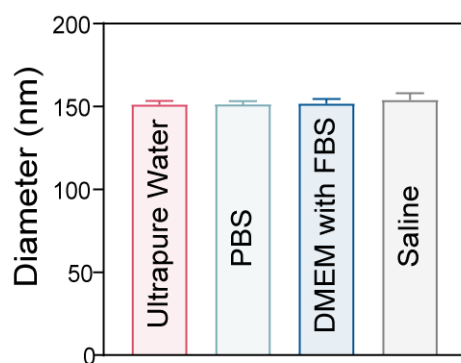


Figure S7. Size distribution of ^{IMTP}Lip@HNP in ultrapure water, PBS buffer, DMEM (with FBS), and saline. Data are mean $\pm$ SD, n = 3.

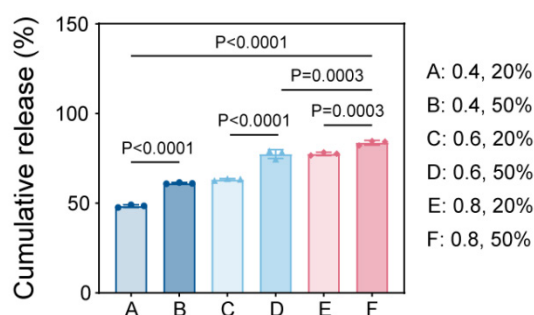


Figure S8. Cumulative NMN release profiles under different ultrasound power intensities and duty cycles. Data are mean $\pm$ SD, n = 3.

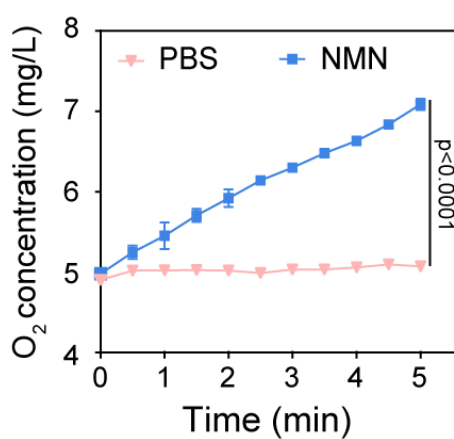


Figure S9. CAT-like activity of free NMN at physiological concentrations. Data are mean $\pm$ SD, n = 3.

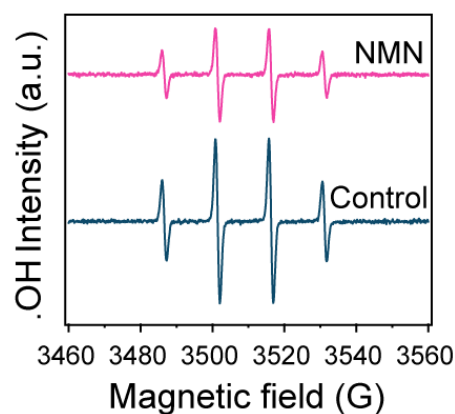


Figure S10. EPR analysis demonstrated that NMN possesses inherent POD-like enzymatic activity.

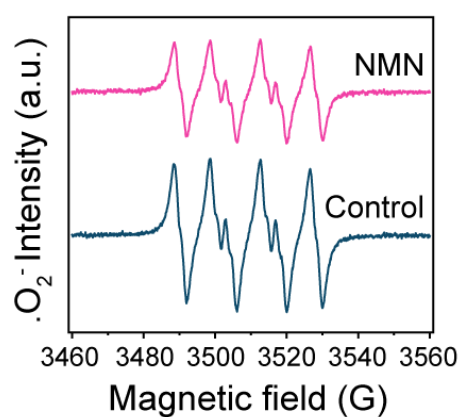


Figure S11. EPR analysis demonstrated that NMN possesses inherent SOD-like enzymatic activity.

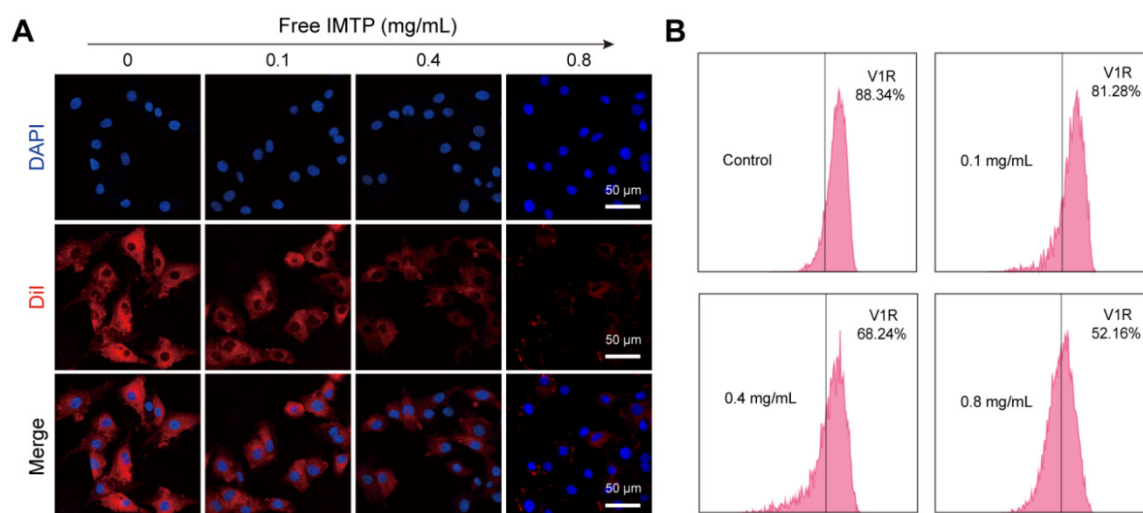


Figure S12. Free IMTP peptide inhibits the cellular uptake of $^{\text{IMTP}}\text{Lip@HNP}$. (A) Representative fluorescence images showing reduced uptake of DiI-labeled $^{\text{IMTP}}\text{Lip@HNP}$ after competition with free IMTP peptide at the indicated concentrations. Scale bar: 50 μm . (B) Flow cytometry analysis demonstrating concentration-dependent inhibition of $^{\text{IMTP}}\text{Lip@HNP}$ uptake by free IMTP peptide in OGD/R-injured H9c2 cells.

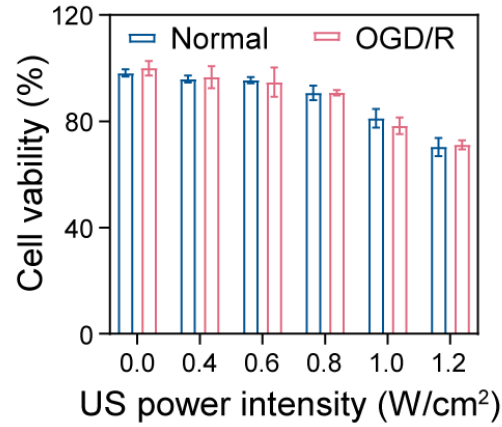


Figure S13. Relative cell viability of normal and OGD/R-injured H9c2 cells under US irradiation at different power intensities for 24 h. Data are mean $\pm$ SD, $n = 3$.

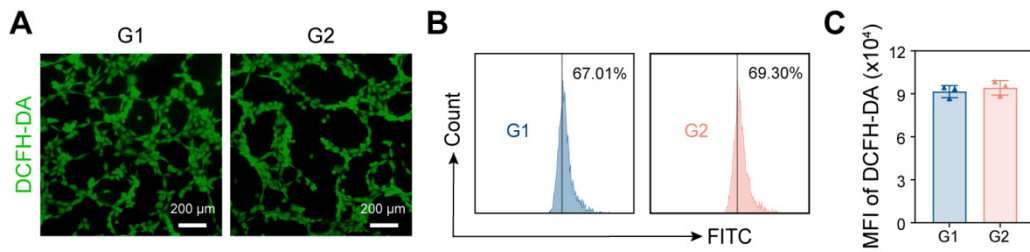


Figure S14. Intracellular ROS levels in H9c2 cells following OGD/R injury. (A) Representative fluorescence images showing ROS production after different treatments. Scale bar: 200 μ m. (B) Flow cytometry analysis and (C) quantitative measurement of intracellular ROS levels under different treatment conditions. Data are mean $\pm$ SD, $n = 3$.

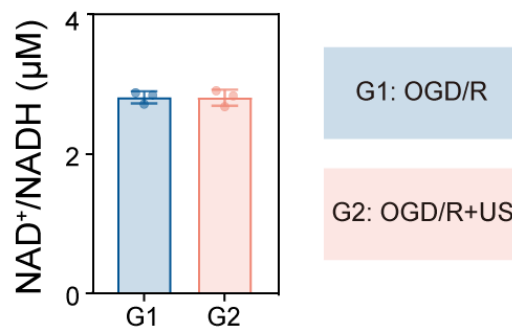


Figure S15. Intracellular NAD⁺/NADH levels in H9c2 cells after different treatments. Data are mean $\pm$ SD, $n = 3$.

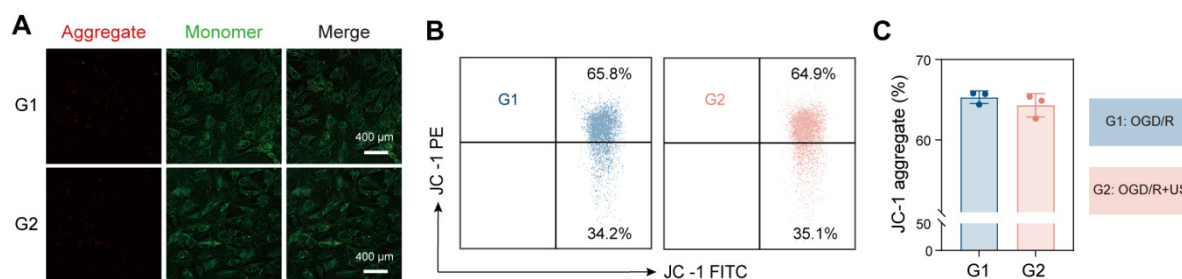


Figure S16. Assessment of mitochondrial membrane potential in H9c2 cells after OGD/R injury using JC-1 staining. (A) Representative fluorescence images of JC-1 staining in H9c2 cells subjected to different treatments. Scale bar: 400 μm. (B) Quantification of mitochondrial membrane potential changes and (C) JC-1 aggregation ratios determined by flow cytometry. Data are mean ± SD, n = 3.

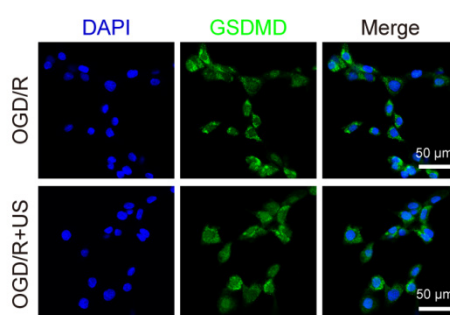


Figure S17. Immunofluorescence analysis of GSDMD expression in H9c2 cells after OGD/R injury. Representative CLSM images showing total GSDMD immunostaining in H9c2 cells following different treatments. The antibody used recognizes both full-length GSDMD and its N-terminal cleavage fragment (GSDMD-N). Scale bar: 50 μm.

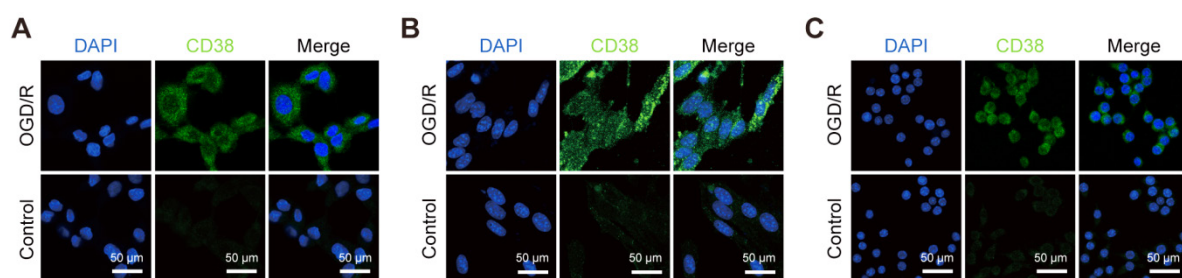


Figure S18. Immunofluorescence analysis of CD38 expression in cardiomyocytes (A), arterial endothelial cells (B), and RAW264.7 cells (C) under normoxia or OGD/R conditions. Scale bar: 50 μm.

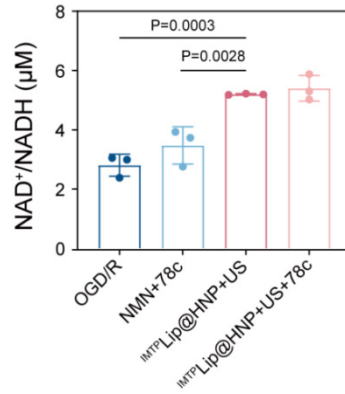


Figure S19. Effect of CD38 inhibition on NAD⁺/NADH levels in OGD/R-injured H9c2 cells. H9c2 cells were subjected to OGD/R injury and treated with CD38 inhibitor 78c + NMN, ^{IMTP}Lip@HNP + US, or 78c + ^{IMTP}Lip@HNP + US. NAD⁺/NADH levels were measured after treatment. Data are mean ± SD, n = 3.

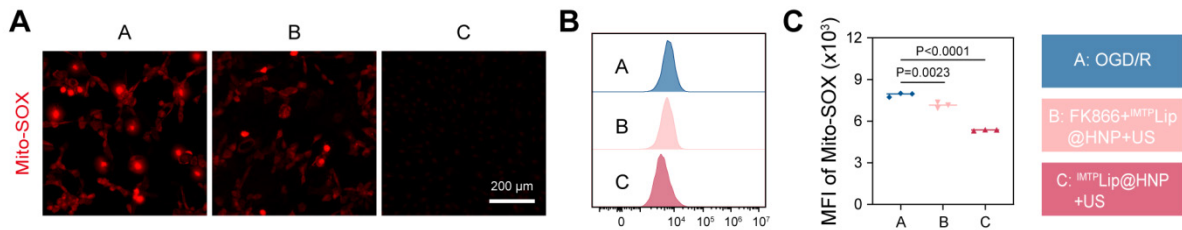


Figure S20. MitoSOX Red staining for mitochondrial superoxide in OGD/R-injured H9c2 cells. (A) Representative confocal images showing mitochondrial superoxide ($\bullet\text{O}_2^-$) levels after different treatments. Scale bar: 200 μm. (B) Flow cytometry analysis and (C) quantification of MitoSOX Red mean fluorescence intensity. Data are mean ± SD, n = 3.

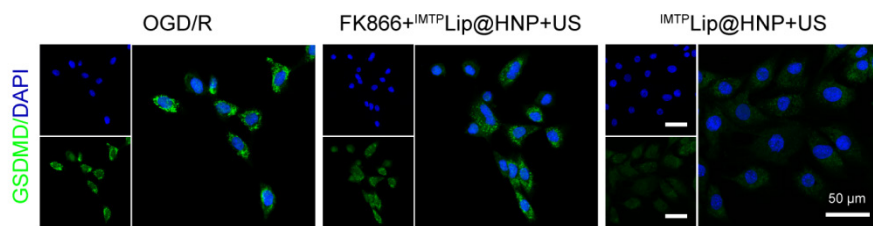


Figure S21. CLSM images of total GSDMD immunostaining in OGD/R-injured H9c2 cells after different treatments. Cells were stained with an anti-GSDMD antibody that detects both full-length GSDMD and its N-terminal cleavage fragment (GSDMD-N). Scale bar: 50 μm.

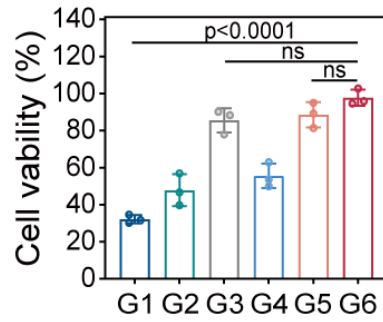


Figure S22. Cell viability after different treatments. Data are mean $\pm$ SD, n = 3.

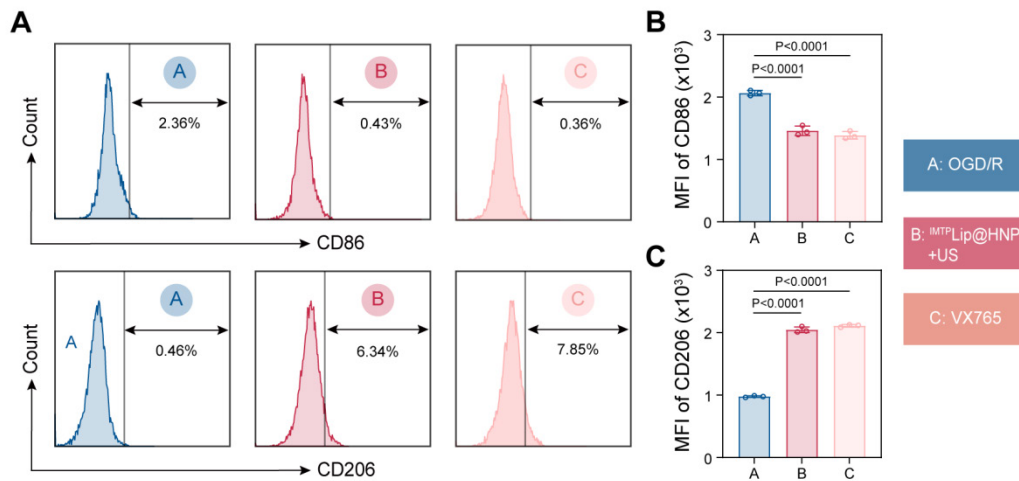


Figure S23. Flow cytometric analysis of macrophage polarization following incubation with conditioned medium derived from differently treated OGD/R-injured H9c2 cardiomyocytes. (A) Representative flow cytometry plots showing RAW264.7 macrophage polarization after exposure to CM collected from H9c2 cells subjected to different treatments. (B, C) Quantitative analysis of CD86- and CD206-positive macrophage populations. Data are mean $\pm$ SD, n = 3.

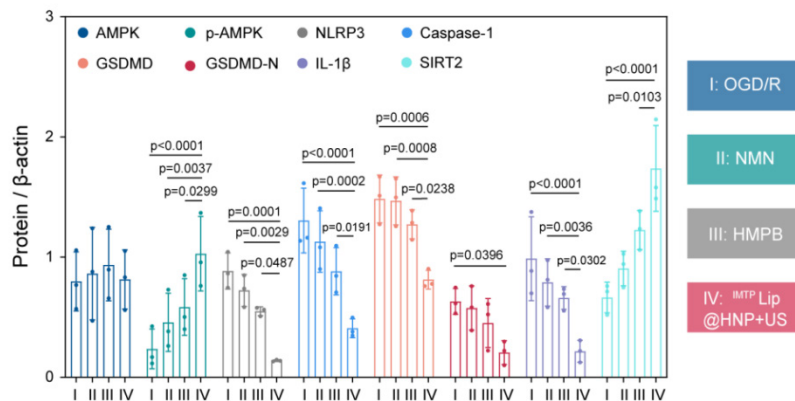


Figure S24. Quantitative analysis of the relative gray values for AMPK, p-AMPK, SIRT2, NLRP3, Caspase-1, GSDMD, GSDMD-N, and IL-1 β . Data are mean $\pm$ SD, n = 3.

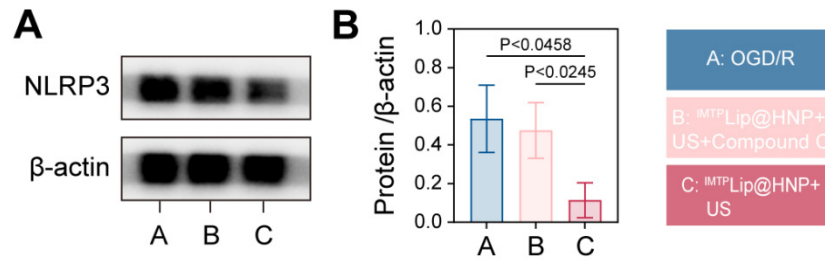


Figure S25. (A) Representative Western blot analysis of NLRP3 expression in OGD/R-injured H9c2 cells treated with ^{IMTP}Lip@HNP + US in the presence or absence of the AMPK inhibitor Compound C. (B) Quantification of the relative NLRP3 protein levels. Data are mean ± SD, n = 3.

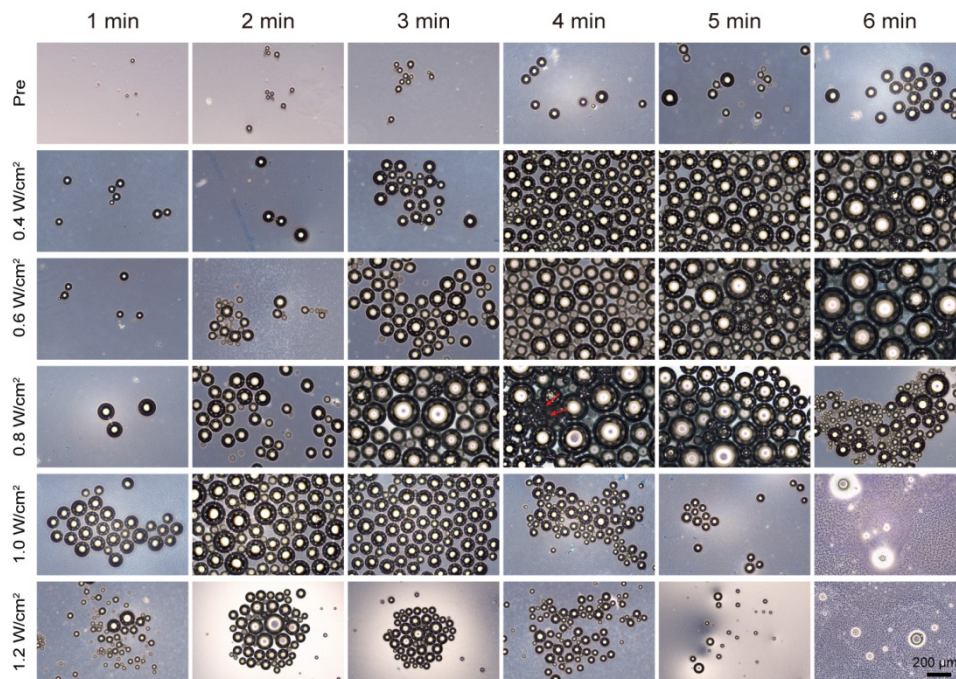


Figure S26. Optical microscopy images showing PFP vaporization in ^{IMTP}Lip@HNP NPs under ultrasound irradiation. Red arrow indicates a microbubble undergoing disruption. Scale bar: 200 μm.

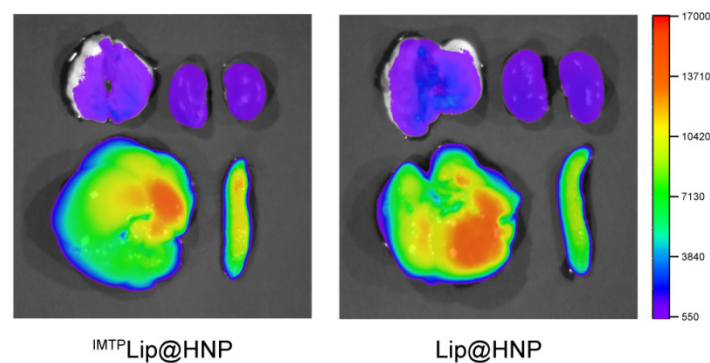


Figure S27. Ex vivo fluorescence images of liver, lung, spleen and kidney.

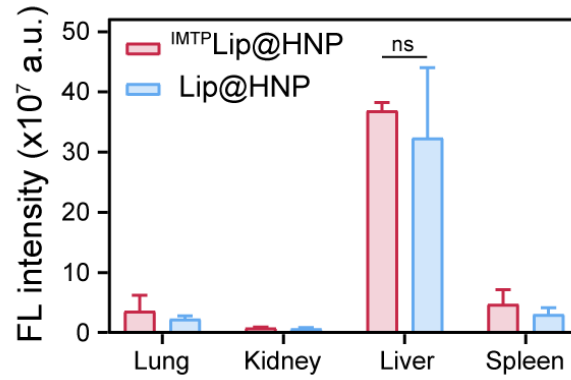


Figure S28. Quantitative data of the accumulation of DiR fluorescent signals in major organs 2 h after intravenous administration. Data are mean $\pm$ SD, $n = 3$.

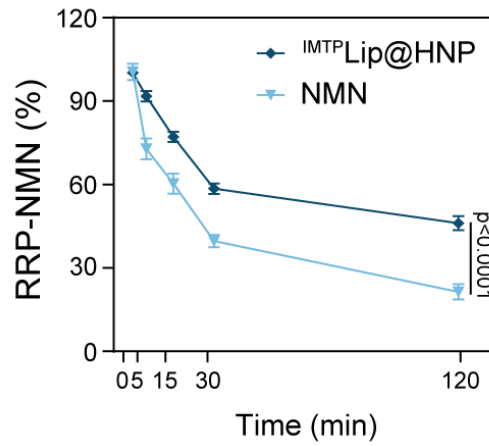


Figure S29. Ex vivo stability of free NMN and ^{IMTP}Lip@HNP in freshly collected whole blood. Data are mean $\pm$ SD, $n = 3$.

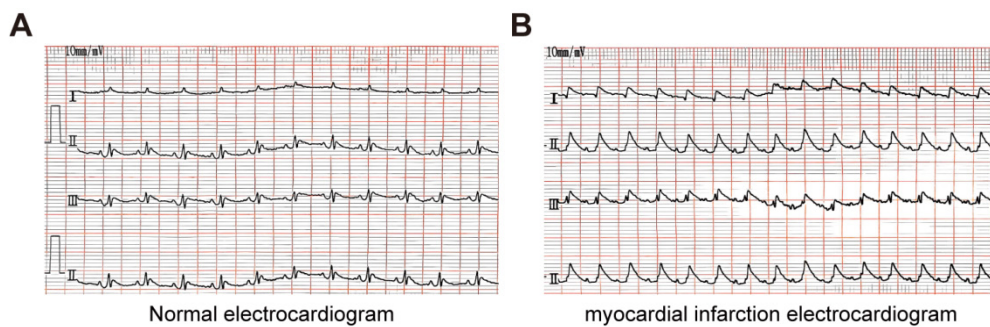


Figure S30. Representative electrocardiogram (ECG) traces of normal (A) and myocardial infarction (B) SD rats.

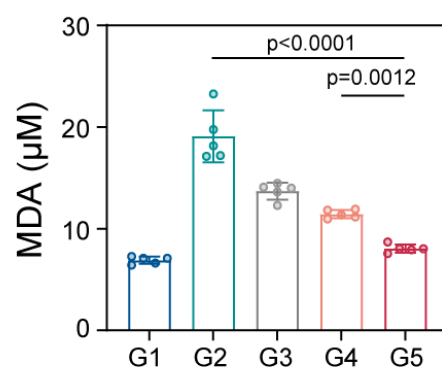


Figure S31. The levels of MDA in serum. Data are mean $\pm$ SD, n = 5.

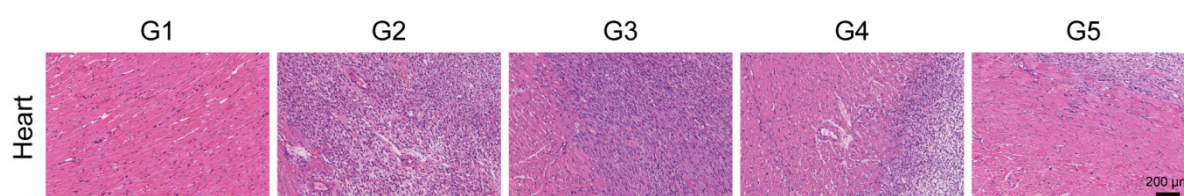


Figure S32. Hematoxylin-eosin (H&E) staining of cardiac tissue. Scale bar: 200 μ m.

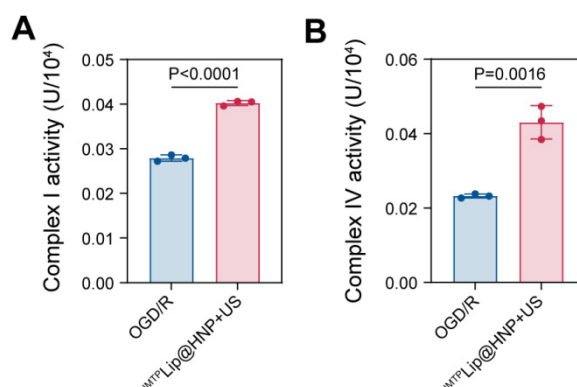


Figure S33. Mitochondrial complex I (A) and complex IV (B) activities in OGD/R-injured H9c2 cells after the indicated treatments. Data are mean $\pm$ SD, n = 3.

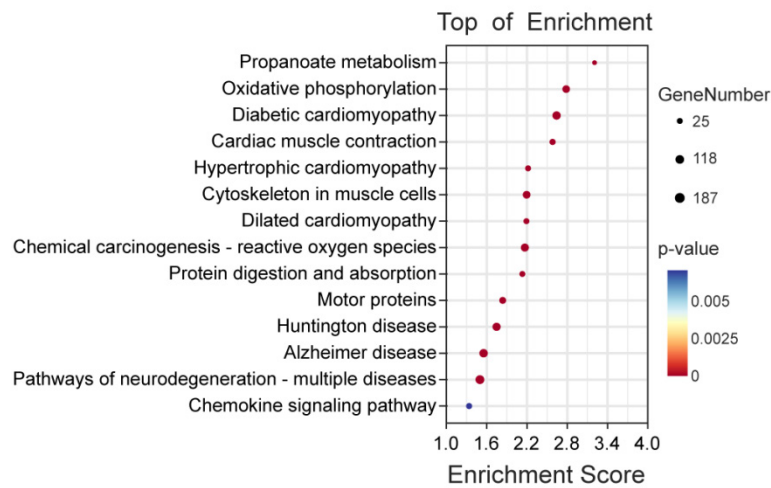


Figure S34. KEGG analysis revealed the significantly enriched biological pathways.

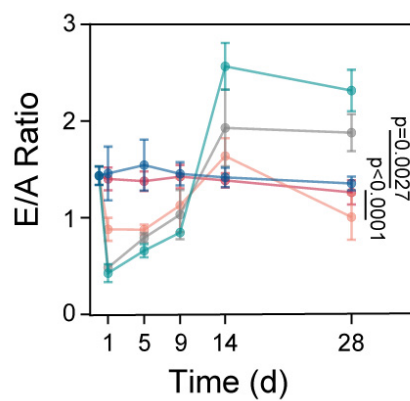


Figure S35. The mitral valve E/A ratio in different treatment groups. Data are mean $\pm$ SD, n = 5.

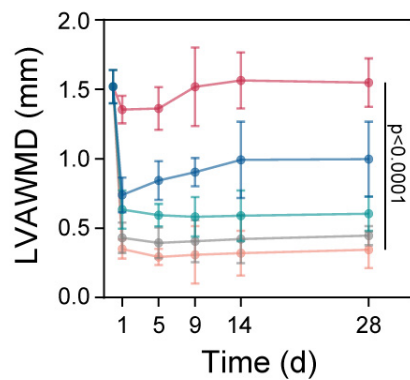


Figure S36. Anterior wall motion amplitude among different treatment groups. Data are mean $\pm$ SD, n = 5.

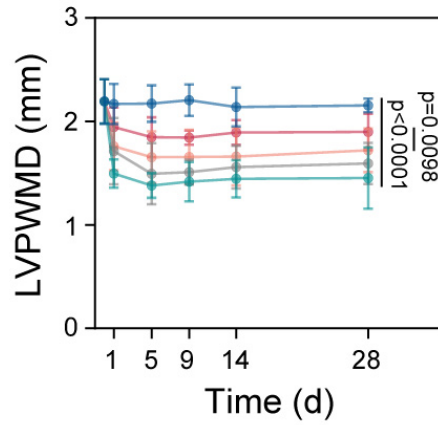


Figure S37. Posterior wall motion amplitude among different treatment groups. Data are mean $\pm$ SD, n = 5.

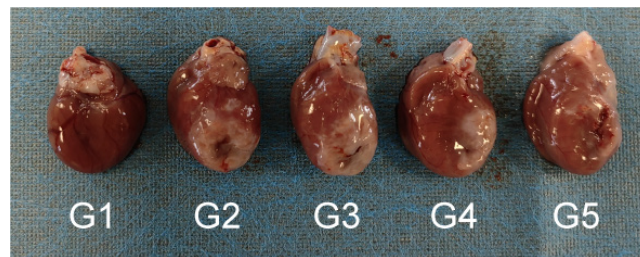


Figure S38. Gross anatomical images of the excised hearts.

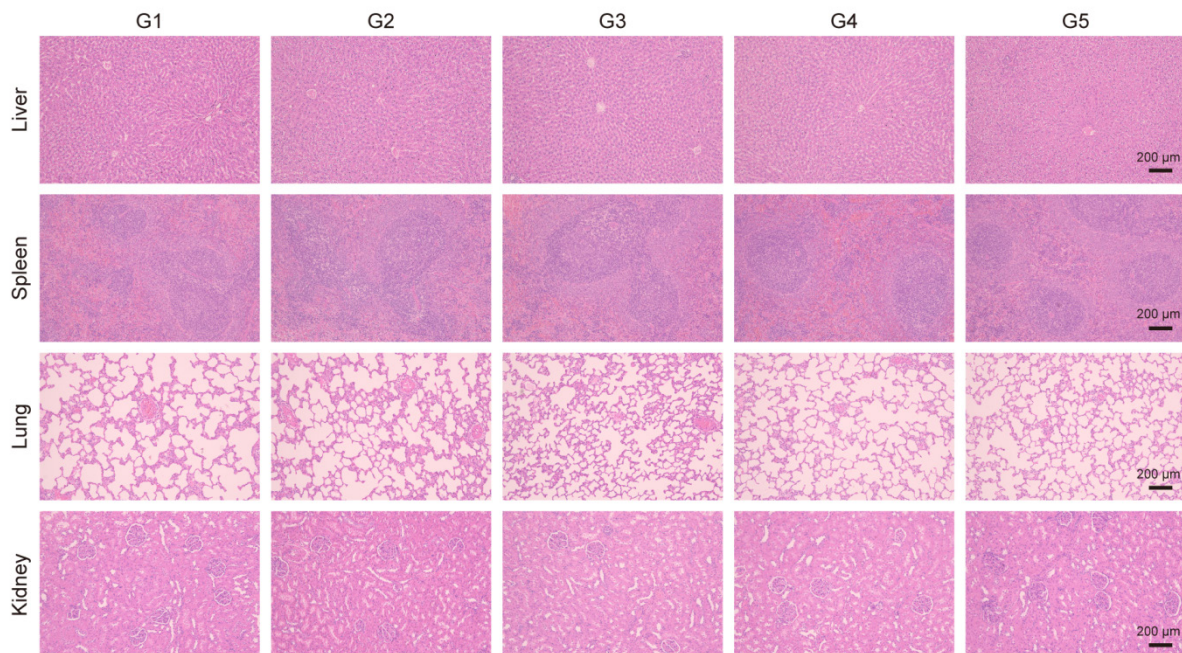


Figure S39. H&E staining of major organs in SD rats with I/R injury at 28 days after different treatments. Scale bar: 200 μ m.

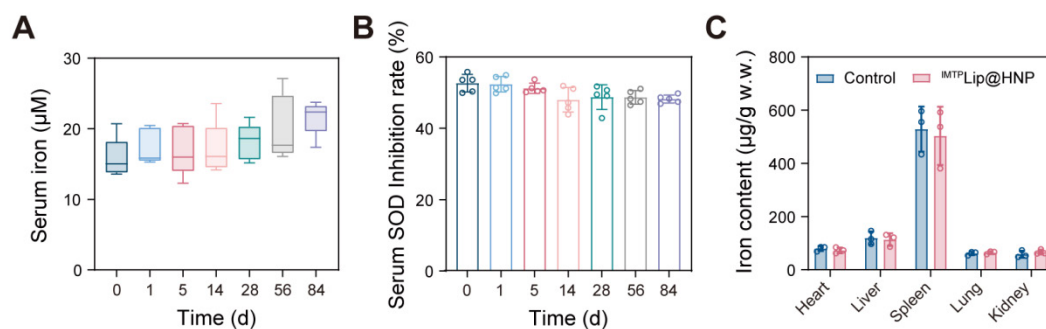


Figure S40. (A) Serum iron levels and (B) serum SOD inhibition rates (%) measured at the indicated time points after intravenous administration of ^{IMTP} Lip@HNP nanoparticles. (C) Quantification of iron content in the heart, liver, spleen, lung, and kidney tissues by ICP-MS at days 0 and 84 after administration. Data are mean $\pm$ SD, $n = 5$.

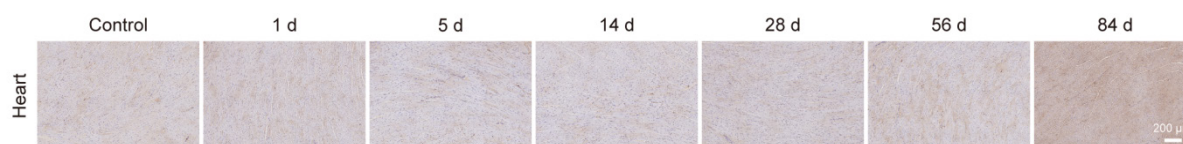


Figure S41. Representative enhanced Prussian blue staining images of myocardial tissues collected from SD rats at different time points after intravenous injection of ^{IMTP} Lip@HNP nanoparticles. Scale bar: 200 μm.

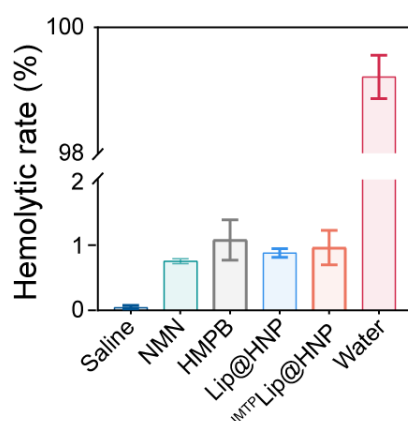


Figure S42. Hemocompatibility test of NMN, HMPB, Lip@HNP, and ^{IMTP} Lip@HNP. Data are mean $\pm$ SD, $n = 3$.

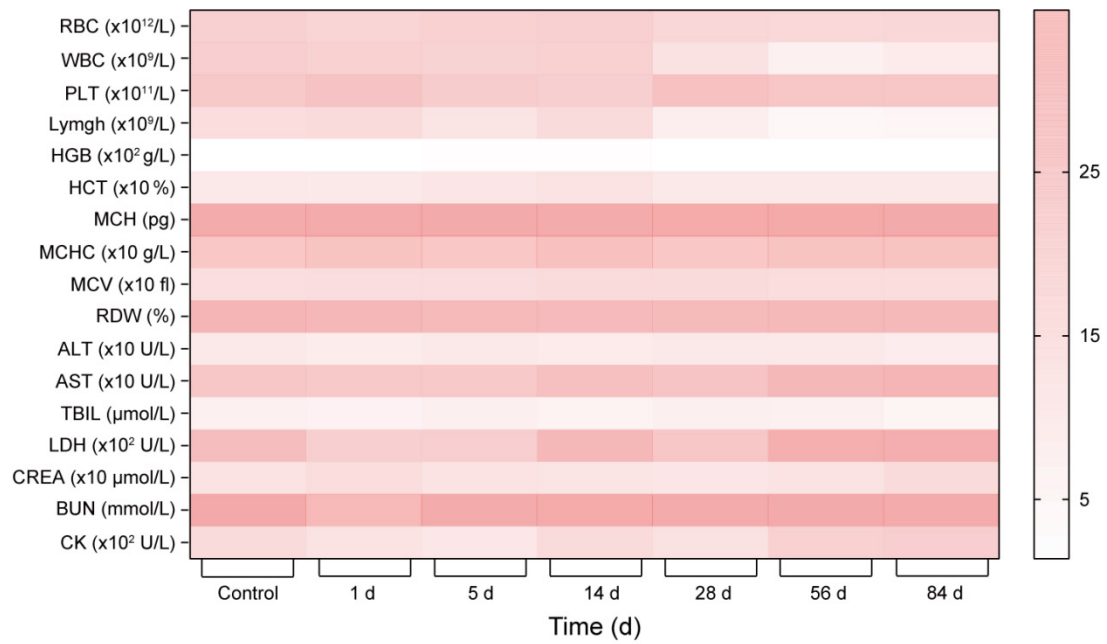


Figure S43. Heat map of routine blood analysis and blood biochemistry in SD rats sacrificed at different time intervals after intravenous administration of ^{IMTP} Lip@HNP NPs. Data are mean $\pm$ SD, n = 5.

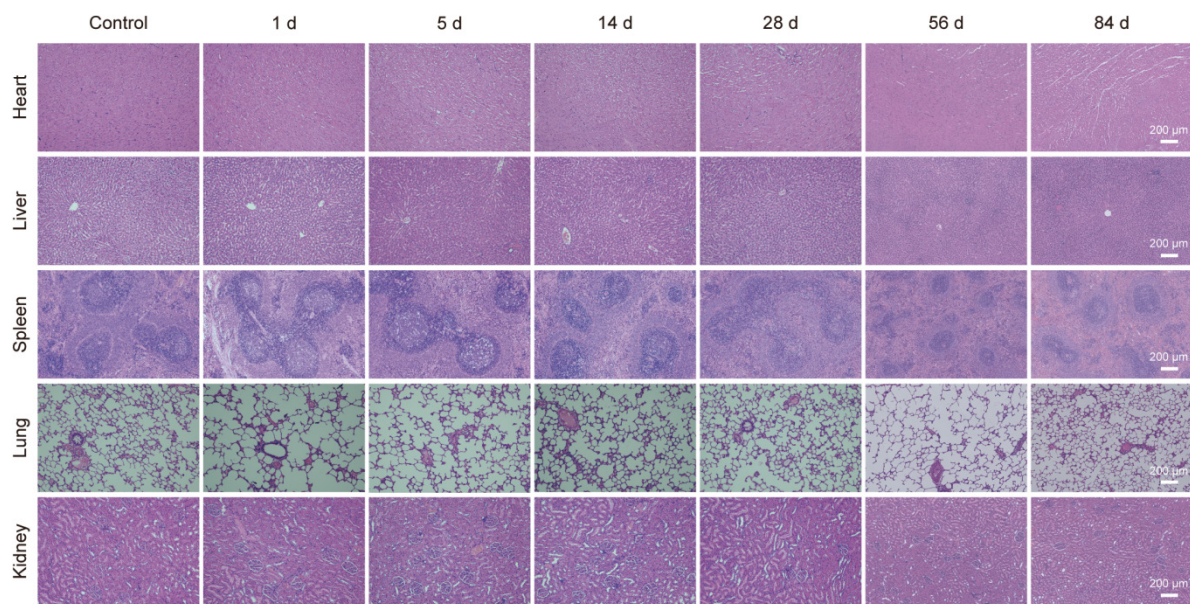


Figure S44. H&E staining of the major organs in SD rats sacrificed at different time intervals after intravenous injection of ^{IMTP} Lip@HNP. Scale bar: 200 μ m.

Vascular Parameter	Group	
	I/R	^{IMTP} Lip@HNP + US
Vascular Volume (μm^3)	1.53612×10^9	3.81791×10^9
Total Sample Volume (μm^3)	4.06781×10^{10}	4.80802×10^{10}
Volume Ratio	0.037762826	0.079407116

Table S1. Quantification results of the microvessel diameter within the injury border zone.

Video S1. Three-dimensional LSFM imaging revealed extensive and spatially heterogeneous α -SMA-positive fibrotic lesions in myocardial tissues of the I/R group. Meanwhile, 3D vascular reconstruction demonstrated pathological dilation of arteries/arterioles within these fibrotic lesions.

Video S2. Three-dimensional LSFM imaging clearly demonstrated that myocardial tissue injury was significantly alleviated in the ^{IMTP}Lip@HNP + US group, with no diffuse fibrotic network observed. Furthermore, 3D vascular reconstruction showed that vascular diameters remained within the physiological range.