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Incorporating nanoparticles in 3D printed scaffolds for bone cancer therapy

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ABSTRACT

The low occurrence rate of bone cancer contributes to delayed diagnosis and treatment; in addition, the surgical resection of bone tumors can cause significant bone defects, further hindering the effective treatment of the disease. 3D printing can help overcome some of these limitations by enabling the design and fabrication of innovative scaffolds loaded with chemotherapeutics and growth factors, stimulating bone regeneration, and delivering targeted cancer treatment. Moreover, advancements in nanotechnology have opened up new possibilities for bone tissue engineering. Nanoparticles (NPs) possess size-dependent physicochemical properties. NPs can also be designed to respond to specific stimuli enhancing localized drug delivery. These unique properties can be harnessed by embedding NPs in 3D-printed scaffolds to develop multifunctional bone scaffolds with enhanced mechanical properties and drug delivery capabilities. This review evaluates the impact of incorporating NPs in 3D-printed scaffolds on bone cancer therapy and bone regeneration. First, various 3D printing techniques employed in the biomedical field are presented and explained. The article then highlights notable achievements by researchers in this area. Finally, the review discusses the current obstacles facing this technology and how they can be addressed to enable translation into clinics.

1. Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and dissemination of abnormal cells in the body forming masses known as tumors [1,2]. According to the American Cancer Society, around 1.9 million new cancer cases are expected to be diagnosed in 2023 in the US alone [3]. The American Cancer Society estimated that for primary cancer of the bones and joints in 2023, about 3970 new cases will be diagnosed [4]. Bone cancer can be divided into primary and metastatic, where the former is caused by cancer cells originating in bone tissue that has metastasized from other primary tumor areas to bone tissue [5]. Primary bone cancer can be further classified into the following (refer to Fig. 1) [6–8]:

- Osteosarcoma: this is the most common form of bone cancer and usually affects children and young adults (in children and young adults, osteosarcoma accounted for 56 % of primary bone cancer cases in 2022). It often develops in the growing ends of long bones, such as the legs or arms.
- Chondrosarcoma: this type of bone cancer arises in the cartilage cells, usually affecting adults and accounted for around 40 % of primary bone cancer cases in adults in 2022. It tends to occur in the pelvis, thigh, or shoulder.
- Ewing sarcoma: primarily affects children and young adults and can develop in the bones or soft tissues (Ewing sarcoma accounted for 34 % of primary cancer cases in 2022). Ewing sarcoma often occurs in the pelvis, chest wall, legs, or arms.

Surgery is usually the first course of action for bone cancer treatment; chemotherapy, radiotherapy, and/or targeted therapy can also be included in the treatment plan, especially if the cancer has metastasized or is in a high-risk or difficult-to-reach region [5]. Despite the availability of various cancer interventions, bone cancer treatment remains a challenge for medical professionals and researchers due to its low incidence rate leading to delayed diagnosis and treatment, tumor heterogeneity, inter-individual variability, systemic side effects associated with some treatment modalities, and cancer recurrence [9,10]. Moreover, bone tumors and surgical interventions can cause large bone defects, usually addressed using autografts, allografts, and artificial

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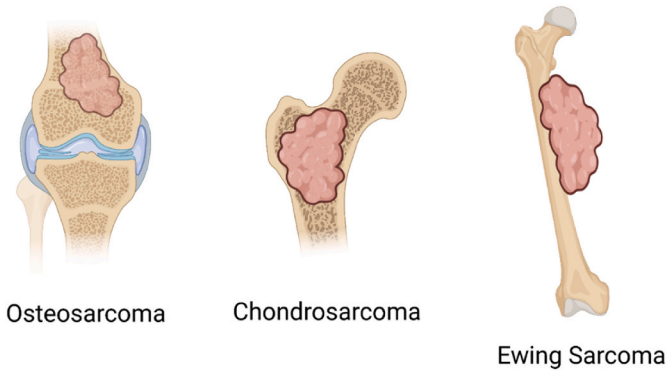


Fig. 1. Types of primary bone cancer (created using BioRender.com).

implants [10]. Autografts are the most suitable option for addressing bone defects due to their innate biocompatibility and non-immunogenicity and their ability to integrate with the existing bone structure to induce bone formation and growth [11]. Nevertheless, autografts also have certain limitations that impact their applicability such as limited availability, inability to repair large bone defects, and a higher likelihood of failure in complex environments [12,13]. Consequently, developing materials capable of repairing and restoring bone defects has become a significant field of research. A promising approach involves using 3D printing to fabricate novel scaffolds from different functional materials and to load these implants with chemotherapeutics and growth factors; such scaffolds would provide mechanical support, promote bone regeneration, and localized cancer treatment [14–16]. Recent studies have also focused on developing stimuli-sensitive-drug-loaded-implants to further enhance the efficiency of bone cancer treatment and promote bone regeneration [5]. Therefore, incorporating stimuli-responsive materials into 3D-printed scaffolds presents a promising technique to control the bone/tumor micro-environment, enhance localized chemotherapeutic/growth factors release, and accelerate bone formation allowing better cell growth and tissue regeneration [17,18]. This review focuses on incorporating NPs into 3D-printed scaffolds to enhance bone cancer therapy and bone regeneration.

2. 3D printing methods

3D printing (3DP), also known as rapid prototyping or additive manufacturing, refers to the process of making 3D solid objects by depositing materials layer-by-layer via computer-aided design (CAD). 3DP was first introduced in the early 1980s in Japan and since its inception, various 3DP techniques have been developed. In 1988, Charles Chuck Hull developed the first commercial 3D printer based on his patented technique known as stereolithography [16,19]. In the early 1990s, the use of 3DP started expanding into the biomedical field and was initially used to create custom implants and prosthetics for cancer patients, improving treatment outcomes [20]. In the early 2000s, researchers started exploring the potential of 3DP for personalized cancer therapy, including patient-specific tumor models for drug testing. Moreover, in the late 2010s, bioprinting emerged as a promising field, allowing the creation of 3D-printed tissues and organoids for cancer research and drug development [21]. The most significant breakthrough came in 2016 when Aprecia Pharmaceuticals launched Spritam®, the first FDA-approved 3D-printed tablet designed to treat epilepsy. Nowadays, 3DP can also be used to devise individualized treatments for cancer patients [22,23]. With respect to bone cancer, 3DP was first introduced in the 2010s for bone tissue engineering, with a focus on creating 3D-printed bone substitutes followed by the introduction of 3D-printed orthopedic implants designed to replace cancer-affected bone segments. Currently, 3DP can be used to fabricate scaffolds at a lower cost, with higher accuracy and repeatability, as well as facilitate the incorporation of other functional agents within the scaffold [5,15,16,24].

Various 3DP techniques have been employed in the biomedical field, including extrusion-based, inkjet-based, laser-assisted, and stereolithography (SLA)-based methods [15,25,26]. Table 1 summarizes the working principle, advantages, limitations, and applications of 3DP techniques relative to cancer therapy.

2.1. Biomaterial inks and bioinks

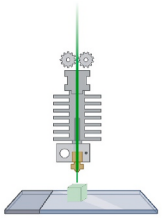
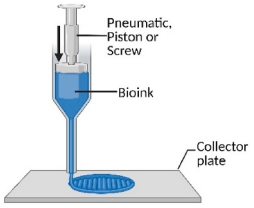
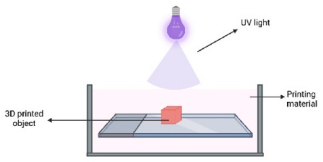
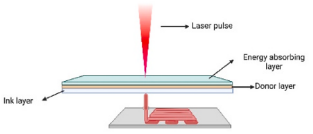
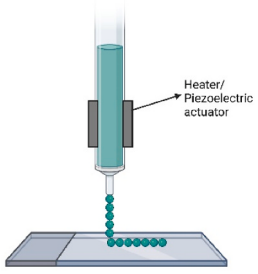
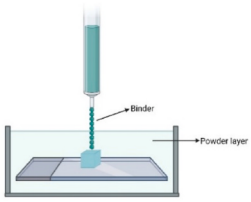
The terms biomaterial ink and bioink are sometimes mistakenly used interchangeably; technically these are different terms as biomaterial inks refer to materials that are biocompatible or designed to interact with biological systems and can serve as ink in 3DP. In contrast, bioinks are defined to contain living cells as a fundamental element, irrespective of the other materials into which the cells are seeded or that serve as the basal matrix (refer to Fig. 2) [16,20,27,28]. Biomaterial inks can be used to print structures such as scaffolds, matrices, and implants that can be used independently or in conjunction with bioprinting to provide mechanical support for the cells [25,27]. Various biomaterial inks have been utilized, including biocompatible metals, ceramics, polymers, and biomolecules, such as enzymes, growth factors, etc. On the other hand, bio-inks include single cells, cells aggregated in spheroids, cells organized into mini-tissues or organoids, cells coated by a thin layer of material, cells seeded onto microcarriers, or cells encapsulated in tailored colloidal microenvironments such as physical hydrogels or hydrogel precursors [27,29,30]. Bioactive hydrogels are commonly used in bioprinting to provide an environment that optimally mimics the native microenvironment of the human body because their structure and composition resemble that of the extracellular matrix (ECM). Hydrogel bioinks can be classified by the matrix surrounding the cells as natural (e.g., collagen, gelatin, alginate, chitosan, hyaluronic acid, cellulose, and fibrin) or synthetic bioinks (e.g., polyurethane, polyethylene glycol (PEG), and Pluronic F127) [15,27,28,31,32].

The properties of bioprintable materials are essential to ensure the quality of the printed structure, as well as to meet the stringent conditions placed by the cellular component(s) of bioinks. Inks should also be composed of biocompatible, biodegradable, nontoxic materials that promote nutrient diffusion and sustain tissue maturation during the post-printing culture phase. Furthermore, biomaterial and bio-ink scaffolds must possess three main qualities [16,33]: printability, functionality, and mechanical strength. The ink needs to be able to be fed and flow through the 3D printer, be processed, and finally result in a scaffold with enough strength to maintain its shape and functionality [31,34,35]. Viscosity is another important rheological parameter because it affects the printing process, i.e., high-viscosity inks are able to maintain their shape and structure; however, they require higher pressures during the printing process. Biomaterial inks with shear-thinning characteristics are more suitable for 3DP, especially for extrusion-based methods, because their viscosities decrease during extrusion, thus limiting the exposure of cells to excessive shear forces that can induce cell membrane damage and lead to reduced cell viability after printing [31,35]. Lower viscosity materials are recommended for droplet-based 3DP, whereas higher viscosity inks can be used in laser-assisted 3DP [16,36].

3. Nanoparticles in 3D printed scaffolds for bone cancer therapy

An emerging trend in 3D-printed scaffolds is the incorporation of nanomaterials or nanoparticles (NPs) in the printed product to enhance the printed systems' properties, functionality, and drug release kinetics [40–42]. NPs are ultrafine particles whose size ranges between 1 and 100 nm, with at least one property being considerably different from its bulk counterpart [43,44]. The size dependence of some properties of NPs arises from their large surface-area-to-volume ratio, which means that there are more atoms exposed at the surface; hence, more

Table 1
Comparison of various 3D printing technologies (adapted from Refs. [14–16,20,37–39]).

Method	Materials	Working Principle	Advantages	Limitations	Schematic
Fused deposition modeling (FDM)/Fused filament fabrication (FFF)	Thermoplastic polymer filaments	Extrusion-based method where a molten thermoplastic polymer filament is extruded through a high-temperature nozzle and is then deposited layer by layer (LbL)	- Produces complex scaffolds with high mechanical strength -Inexpensive -Can be used with simple desktop 3D printers -Uses readily available filaments, reducing post-processing needs	-Not suitable for bioprinting because high temperatures can cause cell degradation -Resolution of printed products limited by nozzle size and printing setup	
Pressure-assisted microsyringes (PAM)	Semi-liquid mixture of polymers and solvents (solution, paste, or dispersion)	Viscous and semi-liquid materials are deposited LbL through a pressurized air piston and a syringe extruder	-Operates at room temperature -Suitable for bioprinting -Continuous flow of aqueous-based materials -Simple, versatile -Wide range of starting materials	-Quality depends on rheological properties -Requires solvents or crosslinking agents -Slower printing speed	
Stereo-lithography (SLA)	Photo-curable liquid resin	Uses light sources from UV to visible light to crosslink or polymerize the ink for the development of 3D structures	-Operates at room temperature -Drugs cast in resin which prevents degradation -High resolution -Speed of fabrication -Creation of smooth surfaces	-Ink must be a photopolymer; however, only a few are approved for pharmaceutical use -Stability issues while storing photo-sensitive resin -Difficulty printing multilayered objects	
Laser-assisted method	Ink solution, laser energy absorbing powders	Based on laser-induced forward-transfer (LIFT) effect. A NIR or UV- a pulsed laser that transfers energy into a liquid photopolymerizable material. Photopolymerization occurs, and the product is created LbL.	-Low heat required, suitable for bioprinting -High resolution -Solvent-free process	-High energy laser might degrade drugs -Only laser energy-absorbing components can be used -Expensive setup	
Drop-on-demand (DOD) inkjet-based printing	Ink—drug solution, substrate—polymer-based films	Two-step process: (1) formation of electrostatically charged ink droplets and directing them toward predefined locations on the substrate and (2) droplet and substrate get to interact	-High resolution -High precision, low cost, and minimizes wastage of material	-Lower drop generating frequency than continuous inkjet -Involves high temperatures, which can cause the degradation of drugs and/or cells	
Continuous inkjet printing			-Higher drop-generating frequencies, which prevent clogging of the nozzle -More suitable for bioprinting	-Sterilization issues -Wastage of material, low resolution, and expensive	
Binder jetting	Binder fluid, powder bed	Liquid binder injected through DOD to selective areas of a spreading layer of powder material. The saturated area solidifies, and inkjet-solidification steps are repeated for each layer until the object is constructed	-Can be performed at room temperature -Wide range of starting materials -Fast-disintegrating dosage forms can be produced	-Post-fabrication processes necessary -Use of organic solvents -Wastage of powder material -Results in fragile dosage forms	

All schematics were created using BioRender.

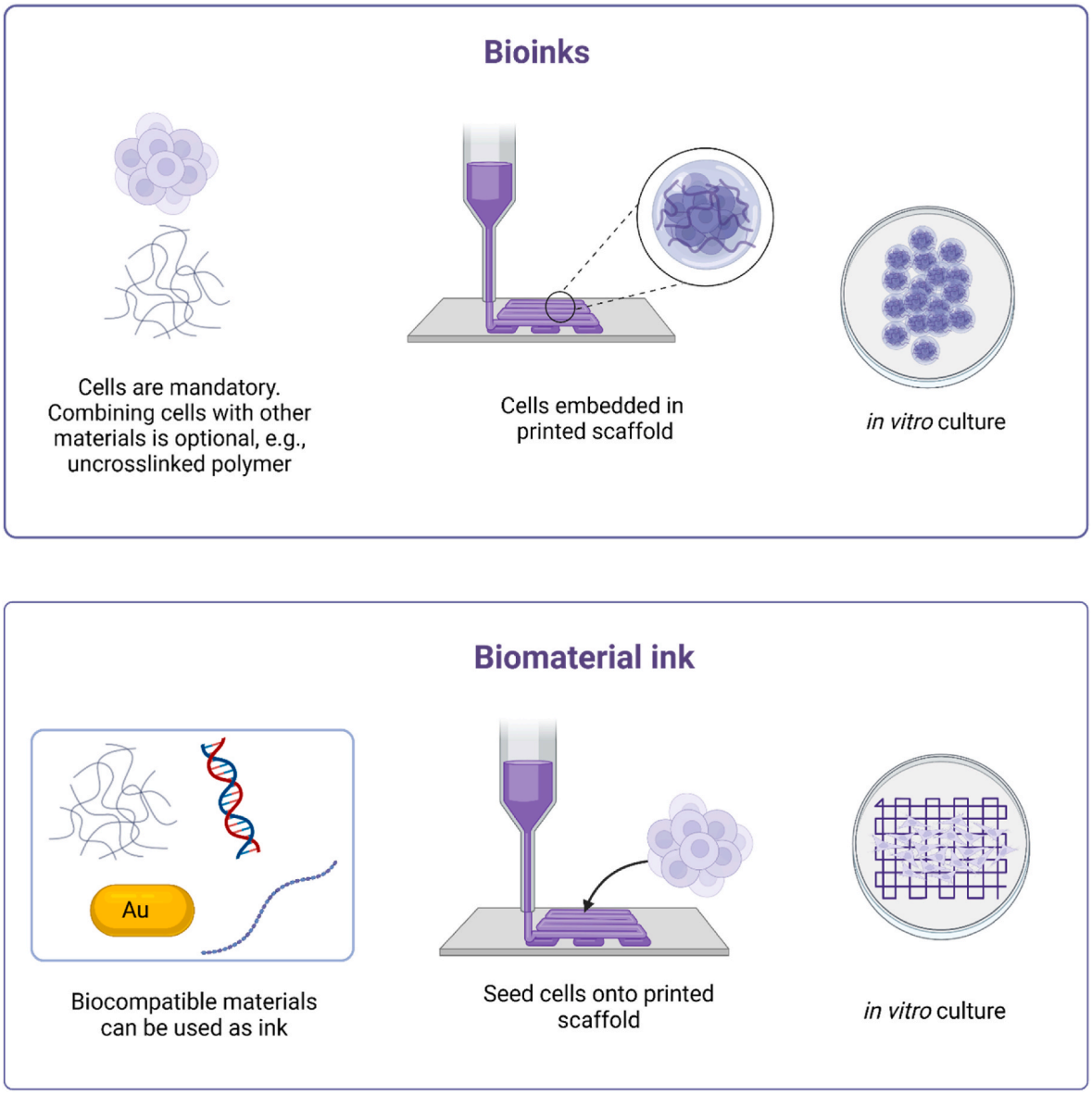


Fig. 2. Comparison between bioink and biomaterials ink (created using BioRender.com).

contribution by surface atoms to said properties [45]. The second reason for size dependence at the nanoscale is quantum confinement, i.e., when the NP size is smaller than the de Broglie wavelength of an electron or hole [46]. Accordingly, NPs exhibit unique physical, chemical, and optical properties. Moreover, depending on their composition, NPs can be classified as organic, inorganic, and carbon-based [47]. Another current trend in 3D-printed scaffolds for bone cancer therapy research is to co-load the scaffold or the embedded NPs with anticancer drugs and bone growth factors to simultaneously kill tumor cells and counteract bone loss/defects caused by surgery and chemotherapy. Osteogenesis and tumorigenesis are two distinct biological processes that involve the growth and development of different types of tissues, each regulated by intricate molecular pathways and cellular interactions. Osteogenesis refers to the formation of bone tissue, whereas tumorigenesis is the formation of abnormal tissue masses resulting from the uncontrolled proliferation of cells [48,49]. Bone growth factors, can exhibit effects of promoting osteogenesis while avoiding tumorigenesis through selective targeting of specific pathways or receptors, promotion of stem cell differentiation into osteoblasts while inhibiting cancerous cell differentiation, immunomodulation, and specific receptor activation/inhibition. However, these properties require meticulous design to ensure safety and efficacy in therapeutic applications, considering factors such as dosage and delivery mechanisms. Growth factors for improving osteogenesis include vascular endothelial growth factors (VEGF), fibroblast growth factors (FGFs), and bone morphogenic proteins (BMPs) [50,51]. Interestingly, some of these growth factors are also being studied for their role in tumorigenesis. One such example is bone morphogenetic protein-2 (BMP-2). BMP-2 is a member of the transforming growth factor-beta (TGF-β) superfamily and is known for its crucial role in promoting bone formation and repair by activating Smad-dependent pathways to induce mesenchymal stem cell differentiation into osteoblasts, upregulating osteogenic transcription factors such as Runx2 and Osterix, and subsequently stimulating the production of essential extracellular matrix proteins like collagen and osteocalcin, vital for bone tissue formation [52,53]. In the context of cancer therapy, BMP-2 was found to exert antiproliferative effects on specific cancer cell types by inducing cell cycle arrest and apoptosis, mediated through the regulation of signaling pathways like Smad and MAPK, while also modulating the tumor microenvironment by affecting angiogenesis and immune regulation, ultimately impeding cancer cell growth and metastasis [54,

55]. However, it is crucial to note that the context of BMP-2 application, including dosage and delivery methods, should be carefully considered to avoid unintended consequences [55–58]. Alternative growth factors such as FGF, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF) have been investigated, demonstrating promising results in pre-clinical models without the side effects of BMP-2 [56,57,59]. Furthermore, 3DP growth factors at specific locations within the scaffold helps minimize the required dosage and promotes spatially defined responses. Additionally, incorporating growth factor(s)-loaded NPs in 3D-printed scaffolds helps further enhance the control over the spatial distribution and temporal delivery of growth factors within scaffolds [60,61]. Therefore, by carefully designing the delivery system, it is possible to regulate the release kinetics and concentrations of these agents, minimizing the risk of any off-target effects.

Several research groups have explored composite inks incorporating different types of NPs in the last few years, particularly in the field of implants to treat bone cancer or tumor-induced bone loss (refer to Fig. 3) [62–64]. Jiang et al. [65] developed a 3D-printed implant that releases chemotherapeutics and growth factors for simultaneous cancer therapy and osteogenesis. Layer-by-layer (LbL) deposition was used to alternatively assemble polydopamine (PDA)-hybridized nanosized zeolitic imidazolate framework-8 (pZIF-8 nanoMOFs) and PDA-decorated-hydroxyapatite nanoparticles (pHA NPs) on the 3D-printed gelatin-based scaffold. The nanoMOFs were used as drug carriers, containing bone morphogenetic protein 2 (BMP-2) and Cisplatin (CDDP). *In vitro* and *in vivo* studies showed that incorporating the nanoMOFs into the scaffold helped improve drug loading and release; it also enabled the device to become responsive to the tumor microenvironment leading to tumor inhibition through the release of CDDP and inducing new bone formation by releasing BMP-2. Oladapo et al. [66] used FDM to synthesize a new poly-ether-ether-ketone calcium hydroxyapatite (PEEK-cHAp) composite bone implant to investigate the impact of cHAp on the mechanical behavior of PEEK bone implants. The 3D-printed composites showed improved tensile strength, stiffness, and Young's elastic moduli compared with the pure epoxy matrix, especially at cHAp of 10 and 20 wt%. Core-shell NPs, liposomes, and micelles have gained significant attention in drug delivery and cancer therapy due to their ability to encapsulate and target therapeutic agents effectively. These nanocarriers offer advantages such as controlled release, improved solubility of hydrophobic drugs, reduced systemic toxicity, and targeted delivery to specific cells or tissues [67]. Incorporating these NPs into 3D-printed matrices for bone cancer therapy has shown promising potential in enhancing treatment outcomes. Core-shell NPs consist of a core material surrounded by a shell that can protect the therapeutic cargo and control its release profile [68]. By incorporating anticancer drugs into the core, and modifying the surface with targeting ligands, core-shell NPs can efficiently deliver drugs to tumor cells while minimizing damage to healthy tissues. Integrating these NPs into 3DP matrices allows for the fabrication of patient-specific implants or scaffolds that can release drugs locally, providing sustained therapeutic effects at the tumor site [14]. Micelles are self-assembled NPs formed from amphiphilic block copolymers, capable of encapsulating hydrophobic drugs within their hydrophobic core. These structures can improve the circulation time of drugs in the body and enhance their accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect [69]. When integrated into 3D printing matrices or tissue engineering scaffolds, micelles enable controlled drug release, facilitating precise spatiotemporal control over therapeutic delivery for effective cancer treatment. Moreover, liposomes are spherical vesicles composed of lipid bilayers, enabling the encapsulation of both hydrophilic and hydrophobic drugs within their aqueous core or lipid layers [70,71]. These structures can improve drug solubility, stability, and bioavailability while minimizing off-target effects. In tissue engineering, liposomes can be incorporated into scaffolds or hydrogels to create drug-releasing constructs that facilitate the localized and sustained delivery of anticancer agents, thereby enhancing the effectiveness of cancer therapy. Sarkar and Bose [72] used porous 3DP-calcium phosphate (CaP) scaffolds containing curcumin-loaded liposomes to study curcumin's anticancer and osteogenic properties. These bifunctional scaffolds showed improved cytotoxicity towards osteosarcoma (MG-63) cells, while also promoting bone proliferation as tested *in vitro* using human fetal osteoblast (hFOB) cells. In another study by Bose et al. [73], curcumin was encapsulated in nanosized polymeric micelles and incorporated in TCP-3D-printed scaffolds. The developed scaffold demonstrates enhanced attachment of osteoblast (hFOB) cells, a 4-fold increase in hFOB cell proliferation, and a 73 % enhancement in hFOB cell differentiation. Additionally, it exhibited cytotoxic effects against osteosarcoma cells, resulting in 61 % lower viability compared to the control. Ma et al. [74] studied Fe–$CaSiO_3$ composite scaffolds (30CS) to provide mechanical support to bone cortical defects and induce anticancer effects. The 30CS possessed remarkable compressive strength; in addition, the inclusion of $CaSiO_3$ within the composite scaffolds resulted in enhanced degradation characteristics, stimulated the growth and differentiation of rat bone-marrow-derived mesenchymal stem cells and further facilitated the formation of bone tissue in living organisms. Fan et al. [75] developed Paclitaxel (PTX) 3D-printed titanium scaffolds (TS) for bone reconstruction and osteosarcoma recurrence prevention. The amphiphilic PEG-acetal-PTX (PEG–acetal–PTX) prodrug polymer self-assembled into micellar structures and was attached to the surface of the TS using polydopamine (PDA). The 3D NP-composite scaffold was tested under physiological (pH of 7.4) and acidic conditions (pH of 6.5) at 37 °C. An accelerated release rate of PTX was observed under acidic conditions (85.33 ± 0.66 %), attributed to the cleavage of the acetal bonds at a lower pH. The *in vitro* study results showed that the treatment of co-cultured five types of human osteosarcoma cells (143 B, MG63, HOS, U2OS, and SAOS2) with the composite scaffold group for 24 h

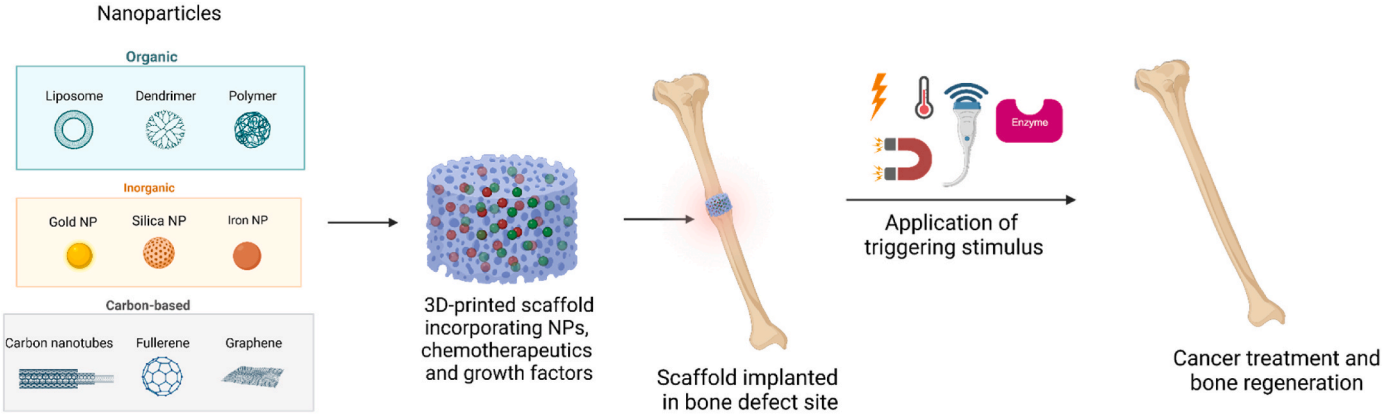


Fig. 3. Incorporating NPs in 3D-printed scaffolds and using stimuli to trigger drug release (created using BioRender.com).

decreased cell activity compared to that of the TS treatment group. However, when the incubation time was extended to 48 and 72 h, there was no statistically significant difference in the cell activity between the two groups (the scaffold group was dominated by late apoptotic cells, accounting for 20.31%–58.21 % of the total cells while for the PTX treated group, the late-stage apoptotic cells accounted for 24.31%–59.64 % of the total cells). Moreover, the *in vivo* performance of the developed system was tested in nude mice. The longest survival time was reached in the composite scaffold group (survival time of 60 days), whereas the survival times of the mice in the control, PTX, and TS groups were 29, 37, and 30 days, respectively.

Another interesting feature of NPs is that they can be designed to respond to internal or external triggers forming what is known as stimuli-sensitive or "smart" NPs [76,77]. Smart NPs can undergo specific changes in their physical and chemical properties or have specific functionalities triggered by various stimuli, e.g., temperature, pH, light, magnetic fields, or chemical agents [70,78–80]. Depending on the desired properties and applications, these NPs can be engineered from a variety of materials, such as polymers, lipids, metals, or hybrid composites. By incorporating them into 3D-printed scaffolds, they allow for precise and targeted delivery of therapeutic agents, imaging agents, or other payloads in biomedical applications, thereby enhancing the efficiency, selectivity, and therapeutic efficacy of drug delivery systems (refer Fig. 3) [81–83]. Lin et al. [84] developed a dual-purpose 3DP scaffold to simultaneously kill cancer cells and repair tumor-associated bone defects. The scaffold was composed of polydopamine (PDA) incorporating Fe and Mg-NPs. Fe-NPs were added to the PDA-based scaffold because Fe^{3+} ions can result in a synergistic effect of combining chemodynamic therapy (CDT) and photothermal therapy (PTT), leading to the effective elimination of tumor cells when triggered using NIR. On the other hand, Mg-NPs were included because Mg^{2+} can enhance osteoblastic differentiation, thereby effectively promoting the repair of bone defects associated with tumors. *In vitro,* results showed that the FeMg-NPs scaffolds could effectively kill tumors even under a short laser irradiation time of 3 min. Similar antitumor effects were observed in mice treated with the FeMg-NPs scaffold group. In addition, the scaffolds containing Fe and Mg-NPs showed remarkably higher bone mineral density, new bone volume, and new bone volume fraction *in vivo*. Zhang et al. [85] fabricated gelatin-based DOX-loaded scaffolds incorporating $SrCuSi_4O_{10}$-β-TCP core/shell filaments to treat bone defects caused by osteosarcoma. The research demonstrated that DOX was released in response to NIR-II triggering, leading to effective chemo-photothermal therapy with synergistic effects for cancer treatment both *in vitro* and *in vivo*. Additionally, the scaffold's transformation to a hollow channeled TCP/SC scaffold, along with the sustained release of bioactive ions (Sr, Cu, Si, and Ca) from bioceramic degradation, was found to promote osteogenesis and angiogenesis *in vitro* and facilitate vascularized bone regeneration *in vivo*. Dang et al. [86] designed MOF Cu-TCPP nanosheets interface-structured β-tricalcium phosphate (TCP) (Cu-TCPP-TCP) scaffold using the solvothermal method and were irradiated with NIR light. The developed Cu-TCPP-TCP scaffolds, when exposed to NIR light with a power density of 1.0 W/cm^2 for 10 min, were able to effectively eliminate osteosarcoma cells by releasing heat energy. The irradiated Cu-TCPP-TCP scaffolds increased the temperature on the surface, with the equilibrium temperatures of 5Cu-TCPP-TCP, 10Cu-TCPP-TCP, 20Cu-TCPP-TCP scaffolds at the time point of 600s reaching 84.58, 101.77, and 108.18 °C at dry conditions and 42.04, 51.35, 55.07 °C at wet conditions, respectively. Furthermore, these scaffolds demonstrated the ability to ablate subcutaneous bone tumor tissues, inhibit their growth by converting NIR light into heat energy, and promote bone regeneration *in vivo*. Hyperthermia NPs, also known as magnetic nanoparticles (MNPs), are a type of NPs, composed of magnetic materials such as iron oxide, that can generate heat when exposed to an alternating magnetic field. When these NPs are targeted to cancer cells and subjected to an alternating magnetic field, they generate localized heat, which can be used to selectively destroy cancer cells. This process, known as magnetic hyperthermia, takes advantage of the sensitivity of cancer cells to elevated temperatures compared to healthy cells. The localized heating can induce cell death in the tumor while minimizing damage to the surrounding healthy tissues. Zhang et al. [87] developed a 3D-printed β-TCP bioceramic scaffold modified with Fe_3O_4 NPs/graphene oxide layers, resulting in a structure exhibiting super-paramagnetic behavior and hyperthermia effects. The magnetic intensity of the scaffold was found to increase proportionally with the Fe_3O_4 content. Careful modulation of the scaffold's temperature between 50 and 80 °C was achieved by adjusting the magnetic intensity and Fe_3O_4 content. The hyperthermia effect of the scaffolds induced more than 75 % cell death for osteosarcoma cells (MG-63) *in vitro*. These findings highlighted the scaffold's potential for treating bone defects caused by tumors through its combined magnetic and osteogenic properties. Table 2 summarizes some relevant studies discussing 3D-printed scaffolds incorporating NPs utilized for bone cancer therapy.

4. Challenges and future directions

Despite the potential demonstrated by 3D-printed scaffolds in bone cancer therapy, they still face several challenges regarding technology, safety, quality control, regulatory aspects, and their translation into clinical applications. The technological limitations of each 3DP technique have been detailed in Table 1 above; as can be seen from the table, the main limitation across different techniques is the risk of drug degradation and the incompatibility of some techniques with heat-sensitive active pharmaceutical ingredients (APIs) [16,37,99]. Choosing the appropriate ink is crucial for 3DP, as it has to fulfill the safety and biocompatibility requirements [100]. Many materials have been employed as 3DP inks, but some can deteriorate or generate toxic substances when heated, extruded, or fused. For instance, certain biodegradable polymers, such as polyglycolic acid (PGA), are commonly used in 3DP for their biocompatibility and biodegradability. However, during the 3DP process, if the temperature and printing conditions are not properly controlled, these polymers can degrade, leading to the generation of harmful substances including particulate matters (PM) and volatile organic compounds (VOCs) such as, toluene, aldehydes, and ethylbenzene. Acrylonitrile butadiene styrene (ABS), a widely used thermoplastic, was also found to emit VOCs during the printing process [101]. Polylactic acid (PLA) is a frequently used biodegradable polymer. However, its hydrophobic nature may impede cell adhesion and proliferation, and also result in the release of acidic by-products during the degradation process [101,102]. Surface treatments have been applied to alter the structure and surface chemistry of PLA, enhancing the hydrophilicity and promoting the attachment of cells and biological compounds to PLA-based structures [102]. Plasma treatment is one of the most investigated methods developed to enhance the surface chemistry of PLA-based parts without affecting their overall properties [103]. Moreover, the crosslinking process involved in forming hydrogel structures can sometimes produce toxic residues or unreacted monomers that may be harmful to the cells or tissues they come into contact with. For example, chemical crosslinking using glutaraldehyde (GA) can lead to cytotoxicity and dysfunction in cells because the GA crosslinking mechanism is a highly nonspecific process that involves most of the lysine residues distributed on the surface of the protein. Ethyl-dimethylaminopropyl-carbodiimide hydrochloride (EDC) can be used as a chemical cross-linking agent to overcome this cytotoxicity since EDC can easily be washed away as a water-soluble urea derivative [104,105]. Although physical crosslinking can avoid the toxicity of the crosslinking agent and the possible interaction between the crosslinking agent and the drug, physically crosslinked hydrogels tend to have low strength and can cause protein denaturation [104,106]. To address these concerns, scientists are actively working on refining printing parameters, exploring innovative crosslinking methods, and developing more stable biomaterials. Their goal is to enhance the safety and effectiveness of 3D-printed biomaterials inks. Enzymatic crosslinking, an emerging

Table 2
Summary of studies discussing 3DP composite scaffolds employed for bone cancer therapy.

Payload	NPs type	3DP technique	Scaffold material	Stimulus	Main Findings	Ref.
–	Fe and Mg NPs	Cryogenic micro-extrusion	PDA	NIR	- Fe^{+3} and Mg^{+2} ions enhanced antitumor effects and stimulated bone regeneration.	[84]
BMP-2 and VEGF	–	LbL deposition	HAP, gelatin, and chitosan	–	-ALP activity significantly improved, i.e., the differentiation to osteogenic cells was enhanced considerably.	[88]
BMP-2 and CT	pZIF-8 nanoMOFs and PDA-decorated- pHA NPs	FDM	Gelatin incorporated with PDA-hybridized	pH	-Incorporation of nanoMOFs improved drug loading and release. -Tumor microenvironment responsive device.	[65]
Curcumin	Liposomes	Binder jetting	Calcium phosphate	–	-MTT results showed 70 % lower cell viability. -ALP assay exhibited higher osteoblast-differentiating ability in the presence of liposome-encapsulated curcumin.	[72]
BMP-2	–	PAM	HAP, chitosan and PVA	–	-The group with 15 wt% HA demonstrated superior mechanical properties. -The 15 wt% HA scaffold showed good biocompatibility and enhanced the attachment and proliferation.	[89]
Aspirin	Liposomes	–	PCL	–	-The composite scaffold exhibited 3-times higher bone volume than the bare scaffold.	[90]
–	Fe_3O_4 NPs	SLS	Polyglycolic acid	Magnetic field	-*In vivo* results revealed that bone regeneration was accelerated with the incorporation of Fe3O4 NPs in the scaffold (bone mineral density = 515 ± 50 mg/cc, and 326 ± 15 mg/cc, in addition, the percentage of bone volume/tissue volume = 92 ± 3.5 %, and 73 ± 5.2 % with NPs and without NPs respectively).	[91]
5-fluorouracil	–	Semi-solid extrusion-based 3D-printer	Calcium phosphate cement, SOL, and PEG	–	-*In vitro* release studies showed that almost 100 % of the drug was released within 2 h for all scaffolds. -Inhibition of cancer cell growth after 5 days.	[92]
5-fluorouracil	–	Drop-on-powder	$CaSO_4$ hydrates, vinyl polymer, and 2-pyrrolidone	–	-*In vitro* release studies showed that about 90 % of the drug had been released from polymeric solutions in 2hrs.	[93]
–	Cu-TCPP MOFs	Extrusion	TCP	NIR	-NIR irradiated scaffolds eliminated osteosarcoma cells and promoted bone regeneration *in vivo*.	[86]
–	MoS_2 nanosheets and HA-NPs	–	PEEK	NIR	-The incorporation of NPs in combination with PTT enhanced adherence and proliferation of bone cells.	[94]
–	CaO_2 and Fe_3O_4 NPs	Extrusion	AKT	Magnetic field	-CaO_2 NPs loaded into AKT scaffolds featured distinct bone-regeneration capabilities due to the release of Ca^{2+} ions. -Magnetic hyperthermia was enabled by Fe_3O_4 NPs and created a synergistic effect with H_2O_2 self-sufficient catalytic therapy of osteosarcoma with enhanced bone-regeneration bioactivity.	[95]
–	BCN nanosheets	Extrusion	AKT	NIR	-BCN-AKT scaffolds caused a tumor clearance rate of 89 % *in vitro*. -BCN-AKT scaffolds showed higher expression of osteogenesis genes *in vitro* and *in vivo*, indicating higher bone regeneration capability.	[96]
–	Nb_2C MXene S-nitrosothiol-grafted mesoporous silica	Bioplotting	Bioactive glass	NIR	-Controlled NO release upon irradiation. -The scaffolds enhanced tumor ablation and increased bone regeneration *in vitro* and *in vivo*.	[97]
Curcumin	Polymeric micelles	Binder jetting	TCP	–	-The developed scaffold exhibited a4-fold increase in hFOB cell proliferation, and a 73 % increase in hFOB cell differentiation. -The scaffold resulted in 61 % lower viability compared to the control.	[73]
DOX	$SrCuSi_4O_{10}$-β-TCP core/shell filaments	Extrusion	Gelatin	NIR	-The *in vitro* and *in vivo* data demonstrated that chemo-photothermal therapy showed a synergetic effect on bone tumors.	[85]
–	Fe_3O_4 NPs, graphene oxide nanocomposites	–	TCP	Magnetic field	-The hyperthermal effect of the scaffolds induced more than 75 % cell death for osteosarcoma cells (MG-63) *in vitro*.	[87]
–	Magnetic graphene oxide @Fe_3O_4 NPs	Extrusion	PVA/SA/HA	Magnetic field	-Adding MGO@Fe_3O_4 NPs to the prepared composite scaffolds improved the biological functions and supported the differentiation of rat BMSCs *in vitro* and showed favourable anti-tumor effects *in vivo*.	[98]

*__TCP/PLGA__, β-tricalcium phosphate/poly(lactic-co-glycolic; __PDA__, Polydopamine; __HAP__, Hydroxyapatite; __PVA__, Poly(vinyl alcohol); __PCL__, Polycaprolactone; __SLS,__ selective laser sintering; __TCP__, β-tricalcium phosphate, __PEEK__, Polyether-ether-ketone; __PTT__, Photothermal therapy; __AKT__, Akermanite ($Ca_2MgSi_2O_7$); __BMP-2__, bone morphogenetic protein 2; __LbL__, Layer-by-layer; __pZIF-8 nanoMOFs__, nanosized zeolitic imidazolate framework-8; __pHA NPs__, hydroxyapatite nanoparticles; __ALP__, alkaline phosphatase; __BCN__, Borocarbonitrides; __PVA/SA/HA__, Polyvinyl alcohol/sodium alginate/hydroxyapatite.

method in hydrogel production, presents numerous benefits, including rapid gelation time, mild aqueous reaction conditions (e.g., physiological temperature), as well as controlled physicochemical properties. Various enzymes, such as horseradish peroxidase, transglutaminase, tyrosinase, phosphopantetheinyl transferase, and lysyl oxidase, have been employed for this purpose, demonstrating the diverse enzymatic options available. However, the careful selection of enzymes is crucial, because using enzymes for crosslinking may introduce unforeseen biological changes *in vivo* [107]. Therefore, it is essential to take sufficient safety measures and adhere to the standard guidelines to reduce the risk of exposure to harmful substances. Rigorous testing and validation protocols should be established to assess the safety and biocompatibility of the printed constructs before their application in various biomedical and research settings [37,108].

Furthermore, various obstacles can hinder the implementation of 3DP technology in hospitals. First, establishing 3D printers in hospitals is expensive and demands proficient technical operators to manage the technical procedures on the premises. Second, maintaining the standard of the printed drug forms is another challenge, especially since there is currently no regulatory framework governing 3D-printed drugs. In 2017, the FDA released guidelines that outlined the regulatory standards for medical device manufacturing using 3DP. Currently, only one 3D-printed pharmaceutical product (Spritam®) has received FDA approval [109], and it is unclear whether regulatory approval will only be limited to the final product or will apply to all aspects of the product's design and manufacturing stages [32,37,110]. Complex UK and EU regulations, along with safety, scalability, and production challenges at the regional level, have posed obstacles for both regulators and applicants, especially since many developments arise from academic institutions rather than businesses. The European Commission's implementation of the Advanced Therapy Medicinal Products (ATMP) regulation (EC 1394/2007) and directive 2009/120 aimed to standardize market availability in the EU and provide marketing authorization guidance, including definitions for these novel technologies [111]. Therefore, improved communication between regulatory bodies and organizations that produce and market tissue engineered products (TEPs) for clinical purposes is vital to effectively tackle these challenges [112]. Furthermore, institutions that adopt such therapies must show their readiness to address the increasing need for these services, including logistical elements such as appropriate transportation, storage, and nearby manufacturing facilities. Additionally, these facilities should be equipped to source donor and autogenous tissue for bioprinting, possibly through collaboration with established clinical organizations, such as blood and transplant services, which manage tissue handling and recipient preparation [112,113]. The importance of incorporating well-designed clinical trials into the regulatory process cannot be overstated. Conducting rigorous clinical trials within hospital settings allows for the comprehensive evaluation of the safety and efficacy of 3D-printed products in real-world patient populations. By implementing well-structured clinical trials, hospitals can gather vital data on the effectiveness and potential risks associated with these innovative therapeutic interventions [114]. However, concerns regarding clinical trials stem primarily from the ethical concerns of testing tissue-engineered organ transplantation on healthy volunteers and the complexities associated with determining the impact of patient-specific cell populations on treatment outcomes versus the bioprinted product. Challenges arise from the inability of patients to withdraw post-implantation and obtaining consent for trial participation becomes problematic when the severity of the problem is unknown. These factors present additional obstacles in trial organization. Consequently, it is necessary to establish a valid and all-encompassing method for assessing the impact of bioprinted interventions before initiating any valuable clinical trials in this field [112,115]. With the rise of artificial intelligence (AI), some researchers are suggesting integrating AI and predictive models into 3DP to ensure the quality, uniformity, release profile, and concentration of the loaded drug(s) [116,117].

As mentioned above, an area of research that is gaining popularity is the use of stimuli-responsive biomaterials in 3DP technology to produce multifunctional products incorporating NPs capable of responding to stimuli or providing diagnostic and therapeutic, i.e., theranostic applications. This trend is expected to expand rapidly in the upcoming years [37,40,118,119]. Despite the reported success in literature, further investigation is still needed to develop biomaterials with sufficient complexity to accurately emulate the bone microenvironment. In the context of bone cancer, the ideal biomaterials would have the ability to sense the most suitable bioactive molecules to release into the tumor microenvironment, thereby achieving successful tumor elimination and tissue regeneration following surgical removal [40,118,120]. In addition, the choice of NPs to be incorporated into the scaffolds is also highly affected by the 3DP method to be used [121]. Incorporating NPs into the printing process might reduce the printing efficiency or place additional demands on the 3D printer [44]. For instance, in SLA, the presence of NPs in the ink reservoir affects light penetration and scattering, resulting in a significant decrease in printing speed [63,122]. Other issues caused by the incorporation of NPs in the 3DP ink include uneven spreading of ink, difficulties in controlling the ink viscosity, and agglomeration [44,63,122]. Additionally, the toxicity and biodegradability of NPs are commonly raised issues when NPs remain in the body for extended periods. Freely circulating NPs can be cleared effectively through the kidney or GI tract to reduce long-term toxicity risks [123–125]. However, NPs incorporated in 3D-printed scaffolds pose the extra challenge of releasing the NPs from the scaffold before they can be cleared from the body, hence reducing their effective biodegradability [63,126,127]. A possible approach to address these limitations is to focus more on organic NPs, such as liposomes, micelles, dendrimers, and solid-lipid NPs, because they have lower toxicity and higher biocompatibility than inorganic NPs [63,128,129]. Moreover, adding NPs into 3D-printed scaffolds introduces complexities in terms of fabrication and processing, which would increase the costs of production and limit their applications in clinical settings [130,131].

The concept of incorporating stimuli-responsiveness in 3D-printed structures has led to the development of an intriguing technology known as four-dimensional printing (4DP) [81]. 4DP evolved from 3DP; therefore, the printing steps and printing methods are similar to 3DP; however, compared to 3DP, this technology adds one more dimension, i.e., time, to the product [129,132,133]. 4D- printed structures can 'fold' or 'unfold' into predetermined shapes in response to specific triggers, including temperature, pressure, humidity, light, magnetic and electric fields [133]. Smart materials that generate 4D-printed structures for biomedical applications include shape-memory alloys and polymers, electroactive polymers, magnetic shape-memory alloys, and smart hydrogels [134,135]. However, 4DP is a relatively new technology, and several aspects need to be further studied and researched. For instance, high-resolution printing techniques are needed to ensure precise shape fabrication and movement, limiting the choice of 3DP methods that can be employed [129]. Moreover, at present, the deformation of 4D-printed structures is relatively basic, often limited to simple actions like folding, which falls short of fulfilling the intricate requirements in clinical applications. The activation/de-activation of these responses needs to be precisely controlled since it introduces an added risk in case the structure does not behave or change its shape as required [81,132]. Smart materials used in 4DP introduce complexities in processing and fabrication that would significantly increase the costs of translating this technology into clinical applications [120]. Additionally, for 4D-printed scaffolds to be widely accepted, the manufacturing process must be both cost-effective and time-efficient. Unfortunately, existing 4DP methods have limited scalability rendering them impractical for large-scale manufacturing. Scalability is a challenge for both 3DP and 4DP bone scaffold because the printed scaffolds need to be customized or personalized to cater to the diverse needs of patients which would increase the time and costs associated with the process [136]. Nonetheless, 4DP is presenting new possibilities in biomedical engineering and is

expected to act as a versatile toolset to address medical challenges by acknowledging the dynamic nature of both the human body and the scaffold used.

5. Conclusion

Many challenges still limit the success and effective treatment of bone cancer using existing methods. The emergence of 3DP and its rising popularity in the biomedical and pharmaceutical fields promises safer and more effective treatment opportunities by enabling the development of novel scaffolds loaded with chemotherapeutics and growth factors. These scaffolds support, stimulate bone regeneration, and enable targeted delivery of drugs. In addition, embedding NPs in these scaffolds, with their unique physicochemical properties, results in versatile bone implants with improved mechanical attributes and drug delivery capabilities. Although this technology is still in its infancy, it appears to be a groundbreaking tool and is expected to revolutionize bone cancer therapy in the near future.

Ethical compliance

Not applicable.

Declaration of competing interest

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

Data availability

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

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