Materials Today Bio 29 (2024) 101276

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Exploring the frontiers: The potential and challenges of bioactive scaffolds in osteosarcoma treatment and bone regeneration

Huaiyuan Zhang [a,1], Yu Wang [a,1], Huifen Qiang [b,1], Dewen Leng [c,1], Luling Yang [d], Xueneng Hu [a], Feiyan Chen [e,**], Tinglin Zhang [b,f,***], Jie Gao [b,f,*], Zuochong Yu [a,****]

[a] Department of Orthopedics, Jinshan Hospital, Fudan University, Shanghai, 201508, China
[b] Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, China
[c] Department of Cardiovascular Surgery, Zhongnan Hospital of Wuhan University, Wuhan, 430071, China
[d] Digestive Endoscopy Center, Shanghai Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200336, China
[e] Department of Orthopedics, Huashan Hospital, Fudan University Shanghai, 201508, China
[f] Shanghai Key Laboratory of Nautical Medicine and Translation of Drugs and Medical Devices, Shanghai, 200336, China

ARTICLE INFO

Keywords:
Surgery
Chemotherapy
Osteosarcoma
Bone regeneration
Integrated bioactive scaffolds

ABSTRACT

The standard treatment for osteosarcoma combines surgery with chemotherapy, yet it is fraught with challenges such as postoperative tumor recurrence and chemotherapy-induced side effects. Additionally, bone defects after surgery often surpass the body's regenerative ability, affecting patient recovery. Bioengineering offers a novel approach through the use of bioactive scaffolds crafted from metals, ceramics, and hydrogels for bone defect repair. However, these scaffolds are typically devoid of antitumor properties, necessitating the integration of therapeutic agents. The development of a multifunctional therapeutic platform incorporating chemotherapeutic drugs, photothermal agents (PTAs), photosensitizers (PIs), sound sensitizers (SSs), magnetic thermotherapeutic agents (MTAs), and naturally occurring antitumor compounds addresses this limitation. This platform is engineered to target osteosarcoma cells while also facilitating bone tissue repair and regeneration. This review synthesizes recent advancements in integrated bioactive scaffolds (IBSs), underscoring their dual role in combating osteosarcoma and enhancing bone regeneration. We also examine the current limitations of IBSs and propose future research trajectories to overcome these hurdles.

1. Introduction

Osteosarcoma, an uncommon yet highly aggressive malignancy, predominantly affects children and adolescents, with a notable prevalence in those aged 10–20 years [1]. The global incidence of this tumor is estimated to be 2 to 3 cases per million individuals, a rate that varies among different geographical regions and populations. The etiology of osteosarcoma remains elusive, although it is hypothesized to be associated with genetic predispositions, radiation exposure, certain chemical exposures, and aberrant osseous growth. In its initial phases, the condition typically manifests as localized pain, which may evolve to include a palpable mass in the affected region, accompanied by significant discomfort. In untreated patients, osteosarcoma can metastasize rapidly, with a propensity for lung involvement, potentially leading to

Abbreviations: (BMSCs), Bone marrow stem cells; (PTT), Photothermal therapy; (CDT), Chemodynamic therapy; (PDT), Photodynamic therapy; (MHT), Magnetic hyperthermia; (SDT), Sonodynamic therapy; (PTAs), Photothermal agents; (PIs), Photosensitizers; (SSs), Sound sensitizers; (MTAs), Magnetic thermotherapeutic agents; (NIR), Near infrared; (PCE), Photothermal conversion efficiency; (ROS), Reactive oxygen species; (ICD), Immunogenic cell death; (TME), Tumor microenvironment; (AMF), Alternating magnetic field; (ICB), Immune checkpoint blockade.

* Corresponding author. Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, China.
** Corresponding author.
*** Corresponding author. Changhai Clinical Research Unit, Shanghai Changhai Hospital, Naval Medical University, Shanghai, 200433, China.
**** Corresponding author. Department of Orthopedics, Jinshan Hospital, Fudan University, Shanghai, 201508, China.
E-mail addresses: zhy2864713204@163.com (H. Zhang), naturewang2022@163.com (Y. Wang), qianghuifen@163.com (H. Qiang), 39921252@qq.com (D. Leng), yllsjtu@qq.com (L. Yang), 1171151853@qq.com (X. Hu), chenfy73@163.com (F. Chen), ztl2107@smmu.edu.cn (T. Zhang), gaojiehighclea@smmu.edu.cn (J. Gao), tjyd327@163.com (Z. Yu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.mtbio.2024.101276
Received 3 August 2024; Received in revised form 16 September 2024; Accepted 25 September 2024
Available online 29 September 2024

respiratory failure and posing a grave risk to patient survival [2]. Prognostic factors influencing osteosarcoma outcomes include tumor stage, size, location, patient age, and histological subtype [3]. Despite therapeutic advancements, the 5-year survival rate for osteosarcoma remains suboptimal, particularly in patients with distant metastasis. Consequently, there is an imperative need for the development of more efficacious therapeutic strategies to increase patient survival rates and overall quality of life.

In contemporary oncology, the management of osteosarcoma has transitioned toward a multimodal therapeutic approach, encompassing surgical intervention, chemotherapeutic regimens, radiotherapy, and the burgeoning fields of targeted and immunotherapies. This integrated model has demonstrated significant efficacy in mitigating disease progression and alleviating patient symptoms. Surgical resection, as the cornerstone of treatment, offers the distinct advantage of directly excising tumor tissue, thereby substantially diminishing the tumor burden and establishing a robust platform for subsequent adjuvant therapies. Chemotherapy, particularly in the neoadjuvant and adjuvant settings, has been instrumental in reducing tumor volume and eradicating microscopic metastatic deposits, consequently increasing 5-year survival rates [4,5]. Radiotherapy, as a localized treatment modality, disrupts tumor cell DNA and curbs proliferation through high-energy irradiation, presenting a viable alternative for patients who are surgically ineligible or at elevated surgical risk [6]. Furthermore, targeted therapy and immunotherapy represent innovative frontiers in osteosarcoma treatment. Targeted therapy precisely targets specific molecular aberrations within tumor cells, thereby inhibiting their proliferation and dissemination [7]. Conversely, immunotherapy leverages the host immune system to combat tumor cells, encompassing strategies such as tumor vaccines, immune checkpoint inhibitors, and adoptive cell transfer [8]. Notably, mivacaftide, an immunomodulatory agent that activates the antitumor functions of monocytes and macrophages, has received European Union approval for combination chemotherapy in nonmetastatic osteosarcoma, heralding a novel dimension in its comprehensive management [9]. As medical research advances, the refinement and innovation of these therapeutic strategies continue to offer renewed hope and improved quality of life for osteosarcoma patients.

Following the establishment of a tumor-free environment via a multidisciplinary treatment approach, postoperative bone healing is initiated through the activation of bone marrow stem cells (BMSCs), the promotion of neovascularization, and the regulation of growth factors, all of which are essential for the regeneration of compromised bone tissue [10]. However, the surgical management of osteosarcoma frequently necessitates the removal of healthy bone margins to ensure complete tumor excision, leading to substantial bone defects. Additionally, while chemotherapy and radiotherapy are instrumental in eradicating neoplastic cells, they can concurrently exert detrimental effects on normal osseous tissue and osteoblasts, thereby hindering the natural bone repair process postoperatively [11]. The magnitude of bone defects, coupled with the potential side effects of adjunct therapies, often surpasses the body's innate regenerative capacity. This scenario underscores the need for innovative therapeutic strategies aimed at enhancing bone regeneration and optimizing patient outcomes following osteosarcoma treatment.

Traditionally, postoperative bone defects have been addressed with autologous or allogeneic bone grafts intended to reconstruct bone structure and function. However, this approach has limitations, including the scarcity of appropriate graft sources, especially for larger defects [12]. The risk of immune rejection associated with allogeneic grafts can hinder integration and recovery and potentially lead to chronic pain and infection [13]. To overcome these obstacles, researchers have sought more effective and safer alternatives, such as bioactive scaffolds. These synthetic substitutes are valued for their mechanical properties, biodegradability, and biocompatibility [14,15]. However, their inherent lack of antitumor properties necessitates the integration of therapeutic agents to enhance their effectiveness against osteosarcoma. Potential additives include chemotherapeutic agents, photothermal agents (PTAs), photosensitizers (PIs), sound sensitizers (SSs), magnetic thermotherapeutic agents (MTAs), and other natural compounds with established antitumor effects. By incorporating these materials into a biocompatible scaffold, a versatile therapeutic platform that targets osteosarcoma cell destruction while promoting bone repair and regeneration can be developed. This dual-functional approach is a promising strategy for the holistic management of osteosarcoma and the restoration of bone integrity.

In recent years, the therapeutic integration of scaffolds has become a focal point in osteosarcoma treatment, presenting new opportunities for accurate tumor removal and subsequent bone regeneration. Pioneering preclinical research, exemplified by the work of Dai et al. [16], has demonstrated the therapeutic potential of polyether ether ketone (PEEK) composite scaffolds, particularly their photothermal capabilities, in both osteosarcoma management and bone repair. In a parallel study, Chen et al. [17] explored the therapeutic application of three-dimensional (3D)-printed polycaprolactone (PCL) composite scaffolds in osteosarcoma therapy and the remediation of postoperative bone defects. Despite the growing body of literature on the convergence of osteosarcoma therapeutics and bone regeneration, a consolidated analysis of the current landscape of integrated bioactive scaffolds (IBSs) is lacking.

This review begins with an overview of advancements in metallic, ceramic, and hydrogel scaffolds, underscoring their critical role in osteosarcoma treatment and postoperative bone defect repair, as illustrated in Fig. 1 and detailed in Tables 1–3. We then proceed to examine the engineering strategies behind the development of IBSs, including biomaterial-directed strategies, drug delivery strategies, environmental response strategies, and multimodal therapeutic strategies, as depicted in Scheme 1. Furthermore, we present a systematic review of the preparation and modification techniques for IBSs, elucidating the effects of various methodologies on scaffold performance. The review concludes with an assessment of the clinical potential of IBSs, considering the challenges and limitations that could arise in future developmental trajectories.

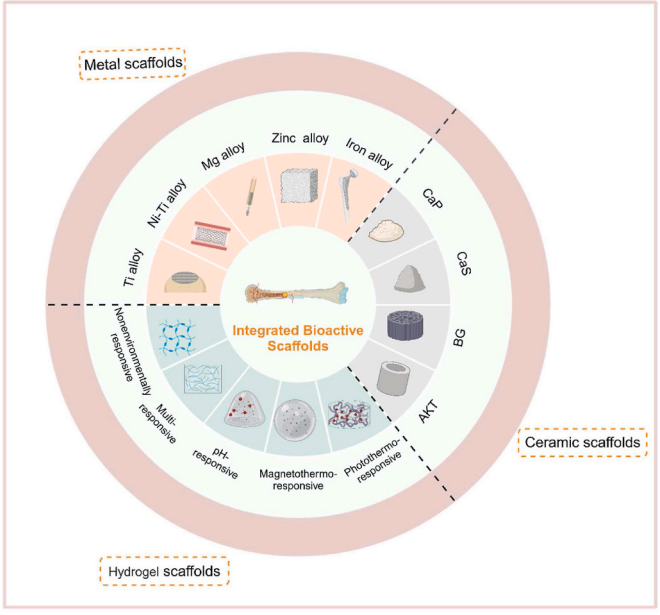
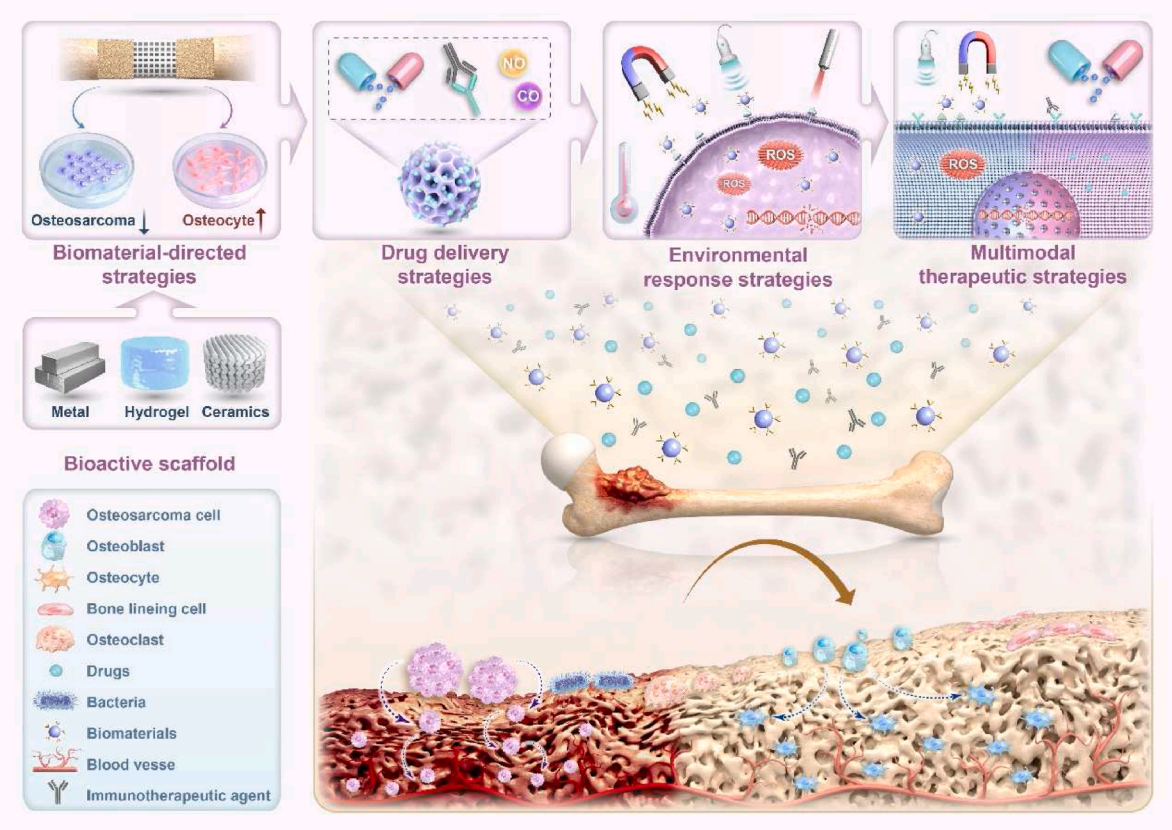


Fig. 1. Summary diagram of the use of IBSs for osteosarcoma treatment and bone regeneration (Created with Biorender.com).



Scheme 1. This paper provides a systematic overview of the utilization of IBSs as a multifaceted platform for osteosarcoma treatment and the facilitation of bone tissue regeneration. This review encompasses a range of strategic approaches, including biomaterial-directed strategies that leverage the inherent properties of scaffold materials, drug delivery strategies that aim to optimize the release of therapeutic agents, environmental response strategies that adapt to the local biological environment, and multimodal therapeutic strategies that combine various treatment modalities to increase overall efficacy. (Created with Biorender.com).

2. Metal scaffolds in the integrated treatment of anti-osteosarcoma and promotion of bone regeneration

Metal scaffolds play pivotal roles in osteosarcoma treatment and bone regeneration. Owing to their exceptional mechanical properties and structural stability, these scaffolds provide substantial mechanical support for bone defects. The degradation of metal scaffolds releases ions that are instrumental in enhancing osteoblast adhesion, proliferation, and differentiation, thus accelerating the reconstruction and repair of bone tissue [18]. The field categorizes metal scaffolds into two principal types on the basis of their degradation profiles: nondegradable and degradable scaffolds, each serving distinct clinical applications (Table 1).

2.1. Nondegradable metal scaffolds

In the realm of osteosarcoma management, the deployment of nonbiodegradable metallic scaffolds is essential for providing enduring and robust mechanical support to osseous defects that arise subsequent to surgical removal of the tumor. These scaffolds play pivotal roles in maintaining the structural integrity and functionality of the bone. Titanium alloys and nitinol have emerged as the materials of choice for scaffold construction due to their exceptional biocompatibility, superior mechanical strength, and significant resistance to corrosion.

2.1.1. Titanium alloy scaffolds

Titanium alloys are esteemed in the field of biomedical engineering for their superior mechanical properties and notable resistance to corrosion. Medical-grade titanium alloys, exemplified by Ti_6Al_4V, are particularly favored for applications involving bone contact due to their elastic modulus, which closely approximates that of human bone. This congruence is pivotal in mitigating stress shielding effects on surrounding healthy tissues [19].

Despite these advantages, the inherent bioinertness of titanium alloys poses a challenge in osteosarcoma treatment and bone tissue regeneration. To overcome this limitation, researchers have introduced innovative strategies, with surface modification technologies standing out as highly effective. These techniques are designed to augment the bioactivity of titanium alloys, conferring properties that can suppress osteosarcoma cells while simultaneously promoting osteoblast adhesion, proliferation, and differentiation, thus significantly enhancing their role in bone tissue engineering. In a pioneering study, Zhang et al. [20] utilized induced suspension plasma spraying (ISPS) to deposit a novel hydrogenated black TiO_2 (H-TiO_2) coating on titanium alloy implants. This coating not only replicated the laminar structure of natural bone at the macroscopic level and surface roughness at the microscopic level, facilitating superior osseointegration but also enhanced the adhesion, proliferation, and differentiation of BMSCs. Moreover, the H-TiO_2 coating displayed exceptional photothermal properties, significantly reducing tumor cell viability following exposure to near-infrared

(NIR) laser irradiation. Building on this research, Zhang et al. [21] developed a novel nanoflake layer of MgO/FeOx (rLDO) on titanium alloy surfaces through a hydrothermal process followed by reductive calcination. This rLDO nanosheet layer demonstrated remarkable photothermal conversion efficiency and peroxidase activity, achieving potent antitumor effects through the synergistic action of photothermal therapy (PTT) and chemodynamic therapy (CDT) (Fig. 2A). Additionally, the nanosheet layer generated a local alkaline microenvironment, which not only suppressed bacterial energy metabolism and enhanced the photothermal antibacterial effect but also promoted the differentiation and migration of osteoblasts and vascular endothelial cells in vitro, suggesting a promising avenue for stimulating bone formation through the release of magnesium ions (Mg^{2+}) and inducing alkaline conditions.

Surface modification techniques have significantly enhanced the bioactivity and therapeutic potential of titanium alloys, particularly those with smooth surfaces, which are traditionally limited in bone tissue engineering applications. Owing to their distinctive 3D structures, porous titanium alloy scaffolds have attracted considerable attention. The porosity of these scaffolds expands the surface area, facilitating cell attachment and proliferation, and more closely mimics the microarchitecture of natural bone, thereby enhancing bone tissue regeneration [22]. Capitalizing on 3D printing technology, Jin et al. [23] fabricated a porous titanium alloy scaffold and seamlessly integrated it with a thermosensitive hydrogel (PLGA-PEG-PLGA) to develop an innovative bone substitute material. This material was designed to fulfill dual roles: exerting anti-osteosarcoma activity and promoting bone repair (Fig. 2B). A hydrogel loaded with the chemotherapeutic agent cisplatin has been shown to markedly reduce tumor size while avoiding systemic side effects through targeted local administration. This method has yielded more precise and safer antitumor effects. Although the incorporation of cisplatin initially appeared to delay bone repair at the 4-week postoperative assessment, by the 8-week mark, the long-term stability and osseointegration of all implants were comparable, with no significant differences observed in bone growth. Collectively, these findings suggest that 3D-printed titanium implants combined with cisplatin-loaded hydrogels demonstrate promising profiles of safety and efficacy in addressing bone defects induced by osteosarcoma, positioning them as a viable option for clinical use.

2.1.2. Nitinol scaffolds

Nitinol, a nickel-titanium (Ni-Ti) shape memory alloy, is renowned for its dual properties of shape memory effect and superelasticity, which make it a superior candidate for implant materials in bone tissue engineering. The shape memory effect enables Nitinol to be plastically deformed at higher temperatures and then return to its original shape upon cooling to body temperature, a phenomenon that greatly facilitates the precision and efficiency of surgical implantation procedures [24]. Additionally, the mechanical properties of nitinol, including its high tensile strength and fatigue resistance, provide the robust structural support required to withstand the physiological loads encountered in the human body, thus fostering bone repair and regeneration.

In addition to their structural utility, Ni-Ti alloys have been the subject of research because of their potential synergy with advanced surface modification techniques to augment osseointegration and impede tumor cell proliferation. Yao et al. [25] illustrated that the in situ growth of nickel (Ni) nanoparticle-doped nickel-titanium oxide ($NiTiO_3$) films on Ni-Ti alloy surfaces yielded a stable and economical photothermal thin film (Fig. 2C). This film not only sustained the integrity of the embedded Ni nanoparticles and their photothermal effect over time but also ensured the sustained release of Ni ions. The gradual release of these ions cultivated a microenvironment reminiscent of hypoxia, which in turn stimulated the expression of angiogenic factors, thereby accelerating both vascularization and bone tissue formation processes. Furthermore, the nanostructured surface topography of the Ni-Ti alloy was instrumental in osteoblast adhesion and differentiation, processes that were essential for bone tissue regeneration. These attributes significantly influenced the orthopedic field, especially in the advancement of implants for osteosarcoma treatment and bone repair. In a complementary study, Ma et al. [26] successfully engineered a multiscale hierarchical structure (Fs-NFs) by integrating 3D micro-nanostructures (Fs-Ni-Ti) with nanoflower-like structures (NFs), utilizing a combination of laser ablation and hydrothermal synthesis techniques. The structure was further enhanced by rapidly depositing a layer of AuPt nanoparticles onto the Fs-NFs via UV reduction, yielding a bimetallic nanomaterial with superior PCE and biocompatibility compared with its monometallic counterparts, which was highly effective for tumor cell ablation. The unique honeycomb porous structure of the coating also enhanced cell contact guidance, promoting cell adsorption, anchoring, and proliferation. Additionally, researchers have decorated Fs-NFs with black scale nanosheets (BPs) [27] and anchored an NIR/pH dual-responsive drug delivery system loaded with the chemotherapeutic drug doxorubicin (DOX) to their surface via polydopamine (PDA). This innovative approach achieved a synergistic effect between PTT and chemotherapy, significantly amplifying antitumor efficacy, and demonstrated excellent photothermal antimicrobial properties, thereby fostering a more conducive microenvironment for bone tissue regeneration (Fig. 2D).

2.2. Degradable metal scaffolds

Biodegradable metal stents represent a groundbreaking innovation in osteosarcoma therapy, revolutionizing traditional approaches to bone repair. In contrast to nonbiodegradable alternatives, these metal scaffolds are engineered to progressively degrade postimplantation, culminating in their safe replacement by the patient's native tissue. This orchestrated biodegradation effectively circumvents a myriad of complications inherent to long-term implants, such as infection, mechanical wear, and material fatigue [28]. Concurrently, the byproducts of this degradation actively participate in the innate regenerative processes of bone, robustly promoting bone tissue formation and repair.

When selecting scaffold materials, biodegradable metals, including magnesium, zinc, or iron alloys, are often favored. Magnesium alloys, known for their swift degradation rate, are especially well suited to meet the dynamic needs of bone healing. Zinc alloys, which are characterized by a moderate degradation rate, mitigate the risk of tissue irritation and structural instability that rapid degradation might induce. On the other hand, iron alloys, with a more gradual degradation profile, provide enduring mechanical support throughout the bone healing process. These metals are biocompatible and release ions—magnesium, zinc, and iron—that are beneficial for osteoblast growth, proliferation, and differentiation during the degradation process. Notably, Mg^{2+} ions are recognized for nurturing a favorable immune microenvironment for bone tissue regeneration by enhancing monocyte-macrophage recruitment and polarization [29]. Zinc ions (Zn^{2+}) modulate osteoclast activity, thus contributing to the regulation of bone resorption and formation [30]. Iron ions (Fe^{3+}), essential trace elements, are integral to key physiological processes such as cellular metabolism and oxygen transport and are equally vital for maintaining healthy bone tissue [31].

2.2.1. Magnesium alloy scaffolds

In the context of bone tissue engineering, biodegradable magnesium alloys have emerged as pivotal agents that facilitate bone repair and

exhibit promising antitumor properties. Recent studies have shown that the degradation products of magnesium alloys, including magnesium hydroxide, hydrogen and Mg^{2+}, have significant antitumor activity. These degradation products act through multiple mechanisms: magnesium hydroxide can alkalize the tumor microenvironment (TME), inhibit tumor cell proliferation and activate antitumor immunity [32]; hydrogen can regulate inflammation, inhibit cellular mitochondrial respiration, and disrupt redox homeostasis, which can lead to the apoptosis and injury of cancer cells [33]; and Mg^{2+} can promote tumor cell apoptosis and damage by affecting intracellular signaling pathways, such as by inhibiting the AKT/mTOR signaling pathway and promoting tumor cell apoptosis while inhibiting tumor cell proliferation [34]. Therefore, although the rapid degradation of magnesium alloys may produce an acidic environment locally, the antitumor effect of their degradation products far outweighs this potential side effect. Philipp Globig [35] and other researchers further confirmed this idea experimentally. They reported that the degradation of magnesium alloy was able to increase the pH around tumors, prompting cancer cells to enter a dormant state, thus effectively inhibiting tumor growth. These findings provide a new perspective on the application of magnesium alloys in the treatment of osteosarcoma and lay the foundation for future research and clinical applications.

Building upon these foundational insights, Zhang et al. [36] made a significant stride in the application of magnesium alloys, introducing a novel strategy that integrates manganese (Mn)-containing layered double hydroxide (LDH) nanosheets into the alloy matrix. This innovative design augmented the photothermal effect, facilitating the synergistic eradication of tumor cells through the generation of reactive oxygen species (ROS) catalyzed by the peroxidase activity of Mn ions (Mn^{2+}). The deliberate release of Mn^{2+} has been shown to enhance cellular adhesion, spreading, and proliferation, thereby accelerating in vivo bone regeneration. The black LDH-coated magnesium alloy also had photothermal bacteriostatic properties, significantly reducing the risk of implant-associated infections, which was imperative for bone tissue repair. Concurrently, Ge et al. [37] developed a biodegradable magnesium rod (MGR) that leverages a vortex effect to synergize magnetic hyperthermia (MHT) with immunotherapy. Their research underscored the potential of MHT to induce immunogenic cell death (ICD) in tumor cells and to mature dendritic cells (DCs), thereby activating the immune response. To mitigate the increase in PD-L1 expression triggered by the vortex effect of MGR, the team has integrated anti-PD-L1 immunotherapy, thereby increasing therapeutic efficacy. Furthermore, MHT combination therapy has been shown to promote the polarization of M1-type macrophages and the infiltration of T cells, fostering a therapeutically advantageous immune milieu. As the MGR degrades, the alkaline microenvironment that ensued was conducive to osteoblast differentiation, presenting a promising avenue for the treatment of bone tumors and pioneering innovative approaches to bone tissue regeneration.

2.2.2. Zinc alloy scaffolds

Although research in this area is nascent, zinc alloys have begun to attract attention within the fields of biomaterials and oncology owing to their potential advantages in the treatment of osteosarcoma and the promotion of bone regeneration. The biocompatibility of zinc alloys, their controlled degradation kinetics, and the osteogenic activity of Zn^{2+} make them promising candidates for facilitating bone repair and regrowth. Additionally, the antimicrobial and antitumor properties of Zn^{2+} present innovative therapeutic avenues for the inclusion of zinc alloys in osteosarcoma treatment protocols [38].

Recent studies have elucidated the impact of Zn^{2+} on tumor cell dynamics, showing that Zn^{2+} can impede cell proliferation, trigger apoptosis, and impede angiogenesis [39]. Specifically, in the context of osteosarcoma therapy, zinc oxide nanoparticles (ZnO NPs) have been found to modulate the expression of β-catenin via the mitochondrial autophagy pathway. This modulation effectively curbs cell migration, invasion, and epithelial-mesenchymal transition (EMT), processes that are pivotal in the prevention of tumor metastasis [40]. The therapeutic potential of ZnO NPs is further enhanced when they are combined with the β-catenin inhibitor ICG-001, a strategy that has been shown to have a synergistic effect on suppressing osteosarcoma lung metastasis and prolonging patient survival rates. Tissue microarray (TMA) analyses have corroborated the significance of β-catenin in osteosarcoma, with elevated levels observed in tumor samples, underscoring its contribution to disease progression.

2.2.3. Iron alloy scaffolds

The burgeoning role of iron alloys in bone regeneration is noteworthy, primarily due to their mechanical robustness and biocompatibility. These alloys exhibit elasticity akin to that of bone, which effectively reduces stress shielding and facilitates more harmonious integration with osseous tissue. The controlled degradation of these ferrous materials liberates Fe^{3+}, which, when present at optimal concentrations, promotes osteoblast proliferation and differentiation and stimulates angiogenesis—a critical process for bone repair and healing [41].

While the exploration of ferroalloys in osteosarcoma therapy is still in its nascent phase, the preliminary findings are encouraging. The magnetic attributes of these alloys allow for the precise application of MHT, a technique that selectively targets and damages tumor cells with minimal collateral damage to the surrounding healthy tissue [42]. Additionally, Fe^{3+} has been implicated in the modulation of osteosarcoma cell behavior, influencing cellular metabolism and signaling pathways. Notably, the accumulation of iron ions and ROS can lead to lipid peroxidation and subsequent tumor cell death, a phenomenon known as "iron death." The induction of this form of cell death in osteosarcoma is a multifaceted process that can be achieved through pharmacological agents that increase intracellular iron levels or by modulating cellular antioxidant defenses [43]. Jiang et al. [44] reported a correlation between reduced expression of miR-144-3p in osteosarcoma cells and disease progression, suggesting that upregulation of this microRNA could suppress tumor growth by triggering iron death through the targeting of ZEB1. This hypothesis has been supported by in vivo studies in a nude mouse model, which demonstrated the inhibitory effects of miR-144-3p on osteosarcoma cell proliferation and lung metastasis.

In conclusion, although metallic scaffolds are conventionally employed for their mechanical strength and stability in the repair of load-bearing bones, their inert characteristics can result in stress shielding and hinder osseointegration [45]. Consequently, interest in the development of ceramic scaffolds has increased. These scaffolds, known for their superior biocompatibility and osteoconductive properties, are pivotal in fostering osteoblast proliferation and hastening the process of bone regeneration. By closely mimicking the mineral composition of natural bone, ceramic scaffolds have emerged as promising therapeutic options for osteosarcoma treatment and bone repair.

Table 1
Summary of metal-based scaffolds.

Compositions	Treatment of osteosarcoma	Bone tissue regeneration	Ref.
H-TiO_2/Ti_6Al_4V	Photothermal therapy	Hierarchical micro/nanotopography of H-TiO_2 coatings improves adhesion, proliferation and osteogenic differentiation of rBMSCs in vitro.	[20]
Cisplatin/PLGA-PEG-PLGA hydrogel/Ti_6Al_4V	Chemotherapy	Porous titanium alloys promote adhesion of rBMSCs and thus promote osseointegration.	[23]
rLDO/Ti	Photothermal therapy and Chemodynamic therapy	Degradation of rLDO nanosheets generates Mg^{2+} and an alkaline microenvironment, which effectively promotes ALP activity and osteogenic gene expression in osteoblasts and enhances migration of vascular endothelial cells.	[21]
F-TiO_2/PC/Ti	Photothermal therapy and Photodynamic therapy	PDA and collagen enhance the proliferation and differentiation of BMSCs.	[46]
LDH-H_2/NiTi	Photothermal therapy	The nanostructures on the surface of Ni-Ti alloy can promote the adhesion and differentiation of osteoblasts. Ni^{2+} can promote the expression of angiogenic factors and accelerate the process of vascular neovascularization and bone tissue formation.	[25]
Fs-NFs-AuPt/NiTi	Photothermal therapy	The unique honeycomb porous structure of the Ni-Ti alloy surface promotes cell adsorption, anchoring, and value addition.	[26]
FS-BP-DOX@PDA/NiTi	Photothermal therapy and Chemotherapy	The multiscale layered structure of the Ni-Ti alloy surface promotes cell adsorption, anchoring, and value-addition. The formation of calcium phosphate by BP degradation contributes to osteoblast differentiation.	[27]
LDH-Mn/Mg	Photothermal therapy and Photodynamic therapy	Mg^{2+} and Mn^{2+} are able to induce adhesion, spreading, proliferation and osteogenic differentiation of osteoblasts and accelerate osteogenesis in vivo.	[36]
MgR	Magnetic hyperthermia and Immunotherapy	Mg^{2+} and alkaline microenvironment formed by MgR degradation can induce osteoblast differentiation and mineralization.	[37]
LDH-C/Mg	Chemotherapy	Celastrol inhibited osteoclast formation and activation by reducing RANKL expression.	[47]

3. Ceramic scaffolds in the integrated treatment of anti-osteosarcoma and promotion of bone regeneration

Ceramic scaffolds, akin to their metallic counterparts, offer stable structural support and serve as templates for bone repair, fostering bone regeneration. They possess unique properties that extend their utility beyond traditional metallic options. Notably, the chemical composition of ceramic scaffolds closely mirrors that of human bone, allowing them to emulate the physical and chemical attributes of natural tissue. This resemblance fosters an environment conducive to bone cell proliferation and differentiation [48]. Additionally, ceramic scaffolds are distinguished by their exceptional biocompatibility and resistance to corrosion, significantly reducing the risk of adverse tissue reactions and postoperative complications such as infections and inflammation, thus increasing treatment safety and efficacy [49].

Researchers classify ceramic scaffolds into two principal categories on the basis of their interaction with surrounding tissues: bioinert and bioactive. Initially, bioinert ceramic scaffolds, prized for their strength and chemical stability, were the preferred choice for human implantation in tissue replacement. However, with an evolving understanding of the mechanisms of interaction between implanted materials and the human body, bioactive ceramic scaffolds have come to the forefront. These scaffolds preserve the stability of their predecessors and exhibit osteoinductivity, stimulating cell growth, proliferation, and differentiation without the need for exogenous growth factors. They are also known as tissue-inductive biomaterials [50]. In this discussion, we concentrate on the latter category, which includes a spectrum of bioactive ceramic scaffolds. These scaffolds can be further divided into calcium phosphate (CaP), bioactive glass (BG), calcium silicate (CaS), and akermanite (AKT) scaffolds on the basis of their composition (Table 2).

3.1. CaP ceramic scaffolds

To date, a wide array of bioceramic products have been successfully commercialized, with extensive applications in the medical field. The cornerstone of these bioceramics is typically composed of calcium phosphate (CaP)-based materials, with hydroxyapatite (HA) and tricalcium phosphate (TCP) being particularly prominent. These materials have been the focus of significant research advancements, yielding substantial insight [51]. The ongoing evolution of biphasic calcium phosphate (BCP), which integrates HA and TCP, has expanded the scope of ceramic scaffolds, increasing their utility in various medical applications.

3.1.1. HA scaffolds

HA, which is known for its biocompatibility, biodegradability, and chemical similarity to the inorganic components of human bone, has become a pivotal material in osteosarcoma treatment and bone tissue regeneration. In the biomedical field, the 3D structure of HA scaffolds not only replicates the microstructure of natural bone, providing an optimal environment for cell attachment, proliferation, and differentiation but also their porous nature offers an ideal conduit for the delivery of trace elements and therapeutic drugs. This dual functionality is instrumental in curbing osteosarcoma cell growth and repairing bone defects [52]. Huang et al. [53] developed composite scaffolds of selenium (Se), strontium (Sr), and zinc (Zn)-doped HA through a hydrothermal method (Fig. 3A). These elements were essential for bone tissue growth and development. Selenium oxide (SeO_3^{2-}) has shown significant antitumor activity, whereas strontium iron (Sr^{2+}) and Zn^{2+} have demonstrated the potential to enhance osteogenic differentiation, with Zn^{2+} also displaying notable antibacterial properties. This three-element-doped HA composite scaffold achieved the multifunctional integration of antitumor, osteogenic, and antibacterial properties. Liu et al. [54] further designed a novel biphasic calcium sulfate/HA (CaS/HA) carrier for the localized, sustained, and controlled release of the chemotherapeutic drug DOX, aiming to improve outcomes for highly proliferative human osteosarcoma. In vitro drug release studies indicated that approximately 28 % and 36 % of the drug was released within 4 weeks at physiological pH (7.4) and acidic pH (5), respectively. The released drug maintained its efficacy against two human osteosarcoma cell lines, MG-63 and 143B. This targeted delivery system could halt the progression of aggressive osteosarcoma by inhibiting angiogenesis and cell proliferation while minimizing systemic side effects. Additionally, HA can be combined with PTAs or MTAs for the in situ eradication of osteosarcoma via advanced techniques such as 3D printing or surface

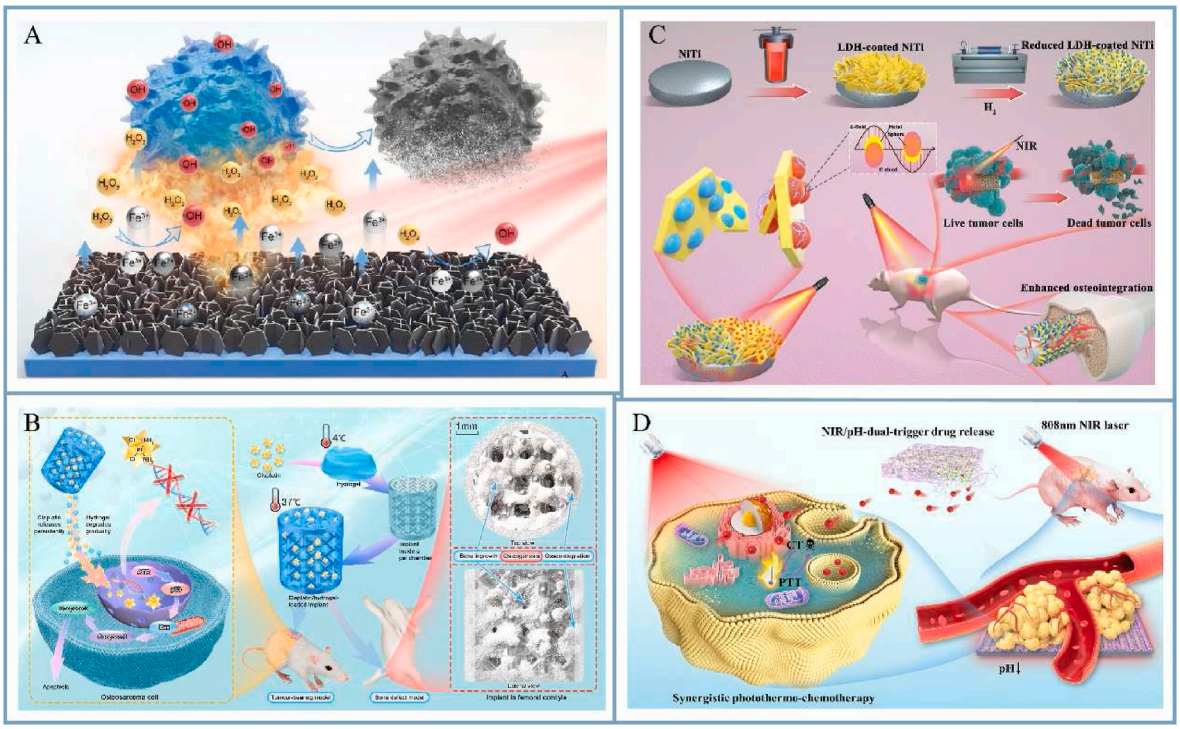


Fig. 2. Metal scaffold. (A) Antitumor mechanism of the rLDO samples. Reproduced with permission from Ref. [21], Copyright @ 2022 Small. (B) Schematic structure of a 3D printed porous titanium alloy scaffold loaded with cisplatin/hydrogel. Reproduced with permission from Ref. [23], Copyright @ 2021 Bioactive Materials. (C) Schematic of the preparation process of LDH-H_2 and its in vivo antitumor and bone-binding properties. Reproduced with permission from Ref. [25], Copyright @ 2022 ACS Applied Materials @Interfaces. (D) Fs-BP-DOX@PDA for synergistic photothermal chemotherapy of osteosarcoma in mice. Reproduced with permission from Ref. [27], copyright @ 2022 ACS Applied Materials @Interfaces.

modification. Employing this strategy, Zhang et al. [55] created a multifunctional nanohydroxyapatite (n-HA)/MXene/g-C_3N_4 composite scaffold that leveraged the properties of PTT and photodynamic therapy (PDT) to rapidly eliminate osteosarcoma cells at a mild temperature of 45 °C within 10 min. The scaffold also exhibited excellent cytocompatibility and the capacity to induce the osteogenic differentiation of BMSCs, thereby not only suppressing the proliferation of bone tumor cells but also enhancing their osteogenic activity.

n-HA has been recognized not only for its indirect effects on inhibiting osteosarcoma cells but also for its direct anti-proliferative impact on a variety of cancer cells [56]. This duality presents a novel therapeutic strategy for osteosarcoma. Capitalizing on these insights, Zhang et al. [57] developed a controlled-release n-HA scaffold, which was implanted into a rabbit tumor model to assess its efficacy in bone defect repair within a simulated tumor setting. After a 5-week period, the n-HA-coated scaffolds significantly diminished the in situ tumor volume by up to 73.8 %, outperforming their uncoated counterparts. Moreover, the n-HA scaffolds were correlated with weight gain, improved health status, and a notable lack of lung metastases in the treated subjects. Microcomputed tomography (micro-CT) analyses revealed that the n-HA scaffolds alleviated tumor-induced osteolysis, and new bone formation was observed on the pore surfaces of the scaffolds. These findings suggest that n-HA coatings potentially inhibit tumor growth while concurrently promoting bone regeneration.

In summary, the distinctive antitumor characteristics of HA, coupled with its osteointegrative properties, make it a prime candidate for osteosarcoma intervention. However, the inherent limitations of these materials, such as their low strength and high brittleness, somewhat restrict their widespread clinical application [58]. To overcome these obstacles, researchers have proposed innovative solutions. For example, the amalgamation of HA with metals or other ceramics, which possess enhanced mechanical attributes, can offer additional structural support, making it more viable for load-bearing applications [59]. Additionally, the incorporation of HA with pliable organic polymers can augment the overall flexibility of the scaffold, enabling it to adapt to diverse biomechanical contexts [60].

3.1.2. *TCP scaffolds*

In addition to HA, TCP also has significant potential in bone reconstruction because of its superior biocompatibility and controllable degradation rate [61]. Scaffolds made from TCP are mainly divided into α-TCP and β-TCP types, each characterized by distinct structural properties and degradation kinetics to address a variety of clinical needs. Notably, α-TCP scaffolds, characterized by a more rapid degradation profile, are particularly well suited for applications requiring swift bone regeneration. On the other hand, β-TCP scaffolds, with their slower degradation rate and enhanced stability, are more appropriate for providing long-term structural support and facilitating the gradual process of bone regeneration.

Advancements in 3D printing technology have increased the application of TCP scaffolds in bone tissue engineering. However, traditional manufacturing methods, which often necessitate high temperatures, risk thermal degradation of temperature-sensitive materials, potentially undermining the bioactivity of embedded drugs or growth factors. To

counteract this issue, cryogenic 3D printing has been introduced, enabling printing at lower temperatures, thus circumventing thermal degradation and reducing thermal stress. This technique importantly maintains the activity of biologically active molecules, a critical factor for tissue engineering and drug delivery applications. For example, α-TCP-based self-setting inks solidify at room temperature through a gelling reaction, eschewing the need for high-temperature processing. Nevertheless, Xu et al. [62] integrated $FePSe_3$ nanosheets onto 3D-printed α-TCP scaffolds to fabricate a bifunctional TCP-$FePSe_3$ scaffold for the synergistic treatment of osteosarcoma (Fig. 3B). This scaffold possessed photothermal properties that rapidly eliminated tumor cells under NIR irradiation, while its rapid degradation released selenium, inhibiting tumor recurrence by activating caspase-dependent apoptosis pathways. In a rat cranial defect model, the scaffold showed osteogenic potential by promoting angiogenesis and bone tissue regeneration through the release of biologically active ions such as iron (Fe), calcium (Ca), and phosphorus (P), thereby enhancing bone defect repair. Moreover, the porous structure of the TCP scaffolds acted as an efficient carrier for drugs and growth factors, facilitating bone defect repair through the localized release of these bioactive molecules. Lu et al. [63] prepared β-TCP scaffolds via 3D printing and incorporated osteogenic factors such as molybdenum disulfide (MoS_2), bone morphogenetic protein-2 (BMP-2), and insulin-like growth factor-1 (IGF-1) onto their surface via PDA. Compared with the control group, the MPBI@β-TCP scaffold group presented increased mineralization and alkaline phosphatase (ALP) activity, promoting the adhesion, proliferation, and differentiation of BMSCs, as evidenced by gene (Runx-2, Col-I, and OCN) and protein (ALP and collagen) analyses. Additionally, the composite scaffolds demonstrated proangiogenic effects in vitro, primarily by promoting the secretion of platelet-derived growth factor (PDGF), a growth factor vital for bone tissue regeneration. Notably, under NIR laser irradiation, the composite scaffolds also produced a photothermal effect, with tumor cell viability significantly reduced to 25 % as the photothermal temperature of the MPBI@β-TCP scaffolds rose from 37 °C to 50 °C.

In addition to 3D printing, advancements in surface modification techniques are garnering increased attention. Dong et al. [64] developed a method for osteosarcoma treatment and bone regeneration that involves coating the surface of β-TCP scaffolds with a carbon aerogel (CA) layer. The CA coating, which was endowed with photothermal properties, could increase the temperature under NIR irradiation, effectively abating osteosarcoma tumors. Its biocompatibility, expansive surface area, high porosity, and tunable nanostructure offered considerable benefits for bone regeneration. The experimental data indicated that the β-TCP-CA scaffolds markedly enhanced the adhesion and proliferation of BMSCs, as well as ALP activity and the expression of genes associated with osteogenesis. This promoted extracellular mineralization and the formation of calcium nodules. These results underscore the potential of CA coating to augment bone regeneration and repair bone defects, suggesting a novel therapeutic strategy for osteosarcoma.

3.1.3. BCP scaffolds

HA scaffolds are renowned for their exceptional biocompatibility and osseointegration capabilities, which stem from their chemical composition closely resembling that of bone minerals. This resemblance facilitates effective integration with the host bone, promoting osteoblast adhesion and proliferation. On the other hand, TCP scaffolds are preferred for their controlled degradation rate and bioresorbability, allowing for gradual resorption that coincides with new bone tissue formation, thus paving the way for bone regeneration. However, the slower degradation rate of HA scaffolds may extend the osseointegration process, whereas the rapid degradation of TCP scaffolds, despite their benefits, may compromise the necessary mechanical strength required for early bone repair.

To harness the combined advantages of HA and TCP while mitigating their individual limitations, researchers have engineered BCP scaffolds. These scaffolds are designed to retain bioactivity and ensure degradability, both of which are crucial for bone tissue engineering [65]. Compared with single-component HA or TCP scaffolds, BCP scaffolds have shown improved biocompatibility and enhanced promotion of bone regeneration. The compressive strength, elastic modulus, degradation profile, and biocompatibility of BCP scaffolds are influenced by the ratio of their composition and macropore architecture. Furthermore, the macropore architecture and pore size significantly impact fluid exchange, ion transport, nutrient supply, and cell migration. An increased macropore architecture can increase the scaffold degradation rate, thereby increasing the osteoinductive potential, but this may also reduce the compressive strength. In a study by Zhao et al. [48], BCP scaffolds with varying macropore architectures (0 %, 30 %, and 50 %) and HA weight ratios (0, 0.20, 0.40, 0.60, 0.80, and 1.00) were fabricated via 3D printing technology to determine the optimal macropore configuration. The study revealed that the degradation rate of the scaffolds decreased with increasing HA content, whereas increased macropore architecture accelerated the degradation process. Scaffolds containing 40 % HA and 50 % macropore architecture were the most effective at supporting cell proliferation, whereas those with 60 % HA and 30 % macropore architecture were the most conducive to osteogenic differentiation. These findings provide valuable insights for in vitro studies on the mechanical properties and biocompatibility of BCP scaffolds and establish a solid foundation for future in vivo research.

In the context of osteosarcoma treatment, Liu et al. [66] introduced an innovative strategy employing BCP as a carrier for a novel polymeric composite. This composite was developed through a layer-by-layer self-assembly process, in which recombinant fibronectin/calmodulin fusion protein (rFN-CDH) and hydrophobically modified chitosan (CS)/paclitaxel nanoparticles (HGC-PTX) were incorporated. This sophisticated material design ensures stable, one-week release of the chemotherapeutic agent paclitaxel (PTX), effectively targeting and neutralizing residual tumor cells postsurgery. Moreover, it provided sustained release of the rFN-CDH fusion protein, which was crucial for osteogenesis and significantly promoted the growth and proliferation of osteoblasts. The successful implementation of this approach presents groundbreaking concepts for the holistic management of osteosarcoma, holding promise for enhancing patient outcomes and quality of life.

3.2. BG scaffolds

The term BG was first introduced by Professor Larry Hench in 1969 and originally referred to a specific class of silicate bioactive glass (SBG). The classic formulation of SBG includes approximately 45 % silica (SiO_2), 24.5 % calcium oxide (CaO), 24.5 % sodium oxide (Na_2O), and 6 % phosphorus pentoxide (P_2O_5) [67]. Since its development, BG has garnered considerable acclaim in the biomedical sector, particularly for bone defect repair and tissue engineering. With the growing demand for bioactive materials and an enhanced understanding of their properties, the scientific community has ventured beyond traditional BG formulations. This exploration has yielded phosphate bioactive glass (PBG) and borate bioactive glass (BBG), each with distinct advantages. PBG, featuring phosphate as a principal component, exhibits superior biocompatibility and a regulated degradation rate, making it an ideal

candidate for bone tissue engineering. Conversely, BBG incorporates borates to strengthen the material's mechanical properties, making it well suited for bone repair scenarios requiring greater mechanical endurance. Additionally, the introduction of mesoporous bioactive glass (MBG) has further broadened the application spectrum of BG. MBG introduces new material options, expanding the potential for bone defect repair, tissue engineering, and drug delivery systems.

Research confirms that BG outperforms other bioactive ceramics in stimulating bone regeneration owing to its unique ability to rapidly induce mineralization and form hydroxyapatite (HCA), which closely resembles the osteocarbon-like composition of bone tissue. This similarity ensures a strong bond with bone tissue, facilitating osteoclast attachment and the formation of new bone [68]. Furthermore, the degradation of BG releases essential elements such as silicon (Si), calcium (Ca), and phosphorus (P), which modulate the genetic pathways of BMSCs, thereby regulating their proliferation and differentiation. These findings demonstrate the significant potential of the BG in repairing bone defects and promoting regeneration. Despite the remarkable efficacy of BG in enhancing bone tissue regeneration, its application as a standalone therapy is often insufficient for treating osteosarcoma, a highly aggressive bone tumor. Effective osteosarcoma treatment requires not only the promotion of bone regeneration but also the critical inhibition of tumor cell growth and metastasis. To overcome these challenges, researchers are exploring the combination of BG with other therapeutic agents or materials, including the incorporation of specific functional groups or bioactive molecules, and their combination with other biocompatible materials to achieve more comprehensive therapeutic outcomes [69,70]. A prevalent strategy involves modifying BGs with metallic materials to bestow them with new functionalities. These modifications allow BGs to retain their original bone tissue regeneration capabilities while acquiring additional antitumor properties. For example, Gu et al. [71] developed transition metal element (Fe, Cu)-doped PBG scaffolds that rapidly increased in temperature and exhibited excellent photothermal stability at a laser power density of 0.48 W/cm^2, effectively killing tumor cells. Over time, PBG scaffolds spontaneously degraded, releasing elements such as P, Ca, Na, and Fe, which further promoted osteoblast proliferation and differentiation. Metallic elements not only directly target tumor tissues through PTT but also generate antioxidant and antimicrobial effects via the Fenton reaction. Wang et al. [72] integrated a highly active single-atom iron catalyst (FeSAC) into a 3D-printed BG scaffold for osteosarcoma treatment, antimicrobial action, and bone defect regeneration. The FeSAC-BG composite scaffold utilized dispersed iron atoms in the catalyst to generate toxic hydroxyl radicals (•OH) in the osteosarcoma-specific microenvironment, achieving effective ablation of osteosarcoma through nanocatalytic therapy augmented by local thermotherapy. Additionally, this scaffold has demonstrated excellent antibacterial properties in ex vivo experiments, effectively inhibiting and eliminating bacteria to prevent chronic osteomyelitis. In bone defect repair, composite scaffolds served multiple functions, providing structural support and promoting BMSCs proliferation and differentiation after implantation into bone defects, thus accelerating bone tissue regeneration.

The utility of BG in osteosarcoma treatment is not limited to its combination with metallic materials; it also extends to its integration with a variety of materials to address the complex challenges of the treatment process. MXenes, a class of two-dimensional materials composed of transition metal carbides or nitrides, have attracted considerable attention because of their exceptional electrical conductivity, biocompatibility, mechanical properties, and thermal stability [73,74]. Pan et al. [75] synthesized Ti_3C_2 MXene nanosheets through a process that involved hydrofluoric acid etching and tetrapropylammonium hydroxide stripping. These nanosheets were integrated with 3D-printed BG scaffolds to fabricate composite scaffolds (TBGSs) (Fig. 3C). TBGS exhibited excellent PCE under NIR irradiation, effectively eliminating bone cancer cells through photothermal ablation. In vivo experiments using a mouse osteosarcoma model demonstrated complete tumor elimination with TBGS. Moreover, the composite scaffold progressively degraded over time, supplying essential minerals and space for new bone tissue formation. The formation of mineralized nodules around the degrading scaffold indicated a dynamic balance between scaffold degradation and new bone tissue growth. In addition to MXenes, semiconductor materials have also become a focal point of research. For instance, Dang et al. [76] employed 3D printing technology in conjunction with a solvothermal method to incorporate $CuFeSe_2$ nanocrystals onto BG scaffold surfaces. This integration endowed the composite scaffolds with superior photothermal properties, which could be adjusted by varying the concentration of the $CuFeSe_2$ nanocrystals and the laser power density. The BG-5CFS composite scaffold was capable of achieving rapid and controlled temperature increases even under low-power-density laser irradiation, effectively eradicating tumor cells. Furthermore, the short-term photothermal effect could stimulate the expression of osteogenic genes in BMSCs, ultimately promoting new bone formation at bone defect sites. This innovative approach represents the first instance of combining the photothermal properties of semiconducting $CuFeSe_2$ nanocrystals with the osteogenic potential of BG scaffolds, offering a novel perspective for the development of biomaterials with dual functionalities in bone tumor therapy and bone regeneration.

3.2.1. MBG scaffolds

MBG is a silicate material characterized by its highly ordered mesoporous structure. This distinctive architecture substantially increases the specific surface area, providing an abundance of attachment sites for cells and thereby enhancing cell adhesion, proliferation, and differentiation. Moreover, the porous framework of MBG can accommodate a variety of functional ions, drugs, or growth factors. This versatility allows MBG to serve not only as a drug delivery platform for controlled and sustained release but also as a multifunctional biomaterial that increases the efficacy of cancer therapy and tissue regeneration [77]. For example, Ravanbakhsh et al. [78] synthesized MBG nanoparticles with a uniform spherical morphology via the sol-gel method, yielding particles with a pore size of 4 nm and an exceptional specific surface area of 354 m^2/g. To improve drug bioavailability and minimize side effects, researchers have employed MBG and aminomethylated MBG (AMBG) as carriers for alendronate (AL). The study revealed that MBG and AMBG achieved high encapsulation efficiencies of 75 % and 85 %, respectively, along with loading efficiencies of 60 % and 63 %. Notably, AMBG displayed a more favorable sustained and controlled release profile for AL. In vitro studies further confirmed that AL released from MBG and AMBG significantly inhibited the proliferation of MG63 cells, even at lower concentrations. Interestingly, in the absence of osteogenic supplements, an increased density of red mineralized nodules was observed with increasing concentrations of MBG and AMBG, suggesting their potential to promote bone regeneration. Additionally, Zhang et al. [79] prepared MBG/PCL composite scaffolds reinforced with magnetic Fe_3O_4 nanoparticles through 3D printing. These composite scaffolds were distinguished by their uniform macroporous structure, high porosity, and remarkable compressive strength. The incorporation of Fe_3O_4 nanoparticles endowed the scaffolds with remarkable magnetic heating

capabilities and upregulated the expression of genes associated with osteogenic differentiation (Runx-2, OCN, BSP, MBP-2, and Col-1), thus promoting the proliferation and differentiation of BMSCs. Furthermore, when DOX was used as a model anticancer drug, the composite scaffold exhibited sustained drug release properties, making it suitable for localized drug delivery therapy. Owing to its enhanced osteogenic activity, localized anticancer drug delivery, and MHT therapeutic capabilities, this 3D-printed Fe_3O_4/MBG/PCL scaffold represents a promising strategy for the regeneration of bone defects following bone tumor resection.

3.3. CaS ceramic scaffolds

CaS, a bioactive material with significant potential, has garnered considerable research interest in the field of bone regeneration [80]. However, CaS faces challenges in practical applications, particularly in meeting the clinical needs of osteosarcoma patients, where its mechanical properties and bone regeneration-promoting effects have yet to meet the desired standards. To address these limitations, researchers are employing various strategies to increase the overall performance of CaS ceramic scaffolds. This includes the exploration of doping with elements such as gadolinium or lithium and the integration of other biocompatible materials such as CS and PCL to bolster the mechanical strength, bioactivity and potentially stimulate angiogenesis.

Recent studies have underscored the role of gadolinium accumulation in human bones and its active contribution to bone tissue regeneration, thereby offering novel perspectives for enhancing the properties of calcium silicate [81,82]. Liao et al. [83] crafted gadolinium-doped mesoporous calcium silicate/chitosan (Gd-MCS/CTS) scaffolds through lyophilization, resulting in superior performance in modulating the expression of osteogenic genes, including ALP, Runx-2, and Col-1. The regulatory impact was positively correlated with the level of gadolinium doping. In vitro studies indicated that Gd doping effectively activated the Wnt/β-catenin signaling pathway, promoting cell proliferation and osteogenic differentiation and thus introducing new possibilities for bone regeneration. Moreover, the integration of exogenous materials not only enhances the osteogenic properties of calcium silicate scaffolds but also paves new avenues for osteosarcoma treatment. Yang et al. [84] designed a multifunctional magnetic mesoporous calcium silicate/chitosan (MCSC) porous scaffold, incorporating M-type ferrite particles ($SrFe_{12}O_{19}$), mesoporous calcium silicate ($CaSiO_3$), and CS. This scaffold demonstrated potent antitumor and bone regeneration capabilities. The mesoporous structure of calcium silicate, in conjunction with the high PCE of the $SrFe_{12}O_{19}$ particles under NIR irradiation, facilitated drug release. Both in vitro and in vivo assays confirmed the excellent antitumor efficacy of the MCSC scaffold through the synergistic effects of DOX drug release and hyperthermia ablation. Additionally, MCSC scaffolds promoted the proliferation and osteogenic differentiation of BMSCs by activating the BMP-2/Smad/Runx-2 pathway. Fu et al. [85] reported on a 3D-printed porous silicone-derived carbon larnite/C-containing scaffold for potential tumor therapy and bone regeneration. This scaffold exhibited notable photothermal effects, effectively targeting human osteosarcoma cells and inhibiting tumor growth in nude mice. Furthermore, the larnite/C scaffold stimulated the expression of osteogenesis-related genes (ALP, OCN, and Runx-2) in rat BMSCs and promoted new bone formation in a rat cranial defect model. The convergence of 3D printing with polymer-derived ceramic strategies enables the fabrication of multifunctional bioceramic scaffolds with promising applications in the treatment of tumor-related bone defects.

3.4. AKT ceramic scaffolds

AKT, a bioceramic material abundant in calcium, magnesium, and silicon, is gaining recognition as a potential candidate for bone tissue engineering because of its excellent biocompatibility, biodegradability, and proangiogenic properties [86]. However, the current bioactivity of AKT and the absence of inherent antitumor characteristics present the main obstacles to its wider application in bone tissue engineering. To overcome these challenges, researchers are concentrating on optimizing the physical and biological attributes of bioceramic scaffolds through the incorporation of exogenous substances [87]. Zhuang et al. [88] successfully incorporated iron (Fe) into AKT scaffolds, thereby increasing their mechanical resilience. In vitro studies have demonstrated that these composite scaffolds exhibited significant PTT and MHT effects under the combined influence of laser irradiation and a magnetic field, achieving a synergistic therapeutic outcome and effectively eliminating tumor cells. Moreover, the release of Fe^{3+} ions from degraded scaffolds has been shown to markedly promote the proliferation and differentiation of BMSCs. In this work, the research team further explored the combined effect of MHT and CDT. Compared with that of the control group, cell viability progressively decreased with increasing temperature induced by MHT, plummeting to as low as 1.54 % in a lower pH (pH 6.5) culture environment, underscoring the therapeutic potential of integrating MHT and CDT in cancer treatment [89].

In addition to the introduction of novel materials, surface modification stands out as an effective strategy for enhancing the physical and chemical attributes of bioceramics [90,91]. MoS_2, as an emerging PTA, has attracted significant interest due to its high absorbance in the NIR region. The absorbance of MoS_2 is approximately 7.8 times greater than that of graphene oxide, enabling it to generate a more potent photothermal effect at lower laser energies and more efficiently achieve thermal ablation of tumor cells. Wang et al. [92] successfully utilized hydrothermal technology to coat the surface of 3D-printed AKT scaffolds with MoS_2 nanosheets. This modification enabled the MS-AKT scaffolds to rapidly increase in temperature to 45 °C within 60 s, effectively inhibiting the viability of tumor cells both in vitro and in vivo. Compared with the original AKT scaffold, the MS-AKT scaffold also promoted in vitro osteogenesis through the release of Mo ions, indicating greater osteogenic potential. Similarly, Zhao et al. [93] introduced 2D boron carbonitride (BCN) nanosheets as a functional coating on AKT scaffolds, creating BCN@AKT scaffolds with dual functionalities (Fig. 3D). The BCN nanosheets not only displayed superior photothermal properties, allowing the composite scaffold to effectively eradicate tumor cells at lower laser power but also the hydroxyl-functional groups (e.g., -OH and -COOH) and boron (B) on their surface promoted the expression of adhesion proteins and the deposition of calcium phosphate (Ca-P), significantly enhancing the osteogenic capacity of the AKT scaffolds. These studies present new insights and opportunities for the application of AKT scaffolds in osteosarcoma treatment and bone tissue regeneration.

In summary, ceramic scaffolds exhibit significant potential for applications in osteosarcoma treatment and the regeneration of bone tissue. They offer several advantages, including exceptional biocompatibility, enhanced osteoconductivity, and a chemical composition akin to that of natural bone minerals. These characteristics collectively facilitate osteoblast adhesion, proliferation, and differentiation, thereby expediting the repair and regeneration of osseous tissue. However, ceramic scaffolds possess relatively inferior mechanical strength, rendering them less suitable for load-bearing applications, and their brittle nature predisposes them to fracture and complicates their customization [94]. In light of these constraints, the scientific community has turned its attention to alternative materials. Owing to their high water content and biocompatibility hydrogel scaffolds, in particular, have emerged as promising candidates. These scaffolds effectively emulate the natural microenvironment of biological tissues, creating conducive conditions for cellular growth. Moreover, their high malleability allows precise shaping and sizing to match damaged tissue, offering tailored and personalized therapeutic solutions [95].

Table 2
Summary of ceramic-based scaffolds.

Compositions	Treatment of osteosarcoma	Bone tissue regeneration	Ref.
CaS/HA	Chemotherapy	HA is able to mimic the structure and composition of human bone tissue, thus promoting the adhesion, proliferation and differentiation of osteoblasts and accelerating the repair and regeneration of bone defect areas.	[54]
CS/HA	Chemotherapy	HA has a similar structure and composition to human bone and promotes adhesion, proliferation and differentiation of osteoblasts.	[96]
n-HA/g-C_3N_4/Mxene	Photothermal therapy and Photodynamic therapy	The presence of n-HA promotes the proliferation and osteogenic differentiation of BMSCs, thereby facilitating the formation of new bone.	[55]
$FePSe_3$/α-TCP	Photothermal therapy and Chemotherapy	Bioactive ions such as Fe, Ca and P released by the degradation of composite scaffolds enhance angiogenesis, which in turn promotes bone regeneration.	[62]
MPBI@β-TCP	Photothermal therapy	Composite scaffolds can promote adhesion, value-addition and differentiation of BMSCs as well as angiogenesis, thereby promoting bone regeneration.	[63]
CA/β-TCP	Photothermal therapy	The CA coating provided additional roughness and high surface area stimulated osteogenic differentiation of BMSCs through FN-mediated signaling pathways, further enhancing bone regeneration.	[64]
Cu-TCPP/β-TCP	Photothermal therapy	Cu^{2+} released from Cu-TCPP nanosheets can play a synergistic role in stimulating new bone formation by stimulating angiogenesis in HUVECs and osteogenesis in HBMSCs.	[97]
rFN-CDH/HGC-PTX/BCP	Chemotherapy	The rFN-CDH fusion protein significantly promoted the growth and proliferation of osteoblasts.	[66]
Fe/PBG or Mn/PBG	Photothermal therapy	P, Ca, Na, Fe and other ions released by PBG degradation can promote the proliferation and differentiation of osteoblasts.	[54
FeSAC/BG	Photothermal therapy and Chemodynamic therapy	The enhanced roughness of the composite scaffold surface contributes to the adhesion, value addition and differentiation of BMSCs.	[72]
2DTi_3C_2MXene/BG	Photothermal therapy	TBGS promotes the adhesion and value addition of BMSCs.	[75]
$CuFeSe_2$/BG	Photothermal therapy	BG-CFS contributes to the adhesion and value-addition of BMSCs, and its degradation releases Ca, Si, and P plasma that can further stimulate osteogenesis and angiogenesis.	[76]
Bi-BG	Photothermal therapy	Bi coating on the surface of BG scaffolds significantly promoted the proliferation of rBMSCs.	[69]
DTC@BG	Photothermal therapy	DTC co-crystals enhance the surface roughness of BG, thus facilitating the attachment and proliferation of hBMSCs.	[98]
MS/MXene-SNO/BG	Photothermal therapy and NO gas therapy	Low concentrations of NO further promote angiogenesis and bone regeneration on top of BG scaffolds.	[99]
AL/MBG	Chemotherapy	The high specific surface area of MBG contributes to the adhesion and value-addition of BMSCs, and its Ca, Si and P further induced osteogenesis.	[78]
Fe_3O_4/MBG/PCL	Magnetic hyperthermia and Chemotherapy	Under the effect of magnetic field, Fe_3O_4 was able to further promote the value-added and differentiation of hBMSCs on the basis of MBG.	[79]
$SrFe_{12}O_{19}$/CS/$CaSiO_3$	Photothermal therapy and Chemotherapy	The porous structure of MCSC scaffolds facilitates the adhesion and diffusion of hBMSCs.	[84]
larnite/C	Photothermal therapy	Free carbon upregulated the expression of osteogenesis-related genes, thereby further enhancing osteogenesis.	[85]
Fe/AKT	Photothermal therapy and Magnetic hyperthermia	Fe doping further promoted the proliferation and differentiation of rBMSCs.	[88]
Fe_3S_4/AKT	Magnetic hyperthermia and Chemodynamic therapy	The microstructure of the composite scaffold surface contributes to the adhesion and value-addition of hBMSCs, and the bioactive ions released by their degradation further promote bone regeneration.	[89]
B-AKT	Photothermal therapy	The micro- and nanostructures on the surface of B-AKT scaffolds contribute to the proliferation, differentiation and differentiation of rBMSCs.	[100]

4. Hydrogel scaffolds in the integrated treatment of anti-osteosarcoma and promotion of bone regeneration

Hydrogel scaffolds represent a unique class of polymeric constructs synthesized from hydrophilic polymers that are cross-linked through covalent or physical bonds to create a porous, 3D matrix. These scaffolds are renowned for their exceptional biocompatibility and hydrophilicity, as well as their ability to maintain structural integrity upon hydration and swelling. These characteristics render hydrogel scaffolds particularly efficacious in the context of bone defect repair [101,102]. The

hydrophilic nature and porous architecture of hydrogel scaffolds facilitate replication of the native microenvironment of biological tissues. This biomimetic design is instrumental in promoting cell infiltration and the proliferation of nascent bone tissues. Additionally, the scaffolds serve as conduits for the controlled release of bioactive molecules, such as growth factors and cytokines, which are pivotal for accelerating osteoblast proliferation and the deposition of the bone matrix [103]. Moreover, the porous framework of the scaffolds can be strategically engineered to function as a delivery system for a variety of antitumor agents. This targeted approach ensures the precise release of therapeutics while minimizing collateral damage to surrounding healthy tissues [104]. The versatility of hydrogel scaffolds is further underscored by the distinction between environmentally responsive and nonresponsive variants. The former undergoes property alterations in response to external stimuli, such as temperature, pH, or light, whereas the latter remains inert to such influences. This categorical distinction is pivotal for the development of hydrogel scaffolds that are tailored to specific therapeutic applications. By harnessing the inherent properties of each hydrogel type, researchers can optimize scaffolds to enhance therapeutic efficacy and precision in treatment regimens (Table 3).

4.1. Environmentally responsive hydrogel scaffolds

Hydrogels with environmental responsiveness are a class of advanced, intelligent polymers that exhibit a remarkable capacity to modulate their physical or chemical attributes in response to specific environmental stimuli. The triggers for these alterations can encompass a spectrum of factors, such as temperature fluctuations, pH variations, exposure to light, and the influence of electromagnetic fields. This adaptive behavior endows these hydrogels with a high degree of sensitivity and selectivity, making them highly versatile for applications in fields ranging from biomedical engineering to environmental monitoring.

4.1.1. Photothermo-responsive hydrogel scaffolds

Photothermo-responsive hydrogels represent a breakthrough in smart materials science and are capable of absorbing light at specific wavelengths and converting it into heat. This process induces reversible alterations in their shape, volume, and physicochemical properties, which are highly useful in bone defect repair [105]. The adaptability of these hydrogels to the contours of a defect, facilitated by the precise manipulation of an external light source, is instrumental in enhancing bone tissue regeneration. In a notable study, Wei et al. [106] harnessed biocompatible materials such as CS, hyaluronic acid, and sodium β-glycerophosphate (GP) to formulate an injectable composite hydrogel system (Gel/CPs) embedded with large carbon particles (CPs). This composite system exhibited temperature sensitivity, transitioning from a sol to a gel state at body temperature, which simplified its application in irregular bone defects, offering a conformal therapeutic approach. Furthermore, the CPs within the composite hydrogel demonstrated superior photothermal conversion capabilities, indicating promise for oncology treatments. By effectively converting NIR laser energy into thermal energy, the system achieved an impressive in vivo tumor inhibition rate, reaching up to 98.4 % following five cycles of laser

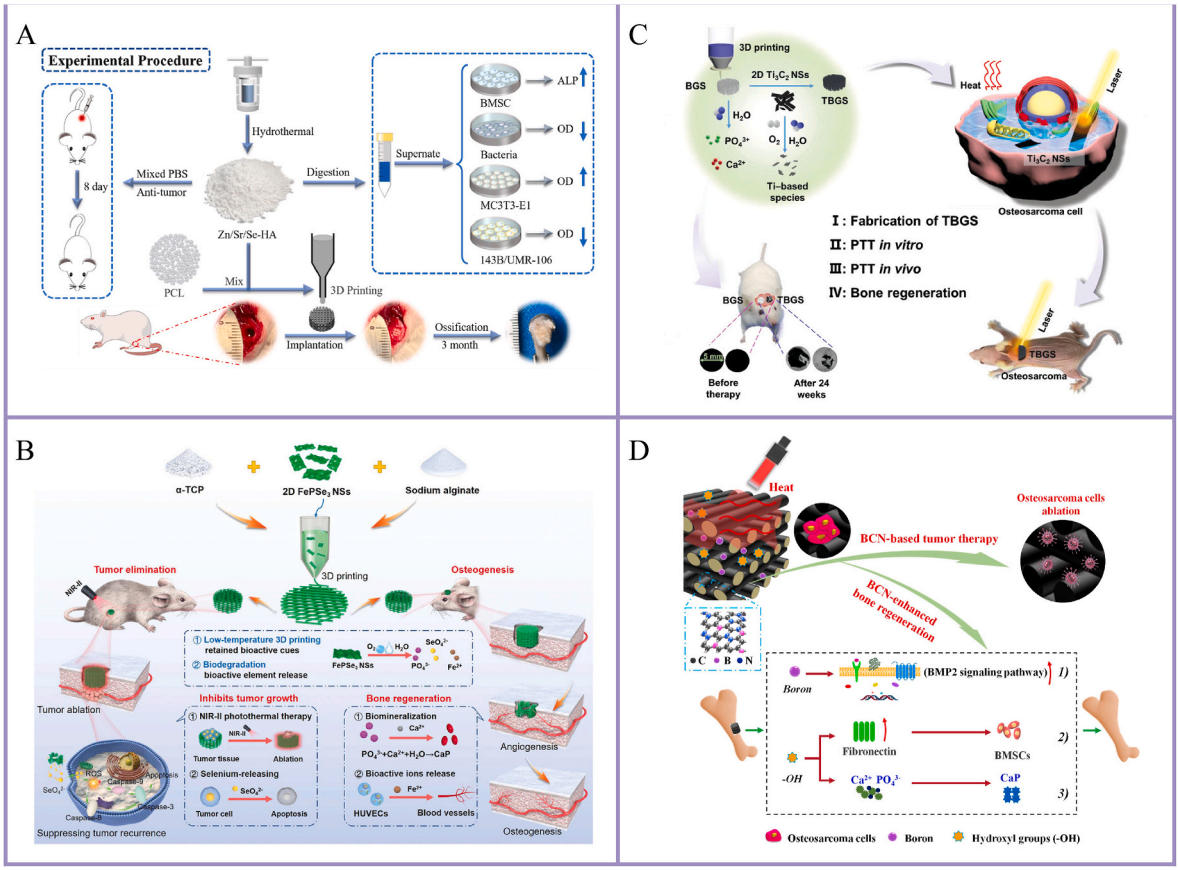


Fig. 3. Ceramic scaffold. (A) Schematic representation of the preparation and function of Se/Sr/Zn-HA and Se/Sr/Zn-HA-PCLs for tumor therapy, bone defect repair and antibacterial treatment. Reproduced with permission from Ref. [53], Copyright @ 2024 Bioactive Materials. (B) A 3D-printed TCP-$FePSe_3$ scaffold was used as an all-in-one platform to inhibit osteosarcoma recurrence and promote bone regeneration after surgery Reproduced with permission from Ref. [62], Copyright @ 2023 Small. (C) Schematic representation of TBGS fabrication, ablation of bone cancer and regeneration of bone tissue. Reproduced with permission from Ref. [75], Copyright @ 2019 Advanced Science. (D) BCN@AKT scaffolds for osteosarcoma cell photothermal therapy and subsequent repair of tumor-induced bone defects as an integrated strategy. Reproduced with permission from Ref. [93], Copyright @ 2020 Chemical Engineering journal.

irradiation. The CPs are distinguished by their abundant surface functional groups, including hydroxyl (-OH) and carboxyl (-COOH) groups, which not only increased the biocompatibility of the material but also provided optimal sites for the nucleation and growth of apatite microcrystals, thereby significantly advancing bone tissue regeneration.

Moreover, the use of photothermal responsive hydrogels represents a paradigm shift in drug delivery systems, offering the potential for on-demand release of therapeutic agents at specific times and locations. By manipulating the light source, these hydrogels can achieve controlled drug release, optimizing therapeutic outcomes while minimizing harm to healthy tissues. Li et al. [107] exemplified this concept by integrating an injectable chitosan (CS)-based hydrogel composite system (BPNS/DOX/CS), which rapidly increased in temperature under NIR radiation (Fig. 4A). This photothermal effect facilitated the initial release of the chemotherapeutic drug DOX, promoting a swift and potent therapeutic response. In vitro assays demonstrated a significant reduction in tumor cell viability to 8.9 %, as corroborated by live/dead staining, underscoring the efficacy of the combined chemotherapy and PTT approach. Furthermore, the capacity of the hydrogel to transition from a sol to a gel at physiological temperatures was advantageous for filling bone defects. Over time, the BPNS component degraded, forming a biocompatible and nontoxic phosphate that enhanced the biomineralization process through a calcium trapping mechanism, thereby promoting bone tissue regeneration. Curcumin (CM), a natural compound with potential inhibitory effects on tumor stem cells [108], faces clinical challenges because of its rapid metabolism and excretion. To overcome this, Tang et al. [109] encapsulated CM with poly(lactic acid)-hydroxyacetic acid copolymer (PLGA), which was then hybridized with methylcellulose and IR820 to create a composite hydrogel (Cur-MPs/IR820 gel). IR820, an indocyanine green derivative, is valued in biomedicine for its NIR absorption efficiency, thermal responsiveness, and biocompatibility [110]. IR820-induced local PTT not only inhibited local tumor growth but also promoted the release of CM from the microspheres, achieving a synergistic effect between PTT and chemotherapy and maximizing the elimination of tumor cells. Additionally, the hydrogel carrier mitigated the metabolic rate of CM, extending its in vivo half-life, effectively targeting residual tumor cells and inducing osteogenic differentiation of BMSCs, thereby providing robust support for bone tissue reconstruction.

4.1.2. Magnetothermo-responsive hydrogel scaffolds

Magnetothermo-responsive hydrogels stand out for their unique physical mechanism, which utilizes an external magnetic field to modulate their properties [111]. This feature allows for effective penetration of biological tissues, enabling precise control over targets that are not easily accessible by light-based systems. This addresses a key limitation of photothermo-responsive hydrogels, which struggle with light penetration depth, thereby positioning magnetothermo-responsive hydrogels as a preferred option for treating deeper tissue damage or tumors. Yu et al. [112] developed a magnetic bone repair hydrogel (MBR) with a liquid-solid phase change capability and triple functionality, demonstrating significant potential in bone defect repair (Fig. 4B). Upon injection into tumor tissue, these fluid MBRs rapidly solidified due to the presence of PLGA, effectively filling bone defect areas and establishing a foundation for bone tissue regeneration. The MBRs contain Fe_3O_4 nanoparticles that could initiate MHT under an alternating magnetic field (AMF), promoting the release of glucose oxidase (GOx). GOx enhanced the thermotherapy sensitivity of osteosarcoma cells by inhibiting ATP production through the oxidation of glucose and reducing the expression of heat shock proteins (HSPs). This approach combined MHT with starvation therapy, offering a novel strategy to increase cancer treatment efficacy. Furthermore, the Mg^{2+} ions released from the degraded MBRs help to regulate the local microenvironment, enhancing bone tissue formation and mineralization through a synergistic effect with the magnetic field, thus accelerating the healing of bone defect areas. In addition, Shi [113] et al. also successfully formulated a composite hydrogel system based on gelatin methacrylate (GelMA) and highly magnetic esterified cobalt ferrite (MECFO) (Fig. 4C). This system exhibited a pronounced MHT effect under the influence of an external magnetic field, effectively targeting osteosarcoma cells. The incorporation of MECFO not only increased the magnetic responsiveness of the hydrogel but also significantly improved the mechanical properties of the composite system, which was crucial for mimicking the mechanical properties of natural bone tissue. Additionally, the internal pore and channel-like structures of the composite hydrogel provided an optimal microenvironment for osteoblasts, facilitating cell migration and nutrient exchange and thereby effectively promoting the bone reconstruction process following osteosarcoma resection.

4.1.3. pH-responsive hydrogel scaffolds

Despite their intelligent material properties, thermo-responsive hydrogels face significant challenges, particularly in terms of their thermal stability [114]. For effective practical application, these hydrogels must maintain their integrity across a broad temperature range. However, existing thermo-responsive formulations often fall short of the necessary performance benchmarks. A critical issue arises when the hydrogel transition temperature surpasses the thermal stability threshold of encapsulated medications, risking drug degradation and efficacy loss.

To address these hurdles, the research community has focused on pH-responsive hydrogels, an emerging class of smart materials. These hydrogels offer enhanced controllability and adaptability, responding sensitively to pH variations in the local environment. This sensitivity allows for precise modulation of the physical and chemical attributes of the hydrogel. Yu et al. [115] introduced an innovative pH-responsive hydrogel scaffold, a composite of N-(2-hydroxyethyl)methacrylamide (HAMA) and silk-filament protein (SF), interspersed with CS nanoparticles encapsulating CM, termed CCNPs. This composite was engineered for efficient CM release at acidic pH values (4–6), which was characteristic of the TME, facilitating targeted cancer therapy. The distinctive 3D network structure of the hydrogel supports a controlled drug release profile, aligns with the prolonged therapeutic requirements of osteosarcoma treatment and enhances its swelling properties. This attribute fostered robust adhesion to surrounding tissues and promoted the adhesion and proliferation of MC3T3-E1 osteoblasts, thereby facilitating bone reconstruction. In parallel, Zhu et al. [116] developed a pH-responsive natriuretic peptide hydrogel featuring the P1 peptide for targeted delivery of the chemotherapeutic agent DOX. The DOX-P1 hydrogel was demonstrated to enable sustained and selective DOX release within the TME, with accumulative release rate of 36.4 % over 120 h at pH 5.8. In vivo experiments confirmed the remarkable efficacy of the DOX-P1 hydrogel in treating in situ osteosarcoma, significantly mitigating the side effects of the drug and effectively curbing tumor growth, with a tumor inhibition rate of 68.11 % relative to that of the nontreatment group. These results underscore the high efficiency of the DOX-P1 hydrogel in targeted drug delivery within tumor tissues and its significant potential as an antitumor therapeutic.

4.1.4. Multi-responsive hydrogel scaffolds

Despite their notable benefits in the realm of smart materials, thermo-responsive and pH-responsive hydrogels have limitations owing to their reactivity to a single external stimulus. Such reactivity can restrict their adaptability and controllability in environments with fluctuating conditions. To address these limitations, the research community is now directing efforts toward hydrogels with dual or multiple responsive properties, enabling more nuanced functional modulation under diverse environmental conditions. In a notable development, Sun et al. [117] introduced composite scaffolds with dual responsiveness (CCPNPs), utilizing CS as a carrier for CM and enhancing the scaffold with both pH-responsive and NIR-responsive properties through PDA functionalization. These CCPNPs exhibited pronounced pH-responsive

release of CM, which was notably augmented by NIR irradiation, particularly at a pH of 5.5. This dual-responsiveness was highly effective against osteosarcoma cells, significantly reducing tumor cell viability within a mere 10 min. Moreover, an optimal concentration of CM was identified to stimulate the proliferation and differentiation of osteogenic stem cells, a critical process for bone regeneration. In parallel with this advancement, Liu et al. [118] developed a dual-responsive GOMP hydrogel that integrated GelMA and the antitumor drug adriamycin. The incorporation of polypyrrole (PPy) endowed the GOMP hydrogel with the ability to efficiently convert light energy into heat, increasing the temperature of the hydrogel for precise thermotherapy of tumor cells. This thermotherapy not only inflicted direct damage to tumor cells but also enhanced cell membrane permeability, facilitating the penetration of chemotherapeutic agents such as adriamycin. The sustained and controlled release of adriamycin from the GOMP hydrogel, in conjunction with the photothermal effect of PPy, suggested a synergistic therapeutic approach. This approach capitalized on the immediacy of thermotherapy and the longevity of chemotherapy for the efficient elimination of tumor cells. Furthermore, the addition of montmorillonite-strontium (MMT-Sr) significantly bolstered the mechanical properties of the hydrogel, enhancing its adaptability to complex in vivo environments and effectively promoting bone tissue regeneration.

In summary, despite the distinct advantages that single-response hydrogels offer in specialized applications, they encounter limitations concerning versatility, adaptability, and controllability. These constraints become particularly evident in complex and dynamic application settings. Consequently, researchers are compelled to meticulously evaluate the merits and demerits of monoresponsive hydrogels in comparison with their multiresponsive counterparts. This assessment must be guided by the specific demands and goals of the application at hand to ensure a judicious selection of material.

4.2. Nonenvironmentally responsive hydrogel scaffolds

In the context of bone tissue engineering, hydrogels that exhibit environmental responsiveness are limited in their adaptability to external stimuli, thereby catering to a spectrum of applications. Conversely, their nonresponsive counterparts are esteemed for their enduring structural integrity and functionality, especially in scenarios necessitating prolonged drug delivery or enduring support frameworks. These hydrogels are renowned for their unwavering efficacy, thereby underpinning the predictability and dependability of their therapeutic impacts. Expanding upon this groundwork, Mahshid Monavari et al. [119] pioneered the fabrication of a multifaceted nanocomposite scaffold, harnessing the precision of 3D printing technology. This innovation integrated lysozyme-laden mesoporous cerium-doped silica-calcium nanoparticles (Lys-Ce-MSNs) within an alginate dialdehyde-gelatin composite matrix (ADA-GELs) (Fig. 4D). In vitro assays have illustrated the progressive degradation of the scaffold, coupled with the sustained release of lysozyme, which not only manifested robust antibacterial properties but also hinted at its antitumor potential. Notably, the inclusion of lysozyme increased the structural integrity of the scaffold, enabling the deposition of an HA layer, thereby catalyzing the osteogenic process. Concurrently, Huang et al. [120] have revealed a groundbreaking core-shell structured hydrogel bone scaffold, termed Mel@Gel/Mel@HF, inspired by the stratified architecture of Janus particles. This scaffold was masterfully crafted to encapsulate melatonin uniformly throughout its core-shell configuration, thereby facilitating the eradication of residual neoplastic cells from the postsurgical site through an initial surge of melatoni. Subsequently, the scaffold sustained a lower concentration release of melatonin, functioning as a potent and enduring catalyst for the osseous repair process, thus markedly propelling the regeneration of osseous tissue. This intricately engineered drug delivery framework encapsulates the synergistic therapeutic advantages of melatonin, presenting a pioneering and promising therapeutic strategy for osteosarcoma management and the revitalization of bone tissue.

Hydrogels hold great potential in the field of bioengineering, with applications ranging from drug delivery to tissue engineering and cellular scaffolding. However, they are not without their challenges, such as inadequate mechanical properties, insufficient tissue integration, and the propensity for rapid payload release, which can lead to suboptimal therapeutic outcomes [121]. To overcome these obstacles, researchers have explored various enhancement strategies. These include the reinforcement of hydrogel matrices through physical cross-linking or the integration of nanoscale materials to increase their strength and resilience [122]. Additionally, the incorporation of bioactive molecules, such as RGD peptides, has been shown to enhance the adhesion of hydrogels to biological tissues [123]. Furthermore, the development of sophisticated controlled-release mechanisms for drugs and bioactive molecules is critical for mitigating the issue of burst release and ensuring a sustained therapeutic effect [124]. Surface modification techniques have also been instrumental in enhancing the biocompatibility and stability of hydrogels, thereby broadening their applicability in biomedical settings without compromising their inherent softness. Notably, Fabian Obregon-Miano et al. [125] constructed an injectable polymer network (SIPN) that exhibited superior physicochemical characteristics. This was achieved by blending porcine bone extracellular matrix (pddECM) with polyethylene glycol diacrylate (PEGDA), yielding a hybrid material that surpasses the limitations of traditional natural polymers in terms of structural integrity and degradation kinetics. The pddECM/PEGDA hydrogel has enhanced porosity and a more intricate porous architecture, which were conducive to cell attachment, proliferation, and the efficient exchange of nutrients and metabolic waste. These features were particularly advantageous for cell engraftment and the promotion of tissue regeneration in the context of tissue engineering. Similarly, inspired by the extracellular matrix (ECM), Wu et al. [126] employed the natural polymer gelatin (GEL) and hydrazide-modified alginate (HAlg) to emulate the structural components of collagen and glycosaminoglycans, respectively. Through a combination of physical and chemical cross-linking methods, they fabricated a high-strength composite hydrogel (GEL-HAlg-DN). This hydrogel not only exhibited remarkable mechanical properties, with a tensile strength of 0.9 MPa and an elongation at break of 177 % but also demonstrated commendable biodegradability and swelling stability. These attributes created an environment that is highly conducive to cell adhesion and proliferation. Collectively, these advancements in hydrogel technology are paving the way for the creation of materials that more closely mimic the native tissue microenvironment, thereby fostering an optimal setting for cell growth and tissue repair.

Overall, in the domain of osteosarcoma therapy, environmentally responsive hydrogels have garnered significant attention owing to their capacity to modulate drug release in accordance with environmental stimuli, thereby facilitating precise therapeutic interventions. Conversely, nonenvironmentally responsive hydrogels, characterized by their straightforward nature, economic viability, and ability to maintain a stable drug release profile, present distinct advantages in specific medical contexts. This makes them a viable alternative for certain treatment modalities. The ongoing pursuit of enhancement and the introduction of novel design paradigms by researchers are propelling the evolution of hydrogel technology. This progress is instrumental in delivering more dependable and efficacious solutions for forthcoming biomedical endeavors.

Table 3
Summary of hydrogel-based scaffolds.

Compositions	Treatment of osteosarcoma	Bone tissue regeneration	Ref.
CP/HA/GP/CS	Photothermal therapy and Chemotherapy	The porous structure of the gel facilitates the exchange of nutrients and promotes the proliferation of osteoblasts; CS, GP, and HA, as active substances, support cell attachment and promote the growth of osteoblasts; and CP improves the deposition of apatite microcrystals and accelerates the formation of new bone.	[106]
BP/DOX/CS	Photothermal therapy and Chemotherapy	BP can promote bone regeneration by forming calcium phosphate deposits through in situ phosphorus driving and subsequent calcium trapping.	[107]
PHA-DDP/OSA/CS	Photothermal therapy and Chemotherapy	PHA particles adhered to cells via PDA and promoted the proliferation and differentiation of BMSCs.	128]
MDA-NPs/CMP@PAM	Photothermal therapy	Mg^{2+} released by degradation of MDA-NPs can upregulate the expression of osteogenic genes, thus promoting osteogenic differentiation of cells.	[127]
PDA@DOX-Alg/GelAGE	Photothermal therapy and Chemotherapy	PDA contributes to the adhesion and value-addition of BMSCs; Sr^{2+} is able to induce osteogenic differentiation and angiogenesis.	[128]
IR820/Cur-MPs	Photothermal therapy and Chemotherapy	The slow release of CM was able to induce value addition and differentiation of BMSCs.	[109]
Fe_3O_4/GOx/$MgCO_3$@PLGA	Magnetic hyperthermia	The Mg^{2+} released from the degradation of MBRs not only help to regulate the local microenvironment, but also enhance the formation and mineralization of bone tissues through synergistic effects with the magnetic field, thus accelerating the healing of the bone defect area.	[112]
MeCFO/GelMA	Magnetic hyperthermia	MeCFO promotes the value-addition, differentiation, and mineralization of BMSCs, which in turn promotes bone regeneration.	[113]
GNRs/n-HA/GelMA	Photothermal therapy	n-HA mimics the natural structure of the ECM in bone, thereby promoting osteoblast proliferation, differentiation and mineralization.	[129]
Odex/MMT-Sr/PPy-PVP/GelMA	Photothermal therapy and Chemotherapy	Sr^{2+} released by MMT-Sr degradation was able to induce the value-added and differentiation of BMSCs.	[118]
SP@MX-TOB/GelMA	Photothermal therapy	GelMA hydrogels have RGD sequences that significantly induce osteogenic differentiation of BMSCs.	[130]
CCNPs-SF/HAMA	Chemotherapy	The porous structure of the gel facilitates the exchange of nutrients and promotes the proliferation of osteoblasts;	[115]
CCPNPs	Photothermal therapy and Chemotherapy	The slow release of CM was able to induce value addition and differentiation of BMSCs.	[117]
Mel@Gel/Mel@HF	Chemotherapy	Low concentrations of melatonin can effectively promote osteogenic differentiation of BMSCs.	[120]
ZA/BG/PL	Photothermal therapy and Chemotherapy	Free ZA induces osteoblasts to increase in value, differentiate and mineralize.	[131]
BPQD/WW/RSF	Photothermal therapy	BPQD has an inhibitory effect on osteoclastogenesis and protein expression; parallel implantation of RSF contributes to osseointegration and vascular regeneration.	[102]
UCNP-Au/Alg	Photothermal therapy	Ca^{2+} supports bone structure and repairs defects	[132]
Nd10%Mn10%-WH-SA-Ca^{2+}	Photothermal therapy	Mn^{2+} and WH can promote the value-added and differentiation of BMSCs.	[133]

5. Design strategy for IBSs

Osteosarcoma, a malignant bone tumor, poses significant therapeutic challenges. Traditional treatments, including surgical resection, radiotherapy, and chemotherapy, are pivotal in managing tumor growth but have inherent limitations. Surgical resection, despite its effectiveness, may not completely eradicate tumor cells and can result in substantial bone loss. Additionally, the systemic side effects of chemotherapy and radiotherapy can adversely affect patients' quality of life and impede the natural processes of bone regeneration and repair. In response to these limitations, a spectrum of innovative therapeutic strategies has been developed. These include biomaterial-based approaches, advanced drug delivery systems, environmentally responsive therapies, and multimodal treatment regimens. The overarching aim of these strategies is to provide more targeted and individualized care, thereby reducing adverse effects and improving the clinical outcomes of osteosarcoma patients.

5.1. Biomaterial-directed strategies

In the therapeutic landscape of osteosarcoma, biomaterial-directed scaffolds have emerged as a significant advancement. These scaffolds fulfill the dual role of providing temporary structural support for bone defects and actively contribute to the healing process through their intrinsic characteristics. Their biocompatibility is a key attribute, as it reduces the likelihood of adverse immune reactions upon contact with human tissues, thus mitigating inflammation and the risk of tumorigenesis. The distinctive porous architecture of these scaffolds further aids in the exchange of nutrients and oxygen, creating a conducive milieu for bone regeneration. Notably, these scaffolds exhibit a dual therapeutic effect, inhibiting the proliferation of osteosarcoma cells while concurrently fostering the regeneration of osteoblasts, all without necessitating supplementary treatments. A case in point is the n-HA controlled-release scaffold, which, upon implantation into bone defects, has been shown to effectively curb the growth of osteosarcoma cells. HA, which closely mimics the mineralized matrix of natural bone, was instrumental in creating a favorable environment for osteoblasts, thereby hastening the repair and regeneration of bone tissue [57] (Fig. 5A). Furthermore, Caitlin Koski et al. [96] underscored the therapeutic potential of biomaterial-guided scaffolds in osteosarcoma treatment by incorporating CS directly onto HA discs. The subsequent degradation and release of CS have been shown to markedly curtail the proliferative capacity of osteosarcoma cells, with a significant reduction in cell viability—up to 96 % compared with that of untreated controls (Fig. 5B). Additionally, the presence of free CS has been found to augment osteoblast adhesion, proliferation, and differentiation, as evidenced by the upregulation of osteoblast bridging protein (OPN) and

collagen I (Col I). While biomaterial-directed scaffolds have demonstrated impressive therapeutic efficacy and a broad scope for application in osteosarcoma treatment, the range of biomaterials suitable for scaffold fabrication is currently constrained. To broaden the clinical utility of these scaffolds, ongoing research is focused on refining existing designs, with a particular emphasis on the development of porous scaffolds for drug delivery, thereby catering to a spectrum of therapeutic needs.

5.2. Drug delivery strategies

Drug delivery strategies represent pivotal advancements in therapeutics and are designed to augment treatment efficacy and concurrently curtail systemic side effects. The core principle involves the encapsulation of pharmaceutical agents within scaffold materials, facilitating localized and sustained release at the disease site [134]. With respect to osteosarcoma management, these strategies have been designed to harness the potential of small-molecule drugs, large-molecule monoclonal antibodies, and traditional chemotherapeutic agents. The overarching objective is to refine the spatial and temporal control of drug delivery, either through targeted systems that release agents in proximity to tumor cells or by activating the patient's immune response to engage in immunotherapy [135]. In the context of bone regeneration, these systems are adept at the continuous dispensation of growth factors and cytokines, which are instrumental in orchestrating bone repair processes, fostering osteoblast proliferation and differentiation and thus accelerating the resolution of bone defects [136].

3D scaffolding in drug delivery systems represents a superior alternative to systemic administration, providing a controlled release mechanism that ensures a consistent drug delivery rate. This method is instrumental in preventing extreme variations in drug concentrations, which in turn minimizes the risk of toxicity to healthy tissues. In an exemplary study, Yao et al. [137] fabricated an innovative chitosan and n-HA (CS/n-HA) composite scaffold for the targeted delivery of zoledronic acid (Zol). Zoledronic acid has been demonstrated to markedly inhibit tumor cell activity, promote apoptosis and curtail osteoclast activity. The integration of n-HA within the scaffold not only replicated the natural bone microenvironment but also augmented the osteogenic differentiation of the BMSCs. Additionally, the chitosan component endowed the scaffold with potent antimicrobial capabilities, significantly reducing the risk of postoperative infection associated with bone grafts. Furthermore, bioactive scaffolds have been utilized for the precise delivery of immunotherapeutic agents, including immunomodulators, vaccines, and immune cells, directly to the tumor site. Zhang et al. [138] developed an avant-garde, implantable 3D-printed scaffold with a distinctive porous architecture. This design facilitated vaccine loading and effectively recruited a variety of naive immune cells. Upon activation within the scaffold by tumor antigens and adjuvants, these cells were poised to accurately target and neutralize tumor cells systemically (Fig. 6A). The porous structure of the scaffold also aided in nutrient delivery and osteoblast adhesion, thus fostering bone tissue regeneration. Gas therapy (GT) has emerged as a promising therapeutic modality for the treatment of deep-seated tumors such as osteosarcoma. This approach utilizes biological scaffolds as a platform for materials that generate bioactive gases, such as nitric oxide (NO), oxygen (O_2), or carbon monoxide (CO). These gases have the capacity to impair the

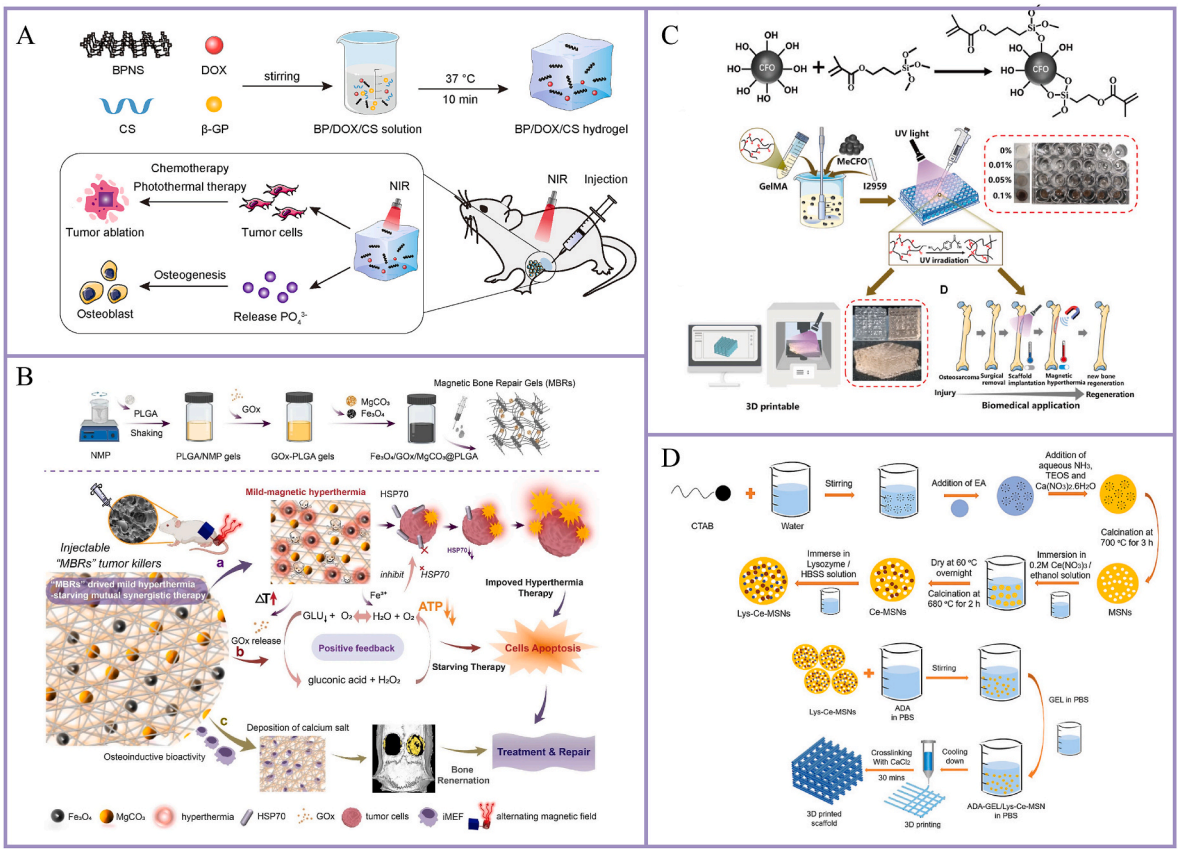


Fig. 4. Hydrogel scaffold. (A) Schematic illustration of synergistic photothermal chemotherapy of bone tumors and enhancement of osteogenesis with the injectable BPNS/DOX/CS hydrogel. Reproduced with permission from Ref. [107], Copyright @ 2023 International Journal of Biological Macromolecules. (B) MBRs induced mild hyperthermia-starvation therapy to treat bone tumors and accelerate bone defect repair. Reproduced with permission from Ref. [112], Copyright @ 2023 Journal of Nanobiotechnology. (C) Synthesis route of the MeCFO/GelMA hydrogel and schematic diagram of magnetothermal therapy. Reproduced with permission from Ref. [113], Copyright @ 2023 Frontiers. (D) 3D-printed ADA-GEL/Lys-Ce-MSN Holder. Reproduced with permission from Ref. [119], Copyright @ 2022 Macromolecular Bioscience.

physiological functions of tumor tissues, triggering tumor cell apoptosis [139]. Moreover, they can modulate cellular behavior, stimulate osteoblast proliferation, differentiation, and migration and expedite the repair of bone defects. Sanika Suvarnapathak et al. [140] engineered a scaffold capable of controlled oxygen release by incorporating microencapsulated calcium peroxide (CaO_2) into PCL and blending it with a GelMA hydrogel (Fig. 6B). This scaffold was designed to progressively release oxygen through the reaction of CaO_2 with water in an oxygen-deprived environment, meeting the oxygen demands of bone tissue and enhancing cellular vitality and tissue development. The mechanical properties, porosity, and biocompatibility of these scaffolds have been meticulously optimized to create a microenvironment conducive to cell growth and the proliferation and osteogenic differentiation of osteoblast precursors. In vivo experimental outcomes have been highly encouraging, with the scaffold demonstrating a substantial improvement in bone regeneration, particularly in the context of critical-size cranial defects. The regenerated bone tissue was found to be comparable to natural bone in volume and density, suggesting the efficacy of the scaffold in bone repair and restoration. Although the application of GT in osteosarcoma treatment and bone regeneration is in its nascent stages, its targeted and minimally invasive nature presents significant advantages over conventional therapies. Future research should investigate the potential of combining GT with other therapeutic strategies to augment treatment efficacy [141].

5.3. Environmental responsive strategies

While drug delivery scaffolds provide a targeted approach to osteosarcoma treatment, prolonged administration of chemotherapeutic and immunotherapeutic agents can engender adverse side effects. Consequently, the scientific community is pivoting toward biomaterials as a viable alternative to conventional pharmaceuticals. This paradigm shift has led to the emergence of a novel category of environmentally responsive scaffolds. These state-of-the-art scaffolds are meticulously designed to detect and react to distinct stimuli present in the TME, including an acidic pH, heightened levels of hydrogen peroxide (H_2O_2), and conditions of oxygen deprivation. Furthermore, they are capable of responding to external stimuli, such as light irradiation, ultrasonic waves, and magnetic fields. Upon activation by these triggers, the physical properties of the scaffold can be dynamically adjusted to meet the precise demands of therapeutic interventions.

5.3.1. Internal environmental responsive strategies

Internally responsive scaffolds have emerged as promising modalities for osteosarcoma therapy and bone tissue engineering. These sophisticated systems are designed to deliver drugs with precision, harnessing the ability to detect and react intelligently to particular stimuli present within the TME. This refined targeting significantly diminishes the proliferation of osteosarcoma cells, concurrently reducing the adverse impact on adjacent healthy tissues. Moreover, these scaffolds are bioengineered to expedite the process of bone regeneration. They are imbued with growth factors and molecules that promote cell adhesion, which collectively cultivate an environment conducive to osteoblast proliferation and the efficient healing of osseous defects.

The integration of CDT with bioactive scaffolds represents a novel therapeutic approach for osteosarcoma treatment and the repair of bone defects. CDT capitalizes on the unique chemical milieu within the TME, particularly the presence of Fe^{3+} and H_2O_2, to initiate the Fenton reaction. This reaction generates a high concentration of -OH, which is capable of damaging DNA, proteins, and other essential cellular components of tumor cells, thereby inducing apoptosis and exerting antitumor effects [142]. Once tumor activity is effectively suppressed, the emphasis transitions to bone defect repair. In this context, bioactive scaffolds play a crucial role in providing structural support akin to the natural 3D framework of bone tissue. These scaffolds are engineered to incorporate growth factors, cell adhesion molecules, and additional bioactive elements that promote bone regeneration. These elements enhance the proliferation and differentiation of osteoblasts, accelerating the formation of new bone tissue and effectively repairing bone defects caused by tumor excision or radiotherapy. Furthermore, the ROS produced during the Fenton reaction in CDT serve dual functions, offering both antitumor and antibacterial capabilities. These capabilities are instrumental in preventing postoperative infections, thereby enhancing the safety of bone repair procedures. An illustrative example is the work of Li et al. [143], who developed an innovative multifunctional nanocomposite scaffold utilizing low-temperature 3D printing technology. This scaffold was designed for a phased therapeutic approach, delivering initial antitumor and antibacterial effects, followed by sustained bone enhancement (Fig. 7A). Notably, the scaffold was capable of the controlled release of H_2O_2 over the first three weeks, triggering apoptosis and ferroptotic cell death in tumor cells through CDT, thus inhibiting the recurrence of osteosarcoma. This process also promoted the polarization of macrophages to the M1 phenotype, activating an antitumor immune response. Over the next 12 weeks, the sustained release of Mg^{2+} from the scaffold stimulated the osteogenic differentiation of the BMSCs by activating the Wnt3a/GSK-3β/β-catenin signaling pathway. This signaling also fostered an osteogenic immune environment through the polarization of macrophages to the M2 phenotype, further supporting bone repair. Additionally, the composite scaffolds exhibited significant antibacterial activity, effectively inhibiting the growth of *Escherichia coli (E. coli)* and *Staphylococcus aureus (S. aureus)*, both in vitro and in vivo. This antibacterial effect was mediated by the release of H_2O_2, which mitigated the risk of bacterial infections and aided in the healing of bone defects.

In summary, the synergistic application of CDT and bioactive scaffolds offers a potent antitumor tool for osteosarcoma treatment and lays a robust foundation for subsequent bone tissue regeneration.

5.3.2. External environmental responsive strategies

Scaffolds that respond to external environmental cues present a unique advantage, as their response mechanisms are not intricately tied to the organism's complex internal milieu. These scaffolds facilitate the exact control of drug release or structural alterations through externally applied, modifiable physical triggers, including light irradiation, electromagnetic fields, and ultrasonic waves. This precise external modulation allows for the strategic and timed delivery of therapeutic agents, enhancing the utility of the scaffold in a clinical setting.

In the therapeutic realm of osteosarcoma, light-responsive scaffolds have become increasingly prominent, offering distinctive advantages for their targeted applications. These scaffolds, integrated with PTAs or PIs, are capable of producing localized hyperthermia or highly reactive free radicals upon exposure to NIR irradiation. Induced hyperthermia can directly inflict thermal injury and induce cell death in tumor cells through photothermal effects, whereas highly reactive free radicals can infiltrate and compromise the integrity of DNA, proteins, and other essential cellular components, thereby instigating apoptosis [144]. Compared with traditional treatment modalities, PTT and PDT are characterized by precision and resistance to conventional drug therapies, enabling accurate targeting of tumor tissues while sparing adjacent healthy tissues [145]. A notable contribution to this area is the work of Liao et al. [129], who engineered a bifunctional hybrid hydrogel consisting of gold nanorods (GNRs) and n-HA. This hydrogel exhibited superior photothermal effects, effectively neutralizing residual postoperative tumor cells and preventing tumor reoccurrence while simultaneously minimizing collateral damage to surrounding healthy tissues due to its localized therapeutic action. This localized approach was particularly advantageous in bone tumor treatments, as it preserved the structural integrity of bone tissue and the surrounding microenvironment to maintain functionality and foster the healing process. Additionally, the heat generated by PTT not only aids in minimally invasive cancer treatment but also enhances blood circulation, which can promote the sustained delivery of therapeutic agents and the

provision of essential nutrients and oxygen to nascent bone tissues, thus further facilitating postoperative bone repair [146].

The challenge of limited light penetration depth for treating deep-seated tissues has prompted researchers to investigate alternative responsive scaffolds. Among these are ultrasound-responsive and magneto-responsive scaffolds, which offer distinctive benefits for therapeutic interventions in deeper tissues. Ultrasound-responsive scaffolds, for example, harness the synergy between ultrasound energy and chemotherapy, particularly through the interaction of ultrasound waves with sensitizing agents within tumor cells. This interaction induces the vibration of sensitizer molecules, enhancing their reactive collisions with neighboring molecules and resulting in the generation of ROS that suppress osteosarcoma cells [147]. A study by He et al. [148] demonstrated that protoporphyrin IX (PpIX) can produce ROS upon ultrasound stimulation, which disrupts the mitochondrial membrane potential of tumor cells, thereby triggering apoptosis (Fig. 7B). Additionally, the mild thermal effect associated with SDT facilitated the degradation of the outer shell of the scaffold and enhanced the release of HA from its inner layer, which was crucial for the precise repair of bone defects. Furthermore, the targeted action of SDT against deep-seated tumors was complemented by its ability to generate ROS that inhibited bacterial growth, thus preventing osteomyelitis and supporting bone tissue regeneration.

Magnetic response scaffolds offer a distinct therapeutic approach by harnessing the capabilities of an external magnetic field to induce thermotherapy through MHT. This method activates MTAs, generating localized heat within the TME, which effectively targets and eliminates tumor cells. The profound tissue penetration capacity of the magnetic field enables MHT to engage deep-seated tissues, presenting a notable advantage over phototherapeutic techniques such as PTT and PDT [149]. Moreover, the influence of a magnetic field aids in the modulation of the bone tissue microenvironment, sustaining osteoblast proliferation and differentiation, fostering the expression of growth factors pivotal for osteogenesis, and thereby hastening the process of new bone formation [150]. Cao et al. [151] reported the successful synthesis of a nanocomposite hydrogel by integrating magnetic Fe_3O_4 nanoparticles within a chitosan/poly(ethylene glycol) (PEG) matrix. This innovative hydrogel demonstrated the ability to safely and efficiently increase the temperature under an AMF, selectively neutralizing tumor cells through magnetic field-induced hyperthermia while sparing adjacent healthy tissues. Notably, compared with traditional heat treatments, this nanoparticle-mediated magnetic thermal therapy markedly augmented the osteogenic differentiation of BMSCs at equivalent temperatures, thereby providing substantial support for the regeneration of bone tissue.

5.3.3. Combined responsive strategies

Despite the efficacy of single-stimuli responsive scaffolds in tailoring drug delivery and cellular responses within defined conditions, they may face challenges arising from the inherent unpredictability of an organism's internal milieu or the limitations imposed by the penetration and accuracy of external stimuli. Such challenges have the potential to lead to therapeutic outcomes that may not align with anticipated results, thereby affecting the precision and effectiveness of the treatment.

In response to the limitations faced by single-stimuli responsive scaffolds, the scientific community has advanced a multifaceted strategy that enlists combined-responsive scaffolds. This innovative approach embeds various responsive mechanisms into a unified scaffold, capable of detecting and reacting to an array of internal biological cues—such as acidic pH, heightened H_2O_2 levels, and hypoxic conditions—as well as external triggers such as light, ultrasound, and magnetic fields. The resulting multi-responsive scaffolds provide a heightened degree of adaptability and specificity, enabling more nuanced modulation of drug delivery and cellular responses in accordance with the intricate microenvironments present within biological systems [152]. A case in point is the work of Wu et al. [46], who crafted a titanium-based bioactive implant enriched with fluorine-doped titanium dioxide (F-TiO_2) nanoparticles, PDA, and collagen. Upon exposure to NIR radiation, the F-TiO_2 nanoparticles exhibited exceptional photothermal and photocatalytic activities. This dual capability facilitated synergistic therapeutic intervention, harnessing localized thermal effects in tandem with ROS production to swiftly neutralize osteosarcoma cells within a mere 10 min. Furthermore, the incorporation of PDA and collagen into the titanium matrix endows it with enhanced osteoconductive characteristics, thereby promoting bone tissue regeneration.

5.4. Multimodal therapeutic strategies

Despite significant progress in osteosarcoma therapeutics, the practical implementation of these treatments faces considerable challenges. Tumors represent intricate biological systems marked by pronounced heterogeneity and adaptability, attributes that hinder the effective management of their multifaceted nature via a one-size-fits-all therapeutic strategy. PTT, for example, is adept at eliminating tumor cells but confronts limitations due to the finite depth of light penetration, which may result in inadequate treatment of deeper or more extensive tumors [112]; conversely, immunotherapy, especially immune checkpoint blockade (ICB) therapy, leverages the patient's immune system to combat the tumor but can produce substandard outcomes in certain individuals and may also elicit a spectrum of immune-mediated adverse effects [153].

To counter the complexities of osteosarcoma, the field of oncology is witnessing a paradigm shift toward multimodal treatment strategies, often termed integrative therapy. This innovative therapeutic paradigm encompasses the concurrent deployment of phototherapeutic techniques, chemotherapy, immunotherapy, and other modalities, which converge to increase therapeutic efficacy. The crux of this strategy lies in the synergistic amalgamation of diverse treatments, which, when integrated, target the tumor from multiple angles. This multifaceted approach not only bolsters the potency and scope of treatment but also mitigates the emergence of drug resistance. A pioneering example is the work of Li et al. [154], who engineered a multifunctional therapeutic scaffold integrating microwave (MW)-responsive zeolitic imidazolium salt framework 8 (ZIF-8) nanomaterials, the chemotherapeutic agent DOX, and an indoleamine 2,3-dioxygenase (IDO) inhibitor. These elements were ingeniously embedded into a 3D-printed titanium scaffold, resulting in a composite scaffold designated TZDI. ZIF-8 assumes dual functionality as both a drug vehicle and a thermosensitive agent under MW irradiation, allowing for the precise release of DOX in response to the TME and MW activation. This orchestrated release induces ICD in cancer cells. Simultaneously, the incorporation of IDO inhibitors invigorated an antitumor immune response, complementing MW thermotherapy and chemotherapy to develop a cohesive antitumor strategy. Moreover, the degradation of ZIF-8 and the subsequent release of Zn^{2+} over time enhanced the osteogenic differentiation of stem cells, thus assisting in bone regeneration. The TZDI scaffold, which encapsulated a myriad of therapeutic functions—MW thermotherapy, chemotherapy, immunotherapy, and bone regeneration promotion—constituted a more holistic therapeutic solution for osteosarcoma treatment.

6. Preparation and modification of IBSs

The fabrication of integrated bioactive scaffolds is an interdisciplinary endeavor involving principles from materials science, engineering, and biological research. This domain is devoted to crafting 3D constructs that replicate the ECM with precision. The initial phase of this process involves the meticulous selection of biomaterials, such as metals, ceramics, or hydrogels, which are renowned for their biocompatibility, to constitute the scaffold matrix. Following this, state-of-the-art techniques, ranging from traditional fabrication approaches to avant-garde 3D and 4D printing technologies, are harnessed to mold the scaffolds into intricate, porous 3D architectures. These architectures are

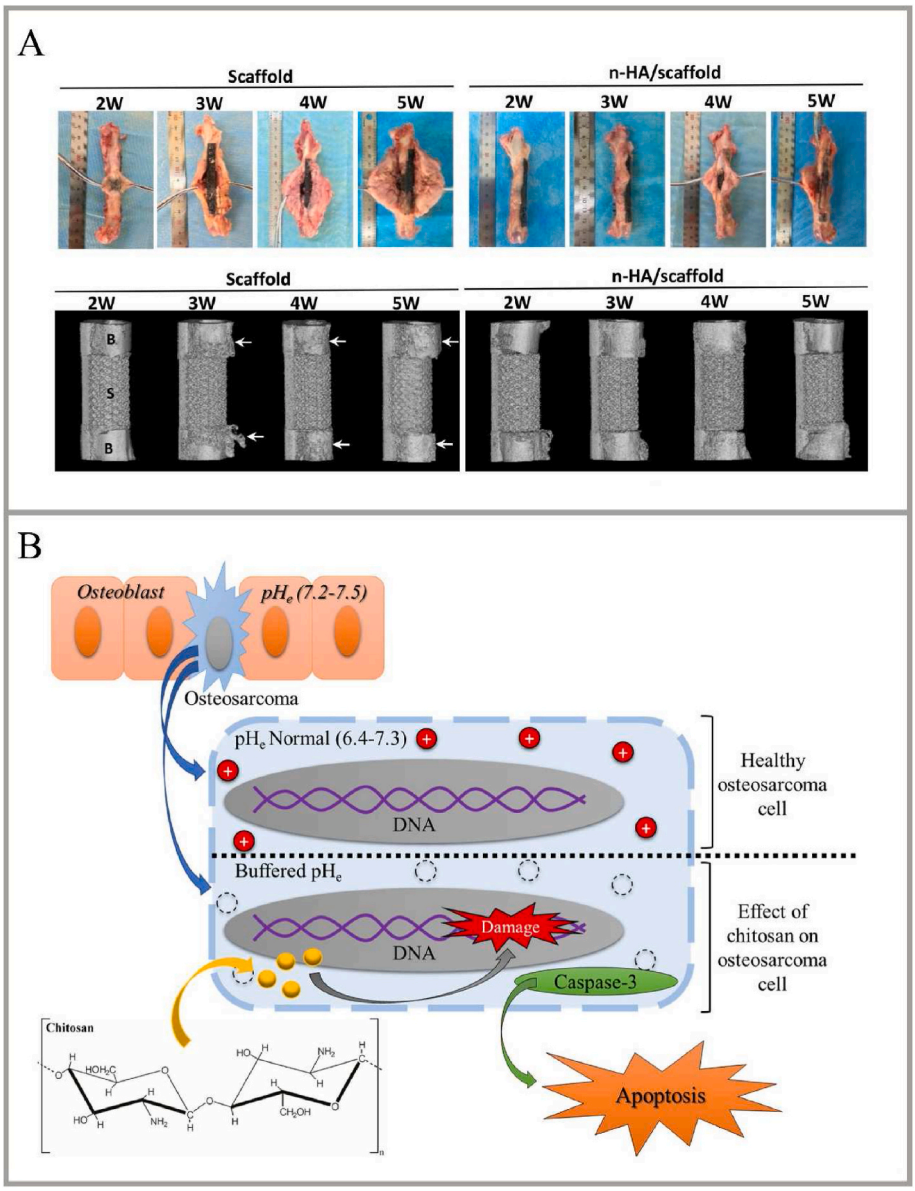


Fig. 5. Biomaterial-directed strategies. (A) Antitumor and segmental bone defect healing capacity of n-HA-loaded titanium scaffolds. Reproduced with permission from Ref. [57], Copyright @ 2019 Science Advances. (B) Mechanism of action of chitosan in tumor suppression. Reproduced with permission from Ref. [96], Copyright @ 2020 Materials Science and Engineering: C.

intricately designed to serve dual roles: enabling the targeted delivery of antitumor medications or growth factors and furnishing an expanded array of cellular attachment sites, thereby fostering cell adhesion and proliferation. This multifunctional design is intended to elicit anti-osteosarcoma responses while simultaneously promoting osseointegration, effectively utilizing the scaffolds as a robust foundation [155]. After fabrication, numerous bioactive scaffolds are subjected to additional surface modifications to further enhance their biocompatibility and bioactivity. For example, physical alterations, such as increasing surface roughness, are implemented to bolster cell attachment and proliferation [156]. Chemical modifications might encompass the covalent bonding of antitumor drugs onto the surface of the scaffold, facilitating the controlled and targeted release of therapeutic agents [157].

6.1. Preparation of IBSs

The evolution of integrated bioactive scaffolds is propelled by an array of fabrication techniques, which are generally categorized into three distinct approaches: traditional methods, 3D printing, and 4D printing technologies.

Traditional fabrication methods rely on established material processing technologies, enabling the creation of scaffolds with adequate porosity and biocompatibility. These methods have been pivotal in the nascent phase of tissue engineering, laying the groundwork for subsequent innovations in scaffold design and function. With the advent of advanced manufacturing technologies, 3D printing has become a preeminent fabrication technique. It permits the customized design of scaffold microarchitectures and intricate geometries through an additive, layer-by-layer assembly process. This precision manufacturing significantly broadens the design possibilities and meets the complex specifications of advanced tissue engineering endeavors [158]. Progressing from the foundation laid by 3D printing, 4D printing introduces a transformative temporal element. This cutting-edge technology integrates materials that exhibit stimuli-responsive properties and react to environmental cues such as temperature, pH, and humidity.

Consequently, 4D-printed scaffolds possess the unique ability to undergo morphological changes or self-adaptation postimplantation, in real time because of the body's dynamic tissue growth and healing mechanisms. This adaptive feature enhances the biomimicry of scaffolds, marking a notable progress in the domain of bioactive scaffold development [159].

6.1.1. Conventional preparation techniques

Bioactive scaffolds play crucial roles in the field of tissue engineering because of their ability to promote cell proliferation and regeneration of new tissue. The manner in which these scaffolds are prepared has a profound impact on their biocompatibility and bioactivity, which are critical determinants of their success in facilitating tissue repair. We present a synopsis of established preparation techniques: solution casting, a method that involves dissolution of the biomaterial in an appropriate solvent and subsequent casting into a mold, leads to solidification of the biomaterial, thereby forming the scaffold structure. The solvent is then eliminated, typically through particle leaching or solvent evaporation, culminating in a scaffold with a porous architecture [160] (Fig. 8A). Phase separation is another technique that initiates a two-phase system within a solution by meticulously controlling the temperature, resulting in the formation of a porous structure from one phase while the other nonporous phase is removed [161] (Fig. 8B). Freeze-drying, or lyophilization, involves the freezing of aqueous biomaterials followed by sublimation under vacuum conditions, yielding a scaffold with an interconnected porous network conducive to cell migration and nutrient transport [162]. These methodologies can be customized and refined to confer the necessary attributes to the scaffold, aligning with the precise demands of diverse biomedical applications.

6.1.2. 3D printing technology

In addition to conventional fabrication techniques, 3D printing has become a transformative innovation in the creation of bioactive scaffolds, providing exceptional precision and the capacity for highly tailored designs. This advanced technology empowers researchers to craft customized scaffolds that are uniquely tailored to address an individual patient's bone defect. These scaffolds not only precisely duplicate the macroscopic geometry of the bone but also replicate its microscopic porous architecture, thereby fostering an environment conducive to cell permeation, adhesion, proliferation, and differentiation [163]. An additional advantage of 3D printing lies in its ability to integrate pharmaceutical agents or growth factors into the scaffolds, with precise spatial control over their distribution during the printing process. This enables targeted and controlled release of bioactive molecules, which can significantly enhance the regeneration of bone tissue [164]. The integration of these therapeutic agents can be executed through two principal methodologies: direct 3D printing, which involves the immediate incorporation of cells and bioactive agents, and indirect 3D printing, which may involve additional steps postprinting for cell seeding or agent incorporation.

The technique of direct 3D printing integrates the preprocessing of bioactive molecules with the printing medium, followed by extrusion through a print nozzle. This method affords exact control over the spatial distribution and temporal release of bioactive agents throughout the fabrication process. A notable benefit of direct 3D printing is its operational simplicity and real-time adjustability, which allows for the meticulous calibration of therapeutic outcomes. Jin et al. [165] demonstrated the efficacy of this method by extruding a composite of PLGA and magnesium (Mg), thereby achieving intricate control over the scaffold's microarchitecture (Fig. 8C). The resulting scaffolds featured biomimetic, hierarchical porosity with optimized pore dimensions, porosity levels, and interconnectivity, all of which were conducive to osteoblast proliferation and the efficient transport of nutrients. Moreover, these scaffolds provided a dual therapeutic mechanism: the Mg particles, when undegraded, produced pronounced photothermal effects that effectively targeted and eliminated residual tumor cells. Concurrently, the release of Mg^{2+} from biodegrading particles contributed positively to the regeneration of bone tissue, playing an essential role in the prevention of osteosarcoma recurrence and the repair of bone defects.

Indirect 3D printing has emerged as a versatile methodology in scaffold fabrication, wherein the structural framework is initially constructed, followed by the targeted infusion of bioactive agents in a subsequent step [166]. This approach enhances flexibility, allowing for postfabrication chemical and biological modifications. Moreover, it enables the incorporation of complex drug delivery systems, such as pulsatile or gradient release profiles, tailored to accommodate the dynamic stages of osteosarcoma treatment. Lu et al. [167] exemplified this by developing a self-assembled cerium-substituted molybdenum blue (CMB) nanowheel crystal. This crystal was integrated into 3D-printed BG scaffolds, resulting in the formation of the CMB@BG scaffold (Fig. 8D). During the early phases of osteosarcoma management, the CMB@BG scaffold rapidly released antitumor agents through photothermal effects, effectively curbing tumor cell recurrence and proliferation. Concurrently, the photothermal catalytic action of CMB expedited

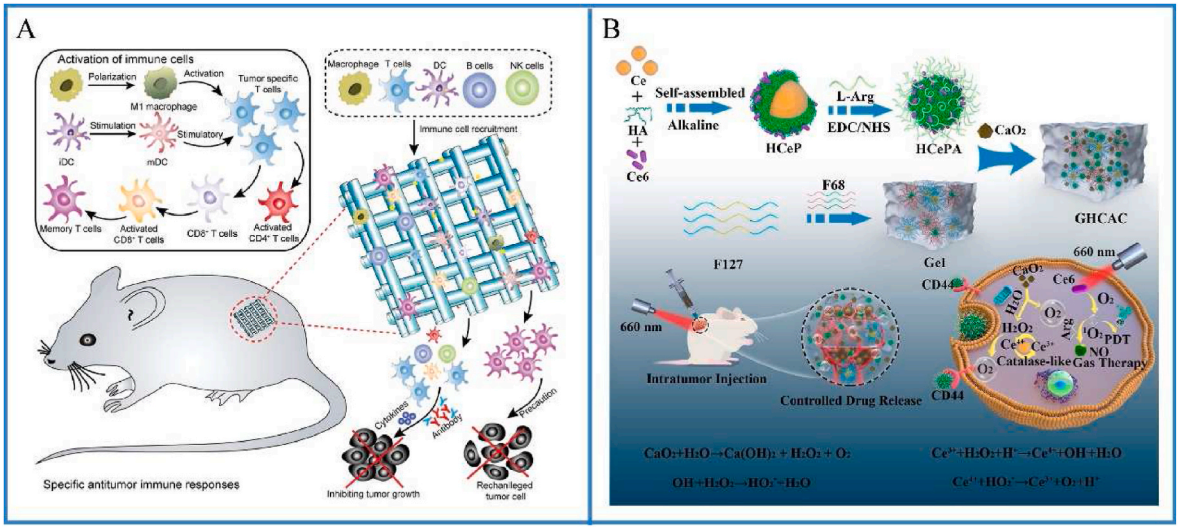


Fig. 6. Drug delivery strategies. (A) Schematic illustration of the in vivo specific antitumor immune response to an implanted 3D scaffolded vaccine. Reproduced with permission from Ref. [138], Copyright @ 2021 Advanced Materials. (B) Schematic of the oxygen-producing hydrogel (GHCAC) used to overcome tumor hypoxia to enhance synergistic photodynamic/gas therapy. Reproduced with permission from Ref. [140], Copyright @ 2020 ACS Applied Materials & Interfaces.

the elimination of ROS, mitigating inflammation and safeguarding adjacent healthy tissues. In the later stages, the scaffold contributed to bone defect repair by progressively releasing osteogenic biomolecules. This scaffold design addressed the multifaceted requirements of osteosarcoma treatment, including tumor ablation, tissue preservation, and bone regeneration, thereby offering an innovative therapeutic strategy for the comprehensive management of osteosarcoma.

In conclusion, both direct and indirect 3D printing methodologies present groundbreaking therapeutic modalities within the realm of bone tissue engineering. These advanced techniques, through the meticulous regulation of bioactive molecule release, hold the promise of markedly increasing the efficacy of bone regenerative therapies and enhancing patient prognoses.

6.1.3. 4D printing technology

While 3D bioprinting has made significant strides in the customization of personalized bioactive scaffolds, the existing technology faces constraints in creating dynamic scaffolds that can meet the sophisticated demands of bone tissue repair dynamics. The process of bone repair transcends the mere establishment of a complex 3D structural framework. It encompasses the intricate and evolving regeneration of diverse heterogeneous tissues, including nerves and blood vessels. These tissues are characterized by their capacity for ongoing property alterations in response to temporal progression and a spectrum of environmental stimuli, thereby highlighting their inherently dynamic and adaptive nature.

The introduction and ongoing evolution of 4D printing technology represent significant advancements in the realm of bioactive scaffolds, addressing the dynamic complexities of tissue repair. This innovative approach augments the capabilities of 3D printing by incorporating a temporal element, allowing for the transformation or adaptation of structures in response to environmental stimuli [159]. The foundation of 4D printing lies in the utilization of intelligent materials, including shape memory alloys, hydrogels, and polymers that exhibit stimulus-responsive behavior, adjusting their form or characteristics in response to conditions such as temperature, humidity, light, or pH. Once implanted, 4D-printed bioactive scaffolds are engineered to evolve in concert with the tissue healing timeline, seamlessly aligning with the developmental and reparative demands of the host tissue. For this purpose, Du et al. [168] have harnessed a biodegradable polyester copolymer to fabricate an innovative bone scaffold through 4D printing techniques. This scaffold integrates a PCL segment with a phase transition temperature close to physiological levels, serving as a molecular switch to initiate the shape memory response. To further augment the scaffold's osteogenic potential, a polypropylene fumarate (PPF) copolymer segment was integrated, allowing for postfabrication cross-linking. In vitro assays revealed that, compared with standard PCL, this copolymer-based scaffold notably enhanced the adhesion and osteogenic differentiation of MC3T3-E1 cells. Subsequent in vivo studies substantiated the capacity of bioactive shape memory scaffolds to swiftly conform to the geometry of bone defects postimplantation, thereby markedly advancing bone regeneration. These findings underscore the potential of 4D printing as a clinically viable strategy for bone defect intervention. Moreover, 4D printing holds the promise of exerting fine-tuned control over drug delivery through the engineering of specific stimulus-response mechanisms, enabling the timed and targeted release of therapeutics, which could substantially iincrease treatment efficacy [169]. While 4D printing remains in the nascent stages of conceptual validation and exploratory research, it has already catalyzed transformative progress in scaffold design and fabrication. This technology facilitates a more sophisticated interaction between scaffolds and host tissues, fostering superior tissue regeneration and functional restoration.

In summary, the progression from traditional scaffold fabrication methods to innovative 3D and 4D printing methods is indicative of the relentless advancements in the technologies underpinning bioactive scaffold preparation. Each technological leap presents distinctive benefits and specific applications, collectively propelling the field of regenerative medicine forward with unprecedented momentum and expansive potential. As these technologies continue to converge and evolve, the anticipation is that they will yield increasingly personalized

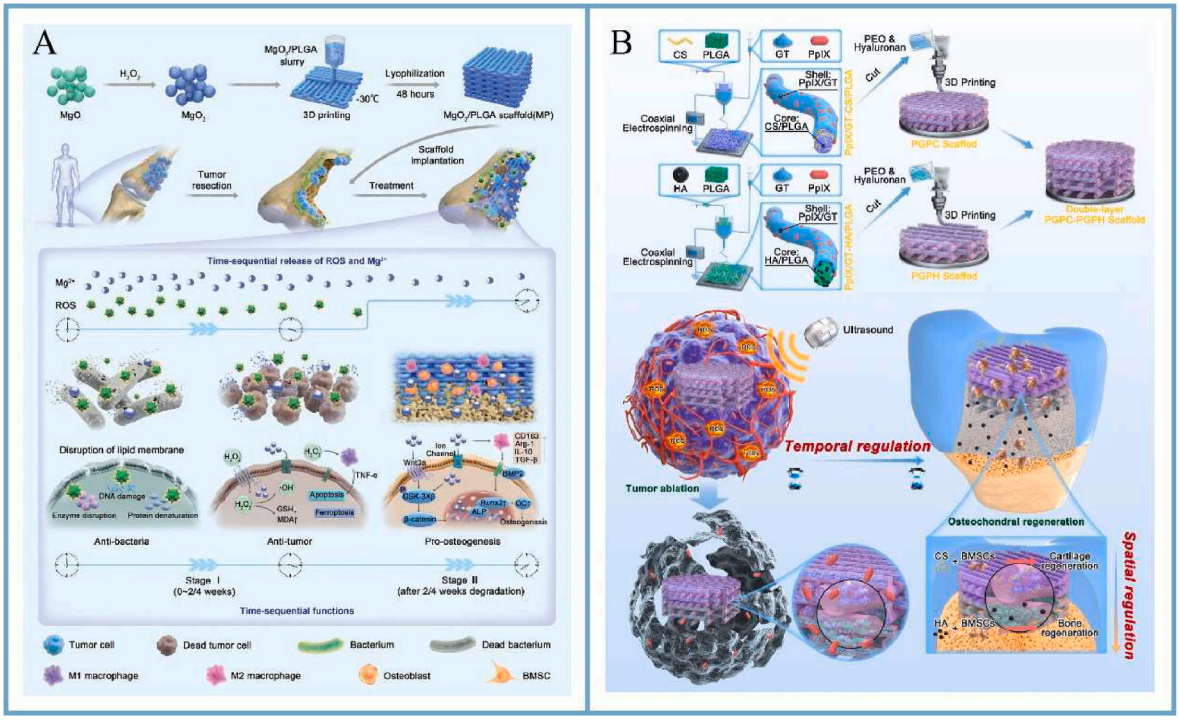


Fig. 7. Environmental response strategy. (A) Schematic of the MgO_2/PLGA composite scaffold preparation and its postoperative antimicrobial, anti-osteosarcoma and bone regeneration mechanisms. Reproduced with permission from Ref. [143], Copyright @ 2023 Advanced Materials. (B) 3D-printed bilayer PGPC-PGPH porous scaffolds and their anti-osteosarcoma and bone-enhancing mechanisms. Reproduced with permission from Ref. [148], Copyright @ 2024 Bioactive Materials.

and efficacious treatment modalities, catering to the unique needs of individual patients.

6.2. Modification of IBSs

Surface modification of bioactive scaffolds is a pivotal aspect of osteosarcoma therapy, significantly influencing the efficacy of the scaffold in bone tissue repair and regeneration. The objective of these strategies is to refine the chemical composition, physical architecture, and biological characteristics of the scaffold, thereby augmenting its integrative potential with the host bone tissue. This optimization is designed to promote the attachment, proliferation, and differentiation of osteoblasts, which are fundamental to the bone healing process. The prevalent approaches to surface modification include physical, chemical, and biological techniques, each serving to tailor the surface of the scaffold to meet specific therapeutic objectives.

6.2.1. Physical modification

Physical modification techniques enhance the surface topography of bioactive scaffolds, preserving the inherent chemical composition of the material. The primary methodologies involve the creation of microscale pores, nanoscale fibers, and tailored surface topographies [170]. According to research by Chinmaya Mahapatra et al. [171], nanofibrous scaffolds that incorporated specific topographical features enhanced cell-substrate interactions, potentially reducing cell-cell contact. This modification significantly facilitated the adhesion and regeneration of BMSCs, thereby augmenting their differentiation and mineralization processes, which were critical for osteogenic activity.

6.2.2. Chemical modification

Chemical modification of scaffolds is a strategic approach that involves altering their surface chemistry by introducing novel chemical groups or modifying existing groups, thereby enhancing interactions with osteocellular components and facilitating cell adhesion. This technique is prevalent in bone tissue engineering, where it is employed to bolster scaffold cytocompatibility and osteoinductive properties [172]. One example is the work of Li et al. [173], who fabricated RGD/GS composite scaffolds. They immobilized RGD peptides onto gelatin (GEL) scaffolds through enzymatic catalysis, leveraging the peptides' cell adhesion sequences to increase the affinity of the scaffold for host cells (Fig. 9A). This specific binding to integrins on the cell surface significantly promoted the recruitment and migration of mesenchymal stem cells (MSCs) in vivo, leading to a robust and evenly distributed cell population with high osteogenic differentiation potential. Subsequent in vivo studies revealed that the implantation of these MSC-enriched RGD/GS scaffolds into a mouse model with critical-size cranial defects markedly stimulated bone regeneration. Moreover, the surface coating of biologically inert scaffolds with bioactive materials represents an effective method for increasing their bioactivity without compromising the scaffold matrix. This approach not only improves the scaffold's biocompatibility but also endows it with additional functionalities, such as the selective promotion of the growth of specific cell types or the provision of localized drug delivery. Bigham et al. [174] exemplified this by employing poly-3-hydroxybutyric acid (P3HB) and ordered mesoporous magnesium silicate (OMMS) composites to enhance the scaffold surface. The ordered mesoporous structure of the OMMS/P3HB coating expanded the surface area of the scaffold, increasing the number of attachment sites for cells and thus promoting cell attachment and spreading. Furthermore, it enhanced the drug

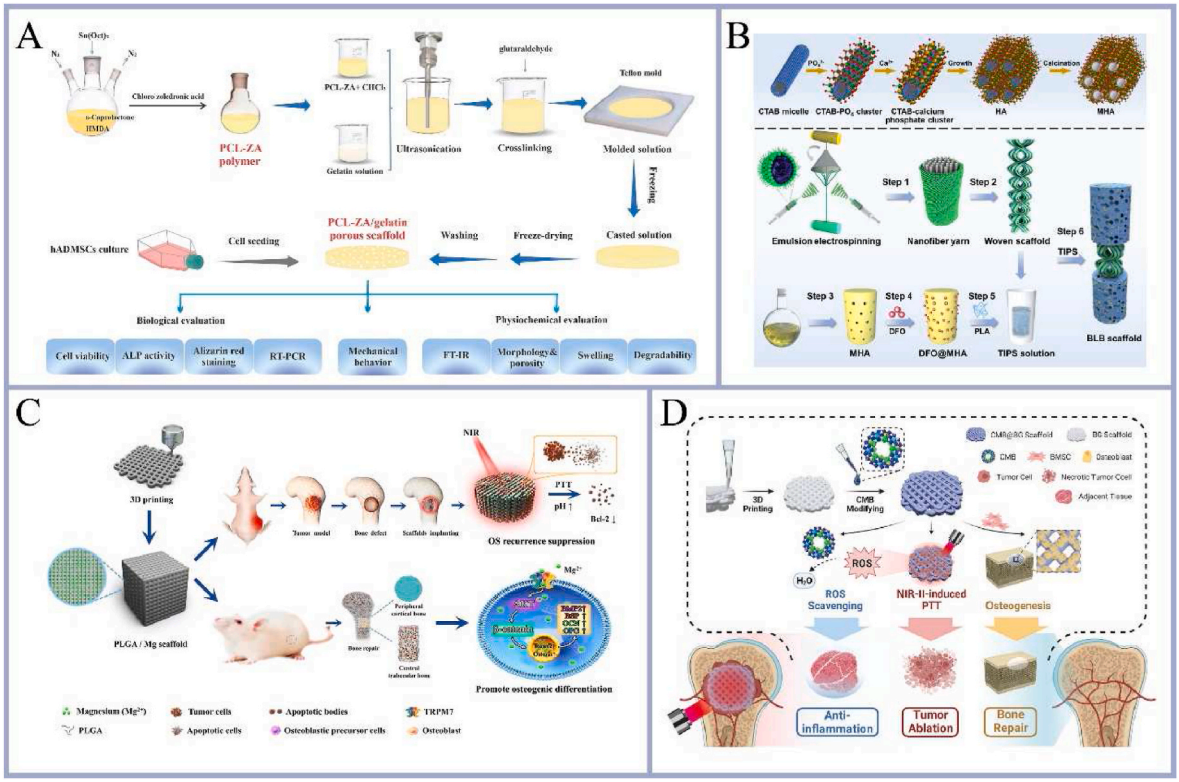


Fig. 8. Preparation of IBSs. (A)Schematic representation of ZA functionalized polycaprolactone scaffold preparation and biological studies. Reproduced with permission from Ref. [160], Copyright @ 2023 International Journal of Biological Macromolecules. (B) Schematic of the design and preparation of a multiphase bone-ligament-osteointegration branch (BLB) for ACL repair. Reproduced with permission from Ref. [161], Copyright @ 2024 Bioactive Materials. (C) Schematic of 3D printed PLGA/Mg scaffolds as an integrated platform for postoperative osteosarcoma recurrence inhibition and bone regeneration. Reproduced with permission from Ref. [165], Copyright @ 2021 Biomaterials. (D) Schematic representation of a CMB@BG scaffold equipped with self-assembled CMB nanowheel crystals with photothermal catalysis as a three-in-one solution for osteosarcoma. Reproduced with permission from Ref. [167], Copyright @ 2023 Advanced Materials.

release profile of the scaffolds, which was pivotal for effective therapeutic intervention in bone defects. The thermogenic properties of the OMMS/P3HB-coated scaffolds highlighted the potential of magnetothermal therapy for bone cancer treatment. The ability of these scaffolds to generate heat in response to an external magnetic field could increase the sensitivity of tumor cells to thermal ablation, thereby increasing the therapeutic efficacy of magnetothermal therapy.

6.2.3. Biomodification

Biomodification is a strategic approach that significantly augments the biocompatibility and biofunctionality of scaffolds through the integration of various biomolecules such as proteins, peptides, and growth factors onto the scaffold surface [175]. A pioneering example is the work of Li et al. [176], who developed a novel 3D nanofiber scaffold fabricated via electrostatic spinning and further enhanced it by immobilizing BMP-2 peptides on its surface using PDA as a facilitator (Fig. 9B). This innovative strategy not only enhanced the immobilization efficiency of BMP-2 peptides but also ensured stable bioactive signaling to cells by regulating the release kinetics of the peptides. Such regulation was critical for promoting cell adhesion, proliferation, and differentiation. In vitro studies demonstrated that these modified scaffolds markedly improved the osteogenic differentiation potential of BMSCs compared with their unmodified counterparts. Furthermore, by integrating genetic engineering techniques, scaffolds can be imbued with specific genes that promote bone formation, enabling gene-level regulation of the bone repair process. This dual-functionality allowed the scaffold to act as both a structural support and a vector for gene therapy, providing continuous biological cues essential for bone regeneration [177]. Collectively, physical, chemical, and biomodification techniques each present unique advantage and often synergize with one another. For example, physical modifications that increase surface roughness can enhance the adherence of chemical modifiers, whereas chemical modifications can introduce functional groups necessary for the immobilization of biomolecules. The integrated application of these techniques enables the design of scaffolds with tailored biological functions, addressing the sophisticated requirements of bone tissue engineering, drug delivery, and other biomedical applications.

7. Conclusions

Osteosarcoma, an aggressive malignant bone tumor, is a profound threat to patient health and life. Conventional therapeutic approaches, including surgical resection, radiotherapy, and chemotherapy, are effective at preventing tumor progression but fail to address postsurgical bone defects and are associated with significant side effects [178]. These adverse effects can impose a physical burden on patients and negatively influence their treatment outcomes and quality of life. In the ccontext of bone defect repair, autologous and allogeneic bone grafts are often regarded as the gold standard. Nevertheless, these grafting methods present challenges, such as pain and donor site dysfunction for autologous grafts and the scarcity of donor bone for allogeneic grafts. Moreover, the risk of immune rejection is a concern that may impede the efficacy of bone healing and result in further complications [179]. Consequently, there is an imperative demand for synthetic bone grafts that are capable of treating osteosarcoma effectively while also facilitating bone defect repair—a task that is notably complex. The advent of tissue engineering has brought integrated scaffold-based therapeutic strategies to the forefront of research. These scaffolds are designed to target both the eradication of osteosarcoma cells and the restoration of tissues or organs impaired by tumorigenesis or therapeutic interventions. This review offers a comprehensive examination of the latest advancements in the fabrication of bioactive scaffolds that possess dual functionalities—combating osteosarcoma and fostering bone regeneration—and explores their design methodologies and

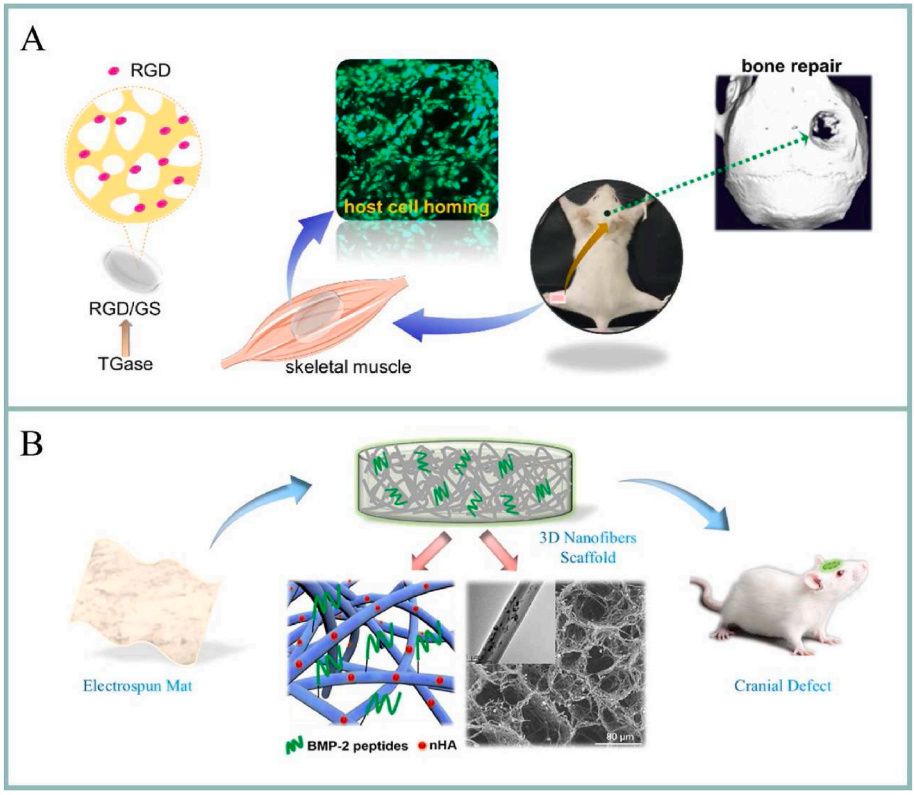


Fig. 9. Modification of IBSs. (A) RGD/GS scaffolds functionalized by site-specific enzymatic reactions were used to recruit MSCs from skeletal muscle, which were then implanted into bone defects. Reproduced with permission from Ref. [173], Copyright @ 2022 Journal of Colloid and Interface Science. (B) Schematic of 3D nanofiber scaffold preparation. Reproduced with permission from Ref. [176], Copyright @ 2019 Journal of Colloid and Interface Science.

manufacturing processes (see Fig. 10).

Addressing the reparative challenges of bone defects post-osteosarcoma surgery, the scientific community is advancing the development of bioactive scaffolds crafted from an array of biocompatible materials, encompassing metals, ceramics, and hydrogels. These scaffolds are considered a viable solution to the intricate demands of postsurgical bone reconstruction. Notably, metal scaffolds, renowned for their exceptional mechanical strength, play a pivotal role in fracture fixation and the repair of bone defects. They offer critical structural support, with the metal ions liberated during their degradation process known to stimulate bone tissue regeneration [180]. However, the inherent biological inertness of metallic scaffolds can hinder their assimilation with native bone tissue, potentially resulting in a stress-masking phenomenon that may decelerate intrinsic healing mechanisms. Ceramic scaffolds, which have a composition akin to that of human bone, are recognized for their capacity to promote bone tissue regeneration [181]. Nonetheless, their fragility and the intricacy of their fabrication processes restrict their utility in regions that endure substantial mechanical stress. On the other hand, hydrogel scaffolds, Owing to their low mass, high moldability, and superior biodegradability, have the potential to be imbued with a spectrum of pharmaceuticals and bioactive molecules, thereby increasing their utility in the treatment of osteosarcoma and the repair of bone defects [182]. Despite these attributes, the mechanical resilience of hydrogels is frequently inadequate for applications requiring the support of substantial loads. Importantly, while metal, ceramic, and hydrogel scaffolds each possess distinctive benefits, their standalone use may not be sufficient to catalyze bone healing and the formation of new bone, especially in instances of extensive bone defects following osteosarcoma surgery. Additionally, the absence of inherent anticancer properties in rudimentary scaffolds may impede their effectiveness in the therapeutic management of osteosarcoma.

Researchers are advancing the frontier of osteosarcoma management and postoperative bone repair through the development of biocompatible scaffolds, integrated with a suite of therapeutic strategies. These strategies are designed to achieve dual therapeutic goals: inhibiting osteosarcoma progression and promoting bone regeneration. The emerging modalities encompass biomaterial-directed, drug delivery, environmental responsive, and multimodal therapeutic approaches. Biomaterial-directed strategies focus on the integration of anti-osteosarcoma and osteoinductive substances within 3D scaffolds. These scaffolds, when implanted, serve the dual purpose of providing mechanical support and actively combat osteosarcoma while simultaneously stimulating bone tissue regeneration. The controlled release of biologically active components from biodegrading scaffolds contributes to the healing process, ensuring a natural transition from temporary structural support to long-term bioremediation. Drug delivery strategies prioritize the targeted and efficient conveyance of therapeutic agents,

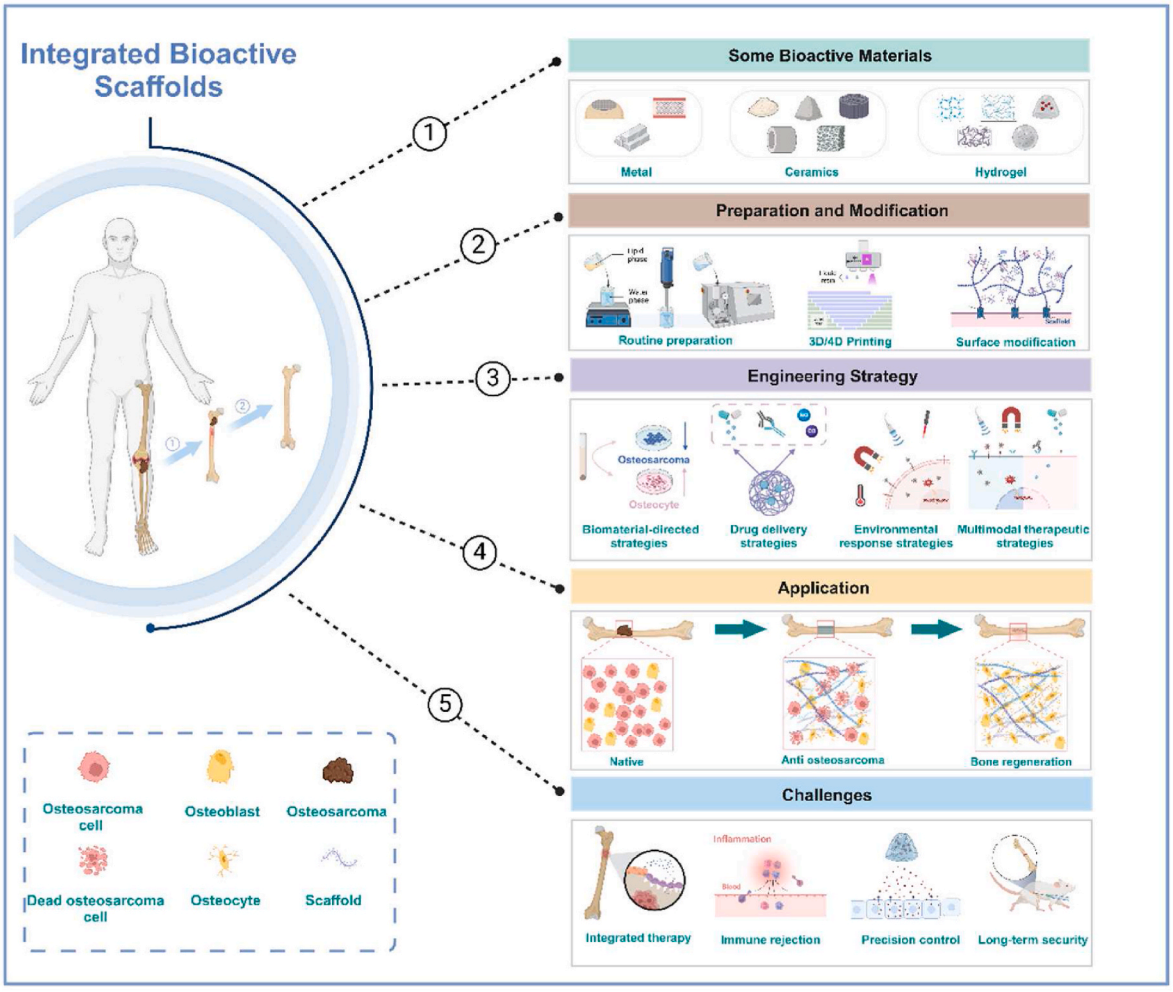


Fig. 10. Summary of IBSs. By carefully selecting and processing a variety of bioactive materials, researchers have successfully developed IBSs. These scaffolds employ a variety of ingenious design strategies that combine anti-osteosarcoma efficacy with the ability to promote bone regeneration, effectively addressing the challenges of tumor cell retention and bone defect repair after osteosarcoma surgery. In the future, research and development of IBSs will focus on three main directions: in situ, precision and long-term treatment (Created with Biorender.com).

such as chemotherapeutics and growth factors, to the site of interest within the patient's body. This targeted approach not only heightens the therapeutic impact but also mitigates the adverse effects on surrounding healthy tissues. The scaffold's capacity to modulate drug release kinetics extends the therapeutic window, offering sustained suppression of osteosarcoma cells and preventing tumor relapse [183]. Moreover, to address the side effects associated with the systemic administration of chemotherapeutic and immunotherapeutic drugs, researchers have developed environmentally responsive biomaterials [184]. These materials are sensitive to changes in the biological milieu, such as changes in pH and the presence of ROS, and can be tailored to respond to endogenous (e.g., TME) or exogenous (e.g., light, magnetic fields) stimuli. Internal environment-responsive materials exploit the unique characteristics of the TME to selectively target cancer cells [185], whereas external environment-responsive materials leverage external stimuli to induce localized hyperthermia or generate ROS, thereby eradicating tumor cells [186]. Induced thermotherapy not only enhances blood circulation and bone tissue regeneration but also synergizes with ROS to suppress bacterial growth, creating a favorable microenvironment for bone repair [187]. As cancer treatment research progresses, the integration of these diverse therapeutic strategies is anticipated to yield a more holistic and personalized approach to cancer therapy, with the potential to significantly improve patient outcomes and quality of life.

The integration of bioactive scaffolds has shown considerable promise in preclinical studies; however, translating this success into clinical practice presents several hurdles. A common limitation in current research is the isolated investigation of subcutaneous antitumor effects and bone regeneration, which overlooks the intricate interplay and synergistic effects between these processes within the bone microenvironment. This multifaceted complexity poses a significant challenge for researchers. Additionally, the biocompatibility of scaffolds and their potential to elicit immune rejection are pivotal concerns for their clinical viability. For optimal integration, scaffolds must harmonize with host tissues, facilitating the proliferation and regeneration of damaged tissue. The quest for high biocompatibility is driving researchers to select materials that naturally complement the host's physiological milieu and to refine scaffold surfaces to augment compatibility, thereby ensuring their in vivo safety and effectiveness [188]. Another critical aspect is the regulation of scaffold degradation rates, which should ideally align with the pace of new bone tissue formation. Striking a balance is essential; scaffolds that degrade too quickly may compromise structural integrity, whereas those that degrade too slowly could impede the formation of new bone tissue [189]. Furthermore, the enduring efficacy and safety profiles of these integrated bioactive scaffolds necessitate extensive validation. Prolonged implantation of nondegradable scaffolds could provoke persistent inflammation and a chronic inflammatory response, potentially detracting from therapeutic efficacy [190]. Thorough clinical surveillance and exhaustive research are imperative to evaluate these risks and guarantee the longevity and safety of such treatments. While challenges persist, the field of bone tissue engineering continues to evolve, and it is anticipated that bioactive scaffolds will undergo substantial refinement. Future advancements are likely to focus on enhancing biocompatibility, modulating degradation rates, and mitigating immune rejection, thereby tailoring these scaffolds to the nuanced demands of clinical applications.

CRediT authorship contribution statement

Huaiyuan Zhang: Writing – original draft. **Yu Wang:** Writing – original draft. **Huifen Qiang:** Writing – original draft. **Dewen Leng:** Writing – original draft. **Luling Yang:** Investigation. **Xueneng Hu:** Investigation. **Feiyan Chen:** Data curation. **Tinglin Zhang:** Supervision. **Jie Gao:** Supervision. **Zuochong Yu:** Supervision.

Declaration of competing interest

The authors do not have any conflicts of interest to declare.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 82473263) and the State Key Laboratory Basic Medicine Innovation Open project (project number: JCKFKT-MS-006).

References

[1] J. Bian, Y. Liu, X. Zhao, C. Meng, Y. Zhang, Y. Duan, G. Wang, Research progress in the mechanism and treatment of osteosarcoma, Chin Med J (Engl). 136 (20) (2023) 2412–2420, https://doi.org/10.1097/CM9.0000000000002800.
[2] H.C. Beird, S.S. Bielack, A.M. Flanagan, J. Gill, D. Heymann, K.A. Janeway, J. A. Livingston, R.D. Roberts, S.J. Strauss, R. Gorlick, Author correction: osteosarcoma, Nat Rev Dis Primers 8 (1) (2022) 82, https://doi.org/10.1038/s41572-022-00416-z.
[3] C. Wu, S. Gong, Y. Duan, C. Deng, S. Kallendrusch, L. Berninghausen, G. Osterhoff, N. Schopow, A tumor microenvironment-based prognostic index for osteosarcoma, J. Biomed. Sci. 30 (1) (2023) 23, https://doi.org/10.1186/s12929-023-00917-3.
[4] I. Lilienthal, N. Herold, Targeting molecular mechanisms underlying treatment efficacy and resistance in osteosarcoma: a review of current and future strategies, Int. J. Mol. Sci. 21 (18) (2020) 6885, https://doi.org/10.3390/ijms21186885.
[5] L. Tang, B. Liu, Lung and bone metastases patterns in osteosarcoma: chemotherapy improves overall survival, Medicine 102 (4) (2023) e32692, https://doi.org/10.1097/md.0000000000032692.
[6] C. Du, M. Zhou, F. Jia, L. Ruan, H. Lu, J. Zhang, B. Zhu, X. Liu, J. Chen, Z. Chai, et al., D-arginine-loaded metal-organic frameworks nanoparticles sensitize osteosarcoma to radiotherapy, Biomaterials 269 (2021) 120642, https://doi.org/10.1016/j.biomaterials.2020.120642.
[7] Y. Chen, R. Liu, W. Wang, C. Wang, N. Zhang, X. Shao, Q. He, M. Ying, Advances in targeted therapy for osteosarcoma based on molecular classification, Pharmacol. Res. 169 (2021) 105684, https://doi.org/10.1016/j.phrs.2021.105684.
[8] C. Chen, L. Xie, T. Ren, Y. Huang, J. Xu, W. Guo, Immunotherapy for osteosarcoma: fundamental mechanism, rationale, and recent breakthroughs, Cancer Lett. 500 (2021) 1–10, https://doi.org/10.1016/j.canlet.2020.12.024.
[9] C. Meazza, S.D. Asaftei, State-of-the-art, approved therapeutics for the pharmacological management of osteosarcoma, Expert Opin Pharmacother 22 (15) (2021) 1995–2006, https://doi.org/10.1080/14656566.2021.1936499.
[10] K. Chen, S. Liao, Y. Li, H. Jiang, Y. Liu, C. Wang, V. Kuek, J. Kenny, B. Li, Q. Huang, et al., Osteoblast-derived EGFL6 couples angiogenesis to osteogenesis during bone repair, Theranostics 11 (20) (2021) 9738–9751, https://doi.org/10.7150/thno.60902.
[11] I.M. Zraik, Y. Hess-Busch, Management of chemotherapy side effects and their long-term sequelae], Urologe 60 (7) (2021) 862–871, https://doi.org/10.1007/s00120-021-01569-7.
[12] A.H. Schmidt, Autologous bone graft: is it still the gold standard? Injury 52 (Suppl 2) (2021) S18–S22, https://doi.org/10.1016/j.injury.2021.01.043.
[13] T.F. Higgins, L.S. Marchand, Basic science and clinical application of reamed sources for autogenous bone graft harvest, J. Am. Acad. Orthop. Surg. 26 (12) (2018) 420–428, https://doi.org/10.5435/JAAOS-D-16-00512.
[14] T.M. Koushik, C.M. Miller, E. Antunes, Bone tissue engineering scaffolds: function of multi-material hierarchically structured scaffolds, Adv Healthc Mater 12 (9) (2023) e2202766, https://doi.org/10.1002/adhm.202202766.
[15] J. Zhou, Biomaterials and nanomedicine for bone regeneration: progress and future prospects, Exploration 1 (2) (2021) 20210011, https://doi.org/10.1002/EXP.20210011.
[16] W. Dai, Y. Zheng, B. Li, F. Yang, W. Chen, Y. Li, Y. Deng, D. Bai, R. Shu, A 3D-printed orthopedic implant with dual-effect synergy based on MoS(2) and hydroxyapatite nanoparticles for tumor therapy and bone regeneration, Colloids Surf. B Biointerfaces 228 (2023) 113384, https://doi.org/10.1016/j.colsurfb.2023.113384.
[17] C. Yang, H. Ma, Z. Wang, M.R. Younis, C. Liu, C. Wu, Y. Luo, P. Huang, 3D printed wesselsite nanosheets functionalized scaffold facilitates NIR-II photothermal therapy and vascularized bone regeneration, Adv. Sci. 8 (20) (2021) e2100894, https://doi.org/10.1002/advs.202100894.
[18] D. Cheng, R. Ding, X. Jin, Y. Lu, W. Bao, Y. Zhao, S. Chen, C. Shen, Q. Yang, Y. Wang, Strontium ion-functionalized nano-hydroxyapatite/chitosan composite microspheres promote osteogenesis and angiogenesis for bone regeneration, ACS Appl. Mater. Interfaces 15 (16) (2023) 19951–19965, https://doi.org/10.1021/acsami.3c00655.

[19] M.L. Lourenco, G.C. Cardoso, K. Sousa, T.A.G. Donato, F.M.L. Pontes, C. R. Grandini, Development of novel Ti-Mo-Mn alloys for biomedical applications, Sci. Rep. 10 (1) (2020) 6298, https://doi.org/10.1038/s41598-020-62865-4.
[20] W. Zhang, J. Gu, K. Li, J. Zhao, H. Ma, C. Wu, C. Zhang, Y. Xie, F. Yang, X. Zheng, A hydrogenated black TiO(2) coating with excellent effects for photothermal therapy of bone tumor and bone regeneration, Mater Sci Eng C Mater Biol Appl 102 (2019) 458–470, https://doi.org/10.1016/j.msec.2019.04.025.
[21] D. Zhang, J. Tan, R. Xu, H. Du, J. Xie, F. Peng, X. Liu, Collaborative design of MgO/FeO(x) nanosheets on titanium: combining therapy with regeneration, Small 19 (5) (2023) e2204852, https://doi.org/10.1002/smll.202204852.
[22] G. Huang, S.T. Pan, J.X. Qiu, The osteogenic effects of porous Tantalum and Titanium alloy scaffolds with different unit cell structure, Colloids Surf. B Biointerfaces 210 (2022) 112229, https://doi.org/10.1016/j.colsurfb.2021.112229.
[23] Z. Jing, R. Ni, J. Wang, X. Lin, D. Fan, Q. Wei, T. Zhang, Y. Zheng, H. Cai, Z. Liu, Practical strategy to construct anti-osteosarcoma bone substitutes by loading cisplatin into 3D-printed titanium alloy implants using a thermosensitive hydrogel, Bioact. Mater. 6 (12) (2021) 4542–4557, https://doi.org/10.1016/j.bioactmat.2021.05.007.
[24] W.A. Brantley, Evolution, clinical applications, and prospects of nickel-titanium alloys for orthodontic purposes, J World Fed Orthod. 9 (3S) (2020) S19–S26, https://doi.org/10.1016/j.ejwf.2020.08.005.
[25] M. Yao, X. Hao, H. Shao, D. Wang, B. Li, S. Xing, X. Zhao, C. Zhang, X. Liu, Y. Zhang, et al., Metallic nanoparticle-doped oxide semiconductor film for bone tumor suppression and bone regeneration, ACS Appl. Mater. Interfaces 14 (42) (2022) 47369–47384, https://doi.org/10.1021/acsami.2c10672.
[26] Y. Ma, L. Jiang, J. Hu, Y. Yuan, Engineering a multiscale multifunctional theragenerative system for enhancing osteosarcoma therapy, bone regeneration and bacterial eradication, Chem. Eng. J. 430 (1) (2022) 132622, https://doi.org/10.1016/j.cej.2021.132622.
[27] Y. Ma, L. Jiang, J. Hu, E. Zhu, N. Zhang, Developing a versatile multiscale therapeutic platform for osteosarcoma synergistic photothermo-chemotherapy with effective osteogenicity and antibacterial capability, ACS Appl. Mater. Interfaces 14 (39) (2022) 44065–44083, https://doi.org/10.1021/acsami.2c10772.
[28] D. Zhao, C. Han, B. Peng, T. Cheng, J. Fan, L. Yang, L. Chen, Q. Wei, Corrosion fatigue behavior and anti-fatigue mechanisms of an additively manufactured biodegradable zinc-magnesium gyroid scaffold, Acta Biomater. 153 (2022) 614–629, https://doi.org/10.1016/j.actbio.2022.09.047.
[29] Z. Zheng, Y. Chen, H. Hong, Y. Shen, Y. Wang, J. Sun, X. Wang, The “yin and yang” of immunomodulatory magnesium-enriched graphene oxide nanoscrolls decorated biomimetic scaffolds in promoting bone regeneration, Adv. Healthcare Mater. 10 (2) (2020) e2000631, https://doi.org/10.1002/adhm.202000631.
[30] S. Li, X. Chen, X. Wang, Y. Xiong, Y. Yan, Z. Tan, X. Yang, Y. Li, Simonkolleite coating on poly(amino acids) to improve osteogenesis and suppress osteoclast formation in vitro, Polymers 11 (9) (2019) 1505, https://doi.org/10.3390/polym11091505.
[31] A.-C.S. Vogt, T. Arsiwala, M. Mohsen, M. Vogel, V. Manolova, M.F. Bachmann, On iron metabolism and its regulation, Int. J. Mol. Sci. 22 (9) (2021) 4591, https://doi.org/10.3390/ijms22094591.
[32] B. Xu, Y. Song, K. Yang, Y. Li, B. Chen, X. Liao, Q. Jia, Magnesium metal and its corrosion products: promising materials for tumor interventional therapy, J. Magnesium Alloys 11 (3) (2023) 763–775, https://doi.org/10.1016/j.jma.2023.02.007.
[33] N. Yang, F. Gong, B. Liu, Y. Hao, Y. Chao, H. Lei, X. Yang, Y. Gong, X. Wang, Z. Liu, et al., Magnesium galvanic cells produce hydrogen and modulate the tumor microenvironment to inhibit cancer growth, Nat. Commun. 13 (2022) 2336, https://doi.org/10.1038/s41467-022-29938-6.
[34] Y. Hsu, Y. Lu, S. Wang, Y. Zheng, D. Xia, Y. Liu, Magnesium alloys in tumor treatment: current research status, challenges and future prospects, J. Magnesium Alloys 11 (10) (2023) 3399–3426, https://doi.org/10.1016/j.jma.2023.08.008.
[35] P. Globig, R. Willumeit-Romer, F. Martini, E. Mazzoni, B.J.C. Luthringer-Feyerabend, Slow degrading Mg-based materials induce tumor cell dormancy on an osteosarcoma-fibroblast coculture model, Bioact. Mater. 16 (2022) 320–333, https://doi.org/10.1016/j.bioactmat.2021.12.031.
[36] D. Zhang, S. Cheng, J. Tan, J. Xie, Y. Zhang, S. Chen, H. Du, S. Qian, Y. Qiao, F. Peng, et al., Black Mn-containing layered double hydroxide coated magnesium alloy for osteosarcoma therapy, bacteria killing, and bone regeneration, Bioact. Mater. 17 (2022) 394–405, https://doi.org/10.1016/j.bioactmat.2022.01.032.
[37] J. Ge, N. Yang, Y. Yang, H. Yu, X. Yang, Y. Wang, T. Wang, S. Cheng, Y. Wang, Z. Han, et al., The combination of eddy thermal effect of biodegradable magnesium with immune checkpoint blockade shows enhanced efficacy against osteosarcoma, Bioact. Mater. 25 (2023) 73–85, https://doi.org/10.1016/j.bioactmat.2023.01.008.
[38] N. Valarmathi, S. Sumathi, Zinc substituted hydroxyapatite/silk fiber/methylcellulose nanocomposite for bone tissue engineering applications, Int. J. Biol. Macromol. 214 (2022) 324–337, https://doi.org/10.1016/j.ijbiomac.2022.06.033.
[39] K. Gao, Y. Zhang, J. Niu, Z. Nie, Q. Liu, C. Lv, Zinc promotes cell apoptosis via activating the Wnt-3a/β-catenin signaling pathway in osteosarcoma, J. Orthop. Surg. Res. 15 (1) (2020) 57, https://doi.org/10.1186/s13018-020-01585-x.
[40] G. He, J.-J. Nie, X. Liu, Z. Ding, P. Luo, Y. Liu, B.-W. Zhang, R. Wang, X. Liu, Y. Hai, et al., Zinc oxide nanoparticles inhibit osteosarcoma metastasis by downregulating β-catenin via HIF-1α/BNIP3/LC3B-mediated mitophagy pathway, Bioact. Mater. 19 (2023) 690–702, https://doi.org/10.1016/j.bioactmat.2022.05.006.
[41] G.B. Im, E. Jung, Y.H. Kim, Y.J. Kim, S.W. Kim, G.J. Jeong, T.J. Lee, D.I. Kim, J. Kim, T. Hyeon, et al., Endosome-triggered ion-releasing nanoparticles as therapeutics to enhance the angiogenic efficacy of human mesenchymal stem cells, J Control Release 324 (2020) 586–597, https://doi.org/10.1016/j.jconrel.2020.05.038.
[42] B. Liang, D. Zuo, K. Yu, X. Cai, B. Qiao, R. Deng, J. Yang, L. Chu, Z. Deng, Y. Zheng, et al., Multifunctional bone cement for synergistic magnetic hyperthermia ablation and chemotherapy of osteosarcoma, Mater Sci Eng C Mater Biol Appl 108 (2020) 110460, https://doi.org/10.1016/j.msec.2019.110460.
[43] R.J. Wen, X. Dong, H.W. Zhuang, F.X. Pang, S.C. Ding, N. Li, Y.X. Mai, S.T. Zhou, J.Y. Wang, J.F. Zhang, Baicalin induces ferroptosis in osteosarcomas through a novel Nrf2/xCT/GPX4 regulatory axis, Phytomedicine 116 (2023) 154881, https://doi.org/10.1016/j.phymed.2023.154881.
[44] M. Jiang, Y. Jike, K. Liu, F. Gan, K. Zhang, M. Xie, J. Zhang, C. Chen, X. Zou, X. Jiang, et al., Exosome-mediated miR-144-3p promotes ferroptosis to inhibit osteosarcoma proliferation, migration, and invasion through regulating ZEB1, Mol. Cancer 22 (1) (2023) 113, https://doi.org/10.1186/s12943-023-01804-z.
[45] P. He, H. Zhang, Y. Li, M. Ren, J. Xiang, Z. Zhang, P. Ji, S. Yang, 1alpha,25-Dihydroxyvitamin D3-loaded hierarchical titanium scaffold enhanced early osseointegration, Mater Sci Eng C Mater Biol Appl 109 (2020) 110551, https://doi.org/10.1016/j.msec.2019.110551.
[46] Z. Wu, Q. Tian, J. Wang, Y. Feng, L. Li, C. Xu, J. Lv, Z. Lv, A bone implant with NIR-responsiveness for eliminating osteosarcoma cells and promoting osteogenic differentiation of BMSCs, Colloids Surf. B Biointerfaces 211 (2022) 112296, https://doi.org/10.1016/j.colsurfb.2021.112296.
[47] S. Cheng, H. Shao, D. Yin, J. Zhou, L. Jian, J. Xie, Y. Zhang, D. Wang, F. Peng, Molecular mechanism underlying the action of a celastrol-loaded layered double hydroxide-coated magnesium alloy in osteosarcoma inhibition and bone regeneration, ACS Biomater. Sci. Eng. 9 (8) (2023) 4940–4952, https://doi.org/10.1021/acsbiomaterials.3c00357.
[48] N. Zhao, Y. Wang, L. Qin, Z. Guo, D. Li, Effect of composition and macropore percentage on mechanical and in vitro cell proliferation and differentiation properties of 3D printed HA/β-TCP scaffolds, RSC Adv. 7 (2017) 43186–43196, https://doi.org/10.1039/c7ra07204j.
[49] S. Prabakaran, M. Rajan, The osteogenic and bacterial inhibition potential of natural and synthetic compound loaded metal–ceramic composite coated titanium implant for orthopedic applications, New J. Chem. 45 (2021) 15996–16010, https://doi.org/10.1039/d1nj02363b.
[50] D. Cao, J. Ding, Recent advances in regenerative biomaterials, Regen Biomater 9 (2022) rbac098, https://doi.org/10.1093/rb/rbac098.
[51] X. Hou, L. Zhang, Z. Zhou, X. Luo, T. Wang, X. Zhao, B. Lu, F. Chen, L. Zheng, Calcium phosphate-based biomaterials for bone repair, J. Funct. Biomater. 13 (4) (2022) 187, https://doi.org/10.3390/jfb13040187.
[52] S.M. George, C. Nayak, I. Singh, K. Balani, Multifunctional hydroxyapatite composites for orthopedic applications: a review, ACS Biomater. Sci. Eng. 8 (8) (2022) 3162–3186, https://doi.org/10.1021/acsbiomaterials.2c00140.
[53] H. Huang, L. Qiang, M. Fan, Y. Liu, A. Yang, D. Chang, J. Li, T. Sun, Y. Wang, R. Guo, et al., 3D-printed tri-element-doped hydroxyapatite/polycaprolactone composite scaffolds with antibacterial potential for osteosarcoma therapy and bone regeneration, Bioact. Mater. 31 (2024) 18–37, https://doi.org/10.1016/j.bioactmat.2023.07.004.
[54] Y. Liu, D.B. Raina, S. Sebastian, H. Nagesh, H. Isaksson, J. Engellau, L. Lidgren, M. Tagil, Sustained and controlled delivery of doxorubicin from an in-situ setting biphasic hydroxyapatite carrier for local treatment of a highly proliferative human osteosarcoma, Acta Biomater. 131 (2021) 555–571, https://doi.org/10.1016/j.actbio.2021.07.016.
[55] G. Zhang, Y. Lu, J. Song, D. Huang, M. An, W. Chen, P. Han, X. Yao, X. Zhang, A multifunctional nano-hydroxyapatite/MXene scaffold for the photothermal/dynamic treatment of bone tumours and simultaneous tissue regeneration, J. Colloid Interface Sci. 652 (PtB) (2023) 1673–1684, https://doi.org/10.1016/j.jcis.2023.08.176.
[56] T.M. Oliveira, F.C.B. Berti, S.C. Gasoto, B. Schneider Jr., M.A. Stimamiglio, L. F. Berti, Calcium phosphate-based bioceramics in the treatment of osteosarcoma: drug delivery composites and magnetic hyperthermia agents, Front Med Technol 3 (2021) 700266, https://doi.org/10.3389/fmedt.2021.700266.
[57] K. Zhang, Application of hydroxyapatite nanoparticles intumor-associated bone segmental defect, Sci. Adv. 5 (8) (2019) eaax6946, https://doi.org/10.1126/sciadv.aax6946.
[58] D.E. Radulescu, O.R. Vasile, E. Andronescu, A. Ficai, Latest research of doped hydroxyapatite for bone tissue engineering, Int. J. Mol. Sci. 24 (17) (2023) 13157, https://doi.org/10.3390/ijms241713157.
[59] M. Gu, W. Li, L. Jiang, X. Li, Recent progress of rare earth doped hydroxyapatite nanoparticles: luminescence properties, synthesis and biomedical applications, Acta Biomater. 148 (2022) 22–43, https://doi.org/10.1016/j.actbio.2022.06.006.
[60] R. Sikkema, B. Keohan, I. Zhitomirsky, Alginic acid polymer-hydroxyapatite composites for bone tissue engineering, Polymers 13 (18) (2021) 3070, https://doi.org/10.3390/polym13183070.
[61] M. Bohner, B.L.G. Santoni, N. Döbelin, β-tricalcium phosphate for bone substitution: synthesis and properties, Acta Biomater. 113 (2020) 23–41, https://doi.org/10.1016/j.actbio.2020.06.022.
[62] XuChao, FePSe3-Nanosheets-Integrated cryogenic-3D-printed multifunctional calcium phosphate scaffolds for synergistic therapy of osteosarcoma, Small 19 (38) (2023) 2303636, https://doi.org/10.1002/smll.202303636.

[63] L. Lu, H. Wang, M. Yang, L. Wang, K. Gan, Three-dimensional-printed MPBI@beta-TCP scaffold promotes bone regeneration and impedes osteosarcoma under near-infrared laser irradiation, FASEB J 37 (2023) e22924, https://doi.org/10.1096/fj.202201991R.
[64] S. Dong, Y.N. Zhang, J. Wan, R. Cui, X. Yu, G. Zhao, K. Lin, A novel multifunctional carbon aerogel-coated platform for osteosarcoma therapy and enhanced bone regeneration, J. Mater. Chem. B 8 (3) (2020) 368–379, https://doi.org/10.1039/c9tb02383f.
[65] S. Mofakhami, E. Salahinejad, Biphasic calcium phosphate microspheres in biomedical applications, J Control Release 338 (2021) 527–536, https://doi.org/10.1016/j.jconrel.2021.09.004.
[66] Z. Liu, Y. Wu, H. Dai, S. Li, Y. Zhu, Y. Chen, Z. Xu, L. Ge, Y. Zhang, A new recombinant fibronectin/cadherin protein-hydrophobically modified glycol chitosan/paclitaxel layer-by-layer self-assembly strategy for the postoperative therapy of osteosarcoma and correlated bone injury, J. Biomed. Nanotechnol. 17 (9) (2021) 1765–1777, https://doi.org/10.1166/jbn.2021.3159.
[67] S. Homaeigohar, M. Li, A.R. Boccaccini, Bioactive glass-based fibrous wound dressings, Burns Trauma 10 (2022) tkac038, https://doi.org/10.1093/burnst/tkac038.
[68] N. Jafari, M.S. Habashi, A. Hashemi, R. Shirazi, N. Tanideh, A. Tamadon, Application of bioactive glasses in various dental fields, Biomater. Res. 26 (1) (2022) 31, https://doi.org/10.1186/s40824-022-00274-6.
[69] J. Du, H. Ding, S. Fu, D. Li, B. Yu, Bismuth-coated 80S15C bioactive glass scaffolds for photothermal antitumor therapy and bone regeneration, Front. Bioeng. Biotechnol. 10 (2022) 1098923, https://doi.org/10.3389/fbioe.2022.1098923.
[70] L. Souza, F.V. Ferreira, J.H. Lopes, J.A. Camilli, R.A. Martin, Cancer inhibition and in vivo osteointegration and compatibility of gallium-doped bioactive glasses for osteosarcoma applications, ACS Appl. Mater. Interfaces 14 (40) (2022) 45156–45166, https://doi.org/10.1021/acsami.2c12102.
[71] J. Gu, X. Liu, P. Cui, X. Yi, Multifunctional bioactive glasses with spontaneous degradation for simultaneous osteosarcoma therapy and bone regeneration, Biomater. Adv. 154 (2023) 213626, https://doi.org/10.1016/j.bioadv.2023.213626.
[72] L. Wang, Q. Yang, M. Huo, D. Lu, Y. Gao, Y. Chen, H. Xu, Engineering single-atomic iron-catalyst-integrated 3D-printed bioscaffolds for osteosarcoma destruction with antibacterial and bone defect regeneration bioactivity, Adv Mater 33 (31) (2021) e2100150, https://doi.org/10.1002/adma.202100150.
[73] M. Malaki, R.S. Varma, Mechanotribological aspects of MXene-reinforced nanocomposites, Adv Mater 32 (38) (2020) e2003154, https://doi.org/10.1002/adma.202003154.
[74] J. Wang, C.F. Du, Y. Xue, X. Tan, J. Kang, Y. Gao, H. Yu, Q. Yan, MXenes as a versatile platform for reactive surface modification and superior sodium-ion storages, Exploration (Beijing) 1 (2) (2021) 20210024, https://doi.org/10.1002/EXP.20210024.
[75] 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. 7 (2) (2020) 1901511, https://doi.org/10.1002/advs.201901511.
[76] W. Dang, T. Li, B. Li, H. Ma, D. Zhai, X. Wang, J. Chang, Y. Xiao, J. Wang, C. Wu, A bifunctional scaffold with CuFeSe(2) nanocrystals for tumor therapy and bone reconstruction, Biomaterials 160 (2018) 92–106, https://doi.org/10.1016/j.biomaterials.2017.11.020.
[77] M. Hu, J. Fang, Y. Zhang, X. Wang, W. Zhong, Z. Zhou, Design and evaluation a kind of functional biomaterial for bone tissue engineering: selenium/mesoporous bioactive glass nanospheres, J. Colloid Interface Sci. 579 (2020) 654–666, https://doi.org/10.1016/j.jcis.2020.06.122.
[78] M. Ravanbakhsh, S. Labbaf, F. Karimzadeh, A. Pinna, A.B. Houreh, M.H. Nasr-Esfahani, Mesoporous bioactive glasses for the combined application of osteosarcoma treatment and bone regeneration, Mater Sci Eng C Mater Biol Appl. 104 (2019) 109994, https://doi.org/10.1016/j.msec.2019.109994.
[79] J. Zhang, S. Zhao, M. Zhu, Y. Zhu, Y. Zhang, Z. Liu, C. Zhang, 3D-printed magnetic Fe(3)O(4)/MBG/PCL composite scaffolds with multifunctionality of bone regeneration, local anticancer drug delivery and hyperthermia, J. Mater. Chem. B 2 (43) (2014) 7583–7595, https://doi.org/10.1039/c4tb01063a.
[80] C. Wang, K. Lin, J. Chang, J. Sun, Osteogenesis and angiogenesis induced by porous β-CaSiO3/PDLGA composite scaffold via activation of AMPK/ERK1/2 and PI3K/Akt pathways, Biomaterials 34 (1) (2013) 64–77, https://doi.org/10.1016/j.biomaterials.2012.09.021.
[81] F. Xiao, J. Shi, X. Zhang, M. Hu, K. Chen, C. Shen, X. Chen, Y. Guo, Y. Li, Gadolinium-doped whitlockite/chitosan composite scaffolds with osteogenic activity for bone defect treatment: in vitro and in vivo evaluations, Front. Bioeng. Biotechnol. 11 (2023) 1071692, https://doi.org/10.3389/fbioe.2023.1071692.
[82] D.-Y. Zhu, B. Lu, J.-H. Yin, Q.-F. Ke, H. Xu, C.-Q. Zhang, Y.-P. Guo, Y.-S. Gao, Gadolinium-doped bioglass scaffolds promote osteogenic differentiation of hBMSC via the Akt/GSK3β pathway and facilitate bone repair in vivo , Int. J. Nanomed. 14 (2019) 1085–1100, https://doi.org/10.2147/ijn.S193576.
[83] F. Liao, X.-Y. Peng, F. Yang, Q.-F. Ke, Z.-H. Zhu, Y.-P. Guo, Gadolinium-doped mesoporous calcium silicate/chitosan scaffolds enhanced bone regeneration ability, Mater. Sci. Eng. C 104 (2019) 109999, https://doi.org/10.1016/j.msec.2019.109999.
[84] F. Yang, J. Lu, Q. Ke, X. Peng, Y. Guo, X. Xie, Magnetic mesoporous calcium sillicate/chitosan porous scaffolds for enhanced bone regeneration and photothermal-chemotherapy of osteosarcoma, Sci. Rep. 8 (1) (2018) 7345, https://doi.org/10.1038/s41598-018-25595-2.
[85] S. Fu, H. Hu, J. Chen, Y. Zhu, S. Zhao, Silicone resin derived larnite/C scaffolds via 3D printing for potential tumor therapy and bone regeneration, Chem. Eng. J. 382 (15) (2020) 122928, https://doi.org/10.1016/j.cej.2019.122928.
[86] N.E. Putra, K.G.N. Borg, P.J. Diaz-Payno, M.A. Leeflang, M. Klimopoulou, P. Taheri, J.M.C. Mol, L.E. Fratila-Apachitei, Z. Huan, J. Chang, et al., Additive manufacturing of bioactive and biodegradable porous iron-akermanite composites for bone regeneration, Acta Biomater. 148 (2022) 355–373, https://doi.org/10.1016/j.actbio.2022.06.009.
[87] A.S. Mertgen, V.T. Trossmann, A.G. Guex, K. Maniura-Weber, T. Scheibel, M. Rottmar, Multifunctional biomaterials: combining material modification strategies for engineering of cell-contacting surfaces, ACS Appl. Mater. Interfaces 12 (19) (2020) 21342–21367, https://doi.org/10.1021/acsami.0c01893.
[88] H. Zhuang, R. Lin, Y. Liu, M. Zhang, D. Zhai, Z. Huan, C. Wu, Three-dimensional-printed bioceramic scaffolds with osteogenic activity for simultaneous photo/magnetothermal therapy of bone tumors, ACS Biomater. Sci. Eng. 5 (12) (2019) 6725–6734, https://doi.org/10.1021/acsbiomaterials.9b01095.
[89] H. Zhuang, C. Qin, M. Zhang, J. Ma, D. Zhai, B. Ma, N. Ma, Z. Huan, C. Wu, 3D-printed bioceramic scaffolds with Fe(3)S(4)microflowers for magnetothermal and chemodynamic therapy of bone tumor and regeneration of bone defects, Biofabrication 13 (4) (2021), https://doi.org/10.1088/1758-5090/ac19c7.
[90] M. Yuan, M. Kermanian, T. Agarwal, Z. Yang, S. Yousefiasl, Z. Cheng, P. Ma, J. Lin, A. Maleki, Defect engineering in biomedical sciences, Adv Mater 35 (38) (2023) e2304176, https://doi.org/10.1002/adma.202304176.
[91] A. Jangizehi, F. Schmid, P. Besenius, K. Kremer, S. Seiffert, Defects and defect engineering in soft matter, Soft Matter 16 (48) (2020) 10809–10859, https://doi.org/10.1039/d0sm01371d.
[92] X. Wang, T. Li, H. Ma, D. Zhai, C. Jiang, J. Chang, J. Wang, C. Wu, NPG Asia Mater. 9 (2017), https://doi.org/10.1038/am.2017.47 e376-e376.
[93] C. Zhao, A. Shen, L. Zhang, K. Lin, X. Wang, Borocarbonitrides nanosheets engineered 3D-printed scaffolds for integrated strategy of osteosarcoma therapy and bone regeneration, Chem. Eng. J. 401 (1) (2020) 125989, https://doi.org/10.1016/j.cej.2020.125989.
[94] Mohammad Sajadi LV. Seyed, Reza Mousavi, Amir Hossein Rahmati, Zoltán Kónya, Kukovecz Ákos, Taib Arif, Tobin Filleter, Robert Vajtai, Peter Boul, Zhenqian Pang, Teng Li, Sekhar Tiwary Chandra, Muhammad M. Rahman, Pulickel M. Ajayan, Damage-tolerant 3D-printed ceramics via conformal coatin, Sci. Adv. 7 (28) (2021) EABC5028, https://doi.org/10.1126/sciadv.abc5028.
[95] B. Zhou, X. Jiang, X. Zhou, W. Tan, H. Luo, S. Lei, Y. Yang, GelMA-based bioactive hydrogel scaffolds with multiple bone defect repair functions: therapeutic strategies and recent advances, Biomater. Res. 27 (1) (2023) 86, https://doi.org/10.1186/s40824-023-00422-6.
[96] C. Koski, A.A. Vu, S. Bose, Effects of chitosan-loaded hydroxyapatite on osteoblasts and osteosarcoma for chemopreventative applications, Mater Sci Eng C Mater Biol Appl. 115 (2020) 111041, https://doi.org/10.1016/j.msec.2020.111041.
[97] W. Dang, B. Ma, B. Li, Z. Huan, N. Ma, H. Zhu, J. Chang, Y. Xiao, C. Wu, 3D printing of metal-organic framework nanosheets-structured scaffolds with tumor therapy and bone construction, Biofabrication 12 (2) (2020) 025005, https://doi.org/10.1088/1758-5090/ab5ae3.
[98] H. Xiang, Q. Yang, Y. Gao, D. Zhu, S. Pan, T. Xu, Y. Chen, Cocrystal strategy toward multifunctional 3D-printing scaffolds enables NIR-activated photonic osteosarcoma hyperthermia and enhanced bone defect regeneration, Adv. Funct. Mater. 30 (25) (2020) 1909938, https://doi.org/10.1002/adfm.201909938.
[99] Q. Yang, H. Yin, T. Xu, D. Zhu, J. Yin, Y. Chen, X. Yu, J. Gao, C. Zhang, Y. Chen, et al., Engineering 2D mesoporous Silica@MXene-integrated 3D-printing scaffolds for combinatory osteosarcoma therapy and NO-augmented bone regeneration, Small 16 (14) (2020) e1906814, https://doi.org/10.1002/smll.201906814.
[100] X. Wang, Y. Liu, M. Zhang, D. Zhai, Y. Wang, H. Zhuang, B. Ma, Y. Qu, X. Yu, J. Ma, et al., 3D printing of black bioceramic scaffolds with micro/nanostructure for bone tumor-induced tissue therapy, Adv Healthc Mater 10 (21) (2021) e2101181, https://doi.org/10.1002/adhm.202101181.
[101] H. Tian, R. Wu, N. Feng, J. Zhang, J. Zuo, Recent advances in hydrogels-based osteosarcoma therapy, Front. Bioeng. Biotechnol. 10 (2022) 1042625, https://doi.org/10.3389/fbioe.2022.1042625.
[102] Z. Hu, J. Lu, A. Hu, Y. Dou, S. Wang, D. Su, W. Ding, R. Lian, S. Lu, L. Xiao, et al., Engineering BPQDs/PLGA nanospheres-integrated wood hydrogel bionic scaffold for combinatory bone repair and osteolytic tumor therapy, Chem. Eng. J. 446 (4) (2022) 137269, https://doi.org/10.1016/j.cej.2022.137269.
[103] Z. Lv, T. Hu, Y. Bian, G. Wang, Z. Wu, H. Li, X. Liu, S. Yang, C. Tan, R. Liang, et al., A MgFe-LDH nanosheet-incorporated smart thermo-responsive hydrogel with controllable growth factor releasing capability for bone regeneration, Adv Mater 35 (5) (2023) e2206545, https://doi.org/10.1002/adma.202206545.
[104] H. Shan, K. Li, D. Zhao, C. Chi, Q. Tan, X. Wang, J. Yu, M. Piao, Locally controlled release of methotrexate and alendronate by thermo-sensitive hydrogels for synergistic inhibition of osteosarcoma progression, Front. Pharmacol. 11 (2020) 573, https://doi.org/10.3389/fphar.2020.00573.
[105] M. Wu, H. Liu, D. Li, Y. Zhu, P. Wu, Z. Chen, F. Chen, Y. Chen, Z. Deng, L. Cai, Smart-responsive multifunctional therapeutic system for improved regenerative microenvironment and accelerated bone regeneration via mild photothermal therapy, Adv. Sci. 11 (2) (2024) e2304641, https://doi.org/10.1002/advs.202304641.
[106] C. Wei, X. Jin, C. Wu, W. Zhang, Injectable composite hydrogel based on carbon particles for photothermal therapy of bone tumor and bone regeneration, J. Mater. Sci. Technol. 118 (2022) 64–72, https://doi.org/10.1016/j.jmst.2021.10.053.

[107] S. Li, Y. Qing, Y. Lou, R. Li, H. Wang, X. Wang, B. Ying, X. Tang, Y. Qin, Injectable thermosensitive black phosphorus nanosheet- and doxorubicin-loaded hydrogel for synergistic bone tumor photothermal-chemotherapy and osteogenesis enhancement, Int. J. Biol. Macromol. 239 (1) (2023) 124209, https://doi.org/10.1016/j.ijbiomac.2023.124209.
[108] K. Mortezaee, E. Salehi, H. Mirtavoos-Mahyari, E. Motevaseli, M. Najafi, B. Farhood, R.J. Rosengren, A. Sahebkar, Mechanisms of apoptosis modulation by curcumin: implications for cancer therapy, J. Cell. Physiol. 234 (8) (2019) 12537–12550, https://doi.org/10.1002/jcp.28122.
[109] B. Tan, Y. Wu, Y. Wu, K. Shi, R. Han, Y. Li, Z. Qian, J. Liao, Curcumin-Microsphere/IR820 hybrid bifunctional hydrogels for in situ osteosarcoma chemo-co-thermal therapy and bone reconstruction, ACS Appl. Mater. Interfaces 13 (27) (2021) 31542–31553, https://doi.org/10.1021/acsami.1c08775.
[110] Y. Jiang, C. Huang, Y. Luan, Lactosylated IR820/DOX Co-assembled nanodrug for synergetic antitumour therapy, Int J Nanomedicine 15 (2020) 4431–4440, https://doi.org/10.2147/IJN.S247617.
[111] X. Chen, H. Wang, J. Shi, Z. Chen, Y. Wang, S. Gu, Y. Fu, J. Huang, J. Ding, L. Yu, An injectable and active hydrogel induces mutually enhanced mild magnetic hyperthermia and ferroptosis, Biomaterials 298 (2023) 122139, https://doi.org/10.1016/j.biomaterials.2023.122139.
[112] K. Yu, H. Zhou, Y. Xu, Y. Cao, Y. Zheng, B. Liang, Engineering a triple-functional magnetic gel driving mutually-synergistic mild hyperthermia-starvation therapy for osteosarcoma treatment and augmented bone regeneration, J. Nanobiotechnol. 21 (1) (2023) 201, https://doi.org/10.1186/s12951-023-01955-7.
[113] Y. Shi, Z. Wang, X. Zhou, C. Lin, C. Chen, B. Gao, W. Xu, X. Zheng, T. Wu, H. Wang, Preparation of a 3D printable high-performance GelMA hydrogel loading with magnetic cobalt ferrite nanoparticles, Front. Bioeng. Biotechnol. 11 (2023) 1132192, https://doi.org/10.3389/fbioe.2023.1132192.
[114] J.P. Jeong, K. Kim, J. Kim, Y. Kim, S. Jung, New polyvinyl alcohol/succinoglycan-based hydrogels for pH-responsive drug delivery, Polymers 15 (14) (2023) 3009, https://doi.org/10.3390/polym15143009.
[115] Q. Yu, Z. Meng, Y. Liu, Z. Li, X. Sun, Z. Zhao, Photocuring hyaluronic acid/silk fibroin hydrogel containing curcumin loaded CHITOSAN nanoparticles for the treatment of MG-63 cells and me3t3-E1 cells, Polymers 13 (2021) 2302, https://doi.org/10.3390/polym13142302.
[116] J. Zhu, R. Gao, Z. Wang, Z. Cheng, Z. Xu, Z. Liu, Y. Wu, M. Wang, Y. Zhang, Sustained and targeted delivery of self-assembled doxorubicin nonapeptides using pH-responsive hydrogels for osteosarcoma chemotherapy, Pharmaceutics 15 (2) (2023) 668, https://doi.org/10.3390/pharmaceutics15020668.
[117] X. Sun, Engineering PDA-coated CM-CS nanoparticles for photothermo-chemotherapy of osteosarcoma and bone regeneration 175 (2021) 108138, https://doi.org/10.1016/j.bej.2021.108138.
[118] X. Liu, Y. Zhang, H. Wu, J. Tang, J. Zhou, J. Zhao, S. Wang, A conductive gelatin methacrylamide hydrogel for synergistic therapy of osteosarcoma and potential bone regeneration, Int. J. Biol. Macromol. 228 (2023) 111–122, https://doi.org/10.1016/j.ijbiomac.2022.12.185.
[119] M. Monavari, R. Medhekar, Q. Nawaz, M. Monavari, M. Fuentes-Chandia, S. Homaeigohar, A.R. Boccaccini, A 3D printed bone tissue engineering scaffold composed of alginate dialdehyde-gelatine reinforced by lysozyme loaded cerium doped mesoporous silica-calcia nanoparticles, Macromol. Biosci. 22 (9) (2022) e2200113, https://doi.org/10.1002/mabi.202200113.
[120] W. Huang, X. Wu, Y. Zhao, Y. Liu, B. Zhang, M. Qiao, Z. Zhu, Z. Zhao, Janus-inspired core-shell structure hydrogel programmatically releases melatonin for reconstruction of postoperative bone tumor, ACS Appl. Mater. Interfaces 15 (2) (2023) 2639–2655, https://doi.org/10.1021/acsami.2c18545.
[121] Z. Liu, W. Xin, J. Ji, J. Xu, L. Zheng, X. Qu, B. Yue, 3D-Printed hydrogels in orthopedics: developments, limitations, and perspectives, Front. Bioeng. Biotechnol. 10 (2022) 845342, https://doi.org/10.3389/fbioe.2022.845342.
[122] Y. Chen, W. Sheng, J. Lin, C. Fang, J. Deng, P. Zhang, M. Zhou, P. Liu, J. Weng, F. Yu, et al., Magnesium oxide nanoparticle coordinated phosphate-functionalized chitosan injectable hydrogel for osteogenesis and angiogenesis in bone regeneration, ACS Appl. Mater. Interfaces 14 (6) (2022) 7592–7608, https://doi.org/10.1021/acsami.1c21260.
[123] C. Qu, Z. Bao, X. Zhang, Z. Wang, J. Ren, Z. Zhou, M. Tian, X. Cheng, X. Chen, C. Feng, A thermosensitive RGD-modified hydroxybutyl chitosan hydrogel as a 3D scaffold for BMSCs culture on keloid treatment, Int. J. Biol. Macromol. 125 (2019) 78–86, https://doi.org/10.1016/j.ijbiomac.2018.12.058.
[124] K.H. Schneider, B.J. Goldberg, O. Hasturk, X. Mu, M. Dotzlhofer, G. Eder, S. Theodossiou, L. Pichelkastner, P. Riess, S. Rohringer, et al., Silk fibroin, gelatin, and human placenta extracellular matrix-based composite hydrogels for 3D bioprinting and soft tissue engineering, Biomater. Res. 27 (1) (2023) 117, https://doi.org/10.1186/s40824-023-00431-5.
[125] F. Obregon-Miano, A. Fathi, C. Rathsam, I. Sandoval, F. Deheghani, A. Spahr, Injectable porcine bone demineralized and digested extracellular matrix-PEGDA hydrogel blend for bone regeneration, J. Mater. Sci. Mater. Med. 31 (2) (2020) 21, https://doi.org/10.1007/s10856-019-6354-3.
[126] T. Wu, L. Liu, Z. Gao, C. Cui, C. Fan, Y. Liu, M. Di, Q. Yang, Z. Xu, W. Liu, Extracellular matrix (ECM)-inspired high-strength gelatin-alginate based hydrogels for bone repair, Biomater. Sci. 11 (8) (2023) 2877–2885, https://doi.org/10.1039/d3bm00213f.
[127] C. Li, W. Zhang, R. Wang, X.-F. Du, D. Jiang, B. Liu, Y. Nie, J. Liao, Y. Chen, X. Liang, et al., Nanocomposite multifunctional hydrogel for suppressing osteosarcoma recurrence and enhancing bone regeneration, Chem. Eng. J. 435 (2022) 134896, https://doi.org/10.1016/j.cej.2022.134896.
[128] S. Chen, Y. Wang, X. Zhang, J. Ma, M. Wang, Double-crosslinked bifunctional hydrogels with encapsulated anti-cancer drug for bone tumor cell ablation and bone tissue regeneration, Colloids Surf. B Biointerfaces 213 (2022) 112364, https://doi.org/10.1016/j.colsurfb.2022.112364.
[129] J. Liao, K. Shi, Y. Jia, Y. Wu, Z. Qian, Gold nanorods and nanohydroxyapatite hybrid hydrogel for preventing bone tumor recurrence via postoperative photothermal therapy and bone regeneration promotion, Bioact. Mater. 6 (8) (2021) 2221–2230, https://doi.org/10.1016/j.bioactmat.2021.01.006.
[130] J. Yin, Q. Han, J. Zhang, Y. Liu, X. Gan, K. Xie, L. Xie, Y. Deng, MXene-based hydrogels endow polyetheretherketone with effective osteogenicity and combined treatment of osteosarcoma and bacterial infection, ACS Appl. Mater. Interfaces 12 (41) (2020) 45891–45903, https://doi.org/10.1021/acsami.0c14752.
[131] R. Borges, T. Zambanini, A.M. Pelosine, G.Z. Justo, A.C.S. Souza, J Jr Machado, J. F. Schneider, D.R. de Araujo, J. Marchi, A colloidal hydrogel-based drug delivery system overcomes the limitation of combining bisphosphonates with bioactive glasses: in vitro evidence of a potential selective bone cancer treatment allied with bone regeneration, Biomater. Adv. 151 (2023) 213441, https://doi.org/10.1016/j.bioadv.2023.213441.
[132] B. Liu, X. Gu, Q. Sun, S. Jiang, J. Sun, K. Liu, F. Wang, Y. Wei, Injectable in situ induced robust hydrogel for photothermal therapy and bone fracture repair, Adv. Funct. Mater. 31 (19) (2021) 2010779, https://doi.org/10.1002/adfm.202010779.
[133] C. Heng, X. Zheng, J. Hui, X. Ma, D. Fan, Neodymium and manganese ions co-doped whitlockite for temperature monitoring, photothermal therapy, and bone tissue repair in osteosarcoma, J. Colloid Interface Sci. 653 (Part B) (2024) 1488–1503, https://doi.org/10.1016/j.jcis.2023.09.186.
[134] D. Fan, C. Zhang, H. Wang, Q. Wei, H. Cai, F. Wei, Z. Bian, W. Liu, X. Wang, Z. Liu, Fabrication of a composite 3D-printed titanium alloy combined with controlled in situ drug release to prevent osteosarcoma recurrence, Mater Today Bio 20 (2023) 100683, https://doi.org/10.1016/j.mtbio.2023.100683.
[135] P. Shi, Z. Cheng, K. Zhao, Y. Chen, A. Zhang, W. Gan, Y. Zhang, Active targeting schemes for nano-drug delivery systems in osteosarcoma therapeutics, J Nanobiotechnology 21 (1) (2023) 103, https://doi.org/10.1186/s12951-023-01826-1.
[136] G. Chen, P. Kong, A. Jiang, X. Wang, Y. Sun, T. Yu, H. Chi, C. Song, H. Zhang, D. Subedi, et al., A modular programmed biphasic dual-delivery system on 3D ceramic scaffolds for osteogenesisin vitroandin vivo, J. Mater. Chem. B 8 (42) (2020) 9697–9717, https://doi.org/10.1039/c9tb02127b.
[137] Y. Lu, M. Li, L. Li, S. Wei, X. Hu, X. Wang, G. Shan, Y. Zhang, H. Xia, Q. Yin, High-activity chitosan/nano hydroxyapatite/zoledronic acid scaffolds for simultaneous tumor inhibition, bone repair and infection eradication, Mater Sci Eng C Mater Biol Appl 82 (2018) 225–233, https://doi.org/10.1016/j.msec.2017.08.043.
[138] Y. Zhang, J. Xu, Z. Fei, H. Dai, Q. Fan, Q. Yang, Y. Chen, B. Wang, C. Wang, 3D printing scaffold vaccine for antitumor immunity, Adv Mater 33 (48) (2021) e2106768, https://doi.org/10.1002/adma.202106768.
[139] R. Liu, Y. Peng, L. Lu, S. Peng, T. Chen, M. Zhan, Near-infrared light-triggered nano-prodrug for cancer gas therapy, J. Nanobiotechnol. 19 (1) (2021) 443, https://doi.org/10.1186/s12951-021-01078-x.
[140] S. Suvarnapathaki, X. Wu, T. Zhang, M.A. Nguyen, A.A. Goulopoulos, B. Wu, G. Camci-Unal, Oxygen generating scaffolds regenerate critical size bone defects, Bioact. Mater. 13 (2022) 64–81, https://doi.org/10.1016/j.bioactmat.2021.11.002.
[141] M. Zhang, X. Liu, Y. Mao, Y. He, J. Xu, F. Zheng, W. Tan, S. Rong, Y. Chen, X. Jia, et al., Oxygen-generating hydrogels overcome tumor hypoxia to enhance photodynamic/gas synergistic therapy, ACS Appl. Mater. Interfaces 14 (24) (2022) 27551–27563, https://doi.org/10.1021/acsami.2c02949.
[142] L. Zhang, C.X. Li, S.S. Wan, X.Z. Zhang, Nanocatalyst-mediated chemodynamic tumor therapy, Adv Healthc Mater 11 (2) (2022) e2101971, https://doi.org/10.1002/adhm.202101971.
[143] C. Li, W. Zhang, Y. Nie, X. Du, C. Huang, L. Li, J. Long, X. Wang, W. Tong, L. Qin, et al., Time-sequential and multi-functional 3D printed MgO(2)/PLGA scaffold developed as a novel biodegradable and bioactive bone substitute for challenging postsurgical osteosarcoma treatment, Adv Mater 36 (34) (2023) e2308875, https://doi.org/10.1002/adma.202308875.
[144] X. Li, J.F. Lovell, J. Yoon, X. Chen, Clinical development and potential of photothermal and photodynamic therapies for cancer, Nat. Rev. Clin. Oncol. 17 (11) (2020) 657–674, https://doi.org/10.1038/s41571-020-0410-2.
[145] Y. Wang, L. Zhang, G. Zhao, Y. Zhang, F. Zhan, Z. Chen, T. He, Y. Cao, L. Hao, Z. Wang, et al., Homologous targeting nanoparticles for enhanced PDT against osteosarcoma HOS cells and the related molecular mechanisms, J. Nanobiotechnol. 20 (1) (2022) 83, https://doi.org/10.1186/s12951-021-01201-y.
[146] X. Zhang, Q. Li, L. Li, J. Ouyang, T. Wang, J. Chen, X. Hu, Y. Ao, D. Qin, L. Zhang, et al., Bioinspired mild photothermal effect-reinforced multifunctional fiber scaffolds promote bone regeneration, ACS Nano 17 (7) (2023) 6466–6479, https://doi.org/10.1021/acsnano.2c11486.
[147] J. Liang, X. Qiao, L. Qiu, H. Xu, H. Xiang, H. Ding, Y. Chen, Engineering versatile nanomedicines for ultrasonic tumor immunotherapy, Adv. Sci. 11 (3) (2024) e2305392, https://doi.org/10.1002/advs.202305392.
[148] W. He, C. Li, S. Zhao, Z. Li, J. Wu, J. Li, H. Zhou, Y. Yang, Y. Xu, H. Xia, Integrating coaxial electrospinning and 3D printing technologies for the development of biphasic porous scaffolds enabling spatiotemporal control in tumor ablation and osteochondral regeneration, Bioact. Mater. 34 (2024) 338–353, https://doi.org/10.1016/j.bioactmat.2023.12.020.

[149] K.-Y. Qian, Y. Song, X. Yan, L. Dong, J. Xue, Y. Xu, B. Wang, B. Cao, Q. Hou, W. Peng, et al., Injectable ferrimagnetic silk fibroin hydrogel for magnetic hyperthermia ablation of deep tumor, Biomaterials 259 (2020) 120299, https://doi.org/10.1016/j.biomaterials.2020.120299.
[150] F.D. Cojocaru, V. Balan, L. Verestiuc, Advanced 3D magnetic scaffolds for tumor-related bone defects, Int. J. Mol. Sci. 23 (24) (2022) 16190, https://doi.org/10.3390/ijms232416190.
[151] Z. Cao, D. Wang, Y. Li, W. Xie, X. Wang, L. Tao, Y. Wei, X. Wang, L. Zhao, Effect of nanoheat stimulation mediated by magnetic nanocomposite hydrogel on the osteogenic differentiation of mesenchymal stem cells, Sci. China Life Sci. 61 (4) (2018) 448–456, https://doi.org/10.1007/s11427-017-9287-8.
[152] H. Gao, Z. Cao, H. Liu, L. Chen, Y. Bai, Q. Wu, X. Yu, W. Wei, M. Wang, Multifunctional nanomedicines-enabled chemodynamic-synergized multimodal tumor therapy via Fenton and Fenton-like reactions, Theranostics 13 (6) (2023) 1974–2014, https://doi.org/10.7150/thno.80887.
[153] Z. Li, X. Lai, S. Fu, L. Ren, H. Cai, H. Zhang, Z. Gu, X. Ma, K. Luo, Immunogenic cell death activates the tumor immune microenvironment to boost the immunotherapy efficiency, Adv. Sci. 9 (22) (2022) e2201734, https://doi.org/10.1002/advs.202201734.
[154] L. Ma, J. Zhou, Q. Wu, G. Luo, M. Zhao, G. Zhong, Y. Zheng, X. Meng, S. Cheng, Y. Zhang, Multifunctional 3D-printed scaffolds eradiate orthotopic osteosarcoma and promote osteogenesis via microwave thermo-chemotherapy combined with immunotherapy, Biomaterials 301 (2023) 122236, https://doi.org/10.1016/j.biomaterials.2023.122236.
[155] J. Wang, Y. Zhang, N.H. Aghda, A.R. Pillai, R. Thakkar, A. Nokhodchi, M. Maniruzzaman, Emerging 3D printing technologies for drug delivery devices: current status and future perspective, Adv. Drug Deliv. Rev. 174 (2021) 294–316, https://doi.org/10.1016/j.addr.2021.04.019.
[156] B. Majhy, P. Priyadarshini, A.K. Sen, Effect of surface energy and roughness on cell adhesion and growth - facile surface modification for enhanced cell culture, RSC Adv. 11 (25) (2021) 15467–15476, https://doi.org/10.1039/d1ra02402g.
[157] M. Khorramnezhad, B. Akbari, M. Akbari, M. Kharaziha, Effect of surface modification on physical and cellular properties of PCL thin film, Colloids Surf. B Biointerfaces 200 (2021) 111582, https://doi.org/10.1016/j.colsurfb.2021.111582.
[158] A. Bandyopadhyay, I. Mitra, S. Bose, 3D printing for bone regeneration, Curr. Osteoporos. Rep. 18 (5) (2020) 505–514, https://doi.org/10.1007/s11914-020-00606-2.
[159] X. Chen, S. Han, W. Wu, Z. Wu, Y. Yuan, J. Wu, C. Liu, Harnessing 4D printing bioscaffolds for advanced orthopedics, Small 18 (36) (2022) e2106824, https://doi.org/10.1002/smll.202106824.
[160] B. Safari, M. Aghazadeh, A. Aghanejad, Osteogenic differentiation of human adipose-derived mesenchymal stem cells in a bisphosphonate-functionalized polycaprolactone/gelatin scaffold, Int. J. Biol. Macromol. 241 (2023) 124573, https://doi.org/10.1016/j.ijbiomac.2023.124573.
[161] X. Xie, J. Cai, D. Li, Y. Chen, C. Wang, G. Hou, T. Steinberg, B. Rolauffs, M. El-Newehy, H. El-Hamshary, et al., Multiphasic bone-ligament-bone integrated scaffold enhances ligamentization and graft-bone integration after anterior cruciate ligament reconstruction, Bioact. Mater. 31 (2024) 178–191, https://doi.org/10.1016/j.bioactmat.2023.08.004.
[162] M.U.A. Khan, S.I.A. Razak, S. Rehman, A. Hasan, S. Qureshi, G.M. Stojanovic, Bioactive scaffold (sodium alginate)-g-(nHAp@SiO(2)@GO) for bone tissue engineering, Int. J. Biol. Macromol. 222 (PtA) (2022) 462–472, https://doi.org/10.1016/j.ijbiomac.2022.09.153.
[163] C. Lyu, C. Cheng, Y. He, L. Qiu, Z. He, D. Zou, D. Li, J. Lu, Graphene hydrogel as a porous scaffold for cartilage regeneration, ACS Appl. Mater. Interfaces 14 (49) (2022) 54431–54438, https://doi.org/10.1021/acsami.2c11307.
[164] G.L. Koons, A.G. Mikos, Progress in three-dimensional printing with growth factors, J Control Release 295 (2019) 50–59, https://doi.org/10.1016/j.jconrel.2018.12.035.
[165] J. Long, W. Zhang, Y. Chen, B. Teng, B. Liu, H. Li, Z. Yao, D. Wang, L. Li, X.F. Yu, et al., Multifunctional magnesium incorporated scaffolds by 3D-Printing for comprehensive postsurgical management of osteosarcoma, Biomaterials 275 (2021) 120950, https://doi.org/10.1016/j.biomaterials.2021.120950.
[166] M.R. Bidgoli, I. Alemzadeh, E. Tamjid, M. Khafaji, M. Vossoughi, Fabrication of hierarchically porous silk fibroin-bioactive glass composite scaffold via indirect 3D printing: effect of particle size on physico-mechanical properties and in vitro cellular behavior, Mater. Sci. Eng. C 103 (2019) 109688, https://doi.org/10.1016/j.msec.2019.04.067.
[167] H. Lu, Z. Li, Z. Duan, Y. Liao, K. Liu, Y. Zhang, L. Fan, T. Xu, D. Yang, S. Wang, et al., Photothermal catalytic reduction and bone tissue engineering towards a three-in-one therapy strategy for osteosarcoma, Adv Mater (2024) e2408016, https://doi.org/10.1002/adma.202408016.
[168] R. Du, B. Zhao, K. Luo, M.-X. Wang, Q. Yuan, L.-X. Yu, K.-K. Yang, Y.-Z. Wang, Shape memory polyester scaffold promotes bone defect repair through enhanced osteogenic ability and mechanical stability, ACS Appl. Mater. Interfaces 15 (36) (2023) 42930–42941, https://doi.org/10.1021/acsami.3c06902.
[169] E. Yarali, M.J. Mirzaali, A. Ghalayaniesfahani, A. Accardo, P.J. Diaz-Payno, A. A. Zadpoor, 4D printing for biomedical applications, Adv. Mater. 36 (31) (2024) e2402301, https://doi.org/10.1002/adma.202402301.
[170] Y.-W. Ge, M. Chu, Z.-Y. Zhu, Q.-F. Ke, Y.-P. Guo, C.-Q. Zhang, W.-T. Jia, Nacre-inspired magnetically oriented micro-cellulose fibres/nano-hydroxyapatite/chitosan layered scaffold enhances pro-osteogenesis and angiogenesis, Materials Today Bio 16 (2022) 100439, https://doi.org/10.1016/j.mtbio.2022.100439.
[171] C. Mahapatra, J.J. Kim, J.H. Lee, G.Z. Jin, J.C. Knowles, H.W. Kim, Differential chondro- and osteo-stimulation in three-dimensional porous scaffolds with different topological surfaces provides a design strategy for biphasic osteochondral engineering, J. Tissue Eng. 10 (2019) 2041731419826433, https://doi.org/10.1177/2041731419826433.
[172] Y. Cui, T. Zhu, D. Li, Z. Li, Y. Leng, X. Ji, H. Liu, D. Wu, J. Ding, Bisphosphonate-functionalized scaffolds for enhanced bone regeneration, Adv. Healthcare Mater. 8 (23) (2019) e1901073, https://doi.org/10.1002/adhm.201901073.
[173] J. Li, Y. Zhang, X. Zhou, S. Wang, R. Hao, J. Han, M. Li, Y. Zhao, C. Chen, H. Xu, Enzymatically functionalized RGD-gelatin scaffolds that recruit host mesenchymal stem cells in vivo and promote bone regeneration, J. Colloid Interface Sci. 612 (2022) 377–391, https://doi.org/10.1016/j.jcis.2021.12.091.
[174] A. Bigham, A.H. Aghajanian, A. Saudi, M. Rafienia, Hierarchical porous Mg2SiO4-CoFe2O4 nanomagnetic scaffold for bone cancer therapy and regeneration: surface modification and in vitro studies, Mater. Sci. Eng. C 109 (2020) 110579, https://doi.org/10.1016/j.msec.2019.110579.
[175] Z. Ma, X. Zhao, J. Zhao, Z. Zhao, Q. Wang, C. Zhang, Biologically modified polyether ether ketone as dental implant material, Front. Bioeng. Biotechnol. 8 (2020) 620537, https://doi.org/10.3389/fbioe.2020.620537.
[176] K. Ye, D. Liu, H. Kuang, J. Cai, W. Chen, B. Sun, L. Xia, B. Fang, Y. Morsi, X. Mo, Three-dimensional electrospun nanofibrous scaffolds displaying bone morphogenetic protein-2-derived peptides for the promotion of osteogenic differentiation of stem cells and bone regeneration, J. Colloid Interface Sci. 534 (2019) 625–636, https://doi.org/10.1016/j.jcis.2018.09.071.
[177] N.Z. Laird, T.M. Acri, K. Tingle, A.K. Salem, Gene- and RNAi-activated scaffolds for bone tissue engineering: current progress and future directions, Adv. Drug Deliv. Rev. 174 (2021) 613–627, https://doi.org/10.1016/j.addr.2021.05.009.
[178] H.C. Beird, S.S. Bielack, A.M. Flanagan, J. Gill, D. Heymann, K.A. Janeway, J. A. Livingston, R.D. Roberts, S.J. Strauss, R. Gorlick, Osteosarcoma, Nat. Rev. Dis. Prim. 8 (1) (2022) 77, https://doi.org/10.1038/s41572-022-00409-y.
[179] D. Fan, Y. Liu, Y. Wang, Q. Wang, H. Guo, Y. Cai, R. Song, X. Wang, W. Wang, 3D printing of bone and cartilage with polymer materials, Front. Pharmacol. 13 (2022) 1044726, https://doi.org/10.3389/fphar.2022.1044726.
[180] S. Li, Y. Cui, H. Liu, Y. Tian, G. Wang, Y. Fan, J. Wang, D. Wu, Y. Wang, Application of bioactive metal ions in the treatment of bone defects, J. Mater. Chem. B 10 (45) (2022) 9369–9388, https://doi.org/10.1039/d2tb01684b.
[181] T. Zhang, J. Li, Y. Wang, W. Han, Y. Wei, Y. Hu, Z. Liang, X. Lian, D. Huang, Hydroxyapatite/polyurethane scaffolds for bone tissue engineering, Tissue Engineering Part B: Reviews 30 (1) (2024) 60–73, https://doi.org/10.1089/ten.teb.2023.0073.
[182] L. Bai, G. Tao, M. Feng, Y. Xie, S. Cai, S. Peng, J. Xiao, Hydrogel drug delivery systems for bone regeneration, Pharmaceutics 15 (5) (2023) 1334, https://doi.org/10.3390/pharmaceutics15051334.
[183] Y. Liu, Q. Li, Q. Bai, W. Jiang, Advances of smart nano-drug delivery systems in osteosarcoma treatment, J. Mater. Chem. B 9 (27) (2021) 5439–5450, https://doi.org/10.1039/d1tb00566a.
[184] G. Wei, Y. Wang, G. Yang, Y. Wang, R. Ju, Recent progress in nanomedicine for enhanced cancer chemotherapy, Theranostics 11 (13) (2021) 6370–6392, https://doi.org/10.7150/thno.57828.
[185] C. Jia, Y. Guo, F.G. Wu, Chemodynamic therapy via Fenton and fenton-like nanomaterials: strategies and recent advances, Small 18 (6) (2022) e2103868, https://doi.org/10.1002/smll.202103868.
[186] H. Miao, R. Shen, W. Zhang, Z. Lin, H. Wang, L. Yang, X.Y. Liu, N. Lin, Near-infrared light triggered silk fibroin scaffold for photothermal therapy and tissue repair of bone tumors, Adv. Funct. Mater. 31 (10) (2020) 2007188, https://doi.org/10.1002/adfm.202007188.
[187] J. You, Y. Li, C. Wang, H. Lv, S. Zhai, M. Liu, X. Liu, Q. Sezhen, L. Zhang, Y. Zhang, et al., Mild thermotherapy-assisted GelMA/HA/MPDA@roxadustat 3D-printed scaffolds with combined angiogenesis-osteogenesis functions for bone regeneration, Adv Healthc Mater 13 (22) (2024) e2400545, https://doi.org/10.1002/adhm.202400545.
[188] O. Cano-Garrido, N. Serna, U. Unzueta, E. Parladé, R. Mangues, A. Villaverde, E. Vázquez, Protein scaffolds in human clinics, Biotechnol. Adv. 61 (2022) 108032, https://doi.org/10.1016/j.biotechadv.2022.108032.
[189] D. Yang, J. Xiao, B. Wang, L. Li, X. Kong, J. Liao, The immune reaction and degradation fate of scaffold in cartilage/bone tissue engineering, Mater Sci Eng C Mater Biol Appl 104 (2019) 109927, https://doi.org/10.1016/j.msec.2019.109927.
[190] J.F. Zheng, Z.W. Xi, Y. Li, J.N. Li, H. Qiu, X.Y. Hu, T. Luo, C. Wu, X. Wang, L. F. Song, et al., Long-term safety and absorption assessment of a novel bioresorbable nitrided iron scaffold in porcine coronary artery, Bioact. Mater. 17 (2022) 496–505, https://doi.org/10.1016/j.bioactmat.2022.01.005.