ABSTRACT: Bioactive glasses (BGs) for biomedical applications are doped with therapeutic inorganic ions (TIIs) in order to improve their performance and reduce the side effects related to the surgical implant. Recent literature in the field shows a rekindled interest toward rare earth elements, in particular cerium, and their catalytic properties. Cerium-doped bioactive glasses (Ce-BGs) differ in compositions, synthetic methods, features, and in vitro assessment. This review provides an overview on the recent development of Ce-BGs for biomedical applications and on the evaluation of their bioactivity, cytocompatibility, antibacterial, antioxidant, and osteogenic and angiogenic properties as a function of their composition and physicochemical parameters.

KEYWORDS: BGs, cerium, bioactivity, cellular activity, ROS

1. INTRODUCTION

The treatment of bone injuries from trauma or disease requires materials with specific mechanical and chemical properties. Among them, bioactive glasses (BGs) have been widely used for the treatment of bone defects due to their ability to bond and integrate with the soft and hard tissues of the living body. This property is associated with the formation of a hydroxycarbonate apatite (HCA) layer on the surface of the glass, following initial glass dissolution. HCA is similar to mineral bone and is thought to interact with collagen fibrils to bond with the host bone; in this process, the release of active ions from the BGs is paramount for bone regeneration.

The first BG (45S5 Bioglass, hereafter abbreviated as 45S5) was developed in 1969 with a weight composition of 45% SiO₂, 24.5% Na₂O, 24.5% CaO, and 6% P₂O₅. “Bioglass” was trademarked by the University of Florida for the 45S5 composition. BGs were doped with therapeutic inorganic ions (TIIs) to improve their properties and reduce postimplantation problems and thus the need for lengthy drug treatments and long recovery times. The addition of TIIs to the BG composition can improve the osteogenesis, angiogenesis, antibacterial activity, and cementogenesis of the material.
prompted the investigation of cerium and its compounds for therapeutic applications.\textsuperscript{30-33} Cerium compounds have been known for some time to have relevant pharmacological properties\textsuperscript{34} and have been used, for example, as antiemetics,\textsuperscript{35,36} bacteriostatics,\textsuperscript{37,38} and antitumors.\textsuperscript{39} There are nevertheless limitations to the use of such compounds in biomedicine, namely, their nonspecific biodistribution, limited cell permeability, and low solubility.\textsuperscript{40} These limitations can be overcome by the use of cerium oxide nanoparticles (CeNPs),\textsuperscript{41} which are cell permeable and can be potentially targeted to specific tissues; furthermore, their solubility can be modulated by coating the material with water-soluble polymers.\textsuperscript{41,42} CeNPs can act as both oxidation and reduction catalyst, depending on the Ce\textsuperscript{3+}/Ce\textsuperscript{4+} ratios and the oxygen defects on the surface.\textsuperscript{43} Their redox activity is due to the quick alternation between the two oxidation states. CeNPs can thus act as a multienzyme mimic or radical scavengers (Figure 2) by dismutating or scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS).\textsuperscript{44-46} In the former case, the Ce\textsuperscript{3+}/Ce\textsuperscript{4+} surface ratio is critical in determining the profile of the system, as CeNPs with high Ce\textsuperscript{3+}/Ce\textsuperscript{3+} surface ratios are effective at catalyzing the dismutation of the superoxide anion O\textsubscript{2}\textsuperscript{−} (superoxide dismutase (SOD) mimetic activity), while CeNPs with low Ce\textsuperscript{3+}/Ce\textsuperscript{4+} surface ratios are effective at catalyzing the dismutation of H\textsubscript{2}O\textsubscript{2} (catalase (CAT) mimetic activity). Furthermore, CeNPs can act as scavengers of other ROS such as the peroxide radical (OH\textsuperscript{•}) and RNS like the nitric oxide radical *NO.\textsuperscript{47}

The toxicity of NPs in general is a major concern for their biomedical applications.\textsuperscript{48,49} Although still controversial, CeNPs are generally considered as low toxicity or biocompatible materials.\textsuperscript{50,51} CeNPs are thought not to induce DNA damage or genotoxicity at certain doses.\textsuperscript{52,53} However, there are also a few reports suggesting that these NPs may be toxic depending on their shape, size, and oxidative status. Their in vivo ADMET (adsorption, distribution, metabolism, excretion, and toxicity) behavior needs thus to be carefully investigated before their biomedical application is granted.\textsuperscript{16,25,24}

Conversely, conventional BGs doped with TII s represent a viable therapeutic strategy for the treatment of a range of conditions and diseases and are routinely used in otology, orthopedics, and dentistry.\textsuperscript{54-57} Other potential applications include treatment of ear diseases (1977, in vivo and clinical trial),\textsuperscript{58} treatment of liver cancer (1987, in vivo and clinical trial),\textsuperscript{59} peripheral nerve repair (1998, in vivo),\textsuperscript{60} wound healing (2000, in vivo),\textsuperscript{61} lung tissue engineering (2004, in vitro),\textsuperscript{62} skeletal muscle and ligament repair (2005, in vitro),\textsuperscript{63,64} gastrointestinal applications (2005, in vitro),\textsuperscript{65} cardiovascular tissue engineering (2010, in vitro),\textsuperscript{66} embolization of uterine fibroids (2012, in vitro and in vivo),\textsuperscript{67} spinal cord repair (2012, in vivo)\textsuperscript{68} and treatment of metastatic colorectal carcinoma of the liver (2018, clinical trial).\textsuperscript{69}

The recent literature reports several detailed studies on cerium-doped bioactive glasses (Ce-BGs) that differ by compositions, synthetic methods, features, and in vitro tests. The purpose of this review is to provide a critical overview on the development and applications of Ce-BGs.

2. SYNTHESIS

Ce-BGs are produced by various synthetic methods, each of which corresponds to a specific Ce-BG category. The three most significant categories are discussed below and illustrated in Figure 3, starting with melt-quenching glasses (MQGs), discovered by Hench in 1969,\textsuperscript{1} followed by the bioactive sol–gel glasses (SGGs), also proposed by Hench in 1991,\textsuperscript{70} and most recently by bioactive mesoporous glasses (MBGs), designed and reported independently by Zhao and Vallet-Regi in 2004 and 2006, respectively.\textsuperscript{71,72}

2.1. Melt-Quenching Glasses (MQGs). In the melt-quenching technique, the glass precursors are melted and successively quenched; the first BG of this kind was 45S5,\textsuperscript{1,73} Ions belonging to the rare-earth group are used to improve the properties of BGs;\textsuperscript{74} these ions possess a high field strength and thus tend to aggregate in clusters when melted with other elements.\textsuperscript{75,76} The solubility of rare-earth ions in pure silicate glass is less than 1 mol % but increases in phosphate-based glass, where the formation of clusters is reduced.\textsuperscript{34-36}

In the particular case of cerium, the easy switch between Ce\textsuperscript{3+} and Ce\textsuperscript{4+} oxidation states is the basis of its catalytic activity. The high temperatures required for melt-quenching influence the Ce\textsuperscript{3+}/Ce\textsuperscript{4+} ratio, which depends also on melting isotherm, glass composition, and the partial pressure of O\textsubscript{2} in the oven atmosphere.\textsuperscript{77,78} Moreover, a higher concentration of cerium in the glass favors the increment of Ce\textsuperscript{3+} concentration, while higher temperature promotes Ce\textsuperscript{3+} formation.\textsuperscript{79} At temperatures >1000 °C, in low-alkali borate and silicate glasses, the Ce\textsuperscript{3+} state prevails, while the Ce\textsuperscript{4+} is favored at higher alkali content.\textsuperscript{80} In sodium phosphate derived glasses, the Ce\textsuperscript{3+} state is favored and oxidation does not occur in the presence of oxygen, even when melting temperature reaches 1000 °C.\textsuperscript{81} Several papers reported that the presence of phosphate (calcium meta-phosphate glasses with high silica) favors the Ce\textsuperscript{4+} state independently of the maximum melting temperature.\textsuperscript{82,83}

The first Ce-BGs were synthesized by Lusvardi et al. in 2002\textsuperscript{84,85} using CeO\textsubscript{2} as the cerium precursor. The glass composition was based on 45S5 doped with different CeO\textsubscript{2} amounts (1.5, 3.2, 5.3, or 13.5 wt %). Although the introduction of the rare earth decreases the viscosity of the melt,\textsuperscript{86} the higher amount of CeO\textsubscript{2} (13.5 wt %) and its low solubility in silicate glasses required higher temperature and
longer isotherm. Attempts were also made to produce glasses with higher CeO$_2$ contents, which resulted in an opaque material with a clear phase separation; higher CeO$_2$ content favors the monazite (CePO$_4$) formation in the glass system $15$SiO$_2$$-15$Al$_2$O$_3$$-70$P$_2$O$_5$$-(0 + x)$CeO$_2$ ($x = 0$−$25$ mol %).$^{57}$

2.2. Sol−Gel Glasses (SGGs). Since the 1990s, the interest toward the sol−gel synthesis has increased; in 1991 some BGs in ternary SiO$_2$$-CaO$$-P_2$O$_5$ systems were synthesized by the sol−gel method. The main steps involved are preparation of sol, casting, gelation, aging, drying, and thermal stabilization.$^{5,60}$ The addition of an acid catalyst (acid water-based solutions, such as HCl, HNO$_3$, and CH$_3$COOH$^{61}$) during the sol−gel process is necessary in order to obtain a 3D reticulated structure. With respect to MQGs, SGGs are purer, more homogeneous in composition, and more porous and have higher specific surface area (SSA, usually $\sim$100−650 m$^2$/g). In contrast, MQGs have no porosity, and their low SSA ($\sim$1−2 m$^2$/g) depends only on the particle size resulting from the grinding of the materials. The porosity of SGGs allows the formation of a hydrated layer inside the material, where biological moieties can enter, maintaining their structural configuration and biological activity; SGGs then can become an indistinguishable part of the host tissue. For example, it has been shown that when trabecular rabbit bone was proliferated on 45S5, large particles were still present even if a structure similar to normal bone was obtained. Conversely, no residual particles were observed when SGGs were utilized.$^{62}$ The formation of HCA takes place much faster on the surface of SGGs than on MQGs; furthermore, HCA formation is observed in SGGs with a SiO$_2$ content up to 90 wt %, while it is only observed in MQGs with 60% or less SiO$_2$. $^{63}$

The most common precursors of cerium in SGGs are Ce(NO$_3$)$_3$·$\times$H$_2$O for Ce$_{3+}$ and (NH$_4$)$_2$Ce(NO$_3$)$_6$ or Ce(SO$_4$)$_2$ for Ce$_{4+}$. $^{64}$ Also, for sol−gel synthesis, the equilibrium between Ce$_{3+}$ and Ce$_{4+}$ mainly depends on thermal treatment, glass composition, and the O$_2$ partial pressure during the thermal stabilization. When a Ce$_{3+}$ precursor is used, trivalent state normally prevails at room temperature; over 100 °C partial oxidation to Ce$_{4+}$ starts, and from 200 to 1000 °C, cerium is completely oxidized to Ce$_{4+}$. In the case of Ce$_{4+}$ precursor, at room temperature a partial reduction to Ce$_{3+}$ takes place, and over 100 °C, it tends to be reoxidized.

2.3. Mesoporous Glasses (MBGs). The discovery of silica mesoporous materials (SMMs) in 1991 by company scientists of Mobil Oil Corporation was recognized as a breakthrough that could lead to a number of important applications as host−guest systems.$^{65,66}$ SMMs are ordered porous structures of SiO$_2$ that show high surface area and pore volume. The pore arrangement is regularly ordered in different geometrical shapes with narrow pore size distribution ranging from 2 to 50 nm that can be controlled and modified by using different synthetic strategies.$^{67}$

The synthesis of MBGs is based on the sol−gel methodology, but the procedure involves the addition of a nonionic surfactant (structure directing agent, SDA) to the alcohol or aqueous solvent before the addition of oxide precursor and the subsequent evaporation-induced self-assembly (EISA) process.$^{68,69}$

The most used SDAs are cetyltrimethylammonium bromide (CTAB), Pluronic P127, and Pluronic P123.$^{70,71}$ In particular, cerium-containing MBGs (Ce-MBGs) were synthesized by using Pluronic P123.$^{72}$

After solvent evaporation, the SDA concentration increases and eventually exceeds the critical micelle concentration (cmc), causing micelles to form in the solution. Subsequently, the co-self-assembly of micelle and silicate matrix leads to the formation of the mesophase. The final MBG is obtained after gelling, drying, and surfactant calcination (700 °C). The calcination of surfactant promotes a porous structure that can be ordered (mesoporous ordered structure) or not-ordered (worm-like structure), and this depends on the glass composition.
Table 1. Evaluation of Bioactivity for Ce-BGs

| Composition | Synthesis | Features (dimensions or shape, maximum time of SBF soaking) | Refs |
|-------------|-----------|----------------------------------------------------------|------|
| 45S doped with CeO₂ (0.75, 1.5, 3.2, 10, 13 wt %) | M | Powders, 250–500 μm, 30 days | 54, 55 |
| 3.7 (wt %) Ca₃₋₅(P₃O₁₀)₂F₂/K₂Mg₆Al₃O₁₀F₂ doped with CeO₂ (1 wt %) | M | Glass-ceramics, 28 days | 112 |
| 80 – x) SiO₂–15CaO–5P₂O₅–xCeO₂ (x = 0.2, 1, 2, 3, 5 mol %) | SGE | MBG, pellets, Φ = 6 mm, 7 days | 72 |
| 80 – x) SiO₂–15CaO–5P₂O₅–xCeO₂ (x = 0.2, 1, 2, 3, 5 mol %) | SGE | MBG, powders, <50 μm, 15 days | 98 |
| 80 – x) SiO₂–15CaO–5P₂O₅–xCeO₂ (x = 0.2, 1, 2, 3, 5 mol %) | SGE | MBG, scaffolds, 7 days | 97 |
| 50SiO₂–(45 – x)CaO–5P₂O₅–xCeO₂ (x = 1, 5, 10 mol %) | SG | MBG, 14 days | 100 |
| xCeO₂–(100 – x)(0.25CaO–0.25SiO₂–0.1Na₂O) (x = 1, 2, 5, 7, 5 mol %) | M | Powders, 300–500 μm, 7 days | 106 |
| 56.6B₂O₃–80SiO₂–5.5Na₂O–11.1K₂O–4.6MgO–3.7P₂O₅ doped with CeO₂ (1, 3, 5 wt %) | M | Scaffolds, d₉₀ = 13.2 μm, 30 days | 113 |
| (53 – x)SiO₂–20CaO–6Na₂O–12K₂O–5MgO–4P₂O₅–xCeO₂ (x = 0, 1, 3, 5 wt %) | SG | Electrospray fibers, Φ = 583 nm; powders, 69 < d₉₀ < 145 μm, 30 days | 105, 123 |
| 79SiO₂–15CaO–5P₂O₅–xCeO₂ (mol %) | SGE | MBG (Φ = 10 μm), 30 days | 101 |
| 50SiO₂–(45 – x)CaO–5P₂O₅–xCeO₂ (x = 1, 5, 10 mol %) | SG | Nanofibers (Φ = 158 nm), 7 days | 107 |
| 52SiO₂–24SrO–16Na₂O–8CaO and 52SiO₂–24SrO–16Na₂O–4CeO₂– 4Y₂O₃ (mol %) | M | Disks, SA 100 mm², 14 days | 108 |
| 45S doped with CeO₂ (1.2, 3.6, 5.3 mol %) | M | Powders, 250–500 μm, 28 days | 91, 94 |
| K50S doped with CeO₂ (1.2, 3.6, 5.3 mol %) | M | Slices, 1.0 cm x 1.0 cm x 2.5 cm, 30 days | 109 |
| 15CaF₂–10CaO–5B₂O₃–(65 – x)P₂O₅–xCeO₂ (x = 0, 1, 2, 3, 4 mol %) | SGE | MBG pellets (Φ = 8 mm), 28 days | 81 |
| 70SiO₂–(26 – x)CaO–4P₂O₅–xCeO₂ (x = 0, 1, 5, 10 mol %) | SG | Pellets (Φ = 8 mm), 15 days | 115 |
| 60SiO₂–(10 – x)B₂O₃–25CaO–5P₂O₅–xCeO₂ (x = 5 mol %) | SGE | MBG powders, <250 μm, 14 days | 80 |
| 80SiO₂–15CaO–5P₂O₅ doped with CeO₂ (5.3 mol %) | M | Powders, <60 μm, 19 days | 93 |
| 80SiO₂–20CaO doped with CeO₂ (5.3 mol %) | SGE | MBG/algnate beads; powders, <250 μm; beads, Ω = 2 mm, 28 days | 116 |
| 100SiO₂ doped with CeO₂ (5.3 mol %) | M | Cubic shape, 21 days | 110 |
| 80SiO₂–15CaO–5P₂O₅ doped with CeO₂ (1.2, 3.6, 5.3 mol %) | SGE | Powders, 130–190 μm, 14 days | 96 |
| 20Na₂O–14CaO–8CeO₂–(66 – x)P₂O₅ (x = 0.1, 0.3, 0.7, 1 wt %) | M | Powders, 130–190 μm, 14 days | 111 |
| K50S doped with CeO₂ (1.2, 3.6, 5.3 mol %) | SG | 45SS, K50S, MBG/algnate beads; powders <250 μm; beads Ω = 2 mm, 28 days | 92 |
| 34SiO₂–8P₂O₅–17MgO–xCeO₂ (41 – x)CaO (x = 0.5, 2.5, 5 mol %) | SGE | Powders, <50 μm, 28 days | 107 |
| 4SSS doped with CeO₂ (4, 5 mol %) | M | Powders, 28 days | 113 |
| K50S doped with CeO₂ (3.6 mol %) | M | Powders, 28 days | 113 |
| 80SiO₂–15CaO–5P₂O₅ doped with CeO₂ (5.3 mol %) | SGE | Powders, <60 μm, 19 days | 93 |
| (45 – x)SiO₂–24.5Na₂O–24.5CaO–6P₂O₅ (x = 0.5, 1, 1.5, 2 wt %) | M | Powders, <60 μm, 19 days | 93 |

The resulting materials present a high SSA (usually ~300–800 m²/g) and a significantly larger pore volume (~1 cm³/g) with respect SGGs. However, the MQGs have enhanced mechanical properties like hardness and flexural strength with respect both SGGs and MBGs.73

MBGs exhibit higher bioactivity than SGGs due to their outstanding textural properties; moreover, MBGs can be loaded more easily in the form of biological importance, which can be released in controlled manner, thus acting as a drug delivery system.74

The formation of ordered mesoporous arrangements is regulated by factors like, among others, surfactant nature, concentration of precursors, solvent, pH, and temperature.75–77 In the case of SiO₂–CaO–P₂O₅ system, CaO acts as a network modifier disrupting the silica network connectivity; when CaO increases, the inorganic/organic volume ratio of the micelles increases with the formation of hexagonal phases rather than cubic.78 P₂O₅ leads to a decrease in the inorganic/organic volume ratio of the micelles resulting in a cubic structure.69, 78, 79

For Ce-MBGs, the glass composition influences the Ce³⁺/Ce⁴⁺ ratio. The presence of P₂O₅ favors the Ce³⁺ state: in ternary SiO₂–CaO–CeO₂ MBG calcined at 700 °C, the Ce³⁺ amount is 80.0 wt %, while in ternary SiO₂–CaO–CeO₂ and binary SiO₂–CeO₂ MBGs, the Ce³⁺ amount decreases to 37.5 and 58.0 wt %, respectively.79

The introduction in the glass network of cerium ions decreases the SSA and the porosity order degree;30 in fact, it is possible to obtain a hexagonal ordered structure until 1 mol % of CeO₂ addition, while for higher concentration, decreased SSA and a worm-like porous structure is obtained. However, it is still possible to enhance the SSA by increasing the concentration of surfactant: during the synthesis of Ce-MBGs the SSA increase around 2.5 times upon the introduction of twice the amount of surfactant (Pluronic P123).81

Similar results were obtained for MBGs without cerium, where the introduction of higher P123 amounts increases SSA, pore diameter, and volume.82 It is also possible to obtain MBGs as nanoparticles by basic catalysis (aqueous ammonia);83, 84 the cerium-doped MBG...
nanoparticles are obtained by immersion in a solution of cerium nitrate after the thermal calcination at 700 °C. This process favors the exchange of Ce⁴⁺ ions from the solution with the Ca²⁺ ions in the glass structure; the final MBGs contain cerium ions on the glass surface.⁶⁴

3. PROPERTIES OF BIOACTIVE GLASSES

3.1. Bioactivity. In the context of synthetic bone grafts, bioactivity concerns the formation of a bond with bone. In the field of bone repair, it is more appropriately defined as a "stimulation of a beneficial biological response".⁶⁵ 4SSS was the first biomaterial able to bond with bone, rather than be encapsulated by fibrous tissue; the bond was so strong that could not be removed without breaking it.¹ The mechanism of the bioactivity⁶⁶ is divided into two macrostages: bone-like apatite layer formation and ionic dissolution products from BGs and osteogenesis.⁴

The general mechanism of formation of the HCA layer is well-known and thus not covered here; we focus instead on the influence of cerium on the bioactivity of Ce-BGs.

As reported in the section 2, the use of different synthetic methods modifies the SSA and the reactivity of BGs. Table 1 reports the features of the Ce-BGs studied for their bioactivity as a function of compositions, dimensions and shape (not always reported), synthetic methods, and maximum soaking time in simulated body fluid (SBF).⁵⁹

In vitro studies have been carried out on BGs of different types, namely, 4SSS,⁵⁵,⁹⁰ Kokubo glass (N25SC55S50, hereafter abbreviated as K50S),¹⁰²,⁹⁵,⁹⁶ MBGs,¹³-⁹³,¹⁰³ and other BGs (BG-106-111 doped with different amounts of cerium and synthesized by melt-quenching ⁵⁴,⁵⁵,⁹¹-⁹³,¹⁰³-¹⁰⁵,¹¹⁰-¹¹ⁱ,¹¹³ s o l–g e l)́¹⁰⁰,¹⁰¹,¹⁰²,¹¹⁶ methods.

The first comments are related to Ce-MQGs in Lusvardi et al.⁵₃ where the cerium content was first reported as improving the chemical durability and retarding the HCA layer formation, mainly due to two factors: (i) the increase in chemical durability and (ii) the formation of insoluble crystalline CePO₄ competitive with HCA. CePO₄ is very insoluble (Ksp(CePO₄) = 10⁻³⁴)¹¹⁷,¹²⁸ and this hampers further solubilization of the glass matrix. This effect is correlated with the CeO₂ content in the glass: for CeO₂ content up to 1 mol %, HCA formation was detectable after 7–14 days, while with higher CeO₂ content (5.3 mol %), the formation of HCA was delayed up to 28 days.⁹² In this study, the formation of insoluble Ce phosphate was detected by SEM analysis, with typical flower-like crystals on the glass surface after SBF soaking (Figure 4).

Subsequently, a similar behavior was detected for SGGs and MBGs.¹⁰⁰,¹⁰³,¹⁰⁵,¹⁰⁶,¹⁰⁷,¹¹⁴,¹¹⁵

In particular, MBGs containing up to 5.3 mol % CeO₂ showed HCA after 7–14 days of SBF soaking.¹¹⁶ Here, the simultaneous presence of both HCA and CePO₄ confirmed that the Ce⁴⁺ ions released by the glass surface react quickly with the phosphate ions of the SBF forming the CePO₄ insoluble phase. This also explains the low level of cerium ions in SBF ²⁻ (cerium concentration <0.05 ppm). In summary, the presence of cerium does not inhibit HCA formation but can delay it at high concentrations due to the competitive cerium phosphate phase, sometimes identified as CePO₄ ²⁻ ⁴³⁻.⁷⁰,¹¹¹,¹²⁸

3.2. Cytocompatibility. Cell culture methods are the main in vitro tool to predict the biological response of the host organism to a biomaterial (Table 2). The cell lines selected for these assays are then typically chosen to model the response likely observed in vivo upon the surgical implant of BGs.¹²²,¹²⁴

Accordingly, the cell types commonly employed to assess the cytocompatibility of BGs have a role in wound healing (fibroblasts) ⁸⁵,¹³³,¹⁴³-¹⁴⁵,¹⁴⁷ bone structure (osteocytes),⁹⁶,¹²⁷-¹³⁰ and bone maintenance and formation (osteoclasts and osteoblasts).¹⁰⁸,¹¹¹,¹¹³,¹¹⁹ As cell cultures are sensitive to changes in variables such as temperature, pH, and nutrient concentration, careful control of the experimental conditions is crucial in correlating cell death to toxicity of the biomaterial rather than to changes in the culture conditions.¹²²

The assessment of cellular response to BGs, and their cytotoxicity in particular is performed by direct tests, carried out in the presence of the BGs, and indirect ones, in which filtered extracts of BGs are added to the cell culture.¹³⁰ Among the latter, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide test (MTT) is the method of choice for the quantification of metabolically active cells upon incubation with BG eluates.⁸¹,⁹⁶,¹⁰⁸,¹⁰⁹,¹⁴³ MTT is a rapid colorimetric test based on the cleavage of a yellow tetrazolium salt to purple formazan crystals by mitochondrial enzymes in metabolically active cells.¹²² Another indirect assay reported on BG extracts is the alamarBlue assay for cell viability (applicable both as a direct and indirect test).¹¹⁶ All the BGs studied show excellent biocompatibility regardless of their cerium content ⁸¹,⁹⁶,¹⁰⁸,¹⁰⁹,¹¹¹,¹⁴³ with specific exceptions for reused materials.¹²⁷ Lactate dehydrogenase (LDH) activity is also used to assess the cytotoxicity of BGs in indirect assays;⁸¹,¹¹⁶ both studies show no significant difference between control

**Figure 4.** SEM micrographs BG-13 Ce glass after 30 days of soaking in SBF Reproduced with permission from ref ⁵⁵. Copyright 2003 Elsevier.

In order to manufacture BGs with higher bioactivity, a suitable morphology can be selected. Some authors ³⁸,¹¹⁶,¹¹⁹,¹²⁰ used Ce-MBGs as a bioactive filler in alginate beads to increase their bioactivity and pro-osteogenic activity. The results indicate that beads with 1.2 and 3.6 mol % CeO₂ are excellent candidates as biocompatible scaffolds.

A final general consideration concerns SBF tests. Direct comparison of literature data on the HCA layer formation is often problematic as the protocols used for SBF testing can vary between research groups. The ISO standard currently in use ¹²¹ refers to materials of standard shape but does not take into account that BGs can have very different specific surface areas and the required amount of SBF should be appropriately chosen. A unified assessment method based on an ISO modified procedure, considering the ratio between BG mass and SBF solution, has been recently proposed.¹²²
Table 2. Evaluation of Cytocompatibility for Ce-BGs

| composition                        | assays and cell lines                                                                 | features                                                                 | ref  |
|------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------|
| 10CaF₂−10Na₂CO₃−15CaO·60P₂O₃−5CeO₂ (mol %) | MTT, human osteoblastic-like cells (MG63) (ATCC, CRL-1427)                           | enhanced cell adhesion and proliferation                                 | 129  |
| 52SiO₂−24SrO−16Na₂O−8CeO₂ (mol %)    | osteoblast viability, cell adhesion MC-3T3-E1 osteoblasts (ATCC CRL-2593)            | cell viability unaffected                                                 | 108  |
| 52SiO₂−24SrO−16Na₂O−4CeO₂−4P₂O₃ (mol %) | MTT, LDH, mouse fibroblast cells (NCTC clone L929)                                   | cell viability above 80% noncytotoxic                                    | 81   |
| 70SiO₂−(26 − x)CaO·4P₂O₃−xCeO₂ (x = 1, 5 mol %) | MTT, mouse lung fibroblast normal cells (WI-38 cells)                               | cell viability improved                                                  | 115  |
| 60SiO₂−(10 − x)BaPO₃−2CaO−5P₂O₃−xCeO₂ (x = 0, 5 mol %) | MTT, LDH, ALP mouse calvaria preosteoblastic cells (MC3T3-E1)                   | cell viability unaffected, cerium enhances cell proliferation and reduces cell differentiation | 116  |
| 80SiO₂−15CaO·5P₂O₃ (mol %) doped with CeO₂ (1, 2, 3, 5, 3 mol %) | NR, MTT, BbDU, MLO-Y4, NIH/3T3 cell lines                                           | cell uptake and viability enhanced                                       | 128  |
| 45S doped with CeO₂ (1, 2, 3, 5 mol %) | MTT, NR, BbDU osteocyte-like cell lines murine long bone (MLO-Y4)                  | cell proliferation and vitality enhanced                                 | 96   |
| 53S doped with CeO₂ (1, 2, 3, 5 mol %) | MTT, human osteosarcoma cells (MG-63)                                              | cerium reduces apoptosis and increases cell viability                     | 111  |
| 46.10SiO₂−2.60P₂O₃−16.90CaO−10.00MgO−19.40Na₂O·5.00CeO₂ (mol %) | MTT, NIH 3T3 mouse fibroblast cells                                                | cerium enhances cell adhesion and spreading                              | 126  |
| 70SiO₂−30CaO impregnated (Ce 0.5, 0.2 M) | MTT                                                                                  | cerium reduces expression of oxidative stress related genes             | 83   |
| 34SiO₂−8P₂O₃−17MgO−xCeO₂−(41−x)CaO (x = 0.5, 2.5, 5 mol %) | MTT                                                                                  | cerium enhances cell viability                                          | 111  |
| 34SiO₂−8P₂O₃−17MgO−xCeO₂−(41−x)CaO (x = 0.5, 2.5, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell viability                     | 111  |
| 45S doped with CeO₂ (1, 2, 3, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 45S doped with CeO₂ (1, 2, 3, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 46.10SiO₂−2.60P₂O₃−16.90CaO−10.00MgO−19.40Na₂O·5.00CeO₂ (mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 70SiO₂−30CaO impregnated (Ce 0.5, 0.2 M) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 34SiO₂−8P₂O₃−17MgO−xCeO₂−(41−x)CaO (x = 0.5, 2.5, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 34SiO₂−8P₂O₃−17MgO−xCeO₂−(41−x)CaO (x = 0.5, 2.5, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 45S doped with CeO₂ (1, 2, 3, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 45S doped with CeO₂ (1, 2, 3, 5 mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 46.10SiO₂−2.60P₂O₃−16.90CaO−10.00MgO−19.40Na₂O·5.00CeO₂ (mol %) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |
| 70SiO₂−30CaO impregnated (Ce 0.5, 0.2 M) | MTT                                                                                  | cerium reduces apoptosis and increases cell proliferation                 | 93   |

Table 3. Evaluation of Antibacterial Activity for Ce-BGs

| composition                        | bacterial strain | antibacterial effect                                                                 | ref  |
|------------------------------------|------------------|--------------------------------------------------------------------------------------|------|
| 50SiO₂−(45 − x)CaO·5P₂O₃−xCeO₂ (x = 1, 5, 10 mol %) | E. coli (ATCC25922) | increasing the amount of cerium increases the antibacterial activity                 | 100  |
| 10CaF₂−10Na₂CO₃−15CaO·60P₂O₃−5CeO₂ (mol %) | S. aureus (ATCC 25923) | antibacterial effect against S. aureus and S. epidermidis                            | 129  |
| 56.6B₂O₅−18.5CaO−5.5Na₂O−11.1K₂O−4.6MgO−3.7Po₃ doped with CeO₂ (1, 3, 5 wt %) | P. aeruginosa | no effects against P. aeruginosa                                                      | 123  |
| (53 − x)SiO₂−20CaO−6Na₂O−K₂O−MgO−P₂O₃−xCeO₂ (x = 3, 5 wt %) | E. coli | no antibacterial response                                                             | 105  |
| 50SiO₂−(45 − x)CaO·5P₂O₃−xCeO₂ (x = 1, 5, 10 mol %) | E. coli (ATCC25922) | no antibacterial response                                                             | 105  |
| 60SiO₂−(10 − x)B₅O₃−2CaO−5P₂O₃−xCeO₂ (x = 5 mol %) | P. aeruginosa (ATCC 27853) | antibacterial activity did not depend on cerium presence                              | 115  |
| 20Na₂O−14CaO−xCeO₂−(66 − x)P₂O₃ (x = 0.1, 0.3, 0.7, 1 wt %) | S. aureus (ATCC 6538) | antibacterial activity enhanced significantly against E. coli and S. aureus as cerium amount increases | 110  |
| 46.15SiO₂−2.60P₂O₃−16.90CaO−10.00MgO−19.40Na₂O−5.00CeO₂ (mol %) | S. aureus | no antimicrobial behavior against B. cereus, B. subtilis, and C. albicans            | 110  |

medium and extracts, confirming the lack of cytotoxicity of BGs.

Direct cytocompatibility has been assessed by a range of assays, including MTT, alamarBlue, and neutral red (NR) for cell viability, bromo-2-deoxyuridine (BrdU) for cell proliferation, and LDH activity for cytotoxicity. Remarkably, all the BGs investigated show little or no effect on...
Among the reported modes of action are the disruption of underlying their antibacterial activity are still under study. At very long (14 days) culture times, cell viability is reported to decrease, and bacterial activity increases with the increase of cerium amount, decreases in presence of phosphate ions, and changes with the environment (higher in water than in SBF). The antibacterial properties can also be induced or improved by the addition of metal ions with bactericidal effects. BGs doped with silver, copper, zinc, or gallium are considered potential candidates as antibacterial agents. Ce-BGs as well are reported as having antibacterial properties, with microbicidal effects toward Escherichia coli and Staphylococcus aureus (Table 3), albeit some studies report the lack of such properties instead. The antibacterial activity of cerium compounds is linked to the inhibition of the oxidation and assimilation of glucose and of endogenous respiration. Various modes of action of cerium compounds on bacteria have been proposed, some of which are based on the direct contact between cerium and the bacterial membrane. These include the impairment of transport exchange through the bacterial membrane followed by reduced growth, reaction of cerium with proteins or transporters within the cell, and induction of oxidative stress.

Table 4. Evaluation of Antioxidant Activity for Ce-BGs

| Composition          | Antioxidant Activity | Features                                                                 | Ref.  |
|----------------------|----------------------|--------------------------------------------------------------------------|-------|
| 45S5 doped with CeO2 (1.2, 3.6, 5.3 mol %) | CMA                  | antioxidant activity increases with the increase of cerium amount, decreases in presence of phosphate ions, and changes with the environment (higher in water than in SBF) | 91, 94, 149–151 |
| K50S doped with CeO2 (1.2, 3.6, 5.3 mol %) | SOD                  | antioxidant activity decreases with high P2O5 amount                     | 80    |
| 80SiO2–15CaO–5P2O5 doped with CeO2 (5.3 mol %) | CMA                  | Ce4+/Ce3+ ratio opposite effects for CMA and SOD                        |       |
| 80SiO2–20CaO doped with CeO2 (5.3 mol %) | SOD                  | cerium-containing glasses exhibit maximum cell viability                |       |
| 80SiO2–20F2O doped with CeO2 (5.3 mol %) | SOD                  | cerium-containing glasses exhibit maximum cell viability                |       |
| 100SiO2 doped with CeO2 (5.3 mol %) | SOD                  | cerium-containing glasses exhibit maximum cell viability                |       |
| 80SiO2–15CaO–5P2O5 doped with CeO2 (1.2, 3.6, 5.3 mol %) | CMA                  | antioxidant activity increases with the increase of cerium amount, decreases in presence of phosphate ions, and changes with the environment (higher in water than in SBF) | 116   |
| 80SiO2–15CaO–5P2O5 doped with CeO2 (1.2, 3.6, 5.3 mol %) | SOD                  | antioxidant activity increases with the increase of cerium amount, decreases in presence of phosphate ions, and changes with the environment (higher in water than in SBF) | 116   |
| 80SiO2–15CaO–5P2O5 doped with CeO2 (1.2, 3.6, 5.3 mol %) | CMA                  | antioxidant activity increases with the increase of cerium amount, decreases in presence of phosphate ions, and changes with the environment (higher in water than in SBF) |       |
| 34SiO2–8P2O5–17MgO–xCeO2–(41–x)CaO (x = 0.5, 2.5, 5 mol %) | CMA, SOD            | oxidative stress induced by H2O2 on MG-63 cells                        |       |
| 45S5 doped with CeO2 (4, 5 mol %) | CMA                  | CMA increases with (i) reduction of glass dimensions and (ii) increment of SSA; alginate coating (beads) does not inhibit CMA | 92    |
| K50S doped with CeO2 (3.6 mol %) | SOD                  | cerium-containing glasses exhibit maximum cell viability                |       |
| 80SiO2–15CaO–5P2O5 doped with CeO2 (3.6 mol %) | CMA                  | cerium-containing glasses exhibit maximum cell viability                |       |

Finally, SEM or confocal microscopy are used to evaluate changes in cell morphology and cell surface to the surface of the BGs. The cell morphology is generally unchanged upon interaction with BGs if not at higher BG concentration; the presence of cerium reduces morphological changes and gives better performance over unfunctionalized BGs. Cell attachment is also favored by the presence of cerium.

3.3. Antibacterial Activity. The efficiency of BGs in bone regeneration is also related to the prevention of bacterial adhesion and proliferation that can occur on the implant surface. While BGs are considered good candidates for preventing or reducing this problem, the mechanisms underlying their antibacterial activity are still under study. Among the reported modes of action are the disruption of prokaryotic cell membranes by glass debris and changes in environmental pH and osmotic pressure. Both those mechanisms are linked to the reactivity of BGs in aqueous solutions, with produces a toxic environment for bacteria. This behavior is associated with an increase of pH and osmolarity in the surrounding environment; an alkaline pH reduces the viability of bacterial suspensions and causes morphological and ultrastructural changes in the bacteria. The antibacterial properties can also be induced or improved by the addition of metal ions with bactericidal effects. BGs doped with silver, copper, zinc, or gallium are considered potential candidates as antibacterial agents. Ce-BGs as well are reported as having antibacterial properties, with microbicidal effects toward Escherichia coli and Staphylococcus aureus, albeit some studies report the lack of such properties instead. The antibacterial activity of cerium compounds is linked to the inhibition of the oxidation and assimilation of glucose and of endogenous respiration. Various modes of action of cerium compounds on bacteria have been proposed, some of which are based on the direct contact between cerium and the bacterial membrane. These include the impairment of transport exchange through the bacterial membrane followed by reduced growth, reaction of cerium with proteins or transporters within the cell, and induction of oxidative stress.

More recent studies, performed between 2014 and 2020, suggest that the antibacterial activity of Ce-BGs is a function of glass composition, cerium amount, and morphology. Ce-BGs possess higher antibacterial activity if the concentration of cerium oxide is in the 5–10 mol % range rather than 1 mol %, Ce-BG-reinforced hydroxyapatite showed a remarkable decrease of bacterial adhesion only for the Staphylococcus strains. Electrosprun fibers and powders based on 13-93 glasses doped with cerium and electrospun poly(lactic acid) (PLA)/chitosan nanofibers coated with cerium-doped glasses are inactive in antibacterial tests; this lack of antibacterial activity can be attributed to the slow release of ions from glass and to the small amount of material adsorbed onto the nanofibers. The antibacterial activity of Ce-nano-BGs is not dependent on the presence of cerium in the glass but rather on the presence of boron, which shows antibacterial activity against a wide range of pathogens. For cerium-containing phosphate glasses, the increase of cerium concentration enhanced the antibacterial activity.
activity against *E. coli* and *S. aureus*, but not against *Bacillus cereus*, *B. subtilis*, and *Candida albicans*.110

Preliminary tests performed on coatings obtained by the laser ablation method and enriched with Ce-BGs suggested high antibacterial activity due to the presence of partially crystallized layers with cerium cations embedded in a glassy matrix, which was more prone to degradation.125

### 3.4. Antioxidant Properties.

Oxidative stress is related to the excessive production of ROS, and these species play an important role in the regulation of cellular functions: inhibition of the differentiation and mineralization of osteoblasts, enhancement of osteoclast activity, and consequent pro-inflammatory bone resorption.142 Their excess can have deleterious effects on the organism with a reduction of antioxidant capacity.143 The implantation of biomedical devices is performed by surgical procedures, which are often followed by tissue damage and inflammation. ROS production linked to inflammation increases and causes a condition of oxidative stress, which in turn enhances inflammation, causing further generation of ROS. Due to this feedback, postsurgery inflammation could need a long time to achieve complete recovery.

The ability to convert ROS to nondangerous species must be a key feature of a biomaterial. In the case of nanoparticles, CeNPs have been widely studied for their antioxidant enzyme-mimetic activity and radical scavenging ability.19,20 In the site of the inflammation, CeNPs favor the conversion of excess free radicals, bringing a faster postsurgery recovery;144 their antioxidant properties are effective against ROS generated in the human body.18 CeNPs can mimic the activity of catalase (CAT)145 and superoxide dismutase (SOD)146 enzymes present in the human body146 (Figure 2).

The antioxidant properties of BGs are strictly correlated to their composition and reactivity. For example, the addition of fluorine (5–15 mol %) to 45S5 increases lipid peroxidation and ROS production in MG-63 osteoblast cells and induces other signs of oxidative stress such as inhibition of the pentose phosphate pathway, the glucose 6-phosphate dehydrogenase activity, and the glutathione activity.147 Similarly, the introduction of copper (1–2.5 wt %) into 45S5 increases ROS production in human osteosarcoma (HOS) cells.148

Table 4 summarizes the results related to Ce-BGs and their potential antioxidant activity.

The antioxidant properties of BGs are strictly correlated to their composition and reactivity. For example, the addition of fluorine (5–15 mol %) to 45S5 increases lipid peroxidation and ROS production in MG-63 osteoblast cells and induces other signs of oxidative stress such as inhibition of the pentose phosphate pathway, the glucose 6-phosphate dehydrogenase activity, and the glutathione activity.147 Similarly, the introduction of copper (1–2.5 wt %) into 45S5 increases ROS production in human osteosarcoma (HOS) cells.148

Table 4 summarizes the results related to Ce-BGs and their potential antioxidant activity.

**CeO**$_2$ (1.2, 3.6, 5.3 mol %) has been added to 45S5 and K50S;91,94,149–151 CAT, evaluated by H$_2$O$_2$ degradation, increases with cerium content and decreases in the presence of phosphate groups. Cerium ions play different structural roles: in phosphate-free glasses cerium is coordinated by nonbridging oxygens (NBOs) originating from the disruption of the silicate network, whereas in phosphate-containing glasses, the NBOs around cerium ions belong to orthophosphate groups. The latter groups stabilize the Ce$^{3+}$ species subtracting them from the interconversion process between Ce$^{3+}$ and Ce$^{4+}$, which is of fundamental importance for CAT. Good catalytic activities were confirmed from SOD mimic activity tests.152 An increase in the cerium content also leads to a significant reduction of the glass *in vitro* bioactivity, which
can be associated with the formation of an insoluble CePO₄ phase that delays or inhibits HCA formation. An optimal compromise between the ability to degrade H₂O₂ and HCA formation was observed with addition of 1.2 and 3.6 mol % CeO₂.

In the case of Ce-MBGs, good bioactivity and antioxidant properties were confirmed. In analogy to what was observed for other BGs, the presence of a high concentration of phosphate groups decreased the catalytic properties. Similarly to CeNPs, also in the case of Ce-BGs the Ce³⁺/Ce⁴⁺ ratio influences the catalytic properties. For Ce-MQGs, during CAT tests, the Ce³⁺/Ce⁴⁺ ratios reached an optimal value around 1−1.5. In the case of Ce-SGBs and Ce-MBGs more oxidized surfaces show improved CAT and lower SOD mimetic activity. CAT increases with smaller dimensions of the BGs and with SSA; while alginate coating (beads) seems to not inhibit the catalytic activity of the glass. CAT changes also with the environment, being higher in water than in SBF.

3.5. Osteogenesis and Angiogenesis. BGs are also known in the field of tissue engineering because of their osteoinductivity and osteoconductivity, which are higher than those of conventional ceramics. TIs, including cerium, have been added do BGs to improve their biological properties. The osteogenic properties of cerium compounds and CeNPs are well-known and linked to the ability of cerium to activate specific cellular pathways such as tumor necrosis factor (TNF) and sucrose nonfermentable (SNF). Ce-MBGs are used as bioactive filler in alginate beads to increase bioactivity and pro-osteogenic activities (Figure 5).

Zheng et al. incorporated cerium into MBGNPs by a two-step approach via post modification method: the nanoparticles exhibited anti-inflammatory response and pro-osteogenic activity (Figure 6).

Most of the studies on Ce-BGs for application in bone tissue regeneration report positive results with regard to osteogenic properties. Recently Westhauser et al. demonstrated that in MBGNs cerium had a positive influence on the viability and the cellular osteogenic differentiation of human bone marrow derived mesenchymal stromal cells exposed to the ionic dissolution products (IDPs) of the respective glasses. The formation and calcification of the osseous extracellular matrix was stimulated in the presence of IDPs of Ce-MBGNs in a positive concentration dependent manner.

Regarding angiogenesis, cerium oxide could improve the vascularization of bone grafts by activating the calcium channel of mesenchymal stem cells. Ce-BGs can modulate the oxygen level in vitro, suggesting their angiogenic potential. In vivo studies on rat cranial defect models revealed that hollow mesoporous Ce-BG scaffolds accelerated collagen deposition, osteoblast formation, and bone regeneration as compared to BG scaffolds (Figure 7); these results indicate these scaffolds a promising platform for healing critical-sized bone defects.

Figure 6. (A) SEM and (B) TEM images of the morphology of MBGN, 0.05 M Ce−MBGN, and 0.2 M Ce−MBGN. MBGN, mesoporous bioactive glass nanoparticle. Reproduced with permission from ref 83. Copyright 2020 Elsevier.

Figure 7. In vivo evaluation of bone formation in rat cranial defects implanted with BG (A) and (B) Ce-BG at 8 weeks postimplantation. The reconstruction images of micro-CT in defect regions. Reproduced with permission from ref 158. Copyright 2019 IOPScience.
4. CONCLUSIONS

BGs are able to stimulate bone regeneration and are used as bone fillers, scaffolds, and implant coatings. To improve their biocompatibility and reduce postimplantation complications, BGs are doped with TIs; among these, cerium is of particular interest due to its biological properties. The purpose of this review is to provide an overview of the state of the art of Ce-BGs by reviewing the effects of cerium on bioactivity, cytocompatibility, and antibacterial, antioxidant, osteogenic, and angiogenic activities of BGs reported in the recent literature.

In order to explain the behavior of a Ce-BG in a biological setting, it is necessary to take into account all the manufacturing and physicochemical parameters that can influence its behavior. For instance, Ce-BG reactivity changes according to the method of synthesis described in section 2, with SGGs being more reactive than MQGs and MBGs being the most reactive glass type. We propose that a correct evaluation of the bioactivity should be performed according to the updated ISO standard and moreover that the bioactivity should be evaluated considering the composition, synthesis, and soaking time in SBF of the material (Table 1). Cytocompatibility and antibacterial and antioxidant activities are reported as a function of the composition with the most important remarks (Tables 2, 3, and 4). While in general the addition of cerium does not alter significantly the in vitro bioactivity of Ce-BGs, except when added in large amounts, it has a positive effect on their biocompatibility, improving their cytotoxicity and antioxidant and antibacterial properties.

Recently, Ce-BGs were also reported to have significant osteogenic properties and to help bone tissue regeneration, while Ce-doped borate BGs exhibited enhanced in vivo bone vessel formation, showcasing the potential benefits of these materials for a range of therapeutic areas.

In comparison with CeNPs, we can say first that CeNPs can have a large range of biomedical applications; even if it is worth considering that their employment, as with all NPs, is quite recent when compared to more established materials like the BGs that have been used for decades in tissue engineering. In addition, the compositional limitations of CeNPs reduce their versatility compared to traditional biomaterials, and the risk of cytotoxicity may be a hurdle for their approval for clinical use and subsequent commercialization.

In summary, the past decade has seen significant progresses in the application of Ce-BGs for therapeutics. Their field of application has broadened considerably and is not limited to the reconstruction of hard tissues such as bone and teeth. Ce-BGs are now explored as therapeutic options for soft tissue and the reconstruction of hard tissues such as bone and teeth. Ce-BGs are able to stimulate bone regeneration and are used as bone fillers, scaffolds, and implant coatings.

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Notes

The authors declare no competing financial interest.

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