ECRONICON OPEN ACCESS

EC ORTHOPAEDICS
Review Article

Nanocomposite Scaffolds for Bone Regeneration, Infection Treatment and Bone Cancer Therapy

Christos D Veros[1] and Dionysios E Mouzakis[2]*

[1]*Medical School, National and Kapodistrian University of Athens, Athens, Greece*

[2]*Department of Mathematics and Engineering Sciences, Hellenic Army Academy, Greece*

***Corresponding Author:** Dionysios E Mouzakis, Department of Mathematics and Engineering Sciences, Hellenic Army Academy, Varis, Koropiou (Evelpidon) Avenue GR-16673, Vari - Greece.

Received: March 27, 2019; **Published:** April 30, 2019

Abstract

Nanocomposite-based scaffolds have been used for many years for bone tissue engineering. Their utilization covers an extended field of bone pathological conditions and a variety of different types of nanocomposites and scaffold types. Plenty of scientific works have been published regarding their characterization and activity. The compilation of the research work done on this interesting, but chaotic field is not an easily accomplishable task. This review aims to concentrate and organize the use of nanocomposite scaffolds, with respect to the major clinical fields, where they are utilized and their intrinsic characteristics, which make them a very promising clinical tool in the future of orthopedics.

Keywords: *Scaffolds; Polymers; Chitin; Chitosan; Nanoceramics; Bone Regeneration; Infection; Bone Tumor; Graphene; SPIONs; Bioglass; Growth Factors; Antimicrobial; Hyperthermia; Drug Delivery*

Abbreviations

PMMA: Poly(Methyl Methacrylate); 3D: Three Dimensional; HA: Hydroxyapatite; SEM: Scanning Electron Microscopy; XRD: X-Ray Diffraction; VEGF: Vascular Endothelial Growth Factor; HIF-1a: Hypoxia-Inducible Factor 1-Alpha; SPIONs: Superparamagnetic Iron Oxide Nanoparticles; PLA: Polylactic Acid; BMP-2: Bone Morphogenetic Protein 2; MBG: Mesoporous Bioglass; MS: Mesoporous Silica; FGF-18: Fibroblast Growth Factor 18; miRNA: Micro RNA; MG-63 Cell Line: Bone Osteosarcoma Cell Line; BG: Bioglass; 2D: Two Dimensional; NIR: Near Infrared; ROS: Reactive Oxygen Species

Introduction

The skeleton plays a central role in supporting the human body and enabling movements to take place. Bones are a highly dynamic tissue, which consists of two separate, but complement phases; an organic, living phase, which includes osteoblasts and several proteins and an inorganic phase, primarily made of hydroxyapatite [1]. Bone injury can occur through mechanical, metabolic and inflammatory agents, along with incidents, such as fractures and diseases, including several tumors, osteoporosis and osteomyelitis, among others. The extent of the arising defect predetermines the self-healing ability of the bone tissue. Nowadays, it is known, that bones with large defects cannot initiate their recovery, as happens when smaller defects take place, for which bone remodeling is the normal process for healing [1,2].

Many different materials have been used for years, in order to artificially remodel large bone defects and enhance their recovery, including PMMA cement, and various metals, such as stainless steel, titanium and cobalt alloys. However, these materials are not bioresorbable, they are brittle and can lead to immunogenic reactions from the host. Hence, scientists today conduct research on nanotechnological and nanomedical approaches to this issue, in terms of manufacturing biocompatible 3D scaffolds. It is attempted that they mimic natural

bone extracellular matrix, which may even include living osteogenic cells and signaling molecules, to provide a more targeted and effective bone regeneration [1]. An optimal 3D scaffold should encompass inter-connective pores, in order to provide the appropriate microenvironment for osteogenic cell migration, differentiation and proliferation. It is known that pores serve as sites of bone mineralization, nutrient and growth factor reservoirs and they can also promote infiltration by osteogenic cells [3]. Additionally, the mechanical properties of the scaffolds should resemble those of the normal bone. The most common biomaterial, that is being used in manufacturing 3D scaffolds is bioactive hydroxyapatite (HA), as seen below [2].

Apart from bone regeneration, a central problem that many orthopedic patients confront is the development of serious bone infections, which are rather difficult to heal and require long term treatment with intensive employment of antimicrobial regimes and surgical debridement. As a result, osteomyelitis emerges as a major challenge for clinicians. Especially when there are implanted orthopedic materials in the site of infection, it is possible that recovery cannot take place, unless these implants are totally removed. Therefore, it is crucial to manufacture orthopedic scaffolds that not only enhance bone regeneration, but also release high concentrations of antibiotics in order to prevent infection, sterilize the surgical site and prevent the creation of bacterial biofilms [4].

A similar principle applies to malignant bone tumors. These are primarily metastatic in nature, deriving mostly breast and prostate cancers. Primary bone tumors are rare. Bone metastases severely affect quality of life, since they are accompanied with pathological fractures and constant pain and they indicate advanced disease with poor prognosis. Modern surgery, chemotherapy, radiotherapy and immunotherapy are common, but their results are not satisfactory. Thus, localized drug delivery through implanted nanocomposite scaffolds and their application in hyperthermia provide new and promising fields of research [5,6]. In this review, we present a thorough approach of the experimental applications of 3D nanocomposite scaffolds in bone tissue engineering, infection treatment and bone cancer therapy.

Bone tissue regeneration

Polymer scaffolds

As mentioned above, there is great need for manufacturing biocompatible 3D scaffolds, that will assist bone repair and regeneration in a wide variety of pathological situations. Hydroxyapatite (HA) plays a central role and can be combined with a variety of other materials, to improve its efficacy. Deepthi., *et al.* suggest chitin and chitosan as highly advantageous materials in terms of nanocomposite scaffold manufacturing. These two materials are easy to manipulate and create various forms, such as nanobeads, nanogels, nanoparticles, nanofibers and highly-porous nanoscaffolds, which enable bone formation *in vitro* and *in vivo*. Although HA alone is not very efficient in bone defect treatment and chitin or chitosan alone do not enhance cell proliferation to a great extent, these materials, when combined, can act as a template for the engineering of bone tissue. Indeed, it has been shown, that the addition of HA in polymeric chitin or chitosan matrices enhances osteoconductiveness, cell differentiation and proliferation. These two polymers resemble the extracellular matrix of the bone, while HA functions as the mineralized tissue. Chitosan and nanoHA composites lead to significant increase in the viability, attachment, differentiation and proliferation of osteoblastic cells. Furthermore, it has been shown that the addition of chitosan in nanoHA leads to better mechanical behavior, as it reduces the resorption of HA and prevents the migration of HA nanoparticles away from the scaffold after its implantation, due to better viscoelastic characteristics. Finally, since the composites are smoother than plain HA, no soft tissue damage takes place around the implant [7].

In a study conducted by Domingos., *et al.* a nanocomposite hydroxyapatite and polycaprolactone scaffold was manufactured and was compared to a microHA-polycaprolactone scaffold. It has been shown that nanoscale dimensions offer optimal characteristics, since the nanocomposite scaffold increased the adhesion of mesenchymal cells. Also, the nanoHA scaffold indicated higher cell viability and alkaline phosphatase activity, which is an indicator of bone formation. On the other hand, HA microparticles formed aggregations, as observed by SEM, reducing cell-to-cell contact and rendering microcomposite scaffolds ineffective [8].

Another combination included the formation of chitosan-gelatin-nanoHA scaffolds, which were created by Peter and his colleagues. His team proved, that these scaffolds are biocompatible and increase osteoblast adhesion and proliferation *in vitro* [9,10].

Furthermore, Meskinfam and his colleagues investigated nanoHA-polyurethane composites as tissue regeneration scaffolds. NanoHA formed a layer on polyurethane foam, as indicated by XRD, resembling natural bone HA. This biomineralization process, attributed optimal mechanical properties to the scaffold and increased its biocompatibility, promoting cell attachment and proliferation. Furthermore, the polyurethane structure is not expected to degrade fast and produce cytotoxic substances [11].

Nanoceramic scaffolds

The research on inert nanoceramics plays a significant role in scaffold formation. Nanoceramics are an extensive category, which includes titanium, zirconium, aluminum and silica nanomaterials among others. These nanocomposites have high mechanical strength and low corrosion rates. They have proven to promote osteochondral formation and osteogenesis, when they are combined with HA. Doping with metal ions assigns them with novel characteristics. For example, doping with magnesium ions further enhances osteogenesis and bone remodeling. Cobalt ions upregulate VEGF and HIF-1a excretion, which leads to increased vascularization of the newly formed bone tissue. Calcium ions promote enhanced implant integration inside the bone, interacting electrostatically with osteoblasts and influencing their attachment, differentiation and proliferation. Other ions, such as zirconium, strontium, silver, nickel, zinc, copper, molybdenum and tin further widen the possible applications of hydroxyapatite-ceramic nanocomposites [1].

Graphene scaffolds

Many studies have indicated the unique abilities of graphene, regarding the improvement of the biological performance of scaffolds and the promotion of adhesion and proliferation of osteoblasts, primarily due to the aromatic structure of plain graphene and graphene oxide. Shadjou., *et al.* manufactured a gelatin-nanoHA scaffold matrix, within which graphene oxide nanoflakes were incorporated. The integration of graphene oxide in the scaffold decreased its brittleness. Later, this scaffold was trialed in cell culture experiments, in two forms. One form included the graphene oxide containing scaffold and the other included the plain gelatin-nanoHA scaffold. Results showed that graphene oxide initiated high osteogenic stem cell differentiation. The same result was obtained by plain gelatin-nanoHA scaffolds only when cells were provided with additional nutritional supplements, including L-ascorbic acid, β-glycerophosphate and dexamethasone [12].

Scaffolds including SPIONs

Several studies suggest the incorporation of SPIONs within the structure of nanocomposite scaffolds, as a way to increase bone formation. The presence of SPIONs is believed to regulate gene expression and activate the MAPK signal pathway, which is involved in osteogenic cell differentiation. Also, the attachment of magnetic nanoparticles on scaffolds is rather easy and is achieved by simple dip-coating of the scaffolds into aqueous solutions, which contain SPIONs. After dip-coating, these are easily integrated into the scaffold pores [13]. In a previous study, gelatin scaffolds, which contained SPIONs were implanted in a rat model. Results have shown enhanced bone regeneration, and better performance of osteoblasts, as compared to rats with gelatin scaffolds without SPIONs. These iron oxide nanoparticles have also proved to have an angiogenetic activity [14].

Another approach suggests the application of external magnetic fields, as well, since these can change the size, charge and other features of SPIONs. Indeed, the magnetic field has shown to increase magnetic nanoparticle accumulation in mesenchymal cells, by inhibiting their release from them. It was also observed that the more nanoparticles a cell included, the greater its osteogenic differentiation was [15,16].

Similar results were obtained by Meng and his team. They created a nanofibrous scaffold, consisting of SPIONs, nanoHA and polylactic acid (PLA). Then the scaffold was implanted in rabbit bone defects and magnets were attached around the cage. The scientists observed better regeneration and bone remodeling, compared with rabbits, whose cages were not surrounded by magnets [17].

Delivery of osteogenesis-promoting factors

Many scaffolds have been employed by scientists to transfer signaling molecules and osteoinductive growth factors in diseased sites and enhance bone formation. The goal is to achieve controlled release of growth factors for specific duration and elicit cellular reactions, that could lead to osteogenic differentiation, bone formation and vascularization of the site. One such factor that has proven to promote

osteogenesis is bone morphogenetic protein 2 (BMP-2). This has successfully been incorporated in mesoporous bioglass (MBG) and mesoporous silica scaffolds (MS), which were doped with magnesium. Results regarding bone regeneration were excellent [3]. In a similar experiment, $CaOP_2O_5$-silica mesoporous scaffolds were manufactured and loaded with BMP-2 growth factor and were able to induce differentiation and proliferation of rabbit mesenchymal cells *in vitro* [18].

Another scientific group proposed the incorporation of more than one growth factors in nanofibrous scaffolds [19]. Also, mesoporous bioactive glass nanospheres have been employed to deliver fibroblast growth factor 18 (FGF18) [3].

Apart from growth factors, miRNA has also been examined as a possible enhancer of bone tissue engineering. MiRNAs are small and non-coding molecules, which can bind on targeted mRNAs. MiRNA-590-5p specifically, is implicated in osteogenic differentiation. It targets and deactivates Smad7, which is a negative regulator of osteoblast function. Balagangadharan., *et al.* formed a triple polymer-nanoceramic-hydroxyapatite nanocomposite scaffold, consisting of chitosan, nanoHA and nano-zirconiumdioxide, which then was loaded with miR-590-5p miRNA molecule. The arising scaffold showed no significant cytotoxicity and promoted osteoblast differentiation of mouse mesenchymal stem cells [20].

Scaffolds and cell conditioning

Samadikuchaksaraei., *et al.* examined the effect of osteoblast conditioning on nanoHA-gelatin nanocomposite scaffolds, regarding their properties, behavior, biocompatibility and biodegradation after implantation. The first step included the fabrication of the nanoHA and gelatin scaffold, followed by the culture of osteoblasts on its surface and their subsequent elimination by repeated freezing and thawing. This scaffold showed optimal effects regarding cell adhesion and growth. Later, it was implanted in rats with critical size calvarium bone defects and it was proved, that the conditioning process further enhanced its biocompatibility and accelerated collagen formation [21].

Antimicrobial 3D scaffolds

Since scaffolds allow for their surface and internal modification, due to their structure and reactive moieties, it is easy to functionalize them with antibiotics or other antimicrobial substances, in order to prevent or tackle infections. In a study conducted by Han., *et al.* titanium scaffolds were constructed and functionalized with oxidized alginate nanoparticles, which were connected with vancomycin molecules. The study showed, that *Staphylococcus epidermidis*, a common pathogen for osteomyelitis, was seriously inhibited. As a result, vancomycin-including scaffolds have been suggested for the prevention of infection during bone defect healing [22].

A very interesting approach includes the use of silver ions for their antibacterial properties. Jiang., *et al.* created nanoHA-polyurethane scaffolds, which were functionalized with Ag3PO4. Silver ions were being released for more than 3 weeks, in a concentration- and time-dependent way. The scaffolds showed good biocompatibility and strong antimicrobial action. In all conducted experiments, the bacteriostatic rate against *Staphylococcus aureus* and *Escherichia coli* was more than 90%. This effect can be explained, since silver ions are absorbed on the bacterial cell wall, react and denaturate its proteins. This phenomenon creates permeable pores on the bacterial cell wall, which leads to internal accumulation of external fluids and cell death [4].

3D scaffold for tumor therapy

3D scaffolds and antitumor drug delivery

Nanocomposite scaffolds can also function as drug delivery systems for antitumor drugs in the diseased site. Shoaib and his colleagues loaded a mesoporous nanobioglass scaffold with imatinib molecules. Imatinib is an antitumor agent, which can be utilized in the treatment of several cancer types, including bone cancer. The scientific group studied the pH-dependent kinetics of imatinib release and the antitumor activity on MG-63 osteosarcoma cell line. Results showed that the scaffold pores played a significant role not only in drug loading, but also in release kinetics. During the first day, the release was burst-like. In that case, it can be utilized for patients with urgent need

for chemotherapeutic delivery. When adjusting pH, drug release can be modified. Maximum release of the drug was observed at pH 4.4, which is close to the pH conditions of the tumor sites. Increasing pH decreases drug release. As a result, this scaffold can be described as a pH-responsive drug delivery nanosystem. The drug-loaded scaffold had a great inhibitory effect on osteosarcoma MG-63 cells [5].

3D scaffolds and hyperthermia

Nanoceramic scaffolds have proved to possess antitumor activities, as well, apart from regeneration capability. As a result, they can be applied after surgery, to regenerate bone formation in the site of defect and simultaneously destroy the residual tumor. Several nanoceramic scaffolds can be utilized for photothermal or magnetothermal therapy, killing only malignant cells and sparing normal ones. The achieved high temperatures lead to protein denaturation, cell damage and apoptosis or necrosis [23].

Photothermal performance can be enhanced by MoS2 nanoparticles on nanoceramic scaffolds, as shown in previous experiments by Wang., *et al.* MoS2 nanosheets display intense and localized surface plasmon resonance effect, which leads to local increase in tissue temperature. These nanosheets, apart from phototherapy, proved to increase rabbit mesenchymal cell adhesion and proliferation [24].

Additionally, other studies showed that bioglass scaffolds can be functionalized with CuFeSe2 nanocrystals and achieve excellent photothermal effect. The simultaneous release of Cu, Se and Fe ions promotes rabbit bone marrow mesenchymal stem cell development. As a result, the scaffold presents a bifunctional effect; antitumor activity and bone regeneration enhancement [23]. Other ions, such as Mn and Co can be also used to dope nanobioglass scaffolds. Liu., *et al.* created such scaffolds, doped with Cu, Fe, Mn and Co. All of them displayed photothermal activity, with the following trend: Cu-BG > Fe-BG > Mn-BG > Co-BG. Cu-BG, Fe-BG and Mn-BG scaffolds inhibited tumor growth *in vitro* and *in vivo*, while Fe-BG and Mn-BG scaffolds also enhanced normal bone formation [25]. In another study, 3D-printed nanobioglass scaffolds were functionalized with 2D black phosphorus nanosheets and were examined for their photothermal activity in tumor-bearing mice xenografts. Mice were divided in 4 categories: those which received only bioglass scaffolds, those that received bioglass scaffolds and were beamed with NIR irradiation, those which received bioglass-black phosphorus scaffolds and those that received nanoglass-black phosphorus scaffolds and were irradiated with NIR irradiation. In the last group, a strong hyperthermal effect was observed and temperature rose up to 58 degrees. Tumors in this group were totally eliminated, without recurrence after 14 days, in contrast to the other groups [26].

Furthermore, photothermal therapy can be combined with reactive oxygen species (ROS) formation for achieving a better synergistic effect. $CaSiO_3$-Fe nanocomposite scaffold are an example, both *in vitro* and *in vivo* [27].

Multifunctional scaffolds

A significant advantage of nanotechnological carriers is the simplicity and convenience of their functionalization, to an extent, that they can obtain novel attributes, by encompassing not only one, but several different molecules on their surface or inside their structure. Bifunctional nanocomposite scaffolds have already been described before, but multifunctionality is a reality as well [28].

Lu and his colleagues functionalized a nanocomposite scaffolds with antitumor, antibacterial and bone regeneration effects, all encompassed in one single structure. The scaffolds consisted of chitosan, nanoHA and zolendronic acid. *In vitro* studies showed significant upregulation of proapoptotic genes and reduction of the osteoclastic activity of the giant cell tumor. These included the activation of the Caspase-3 signal pathway and is attributed to the zolendronic acid. A very interesting observation was that zolendronic acid also increased biocompatibility and osseoinductivity. Furthermore, the antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* was obvious [28].

Discussion and Conclusions

In this review, we present all major categories of nanocomposite scaffolds and their biomedical applications. These include extensive clinical fields, such as bone regeneration and tissue engineering, infections and the treatment of malignant bone tumors. Since nanotechnology allows the easy manipulation of the matter, many different materials can be used to create and modify scaffolds, providing them with many different and novel attributes. Such materials include organic polymers, for example, chitin, chitosan, polyurethane and caprolactone and inorganic compounds, such as several nanoceramic materials. Also, many other materials, such as graphene and metallic nanoparticles can be exploited. Still a lot of laboratory research must be conducted, both *in vitro* and *in vivo*, regarding the biocompatibility, effectiveness, biodegradation and toxicity of nanocomposite scaffolds before they can move from bench to bedside and into clinical practice.

Conflict of Interest

There is no financial interest or any other conflict of interest.

Bibliography

1. Sethu SN., *et al*. "Nanoceramics on osteoblast proliferation and differentiation in bone tissue engineering". *International Journal of Biological Macromolecules* 98 (2017): 67-74.

2. Farshadi M., *et al*. "Nanocomposite scaffold seeded with mesenchymal stem cells for bone repair". *Cell Biology International* (2019).

3. Shadjou N and Hasanzadeh M. "Silica-based mesoporous nanobiomaterials as promoter of bone regeneration process". *Journal of Biomedical Materials Research Part A* 103.11 (2015): 3703-3716.

4. Jiang J., *et al*. "Antibacterial nanohydroxyapatite/polyurethane composite scaffolds with silver phosphate particles for bone regeneration". *Journal of Biomaterials Science, Polymer Edition* 27.16 (2016): 1584-1598.

5. Shoaib M., *et al*. "Mesoporous nano-bioglass designed for the release of imatinib and in vitro inhibitory effects on cancer cells". *Materials Science and Engineering C: Materials for Biological Applications* 77 (2017): 725-730.

6. John Ł., *et al*. "Designing of macroporous magnetic bioscaffold based on functionalized methacrylate network covered by hydroxyapatites and doped with nano-MgFe(2)O(4) for potential cancer hyperthermia therapy". *Materials Science and Engineering C: Materials for Biological Applications* 78 (2017): 901-911.

7. Deepthi S., *et al*. "An overview of chitin or chitosan/nano ceramic composite scaffolds for bone tissue engineering". *International Journal of Biological Macromolecules* 93.B (2016): 1338-1353.

8. Domingos M., *et al*. "Three-dimensional printed bone scaffolds: The role of nano/micro-hydroxyapatite particles on the adhesion and differentiation of human mesenchymal stem cells". *Proceedings of the Institution of Mechanical Engineers, Part H* 231.6 (2017): 555-564.

9. Swetha M., *et al*. "Biocomposites containing natural polymers and hydroxyapatite for bone tissue engineering". *International Journal of Biological Macromolecules* 47.1 (2010): 1-4.

10. Peter M., *et al*. "Novel biodegradable chitosan–gelatin/nano-bioactive glass ceramic composite scaffolds for alveolar bone tissue engineering". *Chemical Engineering Journal* 158.2 (2010): 353-361.

11. Meskinfam M., *et al*. "Polyurethane foam/nano hydroxyapatite composite as a suitable scaffold for bone tissue regeneration". *Materials Science and Engineering C: Materials for Biological Applications* 82 (2018): 130-140.

12. Shadjou N., *et al*. "Graphene based scaffolds on bone tissue engineering". *Bioengineered* 9.1 (2018): 38-47.

13. Xia Y., *et al*. "Magnetic field and nano-scaffolds with stem cells to enhance bone regeneration". *Biomaterials* 183 (2018): 151-170.

14. Hu S., *et al*. "Enhanced bone regeneration and visual monitoring via superparamagnetic iron oxide nanoparticle scaffold in rats". *Journal of Tissue Engineering and Regenerative Medicine* 12.4 (2018): e2085-e2098.

15. Shanehsazzadeh S., *et al*. "External magnetic fields affect the biological impacts of superparamagnetic iron nanoparticles". *Colloids and Surfaces B: Biointerfaces* 136 (2015): 1107-1112.

16. Jiang P., *et al*. "Fe(3)O(4)/BSA particles induce osteogenic differentiation of mesenchymal stem cells under static magnetic field". *Acta Biomaterialia* 46 (2016): 141-150.

17. Meng J., *et al*. "Super-paramagnetic responsive nanofibrous scaffolds under static magnetic field enhance osteogenesis for bone repair in vivo". *Scientific Reports* 3 (2013): 2655.

18. Braem A., *et al*. "Novel anti-infective implant substrates: controlled release of antibiofilm compounds from mesoporous silica-containing macroporous titanium". *Colloids and Surfaces B: Biointerfaces* 126 (2015): 481-488.

19. Kang MS., *et al*. "Therapeutic-designed electrospun bone scaffolds: mesoporous bioactive nanocarriers in hollow fiber composites to sequentially deliver dual growth factors". *Acta Biomaterialia* 16 (2015): 103-116.

20. Balagangadharan K., *et al*. "Chitosan/nano-hydroxyapatite/nano-zirconium dioxide scaffolds with miR-590-5p for bone regeneration". *International Journal of Biological Macromolecules* 111 (2018): 953-958.

21. Samadikuchaksaraei A., *et al*. "Fabrication and in vivo evaluation of an osteoblast-conditioned nano-hydroxyapatite/gelatin composite scaffold for bone tissue regeneration". *Journal of Biomedical Materials Research Part A* 104.8 (2016): 2001-2010.

22. Han L., *et al*. "Porous titanium scaffolds with self-assembled micro/nano-hierarchical structure for dual functions of bone regeneration and anti-infection". *Journal of Biomedical Materials Research Part A* 105.12 (2017): 3482-3492.

23. Ma H., *et al*. "3D-printed bioceramic scaffolds: From bone tissue engineering to tumor therapy". *Acta Biomaterialia* 79 (2018): 37-59.

24. X Wang., *et al*. "A 3D-printed scaffold with MoS2 nanosheets for tumor therapy and tissue regeneration". *NPG Asia Materials* 9 (2017): e376-e314.

25. Liu Y., *et al*. "3D-printed scaffolds with bioactive elements-induced photothermal effect for bone tumor therapy". *Acta Biomaterialia* 73 (2018): 531-546.

26. Yang B., *et al*. "2D-Black-Phosphorus-Reinforced 3D-Printed Scaffolds: A Stepwise Countermeasure for Osteosarcoma". *Advanced Materials* 30.10 (2018).

27. H Ma., *et al*. "3D printing of high-strength bioscaffolds for the synergistic treatment of bone cancer". *NPG Asia Materials* 10 (2018): 31-44.

28. Lu Y., *et al*. "High-activity chitosan/nano hydroxyapatite/zoledronic acid scaffolds for simultaneous tumor inhibition, bone repair and infection eradication". *Materials Science and Engineering C: Materials for Biological Applications* 82 (2018): 225-233.

Volume 10 Issue 5 May 2019