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REVIEW

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Functional anti-bone tumor biomaterial scaffold: construction and application

Biaotong Huang,†[abc] Zhifeng Yin,†[d] Fengjin Zhou*[e] and Jiacan Su *[ab]

Bone tumors, including primary bone tumors and bone metastases, have been plagued by poor prognosis for decades. Although most tumor tissue is removed, clinicians are still confronted with the dilemma of eliminating residual cancer cells and regenerating defective bone tissue after surgery. Therefore, functional biomaterial scaffolds are considered to be the ideal candidates to bridge defective tissues and restrain cancer recurrence. Through functionalized structural modifications or coupled therapeutic agents, they provide sufficient mechanical strength and osteoinductive effects while eliminating cancer cells. Numerous novel approaches such as photodynamic, photothermal, drug-conjugated, and immune adjuvant-assisted therapies have exhibited remarkable efficacy against tumors while exhibiting low immunogenicity. This review summarizes the progress of research on biomaterial scaffolds based on different functionalization strategies in bone tumors. We also discuss the feasibility and advantages of the combined application of multiple functionalization strategies. Finally, potential obstacles to the clinical translation of anti-tumor bone bioscaffolds are highlighted. This review will provide valuable references for future advanced biomaterial scaffold design and clinical bone tumor therapy.

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1 Introduction

Primary bone tumors are unusual neoplasms, most of them have high mortality and usually poor prognosis. Some malignant bone tumors are more common in children, adolescents, and young adults.[1,2] According to clinical studies, the skeleton is one of the most popular metastatic destinations of malignant tumors, including prostate, lung, and breast cancers, and metastatic tumors occupy a higher proportion than primary ones in the bone.[3–5] Bone metastases take place in approximately one in three or five cancer patients.[6] After removal of the bone tumour,

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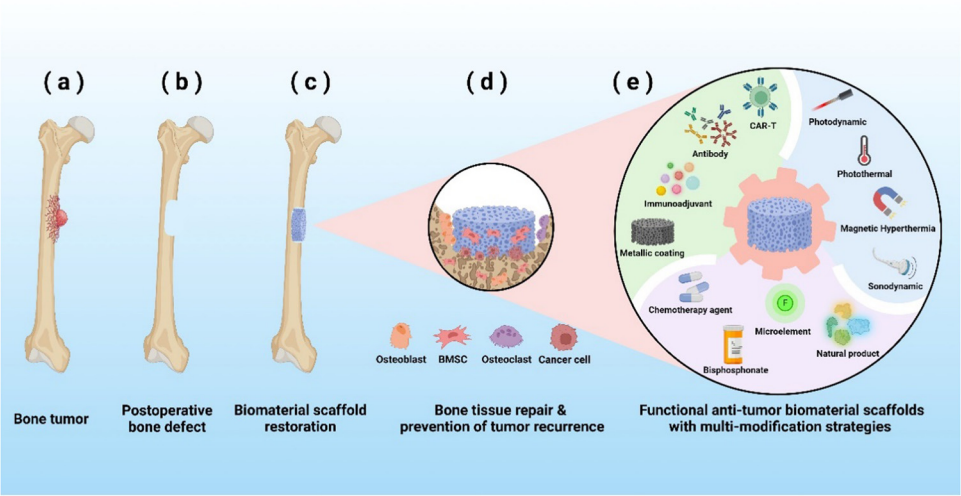

Fig. 1 Schematic illustration of an anti-tumor functional biomaterial scaffold for bone tumor repair. Created with https://BioRender.com.

clinicians require scaffold materials with osteogenic, osteoconductive and osteoinductive properties to restore tissue architecture.[7] Meanwhile, due to the potential risk of postoperative recurrence, these materials should also have the anti-tumor function to eliminate residual tumor cells and prevent recurrence.[8,9] Some novel methods, such as biomaterial-mediated therapies, including targeted chemotherapy and functional response, have demonstrated definite anticancer efficiency and low systemic side effects.[10]

Recent research has focused on the design and fabrication of scaffolds for bone cancer. Multiple methods have been devised to increase the performance of the scaffolds by tuning their properties.[11–14] The usage of biomaterial-based scaffolds for anticancer drug delivery to target sites helps effective and sustained treatment, and improves local drug accumulation.[15–19] Under external stimuli such as ultrasound, light, and magnetic fields, many functional scaffolds may generate heat and consequently lead to irreversible thermal denaturation of proteins, damage to cell membranes, and progressive apoptosis.[20–23] In response to external stimuli, these multifunctional biomaterial scaffolds release chemotherapeutic agents or immunomodulators *in situ* to cure bone tumors.[24–27] With the participation of functional biomaterial scaffolds, metastasis and recurrence of bone tumors can be effectively prevented while promoting bone repair at the defect site (Fig. 1).

Biomaterial-based scaffolds have a successful history and significant promising advances for bone cancer treatment. Here, we highlight the functionalization strategies of bone bioscaffolds to obtain or improve cancer-fighting efficacy. The current challenges and future developments of bone scaffold anticancer therapy are also discussed. This review aims to learn from the past to optimize the design and functionality of bone bioscaffolds for the treatment of bone tumors.

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2 Functionalized bone bioscaffold therapeutic strategy

Biomaterial scaffolds are medical materials used to replace, repair or reconstruct tissue or organ defects.[28] In order to perform anti-cancer effects more precisely and efficiently, it is frequently necessary to functionalize them to exhibit specific functions.[29] That is, active molecules or coatings are introduced on the surface or internal structure to give the scaffold the ability to generate heat, active oxygen, and directional magnetic fields to accelerate the therapeutic process.[30,31] The following methods are commonly used for the functionalization of biomaterial scaffolds: (1) Surface modification: bioactive molecules (*e.g.* peptides, proteins, polysaccharides, *etc.*) are covalently bonded to reactive groups (*e.g.* carboxyl, amino, hydroxyl, *etc.*) on the surface of biomaterial scaffolds to form biomaterials with specific functions.[32] This method is simple and easy to implement, but is influenced by factors such as surface modification density, stability and spatial site resistance.[32] (2) Adsorption: bioactive molecules are adsorbed directly onto the surface of the biomaterial scaffold, using non-covalent bonding forces such as electrostatic forces and hydrophilic/hydrophobic interactions to achieve adsorption.[33,34] This method is easy to operate and does not require chemical reactions, but has low stability and is easily eluted.[34] (3) Cross-linking: bioactive molecules are cross-linked with groups on the surface of the biomaterial scaffold to form a network structure to improve the stability and bioactivity of the biomaterial *in vivo*.[35] This method requires strong chemical reaction conditions and technical support, but the functionalisation effect is better.[35] (4) Electrochemical deposition: bioactive molecules, such as peptides and proteins, are deposited on the surface of biomaterial scaffolds using an applied voltage.[36] This method requires high physical and chemical properties of the material surface, as well as the preparation of electrodes and control of the conditions of the electrode reaction.[36] (5) 3D printing: the carrierization of biologically active molecules is achieved by altering the surface structure or building pores of biomaterial scaffolds through 3D printing techniques.[37] This approach requires sophisticated 3D printing techniques and equipment, but allows for highly and porosity personalized biomaterial scaffolds.[37] These construction methods achieve different therapeutic strategies by incorporating functional agents into biomaterial scaffolds. In this section, the therapy strategies for the different functionalisation modalities are reviewed separately.

2.1 Photodynamic therapy (PDT)

PDT is a novel anti-neoplastic therapeutic approach, which requires photodynamic action of three basic components: photons (usually visible light), photosensitizer, and oxygen. Photosensitizers are administered and activated by a specific wavelength in the absence of oxygen to generate singlet oxygen and other reactive oxygen species (ROS), leading to tumor death *via* apoptosis, necrosis, or autophagy.[38] ROS, including single oxygen ($^1O_2$), hydroxyl radicals ($^{\bullet}OH$), superoxide radicals ($O_2^{\bullet-}$), and peroxides (O_2^{2-}), can functionally regulate cell signaling, adhesion, and migration at a lower concentration.[39] Nevertheless, increased levels of ROS could lead to irreversible vital organ or DNA damage.[39] Cancer cells, compared to normal cells, produce a large amount of ROS to maintain their malignant phenotype and are more vulnerable to exogenous ROS-mediated damage.[40] Therefore, researchers could design additional ROS-generating systems to induce excessive oxidative stress for tumor therapy.

There is a variety of photosensitizers available for PDT.[41] The first officially approved photosensitizing drug for clinical use in PDT is known as Photofrin.[42] It is a first-generation photosensitizer that belongs to the group of porphyrins. The usage of this photosensitizer is limited to superficial tumors since they absorb light weakly at 630 nm. Compared to the first generation, the second generation photosensitizer chlorin e6 (Ce6) and Talaporfin sodium (NPe6) have improved efficacy and fewer side effects.[43] Common limitations of second-generation photosensitizers include poor body clearance and lack of tumor selectivity.[44] The third-generation photosensitizers, such as glycosylated phthalocyanines, can be combined with exceptional carriers or modified by polar groups to adjust their polarities or increase uptake efficacy, and they contribute to selective attack on malignant tumor cells without affecting healthy tissue.[45] Compared to conventional cancer treatments, PDT has demonstrated numerous advantages, such as a low risk of bleeding or complications, little trauma, precise control of treatment, and good selectivity.[46]

PDT has proven to be remarkably promising for treating bone tumors.[47] In osteosarcoma cases, 5,15-bis(2-bromo-5-hydroxyphenyl) porphyrin has been administered and PDT performed after 72 h. The tumor dimensions were dramatically diminished in the PDT group compared to the control group.[48] The authors used vertebral and cranial osteosarcoma models to confirm that photodynamic therapy resulted in increased areas of necrotic cancer tissue while restoring bone-like material. According to the studies by He and colleagues, the photosynthetic and photosensitive Ce6-containing cyanobacteria were integrated into $CaCO_3$-PCL scaffolds (Fig. 2a and b). Under 660 nm laser irradiation, 3D printed CaPC scaffolds produce O_2 and consequently trigger Ce6, producing abundant cytotoxic $^1O_2$, which performs a highly efficient PDT for the treatment of OS.[49] These singly linear oxygen species generate a local ROS storm to inhibit cell proliferation and induce apoptosis. At the same time, photosynthesis raises oxygen concentrations that appear to increase the expression of osteogenic genes, including OCN, achieving osteogenic effects. Nigoghossian *et al.* developed a composite scaffold with the up-conversion property. The system combines polycaprolactone (PCL) polymer, up-conversion nanoparticles apatite, and a PDT photosensitizer erythrosine B (Fig. 2c and d). PS-PCL/UCNPs-apatite composite produced singlet oxygen and displayed PDT properties while the 3D printed scaffold had no effect on optical properties.[50] However, PCL/UCNPs-apatite is genotoxic and mutagenic toward CHO-K1 cells at higher concentrations of rare earth elements and can currently only be used at lower biosafe concentrations.

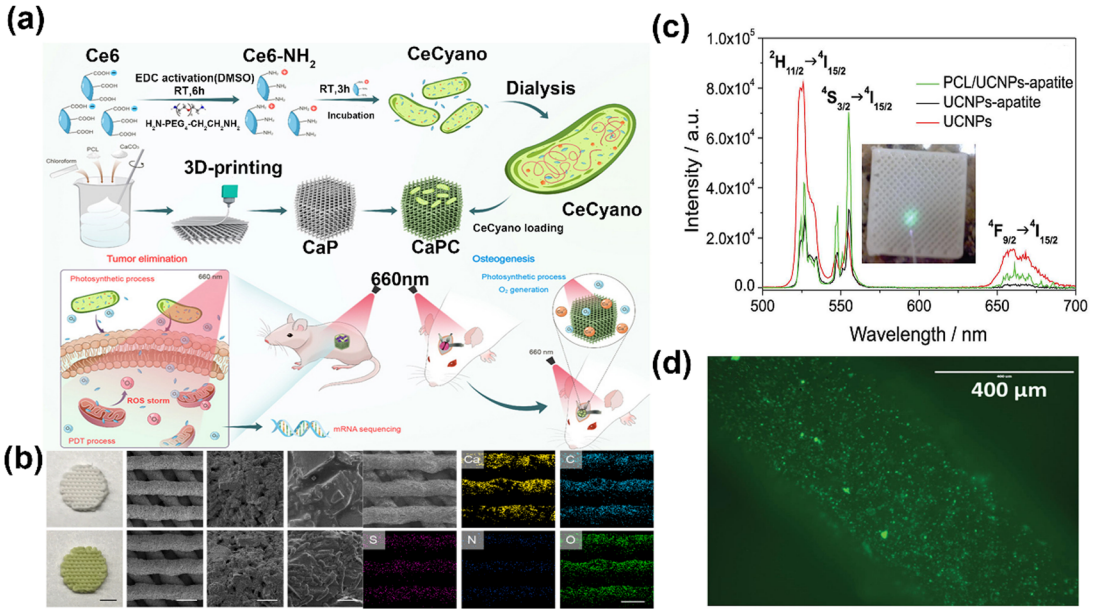

Fig. 2 (a) Schematic illustration of the engineered CaPC 3D-printing scaffolds with profound photodynamic therapy (PDT) efficacy against OS and promoted osteogenesis characteristics. (b) Digital and SEM photographs of a CaP scaffold (upper row) and CaPC scaffold (lower row). Copyright 2021, Elsevier. (c) Upconversion emission spectra (λ_{ex} 980 nm) of UCNPs, UCNPs-apatite and PCL/UCNPs-apatite. Inset: corresponding luminescent photograph of the material. (d) Luminescence microscope image of PCL/UCNPs-apa. Copyright 2022, Royal society of chemistry.

ROS-induced cancer apoptosis is observed to be the dominant mechanism of PDT.[47] The photosensitizer produces ROS under light irradiation at the lesion site where the scaffolds are implanted.[51] PDT consumes local oxygen and affects the tumor vasculature, leading to a hypoxic tumor microenvironment, usually resulting in less effective PDT treatment and poor responses to subsequent radiation therapy or chemotherapy.[52,53] As such, different therapeutic strategies often need to act synergistically with PDT to improve neoplastic tissue oxygenation and maximize the therapeutic efficacy, which could enhance the anti-tumor efficacy and reduce side effects.[46,54]

2.2 Photothermal therapy (PTT)

PTT is another novel photosensitizer-enhanced phototherapy due to its advantages such as high efficacy and less damage to normal tissues.[55] PDT utilizes photosensitizers to generate ROS by light to destroy tumors, while PTT achieves apoptosis through light-induced partial thermotherapy with phototherapeutic agents.

Hyperthermia, which is an effective clinical approach to treat some malignant tumors by raising the local temperature to nearly 44 °C, after which some tumor cells could be significantly damaged through protein denaturation and cell membrane rupture.[56] In addition, it is capable of enhancing efficacy by other therapeutic means (*e.g.* radiotherapy, chemotherapy or immunotherapy) through increasing perfusion and blood flow inside the tumor tissue. According to the previous findings, cells undergo apoptosis within the temperature range 42–46 °C.[56] While above a certain threshold temperature, *i.e.* around 48 °C, the major type of cell death changes from apoptosis to necrosis.[56] However, tumor blood vessels are often unorganized and dysfunctional. Leaky tumor vessels and low blood flow are found in tumor tissues compared to normal vessels of normal tissues, meaning that tumors cannot diffuse heat by increasing blood flow during hyperthermia treatment. Therefore, tumor cells could be theoretically killed if heated to more than 42 °C. On the contrary, normal cells can survive under conditions of even a few degrees exceeding this temperature on account of their better blood flow.[57]

Hyperthermia can be generated in many ways, such as microwave, ultrasound, electromagnetic wave, infrared radiation, and magnetic fluid.[58] Compared with applying the photothermal agents to the whole body, photothermal agents combined with the bone scaffold implanted in the lesion site can make them concentrate around the residual tumor.[58] Through local irradiation, they can maximize the effect of the photothermal agents and reduce the risk of tissue damage.[59] The use of photothermal agents on bone scaffolds is thus a very promising approach.

As an effective and minimally invasive therapeutic strategy, PTT has boasted great success in the treatment of cancer. The efficiency of PTT is mainly dependent on photothermal agents, which transform near-infrared (NIR) light into cytotoxic heating. Various photothermal agents have been discovered during recent decades, including Au-based nanoplatforms, carbon-based biomaterials, chalcogenides, organic nanoparticles, and so on.[60–65]

A wide range of photothermal agents has also been used to fabricate bioscaffolds for bone tumor treatment. Two-dimensional (2D) materials are commonly used because of their efficient photothermal energy conversions, such as carbon-based nanomaterials, transition metal dichalcogenides, Xenes (*e.g.* black

phosphorus), and MXenes. After the successful fabrication of ultrathin 2D Ti_3C_2 MXene nanosheets, Pan and coresearchers integrated it with a 3D printing bioactive glass scaffold (BGS) to fabricate a multifunctional biomaterial scaffold (TBGS) for bone cancer treatment (Fig. 3a and b). Irradiated with an 808 nm laser, the temperature of TBGS increased by 20 °C in 10 min, indicating a strong photothermal conversion capacity and excellent heat stability. In further studies of the photothermal ability of TBGS, it was determined that bone tumor ablation was induced by NIR-triggered photothermal hyperthermia.[66] The high temperature of nearly 60 °C caused a decrease in Ki67-positive cells and an increase in TUNEL-labeled necrotic cells in the cancer tissue, indicating the ablation of cancer cells. Calcein-AM labeling showed that TBGS enhanced new bone formation at the defect site while removing cancer cells. Strontium copper tetrasilicate ($SrCuSi_4O_{10}$, denoted SC) has recently been exfoliated in nanosheets combined with PCL to prepare 3D printed composite scaffolds. This bifunctional SC/PCL therapeutic implant could kill bone tumor cells by hyperthermia of SC nanosheets, improve bone mesenchymal stem cells (BMSCs) osteogenesis and endothelial cells angiogenesis.[67] Similarly, 2D BP nanosheets were integrated into 3D printed BGS to prepare a bifunctional BP-BGS for PTT of osteosarcoma. For photothermal ablation of bone tumors, BP nanosheets showed superior performance with photothermal therapy.[68] Graphene oxide (GO) has also been extensively studied in bone bioscaffolds due to its excellent NIR light absorption and high photothermal transformation efficiency. Ma *et al.* fabricated a multifunctional nanohydroxyapatite/graphene oxide/chitosan (nHA/GO/CS) scaffold (Fig. 3c). Under 808 nm NIR irradiation, the scaffold could effectively kill human osteosarcoma cells by heating and facilitate human BMSC osteogenesis at 42 ± 0.5 °C while cooperating with nHA.[69] Normal tissue ingrowth was observed in both the GO/CS+ and nHA/GO/CS+ groups, with significant skin collagen deposition. The expression of Smad1, Smad5 and p-Smad1/5 was increased in these two groups. It may be that local thermal effects activate the expression of Hsp47 and BMP-2 in hBMSC to induce osteogenic differentiation *via* the Smad signaling pathway. Surfaced modified GO could be further compounded with β-tricalcium phosphate (TCP) to prepare a bifunctional scaffold. The composite scaffold exhibits remarkable photothermal effects, which result in over 90% osteosarcoma cell death *in vitro*. Moreover, it effectively reduces tumor size and inhibits tumor growth in mice.[70] Borocarbonitrides (BCN) nanomaterials are demonstrated to incorporate hexagonal BN and graphene structural regions,[71] suggesting the possibility for exceptional photothermal conversion efficiency comparable to graphene. A novel scaffold was built by introducing BCN nanosheets as a responsive coating on 3D printed akermanite (AKT) scaffolds. BCN nanosheets' high light absorption properties led to a unique photothermal effect that caused apoptosis and necrosis of osteosarcoma cells.[72] Similar to graphene, MoS_2 is also a new type of single layer 2D nanomaterial, which has shown high NIR absorbance as well as excellent photothermal conversion efficiency.[73,74] Wang *et al.* fabricated a novel scaffold by doping MoS_2 on the surface of bioceramics. Under NIR irradiation, MoS_2-modified AKT (MS-AKT) scaffolds dramatically lowered the osteosarcoma cell survivability and restrained tumor expansion.[75] In addition, in a study by Wang and coworkers, the MoS_2-PLGA film was covered on the surface of borosilicate bioactive glass (BG) to prepare anti-tumor/bone repairing scaffolds (Fig. 3d), which displayed high photothermal instability and evoked cancer cell apoptosis.[76] Increased late osteogenic markers BMP and Runx2-positive cells in rat skull defects indicate the skeletal regenerative capacity of PTT. There was a similar trend in the proportion of

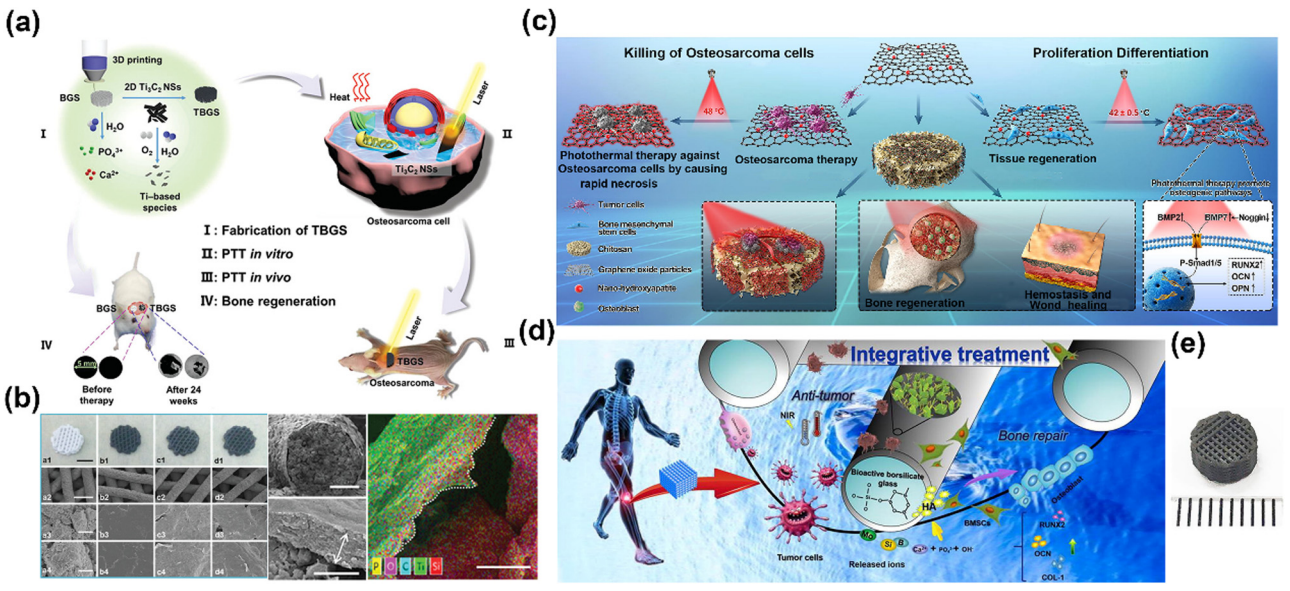

Fig. 3 (a) Schematic illustration of the fabrication of TBGS, ablation of bone cancer, and regeneration of bone tissue. (b) Digital photographs and SEM images of pure BGS and TBGS. Copyright 2019, Wiley-VCH. (c) Schematic illustration of the fabrication of nHA/GO particles, nHA/GO/CS scaffolds, and their bio application. Copyright 2020, Elsevier. (d) Schematic diagram for the investigation on the integrative treatment of anti-tumor/bone repair with a 3D-printed BGM scaffold. (e) The image of a printed 3D BG scaffold. Copyright 2020, Elsevier.

new bone volume and bone density. These data all point to the promising nature of anti-cancer and bone regeneration through controllable photothermal agents.

As well as graphene, other carbonaceous systems can also be used for photothermal therapy utilizing NIR wavelengths. In a recent study by Geng *et al.*, carbon dots were electrostatically attached to WS_2 to prepare nanosheets for photothermal therapy of osteosarcoma (Fig. 4a). The result showed that MG-63 cell viability was only 6% after 1064 nm laser irradiation for 5 min. In addition, tumor growth in mice was observed to be completely inhibited.[77] Interestingly, by incorporating sculpting and composition of ceramic materials, bioscaffold fabrication could be simplified. During polymer-to-ceramic conversion, some bioceramics can be manufactured from organosilicon polymers, in which carbon atoms could be pyrolyzed to free carbon. A free carbon embedding larnite scaffold fabricated by Fu *et al.* was capable of absorbing NIR light and having a highly effective photothermal conversion to inhibit tumorigenesis in bone (Fig. 4b).[78]

Nanoparticles of precious metals, such as Au, Ag, and Pt, are the most researched photothermal materials.[79,80] Because of their low biodegradability, most of them are not suitable for medical applications. Recently, metallic–non-metallic compounds such as CuS and organic semiconductor materials have been exploited for photothermal applications. With their superior light absorption capability, metal sulfides are promising candidate photothermal agents. CuS nanoparticles could be assembled onto mesoporous silica nanoparticles and exhibited an excellent anti-tumor effect *in vitro*.[64] As a kind of copper-based semiconductor, $CuFeSe_2$ nanocrystals have potential application in the photothermal area. $CuFeSe_2$ can grow on the surface of 3D printed BG scaffolds. When exposed to an 808 nm laser, the combined scaffolds acquired anti-tumor bioactivity.[65]

Another technique for performing anti-neoplastic effects of metals is to dope its element into other biomaterials such as bioactive glasses. Researchers reported a novel type of Bi-doped glass and assessed its biocompatibility, HAp formation, and photothermal efficacy, which demonstrated that Bi-doped glass can ablate bone tumors promptly under irradiation with NIR light and facilitate osteogenic cell proliferation, differentiation, and mineralization.[81] The potential of high photothermal conversion of Bi was first reported in this study. Recently, elements (Cu, Fe, Mn, and Co) were incorporated into Ca–Si-based bioactive glass ceramics (BGC) (Fig. 4c). The metal-doped scaffolds showed excellent photothermal properties, with anti-tumor activity achieved by the thermal energy generated by 5Cu-BGC, 5Fe-BGC and 5Mn-BGC. Furthermore, element-doped scaffolds greatly enhanced the expression of VEGF of rat BMSCs and ionic products (Si, Ca) freed from scaffolds motivated osteogenic differentiation of rat BMSCs.[82] This is attributed to the ability of Cu^{2+} and Co^{2+} to mimic the hypoxic environment by stabilizing HIF-1α and stimulating the expression of osteogenic-related genes, demonstrating the biological activity of element-doped scaffolds. Overall, the PTT strategy is able to trigger angiogenesis and osteoblast differentiation while ablating cancer cells through hyperthermia. Its excellent operability and controllability become a prerequisite for clinical translation.

2.3 Magnetic hyperthermia therapy (MHT)

Magnetic hyperthermia therapy (MHT) is an alternative approach for hyperthermia-based treatments, in which biomaterials are

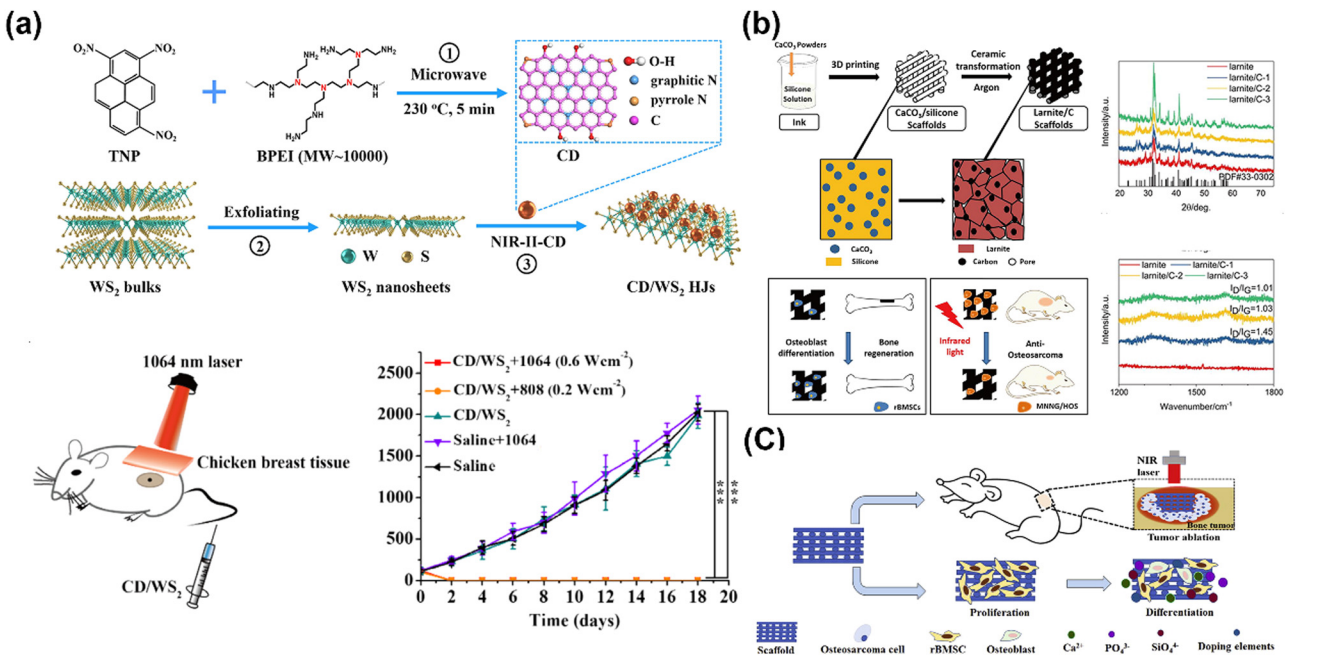

Fig. 4 (a) Schematic illustration for the preparation procedure of CD/WS2 HJs and their functions for tumor therapy. Copyright 2020, Elsevier. (b) Schematic illustration for the fabrication process of the larnite/C scaffolds and their functions for tumor therapy and bone regeneration. Copyright 2020, Elsevier. (c) Schematic illustration for the functions of elements (Cu, Fe, Mn, Co)-doped bioactive scaffolds for tumor therapy and bone regeneration. Copyright 2018, Elsevier.

made to respond to an external magnetic field. Conductive material in an electromagnetic field would be heated by Néel relaxation, Brownian relaxation, and hysteresis.[83] Thus, magnetic nanostructures injected into malignant tissues could be inspired by an alternating current magnetic field to induce a temperature increase in tumor tissue *via* conversion of magnetic energy, thus ablating tumors, inhibiting their growth, and improving chemotherapy or radiotherapy efficacy. The first application of magnetic materials for hyperthermia tumor treatment was reported in 1957 by Gilchrist *et al.*[84] Since then, MHT has been widely researched as a result of the application of magnetic nanoparticles (MNPs). MNPs generally refer to a class of elements including iron, nickel, cobalt, and their alloys or oxides of magnetic elements. Although every magnetic material may exhibit a magnetocaloric effect, which has many advantages, such as large surface area, good biocompatibility, superparamagnetic properties and easy controllability *via* external magnetic field conditions.[85] Even though every magnetic material may exhibit a magnetocaloric effect, superparamagnetic nanoparticles are still the most promising nanomaterials for magnetic hyperthermia treatment. The concept of superparamagnetism refers to the phenomenon that a single domain can be formed to induce strong magnetization of magnetic materials at a certain small size. The magnetization of superparamagnetic materials will not continue to be maintained when the magnetic field is removed.

Due to magneto-thermal effects, magnetic nanostructures can be designed to obtain functional magnetic scaffolds that can be used in bone tumor magneto-thermal treatments. We can develop an inherently magnetic scaffold or incorporate MNPs into a prefabricated scaffold to obtain the MHT materials. In the presence of a magnetic field, heat is released, followed by inhibition or ablation of tumor cells. In a study by Kamitakahara *et al.*, porous hydroxyapatite (HA) granules composed of rod-shaped particles were prepared and stably supported with magnetic nanoparticles composed of γ-Fe_2O_3 with a small amount of Fe_3O_4. Under an alternating magnetic field of 300 Oe at 100 kHz, the temperature of the magnetic and HA nanoparticle composites increased to more than 45 °C within 80s.[86] Elevated temperature has been reported to kill tumor cells.[87] As an FDA-approved biomaterial, polymethylmethacrylate (PMMA) bone cement has been extensively applied in bone disease therapy due to its favorable biocompatibility, good mechanical strength, and stable solidifying process. Fe_3O_4 nanoparticles could also be interfused into PMMA bone cement to prepare a multifunctional bone cement, which could be injected into bone tumor, with anti-tumor properties.[88] Hyperthermia induced by Fe_3O_4 nanoparticles not only caused obvious tumor ablation but also enlarged the synergistic chemotherapeutic efficacy.[89] Recently, Zhang *et al.* loaded the GO sheets with Fe_3O_4 nanoparticles to prepare GO–Fe_3O_4 nanocomposite layers and then modified them on the β-TCP scaffolds surface (Fig. 5). The low content of Fe_3O_4 in β-TCP–8Fe–GO scaffolds exhibited a super paramagnetic effect and hyperthermal properties. With alternating magnetic fields, the scaffold temperature was elevated within the range of 50 to 80 °C in 15 minutes and consequently resulted in the death of more than 75% of osteosarcoma cells *in vitro*.[90] More interestingly, BMSCs cultured in magnetothermal scaffolds had stronger osteogenic potential. β-TCP-4Fe-GO scaffolds showed significantly higher expression levels of osteogenic markers (ALP, OPN, Runx2, OCN, BSP) than β-TCP scaffolds. The data imply that the slow release of Fe^{3+} from the scaffold has a positive effect on osteogenic differentiation. A multifunctional Mg_2SiO_4–

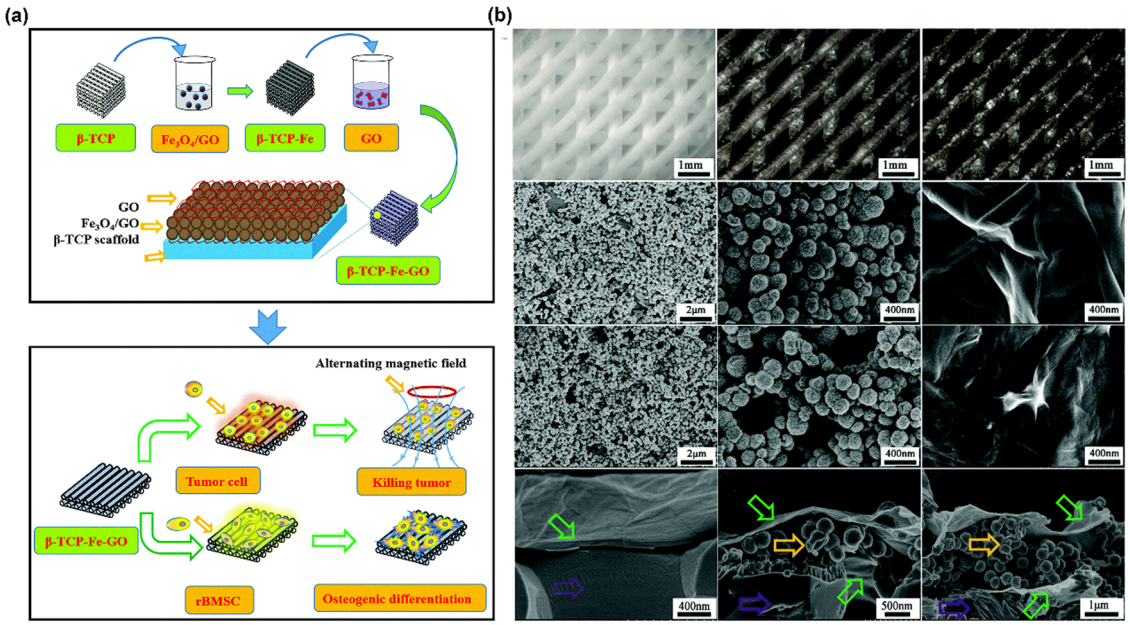

Fig. 5 (a) Schematic for the synthetic route and the bifunctional properties (killing tumor cells and stimulating osteogenic differentiation) of magnetic scaffolds. (b) Optical micrographs of b-TCP, b-TCP–4Fe–GO and b-TCP–8Fe–GO scaffolds, and SEM images of b-TCP–4Fe, b-TCP–8Fe, b-TCP–4Fe–GO and b-TCP–8Fe–GO scaffolds. Copyright 2016, Royal society of chemistry.

$CuFe_2O_4$ nanocomposite was synthesized by sol–gel combustion and surfactant-assisted sol–gel methods. With the performance of these elements, including Mg, Cu, and Fe, this nanocomposite not only had the ability of antibacterial to prevent bone graft infection but also had the heating proficiency to kill bone tumor cells.[91]

Several clinical research studies have been reported on MHT to treat bone tumors. Superparamagnetic iron oxide nanoparticles, such as magnetite (Fe_3O_4) and maghemite (Fe_2O_3), have already been approved for clinical applications by the FDA.[92] A research work compared two different treatment methods for metastatic bone tumors. A group patient was cured by MHT and another group patient was subjected to oncological surgical resection. In this clinical research, calcium phosphate cement containing Fe_3O_4 nanoparticles was used to achieve the magnetic hyperthermal effect and resulted in better outcomes than surgical resection alone.[93]

Like other forms of hyperthermia treatments, the ideal approach of MHT requires the capacity to locally heat the tumor to an efficient temperature but with minimal injury to normal tissues. The transformation ability of magnetic energy to thermal energy is affected by size, shape, surface modifications, *etc.* It has been established that the target therapeutic temperature can be tuned by regulating their sizes, morphologies, and compositions of MNPs. In addition, coupled with a fast phase-transformation strategy introduction, we could use magnetic materials to fabricate a magnetic nano-emulsion hydrogel to securely restrict intra-tumor heating without damaging the surrounding normal tissue.[94] To summarize, initial explorations of MTH have successfully shown great potential in the construction of bone scaffolds for clinical applications.

2.4 Sonodynamic therapy (SDT)

As a type of mechanical wave, ultrasound has a frequency greater than 20 KHz, which exceeds the audible range of mankind. It could be used not only for diagnostic purposes with low energy irradiation to avoid tissue damage, but also for therapeutic aims with a higher dose of energy irradiation to induce its biological actions. Ultrasound can induce bioeffects, including both thermal and nonthermal effects, in biological tissues. High intensity irradiation can lead to significant thermal effects, whereas low frequency irradiation can cause acoustic cavitation, which in turn generates shockwaves and light (known as sonoluminescence).[95,96] Hence, high intensity focused ultrasound (HIFU) was invented to obtain thermal effects of high energy density for ablation of tumor tissues, and focused ultrasound (FUS) is able to transfer the ultrasound energy to a sufficiently high temperature at the focused tumor site and damage tumor tissues.[97] While low-intensity ultrasound could be used as SDT, a noninvasive treatment, together with a sonosensitizer.

Yumita *et al.* demonstrated that hematoporphyrin could be applied as a sensitizer to enhance the anti-tumor effect of ultrasound,[98] and believed that the mechanism of the hematoporphyrin sensitization was similar to photosensitization to laser light.[99] This is the first report about SDT. SDT is triggered by ultrasound, and then a class of sound-responsive materials called sonosensitizers react with surrounding oxygen and even water molecules and form ROS for subsequent degradation and death of tumor tissue.[100] During the SDT process, sonosensitizers are recognized as vital components. Among the various reagents, the most broadly applied are porphyrin-based or xanthene-based sonosensitizers. To create bone scaffolds that encompass the approach of SDT, more and more researchers are committed to the design and development of various novel sonosensitizers.

Hematoporphyrin monomethyl ether (HMME) is an efficient sonosensitizer. HMME and ultrasound radiation appeared to increase the cell death rate of osteosarcoma cells, and the growth of osteosarcoma cells was markedly inhibited.[101] Another study further revealed that the enhancement of cell killing was caused by not only intracellular ROS but also Ca^{2+} elevation.[102] 5-aminolevulinic acid (5-ALA), which can metabolize into the biological precursor of protoporphyin IX (PPIX), is a novel sonosensitizer to mediate SDT for cancer cells. A study showed that 5-ALA could undergo metabolic steps to be a sonosensitizer and significantly strengthened ultrasound-mediated osteosarcoma cell suppression and ultrasound-induced decrease in cell viability of UMR-106 cells.[103] Cell apoptosis *via* the mitochondria pathway assumed a very important role in the deletion of rumor cells.[104]

The electron's transition from the valence band to the conduction band due to sonosensitizers is one of the chief mechanisms of SDT. The narrowed band gap can yield easier electron excitation motivated by external stimulation. Some inorganic sonosensitizers, such as titanium oxide (TiO_2) nanomaterials, are also used for cancer SDT owing to their strong chemical stability, nontoxicity, and low production cost.[105] Doping with different metallic/non-metallic elements can indeed reduce the band gap of TiO_2, and leads to an efficient photon-to-current conversion and a better therapeutic effect.[106] Ultrasmall iron-doped TiO_2 has demonstrated to decrease the band gap and enhance the ROS generation efficiency, improving the sonodynamic effect of TiO_2 nanodots.[107] Vanadium doped TiO_2 could also reduce the TiO_2 nanospindles band gap and significant enlarged the efficiency of ROS generation triggered by ultrasound.[108] In human-derived osteosarcoma mice models, a 35.0×5.2 nm ultrafine W-TiO_2 nanorod displayed a better SDT efficiency than undoped TiO_2 nanorods.[109]

The exposure of sonosensitizers to ultrasound and subsequent generation of free radicals is believed to be similar light irradiated photosensitizers. At present, as mentioned earlier, most sonosensitizers are parts of photosensitizers. SDT can deeply penetrate into target tissues, which overcomes the disadvantages of PDT. But both have the major common side effect of potential phototoxicity and skin sensitivity.[110] If the novel sonosensitizer that only show sensitivity to ultrasound with its SDT effects achieved by the mechanisms of cavitation and collapsing energy, but not sonoluminescence, could be well prepared, it could serve as a promising material for tumor SDT without photosensitivity.[111,112]

2.5 Chemodynamic therapy (CDT)

Chemodynamic therapy refers to the mode of cancer treatment induced by chemical stimulation and produces ROS. To treat

cancer with nano-catalysts, particular chemical reactions, especially the Fenton reaction or Fenton-like reaction in the tumor, have been induced by the unique biochemistry of the tumor microenvironment.[113] Since the first study that employed a Fenton reaction that was induced by the specific properties of the tumor microenvironment was reported in 2016,[114] the study of CDT has gained increasing attention from researchers around the world. A large number of nanomaterials have been studied for CDT, among which iron oxide nanoparticles (IONPs) are the most investigated biomaterials. In the acidic extracellular environment commonly found in tumors, IONPs could catalyze the overproduced H_2O_2 into hydroxyl radicals, which contribute to the anti-tumor activity.[115]

In bone tumors, certain tumor microenvironment characteristics are also present, including mild acidity, high amounts of hydroxyl peroxide, and hypoxia, which make them ideal candidates for CDT. A 3D-printed AKT bioceramic scaffold was developed by constructing a Fe_3S_4 surface layer *via* a hydrothermal method. The existence of ferrous ion in the Fe_3S_4 layer ensured the progress of the CDT, which could be promoted by hyperthermia under an alternating magnetic field.[116]

H_2O_2 is significantly increased in tumor microenvironments, providing reactive substances for CDT. However, there is a certain limit to the increase of its concentration, which do not provide sufficient H_2O_2 to maintain the production of $^{\bullet}OH$.[117] It potentially fails to achieve the desired effects. Therefore, additional catalytic reactions need to be designed to utilize other intracellular substances as another source of H_2O_2, so that sufficient generation of $^{\bullet}OH$ can be sustained for therapeutic purposes. For example, nano-CaO_2 has the capability to produce H_2O_2 in an acidic environment. It was loaded together with Fe_3O_4 nanoparticles into a 3D printed AKT scaffold. The result showed that combining hyperthermia with a catalytic Fenton reaction achieved by Fe_3O_4 and CaO_2 NPs showed exciting curative outcomes for osteosarcoma. In this study, CaO_2 NPs supplied adequate H_2O_2 and released Ca^{2+} ions continuously, while Fe_3O_4 NPs produced $^{\bullet}OH$, which was accelerated by magnetic hyperthermia. The result enlightened a future application for osteosarcoma treatment by the multifunctional biomaterial platforms.[118] CaO_2 sustains the iron oxide (IO) nanoparticle-mediated catalytic Fenton reaction and liberates highly toxic $^{\bullet}OH$ for inducing tumor cells apoptosis. Meanwhile, the $^{\bullet}OH$ production was further promoted by the photothermic effect of the Nb_2C-IO-CaO_2 nanomaterials under NIR at the second biowindow.[119] Engineered microorganisms could also generate enough hydrogen peroxide for the process by themselves. The Fenton-like reaction was used by Fan *et al.* to create modified bacteria for tumors. They employed the anticipated alterations to select non-pathogenic *E. coli* MG1655 (Ec) to acquire Ec@pE@MNPs. Ec had the ability to localise at tumour sites and boosted native H_2O_2 yield owing to overexpression of the NDH-2 enzyme (respiratory chain enzyme II). Ec were then covalently bonded to the magnetic Fe_3O_4 nanoparticles, which acted as a catalyst. As a result of the modified bacteria's H_2O_2, a Fenton-like reaction takes place, resulting in harmful $^{\bullet}OH$ and killing tumor cells. Moreover, this medicinal method was found to be biosecure by toxicological tests.[120]

Single-atom catalysis is also an important and emerging field. Single-atom Fe-containing nanocatalysts are widely applied to initiate the local Fenton reaction for CDT.[121] Wang *et al.* used a 3D printed BG scaffold to incorporate highly vibrant single-atomic iron catalysts (FeSAC) (Fig. 6). The modified FeSAC exhibited strong Fenton catalytic activity, generating harmful $^{\bullet}OH$ in osteosarcoma microenvironments. In the presence of NIR and physiological concentrations of H_2O_2, *Staphylococcus aureus* and *Escherichia coli* were completely eradicated by 250 μg mL^{-1} FeSAC on agarose plates in only 4 h, demonstrating the remarkable antibacterial performance of FeSAC. This suggests that complex osteosarcoma treatment, bacterial clearance, and subsequent osteogenesis were achieved incredibly synchronously. Research presented here outlines a comprehensive, therapeutically viable strategy for osteosarcoma and bacterial.[122]

3 Drug-loaded bone bioscaffold therapeutic strategy

Chemotherapy has always been one of the most effective treatments for bone tumors, which could use toxic compounds to restrain the rapid cancer cell proliferation to achieve anti-tumor effects.[123] Since the first batch of chemotherapy drugs was approved for clinical application in the 1940s and 1950s, more and more varieties of drugs have been used for cancer treatment, such as methotrexate, cisplatin (DDP), paclitaxel, *etc.*[123] Although chemotherapy drugs could obviously inhibit or kill tumor cells, they also have obvious toxic side effects, including hair loss, nausea, and gastrointestinal reactions. This is mainly because the toxicity of the drug itself affects the fast-growing normal cells.[124] On the other hand, since chemotherapeutic drugs are applied systemically, and it is difficult for drugs to spread in hard tissue, larger doses of anti-tumor drugs must be administered so that the drug at the tumor site could achieve an effective concentration, which also increases the negative impact on normal tissue cells.[125]

By implanting the bone scaffold directly at the site where the tumor was removed, drugs could be loaded into the scaffold and delivered directly to the sites nearest the residual tumor cells, with an immediate release or sustained release to the local site.[123] Not only could this achieve the advantages of local drug administration and reduce the unwanted side effects of systemic drugs, it could also achieve continuous anti-tumor effects for several weeks, months or even years through slow release or controlled release. Previous experiments have shown that anticancer drug delivery scaffolds could achieve a combined delivery of multiple chemotherapeutic agents and sustainable therapeutic drugs release.[123] As a result, they increased local drug concentrations, enhanced pharmacodynamics and reduced side effects from systemic chemotherapy.[126] Many drugs could be loaded into a scaffold, and these could be subdivided into the following categories:

3.1 Basic anticancer drug

In addition to surgery, chemotherapy has been used for decades in the treatment of osteosarcoma, and it has significantly improved the clinical effect of simple operation.[127] Studies have

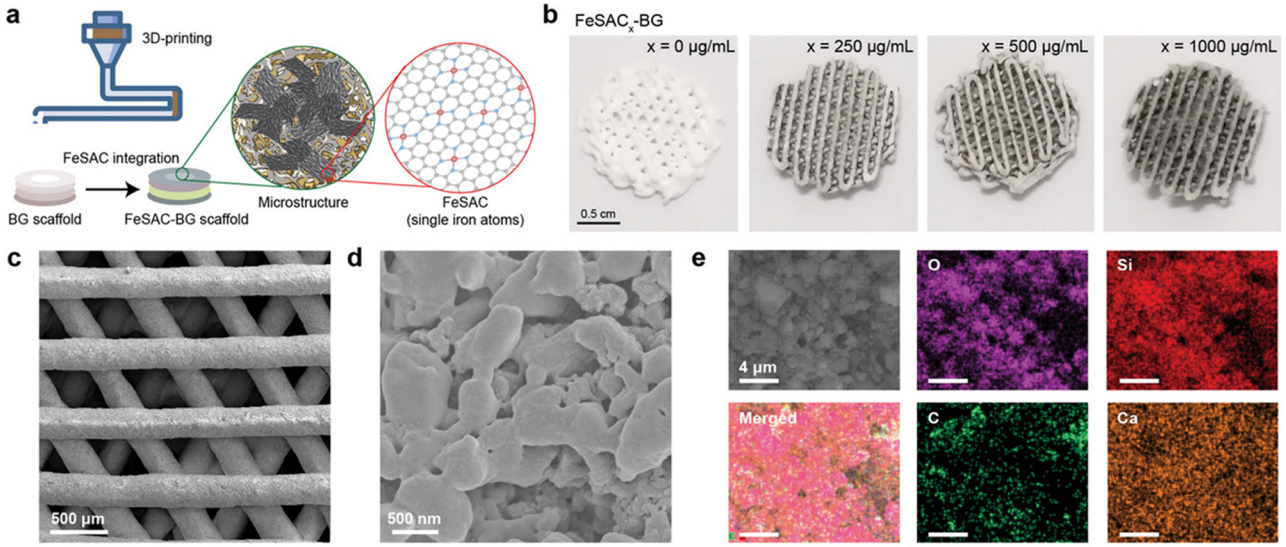

Fig. 6 (a) Schematic illustration of the construction of FeSAC-BG scaffolds. (b) Digital photographs of FeSAC-BG scaffolds with varied initial impregnating FeSAC concentrations: 0, 250, 500, and 1000 μg mL^{-1}. (c and d) SEM images of FeSAC500-BG scaffolds at varied magnification and (e) the corresponding elemental mappings of O, Si, C, and *Ca*. Copyright 2021, Wiley-VCH.

shown that MAP (methotrexate, doxorubicin (DOX), DDP) regimen is the classic treatment and gold standard for the chemotherapy of osteosarcoma,[128] requiring large dose applications of anti-tumor drugs, which usually leads to many acute and chronic side effects.[129] To avoid this, the researchers loaded these drugs with a variety of biomaterials to achieve the same anti-tumor effect while reducing the total amount of drugs, thereby reducing side effects. Using the poly(D,L-lactide) (PDLLA) as the medium, coated with TiN particles and DOX on the surface of TCP scaffolds, accurate photothermal therapy and local controlled release chemotherapy for osteosarcoma could be achieved, and good therapeutic effects had been achieved both *in vivo* and *in vitro*. Moreover, this scaffold could also be used as a general drug delivery platform for loading different types of drugs.[130] Not only TCP, but calcium sulfate and HA could also be used to prepare custom scaffolds for loading DOX, and have achieved the purpose of improving the chemotherapy effects of bone tumors.[131,132] Another study showed dopamine modified zeolitic imidazolate framework-8 metal organic frameworks (MOFs) could be prepared into gelatin scaffolds and loaded with BMP-2 and DDP, so that the scaffolds could effectively release DDP and restrain tumor growth according to the stimulation of the local microenvironment.[133] This scaffold possessed a smart ability and environmentally sensitive property. It shows that it utilizing an innovative strategy to delivery traditional effective antineoplastic drugs is a feasible measure and crucial. 5-Fluorouracil (5-FU) is also a common antineoplastic drug. 5-FU coated calcium phosphate cement (CPC) scaffolds showed significant cell growth inhibition *in vitro* cell culture using two different cancer cell lines, and could be used as a therapeutic material for bone tumors.[134] Interestingly, different types of anticancer agents could also be loaded with biological materials and released in a controlled way in different modes to achieve the superposition, synergism or antagonism effects of drug therapy. The combined release of DDP and DOX showed a synergistic effect in calcium phosphate beads and matrix scaffolds. DDP was burst released within a short period of time, while DOX was continuously released for more than 40 days during the measurable study period.[135]

3.2 Melatonin

Melatonin is a circadian hormone secreted by the pineal gland or other similar organs, and its synthesis and secretion are modulated by the central circadian clock. Melatonin is involved in immune modulation, antioxidation and hematopoiesis, and plays an important role in maintaining appropriate homeostatic metabolic rhythm. In addition, accumulating evidence shows that melatonin possesses a variety of biological activities and shows a wide range of anti-tumor effects.[136] MT1 is one of the main receptors affected by melatonin, which is mainly responsible for regulating the downstream effect of melatonin. MT1-mRNA was proved to be highly exploited in human osteosarcoma cells and other malignant or non-malignant bone tumors.[137] Especially in osteosarcoma cells, melatonin shows convincing cytotoxicity and anti-metastatic activity.[138,139] Due to the rapid clearance of melatonin, it makes sense to encapsulate them in drug delivery particles or scaffolds to control release. Poly(D,L-lactide-*co*-glycolide) (PLGA) micro/nanoparticles loaded with melatonin could be taken up by MG-63 cells and release melatonin explosively, which performed a remarked suppression on osteosarcoma.[140] Chitosan scaffolds could also be used to load melatonin/2-hydroxypropyl-β-cyclodextrin (HPβCD) inclusion complexes, and the release of melatonin could result in time-dependent death of osteosarcoma cells by reducing the proportion of cells in the G2/M phase rather than S phase.[141] The cell-in-cell structure (CIC) also has a function in the occurrence and development of cancers by altering the energy metabolism of tumor cells. The expression of MT1 and CIC increased in osteosarcoma tissues and cells. Through experiments *in vivo* and *in vitro*, it had been found that a 3D printed magnesium–PCL

scaffold containing melatonin (MG-PCL-MT) inhibited the key CIC pathway through a cAMP/PKA signaling pathway, affecting the mitochondrial function of cells, leading to anti-invasion and anti-metastasis functions. In the *in vivo* model, MG-PCL-MT had a significant inhibitory effect on distant organ metastasis of osteosarcoma.[142]

Melatonin could also be loaded into two types of melatonin-carrying and -releasing systems and incorporated into the 3D porous tissue scaffolds. These porous scaffolds loaded with two carrier systems could achieve biphasic release of melatonin, that is, the HPβCD inclusion complex could rapidly release melatonin within 24 hours and inhibit osteosarcoma cells, while the melatonin-loaded PLGA microparticles could have sustained release for 40 days, to support bone regeneration. This indicates that the osteoinductive and anticancer properties of melatonin could effectively act together by using a 3D scaffold-based system, which would be a promising human osteosarcoma treatment system.[143]

3.3 Inorganic element-selenium

Selenium (Se) is an essential trace element for organisms. Both humans and animals need to supplement selenium. Se has many properties, such as antioxidant defense, immune surveillance, regulating cell proliferation, inhibiting cancer cell invasion and so on, so it is used in a variety of anti-cancer materials. Its main mechanism of anti-tumor activity is to promote ROS generation and lead to apoptosis of tumor cells, such as osteosarcoma cells.[144,145] Se/MBG nanospheres prepared by a novel therapeutic ion Se and mesoporous BG had selective cytotoxicity to osteosarcoma cells MG-63 and could effectively regulate the release of loaded DOX. Se and DOX in nanospheres had synergistic effects and displayed a prolonged inhibitory effect on the survival of osteosarcoma cells.[146] Li *et al.* prepared selenium-doped HA (Se/HA) nanoparticles and found that Se/HA nanoparticles exhibit a significant inhibition on tumor growth in the model of orthotopic osteosarcoma tibial, and the inhibitory effect increased gradually with the extension of treatment time.[20] Moreover, the anticancer effect of Se/HA nanocomposites could be enhanced by catechin modification *via* inducing tumor cells apoptosis.[147] Karahaliloglu *et al.* employed Se-nanoparticles to improve the anticancer and antibacterial performances of PMMA and TCP bone cement. Results showed that the apoptosis incidence in Saos-2 cells of Se-nanoparticle containing groups was dramatically increased compared with the others.[148] A biomimetic three-phase composite scaffold composed of porous Ti_6Al_4V (pTi), chitosan (CS) and selenium-doped hydroxyapatite (HAP) nanoparticles (HAP-Se), called pTi/CS/HAP-Se, promoted osteoblast proliferation and inhibited tumor cell growth and bacterial survival (Fig. 7a). The scaffold had a multistage porous structure, similar to natural bone tissue, showing its promising applications in osteosarcoma management.[149] Also due to the doping of Se elements and CS, the antimicrobial ability is enhanced along with the anti-tumor ability of the scaffold. Compared with the pTi scaffold, the osteoblasts on the composite scaffold showed spindle-shaped adhesion, which was more favorable for differentiation to osteoblasts. Meanwhile, the larger specific surface area of the composite scaffold provides a superior cell survival environment for osteogenic differentiation. Inorganic elements induce tumor cell apoptosis through the inherent caspase-dependent apoptosis pathway and cooperate with the production of ROS to inhibit tumor growth. This mechanism has been further verified in selenium-doped HA nanoparticles.[150]

3.4 Metal-based drugs

Since the anti-tumor activity of DDP was discovered and effectively used in the clinic, the exploitation in new metal-based anticancer reagents has attracted lots of attention. Various metal-based drugs with different methods are currently under research, such as platinum, ruthenium, gold and titanium, *etc.*,[151] which are also effective for osteosarcoma. Previous studies indicated that

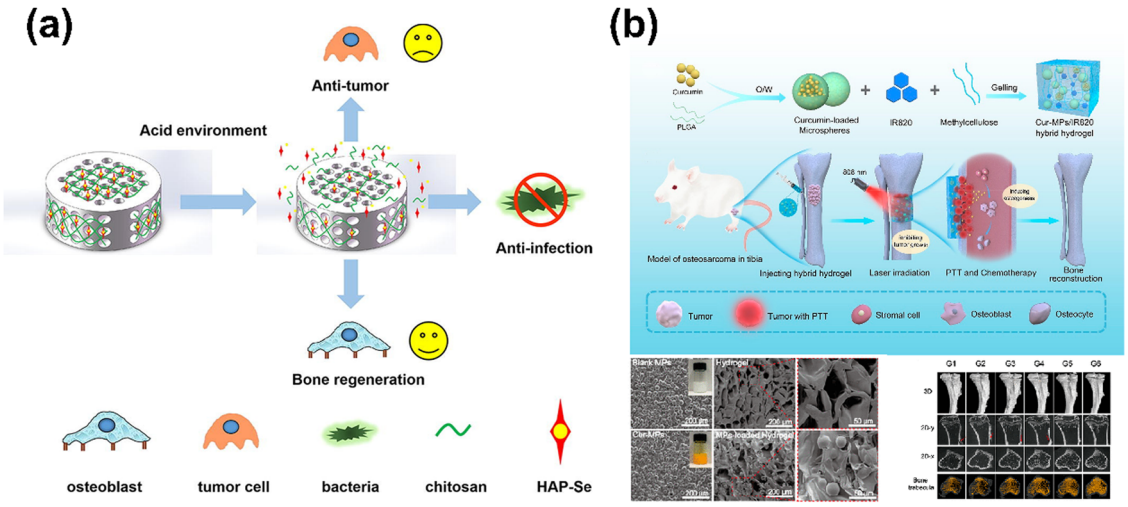

Fig. 7 (a) Schematic illustration of the fabrication and application of biomimetic triphase composite scaffolds for osteosarcoma therapy. Copyright 2019, Elsevier. (b) Illustration of the Cur-MP/IR820 hybrid hydrogel applied in osteosarcoma chemo-photothermal combined therapy and followed by bone reconstruction. Copyright 2021, ACS publications.

ruthenium-loaded PEGylated liposomes were introduced into silica nanoparticle/PCL porous scaffold, and the results showed that the composite could sustain drug release for more than 48 hours and led to mitochondrial dysfunction and apoptotic death of osteosarcoma cells MG-63.[152]

Metallic magnesium (Mg) has obvious anti-tumor properties in living organisms, and is a potential candidate to deal with malignant bone tumors.[153] Degradation of Mg in physiological environments releases Mg^{2+} ions, which could suppress osteosarcoma cell proliferation and promote apoptosis. Bisphosphonate-coated Mg particles could destroy osteosarcoma cells and prevent tumor recurrence through synergistic degradation of Mg and the release of micro-arc oxidation.[154] Mg-coated Ti_6Al_4V scaffolds significantly inhibited the proliferation and migration of osteosarcoma cells. Further evidence of AMPK/mTOR/ULK1 activation was observed *in vivo* and *in vitro*, which might be one of the essential underlying mechanisms of its inhibition of osteosarcoma cells.[155] Reactive oxygen assumes a critical role in bone cancer deterioration. A recently study showed that hydrogen (H_2), a selective antioxidant, released during magnesium deterioration effectively cleared scavenging free radicals in the Fenton reaction system and bone cancer cells, which was expected to prevent metastasis and recurrence of bone cancer while repairing bone defects.[156] In addition to H_2, magnesium hydroxide is produced during the degradation process, creating an alkaline environment of high pH, which has obvious cytotoxicity toward bone tumors.[157] Mg based implants were applied to neutralize the tumor-associated acidic microenvironment. Li *et al.* formulated a novel biomaterial, in which the calcium phosphate coated Mg–Sr alloys were loaded with a small molecule (Zoledronic acid, ZA). ZA-loaded Mg–Sr alloys not only induced apoptosis *via* the mitochondrial pathway of giant cell tumors of bone (GCTB) cells, but also significantly inhibited the activation of NF-κB in the GCTB cells.[158]

Another metal element that could be added is gallium (Ga), a promising candidate element with antibacterial, anti-bone resorption and anti-tumor properties.[159] The anti-tumor effects of gallium ions are achieved mainly through a variety of physiological interference mechanisms, which are mainly involved in DNA replication and destruction of its spiral structure. It could replace Fe iron in transferrin to inhibit ribonucleotide reductase (a key enzyme involved in DNA replication) and is considered to be a non-functional mimic of Fe. The effect of gallium-releasing BGs on bone cancer cells wasfirst researched and the result showed 15 wt% Ga could enhance the viability of preosteoblasts while decreasing the viability of osteosarcoma cells, acting through the suppression of proliferation.[160]

3.5 Natural products

Nature is the best inexhaustible source of anticancer drugs for human beings. In recent decades, about two thirds of the newly discovered anticancer drugs have come from nature. The anticancer effects of these natural products are mediated using a variety of mechanisms, including inducing apoptosis, regulating immune function and inhibiting angiogenesis.[161] Various natural product-loaded delivery scaffolds have also been considered to treat bone cancer. Herein, we focus on highlighting several representative natural phytochemicals such as curcumin, capsaicin, crocin, baicalein, and genistein.

3.5.1 Capsaicin. Capsaicin is the key bioactive component of red pepper and hot pepper. Abundant studies have demonstrated the strong anti-tumor potential of capsaicin. Capsaicin was reported to affect the transcription of several genes related to cancer cell survival, growth arrest, angiogenesis and metastasis, and affect multiple signaling pathways.[162] Capsaicin loaded HAP/poly(xylitol sebacate) (PXS) composites were prepared and their exhibition of antioxidant properties toward osteosarcoma cells was evaluated. Based on the analysis of endocytosis, apoptosis, and ROS, it was concluded that capsaicin induced Saos-2 cells apoptosis and demonstrated an unmatched capability to scavenge H_2O_2. The CAP/HAP/PXS nanocomposite might serve as a promising scaffold for anti-tumor roles in bone tissue engineering.[163]

3.5.2 Baicalein. Baicalein is one of the main active ingredients of Scutellaria baicalensis Georgi, a Chinese herb. The flavonoid baicalein has an array of medicinal properties, including antibacterial, anti-oxidation, anti-cancer, and antiviral actions.[164,165] The anti-tumor molecular mechanisms of baicalein mainly consists of inhibiting cyclin to regulate the cell cycle, scavenging oxidative free radicals, inducing apoptosis, and suppressing tumor invasion and metastasis. Substantial evidence has implied that baicalein may be an potential candidate agent for osteosarcoma therapy in the future.[166,167] Bachimam K and coworkers integrated and characterized a baicalein containing hyaluronic acid-polyethylene oxide-transforming growth factor beta-2-polyvinyl alcohol nanofiber scaffold by electrospinning. The results suggested that baicalein loaded nanofiber scaffolds could be used to prevent local recurrence of bone tumors due to their broad applicability as biomedical materials.[168]

3.5.3 Crocin. Crocin, the main bioactive substance of saffron, is a monosaccharide or disaccharide polyenyl ester, which has been proved to protect cells and tissues against oxidative damage by inhibiting free radicals.[169] As a free radical scavenger, crocin could effectively inhibit the activity of oxygen radicals, inhibiting neoplastic processes at the cellular and molecular levels.[170] Crocin and bicarbonate (a neutralizing agent) were loaded directly into HA disks to evaluate their release *in vitro* and their efficacy on human osteoblasts and osteosarcoma cell lines. Compared with the control samples, crocin and bicarbonate decreased the viability of osteosarcoma cells by almost 50%, and led to clear changes in cell morphology and diffusion. In addition, they significantly reduced the generation of inflammatory cells *in vivo*. Taking these results into account, crocin and bicarbonate may be two interesting therapeutic candidates for osteosarcoma and anti-inflammatory applications.[171]

3.5.4 Curcumin. Curcumin is a yellow polyphenol extracted from the rhizoma of turmeric. It is not only a common spice and dietary supplement, but also a component of many traditional medicines. Anti-inflammatory, antimicrobial, and anticarcinogenic activities of curcumin have been demonstrated in recent decades.[172,173] Curcumin could not only induces apoptosis of cancer cells by regulating a variety of pro-inflammatory factors, growth factors and receptors at the molecular level, but also

inhibits cancer cell proliferation and metastasis. Many preclinical studies have suggested its potential prophylactic and therapeutic uses in the treatment of various cancers.[174] However, its bioavailability is very low, primarily due to the poor water solubility and easy degradation in alkaline environments.[175] To work appropriately, it is necessary to deliver curcumin using some carrier matrixes to retain it for the required time and improve its aggregation in the pathological site.[176] Thus, curcumin is often chosen as a candidate agent loaded in bioscaffolds for bone cancer therapies. Tan *et al.* designed an injectable hydrogel composed of curcumin microspheres and IR820 to treat osteosarcoma and repair bone defects (Fig. 7b). This is a light and thermal dual response delivery system. Under the irradiation of an 808 nm laser, the photosensitizer IR820 releases a large amount of thermal energy, ablating the majority of cancer cells while releasing curcumin. In the more informative and clinically relevant *in situ* bone tumor models, the continuous release of curcumin in hydrogels is helpful to inhibit residual tumor cells and repair bone tissue, which shows good results of chemotherapy and great potential applications.[177] In a recent study, curcumin and vitamin K2 were loaded in a HA coating Ti implant to realize post-surgical repair of tumor-associated bone defects. The showed sustained release from the HA coating and severe cytotoxicity against osteosarcoma cells.[178] In Sarkar N's study, curcumin was encapsulated in a liposome and incorporated onto 3D printed calcium phosphate scaffolds to enhance its bioavailability. Liposome curcumin released from scaffolds exhibited marked cytotoxicity toward osteosarcoma cells and also promoted osteoblast proliferation, suggesting promising application in bone tissue engineering.[179]

3.5.5 Norcantharidin. Norcantharidin (NCTD), a cancer-fighting drug independently developed in China, is the demethylated form of cantharidin. Previously, NCTD could inhibit the development of various cancers, including osteosarcoma cells, *via* suppressing DNA replication and inducing cells apoptosis.[180,181] Huang *et al.* developed a novel strontium/chitosan/hydroxyapatite/norcantharidin (Sr/CS/HAP/NCTD) composite, which might be a promising technique for osteosarcoma treatment and repair of tumor-related bone defects. The inhibitory effect was found to induce apoptosis by increasing proapoptotic gene transcription.[182]

3.5.6 Soy isoflavones. Soybean is one of the primarily dietary sources of isoflavones, a type of phytoestrogen.[183] There are mainly three kinds of isoflavones in soybeans, which are genistein, daidzein and glycitein. Among them, genistein could selectively destroy tumor cells without damaging normal cells. Daidzein has estrogenic effects on reducing bone resorption and increasing bone mineral density. The researchers combined three major soybean isoflavones with porous 3D printed TCP scaffolds, in a ratio mimicking their original proportion in soy, to evaluate their effects on osteoblast proliferation and the prevention of osteosarcoma. Unsurprisingly, soy isoflavones released from the 3D printed TCP scaffolds resulted in a significant decrease in MG-63 cell viability and proliferation, suggesting their potential application in bone cancer treatment as a chemopreventitive agent.[184]

3.6 Bisphosphonates

Known as "antiresorptive drugs", bisphosphonates inhibit bone resorption and are commonly used to treat osteoporosis. Studies in pre-clinical models have shown that bisphosphonates have a range of anti-tumor effects, such as inhibiting bone metastasis, inducing apoptosis in cancer cells, and triggering anti-neovascularization.[185] In addition, bisphosphonates have a high affinity with bone minerals, making them suitable bone-targeting compounds to increase a drug's selectivity against bone tumors. Just as cited earlier, zoledronic acid (ZA) released from the ZA-loaded Mg–Sr alloys could significantly activate mitochondria-mediated apoptotic pathways and suppress the NF-κB pathway in the GCTB cells.[158] In Lu's study, highly active chitosan/nano-hydroxyapatite (CS/NHA) scaffolds containing zoledronic acid were prepared using a simple method. The prepared scaffold displayed a potent anti-cancer efficacy on GCTB *in vitro*. It could induce apoptosis through up-regulation of the pro-apoptotic genes and decrease tumor-induced osteoclast-related gene expression. The scaffolds showed a multi-function of tumor resistance, bone repair and antibacterial effect, presenting a new approach for bone cancer treatment.[186]

4 Immunomodulatory bone bioscaffold therapeutic strategy

Cancer immunotherapy is a novel field for tumor treatment, which has been explored for a long-standing history since bacterial toxins were reported for use in bone and soft-tissue sarcoma immunotherapy.[187] Antigens derived from apoptotic or necrotic tumor cells could be captured by dendritic cells (DCs) and then activate immature T cells, resulting in specific recognizing and killing the targeted tumor cells.[188] Cancer immunotherapy induces immune responses to kill tumor cells by improving the systemic immune system or reverse the immunosuppression of the tumor microenvironment. On the one hand, various immunotherapeutic agents, such as antigens, antibodies, adjuvants, cytokines, and even immune cells, could be used to enhance the immune response.[189] On the other hand, immunosuppressive factors in the TME could be damaged to overcome the suppression of T cell function in tumors.

Biomaterial scaffolds could be pre-designed with specific physiochemical and biological properties to load immunotherapeutic agents and locally release them in a sustained and controllable way. Sialic acid-binding immunoglobulin-like lectin 15 (Siglec-15) has been previously proved to be a macrophage-associated T cell immunosuppressive molecule, regulating cell growth to suppress antigen-specific T cell responses. Siglec-15 monoclonal antibody could reverse immune suppression, activate T cell responses, and inhibit the growth of tumors.[190] Micro-nano bioactive glass scaffolds loaded with siglec-15 monoclonal antibody was shown to decrease the development of tumor by promoting osteosarcoma cell apoptosis.[191] Imiquimod (R837) is so far the only approved TLR7 agonist for human use, stimulating TH-1 immunity and $CD8^+$ T cell responses by activating dendritic cells.[192] As an immune adjuvant, R837 was loaded into Nb_2C MXene-modified 3D-printing bioglass scaffolds and exhibited

vaccine-like functions together with released tumor debris, significantly triggering the immune response and ultimately resulting in an inhibition of tumor cell bone metastases in combination with immune check-point blockade therapy.[193] Immune checkpoint blockade therapy has also been proved to enhance the anti-tumor activity of T lymphocytes through blocking programmed-cell-death protein 1 (PD1) and its ligand PD-L1 or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[194] Biomaterial scaffolds could also deliver chimeric antigen receptors (CAR) T cells and stimulator of IFN genes (STING) agonists to the targeted tumor location. The former performed a more sustained and effectively anti-tumor effect than systemic injections of the same cells, and the latter upregulated CD86 and MHC II expression, triggering host anti-tumor immunity to kill tumor cells and inhibit metastases.[195]

Some features of biomaterial scaffolds themselves, such as their size, shape, surface morphology and charge, have unique immunomodulatory functions that ultimately influence immune responses. Coating materials on the surface of a scaffold, such as a magnesium nanotube array coating on the titanium, endowed the scaffold surface with immune-modulate functions and negatively regulated the inflammatory responses of macrophages.[196] It has been found that roughened titanium caused a polarization of anti-inflammatory macrophages and increased the release of inflammatory cytokines, thus enhancing the osseointegration of roughened titanium implants.

Similar to other tumor microenvironments, the bone tumor microenvironment also has various neoantigens and complex immune cell functions, showing characteristics of an immunosuppressive microenvironment.[197] Varieties of tumor-associated cells and cytokines or chemokines could be regulated to activate tumor-specific T cells and awaken or restart the immune responses of tumor microenvironments.

By manipulating the microenvironment around the tumor, scaffolds could also affect the spread of tumor cells. For example, all-trans retinoic acid could reduce the migration of osteosarcoma cells by restraining tumor-associated macrophages M2 polarization. In intravenous injection and orthotopic transplantation models, it could reduce the number of lung metastatic lymph nodes in osteosarcoma.[198] When tumor cells were incubated with the medium produced by tumor immune cells of mice implanted with scaffolds, the invasion of tumor cells *in vitro* and the activity of transcription factors promoting invasion were significantly reduced.[199]

5 Multimodal therapeutic strategy

The formation of local tumors may be driven by the co-activation of a range of tumor survival signal pathways, which could encourage the expansion of invasiveness and metastasis, as more individuals become aware of the intricacy of cancer occurrence.[200] With the in-depth research of tumor etiology, a growing number of therapy strategies have been created to treat tumors using various mechanisms and methodologies, with positive clinical outcomes. However, each approach has a flaw: either the treatment indication is limited, or the drug develops drug resistance, or the treatment has a variety of undesirable side effects, all of which restrict the efficacy of these procedures.[201,202] The intricacy of cancer genesis and invasion necessitates the development of novel tumor treatment strategies. As a result, multi-mode therapy for osteosarcoma and other bone malignancies, such as chemotherapy/PTT, PTT/PDT, and PDT/chemotherapy, is a novel therapeutic method. Multi-mode therapy may focus on tumor, coordinate time and space, decrease toxicity and side effects, and create a new door for successful tumor treatment when compared to equivalent monotherapy and traditional drug formula combination therapy.[203] The combined application of multimodal strategies may break promising ground for bone tumor therapy.

5.1 Functionalized drug-loaded bone bioscaffolds

Functionalized bioscaffolds are designed as triggers to achieve precise release of drugs while assisting in the elimination of cancer cells. Photothermal treatment could not only destroy tumor cells, but it could also utilize heat to stimulate the release of chemotherapy medications in scaffolds, and even boost the toxicity of chemotherapeutic drugs to tumor cells through a synergistic effect, improving tumor ablation effectiveness and lowering the total chemotherapeutic drug dose.[204] Cryogenically 3D printed nanocomposite scaffolds were made from water/poly(lactic-*co*-glycolic acid)/dichloromethane emulsions containing -TCP, 2D BP nanosheets, DOX, and high-dose osteogenic peptide (Fig. 8a). The multifunctional scaffold has a multistage porous bionic structure, sufficient mechanical strength (comparable to human cancellous bone), excellent photothermal effects, and controlled release of DOX with hydrophilic osteogenic peptides. In *in vivo* and *in vitro* studies, the multifunctional scaffold achieved sustained release of extremely low local DOX concentrations and upregulated BMSC osteogenic differentiation for tissue regeneration. In particular, BP nanosheets in scaffolds greatly decreased the long-term toxicity of released DOX.[205] TCP scaffolds were developed by loading both photothermal agents (TiN) and chemotherapy medicines (DOX) in Dang's study. TCP-TiN scaffolds offered good photothermal characteristics, thanks to the TiN particles on the scaffold surface. Under the same NIR irradiation circumstances, different dosages of DOX coated TCP-TiN scaffolds greatly increased the lethal effect. Chemotherapy and photothermal treatment killing effects were greatly enhanced in the TCP scaffold coated with TiN and DOX, with the inhibitory impact on osteosarcoma development (Fig. 8b).[130] Under NIR laser irradiation, the graphene nanosheets in the scaffold developed by Zhu *et al.* as an efficient photothermal agent enable the scaffold to perform photothermal conversion on demand. With the help of NIR laser-induced heating, antibiotic stearoyl trimethyl ammonium chloride (STAC) and/or anticancer drug DDP could effectively eradicate drug-resistant bacteria and ablate osteosarcoma cells, and the therapeutic effect could be further improved by laser-induced heating as needed. BSA-IrO2NP (bovine serum albumin-iridium oxide nanoparticles) is a protein-based nanocarrier with outstanding biocompatibility and high adriamycin loading (27.4 percent by weight). It has a strong photothermal conversion capacity (54.3%) under NIR laser

irradiation, which may be used for drug delivery and cancer therapy, resulting in an efficient synergistic chemical-photothermal therapy for human osteosarcoma.[206]

Magnetic hyperthermia has been utilized to selectively elevate temperature to ablate tumors throughout the last decade as a viable non-invasive therapy.[56] Magnetic hyperthermia has been utilized to transform electromagnetic energy into thermal energy in an external AMF throughout the last decade as a potential non-invasive therapy, selectively boosting the temperature to ablate tumors. To work with MH ablation and OS treatment, Liang *et al.* created a multi-functional bone cement filled with nano-Fe_3O_4 and the anticancer medication doxorubicin (DOX/Fe_3O_4@PMMA). The DOX/Fe_3O_4@PMMA bone cement is designed to be both a transporter for therapeutic pharmaceuticals and a material capable of magnetically driven synergistic drug release. It regulates DOX production, enhances OS tissue apoptosis, and inhibits the proliferation of tumor cells, and shows the synergistic effect of MH ablation and OS chemotherapy *in vivo*.[207] By combining chemotherapy with hyperthermia, magnetic bioactive glasses (MBGs) might be promising candidates for controlled release of anticancer medications against bone cancer. Chitosan-grafted poly (–caprolactone) (PCL) nanofibers were doped with MBGs/Cisplatin. By treating MG-63 osteosarcoma cells with Cs-*g*-PCL/MBGs/Cisplatin in an alternating magnetic field, the simultaneous impact of chemotherapy and hyperthermia was achieved. The chromatin morphological alterations of MG-63 cells treated with nanofibers containing MBGs/Cisplatin were compared, and it was discovered that the synergistic chemotherapy and hyperthermia combination treatment was clearly superior to solo chemotherapy or single hyperthermia.[208]

5.2 Functionalized immunomodulatory bone bioscaffolds

Due to the high local clearance of immune adjuvants or cancer vaccines, suitable functionalized bioscaffolds are available for prolonged retention and enhanced efficacy. PTT has the ability to cause ICD to release TAA, as well as suppress and stimulate immunological responses. After all, PTT's anti-tumor immune action is limited, and its synergistic effect with cancer vaccines, immune adjuvants, immune checkpoint inhibitors, and macrophage-mediated immunotherapy could boost the immune response and destroy cancer cells. As a result, He and his colleagues created and built a 3D printed biodegradable scaffold (BG@NbSiR) that was modified with immune adjuvant (R837) and carbonized Nb (Nb_2C) MXene to effectively treat breast cancer bone metastases. The two-dimensional Nb_2C MXene nanoparticles covered with mesoporous silica not only provide good photothermal characteristics under NIR irradiation, but also promote bone regeneration through the degradation of Nb-based and Si-based products. By blocking checkpoints, BG@NbSiR engineering scaffolds could eliminate primary tumors, activate an immune response, inhibit metastasis, prevent tumor recurrence (long-term immunological memory), and promote osteogenesis.[193] It is associated with the prolonged residence of R837 at the tumor site by the bioscaffolds.

5.3 Drug-loaded immunomodulatory bone bioscaffolds

The single use of conventional chemotherapy drugs usually fails to completely kill cancer cells *in vivo*, especially metastatic cells that have begun to spread. Many compounds have been reported to increase the immunogenicity of tumors in order to initiate immune cells.[209] Therefore, combined drug delivery and immunomodulation bioscaffolds have received much attention. Wang *et al.* designed an *in situ* scaffold loaded with gemcitabine (GEM) and anti-PD-L1 blocking antibody (aPDL1) to overcome the poor chemotherapy effect due to low immunogenic tumors.[210] When implanted at the tumor site, the large amount of ROS in the tumor tissue gradually triggers the ablation of the scaffold, followed by the release of chemotherapeutic agents and immunomodulators in a programmed manner. Neither systemic nor local injection of aPDL1-GEM was able to completely obliterate cancer cells in mice within 20 days, whereas the composite scaffold entirely eliminated tumor tissue after 15 days. Similarly,

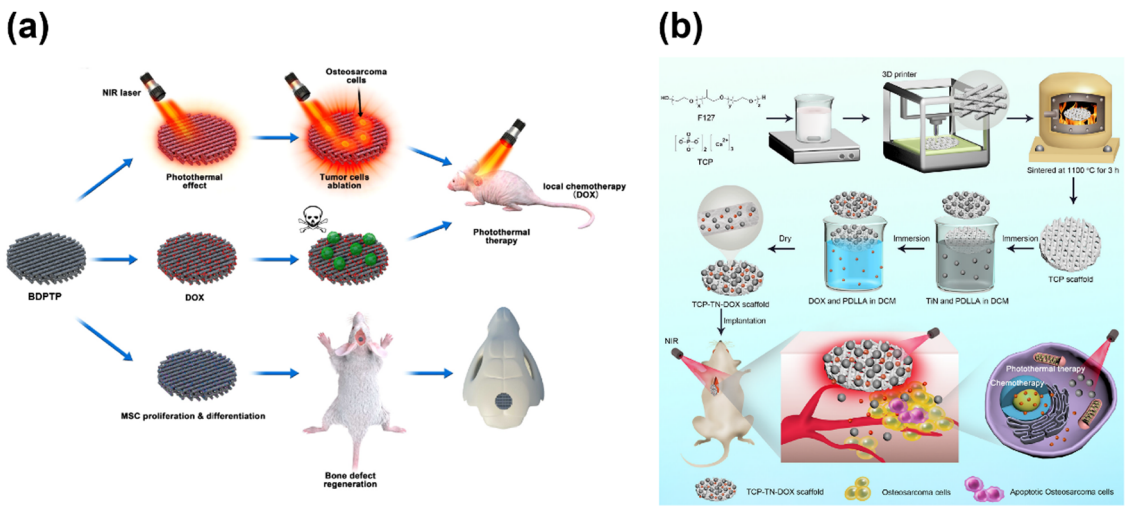

Fig. 8 (a) Schematic illustration of BDPTP for post-operative bone defect repair after tumor surgery. Copyright 2020, IOP publishing. (b) Schematic illustration of the fabrication and application of TCP–TN–DOX scaffolds for osteosarcoma therapy. Copyright 2021, ACS publications.

by introducing immune adjuvants and bioengineered vaccines into the porous scaffold, the killing ability of GEM against cancer cells is dramatically increased.[211] The macropore scaffold cross-linked with collagen and hyaluronic acid forms a continuous release of GEM and cancer vaccine over a week while recruiting activated T cells and dendritic cells. This artificial native immune microenvironment is conducive to the reversal of recurrence and metastasis after malignant tumor resection. The synergistic impact of multimodal treatment for bone cancers has been well studied and confirmed by several studies. The key focus right now is to determine the best materials and procedures to optimize the synergistic impact.

Conclusions

Development of biological scaffolds for the treatment of bone tumors is an on-going and challenging process. Future breakthroughs of these studies will benefit a large number of patients with bone cancers. The treatment options for bone tumors vary widely, with their own advantages and disadvantages. In order to achieve the optimum therapeutic effect, bone tumor therapy is frequently a thorough, multi-measure coordination. Biomaterial scaffolds with multiple functions hold enormous promise in bone scaffold research, despite the benefits of single-functioning scaffolds. Over the next several years, bone tumor research will focus on developing a series of treatment modalities that could be utilized in cooperation with their unique nature. We believe that the following aspects of anti-tumor bone biological scaffold research should be given more attention and breakthroughs: (1) Maximizing the effect and aggregation of the treatment within the local region of the tumor, without damaging the surrounding healthy tissues; (2) the scaffold material is biodegradable and could match with the healing speed of bone defects, so as to realize the substitution of bone structure and function; (3) integration and optimization of multi-functional functions, including anti-tumor, bone repair, antibacterial effect, and prevention of bone metastasis, without causing the accumulation of irreversible cellular damage; (4) to realize a clinical transformation, in addition to the biomaterial itself, we must also take its cost and technological operability into account, so that it could be applied to patients as soon as possible. Overall, the anti-bone tumor bioscaffolds have demonstrated exciting preclinical study efficacy. The unknown and sophisticated regulatory mechanisms and potential long-term toxicity of anti-tumor bioscaffolds, especially scaffold particles and local chronic inflammation, still deserve to be thoroughly investigated. With the continuous breakthroughs in material technology, it may be possible in the future to customize the bioscaffolds according to the patient's defect site, with higher precision and patient adaptability. Rational functionalized designs will create promising clinical translation opportunities for anti-tumor bone bioscaffolds. This work will provide a reference for structural design and specific functionalized modifications for the application of biomaterials in cancer therapy. This means, based on current clinical practice and the above-mentioned research progress, we may be able to develop more personalized anti-cancer scaffold biomaterials for patients. This review will provide promising inspiration for the translation of anti-bone tumor scaffolds from bench to bedside. In summary, it is believed that an advanced bioscaffold based bone tumor therapeutic strategy will be available in the near future.

Abbreviations

PDT	Photodynamic therapy
ROS	Reactive oxygen species
$^1O_2$	Single oxygen
$^{\bullet}OH$	Hydroxyl radicals
$O_2^{\bullet -}$	Superoxide radicals
O_{22}^{-}	Peroxides
Ce6	Chlorin e6
NPe6	Talaporfin sodium
PCL	Polycaprolactone
PTT	Photothermal therapy
NIR	Near-infrared
2D	Two-dimensional
BGS	Bioactive glass scaffold
BMSCs	Bone mesenchymal stem cells
GO	Graphene oxide
TCP	β-tricalcium phosphate
BCN	Borocarbonitrides
AKT	Akermanite
BG	Bioactive glass
BGC	Bioactive glass ceramics
MHT	Magnetic hyperthermia therapy
HA	Hydroxyapatite
PMMA	Polymethylmethacrylate
SDT	Sonodynamic therapy
HIFU	High intensity focused ultrasound
FUS	Focused ultrasound
HMME	Hematoporphyrin monomethyl ether
5-ALA	5-Aminolevulinic acid
PPIX	Protoporphyin IX
TiO2	Titanium oxide
CDT	Chemodynamic therapy
IONPs	Iron oxide nanoparticles
IO	Iron oxide
DPP	Cisplatin
DOX	Doxorubicin
PDLLA	Poly(D,L-lactide)
MOF	Metal organic framework
5-FU	5-Mluorouracil
CPC	Malcium phosphate cement
PLGA	Poly(D,L-lactide-*co*-glycolide)
HPβCD	2-Hydroxypropyl-β-cyclodextrin
CIC	Cell-in-cell structure
CS	Chitosan
HAP	Hydroxyapatite
Mg	Metallic magnesium

H_2	Hydrogen
ZA	Zoledronic acid
GCTB	Giant cell tumors of bone
PXS	Poly(xylitol sebacate)
NCTD	Norcantharidin
ZA	Zoledronic acid
DCs	Dendritic cells
Siglec-15	Sialic acid-binding immunoglobulin-like lectin 15
PD1	Programmed-cell-death protein 1
PDL1	Programmed-cell-death ligand 1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CAR	Chimeric antigen receptors
STAC	Stearoyl trimethyl ammonium chloride
MBGs	Magnetic bioactive glasses
PCL	Poly (caprolactone)
GEM	Gemcitabine
aPDL1	anti-PD-L1 blocking antibody

Conflicts of 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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