Supplemental Information

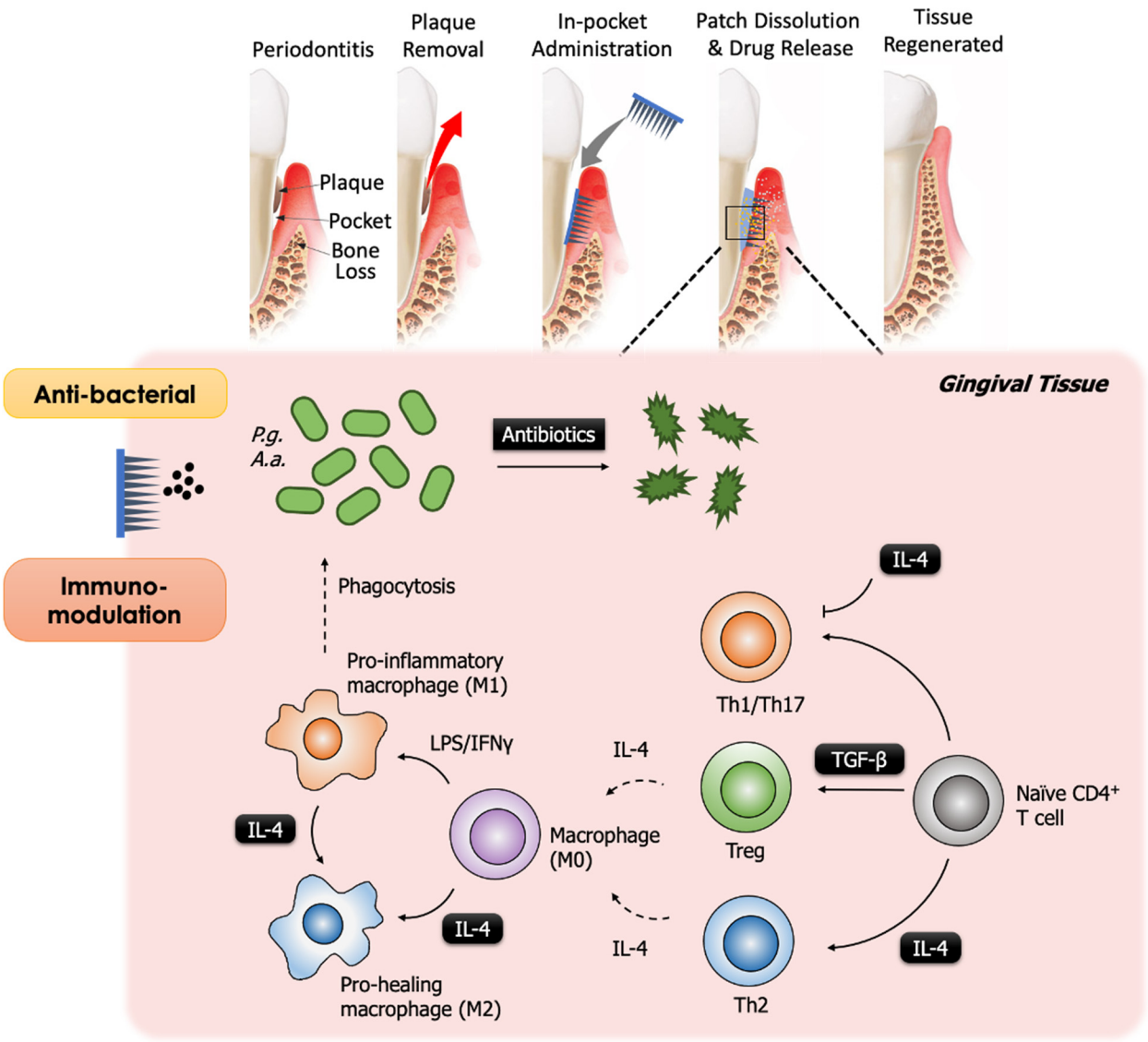


Figure S1. Proposed working mechanism of designed immunotherapeutic periodontal patch. Microneedle (MN) patch is designed to provide transgingival administration of antibiotics and anti-inflammatory cytokines. Following administration, MNs are detached from the base membrane (Gelatin) upon its dissolution, stay in gingival tissue, release their cargos, and finally degrade. The release therapeutics from MNs inside gingival tissue will alter local immune microenvironment to suppress bacterial infection, convert the pro-inflammatory macrophages and T cells into pro-healing phenotypes, and promote periodontium regeneration.

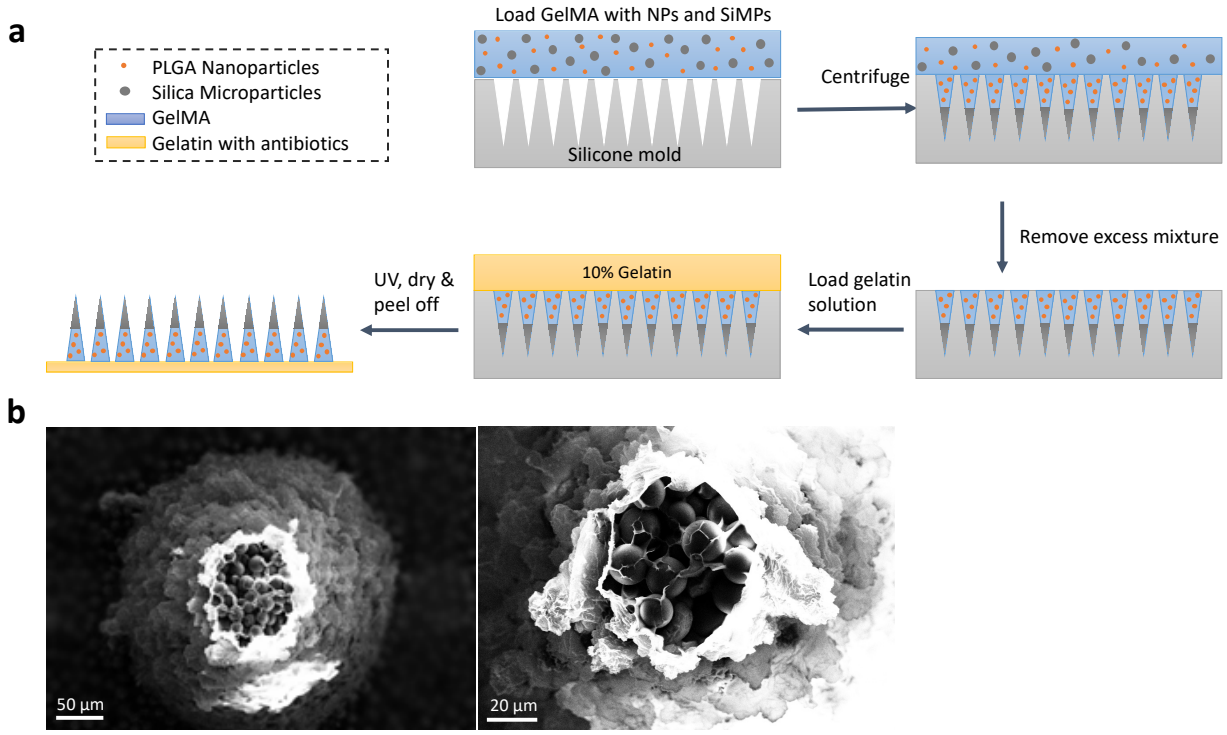


Figure S2. **Fabrication of particles loaded microneedle patch. a,** Schematic representation of the MN patch fabrication procedure. **b,** Encapsulated SiMPs can be seen inside the truncated MNs (from the top of the MNs) at two magnifications.

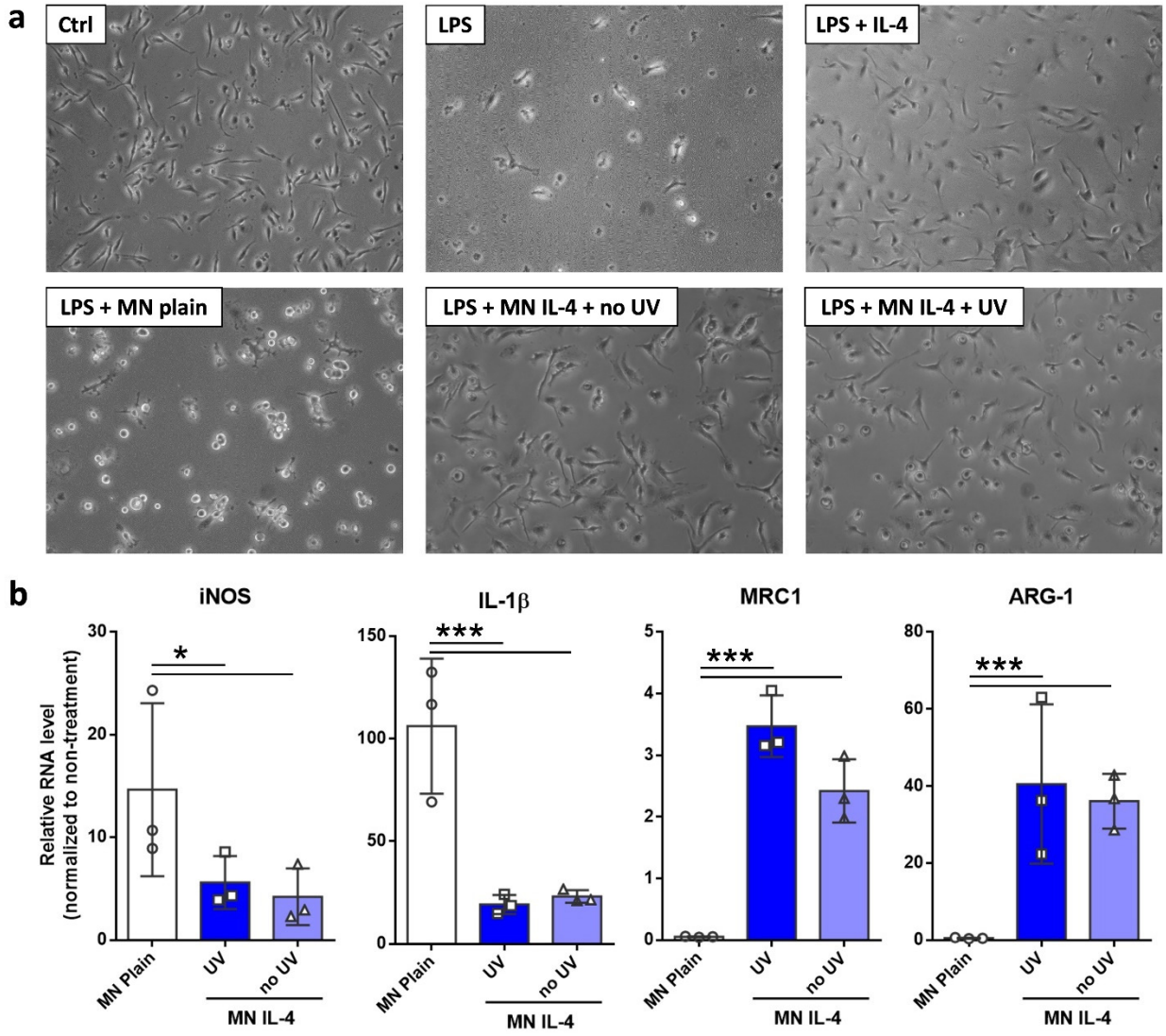


Figure S3. Co-culture of primary bone marrow derived murine macrophages with IL-4-containing MNs with and without UV curing. a, bright field microscopic images of macrophages treated with complete DMEM medium as a control (Ctrl), LPS (10ng/ml lipopolysaccharide), LPS+IL-4 (LPS for 6 hours and then 25ng/ml IL-4), LPS + blank MN (LPS for 6 hours and then placed blank MNs), LPS + IL-4 MN (LPS for 6 hours and then placed IL-4 containing MNs *without* UV crosslink), LPS + IL-4 MN + UV (LPS for 6 hours and then placed IL-4 containing MNs *with* UV crosslink). Images were taken 24 hours after LPS treatment. **b,** Quantitative polymerase chain reaction (qPCR) analysis of mRNA expression of surface markers and cytokines in macrophages in co-culture with MNs with and without UV curing. There is no significant change in the effects of IL-4 macrophage marker expression following the UV curing of the GelMA-based MNs.

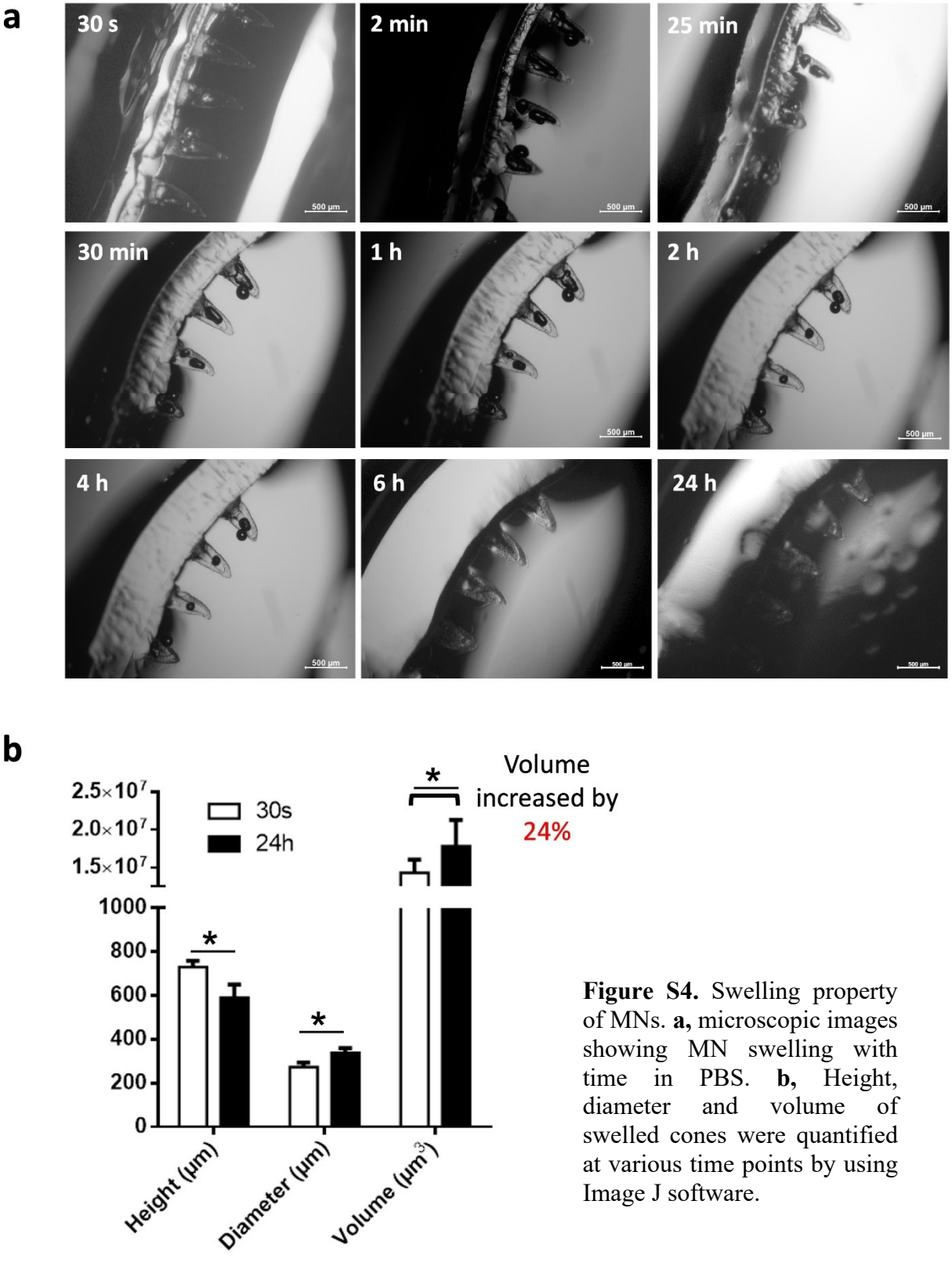


Figure S4. Swelling property of MNs. **a,** microscopic images showing MN swelling with time in PBS. **b,** Height, diameter and volume of swelled cones were quantified at various time points by using Image J software.

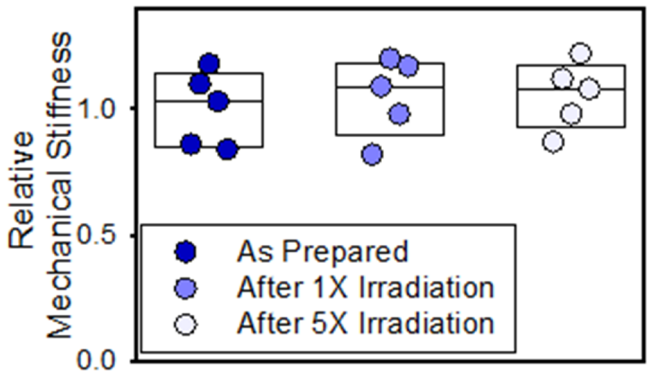


Figure S5. Sterilization with x-ray irradiation. No significant change in mechanical properties of GelMA-based MNs after 1 or 5 times of x-ray irradiation at 25 kGy dose as compared to freshly prepared samples.

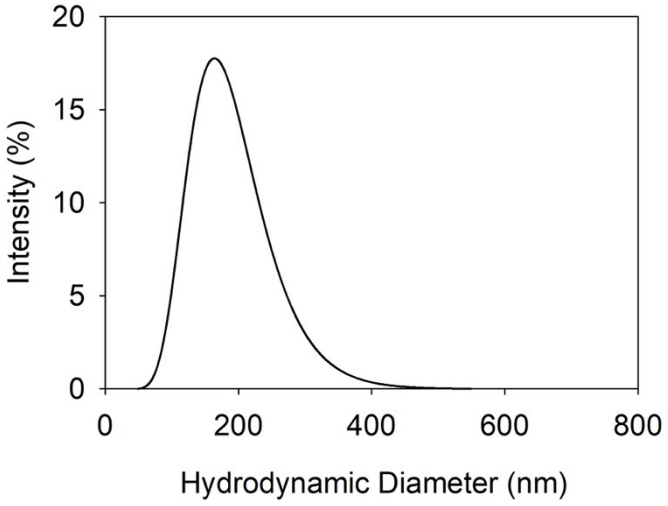
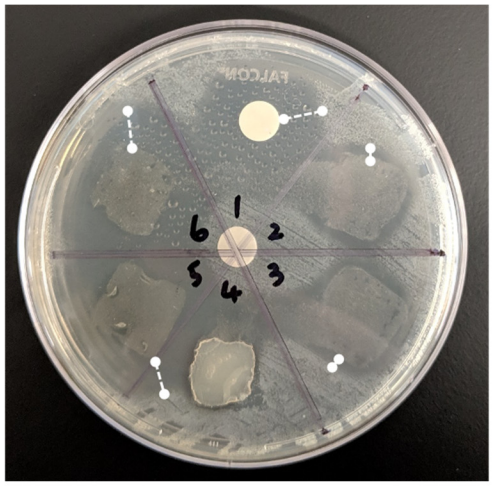


Figure S6. Dynamic light scattering (DLS) was used to measure hydrodynamic diameter of PLGA-tetracycline NPs.



Sample #	Formulation	Inhibition Zone (mm)
1	Tet. Disk (30μg)	8.56
4	Blank MN patch (0μg)	0
2,3	Full Tet. MN patch (30μg)	2.6±0.1
5,6	Full Tet. MN patch (300μg)	13.4±0.1

Figure S7. Antibacterial test. Kirby-Bauer inhibition assay was used to assess antibacterial properties of drug-loaded patches against *E. coli*. Tetracycline disk was prepared by adding tetracycline solution to sterile paper disks and were air-dried in a biosafety cabinet. These disks and MN patches were placed in agar plates inoculated with bacteria at 37°C. The inhibition zones were measured after 48 hours.

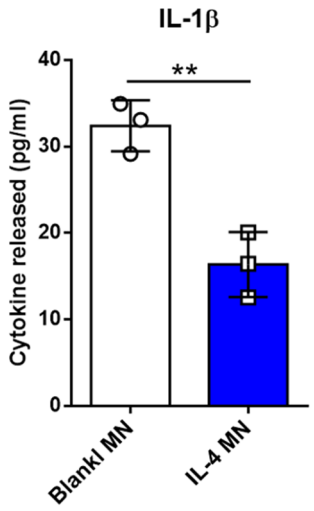


Figure S8. Secreted IL-1β level after treatment of IL-4-loaded MN patches. Change in the level of secreted IL-1β by macrophages after LPS treatment in the presence of blank MN or IL-4-loaded MN patches as assessed by using ELISA (n = 3). The results were analyzed by using one-way ANOVA. Statistical significance is indicated by * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

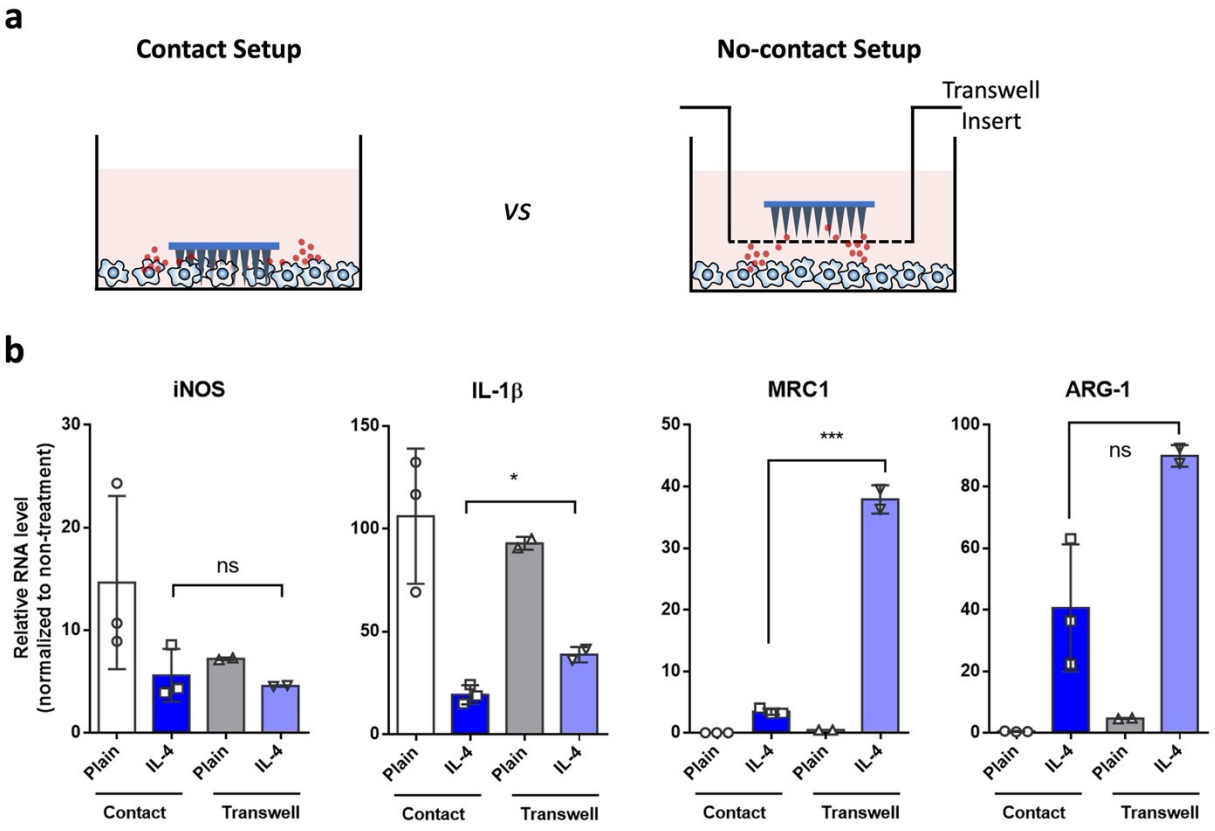


Figure S9. Effects of MN in contact with cells *in vitro*. a, *In vitro* setup for macrophage repolarization experiments. MN patches were placed directly in plates (in contact with cells) or in Transwells (no-contact with cells) and co-cultured with BMDMs for 3 days. **b,** Changes in expression of surface markers and cytokines in macrophages after LPS treatment in the presence of blank MN or IL-4-loaded MN patches as assessed by using qPCR (n = 3). The results were analyzed using one-way ANOVA. Statistical significance is indicated by * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$; ns= not significant.

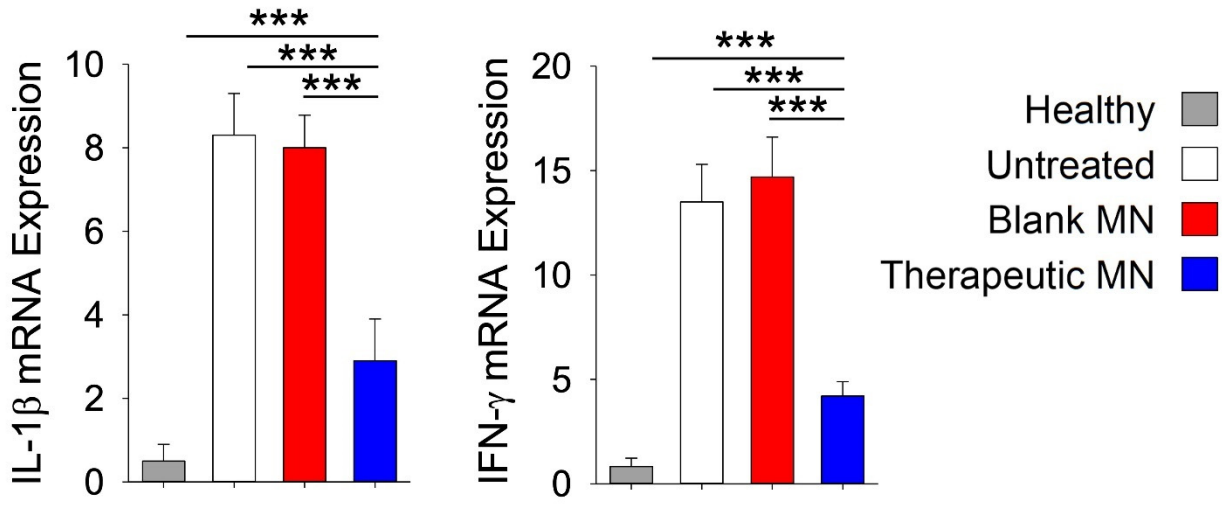


Figure S10. *In vivo* evaluation of the immunomodulatory effects in a rat model of periodontitis. At 8-weeks post MN insertion, buccal and palatal tissues of maxillary molars were isolated and dissociated to assess the inflammatory status of tissue microenvironment. Relative mRNA expression levels of pro-inflammatory (IL-1β and IFN-γ) genes in the periodontal tissue were quantified by qPCR. Healthy: healthy rats; Untreated: untreated periodontitis; Blank Patch: MN patches without any therapeutic cargo; Therapeutic Patch: MN patches containing both tetracycline- and cytokines-loaded particles. The presented data are expressed as mean ± SD (n= 5). The results were analyzed by using one-way ANOVA with post-hoc analysis. Statistical significance is indicated by * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.