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2D materials for bone therapy

Xiangjiang Wang [a,1], Xianjing Han [a,1], Chaozhou Li [b,1], Zhi Chen [b,1], Hao Huang [b], Jindong Chen [a], Chenshuo Wu [b], Taojian Fan [c], Tianzhong Li [f], Weichun Huang [d], Omar A. Al-Hartomy [g], Ahmed Al-Ghamdi [g], Abdullah Swelm. Wageh [g], Fei Zheng [b], G. Al-Sehemi [h], Guiqing Wang [a,*], Zhongjian Xie [e,f,*], Han Zhang [b,*]

[a] The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan 511518, Guangdong, China
[b] Shenzhen Engineering Laboratory of Phosphorene and Optoelectronics, International Collaborative Laboratory of 2D Materials for Optoelectronics Science and Technology of Ministry of Education, College of Optoelectronic Engineering, Shenzhen University, Shenzhen 518060, China
[c] College of Health Science and Environmental Engineering, Shenzhen Technology University, Shenzhen 518118, China
[d] Nantong Key Lab of Intelligent and New Energy Materials, School of Chemistry and Chemical Engineering, Nantong University, Nantong 226019, Jiangsu, PR China
[e] Institute of Pediatrics, Shenzhen Children's Hospital, Shenzhen 518038, Guangdong, PR China
[f] Shenzhen International Institute for Biomedical Research, Shenzhen 518116, Guangdong, China
[g] Department of Physics, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[h] Department of Chemistry, Faculty of Science, Research Center for Advanced Materials Science (RCAMS), King Khalid University, Abha 61413, P.O. Box 9004, Saudi Arabia

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ABSTRACT

Due to their prominent physicochemical properties, 2D materials are broadly applied in biomedicine. Currently, 2D materials have achieved great success in treating many diseases such as cancer and tissue engineering as well as bone therapy. Based on their different characteristics, 2D materials could function in various ways in different bone diseases. Herein, the application of 2D materials in bone tissue engineering, joint lubrication, infection of orthopedic implants, bone tumors, and osteoarthritis are firstly reviewed comprehensively together. Meanwhile, different mechanisms by which 2D materials function in each disease reviewed below are also reviewed in detail, which in turn reveals the versatile functions and application of 2D materials. At last, the outlook on how to further broaden applications of 2D materials in bone therapies based on their excellent properties is also discussed.

Contents

* Corresponding authors at: Institute of Pediatrics, Shenzhen Children's Hospital, Shenzhen 518038, Guangdong, PR China (Z. Xie).
E-mail address: hzhang@szu.edu.cn (H. Zhang).
[1] Contributed equally to this work.

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1. Introduction

Two-dimensional (2D) materials are nanomaterials with a free-standing sheet-like feature[1]. Usually, the lateral size can be as large as from tens of nanometers to tens to micrometers or higher, but the thickness, however, is ranged from only a few angstroms to a few nanometers[2]. This feature results in a high ratio of their lateral size to their thickness[3]. Nowadays, we have found a large variety of 2D materials such as graphene and its derivatives including graphene oxide (GO) and reduced GO (rGO), MXene, graphitic carbon nitride (g-C_3N_4), black phosphorus (BP), black arsenic phosphorus (b-AsP), transition metal dichalcogenides (TMDCs), layered double hydroxides (LDHs), hexagonal boron nitride (h-BN), and so on[4–9].

Compared to their bulky parents, 2D materials have prominent properties including excellent high specific surface area, optical properties, ultrahigh carrier mobility, and high thermal conductivity, therefore, they are broadly employed in the field of optics [10,11], photonic[12–14], energy storage[15,16], sensor[17], electronic[18,19], phototherapy[20] and theranostics[21], etc. because of their unique planar structures. Besides, the remarkable physiochemical properties of 2D materials facilitated their applications in biomedicine. It is becoming a more and more attractive field for researchers. For instance, some 2D materials such as BP, MoS_2, WSe_2, and h-BN, have a broad optical absorption range due to their highly tunable band gap, which promotes their applications in biosensing, photoacoustic imaging, and photodynamic therapy, etc.[22–27]. 2D materials with a high ON-OFF current ratio are suitable to be applied as field-effect transistor-based immunosensors with high sensitivity[28]. Furthermore, some 2D materials with excellent electrical conduction are ideal candidates for the detection of biomolecules with positive or negative charge [29,30]; Some 2D materials show good biocompatibility and biodegradability, which facilitates their application in biomedicine[31,32]; What's more, 2D materials could be integrated with various photonic materials or be applied as a component of vertical heterostructures[33] since their surfaces are naturally passivated without any dangling bonds, providing an alternative method to improve the biocompatibility, biodegradability or stability of some 2D materials and further developing the application of 2D materials in biomedicine.

To date, some researchers had reviewed the application of 2D materials in bone therapy, but most of them focused on the application of 2D materials as a composite of the bio-scaffold for bone tissue engineering (BTE) which is a method based on the stem cells or bone cells, utilizing the admirable properties of 2D materials to improve the mechanical properties, biocompatibility or stability of the bio-scaffold and therefore promotes the stem cell growth, attachment, and differentiation[34–37]. However, the outstanding physicochemical properties of 2D materials are also able to be employed in other bone therapies such as bone tumor therapy[38], joint lubrication, antibacterial[39], and so on. Here, we first comprehensively review the versatile applications of 2D materials in different bone therapy and discuss their potential application in bone therapy in the future based on their properties.

2. Popular 2D materials in biomedical application

2.1. Graphene and its derivatives

Graphene is the first 2D material and the single-layer graphene was isolated from graphite in 2004 by Andre Geim and Nosovelov [40]. Structurally, graphene presented as an almost transparently single atomic sheet that consisted of sp^2 carbon atoms crosslinked in a honeycomb-like lattice. Graphene might be the strongest and stiffest material though it is also the lightest and thinnest material [41] with a thickness of<10 nm[42]. Besides, Graphene has a large surface area which is about 2600m^2g^{-1} and it is flexible. Because of its structural characteristics, graphene possesses some excellent properties, such as outstanding thermal and chemical stability, high electron mobility, and large loading capacity. What's more, graphene is easy to be functionalized in both a covalent and non-covalent style, which is a vital way for the application of graphene in biomedicines. The covalent functionalization of graphene is based on the reaction between its sp^2 carbon atoms and radicals including fluorine[43] and diazonium salts[44] etc. However, non-covalent functionalization is usually involved in the formation of Van der Waals forces, electrostatic interactions, or π-π interaction[45] between graphene and functionalization reagents. And the non-covalent functionalization of graphene is a common way for promotion of its properties such as stability.

GO and rGO are two important derivatives of graphene. Graphene could be oxidized to be an amphiphile graphene oxide (GO) and GO could be further reduced and then leads to the production of the reduced graphene oxide (rGO)[46]. Relative to graphene and rGO, GO is more available to achieve functionalization as it contains different kinds of functional groups including carboxyl, hydroxyl, and epoxy groups which are easy to bind various biomolecules, broadening the bio-applications of graphene. Due to the various properties and availability in functionalization, graphene and its derivatives could be applied in various fields such as electronics, sensing, catalysis, energy storage as well as biomedicines. In biomedicines, graphene and its derivatives could be applied as a delivery vehicle for drugs[42], photothermal reagents (PTAs) and photosensitizer (PS) for phototherapy in cancer treatment[47,48], biosensors, the component of tissue engineering, anchor for growth and differentiation of cells and so on. However, it is of note that, pristine graphene has less compatibility than pristine graphene was found to be toxic for cells. It was reported that the hydrophobic graphene might interrupt the interaction between membrane-associated proteins, eventually leading to cellular toxicity[49]. Nevertheless, the functionalization of graphene was shown to be an effective way to the reduction of its toxicity. Therefore, it is necessary and advantageous to develop different strategies of functionalization of graphene for minimizing its toxicity before its clinical application.

2.2. Black phosphorus (BP)

Phosphorus has various allotropes, such as BP, white phosphorus, violet phosphorus, and red phosphorus as well as the A7 phase. And among them, BP is the most stable one under ambient

conditions[50,51]. BP also knew as phosphorene, whose nanosheets were first exfoliated from bulk BP in 2014[52]. There are several forms of 2D BP, including BP nanosheets (BPNSs)[53], BP nanoparticles (BPNPs)[54], and BP quantum dots (BPQDs)[55]. Structurally, in monolayer BP, the phosphorus atom and three neighboring atoms were bonded together by the covalent bond in an sp^3 hybridized orbitals while the interaction between layers was maintained by weak Van Der Waals forces[56]. Therefore, layers BP was easy to be exfoliated from the bulk crystal. Because of the existence of lone electron pairs in BP, BP is reactive to air and easy to be degraded[57]. One of the methods for improving the stability of BP in humid and light conditions as well as in physiological environments is that surface functionalization. And nowadays, many organic polymers were usually used to modify the BP as polymers themselves' characteristics of low cost and degradability[51,58].

BP possesses many exceptional properties including high carrier mobility, high ON-OFF current ratio, large tunable energy bandgap, and ambipolar electrical conduction, etc. Due to its versatile properties, BP has been applied in many fields such as energy storage[59], sensors, optoelectronics[60], electronics[61], and drugs delivery in bio-application, etc. Besides, BP has inherently excellent biocompatibility and degradability because phosphate, the physiological product of BP degradation, is not only harmless but also a raw material involves in osteogenesis[62]. The cytotoxicity of BP itself was reported to be concentration and size-dependent, therefore it is feasible to control the cytotoxicity of BP by regulating the concentration and size of the application, which greatly facilitate the application of BP in biomedicines[63,64]. Nowadays, in biomedicines, the application of BP in phototherapy for cancers [65] or bacterial infection treatments were promising and aroused great interest of researchers because of its broad light absorption range from visible to near-infrared. What's more, BP had also been employed in biosensors[66], bioimaging[67], theranostics[68–70], drug delivery[71], and so on.

2.3. Mxenes

Because of their brilliant prosperities, 2D MXenes attracted a lot of attention from researchers and got fasted development since it was discovered in 2011[72]. MXenes is an emerging family of 2D metal carbides including a large class of transition metal carbides, nitrides, and carbonitrides[73,74]. MXenes could be produced by etching and delamination of MAX phases which are constituted by ternary carbides and nitrides with a pristine formula of $M_{n+1}AX_n$ (n = 1–3) where M, A, and X, respectively represent the early transition metals (Ti, Hf, Sc, Ta, Mo, Cr, Zr, Nb, V, etc.), main-group sp elements and both C and N atoms. However, MXenes are chemically formulated as $M_{n+1}X_n$ or $M_{n+1}X_nT_x$ (n = 1–3). The Character M in the formula is on behalf of a transition metal and X represents carbon and/or nitrogen while T indicates the functional groups of surface such as hydroxyl, fluorine, or oxygen [75,76].

Due to the big variations of MAX phases, 30 varieties of MXenes were discovered at least to date[77]. Different MAX phases would be fabricated to various MXenes with different properties[78]. Besides, the properties of MXenes would be also affected by different functionalization, which further is conducive to promote the variety of the MXenes superfamily. For instance, $Ti_3C_2T_x$ MXene possesses a high volumetric capacitance, making it suitable for applicating in the battery industry while the Ti_2C has prominent gravimetric hydrogen storage capacities because of its biggest specific area, endowing it an important role in energy storage [73]. MXenes possesses many brilliant physicochemical properties such as chemical stability[79], large surface area and thermo/electrical conductivity[80,81], tunable lateral size as well as hydrophilicity endowed by its surface functional groups, making MXenes could be applied in many fields including catalysis, energy storage, sensing, semiconductor, environmental applications and biomedicines[82–86]. Due to some attractive properties of MXenes, they are more predominant than some other 2D materials while applied in biomedicines. First of all, the hydrophilic nature of MXenes makes them easy to disperse in the physiological environment[77]. Besides, some of MXenes are biocompatible to living organisms with negligible toxicity because such as Ti, Ta and Nb are relatively inert in physiological conditions and some recent studies had shown the degradability of MXenes in mice[87,88]. Then MXenes have strong light absorption in the NIR region, making them suitable and powerful in phototherapy and photoacoustic imaging (PAI)[24,89]. Last but not least, different functionalization of MXenes could be achieved by flexible modification, affording a way for designing the optimal MXenes-based drugs compound for bio-applications. Up to now, MXenes had been employed in thermotherapy for cancers[90] or antimicrobial treatments[91], tissue engineering[91], drug delivery[92], biosensing[93], and theranostics[94], etc. in biomedicines.

2.4. Transition metal dichalcogenides (TMDCs)

Structurally, TMDCs whose stoichiometry is MX_2, present as two layers of chalcogen atoms (X stands for S, Se, or Te) with a hexagonal layer of transition metal atoms (M represents V, Mo, W, Ta, Nb, Ti, Hf, Zr, Tc, and Re) sandwiched in the middle [95,96]. The van der Waals is responsible for the interaction of adjacent sheets leading to the production of 2D TMDCs by exfoliation. Similar to MXenes, 2D TMDCs could be also produced from different bulk parents, bring them many varieties with different properties as well as endowing them a cheaper and more available advantage during application. For example, there are 40 different TMDCs at least. However, some of them are metals (e.g., TiS_2 and VSe_2) while some are semimetals ($MoTe_2$ and WTe_2). Some of them could be employed as conductors (e.g., TaS_2 and NbS_2) and semiconductors (e.g., WS_2, WSe_2, $MoSe_2$, and MoS_2) while some function as insulators.

Like other 2D materials, 2D TMDCs also possesses a series of commonly remarkable capacities such as large specific surface area, high light absorption near NIR, photothermal stability, large and adjustable bandgap as well as biocompatibility[97], leading to the availability of applying them in various fields such as catalysis[98], sensors[99], electronics[100], energy storage[101], biomedicines[97] and so on. Besides, 2D TMDCs could be further functionalized though it is chemically inert. There are two main kinds of methods for functionalization of 2D TMDCs, that is, they could be functionalized both chemically and physically. The chemical functionalization of TMDCs always involved the addition of organic bond modifiers to TMDCs via the formation of coordination bonds or covalent bonds. However, physical functionalization refers to the process that integrates the modifiers with 2D TMDCs possessing a high specific surface area by electrostatic attraction, hydrogen bonding force and van der Waals force etc. Through functionalization, the properties of TMDCs would be further promoted and their application would be more adjustable.

Based on the versatile properties and the availability of functionalization as well as biocompatibility revealed by the promotion of proliferation of pre-osteoblast cells[102], TMDCs are also applied broadly in biomedicines. Compared to some other 2D materials, 2D TMDCs have some advantages for bio-applications. For example, 2D TMDCs have more varieties relative to graphene, which makes them more flexible for applications. What's more, in contrast to graphene, 2D TMDCs are more hydrophilic, leading to better dispersion in the physiological environment. And compared with black phosphorus, TMDCs are more stable in ambient conditions, endowing them with convenience in preparation and

application. The versatile properties of TMDCs greatly promote their application in biomedicines. Nowadays, TMDCs are broadly applied in biosensing, bioimaging, phototherapy, drugs delivery, and tissue engineering, etc. in biomedicines[103,104].

3. 2D materials preparation and modification

3.1. Preparation method for 2D materials

Nowadays, various methods for the production of 2D materials are available. Conventionally, these methods could be divided into two kinds: the gas-phase synthesis methods and solution-based methods. The common gas-phase synthesis method could further be divided into chemical vapor deposition (CVD)[105] and physical vapor deposition (PVD)[106]. The solution-based method includes exfoliation and chemical synthesis[107]. Besides, in recent years, a promising method named topochemical synthesis attract interests from researchers, by which the elements are added to, extracted, or substituted from precursors in a condition of gas or liquid without changes on the morphology or structure of precursors[108]. Common topochemical synthesis includes topochemical deintercalation and transformation. Among them, deintercalation represents a process that some compounds or element layers that were selectively removed from the precursors. A way for production of 2D MXenes via selective etching the element A from the MAX precursor is a typical kind of topochemical deintercalation[109,110]. However, topochemical transformation involves addition elements to the parent precursors or replacement of elements the parent precursors.

All these synthesis methods are mainly based on two strategies that are, bottom-up strategy and top-down strategy[111]. The bottom-up strategy refers to the assembly of 2D materials from atoms or molecules, which is usually used for the combination of large and more compounds with smaller components. The CVD and PVD as well as solvo-thermal synthesis methods are common synthesis methods based on bottom-up strategy. The top-down strategy involved in the destruction of the Van der Waals interaction between the adjacent layers of parent precursors by the employment of external forces or insertion of molecules to achieve controllable production of single-layer sheets[112]. Common methods based on top-down strategy include mechanical cleavage (MC), liquid-phase exfoliation (LPE) and chemical exfoliation, etc. [113]. For instance, MC is a common means for the production of graphene with few layers from graphite via the application of adhesive tape[114]. Based on the bottom-up strategy, it is feasible to obtain 2D materials with higher quality and bigger domain sizes relative to the top-down strategy. However, the bottom-up strategy could not achieve scalable production of 2D materials, which impedes the suitability of 2D materials for practical applications [4]. The top-down strategy, except MC, makes it simple and fast to produce 2D materials on large scale with high reproducibility. However, the top-down strategy is energy-intensive that requires high shear and temperature, which might lead to destruction in the surface structure[115].

Besides, different synthesis methods have their advantages and disadvantages, and 2D materials fabricated by different synthesis methods might have different properties and are suitable for different applications. For instance, the production of 2D materials synthesized through CVD or PVD synthesis is enough for electronics devices but is not sufficient for some other applications such as energy storage[116,117]. As for solution-based methods, higher yields could be achieved. However, solution-based methods are only suitable for those precursors compounds whose interaction of layers was maintained by weak van der Waals forces along one direction[118]. Therefore, it is necessary to be cautious to choose the best synthesis method so that produce 2D materials meeting the actual need for given applications.

3.2. Surface functionalization/ modification of 2D materials

To promote the properties of 2D materials, enhance their biocompatibility as well as stability, and therefore broaden their applications when applied in biological systems, surface functionalization/ modification of nanomaterials is an important mean [115,119]. Various kinds of molecules and compounds such as polymers, metals, biomolecules, radioisotopes, and drugs, etc. have been successful to be employed to modify 2D materials[115]. Currently, there are many surfaces modification means had been employed to achieve the improvement of properties of 2D nanomaterials for biomedical applications and most of them are based on covalent or noncovalent strategies[120–123].

Covalently functionalizing the 2D nanomaterials is a process that forming chemical bonds among the functionalization materials and 2D materials. For instance, many kinds of functional molecules or polymers could be used to chemically modify 2D black phosphorus via the direct formation of P-C and/ or P-O-C bonds between them[53]. For example, some commonly used polymers for functionalization of 2D materials such as amine or amino-modified polyethylene glycol (PEG), which had been reported to be able to modify graphene oxide or TMDCs, leading to improvement of their stability in various applications[124,125]. A mechanochemical method named high-energy ball milling (HEBM) could be used to achieve covalent bonding[126,127].

Besides covalent modification, functionalization with noncovalent methods is another way for modification of 2D materials frequently, which involves hydrogen bonding, hydrophobic action, electrostatic interactions, π-stacking, and van der Waals forces, etc.[122,128–130]. For example, some 2D materials with negative charges, e.g., black could effectively absorb cationic polymers such as polyethyleneimine (PEI) and amino polyethylene glycol (PEG-NH2) through electrostatic interaction[131]. Silk fibroin is found to attach to the surface of BP firmly via powerful hydrophobic action[132]. At last, modification of 2D materials could be simply achieved by wrapping them in polymersomes/ polymeric vesicles with a bilayered membrane[133].

There are many polymers such as soybean phospholipids (SPs) [2], amphiphilic PEG-grafted poly (maleic anhydride-alt-1-octadecene, C18PMH-PEG)[134], polyethyleneimine (PEI)[135], distearo-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol) (DSPE-PEG) polymers[136], polyvinyl pyrrolidone [137] et al. have been used to noncovalently modify 2D materials, effectively enhanced their physicochemical properties. Despite there are various advantages of noncovalent modifications, interactions formed by noncovalent modifications between 2D materials and functionalization reagents are weaker than those formed covalently. For instance, desorption might happen toward intravenous administration is a worrying problem of electrostatic interaction. Therefore, researchers should choose the most suitable way to modify the 2D materials for different applications.

There are many kinds of molecules and compounds such as polymers, metals, biomolecules, radioisotopes, and drugs, etc. have been successful to be employed to modify 2D materials[94]. For example, PEG, a kind of polymer, was used to modify 2D WS_2 through the formation of covalent bonds, which promoted the stability of 2D WS_2 in physiological solutions and therefore induced a longer blood circulation time of 2D WS_2[138]. Sushmitha and coworkers developed a novel biosensor for qualitative and quantitative detection of neurological drugs by functionalizing the 2D MoS_2 with metals including aluminum/ cuprum etc. It was found that sensors of metal-functionalized 2D MoS_2 showed high sensitivity and selectivity as well as stability upon detection of neurological drugs. Biological molecules such as hyaluronic acid, folic acid, arginylglycylaspartic acid, and biotin, etc. are usually used for guiding 2D materials to specific tissues and cells because of their

high affinity toward the cell membrane or the extracellular matrix. Besides, some biological molecules such as phospholipids (PLs) were found to be able to promote the stability and biocompatibility of 2D materials in physiological conditions by improving the interaction of 2D materials and the cell membrane[115,139]. As for radioisotope, the functionalization of 2D materials with a radioisotope is an effective strategy for monitoring the biodistribution of nanomaterials in the physiological environment. In an experiment led by Liang Cheng and colleagues, ^{64}Cu isotope was labeled to $FeSe_2$-decorated Bi_2Se_3 nanosheets to fabricate a multimodal imaging technique through the promotion of its sensitivity[140]. Last, functionalization of 2D materials with some drugs to fabricate a multi-model therapy might achieve a synergistic therapeutic effect. For example, doxorubicin, a common drug of chemotherapy, could be loaded to some 2D materials with NIR light absorption for the combination of chemotherapy and phototherapy, which provides a potently synergistic mean for cancer therapy[141].

3.3. Surface functionalization of 2D materials for bone therapies

Due to the versatile properties of 2D materials and their various applications in biomedicines, 2D materials are drawing wide attention from researchers who are occupying in treating bone diseases. For instance, the broad light absorption and the excellent property of photothermal conversion make some 2D materials including 2D BP and MXene, etc. suitable for bone tumor therapy. And some 2D materials were found to be adhesive to stem cells as well as have the ability of osteoconductivity of stem cells which makes them an important role in bone tissue regeneration. However, some intrinsic demerits of 2D materials such as the instability of BP in ambient conditions, the insufficient mechanical strength of MXene in the physiochemical environment, greatly impairs their therapeutic effect and impedes their applications. Fortunately, the functionalization of 2D materials is a powerful means to solve this problem.

Here, we concluded some strategies employed in different studies about the functionalization of 2D materials for bone therapy (Table 1). In an experiment led by Chong Wang et al., 2D BP is functionalized by being combined with doxorubicin hydrochloride (DOX), β-tricalcium phosphate (β-TCP), osteogenic peptide, followed by being contained in water/poly(lactic-co-glycolic acid)/dichloromethane emulsions to realize tissue regeneration after tumor resection and prevent tumor recurrence. Upon such a strategy, BP and DOX were applied for tumor resection via photothermotherapy and chemotherapy respectively. Meanwhile, β-TCP and osteogenic peptide were used for the achievement of bone tissue regeneration. As shown in the results, this strategy achieved rapid tumor resection and lasting suppression of tumor recurrence [142]. 2D MXene was found to possess potential osteoinductivity and good biocompatibility. However, the mechanical strength of MXene in physiochemical conditions was not sufficient for cell adhesion. Hydroxyapatite (HAP) also showed favorable bioactivity and osteoconductivity. Meanwhile, HAP could also be used as a reinforcing agent for enhancing the mechanical and biological properties of the composites. Based on the properties of MXene and HAP, Yu Fu and co-workers functionalized 2D MXene with 1D hydroxyapatite nanowires to fabricate a nanocomposite membrane with enhanced mechanical and biological properties, which effectively promoted the cell adhesion and cell proliferation as well as osteogenic differentiation. Besides, in a rat calvarial bone defect model, functionalization of MXene with HAP also pronouncedly induced bone regeneration[143]. In another experiment led by Na Young Shim and co-workers, polydopamine (PDA) was employed in the functionalization of 2D GO due to its mussel-derived adhesive properties to achieve enhanced cell adhesion ability and osteoinductivity. They found that embryonic stem cells (ESCs) cultured on composites coated by 2D GO modified by PDA (PDA/GO) had higher viability. Besides, PDA/GO significantly promoted the osteogenic potency of ESCs cultured on it[144].

From the above examples, it is easy to see that the motif of functionalization of 2D materials includes two aspects. On the one hand, functionalization could remedy the inherent defects such as enhancing the stability and mechanical properties, ensuring their application in bone disease treatments. On the other hand, 2D materials could be functionalized with a variety of materials with the ability on treating bone diseases to achieve synthetic effects for diseases treatment, which would amplify the therapeutic effect. In a word, functionalization of 2D materials is a process of replenishing what is still lacking for the treatment of a disease.

Table 1
A summary of various kinds of molecules and compounds used for functionalization of 2D materials and their subsequent applications in biomedicines (mainly in bone therapies).

2D materials	Functionalization	Property	Disease's treatment	Ref
BP	silk fibroin	stability and facile solution-processability	wound repair	[132]
BP	poly(lactic-co-glycolic acid)	efficient NIR photothermal response/photothermal osteogenesis	bone regeneration	[145]
BP	BP/β-TCP/DOX/Peptide 3D printed scaffold	sufficient mechanical strength; excellent photothermal effect; controlled release	tumor resection-induced bone defects	[142]
BP	poly(ε-caprolactone)/collagen nanofiber	cell attachment and proliferation	osteodifferentiation	[146]
MXene	3D-printed bone-mimetic scaffolds	phototherapy and angiogenesis	osteosarcoma and angiogenesis/ osteogenesis of bone defects	[147]
MXene	ultralong hydroxyapatite nanowires	mechanical properties, hydrophilicity and biocompatibility	bone regeneration	[143]
MXene	S-nitrosothiol/mesoporous silica/3D-printing bioactive glass scaffolds	photonic hyperthermia for nitric oxide production, in situ production of phosphorus and calcium components	osteosarcoma treatment and bone regeneration	[148]
MoS_2	Al/Cu/Sn/Ti	probing for aspirin, caffeine, tramadol and nicotine	detection of numerous bioanalytes in body fluids	[149]
MoS_2	Polydopamine/ arginine-glycine-aspartic acid (RGD)/titanium	osteogenesis, antibacterial ability	bacterial infection and osseointegration	[150]
GO	polydopamine	adhesive properties	osteogenic differentiation of ESCs	[144]
GO	Chitosan/Polyvinyl alcohol/ Hydroxyapatite/gold films	antibacterial ability, osteoblast differentiation	bone tissue engineering	[151]
GO	polydopamine nanofilm/ polyetheretherketone/oligopeptide	cytocompatibility, osteogenesis, antibacterial ability	bone infection	[152]
GO	BP/3D poly(propylene fumarate) scaffolds	cell attachment, phosphate supply	osteogenesis	[153]
Bi_2Se_3	radioisotope ^{64}Cu	monitoring the biodistribution of Bi_2Se_3	cancer theranostics	[140]

4. Applications of 2D materials in various bone diseases therapies

4.1. Application of 2D materials in bone tissue engineering (BTE)

Bone is an important organ in human bodies since it not only plays a vital role in the structural support of the body, load-bearing for movement, and physical protection of the inner organs but also functions as a foundation of hematopoiesis and bone regeneration because the bone marrow reserve a lot of hematopoietic stem cells (HSCs) as well as bone marrow-derived mesenchymal stem cells (BMSCs) that could differentiate into various kinds of blood cells and osteocytes[154–156]

]. However, repair of bone defects caused by trauma or some diseases such as tumors is still a challenging issue clinically [157,158]. Normally, bone graft transplantation autologously, allogeneiclly, or substitution of synthetic bone is a conventionally clinical therapy[159,160]. Nevertheless, it's worth noting that there are also some problems including donor site complications, limited availability of tissue, and immunological rejection, etc. that need to be solved when applying these methods[161]. Therefore, it is no doubt that the development of new strategies without shortcomings of conventional therapies is urgent and significant for the repair of the bone defect.

BTE, a method that combines biomaterials, cells, and osteogenic factors to promote bone regeneration in bone defects sites [162,163]. Recently, due to the excellent physicochemical properties of 2D materials including biocompatibility and biodegradability, unique mechanical properties as well as loading capacity, and so on, the application of 2D materials in BTE has attracted extensive attention from researchers. For example, 2D materials such as BP have excellent biodegradability that could degrade into non-toxic PO_4^{3-} in vivo, which could supply the phosphorus element for bone regeneration[63].

Due to the versatile properties of 2D materials, they could function in different ways to be applied in BTE. First of all, some 2D materials could be applied as one kind of raw material for bone regeneration. Take BP as an example, on the one hand, BP is an allotrope of phosphorus with the most stable and the least reactive nature[164] and phosphorus is an important element in the human skeletal system that bones and teeth contain 85% of phosphorus of human body[165,166]. On the other hand, PO_4^{3-}, the degradation product of BP, could coordinate with Ca^{2+} to achieve in situ phosphorus-driven biomineralization[167]. Therefore, it is reasonable to believe that incorporation of BP into BTE to achieve repair of the bone defect is feasible. Huang et al. fabricated a BP/polymer-based hydrogel scaffold for bone regeneration based on a strategy that accelerating biomineralization and bone regeneration by capturing calcium ions through phosphorus provided by BP photoresponsive degradation. They found the photoresponsively released phosphate from BP/polymer-based hydrogel scaffold could accelerate mineralization by capturing Ca^{2+} in vitro as well as successfully promoted bone regeneration in bone defect site in rabbit (Fig. 1)[168]. Similarly, Wang and colleagues transported BP by a cell-targeting aptamer-modified bioinspired Matrix vesicles (MVs) to special bone-related functional cells with ability of regulating biomineralization. Under the guiding of aptamer, MVs concentrated around special bone cells and further leading to an increase of concentration of inorganic phosphate in a photoresponsive manner, which ultimately promoted the biomineralization of osteoblasts and bone regeneration (Fig. 2)[169].

Secondly, 2D materials could also function by enhancing the properties of the biocompatible scaffold in BTE. For example, the incorporation of 2D materials would promote the performance of scaffolds on cell adhesion, proliferation, and differentiation[170].

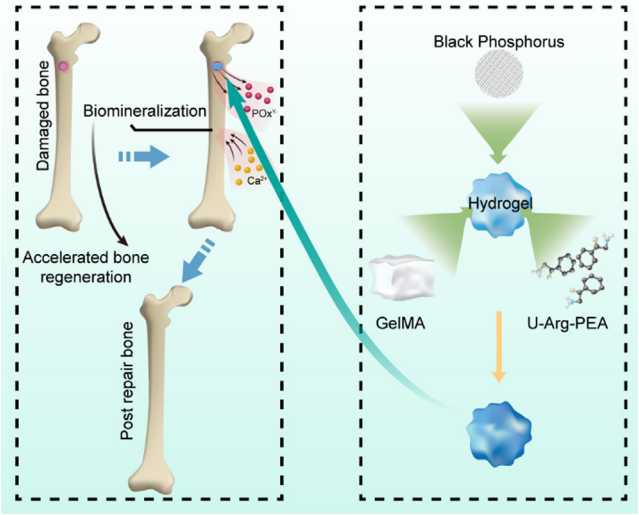

Fig. 1. Schematic of a 3-D hydrogel platform that promotes bone regeneration: PO_4^{3-} produced by the degradation of BPNs encapsulated in the hydrogels could capture calcium ions to promote in situ biomineralization. Reprinted with permission from Black Phosphorus Hydrogel Scaffolds Enhance Bone Regeneration via a Sustained Supply of Calcium-Free Phosphorus. Copyright 2019 American Chemical Society [168].

It had been reported that the characteristics on the material surface and the forces derived from the cell/material interfaces are two key important factors for mediation of cell attachment and cell differentiation[171,172]. However, some polymers including polycaprolactone (PCL) and poly-L-lactic acid (PLLA) which are often applied as the major components of the bio-scaffold used in BTE, were unsatisfied for cell attachment and differentiation because of the lack of sites for cell adhesion. Therefore, it is requisite to add a chemical modification to make them suitable for cell attachment[34]. Kim et al. fabricated a reduced graphene oxide (RGO)-incorporated chitosan substratum for stem cell engineering. Relative to the chitosan substrata group, incorporation of RGO not only showed enhanced cell adhesion and cell differentiation of human mesenchymal stem cells (hMSCs) but also were more beneficial to osteogenesis of hMSCs even in the absence of differentiation-inducing chemicals because RGO–chitosan substrata could provide an environment favorable for the adhesion and proliferation of hMSCs as well as promote the interaction between cell-substrate and cell–cell contacts[173]. In another experiment led by Duan and colleagues, a similar result was found, that is incorporation of the graphene into nanofibrous poly (L-lactic acid) scaffolds could significantly enhance the cell adhesion, proliferation, and osteogenic differentiation of bone mesenchymal stem cells [174]. Besides, some 2D materials were found to have a synergistic effect in promoting the surface properties of scaffolds. Liu et al. coated the GO nanosheets with BP followed by absorption of them together onto 3D poly (propylene fumarate) (PPF) scaffolds. In such a scaffold, it was expected that incorporation of GO nanosheets would enhance cell attachment by increasing the surface area and achieve a continuous supply of phosphate for osteoblast differentiation through slow oxidation of BP nanosheets, finally leading to a goal of new bone formation. Consequently, they did found that corporation of BP together with GO nanosheets achieved a synergistic effect on cell osteogenesis as revealed by that the cell proliferation rate and abundance of cellular osteogenic markers, as well as the biomineralization, was higher in these scaffolds than those with only one of the incorporation of the 2D materials (Fig. 3)[153].

Last, the incorporation of 2D materials could also reinforce the physicochemical properties of the bio-scaffold. As Shear-thinning

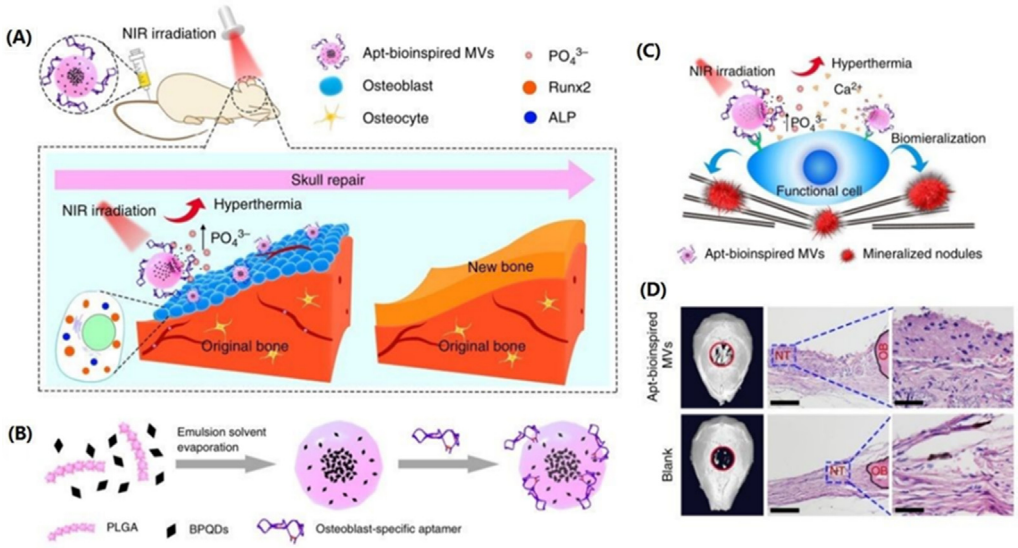

Fig. 2. (A) Schematic illustration of acceleration of mineralization induced by Apt-bioinspired MVs. (B) Synthetic route of Apt-bioinspired MVs. (C) Schematic of illustration that biomineralization induced by Apt-bioinspired MVs. (D) In vivo examination of the effect of Apt-bioinspired MVs on bone issue reconstruction. Reprinted with permission from Springer Nature [169].

injectable hydrogels could shield the encapsulated cell from high shear forces so they promoted the viability of cells and enhanced the outcome of cell-based therapeutics. Recently, methods for obtaining injectable biomaterials have been developed extensively. Thakur et al. fabricated a kappa-carrageenan (κCA) hydrogel scaffold and reinforced it by incorporation of 2D nanosilicates to obtain injectable hydrogels. They found that at the presence of 2D nanosilicates, the hydrogel scaffold presented shear-thinning characteristics, elastomeric properties, and enhanced mechanical stiffness, as well as physiological stability. What's more, encapsulated cells in these nanocomposite hydrogels showed high viability after injection, indicating this injectable nanoengineered system achieved by incorporation of 2D materials possessed the potential on delivery of cells for tissue regeneration such as BTE[175].

4.2. Application of 2D materials in joint lubrication

In recent years, employing 2D materials in lubrication has aroused a lot of interest since superlubricity was found to exist in some layered 2D materials including MoS_2 and boron nitride (BN)[176,177]. Studies had shown that due to their ultra-thin layer structures and the negligible shear strength among the layers, it is easy for 2D materials to enter the friction surfaces, which prevents the friction surfaces to directly contact each other and eventually decreasing the coefficient of friction. Currently, the mechanisms that 2D materials could be applied in lubrication could be divided into 3 aspects (Fig. 4)[4,178]. First of all, the film formation mechanism that 2D materials could be absorbed to form a physical adsorption film, and could deposit directly to form a deposited film as well as form a chemical reaction film through a chemical reaction. The film formed by 2D materials not only reduces the friction between the asperities but also protects the substrate from damage by friction[179]. The anti-wear capacity of the film formed by 2D materials might be positively correlated with the thickness and mechanical strength of the film[180]. Secondly, 2D materials could be used as a filler to compensate for the mass loss of the cavity on the friction surface so that reducing wear and tear, which is known as the self-healing mechanism. Last, the ball bearing mechanism by which 2D materials could form "class bearings" at the contact surfaces and therefore converted the sliding friction of the contact surface between two substrates into rolling friction between the contact surface of substrate and the 2D materials to reduce the friction and wear. Meanwhile, balls formed by 2D materials also direct prevent surface contact of two substrates [181,182].

Besides MoS_2 and BN, some other 2D materials had also been found to be able to be applied in lubrication. For instance, it was reported that even 0.075 wt% graphene platelets incorporated into oil could effectively promote the lubrication performance of oil and improve the wear resistance of the machine[183]. Researchers had found that the production of phosphorus oxides from the degradation of about 50% black phosphorus (BP) leading to the reduction of friction force, indicating that the degradation of BP might be potentially favorable for its application in lubrication[184]. Yanan Meng and colleagues coated hot rolled surface as well as the metallographic structure of steel strips with nano-TiO_2 lubricating fluid to improve the anti-friction performance. They found the defects of the hot-rolled surface, as well as the grain size of rolled steel strips, could be decreased significantly with the application of nano-TiO_2 lubricating fluid[185].

What's more, 2D materials not only could be fabricated to be lubricants on their own but also could be combined with other 2D materials to form a compound and therefore functioned as a lubricant. The nanocomposite of copper oxide/reduced graphene oxide (CuO/rGO) was fabricated and its lubricating effect was investigated in a research group. It was found that about even 0.06 wt% CuO/rGO incorporation could significantly reduce the 46.62% friction coefficient and 77.05% wear rate. Besides, the lubricating effect endowed by CuO/rGO nanocomposite displayed much better lubricating performance than rGO or CuO alone[186]. To improve the anti-wear performance, Wu et al. combined the hydroxide/reduced graphene oxide with the nano-lanthanum to fabricate a nano-La(OH)3/RGO composite followed by the addition of it into the diesel engine oil. They found that the addition of 0.1 wt% nano-La(OH)3/RGO composites could induce a 44% increase in the anti-wear effect of diesel engine oil[187]. Zhang et al. combined crumpled graphene balls (CGB) and nano-magnesium silicate hydroxide (MSH) to synthesize MSH/CGB composites. Then, the oleic acid and stearic acid were added to the MSH/CGB composites to obtain lipophilic composites (ML-MSH/CGB). It was shown that incorporation of 0.005 wt% ML-MSH/CGB composites into the base oil achieved the most powerful

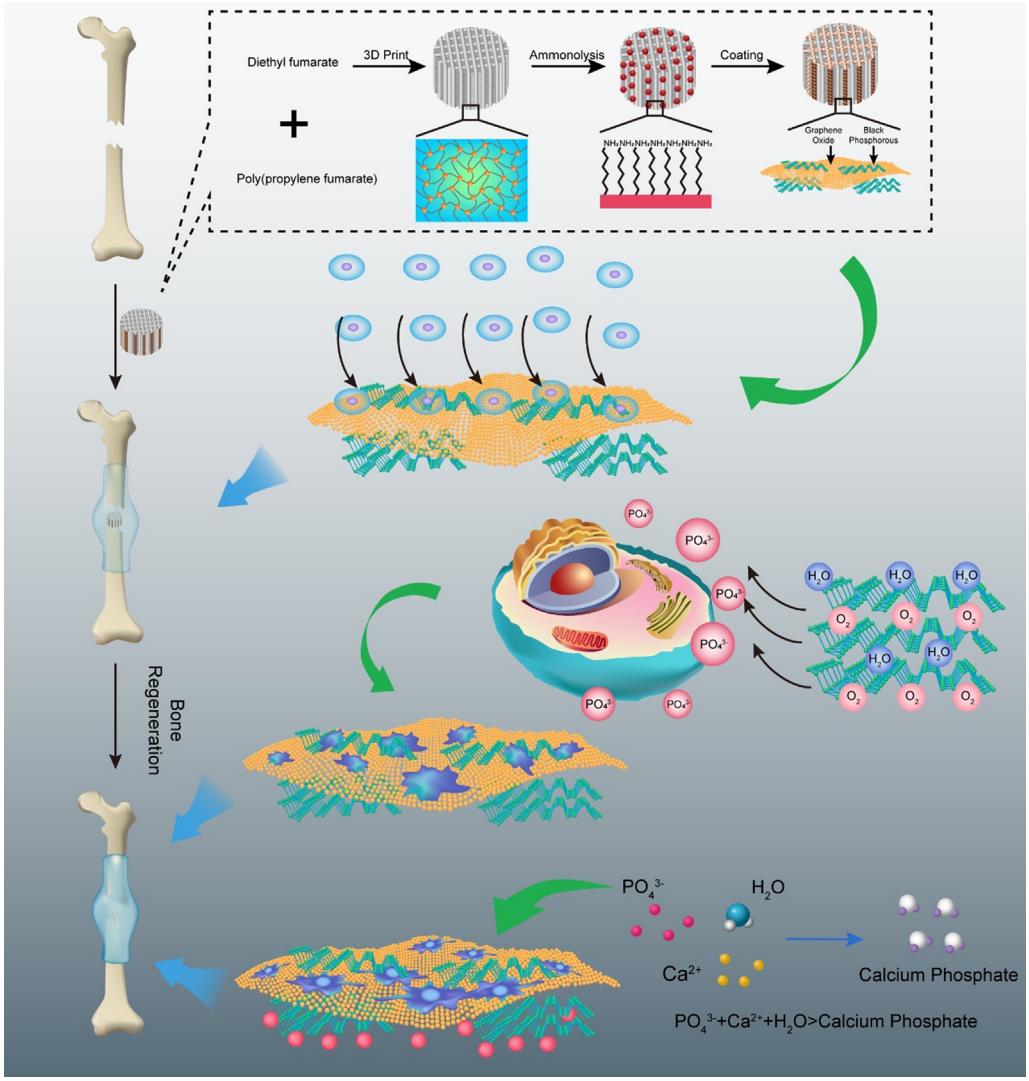

Fig. 3. Schematic illustration of 3D scaffolds incorporated with 2D GO and BP for bone regeneration. Reprinted with permission from Two-Dimensional Black Phosphorus and Graphene Oxide Nanosheets Synergistically Enhance Cell Proliferation and Osteogenesis on 3D Printed Scaffolds. Copyright 2019 American Chemical Society [153].

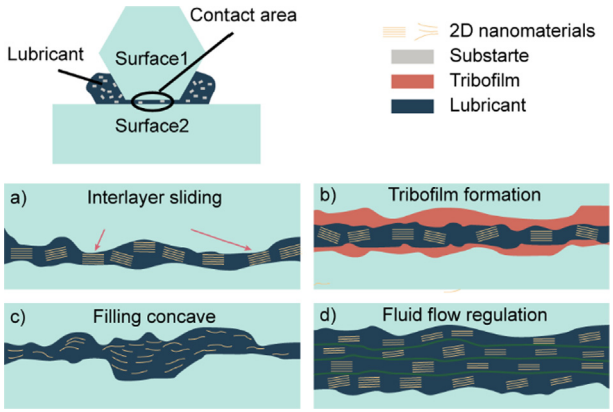

Fig. 4. Schematic illustration of the mechanism by which 2D materials functioned in lubrication[178].

anti-friction performance. The average friction coefficient and wearing degree, as well as wear scar diameter, were decreased by about 25%, 22%, and 17% respectively[188]. Overall, 2D materials are believed to be a kind of promising novel lubricant.

Normally, articular cartilage in healthy people is a self-lubricating system. Some diseases of joint such as OA is believed to begin with injuring in the cartilage, causing the collapse of lubrication, which in turn aggravates the damage in structure and function of cartilage tissue and the subchondral bone[189,190]. Hence, improvement of the lubrication in joints with diseases might be an effective way for protecting the damaged cartilage and inhibiting the deterioration of joint diseases. As we mentioned above, the self-healing mechanism, one of the mechanisms that 2D materials function as lubricants is that 2D materials could be filled into the cavity on the friction surface to neutralize the mass loss and reduce the wear and tear. Therefore, it is reasonable to believe that in the future, those 2D materials with good biocompatibility might be able to be filled directly onto the surface of damaged cartilage to restore the structural integrity of cartilage and therefore restore the lubrication on the surface of the cartilage and relieve patients from pain.

Currently, the application of artificial joints is a kind of treatment for patients with damaged joints to relieve arthritis pain [191]. However, ultra-high molecular weight poly ethylene (UHMWPE), the major component of artificial joints, is easy to be worn out and finally reducing the service life of artificial joints [192]. On the one hand, it was reported that incorporation of some

nanofiller additives with good tribological characteristics such as graphene[193], carbon nanofiller[192], and carbon nanofiber [194], would strengthen the wear resistance. On the other hand, based on the film formation property of 2D materials, we presume that, theoretically, the incorporation of 2D materials into the contact surface of artificial joints could be an effective way to elevate the service life of artificial joints by promoting the lubrication and reducing the friction.

4.3. Application of 2D materials in antibacterial for orthopedic implants

An orthopedic implant is a common surgical intervention for orthopedic disorders which is usually applied to fix fractures, correct the deformities, achieve joint replacements, etc., therefore relieves patients from paint and promotes early mobilization as well as the early return of function[195]. Metals such as titanium alloys, stainless steel, and cobalt alloys, and so on are commonly vital components of orthopedic implants[196–198]. However, the application of any orthopedic implant always poses patients with the risk of infection, which eventually causes implant failures [195]. It was reported that in the USA, about 5% of orthopedic procedures with infection happened a year, and leading to costing of 15,000 dollars per incidence[199]. Nevertheless, because the drug resistance to traditional antibiotics is currently a growing problem, therefore, it is in urgent need of developing new strategies to enhance the antibacterial activities of orthopedic implants [200,201].

Because of their unique structures, 2D materials have fascinating physicochemical properties and therefore possess versatile applications including antibacterial[202]. The mechanisms that 2D materials could act as antibacterial agents could be mainly attributed to several aspects such as oxidative stress including reactive oxygen species (ROS) dependent and ROS independent, physical contact destruction, and photothermal antibacterial [203,204].

Oxidative stress could destroy some components key for bacterial metabolism such as DNA, and therefore killing bacteria [205,206]. As demonstrated by previous studies, many 2D materials could function as photosensitizer (PS) for cancer therapy because of their capability of inducing ROS production[207–209]. Generally speaking, oxidative stress-mediated by 2D materials could be divided into ROS-dependent oxidative stress or ROS-independent oxidative stress. Common ROS includes hydroxyl radicals (•OH), hydrogen peroxide (H_2O_2), and singlet molecular oxygen ($^1O_2$) as well as superoxide anions ($\bullet O_2^-$). Recently, more and more 2D materials have been demonstrated to function as antibacterial agents by inducing the production of ROS. Karunakaran and co-workers achieved a nanomaterial-based antibiotic effect with a long-term (>8 months) stability and enhanced bactericidal capacity by innovatively exfoliating and functionalizing 2D 2H-MoS_2 nanosheets with different thiol surfactants. Based on the previous reporting that vertically aligned 2H-MoS_2 could induce the production of ROS[210], they investigated whether the ROS was responsible for the antibacterial activity of 2H-MoS_2 by Ellman's assay in this work. As a result, 2H-MoS_2 caused a severe loss of glutathione (GSH), a kind of vital reductant in organisms, indicating a great production of ROS induced by 2H-MoS_2 (Fig. 5)[211]. In another work, Yang and colleagues employed 2D exfoliated MoS_2 (ce-MoS_2) in the antibacterial examination. The viability of the bacterium was reduced effectively both in a dose and time-dependent manner upon the treatment with ce-MoS_2. Meanwhile, the concentration of superoxide anion ($O_2^{\bullet-}$) was found to be greatly elevated by ce-MoS_2, but the concentration of GSH was decreased significantly, suggesting that ROS induced by ce-MoS_2 was partly responsible for the antibacterial performance at least [212].

Besides, ROS-independent oxidative stress also plays a vital part in the antibacterial performance of 2D materials. In a study led by Rasool et al., 2D $Ti_3C_2T_x$, a kind of MXene, was tested for its antibacterial properties against both Gram-positive bacterium and Gram-negative bacterium. In comparison with GO, an acknowledged antibacterial agent, $Ti_3C_2T_x$ was more potent in inhibiting the antibacterial activity toward both bacteria. To find out the mechanism that $Ti_3C_2T_x$ functioned as an antibacterial agent, GSH concentration was detected. The results showed that $Ti_3C_2T_x$ could promote the oxidation of GSH, revealing the induction of oxidative stress by $Ti_3C_2T_x$. Then, XTT assay was carried out to determine the production of superoxide anion ($O_2^{\bullet-}$). However, no noticeable $O_2^{\bullet-}$ was detected at different $Ti_3C_2T_x$ concentrations, implying that ROS might play an insignificant role in the mediation of $Ti_3C_2T_x$ antibacterial activity[213].

The structural integrity of the bacterial membrane is vital for the survival of bacteria, suggesting that destroyed the integrity of the bacterial membrane might be an effective means to kill the bacteria[204]. Physical contact destruction is a powerful means that could break up the bacterial membrane based on this mechanism. Graphene-based nanomaterials were the first ones to be proposed to function by this mechanism. Initially, physical contact destruction was thought to work based on the sharp edges of nanosheets, because the sharp edges of nanosheets were viewed to have the lowest energy barrier which contributes to nanosheets penetrating the lipid bilayer[214,215]. Subsequently, Lu et al. found that the antibacterial activity of graphene oxide nanosheets was orientation-dependent which is affected by the orientation of GO nanosheets aligned. As a result, GO nanosheets with vertical orientation were found to be more powerful in inhibiting the activity of bacteria compared with random and horizontal orientations. The authors thought that, relative to the horizontal orientations, alignment in vertical increased the density of edges of GO nanosheets when in contact with the bacteria [214]. In consideration of the problem that orthopedic implants were usually suffered from the colonization of bacteria followed by biofilms formation, leading to infection and the final implant failure, Wang et al developed a novel idea that in situ formations of 2D nanoflakes with non-leaching surfaces on magnesium (Mg) through hydrothermal treatments, which not only resolved the problem that leaching magnesium alloy always caused the uncontrolled release of Mg^{2+} and augment of pH leading to systemic side effects eventually, but also enhanced the antibacterial capacity of Mg^{2+} by physical–mechanical forces. As the in vitro experiment showed, the formation of 2D nanoflake on the surface effectively promoted the antibacterial capacity of magnesium alloy, and the augment of antibacterial capacity is positively related to the density of the nanoflake. Meanwhile, as revealed by the SEM, in the control group, *S. aureus* and *E. coli* presented a normal morphology with membranal integrality. However, in the contrast, the group treated with 2D magnesium flake, *S. aureus* showing concavities on the membrane contacting directly with the nanoflakes while the *E. coli* cells showed a stretched but shriveled morphology, indicating that severe deformation of the membrane caused by physical force contributed to the cell death of bacteria (Fig. 6). Finally, the antibacterial performance and anti-inflammatory effect were tested in vivo by implanting different alloy samples into a soft issue of rats followed by injection of the bacteria. As a result, the Mg group and the 2D Mg nanoflakes group presented similar antibacterial performance which was better than the control group. Besides, serious inflammation was observed in the control group and the Mg group while the group treated with 2D nanoflakes just showed a mild inflammation (Fig. 7)[216].

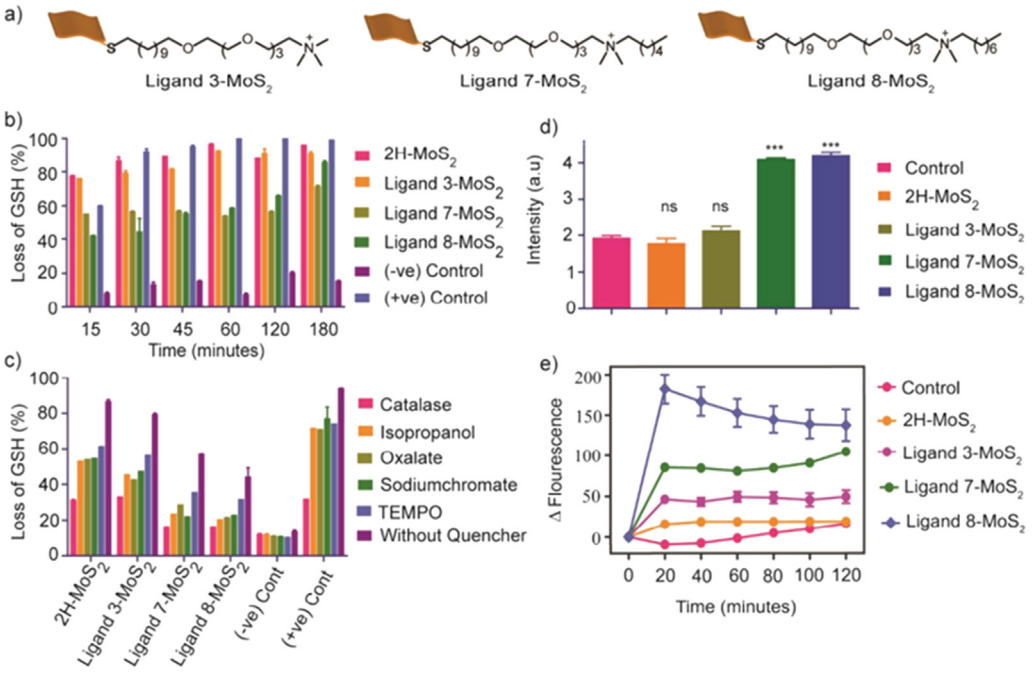

Fig. 5. Determination of the antibacterial property of functionalized MoS_2. a) Structural representation of ligand 3-MoS_2, ligand 7-MoS_2, and ligand 8-MoS_2. b) Evaluation of abiotic oxidative stress through Ellman's assay with 0.4 mM glutathione. All values are statistically significant versus negative control ($P < 0.0001$). c) ROS species determination. All the values are statistically significant versus the without quencher group ($P < 0.0001$). d) Determination of intracellular ROS by fluorescent probe DCFDA. ***, $P < 0.0001$ vs control; ns, $P > 0.05$ vs control. e) Quantification of membrane depolarization of MRSA. Reprinted with permission from Simultaneous Exfoliation and Functionalization of 2H-MoS_2 by Thiolated Surfactants: Applications in Enhanced Antibacterial Activity. Copyright (2018) American Chemical Society. [211].

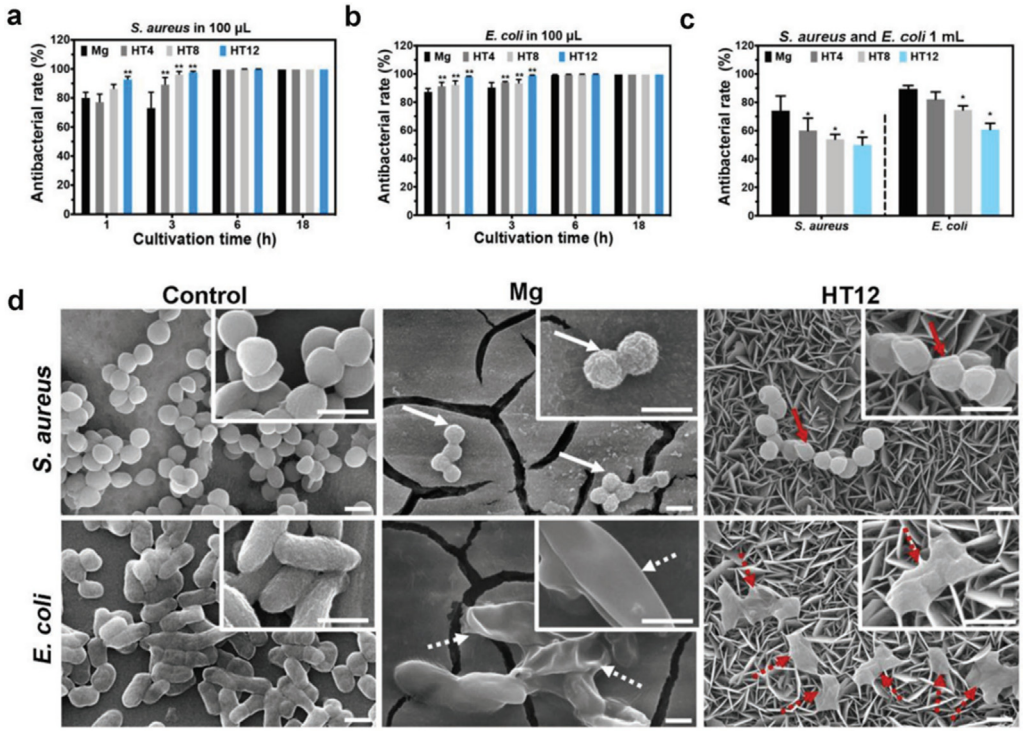

Fig. 6. Antibacterial properties examination: Time-dependent antibacterial effect against a) S. aureus and b) E. coli, respectively; c) Determination of antibacterial effect against S. aureus and E. coli after been cultivated for 3 h; d) Morphological characteristics of S. aureus and E. coli upon treatment with different samples for 3 h. Arrows indicated the deformed morphology. *, $P < 0.05$ and **, $P < 0.01$ versus Mg group. Reproduction from Guomin Wang et al. [216].

However, the sharped edges related mechanism of antibacterial capacity was controversial, because a subsequent work emphasized that the electron transfer between the graphene surface and the bacterial membrane was responsible for the antibacterial performance of GO, suggested that it was the surface but not the edge of GO endowed itself the antimicrobial activity

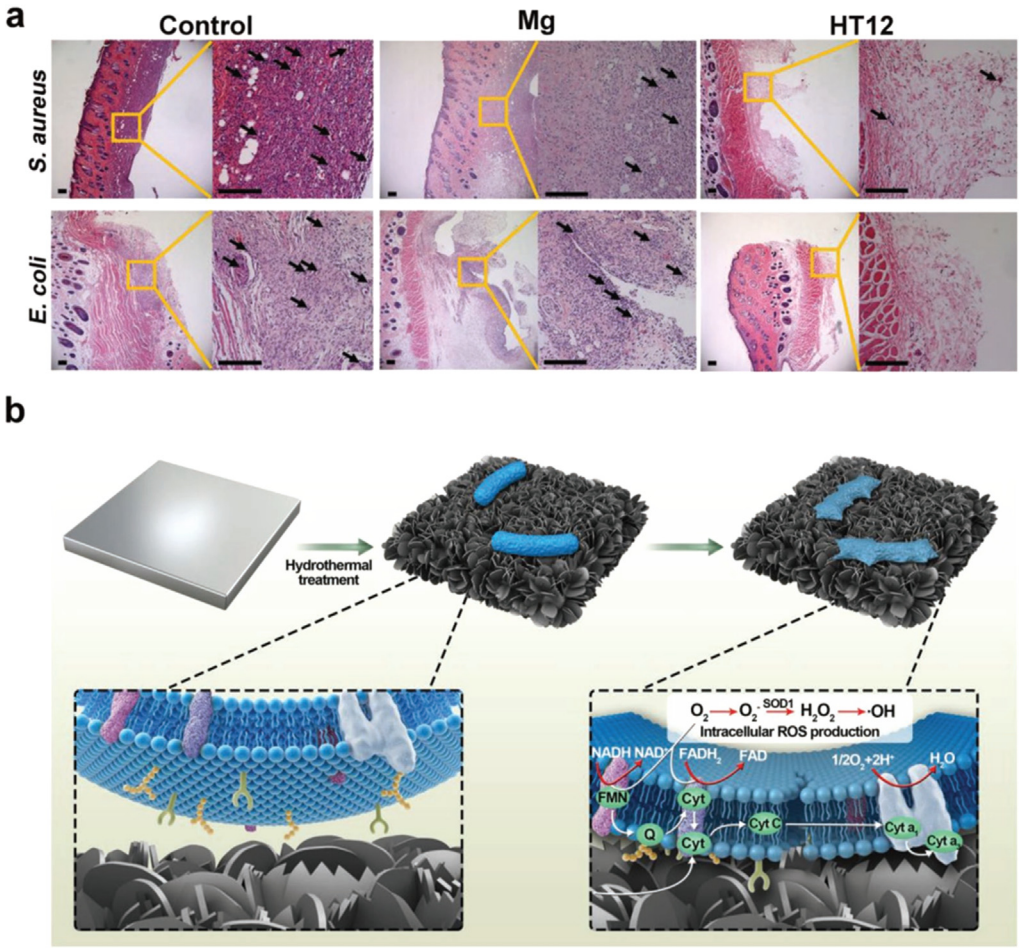

Fig. 7. Anti-inflammation performance and potential antibacterial mechanism: a) Hematoxylin and Eosin (H&E) staining for inflammation examination at day 10 (significant infiltration of inflammatory cells are indicated by black arrows, Scale bar = 200 μm); b) The potential antibacterial mechanism. Reproduction from [216].

[217]. Therefore, to fully elucidate the mechanism that physical contact destruction functions, more work was necessary for the future.

On the one hand, because many 2D materials were demonstrated to possess excellent performance on the conversion of NIR laser to heat, on the other hand, because NIR lasers could deeply penetrate the biological tissues with negligible damage to healthy tissues, utilizing the photothermal conversion ability of 2D materials in the antibacterial application has been considered as a promising antibacterial mean[202]. Inspired by the high efficiency of MoS_2-based nanostructures for photothermal therapy of cancer, Zhang and co-workers fabricated a novel antibacterial agent by integrating the chitosan (CS), magnetic MoS_2, and iron oxide nanoparticles (CFM). In this composite, MoS_2 was responsible for the conversion of the NIR laser to heat to kill the bacteria. CS was introduced for its abundance in amino groups, which is key for nonspecifically cross-linking bacterial cells. And iron oxide nanoparticles played an important role in bacterial enrichment performance. As a result, they found CFM could effectively enrich the bacteria and form CFM – bacteria aggregates within 1 min in vitro. Then in mouse models which have subcutaneous abscess induced by *S. aureus*, upon exposure to NIR laser (2 W/cm^2), bacteria in the infection site were quickly eliminated, indicating MoS_2 in this composite could function with biocompatibility and efficiency for focal infection treatment in vivo through photothermal conversion[218]. According to some previous studies that BP based hybrid materials possess better antibacterial activity compared to the bare BP nanosheets[219,220], Aksoy et al. developed a nanocomposite by incorporating the gold nanoparticles (Au) to BP nanosheets for achieving an enhanced antibacterial capability of BP. As was expected, BP/Au nanocomposites were not only showed to be more potent in the production of heat, but also had more powerful antibacterial capacity than the bare BP nanosheets upon irradiation with NIR lasers[221]. This work further implies that a combination of different 2D materials might be an easy way to achieve antibacterial agents with high efficiency. A multifunctional platform combined with 2D graphene oxide (GO) nanosheets, polydopamine (pDA) nanofilm, and oligopeptide, as well as porous sulfonated polyetheretherketone (PEEK) (GO-SPEEK-BFP), was fabricated by Wang and colleagues to overcome the issue that clinic application of PEEK in orthopedic is always suffered from the infection. Upon exposure to 808 nm NIR laser, GO incorporated SPEEK showed excellent performance on photothermal conversion, which might endow itself with antibacterial capacity. As was expected, the growth of bacteria treated with GO-SPEEK or GO-SPEEK-BFP was significantly inhibited, and their viability was further decreased when exposed to 808 nm NIR laser. Meanwhile, it's worth noting that both in vitro and in vivo, GO-SPEEK-BFP showed great property on osteogenic induction[39]. Besides, other 2D materials such as metal-based nanomaterials, MoS_2, Sb_2Se_3, etc. were also demonstrated to be effective antibacterial agents through photothermal conversion[222–225].

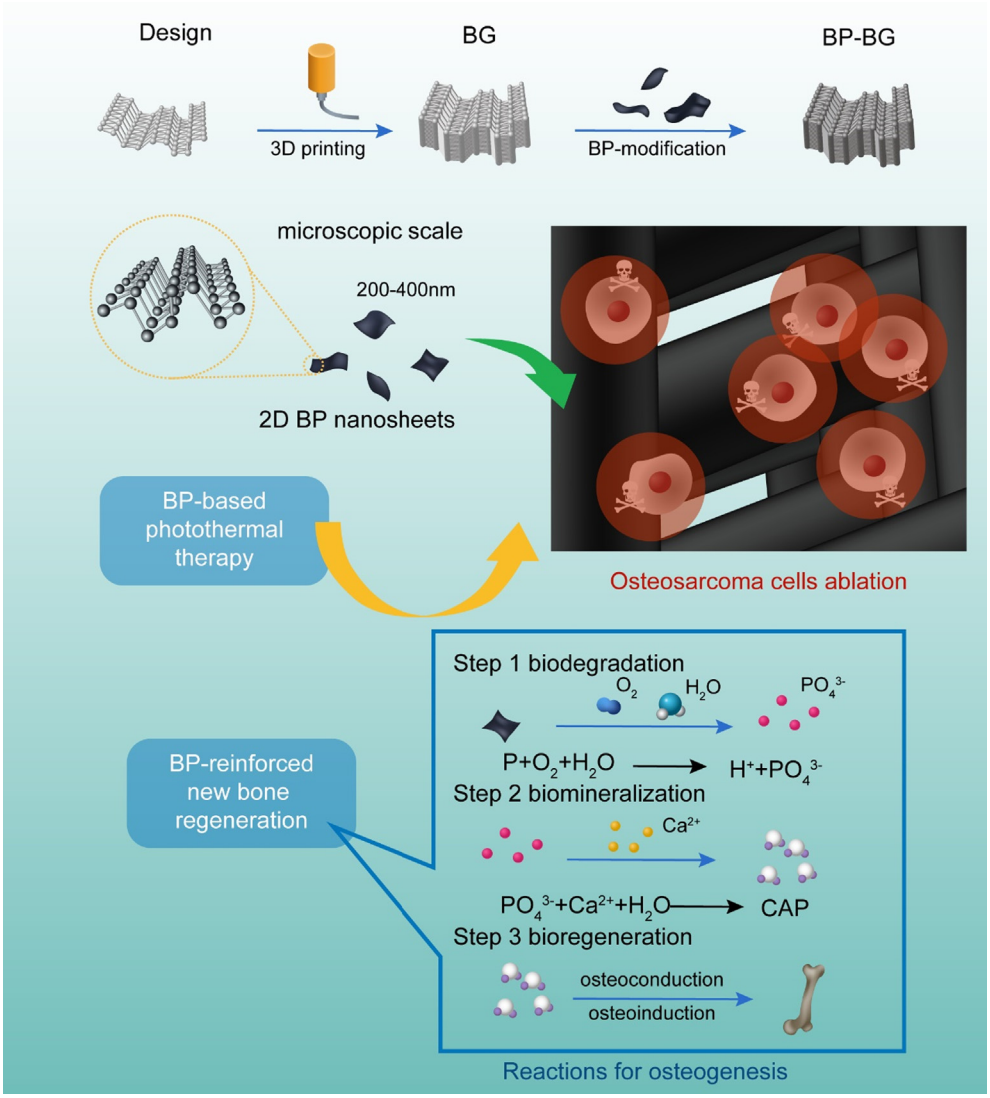

Fig. 8. The preparation process of BP-BG scaffolds and the mechanism that they kill osteosarcoma cells and induce subsequent osteogenesis. Reprinted with permission from 2D-Black-Phosphorus-Reinforced 3D-Printed Scaffolds: A Stepwise Countermeasure for Osteosarcoma [250].

4.4. Application of 2D materials in bone cancers therapies

There are some common bone malignant tumors that are extremely dangerous to patients and are very tough to handle such as osteosarcoma, chondrosarcoma, and Ewing's sarcoma[226–228]. Nowadays, the main methods for cancer therapy include surgical resection, chemotherapy, radiation therapy, and emerging immunotherapy[229–231]. However, some shortcomings still exist between them, for instance, the surgical resection cannot achieve a satisfactory result while tumor metastasis happened and often causes trauma. As for radiotherapy and chemotherapy, the severely systemic side effects with toxicity destroy the healthy organs and tissues in patients[232–234]. Last, recurrence of cancers in some patients who received immunotherapy due to immune escape caused by down-regulation of tumor antigen is still a problem, which also imposed additional financial burdens on patients [234]. Thus, it is necessary to innovate current cancer therapies to achieve a satisfactory method for the treatment of cancers.

Due to their intrinsic optical properties as well as loading capacities endowed by their large specific surface area, 2D materials are currently applied broadly in phototherapy for tumor therapy[235–239]. Phototherapy includes photothermal therapy (PTT) and photodynamic therapy (PDT), which is an innovative cancer therapy that functioned by converting the NIR light into heat with high temperature or into reactive oxygen species (ROS) for destroying the cancer cells respectively[240–243]. 2D materials were employed as photothermal reagents (PTAs) in PTT[244,245]. However, in PDT, 2D materials were applied as photosensitizer (PS) [246,247]. In recent years, a lot of studies had demonstrated that many 2D materials including GO, TMDCs and BP, etc., could be applied in different patterns in phototherapy for the treatment of many kinds of tumors including bone malignant tumors, and achieved great success. 2D materials currently could not only be applied as PTAs or PS in phototherapy but also be employed as the carrier for traditional PTAs or PS because of their excellent drug loading capacities and therefore functioned in the phototherapy for cancer treatment[65,138,223,248,249].

Here we mainly reviewed recent advances in bone malignant tumors treated with 2D materials. Yang and colleagues developed a novel strategy of PTT for osteosarcoma and the subsequent bone regeneration of the bone defects caused by PTT, which a 3D scaffold was fabricated by incorporating the 2D BP nanosheets for the achievement of PTT and the subsequent phosphorus supply from BP degradation would drive the in situ biomineralization

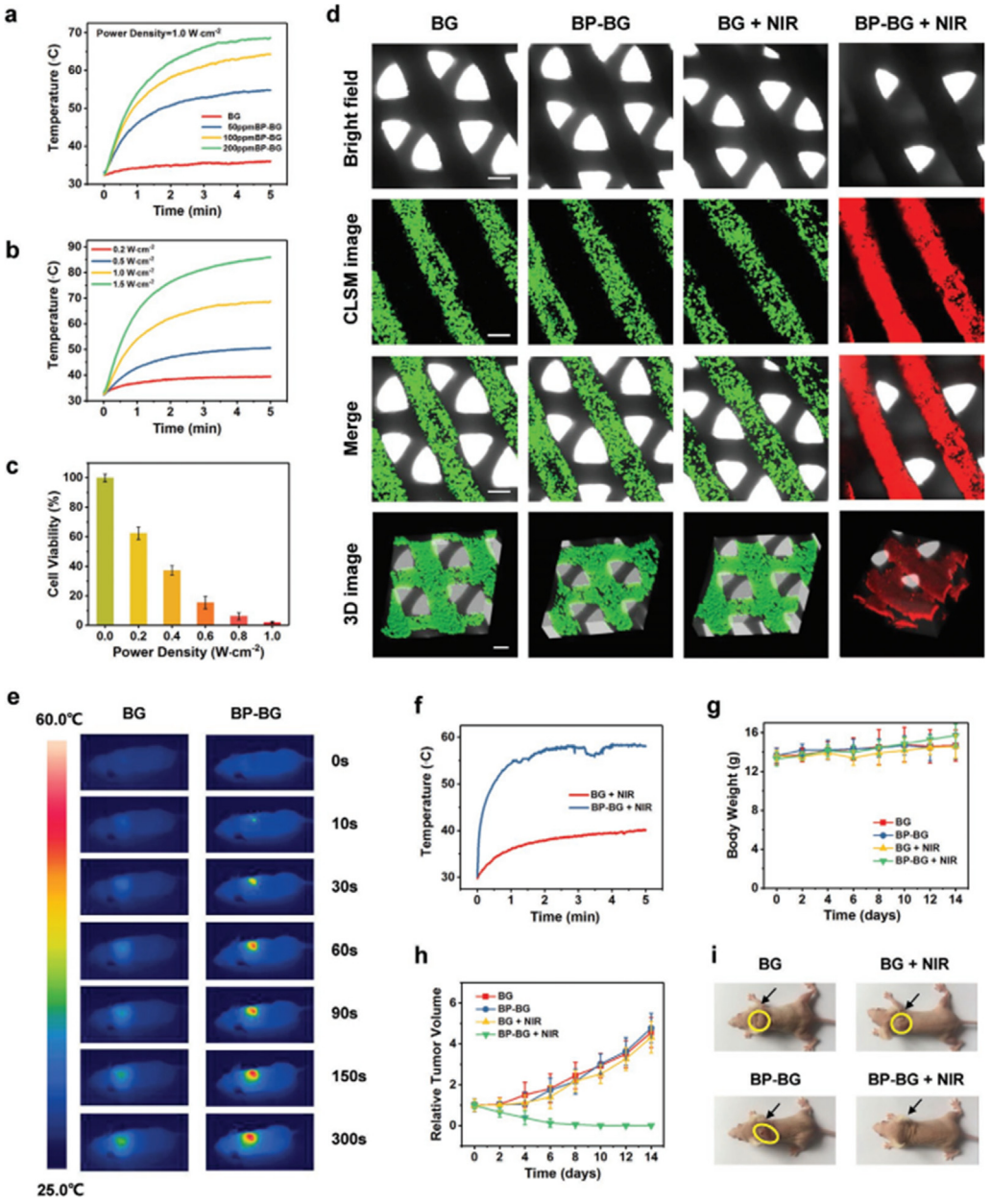

Fig. 9. Examination of photothermal performance in vitro and in vivo. a) Changes in temperature of BP-BG scaffolds with different BP concentrations in vitro. b) Changes in temperature of BP-BG scaffolds with different laser power densities of NIR in vitro. c) Cell viability of Saos-2 cells upon treatment with different power densities of NIR. d) Toxicity of BG and BP-BG scaffolds on Saos-2 cells detected by calcein AM (green fluorescence indicates live cells) and PI (red fluorescence indicates live cells). Scale bar = 200 μm. e) Infrared thermographic photographs of the tumor-bearing nude mice post-implanted with BG and BP-BG scaffolds upon irradiation of 808 nm laser (1 W·cm^{-2}) for different time intervals. f) Real-time temperature change in osteosarcoma tissue corresponding to (e). g) Change of body weight of nude mice after different treatments (n = 7, mean ± SD). h) Change of tumor volume of the mice after different treatments. i) Images of mice with xenografted osteosarcoma after different treatments on day 14. Reprinted with permission from 2D-Black-Phosphorus-Reinforced 3D-Printed Scaffolds: A Stepwise Countermeasure for Osteosarcoma [250]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Fig. 8). Under the irradiation with the 808 nm lasers, the BP incorporated group released a lot of heat and the cell viability of the BP incorporated group was significantly decreased in a NIR power densities dependent manner. As was expected, the volume of tumors of osteosarcoma-bearing mice in the BP incorporated group with irradiation, reduced obviously in a time-dependent manner (Fig. 9)[250]. In another work lead by Wang and colleagues, based on a strategy that "kill first, then regenerate", a 3D scaffold consisted of water/ poly(lactic-co-glycolic acid)/dichloromethane emulsions incorporating with 2D BP nanosheets, β-tricalcium phosphate (β-TCP), osteogenic peptides as well as doxorubicin hydrochloride (DOX)was fabricated for tumors ablation and regeneration of tumor resection-induced bone defects. In such a scaffold, BP was applied as PTAs for PTT and DOX was for chemotherapy, which synergistically functioned for destroying xenograft osteosarcoma. Then, β-TCP and osteogenic peptides were employed for the regeneration of bone defects. As a result, the temperature of the scaffold was significantly elevated and was positively related to the laser density, indicating the suitability of the scaffold in PTT for tumor ablation. Subsequently, upon exposure to irradiation of 808 nm laser, the scaffold reduced cell viability in vitro and effectively inhibited the growth of xenograft osteosarcoma in vivo.

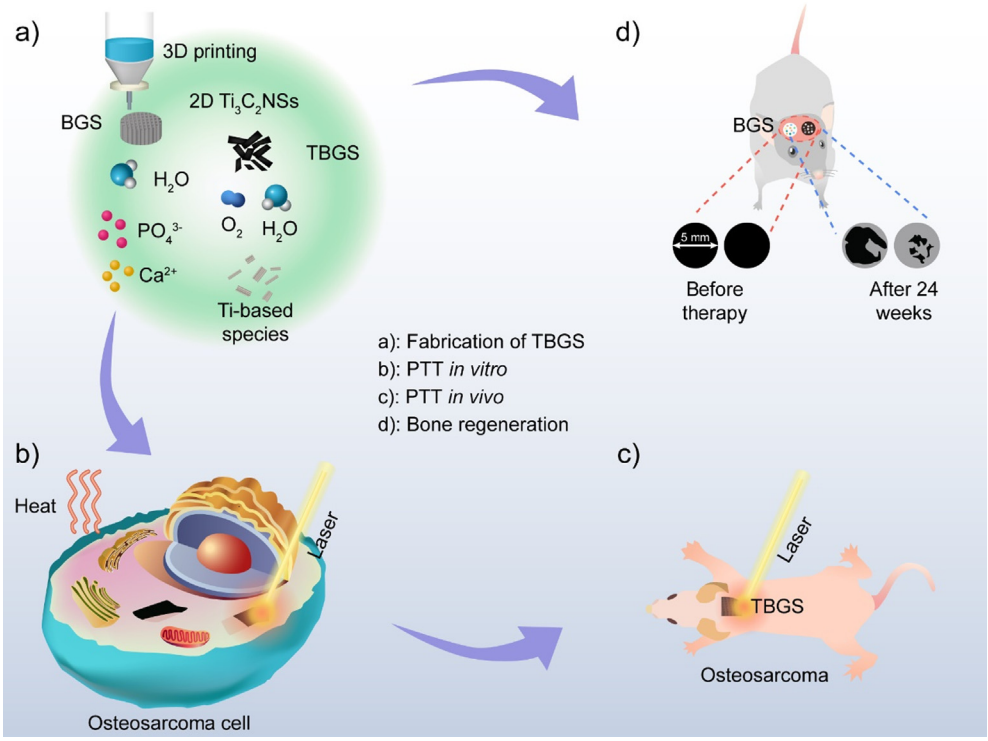

Fig. 10. Preparation progress of TBGS and its application in osteosarcoma treatment[89].

Besides, the scaffold was found to promote the osteogenic differentiation of rat BMSCs in vitro and promote the in vivo bone regeneration of rat cranial[142].

Besides, other 2D materials were also be demonstrated to play an important role in bone tumor therapy. For instance, the Chen group developed a unique strategy for destroying the bone tumors and meanwhiles repairing the bone defects based on the 2D Ti_3C_2 MXenes, because 2D Ti_3C_2 is not only highly biocompatible with excellent photothermal-conversion property, but also capable to promote bone reconstruction through its biodegradation products. In their work, a multifunctional biomaterial scaffold was constructed by integrating the 2D Ti_3C_2 MXenes with a typical biomaterial for bone-tissue regeneration named 3D-printing bioactive glass (BG) scaffold (designated as Ti_3C_2-BG scaffold or TBGS) (Fig. 10). Under the irradiation of 808 nm laser (1.0 W cm^{-2}), the temperature of the scaffold was approximately increased to 60 °C within about 150 s and the augment of temperature was in a power densities dependent manner. As was expected, TGBS with laser exposure significantly reduced the cell viability in vitro and inhibited the growth of osteosarcomas in mice with high effectivity. In the contrast, the scaffold without 2D Ti_3C_2 hardly functioned. Besides, the TBGS show much higher potency in promoting the expression of the osteogenic genes including COL1, RUNX2, OPN, and OCN of hBMSCs in vitro as well as promoting the formation of calcified tissues in the defect in vivo[89]. In another study led by Yang et al., a similarly favorable therapeutic effect on treating malignant bone tumors and bone regeneration was achieved through a 2D Nb_2C MXene incorporated 3D-printing BG scaffolds (Fig. 11)[148].

From what we reviewed above, it is obvious that it is of high efficiency to apply 2D materials in phototherapy for bone tumors treatment and the subsequent bone regeneration. However, researches on the application of 2D materials in bone tumors therapy are at the initial period and most of them concentrated on the application of 2D materials in PTT for osteosarcoma treatment. Most studies had demonstrated that 2D materials could function in various tumors in different ways such as act as PTAs, PS as well as carriers for traditional PTAs and PS. Therefore, it is reasonable to believe that the application of 2D materials in PDT or delivery of drugs for various bone tumors would also be feasible and effective, which would also be conducive to broaden the application of 2D materials in bone tumors therapy.

4.5. Application in cartilage regeneration for osteoarthritis Treatment/ osteochondral repair

Osteoarthritis (OA), the most common disease in joint, is highly associated with age and trauma. The disease is complicated and majorly characterized by cartilage damage, eventually leading to the disability of the joint[251,252]. The hyaline cartilage is a kind of cartilage with the highest content in the body with capabilities of withstanding the repetitive low-friction and providing the high-load activities, which plays a vital role in function realization of the joint[253]. However, damaged cartilage easily results from sports injuries, accident traumas, or degeneration with aging, etc., which commonly lead to pain, joint deformity, and knee functional disability[254–256]. Because of the scarcity of vascularity and poor proliferation of chondrocytes in mature cartilage, cartilage defects cannot be repaired by themselves[257,258]. Thus, cartilage regeneration is critical for restoring the capability of joints[259]. Nowadays, there are some common treatments for cartilage injuries, for instance, systemic administration[260] or intra-articular injection of drugs favorable for cartilage regeneration[261], operative treatments such as abrasion arthroplasty[262], and so on[257]. However, both these methods are unsatisfactory. Firstly, because of the highly negatively charged microenvironment of cartilage tissue caused by a large number of proteoglycans contained in the extracellular matrix (ECM) of chondrocytes, drugs with intra-articular injection are difficult to penetrate the cartilage[263,264]. Meanwhile, due to the rapid clearance of drugs by the vasculature or

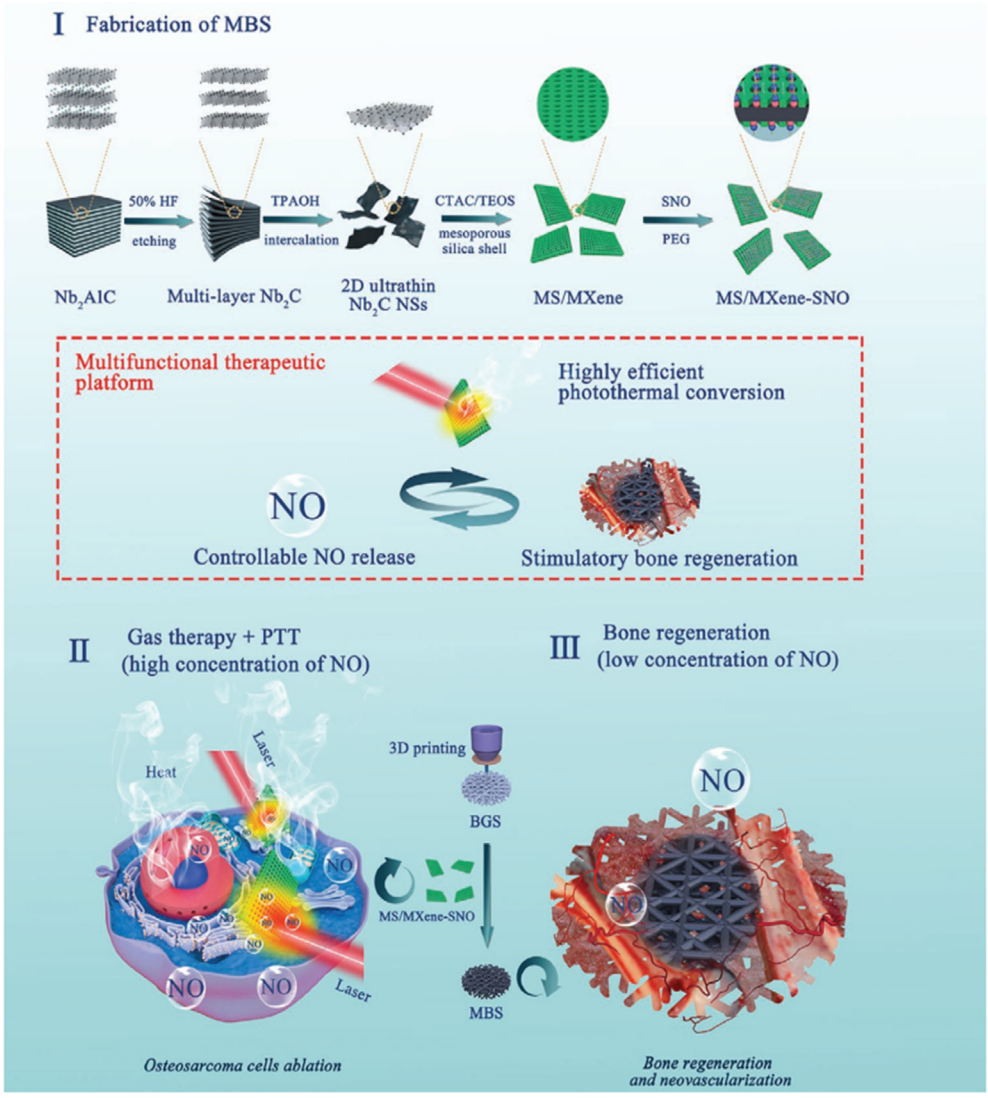

Fig. 11. Preparation progress of TBGS and its application in osteosarcoma treatment and subsequent bone regeneration. Reprinted with permission from Engineering 2D Mesoporous Silica@MXene-Integrated 3D-Printing Scaffolds for Combinatory Osteosarcoma Therapy and NO-Augmented Bone Regeneration [148].

lymphatics in the synovium, drugs administrated intra-articularly merely have a very short retention time, severely limiting the therapeutic effects[265–269]. Then, side effect resulted from systemic administration is still a worrying problem. Last, as for the operative treatments, the healthy cartilage might be damaged and the wound infection might be caused during surgical procedures are still troublesomes[257]. Cartilage regeneration engineering is currently viewed as a promising means for cartilage injury repair [270], functioning by combining the primary chondrocytes, stem cells, or injecting drugs favorable for growth and development of chondrocytes with suitable scaffolds to promote the remodeling of cartilage tissue[257].

Due to the versatility of 2D materials, the application of 2D materials for cartilage regeneration has attracted wide attention from researchers[255]. There are different ways for taking advantage of 2D materials in cartilage regeneration. Firstly, as we stated above, how to realize a continuous drug-releasing to obtain a longer retention time in cartilage is one of the key factors influencing the therapeutic effect of drugs. Michael Morgen and colleagues fabricated cationic polymeric nanoparticles for the delivery of drugs into cartilage. Wenzhen Pan et al. designed a novel therapeutic system that combining platelet-rich plasma (PRP), black phosphorus nanosheets (BPNs), and chitosan thermoresponsive hydrogel. In this smart system, conversion of NIR light to topical heat was induced by the BPNs, which consequently degraded the hydrogel and eventually released the PRP into the articular cavity (Fig. 12). They found that this system significantly increased the retention time of drugs in the articular cavity and improved the pathogenic condition of mice with rheumatoid arthritis[271]. It was reported that shapes of multiphasic systems could be affected by 2D nanoparticles (NPs), leading to the potential application in controlled molecular diffusion. Based on that, and inspired by a biological phenomenon that membrane proteins of cells functioned as ion channels for controlled substances such as nutrients into and out of cells upon response to physiological cues such as specific ligands, Luo et al. fabricated a pH-responsive molecular controlled release system (SJPs) by combing the 2D kaolinite NPs and negatively charged cationic polymer with poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) as well as hydrophobic poly(lauryl methacrylate) (PLMA). In this smart system, 2D kaolinite NPs were intramolecularly attracted to each other by oppositely charged groups grafted on their surface to achieve a lock state, while the unlock state would be presented because PDMAEMA polymers at low pH value would be fully

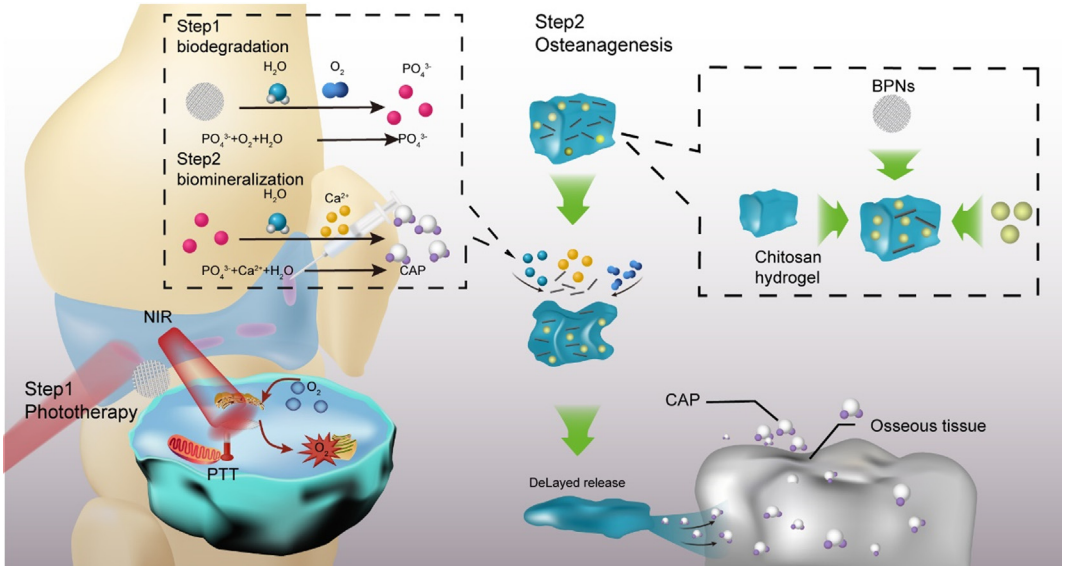

Fig. 12. Schematic illustration of the fabrication of drugs controlled-release smart system. Reprinted with permission from PRP-chitosan thermoresponsive hydrogel combined with black phosphorus nanosheets as an injectable biomaterial for biotherapy and phototherapy treatment of rheumatoid arthritis [271].

protonated and lead to a strong electrostatic repulsion, eventually achieving a pH-responsive molecular controlled release (Fig. 13) [272]. It is worth noting that such an encouraging smart system has great potential to be applied in the treatment of cartilage regeneration or osteoarthritis, for instance, the upregulated osteoarthritis markers such as matrix metalloproteinase 13 (MMP13)[273] or the high density of negative charge in the ECM of chondrocytes[274] are excellent biological cues to achieve the transition between the lock state and unlock state of the smart system for controlled release of drugs. This novel system indicates a new way to apply 2D materials for osteoarthritis treatment.

Besides, the ECM microenvironment of cartilage tissue is compact and full of a negative charge, which hindered drugs with the same negative charge to penetrate the ECM into chondrocytes [275]. Therefore, packaging the drugs with positive 2D materials might be a potential way for delivery of the drugs into cartilage. At an experiment led by Li and colleagues, a nano-vehicle for treatment of chronic obstructive pulmonary disease (COPD) was developed by an assembly of BP and chitosan (CS) with the decoration of hydrophilic polyethylene glycol (PEG), in which positively charged CS nanoparticles are responsible for directing the nano-vehicle to the epithelium with negative charges by electrostatic interaction while the BP functioned in promoting the release of drugs by increasing dissociation of PEGylated CS nanospheres through degradation of itself (Fig. 14). As a result, this nano-vehicle showed a controlled release of loading drugs and rapid penetration ability in vitro experiments. Besides, in vivo experiment, this nano-vehicle presented significantly enhanced therapeutic effect toward COPD mouse models compared with the bare drugs group[276]. Such a strategy employed in this study seems to be feasible in osteoarthritis treatment. On the one hand, as it is known that the ECM of cartilage is compact and is full of negative charge due to the existence of proteoglycan, which makes it difficult for drugs to penetrate the ECM and further enter the chondrocyte. Therefore, fabrication of drug delivery by loading drugs on 2D materials with positive charges might be a feasible way to deliver drugs for chondrocytes of patients with osteoarthritis. On the other hand, we could achieve a controllable release of drugs of osteoarthritis by fabrication of an analogous nanocarrier whose dissociation is also determined by the degradation of BP. Meanwhile, we could also control the degradation of BP by NIR laser to regulate the dissociation of the nanocarrier and the final release of drugs. Such a way of smartly controllable release of drugs could effectively enhance the retention time of drugs in the articular cavity. At last, phosphates, the degradation products of BP, are raw materials involves in osteogenesis. Therefore, it is reasonable to believe that the application of 2D materials in a similar way would also overcome the problem of the penetration of drugs into the cartilage as well as the problem of retention of drugs in the articular cavity, and eventually achieve osteoarthritis treatment.

5. Conclusions

Relative to their bulk parents, ultrathin 2D materials have versatile properties such as excellent high specific surface area, electrical properties, high surface reactivity, and adsorption activity [15,19,72,277–279], making them suitable for various applications in the field of optics, energy storage, sensor, electronic and well as biomedicine. Besides, due to the easy accessibility of functionalization that 2D materials could be modified easily[53], further improving the capacities of 2D materials such as biodegradability [280], and therefore broadening their applications.

Currently, due to their versatile properties, the application of 2D materials in bone diseases therapy has attracted a lot of attention. On the one hand, 2D materials could function by themselves in different aspects because of their intrinsic properties. For example, because of their exceptional optical properties, 2D materials could be employed as PTAs[281] or PS[242] in phototherapy for different kinds of application in bone diseases therapies such as antibacterial and anti-cancer through conversion of light into heat or ROS respectively. Besides, because of the superlubricity in layered 2D materials[176,177], they could also be used as lubricants for joint lubrication. On the other hand, 2D materials could also be employed as additives to improve the performance of the subject. For instance, in BTE, 2D materials are always added to enhanced the physicochemical properties of the bio-scaffolds. Moreover, 2D materials could function as carriers of drugs for cancer therapy [237,282] or BTE due to their large surface area[283,284]. Here, this review first comprehensively summarized applications of 2D materials for various bone diseases including BTE, osteoarthritis, joint lubrication, infection in orthopedic implants as well as bone tumors, which in turn revealed the versatility of 2D materials. As

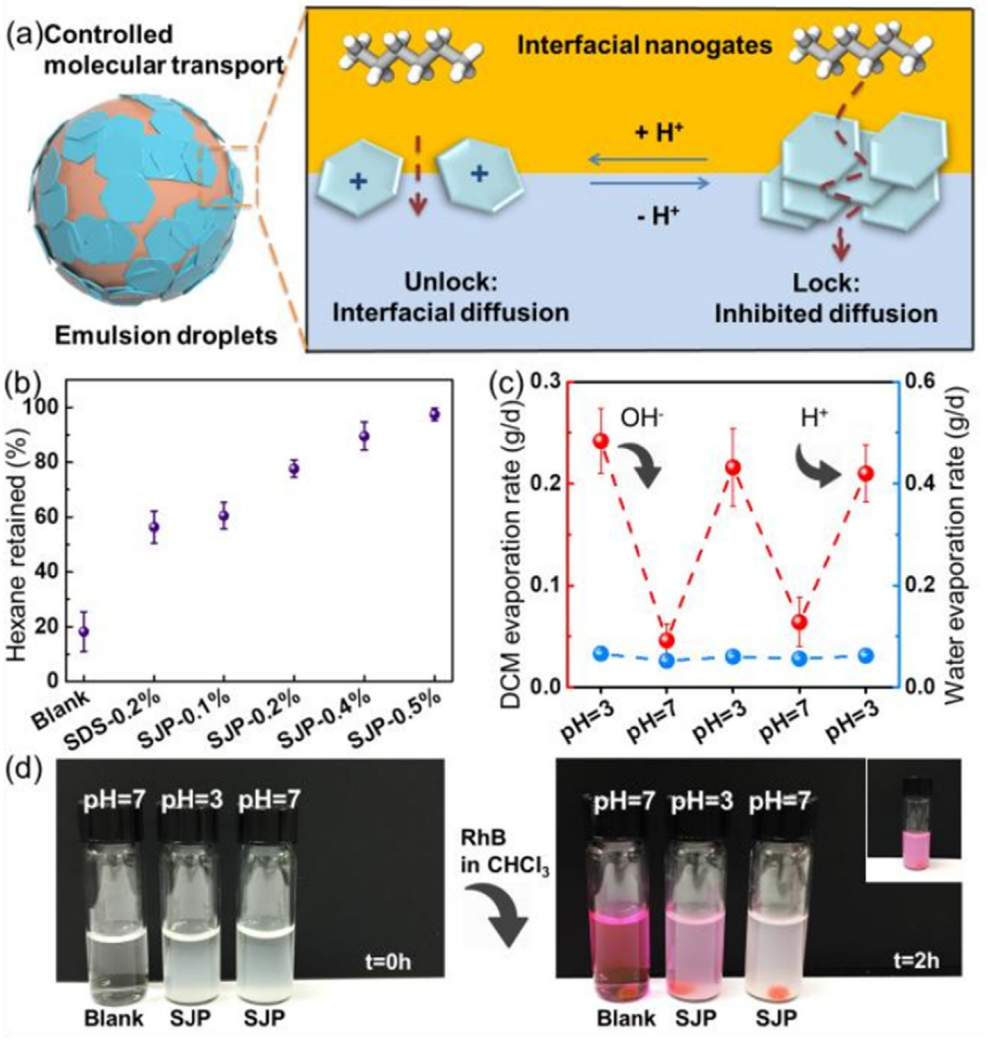

Fig. 13. Examination of performance of SJPs on controlling the molecular release. (a) Schematic illustration of how SJPs functions. (b) Performance of SJPs on controlled release of hexane. (c) Molecular transport with reversible "unlock state" and "lock state" at DCM/water interfaces. (d) Illustration of controlled RhB release from chloroform to water upon treatment with SJPs. In DI water (blank), RhB (red) diffused quickly whereas little diffusion of RhB was observed in SJP solution of 0.5 wt% (pH = 7) after 2 h. The pictures showed, in the aqueous phase, the addition of H^+ led to fast diffusion of RhB. Reprinted with permission from Electrostatic-Driven Dynamic Jamming of 2D Nanoparticles at Interfaces for Controlled Molecular Diffusion [272]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

different 2D materials do well in different aspects, for example, some of them might have the optimal optical property, others might have the largest surface area. Therefore, in the future, the exploration of combining and taking the advantage of different 2D materials to obtain a synergetic effect might be a way to achieve the best therapeutic effect and further broaden the application of 2D materials in biomedicine.

However, there are still some problems that need to be noted and solved. First of all, the toxicity of the 2D materials themselves is still a worrying problem. For example, BP is thought to be of high compatibility because it is unstable in physiological conditions and is easy to degrade into phosphate which is harmless to cells[164]. However, recently, Shao et al. found that 2D BP could target and bind to Polo Like Kinase 1 (PLK1) in centrosome which is crucial for the cell cycle. Upon binding with 2D BP, the activity of PLK1 would be inhibited and then the cell cycle would be blocked in the M phase, finally leading to cell death[285]. This finding revealing that 2D BP may be a potentially effective drug for tumor treatment. Meanwhile, it also reminds us to be cautious when the application of 2D BP in human diseases treatment. On the one hand, it might need more experiments in vitro and in vivo to explore a concentration range with less cytotoxicity before application of 2D BP in treating diseases. Besides, whether there exits similarly intrinsic cytotoxicity of other 2D materials when applied in biomedicines also needs to be further elucidated since some 2D materials were able to interact with biological components and therefore lead to toxicity. Overall, we should be cautious and try our best to reduce the cytotoxicity of 2D materials when employed in bone therapies, which might be achieved via the innovation of functionalization of 2D materials. On the other hand, the finding of intrinsic cytotoxicity of 2D BP hints that 2D materials have similar intrinsic cytotoxicity might be more powerful in the treatment of bone tumor or infection of orthopedic implants, which would make full use of the advantages and effectively avoid the side effects.

Another problem worth noting is that researchers should do their best to reduce the off-target effect when 2D materials function destructively. For example, theoretically, those strategies combining thermoresponsive hydrogel and 2D materials with excellent property of photothermal conversion is a perfect way to achieve control release of drugs. And such strategies are especially suitable for the treatment of osteoarthritis because they

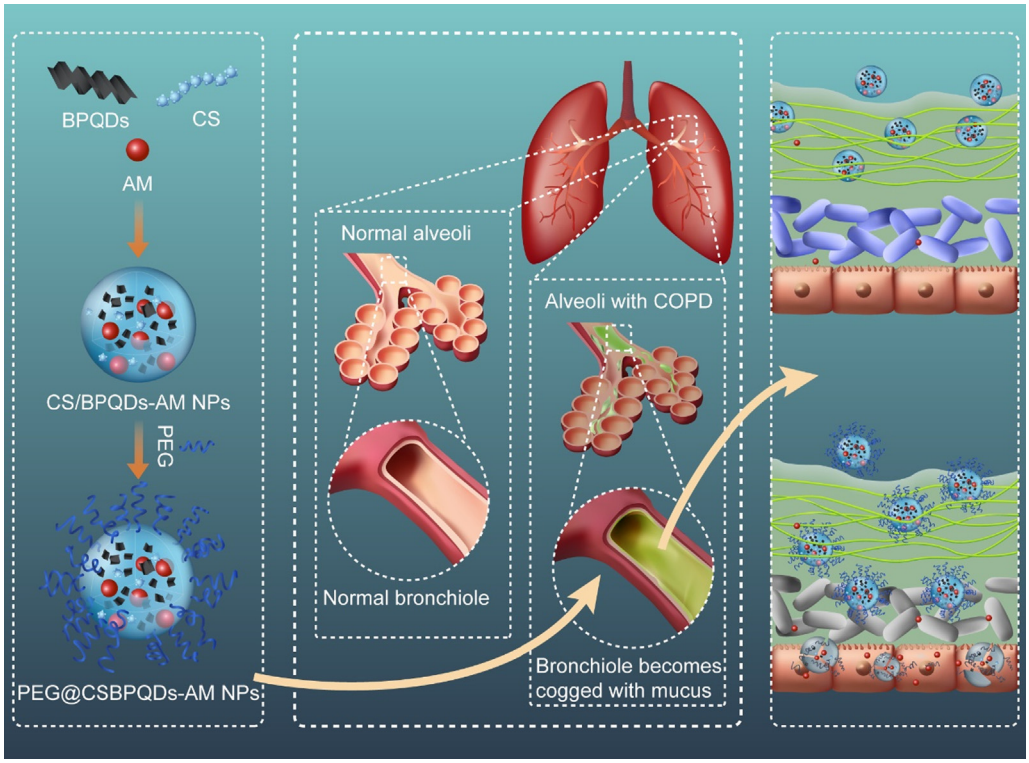

Fig. 14. Schematic illustration of the preparation of PEG@CS/BPQDs-AM NPs as well as their application in COPD. Reprinted with permission from Mediated Drug Release from Nanovehicles by Black Phosphorus Quantum Dots for Efficient Therapy of Chronic Obstructive Pulmonary Disease [276].

could achieve a longer retention time of drugs in the articular cavity. However, a problem may be ignored by researchers who employ such strategies to treat osteoarthritis. Because in such a strategy, another application of 2D materials is the destruction of the inflammatory tissue through the production of high temperature and ROS. Now that the high temperature could damage the inflammatory tissue, it is of the high possibility that the ambient normal tissues such as the cartilage and meniscus might be also destroyed by the high temperature. Therefore, it was necessary for researchers who apply this kind of strategies to afford evidence that other normally adjacent tissues are not affected by the high temperature or ROS derived from the process of photothermal conversion of 2D materials. And functionalization of 2D materials with the ability to target specific tissues or cells such as modifying them with specific antibodies or functionalizing them with polymers to respond to some special environmental clues including temperatures, light, and pH[286] is a potential way to solve this problem. For instance, sodium alginate (SA) is a kind of polymer that could be used to covalently modified 2D materials to achieve intelligently controlled release by responding to the environmental pH. Drugs loaded in the SA-functionalized 2D materials were released lowly in physiological conditions but released fast in the acidulous tumor cell microenvironment[287].

We believe, with the efforts of exploring the advantages of 2D materials suitable for application in bone therapies and improvement in their use safety, the application of 2D materials in bone diseases would be further promoted and the disease treatments would be further benefited too.

Declaration of Competing Interest

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

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References

[1] E.P. Gray, C.L. Browning, M. Wang, K.D. Gion, E.Y. Chao, K.J. Koski, A.B. Kane, R. H. Hurt, Biodissolution and Cellular Response to MoO3 Nanoribbons and a New Framework for Early Hazard Screening for 2D Materials, Environ Sci Nano 5 (2018) 2545–2559.
[2] L. Cheng, X. Wang, F. Gong, T. Liu, Z. Liu, 2D Nanomaterials for Cancer Theranostic Applications, Adv Mater 32 (2020) e1902333.
[3] C.E. Machnicki, F. Fu, L. Jing, P.Y. Chen, I.Y. Wong, Mechanochemical engineering of 2D materials for multiscale biointerfaces, J Mater Chem B 7 (2019) 6293–6309.
[4] X. Cai, Y. Luo, B. Liu, H.M. Cheng, Preparation of 2D material dispersions and their applications, Chem Soc Rev 47 (2018) 6224–6266.
[5] T. Tan, X. Jiang, C. Wang, B. Yao, H. Zhang, 2D Material Optoelectronics for Information Functional Device Applications: Status and Challenges, Adv Sci (Weinh) 7 (2020) 2000058.
[6] K.S. Novoselov, A.K. Geim, S.V. Morozov, D. Jiang, Y. Zhang, S.V. Dubonos, I.V. Grigorieva, A.A. Firsov, Electric field effect in atomically thin carbon films, Science 306 (2004) 666–669.
[7] D. Li, M.B. Muller, S. Gilje, R.B. Kaner, G.G. Wallace, Processable aqueous dispersions of graphene nanosheets, Nat Nanotechnol 3 (2008) 101–105.
[8] C.Y. Zhi, Y. Bando, T. Terao, C.C. Tang, H. Kuwahara, D. Golberg, Chemically activated boron nitride nanotubes, Chem Asian J 4 (2009) 1536–1540.
[9] Z. Zhang, S. Yao, X. Hu, F. Okejiri, K. He, P. Liu, Z. Tian, V.P. Dravid, J. Fu, X. Zhu, S. Dai, Sacrificial Synthesis of Supported Ru Single Atoms and Clusters on N-doped Carbon Derived from Covalent Triazine Frameworks: A Charge Modulation Approach, Adv Sci (Weinh) 8 (2021) 2001493.
[10] L. Wu, Z. Xie, L. Lu, J. Zhao, Y. Wang, X. Jiang, Y. Ge, F. Zhang, S. Lu, Z. Guo, J. Liu, Y. Xiang, S. Xu, J. Li, D. Fan, H. Zhang, Few-Layer Tin Sulfide: A Promising Black-Phosphorus-Analogue 2D Material with Exceptionally Large Nonlinear Optical Response, High Stability, and Applications in All-Optical Switching and Wavelength Conversion 6 (2018) 1700985.

[11] Z. Xie, X. Meng, X. Li, W. Liang, W. Huang, K. Chen, J. Chen, C. Xing, M. Qiu, B. Zhang, G. Nie, N. Xie, X. Yan, H. Zhang, Two-Dimensional Borophene: Properties, Fabrication, and Promising Applications, Research (Wash D C) 2020 (2020) 2624617.
[12] Z. Xie, F. Zhang, Z. Liang, T. Fan, Z. Li, X. Jiang, H. Chen, J. Li, H. Zhang, Revealing of the ultrafast third-order nonlinear optical response and enabled photonic application in two-dimensional tin sulfide, Photon. Res. 7 (2019) 494–502.
[13] C. Xing, W. Huang, Z. Xie, J. Zhao, D. Ma, T. Fan, W. Liang, Y. Ge, B. Dong, J. Li, H. Zhang, Ultrasmall Bismuth Quantum Dots: Facile Liquid-Phase Exfoliation, Characterization, and Application in High-Performance UV–Vis Photodetector, ACS Photonics 5 (2018) 621–629.
[14] C. Xing, Z. Xie, Z. Liang, W. Liang, T. Fan, J.S. Ponraj, S.C. Dhanabalan, D. Fan, H. Zhang, 2D Nonlayered Selenium Nanosheets: Facile Synthesis, Photoluminescence, and Ultrafast Photonics 5 (2017) 1700884.
[15] B. Zhang, T. Fan, N. Xie, G. Nie, H. Zhang, Versatile Applications of Metal Single-Atom @ 2D Material Nanoplatforms, Adv Sci (Weinh) 6 (2019) 1901787.
[16] Z. Xie, Y.-P. Peng, L. Yu, C. Xing, M. Qiu, J. Hu, H. Zhang, Solar-Inspired Water Purification Based on Emerging 2D Materials, Status and Challenges 4 (2020) 1900400.
[17] H. Cui, K. Zheng, Z. Xie, J. Yu, X. Zhu, H. Ren, Z. Wang, F. Zhang, X. Li, L.Q. Tao, H. Zhang, X. Chen, Tellurene Nanoflake-Based NO2 Sensors with Superior Sensitivity and a Sub-Parts-per-Billion Detection Limit, ACS Appl Mater Interfaces 12 (2020) 47704–47713.
[18] W. Huang, M. Wang, L. Hu, C. Wang, Z. Xie, H. Zhang, Recent Advances in Semiconducting Monoelemental Selenium Nanostructures for Device Applications 30 (2020) 2003301.
[19] S. Meng, T. Kong, W. Ma, H. Wang, H. Zhang, 2D Crystal-Based Fibers: Status and Challenges, Small 15 (2019) e1902691.
[20] H. Wang, L. Chai, Z. Xie, H. Zhang, Recent Advance of Tellurium for Biomedical Applications, Chemical Research in Chinese Universities 36 (2020) 551–559.
[21] Y. Zhu, Y. Liu, Z. Xie, T. He, L. Su, F. Guo, G. Arkin, X. Lai, J. Xu, H. Zhang, Magnetic black phosphorus microbubbles for targeted tumor theranostics %J Nanophotonics, (2021).
[22] J.R. Choi, K.W. Yong, J.Y. Choi, A. Nilghaz, Y. Lin, J. Xu, X. Lu, Black Phosphorus and its Biomedical Applications, Theranostics 8 (2018) 1005–1026.
[23] A. Pandey, A.N. Nikam, G. Fernandes, S. Kulkarni, B.S. Padya, R. Prassl, S. Das, A. Joseph, P.K. Deshmukh, P.O. Patil, S. Mutalik, Black Phosphorus as Multifaceted Advanced Material Nanoplatforms for Potential Biomedical Applications, Nanomaterials (Basel) 11 (2020).
[24] A. Szuplewska, D. Kulpinska, A. Dybko, M. Chudy, A.M. Jastrzebska, A. Olszyna, Z. Brzozka, Future Applications of MXenes in Biotechnology, Nanomedicine, and Sensors, Trends Biotechnol 38 (2020) 264–279.
[25] S. Iravani, R.S. Varma, MXenes for Cancer Therapy and Diagnosis: Recent Advances and Current Challenges, ACS Biomater Sci Eng, (2021).
[26] W. Huang, Z. Xie, T. Fan, J. Li, Y. Wang, L. Wu, D. Ma, Z. Li, Y. Ge, Z.N. Huang, X. Dai, Y. Xiang, J. Li, X. Zhu, H. Zhang, Black-phosphorus-analogue tin monosulfide: an emerging optoelectronic two-dimensional material for high-performance photodetection with improved stability under ambient/harsh conditions, Journal of Materials Chemistry C 6 (2018) 9582–9593.
[27] Z. Xie, S. Chen, Y. Duo, Y. Zhu, T. Fan, Q. Zou, M. Qu, Z. Lin, J. Zhao, Y. Li, L. Liu, S. Bao, H. Chen, D. Fan, H. Zhang, Biocompatible Two-Dimensional Titanium Nanosheets for Multimodal Imaging-Guided Cancer Theranostics, ACS Appl Mater Interfaces 11 (2019) 22129–22140.
[28] H. Zhao, Y. Yan, X. Song, Z. Ma, T. Tian, Y. Jiang, X. Li, C. Xia, J. Li, Few-layer In4/3P2Se6 nanoflakes for high detectivity photodetectors, Nanoscale 13 (2021) 3757–3766.
[29] A.T.E. Vilian, B. Dinesh, S.M. Kang, U.M. Krishnan, Y.S. Huh, Y.K. Han, Recent advances in molybdenum disulfide-based electrode materials for electroanalytical applications, Mikrochim Acta 186 (2019) 203.
[30] Y. Zhang, Y. Zhou, Z. Li, H. Chen, L. Zhang, J. Fan, Computational investigation of geometrical effects in 2D boron nitride nanopores for DNA detection, Nanoscale 12 (2020) 10026–10034.
[31] L. Ma, X. Song, Y. Yu, Y. Chen, Two-Dimensional Silicene/Silicon Nanosheets: An Emerging Silicon-Composed Nanostructure in Biomedicine, Adv Mater (2021) e2008226.
[32] C. Martin, K. Kostarelos, M. Prato, A. Bianco, Biocompatibility and biodegradability of 2D materials: graphene and beyond, Chem Commun (Camb) 55 (2019) 5540–5546.
[33] W. Zheng, B. Zheng, C. Yan, Y. Liu, X. Sun, Z. Qi, T. Yang, Y. Jiang, W. Huang, P. Fan, F. Jiang, W. Ji, X. Wang, A. Pan, Direct Vapor Growth of 2D Vertical Heterostructures with Tunable Band Alignments and Interfacial Charge Transfer Behaviors, Adv Sci (Weinh) 6 (2019) 1802204.
[34] N. Dubey, R. Bentini, I. Islam, T. Cao, A.H. Castro Neto, V. Rosa, Graphene, A Versatile Carbon-Based Material for Bone Tissue Engineering, Stem Cells Int (2015, 2015,) 804213.
[35] S.P. Adithya, D.S. Sidharthan, R. Abhinandan, K. Balagangadharan, N. Selvamurugan, Nanosheets-incorporated bio-composites containing natural and synthetic polymers/ceramics for bone tissue engineering, Int J Biol Macromol 164 (2020) 1960–1972.
[36] Y. Zheng, X. Hong, J. Wang, L. Feng, T. Fan, R. Guo, H. Zhang, 2D Nanomaterials for Tissue Engineering and Regenerative Nanomedicines: Recent Advances and Future Challenges, Adv Healthc Mater 10 (2021) e2001743.
[37] H. Xie, T. Cao, F.J. Rodriguez-Lozano, E.K. Luong-Van, V. Rosa, Graphene for the development of the next-generation of biocomposites for dental and medical applications, Dent Mater 33 (2017) 765–774.
[38] M.G. Raucci, I. Fasolino, M. Caporali, M. Serrano-Ruiz, A. Soriente, M. Peruzzini, L. Ambrosio, Exfoliated Black Phosphorus Promotes in Vitro Bone Regeneration and Suppresses Osteosarcoma Progression through Cancer-Related Inflammation Inhibition, ACS Appl Mater Interfaces 11 (2019) 9333–9342.
[39] S. Wang, C. Duan, W. Yang, X. Gao, J. Shi, J. Kang, Y. Deng, X.L. Shi, Z.G. Chen, Two-dimensional nanocoating-enabled orthopedic implants for bimodal therapeutic applications, Nanoscale 12 (2020) 11936–11946.
[40] S. Wang, X. Yang, L. Zhou, J. Li, H. Chen, 2D nanostructures beyond graphene: preparation, biocompatibility and biodegradation behaviors, J Mater Chem B 8 (2020) 2974–2989.
[41] C. Lee, X. Wei, J.W. Kysar, J. Hone, Measurement of the elastic properties and intrinsic strength of monolayer graphene, Science 321 (2008) 385–388.
[42] , Graphene and its derivatives: Opportunities and challenges in dentistry 102 (2019) 171–185.
[43] R.R. Nair, W. Ren, R. Jalil, I. Riaz, V.G. Kravets, L. Britnell, P. Blake, F. Schedin, A. S. Mayorov, S. Yuan, M.I. Katsnelson, H.M. Cheng, W. Strupinski, L.G. Bulusheva, A.V. Okotrub, I.V. Grigorieva, A.N. Grigorenko, K.S. Novoselov, A. K. Geim, Fluorographene: a two-dimensional counterpart of Teflon, Small 6 (2010) 2877–2884.
[44] A. Sinitskii, A. Dimiev, D.A. Corley, A.A. Fursina, D.V. Kosynkin, J.M. Tour, Kinetics of diazonium functionalization of chemically converted graphene nanoribbons, ACS Nano 4 (2010) 1949–1954.
[45] V. Georgakilas, J.N. Tiwari, K.C. Kemp, J.A. Perman, A.B. Bourlinos, K.S. Kim, R. Zboril, Noncovalent Functionalization of Graphene and Graphene Oxide for Energy Materials, Biosensing, Catalytic, and Biomedical Applications, Chem Rev 116 (2016) 5464–5519.
[46] Y. Qu, F. He, C. Yu, X. Liang, D. Liang, L. Ma, Q. Zhang, J. Lv, J. Wu, Advances on graphene-based nanomaterials for biomedical applications, Mater Sci Eng C Mater Biol Appl 90 (2018) 764–780.
[47] K. Yang, S. Zhang, G. Zhang, X. Sun, S.T. Lee, Z. Liu, Graphene in mice: ultrahigh in vivo tumor uptake and efficient photothermal therapy, Nano Lett 10 (2010) 3318–3323.
[48] Y. He, A. Del Valle, Y. Qian, Y.F. Huang, Near infrared light-mediated enhancement of reactive oxygen species generation through electron transfer from graphene oxide to iron hydroxide/oxide, Nanoscale 9 (2017) 1559–1566.
[49] B. Luan, T. Huynh, L. Zhao, R. Zhou, Potential toxicity of graphene to cell functions via disrupting protein-protein interactions, ACS Nano 9 (2015) 663–669.
[50] S. Wu, K.S. Hui, K.N. Hui, 2D Black Phosphorus: from Preparation to Applications for Electrochemical Energy Storage, Adv Sci (Weinh) 5 (2018) 1700491.
[51] Y. Xu, Z. Shi, X. Shi, K. Zhang, H. Zhang, Recent progress in black phosphorus and black-phosphorus-analogue materials: properties, synthesis and applications, Nanoscale 11 (2019) 14491–14527.
[52] L. Li, Y. Yu, G. Ye, Q. Ge, X. Ou, H. Wu, D. Feng, X. Chen, Y.J.N.n. Zhang, Black phosphorus field-effect transistors, 9 5 (2014) 372-377.
[53] S. Thurakkal, X. Zhang, Recent Advances in Chemical Functionalization of 2D Black Phosphorous Nanosheets, Adv Sci (Weinh) 7 (2020) 1902359.
[54] X. Meng, X. Wang, Z. Cheng, N. Tian, M.C. Lang, W. Yan, D. Liu, Y. Zhang, P. Wang, Photoluminescence Lifetime of Black Phosphorus Nanoparticles and Their Applications in Live Cell Imaging, ACS Appl Mater Interfaces 10 (2018) 31136–31145.
[55] R. Gui, H. Jin, Z. Wang, J. Li, Black phosphorus quantum dots: synthesis, properties, functionalized modification and applications, Chem Soc Rev 47 (2018) 6795–6823.
[56] W. Lei, G. Liu, J. Zhang, M. Liu, Black phosphorus nanostructures: recent advances in hybridization, doping and functionalization, Chem Soc Rev 46 (2017) 3492–3509.
[57] A. Castellanos-Gomez, Black Phosphorus: Narrow Gap, Wide Applications, J Phys Chem Lett 6 (2015) 4280–4291.
[58] H. Qiao, Z. Huang, X. Ren, S. Liu, Y. Zhang, X. Qi, H. Zhang, Self-Powered Photodetectors Based on 2D Materials 8 (2020) 1900765.
[59] V.V. Kulish, O.I. Malyi, C. Persson, P. Wu, Phosphorene as an anode material for Na-ion batteries: a first-principles study, Phys Chem Chem Phys 17 (2015) 13921–13928.
[60] V. Eswaraiah, Q. Zeng, Y. Long, Z. Liu, Black Phosphorus Nanosheets: Synthesis, Characterization and Applications, Small 12 (2016) 3480–3502.
[61] H. Liu, Y. Du, Y. Deng, P.D. Ye, Semiconducting black phosphorus: synthesis, transport properties and electronic applications, Chem Soc Rev 44 (2015) 2732–2743.
[62] Y. Qing, R. Li, S. Li, Y. Li, X. Wang, Y. Qin, Advanced Black Phosphorus Nanomaterials for Bone Regeneration, Int J Nanomedicine 15 (2020) 2045–2058.
[63] D. An, J. Fu, Z. Xie, C. Xing, B. Zhang, B. Wang, M. Qiu, Progress in the therapeutic applications of polymer-decorated black phosphorus and black phosphorus analog nanomaterials in biomedicine, J Mater Chem B 8 (2020) 7076–7120.
[64] L. Peng, N. Abbasi, Y. Xiao, Z. Xie, Black Phosphorus: Degradation Mechanism, Passivation Method, and Application for In Situ Tissue Regeneration 7 (2020) 2001538.

[65] H. Wang, X. Yang, W. Shao, S. Chen, J. Xie, X. Zhang, J. Wang, Y. Xie, Ultrathin Black Phosphorus Nanosheets for Efficient Singlet Oxygen Generation, J Am Chem Soc 137 (2015) 11376–11382.
[66] L. Kou, T. Frauenheim, C. Chen, Phosphorene as a Superior Gas Sensor: Selective Adsorption and Distinct I-V Response, J Phys Chem Lett 5 (2014) 2675–2681.
[67] Y.T. Yew, Z. Sofer, C.C. Mayorga-Martinez, M. Pumera, Black phosphorus nanoparticles as a novel fluorescent sensing platform for nucleic acid detection, Materials Chemistry Frontiers 1 (2017) 1130–1136.
[68] S. Anju, J. Ashtami, P.V. Mohanan, Black phosphorus, a prospective graphene substitute for biomedical applications, Mater Sci Eng C Mater Biol Appl 97 (2019) 978–993.
[69] S. Mukherjee, L. Kavalsky, C.V. Singh, Ultrahigh Storage and Fast Diffusion of Na and K in Blue Phosphorene Anodes, ACS Appl Mater Interfaces 10 (2018) 8630–8639.
[70] C. Xing, S. Chen, M. Qiu, X. Liang, Q. Liu, Q. Zou, Z. Li, Z. Xie, D. Wang, B. Dong, L. Liu, D. Fan, H. Zhang, Conceptually Novel Black Phosphorus/Cellulose Hydrogels as Promising Photothermal Agents for Effective Cancer Therapy, Adv Healthc Mater 7 (2018) e1701510.
[71] X. Ling, H. Wang, S. Huang, F. Xia, M.S. Dresselhaus, The renaissance of black phosphorus, Proc Natl Acad Sci U S A 112 (2015) 4523–4530.
[72] H. Lin, Y. Chen, J. Shi, Insights into 2D MXenes for Versatile Biomedical Applications: Current Advances and Challenges Ahead, Adv Sci (Weinh) 5 (2018) 1800518.
[73] X. Li, C. Wang, Y. Cao, G. Wang, Functional MXene Materials: Progress of Their Applications, Chem Asian J 13 (2018) 2742–2757.
[74] W. Huang, L. Hu, Y. Tang, Z. Xie, H. Zhang, Recent Advances in Functional 2D MXene-Based Nanostructures for Next-Generation Devices 30 (2020) 2005223.
[75] D. Magne, V. Mauchamp, S. Celerier, P. Chartier, T. Cabioc'h, Site-projected electronic structure of two-dimensional Ti3C2 MXene: the role of the surface functionalization groups, Phys Chem Chem Phys 18 (2016) 30946–30953.
[76] J. Xuan, Z. Wang, Y. Chen, D. Liang, L. Cheng, X. Yang, Z. Liu, R. Ma, T. Sasaki, F. Geng, Organic-Base-Driven Intercalation and Delamination for the Production of Functionalized Titanium Carbide Nanosheets with Superior Photothermal Therapeutic Performance, Angew Chem Int Ed Engl 55 (2016) 14569–14574.
[77] H.E. Karahan, K. Goh, C.J. Zhang, E. Yang, C. Yildirim, C.Y. Chuah, M.G. Ahunbay, J. Lee, S.B. Tantekin-Ersolmaz, Y. Chen, T.H. Bae, MXene Materials for Designing Advanced Separation Membranes, Adv Mater 32 (2020) e1906697.
[78] B. Anasori, Y. Xie, M. Beidaghi, J. Lu, B.C. Hosler, L. Hultman, P.R. Kent, Y. Gogotsi, M.W. Barsoum, Two-Dimensional, Ordered, Double Transition Metals Carbides, MXenes, ACS Nano 9 (2015) 9507–9516.
[79] M. Jeon, B.M. Jun, S. Kim, M. Jang, C.M. Park, S.A. Snyder, Y. Yoon, A review on MXene-based nanomaterials as adsorbents in aqueous solution, Chemosphere 261 (2020) 127781.
[80] R. Li, L. Zhang, L. Shi, P. Wang, MXene Ti3C2: An Effective 2D Light-to-Heat Conversion Material, ACS Nano 11 (2017) 3752–3759.
[81] C. Dai, Y. Chen, X. Jing, L. Xiang, D. Yang, H. Lin, Z. Liu, X. Han, R.J.A.n. Wu, Two-Dimensional Tantalum Carbide (MXenes) Composite Nanosheets for Multiple Imaging-Guided Photothermal Tumor Ablation, 11 12 (2017) 12696-12712.
[82] A. Zhang, R. Liu, J. Tian, W. Huang, J. Liu, MXene-Based Nanocomposites for Energy Conversion and Storage Applications, Chemistry 26 (2020) 6342–6359.
[83] J. Nan, X. Guo, J. Xiao, X. Li, W. Chen, W. Wu, H. Liu, Y. Wang, M. Wu, G. Wang, Nanoengineering of 2D MXene-Based Materials for Energy Storage Applications, Small 17 (2021) e1902085.
[84] X. Li, S. Fu, S. Chen, A.S. Uzun, C.E. Levitt, W. Shuck, Y. Han, Gogotsi, Hydrophobic and Stable MXene-Polymer Pressure Sensors for Wearable Electronics, ACS Appl Mater Interfaces 12 (2020) 15362–15369.
[85] Y. Zhou, X. Zhuge, P. An, S. Du, First-principles investigations on MXene-blue phosphorene and MXene-MoS2 transistors, Nanotechnology 31 (2020) 395203.
[86] M. Soleymaniha, M.A. Shahbazi, A.R. Rafieerad, A. Maleki, A. Amiri, Promoting Role of MXene Nanosheets in Biomedical Sciences: Therapeutic and Biosensing Innovations, Adv Healthc Mater 8 (2019) e1801137.
[87] K. Chen, N. Qiu, Q. Deng, M.H. Kang, H. Yang, J.U. Baek, Y.H. Koh, S. Du, Q. Huang, H.E. Kim, Cytocompatibility of Ti3AlC2, Ti3SiC2, and Ti2AlN, Vitro Tests and First-Principles Calculations, ACS Biomater Sci Eng 3 (2017) 2293–2301.
[88] H. Lin, S. Gao, C. Dai, Y. Chen, J. Shi, A Two-Dimensional Biodegradable Niobium Carbide (MXene) for Photothermal Tumor Eradication in NIR-I and NIR-II Biowindows, J Am Chem Soc 139 (2017) 16235–16247.
[89] S. Pan, J. Yin, L. Yu, C. Zhang, Y. Zhu, Y. Gao, Y. Chen, 2D MXene-Integrated 3D-Printing Scaffolds for Augmented Osteosarcoma Phototherapy and Accelerated Tissue Reconstruction, Adv Sci (Weinh) 7 (2020) 1901511.
[90] E.A. Hussein, M.M. Zagho, G.K. Nasrallah, A.A. Elzatahry, Recent advances in functional nanostructures as cancer photothermal therapy, Int J Nanomedicine 13 (2018) 2897–2906.
[91] G. Basara, M. Saeidi-Javash, X. Ren, G. Bahcecioglu, B.C. Wyatt, B. Anasori, Y. Zhang, P. Zorlutuna, Electrically conductive 3D printed Ti3C2Tx MXene-PEG composite constructs for cardiac tissue engineering, Acta Biomater (2020).
[92] Y. Liu, Q. Yu, J. Chang, C. Wu, Nanobiomaterials: from 0D to 3D for tumor therapy and tissue regeneration, Nanoscale 11 (2019) 13678–13708.
[93] H.L. Chia, C.C. Mayorga-Martinez, N. Antonatos, Z. Sofer, J.J. Gonzalez-Julian, R.D. Webster, M. Pumera, MXene Titanium Carbide-based Biosensor: Strong Dependence of Exfoliation Method on Performance, Anal Chem 92 (2020) 2452–2459.
[94] Z. Liu, M. Zhao, H. Lin, C. Dai, C. Ren, S. Zhang, W. Peng, Y. Chen, 2D magnetic titanium carbide MXene for cancer theranostics, J Mater Chem B 6 (2018) 3541–3548.
[95] K. Kalantar-zadeh, J.Z. Ou, T. Daeneke, M.S. Strano, M. Pumera, S.L. Gras, Two-Dimensional Transition Metal Dichalcogenides in Biosystems 25 (2015) 5086–5099.
[96] J.N. Coleman, M. Lotya, A. O'Neill, S.D. Bergin, P.J. King, U. Khan, K. Young, A. Gaucher, S. De, R.J. Smith, I.V. Shvets, S.K. Arora, G. Stanton, H.Y. Kim, K. Lee, G.T. Kim, G.S. Duesberg, T. Hallam, J.J. Boland, J.J. Wang, J.F. Donegan, J.C. Grunlan, G. Moriarty, A. Shmeliov, R.J. Nicholls, J.M. Perkins, E.M. Grieveson, K. Theuwissen, D.W. McComb, P.D. Nellist, V. Nicolosi, Two-dimensional nanosheets produced by liquid exfoliation of layered materials, Science 331 (2011) 568–571.
[97] S. Meng, Y. Zhang, H. Wang, L. Wang, T. Kong, H. Zhang, S. Meng, Recent advances on TMDCs for medical diagnosis, Biomaterials 269 (2021) 120471.
[98] H. Li, Y. Tan, P. Liu, C. Guo, M. Luo, J. Han, T. Lin, F. Huang, M. Chen, Atomic-Sized Pores Enhanced Electrocatalysis of TaS2 Nanosheets for Hydrogen Evolution, Adv Mater 28 (2016) 8945–8949.
[99] Y. Sun, S. Gao, F. Lei, Y. Xie, Atomically-thin two-dimensional sheets for understanding active sites in catalysis, Chem Soc Rev 44 (2015) 623–636.
[100] M. Acerce, D. Voiry, M. Chhowalla, Metallic 1T phase MoS2 nanosheets as supercapacitor electrode materials, Nat Nanotechnol 10 (2015) 313–318.
[101] T. Stephenson, Z. Li, B. Olsen, D.J.E. Mitlin, E. Science, Lithium ion battery applications of molybdenum disulfide (MoS2) nanocomposites, 7 (2014) 209-231.
[102] M.H. Shin, S.M. Baek, A.V. Polyakov, I.P. Semenova, R.Z. Valiev, W.B. Hwang, S. K. Hahn, H.S. Kim, Molybdenum Disulfide Surface Modification of Ultrafine-Grained Titanium for Enhanced Cellular Growth and Antibacterial Effect, Sci Rep 8 (2018) 9907.
[103] T. Shao, J. Wen, Q. Zhang, Y. Zhou, L. Liu, L. Yuwen, Y. Tian, Y. Zhang, W. Tian, Y. Su, Z. Teng, G. Lu, J. Xu, NIR photoresponsive drug delivery and synergistic chemo-photothermal therapy by monodispersed-MoS2-nanosheets wrapped periodic mesoporous organosilicas, J Mater Chem B 4 (2016) 7708–7717.
[104] S. Wang, Y. Chen, X. Li, W. Gao, L. Zhang, J. Liu, Y. Zheng, H. Chen, J. Shi, Injectable 2D MoS2 -Integrated Drug Delivering Implant for Highly Efficient NIR-Triggered Synergistic Tumor Hyperthermia, Adv Mater 27 (2015) 7117–7122.
[105] M. Saeed, Y. Alshammari, S.A. Majeed, E. Al-Nasrallah, Chemical Vapour Deposition of Graphene-Synthesis, Characterisation, and Applications: A Review, Molecules 25 (2020).
[106] G. Li, S.H. Huang, Z. Li, Gas-phase dynamics in graphene growth by chemical vapour deposition, Phys Chem Chem Phys 17 (2015) 22832–22836.
[107] J. Kang, V.K. Sangwan, J.D. Wood, M.C. Hersam, Solution-Based Processing of Monodisperse Two-Dimensional Nanomaterials, Acc Chem Res 50 (2017) 943–951.
[108] X. Xiao, H. Wang, P. Urbankowski, Y. Gogotsi, Topochemical synthesis of 2D materials, Chem Soc Rev 47 (2018) 8744–8765.
[109] M. Ghidiu, M. Naguib, C. Shi, O. Mashtalir, L.M. Pan, B. Zhang, J. Yang, Y. Gogotsi, S.J. Billinge, M.W. Barsoum, Synthesis and characterization of two-dimensional Nb4C3 (MXene), Chem Commun (Camb) 50 (2014) 9517–9520.
[110] M. Naguib, O. Mashtalir, J. Carle, V. Presser, J. Lu, L. Hultman, Y. Gogotsi, M.W. Barsoum, Two-dimensional transition metal carbides, ACS Nano 6 (2012) 1322–1331.
[111] T.H. Le, Y. Oh, H. Kim, H. Yoon, Exfoliation of 2D Materials for Energy and Environmental Applications, Chemistry 26 (2020) 6360–6401.
[112] J. Wang, N. Li, Y. Xu, H. Pang, Two-Dimensional MOF and COF Nanosheets: Synthesis and Applications in Electrochemistry, Chemistry 26 (2020) 6402–6422.
[113] X. Zhou, H. Sun, X. Bai, Two-Dimensional Transition Metal Dichalcogenides: Synthesis, Biomedical Applications and Biosafety Evaluation, Front Bioeng, Biotechnol 8 (2020) 236.
[114] O. Erol, I. Uyan, M. Hatip, C. Yilmaz, A.B. Tekinay, M.O. Guler, Recent advances in bioactive 1D and 2D carbon nanomaterials for biomedical applications, Nanomedicine 14 (2018) 2433–2454.
[115] C. Murugan, V. Sharma, R.K. Murugan, G. Malaimegu, A. Sundaramurthy, Two-dimensional cancer theranostic nanomaterials: Synthesis, surface functionalization and applications in photothermal therapy, J Control Release 299 (2019) 1–20.
[116] X. Xu, Z. Zhang, L. Qiu, J. Zhuang, L. Zhang, H. Wang, C. Liao, H. Song, R. Qiao, P. Gao, Z. Hu, L. Liao, Z. Liao, D. Yu, E. Wang, F. Ding, H. Peng, K. Liu, Ultrafast growth of single-crystal graphene assisted by a continuous oxygen supply, Nat Nanotechnol 11 (2016) 930–935.
[117] C. Xu, L. Wang, Z. Liu, L. Chen, J. Guo, N. Kang, X.L. Ma, H.M. Cheng, W. Ren, Large-area high-quality 2D ultrathin Mo2C superconducting crystals, Nat Mater 14 (2015) 1135–1141.
[118] K.R. Paton, E. Varrla, C. Backes, R.J. Smith, U. Khan, A. O'Neill, C. Boland, M. Lotya, O.M. Istrate, P. King, T. Higgins, S. Barwich, P. May, P. Puczkarski, I. Ahmed, M. Moebius, H. Pettersson, E. Long, J. Coelho, S.E. O'Brien, E.K. McGuire, B.M. Sanchez, G.S. Duesberg, N. McEvoy, T.J. Pennycook, C. Downing, A. Crossley, V. Nicolosi, J.N. Coleman, Scalable production of large quantities of defect-free few-layer graphene by shear exfoliation in liquids, Nat Mater 13 (2014) 624–630.

[119] Z. Li, S.L. Wong, Functionalization of 2D transition metal dichalcogenides for biomedical applications, Mater Sci Eng C Mater Biol Appl 70 (2017) 1095–1106.
[120] M.C. Rodriguez Gonzalez, A. Brown, S. Eyley, W. Thielemans, K.S. Mali, S. De Feyter, Self-limiting covalent modification of carbon surfaces: diazonium chemistry with a twist, Nanoscale, 12 (2020) 18782-18789.
[121] N. Zheng, Y. Feng, Y. Zhang, R. Li, C. Bian, L. Bao, S. Du, H. Dong, Y. Shen, W. Feng, Reversible Modification of Nitrogen-Doped Graphene Based on Se-N Dynamic Covalent Bonds for Field-Effect Transistors, ACS Appl Mater Interfaces 11 (2019) 24360–24366.
[122] H. Ghodrati, N. Antonatos, Z. Sofer, Noncovalent Functionalization of Pnictogen Surfaces: From Small Molecules to 2D Heterostructures, Small 15 (2019) e1903495.
[123] J. Ji, J. Wen, Y. Shen, Y. Lv, Y. Chen, S. Liu, H. Ma, Y. Zhang, Simultaneous Noncovalent Modification and Exfoliation of 2D Carbon Nitride for Enhanced Electrochemiluminescent Biosensing, J Am Chem Soc 139 (2017) 11698–11701.
[124] T. Zhou, B. Zhang, P. Wei, Y. Du, H. Zhou, M. Yu, L. Yan, W. Zhang, G. Nie, C. Chen, Y. Tu, T. Wei, Energy metabolism analysis reveals the mechanism of inhibition of breast cancer cell metastasis by PEG-modified graphene oxide nanosheets, Biomaterials 35 (2014) 9833–9843.
[125] J. Yoon, J.W. Shin, J. Lim, M. Mohammadniaei, G. Bharate Bapurao, T. Lee, J.W. Choi, Electrochemical nitric oxide biosensor based on amine-modified MoS2/graphene oxide/myoglobin hybrid, Colloids Surf B Biointerfaces 159 (2017) 729–736.
[126] C. Sun, L. Wen, J. Zeng, Y. Wang, Q. Sun, L. Deng, C. Zhao, Z. Li, One-pot solventless preparation of PEGylated black phosphorus nanoparticles for photoacoustic imaging and photothermal therapy of cancer, Biomaterials 91 (2016) 81–89.
[127] L. Deng, Y. Xu, C. Sun, B. Yun, Q. Sun, C. Zhao, Z. Li, Functionalization of small black phosphorus nanoparticles for targeted imaging and photothermal therapy of cancer, Science Bulletin 63 (2018) 917–924.
[128] J. Sturala, Z. Sofer, M. Pumera, Chemistry of Layered Pnictogens: Phosphorus, Arsenic, Antimony, and Bismuth, Angew Chem Int Ed Engl 58 (2019) 7551–7557.
[129] A. Hirsch, F. Hauke, Post-Graphene 2D Chemistry: The Emerging Field of Molybdenum Disulfide and Black Phosphorus Functionalization, Angew Chem Int Ed Engl 57 (2018) 4338–4354.
[130] Y. Zhang, Q. Wan, N. Yang, Recent Advances of Porous Graphene: Synthesis, Functionalization, and Electrochemical Applications, Small 15 (2019) e1903780.
[131] G. Zeng, Y. Chen, Surface modification of black phosphorus-based nanomaterials in biomedical applications: Strategies and recent advances, Acta Biomater 118 (2020) 1–17.
[132] X.W. Huang, J.J. Wei, M.Y. Zhang, X.L. Zhang, X.F. Yin, C.H. Lu, J.B. Song, S.M. Bai, H.H. Yang, Water-Based Black Phosphorus Hybrid Nanosheets as a Moldable Platform for Wound Healing Applications, ACS Appl Mater Interfaces 10 (2018) 35495–35502.
[133] J. Shao, H. Xie, H. Huang, Z. Li, Z. Sun, Y. Xu, Q. Xiao, X.F. Yu, Y. Zhao, H. Zhang, H. Wang, P.K. Chu, Biodegradable black phosphorus-based nanospheres for in vivo photothermal cancer therapy, Nat Commun 7 (2016) 12967.
[134] H. Zhao, Y. Chao, J. Liu, J. Huang, J. Pan, W. Guo, J. Wu, M. Sheng, K. Yang, J. Wang, Z. Liu, Polydopamine Coated Single-Walled Carbon Nanotubes as a Versatile Platform with Radionuclide Labeling for Multimodal Tumor Imaging and Therapy, Theranostics 6 (2016) 1833–1843.
[135] M. Wang, J. Yang, S. Liu, C. Hu, S. Li, J. Qiu, Polyethyleneimine-Mediated Fabrication of Two-Dimensional Cobalt Sulfide/Graphene Hybrid Nanosheets for High-Performance Supercapacitors, ACS Appl Mater Interfaces 11 (2019) 26235–26242.
[136] Y. Talukdar, J. Rashkow, G. Lalwani, S. Kanakia, B. Sitharaman, The effects of graphene nanostructures on mesenchymal stem cells, Biomaterials 35 (2014) 4863–4877.
[137] Y. Zhu, Y. Wang, G.R. Williams, L. Fu, J. Wu, H. Wang, R. Liang, X. Weng, M. Wei, Multicomponent Transition Metal Dichalcogenide Nanosheets for Imaging-Guided Photothermal and Chemodynamic Therapy, Adv Sci (Weinh) 7 (2020) 2000272.
[138] L. Cheng, J. Liu, X. Gu, H. Gong, X. Shi, T. Liu, C. Wang, X. Wang, G. Liu, H. Xing, W. Bu, B. Sun, Z. Liu, PEGylated WS(2) nanosheets as a multifunctional theranostic agent for in vivo dual-modal CT/photoacoustic imaging guided photothermal therapy, Adv Mater 26 (2014) 1886–1893.
[139] Z. Liu, H. Lin, M. Zhao, C. Dai, S. Zhang, W. Peng, Y. Chen, 2D Superparamagnetic Tantalum Carbide Composite MXenes for Efficient Breast-Cancer Theranostics, Theranostics 8 (2018) 1648–1664.
[140] L. Cheng, S. Shen, S. Shi, Y. Yi, X. Wang, G. Song, K. Yang, G. Liu, T.E. Barnhart, W. Cai, Z. Liu, FeSe2-Decorated Bi2Se3 Nanosheets Fabricated via Cation Exchange for Chelator-Free (64)Cu-labeling and Multimodal Image-Guided Photothermal-Radiation Therapy, Adv Funct Mater 26 (2016) 2185–2197.
[141] Y. Liu, Q. Han, W. Yang, X. Gan, Y. Yang, K. Xie, L. Xie, Y. Deng, Two-dimensional MXene/cobalt nanowire heterojunction for controlled drug delivery and chemo-photothermal therapy, Mater Sci Eng C Mater Biol Appl 116 (2020) 111212.
[142] C. Wang, X. Ye, Y. Zhao, L. Bai, Z. He, Q. Tong, X. Xie, H. Zhu, D. Cai, Y. Zhou, B. Lu, Y. Wei, L. Mei, D. Xie, M. Wang, Cryogenic 3D printing of porous scaffolds for in situ delivery of 2D black phosphorus nanosheets, doxorubicin hydrochloride and osteogenic peptide for treating tumor resection-induced bone defects, Biofabrication 12 (2020) 035004.
[143] Y. Fu, J. Zhang, H. Lin, A. Mo, 2D titanium carbide(MXene) nanosheets and 1D hydroxyapatite nanowires into free standing nanocomposite membrane: in vitro and in vivo evaluations for bone regeneration, Mater Sci Eng C Mater Biol Appl 118 (2021) 111367.
[144] N.Y. Shim, J.S. Heo, Performance of the Polydopamine-Graphene Oxide Composite Substrate in the Osteogenic Differentiation of Mouse Embryonic Stem Cells, Int J Mol Sci 22 (2021).
[145] L. Tong, Q. Liao, Y. Zhao, H. Huang, A. Gao, W. Zhang, X. Gao, W. Wei, M. Guan, P.K. Chu, H. Wang, Near-infrared light control of bone regeneration with biodegradable photothermal osteoimplant, Biomaterials 193 (2019) 1–11.
[146] Y.B. Lee, S.-J. Song, Y.C. Shin, Y.J. Jung, B. Kim, M.S. Kang, I.K. Kwon, S.-H. Hyon, H.U. Lee, S.-H. Jung, D. Lim, D.-W. Han, Ternary nanofiber matrices composed of PCL/black phosphorus/collagen to enhance osteodifferentiation, Journal of Industrial and Engineering Chemistry 80 (2019) 802–810.
[147] J. Yin, S. Pan, X. Guo, Y. Gao, D. Zhu, Q. Yang, J. Gao, C. Zhang, Y. Chen, Nb2C MXene-Functionalized Scaffolds Enables Osteosarcoma Phototherapy and Angiogenesis/Osteogenesis of Bone Defects, Nanomicro Lett 13 (2021) 30.
[148] Q. Yang, H. Yin, T. Xu, D. Zhu, J. Yin, Y. Chen, X. Yu, J. Gao, C. Zhang, Y. Chen, Y. Gao, Engineering 2D Mesoporous Silica@MXene-Integrated 3D-Printing Scaffolds for Combinatory Osteosarcoma Therapy and NO-Augmented Bone Regeneration, Small 16 (2020) e1906814.
[149] S. Veeralingam, S. Badhulika, X (metal: Al, Cu, Sn, Ti)-functionalized tunable 2D-MoS2 nanostructure assembled biosensor arrays for qualitative and quantitative analysis of vital neurological drugs, Nanoscale 12 (2020) 15336–15347.
[150] Z. Yuan, B. Tao, Y. He, J. Liu, C. Lin, X. Shen, Y. Ding, Y. Yu, C. Mu, P. Liu, K. Cai, Biocompatible MoS2/PDA-RGD coating on titanium implant with antibacterial property via intrinsic ROS-independent oxidative stress and NIR irradiation, Biomaterials 217 (2019) 119290.
[151] J. Prakash, D. Prema, K.S. Venkataprasanna, K. Balagangadharan, N. Selvamurugan, G.D. Venkatasubbu, Nanocomposite chitosan film containing graphene oxide/hydroxyapatite/gold for bone tissue engineering, Int J Biol Macromol 154 (2020) 62–71.
[152] S. Wang, C. Duan, W. Yang, X. Gao, J. Shi, J. Kang, Y. Deng, X.L. Shi, Z.G. Chen, Correction: Two-dimensional nanocoating-enabled orthopedic implants for bimodal therapeutic applications, Nanoscale 12 (2020) 17555–17556.
[153] X. Liu, A.L. Miller 2nd, S. Park, M.N. George, B.E. Waletzki, H. Xu, A. Terzic, L. Lu, Two-Dimensional Black Phosphorus and Graphene Oxide Nanosheets Synergistically Enhance Cell Proliferation and Osteogenesis on 3D Printed Scaffolds, ACS Appl Mater Interfaces 11 (2019) 23558–23572.
[154] J.A. McGovern, M. Griffin, D.W. Hutmacher, Animal models for bone tissue engineering and modelling disease, Dis Model Mech 11 (2018).
[155] A.A. El-Rashidy, J.A. Roether, L. Harhaus, U. Kneser, A.R. Boccaccini, Regenerating bone with bioactive glass scaffolds: A review of in vivo studies in bone defect models, Acta Biomater 62 (2017) 1–28.
[156] N. Su, J. Yang, Y. Xie, X. Du, H. Chen, H. Zhou, L. Chen, Bone function, dysfunction and its role in diseases including critical illness, Int J Biol Sci 15 (2019) 776–787.
[157] M. Majidinia, A. Sadeghpour, B. Yousefi, The roles of signaling pathways in bone repair and regeneration, J Cell Physiol 233 (2018) 2937–2948.
[158] E. Garcia-Gareta, M.J. Coathup, G.W. Blunn, Osteoinduction of bone grafting materials for bone repair and regeneration, Bone 81 (2015) 112–121.
[159] R. Dimitriou, E. Jones, D. McGonagle, P.V. Giannoudis, Bone regeneration: current concepts and future directions, BMC Med 9 (2011) 66.
[160] C. Nunziato, J. Williams, R. Williams, Synthetic Bone Graft Substitute for Treatment of Unicameral Bone Cysts, J Pediatr Orthop 41 (2021) e60–e66.
[161] P.C. Wong, C.Y. Wang, J.S. Jang, C.H. Lee, J.L. Wu, Large-Pore Platelet-Rich Fibrin with a Mg Ring to Allow MC3T3-E1 Preosteoblast Migration and to Improve Osteogenic Ability for Bone Defect Repair, Int J Mol Sci 22 (2021).
[162] Z. Peng, T. Zhao, Y. Zhou, S. Li, J. Li, R.M. Leblanc, Bone Tissue Engineering via Carbon-Based Nanomaterials, Adv Healthc Mater 9 (2020) e1901495.
[163] L. Roseti, V. Parisi, M. Petretta, C. Cavallo, G. Desando, I. Bartolotti, B. Grigolo, Scaffolds for Bone Tissue Engineering: State of the art and new perspectives, Mater Sci Eng C Mater Biol Appl 78 (2017) 1246–1262.
[164] L. Cheng, Z. Cai, J. Zhao, F. Wang, M. Lu, L. Deng, W. Cui, Black phosphorus-based 2D materials for bone therapy, Bioact Mater 5 (2020) 1026–1043.
[165] L. Cui, D.A. Houston, C. Farquharson, V.E. MacRae, Characterisation of matrix vesicles in skeletal and soft tissue mineralisation, Bone 87 (2016) 147–158.
[166] R. Gusmao, Z. Sofer, M. Pumera, Black Phosphorus Rediscovered: From Bulk Material to Monolayers, Angew Chem Int Ed Engl 56 (2017) 8052–8072.
[167] J. Shao, C. Ruan, H. Xie, P.K. Chu, X.F. Yu, Photochemical Activity of Black Phosphorus for Near-Infrared Light Controlled In Situ Biomineralization, Adv Sci (Weinh) 7 (2020) 2000439.
[168] K. Huang, J. Wu, Z. Gu, Black Phosphorus Hydrogel Scaffolds Enhance Bone Regeneration via a Sustained Supply of Calcium-Free Phosphorus, ACS Appl Mater Interfaces 11 (2019) 2908–2916.
[169] Y. Wang, X. Hu, L. Zhang, C. Zhu, J. Wang, Y. Li, Y. Wang, C. Wang, Y. Zhang, Q. Yuan, Bioinspired extracellular vesicles embedded with black phosphorus for molecular recognition-guided biomineralization, Nat Commun 10 (2019) 2829.
[170] R. Guo, M. Xiao, W. Zhao, S. Zhou, Y. Hu, M. Liao, S. Wang, X. Yang, R. Chai, M. Tang, 2D Ti3C2TxMXene couples electrical stimulation to promote proliferation and neural differentiation of neural stem cells, Acta Biomater (2020).

[171] K. Rezwan, Q.Z. Chen, J.J. Blaker, A.R. Boccaccini, Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering, Biomaterials 27 (2006) 3413–3431.
[172] W. Qi, W. Yuan, J. Yan, H. Wang, Growth and accelerated differentiation of mesenchymal stem cells on graphene oxide/poly-l-lysine composite films, J Mater Chem B 2 (2014) 5461–5467.
[173] J. Kim, Y.R. Kim, Y. Kim, K.T. Lim, H. Seonwoo, S. Park, S.P. Cho, B.H. Hong, P.H. Choung, T.D. Chung, Y.H. Choung, J.H. Chung, Graphene-incorporated chitosan substrata for adhesion and differentiation of human mesenchymal stem cells, J Mater Chem B 1 (2013) 933–938.
[174] S. Duan, X. Yang, F. Mei, Y. Tang, X. Li, Y. Shi, J. Mao, H. Zhang, Q. Cai, Enhanced osteogenic differentiation of mesenchymal stem cells on poly(L-lactide) nanofibrous scaffolds containing carbon nanomaterials, J Biomed Mater Res A 103 (2015) 1424–1435.
[175] A. Thakur, M.K. Jaiswal, C.W. Peak, J.K. Carrow, J. Gentry, A. Dolatshahi-Pirouz, A.K. Gaharwar, Injectable shear-thinning nanoengineered hydrogels for stem cell delivery, Nanoscale 8 (2016) 12362–12372.
[176] J. Sun, Y. Zhang, Z. Lu, Q. Li, Q. Xue, S. Du, J. Pu, L. Wang, Superlubricity Enabled by Pressure-Induced Friction Collapse, The journal of physical chemistry letters 9 (2018) 2554–2559.
[177] A. Merlo, V. Mokkapati, S. Pandit, I. Mijakovic, Boron nitride nanomaterials: biocompatibility and bio-applications, Biomaterials science 6 (2018) 2298–2311.
[178] L. Liu, M. Zhou, X. Li, L. Jin, G. Su, Y. Mo, L. Li, H. Zhu, Y. Tian, Research Progress in Application of 2D Materials in Liquid-Phase Lubrication System, Materials (Basel) 11 (2018).
[179] I.E. Uflyand, V.A. Zhinzhilo, V.E. Burlakova, Metal-containing nanomaterials as lubricant additives: State-of-the-art and future development, Friction 7 (2019) 93–116.
[180] F. Gustavsson, S. Jacobson, Diverse mechanisms of friction induced self-organisation into a low-friction material – An overview of WS2 tribofilm formation, Tribology International 101 (2016) 340–347.
[181] M. Gulzar, H.H. Masjuki, M.A. Kalam, M. Varman, N.W.M. Zulkifli, R.A. Mufti, R. Zahid, Tribological performance of nanoparticles as lubricating oil additives, Journal of Nanoparticle Research 18 (2016).
[182] M. Gulzar, H.H. Masjuki, M.A. Kalam, M. Varman, N.W.M. Zulkifli, R.A. Mufti, R. Zahid, Tribological performance of nanoparticles as lubricating oil additives, Journal of Nanoparticle Research 18 (2016) 223.
[183] J. Lin, L. Wang, G. Chen, Modification of Graphene Platelets and their Tribological Properties as a Lubricant Additive, Tribology Letters 41 (2010) 209–215.
[184] S. Wu, F. He, G. Xie, Z. Bian, J. Luo, S. Wen, Black Phosphorus: Degradation Favors Lubrication, Nano letters 18 (2018) 5618–5627.
[185] Y. Meng, J. Sun, P. Wu, C. Dong, X. Yan, The Role of Nano-TiO2 Lubricating Fluid on the Hot Rolled Surface and Metallographic Structure of SS41 Steel, Nanomaterials 8 (2018).
[186] Y. Meng, F. Su, Z. Li, Boundary and Elastohydrodynamic Lubrication Behaviors of Nano-CuO/Reduced Graphene Oxide Nanocomposite as an Efficient Oil-Based Additive, Langmuir : the ACS journal of surfaces and colloids 35 (2019) 10322–10333.
[187] B. Wu, H. Song, C. Li, R. Song, T. Zhang, X. Hu, Enhanced tribological properties of diesel engine oil with Nano-Lanthanum hydroxide/reduced graphene oxide composites, Tribology International 141 (2020) 105951.
[188] T. Zhang, J. Zhao, J. Zhang, S. Zhang, J. Li, S. Li, X. Li, J. Zhang, Nano-Magnesium Silicate Hydroxide/Crumpled Graphene Balls Composites, a Novel Kind of Lubricating Additive with High Performance for Friction and Wear Reduction, Materials 13 (2020) 3669.
[189] S. Jahn, J. Seror, J. Klein, Lubrication of Articular Cartilage, Annual review of biomedical engineering 18 (2016) 235–258.
[190] Y. Krishnan, A.J. Grodzinsky, Cartilage diseases, Matrix Biol 71–72 (2018) 51–69.
[191] S.C. Scholes, A. Unsworth, The effects of proteins on the friction and lubrication of artificial joints, Proc Inst Mech Eng H 220 (2006) 687–693.
[192] S. Yousef, A. Visco, G. Galtieri, D. Nocita, C. Espro, Wear behaviour of UHMWPE reinforced by carbon nanofiller and paraffin oil for joint replacement, Mater Sci Eng C Mater Biol Appl 73 (2017) 234–244.
[193] V. Sharma, S. Bose, B. Kundu, S. Bodhak, D. Mitun, V.K. Balla, B. Basu, Probing the Influence of gamma-Sterilization on the Oxidation, Crystallization, Sliding Wear Resistance, and Cytocompatibility of Chemically Modified Graphene-Oxide-Reinforced HDPE/UHMWPE Nanocomposites and Wear Debris, ACS Biomater Sci Eng 6 (2020) 1462–1475.
[194] S.V. Panin, L.A. Kornienko, V.O. Alexenko, D.G. Buslovich, S.A. Bochkareva, B.A. Lyukshin, Increasing Wear Resistance of UHMWPE by Loading Enforcing Carbon Fibers: Effect of Irreversible and Elastic Deformation, Friction Heating, and Filler Size, Materials (Basel) 13 (2020).
[195] U. Filipovic, R.G. Dahmane, S. Ghannouchi, A. Zore, K. Bohinc, Bacterial adhesion on orthopedic implants, Adv Colloid Interface Sci 283 (2020) 102228.
[196] Y. Guo, D. Chen, M. Cheng, W. Lu, L. Wang, X. Zhang, The bone tissue compatibility of a new Ti35Nb2Ta3Zr alloy with a low Young's modulus, Int J Mol Med 31 (2013) 689–697.
[197] A. Jemat, M.J. Ghazali, M. Razali, Y. Otsuka, Surface Modifications and Their Effects on Titanium Dental Implants, Biomed Res Int 2015 (2015) 791725.
[198] T. Xue, S. Attarilar, S. Liu, J. Liu, X. Song, L. Li, B. Zhao, Y. Tang, Surface Modification Techniques of Titanium and its Alloys to Functionally Optimize Their Biomedical Properties: Thematic Review, Front Bioeng Biotechnol 8 (2020) 603072.
[199] T.F. Moriarty, U. Schlegel, S. Perren, R.G. Richards, Infection in fracture fixation: can we influence infection rates through implant design?, J Mater Sci Mater Med 21 (2010) 1031–1035
[200] A. Anand, B. Unnikrishnan, S.C. Wei, C.P. Chou, L.Z. Zhang, C.C. Huang, Graphene oxide and carbon dots as broad-spectrum antimicrobial agents - a minireview, Nanoscale Horiz 4 (2019) 117–137.
[201] C.F. Pope, D.M. O'Sullivan, T.D. McHugh, S.H. Gillespie, A practical guide to measuring mutation rates in antibiotic resistance, Antimicrob Agents Chemother 52 (2008) 1209–1214.
[202] L. Mei, S. Zhu, W. Yin, C. Chen, G. Nie, Z. Gu, Y. Zhao, Two-dimensional nanomaterials beyond graphene for antibacterial applications: current progress and future perspectives, Theranostics 10 (2020) 757–781.
[203] W. Sun, F.G. Wu, Two-Dimensional Materials for Antimicrobial Applications: Graphene Materials and Beyond, Chem Asian J 13 (2018) 3378–3410.
[204] H. Miao, Z. Teng, C. Wang, H. Chong, G. Wang, Recent Progress in Two-Dimensional Antimicrobial Nanomaterials, Chemistry 25 (2019) 929–944.
[205] K. Kaarniranta, E. Pawlowska, J. Szczepanska, A. Jablkowska, J. Blasiak, Role of Mitochondrial DNA Damage in ROS-Mediated Pathogenesis of Age-Related Macular Degeneration (AMD), Int J Mol Sci 20 (2019).
[206] T.H. Lee, T.H. Kang, DNA Oxidation and Excision Repair Pathways, Int J Mol Sci 20 (2019).
[207] Z. Gao, F. Chen, Y. Li, Y. Zhang, K. Cheng, P. An, B. Sun, A small-sized and stable 2D metal-organic framework: a functional nanoplatform for effective photodynamic therapy, Dalton Trans 48 (2019) 16861–16868.
[208] A. Gazzi, L. Fusco, A. Khan, D. Bedognetti, B. Zavan, F. Vitale, A. Yilmazer, L.G. Delogu, Photodynamic Therapy Based on Graphene and MXene in Cancer Theranostics, Front Bioeng Biotechnol 7 (2019) 295.
[209] Y. Sun, H. Chen, G. Liu, L. Ma, Z. Wang, The controllable growth of ultrathin MnO2 on polydopamine nanospheres as a single nanoplatform for the MRI-guided synergistic therapy of tumors, J Mater Chem B 7 (2019) 7152–7161.
[210] C. Liu, D. Kong, P.C. Hsu, H. Yuan, H.W. Lee, Y. Liu, H. Wang, S. Wang, K. Yan, D. Lin, P.A. Maraccini, K.M. Parker, A.B. Boehm, Y. Cui, Rapid water disinfection using vertically aligned MoS2 nanofilms and visible light, Nat Nanotechnol 11 (2016) 1098–1104.
[211] S. Karunakaran, S. Pandit, B. Basu, M. De, Simultaneous Exfoliation and Functionalization of 2H-MoS2 by Thiolated Surfactants: Applications in Enhanced Antibacterial Activity, J Am Chem Soc 140 (2018) 12634–12644.
[212] X. Yang, J. Li, T. Liang, C. Ma, Y. Zhang, H. Chen, N. Hanagata, H. Su, M. Xu, Antibacterial activity of two-dimensional MoS2 sheets, Nanoscale 6 (2014) 10126–10133.
[213] K. Rasool, M. Helal, A. Ali, C.E. Ren, Y. Gogotsi, K.A. Mahmoud, Antibacterial Activity of Ti(3)C(2)Tx MXene, ACS Nano 10 (2016) 3674–3684.
[214] X. Lu, X. Feng, J.R. Werber, C. Chu, I. Zucker, J.H. Kim, C.O. Osuji, M. Elimelech, Enhanced antibacterial activity through the controlled alignment of graphene oxide nanosheets, Proc Natl Acad Sci U S A 114 (2017) E9793–E9801.
[215] Y. Li, H. Yuan, A. von dem Bussche, M. Creighton, R.H. Hurt, A.B. Kane, H. Gao, Graphene microsheets enter cells through spontaneous membrane penetration at edge asperities and corner sites, Proc Natl Acad Sci U S A 110 (2013) 12295–12300.
[216] G. Wang, W. Jiang, S. Mo, L. Xie, Q. Liao, L. Hu, Q. Ruan, K. Tang, B. Mehrjou, M. Liu, L. Tong, H. Wang, J. Zhuang, G. Wu, P.K. Chu, Nonleaching Antibacterial Concept Demonstrated by In Situ Construction of 2D Nanoflakes on Magnesium, Adv Sci (Weinh) 7 (2020) 1902089.
[217] J.D. Mangadlao, C.M. Santos, M.J. Felipe, A.C. de Leon, D.F. Rodrigues, R.C. Advincula, On the antibacterial mechanism of graphene oxide (GO) Langmuir-Blodgett films, Chem Commun (Camb) 51 (2015) 2886–2889.
[218] W. Zhang, S. Shi, Y. Wang, S. Yu, W. Zhu, X. Zhang, D. Zhang, B. Yang, X. Wang, J. Wang, Versatile molybdenum disulfide based antibacterial composites for in vitro enhanced sterilization and in vivo focal infection therapy, Nanoscale 8 (2016) 11642–11648.
[219] J. Ouyang, R.Y. Liu, W. Chen, Z. Liu, Q. Xu, K. Zeng, L. Deng, L. Shen, Y.N. Liu, A black phosphorus based synergistic antibacterial platform against drug resistant bacteria, J Mater Chem B 6 (2018) 6302–6310.
[220] Q. Wu, M. Liang, S. Zhang, X. Liu, F. Wang, Development of functional black phosphorus nanosheets with remarkable catalytic and antibacterial performance, Nanoscale 10 (2018) 10428–10435.
[221] I. Aksoy, H. Kucukkececi, F. Sevgi, O. Metin, I. Hatay Patir, Photothermal Antibacterial and Antibiofilm Activity of Black Phosphorus/Gold Nanocomposites against Pathogenic Bacteria, ACS Appl Mater Interfaces, 12 (2020) 26822-26831.
[222] S. Tan, X. Wu, Y. Xing, S. Lilak, M. Wu, J.X. Zhao, Enhanced synergetic antibacterial activity by a reduce graphene oxide/Ag nanocomposite through the photothermal effect, Colloids Surf B Biointerfaces 185 (2020) 110616.
[223] S.S. Chou, B. Kaehr, J. Kim, B.M. Foley, M. De, P.E. Hopkins, J. Huang, C.J. Brinker, V.P. Dravid, Chemically exfoliated MoS2 as near-infrared photothermal agents, Angew Chem Int Ed Engl 52 (2013) 4160–4164.
[224] X. Wang, F. Lv, T. Li, Y. Han, Z. Yi, M. Liu, J. Chang, C. Wu, Electrospun Micropatterned Nanocomposites Incorporated with Cu2S Nanoflowers for Skin Tumor Therapy and Wound Healing, ACS Nano 11 (2017) 11337–11349.
[225] Z. Miao, L. Fan, X. Xie, Y. Ma, J. Xue, T. He, Z. Zha, Liquid Exfoliation of Atomically Thin Antimony Selenide as an Efficient Two-Dimensional Antibacterial Nanoagent, ACS Appl Mater Interfaces 11 (2019) 26664–26673.
[226] W. Zeng, R. Wan, Y. Zheng, S.R. Singh, Y. Wei, Hypoxia, stem cells and bone tumor, Cancer Lett 313 (2011) 129–136.

[227] R.A. Durfee, M. Mohammed, H.H. Luu, Review of Osteosarcoma and Current Management, Rheumatol Ther 3 (2016) 221–243.
[228] N.J. Balamuth, R.B. Womer, Ewing's sarcoma, Lancet Oncol 11 (2010) 184–192.
[229] R.K. Heck Jr., T.D. Peabody, M.A. Simon, Staging of primary malignancies of bone, CA Cancer J Clin 56 (2006) 366–375.
[230] Z. Chen, P. Zhang, Y. Xu, J. Yan, Z. Liu, W.B. Lau, B. Lau, Y. Li, X. Zhao, Y. Wei, S. Zhou, Surgical stress and cancer progression: the twisted tango, Mol Cancer 18 (2019) 132.
[231] S. Son, J.H. Kim, X. Wang, C. Zhang, S.A. Yoon, J. Shin, A. Sharma, M.H. Lee, L. Cheng, J. Wu, J.S. Kim, Multifunctional sonosensitizers in sonodynamic cancer therapy, Chem Soc Rev 49 (2020) 3244–3261.
[232] F. Danhier, To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine?, J Control Release 244 (2016) 108–121
[233] J. Xie, C. Wang, F. Zhao, Z. Gu, Y. Zhao, Application of Multifunctional Nanomaterials in Radioprotection of Healthy Tissues, Adv Healthc Mater 7 (2018) e1800421.
[234] Y. Liu, X. Cao, Immunosuppressive cells in tumor immune escape and metastasis, J Mol Med (Berl) 94 (2016) 509–522.
[235] Y. Gao, X. Wu, L. Zhou, Y. Su, C.M. Dong, A sweet polydopamine nanoplatform for synergistic combination of targeted chemo-photothermal therapy, Macromol Rapid Commun 36 (2015) 916–922.
[236] Z. Xie, T. Fan, J. An, W. Choi, Y. Duo, Y. Ge, B. Zhang, G. Nie, N. Xie, T. Zheng, Y. Chen, H. Zhang, J.S. Kim, Emerging combination strategies with phototherapy in cancer nanomedicine, Chem Soc Rev 49 (2020) 8065–8087.
[237] Z. Xie, M. Peng, R. Lu, X. Meng, W. Liang, Z. Li, M. Qiu, B. Zhang, G. Nie, N. Xie, H. Zhang, P.N. Prasad, Black phosphorus-based photothermal therapy with aCD47-mediated immune checkpoint blockade for enhanced cancer immunotherapy, Light Sci Appl 9 (2020) 161.
[238] Z. Liu, Z. Xie, W. Li, X. Wu, X. Jiang, G. Li, L. Cao, D. Zhang, Q. Wang, P. Xue, H. Zhang, Photodynamic immunotherapy of cancers based on nanotechnology: recent advances and future challenges, J Nanobiotechnology 19 (2021) 160.
[239] X. Liang, X. Ye, C. Wang, C. Xing, Q. Miao, Z. Xie, X. Chen, X. Zhang, H. Zhang, L. Mei, Photothermal cancer immunotherapy by erythrocyte membrane-coated black phosphorus formulation, J Control Release 296 (2019) 150–161.
[240] D. Zhi, T. Yang, J. O'Hagan, S. Zhang, R.F. Donnelly, Photothermal therapy, J Control Release 325 (2020) 52–71.
[241] Y.J. Hou, X.X. Yang, R.Q. Liu, D. Zhao, C.X. Guo, A.C. Zhu, M.N. Wen, Z. Liu, G.F. Qu, H.X. Meng, Pathological Mechanism of Photodynamic Therapy and Photothermal Therapy Based on Nanoparticles, Int J Nanomedicine 15 (2020) 6827–6838.
[242] J. Chen, T. Fan, Z. Xie, Q. Zeng, P. Xue, T. Zheng, Y. Chen, X. Luo, H. Zhang, Advances in nanomaterials for photodynamic therapy applications: Status and challenges, Biomaterials 237 (2020) 119827.
[243] X. Wu, X. Jiang, T. Fan, Z. Zheng, Z. Liu, Y. Chen, L. Cao, Z. Xie, D. Zhang, J. Zhao, Q. Wang, Z. Huang, Z. Chen, P. Xue, H. Zhang, Recent advances in photodynamic therapy based on emerging two-dimensional layered nanomaterials, Nano Research 13 (2020) 1485–1508.
[244] Y. Liu, P. Bhattarai, Z. Dai, X. Chen, Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer, Chem Soc Rev 48 (2019) 2053–2108.
[245] Z. Xie, D. Wang, T. Fan, C. Xing, Z. Li, W. Tao, L. Liu, S. Bao, D. Fan, H. Zhang, Black phosphorus analogue tin sulfide nanosheets: synthesis and application as near-infrared photothermal agents and drug delivery platforms for cancer therapy, J Mater Chem B 6 (2018) 4747–4755.
[246] H. Abrahamse, M.R. Hamblin, New photosensitizers for photodynamic therapy, Biochem J 473 (2016) 347–364.
[247] A. Sundaram, L. Peng, L. Chai, Z. Xie, J.S. Ponraj, X. Wang, G. Wang, B. Zhang, G. Nie, N. Xie, M. Rajesh Kumar, H. Zhang, Advanced nanomaterials for hypoxia tumor therapy: challenges and solutions, Nanoscale 12 (2020) 21497–21518.
[248] S. Liu, X. Pan, H. Liu, Two-Dimensional Nanomaterials for Photothermal Therapy, Angew Chem Int Ed Engl 59 (2020) 5890–5900.
[249] J. Ge, M. Lan, B. Zhou, W. Liu, L. Guo, H. Wang, Q. Jia, G. Niu, X. Huang, H. Zhou, X. Meng, P. Wang, C.S. Lee, W. Zhang, X. Han, A graphene quantum dot photodynamic therapy agent with high singlet oxygen generation, Nat Commun 5 (2014) 4596.
[250] B. Yang, J. Yin, Y. Chen, S. Pan, H. Yao, Y. Gao, J. Shi, 2D-Black-Phosphorus-Reinforced 3D-Printed Scaffolds: A Stepwise Countermeasure for Osteosarcoma, Adv Mater 30 (2018).
[251] P.M. van der Kraan, W.B. van den Berg, Chondrocyte hypertrophy and osteoarthritis: role in initiation and progression of cartilage degeneration?, Osteoarthritis Cartilage 20 (2012) 223–232
[252] M.H. van den Bosch, A.B. Blom, V. Kram, A. Maeda, S. Sikka, Y. Gabet, T.M. Kilts, W.B. van den Berg, P.L. van Lent, P.M. van der Kraan, M.F. Young, WISP1/CCN4 aggravates cartilage degeneration in experimental osteoarthritis, Osteoarthritis Cartilage 25 (2017) 1900–1911.
[253] A.J. Schreiner, A.M. Stoker, C.C. Bozynski, K. Kuroki, J.P. Stannard, J.L. Cook, Clinical Application of the Basic Science of Articular Cartilage Pathology and Treatment, J Knee Surg (2020).
[254] K. Shimomura, Y. Moriguchi, C.D. Murawski, H. Yoshikawa, N. Nakamura, Osteochondral tissue engineering with biphasic scaffold: current strategies and techniques, Tissue Eng Part B Rev 20 (2014) 468–476.
[255] C. Deng, C. Xu, Q. Zhou, Y. Cheng, Advances of nanotechnology in osteochondral regeneration, Wiley Interdiscip Rev Nanomed Nanobiotechnol 11 (2019) e1576.
[256] J. Chang, W. Wang, H. Zhang, Y. Hu, M. Wang, Z. Yin, The dual role of autophagy in chondrocyte responses in the pathogenesis of articular cartilage degeneration in osteoarthritis, Int J Mol Med 32 (2013) 1311–1318.
[257] M. Falah, G. Nierenberg, M. Soudry, M. Hayden, G. Volpin, Treatment of articular cartilage lesions of the knee, Int Orthop 34 (2010) 621–630.
[258] D.J. Huey, J.C. Hu, K.A. Athanasiou, Unlike bone, cartilage regeneration remains elusive, Science 338 (2012) 917–921.
[259] (!!! INVALID CITATION !!! [225, 226]).
[260] T. Sasaki, R. Akagi, Y. Akatsu, T. Fukawa, H. Hoshi, Y. Yamamoto, T. Enomoto, Y. Sato, R. Nakagawa, K. Takahashi, S. Yamaguchi, T. Sasho, The effect of systemic administration of G-CSF on a full-thickness cartilage defect in a rabbit model MSC proliferation as presumed mechanism: G-CSF for cartilage repair, Bone Joint Res 6 (2017) 123–131.
[261] T.E. McAlindon, M.P. LaValley, W.F. Harvey, L.L. Price, J.B. Driban, M. Zhang, R. J. Ward, Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial, JAMA 317 (2017) 1967–1975.
[262] V. Sansone, L. de Girolamo, W. Pascale, M. Melato, V. Pascale, Long-term results of abrasion arthroplasty for full-thickness cartilage lesions of the medial femoral condyle, Arthroscopy 31 (2015) 396–403.
[263] F.A. Formica, G. Barreto, M. Zenobi-Wong, Cartilage-targeting dexamethasone prodrugs increase the efficacy of dexamethasone, J Control Release 295 (2019) 118–129.
[264] E.A. Aisenbrey, S.J. Bryant, Mechanical loading inhibits hypertrophy in chondrogenically differentiating hMSCs within a biomimetic hydrogel, J Mater Chem B 4 (2016) 3562–3574.
[265] C. Larsen, J. Ostergaard, S.W. Larsen, H. Jensen, S. Jacobsen, C. Lindegaard, P.H. Andersen, Intra-articular depot formulation principles: role in the management of postoperative pain and arthritic disorders, J Pharm Sci 97 (2008) 4622–4654.
[266] C.H. Evans, V.B. Kraus, L.A. Setton, Progress in intra-articular therapy, Nat Rev Rheumatol 10 (2014) 11–22.
[267] T.J. Brown, U.B. Laurent, J.R. Fraser, Turnover of hyaluronan in synovial joints: elimination of labelled hyaluronan from the knee joint of the rabbit, Exp Physiol 76 (1991) 125–134.
[268] C. Albert, O. Brocq, D. Gerard, C. Roux, L. Euller-Ziegler, Septic knee arthritis after intra-articular hyaluronate injection, Two case reports, Joint Bone Spine 73 (2006) 205–207.
[269] C.B. Carballo, Y. Nakagawa, I. Sekiya, S.A. Rodeo, Basic Science of Articular Cartilage, Clin Sports Med 36 (2017) 413–425.
[270] J. Zou, B. Bai, Y. Yao, Progress of co-culture systems in cartilage regeneration, Expert Opin Biol Ther 18 (2018) 1151–1158.
[271] W. Pan, C. Dai, Y. Li, Y. Yin, L. Gong, J.O. Machuki, Y. Yang, S. Qiu, K. Guo, F. Gao, PRP-chitosan thermoresponsive hydrogel combined with black phosphorus nanosheets as injectable biomaterial for biotherapy and phototherapy treatment of rheumatoid arthritis, Biomaterials 239 (2020) 119851.
[272] J. Luo, M. Zeng, B. Peng, Y. Tang, L. Zhang, P. Wang, L. He, D. Huang, L. Wang, X. Wang, M. Chen, S. Lei, P. Lin, Y. Chen, Z. Cheng, Electrostatic-Driven Dynamic Jamming of 2D Nanoparticles at Interfaces for Controlled Molecular Diffusion, Angew Chem Int Ed Engl 57 (2018) 11752–11757.
[273] M. Wang, E.R. Sampson, H. Jin, J. Li, Q.H. Ke, H.J. Im, D. Chen, MMP13 is a critical target gene during the progression of osteoarthritis, Arthritis Res Ther 15 (2013) R5.
[274] J. Yang, Y. Xiao, Z. Tang, Z. Luo, D. Li, Q. Wang, X. Zhang, The negatively charged microenvironment of collagen hydrogels regulates the chondrogenic differentiation of bone marrow mesenchymal stem cells in vitro and in vivo, J Mater Chem B 8 (2020) 4680–4693.
[275] A.G. Bajpayee, R.E. De la Vega, M. Scheu, N.H. Varady, I.A. Yannatos, L.A. Brown, Y. Krishnan, T.J. Fitzsimons, P. Bhattacharya, E.H. Frank, A.J. Grodzinsky, R.M. Porter, Sustained intra-cartilage delivery of low dose dexamethasone using a cationic carrier for treatment of post traumatic osteoarthritis, Eur Cell Mater 34 (2017) 341–364.
[276] Z. Li, G. Luo, W.P. Hu, J.L. Hua, S. Geng, P.K. Chu, J. Zhang, H. Wang, X.F. Yu, Mediated Drug Release from Nanovehicles by Black Phosphorus Quantum Dots for Efficient Therapy of Chronic Obstructive Pulmonary Disease, Angew Chem Int Ed Engl 59 (2020) 20568–20576.
[277] C.R. Dean, A.F. Young, I. Meric, C. Lee, L. Wang, S. Sorgenfrei, K. Watanabe, T. Taniguchi, P. Kim, K.L. Shepard, J. Hone, Boron nitride substrates for high-quality graphene electronics, Nat Nanotechnol 5 (2010) 722–726.
[278] X. Chen, K. Shehzad, L. Gao, M. Long, H. Guo, S. Qin, X. Wang, F. Wang, Y. Shi, W. Hu, Y. Xu, X. Wang, Graphene Hybrid Structures for Integrated and Flexible Optoelectronics, Adv Mater 32 (2020) e1902039.
[279] Y. Liu, Y. Huang, X. Duan, Van der Waals integration before and beyond two-dimensional materials, Nature 567 (2019) 323–333.
[280] B. Ma, C. Martin, R. Kurapati, A. Bianco, Degradation-by-design: how chemical functionalization enhances the biodegradability and safety of 2D materials, Chem Soc Rev 49 (2020) 6224–6247.
[281] Q. Zhang, Q. Guo, Q. Chen, X. Zhao, S.J. Pennycook, H. Chen, Highly Efficient 2D NIR-II Photothermal Agent with Fenton Catalytic Activity for Cancer Synergistic Photothermal-Chemodynamic Therapy, Adv Sci (Weinh) 7 (2020) 1902576.
[282] Q. Liu, Z. Xie, M. Qiu, I. Shim, Y. Yang, S. Xie, Q. Yang, D. Wang, S. Chen, T. Fan, B. Ding, Z. Guo, D. Adah, X. Yao, Y. Zhang, H. Wu, Z. Wu, C. Wei, H. Wang, H.S. Kim, Q. Zou, Q. Yan, Z. Cai, J.S. Kim, L.P. Liu, H. Zhang, Y. Cao, Prodrug-Loaded

Zirconium Carbide Nanosheets as a Novel Biophotonic Nanoplatform for Effective Treatment of Cancer, Adv Sci (Weinh) 7 (2020) 2001191.
[283] V. Urbanova, M. Pumera, Biomedical and bioimaging applications of 2D pnictogens and transition metal dichalcogenides, Nanoscale 11 (2019) 15770–15782.
[284] L.-X. Chai, X.-X. Fan, Y.-H. Zuo, B. Zhang, G.-H. Nie, N. Xie, Z.-J. Xie, H. Zhang, Low-dimensional nanomaterials enabled autoimmune disease treatments: Recent advances, strategies, and future challenges, Coordination Chemistry Reviews 432 (2021) 213697.
[285] X. Shao, Z. Ding, W. Zhou, Y. Li, Z. Li, H. Cui, X. Lin, G. Cao, B. Cheng, H. Sun, M. Li, K. Liu, D. Lu, S. Geng, W. Shi, G. Zhang, Q. Song, L. Chen, G. Wang, W. Su, L. Cai, L. Fang, D.T. Leong, Y. Li, X.F. Yu, H. Li, Intrinsic bioactivity of black phosphorus nanomaterials on mitotic centrosome destabilization through suppression of PLK1 kinase, Nat Nanotechnol (2021).
[286] H. Zhang, T. Fan, W. Chen, Y. Li, B. Wang, Recent advances of two-dimensional materials in smart drug delivery nano-systems, Bioact Mater 5 (2020) 1071–1086.
[287] L. Fan, H. Ge, S. Zou, Y. Xiao, H. Wen, Y. Li, H. Feng, M. Nie, Sodium alginate conjugated graphene oxide as a new carrier for drug delivery system, Int J Biol Macromol 93 (2016) 582–590.