



# Graphene oxide/gallium nanoderivative as a multifunctional modulator of osteoblastogenesis and osteoclastogenesis for the synergistic therapy of implant-related bone infection

Yang Yang<sup>a,b,d,\*</sup>, Min Li<sup>c</sup>, Bixia Zhou<sup>a,d</sup>, Xulei Jiang<sup>a,d</sup>, Dou Zhang<sup>b</sup>, Hang Luo<sup>b,\*\*</sup>

<sup>a</sup> Department of Plastic Surgery, Xiangya Hospital, Central South University, Changsha, 410008, China

<sup>b</sup> State Key Laboratory of Powder Metallurgy, Central South University, Changsha, 410083, China

<sup>c</sup> Department of Oncology, Changsha Central Hospital, University of South China, Changsha, 410006, China

<sup>d</sup> National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, 410008, China

## ARTICLE INFO

### Keywords:

Nanocomposites  
Antimicrobial potency  
Implant-associated bone infections  
Osteogenesis  
Osteoclastogenesis

## ABSTRACT

Currently, implant-associated bacterial infections account for most hospital-acquired infections in patients suffering from bone fractures or defects. Poor osseointegration and aggravated osteolysis remain great challenges for the success of implants in infectious scenarios. Consequently, developing an effective surface modification strategy for implants is urgently needed. Here, a novel nanoplateform (GO/Ga) consisting of graphene oxide (GO) and gallium nanoparticles (GaNPs) was reported, followed by investigations of its *in vitro* antibacterial activity and potential bacterium inactivation mechanisms, cytocompatibility and regulatory actions on osteoblastogenesis and osteoclastogenesis. In addition, the possible molecular mechanisms underlying the regulatory effects of GO/Ga nanocomposites on osteoblast differentiation and osteoclast formation were clarified. Moreover, an *in vivo* infectious microenvironment was established in a rat model of implant-related femoral osteomyelitis to determine the therapeutic efficacy and biosafety of GO/Ga nanocomposites. Our results indicate that GO/Ga nanocomposites with excellent antibacterial potency have evident osteogenic potential and inhibitory effects on osteoclast differentiation by modulating the BMP/Smad, MAPK and NF- $\kappa$ B signaling pathways. The *in vivo* experiments revealed that the administration of GO/Ga nanocomposites significantly inhibited bone infections, reduced osteolysis, promoted osseointegration located in implant-bone interfaces, and resulted in satisfactory biocompatibility. In summary, this synergistic therapeutic system could accelerate the bone healing process in implant-associated infections and can significantly guide the future surface modification of implants used in bacteria-infected environments.

## 1. Introduction

Despite significantly improved technology of medical sterilization and asepsis, bacterial infections and bone osteolysis caused by infection remain great challenges in repairing severe bone fractures or defects in orthopedic or plastic surgeries [1]. Bacterial invasion characterized by colonization or even biofilm formation in wounded regions could unavoidably contribute to implant failure, resulting in substantial costs to society and patient morbidity [2,3]. Conventional implants without antimicrobial properties are vulnerable to biocontamination, which may provide a foothold for the rapid growth of adhered bacterial cells [2].

More importantly, continuous infections surrounding implants most frequently cause osteomyelitis. Implant-related osteomyelitis is mainly generated from *S. aureus* or *S. epidermidis* infections and is characterized by serious inflammation of bone and bone marrow [4,5]. Osteomyelitis is anticipated to produce devastating complications, such as prosthetic loosening and bone necrosis, during the rehabilitation of patients with bone injury, especially diabetic patients [6]. Considering the substantial financial burden and health concerns originating from implant-associated osteomyelitis, the development of anti-infection strategies for clinically used implants in patients at a high risk of bacterial invasion is urgently needed.

Peer review under responsibility of KeAi Communications Co., Ltd.

\* Corresponding author. Department of Plastic Surgery, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, 410008, Hunan, PR China.

\*\* Corresponding author. State Key Laboratory of Powder Metallurgy, Central South University, 932 South Lushan Road, Changsha, 410083, Hunan, China.

E-mail addresses: [forever\\_yang@csu.edu.cn](mailto:forever_yang@csu.edu.cn) (Y. Yang), [hangluo@csu.edu.cn](mailto:hangluo@csu.edu.cn) (H. Luo).

<https://doi.org/10.1016/j.bioactmat.2022.07.015>

Received 8 April 2022; Received in revised form 24 June 2022; Accepted 12 July 2022

Available online 21 July 2022

2452-199X/© 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).