Nanostructured bioactive glasses: A bird's eye view on cancer therapy

Nanostructured Bioactive Glass (NBGs): A Bird's Eye View on Cancer Therapy

S. Kargozar, A. Moghanian, A. Rashvand, A.K. Miri, S. Hamzehlou, F. Baino, M. Mozafari, A.Z. Wang

Abstract

Bioactive glasses (BGs) are well-known for their successful applications in tissue engineering and regenerative medicine; moreover, recent experimental studies witness their usability in oncology, too, either alone or in combination with other biocompatible materials (e.g., biopolymers). On this object, direct contact with BG particles was shown to cause toxicity and death in specific cancer cells (bone-derived neoplastic stromal cells) *in vitro*. BG nanoparticles (NBGs) can be doped with anticancer elements (e.g., gallium) to enhance their toxic effects against tumor cells. However, molecular mechanisms and intracellular targets for anticancer compositions of NBGs need more clarification. NBGs have been successfully evaluated for use in various well-established cancer treatment strategies including cancer hyperthermia, phototherapy, and anticancer drug delivery. Overall, the existing results indicate that NBGs not only enhance cancer cell death but can also participate in the regeneration of lost, healthy tissues. However, it seems that the application of NBGs in oncology is in its first stages and numerous unanswered questions should be addressed. For example, the impact of the composition, biodegradation, size, and morphology of NBGs in their anticancer efficacy should be defined for each type of cancer and treatment strategy. Moreover, it should be more clearly assessed whether NBGs can shrink tumors, slow/stop cancer progression, or totally cure cancer. In this regard, the use of computational studies (in silico methods) is highly suggested in order to design the most effective glass formulations for cancer

therapy approaches as well as to predict, to some extent, the relevant properties, efficacy, and outcomes.

Keywords: Bioactive Glass Nanoparticles; Cancer therapy; Hyperthermia; Photothermal therapy; Drug delivery; Oncology; Tissue engineering

1. Introduction

There is a long history of the use of nanoparticles for cancer therapy and diagnostic (theranostic) strategies. As therapeutic and imaging agents, nano-sized particles (1–100 nm) offer outstanding features in oncology such as high surface area-to-volume ratios, enhanced permeability and retention (EPR) effect, and the ease of surface engineering for reducing their nonspecific uptake [1, 2]. Focusing on inorganic materials, iron and gold nanoparticles are among the most evaluated materials for cancer theranostic applications. In this regard, iron oxide nanoparticles (IONs) were previously approved by the USA Food and Drug Administration (FDA) under the name of Feraheme™ (ferumoxytol) for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD) [3]. In addition, superparamagnetic IONS (SPIONs) are being used as a contrast agent for magnetic resonance imaging (MRI) [4]. However, there are some critical limitations ahead of extensive use of IONs in the clinic, including quick removal from the body and thereby need for repetitive administration as well as potential toxicity. Accordingly, other inorganic materials (e.g., bioceramics) have been investigated in order to develop the next generation of inorganic anticancer substances. In this regard, bioactive glass (BG) nanoparticles (NBGs) have achieved huge attention in oncology in recent years.

BGs are amorphous solids that belong to the bioceramics superfamily. The first produced BG, the so-called 45S5 Bioglass®, was developed by Prof. Larry L. Hench and colleagues at the University

of Florida in the late 1960s [5]. This glass with a chemical composition of $45SiO_2$– 24.5CaO– 24.5NaO– $6P_2O_5$ (wt%) is regarded as the parent of silicate-based biocompatible glasses [6]. 45S5 Bioglass® is also known as the first example of the third-generation of biomaterials that can induce particular cellular responses at the molecular level due to the release of ionic dissolution by-products (e.g., SiO_4^{4-} ions) into the surrounding physiological environment [7]. Two other categories of BGs, i.e., phosphate- and borate-based BGs, were later developed for a wide range of biomedical applications [8, 9]. BGs represent multipurpose materials in biomedicine due to their outstanding inherent properties, including excellent biocompatibility, the ability to bond to soft and hard tissues, promotion of angiogenesis and tissue regeneration, as well as antibacterial and anti-inflammatory activities [10]. Having these characteristics, BGs have been extensively employed for the treatment of a broad spectrum of tissue diseases and disorders. In recent years, particular formulations of BGs have been well-proven as effective biomaterials for cancer therapy, as well [11, 12]. On this matter, BG particles were reported to cause toxic effects against giant tumor cells of bone-derived neoplastic stromal cells while they had no significant adverse effect on normal bone marrow-derived stromal cells [13]. Anticancer dopants (e.g., gallium) can be added to the basic composition of BGs to enhance their toxic impacts on cancer cells [14]. In addition, magnetic BGs can be easily prepared by adding magnetic nanoparticles (e.g., iron oxide nanoparticles) to their structure for use in cancer hyperthermia [15]. In some studies, properly-doped BGs were employed for photothermal therapy of cancers due to their ability to develop heat – thus killing cancer cells – upon NIR irradiation [16]. Furthermore, specific formulations of BGs may be utilized for brachytherapy applications after incorporating radioisotopes (e.g., holmium) into their network [17]. It should be highlighted that a subgroup of nano-structured BGs, i.e., mesoporous BGs (MBGs), can also serve as suitable vectors for the loading and delivery of anticancer drugs [18, 19]. Even

more, targeted drug therapy of tumor cells is imaginable by NBGs as regards the possibility of their surface functionalization and modifications by various biomolecules (e.g., folate) [20, 21]. Although there are several *in vitro* studies in the literature that introduce BGs as suitable and potent anticancer substances, still limited studies have dealt with the evaluations of BGs *in vivo* (animal models and clinical trials). Furthermore, the possible applications of BGs for multimodal anticancer therapy are other important issues that are an interesting topic for future studies.

In the present review, we aim to provide a realistic view of the potential of NBGs in oncology according to previously published reports and highlight the main remaining challenges ahead and possible solutions. The first sections of this review deal with the preparation and physico-chemical properties of NBGs and the following sections give an in-depth survey on the potential of NBG in cancer treatment, including cancer hyperthermia, photothermal therapy (PTT), brachytherapy, and targeted drug therapy.

2. Bioactive Glasses (BGs): from Micro- to Nano-Scale

Biomedical glasses can be viewed as mixtures of different inorganic oxides acting as (I) network formers (e.g., SiO_2, B_2O_3, and P_2O_5), (II) network modifiers (e.g., Na_2O, CaO, MgO, and K_2O), and (III) intermediate agents (e.g., Al_2O_3, ZnO, ZrO_2, and TiO_2) (See Figure 1). Depending on the network-forming oxide, BGs are generally categorized into three different types, including silicate-, phosphate-, and borate-based glasses. In silicate-based glasses, SiO_4^{4-} tetrahedron serves as the structural unit, which can be linked to a maximum of four other silica tetrahedra via its corner oxygens. In the case of phosphate glasses, orthophosphate tetrahedron (PO_4^{3-}) acts as the building block and can attach a maximum of three neighboring units to form a 3D network. In borate-based BGs, boron trioxide (B_2O_3) plays the role of the network-forming oxide and the planar BO_3^{3-}

trigonal group forms the structural unit. These three main groups of BGs possess their unique inherent properties; for example, borate-based BGs show higher dissolution rates and apatite-forming ability in physiological fluids compared to silicate BGs, while phosphate glasses can even be fully resorbable in aqueous media.

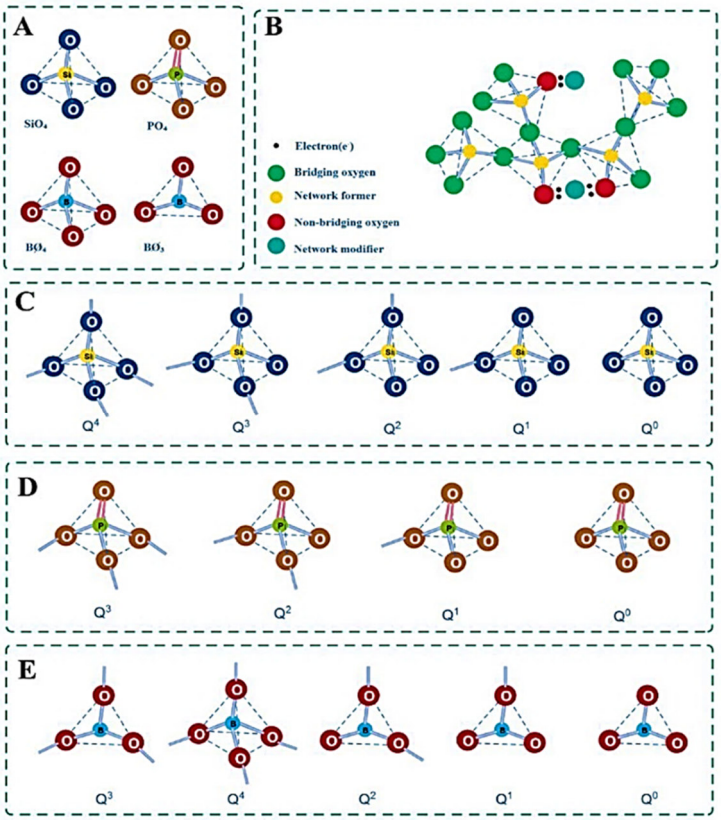


Figure 1. Schematic illustration of structural units of silicate-, phosphate-, and borate-based BGs (A). Bridging oxygens and non-bridging oxygens are present in the silicate glass structure (B). The possible Q^n species in silicate-, phosphate-, and borate-based glasses (C, D, and E, respectively). "n" denotes the number of bridging oxygens. Reproduced with permission from 22.

In general, BGs are synthesized through two well-known methods, i.e., the melt-quenching and the sol-gel routes. The first generation of BGs (45S5 Bioglass®) was developed via the traditional

melt-quenching technique by Prof. Lary L. Hench at the University of Florida (USA) 5. In the melting process, desired amounts of the glass precursors (oxides, fluorides, carbonates, etc.) are placed in a crucible (typically a platinum crucible to avoid contaminations) and heated in an electrical furnace at high temperatures (between 1000 °C and 1500 °C, depending on the composition) 23. The whole process is usually straightforward with reasonable economic justification, especially in the case of simple formulations like 45S5 Bioglass®. However, some cautions should be considered when synthesizing melt-derived glasses. The first one is related to the potential risk of contamination with the crucible elements and thereby the presence of impurities in the final glass product 24. Additionally, it is difficult to precisely control the final product characteristics (e.g., particle shape and size). Moreover, expensive and special equipment (e.g., high-temperature electrical furnaces) is necessary for producing melt-derived BGs 24. It should be noted that the final BG products obtained by the traditional melt-quenching method are either cast bulk pieces or microparticles (from a "frit" in water) with a dense structure, which usually need additional processing (e.g., milling and polishing) for biomedical applications. As an illustration, top-down approaches (e.g., ball milling) are commonly applied to break down the bulk glass into nanometer particles to produce more potent materials in terms of tissue engineering and cancer therapy.

The production of homogenous BG particles by the sol-gel method was introduced by Li et al. in 1990 6. This method is based on wet chemistry in which an inorganic network is formed through mixing organic precursors (e.g., organometallic alkoxides) in a solution. For instance, tetraethyl orthosilicate (TEOS) and triethyl phosphate (TEP) are used in the synthesis procedure as the precursors of the network formers for silicate and silico-phosphate BGs. Besides, nitrate or carbonate salts may be added to the reaction as the precursors of the network modifiers (e.g., Na_2O

and CaO). After the preparation of the sol, the gelation process begins and is followed by the aging and initial thermal treatment of the produced gel. Finally, the drying step (thermal treatment at 500–900°C) is performed in order to remove the sub-products (e.g., nitrate ions) from the gel. The resulting BG particles are at the nanometer scale and possess an inherent mesoporous (pore range 2-50 nm) or even microporous structure (pore diameter below 2 nm) [25]. It should be mentioned that the properties of the resulting glass particles may vary based on the applied synthesis condition, i.e., the acidic or basic (e.g., Stöber method) conditions [26, 27]. In acidic conditions (pH < 2.5), a weakly branched polymeric sol is formed which then is cast and milled to achieve glass particles [28-30].

In 2004, Yan et al. introduced a new generation of sol-gel silicate BGs, named ordered mesoporous BGs (MBGs), through the combination of the sol-gel technique with supramolecular chemistry. In this regard, a structure-directing agent (e.g., cetyltrimethylammonium bromide (CTAB), F127 (EO_{106}-PO_{70}-EO_{106}), or P123 (EO_{20}-PO_{70}-EO_{20})) is used in the sol-gel process and then an evaporation-induced self-assembly (EISA) stage follows in order to form self-organized spherical or cylindrical micellar structures. The whole process leads to produce nanosized glass particles with a well-ordered porous structure (pore diameters ~ 2–50 nm) with well-defined arrangement and symmetry (e.g. hexagonal, cubic etc.). Having well-ordered pores, nanostructured MBGs were proven as suitable platforms for drug delivery applications. In addition, the sol-gel glasses exhibit superior textural characteristics (e.g., higher surface area) as compared to melt-derived BGs due to their nanostructured nature. This may directly affect apatite-forming ability, cellular and molecular events (e.g., protein adsorption as well as cell viability and attachment) and, therefore, the overall biological performance of the biomaterial in a desirable way [10, 31]. In this regard, it is

worth highlighting that sol-gel glasses are bioactive over a wider compositional range compared to melt-derived materials; for example, silicate melt-derived glasses are nearly inert if the amount of silica exceeds 60 mol.%, but this threshold can be increased up to 90 mol.% in sol-gel BGs due to the higher reactivity associated to the higher specific surface area [ref]. Furthermore, sol-gel glasses typically exhibit a higher purity than melt-derived materials, which have to face possible batch-to-batch variations. However, producing sol-gel glasses with complex multi-oxide compositions is a difficult task: binary or ternary sol-gel BGs are the most common ones, while including more alkali or earth-alkali metal oxides requires incorporating more precursors (e.g. salts, alkoxides) with different solubilities in the sol, which could yield unwanted reactions and precipitation of crystalline phases. Moreover, during the fabrication of NPs or nanofibers based on sol-gel-derived BGs, complications can occur due to residual solvents or remaining water. Additionally, the sol-gel method is more time-consuming than the melt-quenching route and carries the challenge of managing the environmentally problematic organic precursors required for advancing the reactions.

Regardless of the synthesis protocol, BGs can be used in medical applications from orthopedics/dental repair[32] to cancer therapy [33] in various shapes and forms, either alone or in combination with other biocompatible materials (e.g., biopolymers).

3. NBGs for Cancer Therapy

Cancer therapy has been among the hottest and most challenging topics in medicine over the last decades [34]. The complicated cellular and molecular mechanisms involved in cancer have made it difficult to provide a straightforward solution for eliminating tumor cells and preventing cancer recurrence. In brief, six hallmarks have been proposed for cancer that empowers tumor growth and

metastatic spread. These hallmarks include (I) sustaining proliferative signaling; (II) evading growth suppressors; (III) resisting cell death; (IV) enabling replicative immortality; (V) inducing angiogenesis; (VI) activating invasion and metastasis 35. Accordingly, therapeutic approaches are being developed to target and disrupt these hallmarks to effectively treat cancer.

Over the last decades, substantial progress has been made in cancer treatment strategies that have led to significant improvements in the life quality and survival rate of patients suffering from this pathology. The current cancer therapies include conventional methods (e.g., surgery, chemotherapy, and radiotherapy) and modern approaches (e.g., immunotherapy, gene therapy, hyperthermia, and photodynamic therapy) 36. More importantly, targeted therapies have gained an outstanding position in cancer research and clinical oncology owing to their ability to precisely identify and attack cancer cells with minimum damage or side effects to normal cells 37. In this regard, nanoscale materials were found as potent substances for monitoring and treating different types of cancer. As previously mentioned, IONs have FDA-approved applications for cancer diagnosis and hyperthermia therapy 38. To the best of the authors' knowledge, IONs are the only inorganic nanomaterials that are currently utilized in cancer research clinically. The reasons for this limitation are associated with inherent drawbacks of inorganic nanoparticles for cancer theranostics, including rapid clearance from the body and long-term toxicity 39. Over the years, scientists and researchers have made great attempts to design and develop other types of inorganic nanoparticles (e.g., mesoporous silica nanoparticles (MSN) and NBGs) that have no above-mentioned limitations for use in cancer research. MSNs have been mainly applied as suitable nanocarriers for delivery of poorly water-soluble drug cargoes to cancer cells. They possess a porous structure with tunable pore size and volume. In addition, MSNs can be empowered using various chemical modifications (e.g., poly(ethylene glycol) (PEG)ylation) with the aim of

developing multimodal anticancer therapeutics 40, 41. MSNs were previously utilized in chemotherapy, radiotherapy, immunotherapy, and gene therapy of cancer 41. However, the toxicity of MSNs to the human organ systems (the nervous, digestive, circulatory systems, etc.) has been shown and is considered as one of the main barriers ahead of their extensive use in the clinic 42. For example, it has been reported that MSNs can cause the excess production of reactive oxygen species (ROS) that negatively affect healthy cells 43. Accordingly, researchers and scientists have evaluated NBGs as a new class of anticancer substances with promising features (see Table 1).

In general, NBGs possess some advantages for use in biomedical sciences that can be summarized as ease of synthesis, versatility in chemical composition, tunable degradability, tissue regenerative potential, antibacterial activity, and fairly inexpensive production costs 44-46. An experimental study has previously proven that BG particles can selectively induce cytotoxicity in giant cell tumor-derived stromal cells (GCTSC)) and encourage MAPK signaling-dependent autophagy 11. The same team reported that silicate-based BGs can kill tumor cells in a dose- and composition-dependent manner 13. Molecular experiments have demonstrated that BGs trigger cell death through apoptosis-independent mechanisms. Indeed, BGs destroyed tumor cells via the disruption of cancer cell membranes and rapid drop of intracellular HMG1 (High Mobility Group Box 1 protein) levels, which yields necrosis 13. The entry of nano- and micro-sized BG particles into mammalian cells has been previously well-documented by Li et al 47. They demonstrated the size-dependent mechanism of intracellular localization and cytotoxicity of spherical BG particles (80% SiO_2–16% CaO–4% P_2O_5 mol%); larger particles (> 174 nm) could escape from the lysosomes after endocytosis and re-localize inside the intra-cytoplasmic vacuoles or randomly in the cytoplasm of cells. The lysosomal escape of the glass particles was considered the main reason for

lysosome damage and induced cell apoptosis. In addition, *in vivo* studies have shown that NBGs/ NBG-containing composites can reduce the tumor volume after their local administration in the tumor sites [48, 49]. In fact, local implantation is the most commonly applied approach for studying the anticancer efficacy of NBGs. Regarding the nature of NBGs, they have been utilized for treating solid tumors, especially bone malignancies. In addition, they have the necessary potential to be used for managing other types of cancers such as soft tissue tumors (e.g., melanoma). More experiments are needed to exactly clarify the possible effects of NBGs in each stage of cancer.

Numerous studies support the usability of NBGs in loading and grafting various anticancer agents (e.g., doxorubicin) and subsequent controlled drug release [50, 51]. In addition, they can be utilized as potential vectors for in situ cancer therapy owing to their potential in facilitating the transport of radioisotopes (e.g., Yttrium-90) into the target tumor [52]. Interestingly, specific kinds of metallic dopants (e.g., Fe) can be incorporated into the basic composition of BGs to enable them for being utilized in other cancer therapy strategies (e.g., hyperthermia) [53]. In the following sections, we aim to comprehensively discuss the NBG possibilities in cancer therapy and diagnosis applications as well as the open questions and directions for future research.

Table 1. A comparative list of different aspects of NBGs and MSNs in cancer research

Material/ Properties	**Therapeutic approaches**								**Toxicity**	**Biodegradability**	**Tissue regeneration capacity**
	Chemotherapy	Radiation therapy	Photodynamic (PDT) therapy	Photothermal therapy (PTT)	Sonodynamic (SDT) therapy	Brachytherapy	Gene therapy	Immunotherapy			

MSNs	*	*	*	*	*		*	*	Toxic effects on various organ systems, including the nervous and digestive systems	Days to Months	Hard tissues (mostly bone)
NBGs	*	*	*	*	-	*	-	-	No significant toxicity against the living organisms	From hours to months depending on the glass type (silicate, phosphate, or borate BGs)	Both hard and soft tissues, including bone, skin, muscle, nerve, etc.

3.1 Doped NBGs: A gateway to cancer research

The chemical structure of BGs provides an outstanding opportunity for adding a wide range of chemical elements (e.g., metals and non-metals) to their classical composition. This variety in the formulation has dramatically increased the therapeutic potential of BGs for medical applications. Concerning cancer research, a series of well-defined elements have been incorporated into the basic composition of BGs to make them potent substances in cancer research, either therapy or imaging applications (See Table 2).

Table 2. A summary of NBGs containing anticancer dopants for potential use in cancer therapy.

Dopant	Glass composition	Remarks	Ref
Iron (Fe)	46.14SiO_2– (26.91-X) CaO-XFe_2O_3–54.4Na_2O-2.55P_2O_5 (X = 0, 1, 2.5, 5, 7.5 mol%)	- The incorporation of 7.5 % Fe into 45S5 BG led to a decrease in the particle size (from 110 nm to 11 nm) while enhancing the specific surface area (from 60 to 270 m_2/g) - Fe-doped MBGs could generate H_2O_2 in a cathodic potential higher than -0.2 V (vs. Ag/AgCl) - Fe-doped MBGs could increase the standard rate constant of ElectroFenton's (EF) reaction up to 38.44 times than the Fe-free glasses.	54

Cobalt (Co)	85SiO_2–(15-X) CaO-XCoO (X = 0, 1, 4 mol%)	- Co-doped NBGs (< 100 nm) showed a uniform spherical morphology, high worm-like mesoporosity (0.41 cm^3/g), and a large specific surface area ca. 787.5 m^2/g -Co-doped NBGs exhibited good bioactivity *in vitro* - 4% Co-doped NBGs were introduced as suitable substances for ferroptosis killing of cancer cells	55
Gallium (Ga)	(46.1−3X) SiO2-XGa_2O_3 –26.9CaO–24.4Na_2O – 2.6P_2O_5 (X= 0,1, 2, and 3% mol%)	- 3% Ga-doped BGs could selectively kill human osteosarcoma cells at a concentration of 10 mg/mL without no adverse effects on normal human osteoblasts - Ga-doped BGs showed excellent osteointegration without any local or systemic toxicity *in vivo*.	14
Tellurium (Te)	60SiO_2–36CaO–4P_2O_5 (mol%) glasses containing 1–5 mol% Te	- Te doping had no adverse effects on the mineralization and degradation of the MBG nanoparticles - Te-doped glasses significantly increased ROS-mediated apoptosis in osteosarcoma cells (from 15 to 50%) due to Te^{4+} ion release	56

Gallium (Ga) is considered the second most commonly-used element for cancer therapy due to its significant cytotoxic effects against a variety of malignant cells 57. Some gallium components (e.g., gallium nitrate (Ganite™)) have been previously approved by FDA for use in managing malignancy-associated hypercalcemia 58. Regarding their high proliferation rate, cancer cells need large quantities of iron compared to normal cells; therefore, more iron receptors (transferrin) are found on their surface. Previous experiments have revealed that Ga^{3+} ions compete with Fe^{3+} ions for entering cells and can accumulate in cancer cells in higher amounts than in healthy cells, which have fewer transferrin receptors. Inside the cancer cells, Ga^{3+} ions bind to ribonucleotide reductase enzyme and thereby disrupt DNA replication and repair, leading to programmed cell death

(apoptosis) through the internal pathway (mitochondrial pathway) 59. However, it should be mentioned that Ga can be localized in cells via transferrin-independent routes, as well 60. There are a couple of studies in which Ga was successfully added to the basic composition of melt-derived BGs to render them anticancer effects 14, 61. For instance, melt-quenched 45S5 BG containing gallium oxide (3 mol %) was reported to selectively reduce the viability of human osteosarcoma cells (up to 41%) while encouraging *in vivo* osteointegration without no local or systemic toxicity (see Figure 2) 14. However, to the best of the authors' knowledge, there is no specific report dealing with the preparation and evaluation of Ga-doped sol-gel BGs for cancer research. So, it can be stated that there is a need for more experiments for determining the real potential of Ga-doped BG nanoparticles in cancer treatment.

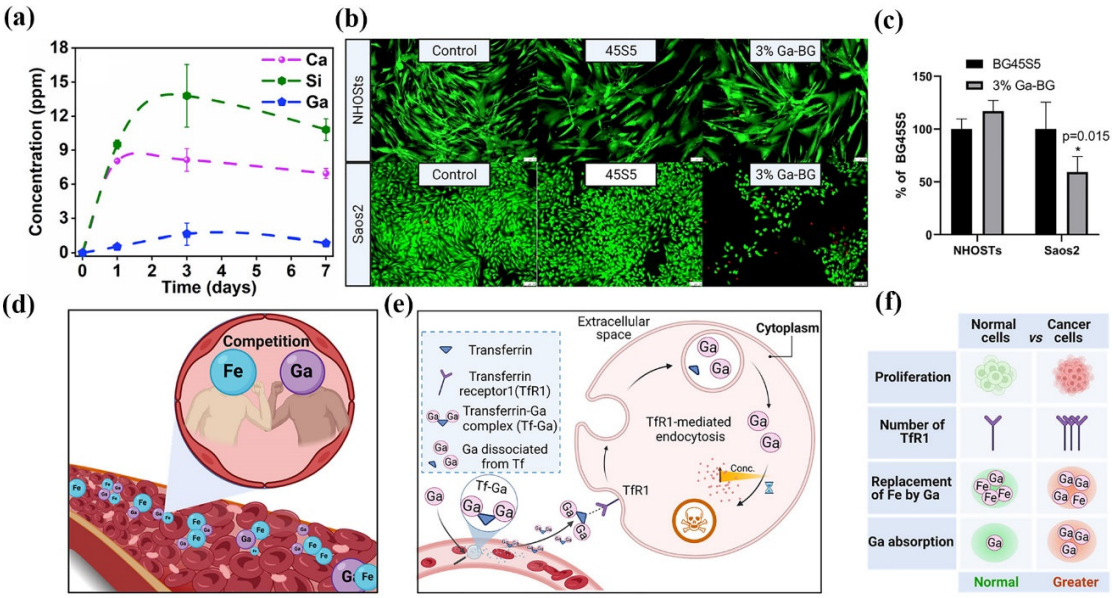


Figure 2. The release profiles of ions (Ca, Si, and Ga) from 3%Ga-doped 45S5 in McCoy's media at pH 7.40 (a). Microscopic images of NHOsts (top row) and Saos-2 (bottom row) cells treated with different samples and stained with calcein AM and ethidium homodimer (b). The results of cell viability (MTT assay) are presented as a percentage of the BG45S5 group (c). Schematic illustration of the competition abiogenic and biogenic ions (Ga^{3+} and Fe^{3+}, respectively) (d). Schematic representation of cellular handling of Ga (e). Ion competition impacts the normal and cancer cells. Reproduced with permission from 14.

Selenium (Se) represent a critical microelement for the human body that can be used for various biomedical applications; for instance, Se-containing compounds were proved to induce cancer cell death via different mechanisms like apoptosis and necrosis 62. Recently, Se-containing MBG nanospheres were successfully developed using a facile sol–gel technique for potential use in bone tissue engineering and cancer therapy 63. The nanoparticles were synthesized based on ternary glass system as 60Si/36Ca/4P/0Se (0Se/MBG), 60Si/35Ca/4P/1Se (1Se/MBG), 60Si/33Ca/4P/3Se (3Se/MBG), and 60Si/31Ca/4P/5Se (5Se/MBG) (mol%). The nanospheres had a uniform spherical morphology, high surface area, and mesopore volume (≈ 400 nm, >400 m^2/g, and ≈0.30 cm^3/g, respectively). The reported results have clarified that the concentration of Se in the glass composition directly affects the bioactivity and drug release capability. The Se/MBG nanospheres showed a selective cytotoxicity against osteosarcoma (MG63 cell line) and normal cells (MC3T3-E1), demonstrating their cell recognition capability *in vitro*. The MBGs doped with low concentrations of Se improved the viability of normal cells with no obvious effect on tumor cells, while glasses containing moderate concentrations of Se only showed toxicity against tumor cells. It should be noted that the MBGs doped with high dosages of Se (5Se/MBG group) significantly

decreased the viability of both cell types, especially tumor cells. Tellurium (Te) is known as another element with promising anti-cancer therapeutic potential [64, 65]. However, there are limited studies (*in vitro* or *in vivo* experiments) on the preparation and characterization of Te-doped glasses with potential application in cancer therapy [66]. In 2022, Zhang et al. could successfully incorporate 1–5 mol% Te into MBGs ($60SiO_2$-$36CaO$-$4P_2O_5$) and produce nanoparticles with uniform spherical morphology [56]. They observed that the MBGs with higher concentrations of the dopant (Te) could significantly enhance apoptosis (from 15 to 50%) in osteosarcoma cells (MG-63 cell line) (Figure 3). This enhancement was associated with the excessive production of reactive oxygen species (ROS) in cancer cells as a result of Te^{4+} ion release from the MBGs over time. The results of confocal laser scanning microscopy (CLSM) clarified that Te-MBG nanoparticles could not enter the cancer cells by endocytosis up to 24 h post-incubation, which could be attributed to the size of the glass particles (500 nm) and their agglomeration. Therefore, the adverse effects of Te-doped MBGs on MG-63 cells may be related to the direct contact of the released Te^{4+} ions with the cells. The authors have concluded that Te-doped MBGs may be presented as suitable substances for bone cancer therapy and regeneration due to their appropriate performance in inducing cancer cells apoptosis, satisfactory bioactivity, and antibacterial activity.

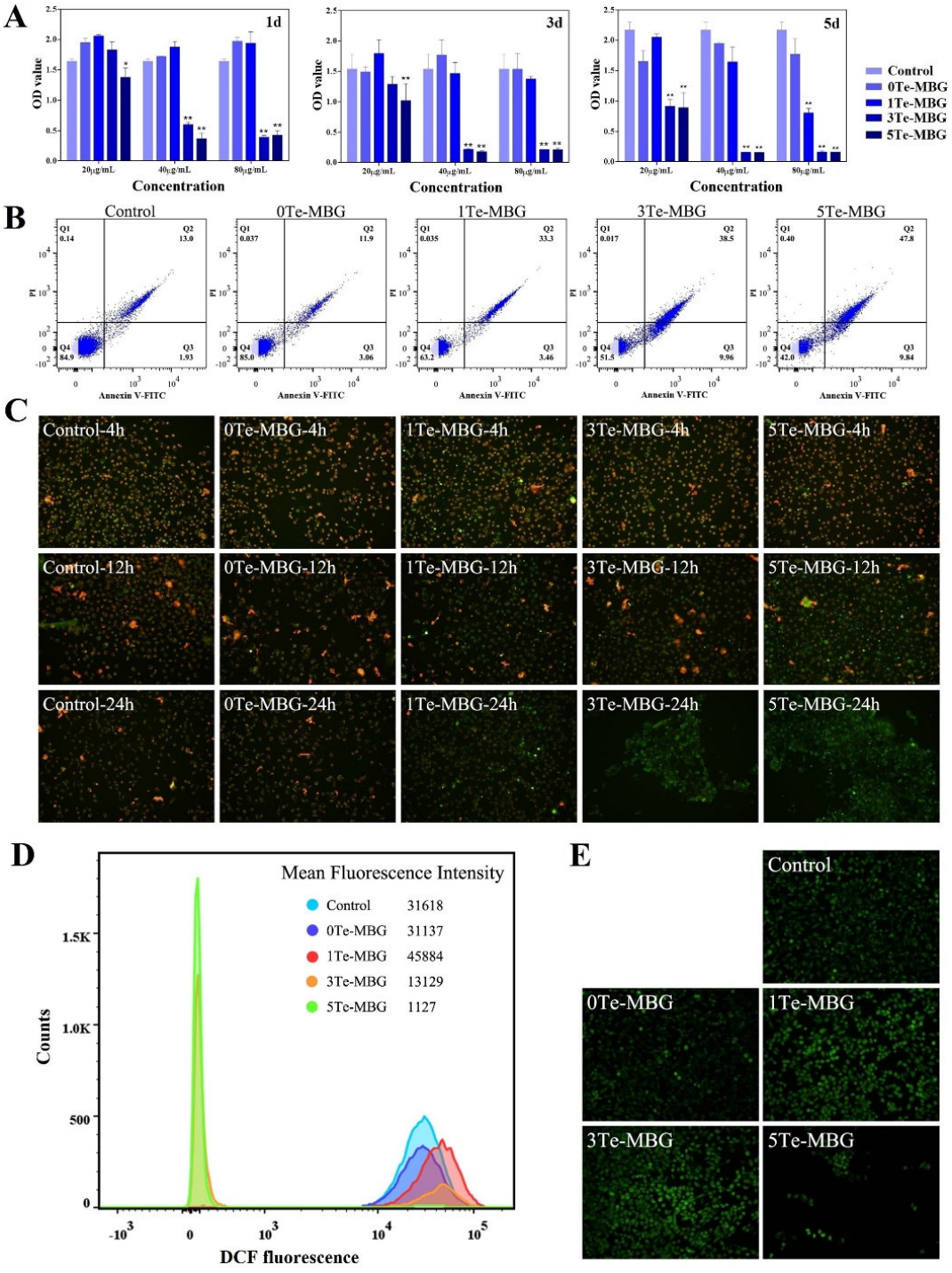


Figure 3. Impact of different concentrations of Te-doped MBG nanoparticles on the viability (A) and the apoptosis of osteosarcoma MG63 cells (B) after 24 h incubation. The measurement of the mitochondrial membrane potential of the Te-MBGs-treated cells with fluorescence microscopy after 4, 12, and 24 h (C). Flow cytometry analysis and fluorescent microscopy images of the cells treated with various concentrations of the Te-MBG nanoparticles after 24 h. The cells were stained with JC-1 dye and DCFH-DA for taking

the images of C and D, respectively. Data were expressed as the mean ± standard deviation of three independent experiments. *: $P < 0.05$, **: $P < 0.01$. Reproduced with permission from ref 56.

The acidic pH of the cancer microenvironment provides a suitable condition for Fenton's reaction since this reaction shows its best performance at pH in a range of 3-4. Some specific ions can be added to the BG composition to mediate Fenton's reaction (iron ions-mediated, Fe^{2+}/Fe^{3+})) or Fenton-like reaction (mediated by copper ions, Cu^{+}/Cu^{2+} or cobalt ions, Co^{2+}/Co^{3+}) 55. In brief, the release of the mentioned ions from BGs can lead to hydrogen peroxide (H_2O_2) decomposition inside the tumor cells and the production of reactive oxygen species (ROS). Eventually, elevated levels of ROS promote ferroptosis (a type of programmed cell death) 67. In this sense, Kermani et al. could synthesize a series of Fe-doped mesoporous 45S5 BG nanoparticles (11–86 nm) with great potential in cancer therapy 54. They reported that Fe_2O_3-containing glasses have a great potential in generating H_2O_2 in a cathodic potential higher than -0.2 V (vs. Ag/AgCl) in an O_2-saturated Na_2SO_4 solution. The incorporation of Fe (2.5 to 7.5 wt%) into BGs not only had no significant negative impact on the bioactivity of the glasses but led to producing smaller particles compared to Fe-free counterparts. In another study, El-Fiqi and Kim reported that adding 10%wt Fe_2O_3 to binary glass systems (85% SiO_2 – 15% CaO) leads to a significant reduction in their particle size (from about 65 nm to < 20 nm) while can increase the specific surface area (SSA) (from 44.7 to 288.1 m^2/g) 68. The sustained release of Fe^{3+} ions (2.20 ± 0.12 ppm/day) with almost

zero-order release kinetics was recorded and mentioned as beneficial for bone cancer treatment through activation of ferroptosis. In apparent contrast with these promising results, however, maghemite (γ-Fe_2O_3)-containing silicate-based 13–93 BGs were previously reported as non-toxic substances against human osteosarcoma cells (Saos-2 cell line) according to the cell viability results (MTT assay) 69. This was probably due to this fact that Fe was stably embedded in maghemite crystals instead of being homogeneously dispersed as Fe^{3+} ions inside the glass network, which is prone to dissolution. Recently, a H_2O_2 self-supplying nanozyme containing glucose oxidase (GOX) and polyethyleneimine was developed based on a Fe-doped phosphate glass with the capability to converting endogenous glucose into toxic hydroxyl radicals 70. In fact, the GOX was loaded to this nanosystem to efficiently consume the glucose molecules in cancer cells and subsequently generated high concentrations of H_2O_2 in tumor microenvironment (TME) that can trigger a Fenton reaction. This biodegradable nanostructured system could suppress the tumor growth by 94.65% in model mice without any side effects living organisms thanks to biodegradability of the system. In summary, the use of doped BGs in cancer therapy is at its beginning steps; therefore, more attempts and *in vitro*/*in vivo* studies should be made to provide precise and detailed information in this area of science. In this sense, the possible adverse effects of SPIONs should be taken into account as they may cause toxicity in the body. The uptake and biocompatibility of SPIONs are mainly determined by their size, surface modifications, concentrations, as well as exposed cells and tissues (e.g., charges of cellular membrane) 71, 72.

The accumulation of high dosages of SPIONs in certain parts of the body (e.g., liver and spleen) were previously detected to cause an imbalance in the iron homeostasis (elevated levels of free Fe ions) and subsequently enhanced cytotoxicity, DNA damages, oxidative stress, and inflammation [73-75].

To the best of our knowledge, most of the conducted experimental studies belong to doped silicate glasses (mainly 45S5 BG) for bone-related cancers; hence, researchers and scientists are suggested to develop simple formulations of borate and phosphate-based BG nanoparticles and investigate their anticancer potential *in vitro* and *in vivo*. In fact, anticancer borate- and phosphate-based NBGs are degraded in the body in a faster trend than their silicate counterparts, eliminating the side effects caused by long-time residence in living organisms [70].

In this regard, metal elements with anticancer capacity (e.g., Mn, Au, Ce, Cu, and Zn) might be added to the BG network and utilized for cancer treatment. In any case, the economic aspects (e.g., cost of valuable metals, like Au) and the availability of dopants should be considered in investigating the feasibility of the next-generation anticancer BGs.

3.2 NBGs for hyperthermia

Hyperthermia, also called thermal therapy, thermal ablation, or thermotherapy is a routine treatment of cancerous tumors in which high temperatures (typically 40–43 °C) are applied for

approximately one hour to kill malignant cells with negligible or no harm to normal tissue cells 76. From a biological point of view, cancer cells are more sensitive to heat because of the difference in the expression profile of heat shock proteins (HSPs) that act against different stressors like heat. Local hyperthermia, regional hyperthermia, and whole-body hyperthermia are the main clinical methods of hyperthermia that are selected for the treatment of cancer depending on the size/spreading of the tumor cells and their location within the body. Different approaches and techniques (e.g., ultrasonic waves, electromagnetic waves, infrared radiations) have been developed for elevating the temperatures of tissue tumors; alternating magnetic field (AMF) is among the most useful methods for hyperthermia. Upon exposure to an AMF, magnetic nanoparticles (e.g., SPIONs) can generate the heat required for destroying cancer cells 77. Recently, magnetic BGs have been considered as potential candidates for common thermoseeds, like superparamagnetic nanoparticles, due to their unique excellent biocompatibility and tissue regeneration capacity 78. The first magnetic BGs were developed by adding iron oxides (magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3)) to their basic composition 79, 80. Over the years, other types of elements were incorporated into Fe-doped BGs and evaluated for their potential in hyperthermia 81-83. In this regard, $BaO–Fe_2O_3$ containing nano-sized BG particles (30-70 nm) have been developed and proven for their capacity in generating enough heat (56.4 °C) for cancer hyperthermia after exposing to an AFM (intensity between 0 and 50 mT, frequency 300 kHz) 15. In another study, the copper oxide was added to Fe-containing BGs (SiO_2, CaO, P_2O_5, and X (X= Fe_2O_3/CuO) to study its impact on the magnetic behavior of the glasses 82. The addition of Cu to the Fe-doped glasses not only led to enhance super-paramagnetic properties of the samples from 0.236 to 1.043 emu/g. In fact, this improvement is associated with the role of Cu in simplifying the entrance of iron oxide into the glass network and subsequent better formation of crystalline

phase of magnetite, hematite, and hedenbergite. Moreover, the addition of Cu to the Fe-doped BGs enhanced their bioactivity, cytocompatibility, and antibacterial activity which is a critical parameters in tissue engineering approaches. Magnetic nanocomposites made of BGs and iron oxides have been previously reported as suitable compositions in magnetic hyperthermia and bone cancer treatment 84. Recently, Borges et al. fabricated superparamagnetic and highly bioactive nanocomposites by adding 10-30 wt% SPIONs to the sol-gel derived 58S BG ($58SiO_2$-33CaO-$9P_2O_5$, wt%) and investigated their potential in magnetic hyperthermia 85. The reported results confirmed the actual embedding of the SPIONs in the sol-gel glass matrix as well as the suitability of these nanocomposites for hyperthermia applications combined with bone regeneration (see Figure 4), as shown by their proper magnetic properties and the absence of any significant negative effect on the bioactivity.

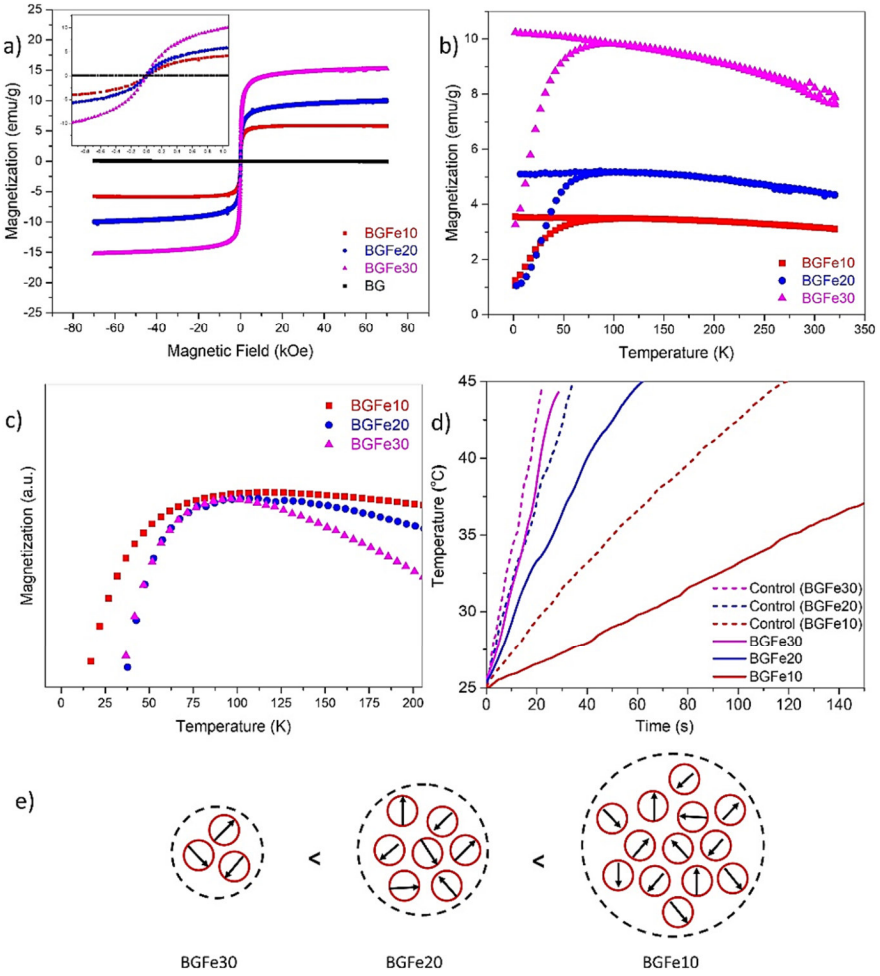


Figure 4. Magnetic properties of SPIONs/BG nanocomposites. M-H curves at body temperature (300 K) (a); Zero-Field-Cooled (ZFC)-Field-Cooled (FC) curves of the prepared samples (b); Intentional overlapping of ZFCs curves of the samples for better visualization of their broadening (c); Calorimetric evaluation under the magnetic field for the nanocomposites and the control groups (water-dispersed SPION) (d); a schematic representation of SPION cluster size in the nanocomposites with different concentrations of Fe (e). Reproduced with permission from 85.

In brief, there are numerous unsolved questions on the application of magnetic BGs in cancer hyperthermia, which should be addressed by future research. For example, the potential effects of the size and shape of magnetic NBGs on their heat generation capacity are of utmost importance

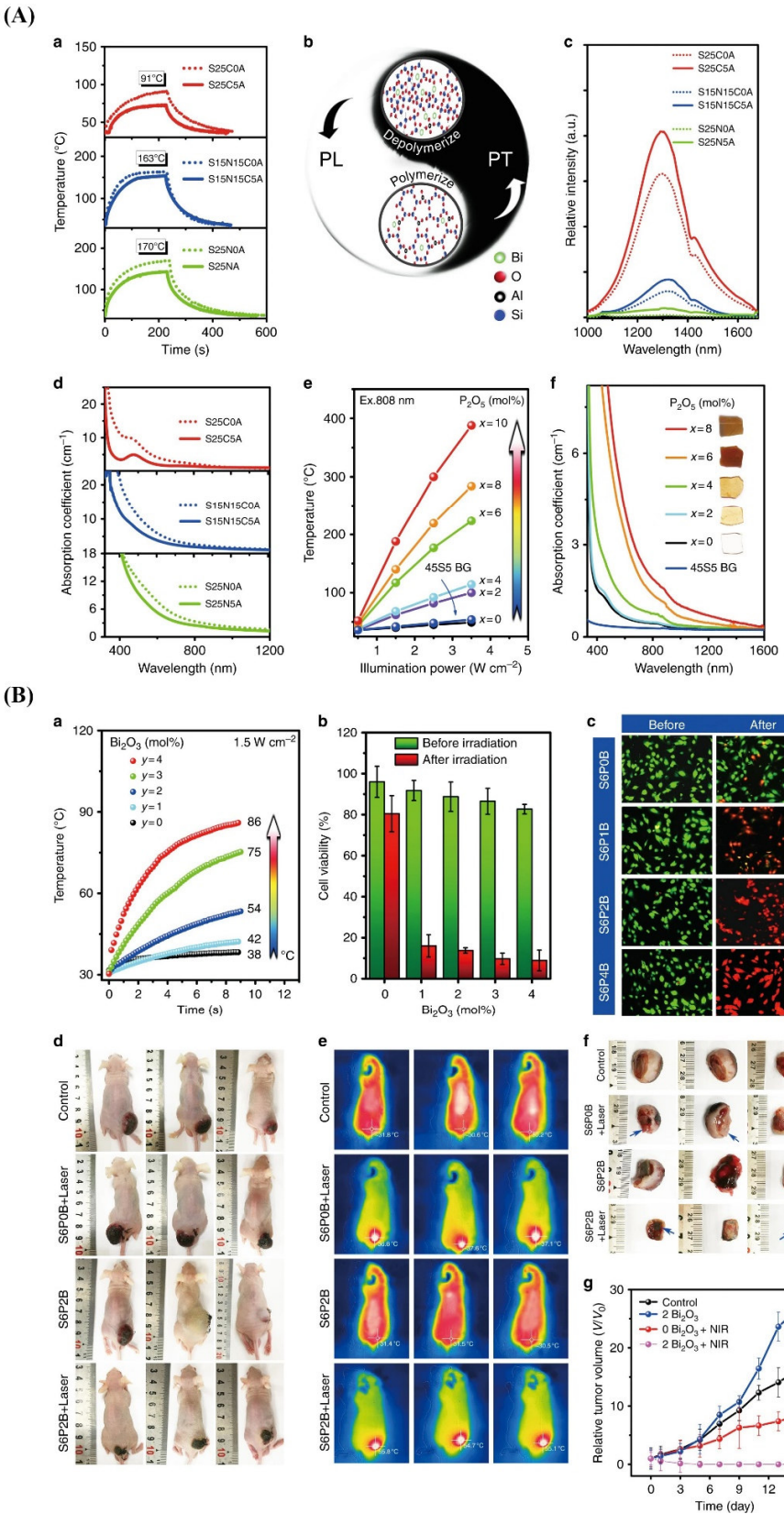
in this area of science. In addition, the combination method of SPIONs to BGs can affect the superparamagnetic properties of final products [84, 86]; for example, SPIONs embedded into/deposited onto the glasses has led to generate NBGs with different particle size and superparamagnetic features [87]. Since physicochemical parameters (e.g., size and shape) of SPIONs can influence their magnetic properties [88-90], BGs containing SPIONs may exhibit vary superparamagnetic characteristics *in vitro* and *in vivo*. For example, reducing the particle size of SPIONs has led to the decrease of magnetic moments of SPIONs and consequently decreased their saturation magnetization [91]. From a medical standpoint, the heat generated by implanted materials should not exceed 44 °C since it can seriously damage healthy cells in the body. Accordingly, designing and developing BGs with a Curie temperature of ~44 °C should be considered for getting ideal outcomes. It should be highlighted that magnetic BGs should have efficacy at the clinical set of magnetic field parameters ($H \times f < 5\times10^9$) [92]. The phase transformations of BGs during heat treatments should be taken into account as another important parameter because it can convert magnetic crystalline phases to other useless phases for hyperthermia. As a matter of fact, a higher quantity of crystallized magnetic content (e.g., magnetite or maghemite) inside the BG network leads to more desirable magnetic characteristics. In this regard, it is feasible to incorporate higher amounts of Fe into the sol-gel BGs as compared to the melt-quench counterparts, which may carry the risk of unpredictable and harmful exothermic reactions during melting and are associated with crucible damage/contamination. Moreover, it is feasible to add previously prepared SPIONs to the synthesis process of BGs during sol-gel formation to create magnetic nanostructured constructs for potential use in cancer hyperthermia [85, 93].

Moreover, the addition of some elements (e.g., cobalt) to Fe-containing NBGs should be studied for clarifying their beneficial effects on the composition (e.g., enhancing specific power loss (SPL)). Furthermore, the preparation and characterization of magnetic phosphate- and borate-based NBGs is an untouched topic in the field that needs to be explored since biodegradable magnetic BGs may be a solution for overcoming the need for further surgery for the removal of the implanted material. Last but not least, conducting *in vivo* animal studies following *in vitro* experiments is of utmost significance for realizing the real potential of magnetic BG nanoparticles in cancer hyperthermia.

3.3 Photothermal therapy

Photothermal therapy (PTT) is one of the latest methods used for cancer treatment in the clinic. In this technique, nano-sized particles are illumined by exposure to a proper wavelength (usually 780–2526 nm) of near-infrared (NIR) light to generate heat (45–50 ºC) in a cancer-bearing tissue and subsequently promote tumor cell death due to damage to the cancer cell membrane, DNA denaturation, and activation of angiogenesis-blocking mechanisms. Up to now, a series of inorganic and organic nanoparticles (mostly metallic nanoparticles like Fe and Au) have been successfully utilized as photothermal agents for PTT applications 94. One of the main restrictions of this technique is related to damage to surrounding healthy tissues due to the excessive applied heat. Therefore, substances with tissue-regeneration capacity may be beneficial in PTT applications since they can help healthy tissue restoration at tumor sites after the therapy. Among different biocompatible materials, BGs were previously introduced and investigated for PTT and tissue repair at the same time. As an illustration, multifunctional melt-quenched bismuth (Bi)-doped BGs were proposed as potent materials with the ability to combine bioactivity and

photothermal (PT) response for concurrent bone tumor treatment and tissue healing 49. In fact, depolymerizing the matrix glass network was suggested to suppress the spontaneous radiation process following NIR excitation and, consequently, enhance the photothermal conversion efficiency and accumulated heat. The presence of Bi^{+3} ions inside the prepared silicate and phosphosilicate glasses led to absorb photon energies following NIR light (808 nm) and subsequent heat generation. In the samples with higher concentrations of Bi, the PT efficiency was obviously enhanced because of luminescence quenching. The prepared samples not only showed bioactivity and biocompatibility but also supported differentiation and mineralization of osteogenic cells *in vitro*, which make a proof of concept for their suitability in bone tissue regeneration. The samples were then implanted into tumor-bearing adult male Balb/c nude mice to determine their PT efficacy *in vivo*. The histological results indicated that treatment of the animals with the 2% Bi-containing glasses and the irradiation (808 nm laser for 10 min at a power density of 1.5 W cm^{-2}) led to reducing and vanishing tumors on days 1 and 3, respectively. More interestingly, all tumor mass disappeared in the animals after two weeks of the treatment, and the growth of normal muscular tissues was visible at the tumor sites (Figure 5).


(A)
a
Temperature (°C)
Time (s)
91°C
S25C0A
S25C5A
163°C
S15N15C0A
S15N15C5A
170°C
S25N0A
S25NA
b
PL
PT
Depolymerize
Polymerize
Bi
O
Al
Si
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Relative intensity (a.u.)
Wavelength (nm)
S25C0A
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S15N15C0A
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P2O5 (mol%)
Absorption coefficient (cm⁻¹)
Wavelength (nm)
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45S5 BG
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°C
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Before irradiation
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Cell viability (%)
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c
Before
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S6P2B
S6P4B
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S6P2B
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f
Control
S6P0B +Laser
S6P2B
S6P2B +Laser
g
Relative tumor volume (V/V0)
Time (day)
Control
2 Bi2O3
0 Bi2O3 + NIR
2 Bi2O3 + NIR

Figure 5. (A) Temperature curves of the Bi-doped silicate glass samples under 1.5 W cm^{-2} irradiation of 808 nm Laser Diodes (LD) (a); schematic illustration of the proposed approach to modulate PT efficiency (b); the emission spectra after excitation of 808 nm (c); the absorption spectra of the samples, (d); the PT effect of the Bi-doped phosphosilicate BG samples SxP2B as a function of illumination power and the content x of P_2O_5 (e); and the absorption spectra of SxP2B and commercial BG 45S5 (f). (B) the temperature curves of the glass samples S6PyB immersed in simulated body fluid (SBF) for different irradiation times at a power density of 1.5 W cm^{-2} (a); the effect of S6PyB on the viability of human osteosarcoma line U2OS cells before and after 808 nm laser irradiation at 1.5 W cm^{-2} for 5 min (b); fluorescence microscopic photographs of the cells treated with S6PyB before and after 808 nm laser irradiation at 1.5 W cm^{-2} for 5 min (c); live cells are green, while dead cells are red due to the fluorescence of calcein and PI-DNA upon the illumination of 490 nm; **d** images of mice in "control", "S6P0B + laser", "S6P2B" and "S6P2B + laser" groups at day 15 (d), the thermal images of mice in the four groups at day 0 (e); tumor tissues of mice in the four groups at day 15 where the blue arrows indicate the location of the glass (f); and the tumor volume evolution of the four groups with times (g). Reproduced from 49.

In another interesting study, Lei's research group could successfully develop a hierarchically multifunctional nanoplatform based on Sr-doped BGs (Si-Ca-Sr glasses) functionalized by polypyrrole (PPy), polydopamine (PDA), and ε-polylysine (EPL) (BSr@PPE) with the aim of integrated tumor photothermal therapy and infection-impaired wound repair 95. The findings indicated that this glass-based nanosystem has tunable photothermal properties, enhanced antioxidant and antibacterial activities, biocompatibility with healthy cells, and UV-shielding capacity for tumor therapy and skin wound healing in A375 tumor-bearing mice after exposure with 808 nm NIR irradiation (1.0 W/cm^2, 10 min). In fact, the presence of PPy and PDA on the glass samples led to absorb NIR light and its conversion into heat. In addition, EPL rendered the glass samples the antibacterial activity due to its role in destroying the bacteria cell structure.

Improving the wound healing rate after any injury (e.g., thermal damage to normal tissues) is of utmost significance for tissue engineering applications. On this subject, composites made of biocompatible polymers and BGs deserve to be considered as promising substitutes for restoration strategies. In 2021, Wang et al. reported a series of polymer/glass composite hydrogels for tissue

regeneration in the site of tumors with antibacterial activity and improved wound healing. For this purpose, they first prepared multifunctional black BGs (CST1, CST3, CST5, CST5.5, (10 − x)(CaO-SiO_2):xTiO_2, x = 10, 30, 50, 55 mol.%) by the containerless melting technique using oxygen (O_2), air, and nitrogen (N_2) levitation. Ti^{3+} ions were added to the BG composition to endow antibacterial and anticancer effects. They added the black glass samples to sodium alginate (SA) to produce hydrogel dressings 96. The reported data showed that the temperature of the group SA/CST5 was raised to ≈58 °C after being irradiated by 808 nm laser (1.5 W cm^{-2} power density) for 300 s, which was comparable with the pure black CST5 glass samples. The samples were then injected into a mouse tumor model to evaluate their real potential in the PTT of the tumor. Similar to *in vitro* results, the *in vivo* data showed that the temperature quickly increased and remained constant at 55 °C after irradiation of the same power laser (808 nm), which resulted in tumor removal while no photothermal effects were observed in the glass-free samples. The implantation of the hydrogels into nude mice chronic wound healing model has clarified that the SA/CST5 composites have a higher healing rate after the laser irradiation in comparison with their counterparts without the irradiation (see Figure 6).

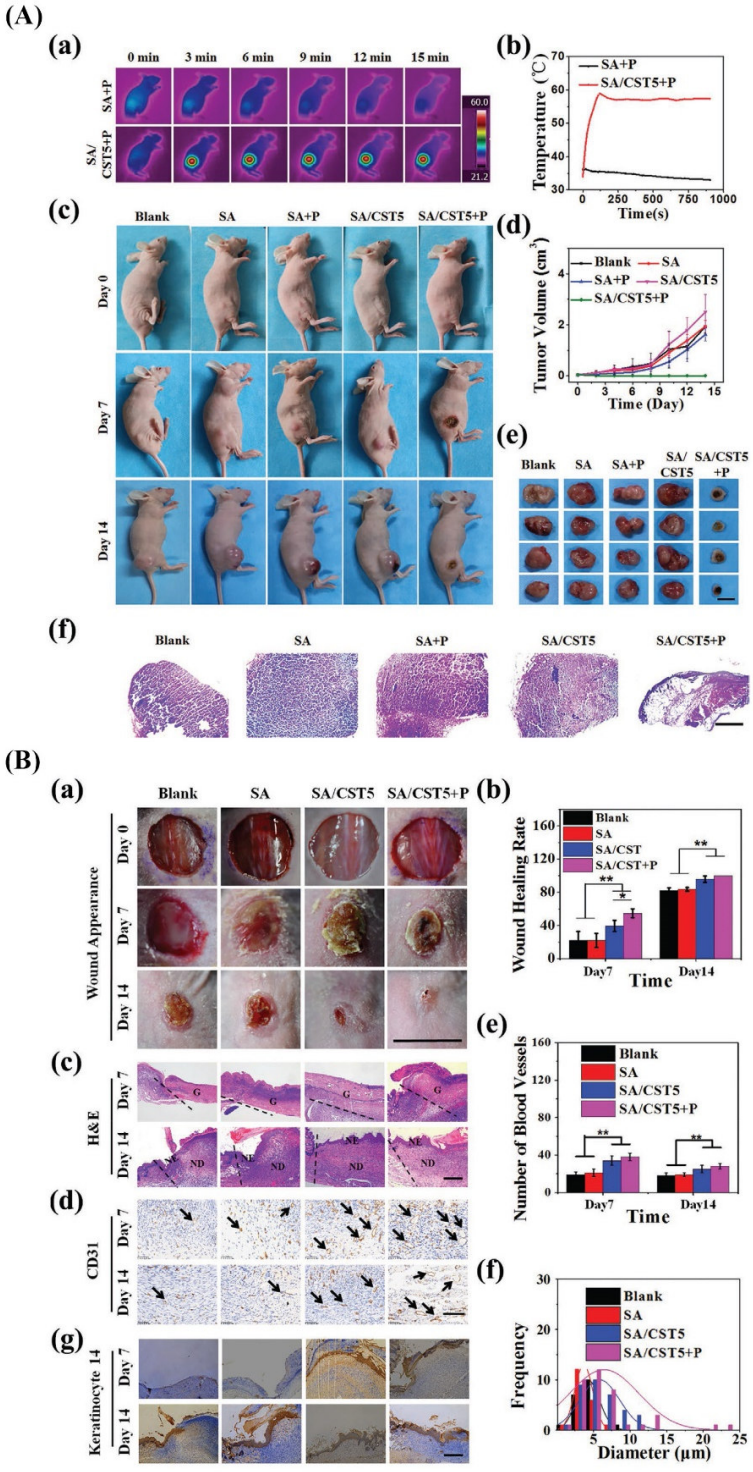

Figure 6. (A) The results of tumors treatment by SA, SA/CST5, SA+P, and SA/CST5+P; infrared thermal photographs of the tumor site in nude mice (a); the temperature curve of the tumor site in the animals treated with SA+P and SA/CST5+P after different irradiation period (b); macroscopic photos of the tumor appearance (c); the tumor volume change with time after the photothermal treatment (d); representative images of the tumor volume in the animals after the treatment (scale bar is 10 mm) (e); histological evaluations of the tumor tissue after 14 days of treatment (scale bar denotes 100 μm). (B) The wound healing potential of SA, SA/CST5, and SA/CST5+P in nude mice; wound

appearance (scale bar is 10 mm) and wound healing rate (a and b); images of hematoxylin & eosin-stained tissue slides (the dotted line indicates the dividing line of old and new tissues; G denotes the granulation tissue; NE means newly formed epidermis; ND signifies newly formed dermis; scale bar is 100 μm) (c); the results of immunohistochemistry staining for CD31 (black arrows point to new blood vessels; scale bar is 100 μm) (d); the number of blood vessels (days 7 and 14) and the diameter size of blood vessels (day 7) (e and f); immunohistochemistry staining for keratinocyte 14 (scale bar is 100 μm) (g). Note: sodium alginate hydrogel dressing (SA), sodium alginate and calcium silicate and titanium dioxide (CST5: $CaSiO_3$:5TiO_2) composite hydrogel dressing (SA/CST5), SA with 808 nm laser (SA+P), SA/CST5 composite hydrogel dressing with 808 nm laser (SA/CST5+P). (*$p < 0.05$, **$p < 0.01$). Reproduced with permission from 96.

Monitoring tissue temperature stands as a key issue for PTT since high temperatures can negatively affect healthy cells and even tissues. There are some traditional methods (e.g., thermocouples and optical fibers) for detecting the temperature but they suffer from poor spatial resolution and low accuracy. In this regard, in situ monitoring of the heat has been proposed as a wise approach for identifying the PTT temperature. For instance, Ma et al. introduced composite hydrogels made of alginate and biocompatible Nd-Ca-Si glasses (Nd:Ca: Si = 1:9:20, Nd/CS1; Nd:Ca: Si = 2:8:20, Nd/CS2; Nd:Ca: Si = 3:7:20, Nd/CS3) as suitable substances for fluorescence thermometry, PTT, and burn tissue repair 97. They observed that the composites emitted fluorescence under 808-nm laser irradiation which had a linear correlation relationship with in situ temperature. The system clarified that the PTT temperature at 53°C is a suitable temperature for eliminating tumors with minimal damage to the surrounding tissues in a mouse model (Figure 7).

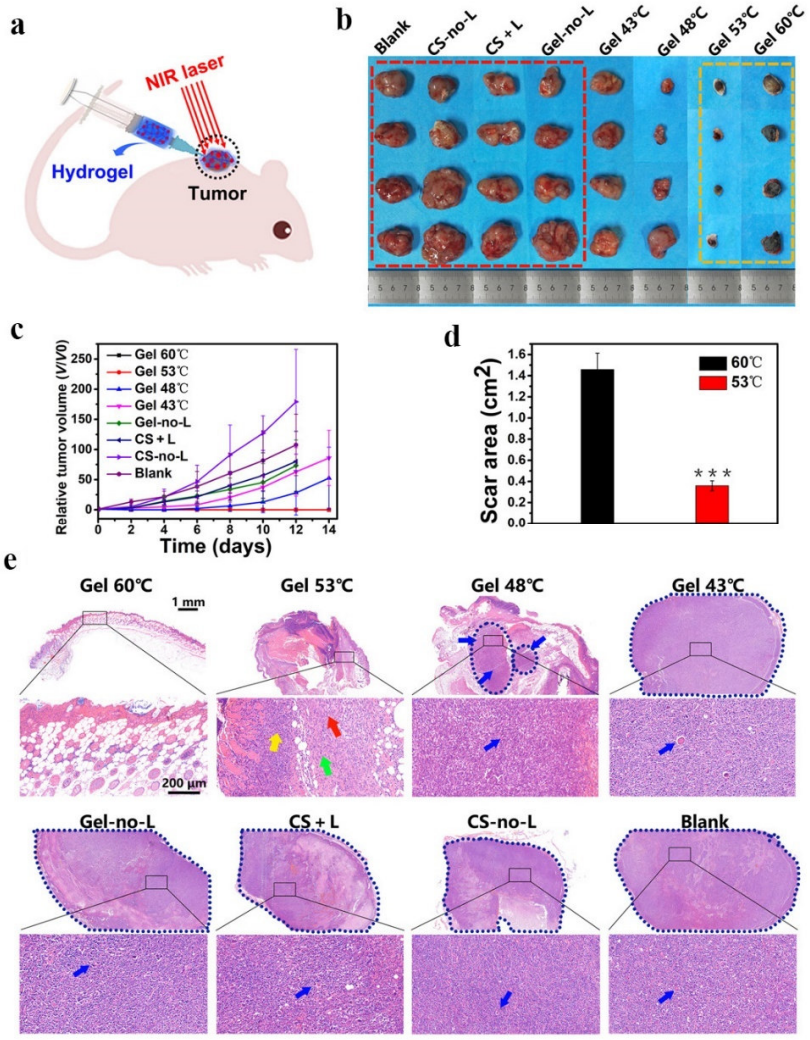

Figure 7. Effects of photothermal therapy of the injectable Nd-Ca-Si bioactive glass/alginate composite hydrogel with different temperatures *in vivo*. Schematic representation of photothermal treatment of tumors (a). Macroscopic images of tumors obtained from animals that received different treatments on day 14 (b) (The red dotted box indicates that the tissues were harvested on day 12 based on the animal welfare rules and the orange dotted box displays the scab of the tumor site of the mouse in the G 53°C and Gel 60°C groups(b). The graph shows the relative tumor volume in the animals over time (n = 4) (c). The scar area of the animals' skin was treated at 60° and 53°C (***P < 0.001) (d). Histological evaluation of the tumor tissue after receiving various temperature treatments on day 14 (blue, red, yellow, and green arrow stand for tumor tissues, fibroblasts, inflammatory cells, and new blood capillaries, respectively). Reproduced from 97.

3.4 NBGs for Brachytherapy

One of the specific forms of radiotherapy is brachytherapy, in which radioactive sources (implantable beta- and/or gamma-ray-emitting seeds or microspheres) are directly placed into or next to solid tumors for killing cancer cells. Accordingly, its efficacy depends on the direct delivery of radiation dose from the source to the intended tumor mass. This approach is usually applied as primary treatment or as adjuvant treatment for various types of cancers (e.g., breast and uterine endometrial cancers) 98. Brachytherapy offers some unique merits in comparison with conventional external-beam techniques, including reducing the risk of exposure of healthy tissues to high doses as well as dosimetric advantages with very sharp radiation dose gradients 98. Commercial seeds are composed of radioisotopes Iodine-125 (^{125}I) and Yttrium-90 (^{90}Y) inside a titanium capsule; the need for a second invasive surgery is mentioned as one of the biggest limitations ahead of their usage in the clinical setting. Accordingly, the use of other types of seeds, including biocompatible glasses, was proposed for brachytherapy over the years.

Radioisotope-containing glasses are the first and only example of biocompatible glasses applied for radioembolization 99. In brief, the following criteria have been suggested for the preparation of biomedical glasses used in brachytherapy: (i) compatibility with living organisms; (ii) high chemical durability (non-biodegradability) in the patient's body (even in low pH environment of cancer) for preventing the release of radioisotopes with long half-life; and (iii) not incorporating specific elements (e.g., Na and Ca) into the glass composition since they can become undesired radioisotopes with long half-life during the neutron activation process. Currently, ^{90}Y glass microspheres (TheraSphere®, MDS Nordion, Ottawa, Canada) are applied for the treatment of liver cancer in clinic 100. In addition, several other formulations of non-degradable biocompatible

glasses have been synthesized and characterized for potential use in brachytherapy applications, including rare earth aluminosilicate (REAS) durable glasses (e.g., $46.8Sm_2O_3$-$18.2Al_2O_3$-$35SiO_2$ (wt.%) and $55Y_2O_3$-$20Al_2O_3$-$25SiO_2$ (wt.%) systems) 101. All these glass systems, which are typically addressed to perform radiation therapy combined with capillary occlusion at the tumor site, are not produced in a nano-sized form but the glass particles are from few to few tens of micrometers.

Over time, degradable biocompatible glasses (e.g., BGs) were also proposed for use in brachytherapy, either alone or in combination with polymeric composites 102. The first use of sol-gel BGs as radioactive implants for brachytherapy was reported by Roberto et al. in 2003 103. They could prepare radioactive ternary glasses by adding ^{153}Sm to the SiO_2-CaO composition and subsequent neutron activation. The rationale for the selection and concentration (4.5 and 11.5 wt.%) of Sm in the glass composition was associated with its short half-life (46.27 h) and ability to provide an effect comparable with ^{125}I seeds. In a following study 104, these radioactive BGs (Si–Ca–Sm-153) were implanted in rabbit livers for investigating their durability *in vivo*. The results of radiological assessments indicated the absorption of the BGs in the animals' livers after 7 months of implantation (Figure 8). Other formulations of silicate-based BGs were also designed for potential use in brachytherapy 105, 106. For example, Cacaina et al. could add Y_2O_3 (5 mol.%) to a multicomponent BG system, SiO_2-Na_2O-P_2O_5-CaO-B_2O_3-K_2O-MgO, without any adverse influence on the bioactivity of the glasses 107.

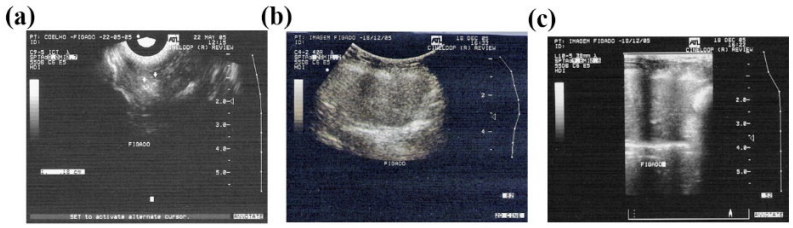

Figure 8. The ultrasound image of two of the three seeds (Si–Ca–Sm-153) implanted in the rabbit's liver of (pointed out by the white arrows) (a); The ultrasonography of the liver after 7 months of the implantation in which no vestige of the implanted seeds is detected (b); The ultrasound image of the liver of the animals receiving the seeds with no sign of the seeds at 7 months after the implantation (c). Represented with permission from 104

In another study, sol-gel-derived 58S-based BGs containing up to 5 wt% holmium (Ho) were developed as promising candidates for brachytherapy applications 17. The reported data indicated that the incorporation of Ho into the 58S BG composition led to the enhanced dissolution of the samples in an early stage while dissolution in the long term decreased, thereby limiting their cytotoxicity. Moreover, Ho did not negatively affect the bioactivity of the BG samples.

Aside from silicate glasses, it seems worthy to develop other subgroups of the BGs family (e.g., borate and borosilicate glasses) and evaluate their potency in brachytherapy strategies 101. In this sense, the specific formulations of borate- and borosilicate glasses can be developed with controlled biodegradation and bioreactivity to provide maximum benefits for brachytherapy.

It should be noted that also radioactive degradable glasses are produced in the form of micrometric particles; nano-sized particles, exhibiting a remarkably larger surface area, would have a higher reactivity/dissolution rate upon contact with biological fluids and, probably, would not be suitable for cancer embolization – although being potentially suitable for radiation therapy. This topic

deserves further research and would benefit from a tight collaboration between glass scientists and clinicians in order to determine which is the best/threshold size for the given application.

Nowadays, computational studies (e.g., molecular dynamics simulations) are commonly carried out for predicting the suitability and properties of biocompatible glasses containing radioisotopes before and/or along with conducting experimental studies [108, 109]. Therefore, glass researchers and scientists may take benefit from in silico studies in order to obtain optimal compositions in the Lab for further *in vivo* experiments.

3.5 NBGs for anticancer drug delivery

As a subgroup of BGs, MBGs are very versatile drug delivery vehicles thanks to their highly ordered porous structure (pore size between 2-50 nm) which provides a high specific surface area [110]. Although these biocompatible materials have been traditionally used in tissue engineering applications, MBGs, either magnetic or non-magnetic, are now recognized as suitable candidates for cancer therapy. It is feasible to load and deliver different anticancer biomolecules and drugs into/from MBGs, either in the form of magnetic or non-magnetic composition. As compared with conventional mesoporous silica nanoparticles, MBGs offer dual functions for cancer therapy and tissue regeneration as they can combine controlled anticancer drug delivery and bone-forming bioactivity [111, 112]. For instance, Mg-doped MBG nanoparticles were prepared using the sol-gel method in the presence of a structure-directing agent (F127) for investigating their capability of delivering mitomycin c (Mc) to osteosarcoma MG-63 cells [113]. The maximum cumulative release (89%) of the drug was observed at pH 6.4. The glass nanoparticles showed no adverse toxic effects on normal cells *in vitro* and *in vivo* while the drug-loaded Mg-MBGs could inhibit the viability of the cancer cells with an IC50 value of 20.8 μg/mL.

The outcome of local chemotherapy with MBGs depends on some parameters, including the pH of the microenvironment, the initial dosage of the loaded anticancer drug, and the degradation rate of glass particles [111, 114, 115]. On this point, MBGs were recently coated with bone-targeting hyaluronic acid-alendronate (HA-ALN) components for loading and delivering DOX to cancer cells drug (See Figure 9) [116]. The sustained release was 1.2 mg/mL with an initial burst release (50% release) at 15 h and 25 h for pH 4.5 and 7.4, respectively. The Van Der Waals force/hydrogen bond interactions between silanol groups on the glasses surface and –COOH groups of DOX assisted in the controlled release of the drug. Higher internalization of MBG particles into endosomes of acidic cancer cells (pH 4.0–5.8) was mentioned as remarkable merit for their usage in cancer therapy; the DOX-loaded MBGs could significantly decrease the viability of MG-63 osteosarcoma cells in comparison with the drug-free MBGs and DOX. Target chemotherapy of cancer cells seems possible with functionalized drug-loaded MBGs [117]. In this sense, anticancer drug-loaded MBGs were surface-functionalized with folic acid since the folate receptor (FR) is overexpressed on several cancer cells (e.g., breast cancer cells and HeLa cells) [117, 118]. Moreover, functionalizing MBG nanoparticles is performed to prolong the release of anticancer cargoes and inhibit their burst release.

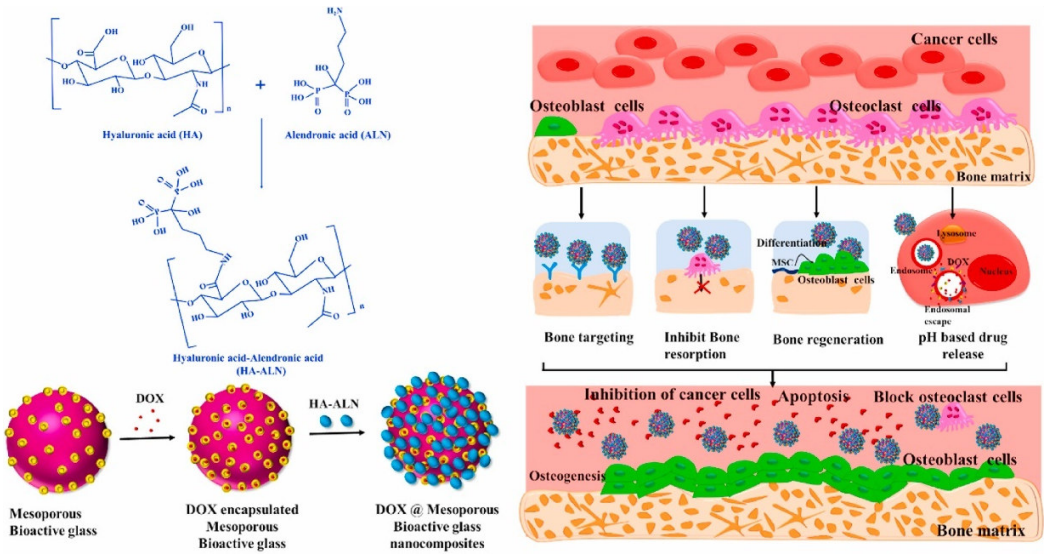

Figure 9. Schematic illustration of preparation of anticancer nanocomposites made of mesoporous bioactive glasses (MBG) coated with hyaluronic acid-alendronate (HA-ALN) with the aim of loading and delivering doxorubicin DOX. This composite was designed to act as a pH-based controlled drug delivery nanosystem for targeting bone, inhibiting bone resorption and cancer cells, as well as inducing osteogenesis. Reproduced with permission from 116

The development of stimuli-responsive glass-based nanosystems can be taken into account for providing a more controlled and specific drug release 50. In this sense, an enzymatic responsive nanosystem was previously developed using the implementation of adenosine triphosphate (ATP) and ε-poly(L-lysine) molecular gates on the MBGs surface. Two portions of the glass mesopores were functionalized with triamine and isocyanates and capped with ATP and ε-poly(L-lysine), respectively. Two molecular gates were opened following the presence of alkaline phosphatase (ALP) and pronase, allowing the controlled release of DOX and levofloxacin cargoes. Concerning cancer research, it can be stated that most of the synthesized MBGs are silicate-based glasses that were investigated for potential use in the treatment of bone-related cancers. Accordingly, it is suggested to develop phosphate- and borate-based glasses and compare their capacity for

anticancer drug delivery with silicate-based counterparts. Due to higher biodegradation rate in the physiological environment, they may provide unique opportunities for cancer therapy, either alone or in combination with other materials. For instance, it has been reported that the fast dissolution of borate glasses in chitosan-coated core/shell glass-hydroxyapatite microspheres may lead to a sharp increase in the environment pH that directly changes the swelling/de-swelling behavior of chitosan, resulting in long-term drug release 119. However, the possibility of pore closure should be taken into consideration in the case of highly reactive MBGs (e.g., borate glasses) as a result of the quick formation of HAp on them following exposure to physiological fluids. Some other crucial aspects include the size, morphology, biodegradation, and cell internalization of MBGs developed for anticancer drug delivery. In addition, the investigation of MBG-based 3D scaffolds for anticancer drug delivery and tissue regeneration can be stated as another hotspot in this area of science. Last but not least, the lack of *in vivo* experimental studies has made it difficult to state the actual potential of MBGs in cancer drug delivery and tissue reconstruction.

4. Concluding Remarks and Challenges

Complexity in cancer biology makes it difficult to present a straightforward solution for its treatment. Moreover, resistance to therapy in cancer is an additional problem for researchers who are working on developing anticancer substances. Up to now, several organic and inorganic nanostructures have been studied and used for the treatment of different types of cancer. Inorganic nanomaterials can act as anticancer agents *per se* or as intelligent vehicles to carry/host and release chemotherapeutics (drugs or ions). The use of BGs for the treatment of cancer has been among the hottest topics in recent years. The main advantages of NBGs in oncology include the relative ease

of synthesis, the tunability of properties, the appropriate stability in physiological environments, and the cost-benefit production process. In addition, they can be easily added to polymeric matrixes to generate biocomposites (e.g., glass-reinforced hydrogels) with improved characteristics (anticancer and antibacterial activities as well as tissue regenerative potential). It is also feasible to create BG-based stimuli-responsive anticancer constructs for drug delivery applications, where the therapeutic agent can be an organic biomolecule – for example, released from MBGs provided with properly functionalized mesopores acting as molecular gates in response to pH, temperature, etc. – or a metallic ion. Furthermore, NBG/polymer composite bio-inks incorporating anticancer agents could be printed to fabricate 3D scaffolds that can replace the resected cancerous tissue (typically bone, but also some soft tissues like skin). These implants show the promise to elicit a multifunctional action, regenerating the tissue and inhibiting the recurrence of cancer. Adding specific elements (e.g., Fe and Ga) to the basic composition of BGs may turn them into more potent anticancer agents with diverse applications in oncology. Regarding the literature, most reports are associated with silicate-based BGs for bone-related tumors. Phosphate- and borate-based glasses may also be considered for cancer therapy and their anticancer capabilities should be compared with silicate counterparts to draw a conclusion for specific cancer types.

As a rule of thumb, NBG show superior physico-chemical and biological characteristics in comparison to their microscale counterparts. Up to now, NBGs were employed for cancer therapy through various well-known approaches, including hyperthermia, PTT, brachytherapy, and drug delivery. As various aspects of BG particles can affect their biological activities, the effect of size, morphology, and surface chemistry of NBGs on their anticancer potential may be an interesting area for research. For example, whether the nanometric size of glass particles is advisable or not

for cancer (radio)embolization still is a matter of debate. Moreover, NBGs can be evaluated for their potential in other cutting-edge cancer therapy approaches such as immunotherapy. In brief, the use of NBGs in cancer therapy is in its first steps and is mainly limited to bone-related cancers and *in vitro* experiments. Therefore, it is strongly suggested that researchers perform follow-up studies in laboratory animals as an important step toward clinical trials. It can be stated that anticancer NBGs with more simple compositions (binary and ternary glasses) are preferred candidates for the path to clinical translational research since the interpretation of the experimental data is less complicated with more predictable outcomes. In this regard, utilizing computational approaches (e.g., molecular dynamics (MD) simulation) can be beneficial for predicting the optimized compositions for cancer therapy. However, the lack of comprehensive experimental data on a single anticancer BG composition is one of the main barriers in translating from *in vitro* to *in vivo* and animal to human trials. On this matter, effective dosages, administration routes, and pharmacokinetics (PK) of selected BGs should be defined and issued as clinical guidelines by international agencies (e.g., Food and Drug Administration (FDA) and European Medicines Agency (EMA)).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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