

Ultrasound-Driven Regulation of Catalysis–Immunity via an In Situ-Doped Sonocatalyst Coating for Infectious Bone Defect Repair

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INTRODUCTION: Infectious bone defects pose a persistent challenge in orthopedic surgery due to biofilm-associated antibiotic resistance, leading to chronic infection and implant failure. Sonocatalytic therapy (SCT) offers a “drug-free” antibacterial strategy through ultrasound-activated generation of reactive species. Among these, nitric oxide (NO) has emerged as a critical signaling molecule generated via ultrasound-driven catalytic reduction of nitrate (NO_3^-), which not only disrupts bacterial biofilms but also interferes with bacterial metabolism without inducing resistance. However, persistent inflammation and oxidative stress after infection clearance often trigger cellular senescence and promote the senescence-associated secretory phenotype (SASP), which exacerbates tissue inflammation and impairs bone regeneration. We hypothesize that a microenvironment-responsive sonocatalytic platform capable of switching from NO-mediated antibacterial activity to spontaneous ROS scavenging-mediated anti-senescence regulation could simultaneously eradicate infection and rejuvenate osteoimmune microenvironments. To validate this hypothesis, we engineered a 3D-printed polyetherketoneketone (PEKK) scaffold coated with a defect-rich Ru-doped LaMnO_3 sonosensitizer (Ru–LMO/PEKK) designed to dynamically regulate infection and immunosenescence.

METHODS: Ru–LMO catalysts were synthesized via a solvothermal reductive route and deposited onto PEKK scaffolds by in situ self-assembly. Ultrasound-triggered NO generation and spontaneous ROS scavenging were characterized using electrochemical and fluorescent assays. In vitro experiments assessed antibacterial efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA), modulation of macrophage polarization, oxidative stress, and expression of senescence markers (β -galactosidase, p16, γ H2AX). Density functional theory (DFT) simulations elucidated the pH-dependent NO_3^- reduction pathway, while transcriptomic and metabolomic analyses elucidated antibacterial and immune rejuvenation mechanisms. In vivo studies in rat infected bone defect models (approved by the Institutional Animal Care and Use Committee of West China Hospital, approval No. 20250908002) evaluated infection eradication, inflammatory resolution, and bone regeneration outcomes.

RESULTS SECTION: Ru–LMO/PEKK scaffolds exhibited well-confined Ru nanoclusters homogeneously dispersed within the defect-rich LMO matrix, forming abundant oxygen vacancies that facilitated ultrasound-driven electron transfer. In acidic infectious conditions, Ru–LMO catalyzed NO_3^- reduction to NO, achieving >99% biofilm removal. Under neutral conditions after infection clearance, the catalyst switched to enzyme-mimetic antioxidative activity, which scavenged intracellular ROS and consequently suppressed SASP-associated cytokines, thereby restoring the osteogenic capacity of BMSCs. This redox modulation further promoted M2 macrophage polarization and upregulated osteogenic gene expression. In vivo, Ru–LMO/PEKK scaffolds effectively eradicated MRSA infection and promoted bone regeneration by alleviating cellular senescence and enhancing vascularization within 8 weeks.

DISCUSSION: This study demonstrates that Ru–LMO/PEKK scaffolds provide a sequential “dynamic antibacterial–static regenerative” response driven by infection microenvironment. The redox-switching mechanism couples ultrasound-activated NO release for biofilm eradication with antioxidative and anti-senescence regulation that suppresses SASP and rejuvenates osteogenic function. These findings support our hypothesis that a sonocatalytic platform with environment-responsive dual behavior can simultaneously eliminate infection and promote bone repair.

SIGNIFICANCE/CLINICAL RELEVANCE: The Ru–LMO/PEKK sonocatalytic scaffold offers a novel, drug-free therapeutic strategy that integrates infection eradication, SASP suppression, and immune rejuvenation, providing a promising translational approach for managing infectious bone defects and age-related implant complications.

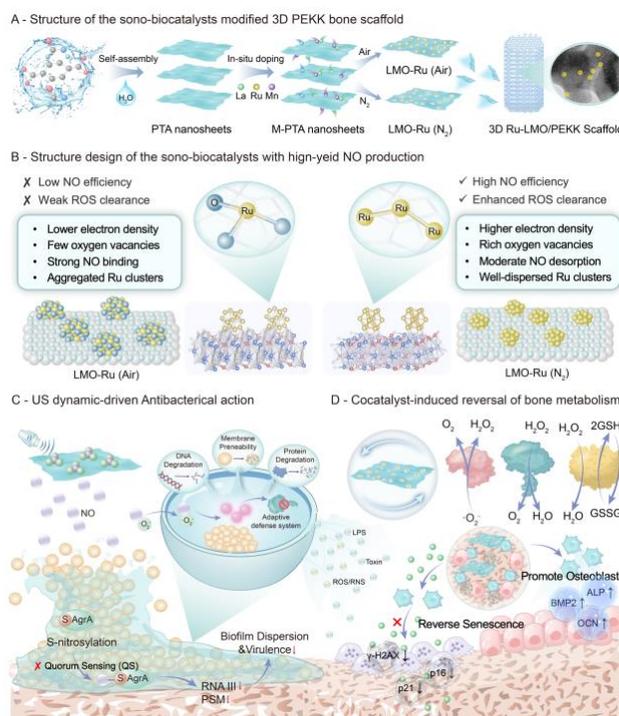


Figure 1. The design and mechanism of the Ru–LMO/PEKK sonocatalytic scaffold for infection eradication and osteoimmune rejuvenation.