
بسم الله الرحمن الرحیم

In the name of God

Department of Bacteriology and Virology

School of Medicine

Ph.D Seminar

Title:

Sonodynamic Therapy for Bacterial Infection

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1 Introduction

- Bacterial infection has posed an enormous threat to public health and the economy for centuries.
- The advent of antibiotics has somewhat slowed down the progression of bacterial infections.
- The evolution of bacteria, drug-resistant bacteria could produce related enzymes to restrict the antibiotics from entering cells.
- The alter membrane permeability, or develop drug efflux pumps protecting themselves from the antibacterial agents.

- Some antibiotics-free and non-invasive approaches have been developed, such as Photodynamic therapy (PDT) and Photothermal therapy (PTT), and Sonodynamic therapy (SDT).

- PTT used electromagnetic radiation (infrared wavelengths) for the treatment of various medical conditions a photosensitizer is excited with specific band light.

- This activation brings the photosensitizer to an excited state where it then releases vibrational energy (heat), which is what kills the targeted cells.

- Photodynamic therapy(PDT) is a form of phototherapy involving light and a photosensitizer used in conjunction with molecular oxygen to leading cell death.

- That light at a specific wavelength (600–800 nm) activates a photosensitizer in the target tissue, which in turn transmits the received energy to **oxygen molecules** in an excited state in the tissue, thereby inducing the generation of reactive oxygen species (ROS).

- Sonodynamic therapy (SDT) shares similarities in mechanism with PDT, but it uses ultrasound(US) rather than light energy for activate sonosensitizer(SS).

- Gram-positive bacteria are more sensitive to SDT because the thick but porous peptidoglycan layer facilitates the entry of SS.

- Gram-negative bacteria due to their complex cell wall structure, SS can only bind to the cell wall.

- That negatively charged phosphate groups on the outer membrane of gram-negative bacteria facilitate the binding of SS.

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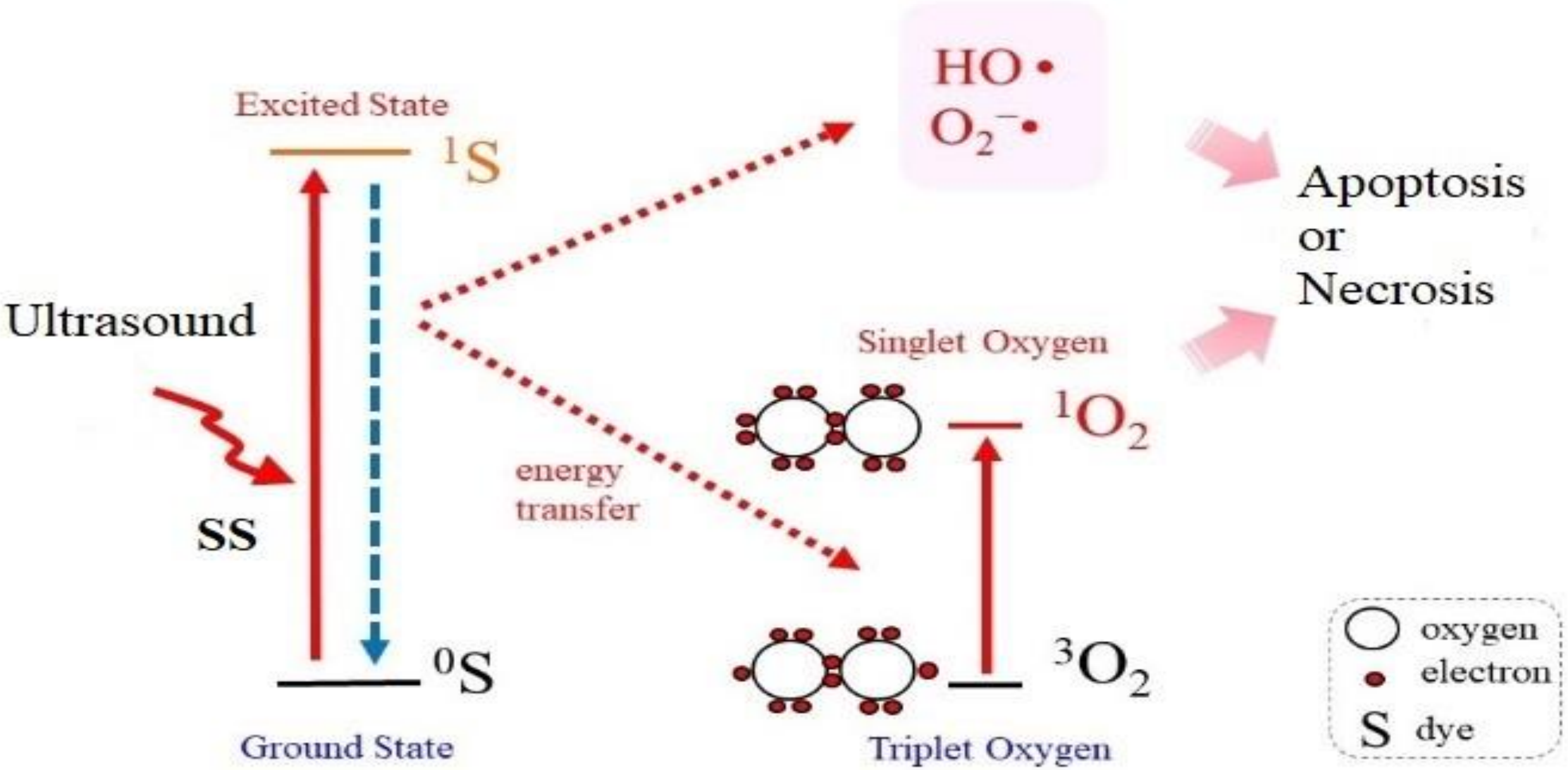
Sonodynamic therapy (SDT)

Sonodynamic therapy (SDT)

- The term ‘‘Sonodynamic therapy” is often used for all non-thermally related therapeutic.
- Sonodynamic therapy (SDT) is a modality of cancer treatment that about 30 years since its emergence.
- SDT is conceptually similar to photodynamic therapy, When a SS is exposed to US, the SS in the ground state (0_S) to that in the excited state (1_S).
- On returning to the ground state 0_S, a part of the released energy can be transferred to oxygen molecules (O_2^3), which results in the electron spin state being altered.
- The received energy to (O_2^3) in the tissue transmit, thereby inducing the generation of ROS and leading to cell damage and even death.



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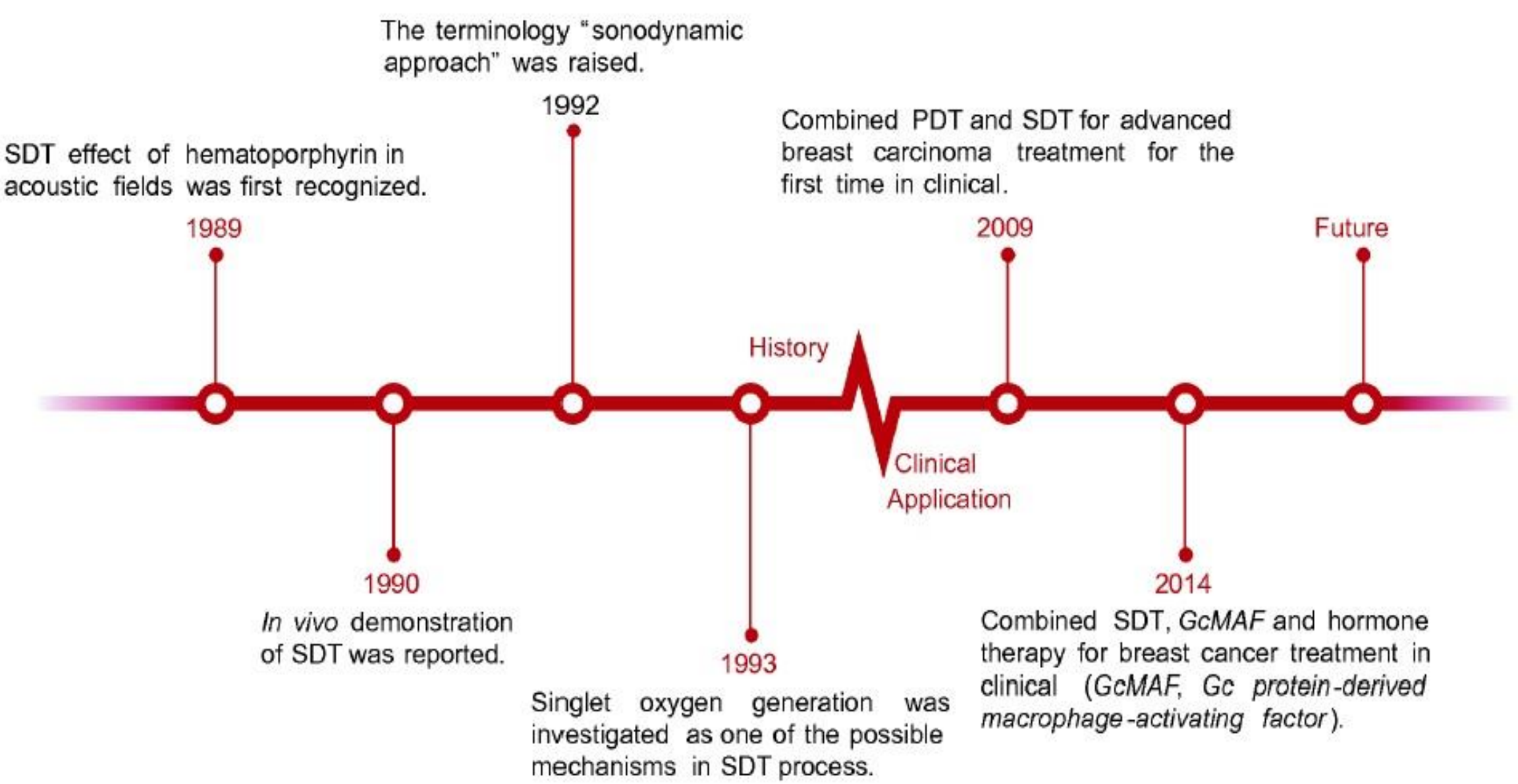

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Ultrasound (US)

- Ultrasound (US) is mechanical waves with periodic vibration of particles in a continuous elastic medium with a frequency equal to or greater than 20kHz.
- The mechanisms of ultrasound action on biological material can be divided into thermal and nonthermal.
- Thermal effects occur when US energy is absorbed and transformed to heat.
- Non-thermal mechanisms can be classified as cavitational and shear stress, Shear stress includes the radiation pressure, radiation force, and acoustic streaming.

Sonosensitizers(SS)

- SS are considered as the most pivotal elements used for the mechanisms of cell apoptosis or necrosis induced by SDT.
- SS are classified into organic-small molecule and inorganic SS.
- **The organic SS** are small fat-soluble molecules such as porphyrin derivatives that good biosafety.
- The organic SS strong hydrophobicity and short circulation time in the physiological environment which limit their further application.

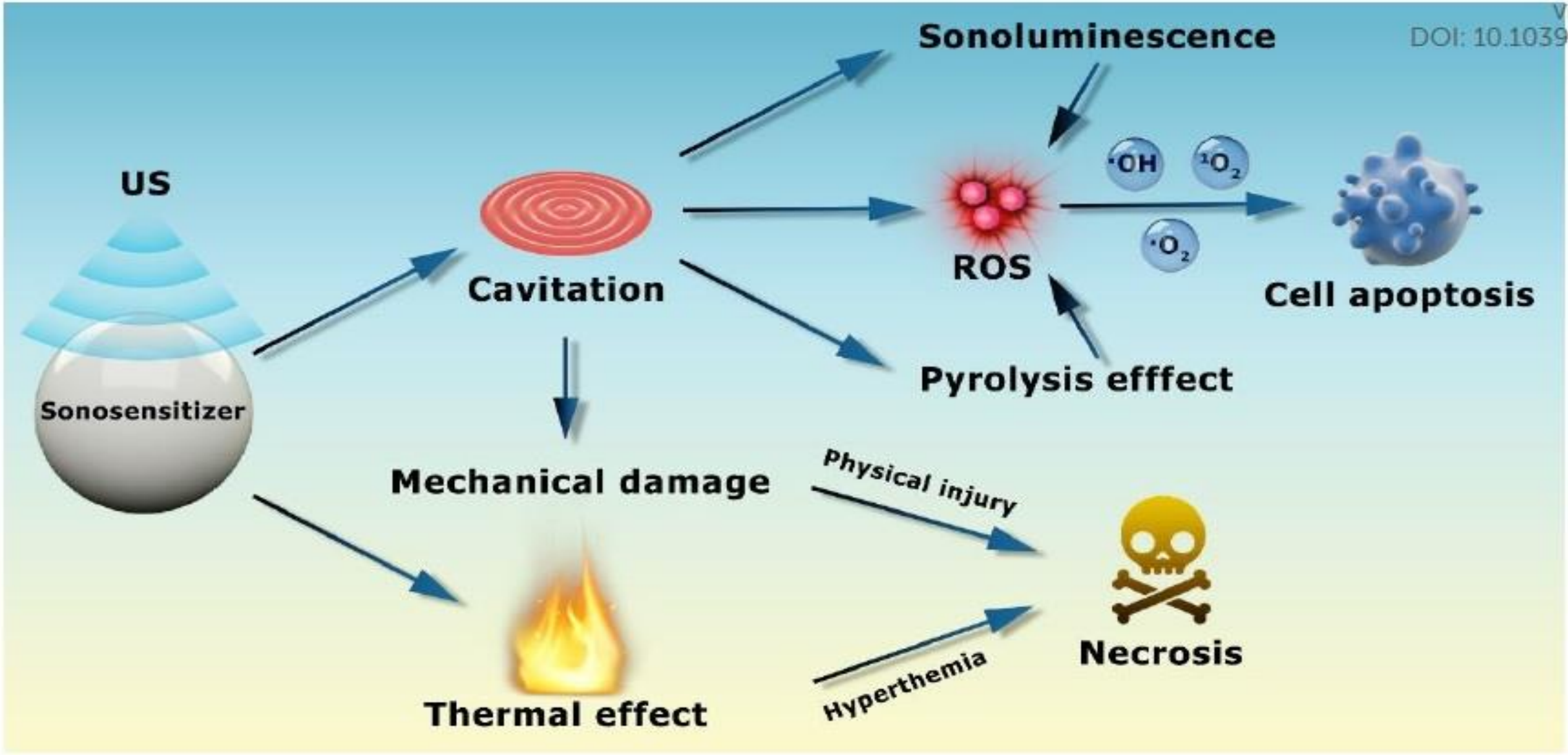
- **The inorganic SS** have better stability, low phototoxicity, and unique composition, structure, and accompanying versatility making them more circulating in the blood.

- Titanium dioxide (TiO_2), as a typical semiconductor.

3 Mechanisms of sonodynamic therapy(SDT)

Mechanisms of sonodynamic therapy(SDT)

- The possible mechanisms SDT including Mechanical damages, Thermal damage and Ultrasonic cavitation effect, generation of ROS, OH and O_2^1 and US-induced direct cell apoptosis.
- When US waves interact with SS in a liquid environment, a phenomenon called Ultrasonic cavitation will occur.
- **Ultrasonic cavitation** is a dynamic phenomenon of US, producing bubbles that are excited.
- Depending on the US intensity, cavitation being divided in non-inertial cavitation (stable cavitation), and inertial cavitation.



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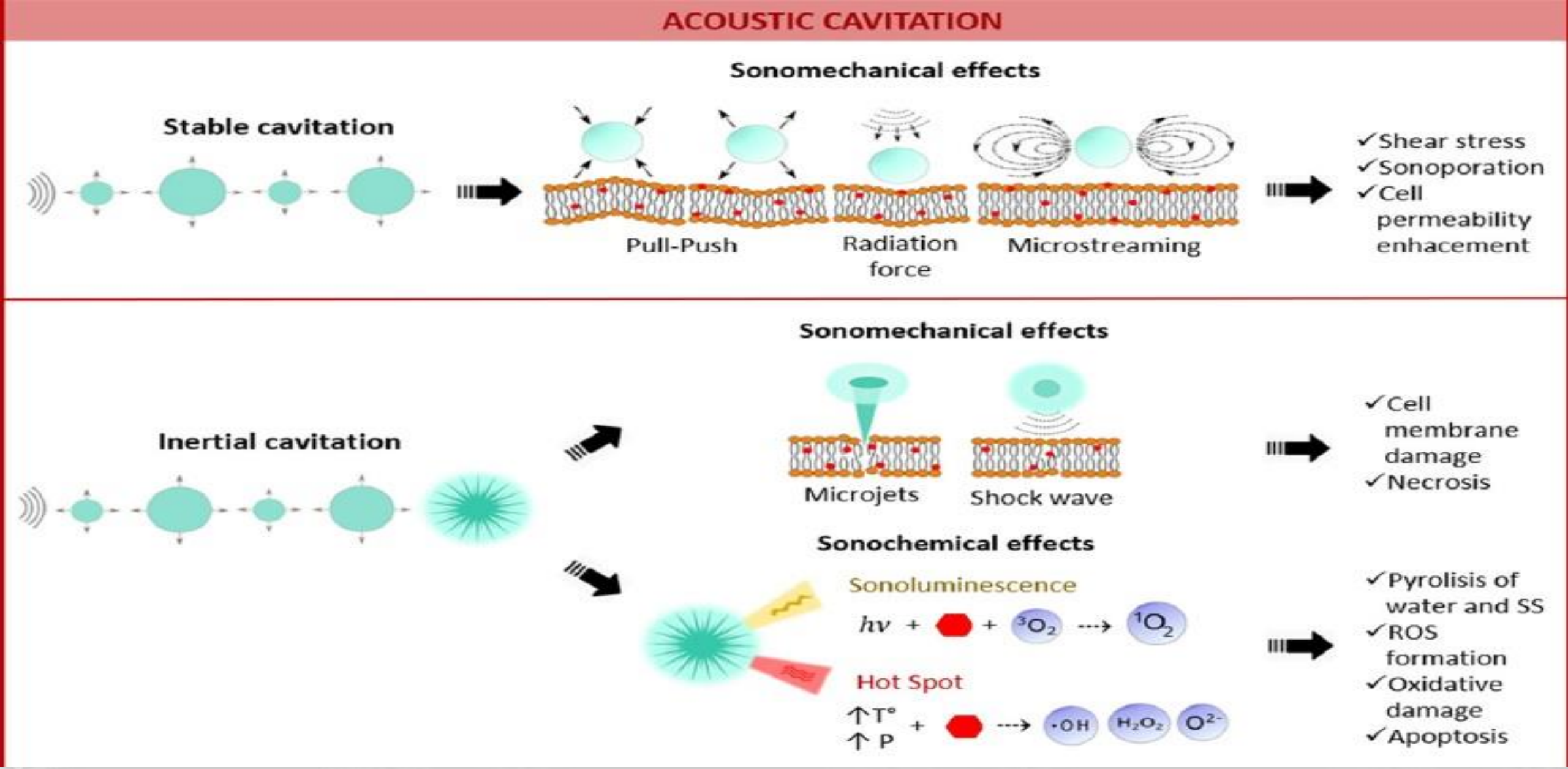

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Review of The Studies

Materials & Design 240 (2024) 112857

Contents lists available at ScienceDirect

Materials & Design

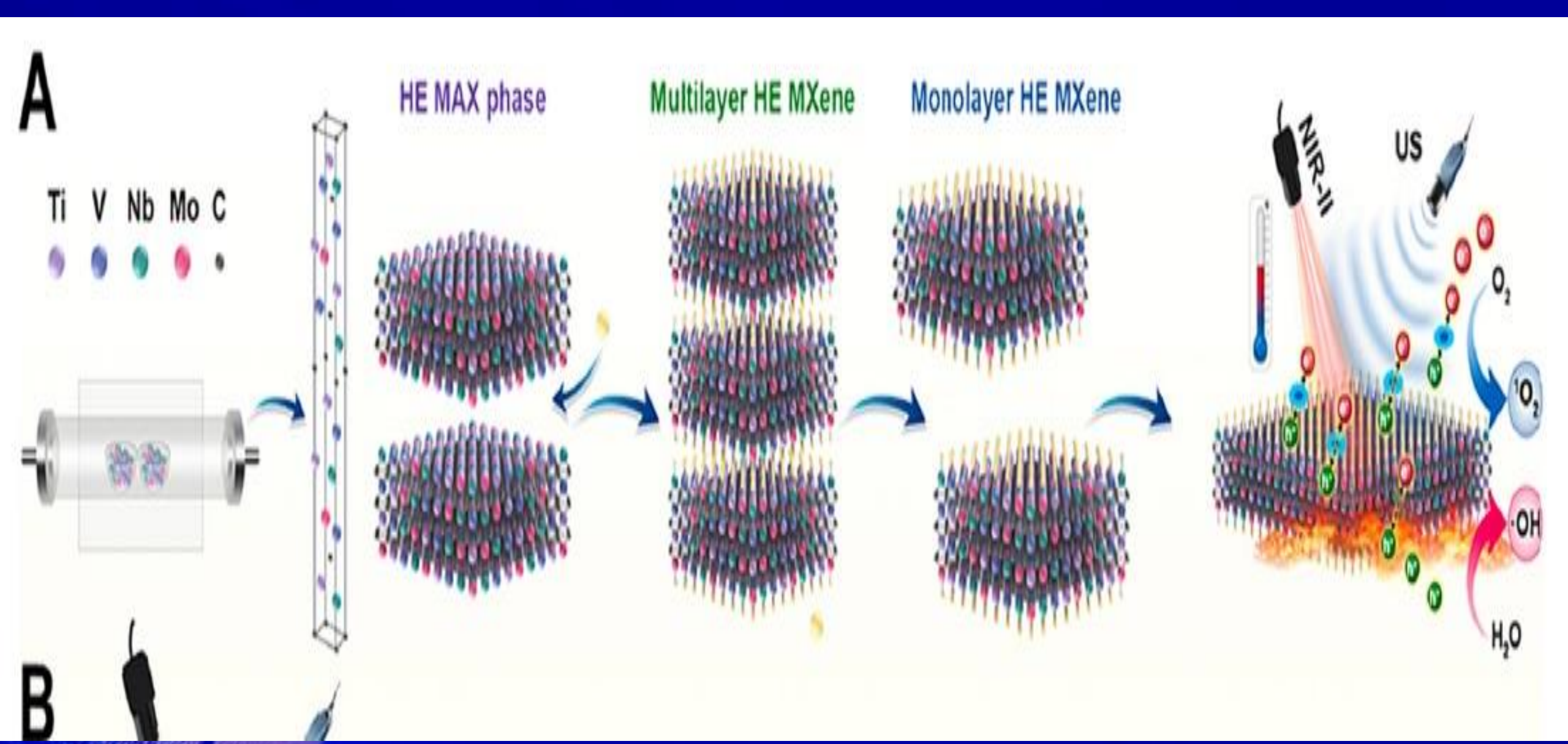
journal homepage: www.elsevier.com/locate/matdes

NIR-II-amplify high-entropy MXene-based sonosensitizer as sonodynamic therapy promotes methicillin-resistant *Staphylococcus aureus*–Infected wound healing

Wei Song [a,1,*], Danyan Wang [c,1], Shuai Xiao [a,1], Xiaojun He [b], Wei Xiong [d,*], Jianliang Shen [b,c,*]

- We developed a high-entropy MXene, after undergoing a single-phase purity, exfoliation, and delamination to give TVNMC MXene for an efficient photothermal enhanced sonodynamic antibacterial therapy.

- Exposure to US and NIR-II invoked rapid conversion of both ultrasound and light for the generation of enormous amounts of toxic ROS for MRSA elimination.



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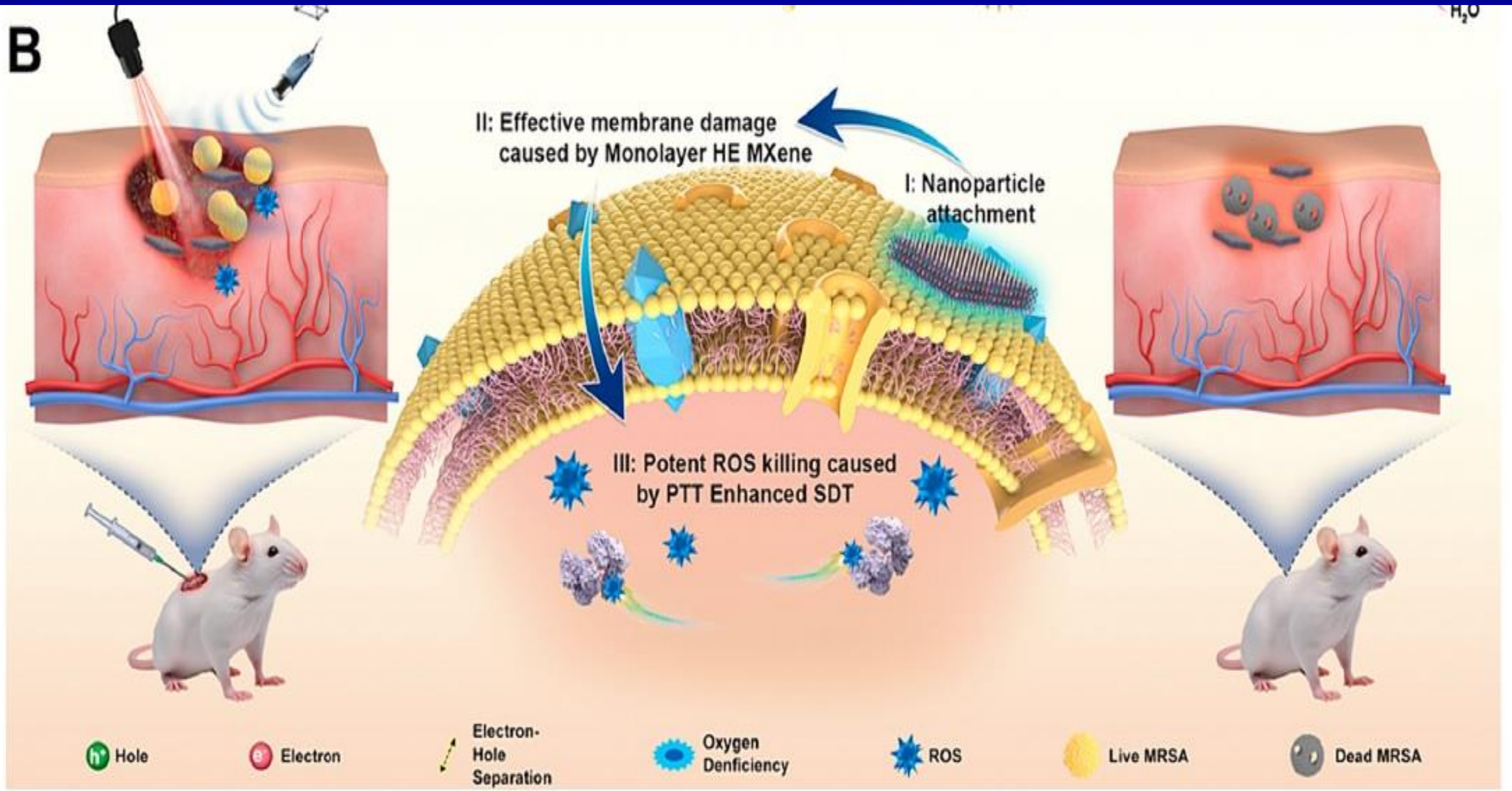
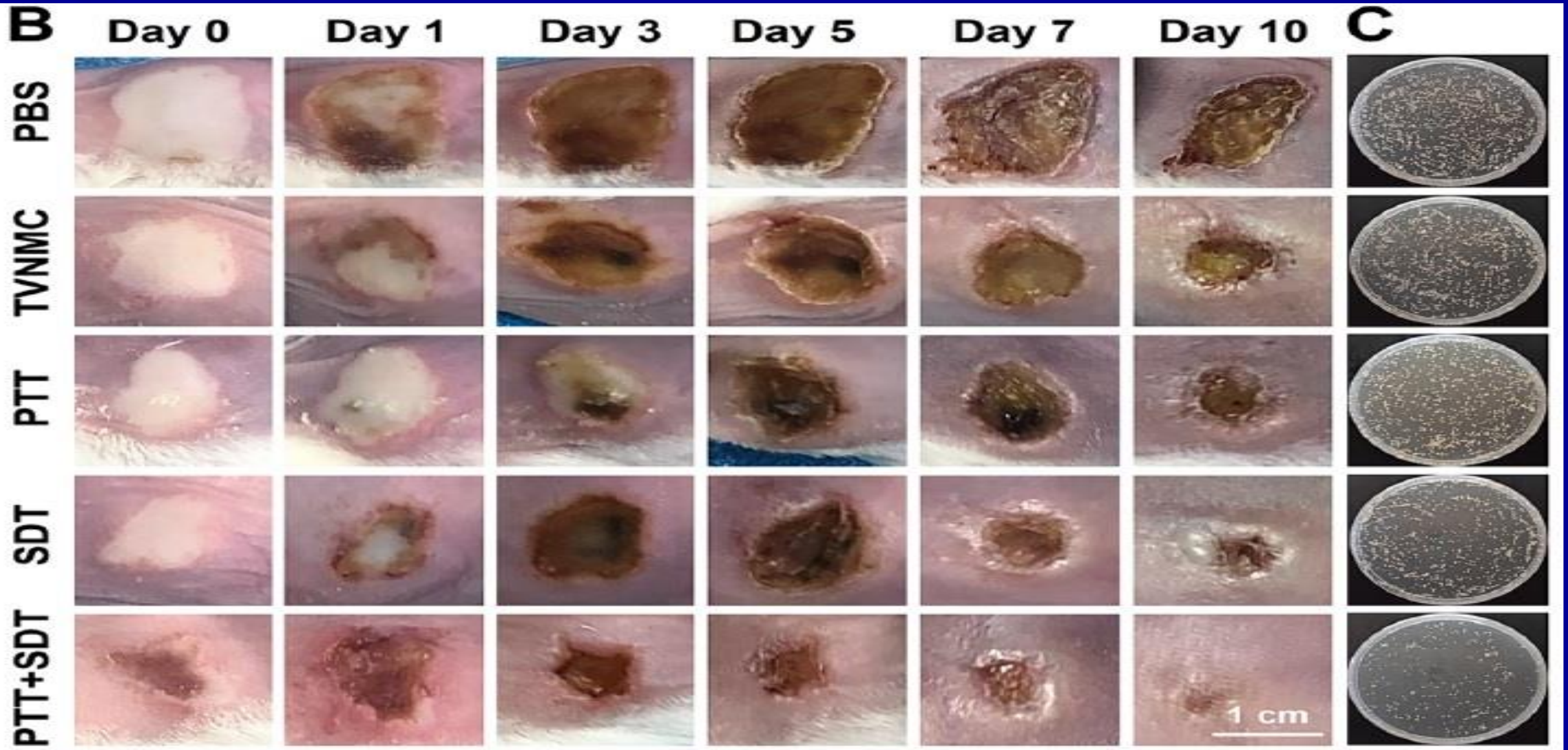
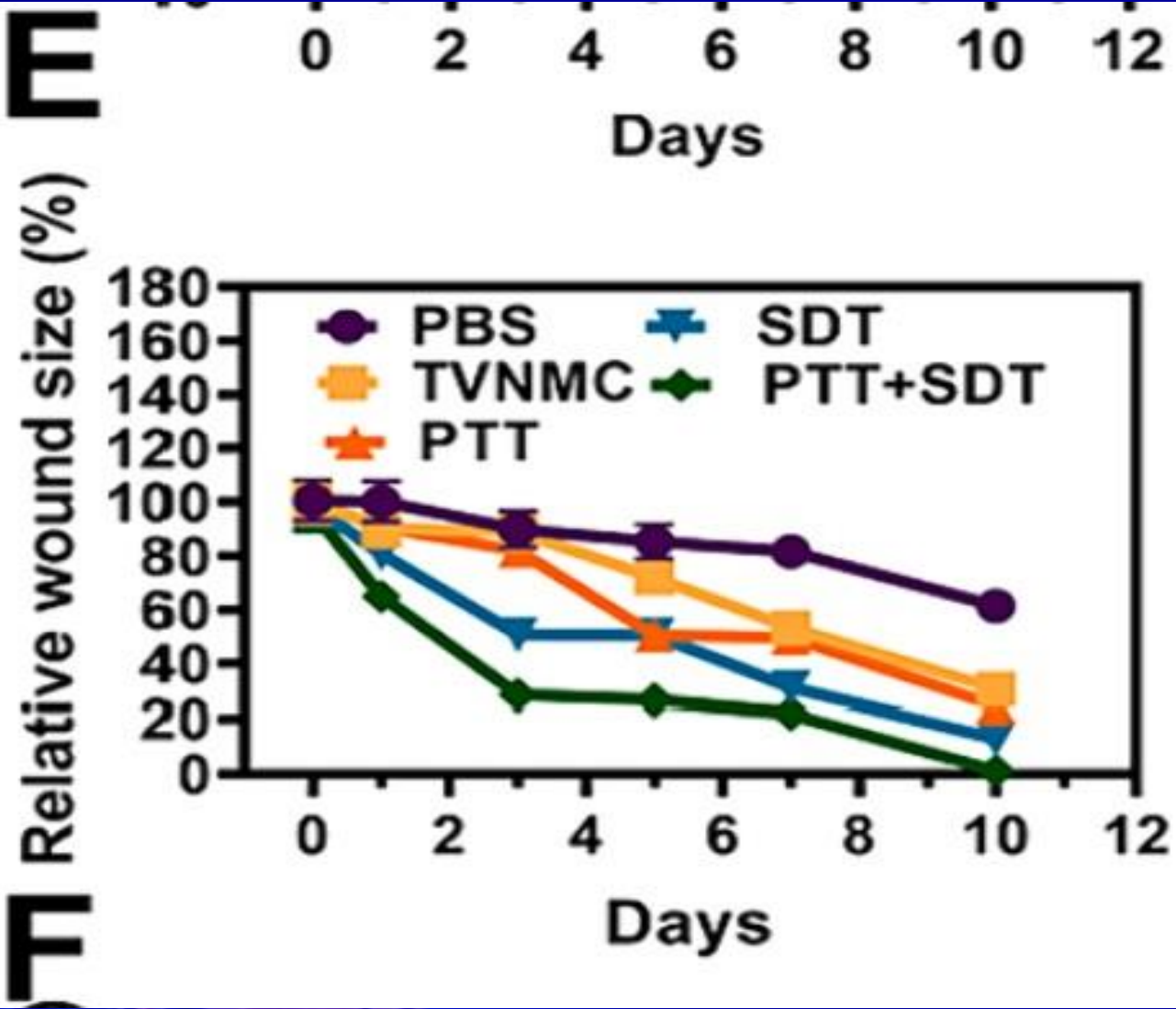
(B) NIR-II mediated ROS generation for enhancing the SDT efficacy against subcutaneous MRSA infection.

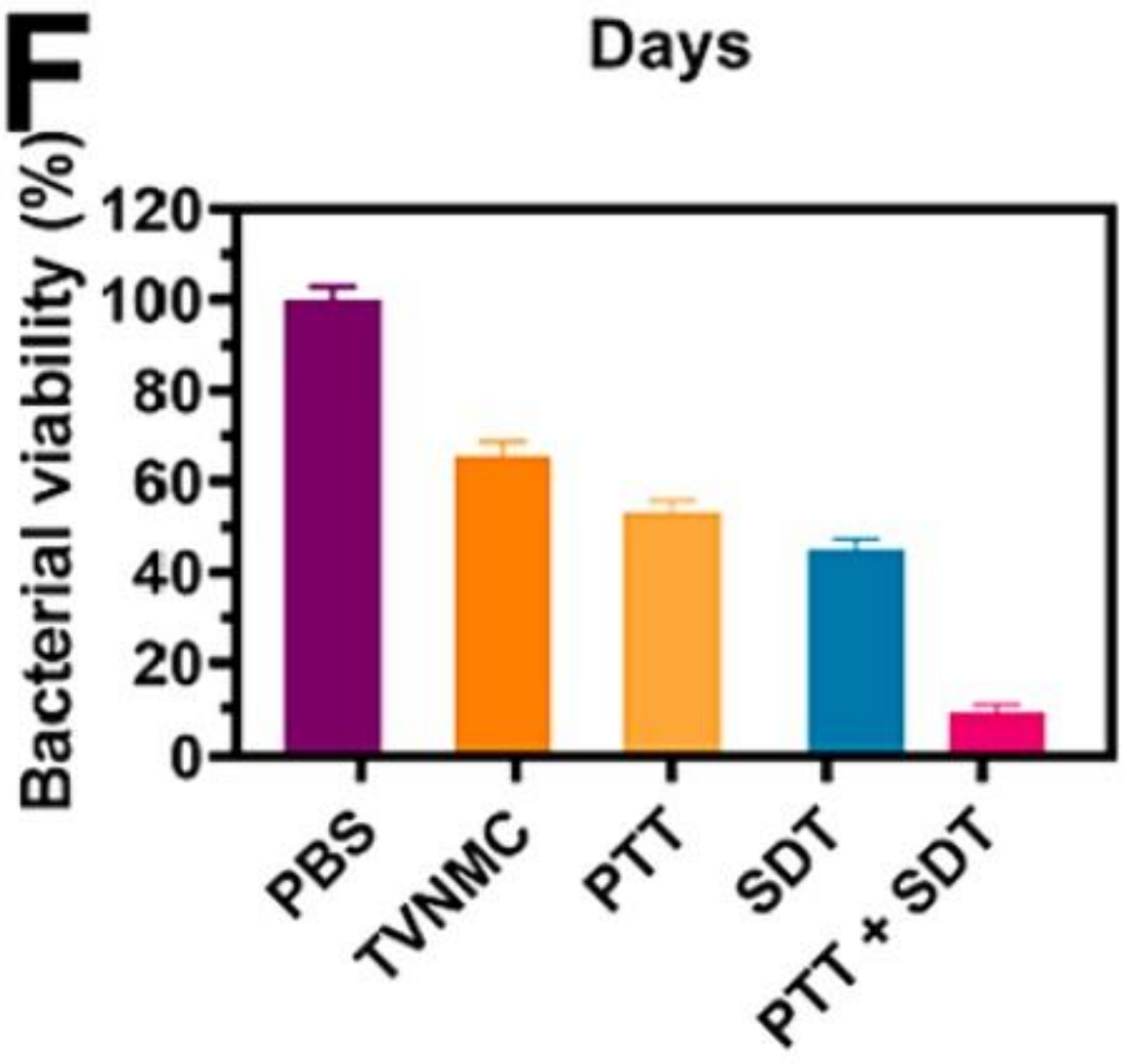


(B) Images of MRSA-infected abscesses from various groups at varying treatment times.
(C) Photographs of the MRSA colonies for the varying treatment groups.

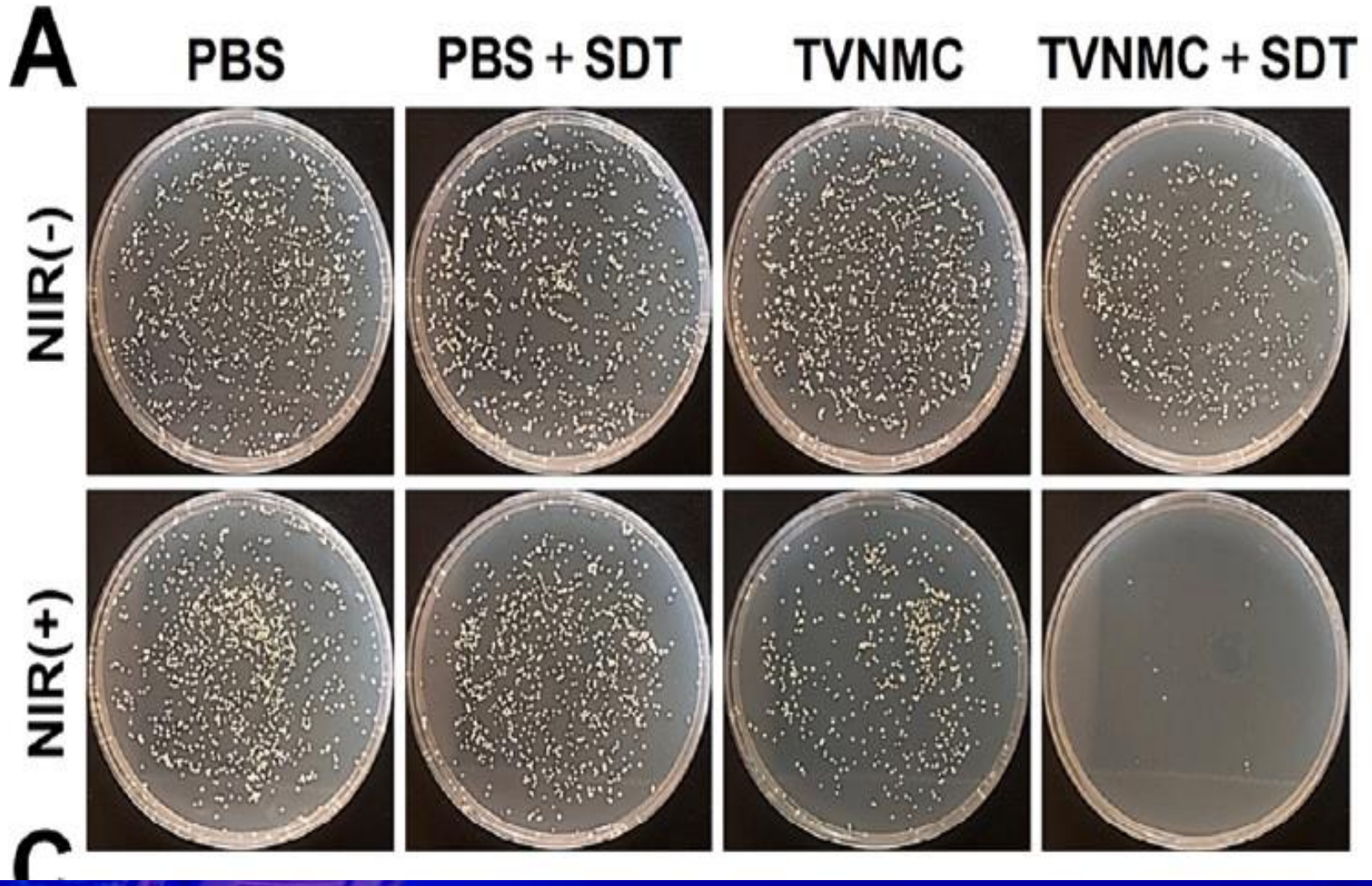


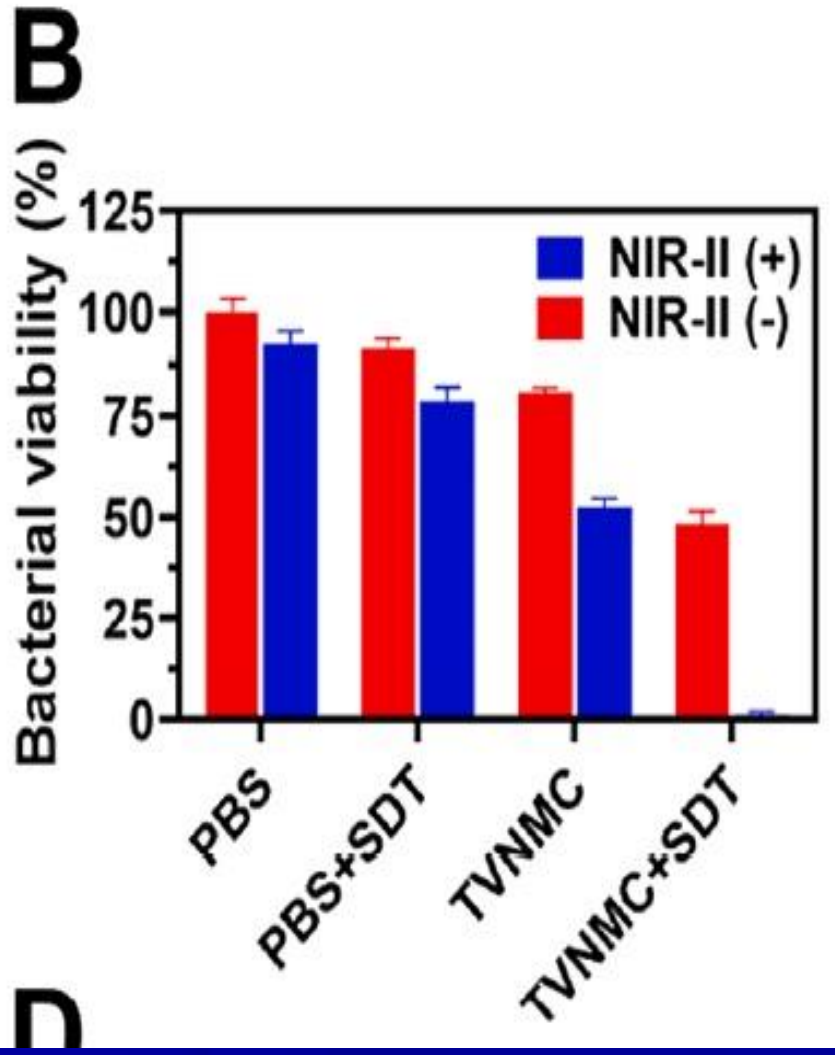
(E) The quantitative statistics of abscess size with time.
(F) Related quantitative information about the MRSA survival rate following treatments in various groups.



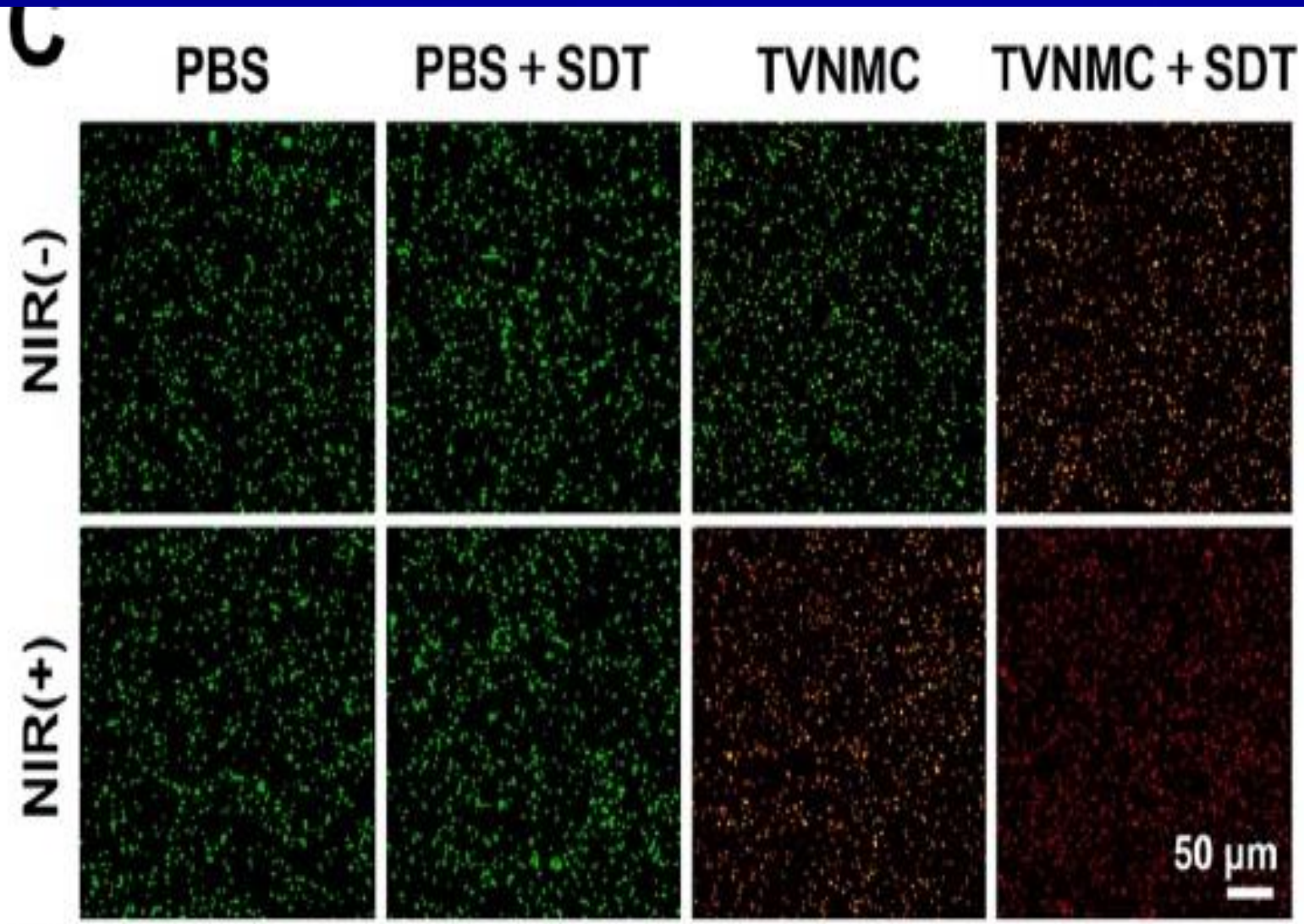


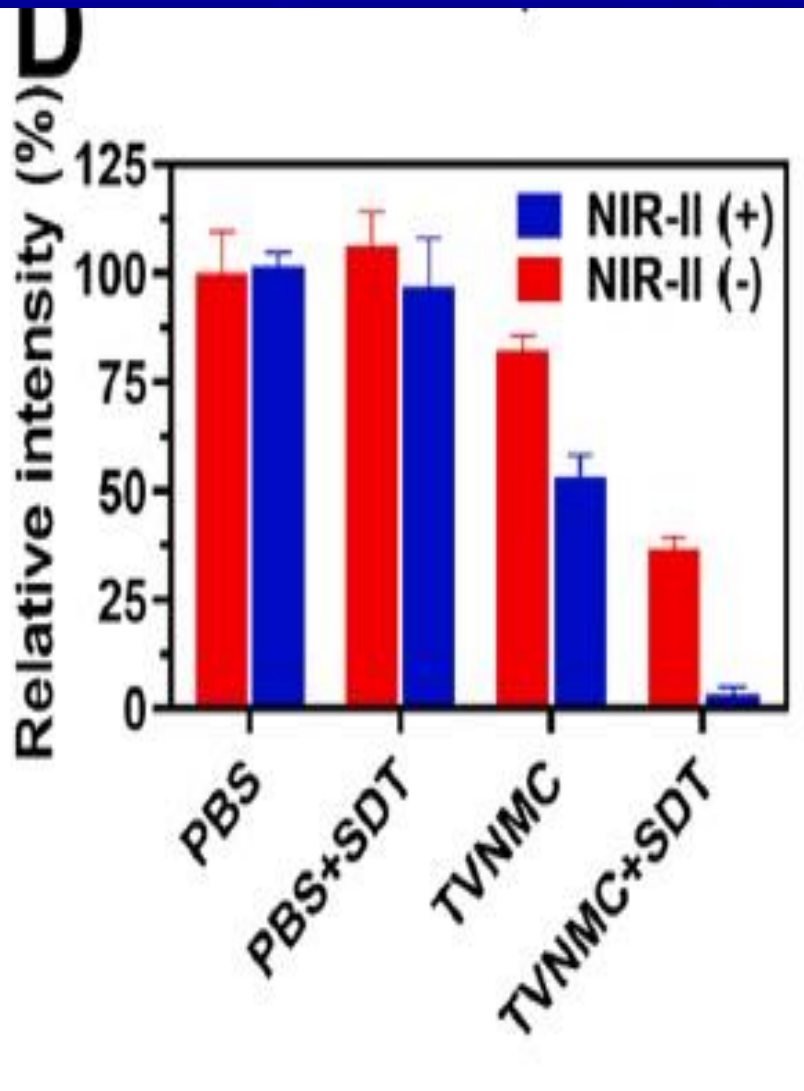
(A) Photographs of a typical agar plate with MRSA bacterial colonies following various treatments.
(B) Related quantitative information about the MRSA survival rate following treatments.





Green/red fluorescence denotes live/ dead bacteria and live/dead staining assay and the associated quantitative statistics are exhibited in (C) and (D).





Nano Today 37 (2021) 101104

Contents lists available at ScienceDirect

Nano Today

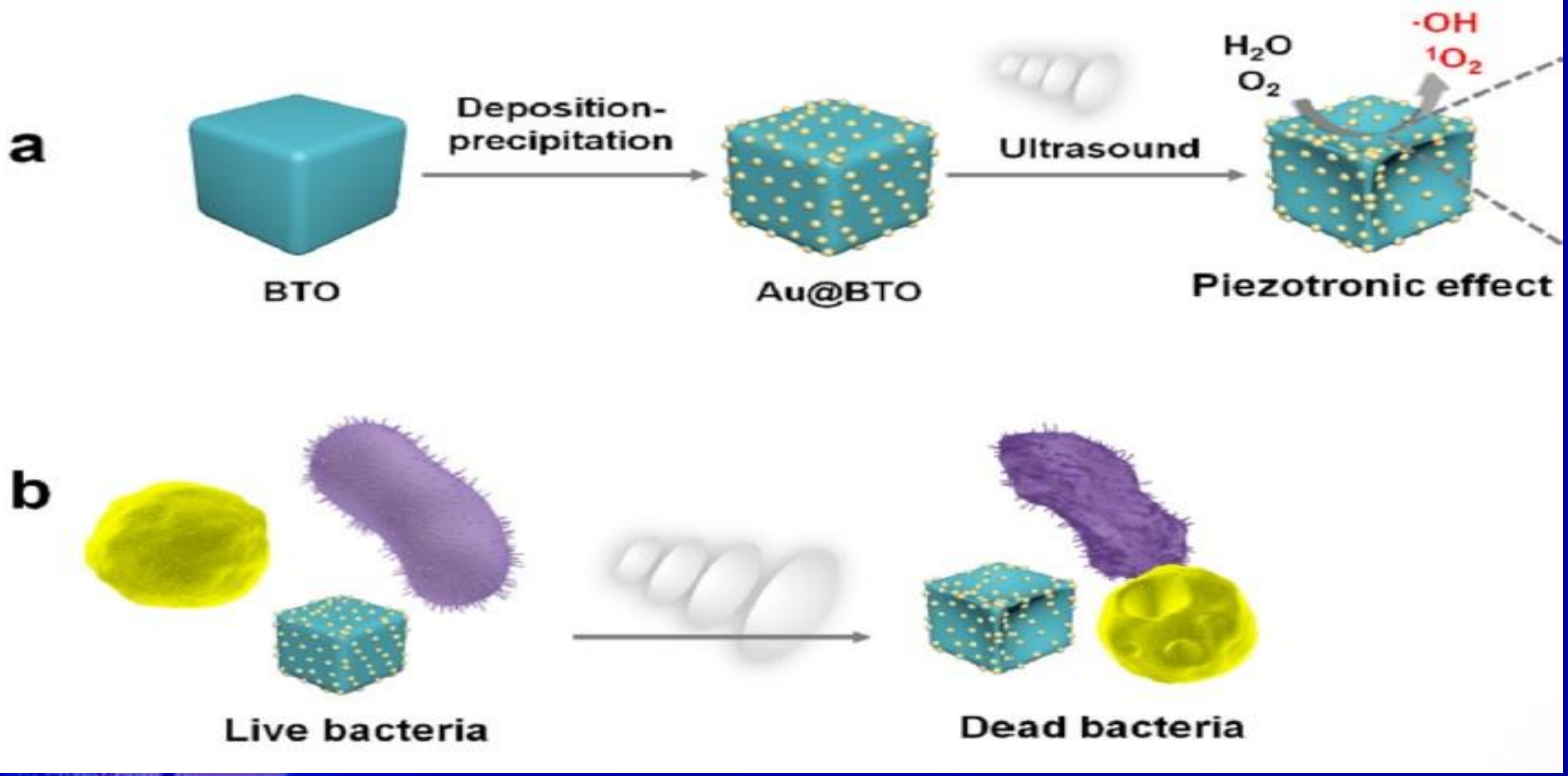
journal homepage: www.elsevier.com/locate/nanotoday

Piezoelectric nanocomposites for sonodynamic bacterial elimination and wound healing

Mengqi Wu[a,b,1], Zeyu Zhang[a,1], Zhirong Liu[a,b], Jiaming Zhang[a,b], Yalong Zhang[a], Yiming Ding[a], Tian Huang[a], Deli Xiang[a], Zhuo Wang[a,b], Yujie Dai[a,b], Xingyi Wan[a,b], Shaobo Wang[a], Huaili Qian[a], Qijun Sun[a,b,*], Linlin Li[a,b,*]

- We have developed a piezoelectric nanocomposite, barium titanate (BaTiO3, BTO) nanocubes with Schottky junction by Au nanoparticles (Au@BTO) as a new kind of SS for high efficient sonodynamic therapy.

- The piezocatalysis can generate ROS through the reaction of the generated charge carriers with surrounding molecular H2O and O2.



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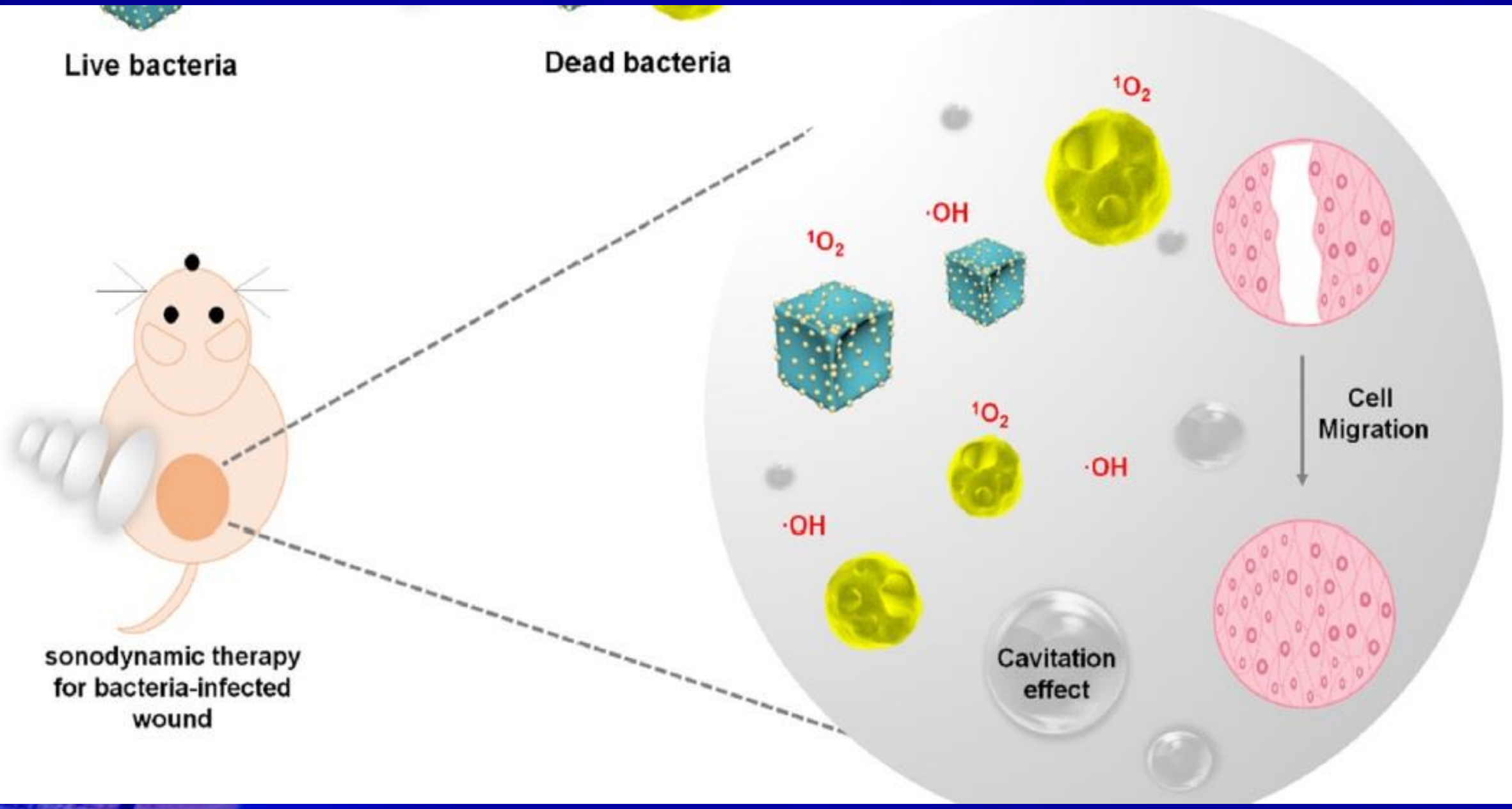
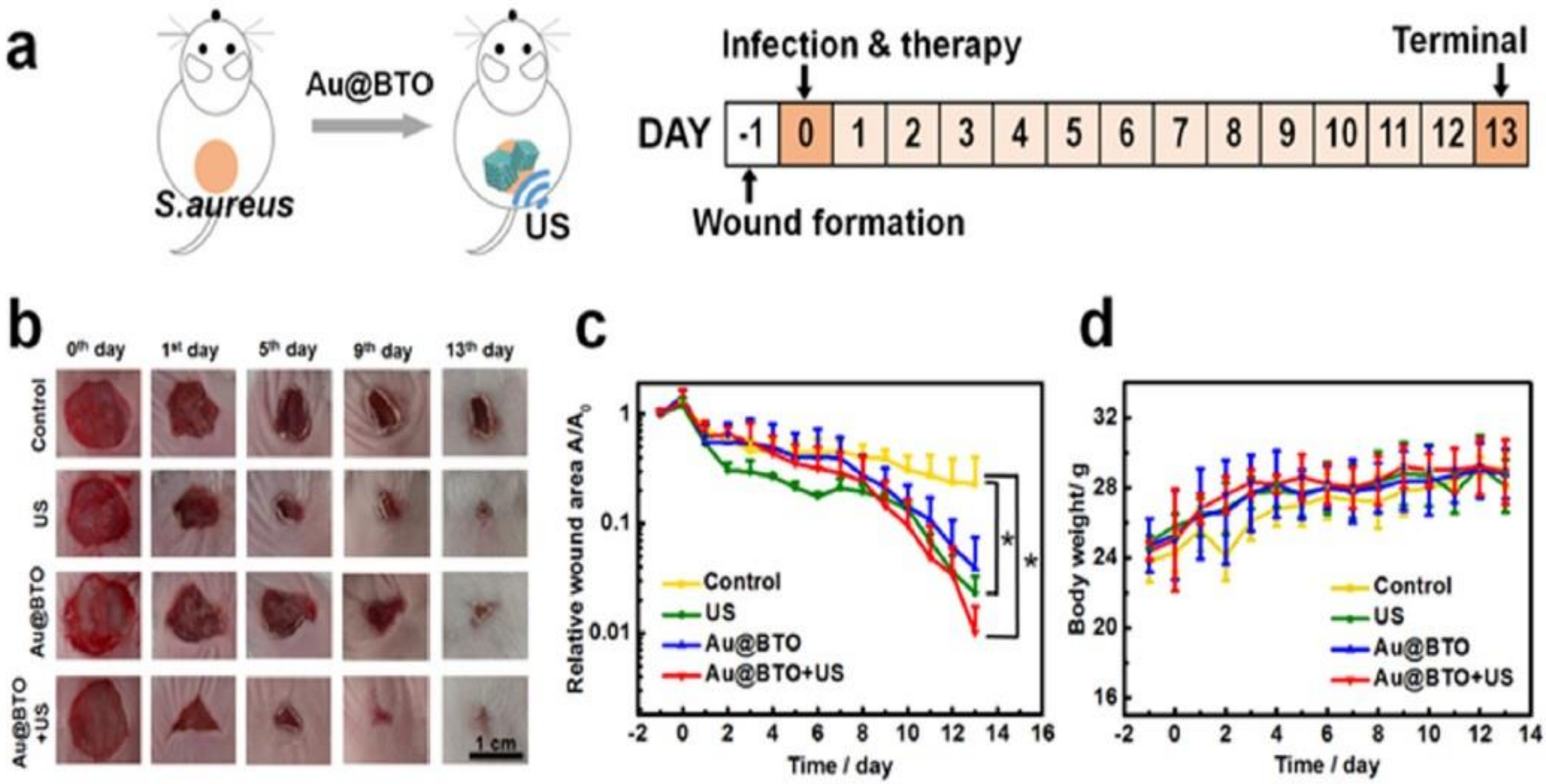
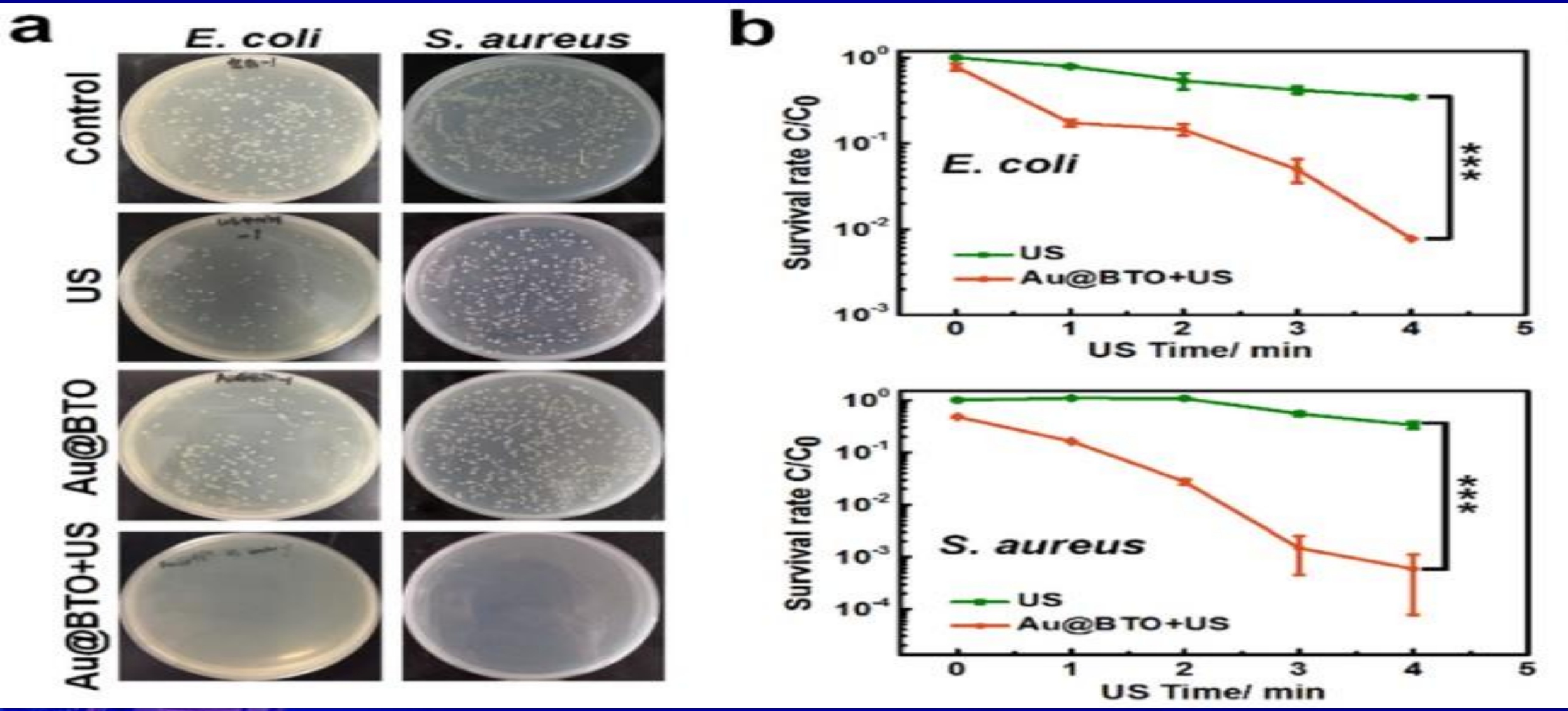
(c) wound healing of Au@BTO in mouse model.



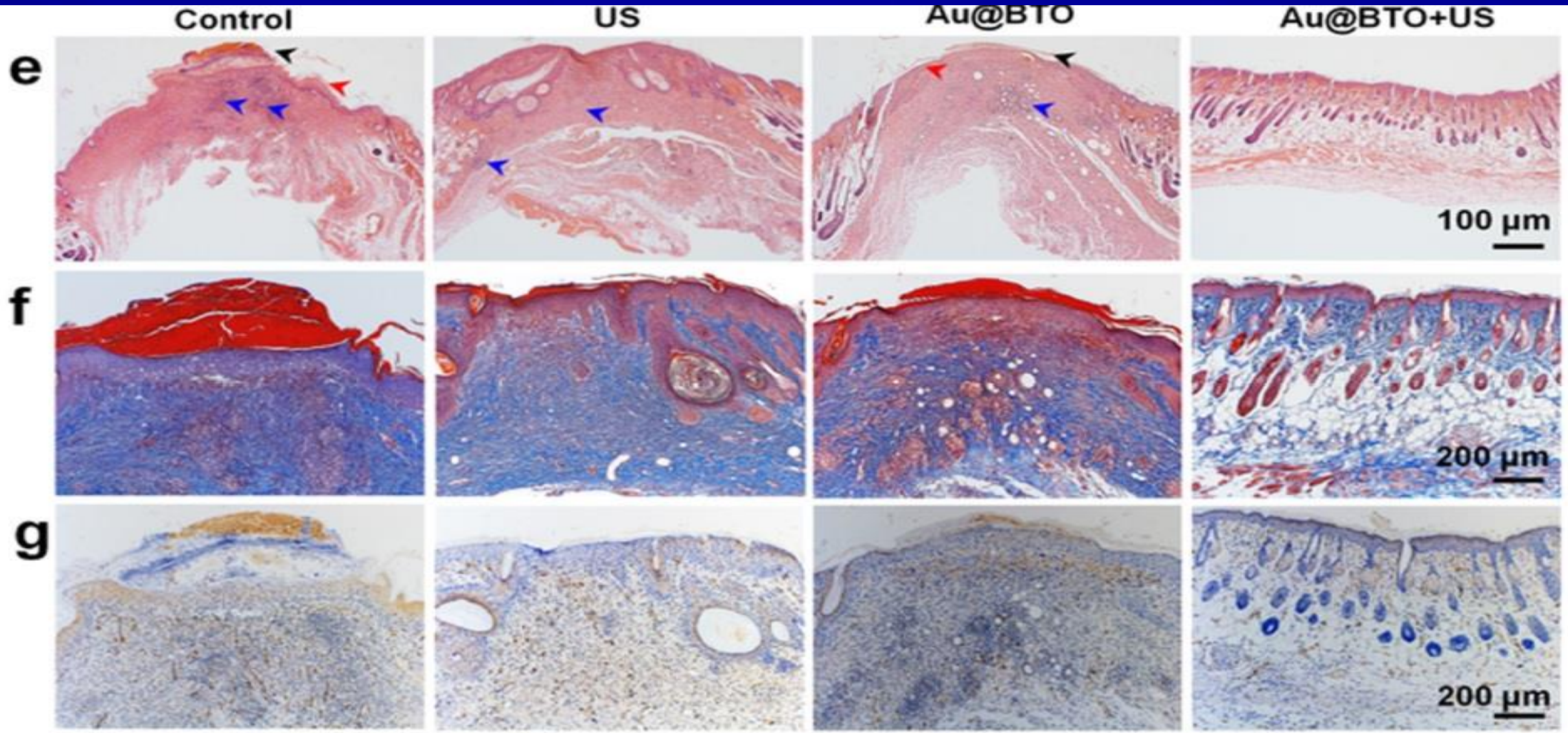
(a) Scheme of the experiment
(b) Representative photographs of the infected wounds at different times during therapy.



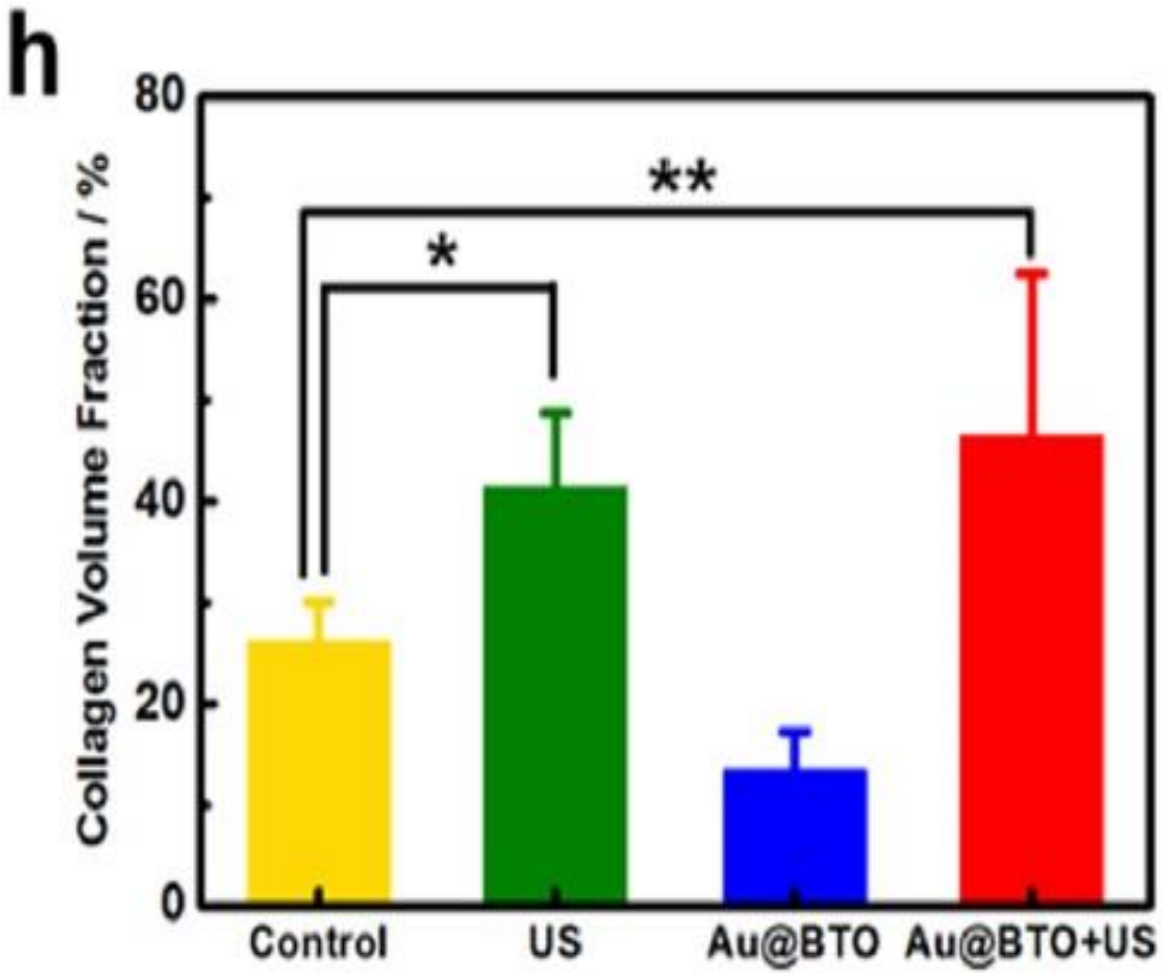
(a) CFU comparison
(b) bacterial survival rate

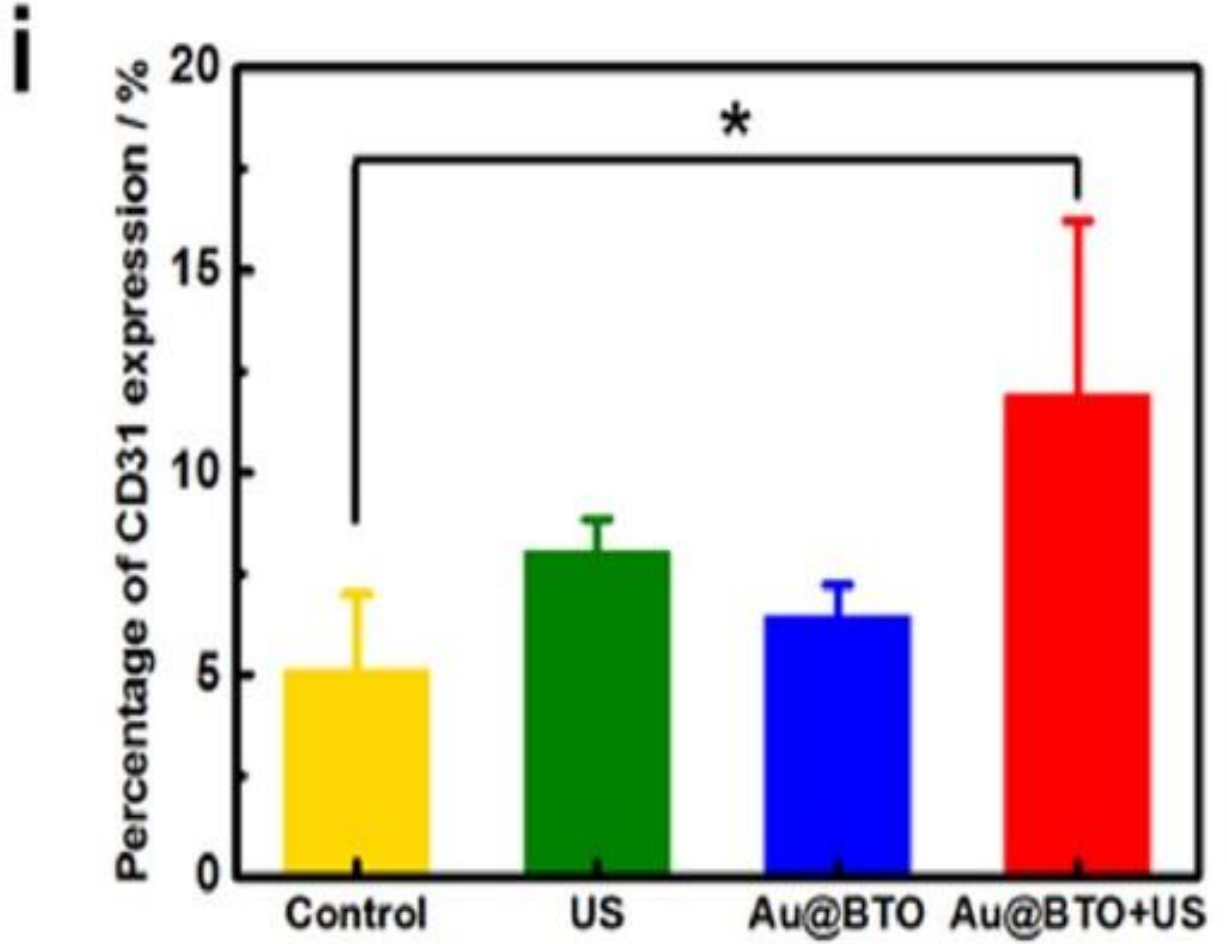


(e) H&E staining,
(f) Masson's trichrome staining and
(g) immunohistochemical staining



(h) the collagen volume fraction and (i) the CD31-labeled structures.





Chemical Engineering Journal 453 (2023) 139839

Contents lists available at ScienceDirect

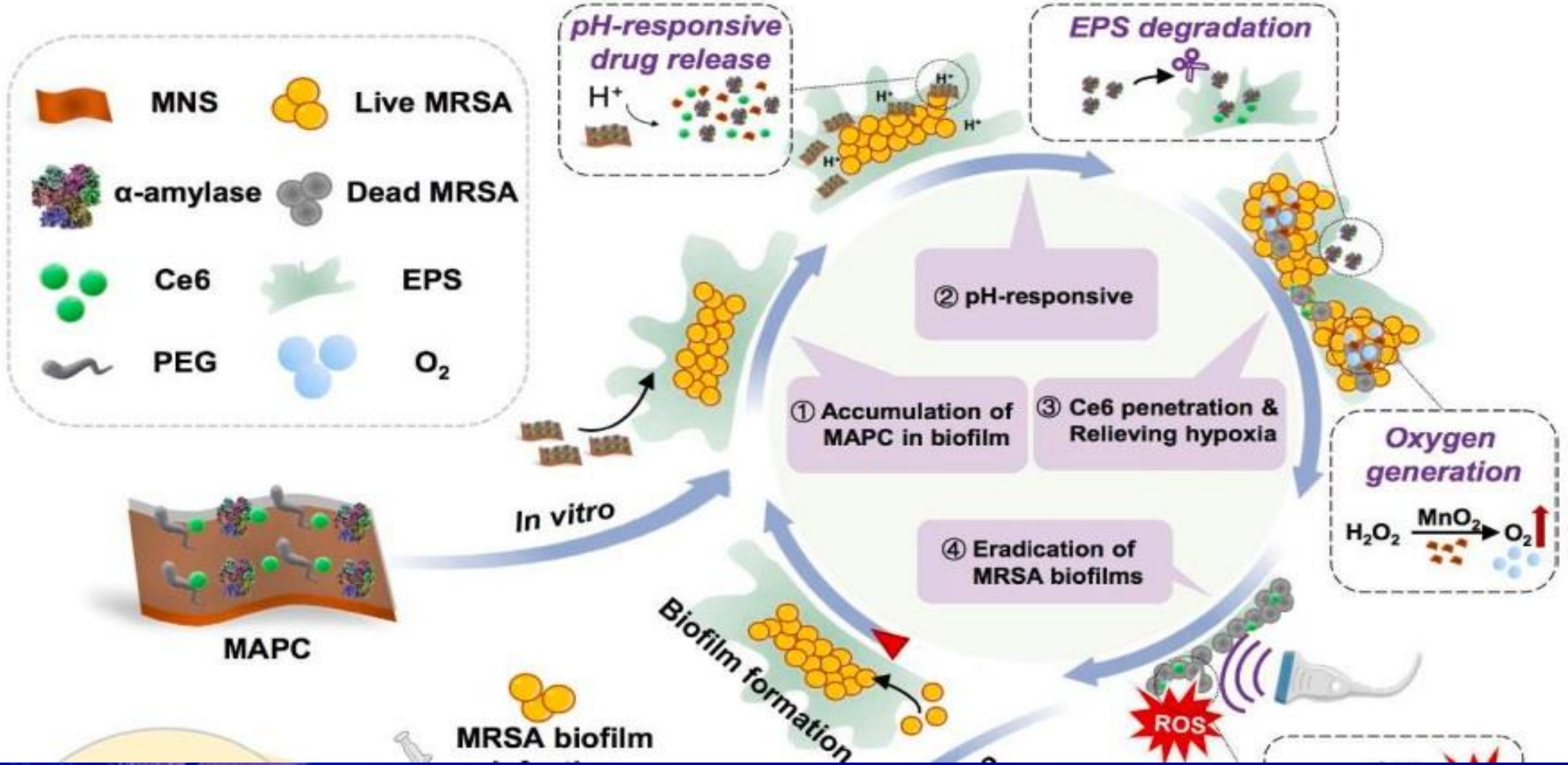
Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

Biofilm microenvironment response nanoplatform synergistically degrades biofilm structure and relieves hypoxia for efficient sonodynamic therapy

Heng Dong [a,1], Weijun Xiu [b,1], Ling Wan [b], Qiang Li [a], Yu Zhang [a], Meng Ding [a], Jingyang Shan [b], Kaili Yang [b], Zhaogang Teng [b,*], Lihui Yuwen [b,*], Yongbin Mou [a,*]

- The nanoplatform was prepared by modifying α-amylase, polyethylene glycol (PEG), and SS chlorin e6 (Ce6) on manganese dioxide nanosheets (MNS) to construct MNS-α-amylase/PEG/Ce6 nanosheets (MAPC).



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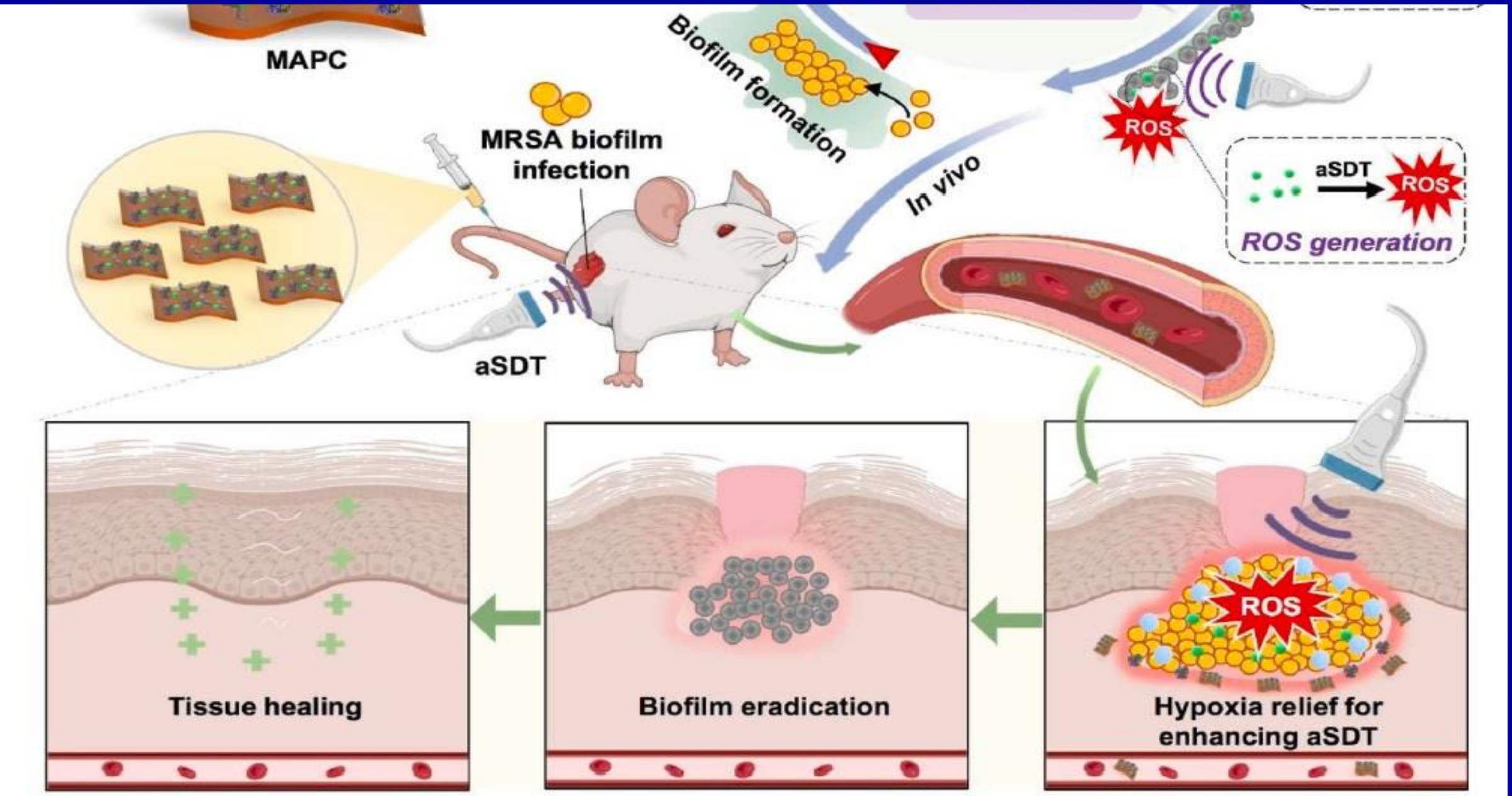
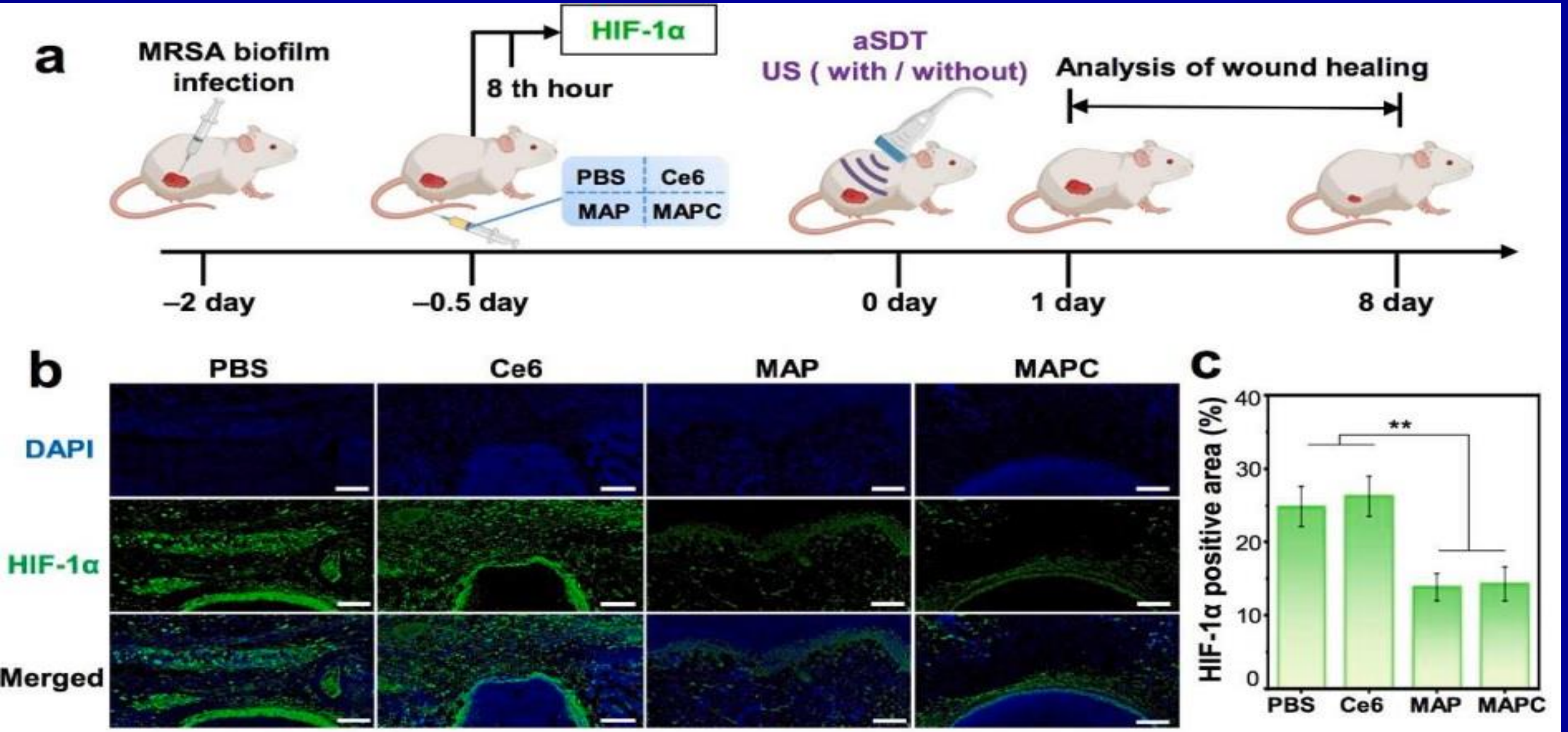
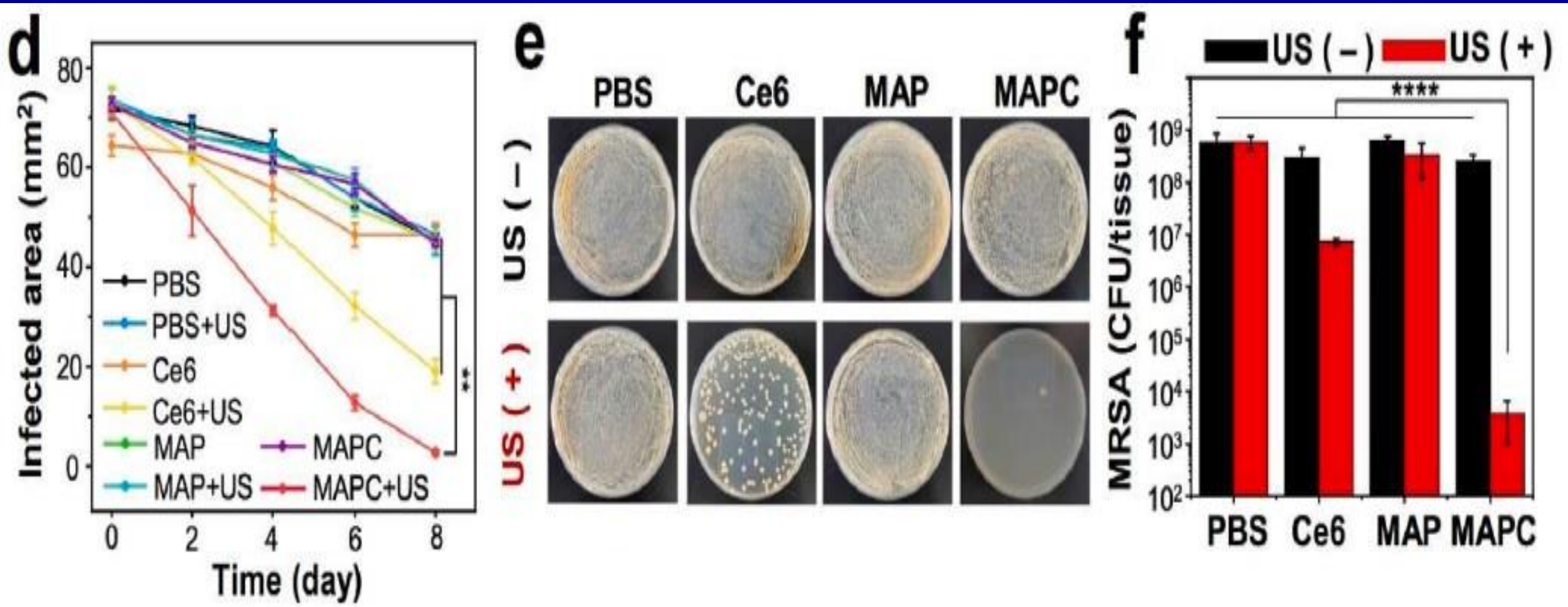
Then eradicates MRSA bacterial biofilms in a mouse model.



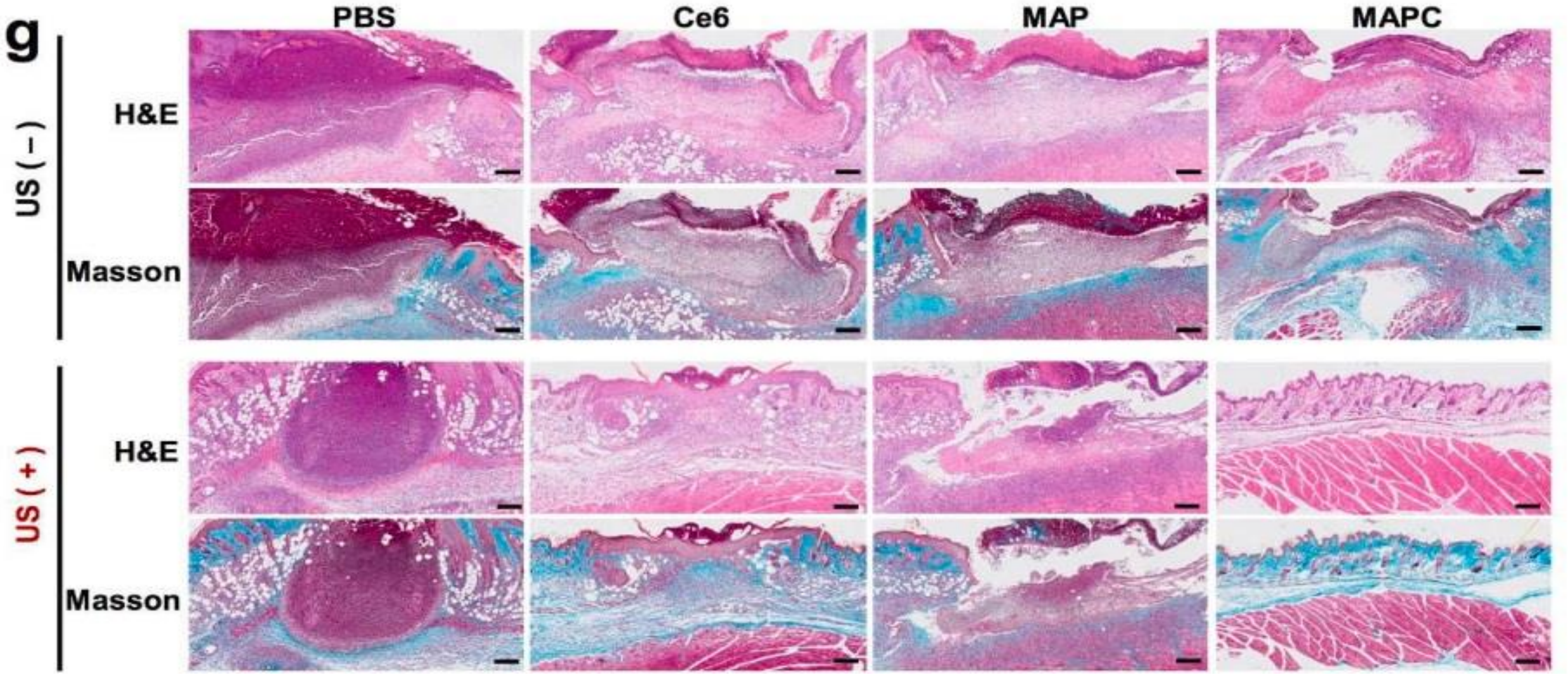
(a) Schematic illustrating the experimental procedure for the treatment of MRSA biofilm-infected mice.
(b) Representative CLSM images of immunofluorescence staining for HIF-1α in infected tissues.
(c) The percentages of HIF-1α-positive areas calculated from the images of immunofluorescence staining.



(d) The areas of biofilm-infected tissue in mice after different treatments for different lengths of time.
(e) Photographs of the MRSA colonies in the infected tissues at 8 d after treatment.
(f) Number of viable bacteria in the biofilm-infected tissues at 8 d post-treatment.



(g) Images of H&E and Masson's trichrome staining images of the infected mouse tissues



5

Advantage and Disadvantages

Advantages

SDT’s deeper penetration

- Ultrasound’s ability to penetrate into deep tissues(10-15 centimeters).

Good repeatability

- After injection of sound-sensitizer, SDT could treat the deep tumor nidus for several times.

Lower cost

- SDT needs no CT/MRI, endoscope and the introduction of laser treatment.

Excellent antibacterial effects

- Combining novel nanomaterials and US techniques produces excellent antibacterial effects.

Disadvantages

- The force and heat caused by ultrasonic cavitation effect may also induce irreversible physical **damage to healthy tissues**.
- The infection microenvironment with **acidic and hypoxic characteristics** limits the further therapeutic performance of US-activated therapy.

6

Conclusion

Conclusion

- **As an emerging therapeutic modality**, nanomaterial-based sonosensitizers exhibit great potential in the treatment of various diseases.

- Sonosensitizers and US stimulation work together to provide desirable therapeutic outcomes, and there are **much less adverse effects than traditional treatments**.

- **Benefiting from the deep tissue-penetrating capability** (<1 cm) of US, SDT showed higher feasibility and better therapeutic efficiency, in deep tissue infections, such as **osteomyelitis and myositis**.

- **Combining novel nanomaterials and US techniques** produces excellent antibacterial effects.

7

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THANK YOU