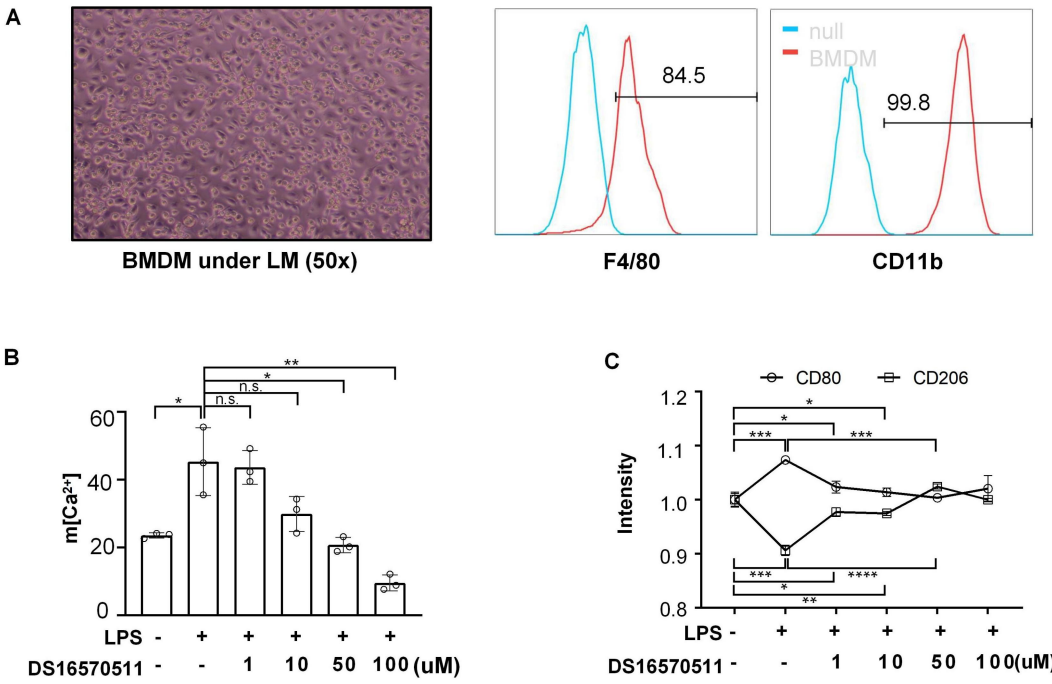
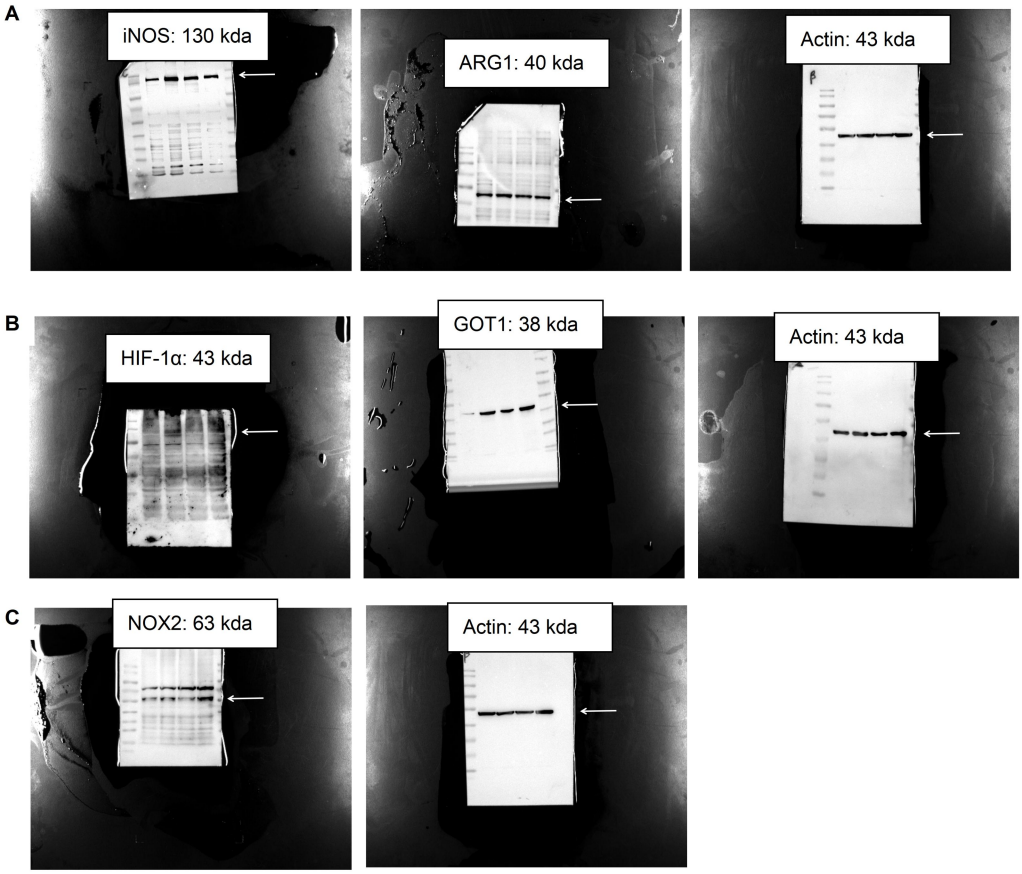
Supplementary Method

PD modeling and administration: C57BL/6 female mice aged 6 weeks were randomly assigned into four groups (n=6). After anesthesia, mice were injected with LPS solution (2 mg/mL) with a dose of 5 μL into the buccal gingiva of the mesial-buccal root of the right first molar with a microsyringe (Envta Technology, Beijing, China) on alternate days for a total of 7 injections. The METP NPs and DS16570511 treatment groups were respectively injected with METP NPs and DS16570511(the same concentration as the KOA injection) along with LPS. Mice were fed normally in SPF animal room after operation (n=8).

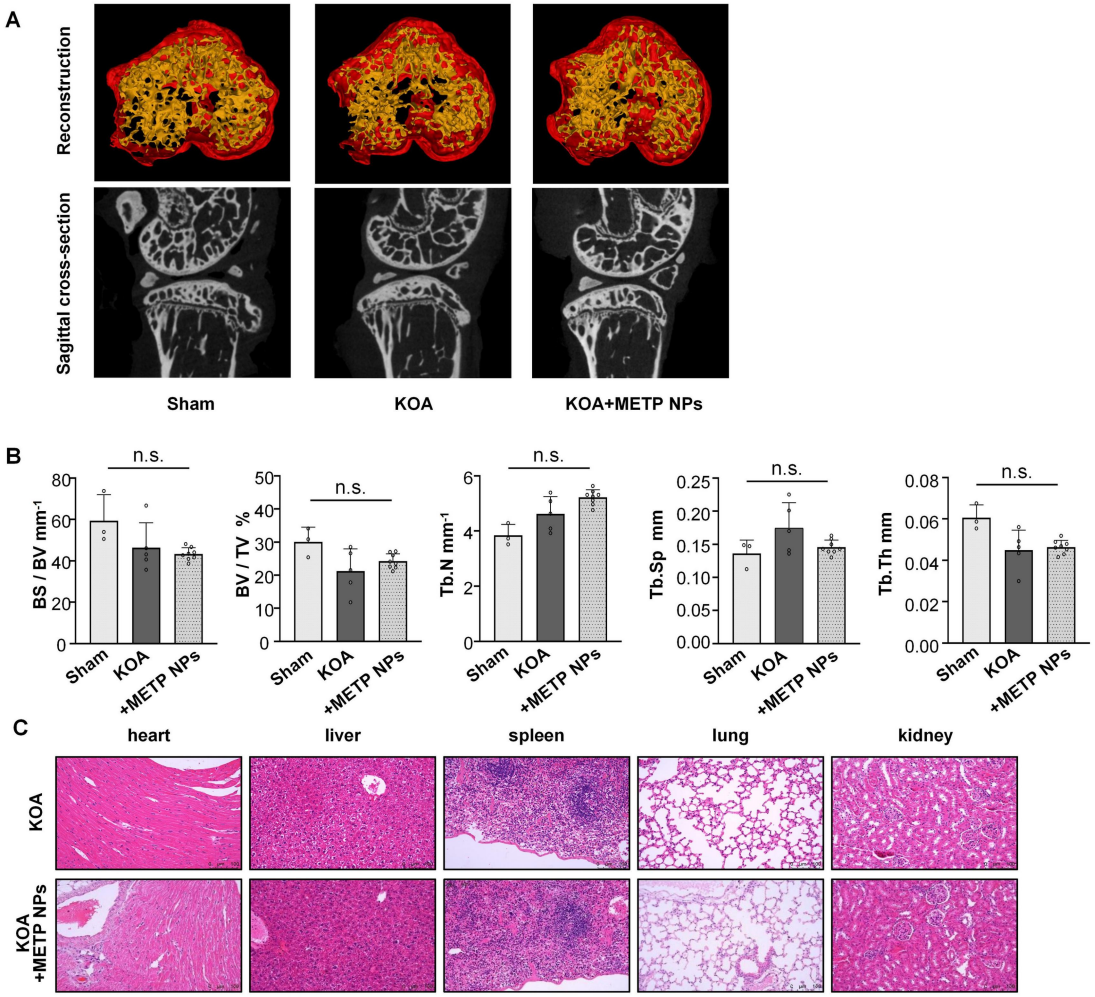
Supplementary Figures



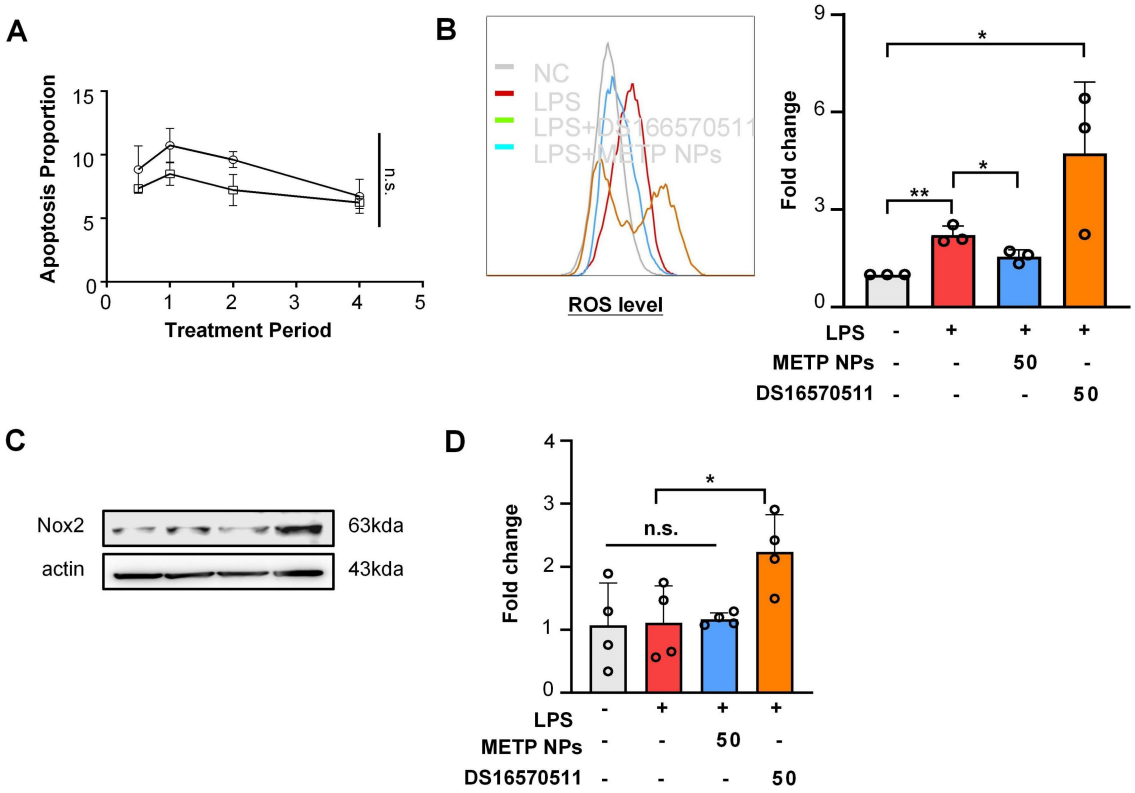
Supplementary Figure 1 (A) BMDM image under light microscope (LM), and BMDM characterization with marker F4/80 and CD11b by flow cytometry; **(B)** Gradient concentration of DS16570511 regulates LPS stimulated BMDM m[Ca^{2+}] level; **(C)** Gradient concentration of DS16570511 regulates expression of surface markers CD80 and C86 in LPS stimulated BMDM, screening the optimal concentration of 50 μM. The concentration of DS16570511 is shown in μM. Data are presented as the mean ± SD. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001; n.s., not significant.



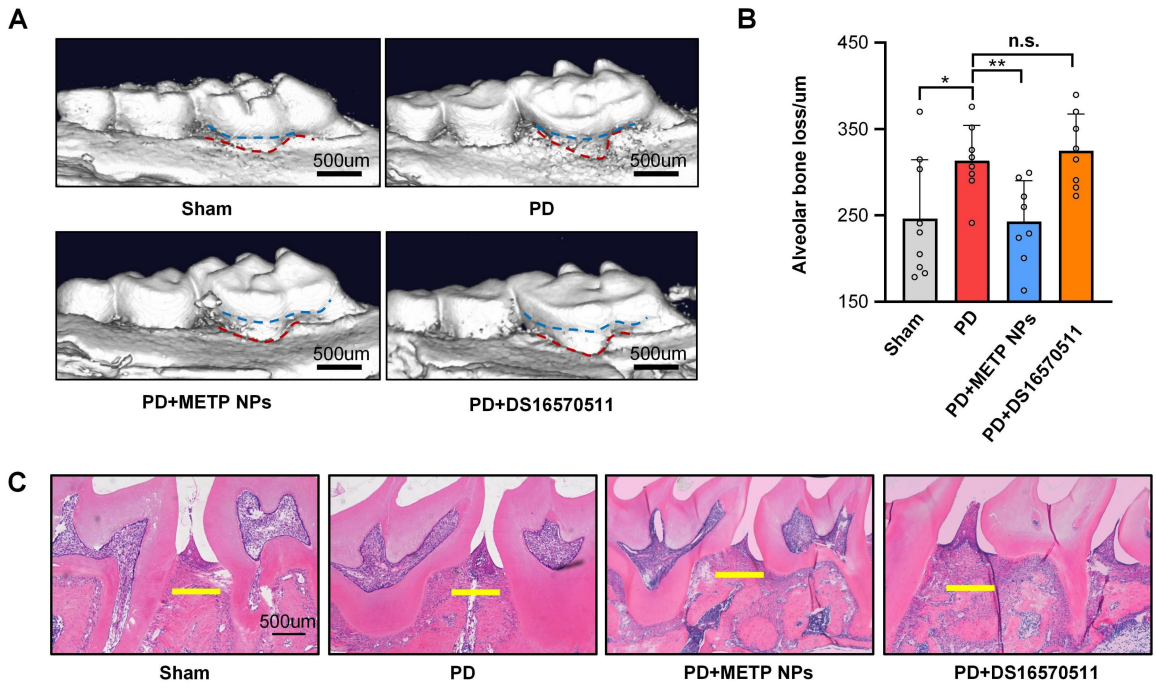
Supplementary figure 2 Uncropped PVDF membrane for **(A)** ARG1, iNOS and Actin corresponding figure 5C; **(B)** GOT1, HIF-1α and Actin corresponding figure 6C; **(C)** NOX2 and Actin corresponding supplementary figure 4C. White arrows marked the target protein bands.



Supplementary Figure 3 (A,B) MicroCT reconstruction, sagittal cross-section and trabecular parameters of mice knee joint; **(C)** Biosafety evaluation of METP NPs with the histological morphology of the heart, liver, spleen, lungs and kidneys *in vivo*. Bone Surface, BS; Bone Volume, BV; Tissue Volume, TV; Trabecular Number, Tb.N; Trabecular Separation/Spacing, Tb.Sp; Trabecular Thickness, Tb.Th; Data are presented as the mean ± SD. n.s., not significant.



Supplementary figure 4 (A) METP NPs cytotoxicity assay on BMDM assessed with cell apoptosis proportion characterized by 7-AAD and Annexin V by flow cytometry; Detection of ROS level in BMDM under LPS stimulation pre-treated with METP NPs or DS16570511 by **(B)** flow cytometry and **(C,D)** western blotting. The concentration of METP NPs is shown in μg/mL, the concentration of DS16570511 is shown in μM. Data are presented as the mean ± SD. *P < 0.05; **P < 0.01; n.s., not significant.



Supplementary figure 5 (A,B) MicroCT reconstruction of alveolar bone in mouse model of periodontitis marking cemento-enamel junction (blue dashed line) and alveolar bone boundary (red dashed line); **(C)** HE staining of sagittal sections of mouse periodontitis tissue marking the alveolar bone loss (yellow line segment). Data are presented as the mean ± SD. *P < 0.05; **P < 0.01; n.s., not significant.

Supplementary Table

Primers information corresponding to Figure 5 E:

Primer	Sequence（5' to 3'）	Bases number	Purification method
m-β-actin-Forward	CATCCGTAAAGACCTCTATGCCAAC	25	ULTRAPAGE
m-β-actin-Reverse	ATGGAGCCACCGATCCACA	19	ULTRAPAGE
m-IL-1β-Forward	CATCAGCACCTCACAAGCAGA	21	ULTRAPAGE
m-IL-1β-Reverse	TGGGGAAGGCATTAGAAACAG	21	ULTRAPAGE
m-IL-6-Forward	GAGCCCACCAAGAACGATAGTC	22	ULTRAPAGE
m-IL-6-Reverse	TTTCTCATTTCCACGATTTCCC	22	ULTRAPAGE
m-TNF-a-Forward	AGTCAACCTCCTCTCTGCCG	20	ULTRAPAGE
m-TNF-a-Reverse	GCAATGACTCCAAAGTAGACCTG	23	ULTRAPAGE
m-NOS2-Forward	TGGAGCGAGTTGTGGATTGTC	21	ULTRAPAGE
m-NOS2-Reverse	GTGAGGGCTTGGCTGAGTGA	20	ULTRAPAGE
m-Cxcl9-Forward	TGAAATCATTGCTACACTGAAG	22	ULTRAPAGE
m-Cxcl9-Reverse	TTTGGCTGATCTTCTTTTCCCA	23	ULTRAPAGE