Surface modification of polyetheretherketone for boosted osseointegration: A review

Yu Chen[1], Zhiyong Chen[1], Kewen Lei[2], Jiandong Ding[1], and Lin Yu[1]*

ABSTRACT

The field of orthopaedic implants has experienced rapid growth in recent decades, evolving from a few obscure examples to become one of the most vibrant domains within regenerative medicine. Polyetheretherketone (PEEK) stands out as a formidable competitor in this field due to its exceptional biocompatibility and appropriate mechanical strength. However, the clinical application of PEEK is limited by its inherent biological inertness. Therefore, numerous studies have focused on overcoming the bio-inert issue of PEEK using surface activation techniques. It is necessary to delve into the intricate effects of these modifications and their corresponding methods. In this review, we provide a comprehensive summary of contemporary research on surface modification for enhancing osseointegration of PEEK implants, categorising them into four parts based on their modification methods and techniques used: (1) physical treatment, (2) wet chemical methods, (3) combination of physical and chemical treatments, and (4) bioactive coating. Finally, we outline the challenges and unmet needs that must be addressed by future designs of PEEK surfaces. Overall, altering the surface morphology and/or surface group of PEEK to obtain a rough, porous, hydrophilic, and bioactive surface, or incorporating bioactive agents/coatings with bone-forming abilities onto the surface of PEEK has shown great potential for promoting osseointegration, which can serve as a solid foundation for subsequent clinical translation.

Keywords:
Coating; Orthopaedic implants; Osseointegration; PEEK; Surface modification

***Corresponding author:**
Lin Yu,
yu_lin@fudan.edu.cn

How to cite this article:
Chen, Y.; Chen, Z.; Lei, K.; Ding, J.; Yu L. Surface modification of polyetheretherketone for boosted osseointegration: A review. *Biomater Transl.* 2025, 6(2), 181-201.

doi: 10.12336/bmt.24.00052

1. Introduction

Bone, as a critical component of the human body, possesses both stiffness and toughness due to its hierarchical organisation of organic matrix and inorganic minerals.[1-3] With its exceptional mechanical properties, bone is capable of providing sufficient load-bearing ability for locomotion and protecting delicate internal organs.[4-6] However, fracture has become a common disease recently due to high energy traumas such as car accidents, sports injuries and industrial injuries, etc.[7] In Europe, it is estimated that there will be an annual rise in fractures by 28% from 2010 to 2025, while age-related fractures in the United States are expected to increase from 2.1 million in 2005 to over 3 million in 2025.[8,9] General speaking, small bone defects can regain their original structure and mechanical strength perfectly without leaving fibrotic scars.[6] However, when the size of a bone defect caused by trauma, developmental deformity, tumor resection, infection, etc. exceeds the critical threshold known as "critical-size defect", self-healing becomes challenging and additional clinical intervention is often required.[6] The concept of critical-size defect was proposed by Schmitz and Hollinge[10] in 1986, and in adult patients, a bone critical-size defect is typically characterised by circumferential loss exceeding 50% or a length greater than 2 cm.[11]

Autologous and allogeneic bone grafts are frequently used to repair large bone defects.[9,12] Yet, they often suffer from the disadvantages of the limited supply of donor bone, blood disease transmission, immune rejection, and high costs.[6] Therefore, with recent advances in materials science, numerous biomaterials with designable and controllable properties have been applied to orthopaedic implants to overcome these problems, such as metals, ceramics, polymers and their composites.[2,13-35] However, each of these materials has certain limitations: (1)

metallic materials may cause stress shielding and undesired release of metal ions; (2) bioceramics are susceptible to fracture owing to their inherent brittleness; and (3) polymers such as poly(L-lactide) and polytetrafluoroethylene lack sufficient strength to meet the mechanical requirements of orthopaedic implants.[35,36]

Polyetheretherketone (PEEK) composed of rigid benzene rings and ether and ketone bonds is a semi-crystalline specialty polymer. PEEK possesses numerous advantages, including suitable mechanical strength, outstanding biocompatibility, good resistance to wear and fatigue, and satisfactory radiation transmittance.[36,37] In particular, the elastic modulus of PEEK closely resembles that of human cortical bone, thus effectively mitigating the "stress shielding effect".[37] Consequently, back in the 1990s, PEEK received approval from the U.S. Food and Drug Administration for use as an orthopaedic implant,[38] and has been successfully utilised in spinal fusion devices, skull reconstruction and dental implants.[37] The medical PEEK market reached approximately $176.6 million in 2017 and is anticipated to grow to $335.8 million by 2025, representing a growth of 90%.[37] However, the lack of active groups in the main chain of PEEK makes it considerable biological inertia, which leads to poor osseointegration with host bone and limits its clinical applications to a great extent.[37]

In general, the strategies to improve the osseointegration ability of PEEK can be categorised into blending modification and surface modification.[37,39] Blending modification refers to a modification method of adding varying amounts of powders, particles, or fibres into the material matrix to obtain a performance-enhanced composite material.[37] This is a commonly used approach to improve the properties of PEEK, including its osseointegration ability. Different from blending modification, surface modification directly activates a material surface through physical or chemical means, thereby boosting its bioactivity without compromising its bulk properties. Numerous studies have shown that the construction of structures on PEEK surfaces that mimic the extracellular matrix of bone tissue, including chemical composition and topological geometry, can promote the osseointegration between its inert surface and natural bone tissue while stimulating the self-regeneration of the damaged bone tissue.[36,40]

In recent years, some reviews have mentioned the surface modification of PEEK, but this topic constitutes only a portion of their content, and the purposes of their modifications are not only to improve the osteogenic effect, but also to improve mechanical properties and other aspects.[39-43] Another recent review has highlighted biomolecule modification strategies on PEEK and its composites for osteogenesis and antibacterial properties.[44] Given the importance of surface modification and its potential for clinical translation, this review concentrates on the strategies to enhance the surface bioactivity of PEEK and their contributions to osseointegration. It is organised into four parts: (1) physical treatment, (2) wet chemical methods, (3) combination of physical and chemical treatments and (4) bioactive coating. Each part is described thoroughly according to the fabrication methods (**Figure 1**), while we introduce the techniques and possible mechanisms behind each modification method and discuss their impacts on osseointegration. The advantages and disadvantages of common surface modification methods are listed in **Table 1**.[45-62] Finally, we highlight the unmet needs and future trends in the development of activated PEEK surfaces for better bone-tissue integration.

2. Retrieval strategy

We searched Web of Science (https://webofscience.clarivate.cn/) with keywords as "(PEEK OR polyetheretherketone) AND (bone OR osteoge*)". The research areas are "Materials Science", "Engineering", "Orthopedics", "Polymer Science", "Chemistry" and "Cell Biology", etc.

3. Physical treatment

Physical treatment can quickly change the properties of material surface, such as roughness, wettability, and surface energy, and can even introduce different reactive groups to boost its biological activity. Meanwhile, these approaches are easy to be combined with following reaction steps to further expand the applications. However, one main drawback of physical treatment is a need for expensive equipment. At present, various physical treatment methods have been employed to physically modify PEEK, and this section highlights some commonly used methods. **Figure 2** presents a schematic diagram of three main physical modification methods.

3.1. Sandblasting

Sandblasting, also known as abrasive blasting, is the operation of propelling abrasive materials or fine particles onto a surface at high speeds to clean, smooth, or roughen the surface. Given that increasing surface roughness can promote various biological responses such as cell adhesion, proliferation and differentiation,[63,64] this method has been used to improve the surface roughness of PEEK. For instance, Ishikawa's group[65] sandblasted PEEK surface with alumina particles to obtain a roughened surface. Scanning electron microscopy observation showed that the surface morphology of the sandblasted PEEK was significantly roughened, and the roughness of the PEEK surface increased from 0.06 μm before treatment to 2.26 μm after sandblasting. *In vitro* experiments revealed that the surface of sandblasted PEEK remarkably improved the adhesion, proliferation, and bone-like nodule formation of rat bone mesenchymal stem cells (BMSCs) compared with untreated PEEK surface. Moreover, *in vivo* results showed that the sandblasted PEEK exhibited a higher pull-out force compared with untreated PEEK after implanting them into the rat femur bone marrow cavities for 2 or 4 weeks, indicating that the sandblasted PEEK has a greater osseointegration

[1]State Key Laboratory of Molecular Engineering of Polymers, Department of Macromolecular Science, Shanghai Stomatological Hospital & School of Stomatology, Fudan University, Shanghai, China; [2]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA

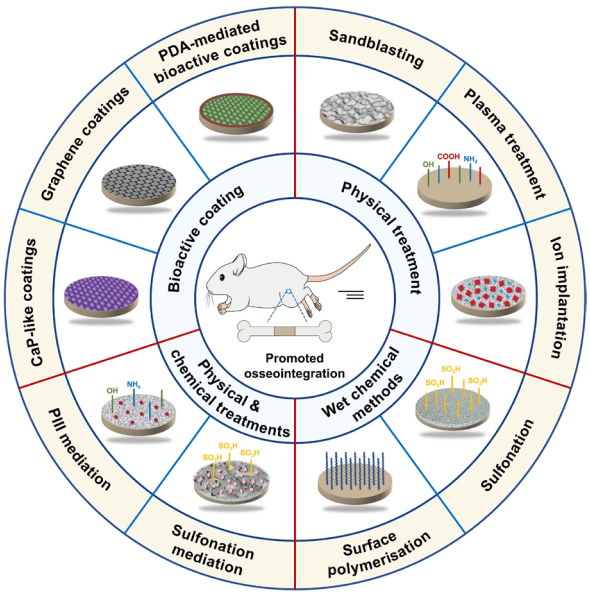

Figure 1. Typical strategies of surface modification for boosting the osseointegration of PEEK. Created with Adobe Illustrator 2020. Abbreviations: CaP: Calcium phosphate; PDA: Polydopamine; PEEK: Polyetheretherketone; PIII: Plasma immersion ion implantation.

Table 1. The advantages and disadvantages of different surface modification techniques

Modification methods	Advantages	Disadvantages
Sandblasting	Increased surface roughness, low-cost, simple and rapid operation[45]	Contamination from the abrasive, difficulty to form nanoscale topography, poor reproducibility[45,46]
Plasma treatment	Increased surface hydrophilicity and roughness, introduction of functional groups, exclusion of the need for solvents, good scalability, uniformity, and repeatability[47-49]	Ageing effect: Partial or full reversibility of enhanced surface wettability[47]
PIII	No line-of-sight limitations, introduction of bioactive substances with strong adhesion, good uniformity and repeatability[50]	Heat generated during the process may cause the deformation of PEEK surface[50]
Sulfonation	Creation of surface porous structure, simple and rapid operation, low cost, applicable to complex shapes, introduction of sulfonyl groups, certain antibacterial activity[51-53]	Residual sulfonic acid is harmful to cells and tissues[53]
Surface polymerisation	Modification of surface chemistry, wettability, and roughness, introduction of various functional groups[54]	Not allowing for precise control of the architecture of the synthesised polymer[55]
CaP-like coatings	Similar to natural bone, good osteoinductivity[56]	Weak bonding strength between the coatings and the substrates[57]
Graphene & GO coatings	Enhanced osteogenic differentiation of human MSCs, antibacterial properties[58-60]	Safety as biomaterials and coatings is still under investigation[60]
PDA-mediated bioactive coatings	Facilely loading a variety of bioactive substances, applicable to complex shapes, strong coating adhesion[61]	'Background adhesion' can decrease the cell viability and migration when PDA coating is exposed[62]

Abbreviations: CaP: calcium phosphate; GO: graphene oxide; MSCs: mesenchymal stem cells; PDA: polydopamine; PIII: plasma immersion ion implantation.

ability. However, previous studies have indicated that the presence of aluminium (Al) ions inhibited the expression of the osteoblastic phenotype *in vitro*, and adversely affected on tissue reactions *in vivo*.[45] Therefore, the possible residue of alumina particles on the surface of PEEK should be concerned. Utilising a more biocompatible substance, such as calcium phosphate (CaP) particles, for sandblasting[66] may represent a better option.

3.2. Plasma treatment

Plasma, often regarded as the fourth state of matter in addition to solid, liquid, and gas, is a fully or partially ionised gas generated by various charge carriers such as ions, electrons, and free radicals.[67] The reactive species generated by this method have higher energies than normal chemical bonds, enabling them to induce the breaking and reorganisation of chemical bonds on the polymer surface.[39] Consequently, this treatment process leads to alterations in both microscopic morphology and chemical composition.[48,68] For example, Liu et al.[48] treated PEEK surface with argon (Ar), nitrogen (N_2), and Ar-N_2 plasma, respectively. The results showed that compared with the other two treatments, N_2 plasma treatment had the most obvious enhancement effect on osteogenic activity of mouse osteoblast precursor cells (MC3T3-E1 cells) due to the maximum roughness, strongest hydrophilicity and the introduction of nitrogen-containing functional groups, all of which have been proved to favour the osteogenic expression of osteoblasts.[36,69] Similarly, oxygen (O_2) and hydrogen-oxygen (H_2-O_2) plasma

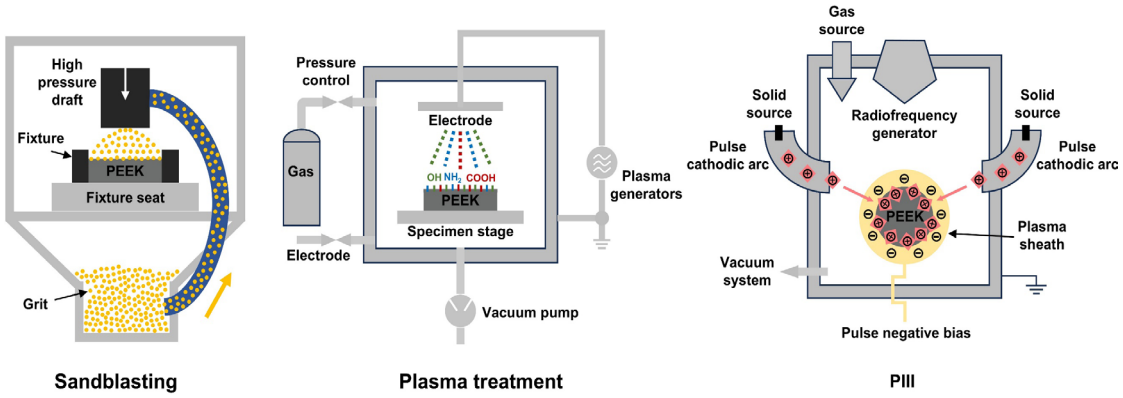

Figure 2. Schematic representation of three typical physical treatments: sandblasting, plasma treatment and PIII. Created with Microsoft PowerPoint 16. Abbreviations: PEEK: Polyetheretherketone; PIII: Plasma immersion ion implantation.

treatments were also conducted onto PEEK surface, which resulted in an improvement of cell adhesion.[49] Although various charge carriers are used, the essence of these plasma treatments is still to introduce different chemical groups on PEEK surface and alter its hydrophilicity and roughness. Obviously, these changes facilitate bone regeneration and integration.

3.3. Ion implantation

Plasma immersion ion implantation (PIII) is a technique for surface modification. In PIII, the sample is surrounded via a high-density plasma and pulse-biased to a high negative potential with respect to the cavity wall, and subsequently ions produced in the plasma shroud are expedited through the sheath formed around the specimen and implanted into the target surface.[70] The efficient transfer of ions from plasma to target surface makes PIII highly suited for high-dose implantation of low-energy ions. Many metal elements have been proved to have excellent osteogenic effects.[42,71] For example, elements such as calcium (Ca), magnesium (Mg), strontium (Sr), and zinc (Zn) play critical roles in bone immunomodulation; copper (Cu), Mg, and Zn are essential for neuromodulation; Mg, Sr, and Zn are pivotal in promoting angiogenesis, while Ca, lithium (Li), Mg, tantalum (Ta), and Sr are instrumental for bone metabolism and regeneration.[71] Therefore, PIII treatment provides an effective way to introduce and bind metal ions stably onto the surface of PEEK, thereby improving the osseointegration/bone remodelling ability of PEEK implants. In this field, Liu's group has done many excellent studies, and they introduced various metal ions such as Ti,[72] Zn,[73] Ca,[74] Ta,[50] Zr,[75] through PIII on the PEEK surface, resulting in varying degrees of improvement in the osteointegration ability of PEEK.

3.4. Other methods

Surface topography of materials also plays a critical role in determining cell behaviour.[76-86] For instance, when cultured on substrates with varying morphologies, cells usually exhibit different spreading shapes, and there is a large amount of evidence suggesting that cell shape affects cell growth, migration, proliferation and differentiation.[87-97]

In bone repair, it is well known that the porous structure of implants has been shown to possess enhanced osteogenic capacity, but the bulk porosity generated by the blending method often leads to a decline in their mechanical properties.[98] In contrast, surface porosity can provide a balance between improving bone integration and maintaining mechanical load bearing. To this end, Evans et al.[98] pressed sodium chloride (NaCl) crystals with the size of approximately 250 μm onto the PEEK surface under high temperature and pressure, and then leached NaCl particles with water. The porous surface obtained could improve bone-implant fixation through enhanced mechanical interlocking, so the modified PEEK showed boosted osseointegration *in vivo*. Similarly, Boschetto et al.[99] introduced NaCl and β-silicon nitride (β-Si_3N_4) particles onto the surface of PEEK by hot pressing. Then, NaCl grains were removed by leaching in water, resulting in a porous PEEK surface embedded with β-Si_3N_4 particles, which improved the osteogenesis and bacteriostasis of PEEK.

Femtosecond laser irradiation can create customised micro-nanostructures and patterns on the surface of various materials to facilitate cell adhesion and osteogenic differentiation.[100,101] This preparation method has the advantages of simplicity, rapidity, accuracy, reproducibility and low oxidation.[102] For instance, Xie et al.[103] fabricated a micro-nanotopography on PEEK surface using femtosecond laser, which significantly elevated the roughness, hydrophilicity and protein adsorption capacity of PEEK surface, thereby promoting the osteogenesis-related gene expression of MC3T3-E1 cells. Additionally, Ji et al.[104] hydroxylated the surface of femtosecond laser-treated PEEK to further stimulate the osseointegration of PEEK.

In a recent study, Zhang et al.[105] used a hot die formation technique to construct patterned nanorod arrays with different diameters on the surface of PEEK (**Figure 3A**). Such approach could obtain evenly distributed nanorod arrays on the PEEK surface**.** *In vitro* studies demonstrated that PEEK embedded with 200-nm nanorod arrays (PEEK 200) exhibited the strongest osteogenic differentiation-inducing ability (**Figure 3B**). Furthermore, both PEEK and PEEK 200 were implanted into the distal femora of Sprague-Dawley rats. Four weeks later, micro-computed tomography observation showed that the extent of new bone formation in the PEEK 200 group was significantly better than that in the PEEK group (**Figure 3C**). Finally, haematoxylin and eosin and Ladewig staining validated

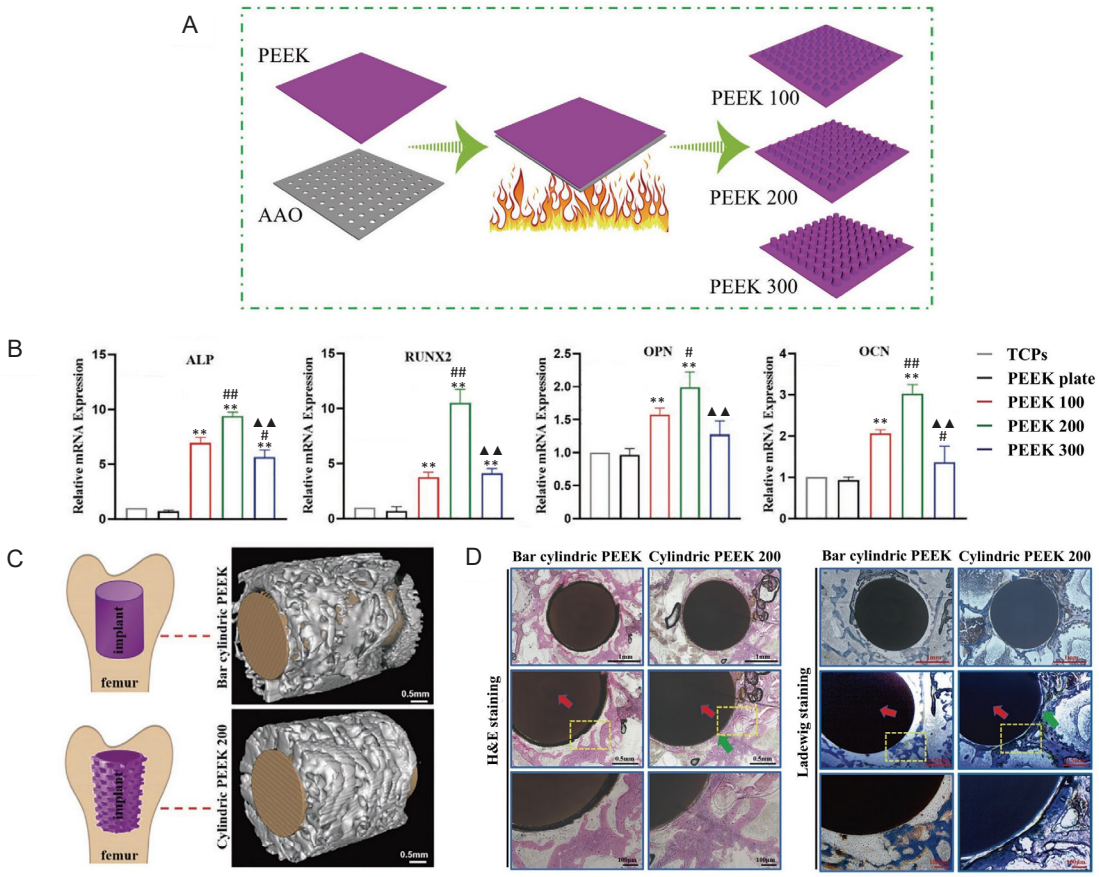

Figure 3. (A) Schematic illustration of the hot die formation technique to establish nanorod arrays with different diameters on PEEK surface. PEEK 100, PEEK 200, and PEEK 300 represent PEEK samples obtained from AAO templates with pore sizes of 100, 200 and 300 nm, respectively. (B) Osteoblast-specific gene analysis on day 14. Data are expressed as mean ± SD. *$P < 0.05$, **$P < 0.01$, *vs.* PEEK plate; #$P < 0.05$, ##$P < 0.01$, *vs.* PEEK 100; ▲$P < 0.05$, ▲▲$P < 0.01$, *vs.* PEEK 200. (C) 3D images of micro-CT scan. Scale bars: 0.5 mm. (D) H&E and Ladewig staining sections. The red arrows represent PEEK implants and the green arrows represent the new bone. Scale bars: 1 mm (upper), 0.5 mm (middle), 100 μm (lower). Reprinted from Zhang et al.[105] Copyright 2021 Wiley-VCH GmbH. Abbreviations: AAO: Anodic aluminium oxide template; ALP: Alkaline phosphatase; H&E: Haematoxylin and eosin; OCN: Osteocalcin; OPN: Osteopontin; PEEK: Polyetheretherketone; RUNX2: Runt-related transcription factor 2; TCPs: Tissue culture plates.

that more new bone (pink in haematoxylin and eosin staining and blue in Ladewig staining) was detected around PEEK 200 (**Figure 3D**), indicating satisfactory osseointegration effects resulting from nanomorphological modification of PEEK.

4. Wet chemical methods

Despite the outstanding chemical stability exhibited by PEEK, several chemical treatment approaches have been exploited for its surface decoration. These methods, collectively known as "wet chemical methods", involve immersing PEEK material into a reaction solution. Therein, surface sulfonation is the most popular wet chemical method. Additionally, some other wet chemical methods, such as surface polymerisation, are mentioned as well.

4.1. Sulfonation

As early as 2001, Huang et al.[106] discovered that the benzene rings on PEEK can be electrophilically substituted with concentrated sulfuric acid to introduce sulfonic acid groups on its main chain (**Figure 4A**). At the same time, by controlling the sulfonation time, a porous structure less than 10 μm can be created on PEEK surface (**Figure 4B**).

The discovery of sulfonation is a considerable milestone in boosting the biological activity of PEEK. Next, Zhao et al.[52] found that the porous structure obtained by sulfonation could enhance the osseointegration of PEEK and bone-PEEK bonding strength *in vivo*, and preliminarily investigated the effects of residual sulfuric acid on cytotoxicity and osteogenesis using two post-treatment methods. Thereafter, they collaborated with Liu's group[51] to explore the effect of hydrothermal treatment temperature after sulfonation on the residual sulfate content and the corresponding cytotoxicity. It was found that hydrothermal treatment at 120°C for 4 hours could reduce the content of residual sulfuric acid to a very low extent, resulting in the sulfonated PEEK (SPEEK) exhibiting the strongest osteogenic activity both *in vitro* and *in vivo*. Furthermore, Ma et al.[107] compared different sulfonation time and post-treatment methods to evaluate their effects on the cytocompatibility of MC3T3-E1 cells. The results indicated that prolonged sulfonation time tended to destroy and dissolve the porous structure formed on the PEEK surface and introduced more cytotoxic sulfur acid, which reduced the survival rate of MC3T3-E1 cells. Conversely, an approximately 5 minutes of treatment achieved the highest cell survival rate on the surface

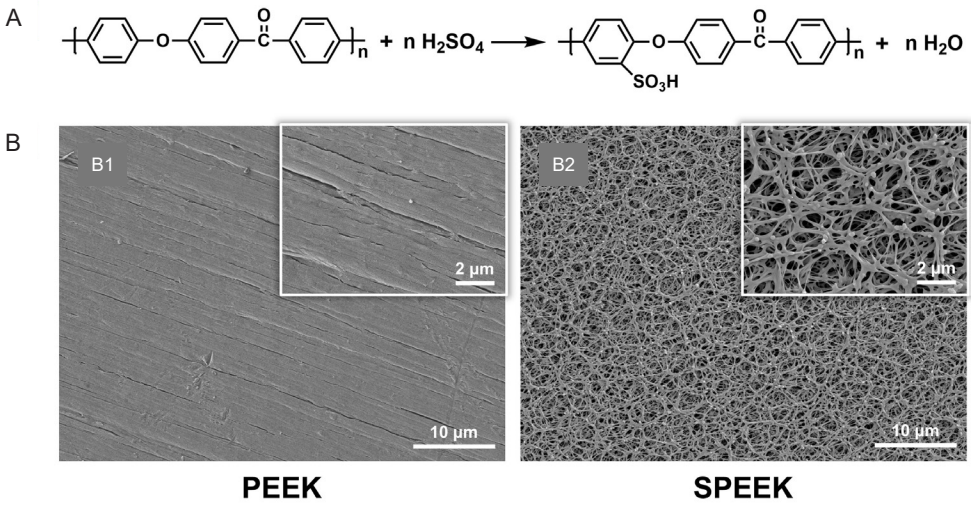

Figure 4. (A) Sulfonation reaction of PEEK. (B) SEM images of untreated PEEK (B1) and SPEEK (B2). Scale bars: 10 μm, 2 μm (enlarged images). Unpublished data. Abbreviations: PEEK: Polyetheretherketone; SEM: Scanning electron microscopy; SPEEK: Sulfonated PEEK.

of PEEK. Additionally, it was revealed that different post-treatment methods such as acetone washing, hydrothermal treatment and sodium hydroxide (NaOH) solution immersion did not differ significantly in the removal effectiveness of residual sulfuric acid.

Subsequently, with the development of research, several approaches have been reported to optimise the sulfonation process, such as the introduction of nitric acid on the basis of sulfuric acid to obtain hierarchical micro-nanostructures on PEEK surface,[108] and the treatment with NaOH solution after sulfonation to further improve its hydrophilicity.[109] Recently, Wan et al.[110] performed a sulfonation reaction on the PEEK surface using sulfur trioxide (SO_3) gas, which displayed better controllability than concentrated sulfuric acid. Similarly, sulfate groups and porous structure were formed, both of which improved the osseointegration ability of PEEK implants.

4.2. Surface polymerisation

Surface polymerisation is a novel surface modification method. One typical way is to generate free radicals on the main chain of PEEK and then to initiate the polymerisation of olefin monomers containing bioactive groups such as sulfonic acid and phosphoric acid, thereby introducing bioactive components onto PEEK surface. For instance, Ma et al.[111] grafted poly(sodium p-styrene sulfonate) onto the surface of PEEK by ultraviolet (UV) induced polymerisation to enhance its osteogenic activity (**Figure 5**). *In vitro* results demonstrated that osteo-differentiation of MC3T3-E1 cells were enhanced after modification and these enhancement effects became more obvious with the increase of grafting amount. In another attempt, Zheng et al.[54] incorporated phosphate groups onto PEEK surface through the UV-initiated graft polymerisation of vinylphosphonic acid. *In vivo* evaluations indicated that the surface-phosphorylated PEEK exhibited improved bone-implant contact. In addition, it was also confirmed that the grafting time could modulate the content of phosphate groups on the PEEK surface, which further affected its osseointegration to a certain extent.[112]

Interestingly, suitable surface polymerisation can also produce specific surface topographies. For instance, polyacrylic acid chains were first grafted onto PEEK surface by UV irradiation. Then, ethylenediamine was added to promote the cross-linking of polyacrylic acid chains.[113] As a result, the modified PEEK surface not only exhibited significantly improved hydrophilicity, but also formed a micrometer-scale porous structure. Such modification further activated the focal adhesion kinase (FAK) pathway and Rho family GTPases, thereby improving cell adhesion and proliferation.

Moreover, in addition to free radicals, surface polymerisation of PEEK can also be carried out by introducing double bonds. For instance, Wang et al.[114] used sodium borohydride to reduce the carbonyl groups on the SPEEK surface to form hydroxyl groups. Next, the resulting samples were reacted with KH570, a silane coupling agent, to introduce C=C bonds. Afterward, a polyacrylic coating was grafted onto the surface and then amidised by ethylenediamine to form an aminated polymer surface. Finally, the samples were treated with excess of sodium hypochlorite to obtain N-Cl groups with antimicrobial activity. After implantation, the N-Cl functionalised surface efficiently prevented microbial infection. As antimicrobial oxidative chlorine atoms continued to be consumed at the bone defect site, the N-Cl groups were gradually turned to pro-osteogenic N-H groups at the later stage. Obviously, this strategy provides dynamic compatible bioactivities for PEEK implants at different stages of osseointegration after implantation *in vivo*.

4.3. Other methods

Some other functional groups have also been introduced to the surface of PEEK through various chemical reactions.[108,115,116] For instance, Zheng et al.[115] modified -COOH, -OH and $-PO_4H_2$ functional groups on the PEEK surface with the aid of silanisation treatment to enhance its bioactivity. Ding et al.[108] fabricated a hierarchical micro-nanoporous structure on the PEEK surface by adjusting the ratio of nitric acid to concentrated sulfuric acid. Subsequently, positively charged NH_2 groups were introduced onto the surface of PEEK by

the Schiff base reaction between the keto carbonyl groups and ethylenediamine. The results showed that such double modification could endow PEEK with antimicrobial and osteogenic activities. In another attempt, Kassick et al.[116] obtained covalently modified hydrophilic PEEK surfaces with improved cell attachment and osseointegration by using the keto carbonyl groups of PEEK to react the same way with different oxyamine and hydrazine nucleophiles bearing polar end groups (**Figure 6A**, and **B**). *In vitro* cell experiments showed that upon addition of bone morphogenetic protein-2, the expression of alkaline phosphatase (ALP) and deposition of mineralised matrix in all the modified PEEK groups surpassed those in the unmodified PEEK group (**Figure 6C**). This indicates that this facile covalent modification method has potential to significantly improve the bone integration of PEEK.

5. Combination of physical and chemical treatments

The combination of physical and chemical treatments can amplify their respective advantages, so as to achieve better modification effects. For example, Wang et al.[53] used sulfonation combined with Ar plasma treatment to obtain a micro/nanotopographic PEEK surface with specific functional groups. Cellular experiments showed that this combination treatment significantly ameliorated the initial adhesion, proliferation and osteogenic differentiation of human osteoblast-like cells (MG-63) on the PEEK surface. In addition, the sulfonation process can soften the surface of PEEK. Taking advantage of this trait, Chen et al.[117] facilely fabricated a hierarchical topological structure on the surface of PEEK through sulfonation combined with "cold pressing" treatment mediated by NaCl porogenic agent (**Figure** 7). Subsequent

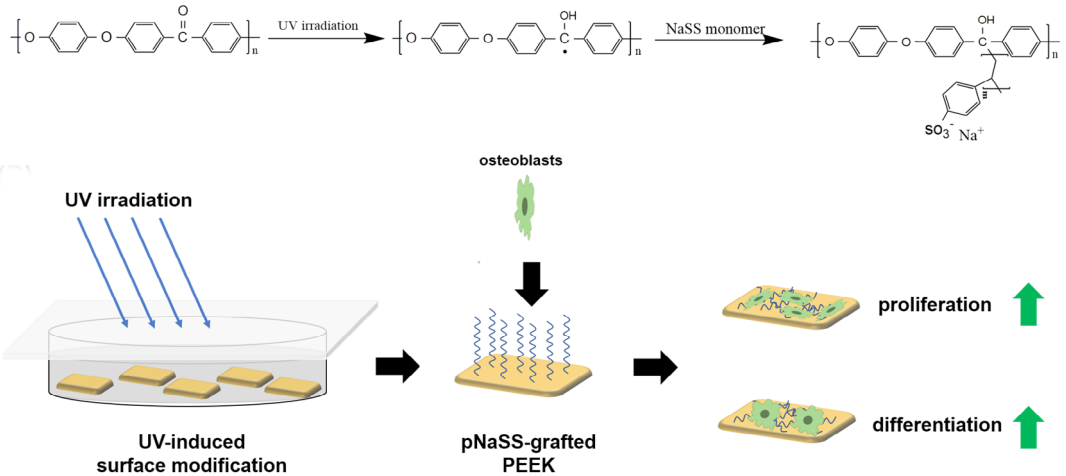

Figure 5. Schematic diagram of the UV-initiated surface grafting polymerisation and *in vitro* evaluation of pNaSS-grafted PEEK. Reprinted from Ma et al.[111] Copyright 2020 Wiley Periodicals, Inc.
Abbreviations: pNaSS: Poly(sodium p-styrene sulfonate); PEEK: Polyetheretherketone; UV: Ultraviolet.

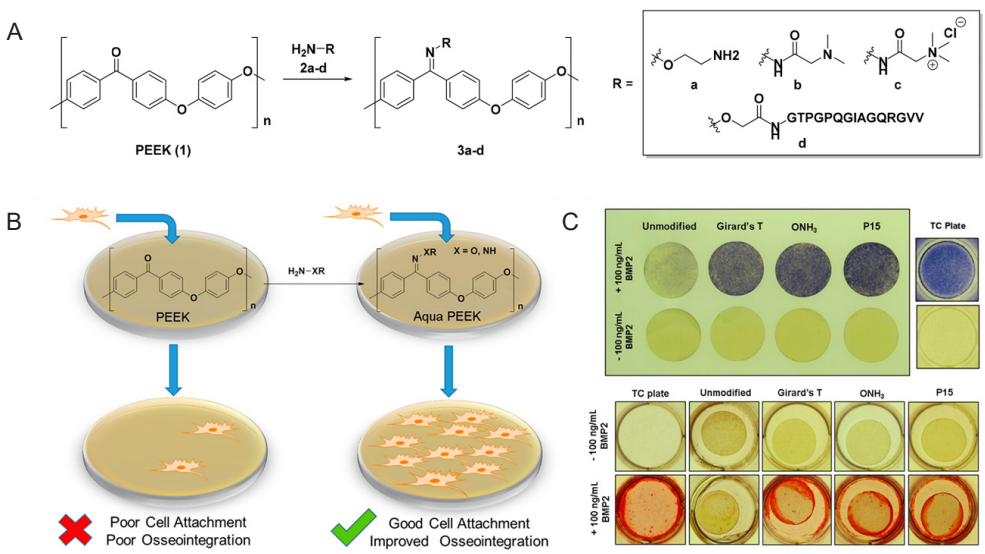

Figure 6. (A) Covalent modification of PEEK surface with oxyamine and hydrazine nucleophiles. (B) Schematic diagram of the covalently modified PEEK surface with improved attachment and osteogenic expression of cells. (C) ALP levels of mouse myoblast cell line with or without BMP2 treatment and mineralisation levels of MC3T3-E1 cells with or without BMP2 treatment on various PEEK surfaces. Reprinted from Kassick et al.[116] Copyright 2018 American Chemical Society.
Abbreviations: ALP: Alkaline phosphatase; BMP2: Bone morphogenetic protein-2; Girard's T: Polymer 3c; ONH_3: Polymer 3a; P15: Polymer 3d; PEEK: Polyetheretherketone; TC: Tissue culture polystyrene.

experiments demonstrated that the superficial porous structure contained 100–200 μm macropores introduced by porogenic agent and 0.5–10 μm micropores generated by sulfonation, which promoted new bone formation and achieved better bone integration with the surrounding host bone compared with pristine PEEK.

Similar to plasma treatment, PIII can also disrupt the molecular chains on PEEK surface and further generate free radicals to activate its surface. With the aid of PIII, researchers have introduced functional groups[118-120] and bioactive agents[121] on the PEEK surface while creating roughened and regular morphology.[118,122]

With the continuous refinement of the sulfonation treatment process, more and more studies have focused on the secondary modification of PEEK after sulfonation to further improve the osseointegration ability of PEEK.[117,123-127] For instance, Yuan et al.[127] added various concentrations of mouse beta-defensin-14 to the SPEEK surface and then immobilised it through lyophilisation. *In vitro* experiments showed that SPEEK incorporating mouse beta-defensin-14 had potent antibacterial activity against both *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa*, and promoted proliferation and osteogenic differentiation of BMSCs. The antibacterial activity and osseointegration potential of mouse beta-defensin-14-modified SPEEK were further confirmed by infected and uninfected rat femur models.

Diabetes-related bone defects have become one of the greatest challenges in bone repair due to the detrimental effects of chronic hyperglycaemia on osseointegration of implants.[128] To address this issue, Wang et al.[129] developed a Zn and Sr co-doped SPEEK implant (Zn&Sr-SPEEK) (**Figure 8A**). Hydrothermal treatment is an efficient method to introduce active substances.[130,131] Here, zinc oxide (ZnO) and strontium hydroxide ($Sr(OH)_2$) nanoparticles were grown firmly onto the SPEEK surface through the electrostatic interaction of the negatively charged groups ($-SO_3$) of SPEEK with Zn and Sr ions during the hydrothermal process. This is then confirmed via Scanning electron microscopy observation (**Figure 8B**). *In vitro* biocompatibility experiments performed in a microenvironment simulating sustained hyperglycaemia demonstrated a significant enhancement in cell proliferation attributed to the sustained release of doped Zn and Sr ions from the Zn&Sr-SPEEK surface (**Figure 8C**). ALP and Alizarin Red S staining further confirmed that the *in vitro* osteogenic capacity of Zn&Sr-SPEEK was substantially improved (**Figure 8D**). Meanwhile, mitochondrial dynamics of MC3T3-E1 osteoblasts cultivated in high glucose medium containing different PEEK sample extracts were also evaluated. Mitotracker red staining results showed that the treatment of Zn&Sr-SPEEK improved the mitochondrial morphology and network structure, forming rod-like, elongated mitochondria and continuous mitochondrial network (**Figure 8E**). Besides, Zn&Sr-SPEEK implants effectively suppressed the overexpression of dynamin-related protein 1 (*Drp1*) gene while reducing the levels of cellular reactive oxygen species, both of which contributed to the regulation of mitochondrial dynamics and functions in a hyperglycaemic micromilieu environment. Ultimately, the femoral/tibia bone defect model of diabetic rats revealed that co-modification with Zn and Sr could significantly promote the *in vivo* osseointegration of PEEK implants (**Figure 8F**).

5.1. Bioactive coating

Another way to improve the bone integration of PEEK is to construct coatings on PEEK surface. Common methods for coating construction include chemical covalent bonding, physical adsorption, or the use of an adhesive medium. The modification methods discussed in the previous subsections only introduce bioactive agents to a portion of the PEEK surface, that is, the "new substance" added is isolated and discontinuous. In contrast, surface coating is to obtain one or more successive layers of "new substance" on the PEEK

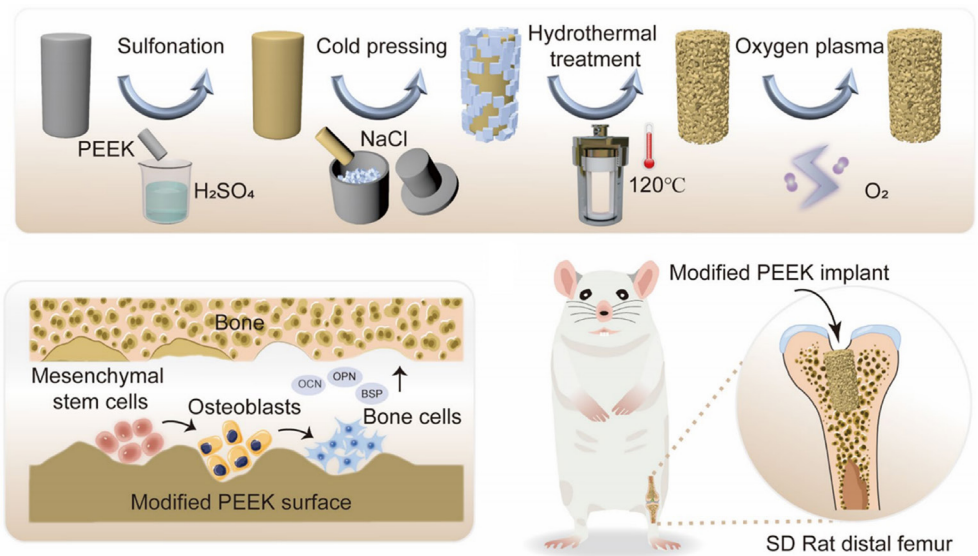

Figure 7. Schematic illustration of the fabrication of a hierarchical porous structure on PEEK surface to enhance osseointegration. Reprinted from Chen et al.[117] Abbreviations: BSP: bone sialoprotein; H_2SO_4: sulfuric acid; O_2: oxygen; OCN: osteocalcin; OPN: osteopontin; PEEK: polyetheretherketone; SD: Sprague-Dawley.

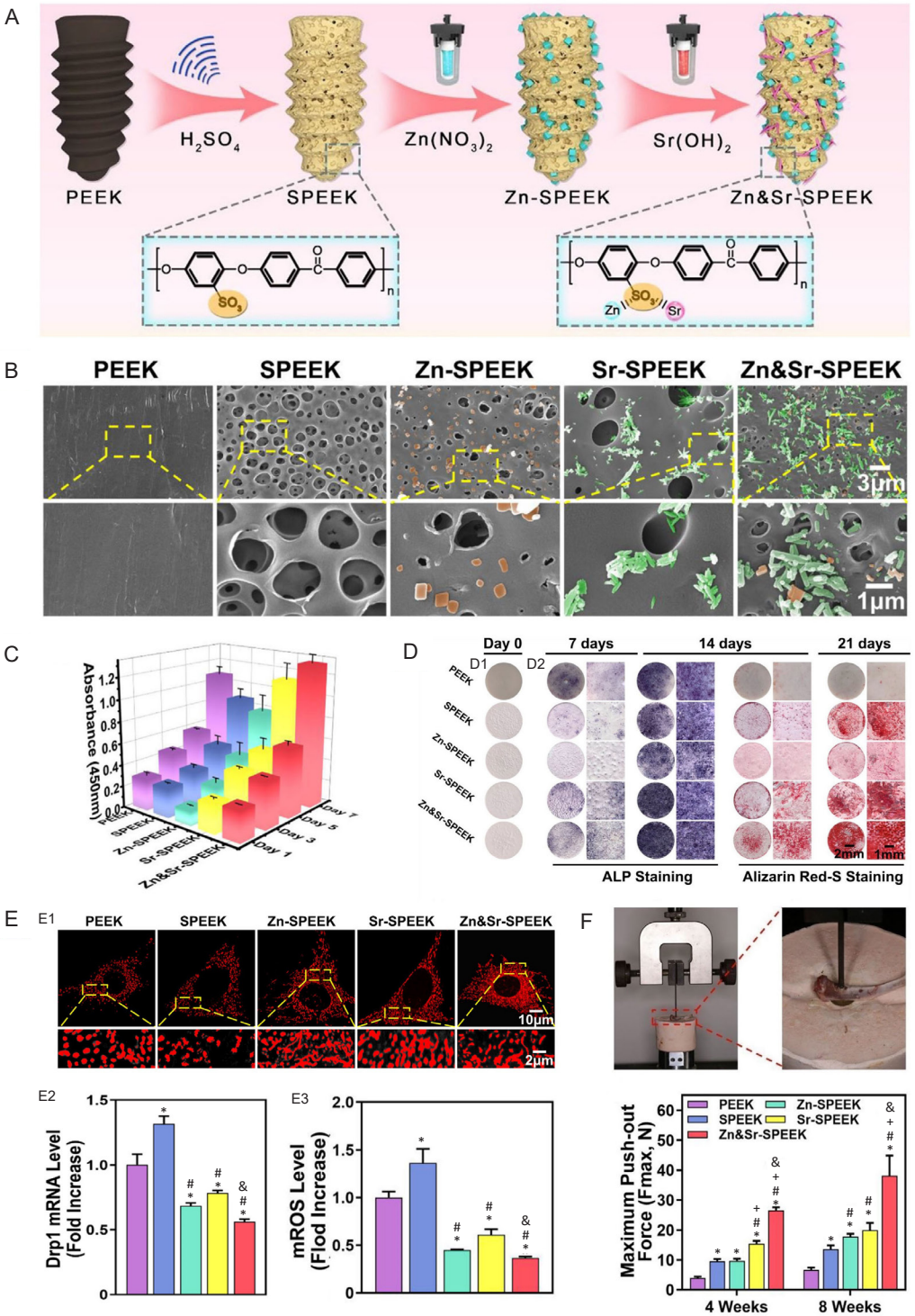

Figure 8. (A) Schematic illustration of the fabrication of Zn and Sr co-decorated PEEK implants. (B) SEM images of different samples. (C) Viability of MC3T3-E1 cells cultured on different substrates for 1, 3, 5, and 7 days. (D1) Photographs of different functionalised PEEK samples. (D2) Photographs of ALP and Alizarin Red S staining of MC3T3-E1 cells on various substrates at indicated time points. Scale bars: 2 mm and 1 mm. (E1) Fluorescence images of Mitotracker Red staining. Scale bars: 10 μm (upper), 2 μm (lower). (E2) Relative expression of *Drp1* gene analysed at 24 hours by qRT-PCR. (E3) Mitochondrial ROS expression confirmed by fluorescent images. (F) Schematic diagram of the push-out experiment and the corresponding maximum push-out force. **P* < 0.05, *vs.* PEEK; #*P* < 0.05, *vs.* SPEEK; +*P* < 0.05, *vs.* Zn-SPEEK; &*P* < 0.05, *vs.* Sr-SPEEK. Reprinted from Wang et al.[129] Abbreviations: ALP: alkaline phosphatase; Drp1: dynamin-related protein 1; mROS: mitochondrial reactive oxygen species; PEEK: polyetheretherketone; qRT-PCR: quantitative real-time polymerase chain reaction; SEM: scanning electron microscopy; SPEEK: sulfonated PEEK; Sr: strontium; Zn: zinc.

surface, thereby forming a new interface in contact with bone tissue. Therefore, the ability of these materials to bind to bone or promote bone growth is their selection criterion. In addition, these coatings can also impact the surface chemistry, morphology, and wettability of PEEK. It should be noted that the strong adhesion between the coating and the substrate is

the key to the coating construction. Once the occurrence of coating shedding, the resulting particle debris may induce inflammation of the surrounding tissue, even causing bone resorption and implant failure.[39]

5.2. CaP-like coatings

Multitudinous studies have confirmed that CaP has an excellent osteogenesis ability.[132-141] Hydroxyapatite (HAp), dicalcium phosphate dihydrate and beta tricalcium phosphate are three common forms of CaP.[142] Inspired by this, Almasi et al.[143] employed friction stir processing to cover HAp and NaCl particles onto the PEEK surface. Then, the sample was immersed in deionised water to leach out NaCl crystals while retaining HAp particles, thus obtaining a porous morphology. *In vitro* results showed that the introduction of HAp particles and porous structure contributed to improving cell adhesion, proliferation and differentiation compared with bare PEEK.

In addition to directly fastening CaP particles onto a material surface, CaP coatings can also be obtained by immersing the activated material in a simulated body fluid for a period of time.[138,144,145] To improve the binding force between the substrate and the coating, the fibre reinforced PEEK was first subjected to sulfonation and plasma treatment, followed by immersion in simulated body fluid solution at pH 8.4 and 25°C and being maintained at 70°C for 24 hours.[146] Scanning electron microscopy observation manifested that such treatment deposited fine amorphous CaP particles in the pores of PEEK and formed a CaP coating with high adhesion strength. After that, the coating-modified sample was implanted into a rabbit tibia model to test its osseointegration.[147] Histological observation and imaging analysis showed that the incorporation of amorphous CaP coating significantly enhanced the bone-implant bonding and promoted the formation of new bone.

It has been the grail to researchers to incorporate a variety of bioactive agents on the implant surface to improve its osseointegration and address other bone repair related issues such as bacterial infection and angiogenesis. In pursuit of this goal, Xue et al.[148] developed a dicalcium phosphate dihydrate coating containing gentamicin sulfate antibiotic on the PEEK surface (PEEK-DCPD-GS) using a layer-by-layer deposition method. *In vitro* antibacterial experiments demonstrated that PEEK-DCPD-GS had superior and sustained antibacterial activity. Meanwhile, the ability of MG-63 cells that are derived from human osteoblasts seeded on PEEK-DCPD-GS to secrete ALP was obviously enhanced compared with bare PEEK. *In vivo* evaluations employing a *S. aureus* infected rat femur defect model validated that PEEK-DCPD-GS could effectively control the occurrence of infection while promoting the formation of new bone. In another study, to orchestrate osteogenesis and angiogenesis during bone regeneration, Dong et al.[56] fabricated a multifunctional coating composed of HAp nanoflowers and nickel hydroxide nanoparticles on the SPEEK surface (SPEEK-Ni-HAp) through a two-step hydrothermal treatment (**Figure 9**). *In vitro* results showed that Ni and Ca ions could be sustainably released from SPEEK-Ni-HAp for over 7 days, and the introduction of Ni ions and HAp significantly enhanced the osteogenicity of SPEEK-Ni-HAp. Meanwhile, the loading and rational release of Ni ions fostered the migration, tube formation and angiogenic gene expression of human umbilical vein endothelial cells, indicating the good angiogenesis of SPEEK-Ni-HAp. Finally, *in vivo* experiments showed that the osseointegration ability of the Ni element and HAp nanoflower dual-modified PEEK was greatly boosted compared with SPEEK.

5.3. Graphene & graphene oxide coatings

Graphene, a two-dimensional material, has received unprecedented attention over the last decade due to its large surface area, high mechanical strength, low mass density, and

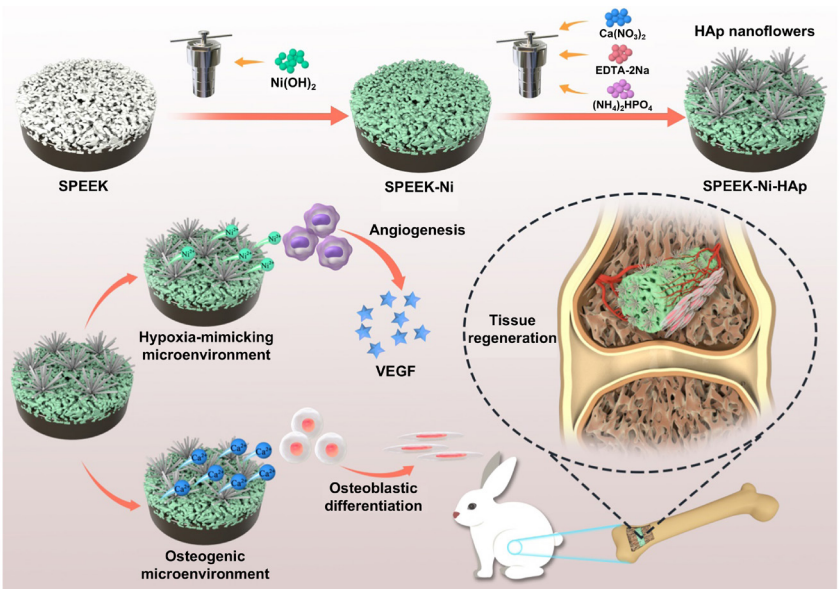

Figure 9. Schematic illustrations of the preparation steps and performance evaluations of SPEEK-Ni-HAp implant. Reprinted from Dong et al.[56] Copyright 2020 American Chemical Society.
Abbreviations: EDTA: ethylenediaminetetraacetate; HAp: hydroxyapatite; SPEEK: sulfonated polyetheretherketone; VEGF: vascular endothelial growth factor.

good thermal and electrical conductivity.[149,150] A large number of studies have demonstrated that graphene can promote osteogenic differentiation of mesenchymal stem cells.[150,151] For instance, Yan et al.[150] transferred graphene onto the surface of carbon fibre-reinforced PEEK. The rabbit extraarticular graft-to-bone healing model confirmed that the graphene modification significantly promoted the osseointegration of carbon fibre-reinforced PEEK implants.

As one of the most popular graphene derivatives, graphene oxide (GO) is a monatomic nanosheet with dense honeycomb-structure composed of sp^2-hybridised carbon atoms, and contains abundant oxygen-containing functional groups (hydroxyl, carboxyl, etc.), which make it easy to achieve good bonding with other substances.[152,153] Meanwhile, some studies have revealed that GO can enhance osteogenic differentiation of mesenchymal stem cells and MC3T3-E1 cells[154,155] and has antiadhesion and antibiofilm activities.[155,156] The contribution of GO to osteogenic differentiation of stem cells may stem from the regulation of mitochondrial dynamics within stem cells,[157] the enhancement of body fluid mineralisation capacity,[158] and the ability to remodel a biomimetic regenerative electrophysiological microenvironment at the defect sites due to its inherent electrical conductivity.[159] Inspired by these studies, Ouyang et al.[160] introduced a GO coating onto the SPEEK surface via a simple dip-coating method. The GO coating exhibited good durability due to the potent π-π stacking interactions between SPEEK and GO. Antibacterial experiments demonstrated that the modification of GO improved the antibacterial performance against *Escherichia coli* (*E. coli*) compared with SPEEK and PEEK. Moreover, GO-modified SPEEK had higher attachment, proliferation, bone-like nodule formation and osteogenic differentiation-related gene expression of MG-63 cells than SPEEK and unmodified PEEK. It should be noted that these studies have demonstrated the efficacy of graphene/GO coatings in animal studies, but their mechanisms of action are not yet clear, which poses a considerable barrier to their clinical translation. Therefore, it is urgent to conduct more in-depth discussion and research on their mechanisms.

5.4. Polydopamine-mediated bioactive coatings

In the past decade, polydopamine (PDA) coatings inspired by marine mussels have attracted considerable attention due to their facile preparation, excellent adhesion and good biocompatibility.[62,161-164] Numerous studies have focused on the construction of PDA coatings on material surfaces and subsequent utilisation of their interactions such as hydrogen bonding, π-π stacking, coordination bonding, and chemical reactions such as Michael addition and Schiff base reactions stemmed from its benzene ring, amino and hydroxyl groups to immobilise a variety of bioactive agents, thereby enhancing the osteogenesis ability of materials.[156,165-168] As its application in PEEK, for instance, Shi et al.[169] fabricated a coating of bionic natural bone composed of collagen and CaP on the PDA-modified PEEK surface through layer-by-layer method combined with in situ mineralisation. The results showed that the introduction of biomimetic interface promoted the osteogenic differentiation of MC3T3-E1 cells *in vitro*, which made the modified PEEK have a stronger osteogenesis effect *in vivo*.

In addition to promoting osteogenesis, PDA coatings also allow the simultaneous introduction of bioactive agents with antibacterial, anti-inflammatory, and angiogenic properties onto the PEEK surface to further enhance the osseointegration capability of PEEK implants.[61,170-175] For example, Meng et al.[170] immobilised the antimicrobial peptide KR-12 on the surface of PEEK with the assistance of PDA coating, which significantly boosted the antimicrobial and osteogenic activities of PEEK both *in vitro* and *in vivo*. Similarly, Xiao et al.[171] constructed a bimetallic-organic framework coating composed of Mg^{2+}, Zn^{2+}, and 2,5-dihydroxyterephthalic acid (Zn-Mg-MOF74) on the PEEK surface (PEEK-74) by using the strong adhesion force and metal ion chelating ability of PDA interlayer, and then loaded the surface of Zn-Mg-MOF74 coating with dexamethasone (DEX) (PEEK-DEX) (**Figure 10A**). *In vitro* osteogenic results showed that the ALP expression and matrix mineralisation formation of BMSCs in the PEEK-DEX group were better than those in the other three groups thanks to the release of Zn and Mg ions and DEX. Blood vessel formation experiments revealed that compared with the other two samples, PEEK-74 and PEEK-DEX exhibited more intersections in the new vascular network (**Figure 10B**), indicating their good angiogenic ability. This was attributed to the release of Mg ions. **Figure 10C** presents the antibacterial activity of various PEEK samples against *E. coli* and *S. aureus*. Similar to blood vessel formation, PEEK-74 and PEEK-DEX showed excellent antibacterial performance. This feature was due to the alkaline microenvironment formed by the degradation of their coatings as well as the release of Zn and Mg ions and 2,5-dihydroxyterephthalic acid. Finally, the rat femoral implant model confirmed that a multifunctional coating (DEX@Zn-Mg-MOF74) on the surface of PEEK-DEX with antibacterial, angiogenic, and osteogenic functions promoted osteointegration *in vivo* (**Figure 10D**).

Interestingly, the roughened and porous SPEEK surface plus the presence of sulfonic acid groups contributes to forming a firmer PDA coating with PEEK substrate. Based on this strategy, using PDA as the interlayer, various bioactive agents/coatings have been introduced onto the SPEEK surface to enhance its osseointegration ability, such as Arg-Gly-Asp tripeptide,[176] gentamicin sulfate,[177] strontium carbonate ($SrCO_3$)/gentamicin-silk protein,[178] moxifloxacin hydrochloride/osteogenic growth peptide,[179] strontium/adiponectin,[130] insulin-like growth factor-1 (IGF-1) and BMP-2,[180] icariin,[181] Cu-Sr bilayer bioactive glass nanoparticles,[182] glucose oxidase,[183] GO/DEX-loaded liposome,[184] copper ferrite ($CuFe_2O_4$)/GO,[185] etc. It should be noted that the sulfonation and subsequent PDA layer (or the PDA layer only) provide almost exclusively the anchoring function, while the osteogenic, angiogenic, and antimicrobial functions of the coatings are generated by the introduced bioactive agents. Therefore, the osseointegration efficiency of modified PEEK is mainly attributed to the attachment-release behaviour of the bioactive agents and their bioactivity in a variety of different situations (e.g., osteoporosis, hyperglycaemia, etc.).

Additionally, with the aid of PDA, Deng-Yang's research group incorporated some biological active agents onto the GO-modified SPEEK surface to further enhance its osteogenesis and antibacterial

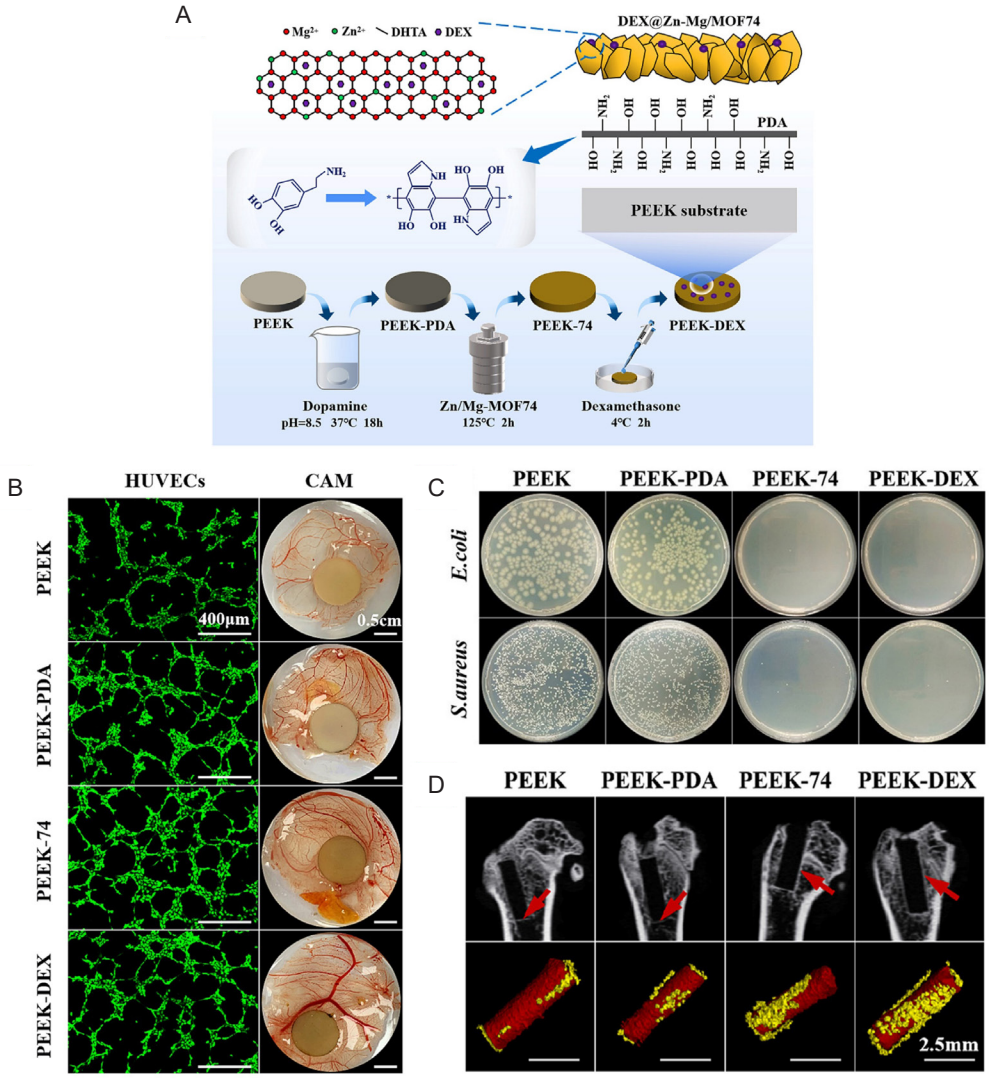

Figure 10. (A) Schematic diagram of the fabrication of multifunctional DEX@Zn-Mg-MOF74 coating on PEEK surface. (B) Representative images of HUVEC angiogenesis assay and *in vivo* CAM assay on various PEEK surfaces. Scale bars: 400 μm (left), 0.5 cm (right). (C) Antibacterial activity of different PEEK samples. (D) Micro-CT observation and reconstructed 3D models. The red arrows mark new bone formation. Scale bars: 2.5 mm. Reprinted from Xiao et al.[171] Copyright 2021 American Chemical Society.
Abbreviations: CAM: chicken chorioallantoic membrane; CT: computed tomography; DEX: dexamethasone; DEX@Zn-Mg-MOF74: zinc-magnesium based metal organic framework loaded with dexamethasone; DHTA: 2,5-dihydroxyterephthalic acid; *E.coli*: *Escherichia coli*; HUVECs: human umbilical vein endothelial cells; MOF: metal-organic frameworks; PDA: polydopamine; PEEK: polyetheretherketone; PEEK-74: PEEK coated with zinc-magnesium based metal organic framework; PEEK-PDA: PEEK coated with PDA; *S.aureus*: *Staphylococcus aureus*.

activities.[186,187] For instance, they coated the GO-modified SPEEK surface with a PDA coating and then introduced a bone-forming peptide, resulting in a multifunctional coating (**Figure 11A**).[186] *In vitro* evaluations showed that the combination of bone-forming peptide and GO increased the viability, ALP expression and calcium nodule formation of MC3T3-E1 cells, thereby achieving the best osteogenesis-promoting effect (**Figure 11B**). *In vivo* experiments based on a rabbit femoral defect model demonstrated that the hybrid coating prominently boosted bone regeneration and osseointegration. Meanwhile, when exposure to 808 nm near-infrared light for 10 minutes, the hybrid coating showed excellent antibacterial activity against *S. aureus* and *E. coli* (**Figure 11C**). This was attributed to the synergetic photothermal/photodynamic efficacy generated by GO nanosheets and PDA interlayer.

5.5. Other bioactive coatings

Inspired from drug delivery systems, many studies began to focus on the construction of drug delivery coatings on the PEEK surface using microspheres, hydrogels, etc., to precisely control the release of loaded bioactive agents.[188-194] Hydrogels, in particular, are suitable as reservoirs for drug delivery due to their simple preparation, good biocompatibility and soft matter nature.[195-207] For example, Dong et al.[194] sulfonated long carbon fibre reinforced PEEK (CP) to obtain a porous CP implant (SCP), and then immersed it into a mixed solution of gelatin methacrylate/acrylamide (GelMA/AM). Under UV irradiation, free radicals were generated on the backbone of SCP, which initiated the polymerisation of GelMA and AM, resulting in the formation of a GelMA/AM gel coating (GC)

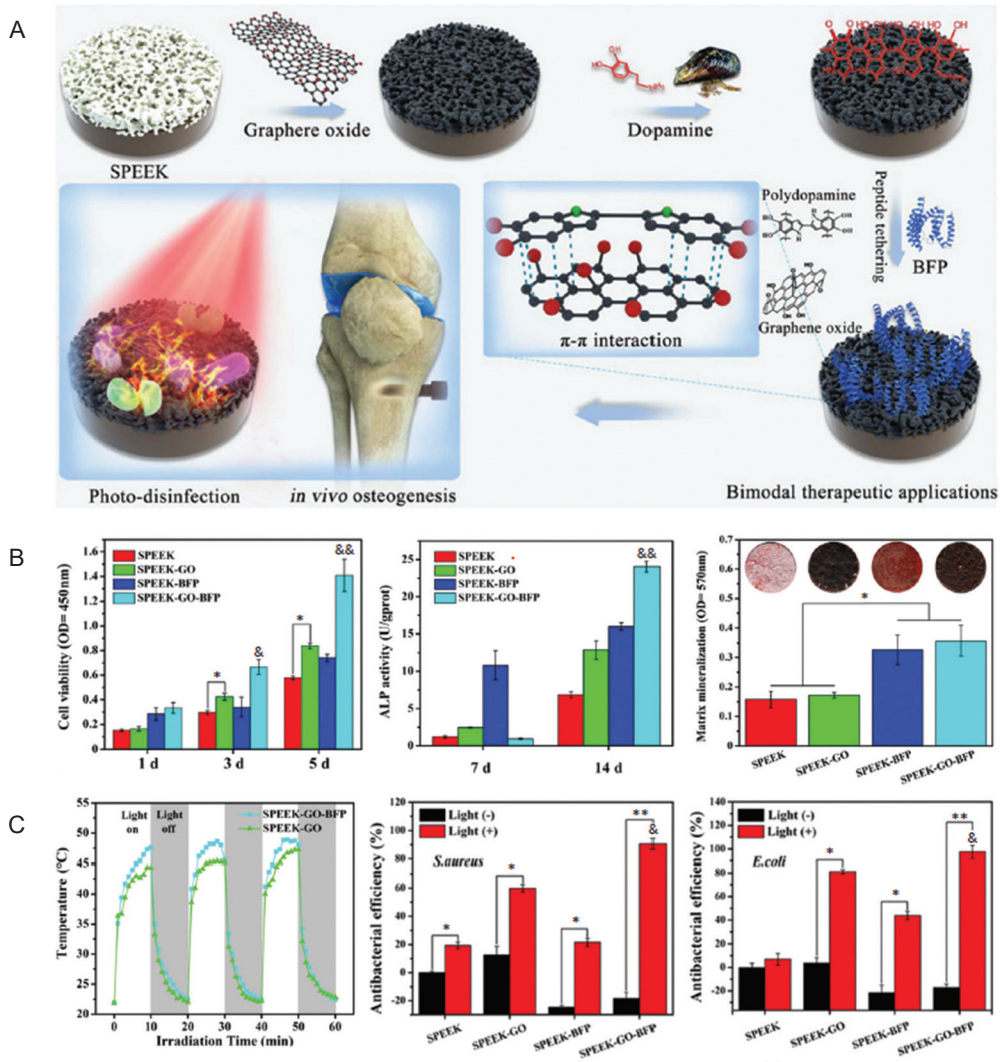

Figure 11. (A) Schematic diagram of the fabrication of GO/BFP-decorated SPEEK implant (SPEEK-GO-BFP). (B) *In vitro* evaluation of cell viability, ALP expression, and matrix mineralisation formation. (C) Photothermal properties and antibacterial activities of the hybrid coating with or without light. Data are expressed as mean ± SD. *$P < 0.05$, **$P < 0.01$; &$P < 0.05$, &&$P < 0.01$, *vs.* other groups. Reprinted from Wang et al.[186] Copyright 2020 The Royal Society of Chemistry.

Abbreviations: ALP: alkaline phosphate; BFP: bone-forming peptide; *E.coli*: *Escherichia coli*; GO: graphene oxide; OD: optical density; PEEK: polyetheretherketone; *S.aureus*: *Staphylococcus aureus*; SPEEK: sulfonated PEEK; SPEEK-BFP: BFP-modified SPEEK; SPEEK-GO: GO-immobilised SPEEK.

on the SCP surface (SCP-GC). Ultimately, DEX was absorbed onto the surface of SCP-GC via hydrogen bonding to harvest DEX-loaded SCP-GC. As a result, a three dimensional network was formed on the GC-modified SCP surface. The components of hydrogel coating coupled with the sustained release of DEX significantly promoted ALP expression and bone-like apatite nodule formation of BMSCs. The rat cranial defect model showed that the DEX-loaded hydrogel coating promoted the formation of new bone around the implant, resulting in a stronger implant-bone interface.

6. Limitations

This review focuses on the material design of PEEK surface modification and its contribution to the osteointegration of PEEK. However, due to the article's length and thematic perspective, this review has the following limitations: (1) In recent years, with the deepening of the understanding of bone repair, researchers have found that stem cells, immune cells and nerve cells, etc. have a strong correlation with bone regeneration. This review does not elaborate on the impact of PEEK surface modification on this aspect. (2) The biological effects of the physicochemical properties of modified PEEK surfaces on tissues and cells are not discussed in depth, and their relevant rules need to be further summarised. (3) The biological mechanisms by which the active substances introduced onto the PEEK surface contribute to pro-osteogenic effects are not much involved.

7. Summary and prospect

This review summarises the main surface modification methods that have been used in recent years to improve the osseointegration of PEEK implants and categorised them into four parts based on the modification methods and techniques used, that is, (1) physical treatment, (2) wet chemical methods, (3) combination of physical

and chemical treatments, and (4) bioactive coating. All of these modification methods have altered the surface state of PEEK to a certain extent, i.e., increasing surface roughness, hydrophilicity, porosity, and/or introducing bioactive groups/agents/coatings, thereby boosting its osseointegration. Meanwhile, we have also demonstrated the powerful capability and numerous applications of sulfonation layer and/or PDA layer as an interlayer to bind bioactive agents/coatings.

Bone defect repair involves various cell types, including osteoblast cell lines, angiogenic cell lines, and immune cells, as well as the corresponding interactions of cells and cell-biomolecules/materials, making it a multi-stage and dynamic process. Tissue engineering is an advanced technique for tissue repair.[208-229] As a matter of fact, the aforementioned modification strategies of PEEK surface align with the prevailing modification strategies employed in bone tissue engineering scaffolds. The essence of tissue engineering scaffold is to design a material structure close to natural bone tissue and incorporate appropriate bioactive molecules to modulate the osteogenic and angiogenic/neurogenic microenvironments, thereby promoting bone regeneration and facilitating bone-implant bonding. Therefore, the key aspect of PEEK surface design lies in achieving a biomimetic interface and precise delivery of bioactive molecules/components. Particularly important is ensuring that the release behaviour of these bioactive molecules/components matches the process of bone repair/regeneration.

Meanwhile, as regenerative medicine advances, there is an increasing demand for precision and personalised treatment among patients. This necessitates constructing customised PEEK implant surfaces tailored to individuals with different bone defect conditions based on accurate diagnoses. 3D-printed PEEK can be a potential development direction. Researchers have proposed some surface modification strategies for 3D-printed PEEK, including a sand casting-inspired technology to produce BG coatings,[230] a combined method of sulfonation and UV-induced grafting to introduce gel coatings,[231] and a PDA coating-mediated approach for the introduction of bioactive metal ions.[232] However, traditional line-of-sight surface modification techniques such as plasma treatment, sandblasting and sputtering are not suitable for the complex topography of 3D-printed PEEK.[230] Consequently, the surface modification of 3D-printed PEEK remains an area that needs to be explored in depth.

Additionally, standardising unmodified PEEK specimens, surface analysis methods and *in vivo* animal models will facilitate comparison across different studies on surface modifications. Finally, before these surface treatments can be implemented clinically, some practical issues such as stability during storage, resistance to sterilisation procedures, and wear resistance must be addressed to ensure that these modifications remain intact during preparation and implantation.

Acknowledgement
None.

Conflicts of interest statement
The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Financial support
This work was supported by the Special Project for Emerging Interdisciplinary Research in the Health Industry of the Shanghai Municipal Health Commission (No. 2022JC030) and National Key R&D Program of China (No. 2020YFC1107102).

Author contributions
Conceptualization: LY; *Writing-original draft:* YC; *Writing-review & editing:* ZC, KL and JD. All authors reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data
Not applicable.

References

1. Reznikov N, Bilton M, Lari L, Stevens MM, Kröger R. Fractal-like hierarchical organization of bone begins at the nanoscale. *Science.* 2018;360:eaao2189. doi: 10.1126/science.aao2189
2. Koons GL, Diba M, Mikos AG. Materials design for bone-tissue engineering. *Nat Rev Mater.* 2020;5:584-603. doi: 10.1038/s41578-020-0204-2
3. Depalle B, McGilvery CM, Nobakhti S, Aldegaither N, Shefelbine SJ, Porter AE. Osteopontin regulates type I collagen fibril formation in bone tissue. *Acta Biomater.* 2021;120:194-202. doi: 10.1016/j.actbio.2020.04.040
4. DiGirolamo DJ, Clemens TL, Kousteni S. The skeleton as an endocrine organ. *Nat Rev Rheumatol.* 2012;8:674-683. doi: 10.1038/nrrheum.2012.157
5. Stevens MM. Biomaterials for bone tissue engineering. *Mater Today.* 2008;11:18-25.
6. Zhu G, Zhang T, Chen M, *et al.* Bone physiological microenvironment and healing mechanism: Basis for future bone-tissue engineering scaffolds. *Bioact Mater.* 2021;6:4110-4140. doi: 10.1016/j.bioactmat.2021.03.043
7. Ho-Shui-Ling A, Bolander J, Rustom LE, Johnson AW, Luyten FP, Picart C. Bone regeneration strategies: Engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives. *Biomaterials.* 2018;180:143-162. doi: 10.1016/j.biomaterials.2018.07.017
8. Lopes D, Martins-Cruz C, Oliveira MB, Mano JF. Bone physiology as inspiration for tissue regenerative therapies. *Biomaterials.* 2018;185:240-275. doi: 10.1016/j.biomaterials.2018.09.028
9. Hu C, Ashok D, Nisbet DR, GautamV. Bioinspired surface modification of orthopedic implants for bone tissue engineering. *Biomaterials.* 2019;219:119366. doi: 10.1016/j.biomaterials.2019.119366
10. Schmitz JP, Hollinger JO. The critical size defect as an experimental model for craniomandibulofacial nonunions. *Clin Orthop Relat Res.* 1986;299-308.
11. Mauffrey C, Barlow BT, Smith W. Management of segmental bone defects. *J Am Acad Orthop Surg.* 2015;23:143-153.doi: 10.5435/JAAOS-D-14-00018
12. Steijvers E, Ghei A, Xia Z. Manufacturing artificial bone allografts: A perspective. *Biomater Transl.* 2022;3:65-80.
13. Deng J, Wang X, Zhang W, *et al.* Versatile hypoxic extracellular vesicles laden in an injectable and bioactive hydrogel for accelerated bone

regeneration. *Adv Funct Mater.* 2023;33:2211664. doi: 10.1002/adfm.202370132
14. Huang J, Zhai D, Xue J, Li T, Ren D, Wu C. Bioinspired laminated bioceramics with high toughness for bone tissue engineering. *Regen Biomater.* 2022;9:rbac055.
15. Tao Z, Yuan Z, Zhou D, *et al.* Fabrication of magnesium-doped porous polylactic acid microsphere for bone regeneration. *Biomater Transl.* 2023;4:280-290. doi: 10.12336/biomatertransl.2023.04.007
16. Wang Y, Feng Z, Liu X, *et al.* Titanium alloy composited with dual-cytokine releasing polysaccharide hydrogel to enhance osseointegration via osteogenic and macrophage polarization signaling pathways. *Regen Biomater.* 2022;9:rbac003. doi: 10.1093/rb/rbac003
17. Shuai C, Wang Z, Zhang H, *et al.* Biosoluble ceramic fiber reinforced poly(L-lactic acid) bone scaffold: Degradation and bioactivity. *Npj Mater Degrad.* 2022;6:87. doi: 10.1038/s41529-022-00297-3
18. Bai Z, Hu K, Shou Z, *et al.* Layer-by-layer assembly of procyanidin and collagen promotes mesenchymal stem cell proliferation and osteogenic differentiation *in vitro* and *in vivo*. *Regen Biomater.* 2023;10:rbac107.
19. Ullah I, Ou P, Xie L, *et al.* Diffusion-driven fabrication of calcium and phosphorous-doped zinc oxide heterostructures on titanium to achieve dual functions of osteogenesis and preventing bacterial infections. *Acta Biomater.* 2024;175:382-394. doi: 10.1016/j.actbio.2023.12.046
20. Zhou Q, Chen W, Gu C, *et al.* Selenium-modified bone cement promotes osteoporotic bone defect repair in ovariectomized rats by restoring GPx1-mediated mitochondrial antioxidant functions. *Regen Biomater.* 2023;10:rbad011. doi: 10.1093/rb/rbad011
21. Jing X, Ding Q, Wu Q, *et al.* Magnesium-based materials in orthopaedics: Material properties and animal models. Biomater Transl. 2021, 2, 197-213.
22. Miao X, Yang S, Zhu J, *et al.* Bioactive mineralized small intestinal submucosa acellular matrix/PMMA bone cement for vertebral bone regeneration. *Regen Biomater.* 2023;10:rbad040. doi: 10.1093/rb/rbad040
23. Zhao F, Gao A, Liao Q, *et al.* Balancing the anti-bacterial and pro-osteogenic properties of Ti-based implants by partial conversion of ZnO nanorods into hybrid zinc phosphate nanostructures. *Adv Funct Mater.* 2024;34:2311812. doi: 10.1002/adfm.202311812
24. Huang L, Gong W, Huang G, Li J, Wu J, Dong Y. The additive effects of bioactive glasses and photobiomodulation on enhancing bone regeneration. *Regen Biomater.* 2023;10:rbad024. doi: 10.1093/rb/rbad024
25. Wang DX, He Y, Bi L, *et al.* Enhancing the bioactivity of poly(lactic-co-glycolic acid) scaffold with a nano-hydroxyapatite coating for the treatment of segmental bone defect in a rabbit model. *Int J Nanomedicine.* 2013;8:1855-1865. doi: 10.2147/ijn.s43706
26. Ma Z, Liu B, Li S, *et al.* A novel biomimetic trabecular bone metal plate for bone repair and osseointegration. *Regen Biomater.* 2023;10:rbad003.
27. Ren Y, Ma C, Yu Y, *et al.* Poly(l-lactic acid)-based double-layer composite scaffold for bone tissue repair. *Regen Biomater.* 2024;11:rbad093. doi: 10.1093/rb/rbad093
28. Qi L, Zhao T, Yan J, *et al.* Advances in magnesium-containing bioceramics for bone repair. *Biomater Transl.* 2024;5:3-20.
29. Zhang B, Yin X, Zhang F, *et al.* Customized bioceramic scaffolds and metal meshes for challenging large-size mandibular bone defect regeneration and repair. *Regen Biomater.* 2023;10:rbad057. doi: 10.1093/rb/rbad057
30. Gao J, Ding X, Yu X, *et al.* Cell-free bilayered porous scaffolds for osteochondral regeneration fabricated by continuous 3D-printing using nascent physical hydrogel as ink. *Adv Healthc Mater.* 2021;10:e2001404. doi: 10.1002/adhm.202001404
31. Duan P, Pan Z, Cao L, *et al.* Restoration of osteochondral defects by implanting bilayered poly(lactide-co-glycolide) porous scaffolds in rabbit joints for 12 and 24 weeks. *J Orthop Translat.* 2019;19:68-80. doi: 10.1016/j.jot.2019.04.006
32. Liang X, Duan P, Gao J, *et al.* Bilayered PLGA/PLGA-HAp composite scaffold for osteochondral tissue engineering and tissue regeneration. *ACS Biomater Sci Eng.* 2018;4:3506-3521. doi: 10.1021/acsbiomaterials.8b00552.s001
33. Pan Z, Duan P, Liu X, *et al.* Effect of porosities of bilayered porous scaffolds on spontaneous osteochondral repair in cartilage tissue engineering. Regen Biomater. 2015;2:9-19. doi: 10.1093/rb/rbv001
34. Sun W, Yang K, Zou Y, *et al. In vitro* and *in vivo* degradation, biocompatibility and bone repair performance of strontium-doped montmorillonite coating on Mg-Ca alloy. *Regen Biomater.* 2024;11:rbae027. doi: 10.1093/rb/rbae027
35. Feng P, Zhao R, Tang W, *et al.* Structural and functional adaptive artificial bone: Materials, fabrications, and properties. *Adv Funct Mater.* 2023:33:2214726. doi: 10.1002/adfm.202214726
36. Buck E, Li H, Cerruti M. Surface modification strategies to improve the osseointegration of poly(etheretherketone) and its composites. *Macromol Biosci.* 2020;20:e1900271. doi: 10.1002/mabi.201900271
37. Chen Z, Chen Y, Ding J, Yu L. Blending strategy to modify PEEK-based orthopedic implants. *Compos B Eng.* 2023;250:110427.
38. Kurtz SM, Devine JN. PEEK biomaterials in trauma, orthopedic, and spinal implants. *Biomaterials.* 2007;28:4845-4869. doi: 10.1016/j.biomaterials.2007.07.013
39. Ma T, Zhang J, Sun S, Meng W, Zhang Y, Wu J. Current treatment methods to improve the bioactivity and bonding strength of PEEK for dental application: A systematic review. *Eur Polym J.* 2023;183:111757. doi: 10.1016/j.eurpolymj.2022.111757
40. He M, Huang Y, Xu H, *et al.* Modification of polyetheretherketone implants: From enhancing bone integration to enabling multi-modal therapeutics. *Acta Biomater.* 2021;129:18-32. doi: 10.2139/ssrn.3797424
41. Pu F, Yu Y, Zhang Z, *et al.* Research and application of medical polyetheretherketone as bone repair material. *Macromol Biosci.* 2023;23:e2300032.
42. Zheng W, Wu D, Zhang Y, *et al.* Multifunctional modifications of polyetheretherketone implants for bone repair: A comprehensive review. *Biomater Adv.* 2023;154:213607.
43. Zheng Z, Liu P, Zhang X, *et al.* Strategies to improve bioactive and antibacterial properties of polyetheretherketone (PEEK) for use as orthopedic implants. *Mater Today Bio.* 2022;16:100402. doi: 10.1016/j.mtbio.2022.100402
44. Han X, Gao W, Zhou Z, *et al.* Application of biomolecules modification strategies on PEEK and its composites for osteogenesis and antibacterial properties. *Colloids Surf B Biointerfaces.* 2022;215:112492. doi: 10.1016/j.colsurfb.2022.112492
45. Jiang P, Zhang Y, Hu R, *et al.* Advanced surface engineering of titanium materials for biomedical applications: From static modification to dynamic responsive regulation. *Bioact Mater.* 2023;27:15-57. doi: 10.1016/j.bioactmat.2023.03.006
46. Oshida Y. Surface modifications. In: *Bioscience and Bioengineering of Titanium Materials.* 2nd ed. Oxford: Elsevier; 2013. p. 341-456. doi: 10.1016/b978-0-444-62625-7.00011-x
47. Petlin DG, Tverdokhlebov SI, Anissimov YG. Plasma treatment as an efficient tool for controlled drug release from polymeric materials: A review. *J Control Release.* 2017;266:57-74. doi: 10.1016/j.jconrel.2017.09.023
48. Liu C, Bai J, Wang Y, *et al.* The effects of three cold plasma treatments on the osteogenic activity and antibacterial property of PEEK. *Dent Mater.* 2021;37:81-93.
49. Fu Q, Gabriel M, Schmidt F, Müller WD, Schwitalla AD. The impact of different low-pressure plasma types on the physical, chemical and biological surface properties of PEEK. *Dent Mater.* 2021;37:e15-e22. doi: 10.1016/j.dental.2020.09.020
50. Lu T, Wen J, Qian S, *et al.* Enhanced osteointegration on tantalum-implanted polyetheretherketone surface with bone-like elastic modulus. *Biomaterials.* 2015;51:173-183. doi: 10.1016/j.biomaterials.2015.02.018

51. Ouyang L, Zhao Y, Jin G, *et al.* Influence of sulfur content on bone formation and antibacterial ability of sulfonated PEEK. *Biomaterials.* 2016;83:115-126.
52. Zhao Y, Wong HM, Wang W, *et al.* Cytocompatibility, osseointegration, and bioactivity of three-dimensional porous and nanostructured network on polyetheretherketone. *Biomaterials.* 2013;34:9264-9277. doi: 10.1016/j.biomaterials.2013.08.071
53. Wang S, Deng Y, Yang L, Shi X, Yang W, Chen ZG. Enhanced antibacterial property and osteo-differentiation activity on plasma treated porous polyetheretherketone with hierarchical micro/nano-topography. *J Biomater Sci Polym Ed.* 2018;29:520-542. doi: 10.1080/09205063.2018.1425181
54. Zheng Y, Liu L, Xiao L, Zhang Q, Liu Y. Enhanced osteogenic activity of phosphorylated polyetheretherketone via surface-initiated grafting polymerization of vinylphosphonic acid. *Colloids Surf B Biointerfaces.* 2019;173:591-598. doi: 10.1016/j.colsurfb.2018.10.031
55. Flejszar M, Chmielarz P. Surface modifications of poly(ether ether ketone) via polymerization methods-current status and future prospects. *Materials* (*Basel*). 2020;13:999. doi: 10.3390/ma13040999
56. Dong T, Duan C, Wang S, *et al.* Multifunctional surface with enhanced angiogenesis for improving long-term osteogenic fixation of poly(ether ether ketone) implants. *ACS Appl Mater Interfaces.* 2020;12:14971-14982. doi: 10.1021/acsami.0c02304.s001
57. Niu Y, Guo L, Hu F, *et al.* Macro-microporous surface with sulfonic acid groups and micro-nano structures of PEEK/nano magnesium silicate composite exhibiting antibacterial activity and inducing cell responses. *Int J Nanomedicine.* 2020;15:2403-2417. doi: 10.2147/ijn.s238287
58. Shin SR, Li YC, Jang HL, *et al.* Graphene-based materials for tissue engineering. *Adv Drug Deliv Rev.* 2016;105:255-274.
59. Cao G, Yan J, Ning X, *et al.* Antibacterial and antibiofilm properties of graphene and its derivatives. *Colloids Surf B Biointerfaces.* 2021;200:111588. doi: 10.1016/j.colsurfb.2021.111588
60. Silveira SR, Sahm BD, Kreve S, Dos Reis AC. Osseointegration, antimicrobial capacity and cytotoxicity of implant materials coated with graphene compounds: A systematic review. *Jpn Dent Sci Rev.* 2023;59:303-311. doi: 10.1016/j.jdsr.2023.08.005
61. Xu X, Li Y, Wang L, *et al.* Triple-functional polyetheretherketone surface with enhanced bacteriostasis and anti-inflammatory and osseointegrative properties for implant application. *Biomaterials.* 2019;212:98-114. doi: 10.1016/j.biomaterials.2019.05.014
62. Yu Y, Wang X, Zhu Y, He Y, Xue H, Ding J. Is polydopamine beneficial for cells on the modified surface? *Regen Biomater.* 2022;9:rbac078.
63. Faia-Torres AB, Charnley M, *et al.* Osteogenic differentiation of human mesenchymal stem cells in the absence of osteogenic supplements: A surface-roughness gradient study. *Acta Biomater.* 2015;28:64-75. doi: 10.1016/j.actbio.2015.09.028
64. Deligianni DD, Katsala ND, Koutsoukos PG, Missirlis YF. Effect of surface roughness of hydroxyapatite on human bone marrow cell adhesion, proliferation, differentiation and detachment strength. *Biomaterials.* 2001;22:87-96. doi: 10.1016/s0142-9612(00)00174-5
65. Sunarso Tsuchiya A, Fukuda N, Toita R, Tsuru K, Ishikawa K. Effect of micro-roughening of poly(ether ether ketone) on bone marrow derived stem cell and macrophage responses, and osseointegration. *J Biomater Sci Polym Ed.* 2018;29:1375-1388. doi: 10.1080/09205063.2018.1461448
66. Citeau A, Guicheux J, Vinatier C, *et al. In vitro* biological effects of titanium rough surface obtained by calcium phosphate grid blasting. *Biomaterials.* 2005;26:157-165. doi: 10.1016/j.biomaterials.2004.02.033
67. Ma C, Nikiforov A, Hegemann D, De Geyter N, Morent R, Ostrikov K. Plasma-controlled surface wettability: Recent advances and future applications. *Int Mater Rev.* 2023;68:82-119. doi: 10.1080/09506608.2022.2047420
68. Aditya T, Mesa-Restrepo A, Civantos A, *et al.* Ion Bombardment-induced nanoarchitectonics on polyetheretherketone surfaces for enhanced nanoporous bioactive implants. *ACS Appl Bio Mater.* 2023;6:4922-4934. doi: 10.1021/acsabm.3c00642
69. Schröder K, Finke B, Jesswein H, *et al.* Similarities between plasma amino functionalized PEEK and titanium surfaces concerning enhancement of osteoblast cell adhesion. *J Adhes Sci Technol.* 2010;24:905-923. doi: 10.1163/016942409x12598231567989
70. Chu PK, Qin S, Chan C, Cheung NW, Larson LA. Plasma immersion ion implantation-a fledgling technique for semiconductor processing. *Mater Sci Eng R Rep.* 1996;17:207-280. doi: 10.1016/s0927-796x(96)00194-5
71. Bai L, Song P, Su J. Bioactive elements manipulate bone regeneration. *Biomater Transl.* 2023;4:248-269. doi: 10.12336/biomatertransl.2023.04.005
72. Lu T, Liu X, Qian S, *et al.* Multilevel surface engineering of nanostructured TiO2 on carbon-fiber-reinforced polyetheretherketone. *Biomaterials.* 2014;35:5731-5740.
73. Lu T, Li J, Qian S, Cao H, Ning C, Liu X. Enhanced osteogenic and selective antibacterial activities on micro-/nano-structured carbon fiber reinforced polyetheretherketone. *J Mater Chem B.* 2016;4:2944-2953.
74. Lu T, Qian S, Meng F, Ning C, Liu X. Enhanced osteogenic activity of poly ether ether ketone using calcium plasma immersion ion implantation. *Colloids Surf B Biointerfaces.* 2016;142:192-198. doi: 10.1016/j.colsurfb.2016.02.056
75. Li J, Qian S, Ning C, Liu X. rBMSC and bacterial responses to isoelastic carbon fiber-reinforced poly(ether-ether-ketone) modified by zirconium implantation. *J Mater Chem B.* 2016;4:96-104.
76. Zhang Y, Wang X, Li Y, *et al.* Cell osteogenic bioactivity mediated precisely by varying scaled micro-pits on ordered micro/nano hierarchical structures of titanium. *Regen Biomater.* 2022;9:rbac046. doi: 10.1093/rb/rbac046
77. Zheng X, Chen L, Tan J, *et al.* Effect of micro/nano-sheet array structures on the osteo-immunomodulation of macrophages. *Regen Biomater.* 2022;9:rbac075. doi: 10.1093/rb/rbac075
78. Chayanun S, Chanamuangkon T, Boonsuth B, Boccaccini AR, Lohwongwatana B. Enhancing PEEK surface bioactivity: Investigating the effects of combining sulfonation with sub-millimeter laser machining. *Mater Today Bio.* 2023;22:100754. doi: 10.1016/j.mtbio.2023.100754
79. Gu Z, Fan S, Kundu SC, Yao X, Zhang Y. Fiber diameters and parallel patterns: Proliferation and osteogenesis of stem cells. *Regen Biomater.* 2023;10:rbad001. doi: 10.1093/rb/rbad001
80. Yao X, Wang X, Ding J. Exploration of possible cell chirality using material techniques of surface patterning. *Acta Biomater.* 2021;126:92-108. doi: 10.1016/j.actbio.2021.02.032
81. Yao X, Liu R, Liang X, Ding J. Critical areas of proliferation of single cells on micropatterned surfaces and corresponding cell type dependence. *ACS Appl Mater Interfaces.* 2019;11:15366-15380. doi: 10.1021/acsami.9b03780
82. Wang X, Li S, Yan C, Liu P, Ding J. Fabrication of RGD micro/nanopattern and corresponding study of stem cell differentiation. *Nano Lett.* 2015;15:1457-1467. doi: 10.1021/nl5049862
83. Yao X, Peng R, Ding J. Cell-material interactions revealed via material techniques of surface patterning. *Adv Mater.* 2013;25:5257-5286. doi: 10.1002/adma.201301762
84. Tang J, Peng R, Ding J. The regulation of stem cell differentiation by cell-cell contact on micropatterned material surfaces. *Biomaterials.* 2010;31:2470-2476. doi: 10.1016/j.biomaterials.2009.12.006
85. Mo S, Tang K, Liao Q, *et al.* Tuning the arrangement of lamellar nanostructures: Achieving the dual function of physically killing bacteria and promoting osteogenesis. *Mater Horiz.* 2023;10:881-888.
86. Dong Z, Han W, Jiang P, Hao L, Fu X. Regulation of mitochondrial network architecture and function in mesenchymal stem cells by micropatterned surfaces. *Regen Biomater.* 2024;11:rbae052. doi: 10.1093/rb/rbae052
87. Li Z, Cao B, Wang X, Ye K, Li S, Ding J. Effects of RGD nanospacing on chondrogenic differentiation of mesenchymal stem cells. *J Mater Chem B.*

2015;3:5197-5209.
88. Peng R, Yao X, Cao B, Tang J, Ding J. The effect of culture conditions on the adipogenic and osteogenic inductions of mesenchymal stem cells on micropatterned surfaces. *Biomaterials.* 2012;33:6008-6019. doi: 10.1016/j.biomaterials.2012.05.010
89. He J, Liu Q, Zheng S, *et al.* Enlargement, reduction, and even reversal of relative migration speeds of endothelial and smooth muscle cells on biomaterials simply by adjusting RGD nanospacing. *ACS Appl Mater Interfaces.* 2021;13:42344-42356. doi: 10.1021/acsami.1c08559
90. He J, Shen R, Liu Q, *et al.* RGD nanoarrays with nanospacing gradient selectively induce orientation and directed migration of endothelial and smooth muscle cells. *ACS Appl Mater Interfaces.* 2022;14:37436-37446. doi: 10.1021/acsami.2c10006.
91. Liu X, Liu R, Cao B, *et al.* Subcellular cell geometry on micropillars regulates stem cell differentiation. *Biomaterials.* 2016;111:27-39. doi: 10.1016/j.biomaterials.2016.09.023
92. Liu Q, Zheng S, Ye K, *et al.* Cell migration regulated by RGD nanospacing and enhanced under moderate cell adhesion on biomaterials. *Biomaterials.* 2020;263:120327. doi: 10.1016/j.biomaterials.2020.120327
93. Zheng S, Liu Q, He J, *et al.* Critical adhesion areas of cells on micro-nanopatterns. *Nano Res.* 2022;15:1623-1635. doi: 10.1007/s12274-021-3711-6.
94. Yao X, Ding J. Effects of microstripe geometry on guided cell migration. *ACS Appl Mater Interfaces.* 2020;12:27971-27983. doi: 10.1021/acsami.0c05024
95. Cao B, Peng R, Li Z, Ding J. Effects of spreading areas and aspect ratios of single cells on dedifferentiation of chondrocytes. *Biomaterials.* 2014;35:6871-6881. doi: 10.1016/j.biomaterials.2014.04.107
96. Yao X, Hu Y, Cao B, Peng R, Ding J. Effects of surface molecular chirality on adhesion and differentiation of stem cells. *Biomaterials.* 2013;34:9001-9009. doi: 10.1016/j.biomaterials.2013.08.013
97. Peng R, Yao X, Ding J. Effect of cell anisotropy on differentiation of stem cells on micropatterned surfaces through the controlled single cell adhesion. *Biomaterials.* 2011;32:8048-8057. doi: 10.1016/j.biomaterials.2011.07.035
98. Evans NT, Torstrick FB, Lee CS, *et al.* High-strength, surface-porous polyether-ether-ketone for load-bearing orthopedic implants. *Acta Biomater.* 2015;13:159-167. doi: 10.1016/j.actbio.2014.11.030
99. Boschetto F, Marin E, Ohgitani E, *et al.* Surface functionalization of PEEK with silicon nitride. *Biomed Mater.* 2020;16:015015. doi: 10.1088/1748-605X/abb6b1
100. Chen P, Aso T, Sasaki R, *et al.* Adhesion and differentiation behaviors of mesenchymal stem cells on titanium with micrometer and nanometer-scale grid patterns produced by femtosecond laser irradiation. *J Biomed Mater Res A.* 2018;106:2735-2743. doi: 10.1002/jbm.a.36503
101. Luo F, Li D, Huang Y, *et al.* Efficient osteogenic activity of PEEK surfaces achieved by femtosecond laser-hydroxylation. *ACS Appl Mater Interfaces.* 2023;15:37232-37246. doi: 10.1021/acsami.3c06430
102. Cai G, Wang H, Jung YK, *et al.* Hierarchically porous surface of PEEK/nMCS composite created by femtosecond laser and incorporation of resveratrol exhibiting antibacterial performances and osteogenic activity *in vitro*. *Compos B Eng.* 2020;186:107802.
103. Xie D, Xu C, Ye C, *et al.* Fabrication of submicro-nano structures on polyetheretherketone surface by femtosecond laser for exciting cellular responses of MC3T3-E1 cells/gingival epithelial cells. *Int J Nanomedicine.* 2021;16:3201-3216. doi: 10.2147/IJN.S303411
104. Ji Y, Zhang H, Ru J, *et al.* Creating micro-submicro structure and grafting hydroxyl group on PEEK by femtosecond laser and hydroxylation to synergistically activate cellular response. *Mater Des.* 2021;199:109413.
105. Zhang S, Feng Z, Hu Y, *et al.* Endowing polyetheretherketone implants with osseointegration properties: *In situ* construction of patterned nanorod arrays. *Small.* 2022;18:e2105589. doi: 10.1002/smll.202105589
106. Huang RYM, Shao P, Burns CM, Feng X. Sulfonation of poly(ether ether ketone)(PEEK): Kinetic study and characterization. *J Appl Polym Sci.* 2001;82:2651-2660.
107. Ma R, Wang J, Li C, *et al.* Effects of different sulfonation times and post-treatment methods on the characterization and cytocompatibility of sulfonated PEEK. *J Biomater Appl.* 2020;35:342-352. doi: 10.1177/0885328220935008
108. Ding R, Chen T, Xu Q, *et al.* Mixed modification of the surface microstructure and chemical state of polyetheretherketone to improve its antimicrobial activity, hydrophilicity, cell adhesion, and bone integration. *ACS Biomater Sci Eng.* 2020;6:842-851. doi: 10.1021/acsbiomaterials.9b01148
109. Cheng QW, Yuan B, Zhu XD, Zhang K, Zhang XD. Surface elemental compositions and *in vitro* bioactivities of the PEEK materials with various sulfonation and alkali treatments. *Gaodeng Xuexiao Huaxue Xuebao.* 2019;40:1757-1765.
110. Wan T, Jiao Z, Guo M, *et al.* Gaseous sulfur trioxide induced controllable sulfonation promoting biomineralization and osseointegration of polyetheretherketone implants. *Bioact Mater.* 2020;5:1004-1017.
111. Ma Z, Li L, Shi X, *et al.* Enhanced osteogenic activities of polyetheretherketone surface modified by poly(sodium p-styrene sulfonate) via ultraviolet-induced polymerization. *J Appl Polym Sci.* 2020;137:49157.
112. Liu L, Zheng Y, Zhang Q, Yu L, Hu Z, Liu Y. Surface phosphonation treatment shows dose-dependent enhancement of the bioactivity of polyetheretherketone. *RSC Adv.* 2019;9:30076-30086.
113. Zhang B, Leng J, Ouyang Z, *et al.* Superhydrophilic and topography-regulatable surface grafting on PEEK to improve cellular affinity. *Biomater Adv.* 2023;146:213310. doi: 10.1016/j.bioadv.2023.213310
114. Wang Z, Tang Y, Wang P, *et al.* Dynamical integration of antimicrobial, anti-inflammatory, and pro-osteogenic activities on polyetheretherketone via a porous N-halamine polymeric coating. *Adv Funct Mater.* 2023;33:2307286.
115. Zheng Y, Liu L, Xiong C, Zhang L. Enhancement of bioactivity on modified polyetheretherketone surfaces with –COOH, –OH and –PO4H2 functional groups. *Mater Lett.* 2018;213:84-87.
116. Kassick AJ, Yerneni SS, Gottlieb E, *et al.* Osteoconductive enhancement of polyether ether ketone: A mild covalent surface modification approach. *ACS Appl Bio Mater.* 2018;1:1047-1055. doi: 10.1021/acsabm.8b00274
117. Chen Z, Chen Y, Wang Y, *et al.* Polyetheretherketone implants with hierarchical porous structure for boosted osseointegration. *Biomater Res.* 2023;27:61. doi: 10.1186/s40824-023-00407-5
118. Zhao Y, Wong HM, Lui SC, *et al.* Plasma surface functionalized polyetheretherketone for enhanced osseo-integration at bone-implant interface. *ACS Appl Mater Interfaces.* 2016;8:3901-3911. doi: 10.1021/acsami.5b10881
119. Wang H, Lu T, Meng F, Zhu H, Liu X. Enhanced osteoblast responses to poly ether ether ketone surface modified by water plasma immersion ion implantation. *Colloids Surf B Biointerfaces.* 2014;117:89-97. doi: 10.1016/j.colsurfb.2014.02.019
120. Gan K, Liu H, Jiang L, *et al.* Bioactivity and antibacterial effect of nitrogen plasma immersion ion implantation on polyetheretherketone. *Dent Mater.* 2016;32:e263-e274. doi: 10.1016/j.dental.2016.08.215
121. Wakelin EA, Yeo GC, McKenzie DR, Bilek MMM, Weiss AS. Plasma ion implantation enabled bio-functionalization of PEEK improves osteoblastic activity. *APL Bioeng.* 2018;2:026109. doi: 10.1063/1.5010346
122. Ouyang L, Chen M, Wang D, *et al.* Nano textured PEEK surface for enhanced osseointegration. *ACS Biomater Sci Eng.* 2019;5:1279-1289. doi: 10.1021/acsbiomaterials.8b01425
123. Bai X, Zhang X, Zhang R, *et al.* Immobilizing enoxacin on implant by polyvinyl butyral coating to promote osseointegration in osteoporosis with infection. *Mater Des.* 2023;227:111749. doi: 10.1016/j.matdes.2023.111749
124. Su XJ, Liu S, Huo SC, *et al.* Polyetheretherketone surface modification

by lithium-doped bioglass nanospheres to regulate bone immunity and promote osseointegration. *Mater Des.* 2024;238:112646.
doi: 10.1016/j.matdes.2024.112646
125. Sun Z, Ouyang L, Ma X, Qiao Y, Liu X. Controllable and durable release of BMP-2-loaded 3D porous sulfonated polyetheretherketone (PEEK) for osteogenic activity enhancement. *Colloids Surf B Biointerfaces.* 2018;171:668-674.
doi: 10.1016/j.colsurfb.2018.08.012
126. Wang C, Wang S, Yang Y, *et al.* Bioinspired, biocompatible and peptide-decorated silk fibroin coatings for enhanced osteogenesis of bioinert implant. *J Biomater Sci Polym Ed.* 2018;29:1595-1611.
doi: 10.1080/09205063.2018.1477316
127. Yuan X, Ouyang L, Luo Y, *et al.* Multifunctional sulfonated polyetheretherketone coating with beta-defensin-14 for yielding durable and broad-spectrum antibacterial activity and osseointegration. *Acta Biomater.* 2019;86:323-337.
doi: 10.1016/j.actbio.2019.01.016
128. Hamann C, Kirschner S, Günther KP, Hofbauer LC. Bone, sweet bone--osteoporotic fractures in diabetes mellitus. *Nat Rev Endocrinol.* 2012;8:297-305.
doi: 10.1038/nrendo.2011.233
129. Wang H, Fu X, Shi J, *et al.* Nutrient element decorated polyetheretherketone implants steer mitochondrial dynamics for boosted diabetic osseointegration. *Adv Sci (Weinh).* 2021;8:e2101778.
doi: 10.1002/advs.202101778
130. Wang S, Yang Y, Li Y, *et al.* Strontium/adiponectin co-decoration modulates the osteogenic activity of nano-morphologic polyetheretherketone implant. *Colloids Surf B Biointerfaces.* 2019;176:38-46.
doi: 10.1016/j.colsurfb.2018.12.056
131. Hu Q, Wang Y, Liu S, Liu Q, Zhang H. 3D printed polyetheretherketone bone tissue substitute modified via amoxicillin-laden hydroxyapatite nanocoating. *J Mater Sci.* 2022;57:18601-18614.
doi: 10.1007/s10853-022-07782-9
132. Surmenev RA, Surmeneva MA, Ivanova AA. Significance of calcium phosphate coatings for the enhancement of new bone osteogenesis--a review. *Acta Biomater.* 2014;10:557-579.
doi: 10.1016/j.actbio.2013.10.036
133. Liu X, Ouyang L, Chen L, *et al.* Hydroxyapatite composited PEEK with 3D porous surface enhances osteoblast differentiation through mediating NO by macrophage. *Regen Biomater.* 2022;9:rbab076.
doi: 10.1093/rb/rbab076
134. Huang S, Li J, Qin K, *et al.* Evaluation of the performance of Ca-deficient hydroxyapatite (CDHA)/MgF_2 bilayer coating on biodegradable high-purity magnesium in a femoral condyle defect model in rabbits. *Regen Biomater.* 2022;9:rbac066.
doi: 10.1093/rb/rbac066
135. D'Adamo A, Salerno E, Corda G, *et al.* Experimental measurements and CFD modelling of hydroxyapatite scaffolds in perfusion bioreactors for bone regeneration. *Regen Biomater.* 2023;10:rbad002.
doi: 10.1093/rb/rbad002
136. Qiang H, Hou C, Zhang Y, *et al.* CaP-coated Zn-Mn-Li alloys regulate osseointegration via influencing macrophage polarization in the osteogenic environment. *Regen Biomater.* 2023;10:rbad051.
doi: 10.1093/rb/rbad051
137. Yang W, Tong Q, He C, *et al.* Mechanically propelled ion exchange regulates metal/bioceramic interface characteristics to improve the corrosion resistance of Mg composite for orthopedic applications. *Ceram Int.* 2024;50:23124-23134.
138. He Y, Wang X, Chen L, Ding J. Preparation of hydroxyapatite micropatterns for the study of cell-biomaterial interactions. *J Mater Chem B.* 2014;2:2220-2227.
doi: 10.1039/C4TB00146J
139. Wei P, Wang N, Zhang Q, *et al.* Nano-ZnO-modified hydroxyapatite whiskers with enhanced osteoinductivity for bone defect repair. *Regen Biomater.* 2024;11:rbae051.
doi: 10.1093/rb/rbae051
140. Huang H, Yang A, Li J, *et al.* Preparation of multigradient hydroxyapatite scaffolds and evaluation of their osteoinduction properties. *Regen Biomater.* 2022;9:rbasc001.
141. Shuai C, Yang W, Feng P, Peng S, Pan H. Accelerated degradation of HAP/PLLA bone scaffold by PGA blending facilitates bioactivity and osteoconductivity. *Bioact Mater.* 2021;6:490-502.
doi: 10.1016/j.bioactmat.2020.09.001
142. Gallo M, Tadier S, Meille S, Chevalier J. Resorption of calcium phosphate materials: Considerations on the *in vitro* evaluation. *J Eur Ceram Soc.* 2018;38:899-914.
doi: 10.1016/j.jeurceramsoc.2017.07.004
143. Almasi D, Lau WJ, Rasaee S, Abbasi K. Fabrication and *in vitro* study of 3D novel porous hydroxyapatite/polyether ether ketone surface nanocomposite. *J Biomed Mater Res B Appl Biomater.* 2022;110:838-847.
doi: 10.1002/jbm.b.34964
144. Ryu J, Ku SH, Lee H, Park CB. Mussel-inspired polydopamine coating as a universal route to hydroxyapatite crystallization. *Adv Funct Mater.* 2010;20:2132-2139.
doi: 10.1002/adfm.200902347
145. Gao Y, Pang Y, Wei S, *et al.* Amyloid-mediated nanoarchitectonics with biomimetic mineralization of polyetheretherketone for enhanced osseointegration. *ACS Appl Mater Interfaces.* 2023;15:10426-10440.
doi: 10.1021/acsami.2c20711
146. Yabutsuka T, Fukushima K, Hiruta T, Takai S, Yao T. Fabrication of bioactive fiber-reinforced PEEK and MXD6 by incorporation of precursor of apatite. *J Biomed Mater Res B Appl Biomater.* 2018;106:2254-2265.
doi: 10.1002/jbm.b.34025
147. Masamoto K, Fujibayashi S, Yabutsuka T, *et al. In vivo* and *in vitro* bioactivity of a "precursor of apatite" treatment on polyetheretherketone. *Acta Biomater.* 2019;91:48-59.
doi: 10.1016/j.actbio.2019.04.041
148. Xue Z, Wang Z, Sun A, *et al.* Rapid construction of polyetheretherketone (PEEK) biological implants incorporated with brushite ($CaHPO_4{\cdot}2H_2O$) and antibiotics for anti-infection and enhanced osseointegration. *Mater Sci Eng C Mater Biol Appl.* 2020;111:110782.
doi: 10.1016/j.msec.2020.110782
149. Geim AK. Graphene: Status and prospects. *Science.* 2009;324:1530-1534.
doi: 10.1126/science.1158877
150. Yan JH, Wang CH, Li KW, *et al.* Enhancement of surface bioactivity on carbon fiber-reinforced polyether ether ketone via graphene modification. *Int J Nanomedicine.* 2018;13:3425-3440.
doi: 10.2147/IJN.S160030
151. Wang CH, Guo ZS, Pang F, *et al.* Effects of graphene modification on the bioactivation of polyethylene-terephthalate-based artificial ligaments. *ACS Appl Mater Interfaces.* 2015;7:15263-15276.
doi: 10.1021/acsami.5b02893
152. Kiew SF, Kiew LV, Lee HB, Imae T, Chung LY. Assessing biocompatibility of graphene oxide-based nanocarriers: A review. *J Control Release.* 2016;226:217-228.
doi: 10.1016/j.jconrel.2016.02.015
153. Dreyer DR, Todd AD, Bielawski CW. Harnessing the chemistry of graphene oxide. *Chem Soc Rev.* 2014;43:5288-5301.
doi: 10.1039/C4CS00060A
154. Luo Y, Shen H, Fang Y, *et al.* Enhanced proliferation and osteogenic differentiation of mesenchymal stem cells on graphene oxide-incorporated electrospun poly(lactic-co-glycolic acid) nanofibrous mats. *ACS Appl Mater Interfaces.* 2015;7:6331-6339.
doi: 10.1021/acsami.5b00862
155. Jia Z, Shi Y, Xiong P, *et al.* From solution to biointerface: Graphene self-assemblies of varying lateral sizes and surface properties for biofilm control and osteodifferentiation. *ACS Appl Mater Interfaces.* 2016;8:17151-17165.
doi: 10.1021/acsami.6b05198
156. Guo C, Lu R, Wang X, Chen S. Antibacterial activity, bio-compatibility and osteogenic differentiation of graphene oxide coating on 3D-network poly-ether-ether-ketone for orthopaedic implants. *J Mater Sci Mater Med.* 2021;32:135.
doi: 10.1007/s10856-021-06614-7
157. An N, Yan X, Qiu Q, *et al.* Human periodontal ligament stem cell sheets activated by graphene oxide quantum dots repair periodontal bone defects by promoting mitochondrial dynamics dependent osteogenic differentiation. *J Nanobiotechnol.* 2024;22:133.
doi: 10.1186/s12951-024-02422-7

158. Zhou C, Liu S, Li J, *et al.* Collagen functionalized with graphene oxide enhanced biomimetic mineralization and *in situ* bone defect repair. *ACS Appl Mater Interfaces.* 2018;10:44080-44091. doi: 10.1021/acsami.8b17636
159. Chen L, Yang J, Cai Z, *et al.* Electroactive biomaterials regulate the electrophysiological microenvironment to promote bone and cartilage tissue regeneration. *Adv Funct Mater.* 2024;34:2314079. doi: 10.1002/adfm.202314079
160. Ouyang L, Deng Y, Yang L, *et al.* Graphene-oxide-decorated microporous polyetheretherketone with superior antibacterial capability and *in vitro* osteogenesis for orthopedic implant. *Macromol Biosci.* 2018;18:e1800036. doi: 10.1002/mabi.201800036
161. Lee H, Dellatore SM, Miller WM, Messersmith PB. Mussel-inspired surface chemistry for multifunctional coatings. *Science.* 2007;318:426-430. doi: 10.1126/science.1147241
162. Liu M, Zeng G, Wang K, *et al.* Recent developments in polydopamine: An emerging soft matter for surface modification and biomedical applications. *Nanoscale.* 2016;8:16819-16840. doi: 10.1039/C5NR09078D
163. Yang F, Lin Y, Shen S, Gu Y, Shuai C, Feng P. Polydopamine chelating strontium on graphene oxide enhances the mechanical and osteogenic induction properties of PLLA/PGA bone scaffold. *Int J Bioprint.* 2024;10:1829. doi: 10.36922/ijb.1829
164. Guo Y, Li B, Xie H, *et al.* The therapeutic efficacy of different configuration nano-polydopamine drug carrier systems with photothermal synergy against head and neck squamous cell carcinoma. *Regen Biomater.* 2024;11:rbae073. doi: 10.1093/rb/rbae073
165. Kwon G, Kim H, Gupta KC, Kang IK. Enhanced tissue compatibility of polyetheretherketone disks by dopamine-mediated protein immobilization. *Macromol Res.* 2018;26:128-138. doi: 10.1007/s13233-018-6018-z
166. Ahmad T, Byun H, Shin HJ, *et al.* Polydopamine-assisted one-step modification of nanofiber surfaces with adenosine to tune the osteogenic differentiation of mesenchymal stem cells and the maturation of osteoclasts. *Biomater Sci.* 2020;8:2825-2839. doi: 10.1039/C9BM01990A
167. Zhu Y, Liu D, Wang X, *et al.* Polydopamine-mediated covalent functionalization of collagen on a titanium alloy to promote biocompatibility with soft tissues. *J Mater Chem B.* 2019;7:2019-2031. doi: 10.1039/C8TB03379J
168. Mao G, Sun Q, Jiang J, *et al.* Dopamine and epigallocatechin-3-gallate cross-linked coating demonstrates improved osteointegration of polyetheretherketone in rabbits. *Mater Des.* 2023;226:111607. doi: 10.1016/j.matdes.2023.111607
169. Shi R, Zhang J, Li W, Zhang Y, Ma Z, Wu C. An effective surface modification strategy to boost PEEK osteogenesis using porous CaP generated in well-tuned collagen matrix. *Appl Surf Sci.* 2021;555:149571. doi: 10.1016/j.apsusc.2021.149571
170. Meng X, Zhang J, Chen J, *et al.* KR-12 coating of polyetheretherketone (PEEK) surface via polydopamine improves osteointegration and antibacterial activity *in vivo*. *J Mater Chem B.* 2020;8:10190-10204. doi: 10.1039/d0tb01899f
171. Xiao T, Fan L, Liu R, *et al.* Fabrication of dexamethasone-loaded dual-metal-organic frameworks on polyetheretherketone implants with bacteriostasis and angiogenesis properties for promoting bone regeneration. *ACS Appl Mater Interfaces.* 2021;13:50836-50850. doi: 10.1021/acsami.1c18088
172. Ma H, Han H, Zhao X, *et al.* Engineering multifunctional polyether ether ketone implant: Mechanics-adaptability, biominerialization, immunoregulation, anti-infection, osteointegration, and osteogenesis. *Adv Healthc Mater.* 2023;12:e2202799. doi: 10.1002/adhm.202202799
173. Yang X, Wang Q, Zhang Y, *et al.* A dual-functional PEEK implant coating for anti-bacterial and accelerated osseointegration. *Colloids Surf B Biointerfaces.* 2023;224:113196. doi: 10.1016/j.colsurfb.2023.113196
174. Zhan X, Yan J, Xiang D, *et al.* Near-infrared light responsive gold nanoparticles coating endows polyetheretherketone with enhanced osseointegration and antibacterial properties. *Mater Today Bio.* 2024;25:100982. doi: 10.1016/j.mtbio.2024.100982
175. Zhang W, Liu L, Zhou H, *et al.* Surface bisphosphonation of polyetheretherketone to manipulate immune response for advanced osseointegration. *Mater Des.* 2023;232:112151. doi: 10.1016/j.matdes.2023.112151
176. Zhu Y, Cao Z, Peng Y, Hu L, Guney T, Tang B. Facile surface modification method for synergistically enhancing the biocompatibility and bioactivity of poly(ether ether ketone) that induced osteodifferentiation. *ACS Appl Mater Interfaces.* 2019;11:27503-27511. doi: 10.1021/acsami.9b03030
177. Sun A, Lin X, Xue Z, *et al.* Facile surface functional polyetheretherketone with antibacterial and immunoregulatory activities for enhanced regeneration toward bacterium-infected bone destruction. *Drug Deliv.* 2021;28:1649-1663. doi: 10.1080/10717544.2021.1960924
178. Sang S, Yang C, Chai H, Yuan X, Liu W, Zhang X. The sulfonated polyetheretherketone with 3D structure modified by two bio-inspired methods shows osteogenic and antibacterial functions. *Chem Eng J.* 2021;420:130059.
179. Gao C, Wang Z, Jiao Z, *et al.* Enhancing antibacterial capability and osseointegration of polyetheretherketone (PEEK) implants by dual-functional surface modification. *Mater Des.* 2021;205:109733. doi: 10.1016/j.matdes.2021.109733
180. Wan T, Li L, Guo M, *et al.* Immobilization via polydopamine of dual growth factors on polyetheretherketone: Improvement of cell adhesion, proliferation, and osteo-differentiation. *J Mater Sci.* 2019;54:11179-11196. doi: 10.1007/s10853-018-03264-z
181. Chai H, Sang S, Luo Y, He R, Yuan X, Zhang X. Icariin-loaded sulfonated polyetheretherketone with osteogenesis promotion and osteoclastogenesis inhibition properties via immunomodulation for advanced osseointegration. *J Mater Chem B.* 2022;10:3531-3540. doi: 10.1039/D1TB02802B
182. Wu Y, Huo S, Liu S, Hong Q, Wang Y, Lyu Z. Cu-Sr bilayer bioactive glass nanoparticles/polydopamine functionalized polyetheretherketone enhances osteogenic activity and prevents implant-associated infections through spatiotemporal immunomodulation. *Adv Healthc Mater.* 2023;12:e2301772. doi: 10.1002/adhm.202301772
183. He M, Wang H, Han Q, *et al.* Glucose-primed PEEK orthopedic implants for antibacterial therapy and safeguarding diabetic osseointegration. *Biomaterials.* 2023;303:122355. doi: 10.1016/j.biomaterials.2023.122355
184. Ouyang L, Qi M, Wang, S, *et al.* Osteogenesis and antibacterial activity of graphene oxide and dexamethasone coatings on porous polyetheretherketone via polydopamine-assisted chemistry. *Coatings.* 2018;8:203. doi: 10.3390/coatings8060203
185. Zhang J, Gao X, Ma D, *et al.* Copper ferrite heterojunction coatings empower polyetheretherketone implant with multi-modal bactericidal functions and boosted osteogenicity through synergistic photo/Fenton-therapy. *Chem Eng J.* 2021;422:130094. doi: 10.1016/j.cej.2021.130094
186. Wang S, Duan C, Yang W, *et al.* Two-dimensional nanocoating-enabled orthopedic implants for bimodal therapeutic applications. *Nanoscale.* 2020;12:11936-11946. doi: 10.1039/D0NR02327B
187. Deng Y, Gao X, Shi XL, *et al.* Graphene oxide and adiponectin-functionalized sulfonated poly(etheretherketone) with effective osteogenicity and remotely repeatable photodisinfection. *Chem Mater.* 2020;32:2180-2193. doi: 10.1021/acs.chemmater.0c00290
188. Qin S, Lu Z, Gan K, *et al.* Construction of a *BMP-2* gene delivery system for polyetheretherketone bone implant material and its effect on bone formation *in vitro*. *J Biomed Mater Res B Appl Biomater.* 2022;110:2075-2088. doi: 10.1002/jbm.b.35062
189. He X, Deng Y, Yu Y, Lyu H, Liao L. Drug-loaded/grafted peptide-modified porous PEEK to promote bone tissue repair and eliminate

bacteria. *Colloids Surf B Biointerfaces.* 2019;181:767-777.
doi: 10.1016/j.colsurfb.2019.06.038
190. Deng LJ, Wu YL, He XH, Xie KN, Xie L, Deng Y. Simvastatin delivery on PEEK for bioactivity and osteogenesis enhancements. *J Biomater Sci Polym Ed.* 2018;29:2237-2251.
doi: 10.1080/09205063.2018.1534668
191. Zheng Y, Gao A, Bai J, *et al.* A programmed surface on polyetheretherketone for sequentially dictating osteoimmunomodulation and bone regeneration to achieve ameliorative osseointegration under osteoporotic conditions. *Bioact Mater.* 2022;14:364-376.
doi: 10.1016/j.bioactmat.2022.01.042
192. Chen Y, Chen Y, Han T, *et al.* Enhanced osteogenic and antibacterial properties of polyetheretherketone by ultraviolet-initiated grafting polymerization of a gelatin methacryloyl/epsilon-poly-L-lysine/laponite hydrogel coating. *J Biomed Mater Res A.* 2023;111:1808-1821.
doi: 10.1002/jbm.a.37589
193. An J, Shi X, Zhang J, *et al.* Dual aldehyde cross-linked hyaluronic acid hydrogels loaded with PRP and NGF biofunctionalized PEEK interfaces to enhance osteogenesis and vascularization. *Mater Today Bio.* 2024;24:100928.
doi: 10.1016/j.mtbio.2023.100928
194. Dong W, Ma W, Zhao S, *et al.* The surface modification of long carbon fiber reinforced polyether ether ketone with bioactive composite hydrogel for effective osteogenicity. *Mater Sci Eng C Mater Biol Appl.* 2021;130:112451.
doi: 10.1016/j.msec.2021.112451
195. Shi J, Yu L, Ding J. PEG-based thermosensitive and biodegradable hydrogels. *Acta Biomater.* 2021;128:42-59.
doi: 10.1016/j.actbio.2021.04.009
196. Wang Y, Yang X, Chen X, *et al.* Sustained release of nitric oxide and cascade generation of reactive nitrogen/oxygen species via an injectable hydrogel for tumor synergistic therapy. *Adv Funct Mater.* 2022;32:2206554.
doi: 10.1002/adfm.202270205
197. Wang Y, Chen X, Chen Z, *et al.* Autophagy inhibition mediated via an injectable and NO-releasing hydrogel for amplifying the antitumor efficacy of mild magnetic hyperthermia. *Bioact Mater.* 2024;39:336-353.
doi: 10.1016/j.bioactmat.2024.05.032
198. Chen X, Wang H, Shi J, *et al.* An injectable and active hydrogel induces mutually enhanced mild magnetic hyperthermia and ferroptosis. *Biomaterials.* 2023;298:122139.
doi: 10.1016/j.biomaterials.2023.122139
199. Cao D, Chen X, Cao F, *et al.* An intelligent transdermal formulation of ALA-loaded copolymer thermogel with spontaneous asymmetry by using temperature-induced sol-gel transition and gel-sol (suspension) transition on different sides. *Adv Funct Mater.* 2021;31:2100349.
doi: 10.1002/adfm.202100349
200. Cao D, Guo W, Cai C, *et al.* Unified therapeutic-prophylactic vaccine demonstrated with a postoperative filler gel to prevent tumor recurrence and metastasis. *Adv Funct Mater.* 2022;32:2206084.
doi: 10.1002/adfm.202206084
201. Zhuang Y, Yang X, Li Y, *et al.* Sustained release strategy designed for lixisenatide delivery to synchronously treat diabetes and associated complications. *ACS Appl Mater Interfaces.* 2019;11:29604-29618.
doi: 10.1021/acsami.9b10346
202. Chen Y, Li Y, Shen W, *et al.* Controlled release of liraglutide using thermogelling polymers in treatment of diabetes. *Sci Rep.* 2016;6:31593.
doi: 10.1038/srep31593
203. Yang X, Chen X, Wang Y, Xu G, Yu L, Ding, J. Sustained release of lipophilic gemcitabine from an injectable polymeric hydrogel for synergistically enhancing tumor chemoradiotherapy. *Chem Eng J.* 2020;396:125320.
doi: 10.1016/j.cej.2020.125320
204. Cao D, Ding J. Recent advances in regenerative biomaterials. *Regen Biomater.* 2022;9:rbac098.
doi: 10.1093/rb/rbac098
205. Xu WK, Tang JY, Yuan Z, *et al.* Accelerated cutaneous wound healing using an injectable teicoplanin-loaded PLGA-PEG-PLGA thermogel dressing. *Chin J Polym Sci.* 2019;37:548-559.
doi: 10.1007/s10118-019-2212-5
206. Yu L, Li K, Liu X, *et al. In vitro* and *in vivo* evaluation of a once-weekly formulation of an antidiabetic peptide drug exenatide in an injectable thermogel. *J Pharm Sci.* 2013;102:4140-4149.
doi: 10.1002/jps.23735
207. Chen J, Cheng X, Yu Z, *et al.* Sustained delivery of NT-3 and curcumin augments microenvironment modulation effects of decellularized spinal cord matrix hydrogel for spinal cord injury repair. *Regen Biomater.* 2024;11:rbae039.
doi: 10.1093/rb/rbae039
208. Wang J, Tang Y, Cao Q, *et al.* Fabrication and biological evaluation of 3D-printed calcium phosphate ceramic scaffolds with distinct macroporous geometries through digital light processing technology. *Regen Biomater.* 2022;9:rbac005.
doi: 10.1093/rb/rbac005
209. Lee SS, Du X, Kim I, Ferguson SJ. Scaffolds for bone-tissue engineering. *Matter.* 2022;5:2722-2759.
doi: 10.1016/j.matt.2022.06.003
210. Cao Y, Sun L, Liu Z, *et al.* 3D printed-electrospun PCL/hydroxyapatite/MWCNTs scaffolds for the repair of subchondral bone. *Regen Biomater.* 2023;10:rbac104.
doi: 10.1093/rb/rbac104
211. McWilliam RH, Chang W, Liu Z, *et al.* Three-dimensional biofabrication of nanosecond laser micromachined nanofibre meshes for tissue engineered scaffolds. *Biomater Transl.* 2023;4:104-114.
doi: 10.12336/biomatertransl.2023.02.005
212. Lu T, Yang L, Li Z, Liu Y, Xu S, Ye C. Immediate implantation of ultrafine fiber slow-release system based on cell electrospinning to induce osteogenesis of mesenchymal stem cells. *Regen Biomater.* 2024;11:rbad113.
doi: 10.1093/rb/rbad113
213. Yang, J, Fatima, K, Zhou, X, He, C. Meticulously engineered three-dimensional-printed scaffold with microarchitecture and controlled peptide release for enhanced bone regeneration. *Biomater Transl.* 2024;5:69-83.
doi: 10.12336/biomatertransl.2024.01.007
214. Qi J, Wang Y, Chen L, *et al.* 3D-printed porous functional composite scaffolds with polydopamine decoration for bone regeneration. *Regen Biomater.* 2023;10:rbad062.
doi: 10.1093/rb/rbad062
215. Gantenbein S, Colucci E, Käch J, *et al.* Three-dimensional printing of mycelium hydrogels into living complex materials. *Nat Mater.* 2023;22:128-134.
doi: 10.1038/s41563-022-01429-5
216. Guo C, Wu J, Zeng Y, Li H. Construction of 3D bioprinting of HAP/collagen scaffold in gelation bath for bone tissue engineering. *Regen Biomater.* 2023;10:rbad067.
doi: 10.1093/rb/rbad067
217. Hua X, Hou M, Deng L, *et al.* Irisin-loaded electrospun core-shell nanofibers as calvarial periosteum accelerate vascularized bone regeneration by activating the mitochondrial SIRT3 pathway. *Regen Biomater.* 2024;11:rbad096.
doi: 10.1093/rb/rbad096
218. Wang C, Huang W, Zhou Y, *et al.* 3D printing of bone tissue engineering scaffolds. *Bioact Mater.* 2020;5:82-91.
doi: 10.1016/j.bioactmat.2020.01.004
219. Aihemaiti P, Jiang H, Aiyiti W, Wang J, Dong L, Shuai C. Mechanical properties enhancement of 3D-printed HA-PLA composites using ultrasonic vibration assistance. *Virtual Phys Prototyp.* 2024;19:e2346271.
doi: 10.1080/17452759.2024.2346271
220. Wu L, Ding J. *In vitro* degradation of three-dimensional porous poly(D,L-lactide-co-glycolide) scaffolds for tissue engineering. *Biomaterials.* 2004;25:5821-5830.
doi: 10.1016/j.biomaterials.2004.01.038
221. Wu L, Ding J. Effects of porosity and pore size on *in vitro* degradation of three-dimensional porous poly(D,L-lactide-co-glycolide) scaffolds for tissue engineering. *J Biomed Mater Res A.* 2005;75:767-777.
doi: 10.1002/jbm.a.30487
222. Jing D, Wu L, Ding J. Solvent-assisted room-temperature compression molding approach to fabricate porous scaffolds for tissue engineering. *Macromol Biosci.* 2006;6:747-757.

doi: 10.1002/mabi.200600079

223. Wu L, Jing D, Ding JA. "Room-temperature" injection molding/particulate leaching approach for fabrication of biodegradable three-dimensional porous scaffolds. *Biomaterials.* 2006;27:185-191. doi: 10.1016/j.biomaterials.2005.05.105
224. Qu Z, Ding J. Physical modification of the interior surfaces of PLGA porous scaffolds using sugar fibers as template. *J Biomater Sci Polym Ed.* 2013;24:447-459. doi: 10.1080/09205063.2012.690285
225. Gao J, Yu X, Wang X, He Y, Ding J. Biomaterial-related cell microenvironment in tissue engineering and regenerative medicine. *Engineering.* 2022;13:31-45. doi: 10.1016/j.eng.2021.11.025
226. Ding X, Gao J, Yu X, *et al.* 3D-printed porous scaffolds of hydrogels modified with TGF-β1 binding peptides to promote *in vivo* cartilage regeneration and animal gait restoration. *ACS Appl Mater Interfaces.* 2022;14:15982-15995. doi: 10.1021/acsami.2c00761
227. Liang X, Qi Y, Pan Z, *et al.* Design and preparation of quasi-spherical salt particles as water-soluble porogens to fabricate hydrophobic porous scaffolds for tissue engineering and tissue regeneration. *Mater Chem Front.* 2018;2:1539-1553. doi: 10.1039/C8QM00152A
228. Shuai C, Peng B, Feng P, Yu L, Lai R, Min A. *In situ* synthesis of hydroxyapatite nanorods on graphene oxide nanosheets and their reinforcement in biopolymer scaffold. *J Adv Res.* 2022;35:13-24. doi: 10.1016/j.jare.2021.03.009
229. Feng P, Wu P, Gao C, *et al.* A multimaterial scaffold with tunable properties: Toward bone tissue repair. *Adv Sci (Weinh).* 2018;5:1700817. doi: 10.1002/advs.201700817
230. Yu J, Zhang Y, Guo J, Shu X, Lu Q, Chen Q. Sand casting-inspired surface modification of 3D-printed porous polyetheretherketone scaffolds for enhancing osteogenesis. *Compos Part A Appl Sci Manuf.* 2024;179:108033. doi: 10.1016/j.compositesa.2024.108033
231. Liu Z, Zhang M, Wang Z, *et al.* 3D-printed porous PEEK scaffold combined with CSMA/POSS bioactive surface: A strategy for enhancing osseointegration of PEEK implants. *Compos B Eng.* 2022;230:109512. doi: 10.1016/j.compositesb.2021.109512
232. Wei X, Zhou W, Tang Z, *et al.* Magnesium surface-activated 3D printed porous PEEK scaffolds for *in vivo* osseointegration by promoting angiogenesis and osteogenesis. *Bioact Mater.* 2023;20:16-28. doi: 10.1016/j.bioactmat.2022.05.011

Received: August 20, 2024
Revised: October 18, 2024
Accepted: December 15, 2024
Available online: June 25, 2025