A critical review of bioactive glasses and glass–ceramics in cancer therapy

A Critical Review of Bioactive Glasses and Glass-ceramics in Cancer Therapy

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Abstract

There is an ongoing profound shift in using glass as a primarily passive material to one that instills active properties. This review aims at clearly demonstrating that bioactive glasses (BGs) and glass-ceramics (BGCs) as functional biomaterials for cancer therapy can transform the world of healthcare in the 21st century. Melt- and gel-derived glasses and glass-ceramics can carry many exotic elements, including less common rare-earth, and trigger highly efficient anticancer properties via the combination of radiotherapy, photothermal therapy, magnetic hyperthermia, along with drug or therapeutic ions delivery. The addition of these dopants modifies the bioactivity, imparts novel functionalities, and induces specific biological effects that are not achievable using other classes of biomaterials. In this paper, we have reviewed and discussed the current knowledge on promising compositions, processing parameters, and applications of BGs and BGCs in treating cancer. We have also highlighted the need for further research on this particular, unique class of biomaterials as well as the major challenges ahead in the field.

Keywords: Glass; Biomaterial; Cancer; Mesoporous; Glass-ceramic

1- Introduction

Cancer is one of the most important reasons for death among the other complex and dangerous diseases that are still largely incurable. However, much progress is being made in this area [1]. Various strategies such as surgery, chemotherapy, radiotherapy, and new targeted therapies have been developed, including hyperthermia, phototherapy, gas therapy, and intelligent drug delivery to combat cancer and associated complications [2]. Surgery can successfully treat the disease in the first stages when the cancer cells have not spread over a long distance in the body. However, surgery is often not recommended in the later stages of cancer due to its invasive nature [3]. Conventional chemotherapy can not also selectively treat cancer as it does not usually differentiate between cancer and healthy cells. A significant portion of the drugs used in this treatment does not affect the target cancerous tissue but causes unwanted side effects [4]. Therefore, controlled drug delivery systems are highly recommended. Many other promising methods are introduced for patients who cannot undergo surgery or chemotherapy. These new methods complement basic techniques, are more accurate and effective, and identify and target only tumor cells [5].

Bioactive glasses (BGs) and glass-ceramics (BGCs) have been introduced since 1969 for various applications in tissue engineering, implantology, and pharmaceutics because of their exceptional properties such as good biocompatibility, controllable degradation rate, osteoinductivity, antibacterial capability, and pro-angiogenic effect, which are key to develop multifunctional systems [6], [7], [8]. These substances have been highly considered for cancer treatment since the beginning of the 21st century [9], [10]. For this purpose, they are modified by using biologically active and rare elements, increasing their performance range and application [11],[12]. Figure 1 summarizes the different cancer treatment approaches using BGs and BGCs, including radiotherapy, drug delivery, phototherapy, and hyperthermia.

Radioactive biomedical glasses are already used to kill cancerous cells through the emission of radioactive beta radiation. These glasses are either non-biodegradable or biodegradable radioactive glasses. Yttria-alumina-silica (YAS) compositional system is one of the most famous non-biodegradable groups of rare earth aluminosilicate (REAS) glasses used in brachytherapy, which is an internal radiation therapy with seeded radionuclides inside or in

the vicinity of the treatment area. When radionuclides are irradiated, the radioembolization effect significantly reduces blood flow to the cancerous tumor and, hence, reduce the tumor mass. This procedure may complement chemotherapy or surgery (Figure 1-A) [13].

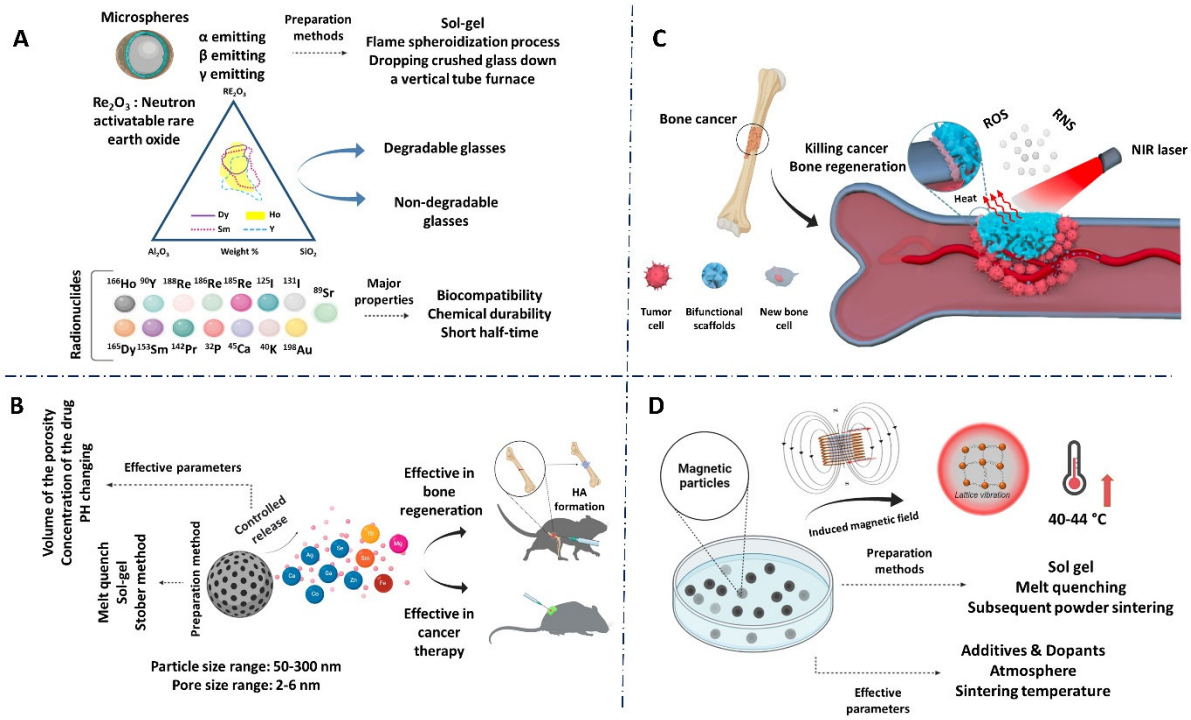

Figure 1. The different cancer treatments with biomedical glass and glass-ceramics: **(A)** Radiotherapy, **(B)** Drug delivery, **(C)** Phototherapy (adapted from ref. [14]) and **(D)** Magnetic hyperthermia.

Mesoporous bioactive glasses (MBGs) can treat cancerous tumors more purposefully; controlled loading and release of drugs are performed in addition to the inherent properties of glasses, such as the ability to regulate gene expression and regeneration of lost tissue, including bone. Emerging drug delivery systems based on pH-triggered drug release by MBGs are designed to selectively enhance chemotherapy of drugs based on the pH distinction between normal and cancer tissues. These smart systems provide more toxicity to cancer cells *in vitro* and show selective damage of tumors *in vivo* (Figure 1-B) [15]–[18].

Various biologically active elements such as copper and bismuth with photothermal (PT) conversion properties have been incorporated in glasses. These glasses in photothermal therapy (PTT) damage cancer cells by absorbing the near-infrared (NIR) light of the laser and converting it into heat. Recent research has shown that heat generation can form reactive nitrogen species (RNS) or reactive oxygen species (ROS) in the patient's body and destroy cancer cells under photodynamic therapy (PDT) or gas therapy (Figure 1-C) [19].

Magnetic BGCs are another group used to combat cancer. The magnetic phases/crystals are formed within the glassy matrix by controlled heat treatment, resulting in the formation of glass-ceramics. When a magnetic field is applied to these substances, the magnetic phase can generate heat, thus yielding a controlled local increment of the temperature under the treatment mechanism of hyperthermia. This overheating kills cancer cells without damaging healthy cells (Figure 1-D) [20].

In the last few years, enormous progress has been made in developing BGs and BGCs for new and intelligent cancer treatment methods [21]. As such, the main focus of this article is to snapshot the application of BGs and BGCs in emerging treatment approaches such as radiotherapy, drug delivery, phototherapy, and hyperthermia. The simultaneous use of several treatment methods to maximize therapeutic effect is also highlighted for future research.

2- Radiotherapy

Unlike chemotherapy and surgery, which are the most typical cancer treatments, radiation is a less invasive strategy that can be applied either from the inside or outside the body. Radiation therapy can destroy tumor cells by damaging the DNA of cancerous cells and losing the competence to divide and proliferate or reduce the size of the malignant mass by applying ionizing radiation as a physical therapeutic agent [22],[23]. Ionizing radiation consists of subatomic particles (photons, protons, and electrons) or electromagnetic waves that have enough energy to ionize atoms or molecules by separating electrons from them [24]. In addition to damaging cancerous cells, radiation therapy is sometimes harmful to normal cells. Still, they can keep their functions due to quicker self-repair than neoplastic ones [25],[26].

There are two strategies for radiation delivery to the injured site. The first case is ab externo (from outside the body, external beam radiation is given to the tumor location) which is the most commonly used clinical approach and typically operates with high-energy gamma rays, X-rays, or electrons (provided by a linear accelerator). The second case is ab interno using a radioactive source that delivers internal radiation from inside the body directly to the cancer site [23]. This radioactive source can be left in situ indefinitely (permanent brachytherapy) or be terminated and periodically replaced to preserve its therapeutic activity (temporary brachytherapy) [27].

In brachytherapy, the radioactive sources are immobilized or sealed in microspheres, capsules, seeds, wires, or pellets. The appropriate radioactive sources for brachytherapy are chosen depending on the patient's clinical conditions, disease stage, and physical aspects of radionuclides such as emitted radiation, the half-life time, associated average energy, and the emitted dose rate [23]. The selected radioisotope usually emits beta-ray with a short half-life and high energy or, in a few cases, alpha radiation for cancer treatment [28]–[30]. Brachytherapy has been successfully used to treat soft tissue cancer (gynecological and prostate malignant tumors) [23] and osseous tumors (Ewing's sarcoma and metastatic bone cancer) [23],[31],[32].

Usually, radioactive seeds for brachytherapy consist of ^{125}I as a radioactive element embedded in a metallic capsule (Ti in most cases) (Figure 2-A) [33]. Still, because of the long half-life of ^{125}I (59.5 days), it can be replaced by ^{90}Y with a shorter half-life (64.2 h) [34]–[36]. However, using this metallic capsule may require invasive extra-surgery for its removal [34]. Therefore, investigations have been conducted to find new materials to replace radioactive sources [36],[37]. Glasses with particular compositions are good candidates for brachytherapy, which host radionuclides in the glassy matrix. They can be non-degradable or degradable [38]. There are also two synthesis methods for radioactive glass fabrication. The first method includes combining the batch material with the radioactive agent and blending them, which causes the radioisotope to become an integral part of the glass. The second method is making radioactive glass from non-radioactive glass (specifically, oxide glasses) by neutron activation. This method is more common than the first one [38]. The remarkable point that must be avoided is the generation of some neutron-activated radioisotopes of Ca, K, and Na (the typical ingredients of oxide glasses) with a long half-life of about thousands of years. Also, the biocompatibility and chemical durability of glass matrices are other critical issues that must be considered [35],[39].

In order to avoid the production of undesirable radioisotopes from highly soluble K and Ca with a long half-life (1.25×10^9 years and 162.7 days, respectively) during neutron activation processes, a rare-earth doped aluminosilicate (REAS) system was studied by Day *et al.* in the early 1980s [35],[40],[41]. REAS consists of three oxides (Al_2O_3-SiO_2-RE_2O_3, where RE_2O_3 is the neutron-activated rare earth oxide) and is a good candidate for radiotherapy agents due to the fast decay of radioisotope produced during neutron activation processes. Furthermore, these glasses have excellent durability in the biological environment and do not release any radioisotope *in vivo*. REAS glasses used in brachytherapy have been produced in

different shapes like rods (based on the $46.8Sm_2O_3$-$18.2Al_2O_3$-$35SiO_2$ wt.% system) (Figure 2-B) or microspheres ($55Y_2O_3$-$20Al_2O_3$-$25SiO_2$ wt.%) (Figure 2-C). REAS includes beta-emitting ^{90}Y (with a half-life of 64.2 h), ^{153}Sm (46.7 h), ^{165}Dy (1.257 minutes), ^{166}Ho (26.7 h), and $^{186}Re/^{188}Re$ (90.6 h/17.0 h). The REAS glasses carrying ^{90}Y or ^{166}Ho present dual functions of avoiding the growth of a tumor and decreasing the mass of the tumor [38].

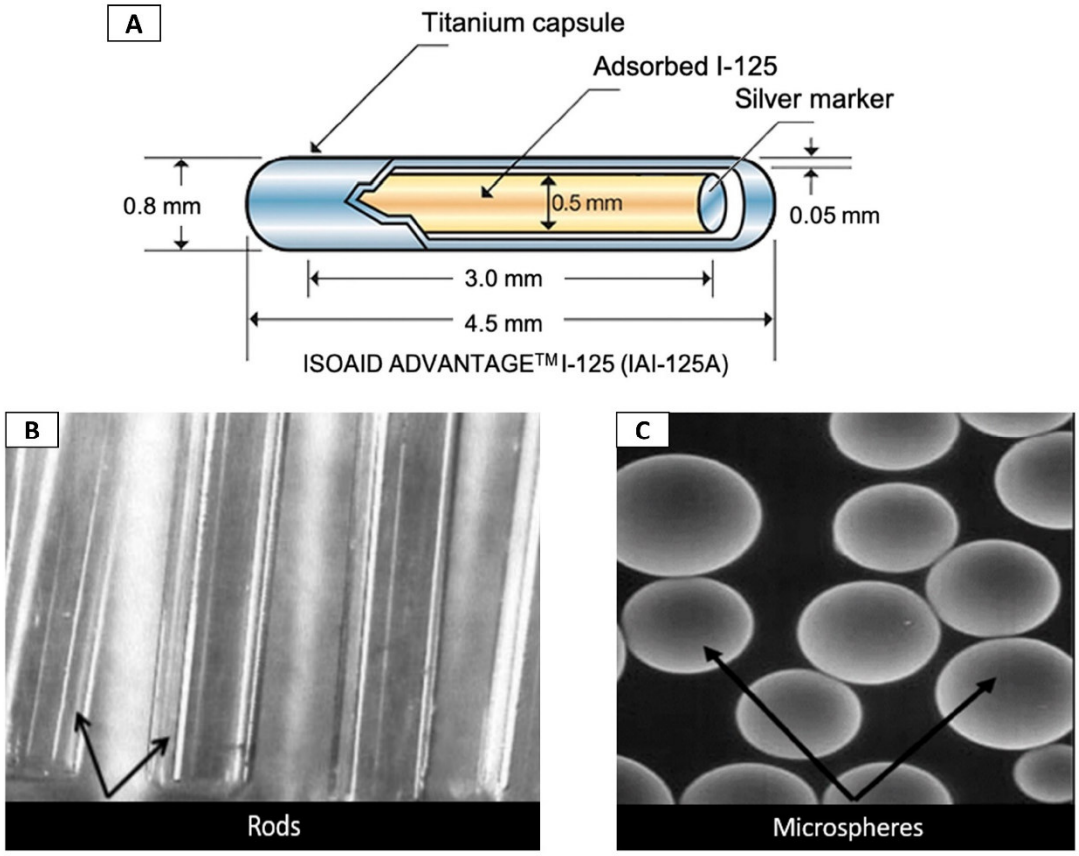

Figure 2. **(A)** A sample of commercial seeds with clinical use for brachytherapy [27]. **(B)** Rods and **(C)** Microspheres made of REAS glass in brachytherapy [28].

Yttria-alumina-silica (YAS) glasses are the most famous family of REAS glasses. These glasses have been synthesized by the flame spheroidization method in the form of microspheres (diameter around 20-30 µm). They kill cancerous cells by simultaneously emitting radiation and performing an embolization effect on the capillaries (radioembolization), which can be used in liver cancer radiotherapy [35],[36],[40],[42]. YAS glasses containing up to 55 wt.% Y_2O_3 have excellent chemical durability. It is also reported that the $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ (wt.%) glass does not release any appreciable amount of ^{90}Y *in vivo* [40]. In 1989, the first clinical trial reported by Boos *et al.* showed a considerably positive outcome in 35 of 46 patients suffering from liver cancer, with full recovery of 1, partial recovery of 6, and disease

stability of 24 cases. Furthermore, the mean survival time for the respondent patients was 16.1 months versus 8.8 months for the unresponsive patients [43].

In 1999, ^{90}Y-containing glass microspheres, after being endorsed by the Food and Drug Administration (FDA), started being commercialized under the TheraSphere® brand (Boston Scientific Corporation, Watertown, MA, USA) [35]. They are currently used to treat patients with primary liver cancer that cannot be removed by surgery (unresectable hepatocellular carcinoma) [44],[45]. This product is clinically applied in more than 200 specialized global centers. The microspheres containing ^{90}Y injected into the hepatic artery can be deposited in the capillary bed by radioembolization effect, decreasing the blood flow to the malignant tumor. Then, other follow-up treatments like transplants or surgery with observed significant reduction of a tumor mass can be performed [40],[35]. In addition, life expectancy has increased in terminal patients from 5-7 months to 12-24 months. Compared to chemotherapy or other cancer therapies, TheraSphere® has minor side effects and only causes flu-like symptoms such as mild fever, fatigue, or abdominal pain that may persist in patients after treatment for several days [40]. In 2006, Bretcanu and Evans provided a comprehensive review of TheraSphere® clinical applications for liver cancer treatment [46]. More recently, Daniel Boyd's team at Dalhousie University, Canada, has developed another radioactive glass that triggers radioembolization and shows promise for treating cancer. This product, trade named Eye 90 Microsphere™ glass, is being commercialized by ABK Biomedical Co. [47]–[49].

Recently, it was observed that TheraSphere®-based therapy combined with chemotherapy had advantageous effects in selected patients with metastatic colorectal liver cancer. Still, even patients with the chemotherapy-resistant disease received some benefits from the treatment [50]. Hence, an investigation for assessing the safety and efficacy of TheraSphere® radioembolization assisted with second-line therapy was launched in 2018 in patients with metastatic colorectal carcinoma of the liver who had disease advancement during or after first-line cancer chemotherapy. Phase 3 pilot studies have begun at 100 sites in Canada, the USA, Asia, and Europe, and investigation is ongoing [51].

One of the main functions of glasses is their capability to release ions *in vivo*, which can help cell proliferation, gene activation, osteogenesis, or elicit angiogenesis, antibacterial, anti-inflammatory effects, leading to more efficient tissue and bone regeneration. Biodegradability can also be helpful along with the radioactivity of glass. When cancer cells are surgically removed, some small-scale cancer cells that cannot be removed may be left behind and

destroyed by the radioactive glass. It is also possible that some tissue or bone may be damaged or removed by surgery, which demands tissue regeneration by bioactivity and ion release properties of BGs.

The critical issue which could not be neglected is the released amount of the therapeutic substance or element from the glass carriers. This issue is truly crucial for biodegradable radioactive glasses as the amount of released radionuclide for brachytherapy must not stimulate the immune system or induce toxic effects in healthy tissue [30].

In 2003, Roberto *et al.* introduced the first radioisotope vectors based on biodegradable glass for therapeutic brachytherapy. In this study, to achieve a similar yield to titanium-encapsulated ^{125}I seeds, a group of biphasic materials combined a SiO_2 gel-derived glass with high chemical stability in the biological fluid, and a biodegradable SiO_2-CaO glass carrying neutron-activated ^{153}Sm radioisotope was used [52]. The ^{153}Sm radioisotope has a shorter half-life than the ^{125}I radioisotope and could operate better in a biodegradable carrier for a short and acceptable duration of several months. However, higher concentrations were used to function comparable with the ^{125}I radioisotope [41]. In 2008, Roberto *et al.* also performed X-ray radiographic imaging on ^{153}Sm seeds implanted in rabbit liver after seven months. However, no presence of carrier glass and ^{153}Sm seeds were reported, thus confirming the uptake of glass particles into the liver [53]. Later, Cacaina *et al.* [53],[54] reported that bioactive silicate glasses exhibited different chemical stability depending on silica content. This type of glass showed good potential as a carrier for their lease of Y_2O_3 in simulated body fluid (SBF) in brachytherapy. The general rule is that the more silica in bioactive glass, the less chemical solubility is. As a result, glasses with lower silica content have more yttrium release. On the other hand, the presence of yttrium increases the chemical stability of the glass [35], thus allowing a multiple control on glass dissolution kinetics.

Other biodegradable glasses for potential use in brachytherapy include melt-derived alkaline borate and borosilicate glasses. When these glasses are not radioactive anymore, they gradually decompose in the body over hours or weeks [38]. For example, during the decomposition of dysprosium-containing lithium-borate (DyLB) glasses, radioisotopes of Dy react with phosphate and calcium in the body fluid and form insoluble phosphates [56]. In principle, the microspheres react nonuniformly by releasing almost entirely soluble constituents (here B and Li), whereas dysprosium phosphate forms. The initial glass loses up to 80% of its weight after 64 days of implantation. 10-mg injected glass into a human joint

forms only 2 mg of an insoluble dysprosium phosphate-rich reaction product. It is assumed that this low amount will create no tissue damage in humans since the1 mg injection into the much smaller mice joint did not cause any damage. To date, studies have been performed on borate glass microspheres containing the ^{153}Sm, ^{90}Y, ^{166}Ho, ^{165}Dy, and ^{186}Re isotopes but have not yet reached the commercialization stage [38]. However, more studies are needed to investigate the dissolution mechanism of these glasses to understand their *in vivo* and *in vitro* behaviors [56].

Nogueira *et al.* [57] showed that sol-gel-derived glasses containing radioisotopes of Ba, Zr, and Ho allow better visualization under radiographic imaging due to the additional role of Ba and Zr as contrast agents. Specifically, the glass sample loaded with Ho and Zr showed a significantly better radiological contrast than the sample loaded with only Ho. The presence of Zr also decreases the degradability and bioactivity of glass. ^{166}Ho-doped glass compared to the Sm-containing one can treat smaller tumors faster due to its higher energy [58].

Recently, Piagentini Delpino *et al.* [59] examined Ho-doped 58S glass for brachytherapy. The results showed that the Ho content significantly affects the kinetics of the hydrolysis reaction: specifically, the addition of holmium ions in the glass structure decreased the energy barrier of hydrolysis reactions, thus accelerating glass dissolution in an early stage, while the strength of Si–O–Ho bonds yields a more stable dissolution in the long term. Although a high concentration of Ho was added into the glass, most of this dopant remains in the glass structure, thus preventing toxicity. Figure 3 summarizes the structure, *in vitro* bioactivity, and cell culture experiments on 58S gel-glass ($60SiO_2$–$36CaO$–$4P_2O_5$ mol%). It was observed that Ho had no adverse effect on glass bioactivity and can stimulate more pre-osteoblast cell proliferation as compared to the Ho-free control sample (58S) (Figure 3) [59]. ^{166}Ho-containing BGs produced more radiation to the tumor tissue than other radioisotopes, and the short-range penetration of beta particles is useful to minimize damages to the adjacent healthy tissue [60],[61].

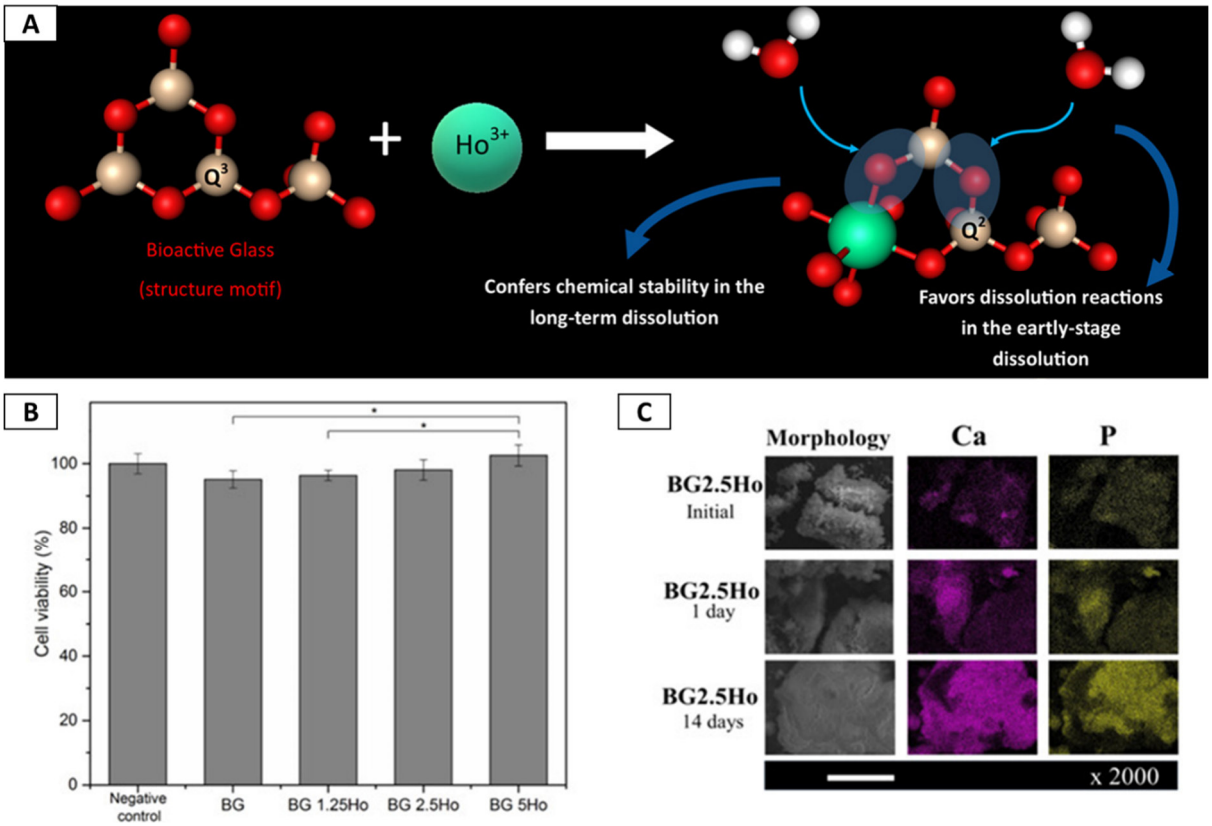

Figure 3. **(A)** Schematic representation of Ho-doped 58S glass structure, containing silicate tetrahedrons with holmium in octahedral coordination. Water attack possibilities in this glass (right side) should be considered for the chemical stability of Ho (radioactive) ion in the long-term degradation and early-stage dissolution of non-radioactive elements. **(B**) Osteoblast cell culture experiments on Ho-doped bioactive glass. **(C)** Results of *in vitro* apatite forming ability on 2.5 mol% holmium-containing glasses before and after 1and 14 days immersed in SBF solution confirm the apatite forming ability of this glass [59].

3-Drug and ion delivery

BGs can act as a powerful local drug delivery system by adsorption, establishing covalent or non-covalent bonds to trap drugs in their cavities [62]–[64]. Compared to other biomaterials, BGs can also act as vehicles for the controlled release of ions that can regulate gene expression of cells, which makes them multifunctional candidates in cancer treatment [65]–[69]. These carriers show slow and continuous *in vitro* sustained drug release due to the dissolution of the glass matrix, which is accompanied by ion release as well [70].

Mesoporous bioactive glasses (MBGs), first synthesized two decades ago, have become an ideal option in topical and targeted tumor therapies due to their ability to deliver drugs along with various therapeutic elements. Figure 4-A illustrates the schematic preparation of drug-loaded MBGs. Active targeting of MBGs is accomplished by functionalizing their surface by factors such as peptides, antibodies, or proteins [71]. One of the most critical issues in cancer

treatment by drug delivery systems is how to differentiate cancer and normal cells and use the differences to achieve a selective and more effective treatment. These dissimilarities include pH differences, redox levels, and expression levels of several enzymes and receptors [17], [18], [72].

The innovative drug delivery systems that have received so much attention are environmental-sensitive carriers [73]. They consist of ionizable components (e.g., amines or carboxyl groups), and their structure changes under pH change [74]. Consequently, the pH gradient will act as the driving force behind the release of the drug from the glass carrier in such systems (Figures 4-B; 3&4, and 4-C) [74].

In some cases, a more finely controlled drug release can be achieved by using pH-sensitive polymer coatings on the surface of glass carriers [75]. The results demonstrated that these smart systems provided higher toxicity for cancer cells *in vitro* and showed a selective increase in tumor death *in vivo* [15], [75]–[86]. After entering the body, the drug goes through four stages, including absorption, release, metabolism, and excretion. The drug should be metabolized after entering the body and reaching the target tissue or cell and easily be eliminated from the body after creating the effect [87]–[92].

Specific surface area, composition, pore size, and particle size are among the key factors influencing the rate of glass degradation as well as their biocompatibility in contact with the biological fluid [65]. On the other hand, drug delivery can be controlled by changing the porosity volume, drug concentration, pH of the environment and by adding different dopants in the glass structure [77], [83], [85], [93]–[101]. Shoaib *et al.* [74] studied the effect of drug loading concentrations and pH for the controlled release of Imatinib (IMT) against cancer cells in MBGs (Figure 4-C and 4-D). IMT was loaded with 77.59% efficiency, and its release was affected by the drug loading concentration (0.2–1.0 mg/mL) and the pH of the medium where the release takes place (4.4-10.4). 81% of IMT was released for 250 h at an acidic pH=4.4 at 12.19 µg/mL of IMT-MBG, and significant inhibitory effects were observed on the viability of MG-63 osteosarcoma cancer cells [74].

It has been proven that hollow spheres of MBGs doped with different ions (Ag, Ca, Sm, Tb, Se) have a higher drug loading capacity and more stable release than dopant-free BGs [77], [83]–[85], [102], [103]. Interaction between ions and drugs can synergistically enhance the anticancer effect and improve drug loading [98], [102]. Rahman *et al.* [84] reported that Ag-doped MBG nanospheres have higher drug storage capacity and more stable release of DOX

than the pure MBG nanospheres. It was shown that Ca-MBG nanospheres loaded with DOX could effectively inhibit tumor growth [102], [103]. MBG nanospheres showed continuous and long-term local release of DOX in many studies [82], [86], [104]. Meng Hu et al.[77] studied the cytotoxicity of DOX-Se-MBG and DOX-free nanospheres (Se-MBG) in the context of bone tissue engineering. It was proved that the cytotoxicity of DOX-Se-MBG and Se-MBG nanospheres depends on release time and drug dosage. The viability of MG63 osteosarcoma cells cultured with DOX-Se-MBG nanospheres was slightly higher than the positive control (DOX-free sample), attributed to the interaction between DOX and Se. Indeed, the effect of this synergy apparently seems not so helpful for cancer therapy. However, although Se-MBG nanospheres had a faster inhibitory effect on MG63 osteosarcoma cells in the short term, DOX-Se-MBG nanospheres provided a long-term inhibitory effect on the same cells [77].

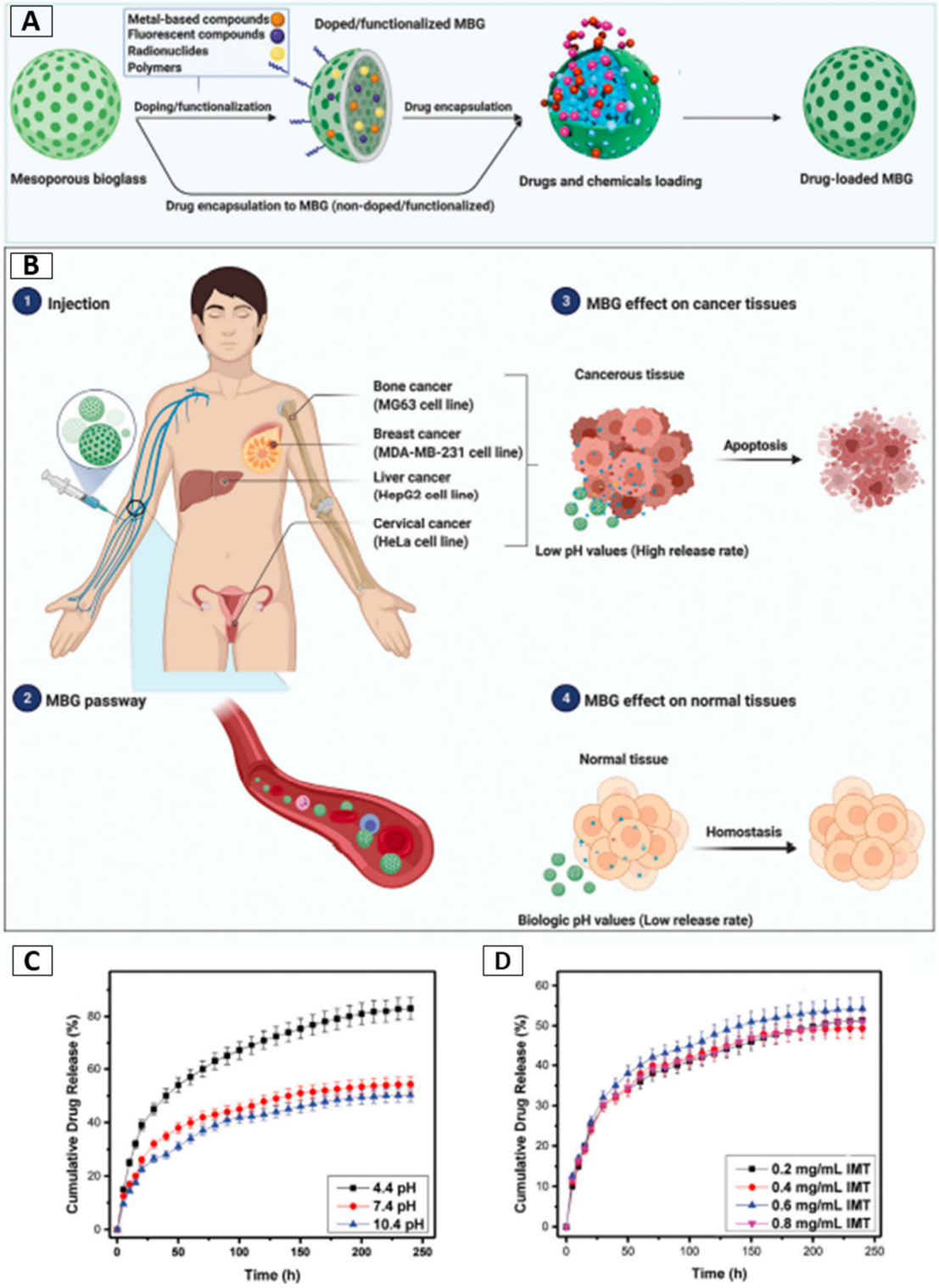

Figure 4. **(A)** Schematic of drug-loaded MBG preparation. **(B)** The effect of MBGs on cancer cells and normal cells [105]. Cumulative drug release profile **(C)** against different pH and **(D)** against different drug loading concentrations [74].

The doping of various elements can influence the microstructural and morphological properties of the MBGs. Ion concentrations can alter drug release due to changes in the number

of ionic bindings [77], [83], [85]. Also, even the type of ions can affect drug loading concentrations. For example, doping with Cu and Se [106], [107] was shown to be associated with drug loading increase, but Mg, Zn [106], [108] reduced the drug loading concentration in MBGs structure. The effect on drug loading capability is related to morphological changes in terms of pore volume, surface area, and pore size of MBGs. For example, adding a certain amount of cerium in the glass structure increases the pore size and reduces the specific surface area [109]. Furthermore, the addition of metal ions into the structure of MBGs changes the surface charges of nanoparticles, yielding a direct impact on particles aggregation [98], [110].

Se [77], [111], Ca [112], Ga [113], Cu, Ag [110], [114]–[116], Zn [117] have shown anticancer properties. Each of these ions exhibits this property via a different mechanism [110], [118], [119]. However, the production of reactive oxygen species (ROS) – stimulated by such ions – has always been a key factor in developing anticancer properties [120].

Concentrations of calcium ions in the glass structure can also be effective in drug release and control [103], [121]. Excessive calcium ion release from the glass structure can damage cells and kill them through apoptosis, thus stimulating the anticancer effect [98]. Released calcium from the glass structure can suppress cancer growth by activating calcium sensor channels on cancer cells with the least damage to healthy cells [112]. Ion doping such as Mg and Co provides anticancer properties if these ions are appropriately released from the glass structure properly. This release can be controlled depending on the concentration of dopants and the pH of the release medium [75], [122]. Low and suitable concentrations of cobalt ions can cause angiogenesis during tissue regeneration due to their hypoxia-mimetic effect. If cobalt ion is released rapidly and extensively in situ, this ion can cause the death of cancer cells by ferroptosis [120], [123]–[138]. Ferroptosis is generally a type of cell death caused by ROS accumulation due to Fenton's or Fenton-like reactions [120], [139]–[141]. On the other hand, we cannot ignore that cobalt has a potent pro-angiogenic effect, which could contribute to cancer development, thus achieving an opposite effect. Oxidative stress of cells and the production of ROS have been shown to be induced by selenium ions [77], [111], [142]. Also, Ga-doped BGs show the ability to suppress cancer cells [143].

Ferroptosis is a type of programmed cell death dependent on iron and is detected by lipid peroxides accumulation. It is biochemically and genetically different from other types of regulated cell death, like apoptosis. Recently this method attracted significant attention in cancer therapy that kills cancer cells by ROS generation via iron ions mediated Fenton's

reaction. Among ferroptosis-based cancer therapies, metal-containing nanomaterials meddling with ferroptosis cancer therapies efficiently induce ferroptosis of tumor cells without complex cellular signal transduction [120]. Also, therapeutic metal elements incorporation into a MBG and controlled release of these soluble therapeutic ions developed MBG with therapeutic properties such as Fe for ferroptosis [144]. The release of Fe ions results in catalytic H_2O_2 decomposition inside the tumor cells and production of ROS, a Fenton's reaction [145]. Fe ions-releasing MBG ultra-small nanoparticles synthesized by a simple one-pot ultrasonic-coupled sol-gel synthesis can be used as a ferroptosis-based bone cancer treatment. Also, adding 10%Fe_2O_3 to 85SiO_2–15CaO (mol%) glass reduced the particle size and simultaneously increased the specific surface area [139].

MBGs can also be effective in other cancer treatment methods such as photothermal therapy and hyperthermia, depending on the type of ions that they carry [110], [137].

4-Phototherapy

A laser-irradiated cancerous region could be locally heated in PTT due to the possibility of controlling laser penetration. In this case, overheated cancer cells are killed without harming other organs or tissues. Various nanoparticles have been utilized as PT conversion agents that absorb NIR-light and transform it into heat [146]. The PT effect caused by optical input can also generate the thermal apoptosis of cancerous cells. Studies showed that metal ions doping in the glass structure could provide PT therapeutic ability. Liu *et al.* [69] reported the first PT effect in BG doped with copper, iron, manganese, and cobalt ions. Bismuth [147] and carbon dots [148] also induced a PT effect in BGs.

One new idea was to make multifunctional glasses for cancer treatment by combining radiotherapy, drug delivery, and PTT and using BGs to regenerate bone. Multifunctional glasses with anticancer and bone regenerative properties can eliminate bone tumors and often lead to new bone formation to achieve optimal bone tumor therapeutic effect. Wang *et al.* [147] fabricated Bi-doped BGs for triggering PT and bioactivity response for tissue repair and bone tumor therapy. A Bi-doped BG equips photo-induced hyperthermia and enriched remineralized bone tissue. The high PT transformation of Bi locally raised the temperature from 42 to 86 °C depending on the irradiation time and Bi concentration (Figure 5-A). The PT effects were managed by controlling the nonradiative and radiative procedures. Also, Bi-doped BGs

demonstrated non-cytotoxicity before and after laser irradiation and showed an effective inhibitory effect on cancerous cells viability. It was proved that more than 80% of human osteosarcoma line U2OS tumor cells were killed under NIR-light (Figure 5-B) [147]. Such dual-functional materials exhibit remarkable bioactivity and tumor therapy, offering a new horizon for bone tumor treatment. Copper is another element that can be added to MBGs, giving PT effect while maintaining bioactivity. Copper-doped BGs provide good opportunities for biomedical applications due to their excellent biocompatibility, antibacterial properties, bone regenerative potential, and cancer theranostics [149]. In PT, it is critical to apply a very homogeneous laser on the treated area, otherwise localized hot spots damage the tissues.

Chang *et al.* [150] synthesized copper-doped MBGs with excellent drug loading capacity, good bioactivity leading to apatite formation and mineralization, and excellent photothermal properties. The photothermal effect could well modulate the drug release, thus allowing a combination of chemotherapy and photothermal therapy to enhance tumor eradication.

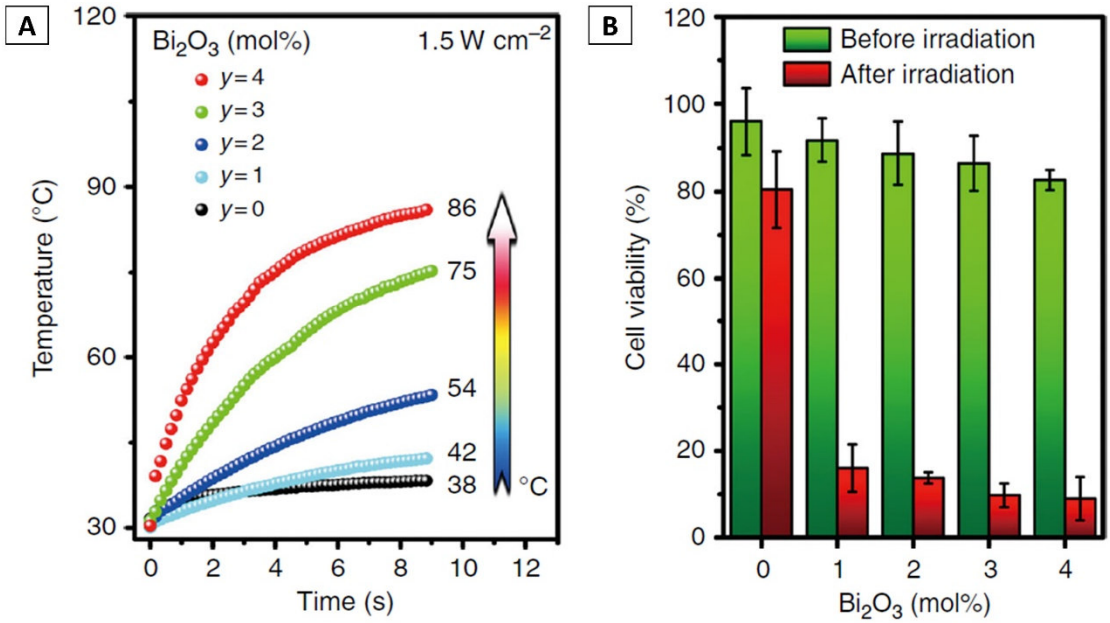

Figure 5. **(A)** Diagram of temperature changes over time for Bi-doped BG samples immersed in SBF solution for various irradiation times (at a power density of 1.5Wcm^{-2}). The temperature of S6PyB rises from 42 °C to 86 °C when the concentration of Bi_2O_3 in the glass extends from 1 to 4 mol%. **(B)** Cell viability of Bi-doped BG before and after laser irradiation (808 nm at 1.5Wcm^{-2} for 5 min) [149].

Another innovative developing method for cancer therapy is gas therapy to generate RNS where adjustable nitric oxide (NO) generation plays a critical role in bone regeneration, combinatory progression of coupled vascularization, and sequential adjuvant tumor ablation.

Multifunctional biomaterial system of 2D Nb_2C MXenes wrapped with S-nitrosothiol-grafted mesoporous silica with 3D-printed BG scaffolds showed the specific characteristics of controllable NO release, stimulatory bone regeneration, and highly efficient PT conversion. This multifunctional biomaterial can be coordinated for multitarget ablation of bone tumors to improve localized osteosarcoma treatment due to the NIR-triggered photonic hyperthermia of MXenes in the NIR-II bio window and controlled release of NO [151].

5-Magnetic hyperthermia

Among the mechanisms of tumor cell death induced by the most common thermo-ablation techniques, hyperthermia uses magnetic materials exposed to an external magnetic field to generate a local temperature increase above 42 °C. This temperature rise destroys cancer cells without significantly damaging normal tissues [146],[152]. Although various biological effects can simultaneously appear like heat-induced alteration of cell signaling pathways, expression of heat-shock proteins, RNA and DNA alterations, the direct cytotoxic effect of heat, and many other biochemical changes, the precise mechanism of hyperthermia is not yet completely understood [153],[154]. This method is associated with less unfavorable side effects than conventional therapies of various tumors such as glioblastoma, prostate, and metastatic bone cancer. Hyperthermia can be combined with other treatments like PTT, PDT, immunotherapy, gene therapy, chemotherapy (drug delivery), and high-intensity focused ultrasounds [20].

Superparamagnetic iron oxide nanoparticles (SPIONs) can significantly reduce or eliminate the population of cancer cells in the patient's body by generating heat due to magnetic hyperthermia. Unlike SPIONs, BGs usually do not exhibit any inherent magnetic behavior unless a magnetic phase, such as Fe_3O_4, is embedded or somehow nucleated in the glass network (e.g., by thermal treatment), thus obtaining magnetic BGCs [155]. Glass-ceramics generally have better mechanical properties and may also inherit – at least partially – the bioactivity of the parent glass. The magnetic crystalline phases in glass-ceramics cause heat generation when exposed to a magnetic field, helping to kill cancer cells [20]. Both melt-derived BGCs and gel-derived mesoporous BGCs with various compositions or dopants were synthesized in order to improve their efficiency for hyperthermia application [156]. It has been shown that MBGs containing iron oxide phase(s) (Fe_3O_4, FeO) are endowed with the double ability of loading/releasing anticancer drugs and eliciting a hyperthermic effect due to the

presence of magnetic crystals via ferrimagnetic properties [76], [78], [86], [157], [158], [157]–[159].

Many fabrication techniques like melt-quenching, powder-sintering, and sol-gel, as well as various compositions such as SiO_2-CaO-Fe_2O_3-ZnO [160], SiO_2-CaO-Na_2O-Fe_2O_3 [161], [162], SiO_2-Na_2O-CaO-P_2O_5-FeO-Fe_2O_3 [163], SiO_2-CaO-Fe_2O_3-B_2O_3-P_2O_5 [164], SiO_2-Fe_2O_3-Li_2O-CaO-MnO-P_2O_5 [165], SiO_2-CaO-P_2O_5-MgO-MnO_2-Fe_2O_3 [166], SiO_2-CaO-P_2O_5-Fe_2O_3-ZnO-Na_2O [167]–[169], and SiO_2-CaO-P_2O_5-MgO-CaF_2-MnO_2-Fe_2O_3 [170]–[172] were investigated so far for hyperthermia.

Fabrication methods, sintering temperature, crystallization [173], [174], synthesis atmosphere [175], additives [176],[177], and dopants [159],[178] are important parameters that affect the structural, magnetic and biological properties of BGs and BGCs. Apart from the conventional fabrication methods, new techniques like the sol-gel method, electrospinning, and 3D printing were also developed to improve the properties of BGs and BGCs. More reactive materials in a wider compositional range are obtained by the sol-gel method as compared to the traditional melt-quenching route due to the unique textural properties (for example, inherent nano-porosity) that directly derives from the sol-gel synthesis process [179]–[181]. However, nucleation and crystallization in sol-gel BGs are more complex and difficult to control compared to melt-derived systems [182].

BG fibers (BGFs), mainly fabricated by the electrospinning method, have potential biomedical applications due to their unique fibrous structure, resembling the structure of fibrin clots. Fe-doped mesoporous BGFs (Fe-MBGFs) fabricated by this method has a weak coercive field and a narrow hysteresis loop. The magnetic property of Fe-MBGFs can be enhanced by more iron salt precipitation into the porous polystyrene fiber template. Multifunctional scaffolds with hyperthermia and local drug delivery functions were constructed from these Fe-MBGFs for bone defects therapy [183].

Magnetic composite scaffolds were fabricated by M. L. Dittler *et al.* [184], who coated a foam-derived 45S5 Bio-glass® structure with iron-doped hydroxyapatite (Fe-HA) nanoparticles. This magnetic 3D Fe-HA-BG scaffold has potential application in biology and nanomedicine as contrast agents for magnetic resonance imaging (MRI), drug carriers, and magnetic hyperthermia application [184].

Multifunctional systems can be fabricated by utilizing 3D printing of scaffolds with glass and magnetic particles. J. Zhang *et al.* [185] studied a 3D-printed multifunctional

Fe_3O_4/MBG/PCL scaffolds with hierarchically meso-macropore architecture and uniform pore size and shape. These scaffolds exhibited sustained anticancer drug delivery, superior apatite-forming ability (bioactivity), and magnetic heating properties due to the presence of Fe_3O_4 nanoparticles. Fe_3O_4 nanoparticles incorporated into the MBG/PCL scaffolds were also beneficial in stimulating the differentiation and proliferation of h-BMSCs [185].

G. Li *et al.* [186] proposed a novel magnetic BGC utilizing graphite-modified magnetite with improved magnetic property. Graphite-modified Fe_3O_4 was incorporated into the BGC via a sol-gel technique and then optimized sintering and quenching procedures enhanced the magnetic properties of the system.

As mentioned, the sintering temperature also affects the properties of glass-ceramics. In $SrFe_{12}O_{19}$-P_2O_5-CaO-Na_2O BGCs, the coercivity of the material increases, and the $SrFe_{12}O_{19}$ crystallite size decreases, respectively, as sintering temperature raises. At the minimum sintering temperature (500 ℃), $SrFe_{12}O_{19}$ phase with the largest crystallite size and highest crystallinity was observed, along with the highest saturation magnetization (M_s) and remanent magnetization (M_r) [173].

Another critical parameter to be taken into account during the fabrication of BGs and BGCs is the control of the atmosphere. Y. Hou *et al.* investigated the effect of the treatment atmosphere on the magnetic properties of CaO-Al_2O_3-SiO_2-Fe_3O_4 glass-ceramics prepared by the powder-sintering method. The magnetic properties of glass-ceramics could be tuned by varying the ratio of Fe^{3+} to Fe^{2+}, which was modified by changing the oxygen partial pressure in the melting process. The air atmosphere during heat treatment causes Fe_2O_3 (hematite) precipitation. On the contrary, using an inert atmosphere such as an argon atmosphere can reduce the amount of oxygen and favour the formation of magnetite [175]. The same authors reported that an increment of heat-treatment temperature decreased the saturation magnetization and remanent magnetization, which was attributed to the reduction of magnetite content because of the remelting of magnetite crystals into the glass matrix at a higher temperature.

Similar conclusions about the effect of the heat-treatment atmosphere (argon vs. air) were also reported by Baino *et al.*, who synthesized Fe-doped silicate glasses and glass-ceramics by the sol-gel method [156].

It was also proven that three main phases of iron oxide (magnetite, hematite, and maghemite) show superparamagnetic properties at the nanoscale. The crystallinity of the

hematite phase was affected by the content of iron oxide in the glass-ceramic composition. However, the final hematite crystal size was not affected by iron oxide content [187]. Also, adding P_2O_5 to magnetic Fe_2O_3-CaO-SiO_2 glass-ceramics promoted the formation of a surface apatite layer (bioactivity) while eliciting low cytotoxicity *in vitro* [188].

Mesoporous lithium-ferrite containing BGs synthesized through the sol-gel technique are another class of promising BGs for hyperthermia. Yazdanpanah *et al.* [189] proved that these glasses are appropriate for use as thermoseeds. The magnetic properties of samples were improved when the content of magnetic crystals increased, and a local temperature of 47.2 °C could be reached under hyperthermic effect.

Koohkan *et al.* [190] synthesized copper-containing MBGs for hyperthermia in bone defect treatment. The addition of copper oxide in Fe-doped BGs increased the magnetic saturation of the sample and improved superparamagnetic behaviors. The presence of copper in the magnetic glass structure caused further calcium release and improved bioactivity. In addition, Fe/Cu-containing MBGs can be used as a multifunctional system combining hyperthermia, therapeutic ion release, and drug delivery. The antibacterial properties of Fe-BG and Cu-BG were also found to be better than those of Fe-Cu-BG [190].

The gradual replacement of B_2O_3 with SiO_2 in a magnetic $20BaO–20Fe_2O_3–xSiO_2–(60-x)B_2O_3–1CeO_2$ glass-ceramic with various compositions (x = 0 − 50 wt%) changed the types of crystalline phases that nucleated in the material, i.e., Fe_2O_3, $Ba_4B_2O_7$, $BaFe_2O_4$, and Fe_3O_4. As a result of this gradual replacement, a “boron abnormal phenomenon” was observed due to the different $[BO_3]/[BO_4]$ ratio in the glass-ceramics composition, which led to a continuous transition from the paramagnetic to the ferromagnetic behavior when x increased from 20 to 30 wt%, accompanied by a significant increase of the saturation magnetization [191].

Glass-ceramic engineering provides versatile flexibility in hyperthermia. It is possible to enhance the magnetic properties or generate heat by developing finely nanostructured glass-ceramic. Shah *et al.* [167] synthesized nano-sized $ZnFe_2O_4$ crystallites with pseudo-single domain structures formed in ferromagnetic zinc/ferrite-containing glass-ceramics by aligning magnetic field.

Some of the most recent studies have focused on the association of hyperthermia with chemotherapy to limit the well-known side effects of chemotherapy. Local heating of tumors increases the sensitivity of malignant cells to drugs, thus allowing a reduction of the drug's dosage and the side effects on the human body [192]. Sometimes a polymeric additive can be

used in the system so that the desired drugs can be embedded in this component. When the magnetic field is applied and the system heats up, the polymer component melts, and the drug is released in a controlled way [193]. Magnetite (Fe_3O_4)-containing MBGs also creates synergy for treating cancer by hyperthermia and concurrent drug delivery, adding value to stimulating bone regeneration [194].

Another approach to enhance BG properties relies on the design and production of composite materials [195]–[197]. H. Tripathi *et al.* [198] combined strontium-containing BG (46.1SiO_2–21.9CaO–24.4Na_2O–2.6P_2O_5–5SrO wt.%) with manganese ferrite ($MnFe_2O_4$) to obtain a dual-phase magnetic composite with enhanced biocompatibility and antimicrobial properties. The results showed that this composite had an antibacterial effect on both Gram-positive (S. Aureus) and Gram-negative (E.coli) bacteria while exhibiting superparamagnetic characteristics and heating capability for potential use in hyperthermia application [198]. In another study, Matteo Bruno *et al.* [199] have dispersed a ferrimagnetic BGC in a polymethylmethacrylate (PMMA) matrix, thus obtaining a composite cement. The glass-ceramic contained magnetite crystals embedded in an amorphous bioactive SiO_2–Na_2O–CaO–P_2O_5–FeO–Fe_2O_3 matrix. The material was recommended as an injectable bone filler for treating osseous tumors by hyperthermia [199]. *In vitro* properties of this composite bone cement were investigated, and a synergistic effect between bioactivity and cell mineralization was observed, i.e., cells seemed to be stimulated in their mineralization process by the ions released from the BGC particles even at the early stages of culture (72 h) [200].

Among the methods described, new treatments have emerged that lead to new substances in the treatment and control of cancer. Developing BGs and BGCs containing two or more therapeutic approaches such as magnetic, drug-release ability, PT, and radioactive properties is a hot spot zone for future research. There is consent that the immense promise comes when multiple therapeutic actions against cancer are activated simultaneously. For example, Figure 6 shows that magnetic hyperthermia can synergistically combine with chemotherapy and PTT.

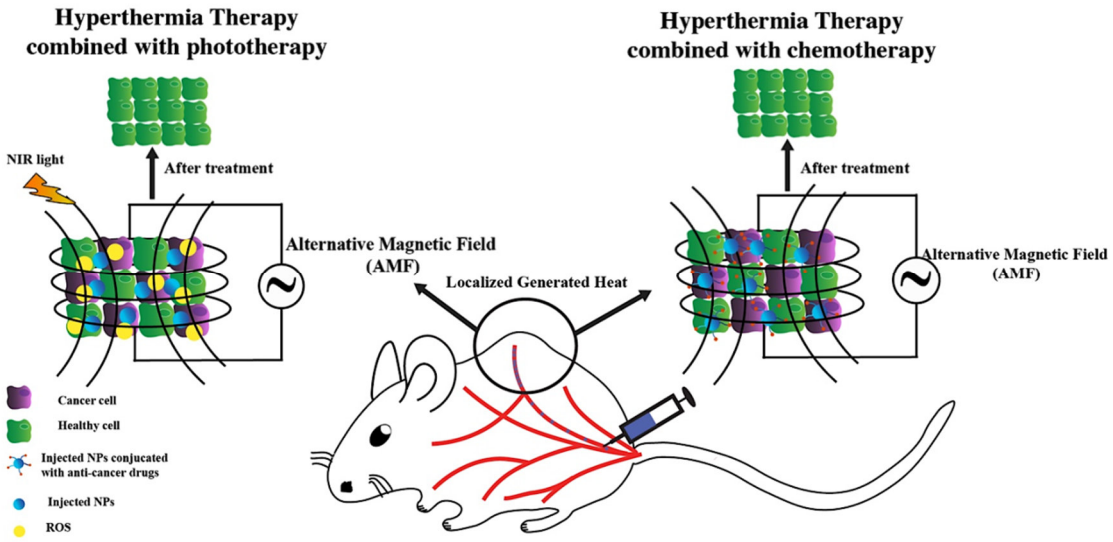

Figure 6. Combining magnetic hyperthermia with chemotheraphy or PTT enhances cancer treatment efficacy.

6- Conclusions and Perspectives

This review paper witnesses that BGs, although being developed more than 50 years ago, still exhibit a great potential in biomedicine and, especially, are highly appealing in the field of cancer therapy. These materials exhibit an exceptional versatility in terms of composition and processing, with an obvious impact on the range of functional properties and biological responses that can be obtained. Hence, the "best" BG option should be designed and tailored depending on the type of cancerous disease and patient's clinical situation as well as taking into account the latest advancments in the field. For example, chemically-inert radioactive glasses have been typically used to treat liver cancer; however, combining radioactive therapy and bio-reactivity of partially-soluble glasses has a great potential to open new treatment perspectives for a broader range of cancer-associated diseases. It is also believed that MBGs are novel systems within the BG family that can stimulate multiple therapeutic actions thanks to their unique composition, easy-to-functionalize nature, and tailorable textural properties such as high surface area, pore size, and pore volume. They are promising platforms that can offer simultaneous controlled drug/ion delivery, healthy tissue regeneration, PT therapy, and hyperthermia, which are all valuable strategies that can be used and/or combined in the fight against cancer. BGCs are also remarkable in terms of having higher mechanical strength and magnetic properties [201]. From the viewpoint of therapeutic response, it is known that combining at least two different strategies is a valuable option as synergistic effects can be achieved by combining different cancer cell death mechanisms. In general, a combination of different therapeutic approaches can yield an improvement of treatment efficacy against

cancer, and BGs/BGCs are indeed a great resource in this regard because of the potential of inherent multifunctionality. These biomaterials also carry other important added values. Today, nanocomposite or hybrid materials that combine biodegradability and bioactivity are extensively researched for 3D bioprinting and tissue engineering. Composite bio-inks incorporating anticancer BGs could permit the development of scaffolds that can replace the resected cancerous tissue (commonly bone), thus regenerating healthy tissue while inhibiting the recurrence of cancer. They can even contribute to 4D bioprinting, where time, pH, or biological parameters are integrated with 3D bioprinting as the fourth dimension. In this regard, BGs can change their functionalities when an external stimulus like pH is imposed or when cell fusion or specific chemical reactions occur. This interesting and emerging research field demands further attention and multidisciplinary collaboration of BG community with other scientific and technological fields.

Future research is envisaged in which theoretical and computational modeling can significantly accelerate the compositional and microstructural design, characterization, synthesis, and application of materials [202]–[204]. In the last 25 years, more than 6 thousand articles and *100 review papers* have highlighted the impact of the discovery of BGs on the pathways of biomaterials research. We applaud these very accurate portrayals of the early days after the discovery of Bioglass® 45S5 by Larry Hench in 1969, the chronology, numerous advances, and future challenges. However, albeit the literature became rich in this topic, few works have addressed data/model-driven approaches to designing new BGs or efficiently predicting their properties. This task should be accelerated as a critical part of the macro-endeavor to decode the "glass genome" [205]. Montazerian *et al.* [206] have recently reviewed all publications that have applied molecular dynamics simulations, machine learning approaches, and meta-analysis for understanding BGs. They argued that more modeling of BGs should be employed to design specific properties of glass, including anticancer properties, in the future. Modeling the therapeutic action of BGs is a complicated but indispensable challenge, which should focus on modeling the biological response of these biomaterials after implantation in terms of impact on processes such as cell proliferation, cell adhesion, protein adsorption, angiogenesis, osteogenesis, bactericidal effects, and anticancer properties.

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