

# A Codispersed Nanosystem of Silver-anchored MoS<sub>2</sub> Enhances Antibacterial and Antitumor Properties of Selective Laser Sintered Scaffolds

Leliang Zheng<sup>1,2,3</sup>, Yancheng Zhong<sup>1,2,3</sup>, Tiantian He<sup>1,2,3</sup>, Shuping Peng<sup>1,2,3\*</sup>, Liuyimei Yang<sup>4\*</sup>

<sup>1</sup>NHC Key Laboratory of Carcinogenesis and Hunan Key Laboratory of Cancer Metabolism of Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine; School of basic Medical Science, Central South University, Changsha, Hunan 410013, China

<sup>2</sup>The Key Laboratory of Carcinogenesis and Cancer Invasion of the Chinese Ministry of Education, Xiangya Hospital, Central South University, Changsha, Hunan China

<sup>3</sup>Hunan Key Laboratory of Non Resolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, Hunan, China

<sup>4</sup>Ganjiang Innovation Academy, Chinese Academy of Sciences, Ganzhou 341119, China

**Abstract:** Tumor recurrence and bacterial infection are common problems during bone repair and reconstruction after bone tumor surgery. In this study, silver-anchored MoS<sub>2</sub> nanosheets (Ag@PMoS<sub>2</sub>) were synthesized by *in situ* reduction, then a composite polymer scaffold (Ag@PMoS<sub>2</sub>/PGA) with sustained antitumor and antibacterial activity was successfully constructed by selective laser sintering technique. In the Ag@PMoS<sub>2</sub> nanostructures, silver nanoparticles (Ag NPs) were sandwiched between adjacent MoS<sub>2</sub> nanosheets (MoS<sub>2</sub> NSs), which restrained the restacking of the MoS<sub>2</sub> NSs. In addition, the MoS<sub>2</sub> NSs acted as steric hindrance layers, which prevented the aggregation of Ag NPs. More importantly, MoS<sub>2</sub> NSs can provide a barrier layer for Ag NPs, hindering Ag NPs from reacting with the external solution to prevent its quick release. The results showed that Ag@PMoS<sub>2</sub>/PGA scaffolds have stronger photothermal effect and antitumor function. Meanwhile, the Ag@PMoS<sub>2</sub>/PGA scaffolds also demonstrated slow control of silver ion (Ag<sup>+</sup>) release and more efficient long-term antibacterial ability. Besides, composite scaffolds have been proved to kill the MG-63 cells by inducing apoptosis and inhibit bacterial proliferation by upregulating the level of bacterial reactive oxygen species. This kind of novel bifunctional implants with antitumor and antibacterial properties provides better choice for the artificial bone transplantation after primary bone tumor resection.

**Keywords:** Selective laser sintering; *In situ* growth; Photothermal therapy; Apoptosis; ROS

**\*Correspondence to:** Shuping Peng, NHC Key Laboratory of Carcinogenesis and Hunan Key Laboratory of Cancer Metabolism of Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine; School of basic Medical Science, Central South University, Changsha, Hunan 410013, China; shuping@csu.edu.cn; Liuyimei Yang, Ganjiang Innovation Academy, Chinese Academy of Sciences, Ganzhou 341119, China; lymyang@gia.cas.cn

**Received:** March 14, 2022; **Accepted:** April 17, 2022; **Published Online:** June 3, 2022

**Citation:** Zheng L, Zhong Y, He T, *et al.*, 2022, A Codispersed Nanosystem of Silver-anchored MoS<sub>2</sub> Enhances Antibacterial and Antitumor Properties of Selective Laser Sintered Scaffolds. *Int J Bioprint*, 8(3):577. <http://doi.org/10.18063/ijb.v8i43.577>

## 1. Introduction

Primary bone tumors such as osteosarcoma, chondrosarcoma, and Ewing's sarcoma as well as bone metastases such as lung cancer seriously threaten the survival prognosis of patients<sup>[1]</sup>. Although surgical treatment

combined with chemotherapy significantly improved the survival rate of patients<sup>[2]</sup>, some challenges such as tumor recurrence from post-operative tumor residue, side effects from chemotherapy, and strong ability of tumor invasion and metastasis still exist<sup>[3]</sup>. In addition, bone grafts are

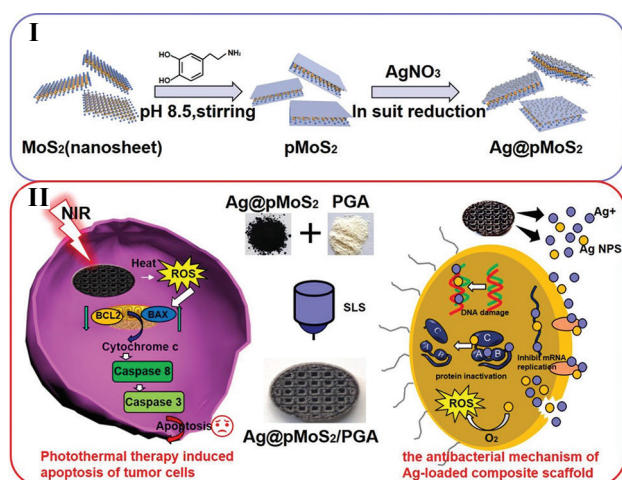
required to guide new bone repair and growth in patients with bone defects after surgery operation<sup>[4,5]</sup>, yet bacterial infection is a serious problem, leading to implant failure during bone reconstruction<sup>[6]</sup>.

Multimodal therapies, such as photothermal therapy/photodynamic therapy (PTT/PDT), chemo-PTT, and PDT/chemotherapy therapy, make it possible to cure tumor recurrence and bacterial infection<sup>[7]</sup>. A study by Li *et al.* designed a multifunctional scaffold consisting of porous Ti6Al4V, chitosan, and selenium-doped hydroxyapatite nanoparticles<sup>[8]</sup> promoted osteoblast proliferation while inhibited tumor cells growth and bacterial viability, which can be potentially used for treating bone defects resulted from surgical resection of osteosarcoma. Some researchers have introduced photothermal agents and drugs into stents to achieve the synergistic treatment of PTT/PDT. For example, Wang *et al.* reported highly active single-atomic iron catalyst modified three-dimensional (3D)-printed bioactive glass scaffold with the ability to generate reactive oxygen species (ROS) and absorb near-infrared (NIR) laser, which can be used for antibacterial and antitumor treatment of osteosarcoma<sup>[9]</sup>. NIR laser-induced heating can also enhance the sensitivity of bacteria to antibiotics, leading to reduced drug dosage and improved treatment efficacy<sup>[10]</sup>. However, multidrug resistance of bacteria and inadequate mechanical properties of scaffolds limit their application in bone replacement materials.

MoS<sub>2</sub> nanosheets (MoS<sub>2</sub> NSs) belong to a novel type of nanomaterial with large specific surface area, easy surface modification, and high NIR photothermal conversion efficiency, which are being developed for cancer diagnosis and treatment<sup>[11-13]</sup>. Chen *et al.* developed a novel MoS<sub>2</sub>/Bi<sub>2</sub>S<sub>3</sub> nanomaterial based on MoS<sub>2</sub>, which can be used for photoacoustic and computed tomography imaging and tumor photothermal therapy<sup>[14]</sup>. Cai *et al.* developed an DOX@Apt-PEG-PDA-MoS<sub>2</sub> nanoplatform based on MoS<sub>2</sub> and adaptor functionalization, which can effectively target breast cancer and cooperate with photothermal therapy<sup>[15]</sup>. Meanwhile, silver and silver-based compounds are recognized as powerful antibacterial agents due to their high bactericidal efficiency, wide bactericidal spectrum, and no bacterial resistance<sup>[5]</sup>. Silver nanoparticles (Ag NPs) not only release silver ion (Ag<sup>+</sup>) to destroy the protein structure of bacterial cell membrane, inhibit the activities of respiratory enzymes and proteins, inhibit DNA transcription and translation, but also upregulate the level of ROS, causing oxidative damage to bacteria<sup>[16]</sup>. Hence, the combination of MoS<sub>2</sub> and silver may be a promising antitumor and antibacterial strategy. However, MoS<sub>2</sub> NSs and Ag NPs tend to agglomerate in the polymer matrix because of their large van der Waals forces, as well as the explosive release of Ag<sup>+</sup> is still a problem in the application of Ag-based antibacterial materials<sup>[17]</sup>.

*In situ* growth of nanoparticles on the carrier is an effective way to solve this problem<sup>[18-21]</sup>. For example, Ali *et al.* synthesized Au@graphene mixed aerogel by *in situ* reduction using NIR radiation, in which gold nanoparticles were uniformly dispersed and enhanced the conductivity of graphene oxide (GO)<sup>[22]</sup>. Nanometer system of *in situ* growth of silver has been developed, Xu *et al.* synthesized a silver modified hollow silicon dioxide (SiO<sub>2</sub>) nanoparticles, which showed good dispersity in ethanol and water, and had good antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*<sup>[23]</sup>. However, the conditions for surface functionalization of nanomaterials are often complex and difficult to control. In general, redox reaction is an effective method to obtain Ag NPs on nanocarriers<sup>[24]</sup>. Polydopamine stands out among reducing agents because of its good biocompatibility and adhesion properties, as well as its large amount of catechol and amine groups<sup>[25]</sup>. More importantly, its catechin group can be adsorbed to nanocarriers by coordination reaction and then reduced to Ag NPs by redox reaction<sup>[26]</sup>, which helps to control the content and size of Ag NPs by the concentration of Ag<sup>+</sup>.

In this study, a codispersed Ag@PMoS<sub>2</sub> nanosystem was developed by *in situ* reduction of Ag NPs on MoS<sub>2</sub> NSs with polydopamine. In the Ag@PMoS<sub>2</sub>, Ag NPs and MoS<sub>2</sub> NSs are separated from each other, where MoS<sub>2</sub> NSs loaded Ag NPs, while Ag NPs acts as steric hindrance to prevent the accumulation of MoS<sub>2</sub> NSs (**Figure II**). Then, Ag@PMoS<sub>2</sub> was mixed with polyglycolic acid (PGA). Finally, the composite scaffold was developed by selective laser sintering (SLS) technology (**Figure III**). The morphology and structure as well as the chemical composition of Ag@PMoS<sub>2</sub> were analyzed. Furthermore, the comprehensive performance of 3D scaffolds was evaluated, including photothermal performance and photothermal stability,



**Figure 1.** Schematic diagram of preparation and antibacterial and antitumor function of multifunctional scaffold. (I) Preparation process of *in situ* growth of Ag NPs on MoS<sub>2</sub>. (II) Mechanism of antibacterial and antitumor of multifunctional therapy.

antitumor and antibacterial ability, and Ag<sup>+</sup> release spectrum. Besides, we explored the potential mechanisms of antitumor and antibacterial stents (Figure III).

## 2. Experimental methods

### 2.1. Materials

PGA was supplied by from Shenzhen Polymtek Biomaterial Co. Ltd. (Shenzhen, China). The average molecular weight of PGA was 100 kDa. MoS<sub>2</sub> NSs were supplied by Nanjing XFNano Materials Tech Co. Ltd. (Jiangsu, China), with diameter in the range of 0.2 – 5 μm and more than 90% monolayer rate. Silver nitrate (AgNO<sub>3</sub>) was purchased from Sinopharm Chemical Reagent Co., Ltd. Tris-HCl and dopamine hydrochloride as well as other reagents of analytical grade were purchased from Sigma (Shanghai, China). All the above raw materials were used as received.

### 2.2. Preparation of Ag@PMoS<sub>2</sub> nanosheets

Figure II shows the preparation of silver by *in situ* reduction on MoS<sub>2</sub> NSs. In general, 0.04 g MoS<sub>2</sub> NSs was added to 100 mL TRIS-HCl buffer (10 mM, pH = 8.5) and ultrasonic stirred for 2 h. Then, 0.2 g dopamine hydrochloride was added and stirred vigorously at room temperature for 12 h. Black precipitate was separated and collected at 6000 rpm for 10 min, and washed with anhydrous ethanol for 5 times. To generate Ag NPs *in situ* on PDA surface, the products obtained in the above experiments were dispersed into 100 mL ethanol under ultrasonic conditions, then 2 mL 0.12 M AgNO<sub>3</sub> solution was added into the reaction system. After mixing well and standing for 24 h, the supernatant was removed and the precipitate was resuspended with 100 mL ethanol. The mixture was added to a 250 mL oil bath and stirred with magnetic force. When the temperature rose to 80°C, 30 mL NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O (14.8 mg/mL) ethanol solution was added to the above mixture, reacting for 20 min. Then, the products were cooled at room temperature for 12 h and washed 6 times with anhydrous ethanol. Finally, the products were dried in a vacuum oven at 60°C for 24 h.

### 2.3. Scaffold preparation

As we know, PGA is a kind of non-toxic and non-immunogenicity biomaterial with excellent biodegradability and biocompatibility, which has been approved by the Food and Drug Administration for human clinical applications. Herein, PGA was used as the matrix material to prepare the composite scaffold. Specifically, the 0.1 g nanometer sample and 9.9 g PGA powder were dispersed into a beaker containing 30 mL anhydrous ethanol for ultrasonic stirring for 30 min. The composite powder was then obtained through filtering, drying, grinding, and other processes. Finally, the self-

developed SLS system was used to build the 3D scaffold layer by layer. SLS could meet the personalized needs of bone implantation due to the controllable external shape and pore size of the scaffold<sup>[27-32]</sup>. Typically, a layer of 0.1 mm thick powder were spread by the roller at a constant speed; then, the powders were selectively fused by the laser beam under the control of the programmed pattern; subsequently, the powder bed was lowered by 0.1 mm and the powder was respread, the sintering process was repeated until the scaffold was complete; the primary processing parameters of the scaffold preparation were hatch distance (0.1 mm), laser power (2.7 W), and scan speed (300 mm/s). The sintered scaffold of pure PGA powder was named PGA, the sintered scaffold was named MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA after mixing MoS<sub>2</sub>, PMoS<sub>2</sub>, and Ag@PMoS<sub>2</sub> NSs with PGA powder, respectively.

### 2.4. Analysis and characterization

The morphology of Ag@PMoS<sub>2</sub>, PMoS<sub>2</sub>, and MoS<sub>2</sub> was observed by transmission electron microscopic (TEM) (Morgagni 268D, FEI, USA). The chemical structure of Ag@PMoS<sub>2</sub>, PMoS<sub>2</sub>, and MoS<sub>2</sub> was analyzed by Fourier-transform infrared spectroscopy. The morphology and elemental composition distribution of Ag@PMoS<sub>2</sub>, PMoS<sub>2</sub>, and MoS<sub>2</sub> and composite scaffolds were observed by scanning electron microscopy (SEM) (EVO LS10, Zeiss, Germany) equipped with energy-dispersive spectroscopy (EDS) (XFlash 6130, Bruker, Germany). The chemical composition of Ag@PMoS<sub>2</sub>, PMoS<sub>2</sub>, and MoS<sub>2</sub> was evaluated by X-ray photoelectron spectroscopy (XPS) (ESCALAB 250, Thermo Scientific, UK). The crystal structure of Ag@PMoS<sub>2</sub>, PMoS<sub>2</sub>, and MoS<sub>2</sub> was observed by X-ray diffractometer (XRD) (Empyrean-100, PANalytical, Netherlands). The Ag<sup>+</sup> release spectrum of composite scaffolds in deionized water was quantitative analyzed by inductively coupled plasma optical emission spectrometer (Optima 8300, Perkin Elmer, USA).

### 2.5. Photothermal performance and photothermal stability of composite scaffolds

The prepared scaffolds were immersed in pure water, and the PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds were irradiated by a NIR laser generator. We designed pure water as the background group because water can absorb a certain amount of NIR energy<sup>[33]</sup>. Under the same laser power density (1 W/cm<sup>2</sup>), the composite scaffold was irradiated with 808 nm laser for about 750 s, and the corresponding solution temperature data were recorded in real time to evaluate the photothermal performance of the composite scaffolds. In addition, the photothermal stability of the Ag@PMoS<sub>2</sub>/PGA scaffold was evaluated by four switching cycles under NIR irradiation.



## 2.6. Photothermal effect of scaffold to MG63 and bone marrow mesenchymal stem cell (BMSC) cells

The composite scaffolds were sterilized with 75% alcohol for 1 h and then ultraviolet for 2 h. human osteosarcoma cells (MG63) and mouse BMSC were cultured with DMEM (10% fetal bovine serum, 1% penicillin, and streptomycin) in a cell incubator (5% CO<sub>2</sub>, 37°C) for 48 h. The cell suspensions were then placed into a composite scaffold and irradiated with or without 808 nm NIR laser for 10 min. Cell Counting Kit-8 reagent was added to each hole and incubate at 37°C for 2 h. Cell survival was evaluated by measuring the absorbance of the supernatant at 450 nm (Beckman, USA). Propidium iodide (PI) and calcein-AM were added, respectively, and the cells live/dead assay was evaluated using a fluorescence microscope (BX60, Olympus, Japan). Apoptosis rate was evaluated according to the instructions of the VFITC/PI Apoptosis Detection Kit (BIOBOX, China). For Western blotting detection of Bcl-2 and Bax expression, the MG63 cells were cocultured with the composite scaffold, then irradiated with or without 808 nm NIR laser (1 W/cm<sup>2</sup>) for 20 min and then incubated for 2 h. Then, the protein was collected and the protein concentration was measured. Finally, the expression of Bcl-2 and Bax was examined by Western blotting.

## 2.7. Antibacterial function of scaffolds

The antibacterial performance of scaffolds was evaluated with Gram-negative bacteria *E. coli*. The composite scaffolds were sterilized with 75% alcohol for 1 h and then ultraviolet for 2 h. *E. coli* suspension (1 × 10<sup>6</sup> CFU/mL) was cultured with sterilized scaffolds and irradiated with or without 808 nm NIR for 10 min at 4 h intervals. After 24 h, the absorbance of the suspension at 600 nm was measured to evaluate the antibacterial activity of the scaffold (Beckman, USA). At the same time, the suspension was imaged by digital camera. Finally, the scaffolds attached with bacteria were fixed with 2.5% glutaraldehyde for 1 h after washed with PBS, then dehydrated in a gradient concentration of ethanol (10, 30, 50, 75, 95, and 100% v/v) for 10 min. The number and morphology of bacteria on the scaffold were observed by SEM. 2',7'-dichlorofluorescein diacetate (DCFH-DA) was used to evaluate the ROS in *E. coli*. In details, *E. coli* suspension (1 × 10<sup>6</sup> CFU/mL) was cultured with sterilized scaffolds and irradiated with or without 808 nm NIR for 10 min at 4 h intervals. After 24 h, *E. coli* was collected, 500 μL phosphate-buffered PBS with 10 μM of DCFH-DA was added and then incubated at 37°C for 30 min in the dark. The images were captured with fluorescence microscope (BX60, Olympus, Japan).

## 2.8. Statistical analysis

In this study, multiple replicate tests were performed for each group of samples and the final experimental results were expressed as mean ± standard deviation. All experimental data were statistically analyzed by SPSS software (ver. 23.0; IBM Corporation, NY, USA). The results were regarded as statistically significant only when  $P < 0.05$ .

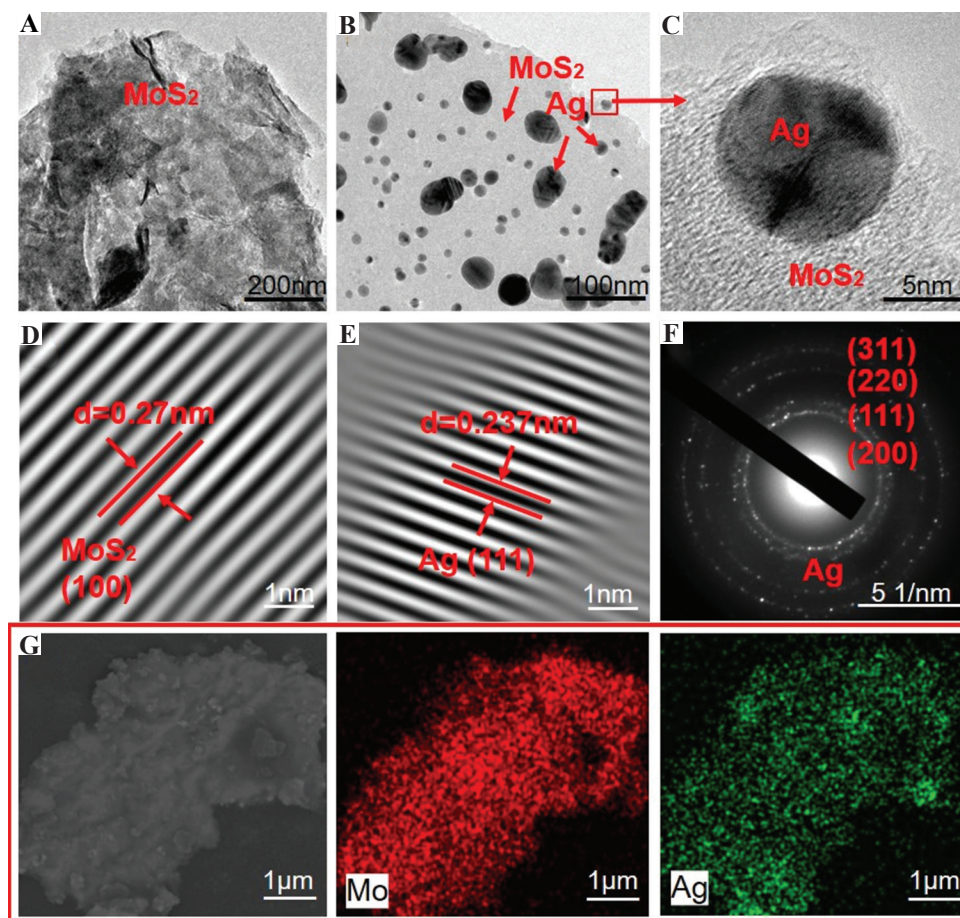
## 3. Results and discussion

### 3.1. Micromorphology of MoS<sub>2</sub> and Ag@PMoS<sub>2</sub>

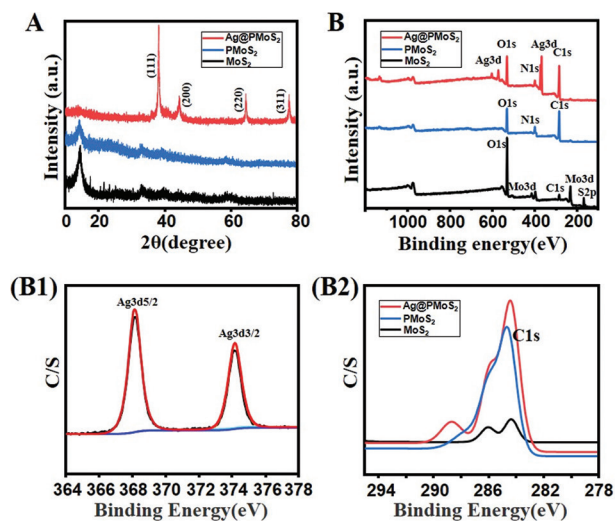
Micromorphology and elemental compositions of the MoS<sub>2</sub> and Ag@PMoS<sub>2</sub> NSs were observed by TEM and SEM equipped with EDS. As shown in **Figure 2A**, the unmodified MoS<sub>2</sub> NSs presented a relative smooth surface. **Figure 2B** shows the TEM images of Ag@PMoS<sub>2</sub> NSs. It can be seen that the size of Ag particles ranges from 5 nm to 20 nm and is evenly distributed on the surface of PMoS<sub>2</sub> NSs. This is because MoS<sub>2</sub> is coated by PDA and has abundant phenols and nitrogenous groups on its surface, which can absorb Ag<sup>+</sup> and help the formation of Ag NPs<sup>[34]</sup>. The high-resolution TEM image of Ag@PMoS<sub>2</sub> nanosheets shows crystal structure with lattice spacing about 0.27 nm for the (100) plane of MoS<sub>2</sub> NSs and 0.237 nm for the (111) plane of metallic Ag (**Figure 2C-E**)<sup>[35,36]</sup>. In the selected area of electron diffraction images (**Figure 2F**), the lattices of (200), (111), (220), and (311) were observed, which further confirmed the formation of Ag NPs. To check the distribution of silver in PMoS<sub>2</sub> NSs, EDS assay was performed. As shown in **Figure 2G**, the silver element is uniformly distributed on the surface of PMoS<sub>2</sub> NSs. Above results indicate that the Ag<sup>+</sup> had been reduced to Ag NPs and distributed uniformly on the surface of PMoS<sub>2</sub> NSs, which could help with the dispersion on each other. On the one hand, the accumulation of MoS<sub>2</sub> NSs may be inhibited by the sandwiched Ag NPs. On the other hand, the aggregation of Ag NPs may be hindered by the MoS<sub>2</sub> nanosheets.

### 3.2. Characterization of Ag@PMoS<sub>2</sub>

XRD and XPS were performed to characterize the crystal structure and chemical component of MoS<sub>2</sub> NSs, PMoS<sub>2</sub> NSs, and Ag@PMoS<sub>2</sub> NSs. As shown in **Figure 3A**, the pattern of the Ag@PMoS<sub>2</sub> exhibited all diffraction peaks associated to Ag and MoS<sub>2</sub>. The diffraction peak near 14° reduces in PMoS<sub>2</sub> NSs and Ag@PMoS<sub>2</sub> NSs due to the stack of MoS<sub>2</sub> layers is disrupted by the PDA coating<sup>[35]</sup>. Compared with PMoS<sub>2</sub> and MoS<sub>2</sub>, it can be observed that four new diffraction peaks at 38.13°, 44.35°, 64.52°, and 77.44° in Ag@PMoS<sub>2</sub>, which belong to the (111), (200), (220), and (311) reflection planes of metallic Ag,



**Figure 2.** Micromorphology of Ag@PMoS<sub>2</sub>. (A) TEM images of MoS<sub>2</sub>, (B-F) TEM images of Ag@PMoS<sub>2</sub>. (G) SEM images and EDS analyze of Ag@PMoS<sub>2</sub>.



**Figure 3.** Characterization of Ag@PMoS<sub>2</sub>. XRD (A) and XPS (B) spectra of MoS<sub>2</sub>, PMoS<sub>2</sub>, and Ag@PMoS<sub>2</sub>. (B1) XPS for Ag3d orbits of metallic Ag@PMoS<sub>2</sub>. (B2) C1s for the samples of MoS<sub>2</sub>, PMoS<sub>2</sub>, and Ag@PMoS<sub>2</sub>.

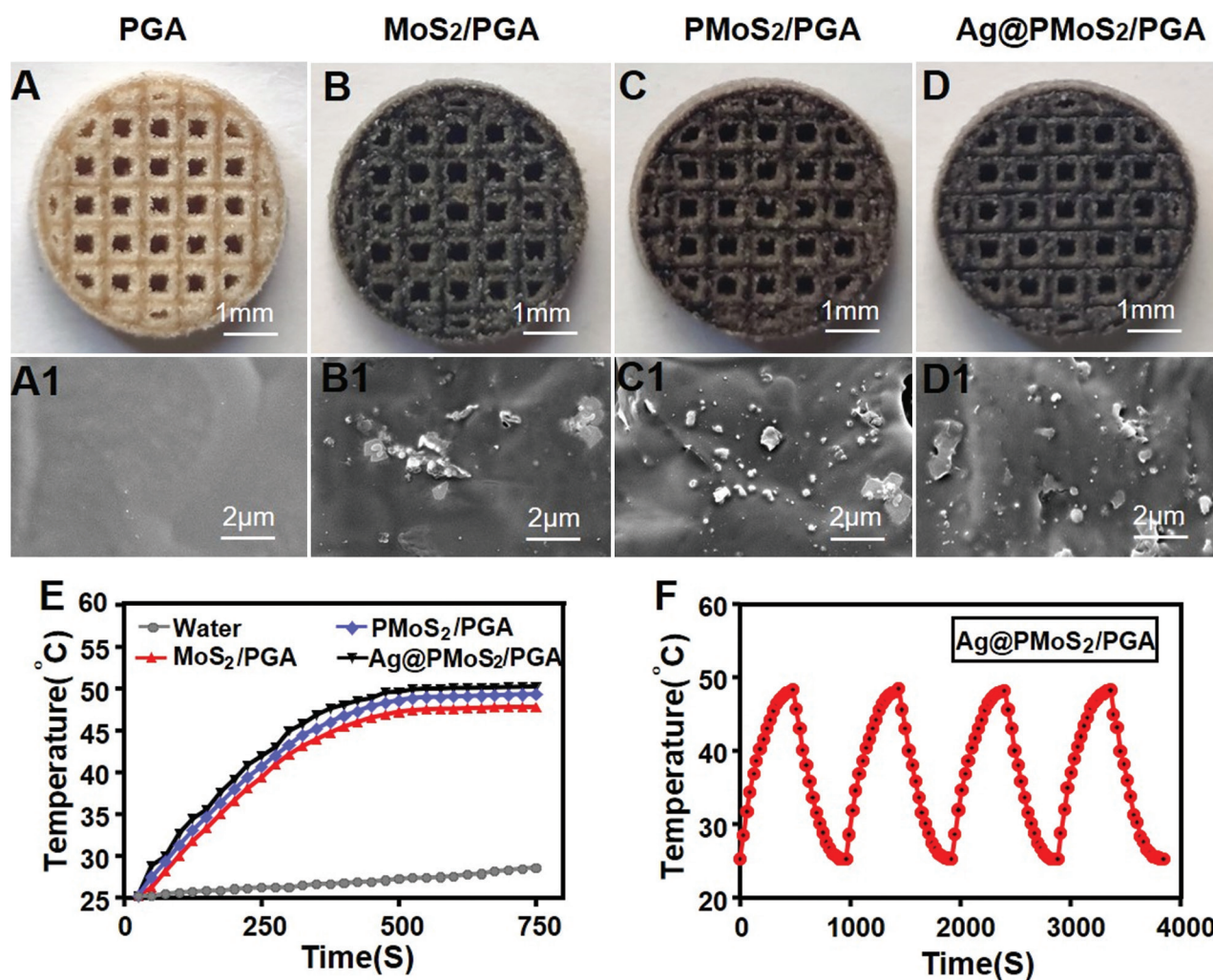
respectively<sup>[37]</sup>. The surface elemental configurations of MoS<sub>2</sub> NSs, PMoS<sub>2</sub> NSs, and Ag@PMoS<sub>2</sub> NSs were

performed by XPS. As shown in **Figure 3B**, the C, N, O, Mo, and Ag elements were detected in Ag@PMoS<sub>2</sub>, in which N and C were assigned to polydopamine. Clearly, the spectrum of Ag@PMoS<sub>2</sub> appeared several new peaks was occurred at 375 – 385 and 578 – 613 eV compared to PMoS<sub>2</sub> and MoS<sub>2</sub>, which were belong to Ag 3d and Ag 3p peaks of metallic Ag, respectively. **Figure 3B1** shows that at 368.1eV and 374.0eV, Ag3d nuclear horizontal spectrum can be divided into two peaks corresponding to Ag3d5/2 and Ag3d3/2 of metallic Ag, respectively<sup>[38]</sup>. As can be seen from **Figure 3B2**, the peak relative strength of Ag@PMoS<sub>2</sub> at about 298 eV is significantly higher than MoS<sub>2</sub> and PMoS<sub>2</sub>, which can be attributed to the C=O band of PDA. It can be inferred that the Ag<sup>+</sup> could oxidize the -C-OH of polydopamine to -C=O, and the metallic Ag can be immobilized on the surface of PMoS<sub>2</sub> by the structure of quinone<sup>[39]</sup>.

### 3.3. Microstructure and photothermal performance of scaffolds

The digital photos of PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds fabricated by SLS technology are shown in **Figure 4A-D**, respectively.





**Figure 4.** The microstructure and photothermal performance of scaffolds. (A-D) Photographs and (A1-D1) SEM images of the cross-section of the composite scaffolds. (E) Real-time temperature of PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds during NIR irradiation. (F) Real-time temperature of Ag@PMoS<sub>2</sub>/PGA scaffolds under “on-off” cycles during the NIR irradiation.

In general, scaffolds suitable for cell adhesion, growth, migration, and appropriate mechanical strength should have an aperture between 100 μm and 1000 μm<sup>[40-43]</sup>. The aperture of the composite scaffolds prepared in this study was about 500 μm, which was within a reasonable range. **Figure 4A1-D1** shows the SEM images of the cross section of the composite scaffolds fractured by liquid nitrogen. It is obvious that there are some aggregates from the MoS<sub>2</sub>/PGA matrix due to the strong van der Waals forces of MoS<sub>2</sub> NSs<sup>[44]</sup>. Conversely, the Ag@PMoS<sub>2</sub> NSs were uniformly distributed in the PGA matrix, which benefited from the synergistic dispersion effect of the Ag NPs and MoS<sub>2</sub> NSs<sup>[45]</sup>. Furthermore, we verify the photothermal performance of composite scaffolds by irradiating 808 nm NIR laser. As shown in **Figure 4E**, Ag@PMoS<sub>2</sub>/PGA scaffolds exhibited better photothermal performance than PMoS<sub>2</sub>/PGA and MoS<sub>2</sub>/PGA. Furthermore, photothermal stability of Ag@PMoS<sub>2</sub>/PGA was examined by over four

laser on/off cycles (1 W/cm<sup>2</sup>). As shown in **Figure 4F**, there was no obvious reduction, which further indicates that the photothermal agent has excellent photostability.

### 3.4. Photothermal antitumor function of scaffolds

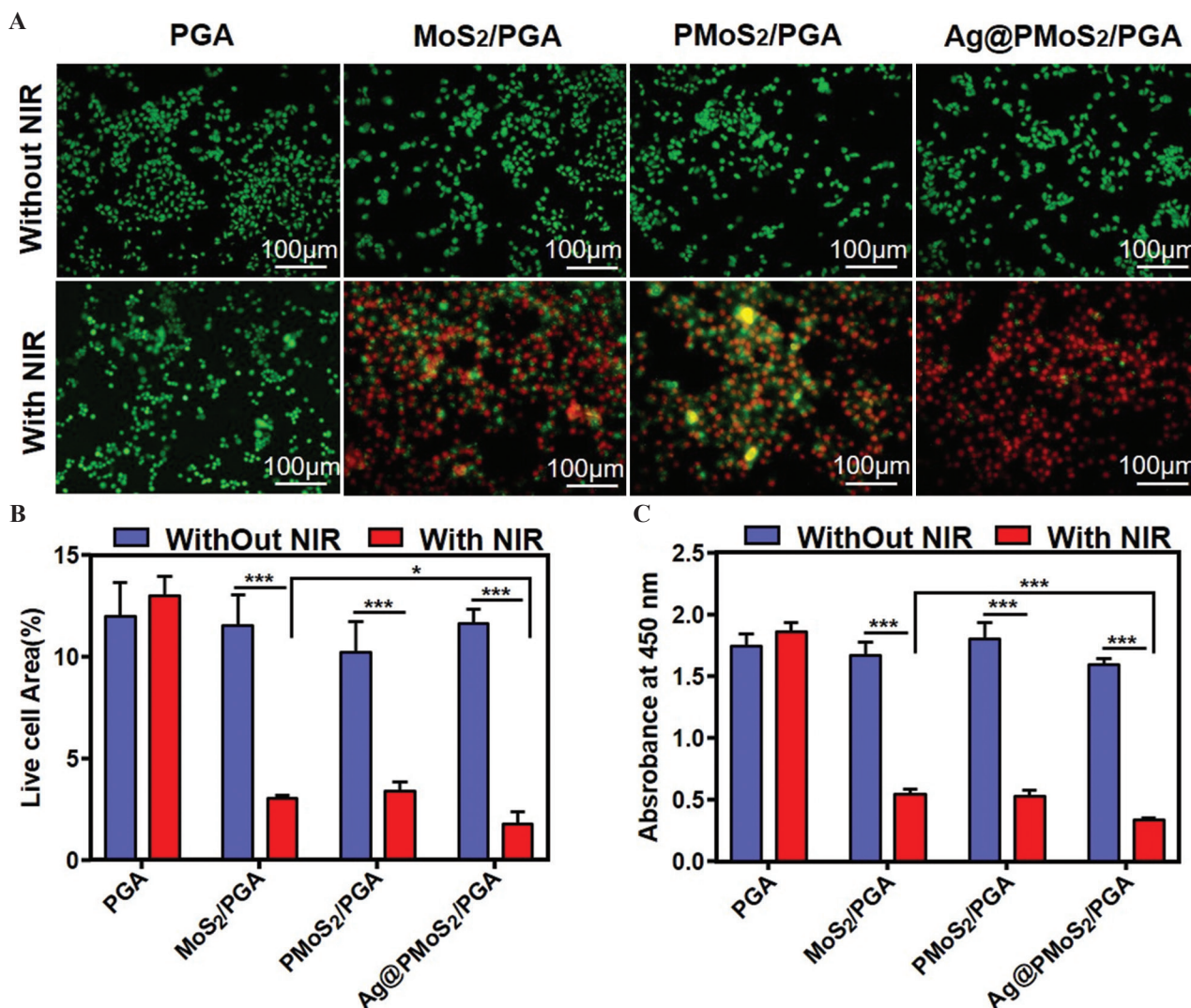
To further confirm the photothermal antitumor efficacy of composite scaffolds, MG63 cells were cultured with sterilized scaffolds and irradiated with or without 808 nm NIR for 10 min. The cells were stained with PI in red and calcein-AM in green, respectively, and the live/dead staining status was evaluated by a fluorescence microscope. The dead cells were stained in red as PI cannot enter living cells and the living cells were stained in green (calcein-AM enters dead cells and dispersed very fast and cannot be detected). As expected, both PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/

PGA scaffolds showed no cytotoxicity without NIR irradiation (**Figure 5A and B**). However, under NIR laser irradiation, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds significantly ablated MG63 cells. The area occupied by living cells decreased on average by 8.4%, which was significant superior to the PGA scaffolds alone (**Figure 5A and B**). More importantly, compared with MoS<sub>2</sub>/PGA, the ablation effect of Ag@PMoS<sub>2</sub>/PGA on tumor cells was significantly enhanced (**Figure 5A and B**). Cell Counting Kit-8 also showed that the survival rate of MG63 cells decreased significantly by 39% (**Figure 5C**).

### 3.5. Effect of photothermal function of scaffold on normal cells

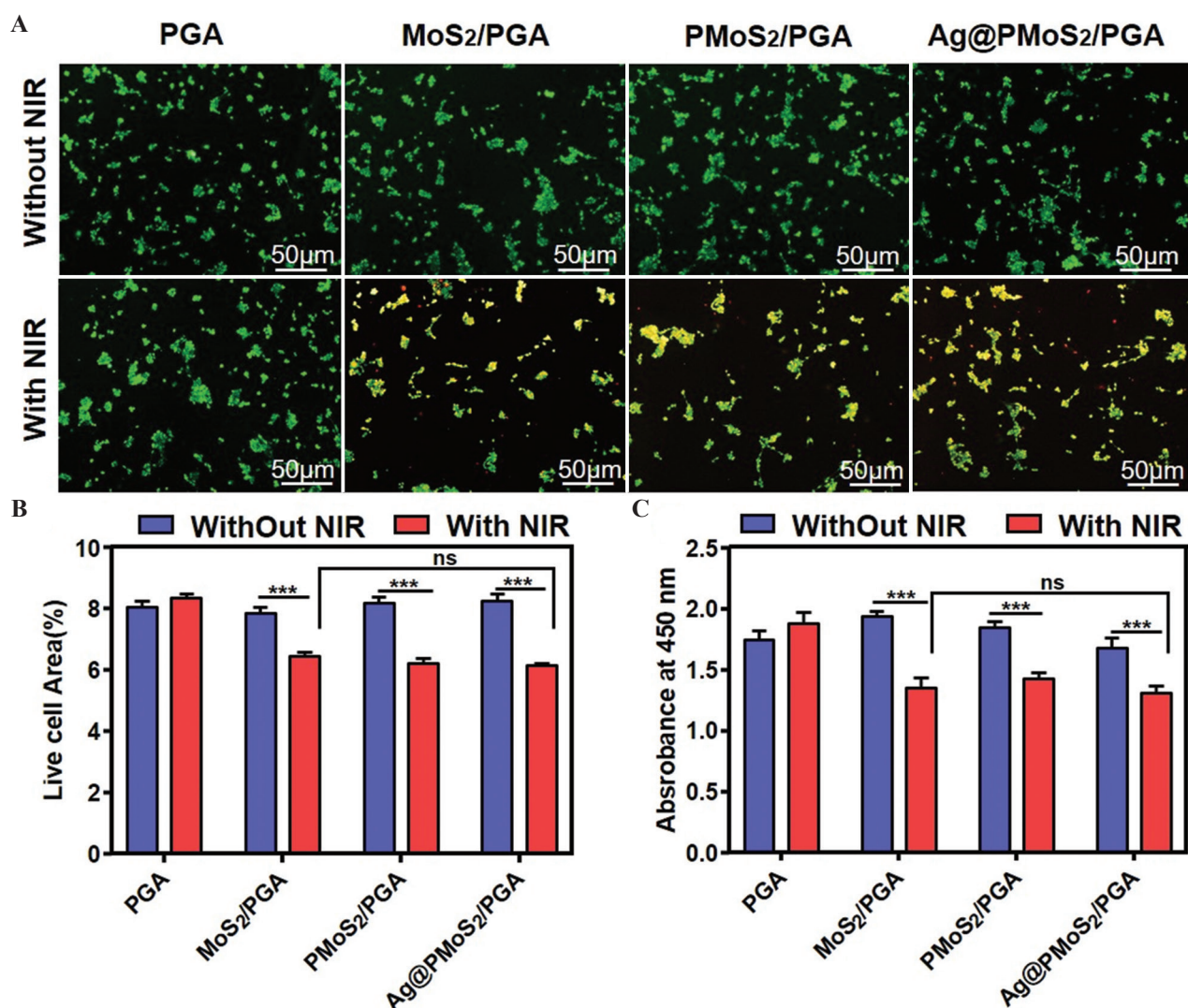
At the same time, we also evaluated the effect of composite scaffolds on normal cells. BMSC cells were cultured with

sterilized scaffolds and irradiated with or without 808 nm NIR for 10 min. As show in **Figure 6A**, under NIR laser irradiation, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds also ablated BMSC cells. The area ratio of living cells decreased by about 2% (**Figure 6B**). However, the ablation effect of these scaffolds on MSC cells was significantly reduced compared with those on MG63 cells. As shown in **Figure 5C and 6C**, two kinds of cells were cocultured with the composite scaffold, respectively, the activity of MG63 cells was about 0.5, while that of BMSC cells was still about 1.4 after NIR irradiation. This is because tumor cells are far less tolerant to heat than normal cells and are easily killed by high temperature. When the tumor tissue was heated at about 43°C, the permeability of tumor cell membrane was increased. When the temperature is above 50°C, the



**Figure 5.** *In vitro* photothermal antitumor role of the composite scaffolds fabricated by SLS. Live/dead staining (A), statistical diagram of living cell proportion area (B), and Cell Counting Kit-8 assay (C) of MG63 cells after incubation with PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds with or without 808 nm NIR irradiation (1 W/cm<sup>2</sup>, 10 min).





**Figure 6.** Photothermal effect of the scaffolds on normal cells. Live/dead staining (A), statistical diagram of living cell proportion area (B), and Cell Counting Kit-8 assay (C) of BMSC cells after incubation with PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds with or without 808 nm NIR irradiation (1 W/cm<sup>2</sup>, 10 min).

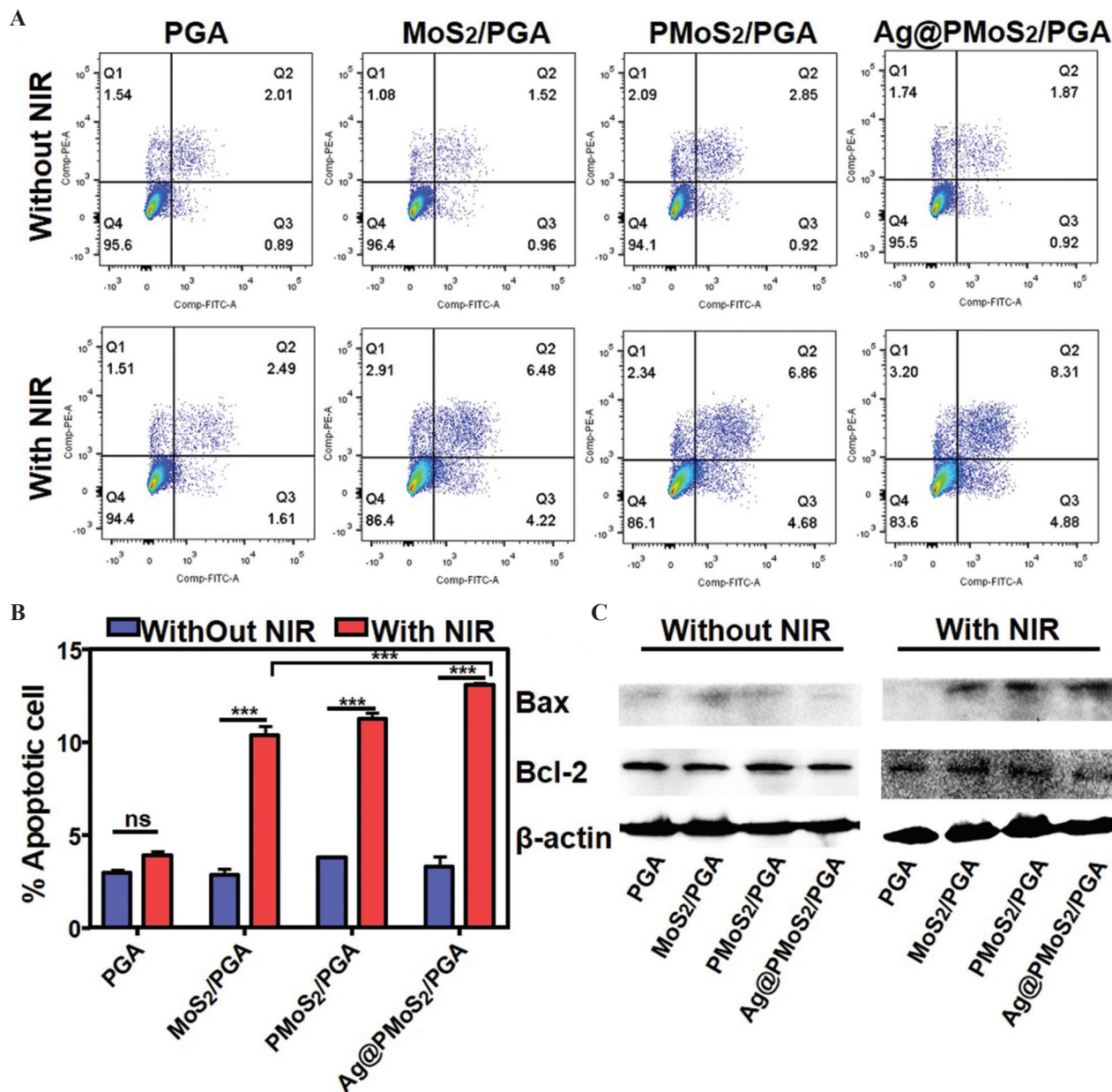
thermal effect will destroy the tumor tissue, resulting in apoptosis and necrosis of tumor cells, thus achieving the purpose of treatment<sup>[46,47]</sup>.

### 3.6. The scaffold selectively induced apoptosis *in vitro*

Above results demonstrate that the composite scaffolds can effectively cause tumor cell death under NIR irradiation. It is well known that apoptosis and necrosis are two common but completely different pathways of cell death. Some studies have shown that photothermal therapy can be used as an antitumor therapy because it can induce apoptosis and necrosis of tumor cells<sup>[48-50]</sup>. In necrosis, cell function is completely destroyed, along with the loss of membrane integrity, in which cell

contents leak out of the cell uncontrollably, causing an inflammatory response<sup>[51]</sup>. In the process of apoptosis, the cell can retain the integrity of plasma membrane, and the phagocytes selectively recognize and quickly engulf the apoptotic cells<sup>[52]</sup>. Recent studies have shown that photothermal therapy at low power density can induce apoptosis rather than necrosis<sup>[53,54]</sup>. To further investigate the mode of tumor cell death induced by composite scaffolds, flow cytometry was performed. As shown in **Figure 7A**, NIR irradiation of MoS<sub>2</sub> samples significantly promoted the apoptosis of MG63 cells. **Figure 7B** shows the statistics of apoptosis rate, it was observed that the rate of cell apoptosis in the MoS<sub>2</sub> sample increased from 3.3% to 11.6% after NIR irradiation, while PGA scaffolds remained unchanged. More importantly, compared with MoS<sub>2</sub>/PGA scaffolds, the apoptosis of MG63 cells





**Figure 7.** The scaffolds selectively induced apoptosis *in vitro*. (A) FCM (flow cytometry) for apoptosis of MG63 cells after incubation with PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds with or without 808 nm NIR irradiation (1 W/cm<sup>2</sup>, 10 min). (B) Statistics analysis of the apoptosis rate. (C) Western blot analysis of Bcl-2 and Bax protein expression in MG63 cells after incubation with PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds with or without 808 nm NIR irradiation (1 W/cm<sup>2</sup>, 10 min).

induced by Ag@PMoS<sub>2</sub>/PGA scaffolds after NIR irradiation was significantly increased by 2.7%, which was consistent with the previous results. Bax and Bcl-2 are Bcl-2 family genes. Bax promotes apoptosis and Bcl-2 inhibits apoptosis. Western blot was performed to detect the expression of Bax and Bcl-2 proteins in cells before and after photothermal treatment. As shown in **Figure 7C**, Bax protein was increased and Bcl-2 protein expression was inhibited after photothermal treatment. Factors reported to influence photothermal therapy-induced cell

death patterns include photothermal conversion efficiency and concentration of photothermal reagents, laser power density, and exposure time<sup>[55]</sup>. Here, the data showed that the scaffolds MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA induced the apoptosis of osteosarcoma cells under NIR irradiation at low density (1 W/cm<sup>2</sup>) for 10 min.

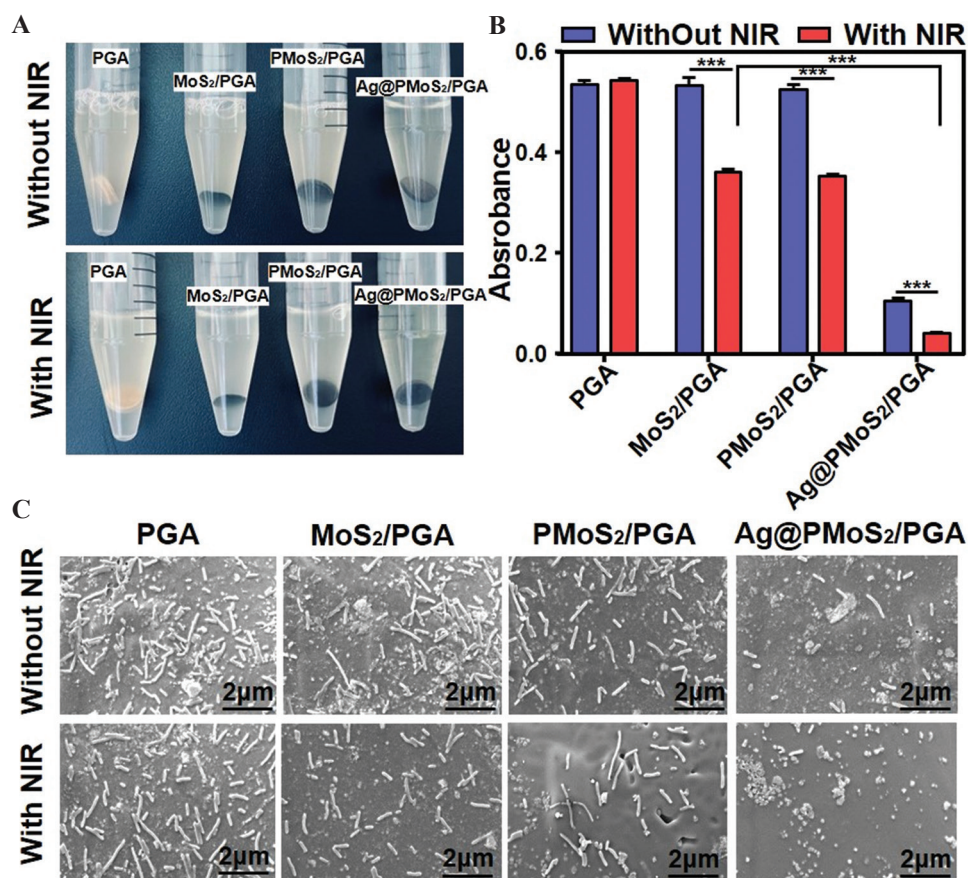
### 3.7. Antibacterial function of scaffolds

Clinically, it was well known that the bacterial infection was one problem causing orthopedic implant failure<sup>[56,57]</sup>.

The antibacterial ability of composite scaffold was evaluated by coculture of scaffolds and bacteria. As shown in **Figure 8A** and **B**, PGA, MoS<sub>2</sub>/PGA, and PMoS<sub>2</sub>/PGA scaffolds have very weak antibacterial activity to *E. coli* without NIR irradiation. While MoS<sub>2</sub>/PGA and PMoS<sub>2</sub>/PGA scaffolds show moderate photothermal antibacterial properties during NIR laser irradiation. Due to the powerful antibacterial properties of Ag, Ag@PMoS<sub>2</sub>/PGA scaffolds have superior antibacterial properties without NIR irradiation. Moreover, the antibacterial activity of Ag@PMoS<sub>2</sub>/PGA scaffolds was enhanced after NIR irradiation. The morphology of bacterial was observed by scanning electron microscope. In the absence of NIR irradiation, a large number of rod-shaped bacteria conglutinated together on the surface of the Ag-free scaffold. In contrast, the content of adherent bacteria decreased significantly in the presence of silver. More importantly, the bacteria's appearance becomes distorted and shrunken, indicating damage to their cellular structure. Compared with the scaffolds without NIR irradiation, the number of bacteria attached to the surface of MoS<sub>2</sub> scaffolds after NIR irradiation was lower and the morphology was more atrophied, especially the Ag@PMoS<sub>2</sub>/PGA scaffolds (**Figure 8C**).

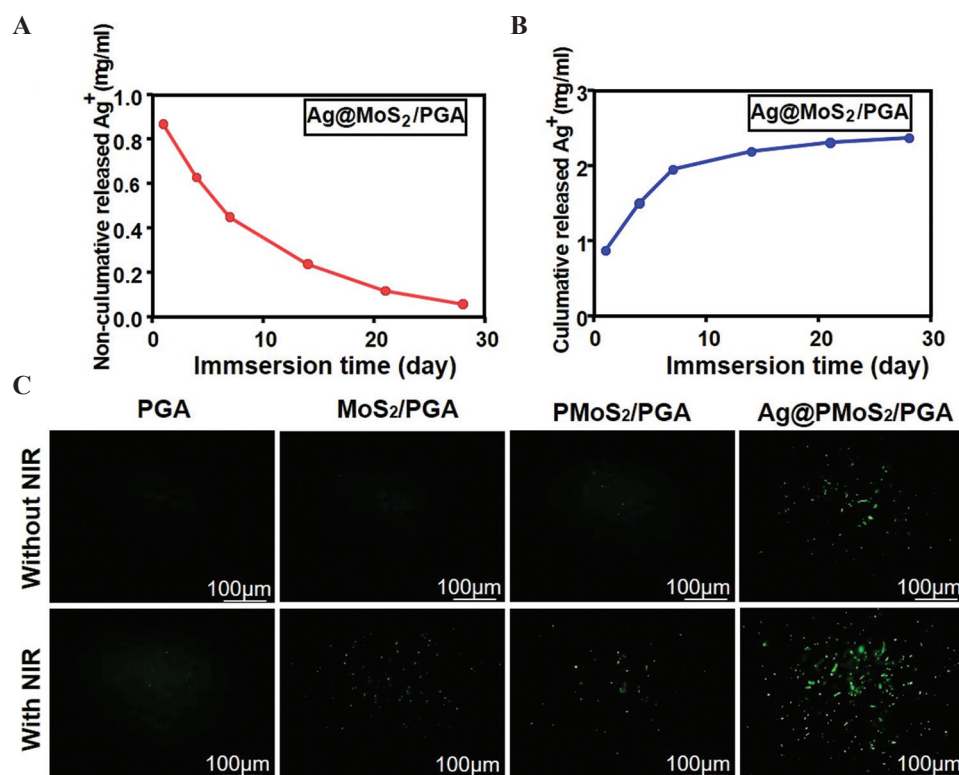
### 3.8. Release of silver ions by scaffold upregulated the level of ROS in bacteria

To explore the mechanism of antibacterial performance of scaffold, the release kinetics of Ag<sup>+</sup> of the Ag@PMoS<sub>2</sub>/PGA scaffold was studied. The amount of non-cumulative Ag<sup>+</sup> release in deionized water is shown in **Figure 9A**. It can be observed that the release amount of Ag<sup>+</sup> is 0.87 μg/mL on the 1<sup>st</sup> day. With the extension of leaching time, the release amount of Ag<sup>+</sup> gradually decreases and tends to be stable. The cumulative release experiment showed that the Ag<sup>+</sup> release gradually increased with time dependence (**Figure 9B**). It was considered that the good stability of Ag NPs formed by *in situ* reduction, the lamellar structure of MoS<sub>2</sub> NSs, and the inclusion of polymer matrix all contribute to the slow release of Ag<sup>+</sup>[58-61]. This sustained release property contributes to long-term antibacterial action without sacrificing its biocompatibility[62]. It has been reported that Ag or Ag<sup>+</sup> ions can upregulate intracellular ROS levels, resulting the destruction of cellular structure and function in many bacteria[63]. Then, we further detected the ROS level in the bacteria, and the results are shown in **Figure 9C**. It can be seen that silver-free scaffolds have no significant



**Figure 8.** The scaffolds selectively inhibit the bacterial proliferation and survival. (A) The photographs of turbidity of bacterial fluid. (B) Absorption value of bacterial culture medium at 600 nm. (C) SEM of the morphologies of *Escherichia coli* on scaffolds.





**Figure 9.** Release of silver ions by scaffold upregulated the level of ROS in bacteria. Non-cumulative (A) and cumulative (B) Ag<sup>+</sup> concentration released of Ag@PMoS<sub>2</sub>/PGA scaffold. (C) Fluorescence microscope images of *Escherichia coli* incubated with DCFH-DA after incubation with PGA, MoS<sub>2</sub>/PGA, PMoS<sub>2</sub>/PGA, and Ag@PMoS<sub>2</sub>/PGA scaffolds with or without 808 nm NIR irradiation (1 W/cm<sup>2</sup>, 10 min).

change in ROS content in bacteria with or without NIR irradiation. While the Ag@PMoS<sub>2</sub>/PGA scaffold can upregulate the ROS level in bacteria without NIR laser. And the ROS level in bacteria was more significantly upregulated when irradiated with NIR laser.

#### 4. Conclusion

A novel antitumor and antibacterial composite scaffold based on MoS<sub>2</sub> NSs loaded with *in situ* grown Ag NPs was designed and constructed by SLS technology. This *in situ* growth mode has a synergistic dispersion effect and helps prevent the agglomeration of Ag NPs and MoS<sub>2</sub> NSs in the polymer scaffold. Meanwhile, MoS<sub>2</sub> NSs can provide a barrier layer for Ag<sup>+</sup> to react with external solution and control its stable release. The data showed that the composite scaffolds had stronger photothermal and antitumor effects and could induce tumor cell apoptosis. The scaffolds also have stronger antibacterial function through upregulation of ROS in bacteria. In conclusion, the porous Ag@PMoS<sub>2</sub>/PGA composite scaffold may be a promising candidate for preventing tumor recurrence and bacterial infection in reconstruction after bone tumor surgery.

#### Acknowledgments

This study was supported by the National Natural Science Foundation of China (No. 51935014, 81871498, 82072084, 81871494), Jiangxi Provincial Natural Science Foundation of China (20192ACB20005), and Innovation for graduate students of Central South University 2020 (2020zzts774, 2020zzts223). Special thanks to the technical platform and experiment assistance of the Institute of Biological Additive Manufacturing of Jiangxi University of Science and Technology.

#### Conflict of interest

The authors declare that there are no competing interests.

#### Author contributions

S.P. guided and supervised the project. L.Z. designed and supervised the experiments. L.Z., Y.Z., and T.H. carried out the experiments. L.Z. interpreted data and wrote the manuscript with support from Y.Z., T.H., and L.Y.; S.P. and L.Y. mentored the technical part of the project. All authors read and approved the manuscript.

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