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**Supplementary Information for**  
**Remodeling Articular Immune Homeostasis with an Efferocytosis-inspired**  
**Nanoimitator Mitigates Rheumatoid Arthritis**

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Chen<sup>1</sup>, Jing Zhang<sup>1</sup>, Ying Liu<sup>1</sup>, Peng Sun<sup>4</sup>, Rui Zhang<sup>1</sup>, Zhenmei Yang<sup>1</sup>, Maosen Han<sup>1</sup>,  
Yan Wang<sup>1</sup>, Xia Wei<sup>5</sup>, Jun Li<sup>5</sup>, Wei Li<sup>2,3</sup>, Mohnad Abdalla<sup>1</sup>, Gongchang Yu<sup>6</sup>, Bin Shi<sup>6</sup>,  
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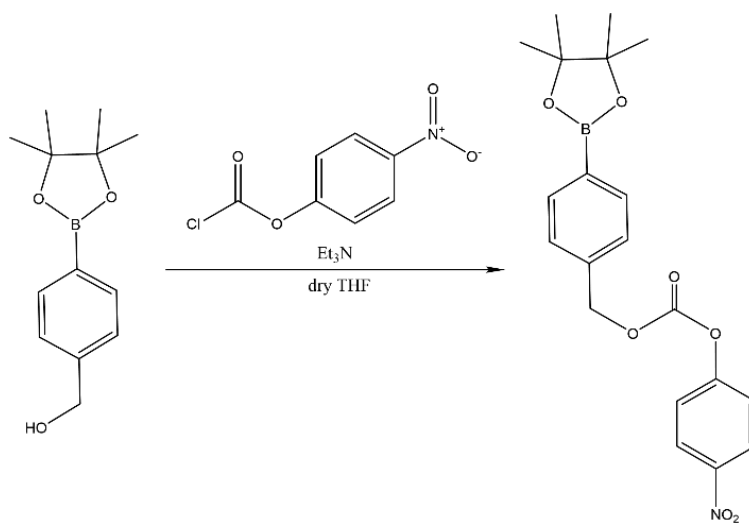
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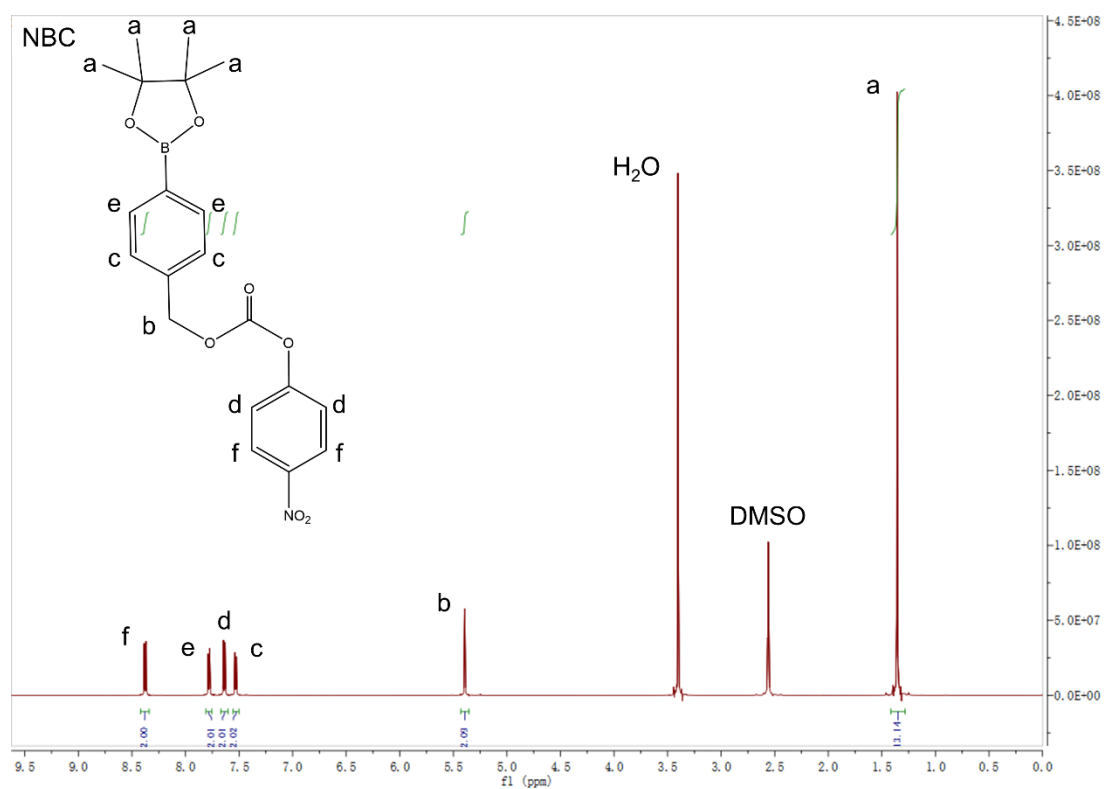
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57 analyses of the TRAP-stained osteoclasts.

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

59 **Supplementary Scheme 1. Synthetic of NBC.**



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62 **Supplementary Figure 1. <sup>1</sup>H NMR spectrum of NBC in DMSO-d<sub>6</sub>.**

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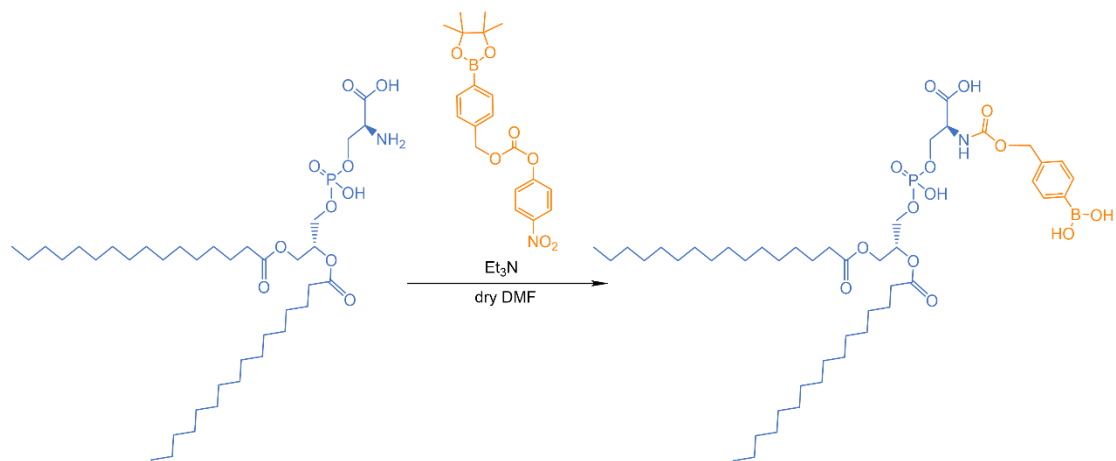
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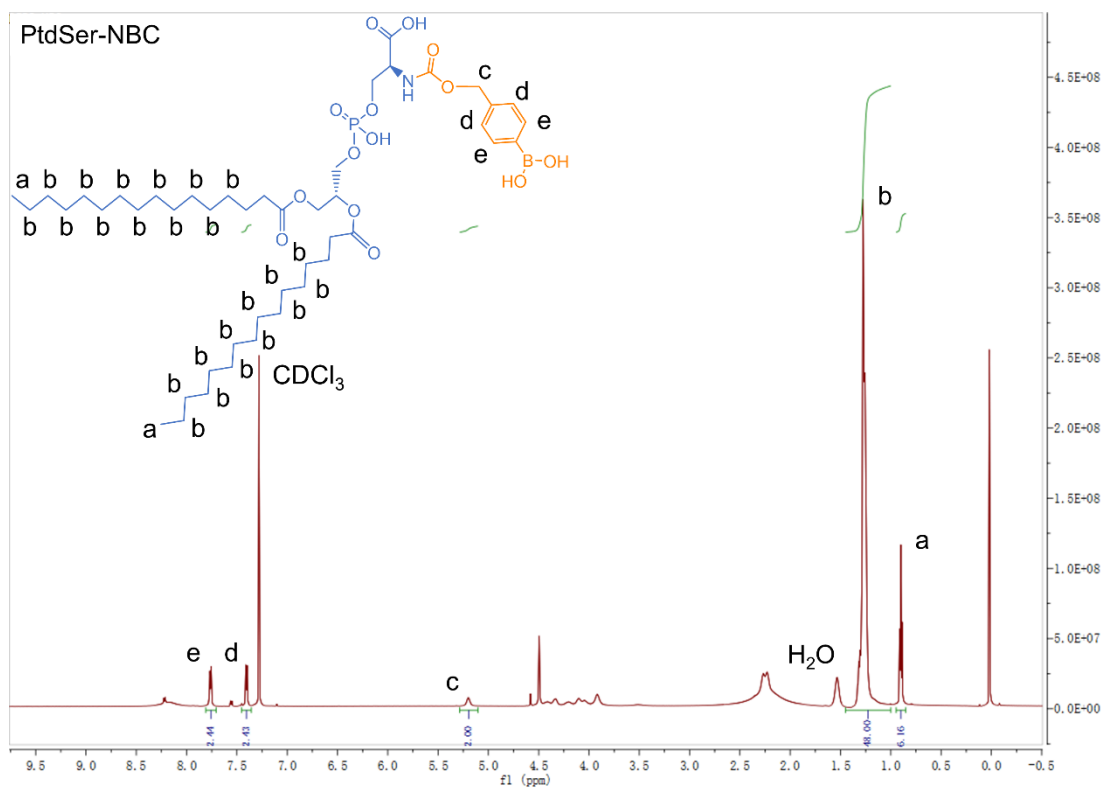
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70 **Supplementary Scheme 2. Synthetic route developed to produce PtdSer-NBC.**



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73 **Supplementary Figure 2. <sup>1</sup>H NMR spectrum of PtdSer-NBC in CDCl<sub>3</sub>.**

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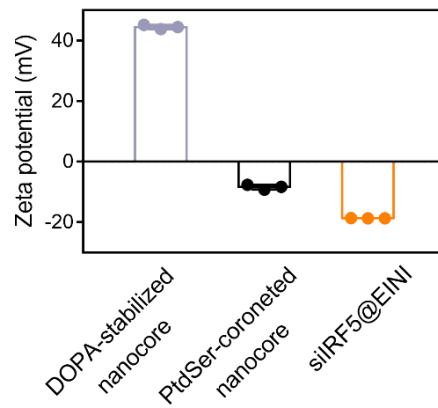
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85 **Supplementary Figure 3. Zeta potential of DOPA-stabilized nanocore, PtdSer-**  
86 **coroneted nanocore and siIRF5@EINI.**

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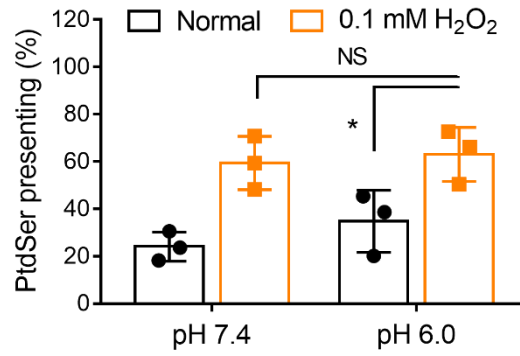
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116 **Supplementary Figure 4. Flow cytometry analysis of PtdSer-presenting.** The  
 117 nanoimitator was resuspended in PBS at pH 7.4 or pH 6.0 respectively, and was  
 118 incubated with or without H<sub>2</sub>O<sub>2</sub> (0.1 mM). Data are presented as the mean  $\pm$  s.d. ( $n = 3$   
 119 independent experiments).  $**P < 0.01$ . NS, not significant.

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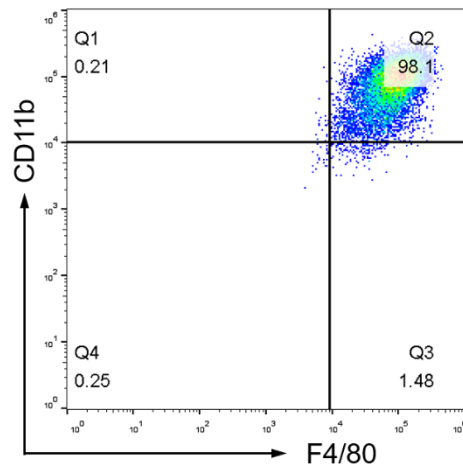
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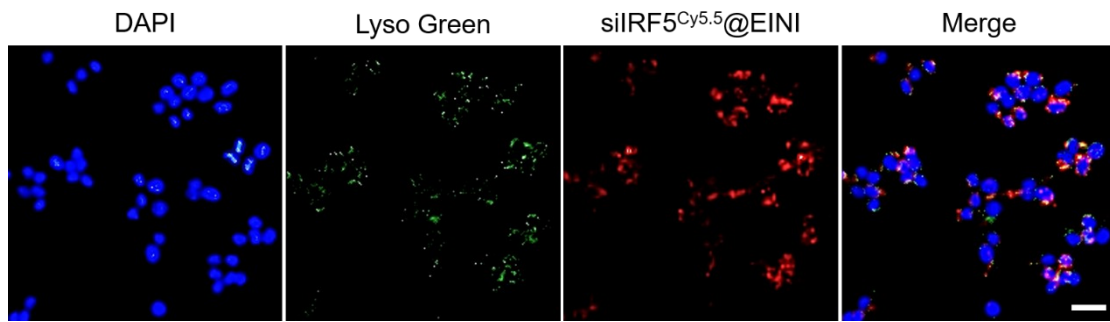
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149 **Supplementary Figure 5. The expression levels of CD11b and F4/80 in BMDMs**  
150 **analyzed by flow cytometry.**

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

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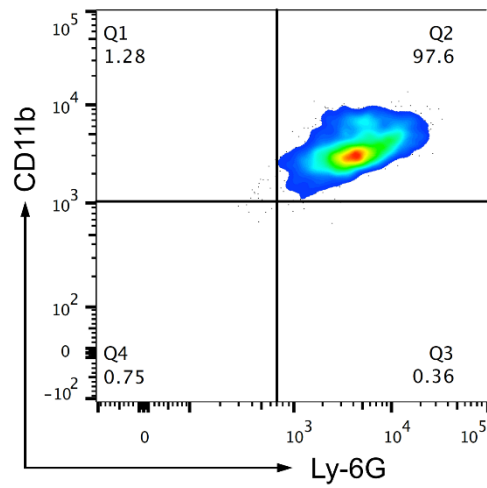
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216 **Supplementary Figure 7. Flow cytometric analysis of the purity of neutrophils**  
217 **doubly stained with FITC-conjugated Ly-6G and PerCP-Cy5.5-conjugated**  
218 **CD11b antibodies.**

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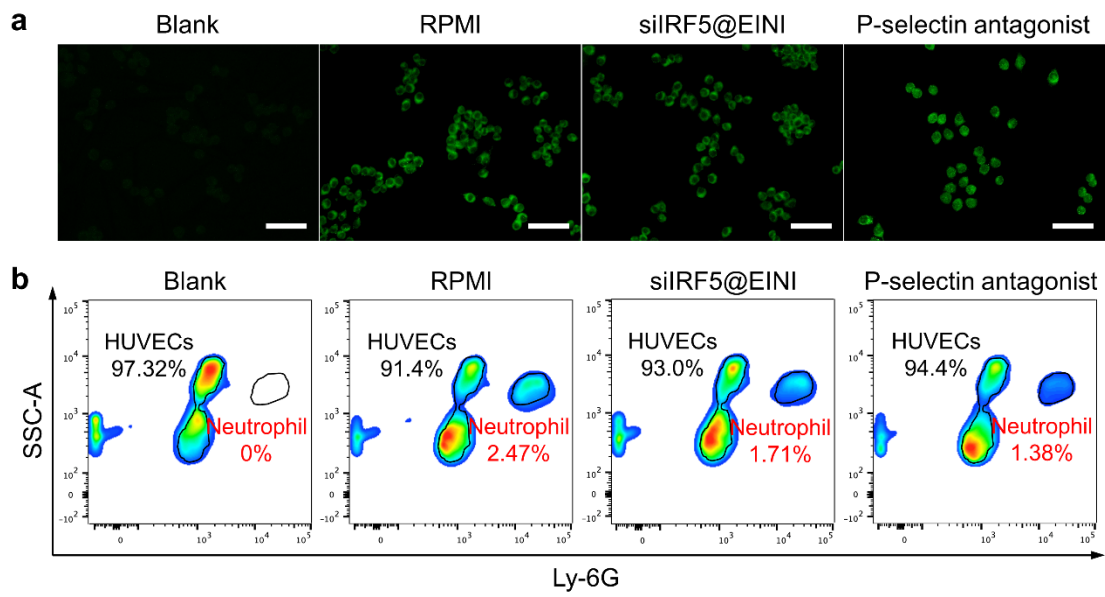
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248 **Supplementary Figure 8. Effective intervention by nanoimitator on inflammatory**  
249 **neutrophils. a**, Evaluation of neutrophil adhesion to a HUVECs monolayer after  
250 incubation with nanoimitator. Scale bars, 50 nm. **b**, FACS analysis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

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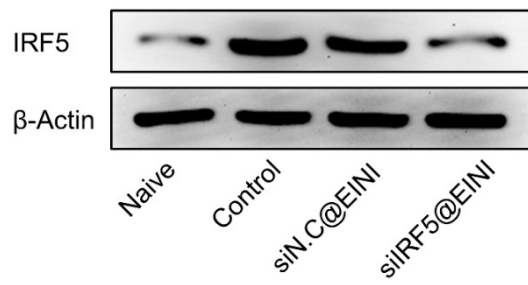
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275 **Supplementary Figure 9. IRF5 expression in macrophages treated with different**  
276 **formulations, detected by western blot.**

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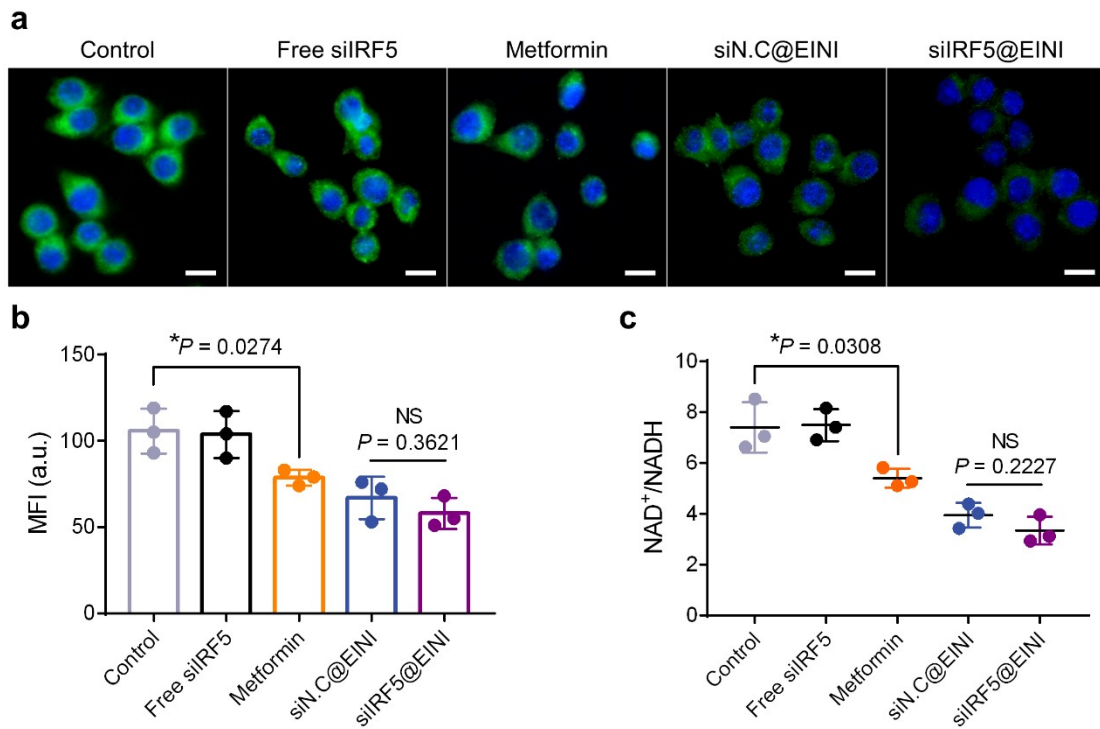
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312 **Supplementary Figure 10. Metformin reprogramming mitochondrial metabolism**  
 313 **in macrophages, which act as mitochondrial complex I (CI) inhibitor directly**  
 314 **inhibit CI-derived ROS. a**, Fluorescence images and the quantification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

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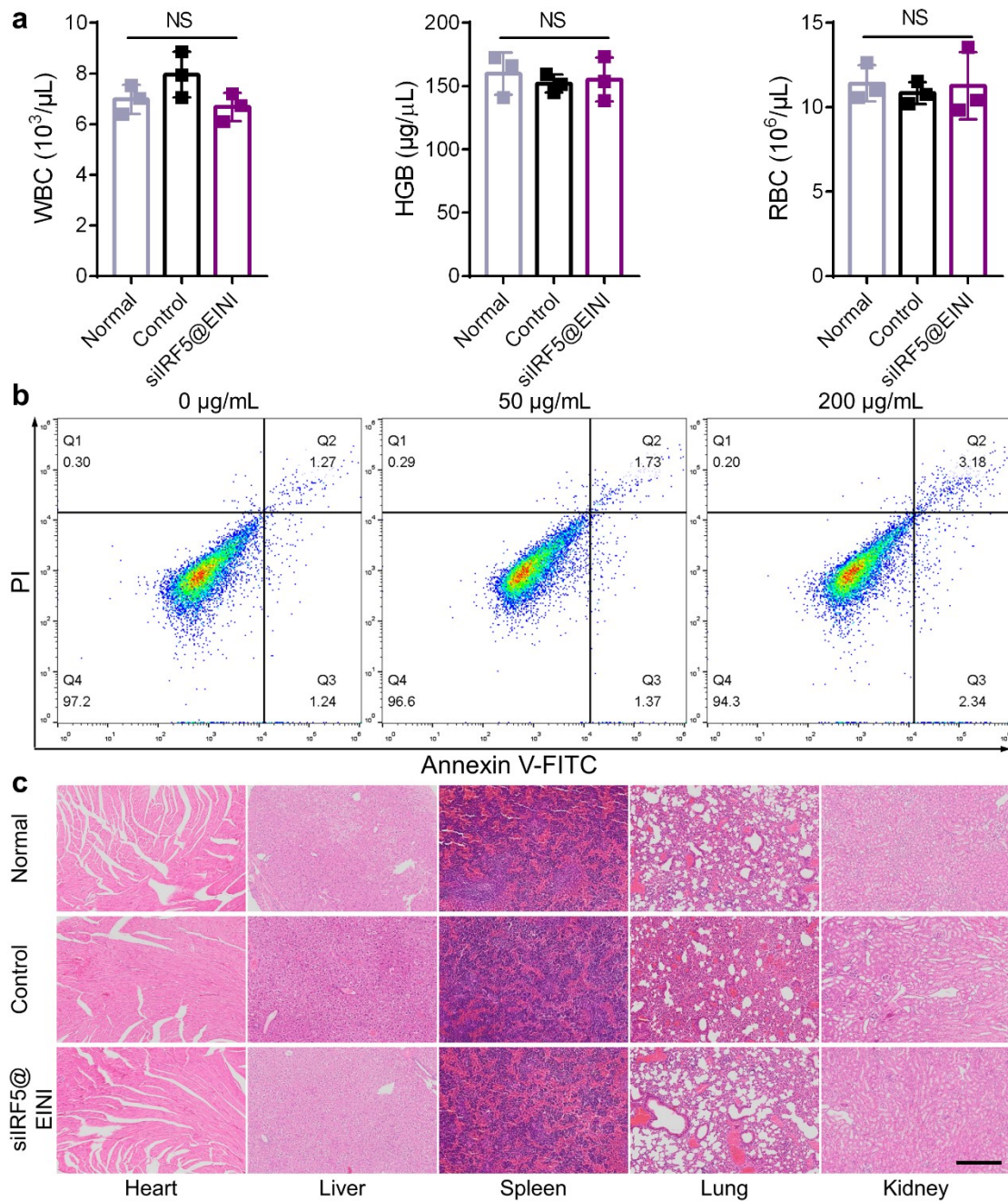
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334 **Supplementary Figure 11. Systemic toxicity evaluation of siIRF5@EINI.** a, During

335 the experimental cycle, mice were followed up to sacrifice on day 60, the change of

336 white blood cell (WBC), hemoglobin (HGB) and red blood cell (RBC) were measured.

337 Data are presented as the mean  $\pm$  s.d. ( $n = 3$  independent experiments). NS, not

338 significant. b, Apoptosis of T cells extracted from the spleens of mice that received i.v.

339 injections of siIRF5@EINI during the experimental cycle. Mice injected with PBS

340 were used as a negative control. c, Histological sections of major organs at 60th day.

341 Scale bar, 50  $\mu\text{m}$ . ( $n = 3$  biologically independent animals).

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343 **Supplementary Figure 12. Representative lesions image from macroscopic**  
344 **observation of the hind paws in different treatment groups. Scale bar, 3 mm. (*n* =**  
345 **5 biologically independent animals).**

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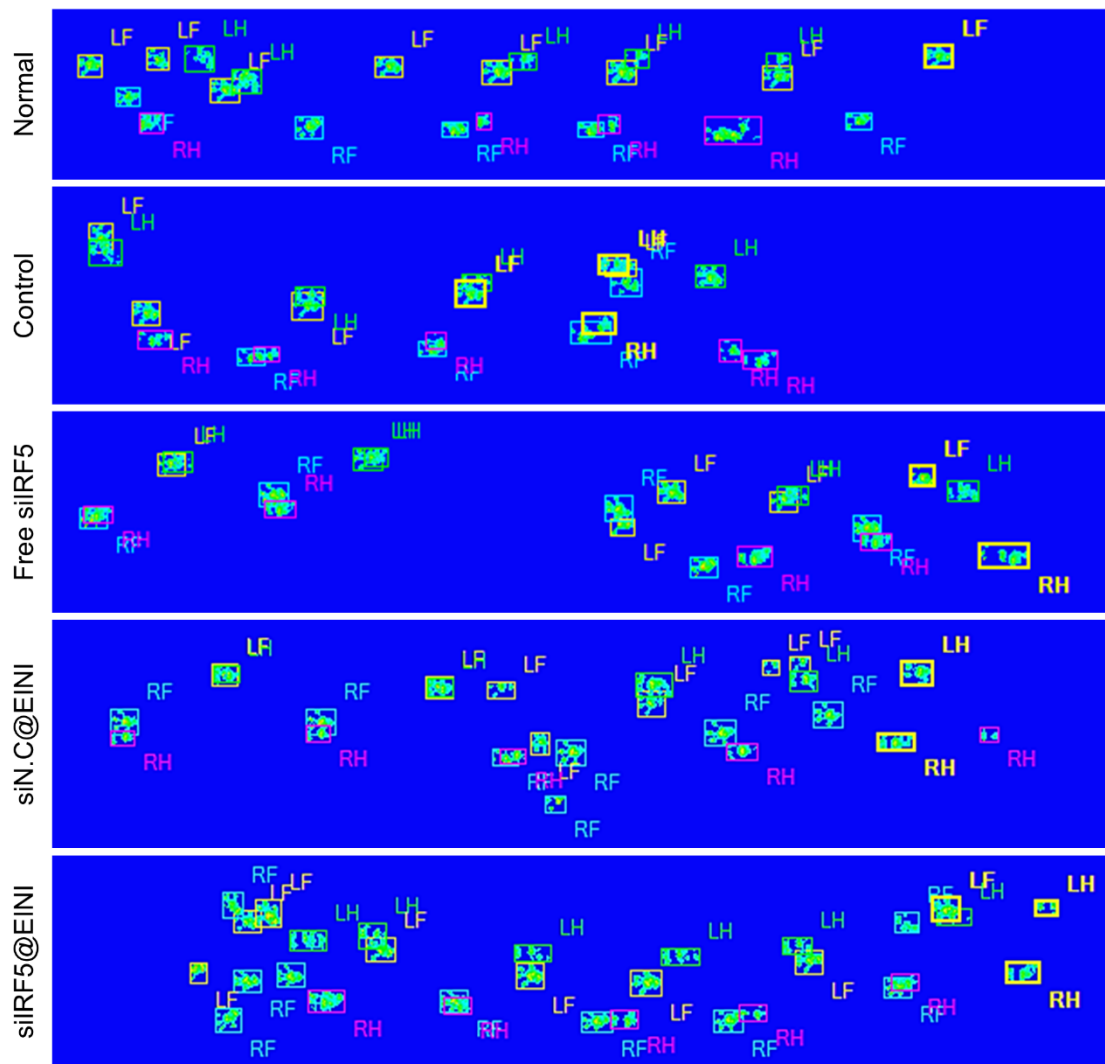
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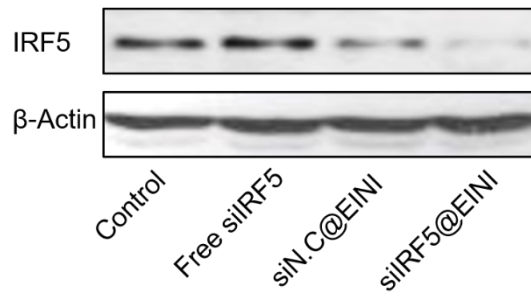
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**Supplementary Figure 13. Representative signal images of the footprint assay.**

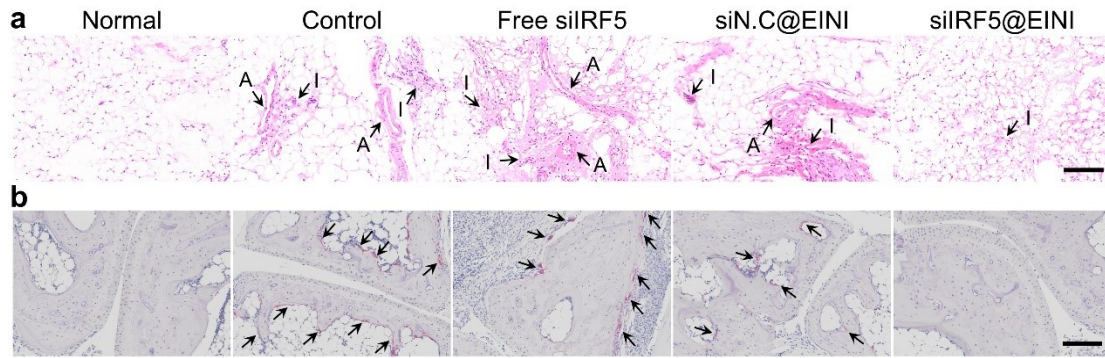
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399 **Supplementary Figure 14. Western blot images of IRF5 protein levels in the**  
400 **synovial macrophages in different formulations treated group.**

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

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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- $\alpha$	Forward	5'-TGGAAGTGGCAGAAGAGGCAC-3'
	Reverse	5'-AGGGTCTGGGCCATAGAAGTGA-3'
Arg1	Forward	5'-TGCTTAGCTCTGTCTGCTTTGC-3'
	Reverse	5'-GAACACGGCAGTGGCTTTAAC-3'
CD206	Forward	5'-GGAGGCTGATTACGAGCAGT-3'
	Reverse	5'-CATAGGAAACGGGAGAACCA-3'
$\beta$ -actin	Forward	5'-CTACAATGAGCTGCGTGTGG-3'
	Reverse	5'-CAGGTCCAGACGCAGGATGGC-3'

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