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2D MoS₂-conformal 3D-printed platform for dual-phototherapy and bone regeneration

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Abstract

Osteosarcoma has poor prognosis owing to its aggressive metastasis and high recurrence rates due to residual cancer cells which are common even after surgical resection. In addition, for irregular defects, site-specific design is essential to ensure anatomical conformity. Consequently, a critical demand exists for a theragenerative approach that simultaneously provides structural reconstruction and functional eradication of residual cancer cells. Herein, we present a patient-specific 3D-printed theragenerative polyetheretherketone (PEEK) scaffold integrated with biofunctional 2D molybdenum disulfide (MoS₂) to impart enhanced bioactivity and dual-phototherapy. 2D monolayer MoS₂ synthesized via nanoseed-initiated atmospheric pressure chemical vapor deposition (APCVD) was subsequently integrated onto the 3D-printed PEEK through a polymer-assisted transfer process. The fabricated 2D MoS₂-conformal 3D-printed PEEK scaffold (MoS₂@PEEK) enabled simultaneous photothermal and photodynamic therapy via the intrinsic photoresponsive properties MoS₂. Under dual-wavelength irradiation, this combined phototherapy effectively induced pronounced cancer cell apoptosis and exhibited antibacterial activity through the synergistic effects of localized hyperthermia and reactive oxygen species generation. In contrast, under the same photothermal stimulation, pre-osteoblasts and vascular endothelial cells exhibited enhanced attachment, proliferation, and differentiation. Therefore, this theragenerative system represents a promising patient-specific platform for simultaneous tumor suppression, infection control, and bone regeneration after osteosarcoma resection.

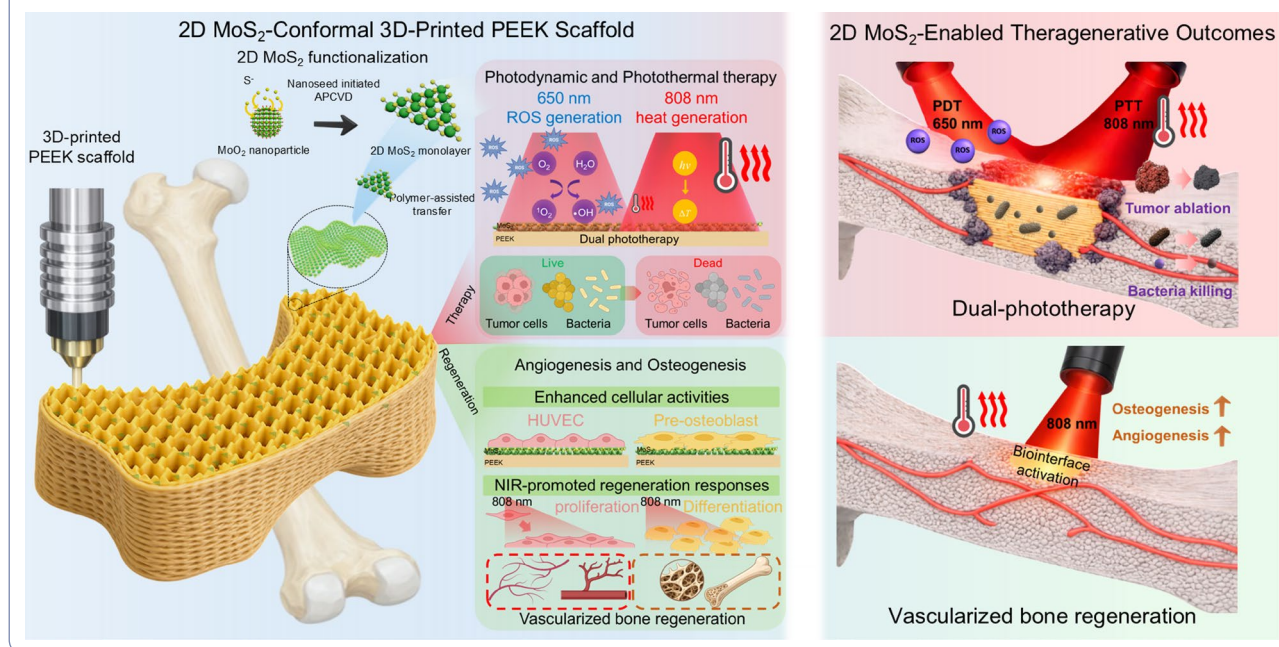
Keywords 3D printing, PEEK scaffold, 2D monolayer MoS₂, Dual-phototherapy, Osteosarcoma treatment, Antibacterial activity, Vascularized bone regeneration

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Graphical abstract**1 Introduction**

Osteosarcoma is a malignant bone tumor that primarily affects pediatric and adolescent populations because of its aggressive local infiltration and high susceptibility to early systemic metastasis, requiring advanced therapeutic treatments beyond conventional strategies [1, 2]. Wide surgical resection is one of the most commonly used treatment approaches, however, it often results in extensive postoperative bone defects [1], which can cause long-term functional disorders and increase the risk of reconstructive failure [3]. In addition, post-resection implant integration carries several clinical risks [3]. The surgical site may be vulnerable to bacterial infection due to reduced blood flow, a weakened immune response, and excessive inflammation [3, 4]. Notably, delayed bone regeneration and dead space facilitate biofilm maturation leading to chronic infection and implant failure [4]. In addition, the potential for minimal residual disease represents a critical oncological challenge, which increases the risk of local recurrence, imposing a severe burden on patients and impacting their long-term quality of life [1]. Furthermore, because bone defect geometries vary significantly between patients following osteosarcoma resection, there is a critical need for patient-specific implant designs tailored to these individual defect characteristics [3, 4]. Consequently, following osteosarcoma resection, there is a need to develop patient-specific bone implants that can simultaneously achieve tumor control and bone regeneration while preventing infection and recurrence.

Polyetheretherketone (PEEK) has attracted considerable attention as a candidate material for orthopedic implants owing to its bone-like elastic modulus, excellent mechanical strength, chemical stability and relatively low imaging artifacts in computed tomography (CT) and magnetic resonance imaging (MRI) [5–9]. In particular, PEEK can effectively mitigate the stress-shielding phenomenon compared with conventional metallic implants due to its similar elastic modulus with that of the bone, while possessing excellent durability that ensures long-term stability in-vivo [1, 4–6, 10]. Furthermore, although PEEK is a challenging material for additive manufacturing due to its high melting temperature, successful 3D printing of PEEK enables patient-specific geometries tailored to complex defects while maintaining superior mechanical integrity [1, 4, 6]. By precisely controlling pore architecture including porosity, pore size and interconnectivity, mechanical integrity and biological fixation can be optimized, facilitating tissue ingrowth for excellent load-bearing performance [4, 11, 12]. However, PEEK is a representative bioinert material with limited capacity to facilitate cellular adhesion and proliferation. The deficiency in surface bioactivity results in a lack of osseointegration and osteogenesis, compromising the initial stability of the bone implant and delaying tissue regeneration [1, 4–6, 11]. Consequently, strategies for surface functionalization to enhance bioactivity are essential for maximizing the clinical performance of PEEK-based orthopedic implants.

Molybdenum disulfide (MoS_2), a transition metal dichalcogenide (TMDC), is gaining attention as a functional material in the biomedical field due to its high surface area, defect-rich surfaces including sulfur vacancies and edge sites with oxygen-containing surface species such as MoO_x and Mo-OH , which can collectively enhance biocompatibility, including cellular adhesion, proliferation and differentiation [13–20]. In addition, MoS_2 exhibits excellent long-term mechanical and chemical stability, making it an ideal candidate for biomedical implant surface functionalization [1, 17, 19, 20]. Notably, MoS_2 exhibits dual phototherapeutic performance, enabling both photothermal therapy (PTT) and photodynamic therapy (PDT) effects in response to external light irradiation [2, 5, 13, 19]. Compared to conventional pharmacological interventions, this light-mediated approach offers a non-invasive, localized antimicrobial and anti-cancer treatment, which can minimize damage to healthy tissue and systemic side effects while accelerating tissue regeneration [1, 5, 10, 11, 19]. PTT can selectively damage tumor cells and bacteria by localized hyperthermia through photothermal conversion under near-infrared irradiation (NIR) [1, 2, 5, 13, 19, 21]. PDT generates reactive oxygen species (ROS) upon light irradiation, thereby inducing cytotoxicity and antibacterial activity [5, 13, 19]. However, the therapeutic efficacy of PTT or PDT monotherapy may be limited. Therefore, synergizing these two phototherapies can significantly enhance therapeutic efficacy and address heterogeneity within tumor and infection microenvironments [2, 5, 13, 19]. Furthermore, numerous studies have reported that mild photothermal stimulation promotes not only osteogenesis but also accelerates angiogenesis [5, 10, 11, 15, 18]. Consequently, precisely controlled photo-stimulation represents a potent strategy to achieve tumor ablation and infection prophylaxis, while simultaneously promoting vascularized bone regeneration.

MoS_2 can be synthesized by mechanical exfoliation, chemical exfoliation, hydrothermal/solvothermal synthesis, metal–organic chemical vapor deposition (MOCVD), and conventional atmospheric pressure chemical vapor deposition (APCVD) [13, 16, 19, 20, 22]. However, these methods often struggle to obtain highly crystalline MoS_2 , require prolonged synthesis times, involve high costs, and pose health, and environmental risks. Notably, these methods have limitations in precisely controlling the layer thickness and uniformity [13, 14, 16, 20, 22]. To overcome these limitations, we utilized the nanoseed-initiated APCVD process, which enables wafer-scale synthesis of 2D monolayer MoS_2 with high crystallinity and uniformity. This approach not only ensures excellent reproducibility and scalability, with a reduced processing time but also reduces potential health and environmental risks. Furthermore, by applying a polymer-assisted

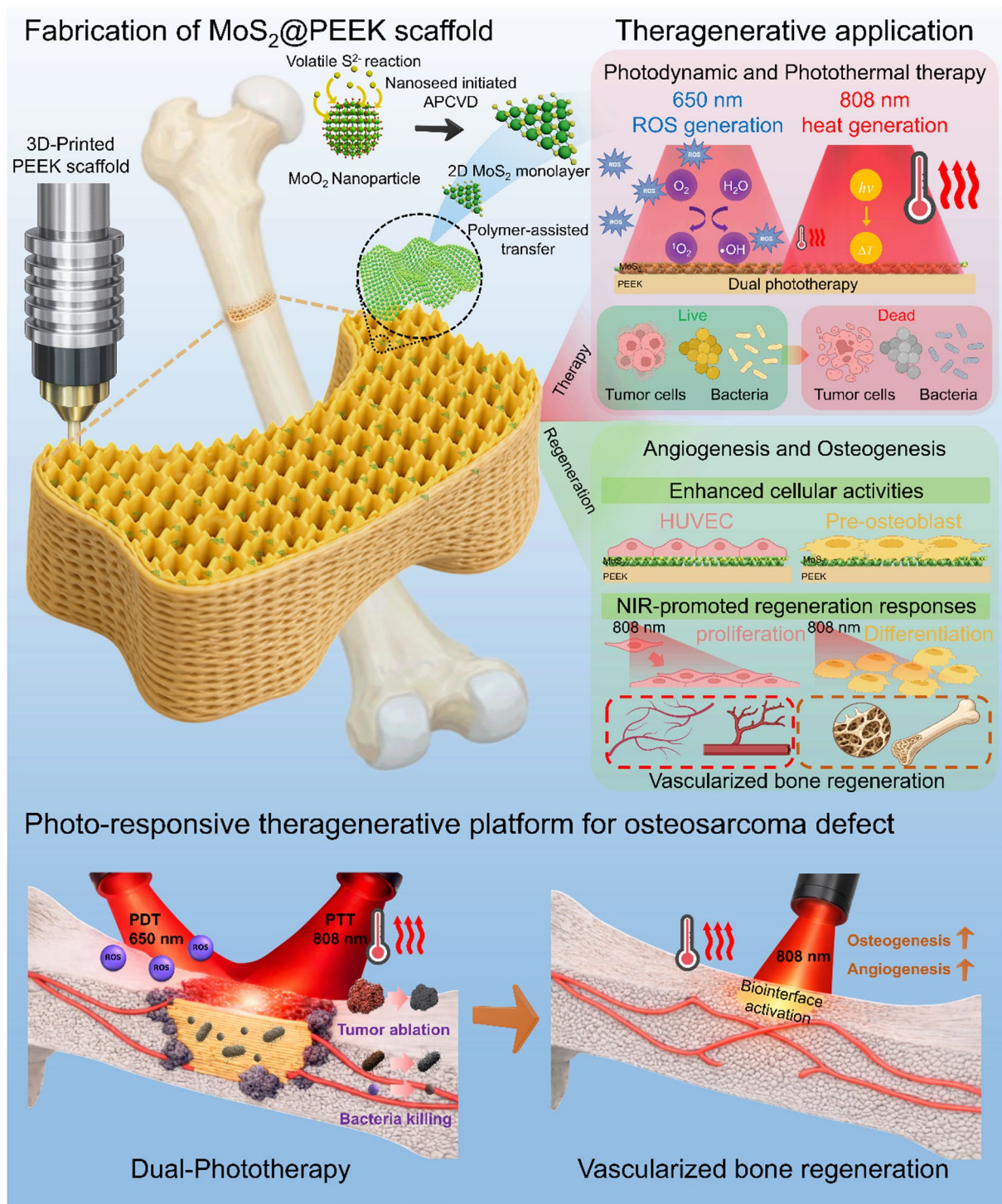
transfer method, MoS_2 can be conformally integrated onto the large surface area of the substrate with complex morphologies. This approach enables functionalization of heat-sensitive polymers such as PEEK which can not withstand the high temperatures of CVD or hydrothermal processes for direct MoS_2 growth, and additionally allows integration onto the irregular surface of 3D scaffolds, thereby significantly enhancing the bioactivity of 3D-printed PEEK.

In this study, we applied MoO_2 nanoseed-initiated APCVD to uniformly synthesize wafer-scale 2D monolayer MoS_2 with high crystallinity, which was subsequently integrated onto the surface of 3D-printed PEEK by a polymer-assisted transfer technique. This process developed 3D-printed PEEK functionalized with 2D MoS_2 termed $\text{MoS}_2@\text{PEEK}$. $\text{MoS}_2@\text{PEEK}$ features a structure optimized for the patient-specific defects and promotes enhanced osteogenesis and angiogenesis. Moreover, $\text{MoS}_2@\text{PEEK}$ exhibits dual phototherapeutic efficacy under dual-wavelength irradiation at 808 and 650 nm, which induces PTT and PDT responses, respectively. This synergistic approach significantly mitigates the risk of postoperative bacterial infection and tumor recurrence while simultaneously accelerating osteogenesis and angiogenesis through a pro-regenerative microenvironment (Scheme 1) [23]. Consequently, by integrating patient-specific bone reconstruction and localized dual-phototherapy into a single implant, this platform represents a next-generation theragenerative strategy to overcome critical challenges that may arise during implant placement and tissue reconstruction following osteosarcoma resection.

2 Materials and methods

2.1 Materials

Polyetheretherketone (PEEK) granule, 6 mm nominal granule size, weight 200 g, PEEK powder, mean particle size 50 μm , weight 100 g, ammonium heptamolybdate powder, ethyl alcohol (EtOH, 99%), acetone (99%), isopropyl alcohol (IPA, 99%), polyvinylpyrrolidone (PVP, molecular weight: 40,000), NaCl powder (99%), SiC sandpapers, polystyrene (PS, molecular weight: 280,000), toluene (99.8%), antibiotic–antimycotic (AA), paraformaldehyde (4%), Triton X-100, bovine serum albumin (BSA), glutaraldehyde, 1,1,1,3,3,3-hexamethyldisilazane, trypsin EDTA solution, and alizarin red S (ARS), sodium phosphate, cetylpyridinium chloride, p-Nitrophenyl Phosphate (pNPP) were purchased from Sigma-Aldrich (USA). Double-side polished C-plane sapphire wafers (0001), 2 inches in diameter and 430 μm in thickness, were obtained from iNexus, Inc (Korea). Argon gas (99.999%, Ar), and Nitrogen gas (99.99%, N_2) were purchased from DAEHAN SPECIAL GAS Co., LTD (Korea). 70% EtOH (99.5%), and methyl alcohol (99.5%)



Scheme 1 Schematic illustration of the fabrication of a 2D MoS₂-conformal 3D-printed PEEK scaffold (MoS₂@PEEK) and its application as a dual photo-responsive theragenerative platform for osteosarcoma defect treatment. Patient-specific PEEK scaffolds were fabricated via melt-extrusion filament fabrication and FDM-based 3D printing. Wafer-scale 2D MoS₂ synthesized by nanoseed-initiated APCVD processes was integrated onto the 3D-printed PEEK through a polymer-assisted transfer, yielding MoS₂@PEEK. Under dual-wavelength irradiation, the MoS₂ enables dual-phototherapy, involving 650 nm-mediated photodynamic therapy (PDT) and 800 nm-mediated photothermal therapy (PTT), for effective tumor ablation and antibacterial activity. Simultaneously, controlled 800 nm-induced hyperthermia promotes vascularized bone regeneration. This integrated theragenerative platform simultaneously achieves oncologic eradication and functional bone repair within a single implant system.

were purchased from DAEJUNG (Korea). Endothelial cell basal medium-2 (EBM) and endothelial cell growth kit (EGM) were obtained from Lonza (Switzerland). Dulbecco's modified Eagle's medium (DMEM), Dulbecco's Phosphate-Buffered Saline (DPBS), and alpha minimum essential medium (α -MEM) were purchased from Welgene (Korea). Fetal bovine serum (FBS) was obtained from Gibco (USA). Singlet oxygen sensor green (SOSG) kit, Live/Dead staining kit (L3224), 4',6-diamidino-2-phenylindole (DAPI), CyQUANT cell proliferation assay kit (C7026), calcein AM, and live and dead bacterial viability kit (L7012) were obtained from Invitrogen (USA). CCK cell viability assay kit (D-Plus) was purchased from Dongin-LS (Korea). Alexa Fluor® 555 phalloidin was purchased from Molecular Probes (USA). BCA protein assay kit was obtained from Thermo Fisher (USA).

2.2 Fabrication of the PEEK filament and 3D-Printed PEEK scaffolds

For the manufacture of PEEK filament, PEEK was mixed in two forms, granules and powder, at a ratio of 80 vol% granules to 20 vol% powder. This composition was designed to maintain the stable melt viscosity of the granule base while allowing the powder to effectively fill the voids between the granules, thereby improving flowability and enhancing extrusion stability. Subsequently, all mixed raw materials were dried in a vacuum oven at 80 °C for 12 h to remove moisture. The dried mixture was extruded at 400 °C using filament manufacturing equipment (3devo B.V., Netherlands), resulting in the production of uniform filaments with a diameter of 1.56 ± 0.01 mm. The manufactured filament was used for 3D printing via a customized FDM system. Printing was performed under the following conditions: nozzle temperature 440 °C, bed temperature 160 °C, chamber temperature 160 °C, printing speed 20 mm/s, and layer thickness 200 μ m. Under these conditions, various structures were printed to realize patient-specific shapes based on diverse CAD designs.

2.3 Preparation of MoO₃ precursor solution

MoO₃ nanoparticles were synthesized by hydrothermal synthesis. 150 mg of Ammonium heptamolybdate powder was dissolved in 22 mL of deionized (DI) water. And 10 mL of EtOH was added to the solution. After 500 mg of PVP powder was dissolved in the solution. Subsequently mixture was stirred for 30 min. The solution was transferred into Teflon-lined stainless-steel autoclave (SCIST, Korea) and heat-treated at 180 °C for 16 h in a muffle furnace. After the reaction, the autoclave was rapidly cooled in 4 °C water. The solution was then centrifuged at 23,000 G, and the supernatant was removed. The precipitate was washed three times with acetone and

EtOH, respectively, followed by drying at 80 °C overnight to prepare MoO₃ nanoparticles. To prepare the MoO₃ precursor solution, 15.2 mg of MoO₃ nanoparticle precursor was dispersed in 30 mL of ethanol by sonication for 30 min to achieve uniform dispersion. Then, 1.2 mL of the MoO₃ solution was mixed with 0.1 mL of ethanol and 26 μ L of 0.1 M NaCl in methanol, followed by sonication for 10 min.

2.4 2D MoS₂ synthesis via nanoseed-initiated APCVD

Sapphire wafer was pretreated at 1000 °C for 4 h in a muffle furnace to remove surface impurities. The pretreated wafer was sequentially washed by sonication in acetone and EtOH for 10 min each, respectively. Afterwards, the wafer was rinsed with IPA and dried by N₂ gas blowing. After the cleaning process, 0.8 mL of the MoO₃ precursor solution was drop-cast on the wafer and uniformly dispersed by spin coating at 3000 rpm for 60 s. The MoO₃ dispersed wafer and sulfur powder were loaded in separate zones within CVD chamber. The distance between the samples was 35 cm. The MoO₃ dispersed wafer was heated to 650 °C for 45 min and maintained at that temperature for 30 min, and the sulfur powder was maintained at 20 °C for 35 min, then heated to 140 °C for 10 min and held at that temperature for 30 min, respectively, under an Ar atmosphere with flow rate of 500 sccm. After the heating process, the samples were cooled to room temperature.

2.5 Polymer assisted transfer of MoS₂ onto 3D-printed PEEK scaffolds

The PEEK was polished in sequence with 800, 1000, 2000, and 3000 grits SiC sandpaper. Polished PEEK was washed sequentially with ethanol and DI water by sonication for 5 min each. A polymer-assisted transfer method was used to transfer MoS₂ onto the PEEK surface. For the supporting polymer, 9 g of PS powder was dissolved in 100 mL of toluene overnight. The PS solution was spin-coated onto MoS₂ grown wafer at 3000 rpm for 60 s and subsequently heat-treated at 90 °C for 5 min on a hot plate to completely dry the solvent. The PS coated MoS₂ wafer was cut into the size of the PEEK substrate and immersed in DI water. Due to the hydrophobic nature of both MoS₂ and PS, water penetrated the interface between MoS₂ and the wafer, separating the PS/MoS₂ layer from the wafer and floating on the water surface. The floating film was carefully transferred onto the PEEK substrate. Then residual water between MoS₂ and PEEK was removed using filter paper and to ensure complete removal of the water, the sample was heat-treated at 90 °C for 5 min. The PS was eliminated by immersing the sample in toluene for 1 h and the sample was rinsed with acetone and dried at room temperature for 30 min. The

resulting MoS₂ transferred PEEK substrate is hereafter referred to as MoS₂@PEEK.

2.6 Characterization of MoS₂ grown wafer and MoS₂@PEEK

The morphology, nanostructure and atomic structure of the materials were analyzed by scanning electron microscopy (SEM, HITACHI S-4800, Japan) and transmission electron microscopy (TEM, JEOL Ltd, JEM-2100F, Japan), equipped with energy-dispersive X-ray spectroscopy (EDX). To investigate the cross-sectional morphology, a TEM specimen was prepared by focused ion beam milling (FIB) using a dual-beam SEM (ZEISS AURIGA, Germany), followed by TEM imaging. The surface chemistry of products was collected by X-ray photoelectron spectroscopy (XPS, AXIS SUPRA, ESCA II, UK). X-ray diffraction (XRD, Rigaku MiniFlex600, Japan) patterns were recorded, diffractometer using Cu K α radiation ($\lambda = 1.5405 \text{ \AA}$) with the 2θ range of $20\text{--}75^\circ$ with an interval of 0.02° . Additionally, Raman spectra were collected using aberration-corrected spectrometer operated with 532 nm laser (NOST, HEDA, Korea).

2.7 The photothermal and photodynamic ability of the MoS₂@PEEK scaffold

The photothermal and photodynamic characteristics of the scaffold were assessed using 808 nm NIR and 650 nm visible-light lasers (OCLA; AMI, Korea), respectively. The 3D-printed scaffold, with dimensions of $10 \times 10 \times 2 \text{ mm}^3$, was positioned within a mold filled with DPBS, measuring $20 \times 20 \times 4 \text{ mm}^3$, to replicate an in vitro environment. Photothermal properties were evaluated by monitoring temperature variations over time under irradiation at power intensities of 1, 2, and 3 W cm^{-2} using the 808 nm laser. Photodynamic properties were examined by assessing the time-dependent production of singlet oxygen ($^1\text{O}_2$) under continuous irradiation with a 650 nm laser (100 mW). During irradiation, temperature changes were recorded in real-time using a thermal imaging camera (FLIR E54; FLIR Systems Inc., USA), and $^1\text{O}_2$ generation was quantified using the SOSG assay. SOSG fluorescence was measured with a hybrid multi-mode reader (Synergy H1, BioTek, USA) at an excitation wavelength of 390 nm and an emission wavelength of 520 nm. The final fluorescence values were obtained by subtracting the signal of the control group and followed by normalization for analysis.

2.8 In vitro dual-phototherapeutic anticancer performance of MoS₂@PEEK scaffolds

Osteosarcoma cells (MG63; CRL-1427, ATCC, USA) were seeded onto sterilized PEEK and MoS₂@PEEK scaffolds ($10 \times 10 \times 2 \text{ mm}^3$) at a density of $2 \times 10^4 \text{ cells mL}^{-1}$ following treatment with 70% ethanol and ultraviolet

(UV) irradiation. The cells were subsequently cultured under standard conditions in DMEM supplemented with 10% FBS and 1% AA. After a 24 h incubation period to facilitate cell attachment and stabilization, photoirradiation was conducted under three different conditions. For PDT alone, a 650 nm laser was applied at 100 mW output for 3 min. For PTT alone, an 808 nm laser was applied at an output density of 2 W cm^{-2} for 3 min. For dual-phototherapy, specimens were sequentially irradiated with a 650 nm laser at 100 mW for 3 min, followed by an 808 nm laser at 2 W cm^{-2} for 3 min. Cell viability was then qualitatively assessed using fluorescent staining with a Live/Dead staining kit and quantitatively analyzed using a CCK-8 assay. Fluorescence images were acquired using a fluorescence microscope (ECLIPS Ti2; Nikon, Japan). Cells were stained to indicate live and dead states with Calcein AM and Ethidium homodimer-1, respectively.

2.9 In vitro dual-phototherapeutic antibacterial effect of MoS₂@PEEK scaffolds

Gram-negative *Escherichia coli* (*E. coli*; ATCC 8739, Rockville, MD, USA) and gram-positive *Staphylococcus aureus* (*S. aureus*; ATCC 6538, Rockville, MD, USA) were employed to assess the NIR-responsive dual phototherapeutic antibacterial efficacy of the theragenerative MoS₂@PEEK platform. Each bacterial strain was cultured for 24 h by inoculating 50 μL of stock solution into 3 mL of LB broth. Subsequently, scaffolds measuring $10 \times 10 \times 2 \text{ mm}^3$, sterilized with 70% ethanol and UV irradiation, were placed in a 24-well plate. Suspensions of *E. coli* ($1 \times 10^3 \text{ CFU mL}^{-1}$) and *S. aureus* ($1 \times 10^4 \text{ CFU mL}^{-1}$), each 60 μL , were seeded onto the respective specimens. Following a 4 h incubation period to facilitate bacterial attachment, photoirradiation was conducted. PDT was executed using a 650 nm laser at 100 mW for 3 min, while PTT was performed using an 808 nm laser at 2 W cm^{-2} for 3 min. For dual-phototherapy, specimens were sequentially irradiated with a 650 nm laser at 100 mW for 3 min, followed by an 808 nm laser at 2 W cm^{-2} for 3 min. Immediately post photoirradiation, the specimens were washed twice with DPBS and fixed with 2.5% glutaraldehyde to observe bacterial morphological changes. A stepwise dehydration process was then conducted using 70%, 90%, and 100% ethanol, followed by treatment with 1,1,1,3,3,3-hexamethyldisilazane, and analysis was performed using FE-SEM. Bacterial viability was assessed using a live/dead bacterial viability kit, with SYTO 9 and propidium iodide applied to each specimen and allowed to react for 15 min in the dark condition, followed by qualitative analysis using a fluorescence microscope. For quantitative evaluation, post-laser irradiation, the specimens were further incubated for 6 h at 37°C and 150 rpm. The specimens were then washed with PBS, transferred into 3 mL of LB broth, and the attached

bacteria were detached by vigorous vortexing for 1 min. The recovered bacterial suspension was serially diluted tenfold up to 10^3 times and subsequently plated onto LB agar plates. After 24 h of incubation at 37 °C, the number of colonies formed was counted, and the average number of colonies was quantified based on high-resolution images.

2.10 In vitro NIR-responsive osteo- angiogenesis of MoS₂@ PEEK scaffolds

The degree of osteogenesis and angiogenesis were analyzed using pre-osteoblast cells (MC3T3-E1; CRL-2593, ATCC, USA), and human umbilical vein endothelial cells (HUVECs; CRL-1730, ATCC, USA), respectively. MC3T3-E1 cells and HUVECs were cultured in α -MEM, and EBM supplemented with EGM bullet kit, respectively. For fluorescence staining, cells were seeded on specimens ($10 \times 10 \times 2$ mm³) at a density of 3×10^4 cells mL⁻¹, fixed with 4% paraformaldehyde, and immersed in 0.1% Triton X-100 and 3% BSA solutions. The nuclei and cytoplasm of the cells were then stained with DAPI and phalloidin, respectively. For quantitative analysis of cell adhesion, cell density based on fluorescence images and cytoplasmic area per cell based on FE-SEM images were each analyzed. Cell proliferation was assessed using the CCK-8 assay; after seeding at a density of 2×10^4 cells mL⁻¹ and allowing an overnight stabilization period, NIR stimuli were applied using an 808 nm laser at 2 W cm⁻² for 3 min, and absorbance at 450 nm was measured using a multi-mode reader at 1 and 3 days. Cell differentiation was analyzed through ARS staining and ALP activity assay. For ARS staining, following NIR stimulation using an 808 nm laser at 2 W cm⁻² for 3 min on days 0 and 3, the specimens were washed twice with DPBS, fixed with 4% paraformaldehyde, and reacted with ARS solution under dark conditions, followed by washing with DW and drying. The degree of mineralization was then photographed using a high-resolution camera. For quantitative analysis, the specimens washed with DW were reacted with 10% cetylpyridinium chloride in 10 mM sodium phosphate (pH 7.0), and absorbance at 560 nm was measured using a multi-mode reader. For the ALP activity assay, following NIR stimulation using an 808 nm laser at 2 W cm⁻² for 3 min on days 0 and 3, cells were collected by trypsin EDTA treatment, then treated with 0.1% Triton X-100 and vortexed, followed by four cycles of freezing at -70 °C and thawing at 37 °C for 5 min each. The samples were then centrifuged at 14,000 rpm and 4 °C for 20 min to separate the supernatant, and samples were prepared according to consistent protein amounts determined by BCA protein quantification. Next, pNPP was dispensed, reacted at 37 °C for 1 h, and absorbance at 405 nm was measured using a multi-mode reader.

2.11 Statistical analysis

The quantitative experimental results are expressed as the mean $\pm$ standard deviation, derived from at least three replicates for each group. The data analysis was conducted using IBM SPSS Statistics 26 (IBM, Armonk, USA). To determine statistical significance, one-way analysis of variance (ANOVA) with Tukey's post hoc test, the Kruskal–Wallis H test, and the Mann–Whitney U test with pairwise comparisons were employed. The p-value of less than 0.05 was considered statistically significant, with significance levels indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, and **** $p < 0.001$.

3 Results and discussion

3.1 Fabrication of 3D-printed PEEK scaffold

The reconstruction of extensive and irregular defects formed after osteosarcoma resection often hindered by the technical limitations of fabricating implant structures that simultaneously satisfy anatomical precision and mechanical compatibility. Therefore, PEEK scaffolds fabricated through 3D printing-based patient-specific structural design must not only ensure precise geometric compatibility with the surrounding tissue but also facilitate simultaneous therapeutic treatment and tissue regeneration through integration with functional materials [24, 25].

Accordingly, this study proposes a strategy to enhance tissue-material interfacial interactions and induce functional reconstruction by integrating 2D monolayer MoS₂ synthesized via MoO₃ nanoseed-initiated APCVD, onto the surface of a 3D-printed PEEK scaffold. Notably, by exploiting the photo-responsivity of 2D MoS₂, we induced localized dual-phototherapeutic effects of combined PTT and PDT, while simultaneously promoting tissue regeneration through the intrinsic bioactivity of MoS₂ [26]. Consequently, a 2D MoS₂-conformal 3D-printed PEEK based theragenerative platform was established, enabling simultaneous eradication of residual cancer cells and bacterial pathogens with accelerated vascularized osteogenesis, as illustrated in Scheme 1.

First, to achieve precise 3D-printed PEEK scaffolds, it is essential to manufacture PEEK filaments with uniform diameters and stable physical properties. However, melt-extruding PEEK into high-quality filaments while preserving its inherent mechanical properties remains a technically challenging task [27]. To ensure the structural stability and printing precision of PEEK filaments, we employed a granule-powder blend with a nominal size of 6 mm and powder with an average size of 50 μ m at an 8:2 (vol%) ratio. While granules offer the advantage of excellent mechanical strength, their high strength and melting characteristics can hinder flowability during filament extrusion. In contrast, powder effectively fills interparticle voids, thereby enhancing flowability and ensuring

extrusion stability. Utilizing this optimized blend, we successfully produced highly uniform filaments with a diameter of 1.56 ± 0.01 mm by a melt extrusion-based compression molding process. By applying the filaments, various structures were fabricated based on computer-aided design (CAD) models under printing conditions of 440°C (Fig. S1). Furthermore, to demonstrate anatomical applicability and clinical scalability, several orthopedic devices traditionally made from metallic alloys including a cranial patch, spinal cage, suture anchor, and bone plate were 3D-printed with high anatomical precision, confirming the feasibility of patient-specific fabrication and its applicability to actual bone defect sites (Fig. S2).

3.2 Fabrication and characterization of MoS_2 @PEEK scaffold

MoS_2 , a member of the TMDC family, has attracted considerable attention as a functional material for biomedical applications owing to its high specific surface area, and superior interfacial reactivity arising from sulfur vacancies, edge defects, and surface-active species such as MoO_x and $\text{Mo}-\text{OH}$, which collectively contribute to its excellent cellular compatibility and adhesive properties [12, 14, 15, 17]. Furthermore, MoS_2 maintains excellent mechanical and chemical stability over prolonged periods while offering great potential as a next-generation biointerfacial material owing to its photo-responsive capabilities such as PTT and PDT [13, 16, 17, 19, 20, 28]. However, to translate these advantages into practical biomedical platforms, highly crystalline 2D MoS_2 with precisely controlled layer thickness over large-area substrates, must be reproducibly synthesized. In parallel, processing strategies are required to enable damage-free integration of MoS_2 onto various substrates, particularly 3D scaffolds with complex geometries. To achieve large-area, highly crystalline 2D MoS_2 , we employed a MoO_2 nanoseed-initiated APCVD process. The as-synthesized 2D MoS_2 was integrated onto 3D-printed PEEK via polymer-assisted transfer to yield the MoS_2 @PEEK platform (Fig. S3).

Based on a previous study, the MoO_2 precursor was synthesized via a hydrothermal method [22]. The crystallographic structure of the synthesized MoO_2 precursor was validated by X-ray diffraction (XRD) analysis. The XRD patterns exhibited the characteristic peaks corresponding to the (100), (002), and (101) planes of MoO_2 , confirming the successful synthesis of the highly crystalline MoO_2 precursor (Fig. S4). The synthesis of a highly crystalline nanoparticle precursor is a critical foundation for achieving highly crystalline MoS_2 during the subsequent nanoseed-initiated APCVD process. This is because the highly crystalline MoO_2 nanoparticles act as self-seeding templates, where the growth of the MoS_2 layer is driven by strong crystallographic correlations and

energetically preferred orientations, rather than simply replicating the crystal structure of MoO_2 [20, 22]. The synthesized MoO_2 precursor was mixed with ethanol, methanol, and NaCl to prepare a MoO_2 solution, which was uniformly dispersed onto the wafer by spin-coating. Scanning electron microscope (SEM) and energy dispersive X-ray spectroscopy (EDX) analyses were performed to examine whether the MoO_2 particles were uniformly distributed on the prepared sapphire wafer (Fig. S5). The results showed that the MoO_2 particles were uniformly distributed across the wafer surface, suggesting spatial homogeneity which is a critical factor in achieving uniform sulfurization and preventing non-uniform island coalescence or unnecessary local defects during the nanoseed-initiated APCVD process [13, 16, 20, 22].

Subsequently, sulfur powder was used as the sulfur source and MoS_2 grown wafer was fabricated by nanoseed-initiated APCVD. As shown in Fig. S6, Optical images and optical microscopy (OM) analyses confirmed that MoS_2 was uniformly grown across the entire large-area wafer with a diameter of 2 inches. Such large-scale uniformity minimizes sample to sample variation, thereby enhancing the reliability of subsequent biological evaluations [14, 22, 29–31]. SEM and EDX analyses further confirmed that the MoS_2 was uniformly grown across the entire wafer (Fig. S7). This indicates that sulfurization did not occur locally but proceeded uniformly across the entire wafer surface, thereby supporting the chemical homogeneity and reproducibility of the process. Transmission electron microscope (TEM) analysis revealed that the synthesized MoS_2 grew in the morphology of triangular island (Fig. S8a), indicating a highly ordered crystalline structure rather than an amorphous phase [20, 22]. Notably, cross-sectional TEM analysis confirmed that the thickness of the synthesized MoS_2 was approximately 6 Å, directly demonstrating the growth of monolayer MoS_2 (Fig. S8b and c) [15, 16, 22]. The significance of the monolayer structure extends beyond its minimal thickness, it maximizes interfacial interactions with the substrate, exposes active surface sites to the external environment, and gives rise to properties that are distinct from those of bulk or few-layer counterparts [13, 14, 18–20, 28]. Therefore, the monolayer and highly crystalline structures obtained in this study can be regarded as a key structural foundation for subsequent cell-material interactions, modulation of surface energy, and the photo-responsive functions. Raman analysis further supported these findings, showing characteristic Raman peaks of the MoS_2 at 386 and 403 cm^{-1} . The 17 cm^{-1} peak separation confirms the formation of monolayer structure of MoS_2 (Fig. S9a) [12, 22]. Furthermore, Mo 3d and S 2p peaks were observed in the full XPS spectra of the MoS_2 grown wafer (Fig. S9b), and Mo 3d₅, Mo 3d₃, S 2p₃, and S 2p₁ peaks were clearly identified in the high-resolution

XPS spectra (Fig. S9c and d), indicating that the chemically stable 2D MoS₂ phase was successfully synthesized without any physically adsorbed byproducts. Consequently, the nanoseed-initiated APCVD process developed in this study can be an effective synthesis strategy to produce highly crystalline 2D monolayer MoS₂ with uniform thickness over a large area.

Subsequently, the 2D monolayer MoS₂ was transferred onto the 3D-printed PEEK using a polymer-assisted transfer process, followed by the removal of polystyrene (PS) with toluene to obtain the MoS₂@PEEK scaffold. This process offers the advantage of preserving the highly crystalline monolayer characteristics achieved during the synthesis without structural damage, while ultimately enabling functional integration onto the surface of a biomedical scaffold. This demonstrates a higher level of technical completeness than conventional transfer methods such as wet transfer, electrochemical delamination, bubble transfer, and dry transfer [22, 31]. The surface characteristics including surface morphology and the chemical structure of the fabricated MoS₂@PEEK were evaluated. Optical images, SEM, and EDX analyses confirmed that MoS₂ was uniformly transferred over a wide area of the 3D-printed PEEK (PEEK) surface (Fig. 1a). This indicates that the transfer was achieved stably across the entire surface of the scaffold, rather than being confined to specific regions. In particular, 3D printed scaffolds may exhibit surface roughness, curvature, and microstructural inhomogeneities, uniform transfer on complex structure is particularly noteworthy from a process engineering perspective. Cross-sectional TEM analysis confirmed that the monolayer MoS₂ with a thickness of approximately 6 Å was functionalized on the PEEK surface (Fig. 1b and c), consistent with the cross-sectional TEM image observed for the MoS₂ grown wafer (Fig. S8b and c). This demonstrates that the transfer process 2D MoS₂ was transferred onto the substrate while preserving the monolayer characteristics and structural integrity established during the synthesis. Raman analysis revealed the characteristic peaks of monolayer MoS₂ at 384 and 403 cm⁻¹ on the MoS₂@PEEK surface, and the 19 cm⁻¹ separation between the two peaks which suit the separation range of 17–19 cm⁻¹ of the monolayer MoS₂ confirming the successful transfer of monolayer MoS₂ (Fig. 1d). Furthermore, the uniformity of the transferred 2D MoS₂, Raman evaluation was performed at predetermined nine spots of MoS₂@PEEK surface, and the characteristic peaks of monolayer MoS₂ were consistently observed in all regions (Fig. S10). The XPS analysis results also strongly supported this finding. Mo 3d and S 2p peaks, which were not observed in PEEK, were clearly identified in the full XPS spectra of MoS₂@PEEK (Fig. 1e), and the high-resolution XPS spectra revealed Mo 3d₅, Mo 3d₃, S 2p₃, and S 2p₁ peaks

identical to those of the MoS₂ grown wafer (Fig. 1f and g). These results demonstrate that this transfer process is not limited to localized functionalization but can achieve a stable and reproducible uniform monolayer coating across the entire surface of the scaffold. This provides an important foundation for minimizing surface location dependent variations in cellular responses and ensuring uniform biological performance in future bio-scaffold applications. The integrated process of nanoseed-initiated APCVD growth, and polymer-assisted transfer can be regarded as a coherent fabrication strategy for integrating highly crystalline 2D monolayer MoS₂ onto the surface of a 3D polymer scaffold without structural damage. This level of process integration is particularly attractive because it demonstrates technical completeness that extends beyond simple material fabrication and is directly applicable to the design of tissue engineering scaffolds and next-generation biointerfaces, representing a key methodological distinction of this study.

The hydrophilicity of the surface was evaluated by measuring the water contact angles of PEEK and MoS₂@PEEK showed that the contact angle of MoS₂@PEEK was higher than that of the PEEK (Fig. S11), showing that the introduction of MoS₂ increased surface hydrophobicity. Although hydrophobicity was increased which may be considered as adverse effect on cellular adhesion, despite its higher hydrophobicity MoS₂@PEEK exhibited enhanced cellular compatibility. This suggests that cell-material interactions are not determined solely by surface hydrophilicity but rather arise from the combined effects of surface chemical composition, defect structures, charge distribution, interfacial reactivity, protein adsorption behavior, and nanoscale surface characteristics [15, 17, 18, 28–30]. In particular, the high specific surface area and exposed active sites of the monolayer MoS₂, together with sulfur vacancies, edge defects, and surface MoO_x/Mo–OH species, may have favorably modulated the interfacial interactions associated with initial protein adsorption and cell adhesion [13, 15, 17–20, 28]. In other words, the enhanced cytocompatibility observed in this study is more reasonably attributed to the biologically activated interface provided by the highly crystalline monolayer MoS₂ with abundant active sites, rather than being explained by the conventional interpretation that it simply depends on increased surface hydrophilicity.

3.3 Photo-stimulated photothermal and photodynamic performance of MoS₂@PEEK scaffolds

With the successful incorporation of 2D MoS₂ onto the surface, the limitations of the biological functionality inherent in conventional PEEK scaffolds were effectively overcome. The introduction of a photoresponsive interface enables a transition from a simple scaffold to an active platform for promoting both therapy and

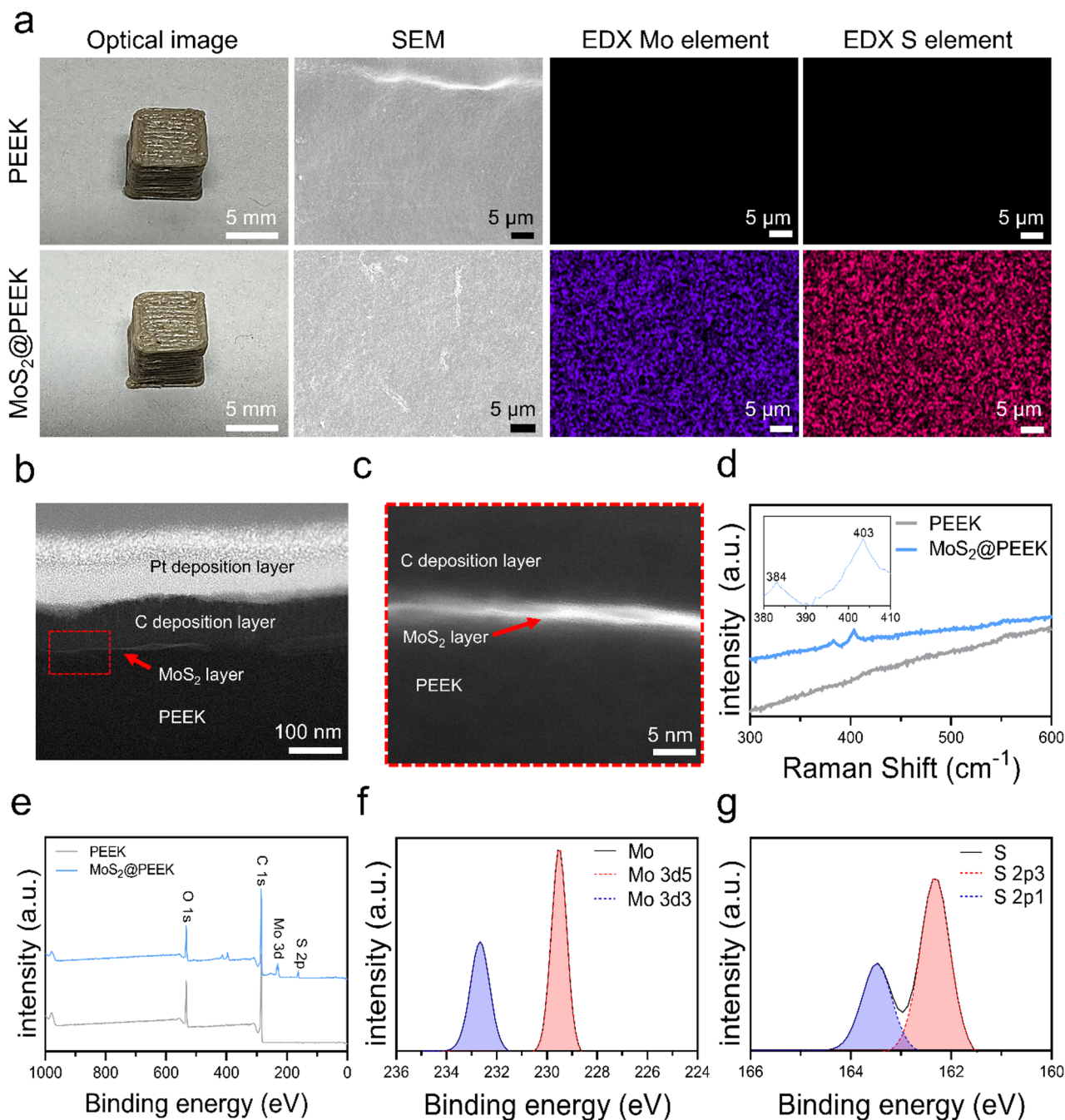


Fig. 1 Surface morphology and chemical analysis of PEEK and MoS₂@PEEK. **(a)** Optical images of 3D-printed PEEK (PEEK) and 2D MoS₂ transferred 3D-printed PEEK (MoS₂@PEEK), and SEM and EDX elemental mapping images of PEEK and MoS₂@PEEK surface. **(b)** Low and **(c)** high magnification of cross-sectional TEM image of MoS₂@PEEK. **(d)** Raman spectra of PEEK and MoS₂@PEEK. **(e)** Full XPS spectra of PEEK and MoS₂@PEEK. Deconvoluted high-resolution XPS spectra of **(f)** Mo 3d and **(g)** S 2p for MoS₂@PEEK

regeneration. Therefore, the wavelength-dependent photoresponsiveness was systematically evaluated.

Monolayer MoS₂ possesses a direct bandgap (~1.8–1.9 eV), which induces both efficient charge generation and surface reactions upon light irradiation. These electronic structural characteristics and high surface exposure provide the foundation for implementing PTT and PDT

within a single platform [32, 33]. When NIR irradiation at 808 nm is applied, the electron energy is converted into lattice vibrations (phonons) rather than being emitted as light. The accumulation of these phonons leads to localized heat generation, resulting in a photothermal effect where light energy is converted into thermal energy [34, 35]. In particular, the monolayer MoS₂ structure induces

a stable temperature rise due to the rapid transfer and diffusion of heat generated through its high surface-to-volume ratio and direct interfacial contact with the PEEK substrate [36, 37]. In contrast, under light irradiation conditions in the 650 nm region (≈ 1.91 eV), generated charges migrate to the surface before recombination, triggering oxidation–reduction reactions with surrounding oxygen and water molecules, which lead to the formation of ROS. Since monolayer MoS₂ has a structure in which all atoms are exposed at the surface, the number of reactive sites is maximized, and the density of edge sites and defects promotes charge transfer reactions. Furthermore, the short charge transport distance increases the probability of participation in surface reactions before recombination, thereby enhancing ROS generation efficiency [38, 39]. Under dual-wavelength irradiation at 808 nm and 650 nm, photothermal and photodynamic effects act complementarily, resulting in a synergistic therapeutic outcome. Consequently, wavelength-selective photoresponsiveness enables a precisely controllable dual therapeutic strategy even on a single-material basis, thereby directly enabling spatiotemporally controlled therapeutic functionality and providing the core principle by which the MoS₂@PEEK scaffold functions as a light-induced theragenerative platform [40–44]. Accordingly, quantitative validation of the degree of photoresponsiveness and the irradiation intensity and duration conditions were performed.

To precisely control the photothermal effect, temperature changes were analyzed as a function of the irradiation intensity and duration of 808 nm NIR, and heat generation was evaluated while immersed in DPBS to simulate a tissue-like environment. As a result, temperature elevation was observed in both the PEEK and the MoS₂@PEEK scaffolds, increasing with respect to NIR irradiation intensity and exposure time. However, while PEEK exhibited only a limited temperature rise even under 3 W cm^{-2} irradiation, MoS₂@PEEK showed a much higher photothermal conversion efficiency with increasing irradiation intensity and duration (Fig. 2a and b). Quantitative analysis revealed that a rapid temperature rise occurred within approximately 30 s after NIR irradiation, followed by a gradual stabilization. Based on the maximum temperature after 3 min of irradiation, the temperature differences were 0.76°C at 1 W cm^{-2} (PEEK: 25.65°C , MoS₂@PEEK: 26.41°C), 7.32°C at 2 W cm^{-2} (PEEK 29.49°C , MoS₂@PEEK 36.81°C), and 11.23°C at 3 W cm^{-2} (PEEK 37.08°C , MoS₂@PEEK 48.31°C) (Fig. 2c and d). These results are attributed to the fact that PEEK, as a polymer that lacks photoactive functional groups, has a very low light absorption coefficient. Thus, the incident light energy is not effectively converted into heat but is largely dissipated without significant thermal conversion. In contrast, in MoS₂@PEEK, heat is continuously

generated due to the repeated creation of photoexcited charges and phonon accumulation resulting from non-radiative recombination. Furthermore, the temperature rise was more pronounced because the heat generation rate remained higher than the heat loss rate during continuous light irradiation [45, 46].

To verify the reproducibility of the photothermal effect, the on–off cycle was repeated three times under 808 nm irradiation conditions. As a result, a reproducible and significant photothermal effect was confirmed in MoS₂@PEEK. Notably, under the 3 W cm^{-2} condition, complete cooling did not occur during the off interval due to excessive heat generation. Consequently, as the cycles were repeated, the degree of temperature rise tended to increase progressively due to accumulated heat relative to the initial temperature (Fig. 2e). Furthermore, when irradiated at 3 W cm^{-2} starting from an initial temperature of 25°C , the temperature of MoS₂@PEEK rose to 48.31°C , representing an increase of approximately 23.31°C , which is a level capable of causing thermal damage to surrounding normal tissue. Therefore, an irradiation intensity of 2 W cm^{-2} , which induces a temperature rise of approximately 11.81°C , was established as the optimal condition for theragenerative applications [47].

Subsequently, SOSG fluorescence analysis was performed to verify the potential for photodynamic therapy in the 650 nm wavelength range. The results showed that ROS generation was not observed in PEEK, whereas a time-dependent increase in ROS generation was confirmed in MoS₂@PEEK (Fig. 2f). This indicates that photodynamic therapy can be applied by controlling the irradiation time. Furthermore, to verify wavelength-dependent photoresponsiveness, temperature changes under 650 nm irradiation conditions were analyzed under 100 mW, 3 min irradiation conditions, and no photothermal effect was observed in either PEEK or MoS₂@PEEK (Fig. S12). Conversely, SOSG fluorescence analysis under 808 nm irradiation conditions revealed no ROS generation in either group (Fig. S13). In the 650 nm region, exciton-driven charge generation promotes surface redox reactions, whereas heat accumulation via non-radiative recombination remains limited. In contrast, in the 808 nm region, sub-bandgap excitation leads to rapid non-radiative recombination, resulting in efficient heat generation but insufficient charge transfer for ROS production. Consequently, this wavelength-selective photoresponsiveness clearly demonstrates that the MoS₂@PEEK system can precisely control the therapeutic mode depending on external light stimulation conditions, providing a key basis for the design of a theragenerative platform capable of applying PTT and PDT both independently and in combination [16, 48].

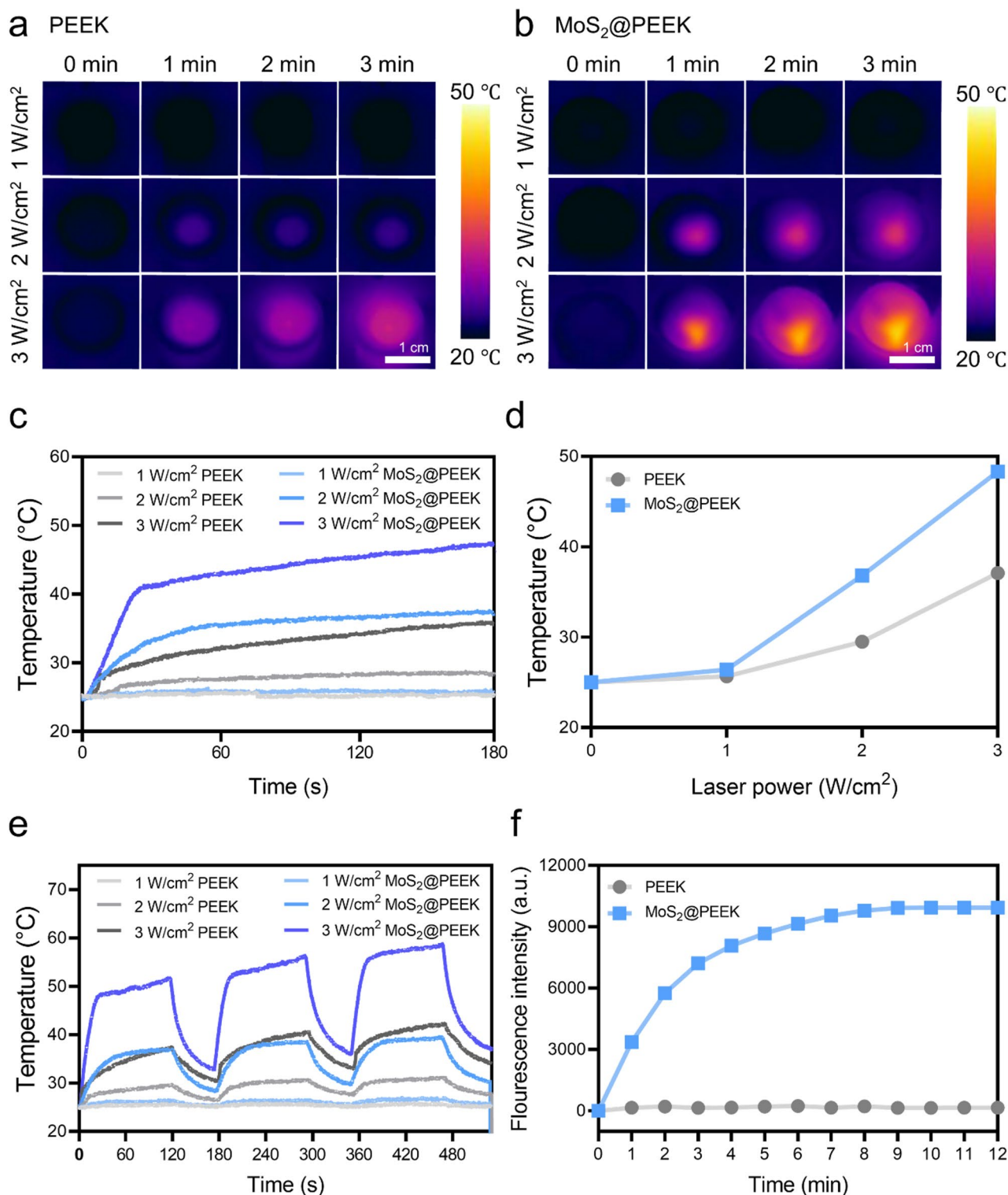


Fig. 2 Dual photo-responsive photothermal and photodynamic performance of PEEK and MoS₂@PEEK. **(a)** Infrared thermal images of PEEK and **(b)** MoS₂@PEEK under 808 nm NIR irradiation at different power densities and irradiation times. **(c)** Temperature elevation profiles as a function of irradiation time under various 808 nm power densities. **(d)** Maximum equilibrium temperatures achieved at different 808 nm power densities. **(e)** Consecutive heating-cooling cycles under repeated 808 nm irradiation for photothermal stability and reproducibility. **(f)** Time-dependent singlet oxygen generation evaluated by SOSG fluorescence intensity under 650 nm irradiation

3.4 In vitro synergistic dual-phototherapeutic antitumor performance of MoS₂@PEEK scaffold

Following osteosarcoma resection, there is a significant risk of recurrence due to residual cancer cells at the surgical site. In particular, residual cancer cells can lead to tumor recurrence by continuously proliferating and invading surrounding tissues and metastasizing, which is a major cause requiring additional surgical resection and anticancer therapy. Therefore, effective elimination of residual cancer cells is critical for preventing recurrence and improving therapeutic outcomes [49, 50]. To address these issues, a light-mediated treatment strategy based on the photoresponsive properties of 2D MoS₂ was introduced. Specifically, we aimed to evaluate the synergistic therapeutic effects by applying PTT and PDT independently, as well as in combination as dual-phototherapy.

Osteosarcoma cells were seeded onto PEEK and MoS₂@PEEK scaffolds. The non-photo-responsive PEEK group was set as a negative control without photoirradiation, while the MoS₂@PEEK group was designated as both the positive control and the phototherapy treatment group. Subsequently, MoS₂@PEEK was irradiated with the light at wavelengths of 650 nm (PDT) and 808 nm (PTT), as well as under dual-phototherapeutic conditions involving sequential irradiation with both wavelengths. As a result, under conditions without light irradiation, osteosarcoma cells maintained high viability on both PEEK and MoS₂@PEEK exhibiting a higher cell attachment density on MoS₂@PEEK, which incorporates the bioactive features of 2D MoS₂, compared to the PEEK. Subsequently, cellular behavior was analyzed after irradiation with 650 nm and 808 nm, either individually or in combination, followed by 1 and 3 days of cell culture. On day 1, partial cell death was observed in the MoS₂@PEEK (PDT) group irradiated with 650 nm only, while the MoS₂@PEEK (PTT) group irradiated with 808 nm only showed a more pronounced cytotoxic effect compared to the PDT group. However, in both conditions, cancer cells were not completely eliminated, and remaining residual cells were observed. In contrast, in the MoS₂@PEEK (Dual) group, where 808 nm irradiation was applied sequentially after 650 nm irradiation, complete cell death with no surviving cells was observed (Fig. S14). By day 3, cells proliferated rapidly in both the PEEK and MoS₂@PEEK groups, confirming high-density cell survival, whereas MoS₂@PEEK (PDT) and MoS₂@PEEK (PTT) groups exhibited moderate cytotoxicity, and the proliferation of residual cancer cells was observed. However, in the MoS₂@PEEK (Dual) group, complete cell death was shown, clearly confirming the synergistic therapeutic effect resulting from the combined application of PDT and PTT (Figs. 3a and S15).

Subsequently, the extent of cancer cell death was evaluated quantitatively as shown in Fig. 3b. Under conditions without photoirradiation, MoS₂@PEEK exhibited

a higher tendency for cell adhesion and proliferation compared to PEEK, and cell viability was significantly increased on day 3. In contrast, in the MoS₂@PEEK (PDT) group, 16.13% cell death was observed on day 1 compared to PEEK. However, on day 3, the survival rate increased by 38.12% due to the proliferation of residual cells. In the MoS₂@PEEK (PTT) group, 48.67% cell death was observed on day 1, indicating higher therapeutic efficacy than the PDT group. However, the survival rate increased by 41.22% on day 3, due to the proliferation of residual cells. In contrast, the MoS₂@PEEK (Dual) group induced complete cell death on day 1, and no proliferation of residual cancer cells was observed thereafter. These results suggest that the combined application of PDT and PTT induces a significantly enhanced anticancer effect compared to monotherapy, and that complete elimination of cancer cells is achievable through the synergistic interaction of the two therapeutic modalities [41, 51]. This can be attributed to the generation of ROS under PDT conditions, which induces lipid peroxidation in cell membranes, compromises membrane integrity, and inhibits enzyme activity and cellular function through the oxidative denaturation of proteins. Furthermore, by disrupting the mitochondrial membrane potential and inhibiting ATP production, ROS disrupts cellular energy metabolism, ultimately leading to cell death or necrosis. However, as ROS is highly reactive, its diffusion within cells is limited, and it can be partially eliminated by intracellular antioxidant systems, which limits to induce uniform and complete cell death throughout the entire cell [52]. In contrast, heat generated under PTT conditions causes nonselective and irreversible damage throughout the cell. The rise in temperature increases the fluidity of the cell membrane and destabilizes the lipid bilayer, thereby increasing membrane permeability, which leads to the leakage of cellular contents and the disruption of ion homeostasis. Simultaneously, thermal denaturation of proteins, enzyme inactivation, mitochondrial dysfunction, and cytoskeletal collapse are induced, leading to cell death. However, as heat dissipates into the surrounding environment, some cells may survive if the local temperature is not maintained above a certain level, and complete elimination of cancer cells is limited due to the adaptive response of cells to heat stress [53, 54]. In contrast, under dual-phototherapy conditions, cell death proceeds irreversibly as initial cell damage caused by ROS and subsequent damage caused by induced heat occur consecutively. Although oxidative damage induced by PDT does not immediately induce cell death, it renders cell membranes and intracellular structures vulnerable and partially disrupts the antioxidant defense system. Under these conditions, when additional thermal stress is applied via PTT, the already damaged cell membranes collapse more easily, and the denaturation of proteins

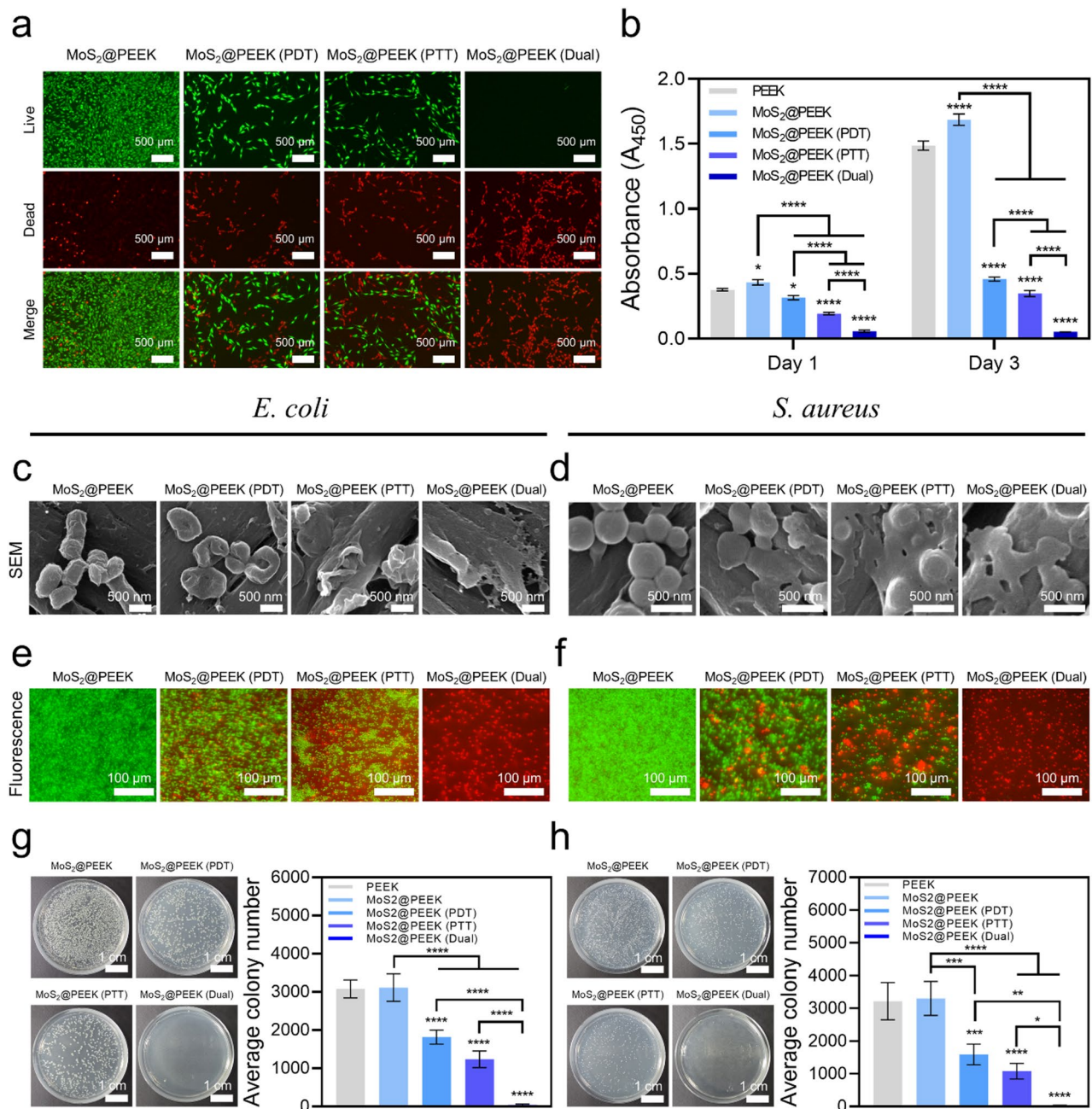


Fig. 3 Synergistic dual-phototherapeutic anticancer and antibacterial effects of MoS₂@PEEK. **(a)** Live and dead staining fluorescence images of cancer cells after 3 days of culturing on different 3D-printed PEEK scaffolds. **(b)** Quantitative analysis of cell viability determined by CCK-8 assay at day 1 and 3 of culture (n=3). Representative SEM images of bacterial morphology on the 3D-printed PEEK scaffolds against **(c)** *E. coli* and **(d)** *S. aureus*, respectively. Fluorescence microscopy images of live and dead staining for **(e)** *E. coli* and **(f)** *S. aureus*, respectively. Representative colony formation images and corresponding quantitative analysis of average colony numbers for **(g)** *E. coli* and **(h)** *S. aureus* (n=3). Data are shown as mean $\pm$ standard deviation (SD). Normality was tested using the Shapiro–Wilk method, and one-way ANOVA followed by Tukey’s HSD post hoc analysis was applied, with significance at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, and **** $p < 0.001$

and organelles accelerates, leading to irreversible loss of cellular function [41]. Furthermore, the rise in temperature increases the reaction rate of ROS and promotes its diffusion within the cell, thereby further amplifying oxidative damage. Consequently, while under single PDT or PTT conditions, the respective damage mechanisms act

partially, leaving residual cells, under dual-phototherapy conditions, chemical and physical damage interact synergistically. This simultaneously disrupts the structural and functional elements essential for cell survival, leading to complete cell death [55].

3.5 In vitro synergistic dual-phototherapeutic antibacterial performance of MoS₂@PEEK scaffold

Along with tumor recurrence, bacterial infection at the surgical site represents another critical clinical challenge. Bacterial infection triggers an inflammatory response, promoting the excessive secretion of inflammatory cytokines, thereby increasing cellular toxicity and delaying tissue healing [56, 57]. To address this challenge, the potential of MoS₂@PEEK scaffolds as a dual-phototherapeutic antibacterial platform utilizing external light stimulation was further investigated. In particular, we aimed to evaluate the antibacterial efficacy induced by PTT and PDT, both individually and in combination (dual-phototherapy), under controlled irradiation conditions. The antibacterial activity under the same phototherapy conditions used for tumor ablation was evaluated. To verify the photoresponsive antibacterial effect of the MoS₂@PEEK scaffold, *Escherichia coli* (*E. coli*), a representative Gram-negative bacterium, and *Staphylococcus aureus* (*S. aureus*), a Gram-positive bacterium, were comprehensively analyzed in terms of morphological changes, bacterial death, and colony-forming ability.

The morphology of each bacterial strain cultured on the samples depending on the phototherapy condition was observed by SEM. SEM morphology revealed that in the PEEK and MoS₂@PEEK groups, which were not subjected to light irradiation, *E. coli* appeared as rod-shaped bacteria, while *S. aureus* appeared as cocci arranged in a grape-like cluster. It was confirmed that both strains maintained their normal structures without cell membrane damage and were stably attached to the scaffold surface (Fig. S16) [58]. In contrast, partial damage and deformation of the cell surface were observed in the MoS₂@PEEK (PDT) group, while more pronounced structural damage, such as cell membrane contraction and collapse, was confirmed in the MoS₂@PEEK (PTT) group. In particular, in the MoS₂@PEEK (Dual) group, severe disruption of the cell membrane and complete loss of bacterial morphology were observed, confirming a significantly enhanced synergistic antibacterial effect compared to each phototherapy condition in both strains (Fig. 3c and d). To confirm the extent of bacterial killing alongside these morphological changes, live/dead fluorescence staining was performed. In the PEEK and MoS₂@PEEK groups, green fluorescence indicating surviving bacteria was predominantly observed for both strains, while red fluorescence indicating death was rarely observed, confirming the high survival rate (Fig. S17). In contrast, partial bacterial death was observed in the MoS₂@PEEK (PDT) and MoS₂@PEEK (PTT) groups, with a higher killing effect observed particularly in the PTT group. In the MoS₂@PEEK (Dual) group, however, only red fluorescence was observed in both strains, indicating complete bacterial death, thereby clearly

confirming the synergistic effect resulting from the combined application of the two phototherapies (Fig. 3e and f). To quantitatively verify these antibacterial effects, a colony-forming ability analysis was performed. In the PEEK and MoS₂@PEEK groups, high levels of colony formation were observed for both bacterial strains, and no statistically significant differences were found (Fig. S18). In contrast, in the MoS₂@PEEK (PDT) and MoS₂@PEEK (PTT) groups, the number of colonies decreased significantly, but the survival of some bacteria was still confirmed. In particular, in the MoS₂@PEEK (Dual) group, almost no colony formation was observed for either strain, indicating that complete bacterial killing was induced (Fig. 3g and h).

Overall, the differences in antimicrobial effects observed in this study are interpreted as resulting from differences in the damage mechanisms acting on the bacteria and their interactions. Under PDT conditions, ROS partially damages the bacterial cell membrane and cell wall and inhibits metabolic functions. However, since the damage is localized, some bacteria can survive [59, 60]. In contrast, under PTT conditions, heat reduces the structural stability of the cell membrane and cell wall and induces morphological collapse; however, due to heat diffusion, there are limitations in completely eliminating all bacteria [61, 62]. Under dual-phototherapy conditions, PTT further acts on bacterial structures weakened by PDT, accelerating the breakdown of the cell membrane and cell wall. This leads to simultaneous leakage of intracellular contents and structural disintegration, resulting in irreversible damage. Consequently, while single-modality therapy results in only partial bacterial killing, dual-phototherapy induces complete bacterial killing through the simultaneous accumulation of structural and functional damage [59, 63].

3.6 In vitro integrated osteogenic and angiogenic regenerative performance of MoS₂@PEEK scaffold

Following the evaluation of therapeutic performances through photoresponsive-based anticancer and antibacterial effects, this study sought to assess cellular behavior during the regeneration phase post-treatment. Consequently, conditions conducive to inducing cellular responses while minimizing phototherapy-induced cell damage were applied during the regeneration stage. Although the same 808 nm NIR irradiation conditions were employed, the extent of thermal stimulation in normal cells was mitigated by cell–substrate interactions and the diffusion environment, unlike in cancer cells and bacteria [64, 65]. The experimental groups comprised four types based on scaffold type and irradiation status: PEEK (–), PEEK (+), MoS₂@PEEK (–), and MoS₂@PEEK (+), where (–) and (+) denote the absence or presence of 808 nm NIR, respectively. The irradiation intensity and

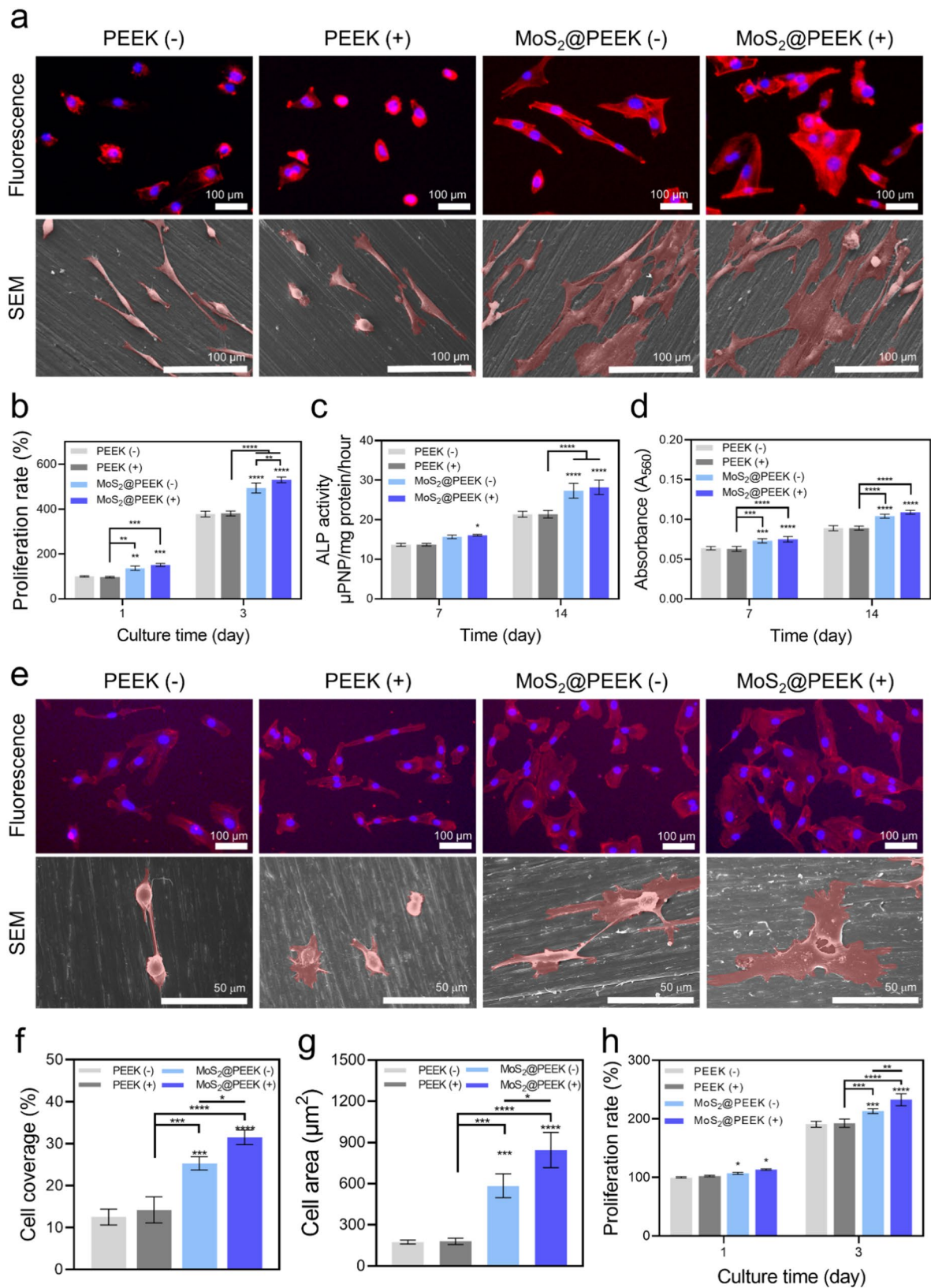


Fig. 4 (See legend on next page.)

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Fig. 4 In vitro osteogenic and angiogenic responses on MoS₂@PEEK under NIR-induced mild hyperthermia. **(a)** Representative SEM and DAPI/Phalloidin-stained fluorescence images of pre-osteoblasts adhesion on different 3D-printed PEEK specimens after 6 h of culture. **(b)** Cell proliferation rate assessed by CCK-8 assay (n = 3). **(c)** Alkaline phosphatase (ALP) and **(d)** Alizarin Red S (ARS) staining to assess differentiation after 7 and 14 days of culture (n = 3). **(e)** Representative SEM and DAPI/Phalloidin-stained fluorescence images of endothelial cells adhesion on different 3D-printed PEEK specimens after 1 day of culture. **(f)** Quantitative analysis of endothelial cell adhesion coverage based on fluorescence imaging (n = 3). **(g)** Quantification of cell spreading area determined from SEM images (n = 3). **(h)** Cell proliferation rate assessed by CCK-8 assay (n = 3). Data are shown as mean ± standard deviation (SD). Normality was tested using the Shapiro–Wilk method, and one-way ANOVA followed by Tukey's HSD post hoc analysis was applied. For non-normally distributed data, statistical analysis was performed using the Kruskal–Wallis H test followed by pairwise comparisons with the Mann–Whitney U test, with significance at **p* < 0.05, ***p* < 0.01, ****p* < 0.005, and *****p* < 0.001

duration were consistent with the conditions utilized in the preceding anticancer and antibacterial experiments, yet were designed to compare variations in cellular responses within the regenerative environment. Using pre-osteoblasts (MC3T3-E1) and HUVECs, we conducted a comprehensive evaluation of cell adhesion, proliferation, and differentiation behavior on the scaffold to verify biological compatibility and the potential for functional vascularized bone regeneration during the post-treatment regeneration stage.

Cell adhesion represents the initial phase in scaffold-based tissue regeneration and is a critical process that influences subsequent cell proliferation and differentiation. Specifically, cell adhesion is intricately linked to the development of an ECM-like environment that facilitates cell–substrate interactions. The binding of cells to substrates, primarily through integrins, leads to the formation of focal adhesion complexes and the activation of intracellular signaling pathways. These mechanical and biochemical signals not only prompt cytoskeletal rearrangement and stabilization of cell morphology but also directly affect cell survival, proliferation, and differentiation via downstream signaling cascades [66–68]. Consequently, the initial cell adhesion characteristics on the scaffold surface serve as a predictive indicator for subsequent cell proliferation, differentiation, and ultimately, the efficacy of tissue regeneration [69, 70]. From this standpoint, examining the initial cell adhesion behavior and morphological characteristics is deemed a crucial process for assessing the regeneration-friendly properties of MoS₂@PEEK scaffolds. At 6 h post-seeding onto the scaffolds, cell adhesion behavior was evaluated using DAPI and phalloidin fluorescence staining as well as SEM analysis. As shown in Fig. 4a, both PEEK (–) and PEEK (+) demonstrated limited cell adhesion, with cells tending to maintain a rounded morphology, showing no significant differences between the two. Conversely, on MoS₂@PEEK, the incorporation of 2D monolayer MoS₂ enhanced biological activity, resulting in cells spreading over a wider area, with the MoS₂@PEEK (+) group under NIR hyperthermia exhibiting the most pronounced cell adhesion behavior.

To quantitatively evaluate cell adhesion, both fluorescence image-based cell adhesion density and SEM observation-based cell spreading area were analyzed.

The fluorescence image analysis revealed no significant difference between PEEK (–) and PEEK (+), with values of $7.97 \pm 1.24\%$ and $7.36 \pm 1.47\%$, respectively. In contrast, MoS₂@PEEK (–) exhibited a 157.21% increase to $20.5 \pm 2.57\%$ compared to PEEK (–), and MoS₂@PEEK (+) demonstrated a 250.69% increase to $27.95 \pm 3.74\%$ (Fig. S19a). SEM analysis of the average cell spreading area per cell indicated no significant difference between PEEK (–) and PEEK (+), but showed an increase to $337.33 \mu\text{m}^2$ in MoS₂@PEEK (–) and $536.99 \mu\text{m}^2$ in MoS₂@PEEK (+) compared to PEEK (–) (Fig. S19b). These findings clearly illustrate the enhanced biological activity on the surface due to MoS₂ incorporation and the improved cell adhesion effect from NIR hyperthermia [16, 28]. Based on this initial cell adhesion, cell proliferation behavior was assessed to determine whether initial adhesion subsequently led to actual cell growth and tissue formation. As shown in Fig. 4b, proliferation analysis showed no significant difference between PEEK (–) and PEEK (+) at both day 1 and day 3, indicating that light irradiation alone had no effect on cell proliferation in the light-inactive PEEK groups. Conversely, MoS₂@PEEK (–) exhibited a 36.27% increase at day 1 and 116.14% at day 3 compared to PEEK (–), while MoS₂@PEEK (+) showed the highest cell proliferation, with increases of 50.94% and 125.62% at day 1 and day 3, respectively, compared to PEEK (–). These results are interpreted as a synergistic effect of increased surface biological activity due to MoS₂ incorporation, alongside NIR-driven photothermal stimulation reinforcing cell–substrate interactions and activating intracellular signaling, thereby effectively promoting cell proliferation [28, 71]. Building on these cell proliferation characteristics, the effect on osteogenic differentiation and functional maturation, beyond simple cell number increase, was analyzed to determine the potential for functional tissue formation. Osteogenic differentiation was assessed using alkaline phosphatase (ALP) activity as an early differentiation marker, and alizarin red S (ARS) staining as a marker for mineral deposition. ALP is a key enzyme expressed during the early stage of osteoblast differentiation, playing a critical role in phosphate metabolism and initiating mineralization by providing inorganic phosphate for hydroxyapatite formation [72–74]. In parallel, ARS staining is employed to evaluate late-stage osteogenic differentiation by quantifying calcium-rich

mineralized matrix deposition, which reflects the formation of mature bone-like tissue [75–77]. ALP analysis showed no significant difference between PEEK (–) and PEEK (+) up to day 14, however, MoS₂@PEEK (–) had a 14.96% increase at day 7 and a 43.70% increase at day 14 compared to PEEK (–). MoS₂@PEEK (+) showed the highest ALP activity, with increases of 17.91% at day 7 and 50.01% at day 14 versus PEEK (–) (Fig. 4c).

The findings indicate that the surface characteristics of MoS₂ and photothermal stimulation significantly enhance enzymatic activity and osteogenic signaling during the initial differentiation phase of osteoblasts. A similar pattern was observed in bone mineralization, as assessed by ARS staining. While the PEEK groups exhibited relatively weak staining intensity, the groups incorporating MoS₂ showed progressively greater red staining intensity, with the most pronounced red deposition observed in the MoS₂@PEEK (+) group under NIR hyperthermia, visually indicating the most active calcium-based mineral accumulation (Fig. S20). Quantitative analysis supported these observations that MoS₂@PEEK (–) increased by 14.55% at day 7 and 23.51% at day 14 compared to PEEK (–), while MoS₂@PEEK (+) increased by 17.75% and 31.38% at day 7 and day 14, respectively, demonstrating the highest level of mineralization (Fig. 4d). From the results, both the enhanced surface biological activity through MoS₂ incorporation and the NIR-based photothermal stimulation were found to sequentially augment not only cell adhesion and proliferation but also early differentiation and late-stage mineral deposition of osteoblasts. This suggests that MoS₂@PEEK scaffolds effectively provide a functional microenvironment conducive to bone regeneration [1, 12].

Effective tissue formation during bone regeneration necessitates not only the activation of osteoblasts but also the provision of oxygen and nutrients through vascularization. Consequently, this study extends beyond osteoblast-based evaluation to analyze the biological behavior of vascular endothelial cells on the scaffold, thereby assessing the potential for vascularization within the regenerative microenvironment [78, 79]. From this perspective, the ability of the scaffold surface to effectively induce the initial attachment interactions of vascular endothelial cells is considered a critical stage in predicting subsequent vascular formation and the potential for functional tissue regeneration [80, 81]. Accordingly, using HUVECs, we initially evaluated the attachment behavior at 1 day post-cell seeding through SEM and DAPI/phalloidin staining. The results indicated that, similar to osteoblasts, the PEEK group without photoresponsiveness exhibited low cell attachment density and limited cytoplasmic spreading, irrespective of NIR irradiation. Conversely, in the MoS₂@PEEK (–) group, cell density and attachment were significantly

enhanced due to increased surface bioactivity and interfacial interactions conferred by the MoS₂ monolayer. Furthermore, as depicted in Fig. 4e, in the MoS₂@PEEK (+) group, where NIR-based hyperthermia stimulation was applied, the most pronounced initial cell attachment behavior was observed, suggesting that the MoS₂-based surface activation and hyperthermia stimulation synergistically enhanced cell attachment. Quantitative evaluation revealed no significant difference in cell attachment density between PEEK (–) and PEEK (+), based on fluorescence image analysis. MoS₂@PEEK (–) demonstrated a 12.8% increase, while MoS₂@PEEK (+) exhibited a 19% increase in cell density compared to PEEK (–) (Fig. 4f). Furthermore, analysis of the average cell spreading area per cell, derived from SEM images, revealed no difference in the PEEK group with or without NIR exposure. In contrast, MoS₂@PEEK (–) and MoS₂@PEEK (+) showed increases of 409.98 μm^2 and 670.54 μm^2 , respectively, over PEEK (–), confirming statistically significant enhancements in cell attachment (Fig. 4g). These findings suggest that interfacial activation resulting from MoS₂ incorporation and NIR-induced hyperthermia effectively enhances initial cell–matrix interactions. To ascertain whether these initial interactions underpin the sustained growth and functional activity of vascular endothelial cells, we assessed cell proliferation behavior. The results indicated no significant difference in the PEEK group between NIR and non-NIR conditions on both day 1 and day 3 post-cell attachment. Conversely, MoS₂@PEEK (–) exhibited a 6.89% increase on day 1 and a 13.33% increase on day 3 compared to PEEK (–), while MoS₂@PEEK (+) showed increases of 22.30% and 41.88% on days 1 and 3, respectively, indicating the highest cell proliferation (Fig. 4h). This suggests that interfacial activation by the MoS₂ monolayer positively influences not only initial attachment but also the cell proliferation phase, with hyperthermia stimulation induced by NIR irradiation further enhancing cellular activation. In conclusion, the synergistic effects of increased surface biological activity due to MoS₂ introduction and hyperthermia stimulation induced by NIR irradiation effectively reinforced cell–implant interactions, significantly promoting cell attachment, proliferation, and functional activation. This trend was consistently observed in both osteoblasts and vascular endothelial cells, indicating that the NIR-stimulated MoS₂@PEEK platform provides an integrated regenerative microenvironment capable of simultaneously inducing vascularization and bone regeneration [82, 83].

4 Conclusion

Our study proposes a personalized orthopedic scaffold-based theragenerative platform that effectively induces antitumor, antibacterial, and vascularized bone tissue regenerative effects. This approach was achieved by

fabricating patient-specific 3D-printed scaffolds using manufactured PEEK filaments, followed by surface functionalization with 2D monolayer MoS₂ synthesized from MoO₃ nanoparticle precursors via a nanoseed-initiated APCVD process and transferred using a polymer-assisted transfer method. The resulting MoS₂@PEEK scaffold, characterized by uniform thin-film structural integrity and fabrication reproducibility, offers high design flexibility to accommodate various anatomical defect sites. Importantly, the MoS₂-based surface exhibits pronounced dual photoresponsiveness, enabling the precise and non-invasive induction of combined photothermal and photodynamic effects under external stimulation. Furthermore, the MoS₂ interface compensates for the previously lacking therapeutic and regenerative functions of PEEK, conferring antitumor and antibacterial capabilities under dual-wavelength irradiation while significantly enhancing cell adhesion, proliferation, and differentiation. Through the synergistic effects of these dual-photoresponsive therapeutic mechanisms, the MoS₂@PEEK scaffold achieved effective tumor cell ablation and significant antibacterial activity. Furthermore, under the same photothermal stimulation conditions, the MoS₂-functionalized interface dynamically regulates the cellular microenvironment, promoting the activation of osteoblasts and vascular endothelial cells and inducing biological behaviors conducive to vascularized bone regeneration. As a result, the MoS₂@PEEK scaffold demonstrated its potential as a multifunctional theragenerative platform capable of integrating tumor suppression, infection control, and tissue regeneration. Although further validation regarding long-term in vivo stability and immune responses is required, the MoS₂@PEEK-based theragenerative platform proposed in this study is suggested to be a promising strategy capable of comprehensively resolving the complex clinical issues arising after surgical resection of osteosarcoma using a single platform. Furthermore, this scaffold, realized through the convergence of 3D printing-based patient-specific design and 2D nanomaterial-based surface engineering, presents significant potential as a next-generation theragenerative platform for future tissue engineering and orthopedic clinical applications.

Supplementary Information

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Supplementary Material 1

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Author contributions

J. H. Seo, and I. H. Choi contributed equally to this work. J. H. Seo, and I. H. Choi wrote the manuscript all of the activities. M.-H. Kang, and H.-D. Jung edited the manuscript. S. J. Bang, H. S. Kang, J. Y. Gwon, C. H. Moon, N. Y. Lee, and G. W. Kim supported the fabrication of the 3D-printed PEEK and performed the structural and mechanical analyses. J. H. Kim, H. J. Joo, J. H. Kim, Y. H. Cho, E. S. Song, and S. J. Choi assisted the synthesis of the 2D monolayer MoS₂. J. W. Park, D. J. Kim, and S. S. Kang contributed to TEM imaging and analyzing the structure. K. S. Yang, G. D. Cha, and S.-H. Lee contributed to explanation of in vitro tests. J. H. Seo, I. H. Choi, M.-H. Kang, and H.-D. Jung contributed to interpretation and discussion of the results.

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Data availability

Data will be made available on request.

Declarations

Competing interests

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this study.

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