



# The journey of multifunctional bone scaffolds fabricated from traditional toward modern techniques

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## Abstract

As a bone scaffold, meeting all basic requirements besides dealing with other bone-related issues—bone cancer and accelerated regeneration—is not expected from traditional scaffolds, but a newer class of scaffolds called multifunctional. From a clinical point of view, being a multifunctional scaffold means reducing in healing time, direct costs—medicine, surgery, and hospitalization—and indirect costs—loss of mobility, losing job, and pain. The main aim of the present review is following the multifunctional bone scaffolds trend to deal with both bone regeneration and cancer therapy. Special consideration is given to different fabrication techniques which have been applied to yield these materials spanning from traditional to modern ones. Moreover, the hierarchical structure of bone plus bone cancers and available medicines to them are introduced to familiarize the potential reader of review with the pluri-disciplinary essence of the field. Eventually, a brief discussion relating to the future trend of these materials is provided.

**Keywords** Multifunctional scaffolds · Bone cancer · Fabrication techniques · Bone tissue regeneration

## Introduction

Bone is perceived as a responsive tissue to its surrounding medium with a complex structure; it is in charge of many important functions throughout the human body—structural

support of internal organs, locomotion, and producing blood cells [1]. Bone is composed of an inorganic phase called hydroxyapatite (~70%) and the rest attributes to proteins mainly collagen (type I) [2]. Bearing in mind, although aging is to blame for increasing the rate of musculoskeletal diseases, high active routines of youth cause the risk of musculoskeletal-related injuries to soar [3]. Taking a glance at statistics is enough to realize that the total costs including both direct and indirect ones are astronomical [4]. Among different types of musculoskeletal-related issues, the majority of recorded cases belong to bone defects caused by tumors, trauma, etc. When a bone defect goes beyond a small size, which can be repaired through an endogenous regenerate process spontaneously, it is called a critical-sized defect requiring an external intervention [5].

Bone tumors are recognized as one of the culprits leaving behind a critical-sized defect after being removed, but before that, an introduction to bone cancer is of great significance here. So far, it is reported that 45 types of bone tumors exist and the most important one is called osteosarcoma [6]. It is noteworthy that compared to other types of cancer which is prevalent among old people, young people are prone to osteosarcoma. The most practical treatments to deal with bone cancer are surgery followed by chemotherapy

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and radiotherapy [7]. To fight other types of cancer, some unconventional methods like hyperthermia, photothermal therapy, and targeted drug delivery are introduced and being applied clinically [8–10]. On the upside, theoretically, the multifunctional nanoparticles are injected through the bloodstream and either actively or passively they find their way through a tumor to get their job done [11]. However, in the case of bone cancer, the situation is different; after removal of a bone tumor, medical practitioners do not have any other choice instead of filling up the defect with an osteoconductive material. In this case, the risk of recurrence of tumors is reported to be high, and some bone substitutes capable of doing multiple tasks like eradication of cancerous cells and bone regeneration are required [12]. Complicating matters when a bone substitute should be designed to not only possess all the basic requirements of load-bearing applications, but it must also address cancerous tissues; this class of bone substitutes is called multifunctional.

As a multidisciplinary field of study, tissue engineering and regenerative medicine (TERM) brings together experts of different fields including materials science, chemistry, mechanical engineering, and medicine under one roof to come up with startling discoveries—restoring and improving the function of the tissues [13]. Bone tissue engineering (BTE) is considered as a subcategory of TERM, and when it comes to a critical-sized bone defect, BTE has made a revelation that traditional bone grafts, which carry a huge cost and pain on the patients, should be gradually replaced with 3D multifunctional bone scaffolds [14]. Based on the reported studies, at the first stage, a 3D bone scaffold intended for load-bearing applications should be biocompatible, highly porous, mechanically matched with the host tissue, and biodegradable in a rate close to the regeneration process [15–17]. On the other hand, besides the mentioned basic requirements, a 3D multifunctional bone scaffold has one or more functions—prevention of bone infection [14], treatment of inflammation [18], extirpating cancerous cells [19], etc. It is critical to bear in mind that the design and fabrication route are pivotal factors to yield a desirable multifunctional bone scaffold.

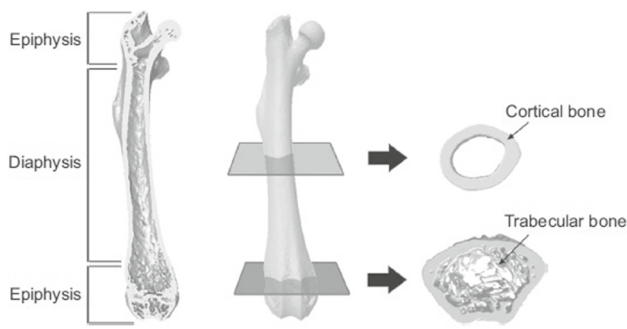
Up to now, there is a variety of techniques adopted to yield 3D multifunctional bone scaffolds—polymer sponge [20], freeze-drying [21], gel casting [22], etc. Although the mentioned methodologies have their advantages, they are regarded conventional mostly due to their incapability to be shaped close to the complex form of defect. Therefore, other techniques like rapid prototyping or 3D printing and electrospinning with more precise control over the design and microstructure of the final product have attracted more attention in recent years in BTE [23].

In recent years, some reviews relating to multifunctional bone scaffolds for bone cancer therapy have been published [19, 24], but none of which has reviewed the field from the

fabrication techniques viewpoint and their subsequent effect on the applicability of the scaffolds. The aim of the present review is to cover multifunctional ceramic-based and composite scaffolds for both bone cancer therapy and regeneration. In the first stage, the structure of bone and its hierarchical nature will be introduced to make the potential reader familiar with its biology. Next, bone cancer, its types, and available medicine to treat them will be discussed followed by introducing bone scaffolds with desirable properties for BTE. The emphasis of this review is on the multifunctional bone scaffolds fabricated through traditional and more up-to-date routes and their advantages and disadvantages; such multifunctional scaffolds are of great concern because they are able to address both eradication of bone tumors and subsequent regeneration process effectively. Eventually, conclusions and a brief future perspective will be outlined as well.

## Bone structure and microstructure

Bone as a connective tissue has an exceptionally mineralized extracellular matrix giving it desirable mechanical compressive and tensile strengths required for daily activities. Besides its mechanical support, which is the most recognized role of bone, it is responsible to protect the internal organs from any potential danger and provide an appropriate substrate for muscle adhesion. Moreover, bone maintains calcium ions balance throughout the body (homeostasis) and controls the formation of blood cells (hematopoiesis) [25]. The anatomy of bone is hierarchical spanning from macroscopic level to the nanoscale. From a macroscopic viewpoint, there are two types of bone tissue—spongy (trabecular) and cortical; these tissues are not different in composition, but their microstructure, function, and distribution [26]. Approximately, up to 80% of total bone mass attributes to the cortical bone that is highly dense with low porosity; these characteristics make this tissue mechanically strong (compressive strength). On the contrary, trabecular or spongy bone has an interconnected porous structure (~50–90%) causing this tissue to have a compressive strength one-tenth that of cortical bone; it is critical to notice that the porous structure of trabecular bone provides a high surface area which means more contact with blood cells followed by controlling over hematopoiesis and homeostasis [27]. Throughout the human body, there are long and short bones, and to exemplify both trabecular and cortical tissues, it is important to introduce different regions of a long bone as an example. Long bone has three main regions including a cylindrical dense shaft made of cortical bone called diaphysis and two parts at the end of the shaft made of trabecular bone called metaphysis (Fig. 1). It is interesting to mention that the tube-like essence of the shaft increases the bending resistance of bone without making the bone heavy [25].



**Fig. 1** A schematic showing the macroscopic anatomy of a long bone. Reproduced with permission from Ref. [25]

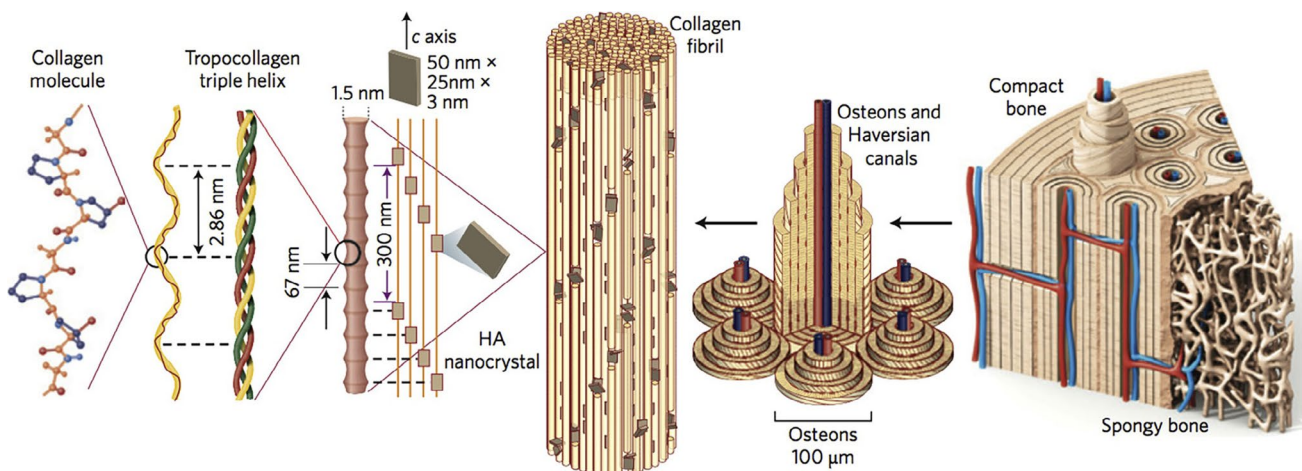
As mentioned earlier, as a composite material, bone is formed by organic and inorganic components—collagen (type I, ~20%), and the remained belongs to carbonated hydroxyapatite and water. It is noteworthy that the majority of the organic part of bone relates to type I collagen, whereas the rest attributes to the other types of collagen; as a fibrous protein, collagen consists of nearly 1000 amino acids and it has a length of about 300 nm with a rope-like morphology. Collagens are normally synthesized throughout the human body spontaneously by osteoblasts. The precursors (procollagen molecules) are first secreted through osteoblast cells, and these molecules are gradually congregated and form collagen fibrils; collagen fibrils are made of two  $\alpha 1$  and an  $\alpha 2$  polypeptide chains. The deposition of mainly calcium phosphate nanocrystals through collagen fibrils leads to the formation of bone composite-like unit cells called osteons yielding the final bone structure [28] (Fig. 2).

## Bone cancer and available medications

The occurrence of bone cancer is more probable in youth rather than old people [6]. The very first action after diagnosis of a bone tumor is resection of the tumor through surgery; surgery plays an integral part in treating bone cancers, combined with other methods [30]. Limb-sparing surgery is generally accomplished when cancer has just affected the patient. Only the affected bone is removed, along with the surrounding cells. It is reported that even after the resection process, there will be remained cancerous tissues in the bone defect’s wall raising the risk of tumor recurrence [31]. If the limb-sparing surgery were unavailable, the next solution would be an amputation. This might be needed in the following cases [19]:

- If the cancer has affected not just the bone but vital blood vessels and nerves.
- In the occurrence of an infection because of the limb-sparing surgery leading to the removal of the graft or prosthetics.
- When cancer develops in a part of the body where the limb-sparing surgery may not be possible such as the ankle.

Through Table 1, different bone cancer types, formation and growth, symptoms, causes, and risk factors are summarized. Although injecting massive chemotherapeutic drugs in the case of bone cancer therapy has catastrophic effects on healthy tissues, there are some drugs which are still being used clinically which are introduced in Table 2. Systemic chemotherapy has failed to address the issue effectively due to the weak bloodstream of bone tissue [32]. Therefore,



**Fig. 2** Step-by-step formation of the bone’s hierarchical structure from collagen molecules and nanohydroxyapatite crystals. Reproduced with permission from Ref. [29]

**Table 1** Different types of bone cancer

Bone cancer type	Description	Formation and growth	Symptoms	Causes	Risk factors	References
Chondrosarcoma	This is a very uncommon form of bone cancer that originates in the bones/soft tissues. The pelvis, shoulder, and hip are common locations for chondrosarcoma tumors	Cartilage is produced by the cells of the chondrosarcoma cancer. The rate of growth can be small if the cancer cells are removed fully; however, they can spread quickly to other organs if the growth rate is high	Fractures, high levels of pain, and any swellings are common symptoms	Certain genetic mutations could be possibly connected with chondrosarcoma. Moreover, conversion of any unharmed cartilage lesion into cancer could be another cause	Middle-aged people are typically affected by this type of cancer. Maffucci syndrome and Ollier disease are conditions where a ballooned number of unharmed cartilage lesions in the body are observed—they have a chance of converting into chondrosarcoma	[38, 39]
Ewing sarcoma	This is also a very rare form of bone cancers originating in long bones/soft tissues. Other spots include soft tissues of the abdomen and arms	Originating from long bones/soft tissues, cancer can quickly spread to the other organs in the body such as bone marrow, other bones, lungs—this will make the treatment a lot more arduous and this cancer can also make a comeback after it has been treated	Fatigue, bone pain which can exacerbate with more work loss, and fractures	Unknown	Unknown	[40, 41]
Osteosarcoma	The forming cells of bones cause osteosarcoma. This type of cancer can originate in long bones and soft tissues	Osteosarcoma forms from the cells that are responsible for the bone formation	Swelling next to a bone, fracture, and joint/bone pain	Unknown	Some inherited and genetic conditions, radiation therapy that may have been performed before	[42, 43]

**Table 2** Available medicines for bone cancers

Drug name	Chemical structure, US and foreign brand name	Usage of the medication	Side effects	References
Dactinomycin (DACT)—used in combination with other medications to treat Ewing sarcoma.	2-Bis[cyclo(N-methyl-L-valyl-sarcosyl-L-prolyl-D-valyl-L-threonyl)]-1,9-dimethyl-4,6,3H-phenoxazinone-3 US—Cosmegen Foreign—Lyovac Cosmegen	The drug in the form of a powder is blended with a liquid that is injected into a vein The duration of this treatment depends on the other drugs taken and the ability of the body to respond to the drug This drug can also be injected into the bone to treat the tumor (Ewing sarcoma)	Vomiting, hair loss, diarrhea, and stomach pain are possible side effects	[44, 45]
Denosumab—used in treating huge cell tumors in the bone that cannot be treated by surgery. It is also used in broken bones and some bone issues	USA—Prolia, Xgeva Foreign—Prolia	Denosumab is a liquid solution that is injected into the upper arm, stomach, or thigh Prolia is used every 6 months Xgeva is used every 4 weeks to treat cancer that has spread to bones and decrease the risk of bone fractures Xgeva can be given once a week to treat a big tumor of the bone	Fever, cough, difficulty in breathing, numbness in the fingers, stiff muscles, unusual bleeding, ear pain are some possible side effects	[46, 47]
Doxorubicin hydrochloride—used in combination with other medications to treat soft tissue and bone sarcomas	14-Hydroxydaunorubicin hydrochloride 3-Hydroxyacetyldaunorubicin hydrochloride Foreign—adriablastin; adriacini; adriablastina; adriblastine	The drug in the form of a powder is blended with a liquid that is injected into a vein The duration of this treatment depends on the other drugs taken and the ability of the body to respond to the drug—it is typically given once every 3/4 weeks	Nausea, sore throat, appetite loss, weight loss, hair loss, diarrhea, fatigue, eye pain are some of the side effects of this drug	[48, 49]
Methotrexate—used in combination with other medications to treat Osteosarcoma	4-Amino-10-methylfolic acid 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic acid Foreign—Brimexate; Emtextate; Emthexat; Emthexate	The drug in the form of a powder is blended with a liquid that is injected into a vein/muscle/artery	Memory loss, vomiting, seizures, itching are some side effects	[50–52]

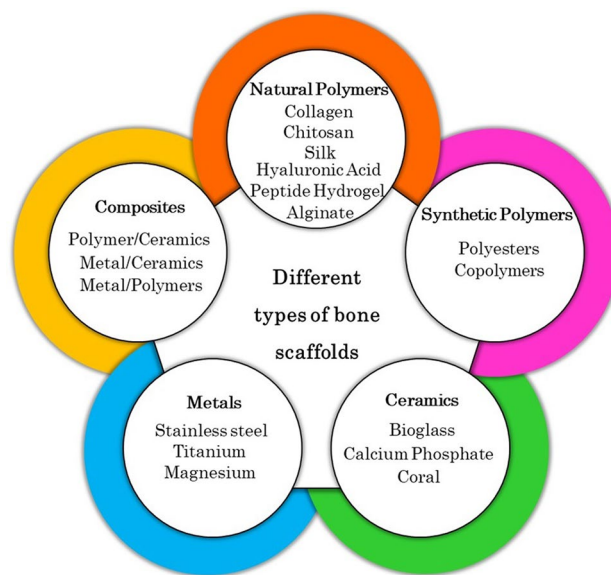


attention is focused on localized treatment through different methods—localized drug delivery, photothermal therapy, and hyperthermia therapy. Through novel drug delivery systems, the pharmaceutical community has focused on two fields to deal with bone cancer—finding new drugs and enhancing the performance of available drugs. From the early of 1990 to now, different kinds of drug delivery systems—polymeric and composite—have been developed and tried among which PLGA/doxorubicin (DOX) [33], chitosan/paclitaxel [34], polyurethane/curcumin [35], gelatin/DOX [36], and collagen/hydroxyapatite/cisplatin [37] can be enumerated. The idea of applying ceramic-based composites is of particular interest because treating bone cancer and bone regeneration should occur simultaneously, and applying drug-loaded hydroxyapatite, which has a similar structure to the inorganic phase of bone, would be killing two birds with one stone.

### Multifunctional bone scaffolds

Before getting into multifunctional bone scaffolds, it is of great significance to get familiar with a bone scaffold's design and basic requirements. As a bone scaffold, it is intended to provide temporal support for accelerating bone tissue regeneration, whereas the scaffold finally will be degraded without triggering any cytotoxicity to its surrounding medium. This biodegradable bone scaffold must be biocompatible, highly porous, and mechanically strong to withstand mechanical loads and its degradation rate should be matched with the tissue regeneration [53]. Besides the mentioned properties, having appropriate surface chemistry provides an ideal surface for the cell's attachment and proliferation [54]. Various materials have been used as bone scaffolds to fulfill the aforementioned requirements including polymers, ceramics, metals, and their composites. This information is summarized in Fig. 3.

That was in the early 1990s that Langer et al. [55] made a revelation discovery by which tissues could be reconstructed through cell-seeded synthetic materials. From that moment on, a huge explosion has happened in the scientific community of TERM and different researchers around the globe came up with different scaffolds made of various materials and fabrication techniques. However, most of them were eliminated by the death valley toward commercialization. From a clinical point of view, generally, there are four parameters when it comes to commercialization of a bone scaffold—form, function, formation, and fixation; the very first one (form) refers to designing and fabrication of a bone scaffold based on the complex form of defect. Function means the tolerance of scaffold—mechanical loads—every day until the regeneration is reached. The formation, briefly, means providing a structural scaffold to accelerate



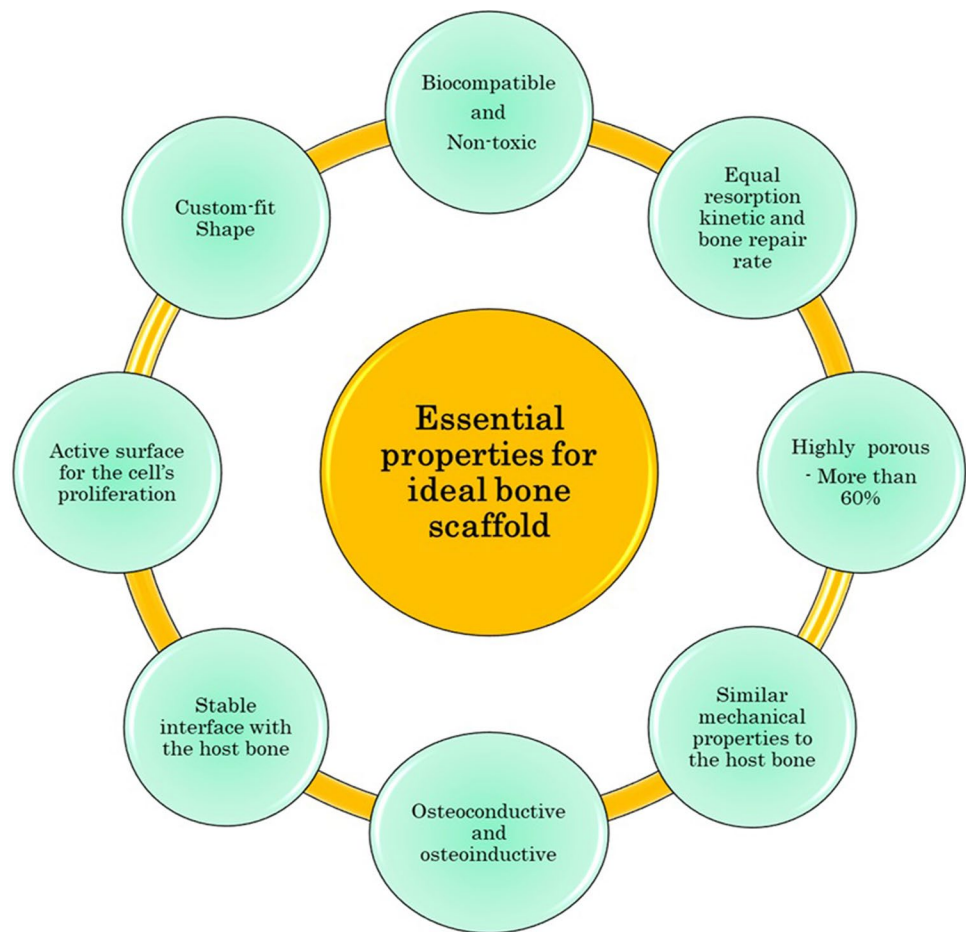
**Fig. 3** Different types of biomaterials including polymers, metals, ceramics, and composites along with their applicable examples of each group for bone tissue regeneration

the regeneration process through releasing biological materials, and finally, fixation relates to making all of the requirements available in a package for easy implantation in clinical practices [56, 57].

It is critical to bear in mind that the structural properties of 3D bone scaffolds are a key factor resulting in the future success of these materials; the aim is to mimic the hierarchical structure of bone consisting different length scales and so fabricating a 3D bone scaffold in harmony with the natural bone [26]. In the former paragraph, the importance of mechanical properties is introduced and now the effects of total porosity, pore size, and interconnectivity of these pores will be discussed. To ensure effective nutrients penetration and waste removal, reaching more than 60% total porosity with the interconnected porous structure in the size of 100–1000  $\mu\text{m}$  is indispensable. Pores with a size smaller than 1  $\mu\text{m}$  improve not only the interaction of proteins with the scaffold, but they also increase the surface area leading to more ions exchange with the surrounding medium and faster formation of carbonated hydroxyapatite. All the properties of an ideal bone scaffold are represented in Fig. 4.

It is reported that the newly formed carbonated hydroxyapatite is capable of making a strong bond with the host bone and so a desirable fixation (bioactivity). Having pores in the range of 1–20  $\mu\text{m}$  provides an appropriate surface on which the cells' attachment, proliferation, and differentiation could be eased [58, 59]. Through Fig. 5, it is observable that a multifunctional bone scaffold with hierarchical porosity is designed and fabricated through the polymer sponge technique. The scaffold's composition consists

**Fig. 4** The essential properties of a bone scaffold potentially suitable for bone tissue regeneration

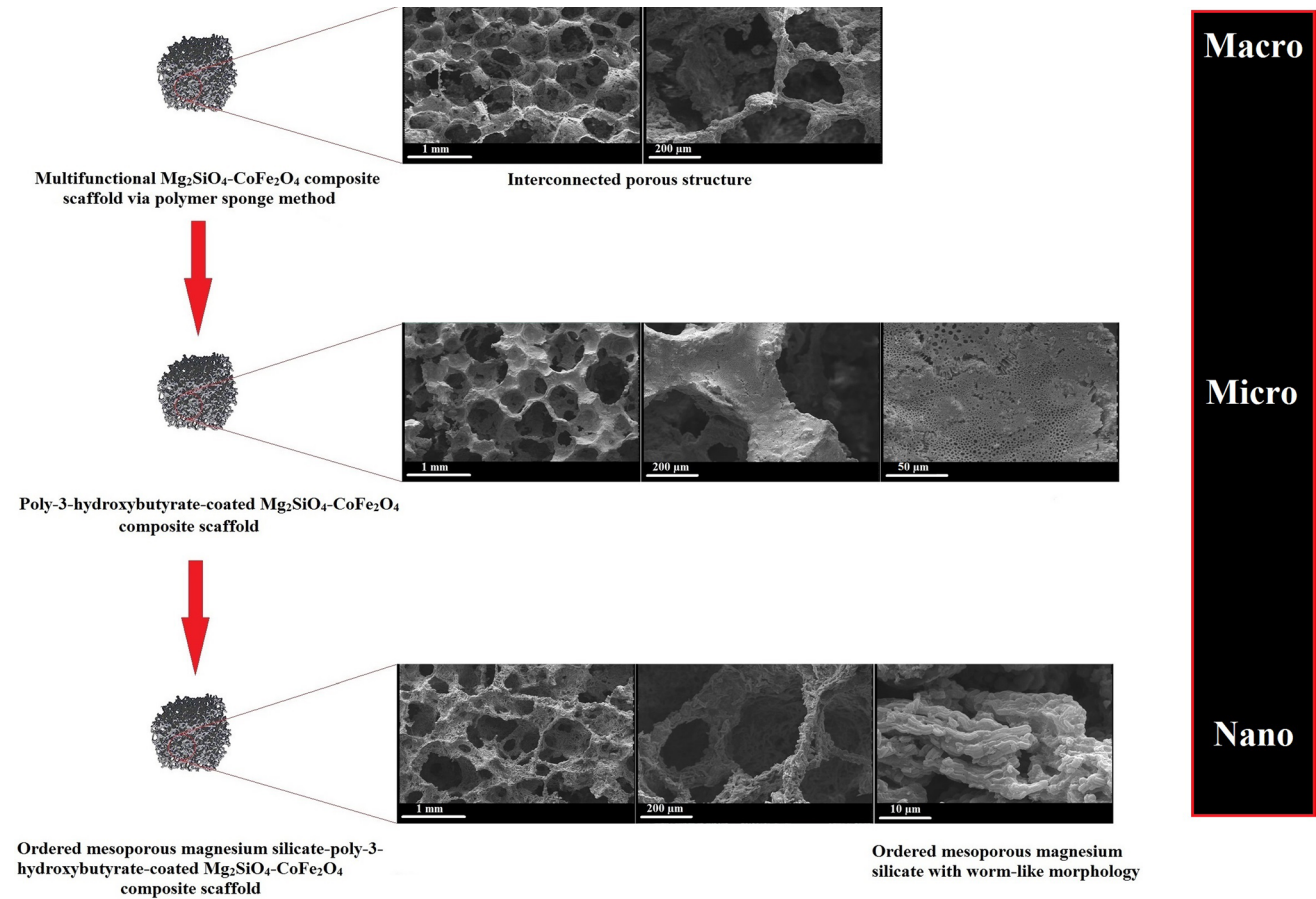


of a magnetic nanocomposite, and then, it is coated with a polymer-ceramic composite to address the issues related to bone cancer therapy and regeneration [60].

### Hyperthermia therapy

When it comes to eradication of a bone tumor followed by repairing the defect left behind after surgery, there are many impediments to traditional bone grafts; the remained cancerous cells in the defect have a high potential to form a new tumor in the site again. Therefore, there is a great need to apply multifunctional scaffolds to fight the cancerous cells on the one hand and supporting the bone regrowth on the other hand. Generally, there are three main approaches toward making a multifunctional bone scaffold for bone cancer therapy—being responsive to an external magnetic field (EMF) (hyperthermia therapy) [61], catalytically active to raise the heat locally (photothermal therapy) [30], and localized release of chemotherapeutic drugs [62]. Through hyperthermia-based therapy, generally, there is a magnetic material by which a scaffold is fabricated or a magnetic agent is introduced to a non-magnetic bone scaffold; when the magnetic bone scaffold is exposed to EMF, the hysteresis and

relaxation loss are governing factors to generate heat. If the magnetic agent is superparamagnetic, there is no hysteresis and so the heat generation is controlled through the relaxation loss—Neel and Brown losses. When a single-domain particle rotates, which leads to raising in the local heat, it is called Brown relaxation, and an increase in the heat through rotation of magnetic moments is called Neel relaxation [63]. Based on the applied temperature, there are three categories relating to hyperthermia-based therapy— $T \leq 41$  °C,  $42 \leq T \leq 46$  °C, and  $T \geq 46$  °C [64]. The first category has either small effects or nothing on the cancerous cells, and its application mainly falls into treating osteoarthritis. Applying a temperature in the range of 42–46 °C is of particular interest for bone cancer therapy because applying this range can kill the cancerous cells, and on the other side, there is no side effect for healthy tissues. The last category belongs to temperatures above 46 °C which is called thermoablation; there is no doubt that the generated heat is high enough to extirpate the cancerous cells, but it severely affects the healthy tissues on the downside. It is important to notice that taking control over the released heat is essential and based on the previous studies, the applied magnetic field and frequency are two governing factors by which the released



**Fig. 5** Multifunctional nanocomposite scaffolds' microstructure including non-coated, polymer-coated, and polymer-ceramic composite-coated scaffolds having a hierarchical porous structure from macro to nano. Reproduced with permission from Ref. [60]

heat from magnetic bone scaffolds can be controlled [20, 65, 66]. Through Fig. 6, a schematic of how a magnetic-responsive bone scaffold can treat remained bone cancerous cells is indicated.

### Photothermal therapy

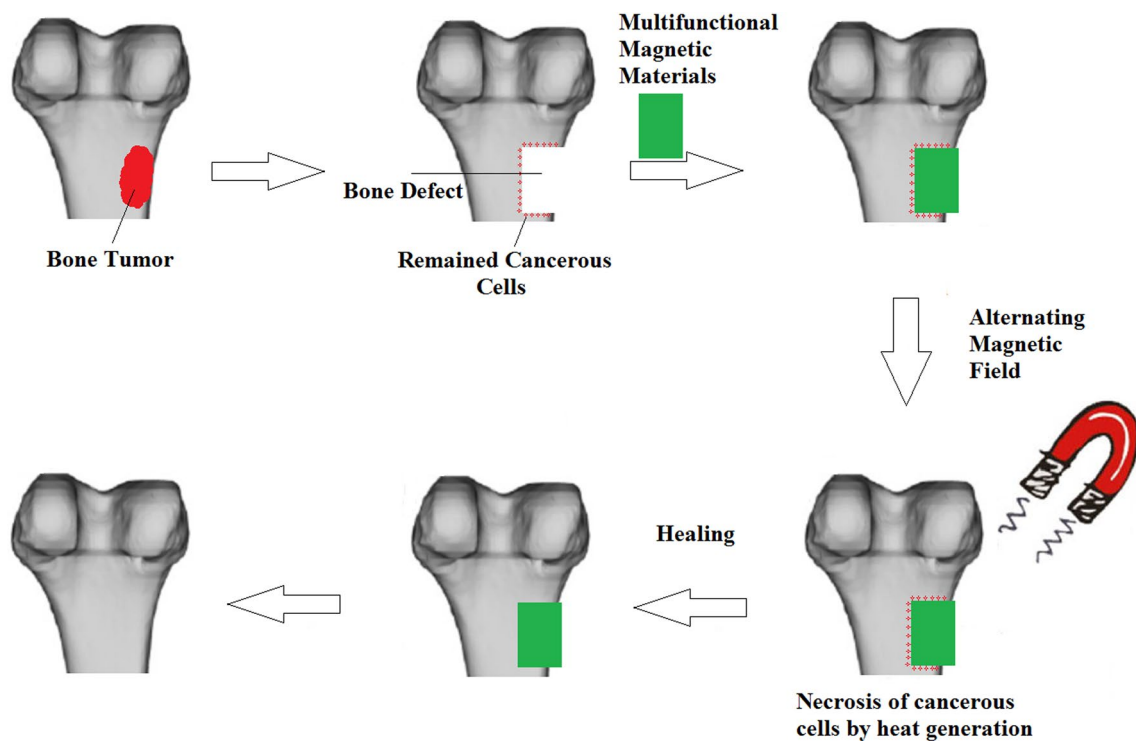
Photothermal therapy as a method with minimal invasiveness has received tremendous attention in recent years. In this method, a near-infrared laser is adopted to excite a catalyst that is embedded in the tumor's site through shedding light on it. The absorption of light is synchronized with releasing heat in the tumor's site [68]. Three parameters are affecting the effectiveness of photothermal therapy—the catalyst, the light's wavelength, and the delivery mode of laser light which can be either interstitial or non-invasive. It is noteworthy that all laser delivery modes focus on raising the local temperature in a manner which is destructive to cancerous cells without any negative effect on the surrounded healthy tissues. It is well known that increase in the tumor's temperature up to 41 °C is ineffective, and through

photothermal therapy, it is reported that raising the temperature of the tumor's center up to 50 °C to reach complete necrosis of cancer cells is required [69, 70]. Taking control over this high temperature to prevent any potential harm to healthy tissues is one of the main challenges of photothermal therapy [71]. Figure 7 illustrates a multifunctional 3D bone scaffold composed of tri-calcium phosphate modified with LaB<sub>6</sub> to deal with both bone cancer cells and regeneration [72].

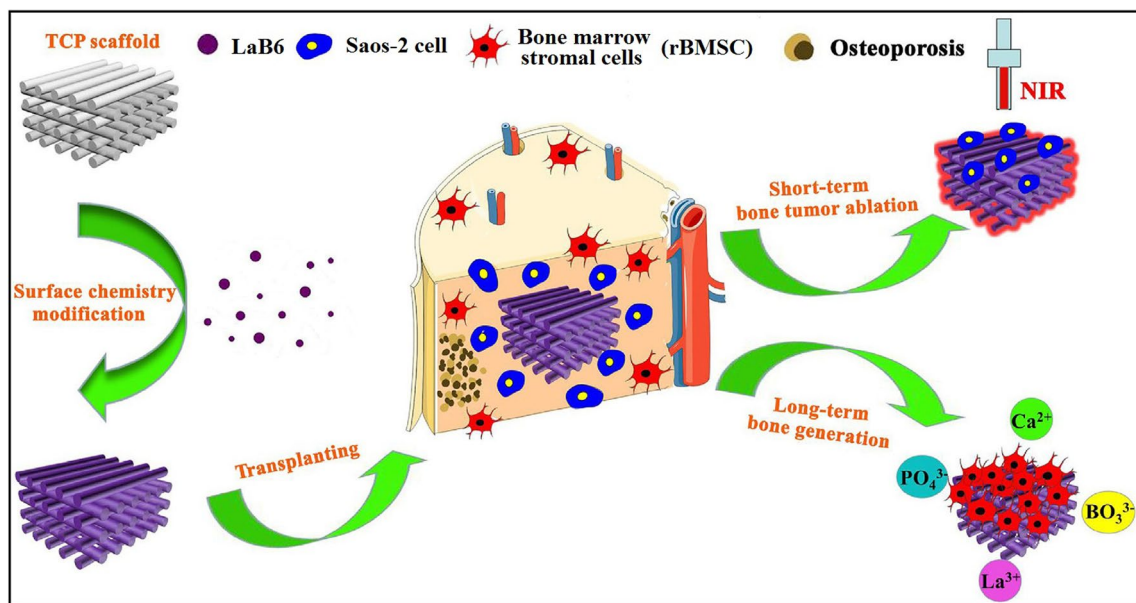
### Localized drug delivery

Through great advances which have been made in drug delivery systems in recent years, the idea of targeted drug delivery or localized controlled release has opened many doors to unsolved issues; ignoring the type of cancer, destroying the cancerous cells while keeping the healthy tissues intact is the main aim of targeted drug delivery systems [12, 73]. The liberation of chemotherapeutic drugs in the targeted site has some advantages—preserving prolonged release and so improving the efficiency, decreasing the side





**Fig. 6** A schematic illustrating how a bone tumor is treated through hyperthermia-based therapy by multifunctional bone scaffolds. Reproduced with permission from Ref. [67]



**Fig. 7** The application of LaB<sub>6</sub>-modified TCP scaffolds for bone tumor therapy through photothermal therapy followed by bone defect repair. Reproduced with permission from Ref. [72]

effects of chemotherapeutic drugs on the surrounded cells and organs, and finally, the applied dose of the drug will be comparatively less than the systemic administration [74, 75].

Following the traditional drug delivery methods, in the case of bone disease, a massive drug dose is required due to poor bloodstream through bone tissue compared to soft tissues

[32, 76]. Therefore, it is clear that when a chemotherapeutic drug in massive concentrations is injected directly through the bloodstream, the effects on healthy organs would be devastating [61, 77]. Up to now, various methods are adopted to equip a bone scaffold with a drug delivery capability—loading drug molecules in the interparticle porosity of bioceramic scaffolds [20], loading the drug into a polymer matrix [78], surface coating of some porous or mesoporous nanoparticles which have a great potential for high drug loading followed by prolonged release [18, 60]. Figure 8 indicates a 3D bone scaffold with meso-macroporosity for both bone tissue regeneration and localized drug delivery applications.

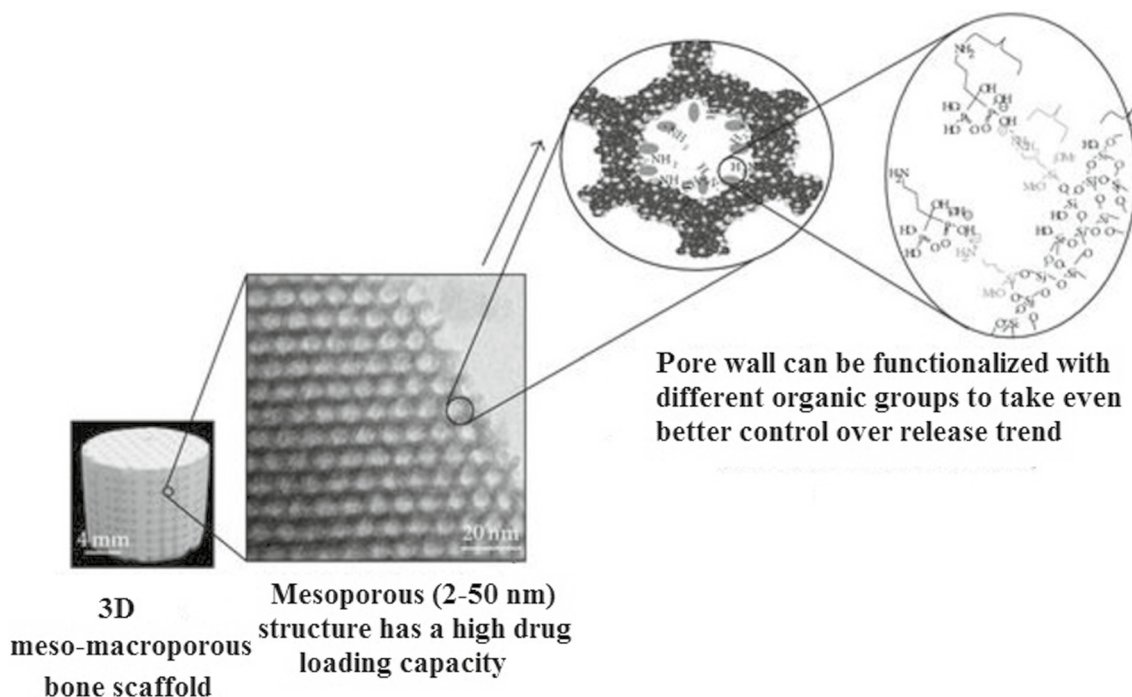
### Fabrication techniques of bone scaffolds

There is quite number of fabrication techniques applied to yield 3D bone scaffolds spanning from traditional routes—polymer sponge (replica) [20], leaching [80], freeze-drying [81], space holder [82], foaming [83], etc.—to the up-to-date ones including 3D printing and electrospinning capable of taking precise control over the final microstructure [84, 85]. In any case, the key aspects that should be accounted for are biocompatibility, hierarchical structure, porosity, mechanical properties, and surface properties. In the following section, a brief explanation of each technique is carried out as follows:

*Foaming* methods entail a foaming agent in the form of direct injection gases, gas incorporation through agitation, gas produced with chemical reactions, or thermal decomposition of peroxides. The foaming techniques have generally an easy process allowing an acceptable control of total porosity, pore size, and also pore shape through changing in the technique's parameters—temperature and the concentration of the reactant agents [86]. However, common issues with these techniques are lack of interconnected porous structure, a non-uniform surface layer, and poor mechanical properties [87].

*The space holder* technique is characterized by the inclusion of sacrificial particles in the green body that is sintered. The porogen particles are polymers, either synthetic such as polyethylene, or natural such as starch or rice husk [88]. This cheap technique allows to obtain good mechanical properties and to control the level of porosity. However, the level of total porosity is difficult to exceed over 70% in volume and the pores interconnectivity tends to be low [89].

*Polymer sponge technique* is ideal to obtain scaffolds similar to the trabecular bone stemming from the sacrificial polymer foam's structure. It is possible to achieve totally interconnected pores, with a level of the void that can reach 90% in volume while maintaining the desired mechanical properties close to the values of trabecular bone [90]. The architecture of scaffolds can be controlled, and the technique is compatible with various materials as well allowing the production of scaffolds made of glass



**Fig. 8** A 3D-printed bone scaffold composed of ordered mesoporous silicate making the scaffold ideal to load huge amounts of drug molecules followed by releasing them in a sustained manner (localized drug delivery applications). Reproduced with permission from Ref. [79]

[91], ceramics [20], metals [92], and composites [60]. This technique suffers from a lack of reproducibility, and also yielding a scaffold with complex shapes is difficult to obtain.

The *freeze-drying* technique involves the sudden and directional freezing, and it is pioneered by Fukasawa et al. [93] to yield porous ceramics; the technique takes the advantage of ice crystals to form columnar porous structures instead of inclusion of an organic matter. Once the formation of long and oriented ice crystals is carried out, the crystals will be sublimated followed by exposing the scaffold to a high temperature to be consolidated [94]. Due to the oriented structure of the crystals, the mechanical properties of the resulting scaffold are excellent, but the process is both energy and time-consuming [59].

*Solvent casting and particulate leaching* techniques are versatile fabrication routes for both polymeric and polymer/ceramic composite scaffolds. The techniques revolve around pouring a polymeric/slurry (polymer-ceramic) solution into a mold followed by the consolidation of solution/slurry through lyophilization or evaporation. As the result, a nanoporous structure is obtained, but in the case of yielding a macroporous structure, preferably, a water-soluble agent is introduced in the polymer/slurry solution before complete consolidation; the final bulk material will then be immersed into the water leading to the removal of the agents and yielding a macroporous scaffold [95, 96]. On the upside, fabrication of scaffolds with total porosity over even 90% is possible, the whole process is cost-effective and also based on the particle size and morphology of leaching agents, the final pore size and shape can be altered. On the downside, the limitation of the final shape, cytotoxicity of the leaching agents remained after immersion into the solvent, and achieving an interconnected porous structure are some drawbacks that should be taken into consideration.

*Electrospinning* is a versatile and simple fabrication technique which adopts an electric field to construct fibrous scaffolds in nano- and microscales; through using this technique, it is possible to produce scaffolds from both polymer and polymer/ceramic solutions [97, 98]. One of the greatest advantages of electrospinning, which has made this technique so popular, is its high surface area resembling the fibrous protein structure found in the natural extracellular matrix [99, 100]. Electrospinning has some fabrication-related parameters—the flow rate, applied voltage, the solution concentration, collector distance, the solution's conductivity, and volatility—by which the textural properties of the final scaffold such as pore size, total porosity, and fiber shape can be manipulated [101].

*3D printing* is formed by a group of techniques, and through their applicability and compatibility with different kinds of materials, they are being applied to fabricate different bone scaffolds [56, 84, 102]. Generally, 3D printing works based on a programmed 3D image and it fabricates a bone scaffold through the deposition of layers [103]. This technique has two important advantages—reproducibility and precise control on the porosity, pore size, pore shape, and mechanical properties which make this technique stand head and shoulders above the rest. Specifically, in the case of bone defects, 3D printing endows the clinical practitioners to design a scaffold based on the complex shape of the defect; once the scan is finished, a bone scaffold will be printed. Through Table 3, the advantages and disadvantages of the mentioned fabrication techniques are summarized. In the next section, four techniques—polymer sponge and space holder as traditional fabrication routes and both electrospinning and 3D printing as more up-to-dated techniques applied to produce multifunctional bone scaffolds for bone regeneration and cancer therapy, are chosen to be discussed more comprehensively.

**Table 3** Fabrication techniques for 3D bone scaffolds

Technique	Advantages	Disadvantages	References
Foaming	Easy process	Difficult to achieve an interconnected porous structure Non-uniform surface layer Poor mechanical properties	[104]
Space holder	Cost-effective Desirable mechanical properties	Difficult to achieve an interconnected porous structure Difficult to achieve a high total porosity	[87, 105]
Polymer sponge	High porosity and interconnectivity	Poor reproducibility Poor mechanical properties for load-bearing applications	[20, 60]
Freeze-drying	High porosity	Costly in both time and energy	[87]
Solvent casting and particulate leaching	High porosity Cost-effective	Difficult to achieve an interconnected porous structure Cytotoxicity attributed to remained leaching agents	[59]
Electrospinning	Easy process Versatility High surface area	Difficult to design macroscopically porous 3D architectures	[106, 107]
3D printing	Reproducible and fast Accurate control on the textural properties	Costly High energy consumption	[23, 108]

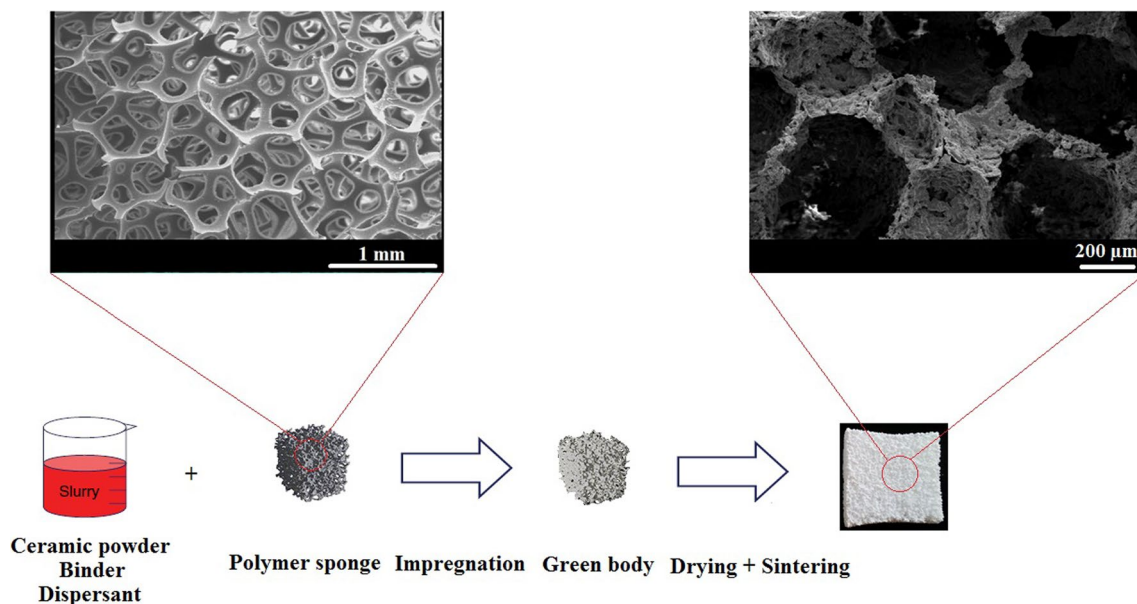
## Fabrication techniques of multifunctional bone scaffolds for bone cancer

### Polymer sponge technique

Polymer sponge technique was initially expanded in 1963 [109], and from that moment on, this technique has been widely applied to construct porous ceramic-based foams for different applications—refractory [110], separation [111], biomedical engineering [112], etc. Through this process, there is a polymeric foam (normally polyurethane sponge (PUS)) which is impregnated in a ceramic slurry; there are other materials including a binder and dispersant besides ceramic particles and water to form an appropriate and stable slurry. After impregnation of the foam, a little squeeze is required to remove additional slurry to prevent clogging the macropores. The PUS plays a sacrificial role, and after being into a furnace followed by raising the temperature, it will be burned out. It is important to notice that a multistep process for the sintering of these materials is required. The sacrificial agent should be slowly and gradually removed, and if not, the green body would be ruined. Therefore, a heating rate of about  $1\text{--}2\text{ }^{\circ}\text{C min}^{-1}$  is applied up to normally  $600\text{ }^{\circ}\text{C}$  plus preserving the scaffold in this temperature for about an hour to remove the backbone of sacrificial agent followed by raising the temperature to the sintering temperature of applied ceramic (normally above  $1000\text{ }^{\circ}\text{C}$ ) [20]. Figure 9 shows the process of the polymer sponge process. As mentioned earlier, the PUS foam

perfectly resembles the porous structure of trabecular bone and that is the reason why this technique has attracted so much attention in bone tissue engineering. Moreover, the polymer sponge technique gives an opportunity to design and fabricate bone scaffolds with adjustable pore dimensions, and based on the bone's defect shape, this technique allows producing scaffolds with irregular shapes [60]. On the other side, the highly porous structure of scaffolds produced by this technique is a double-edged sword. The compressive strength of these scaffolds normally is not high enough to withstand load-bearing applications and so the scaffolds require complete sintering plus a reinforcement agent (normally a polymer) to improve both the natural brittleness of ceramic-based scaffolds and other properties—compressive and tensile strengths.

In 2011, Wu et al. [91] fabricated a multifunctional bone scaffold made of mesoporous bioactive glass (MBG) through the polymer sponge technique. In this study, Fe ions with different concentrations are introduced in the crystal structure of MBG particles as a new way of making the MBG particles magnetic-responsive without ruining the mesoporous structure. It is well known that the incorporation of different ions into the crystal structure of a silica-based mesoporous material negatively alters the ordered mesoporous structure [113]. Wu et al. have obtained a meso-macroporous scaffold successfully and the magnetization saturation ( $M_s$ ) reached nearly  $1\text{ emu g}^{-1}$ ; dexamethasone (DEX) is used as a drug model to assess the controlled release capability of scaffolds as well. Based on their results, the Fe-incorporated MBG scaffolds can be applied for both hyperthermia-based



**Fig. 9** Step-by-step process of the polymer sponge technique to yield 3D porous bone scaffolds—slurry preparation, impregnation, drying, and sintering



bone cancer therapy and localized chemotherapeutic drug release. Although they were successful to fabricate a meso-macroporous multifunctional bone scaffold with nearly 80% total porosity and promising cell compatibility, the compressive strength is poor limiting its application. In a similar study, Zhu et al. [114] have worked on the same composition reported in the Wu's study, but through the newer study, it is mentioned that due to the calcination of Fe-incorporated MBG scaffolds under an air atmosphere, an undesirable phase of  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> is formed and caused the Ms to reduce dramatically in the Wu's study. Therefore, Zhu et al. have applied a modified calcination process in which the scaffolds are first calcined at 700 °C (heating rate of 2 °C min<sup>-1</sup>) for 8 h followed by reducing the scaffolds in 10% (H<sub>2</sub>)/90% (Ar) at 400 °C (3 h). The calcination process was successful to prevent the  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> formation, and as a result of that, a superparamagnetic property is achieved with the Ms of 1.75 emu g<sup>-1</sup>. The heat generation capacity of scaffolds is scrutinized as well through applying an EMF whose magnetic field strength and frequency are chosen to be 1.47 kA m<sup>-1</sup> and 232 kHz, respectively. It is observed that the applied field strength and frequency caused the temperature to rise from 36 °C to 44.25 °C after 25 min; in a parallel manner, a vial without any scaffold is also exposed the same EMF and frequency and it turned out that the temperature just increased from 36 °C to 36.5 °C after the same time.

In 2017, Farzin et al. [62] developed a bifunctional magnetic calcium-zinc-silicate scaffold through polymer sponge to address bone regeneration and cancer therapy simultaneously. The substitution of Fe<sup>3+</sup> instead of Ca<sup>2+</sup> was the way by which the magnetism property has been added to the scaffolds. The results show that the obtained Ms reached nearly 1 emu g<sup>-1</sup> without the appearance of any Fe-based phase—magnetite or maghemite. The compressive strength reported being in the range of 1.8–2.5 MPa which is in the range of trabecular bone. Nonetheless, through applying a magnetic field strength and frequency of 0.8 kA m<sup>-1</sup> and 750 kHz, respectively, the temperature generated from the scaffold has reached 50 °C after 350 s. It is noteworthy that the drug delivery of scaffolds is assessed through-loading cisplatin followed by evaluation of its release rate; the results indicate that a sustained release is obtained after an initial burst release during the first 24 h. In 2019, a study is reported by Bigham et al. [20] in which a multifunctional bone scaffold is made of a core-shell nanocomposite. The nanocomposite consists of CoFe<sub>2</sub>O<sub>4</sub> as the core and Mg<sub>2</sub>SiO<sub>4</sub> as the shell. The scaffold made of the nanocomposite has shown 84% total porosity with a compressive strength of 2 MPa. The Ms of scaffold is reported to be 15 emu g<sup>-1</sup> which is higher than that of other similar studies; through hyperthermia assessment *in vitro*, a range of magnetic fields with different strengths including 7.95, 9.95, 11.94, and 15.91 kA m<sup>-1</sup> along with a constant frequency of 200 kHz is adopted. The

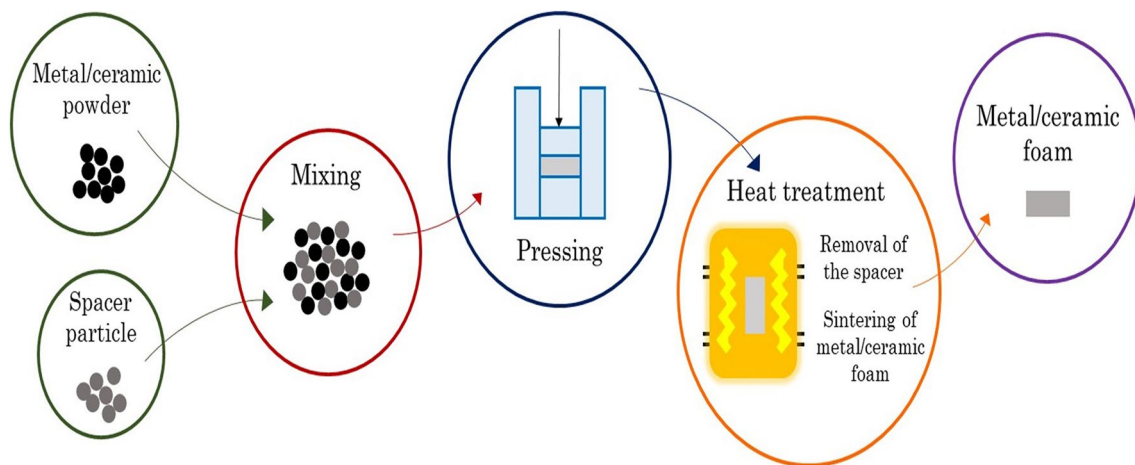
results reveal that a progressive increase in the magnetic field results in an increase in temperature up to 500 s. Nevertheless, the drug delivery potential of a nanostructured scaffold is assessed as well through loading an antibiotic, and the related results evidence that the multifunctional Mg<sub>2</sub>SiO<sub>4</sub>-CoFe<sub>2</sub>O<sub>4</sub> scaffold has a promising potential to keep drug availability for about 100 h. In a complementary study carried out by Bigham et al. [60], the surface coating of a multifunctional Mg<sub>2</sub>SiO<sub>4</sub>-CoFe<sub>2</sub>O<sub>4</sub> scaffold is carried out to not only reinforce the mechanical properties but also take better control over the release rate of the scaffold. The scaffold is coated with poly-3-hydroxybutyrate (P3HB)-ordered mesoporous magnesium silicate (OMMS) composite. The polymeric phase has significantly improved the compressive strength of the scaffold up to 3 MPa and the OMMS microparticles by having ordered mesoporous structure (4 nm) provided a carrier to load high amounts of drug molecules followed by liberating the molecules in a controlled way. It is important to remind that coating of the scaffold has decreased the Ms, but through applying a magnetic field of 19.9 kA m<sup>-1</sup>, that shortcoming was reported to be compensated.

### Space holder technique

Space holder technique can be regarded as a derivative of the traditional powder sintering process in which metal or ceramic powder particles are compacted followed by sintering at high temperatures; the porous structure is formed as the result of rearrangement of particles during sintering procedure [115, 116]. The final pore size and shape totally depend on the morphology of initial powders, but through applying the powder sintering process, a maximum total porosity of 35% can be achieved [117]. Space holder technique adopts different temporary pore-forming agents, and these agents are embedded through either ceramic or metal starting particles; elimination of the agents either before or during the sintering process forms a porous structure in the final ceramic/metal material [118, 119]. To fabricate a bone scaffold through space holder technique, the following steps are generally applied [120, 121] (Fig. 10):

1. Preparation of a mixture of the starting powder (ceramic/metal) and pore-forming agents.
2. Compaction of the obtained mixture.
3. Elimination of the pore-forming agents through the compacted material.
4. Consolidation of the scaffold through the sintering process.

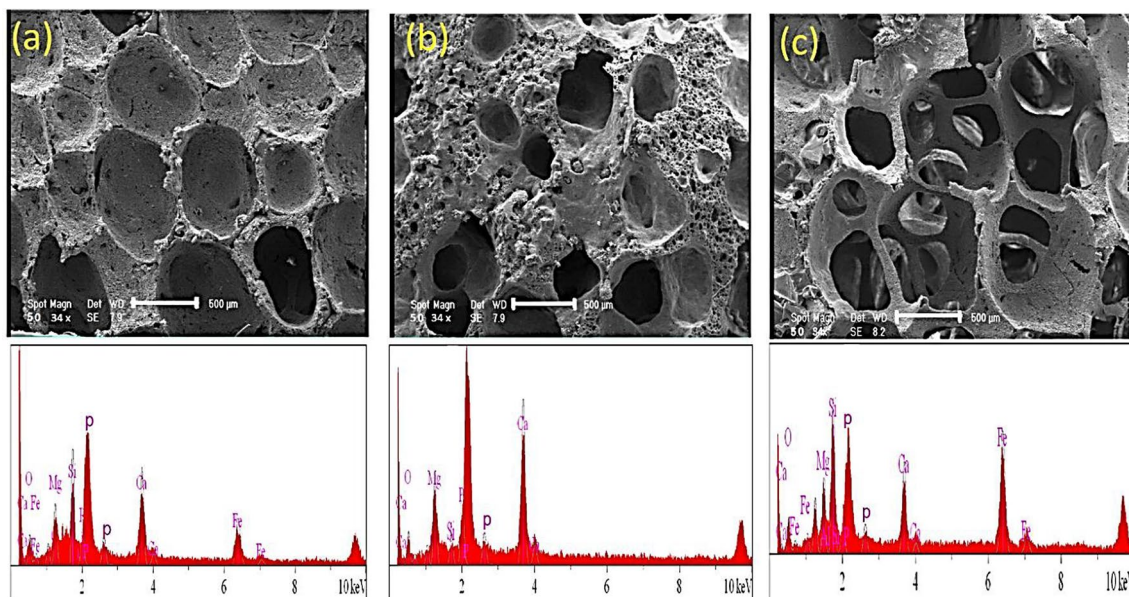
It is critical to bear in mind that choosing an appropriate space holder agent has direct effects on the textural and mechanical properties of the scaffold and it may indirectly



**Fig. 10** A schematic showing the space holder technique's process step-by-step; mixing the initial powder with the space holder agent followed by pressing the mixture and finally the sintering of the green body

have the potential to trigger cytotoxicity in the case of incomplete removal. Therefore, some parameters including the agent's biocompatibility, chemical stability, and removal capability are of great importance in this technique. Up to now, various pore-forming agents are used in space holder technique—sodium chloride (NaCl) [122], carbamide [117], ammonium hydrogen carbonate [123], etc. To minimize the negative effects of remained pore-forming agents on cell compatibility, some researchers have used food-grade powders—cornstarch [124], NaCl [125], and saccharose [126].

In 2018, Abdellahi et al. [105] developed a novel composite scaffold composed of diopside ( $\text{CaMgSi}_2\text{O}_6$ )-magnetite ( $\text{Fe}_3\text{O}_4$ ) to be applied in bone cancer therapy and regeneration. Different amounts of  $\text{Fe}_3\text{O}_4$  are used in the scaffold's structure, and their effects on the bioactivity, heat generation capability, and mechanical properties of scaffolds are assessed in vitro. Figure 11 exhibits the scaffolds with different amounts of  $\text{Fe}_3\text{O}_4$ . The results related to the scaffolds' microstructure reveal that the increase in the  $\text{Fe}_3\text{O}_4$  content results in the improvement in the pore's interconnectivity and heat generation capability. Increasing the



**Fig. 11** The microstructure of diopside-magnetite scaffolds with different magnetite contents: **a** 10 wt% **b** 20 wt% **c** 30 wt%. Reproduced with permission from Ref. [105]

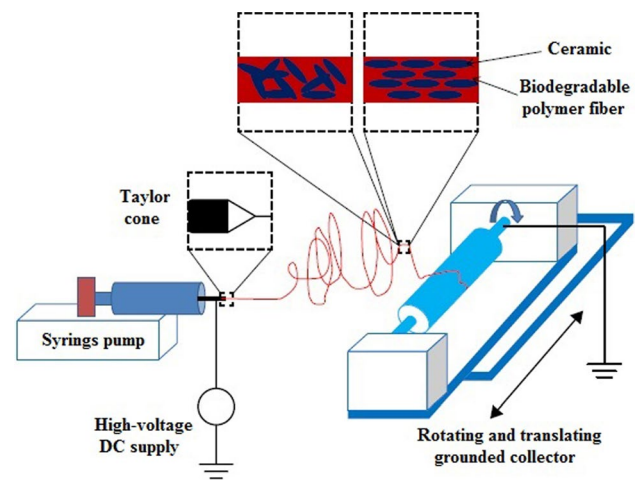
porous structure is a double-edged sword because on the one side, these pores ensure penetration of nutrients and waste removal, and on the other side, the mechanical properties weaken significantly. In the same year, Najafinezhad et al. [127] reported a research job in which a hexaferrite composition ( $\text{SrFe}_{12}\text{O}_{19}$ ) was mixed with hydroxyapatite to fabricate a multifunctional bone scaffold for hyperthermia-based therapy. It is worth mentioning that applying hard ferrites in hyperthermia have always been debatable due to their high anisotropy. The effects of  $\text{SrFe}_{12}\text{O}_{19}$  contents plus gelatin coating on the heat generation capacity and compressive strength of hydroxyapatite scaffolds are assessed. Based on the reported results, the HA-20 wt%  $\text{SrFe}_{12}\text{O}_{19}$  scaffold had a larger pore size leading to the absorption of more gelatin and better compressive strength compared to other scaffolds.

In 2020, Sahmani et al. [128] designed and fabricated a multifunctional Ha- $\text{Fe}_3\text{O}_4$  bone scaffold through space holder technique with different  $\text{Fe}_3\text{O}_4$  contents—0 wt%, 5 wt%, 10 wt%, and 15 wt%. Next, a coating containing ibuprofen and gelatin is developed on the scaffolds to monitor the controlled release rate along with the hyperthermia capability. The overall results show that the addition of  $\text{Fe}_3\text{O}_4$  reduces the scaffolds' interconnected porous structure on the downside, but it improves the degradation rate and effectiveness of hyperthermia therapy on the upside. Moreover, the release trend of ibuprofen is reported to depend on the Ha content.

## Electrospinning

Through applying high voltages, electrospun macro-/nanofibers are fabricated from electrified jets; due to a repulsive interaction of the applied solvent and surface charge, fibers are being elongated continuously during the fabrication process [129]. As mentioned earlier, yielding a fibrous scaffold with a high surface area similar to the extracellular matrix is considered as one of the most important features of the electrospinning technique [130]. Moreover, the compatibility of technique with various materials—natural and synthetic polymers, ceramics, metals, and also their combinations—has made it an easy-to-use technique [131]. Although electrospinning has numerous advantages, designing and fabrication of densely packed fibers with the entangled structure were difficult to achieve [132]. Therefore, the rotating collectors are applied in the technique to compensate for the setback [133]. Figure 12 indicates a typical electrospinning system adopting a high voltage to obtain macro-/nanofibrous scaffolds.

As it is well known that the scaffold's topography directly affects the cell adhesion and proliferation, electrospinning is capable of taking control over the size and shape of the fibers, and total porosity as well [134]. There are some criteria when it comes to designing electrospun fibers for a specific



**Fig. 12** A typical electrospinning system yielding fibrous scaffolds for different applications. Reproduced with permission from Ref. [59]

application in tissue engineering—choosing an appropriate material based on the desired need, total porosity, surface modification, and fibers orientation (aligned vs. random) [135]. Through controlling the fiber size and orientation, the final pore size and total porosity will be optimized for an intended application [136]. Moreover, after the fabrication process, because of the high surface area of scaffolds, the surface can be modified through different kinds of bioactive molecules [137]. Applying single-phase electrospun scaffolds (normally a natural/synthetic polymer) has expansively assessed for different applications, but recently, obtaining an electrospun composite scaffold consists of a bioceramic and a polymer for bone tissue regeneration is of particular interest; different bioceramics including hydroxyapatite, bioactive glass, etc. have been incorporated into the matrix of various polymers—PCL, gelatin, PVA, etc. [98, 138–141].

Designing an electrospun multifunctional scaffold comes back to 2013 when Gloria et al. [142] developed a magnetic scaffold composed of PCL/ $\text{Fe}$ -doped hydroxyapatite for advanced bone tissue engineering. The main aim of their study was to fabricate a fully degradable multifunctional scaffold to deal with different bone-related issues—cancer and regeneration. The results show that the fibrous nanocomposite has a superparamagnetic character and  $M_s$  is directly related to the  $\text{Fe}$ -doped hydroxyapatite content and the heat generation ability of scaffolds for hyperthermia-based therapy is evident; the osteogenic differentiation is also accelerated through applying an EMF. In the same year, Amarjargal et al. [143] studied the effects of  $\text{Fe}_3\text{O}_4$  nanoparticles on the physical and chemical properties of polyurethane fibers. The novelty of this work revolves around the immobilization of  $\text{Fe}_3\text{O}_4$  nanoparticles on the fibers through a simple immersion of the fibrous scaffolds into a polyol solution. The addition of  $\text{Fe}_3\text{O}_4$  nanoparticles led to obtaining the  $M_s$  of 33.12



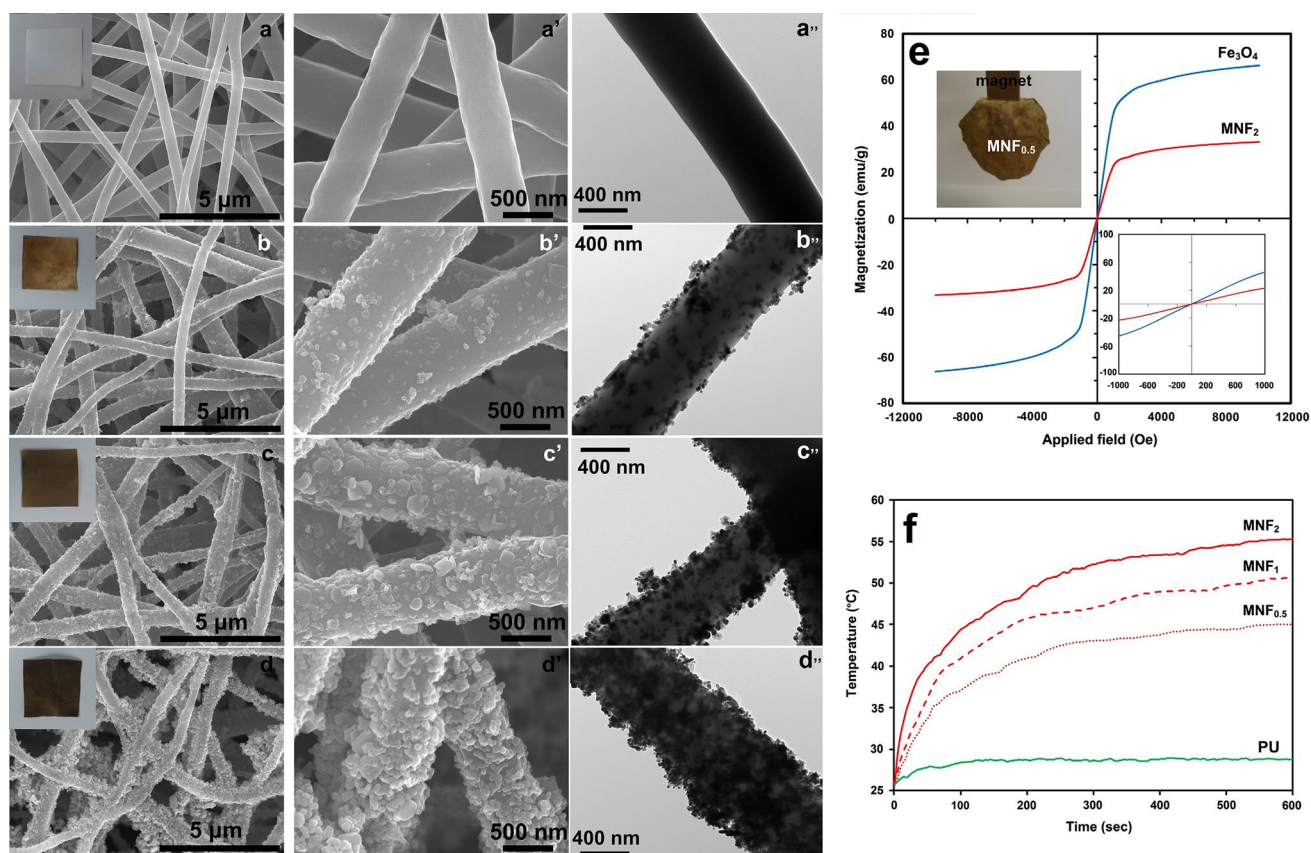
emu  $g^{-1}$  that is suitable for hyperthermia-based therapy. The thermal activity of nanocomposite is very promising, and the sample containing the highest amounts of  $Fe_3O_4$  nanoparticles called  $MNF_2$  raised the temperature around  $55\text{ }^\circ\text{C}$  in 600 s when it exposed to an EMF. The SEM and TEM micrographs of polyurethane and polyurethane- $Fe_3O_4$  nanoparticles along with the related VSM and hyperthermia studies are exhibited in Fig. 13.

Another composite fibrous scaffold containing polylactic acid (PLA), hydroxyapatite, and  $\gamma\text{-}Fe_2O_3$  is developed by Meng et al. [144] through electrospinning technique. The Ms scaffold is found to be  $0.049\text{ emu }g^{-1}$ , and the scaffold is implanted into a bone defect of white rabbit; the rabbit models are permanently exposed to an EMF during the test to assess whether the magnetic property of scaffold accelerates the bone regeneration rate. The results reveal that the magnetic scaffold has a promising potential to regenerate the bone defect and alleviate the postsurgery period. In 2018, a doxorubicin hydrochloride-loaded electrospun scaffold composed of chitosan/cobalt ferrite/titanium oxide was fabricated for both chemotherapy and hyperthermia therapy by Radmansouri et al. [145]. It turned out that the fiber size of

the composite scaffold is in the range of 90–110 nm. The thermal activity of the scaffold is assessed in vitro in the exposure of an EMF and the temperature reached  $44.7\text{ }^\circ\text{C}$  after 900 s (strength of magnetic field =  $1\text{ kA }m^{-1}$ , frequency = 290 kHz). The drug release study is performed in both the presence and absence of EMF up to 72 h, and the results exhibit that after a burst release in the initial hours of soaking, there is a steady rate up to 72 h. Moreover, the magnetic field applied in the release study caused the liberation trend to become faster stemming from the vibration-related effects of magnetism on the magnetic materials.

### 3D printing

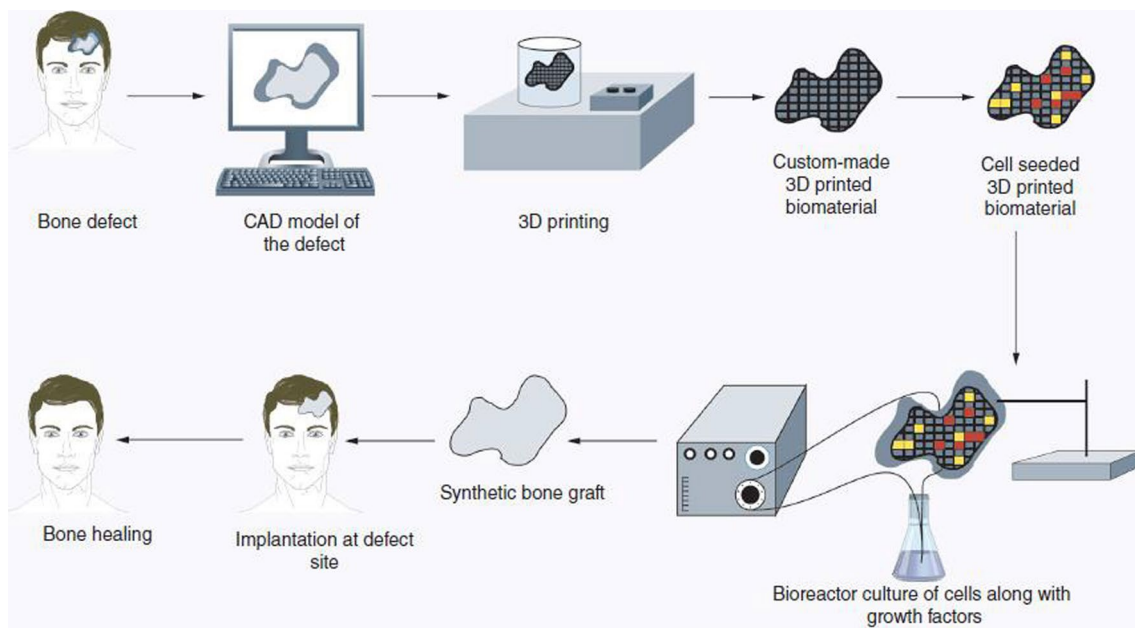
Nowadays, 3D printing technologies have changed the traditional prostheses and presented a sufficient method to replace tumors with patient-matched devices. Figure 14 shows a hypothetical model for a working plan to produce patient-specific devices. Besides theoretical and laboratory models, 3D-printed prostheses have earned the approval for successful clinical trials. It should be noted that the most important feature about 3D-printed prostheses is that their



**Fig. 13** The FESEM and TEM micrographs of the electrospun membranes: (a, a', and a'') PU; (b, b', and b'')  $MNF_{0.5}$ ; (c, c', and c'')  $MNF_1$ ; (d, d', and d'')  $MNF_2$ ; magnetic hysteresis loops of  $Fe_3O_4$  and

$MNF_2$  membrane (e); heat generation vs. time curves of the membranes in the exposure of an EMF (f). Reproduced with permission from Ref. [143]





**Fig. 14** The path of making patient-specific devices via 3D printing. Reproduced with permission from Ref. [146]

contour should be able to accurately fit the injured bone. In addition, 3D printing can help in producing porous devices. Porous devices not only promote bone ingrowth but also reduce the modulus, which can prevent prolonged mechanical issues such as fracture and loosening. Porous 3D-printed scaffolds have shown to possess a high potential for bone-related problems. In practice, interconnected networks are necessary to provide enough space for cell bioactivity, cell feeding, and interactions. In the meantime, the 3D-printed surface with a specified design explicitly affects cell interactions and formation. Therefore, producing a porous scaffold by the 3D printing method is of great interest and importance for developing bone formation. Figure 15 shows a 3D-printed prosthesis for a 13-year-old girl, who showed a diagnosis of osteosarcoma.

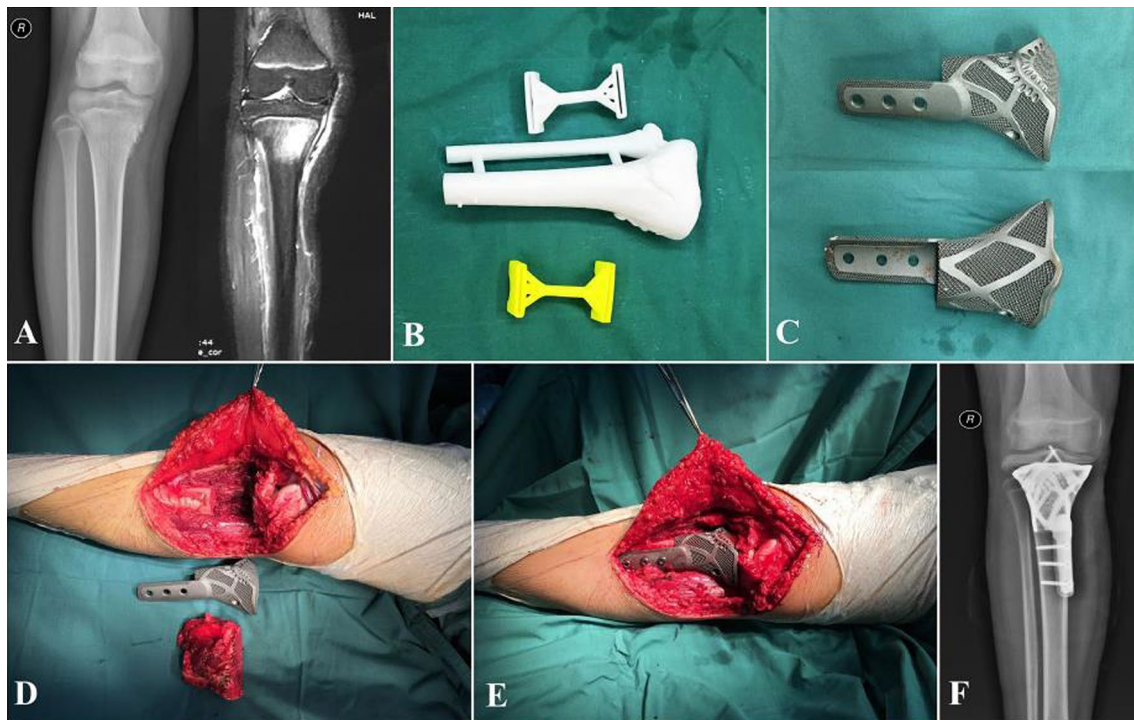
3D printing provides a unique feature to produce an architecturally complicated design with high reproducibility. Regarding conventional methods, a wide range of polymers have been printed using techniques which are mostly based on extrusion of materials, for instance, fused filament fabrication to make scaffolds and devices with controllable porosity. The good point about them is that they can offer high mechanical properties. However, the cons about them are related to the low resolution and cell culture has to be done after fabrication. Moreover, printing materials are limited and the high printing temperatures during fused filament fabrication do not allow for the incorporation of cells and biomolecules during manufacturing. On the contrary, 3D bioprinting techniques provide in situ incorporation of cells such as direct-ink writing and

inkjet printing. However, there are some issues about utilizing inkjet printing which is needle clogging for viscous inks and exposing cells to severe shear forces. Respecting other useful methods which can incorporate cell at the time of printing, stereolithography should be mentioned which shows great resolution as well as favorable properties. It should be noted that the toxicity related to monomers and utilizing UV radiation for curing may cause some viability problems for cells in long times. Table 4 demonstrates available additive manufacturing methods used for bone scaffold production including their advantages and disadvantages [18]. There are five different approaches in additive manufacturing of bone scaffolds—direct-ink writing, laser-assisted bioprinting, selective laser sintering, stereolithography, and fused deposition modeling.

*Direct-ink writing* technique refers to applying a slurry-based ink which is highly concentrated, and it should be able to carry its weight during the assembly while not being deformed; the composition should be carefully chosen and its viscoelastic properties must be taken into account.

*Laser-assisted bioprinting* has vast applicability in tissue engineering rooting in its physical mechanisms giving an ample opportunity to print liquid materials plus cells. The technique is very promising because it allows the engineers to control the cell density carefully and also organizing the 3D tissue construct.

*Selective laser sintering* through adopting a CO<sub>2</sub> laser beam applies heat during the printing process to consolidate the layers; the technique is compatible with polymers, ceramics, and the combinations.



**Fig. 15** **a** X-ray and MRI image, **b** 3D model of the tumor and bone plate, **c** patient-matched, **d** tumor and bone defect, **e** the matched contour to the patient, **f** One month after surgery. Reproduced with permission from Ref. [147]

**Table 4** Additive manufacturing techniques characteristics for bone scaffold production

Technique	Processing specifications	Advantages and disadvantages	Ref.
Direct-ink writing	Extrusion of viscous solution due to the designed structure Fixed pressure Layer by layer deposition at a fixed extrusion rate	<i>Pros</i> The possibility of incorporation of medicine, cells, and biomolecules <i>Cons</i> Heat treatment requirement of some materials prevents the incorporation of biomolecules	[148, 149]
Laser-assisted bioprinting	The intended materials are coated on the ribbon The accuracy of the deposition is controlled by laser energy Resolution is controlled by spot size, a distance of quartz disk, and step motion	<i>Pros</i> Quantitatively controllable, applicable for a wide range of materials <i>Cons</i> Ribbons must be homogenous	[150, 151]
Selective laser sintering	Powder bed preparation Layer by layer deposition of powder Utilizing laser resource to sintering each layer due to the pre-designed structure	<i>Pros</i> Thorough method with no support, no more process is needed after production <i>Cons</i> Laser diameter affects the quality of resolution	[152, 153]
Stereolithography	The platform needs to be immersed in a photopolymer solution Light is exposed according to the intended design Polymer solidification Fabrication is carried out layer by layer	<i>Pros</i> Applicable for complicated internal characteristics, usable for incorporating of cells and biomolecules <i>Cons</i> Just for photopolymers	[152, 154]
Fused deposition modeling	Polymer heating Extrusion through nozzle	<i>Pros</i> Platform is not required <i>Cons</i> A smaller range of materials can be used due to the requirement of the molten phase	[155, 156]
Inkjet printing	Pumping of ceramic suspensions Accumulation of the feedstock as droplets	<i>Pros</i> Applicable for fabricating complicated ceramic structures, timely efficient <i>Cons</i> Poor adhesion among printed layers	[157, 158]

The *stereolithography* technique is based on using a light-responsive polymer which means after or during the deposition of a layer, light is being emitted on the polymer resulting in the solidification of layers.

*Fused deposition modeling* is based on using a thermo-plastic filament; before the extrusion of filament, it exposes to heat through a liquefier-head, and then it will be extruded through a nozzle to form the layers.

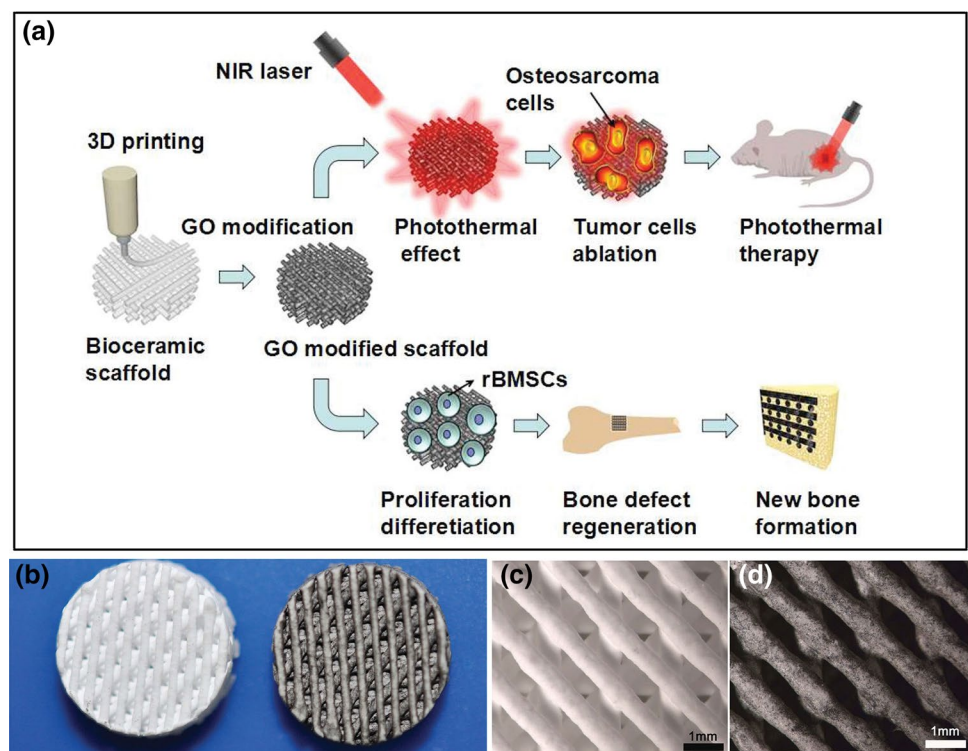
*Inkjet printing* is one of the most useful 3D printing techniques for the fabrication of bone scaffolds. In this technique, a ceramic suspension is pumped and the droplets of the suspension are accumulated on the printing bed to form the final design of the product.

Generally, after printing scaffolds, it is needed to culture cells on the printed device prior to implantation in the body. Hence, it should be noted that some of these approaches, such as direct-ink writing and stereolithography, are able to incorporate medicine, cells, and biomolecules while printing the scaffold. However, each of these methods has some limitations which are completely discussed in Table 4.

Designing and applying 3D-printed multifunctional ceramic bone scaffolds for simultaneous bone cancer therapy and regeneration traces back to 2016 when Ma et al. [159] developed a 3D-printed tri-calcium phosphate scaffold modified with graphene oxide to deal with bone tumors through photothermal therapy. Besides possessing appropriate microstructural and mechanical properties, it is found that based on the graphene oxide concentration, the heat

generation of the modified scaffold can be altered in the range of 40–90 °C, whereas the unmodified scaffold did not raise the temperature in the presence of near-infrared laser. Moreover, the modified scaffold is turned out to successfully stimulate rabbit bone mesenchymal stem cells toward osteogenic cells (Fig. 16). The same group accomplished another work on 2016 [160] in which a calcium-silicate-phosphate called Nagelschmidite ( $\text{Ca}_7\text{Si}_2\text{P}_2\text{O}_{16}$ ) is printed followed by a surface modification on the scaffolds consisting of Ca-P/polydopamine. The in vitro and in vivo studies together suggest that the surface-modified scaffold is a promising candidate for large bone defects caused by the removal of bone tumors to not only accelerate the regeneration process but also reducing the risk of tumor recurrence. In 2017, Khandan et al. [161] prepared a 3D-printed nanocomposite bone scaffold composed of  $\text{Ca}_7\text{MgSi}_4\text{O}_{16}$ - $\text{Fe}_3\text{O}_4$  for hyperthermia-based bone cancer therapy. Based on the results, incorporation of 30% wt  $\text{Fe}_3\text{O}_4$  leads to a significant improvement in the physical, chemical, and biological-related properties of  $\text{Ca}_7\text{MgSi}_4\text{O}_{16}$  scaffold and the magnetic nanoparticles endow hyperthermia capability to the scaffold as well. Up to now, various modifiers being responsive to near-infrared laser have been investigated for bone cancer therapy such as  $\text{CuFeSe}_2$  [30],  $\text{SrFe}_{12}\text{O}_{19}$  [162],  $\text{LaB}_6$  [72], carbon [108], and  $\text{MoS}_2$  [163]. Although all of them were well established and successfully getting the osteosarcoma cells killed, a sufficient and easy way is introduced by Liu et al. [164, 165] which is doping metallic elements into

**Fig. 16** **a** A schematic showing 3D printing and surface modification of the scaffolds followed by applying for bone regeneration and cancer therapy; **b** digital photographs relating to 3D-printed TCP scaffolds (left) and surface-modified TCP scaffolds (right) scaffolds; the microstructure of **c** TCP and **d** surface-modified TCP scaffolds. Reproduced with permission from Ref. [159]





the crystal structure of a bioactive ceramic-like bioglass. They have developed 3D-printed Cu, Fe, Mn, and Co-doped bioactive glass–ceramic scaffolds for bone cancer therapy. Besides, some of these elements are reported to have angiogenesis and antibacterial properties which are added values to take into consideration [65, 66, 166–168]. The added elements show an excellent photothermal ability besides playing another key role which is being a sintering aid increasing the mechanical properties. The overall results exhibit that this approach is a smart strategy to develop bone scaffolds with multiple capabilities—bone cancer therapy, desired mechanical properties, accelerated bone regeneration, antibacterial activity, and angiogenesis (Fig. 17).

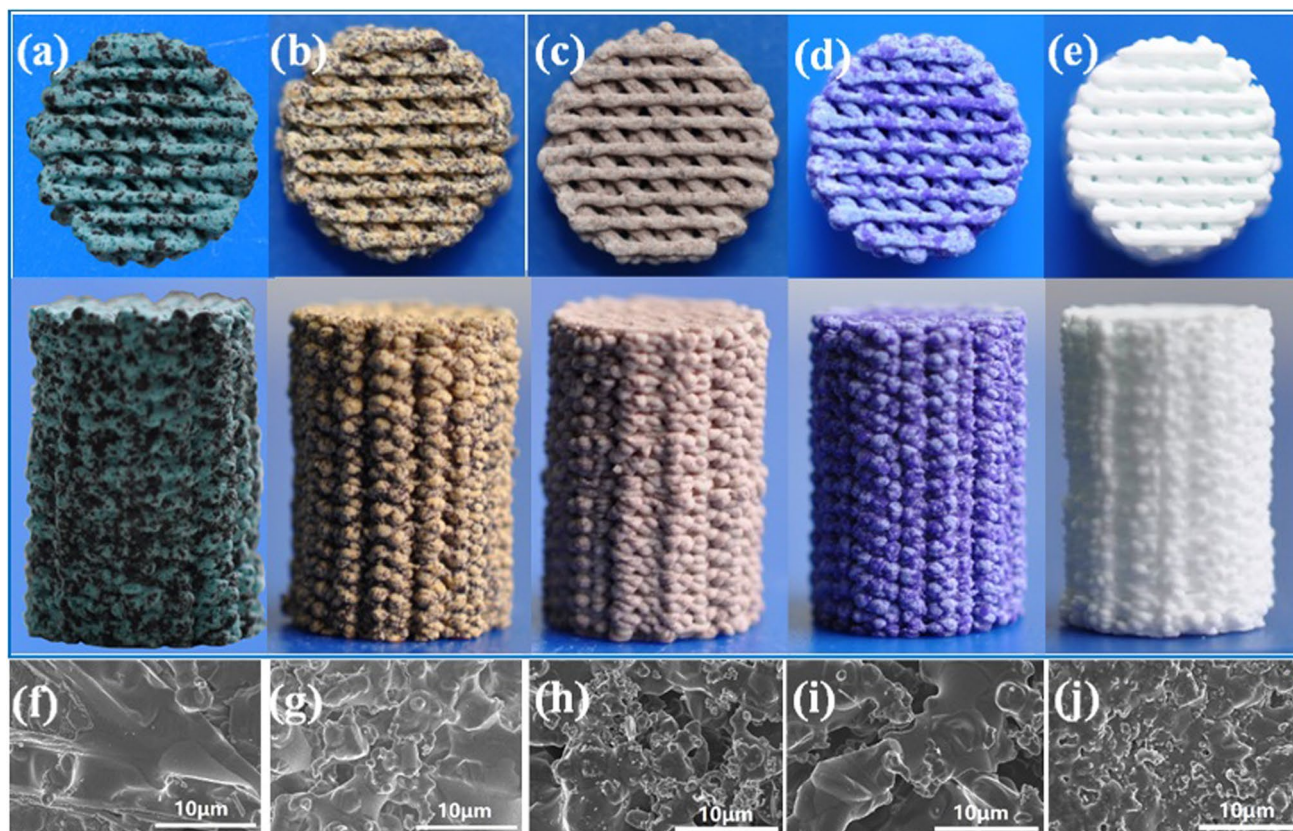
Below each digital photograph, there is the related SEM micrograph of scaffolds doped with different elements. Reproduced with permission from Ref. [165].

## Conclusions

Due to a high risk of bone tumor recurrence, filling up a large-sized bone defect caused by a tumor removal with a multifunctional bone scaffold is killing two birds with one

stone. The multifunctional scaffolds are able to address the remained bone cancerous cells in the defect's wall through hyperthermia, photothermal, and localized drug delivery besides regenerating the bone tissue. Various fabrication techniques are applied in recent years to yield multifunctional scaffolds with desirable properties like polymer sponge, space holder, electrospinning, and 3D printing. Despite yielding 3D scaffolds with a porous structure similar to bone, polymer sponge and space holder techniques are suffering from a lack of precise control over microstructure and reproducibility. Modern techniques—electrospinning and 3D printing—are proven to be practically applicable when it comes to designing a bone scaffold based on the complex shape of a bone defect. Through this review, we aimed to shed light on the multifunctional bone scaffolds potential for both bone cancer therapy and regeneration, in particular, different fabrication techniques adopted to construct these scaffolds are reviewed.

With the advent of 3D printing in bone tissue engineering, this field has undergone a fundamental change since then. Therefore, it is clear that 3D printing's excellent properties—precise control on morphology and reproducibility—have made the researchers put aside the traditional



**Fig. 17** Digital photographs relating to 3D-printed bone scaffolds, 5Cu—bioactive glass–ceramic (a), 5Fe—bioactive glass–ceramic (b), 5Mn—bioactive glass–ceramic (c), 5Co—bioactive glass–ceramic (d), and pure bioactive glass–ceramic (e)



techniques. Despite the advantages of 3D printing compared to traditional techniques, it requires permanent progress in its accuracy and resolution. Moreover, working with up-to-date 3D printing systems is costly and so cooperation between different fields to reduce the costs is necessary. It is worth mentioning that 3D-printed ceramic scaffolds are much more difficult to obtain than polymeric ones; preparation of ceramic-based slurries with high flowability for 3D printing requires an appropriate binder, dispersant, and solvent in the first stage. Next, to be mechanically strong for load-bearing applications, it needs to be sintered at high temperatures leading to shrinkage followed by the appearance of cracks. Therefore, it can be expected that through the near future, we will witness vast progress in the 3D printing techniques resulting in more structurally accurate multifunctional scaffolds for bone cancer therapy.

**Authors contribution** AB, FF, and ERG summarized the literature and wrote a major part of the manuscript. MR, REN, and SR conducted the deep review, editing, guidance, and supervision. All authors have read and approved the article for publication.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights** This article does not contain any studies with human or animal subjects performed by any of the authors.

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