

# The Dual Effect of 3D-Printed Biological Scaffolds Composed of Diverse Biomaterials in the Treatment of Bone Tumors

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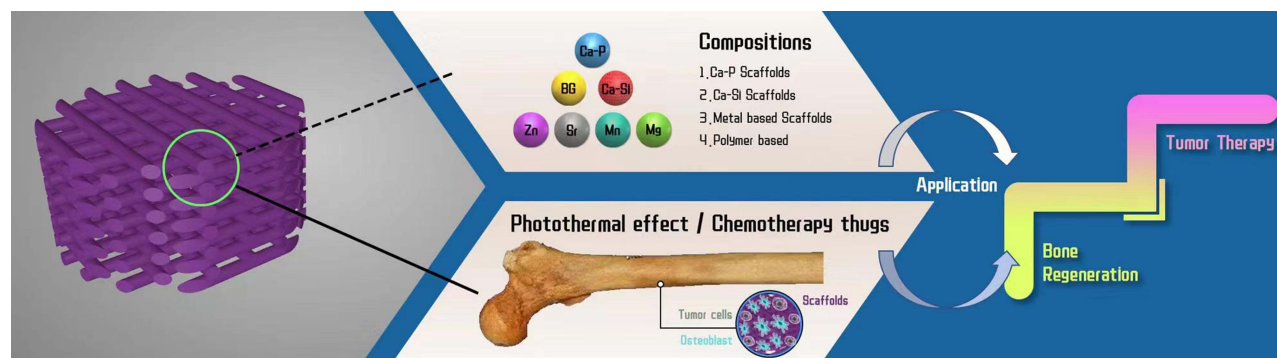
**Abstract:** Bone tumors, including primary bone tumors, invasive bone tumors, metastatic bone tumors, and others, are one of the most clinical difficulties in orthopedics. Once these tumors have grown and developed in the bone system, they will interact with osteocytes and other environmental cells in the bone system's microenvironment, leading to the eventual damage of the bone's physical structure. Surgical procedures for bone tumors may result in permanent defects. The dual-efficacy of tissue regeneration and tumor treatment has made biomaterial scaffolds frequently used in treating bone tumors. 3D printing technology, also known as additive manufacturing or rapid printing prototype, is the transformation of 3D computer models into physical models through deposition, curing, and material fusion of successive layers. Adjustable shape, porosity/pore size, and other mechanical properties are an advantage of 3D-printed objects, unlike natural and synthetic material with fixed qualities. Researchers have demonstrated the significant role of diverse 3D-printed biological scaffolds in the treatment for bone tumors and the regeneration of bone tissue, and that they enhanced various performance of the products. Based on the characteristics of bone tumors, this review synthesized the findings of current researchers on the application of various 3D-printed biological scaffolds including bioceramic scaffold, metal alloy scaffold and nano-scaffold, in bone tumors and discussed the advantages, disadvantages, and future application prospects of various types of 3D-printed biological scaffolds. Finally, the future development trend of 3D-printed biological scaffolds in bone tumor is summarized, providing a theoretical foundation and a larger outlook for the use of biological scaffolds in the treatment of patients with bone tumors.

**Keywords:** 3D-printed, scaffolds, bone tumors, nanomaterials

## Introduction

Bone is a natural composite material that has yet to be properly replicated by man-made materials. As a result, the development of biological materials capable of repairing bone defects has become a significant focus of study in clinical orthopedics. In addition to tumors damaging the bone's physical structure, the surgery for bone tumors will also result in bone defects.<sup>1</sup> Bone tumors are categorized into primary bone tumors (osteosarcoma), invasive bone tumors (melanoma), and metastatic bone tumors (eg, lung cancer, prostate cancer, and others).<sup>2-5</sup> Without exception, these tumors can impair the physical connections between bones by interacting with normal bone cells. In order to assure complete resection, surgical resection, the gold standard for the treatment of bone tumor disorders, will also cause harm to normal bone tissue.<sup>6-8</sup> Nevertheless, tumor cells will persist in the bone tissue after surgery.<sup>9,10</sup> Therefore, we require a substance that is not only capable of promoting bone tissue regeneration and repairing bone defect, but also of destructing residual bone tumor cells. In bone tissue engineering, scaffolds serve a critical role by creating a three-dimensional (3D) environment for cell adhesion and proliferation.<sup>11-13</sup> A number of biological scaffolds, including bioceramics and metal nanoparticles, have been developed by simulating the structures and physical characteristics of normal bone tissue. In addition to effectively filling bone defects, these

## Graphic Abstract



scaffolds can also kill residual tumor cells through their own physical and chemical properties or loaded drugs, thereby reducing postoperative complications of bone tumors and enhancing the life quality and survival time of patients.<sup>14–16</sup> 3D printing offers a rapid transition from product design or conceptual models to rapid prototyping and functional part manufacturing, allowing for the rapid fabrication of diverse complicated structural components without specialized tools.<sup>17,18</sup> 3D printing techniques make it possible to precisely adjust the geometry, connectivity, and porosity of biological scaffolds, allowing them to better adapt to cell growth and tissue regeneration.<sup>19–22</sup> Based on an understanding of the current clinical difficulties of treating patients with bone tumors, such as irreparable bone defects, and tumor recurrence, this review summarized the current role of 3D-printed biological scaffolds in treating the patients with bone tumors, as well as the differences, advantages, and disadvantages of various types of scaffolds. In addition to offering a reference scheme for the current treatment of bone tumors with biological scaffolds, it is anticipated that the future trend of 3D printing biological scaffolds will give researchers with new ideas.

## Destruction of Bone Structure by Bone Tumors

According to its macroscopic structure, bone is composed of cortical bone on the outside and trabecular bone on the inside. The cortical bone structure is extraordinarily dense (6% porosity and 130–190mpa compressive strength). Trabeculae cross-arrange in the internal bone to generate cancellous bone, which has a loose structure, but its arrangement and thickness are crucial for the bone to withstand pressure and weight.<sup>23–26</sup> Bone tissue is made up of bone matrix and other cells at the microscopic structure. The bone matrix is composed of both inorganic and organic substances. These inorganic substances are predominantly made of hydroxyapatite crystals (calcium and phosphorus), compounds (sodium, potassium, magnesium, and fluorine), salts (chloride), and some trace elements (silicon, zinc, and copper). The majority of these organic substances consists of collagen fibers, osteocalcin, osteophosphoprotein, and other compounds.<sup>27–30</sup>

Most primary bone tumors are amenable to surgical treatment. The tumor resection will also result in bone defects at the resection site. Due to the presence of leftover tumor cells at the defect site, recurrence of bone tumors is often a significant source of distress for patients.<sup>31</sup> In addition, although some invasive and metastatic bone tumors do not undergo surgical excision, the tumor cells themselves interact with bone cells and inorganic mineralized bone matrix, and can produce substances like parathyroid hormone-related protein (PTHrP) and other factors; these factors stimulate osteoclast aggregation and generates a cascade reaction, ultimately resulting in the transition of bone from the pre-osteolytic to the osteolytic phase.<sup>32–34</sup> In addition, research on the relationship between breast cancer cells and bone matrix reveals that breast cancer cells inhibit bone formation by inhibiting the proliferation of osteoblasts and mesenchymal stem cells (MSC) and the activity of alkaline phosphatase (ALP), which leads to bone loss caused by metastatic bone tumors.<sup>35</sup> It is evident that many forms of bone tumors can result in bone defects for various reasons. The introduction of biological scaffolds for such bone deficiency has inspired optimism. Biological scaffolds can not only mimic the chemical composition and layered structure of bone so that their physical and chemical properties are similar

to those of human bone, but they can also transport cells, nutrients, oxygen and growth factors to promote tissue regeneration.<sup>36,37</sup> Besides, the transporting of medications or the loading of particular metal ions and nanoparticles can provide biological scaffolds the power to inhibit or even kill tumor cells, which is a significant step forward for the application of biological scaffolds in bone tumors.<sup>38</sup> Due to the various site and shape of bone defects, however, biological scaffolds are frequently unable to suit the needs of specific sites and shapes. The advent of 3D printing can compensate for this flaw.

## Introduction of 3D Printing Technology, Different 3D Printing Methods and Their Advantages and Disadvantages

The conventional biological scaffolds are prepared by methods of gas flocculation, particle rinsing, and phase isolation.<sup>39–41</sup>

However, these preparation methods are incapable of customizing product properties like as porosity, permeability, and connection. Professor Sachs of the Massachusetts Institute of Technology innovatively created 3D printing technology, often known as additive manufacturing or fast printing prototype, to overcome these restrictions.<sup>42</sup> Through layer-by-layer deposition, curing, and material fusion, the 3D digital model is finally transformed into a physical model. This manufacturing process not only successfully controls costs, but also allows for the modification of the 3D digital model based on specific requirements, the rapid and efficient realization of the design scheme, and the ultimate creation of customized products. Over time, the 3D printing technology has evolved from photosculpture and geomorphology to selective laser sintering (SLS), fused deposition modeling (FDM), and stereolithography (SLA), ink jet 3D printing, adhesive droplet and powder bed-based AM, digital laser processing, continuous liquid interface production.<sup>43–46</sup> Using powder bed melting technology, SLS fabricates scaffolds in a directional layering manner by the repetitive deposition of powder particle materials and laser or electron beam melting or sintering, which is mostly used for metallic printing. FDM is the most common technique for printing polymers, which entails injecting thermoplastic polymers into a heating chamber, melting them, and extruding them through a nozzle under pressure.<sup>44</sup> For printing, the tiny filament-like material was layered from bottom to top, row by row, while the heated nozzle moved over the layer contour. Currently, FDM is economic and frequently used.<sup>47</sup> SLA printing process is similar to SLS, with the exception that powder is deposited on the print bed instead of a liquid photosensitive resin, and a laser (DLP utilizes a photomask instead of a laser) is used to track the product layer by layer until it is produced. Both SLA and DLP have the capacity to print high-resolution, structurally complicated items. However, the implementation of these two technologies is limited by the toxicity of the photosensitive resins employed as raw materials and the expense of printing equipment. Inkjet printing has limited use, and its application concept is comparable to that of 2D inkjet printing, which is often used to create product molds rather than the actual product.<sup>47</sup> The benefit of 3D-printing printing is the ability to alter the product's shape, porosity/pore size, and other mechanical properties as needed, instead of having fixed qualities like natural and manufactured substances. In addition, 3D printing allows for the rapid production of products and the reduction of experimental repetition time.<sup>48</sup> (Table 1) In recent years, since 3D printing has garnered broad interest in the field of biomedicine, it has been regarded as the most optimal technical method for the advancement of scaffold-based tissue engineering.

**Table 1** Different Technical Means Applied to 3D Printing

	<b>Stereolithography (SLA)</b>	<b>Selective Laser Sintering (SLS)</b>	<b>Fused Deposition Modeling (FDM)</b>	<b>Binder-Based 3DP</b>
Technical principle	Ultraviolet laser irradiation	Laser radiation	Extruded from the hot nozzle	Adhesive, adhesive powder
Product	Bioceramics, polymers	Bioceramics, metals, polymers	Bioceramics, polymers	Bioceramics, polymers
Cost	High	High	Low	Low
Form of raw material	Liquid	Powder	Solid	Powder

## Application of Different Types of 3D Printed Biological Scaffolds in Bone Tumors

The biological scaffolds utilized in the treatment of bone tumors should have the following characteristics: 1) a porous structure, which facilitates the transport of nutrients, medicines, and cell migration. 2) Biocompatibility and biodegradability: the biocompatibility ensure the scaffolds are not rejected by the immune system in vivo and decreases the inflammatory response; the biodegradability assures that the scaffolds do not create substances that can harm the human body. 3) Diversified mechanical strength, allowing the scaffolds to accommodate various defect sites. 4) Biological activity, which causes biochemical reactions with bodily tissues, resulting in the establishment of unique chemical linkages between organisms and substances.<sup>49–51</sup> The mechanical strength of 3D-printed biological scaffolds can be precisely adjusted to accommodate a variety of clinical scenarios, and their pore sizes can be tuned to meet specific functional requirements. Currently, bioceramics, metal alloy scaffolds, polymer scaffolds, nanoscaffolds, and composite scaffolds comprise the majority of 3D-printed biological scaffolds applied to patients with bone tumors<sup>52,53</sup> (Table 2).

**Table 2** Application of 3D-Printed Scaffold of Different Materials in Bone Tumors

Scaffold Type	Composition	Characteristic	Application	Literature
HA scaffold	HA, HACC, PLGA, PCL, DOX	Excellent antibacterial property, bone conductivity, and good biological and mechanical properties	Improve osteoblast proliferation, promote bone defect regeneration, anti-infection, load chemotherapy drugs anti-tumor	[58–63]
BCP scaffold	HA, $\beta$ -TCP, ZrO <sub>2</sub>	Good bone conductivity, biocompatibility, suitable mechanical property	Bone defect substitute and promoting the differentiation of human mesenchymal stem cells (hMSCs)	[66,67]
Bioactive glass scaffold	Na <sub>2</sub> O, CaO, SiO <sub>2</sub> , P <sub>2</sub> O <sub>5</sub> , HM, DOX	Able to form a binding interface with the surrounding tissue and has excellent bone conductivity	Promoting the proliferation and differentiation of stem cells, anti-tumor using chemical drugs and photothermal effect, and MBG nanolayer applied on $\beta$ -TCP can significantly improve the osteogenic ability and promote bone angiogenesis.	[68–72]
Calcium silicate scaffold	CaSiO <sub>3</sub> , PLGA, $\beta$ -TCP	The process is simple and has good mechanical property	Inducing hydroxyapatite (HA) formation, promoting cell growth, enhancing angiogenesis and osteoinduction, and stimulating secretion of PDGF-BB and chemokine matrix derived factor-1 (CXCL12) into the surrounding environment.	[76,77]
Metal support	Ti, Mg, Ta, Cu, MOF, PLGA, PLLA	Excellent compressive strength, excellent osteogenic activity, biodegradability, good biocompatibility, and excellent photothermal property	Anti-tumor therapy with photothermal therapy	[80,84,87–91]
Polymer scaffold	Sodium alginate (SA)/gelatin (Gel) hydrogel, alginate dialdehyde-gelatin (ADA-gel) hydrogel, nanoparticles	Excellent anti-infection property, able to load cells, nanoparticles.	Promoting stem cell proliferation and osteoblast differentiation, loading with drugs for anti-tumor, loading with nanoparticles for photothermal therapy and enhancing antibacterial effect	[92,93]
Nanocomposite scaffold	Nano-liposome particles, gold nanoparticles (AuNP), silver nanoparticles (AgNP), polymer nanoparticles	Magnetocaloric properties, Photothermal properties	Photothermal therapy and magnetothermal therapy for anti-tumor treatment and promotion of bone regeneration	[95–99]

## 3D-Printed Bioceramic Scaffolds

Due to their similarity to inorganic bone components, bioceramic scaffolds are now the most commonly utilized 3D-printed scaffolds for bone defects. Compositionally, bioceramics are categorized primarily as calcium-phosphate-based bioactive materials and calcium-silica-based bioactive materials.<sup>40</sup> Calcium-phosphorus-based bioactive materials include hydroxyapatite (HA),  $\beta$ -tricalcium phosphate ( $\beta$ -TCP), and biphasic calcium phosphate (BCP), whereas calcium-silica-based bioactive materials include bioactive glass, calcium silicate, tricalcium silicate, akermanite, and calcium silicate. These materials offer good bone conductivity, biocompatibility, and bioactivity, as well as robust compression qualities.<sup>54–56</sup> However, conventional 3D-printed bioceramics scaffolds also exhibit disadvantages such as single function, difficulty inducing angiogenesis, low bone formation efficiency, inability to treat tumors, and ease of bacterial reproduction, which hinder the development of bioceramics scaffolds.<sup>57</sup> Due to the advancement of research, bioceramic scaffolds composed of a single material are rarely employed. Based on traditional calcium phosphate-based and calcium silicon-based materials, 3D-printed bioceramics scaffolds are further optimized by methods such as apparent function change, trace element doping, and nanostructure construction, making them an ideal alternative material in bone tissue engineering.<sup>8,58</sup>

### Calcium-Phosphorus-Based Bioceramic Scaffolds

#### Hydroxyapatite(HA)

HA bioceramics are the most prevalent calcium-phosphate-based bioceramics, which have positive effects on osteoblast proliferation and adhesion, due to their comparable chemical structure to human bone.<sup>59–61</sup> However, scaffolds supported by HA degrade slowly and have poor mechanical strength, which inhibits bone repair and raises the risk of infection. Infection is one of the leading reasons of nonunion after trauma or tumor removal.<sup>62,63</sup> Through 3D printing technology, Ying Yang et al prepared quaternized chitosan (HACC)-Grafted Polylactide-co-glycolide (PLGA)/ (HA) scaffolds, and their good antibacterial characteristics and bone conductivity were validated in vitro. HACC exhibits excellent antibacterial properties by electrostatically binding to bacterial membranes, thereby reducing the risk of bacterial resistance by a substantial margin. The biological properties of Hacc-coated bone scaffolds, titanium implants, and absorbable sutures are satisfactory both in vitro and in vivo. By varying the substitution degree (DS) of quaternary ammonium salt, the cytocompatibility and antibacterial activity of HACC were enhanced.<sup>64</sup> They also demonstrated that PLGA/HA scaffolds transplanted with HACC exhibited significantly increased anti-infection and bone regeneration properties on rat and rabbit cortical bone defects. They also hypothesized that the degradation velocity of the scaffolds was strongly tied to its antibacterial effect, which would explain why many scaffolds with poor biodegradability had a greater risk of infection. This is a typical example of constructing composite scaffolds using polymers and HA.<sup>65</sup> Likewise, Fan Liu et al fabricated biodegradable PCL/HA composites using poly- $\epsilon$ -caprolactone (PCL) and hydroxyapatite (HA) nanoparticles. Using melt deposition formation, PCL/HA scaffolds were prepared from PCL/HA composites. A series of in vitro assessments revealed that PCL/HA composites had strong biodegradability, low cytotoxicity, and good biocompatibility, hence enhancing the osteoblasts MC3T3-E1 cell proliferation. Moreover, multifunctional 3D-printed PCL/HA/DOX scaffolds with a composite design loaded with anticancer pharmaceuticals (doxorubicin, DOX) and attaining sustained drug release qualities might accelerate bone healing and are anticipated to inhibit tumor cells following removal of malignant bone tumors.<sup>66,67</sup> Consequently, the development of suitable 3D-printed scaffolds can not only repair bone defects produced by bone tumors, but also inhibit tumor cells, but also delay tumor development, playing a role in preventing the recurrence and metastasis of bone tumors. As a form of additive manufacturing, 3D printing permits the customization of product parameters. For example, the 3D high-resolution ( $<210\ \mu\text{m}$ ) printing at room temperature was used to create scaffolds with regulated HA components. Yoontae Kim et al manipulated the formation rate and amount of HA by adjusting the concentration of  $\text{Na}_2\text{HPO}_4$  in order to produce bioceramic scaffolds with varying amounts of HA in order to optimize the scaffolds' mechanical characteristics, porosity, and osteoclast activity.<sup>68,69</sup>

#### Biphasic Calcium Phosphate (BCP)

BCP bioceramics are a blend of hydroxyapatite (HA) and  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) in varying proportions, achieving good chemical bone bonding capacity and biological absorption qualities.<sup>70</sup> TCP's utility cannot be questioned. By continuously coating tricalcium phosphate (TCP) scaffolds with TiN microparticles and doxorubicin (DOX), Dang et al were able to achieve the combined effect of photothermal therapy and chemotherapy on osteosarcoma. By immersing the



scaffold in a solution containing varied concentrations of TiN and DOX, it was possible to alter the quantity of TiN and DOX present in the scaffold. In vitro and in vivo, both precision photothermal treatment and local controlled release chemotherapy have shown positive therapeutic results.<sup>71</sup> However, it has been demonstrated in vitro, in vivo, and in clinical models that BCP has superior biocompatibility, bone conductivity, and safety.<sup>72</sup> Moreover, investigations have demonstrated that the bioceramic mixture of 60%HA and 40%  $\beta$ -TCP has a superior capacity for bone tissue regeneration and can be employed as a filler for bone defects produced by bone tumors or other factors.<sup>73</sup> Using fused deposition modeling (FDM), Min-woo Sa et al effectively created 3D slurry foams including mixes. The microstructure and shape of BCP/ZrO<sub>2</sub> scaffolds were validated by scanning electron microscopy (SEM), and the biocompatibility of BCP and BCP/ZrO<sub>2</sub> scaffolds was assessed by measuring the mechanical strength using a compression testing machine. We examined their impact on MG63 cells by measuring cell proliferation. Human mesenchymal stem cells (hMSCs) were seeded onto BCP or BCP/ZrO<sub>2</sub> to show the efficacy of BCP/ZrO<sub>2</sub> for bone tissue engineering applications. By removing the combined material following a high-temperature sintering procedure, they obtained BCP/ZrO<sub>2</sub> composite scaffolds with particular pore characteristics, porosity, and size. Not only did the inclusion of ZrO<sub>2</sub> increased the mechanical strength of BCP scaffolds, but it was also shown that BCP/ZrO<sub>2</sub> scaffolds were biocompatible for the proliferation of MG63 cells for 7 days and were favourable to the differentiation of human mesenchymal stem cells (hMSCs).<sup>74</sup>

## Calcium Silicon-Based Bioceramic Scaffolds

### Bioactive Glass Scaffold

The most prevalent calcium-silica-based bioceramic scaffolds are bioactive glass scaffolds, whose primary components are Na<sub>2</sub>O, CaO, SiO<sub>2</sub> and P<sub>2</sub>O<sub>5</sub>. Bioactive glasses need to be bone conductive and bone potent in order to promote stem cell proliferation and differentiation.<sup>75,76</sup> It has also been established that bioactive glass degradation products could impact the cell cycle of osteoblasts and promote bone tissue formation. The production of a layer of bioactive hydroxyapatite (HA) and hydroxy-carbonate apatite (HCA) on the surface in contact with bodily fluids, which offers a binding interface between bioactive glass and surrounding tissue is a common denominator of bioactive glass function.<sup>77</sup> Wentao Dang et al investigated the use of bioactive scaffolds to fill bone defect, sustain bone tissue, and stimulate bone formation, as well as to reduce drug resistance and tumor recurrence following continuous chemotherapy following surgical excision of osteosarcoma.<sup>78</sup> They prepared multifunctional scaffolds by applying heme and doxorubicin (DOX) to the surface of 3D-printed bioactive glass (BGC-HM-DOX). BGC-HM-DOX scaffolds had an exceptional photothermal sensitivity to NIR laser irradiation because to the heme particles on their surface. Combining photothermal therapy with DOX chemotherapy enabled the BGC-HM-DOX scaffolds with to kill osteosarcoma cells in vitro and inhibit tumor growth in vivo. This 3D-printed bioactive glass scaffold with multifunction is a significant improvement over the conventional 3D-printed scaffolds, the latter of which is only utilized to fill bone defects caused by bone tumors. Patients with bone tumors benefit greatly from it.

In addition, research on mesoporous bioactive glass (MBG) is ongoing. Due to its organized mesoporous (nanoporous) structure, MBG has much improved surface area and pore volume than conventional bioactive glasses. The presence of silanol groups on the surface of MBG makes it simple to functionalize submicroparticles for a variety of drug delivery applications. M. Ravanbakhsh et al created submicron MBG particles of uniform size and shape for local drug delivery. Due to the negatively charged surface of MBG, the researchers introduced amine groups to change the surface charge to a positive charge to improve drug attachment and loading efficiency.<sup>79</sup> Considering the unusual mesoporous structure and biological activity of MBG, its application to modify porous bioceramic scaffolds is of major importance.<sup>80,81</sup> Yali Zhang et al constructed  $\beta$ -TCP porous scaffolds using 3D printing. The MBG nanolayers were then uniformly coated on the  $\beta$ -TCP scaffolds using a spin coating technique. MBG- $\beta$ -TCP ultimately demonstrated more osteogenic and angiogenesis-related gene expression than BG-TCP. Compared to the  $\beta$ -TCP scaffold alone, the osteogenic capacity of the MBG- $\beta$ -TCP scaffold was dramatically enhanced.<sup>82</sup>

### Calcium Silicate Scaffold

Calcium silicate ceramics are a particular bioactive compounds that have been demonstrated to promote bone regeneration. Using 3D printing to construct CS scaffolds is a straightforward method with good mechanical properties.<sup>83</sup> In 2005, Wenyan Zhao et al investigated the in vitro biological activity of CaSiO by soaking it in simulated bodily fluid (SBF) for various

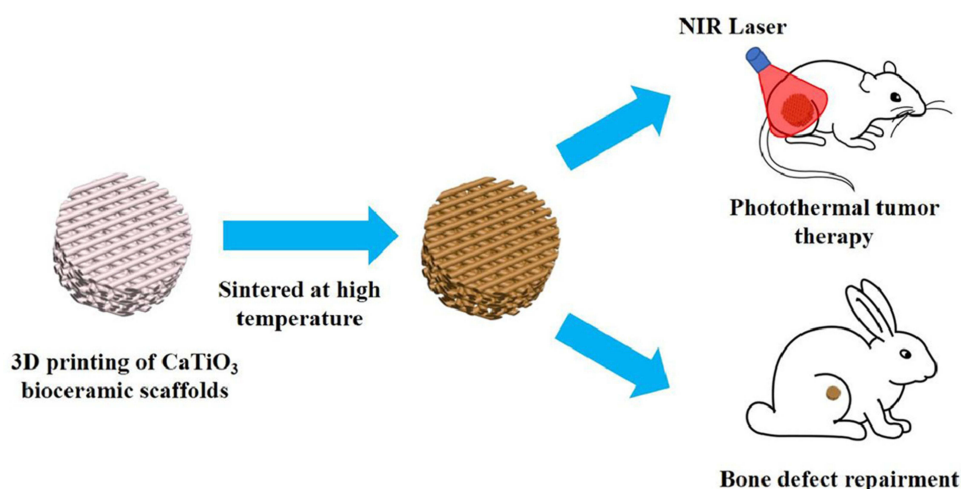
durations.<sup>84</sup> CaSiO slurry was found to stimulate hydroxyapatite (HA) production and dissolve slowly in SBF. CaSiO paste enhanced cell proliferation within a specific concentration range, as determined by indirect cytotoxicity screening. In a co-culture system of human bone marrow stromal cells (hBMSC) and human umbilical vein endothelial cells (HUVECs), the (PLGA)/calcium silicate scaffold raised the level of VEGF, resulting in a significant osteogenic and angiogenic synergy. Compared to  $\beta$ -TCP alone, 5% CaSiO<sub>3</sub>- $\beta$ -TCP scaffolds increased angiogenesis and osteoinduction and encouraged the release of PDGF-BB and chemokine matrix derived factor-1 (CXCL12) into the surrounding environment.<sup>85</sup>

### 3D Printed Metal Composite Scaffolding

Metal implants have traditionally been a crucial material for repairing bone defects. The markers that define the suitability of metal materials are mechanical stability and biological reactivity, which may be done more effectively through 3D printing's customization.<sup>86</sup>

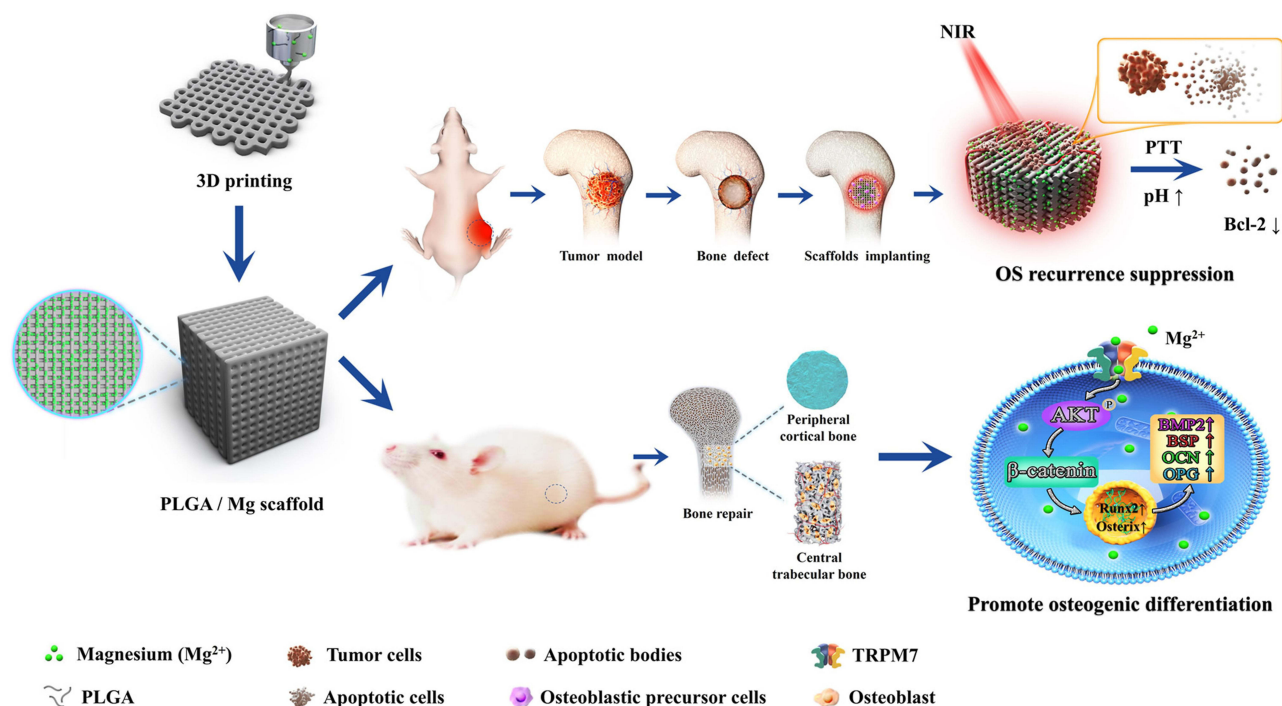
Using 3D printing technologies to make metal implants may lessen the stiffness of metal implants by producing pores, hence decreasing overall stress shielding to obtain a closer resemblance to human bone and providing space for bone regeneration. In addition, metal ceramic materials, which are made by mixing metal materials with bioceramic materials, may complement the two substantially.<sup>87</sup> Titanium (Ti), magnesium (Mg), and tantalum (Ta) are commonly used metals.<sup>88–90</sup> The combining of metallic materials and bioceramic materials to prepare a ceramic-metal composition could significantly complement both substances. Xin Wang et al<sup>91</sup> used 3D printing technology based on digital laser processing (DLP) to fabricate CaTiO<sub>3</sub> bioceramic scaffolds and discovered that the color of the scaffolds became darker as the sintering temperature increased; when the color reached pink exposed to NIR laser, CaTi scaffolds exhibited the highest compressive strength and satisfactory photothermal properties. This permits the use of CaTi scaffolds as photothermal biomaterials for the effective in vitro and in vivo treatment of bone tumors. (Figure 1) In addition, both in vitro and in vivo bone formation was observed in the pink CaTi scaffolds. Therefore, the use of this biphasic metal-ceramic material to cure bone defects induced by malignancies is a potential method.<sup>92</sup>

Due to its appropriate mechanical qualities, biodegradability, and good osteogenic activity, magnesium metal is also regarded a viable bioactive material for bone regeneration. However, pure magnesium scaffolds deteriorate too rapidly, and the enormous amount of hydrogen created would harm the human body's normal tissue structure.<sup>93,94</sup> To create composite scaffolds, the researchers decided to include Mg particles into a biodegradable polymer matrix (such as poly (Lactide-co-Glycolide), PLGA; Poly-L-lactide, PLLA). Recent investigations<sup>95</sup> have demonstrated that the developed PLGA/Mg composite scaffold has outstanding osteogenic activity, biodegradability, and biocompatibility, and that its photothermal properties make it an essential antitumor medium for photothermal therapy. (Figure 2) These characteristics satisfy the



**Figure 1** DLP-based 3D printed bifunctional calcium titanate scaffolds for photothermal therapy and bone regeneration.

**Notes:** Reprinted from *Journal of Materials Chemistry*, 22(24), Wu C, Fan W, Zhou Y, Luo Y. 3D-printing of highly uniform CaSiO<sub>3</sub> ceramic scaffolds: preparation, characterization and in vivo osteogenesis. 12288–12295, Copyright 2012, with permission from Elsevier.<sup>83</sup>



**Figure 2** Schematic illustration of the 3D printed PLGA/Mg scaffold used to inhibit postoperative osteosarcoma recurrence and promote bone regeneration.

**Notes:** Reprinted from Zadpoor AA, *J Mech Behav Biomed Mater*, 70, Mechanics of additively manufactured biomaterials. 1–6, Copyright 2017, with permission from Elsevier.<sup>87</sup>

prerequisites for future clinical translation. Similarly, porous tantalum (Ta) scaffold is a novel form of metallic scaffolding material. Utilizing selective laser melting (SLM) technology, researchers have created porous Ta scaffolds. In comparison to conventional Ta scaffolds, 3D-printed Ta scaffolds not only have regular pore structure and connectivity, but they also have a tunable elastic modulus and compressive strength, and their osteogenic impact in vitro and in vivo is greatly enhanced.<sup>96</sup>

Metal-organic frameworks (MOFs) are a recently found type of metal-organic frameworks that are often composed of metal ions or clusters of polytopic organic ligands. MOF-based compounds are frequently utilized as chemical drug carriers, and PTT reagents for tumor therapy are created by converting near-infrared light into thermal energy.<sup>97,98</sup> Consequently, bioscaffolds prepared using these MOFs may be beneficial for chemotherapy or photothermal therapy of bone tumors. By means of a solvothermal reaction, Wentao Dang et al coated the surface of 3D-printed TCP scaffolds with Cu-TCPP nanosheets of around 50 nm in thickness. Due to the photothermal characteristics of Cu-TCPP nanosheets, it was experimentally proven that Cu-TCPP-TCP scaffolds effectively kill osteosarcoma cells in vitro and in vivo.<sup>99</sup>

### 3D-Printed Polymer Scaffolds

In addition to assisting bioceramic or metallic particles in preparing composite scaffolds, polymers have a promising future.<sup>100,101</sup> By means of 3D printing, Ce Zhu et al prepared PEEK/graphene composite scaffolds. The scaffolds were subsequently electrophoretically deposited (EPD) with drug-loaded bioactive coatings based on hydroxyapatite (HA). HA is the predominant inorganic component of bone, and its release of Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> may stimulate bone repair. The in-scaffold graphene nanosheets function as potent PT conversion agents, whilst the loaded pharmaceuticals, such as antibacterial stearyl trimethylammonium chloride (STAC) and/or anticancer medication cisplatin (DDP), destroy tumor cells and bacteria through NIR laser-induced heating. This scaffold has been effectively used to the multimodal treatment of bone regeneration, tumor therapy, and antimicrobial therapy.<sup>102</sup> Studies have demonstrated that 3D-printed sodium alginate (SA)/gelatin (Gel) hydrogel scaffolds promoted stem cell proliferation and osteoblast differentiation, and an obvious mineralization effect was observable in simulated body fluids after doping with different concentrations of nano-attapulgit, making them ideally suited for bone regeneration and defect repair.<sup>103</sup> Nonetheless, a unique 3D-printed



composite scaffold including alginate dialdehyde-gelatin (ADA-GEL) hydrogel has been developed, which is enhanced by lysozyme-loaded mesoporous cerium desilica-calcium nanoparticles (Lys-CE-MSN). In a simulated humoral environment, Lys-Ce-MSN could increase the mechanical strength of hydrogel composite scaffolds and trigger surface apatite mineralization. This ADA-GEL/Lys-Ce-MSN nanocomposite inhibits the formation and growth of malignancies in addition to inducing bone regeneration and resolving the infection.<sup>104</sup>

### 3D Printing Nano Material Composite Scaffolding

Nanomaterials are frequently employed in tissue engineering because they not only have sizes and shapes that penetrate most physiological barriers, but also imitate the functions of many spherical biological macromolecules.<sup>105</sup> In bone tissue engineering, nanoparticles are thus often used as drug delivery vehicles, or play roles depending on their inherent electromagnetic and optical capabilities. In addition to mesoporous biological scaffolds previously mentioned, researchers frequently incorporate nanoparticles, such as nano-liposome particles,<sup>106</sup> gold nanoparticles (AuNP),<sup>107</sup> silver nanoparticles (AgNP),<sup>108</sup> and polymer nanoparticles,<sup>109</sup> into 3D-printed scaffolds to promote bone regeneration and inhibit the tumor cells growth. A set of investigations on the creation of nanocomposites for bone tissue engineering applications, including the cost-effective preparation of akermanite (CaMgSiO) nano-bioceramic, have provided considerable insight. Coating this nanoceramic solution onto a 3D filament-printed poly-lactic acid (EC-PLA) scaffold significantly increased its chemical stability and stress tolerance. The scaffold was then infused with Magnetic Nanoparticles (MNPs), and its porosity was remarkably comparable to that of regular bone tissue. In addition, the heat and magnetic properties of MNPs might attract cancer cells to separate and kill them, as well as restrict their proliferation.<sup>110–114</sup> Sarkar et al integrated curcumin-encapsulated nano-liposomes into calcium phosphate 3D-printed scaffolds, which not only stimulated the bone formation but also shown antitumor effect.<sup>106</sup> Moreover, it has been shown that both AuNPs and AgNPs produce anti-tumor effects in vitro owing to their superior features, such as their multi-functionalization capacity, high surface area-to-volume ratio, and high permeability. AgNP-prepared Ag-GO composite nanoparticles were incorporated into 3D-printed  $\beta$ -TCP scaffolds. The composite scaffolds not only had excellent osteogenic activity, but also induced oxidative stress in tumor cells after the generation of reactive oxygen species (ROS) by AgNP and promoted tumor cell apoptosis.<sup>107–109</sup>

Fe<sub>3</sub>O<sub>4</sub> nanoparticles have magnetic thermal characteristics and are often used in tumor magnetic thermal treatment. Some pieces of research have combined calcium peroxide (CaO<sub>2</sub>) and iron oxide (Fe<sub>3</sub>O<sub>4</sub>) nanoparticles into 3D-printed AKT-Fe<sub>3</sub>O<sub>4</sub>-CaO<sub>2</sub> scaffolds to achieve H<sub>2</sub>O<sub>2</sub>-self-sufficient chemodynamic therapy (CDT) for osteosarcoma, employing CaO<sub>2</sub> nanoparticles as a source of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and the magnetic heating action of Fe<sub>3</sub>O<sub>4</sub> to accelerate the CDT process. Obtaining H<sub>2</sub>O<sub>2</sub>-independent CDT osteosarcoma treatment. Adequate calcium ion (Ca<sup>2+</sup>) also stimulates osteogenesis. This approach of interdisciplinary research blends nanoparticles with 3D-printed scaffolds to enable the advancement of the present frontier research-CDT for tumor therapy.<sup>115</sup>

### Conclusion and Prospect

Despite the fact that bone tissue has a robust capacity for self-repair, it is difficult for patients with bone tumors to repair themselves due to the ongoing destruction of their own tissue or bone defects induced by surgical resection. The purpose of conventional biological scaffolds is to fill the defects. Due to the constraints of the preparation processes, however, the mechanical and biological qualities (biodegradability and biocompatibility) required to fulfill a variety of clinical circumstances are frequently not obtained. This disadvantage is remedied with the advent of 3D printing, which is able to suit specific needs by carefully regulating parameters and computer-controlled editing of objects with variable parameters. Initially, the most basic bioceramic scaffolds could cover the majority of application cases. It has gradually been obvious that just filling a defect in patients with bone tumors is of limited benefit. The true influence on life expectancy and life quality is the recurrence and progression of the tumor. Consequently, 3D-printed biological scaffolds for the treatment of tumors have increasingly entered the public consciousness. Researchers have mixed bioceramics with metal particles, polymers, and other materials to take advantage of the drug-loading and photothermal capabilities of the materials in the treatment of tumors, and even to overcome the faults of scaffolds that are prone to infection. Researchers have employed 3D printing as a manufacturing method to continually develop biological scaffolds suitable for the

patients with bone tumors, compensating for the positive and negative properties of these materials. However, clinical application of these scaffolds is still some time away. In addition to upgrading the current 3D printing technology, the mechanical strength and durability of its products may be continuously modified to suit the actual clinical environment. Researchers should also begin at the microscopic molecular level of bone, while simulating the macroscopic bone structure, and improve the degree of fit between biological scaffolds and bone at the microscopic level, so that biological scaffolds can more accurately simulate the function of bone tissue and regenerative medicine can reach a new plateau.

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## Disclosure

The authors report no conflicts of interest in this work.

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