Supplementary Information for

Remodeling Articular Immune Homeostasis with an Efferocytosis-inspired Nanoimitator Mitigates Rheumatoid Arthritis

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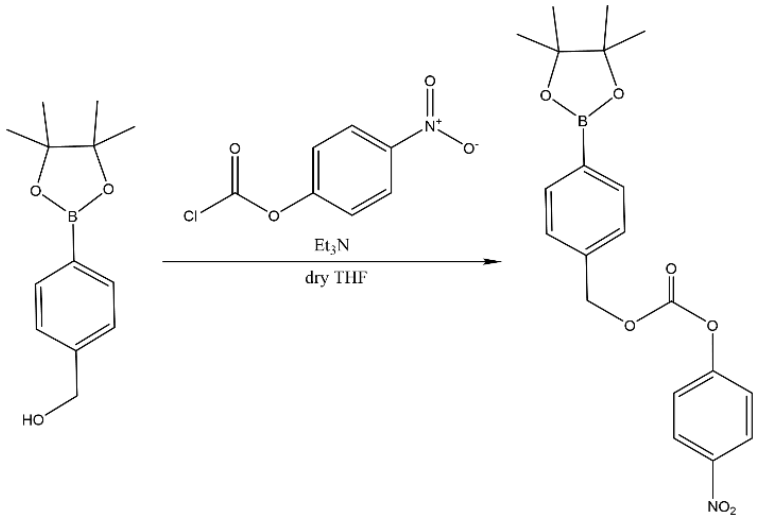
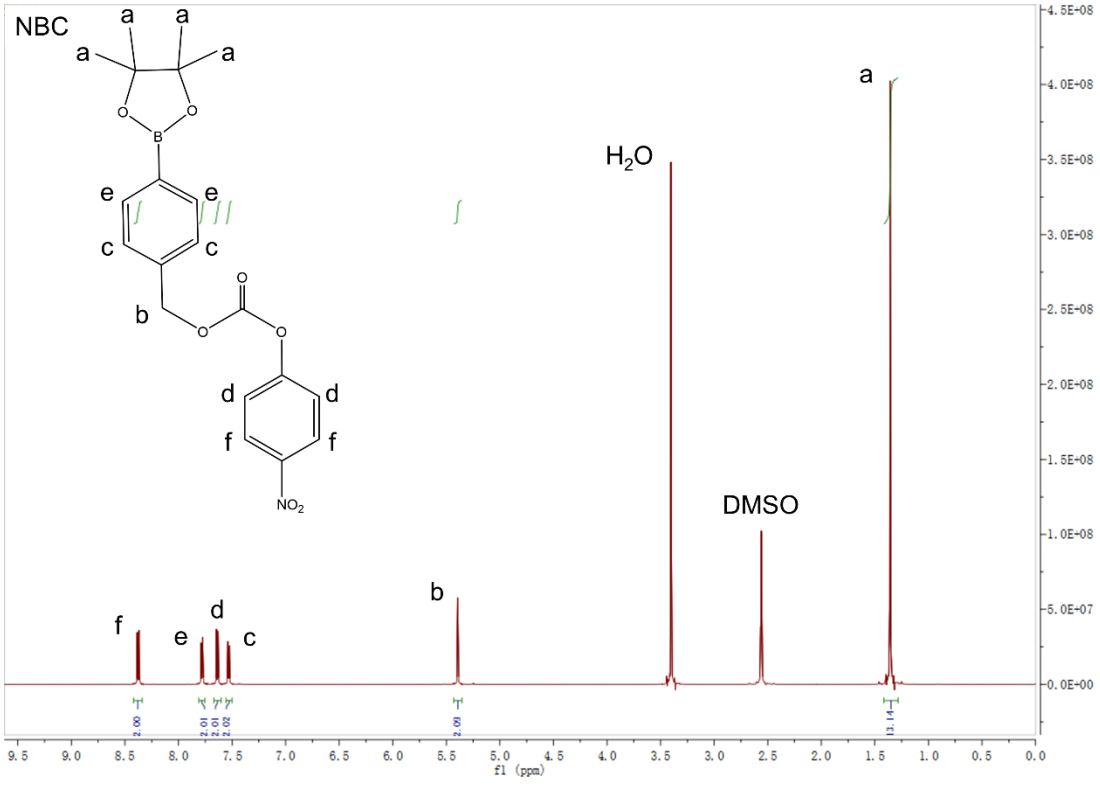
Contents

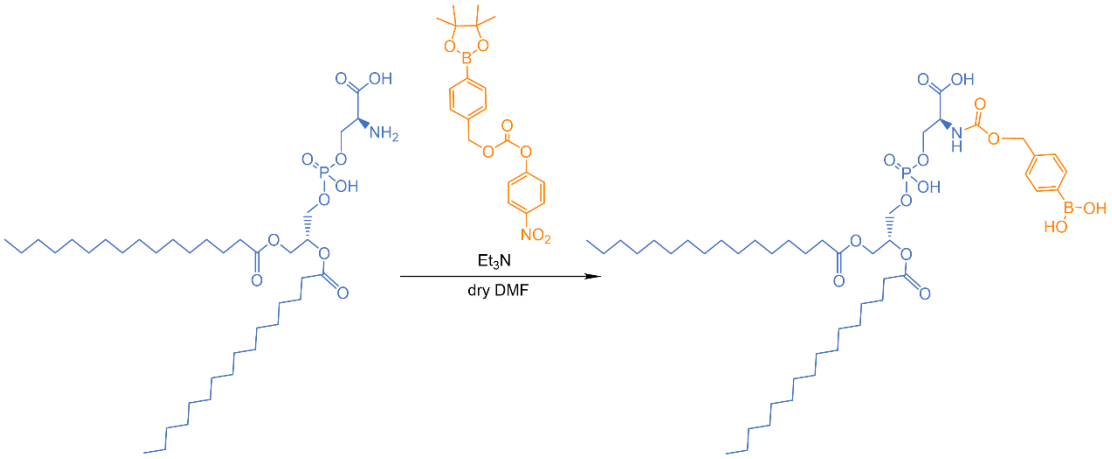
Supplementary Scheme 1. Synthetic of NBC.

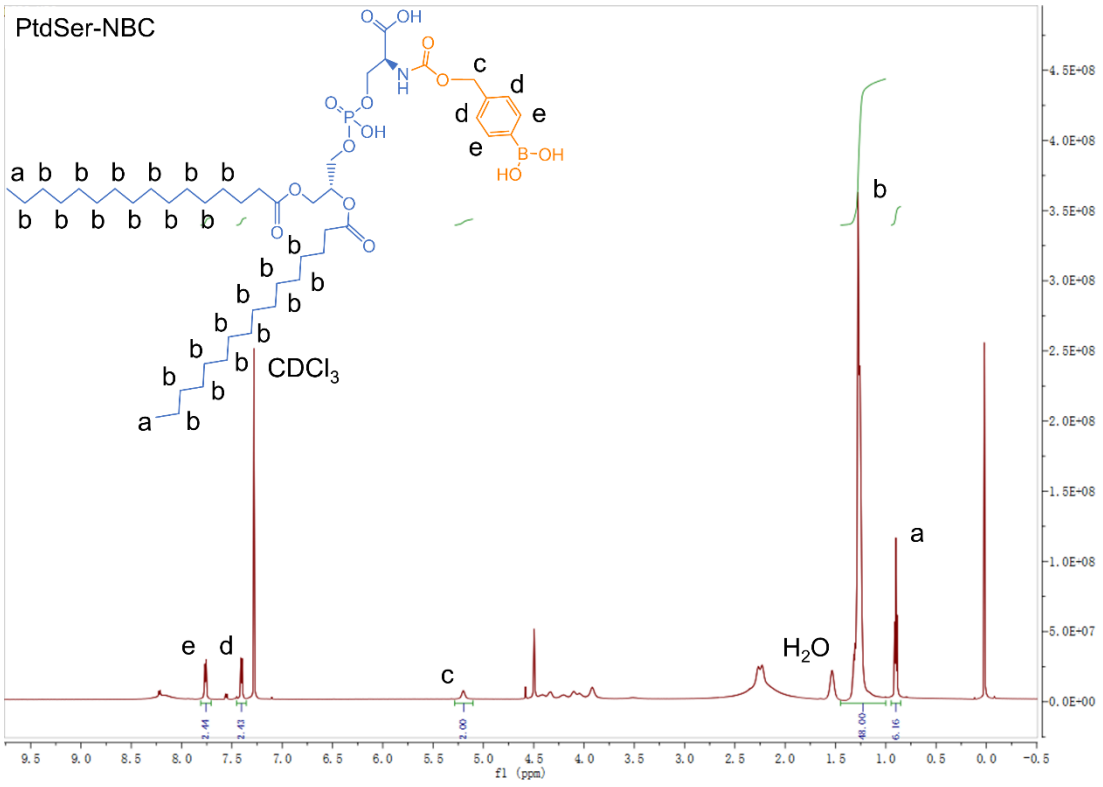




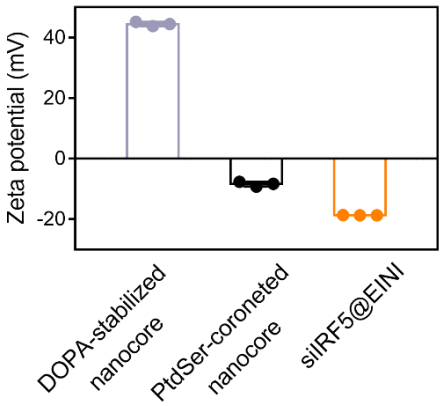
Supplementary Figure 1. ^{1}H NMR spectrum of NBC in DMSO-d6.

Supplementary Scheme 2. Synthetic route developed to produce PtdSer-NBC.

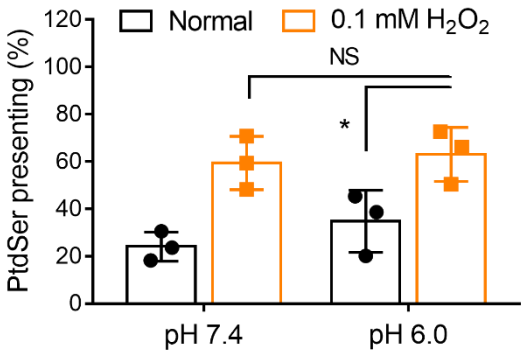




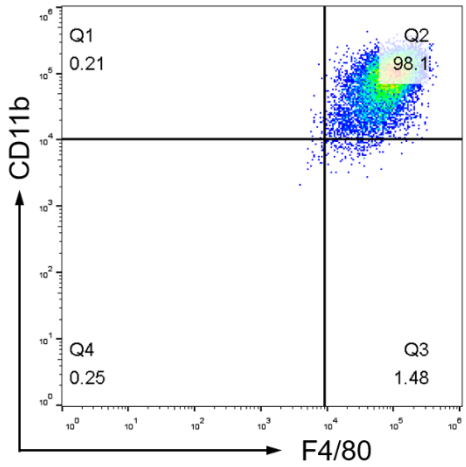
Supplementary Figure 2. ^{1}H NMR spectrum of PtdSer-NBC in $CDCl_3$.



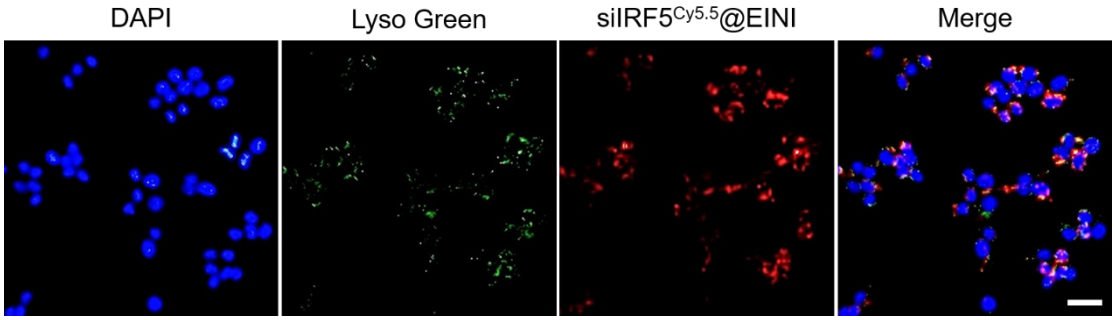
Supplementary Figure 3. Zeta potential of DOPA-stabilized nanocore, PtdSer-coroneted nanocore and siIRF5@EINI.



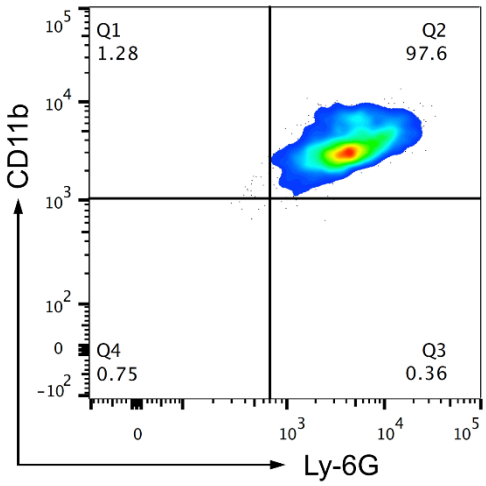
Supplementary Figure 4. Flow cytometry analysis of PtdSer-presenting. The nanoimitator was resuspended in PBS at pH 7.4 or pH 6.0 respectively, and was incubated with or without H_2O_2 (0.1 mM). Data are presented as the mean ± s.d. ($n = 3$ independent experiments). $^{**}P < 0.01$. NS, not significant.



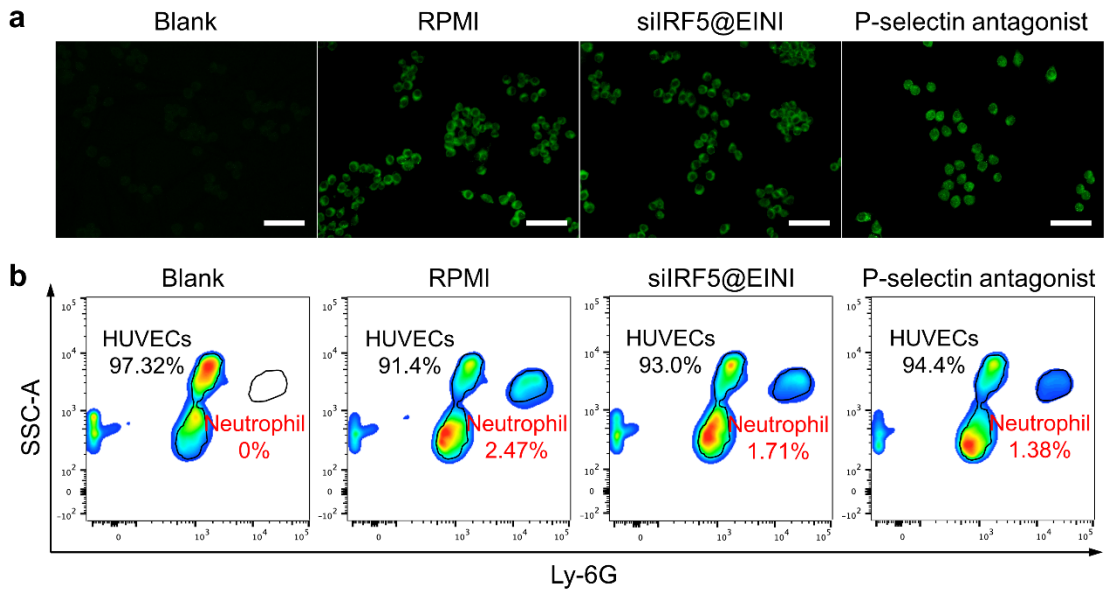
Supplementary Figure 5. The expression levels of CD11b and F4/80 in BMDMs analyzed by flow cytometry.



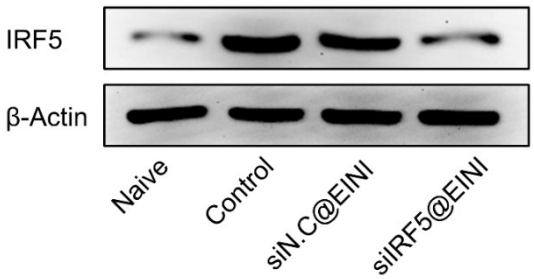
Supplementary Figure 6. Fluorescent visualization of siRNA localization in macrophages 6 hours after incubation with nanoimitator. Scale bars, 50 nm.



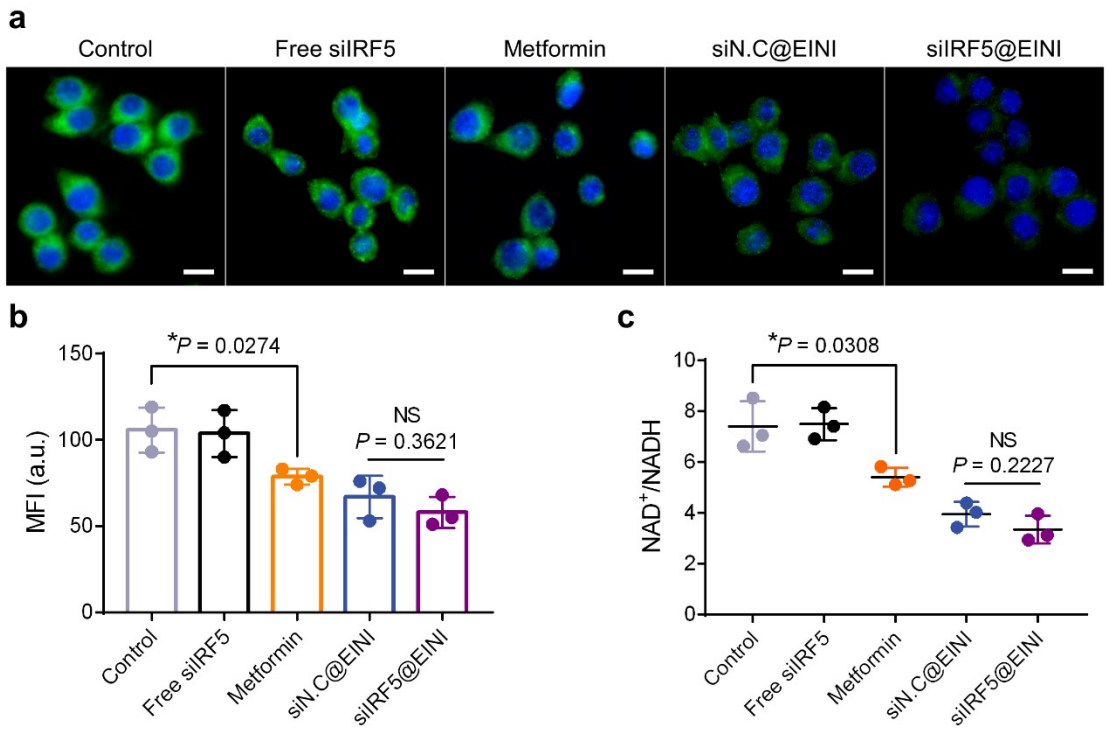
Supplementary Figure 7. Flow cytometric analysis of the purity of neutrophils doubly stained with FITC-conjugated Ly-6G and PerCP-Cy5.5-conjugated CD11b antibodies.



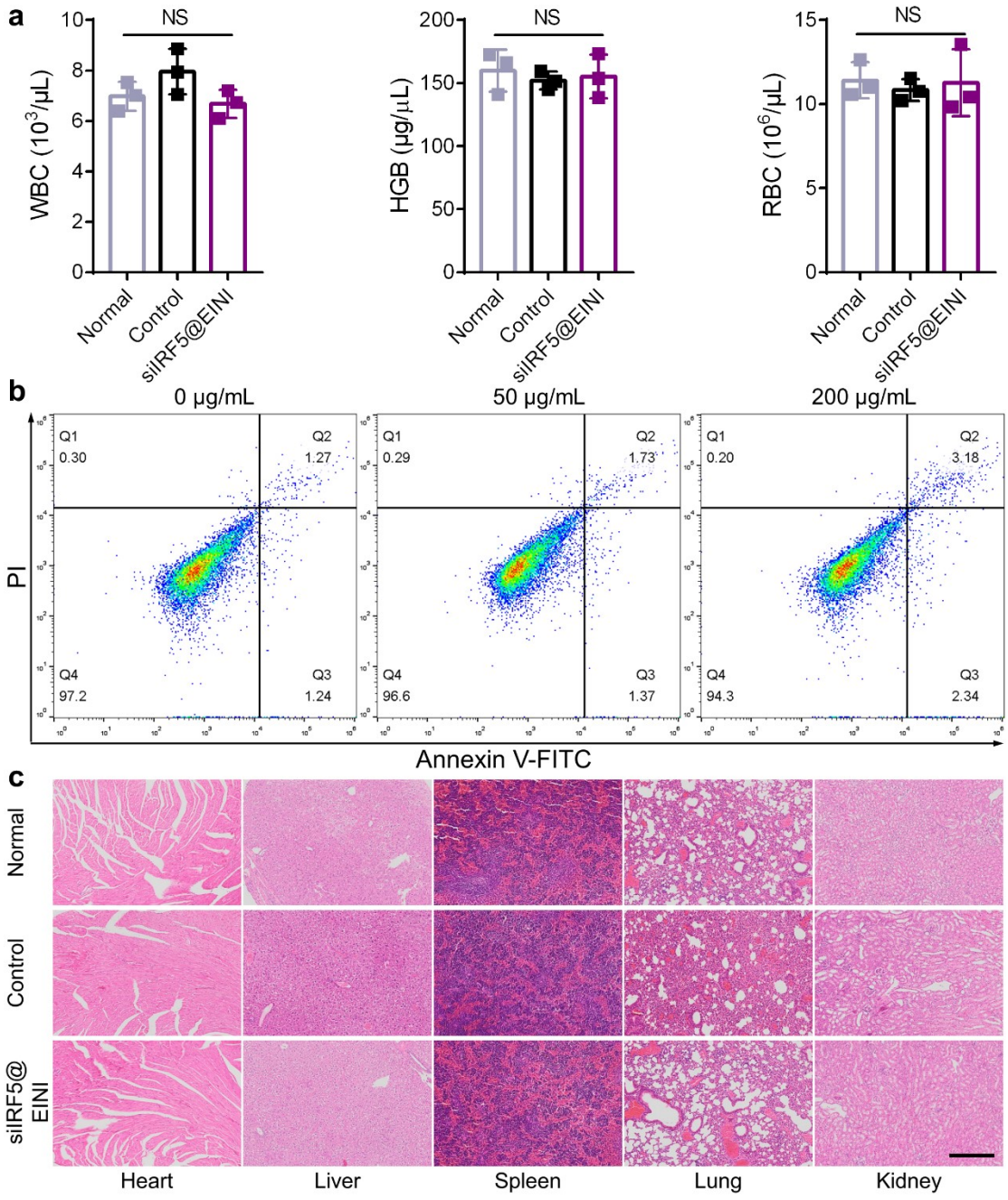
Supplementary Figure 8. Effective intervention by nanoimitator on inflammatory neutrophils. a, Evaluation of neutrophil adhesion to a HUVECs monolayer after incubation with nanoimitator. Scale bars, 50 nm. **b**, FACS analysis of neutrophil adhesion to HUVECs. All values are expressed as the mean ± s.d. (n = 3 independent experiments).



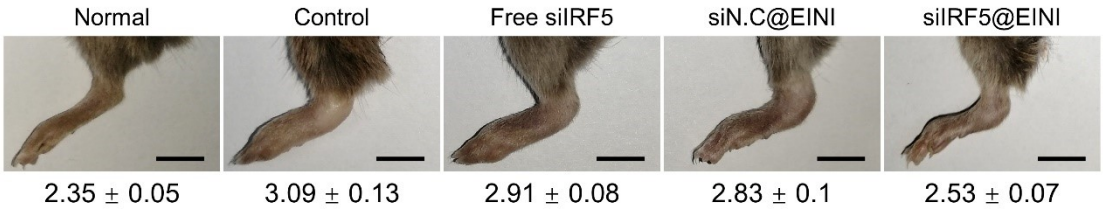
Supplementary Figure 9. IRF5 expression in macrophages treated with different formulations, detected by western blot.



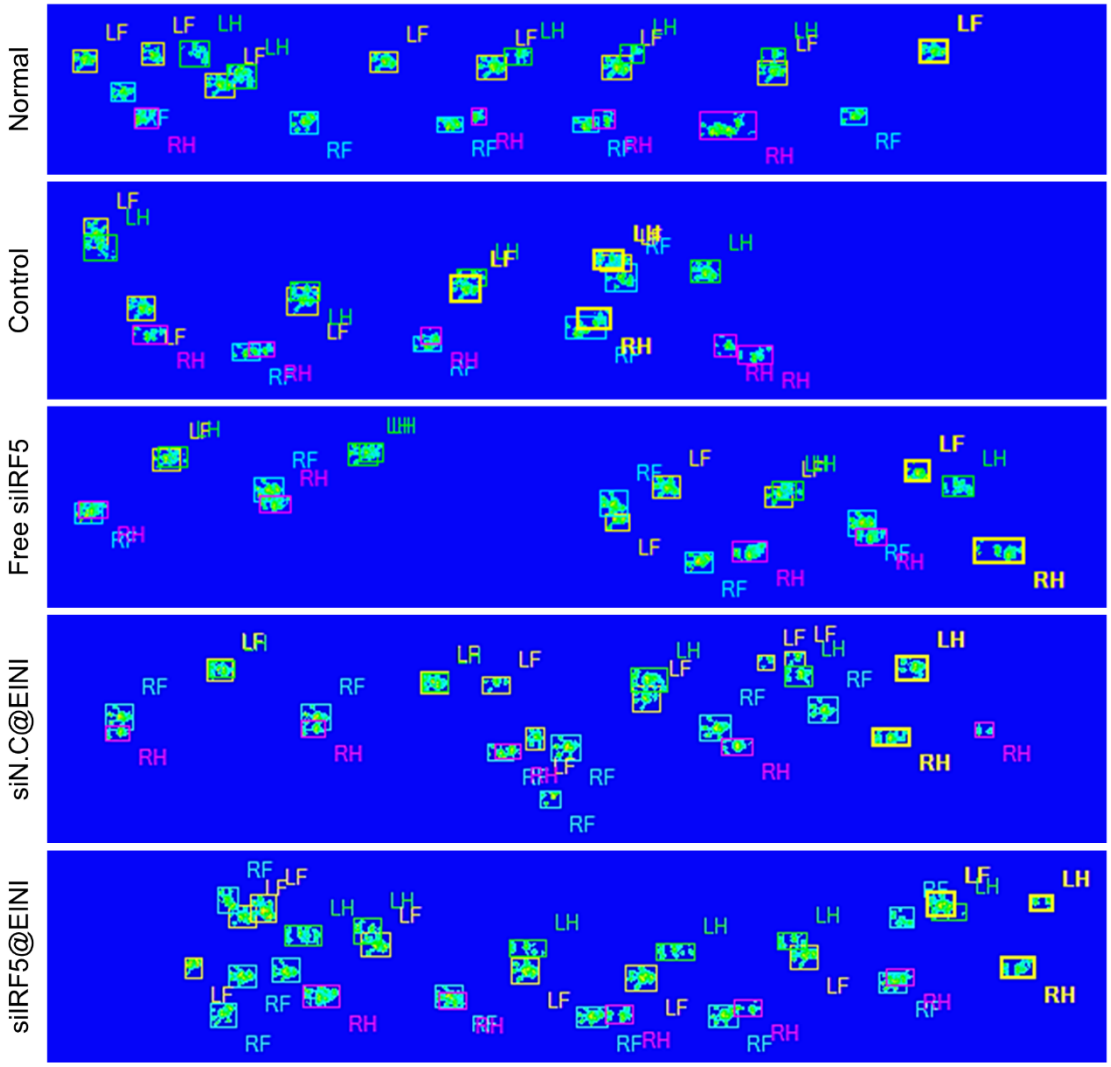
Supplementary Figure 10. Metformin reprogramming mitochondrial metabolism in macrophages, which act as mitochondrial complex I (CI) inhibitor directly inhibit CI-derived ROS. a, Fluorescence images and the quantification result (**b**) of intracellular ROS generation in macrophages stained with DCFH-DA. The scale bars were 20 μm. **c**, The levels of oxidized and reduced nicotinamide adenine dinucleotide (NAD^+/NADH) were measured in macrophages using a colorimetric assay. All values are expressed as the mean ± s.d. (n = 3 biologically independent animals). *P < 0.05. NS, not significant.



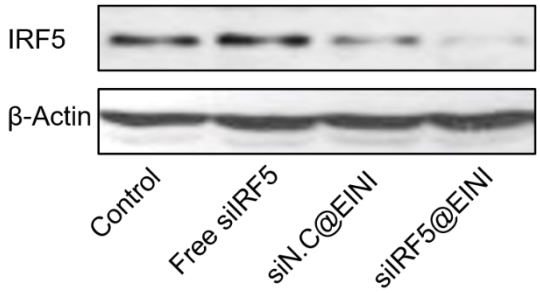
Supplementary Figure 11. Systemic toxicity evaluation of siIRF5@EINI. a, During the experimental cycle, mice were followed up to sacrifice on day 60, the change of white blood cell (WBC), hemoglobin (HGB) and red blood cell (RBC) were measured. Data are presented as the mean ± s.d. (n = 3 independent experiments). NS, not significant. **b**, Apoptosis of T cells extracted from the spleens of mice that received i.v. injections of siIRF5@EINI during the experimental cycle. Mice injected with PBS were used as a negative control. **c**, Histological sections of major organs at 60th day. Scale bar, 50 μm. (n = 3 biologically independent animals).



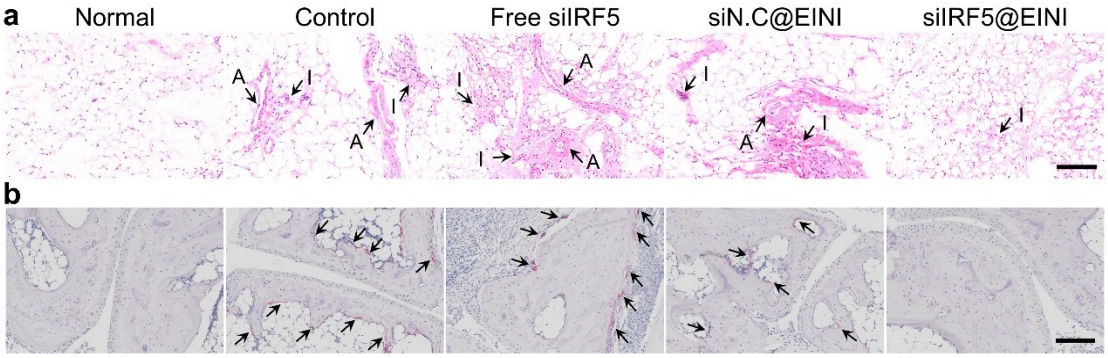
Supplementary Figure 12. Representative lesions image from macroscopic observation of the hind paws in different treatment groups. Scale bar, 3 mm. (*n* = 5 biologically independent animals).



Supplementary Figure 13. Representative signal images of the footprint assay.



Supplementary Figure 14. Western blot images of IRF5 protein levels in the synovial macrophages in different formulations treated group.



Supplementary Figure 15. H&E staining of synovium and immunohistochemical analyses of the TRAP-stained osteoclasts. a, H&E staining of synovium extracted from mice of different treatment groups. I, immune cell infiltration; A, angiogenesis. Scale bars = 50 μm. (*n* = 5 biologically independent animals). **b**, Immunohistochemical analyses of the TRAP-stained osteoclasts in the joint tissues from rats receiving the indicated treatment. Scale bar = 100 μm. (*n* = 5 biologically independent animals).

Supplementary Table 1. List of primers used for real-time PCR

IRF5	Forward	5’-CATTCAGCGGGAAGTCAAGA-3’
	Reverse	5’-TGTCTGCCGACCAAGAAAGC-3’
CXCL1	Forward	5’-CACCCAAACCGAAGTCATAGC-3’
	Reverse	5’-GGGGACACCTTTTAGCATCTTT-3’
iNOS	Forward	5'-AGCCAAGCCCTCACCTACTT-3’
	Reverse	5'-CTCTGCCTATCCGTCTCGTC-3’
TNF-α	Forward	5’-TGGAACTGGCAGAAGAGGCAC-3’
	Reverse	5’-AGGGTCTGGGCCATAGAACTGA-3’
Arg1	Forward	5’-TGCTTAGCTCTGTCTGCTTTGC-3’
	Reverse	5’-GAACACGGCAGTGGCTTTAAC-3’
CD206	Forward	5’-GGAGGCTGATTACGAGCAGT-3’
	Reverse	5’-CATAGGAAACGGGAGAACCA-3’
β-actin	Forward	5'-CTACAATGAGCTGCGTGTGG-3’
	Reverse	5'-CAGGTCCAGACGCAGGATGGC-3’