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## **How can bioactive glasses be useful in ocular surgery?**

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### **Abstract**

In the last few decades the introduction of bioactive glasses, a special class of bioceramics that are able to bond to living tissues stimulating new tissue growth, has improved both treatment procedures via reconstructive surgery and the quality of life of rehabilitated patients in orthopaedics and dentistry. While bioactive glasses have been extensively investigated for applications in these two surgical fields, there has been relatively little research on their use in other medical areas. Glass has been used for centuries to produce external refractive lenses and the intraocular implantation of small glass disks to correct visual deficiencies has been documented since the mid 1700s. Moreover, some evidences reported in the recent literature seem to demonstrate that the success of three specific types of ophthalmic devices, i.e. synthetic grafts for eye orbit bone repair, orbital implants replacing the whole ocular globe and keratoprotheses (artificial cornea), could significantly benefit by the use of bioactive glass. A prospective view as well as a state-of-the-art review on this topic are currently lacking in the literature. The present article aims to give a

comprehensive picture of the bioactive glass-based implants that have been developed in the context of ocular surgery; the strengths and shortcomings of the existing devices are outlined in order to provide useful stimuli for future research. Promising research directions are also proposed, emphasizing the added values that bioactive glasses could carry in ophthalmology in the light of recent findings in tissue engineering and regenerative medicine.

Keywords: Bioactive glass; Eye orbit; Artificial cornea; Tissue integration; Angiogenesis.

## INTRODUCTION

Glass had and currently still has a great importance in ophthalmology due to a number of attractive features, including transparency to visible light, biocompatibility and relative ease of processing; it is commonly considered a valuable material to fabricate external lenses to correct refractive deficiencies of eyes. Furthermore, the use of some special glasses and glass-ceramics, that are defined “bioactive” due to their unique capability of stimulating cell activity and tissue regeneration *in vivo*, could disclose new, fascinating scenarios in ocular surgery.

In biomaterials science, the word “bioactive” generally means that the material stimulates an advantageous biological response from the body on implantation. The term was coined by Larry Hench in the early 1970s, when he and his colleagues at the University of Florida invented 45S5 Bioglass<sup>®</sup>, the first material able to form a strong bond to bone.<sup>1,2</sup> This discovery launched the field of bioactive glasses (BGs) and glass-ceramics (BGCs) and, even most importantly, introduced the basic concept of modern regenerative medicine, i.e. some special materials not only are not rejected by living tissues but can elicit a therapeutic action in the human body. Initially, bioactivity referred to materials that could bond to bone (osteoconduction), but 45S5 Bioglass<sup>®</sup> was later found to stimulate new bone growth (osteinduction) and to bond to soft tissues.<sup>3</sup>

The applications of BGs and BGCs in the medical field have been mainly related to the repair of hard tissues, like bone and teeth, and over the years tens of compositions have been investigated and clinically tested in orthopaedics and dentistry.<sup>4-9</sup> The use of BGs and BGCs in ocular surgery might seem an unusual and marginal application, since the eye comprises a variety of soft, delicate structures that, apparently, are mechanically unmatchable with stiff and brittle BGs; in this regard, polymeric substances, in form of injectable gels or flexible products, would seem much more suitable and effective.<sup>10-14</sup> Reviewing the available literature, however, we found that BGs and BGCs have been applied with promising outcomes in three sub-areas of ophthalmology: (i) oculoplastic surgery for the repair of eye orbit floor, (ii) orbital implants for anophthalmic surgery and (iii) artificial cornea.

Facial trauma to the midface can lead to fractures in the inferior/medial orbit wall<sup>15</sup> with herniation of the orbital contents into the maxillary sinus located underneath (Fig. 1). Surgical intervention is necessary to treat this type of injury: the implant aims to act as a bone graft ensuring structural support at the bone defect site (fracture) and is often designed as a porous scaffold to promote bone in-growth and a safe anchorage to surrounding host tissues.<sup>16</sup> Autologous bone graft is usually the preferred option to repair the defect, although it carries the need for extra-surgery at the harvesting site. Porous hydroxyapatite (HA) and polyethylene (PE) implants are also used, but problems of brittleness occur with the former during implantation and the latter does not induce new bone in-growth.<sup>16</sup>

Porous HA, PE and alumina are also the most commonly-used materials for producing orbital implants (Fig. 2) to be placed in the patient's anophthalmic socket after evisceration or enucleation due to trauma or otherwise untreatable diseases (e.g. tumours especially in infancy).<sup>17</sup> The presence of an interconnected macroporous network in these materials is crucial to obtain an adequate postoperative fibrovascularization of the porous orbital implant, which is a desirable characteristic in view of exposure-related infections as vascular in-growth helps to anchor the implant, permits immune surveillance and makes possible the treatment via systemic antibiotics.

As to the third application it is impressive to mention that, according to the World Health Organization,<sup>18</sup> corneal diseases (e.g. age-related degeneration, infections, chemical/thermal/mechanical injuries) are the 4<sup>th</sup> largest cause of blindness worldwide. Although corneal transplantation is the most common treatment of corneal blindness, the limitation in the storage of corneal tissue as well as cultural or religious barriers remain a problem; furthermore, failure of the transplanted graft is not uncommon.<sup>19</sup> An interesting alternative is the implantation of a keratoprosthesis (artificial cornea), generally comprising a transparent optical core supported by a skirt that anchors the implant within the host corneal tissue. Many types of keratoprostheses have been developed and are currently used in the clinical practice; most of them are fully constituted by polymeric materials, like the so-called “Boston keratoprosthesis” entirely made of poly(methylmetacrylate) (PMMA) or other models comprising an optical element made of PMMA or transparent hydrogel supported by a porous polymeric skirt.<sup>19</sup> With the aim to enhance the bond between keratoprosthesis and surrounding tissues through the promotion of better cell adhesion, Strampelli pioneered the use of the osteo-odonto-keratoprosthesis (OOKP) (Fig. 3), wherein a lamina prepared from a single-root tooth extracted from the patient is used to form a biocompatible skirt around the PMMA core.<sup>20</sup> A relatively good, long-term clinical outcome can be achieved with the OOKP also in dramatic cases (e.g. patients with dry eye or Stevens-Johnson syndrome<sup>1</sup>); however, the complexity of OOKP surgery and the need for sacrificing the autologous tissues make this approach stressful for patients. Furthermore, local inflammation can decrease the pH of the tissue, thereby causing the degradation of the tooth-derived prosthetic skirt, device instability and final loss of the OOKP.<sup>21</sup>

The use of BGs and BGCs in all these three contexts of application could contribute to overcome some shortcomings related to the existing devices, thus opening new research directions. After

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<sup>1</sup> Stevens-Johnson syndrome (SJS) is a form of life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. This syndrome is thought to arise from a disorder of the immune system, leading to a hypersensitivity complex that affects the skin and the mucous membranes. The immune reaction can be triggered by drugs administered to treat other pathologies (in most cases), infections or, more rarely, cancer. Outcomes of SJS include serious organ damage as well as corneal disease which may eventually cause blindness.

giving the reader an overview about the use of glass in ocular surgery, this article focuses on the ocular applications of BGs and BGCs and highlights the challenges and promises for the future, especially in the light of the recent findings in tissue engineering. Finally, some methodological remarks about the need to elaborate standard guidelines for selecting and testing potentially implantable BGs and BGCs for ophthalmic use are presented at the end of the work.

## **TRADITIONAL GLASS-BASED IMPLANTS IN OCULAR SURGERY: A HISTORICAL OVERVIEW**

Glass has been employed for making external corrective lenses since the Roman Age (e.g. the famous philosopher Seneca reports the use of glass spheres to magnify objects in the 1<sup>st</sup> century AD), but its use as an implantable material in ophthalmology is more recent, dating back to the mid 1700s. The first evidence was reported in the book “The Memoirs of Casanova”, where the great lover described a meeting with an Italian itinerant ophthalmologist, Tadini, at a dinner in Warsaw in 1765.<sup>22</sup> Tadini showed him some polished glass spheres in a box and claimed that he could implant them underneath the cornea to replace the crystalline lens. A fellow guest, an unnamed German ophthalmologist, ridiculed the claim in print and Tadini never mentioned the spheres again, but Casanova may have been responsible for conveying the idea to the Court at Dresden where, few years later, the ophthalmologist Casaamata unsuccessfully tried to insert a glass lens underneath a corneal wound.<sup>22</sup> This is recognized as the first (failed) attempt to correct aphakia via implantation of a glass intraocular lens (IOL). Only almost two centuries later, in 1950, Sir Harold Ridley successfully performed the first implantation of a IOL during cataract surgery using a lens of PMMA, that is the material commonly used till now; glass is considered unsuitable for this application due to its too high density.<sup>23</sup>

Glass was also the first material employed to make a keratoprosthesis device. Pellier de Quengsy is traditionally considered as the first who proposed an artificial cornea in his comprehensive treatise

of ocular surgery published in 1789:<sup>24</sup> he suggested the use of a thin silver-rimmed convex glass disc as a keratoprosthesis and described in great detail the surgical instruments suitable for its insertion. According to the studies by Chirila and Hicks,<sup>25</sup> Pellier de Quengsy was also the first to suggest a porous periphery (skirt) for the keratoprosthesis, thus anticipating an important strategy for the prosthesis anchorage which will be developed only several years later. However, there is no proof that an actual implantation of this device was ever performed and only 60 years later Von Nussbaum implanted in rabbits and human patients a glass keratoprosthesis.<sup>26</sup> Since then, the use of glass to manufacture the optical core of keratoprostheses was accompanied by controversial results and, after the Second World War (WWII), it was commonly substituted by the lighter PMMA. In recent years, the unique exception has been represented by the “champagne cork” keratoprosthesis, developed by Worst and co-workers in the 1980s.<sup>27</sup> This model had a shape similar to a mushroom and consisted of a glass core mounted in a platinum cylinder provided with a flange, through which four stainless steel wires were passed for the fixation to the sclera.<sup>28</sup> This keratoprosthesis was initially implanted in a large number of cases in India from the 1980s to the early 1990s with a high rate of success.<sup>29</sup> However, as pointed out by Chirila et al.,<sup>30</sup> these apparently good outcomes are questionable as they refer only to the immediate postoperative follow-up and most of patients never came back for subsequent, long-term examination. This prosthesis has been still used more recently because it provides a significantly wider range of vision in comparison to other models,<sup>31</sup> but it suffers from late problems with the tension on the stainless steel sutures that causes them to erode through the tissues, thus leading to instability of the implant and damage to the eye.

Apart from being used to correct visual deficiencies, glass was also employed for aesthetic purposes in the fabrication of artificial eyes. In this regard, the first evidences of the so-called “glass eyes” date back to the end of 18<sup>th</sup> century, when Venetian glassmakers, taking inspiration from dolls’ eyes, began to produce prosthetic human eyes in the form of thin, highly brittle glass shells.<sup>32</sup> In 1885 Mules first described in detail the surgical placement of a hollow glass sphere into an eviscerated globe.<sup>33</sup> Since the early 1900s, glass ocular prostheses began to be coupled with an

orbital implant in order to restore a better aesthetic appearance to the patient's face; the prosthesis was a glass shell placed between the closed conjunctival surface covering the orbital implant (bulbar conjunctiva) and the eyelids (palpebral conjunctiva) (as shown in Fig. 2). Glass eyes had to be worn with caution as they were brittle and prone to implosion with acute changes in temperature; furthermore, they became etched from exposure to body secretions. Glass remained the standard material for making ocular prostheses and orbital implants (hollow sphere) until WWII, when they were progressively replaced by PMMA devices<sup>34</sup> that definitely overcame the problems of brittleness, permitted custom fitting at a relatively low cost and allowed better motility of the prosthesis. In the last decades, the use of glass spheres as orbital implants has been almost totally abandoned; occasionally, however, glass has been still employed in selected cases. In the late 1980s Helms et al.<sup>35</sup> implanted a glass sphere in 1 patient and unfortunately the device underwent posterior intracranial migration. One decade later Christmas et al.<sup>36</sup> used a glass implant in a single patient without reporting any complication after a 2-year follow-up.

## **CURRENT APPLICATIONS OF BGs AND BGCs IN OPHTHALMOLOGY**

In all the “traditional” applications presented in the previous section glass has been employed as an optical or aesthetic element of implantable ocular devices; on the contrary, the concept behind the use of BGs and BGCs lies on a completely different approach. Essentially, the experimentation of BGs and BGCs as eye orbit floor grafts, orbital implants and keratoprosthesis skirts was proposed in the attempt to improve implant biointegration, which is tightly related to the postoperative success of the implanted device.

Table I collects the currently-available clinical or experimental studies dealing with the use of BGs and BGCs in ocular surgery; the specific applications and essential characteristics of the related devices are also summarized for the reader's benefit. These studies are reviewed and critically discussed in the following three subsections, depending on the context of application.

## Eye orbit floor repair

To date, the use of BGs for orbital floor repair is limited to a series of studies performed from the late 1980s to the early 2000s on four series of human patients by two teams of Finnish researchers. In all those studies, the aim was to investigate the suitability of curved plates obtained from cast S53P4 silicate glass (oxide weight composition: 53% SiO<sub>2</sub>, 23% Na<sub>2</sub>O, 20% CaO, 4% P<sub>2</sub>O<sub>5</sub>) as synthetic grafts to repair orbital fractures.

Suominen and Kinnunen,<sup>37</sup> affiliated to the Helsinki University Central Hospital, first implanted S53P4 granules and plates at 36 sites in 13 patients, comparing the behaviour of this material with that of bone grafts at 16 sites in the same patients. BG granules were used in facial bone defects in subperiosteal pockets and to obliterate frontal sinuses, whereas the plates were employed for orbital wall reconstruction. Clinical examination, middle face radiographs and computed tomography (CT) scanning showed that the BG was generally well tolerated. The glass plates retained their density, did not change in size and were characterized by tighter contact with the host bone in comparison to BG granules and bone grafts. The clinical outcome showed no relapses after a 1-year follow-up and no further operations were needed to remove or adjust the implanted material.

On the basis of these promising results, the studies were continued by another research group at the Turku University Hospital. Kinnunen et al.<sup>38</sup> compared the use of melt-derived S53P4 glass plates with conventional cartilage grafts for the treatment of traumatic orbital floor fractures in 28 patients operated from 1991 to 1995 and evenly split in two groups of 14 people. None of 14 patients receiving the S53P4 plate showed significant evidence of implant-related postoperative complications; in addition, their clinical outcomes (only 1 case of infraorbital nerve paraesthesia and 1 case of entropion<sup>2</sup> were registered) were better than those the cartilage group (3 cases of

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<sup>2</sup> Folding inwards of the eyelid (usually the lower eyelid), which causes the eyelashes to constantly rub against the cornea.

diplopia, 2 case of infraorbital nerve paraesthesia and 1 case of enophthalmos<sup>3</sup>). The authors of this study concluded that the use of BGs plates led to less morbidity as no donor site operation is needed and S53P4 glass provided favourable healing due to its ability to stimulate new bone formation, which encouraged further investigations. Aitasalo et al.<sup>39</sup> reported a retrospective study of 36 patients operated from 1995 to 1999: after a 1-year follow-up, the S53P4 glass implants caused no foreign body reaction in the bone or soft tissue as well as no infection, haemorrhage and implant displacement/extrusion<sup>4</sup>; CT scanning qualitatively demonstrated new bone growth around the implanted BG plates. Peltola et al.<sup>40</sup> reviewed the postoperative outcomes of 49 patients receiving a S53P4 glass plate from 1998 to 2001 (Fig. 4). These authors developed a set of stainless steel templates to guide the selection of the correct glass plate so that it almost perfectly fitted the surrounding orbit bone defect margins and anatomy. No signs of implant-related infection, extrusion or displacement were observed over a 2-year postoperative follow-up; furthermore, the implants caused no foreign body reaction, new bone formation was observed around the glass plates and only a minor resorption was found on the margins of the implants. Part of these results was also presented in the form of a conference abstract by Aitasalo et al.<sup>41</sup>

From the data reported in this series of studies, BG plates appear a promising and reliable solution for orbital floor reconstruction; specifically, S53P4 glass is biocompatible, bioactive (i.e. able to stimulate new bone growth) and slowly biodegradable (thereby ensuring adequate structural support while bone regenerates); furthermore, if the glass implant size and shape are properly selected, excellent functional and aesthetic results can be achieved.

## **Orbital implants**

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<sup>3</sup> Recession of the ocular globe or orbital implant within the orbit; it may be acquired as a result of trauma (e.g. blow-out fracture of the orbit) or related to postoperative complications of oculo-orbital surgery.

<sup>4</sup> “Extrusion” is the commonly used surgical term to describe the expulsion or spontaneous removal of an ocular implant from the host tissue, without any connotation of its meaning in polymer technology.

Silicate BG and BGC formulations have been also proposed for the manufacture of porous orbital implants in the form of single-phase materials or as a second phase added to a polymeric matrix (composites). There is a general paucity of scientific literature on this topic; most of available studies were performed by four groups of Chinese researchers.

In the late 1990s, Xu and co-workers<sup>42</sup> implanted BGC porous orbital implants in enucleated rabbits and observed no rejection during a 6-month postoperative follow-up; ultrasound examination revealed a venous-flow-like spectra in the implants after 3 months and histological analysis showed that around 90% of the implant pores were filled by fibrovascular tissue after 6 months from operation. Encouraged by these promising results, the same authors implanted the BGC orbital implants in 102 human patients, declaring a success rate of 96.1% (98 cases).<sup>43</sup> In 4 cases the conjunctiva was torn partly when suture stitches were taken out of the wound, and the orbital implant removal was necessary in 1 patient. There were no reported complications after a follow-up of 6 months to 2 years and all patients were satisfied with their cosmetic appearance, although implant drilling and placement of the motility peg to connect the implant to the ocular prosthesis were not performed as a secondary procedure.

After a time gap of 10 years, BG was recently experimented to fabricate PE-based composite porous implants. In 2006, Choi et al.<sup>44</sup> analyzed the effect of BG particulate on the fibrovascular in-growth occurring in porous PE-based orbital implants in rabbits. Forty-eight rabbits were divided into 4 equally-sized groups, according to the different surgical techniques and implanted materials employed: groups 1 and 2 received a porous PE sphere after enucleation or evisceration, respectively (reference groups), whereas groups 3 and 4 received a porous BG/PE composite implants after enucleation or evisceration, respectively. Histological examinations revealed that there was no statistically significant difference with regard to fibrovascular in-growth among the 4 groups after a 8-week postoperative follow-up. Therefore, in this preliminary study the authors concluded that inclusion of BG particulate did not significantly promote the rate of fibrovascular in-growth into porous PE-based orbital implants. In 2011, Ma et al.<sup>45</sup> reviewed the clinical outcomes

of 170 human patients after placement of porous BG/PE composite orbital implants for primary enucleation or secondary implantation. The majority of patients (161 cases) experienced no complications, the implant motility was generally good and no cases of implant-related conjunctival thinning or inflammation were observed. Excessive discharge and implant postoperative exposure occurred in 2 and 7 cases, respectively; additional surgery was necessary in 8 patients. These results suggest that the porous glass/PE composite orbital implant may be a useful alternative to other existing options, although its real advantages are currently unclear. Comparative studies are still necessary to definitely estimate their performance with respect to the commonly available and routinely used implants.

It is interesting to mention a very recent study by Ye et al.,<sup>46</sup> who coated porous HA orbital implants with a sol-gel derived CuO-containing mesoporous BG (Cu-MBG) (Fig. 5). The aim was to combine the antibacterial effect (copper shows potent antibacterial activity in suppressing a range of bacterial pathogens involved in hospital-acquired infections<sup>47</sup>) and drug delivery capacity (drug molecules can be hosted within the mesopores<sup>48</sup>) of the Cu-MBG coating to improve the final outcomes of anophthalmic socket surgery. Cu-MBG coatings with 0-5 mol.% of CuO were directly prepared in the pore walls of porous HA implants by dipping in the sol precursor of the glass, followed by evaporation and ageing. With the peculiarity of releasing antibacterial ions as the Cu-MBG degrades (viability of *Staphylococcus Aureus* (*S. Aureus*) and *Escherichia Coli* (*E. Coli*) was inhibited) and good drug uptake/delivery ability (in this study ofloxacin), Cu-MBG-coated porous HA orbital implants are promising in the prevention of implant-related infections. Moreover, there is an additional, perhaps even more important reason why the approach pioneered by these authors is so fascinating: it was demonstrated that Cu<sup>2+</sup> induces migration and proliferation of endothelial cells during *in vitro* culture, which could lead to an improved fibrovascularization of the orbital implant *in vivo*. Looking at the future, appropriate design of BG composition could impart angiogenetic properties to the material for enhancing the fibrovascular in-growth, which would actually represent a key added value for orbital implants.

The use of BGs to fabricate orbital implants was also claimed in a recent patent by Richter et al.<sup>49</sup> but, to the best of the author's knowledge, no manufacturing or clinical studies have been reported yet in the literature on this type of implant.

Another interesting application was reported by Heringer and Ng,<sup>50</sup> who proposed the use of BG as a "contingency plan" to fill old peg tracts and to permit re-pegging in porous HA orbital implants, if the initial drilled tunnel was not perpendicular and central to the implant surface. These authors removed the implant pegs and/or sleeves of 3 patients who had pegged HA orbital implants with related complications and, over a 2-year period, did not respond to conservative treatment. Peg tracts were subsequently filled with BG and no subsequent complications occurred in any case during 3 years of follow-up. After 2 months, 2 patients underwent successful re-drilling of the peg site with insertion of titanium pegs with good outcomes (the third patient deferred re-pegging at that time) and satisfactory connection to the ocular prosthesis.

### **Keratoprotheses**

Glass has been traditionally used to fabricate the optical core of keratoprotheses (especially in the early models) due to its transparency to visible light. On the contrary, the concept behind the use of BGs and BGCs is completely different: over the last 35 years, some of these special glasses have been employed in the manufacturing of keratoprosthetic skirts with the final aim of improving biointegration. As pointed out by Chirila,<sup>51</sup> the skirt material should preferably be hydrophilic in order to encourage the penetration of biological fluids from the host tissue, as an initial step in the biocolonization of the porous skirt. In principle, this requirement could be successfully fulfilled by BGs and BGCs, that are able to expose hydroxyl groups after contact with aqueous solutions and are characterized by a good water wettability. In the late 1970s, some BGC formulations belonging to the group called "Ceravital" were proposed to fabricate an anchorage skirt around experimental OOKP,<sup>52-55</sup> however, the tendency of these materials to progressively dissolve after contact with

biological fluids caused concerns about their suitability *in vivo* due to the consequent loss of their supporting function and, therefore, the investigations were discontinued. After a time gap of 15 years, Krause reported a concise study about the intracorneal biocompatibility of Bioverit® I and II in rabbit eyes:<sup>56</sup> the materials were incorporated into the host corneal tissue almost without irritation and no toxic or immune reactions were observed. Few years later, Linnola et al.<sup>57</sup> investigated the suitability of an apatite/wollastonite (A/W) glass-ceramic coating to solve a specific problem related to keratoprotheses, i.e. the in-growth of corneal or conjunctival epithelium into the anterior chamber, which may lead to infections and extrusion of the implant as well as to the development of retroprosthetic membrane and secondary glaucoma. The concept behind this study was that a material able to fasten the prosthesis to the corneal tissue before the epithelium grows inward could prevent these complications. The experimented keratoprotheses had a PMMA optical core supported by a titanium flange coated or not with a A/W glass-ceramic layer; 11 keratoprotheses for each of the two series were implanted in rabbit corneas. Histological analysis showed no significant in-growth of epithelium in 83% and 73% of the analysed areas of the A/W glass-ceramic coated and bare titanium protheses, respectively; therefore, the authors of this study concluded that the use of a BGC coating was an effective strategy to hinder the corneal epithelium in-growth.

After another time gap of 15 years, some very interesting studies have been published by different research groups. Santos et al.<sup>58</sup> investigated the properties of a glass-reinforced HA (GRHA) porous composite for potential use as a new synthetic material for the skirt of artificial cornea (Fig. 6(a)). This study is valuable also from a methodological viewpoint as the authors justified the suitability of the prepared material according to a defined protocol that included evaluation of pores characteristics, degradation in biological media at different pH (following the relevant ISO standard<sup>59</sup>) and *in vitro* cell viability (human dermal fibroblasts were used). GRHA was obtained through the addition of 2.5 wt.% of a phosphate glass (molar composition: 65P<sub>2</sub>O<sub>5</sub>–15CaO–10CaF<sub>2</sub>–10Na<sub>2</sub>O) to HA powder prepared by chemical precipitation. Poly(vinyl alcohol) was added as a porogen agent (10-50 vol.%) to the powder mix, that was pressed and finally sintered at 1300

°C for 1 h to obtain small porous disks. Degradation studies showed that no mass loss was found under simulated physiologic conditions (immersion in Tris solution); on the contrary, a significant mass loss was observed under acidic conditions (immersion in citric acid solution). The biological performance of these samples was satisfactory when cultured with human fibroblasts, that invaded the material porous network, grew and proliferate over a 14-day culture period. The mean pore size of 110 µm was found adequate to allow implant colonization by cells.

In the search for a suitable synthetic substitute of the dental laminate of OOKP, Laattala et al.<sup>60</sup> proposed a PMMA-based composite in which BG particles (40 wt.%) were added to the polymer matrix; four different glass compositions, including 45S5 Bioglass<sup>®</sup>, S53P4 and two other experimental formulations, were tested. These authors tried to solve the problems of the loosening of the optical cylinder in the Strampelli's OOKP due to the reabsorption of the autologous skirt. PMMA was chosen as a potentially suitable material to firmly anchor the keratoprosthesis, but it was too inert to be used on its own; therefore, a BG phase was added to enhance the bioactivity of the device, intended in this case as the ability to promote corneal cells adhesion. The dissolution behaviour of the composites in simulated aqueous humour, as well as the changes in the compressive strength and Young's modulus after soaking for 6 weeks in this testing solution, were investigated. A decrease of the mechanical properties after soaking in simulated aqueous humour was observed due to BG particles dissolution with an associated porosity increase; this behaviour was partially suppressed by the formation of apatite on the BG particle surface. In general, it should be taken into account that the progressive BG dissolution and the weak interfaces between BG particles and PMMA matrix (due to the lack of a covalent bond) permitted the penetration of water molecules into the composite, which could eventually lead to local disintegration; this issue deserves careful investigation as the maintenance of the device integrity *in vivo* is a key goal to be achieved. Another drawback related to the use of these composites is that the actual exposure on surface of BG particles, and hence their actual efficacy, was not known since the BG particles were dispersed within the polymeric matrix. Furthermore, the authors observed the presence of a thin

PMMA skin layer that covered the BG particles after the manufacturing of the composite; this polymeric layer could be eliminated from the outermost surface by grinding or manipulating with an organic solvent. Promising prototypes were obtained demonstrating the feasibility of the proposed approach (Fig. 6(b),(c)), but *in vitro* tests with cells (e.g. keratocytes) will be necessary to assess the actual suitability of the composite skirt for clinical use.

In 2013, Huhtinen et al.<sup>61</sup> investigated two experimental silico-boro-phosphate BGs of different compositions (1-98: 5.9Na<sub>2</sub>O-7.1K<sub>2</sub>O-7.6MgO-23.9CaO-0.9B<sub>2</sub>O<sub>3</sub>-0.9P<sub>2</sub>O<sub>5</sub>-53.8SiO<sub>2</sub>; 28-04: 4.9Na<sub>2</sub>O-7.2K<sub>2</sub>O-9.0MgO-16.2CaO-2.6B<sub>2</sub>O<sub>3</sub>-60.1SiO<sub>2</sub>, mol.%) as potential substitutes of the tooth-derived skirt of the OOKP. The glasses were produced by melting-quenching route, crushed and sieved into the 250-315 and 315-500 µm size ranges to assess the influence of different dimensional ranges besides that associated to composition; the particles were then sintered in a graphite mould into ring-shaped structures with interconnected porosity. *In vitro* tests with keratocytes showed that none of the porous BG structures induced a cytokine driven inflammatory response and the adherent keratocytes exhibited a typical elongated, spindle-shaped morphology which suggested a good adhesive potential. These preliminary investigations support the use of porous BG as a synthetic OOKP skirt, even if dissolution of the glass over time may destabilise the OOKP, indicating that a composite system with a stable backbone structure would be necessary to maintain the optical core in the correct position while the BG chemically dissolves; in this regard, the study by Laatala et al.<sup>60</sup> (previously presented) can provide useful research inputs. Future studies in an animal model would be necessary to explore the systemic effects of the dissolution products from these BGs as well as the impact of ion release and pH change in the eye.

An interesting *in vivo* investigation was reported by Liang et al.,<sup>62</sup> who implanted experimental BGC disks (diameter 8 mm, thickness 0.5 mm, pore diameter 20-70 µm, porosity 37-62 vol.%) in 11 albino rabbit corneas. The implants with higher porosity (51-62 vol.%) were all extruded due to breakage (5 cases); the other major complications included corneal oedema with severe degrees of corneal neovascularization within 1 month postoperatively, opacity of the corneal lamella after 2

months and lipid deposits (4 cases). Furthermore, the implant was too hard to be cut, thus making difficult the histological examination. Therefore, the authors of this study judged the chosen BGC unsuitable as peripheral keratoprosthesis materials because of excessive roughness, hardness, thickness and tendency to breakage; perhaps, an optimization of the structural design parameters (e.g. implant thickness, pore size and interconnectivity) maintaining unaltered the material formulation may lead to more satisfactory results.

## **TOWARDS TARGETED THERAPEUTIC APPLICATIONS AND EYE TISSUE ENGINEERING USING BGs AND BGCs: PROMISES, CHALLENGES AND CRUCIAL ISSUES**

Possible advances provided by the use of BGs and BGCs in ocular surgery over the existing state-of-the-art solutions are briefly summarized in Table II; these concepts will be discussed in the details in the following paragraphs.

With respect to the currently-employed biomaterials for ocular surgery (e.g. HA, PE, alumina), the most fascinating added value of BGs and BGCs is the unique ability to release appropriate ions with the aim of inducing a specific, desired response *in vivo*. It has been demonstrated that ionic dissolution products play a key role in affecting the biological response of biomedical materials *in vitro* and *in vivo*, stimulating cell activity or exerting other appropriate functions (e.g. antibacterial effect); in this regard, BGs have received great attention by researchers due to their adjustable reactivity in the biological environment.<sup>63,64</sup> Since many trace elements present in the human body are known for their anabolic effects in cells metabolism, a new approach for designing BG-derived products able to elicit a specific biological response for targeted applications could be based on the introduction of therapeutic ions into the BG formulation. The subsequent release of these ions after exposure to a physiological environment can exhibit osteogenetic,<sup>63</sup> antibacterial,<sup>65</sup> anti-inflammatory<sup>66</sup> or angiogenetic effects.<sup>67-72</sup> This fascinating scenario was impressively called

“genetic design of bioactive glass” by Prof. Hench, the inventor of 45S5 Bioglass<sup>®</sup> who entitled in this way one of his publications.<sup>63</sup> In the specific context of ocular surgery, the ability to bond to bone stimulating new bone formation is a key property for orbital floor implants; antibacterial action would be generally very useful for all ocular implants; finally, BGs able to promote angiogenesis can open interesting perspectives in the field of porous orbital implants, whose fibrovascularization is a crucial requirement to maintain the implant in place and to reduce the risk of exposure-related infections. *In vitro* experiments have shown that BGs stimulate the secretion of angiogenic growth factors in fibroblasts, the proliferation of endothelial cells and the formation of endothelial tubules;<sup>67,69</sup> early *in vivo* results assessed the neovascularization of porous BG implanted in rats.<sup>69-71</sup>

BG and BGC compositions can be properly designed to obtain materials with different degrees of solubility by varying the ratios between the constituent oxides (e.g. SiO<sub>2</sub>, P<sub>2</sub>O<sub>5</sub>, Na<sub>2</sub>O and CaO) and/or incorporating additional metal oxides; in this regard, biocompatible phosphate glasses can offer a wide range of dissolution kinetics.<sup>73</sup> It has been demonstrated that metal oxides such as TiO<sub>2</sub>, CuO, AgO and Fe<sub>2</sub>O<sub>3</sub>, apart from modulating the phosphate glass solubility, are also useful in exerting an antibacterial effect via the release of the relevant metal ions. In this regard, the recent – and currently unique – study by Ye et al.<sup>46</sup> about the antibacterial effect of Cu<sup>2+</sup> released from MBG-coated HA porous orbital implants opens interesting perspectives for the development of novel ocular devices with antiseptic functionalities.

The use of soluble materials as ocular implants, however, deserves careful attention depending on the context of use. Potentially suitable BGs and BGCs for orbital floor repair are expected to exhibit an adequate surface reactivity to promote the bond to the host bone via the series of ion-exchange reactions described by Hench et al.;<sup>1</sup> as a general rule, the implant solubility must be compatible with bone healing rate. In this regard, the solubility of S53P4 glass orbital plates, that are currently the unique BG implants clinically employed for this purpose, is quite moderate.<sup>37-41</sup> On the contrary, orbital implants should be conceived as permanent devices, i.e. they must remain *in situ*

indefinitely during the patient's whole life without undergoing degradation to ensure an adequate socket volume replacement. An interesting exception was disclosed in a patent deposited in the late 1990s by Durette,<sup>74</sup> who proposed an orbital implant preferably made of biodegradable material (including glass) and having a matrix with random voids throughout to enhance tissue in-growth. The use of a partially absorbable orbital implant able to increase its porosity *in vivo*, thereby allowing an improved fibrovascularization postoperatively, represents a fascinating concept; however, this approach poses several problems which should be carefully and critically examined, especially concerning the kinetics of socket volume replacement by tissue while the implant resorbs and the ocular prosthesis motility in the partial or total absence of an orbital implant that can transfer movement to it. In the field of artificial cornea, resorption of the porous skirt around the optical core is an unwanted effect that would lead to the loosening of the keratoprosthesis;<sup>21</sup> this problem was the major reason why synthetic alternatives to the tooth-derived skirt of Strampelli's OOKP have been proposed, including BG-based materials.<sup>58,60,61</sup> Therefore, the use of BGs and BGCs able to maintain adequate integrity over time *in vivo* is recommended for this specific application. On the other hand, it cannot be ignored that chemical and biological stability competes with the capability of BGs to release therapeutic ions via controlled dissolution. This specific problem is only one of the aspects of a wider issue concerning the surgical applications of BGs and BGCs, that are excellent biomaterials to be replaced or invaded (if porous) by regenerating tissues but, if used as connecting or joining elements between various prosthetic permanent components (as in the case of synthetic OOKP), they must ensure indefinite and safe stability and should not dissolve in biological fluids.

BGs and BGCs are attractive also from a technological viewpoint due to the relative ease of processing associated to their production. BGs can be employed in the form of powder to produce 3-D porous scaffolds with different size, shapes, pore architecture and mechanical properties through a number of relatively easy, inexpensive methods like sponge replica technique,<sup>75,76</sup> sol-gel foaming<sup>77</sup> and polymeric particles burning-out.<sup>78</sup> Rapid prototyping techniques, such as selective

laser sintering<sup>79</sup> and robocasting,<sup>80</sup> can allow custom-made porous BG implants to be fabricated. A clever approach could involve the use of microCT- or MRI-derived files as input data for CAD/CAM manufacturing systems in order to produce scaffolds exactly matching the required anatomical dimensions. This strategy was already successfully applied for the production of HA porous implants for oculoplastic surgery.<sup>81-83</sup> In this way, the size of porous plates for orbital floor repair could reproduce the contour of the bone fracture, the orbital implant volume could be properly adapted to fit the individual eye socket, and the porous skirt of synthetic OOKP could be tailored according to the features of each patient's eye.

BGs can be also produced in form of mesoporous materials (MBGs, with an ordered pore arrangement with pore size within 2-50 nm)<sup>84</sup> that, hosting anti-inflammatory drugs or antibiotics, could impart a significant added value to implantable ocular devices since intra- or postoperative infections are one of the major causes of failure of ophthalmic implants. Before implantation, porous ocular biomaterials are usually soaked by the ophthalmic surgeons into an antibiotic solution; however, this common practice is quite rough and the antibiotic is released as a burst after contact with biological fluids *in situ*. Drug release from MBGs would allow a prolonged therapy to be performed, with a higher control on the amount of incorporated drug and the release kinetics, which both can be pre-determined as a function of the mesopores shape and size. A serious drawback of MBG constructs is the high brittleness due to the presence of an intrinsic mesoporous texture (compressive strength within 50-250 kPa<sup>85</sup>), which poses serious problems for material shaping at the time of surgery and safe implantation without loss of integrity. High solubility of MBGs related to the high surface exposed to biological fluids is another issue to be taken into account. The use of MBGs as coatings on a mechanically and chemically stable porous backbone, as proposed by Ye et al.,<sup>46</sup> could be an effective solution to these shortcomings.

Looking at the future, the use of BGs and BGCs in ophthalmology could also disclose new therapeutic approaches for the treatment of ocular tumours. Tumours affecting the orbital bone or ocular tissues are one of the main non-traumatic causes requiring the surgical resection of the

orbital bone or the removal of the ocular globe. The surgical procedure typically comprises two stages: (i) removal of the diseased tissue (orbital bone portions and/or the ocular globe) and (ii) implantation of an appropriate biomaterial or device (orbital bone graft and/or orbital implant replacing the socket volume). Therefore, the clinical challenge is twofold: it is necessary not only to successfully restore the surgically-induced defect, but also to avoid the re-development of the tumour. In this regard, hyperthermia using implantable magnetic BGs and BGCs has emerged as a promising option for the localized treatment of malignant tumours.<sup>86</sup> At present, the researches and clinical applications of hyperthermia mediated by magnetic materials are mainly addressed to the treatment of bone tumours; the suitability of this approach to treat orbital bone/intra-orbital malignancies would deserve consideration in the next future. In this regard, for the sake of discussion it is instructive to mention a recent work by Wu et al.,<sup>87</sup> who proposed an innovative approach combining hyperthermia therapy and local drug delivery in a multifunctional Fe-containing hierarchical porous MBG scaffold prepared through a co-templating method. Large macropores are useful to permit healthy tissue in-growth, mesopores allow sustained drug release and the magnetic properties of the Fe-containing glass can be exploited for *in situ* cancer treatment by hyperthermia. As mentioned above, high brittleness of MBG constructs is a serious shortcoming that limits the clinical applications; perhaps, injectable magnetic MBG pastes could be suitable for the repair of cancer-derived orbital bone defects or be introduced intraorbitally in the region around the severed optic nerve to kill the residual cancer cells that might migrate through it after enucleation. MBGs hosting and releasing antineoplastic drugs could be also considered for the treatment of orbital bone tumours or intra-orbital malignancies, like retinoblastoma, which is the major cause of enucleation in children.

Use of radioactive BGs, initially proposed by Day and Day<sup>88</sup> for the treatment of liver cancer, deserves to be mentioned in this review as a possible stimulus for future research, in the attempt at developing less invasive approaches to treat ocular tumours, decreasing the radiation dosage required to kill the cancer cells and minimizing the overall side effect toxicities. In current

applications,  $^{89}\text{Y}$ -containing glasses in the  $\text{Y}_2\text{O}_3\text{-Al}_2\text{O}_3\text{-SiO}_2$  ternary system were produced in the form of 20 to 30  $\mu\text{m}$  microspheres (TheraSphere<sup>®</sup>); before arterial infusion, the glass beads were bombarded by neutrons that create  $^{90}\text{Y}$ , a radioisotope that is a short-half-life (64 h), short-range  $\beta$ -rays emitter. In this way, a localized dosage of up to 15000 rad was delivered, whereas a maximum of 3000 rad under external radiation can be tolerated by the patient. The selected ternary glass system provided excellent chemical durability in the body in order to avoid dissolution and migration of the radioisotope via the blood circulation; at present, radioactive glass microspheres are clinically used as an adjuvant to liver surgery at a number of clinical centres in USA, Canada and EU countries after receiving FDA approval in 1999.

A very versatile way to impart special properties to BGs and BGCs involves surface modifications. It has been demonstrated that in aqueous environment silicate BGs and BGCs can expose reactive hydroxyls groups on their surface, that can be employed for the grafting of appropriate biomolecules to improve bioactivity or elicit specific therapeutic actions.<sup>89</sup> In this context, functionalization of MBG pore walls has been successfully experimented.<sup>86</sup> Looking at possible ophthalmic applications, the idea of grafting specific growth factors, like the vascular endothelial growth factor (VEGF) to enhance vascularization, or drugs to reduce inflammation and infection, could be of high interest in the field of orbital implants. Another strategy to impart added values to biomaterials is the deposition of a coating on the implant surface. Since implant-related ocular infections are responsible for serious postoperative problems requiring expensive and stressful extra-treatments for the patients,<sup>90-93</sup> a smart coating able to elicit an antibacterial/antifungal effect would be of great importance for ophthalmic biomaterials. In this regard, Bairo et al.<sup>94</sup> disclosed in a recent patent the application of an antibacterial oxide-based composite film on the surface of orbital implants and ocular prostheses. The coating, whose thickness can be modulated from 10 nm to 1  $\mu\text{m}$ , is produced by radio-frequency co-sputtering of silver and silica and is constituted by silver nanoclusters embedded in an amorphous silica (silica glass) matrix. The antiseptic effect was demonstrated *in vitro* (using *S. Aureus*) and is due to the release of silver ions,<sup>95-97</sup> that are not

associated to problems of bacterial resistance like in the case of antibiotic treatments. This approach is promising but further *in vitro* tests with the relevant cell types (e.g. orbital fibroblasts) and *in vivo* studies in an animal model have to be performed to draw definite conclusions about the suitability of the coating: in fact, the ocular environment is highly complex and several parameters should be taken in account, including the solubility of the silica matrix, the interaction of released metal ions with the tears and the possible ion-induced eye tissue necrosis. This field of research being very new, the existing literature is very scarce, also due to the difficulty in detecting the toxic effect. In this regard, Hau and Tuft recently described corneal argyrosis associated with silver nitrate-coated cosmetic soft contact lenses that a 67-year-old woman wore for 17 years:<sup>98</sup> this is a typical example of an apparently unexpected side effect detectable only after many years of follow-up. Matusiewicz recently published a comprehensive review article about the toxicity associated to metal ions released from orthopaedic and dental implants;<sup>99</sup> the provided guidelines to assess and quantify the toxic effect could be a valuable starting point and a stimulus to extend such investigations to ocular devices.

As a fascinating promise for the future, it is also instructive to mention the case of retinal implants, whose development might benefit by the use of BGs. Despite enormous efforts and advances in clinical treatment of eye diseases, there is no established method to prevent or cure degenerative processes in eye, such as age-related macular degeneration (ARMD) and retinitis pigmentosa (RP); the latter disease can lead to blindness when photoreceptors in the retina are completely degenerated. Recent advances in microtechnologies have paved the way to pursue the idea for developing an implantable device, commonly referred to as artificial retina, visual prosthesis or bionic eye, that can substitute degenerated visual photoreceptors and neural structures for stimulating intact neural tissue so that a meaningful visual sensation is obtained. The subretinal implant is based on the concept to place a silicon-based microphotodiode array (MPDA) in the subretinal space in order to replace the degenerated photoreceptors; a photovoltaic charge is generated in each photodiode cell and transferred to the adjacent microelectrode for stimulation of

the bipolar cells. An external camera connected to a pair of glasses transmits wirelessly the electromagnetic signals to the implanted device. In the late 1990s, a group of German researchers manufactured a MPDA on a silicon wafer using complementary metal-oxide semiconductor (CMOS) process technology.<sup>100</sup> After completion of electrically active structures, a 500-nm thick passivation layer consisting of amorphous silicon oxide (silica glass) was applied using tetraethylorthosilicate (TEOS) as a precursor. *In vivo* experiments (rabbits and pigs) revealed a decay of the silicon oxide passivation layer and pit corrosion of the underlying silicon for implantation periods above 6 months. Therefore, this material has been substituted by stimulation microelectrodes made of nanoporous titanium nitride, that demonstrated good biostability over an implantation period exceeding 18 months, and other passivation layers, such as polyimide, benzocyclobutene (BCB), and parylene C, were selected. Although the choice of amorphous silicon oxide as a passivation layer was not the most fortunate, it is an interesting example (at present the unique one) about the use of a biocompatible glass as a thin passivation film in a bionic device (retinal implant). In the last two decades, many other types of artificial retinas have proposed by several research groups around the world; the interested reader can find a comprehensive picture of this topic in a recent review by Ong and Da Cruz.<sup>101</sup> The development of functional microdevices that fit in the human eye and take over lost biological functions to restore vision is a challenge bridging different research fields including materials science, microelectronics and ophthalmology; at present, only one retinal implant, Argus II (60 electrodes),<sup>102</sup> has received approval for commercial use in Europe (2011) and USA by the FDA (2013). In the next few years an increasing cooperation among biomaterials scientists, biologists, ophthalmologists and researchers in the medical implant industry would be desirable to understand whether BGs and BGCs can play a role in the treatment and, hopefully, repair of diseased retina, thus opening new perspectives to further improve the patient's quality of life.

## **CRITERIA AND GUIDELINES FOR SELECTING AND TESTING SUITABLE BG-BASED MATERIALS FOR OPHTHALMIC APPLICATIONS**

Taking the existing literature as a starting point, this section collects some methodological remarks in the attempt to provide useful suggestions towards the development of more effective implantable BG-based ocular devices, with particular reference to oculo-orbito-plastics (BG/BGC orbital floor grafts and orbital implants) and artificial cornea (BG/BGC keratoprosthesis).

### **Design concept and implants fabrication**

First, the ocular implant specifications, such as size, shape, pores features and possible need for bioresorption, have to be defined. Implant geometry can be customized on the basis of the patient's anatomy evaluated through CT scanning and/or MRI. Open and highly interconnected macroporosity would be a desirable characteristic for all the three types of implants mentioned above in order to allow cell invasion *in vivo* and new tissue in-growth; with regard to BG orbital floor grafts, at present only pore-free melt-derived plates were produced and successfully experimented in human patients.<sup>37-41</sup> Looking at the future, porous implants for the repair of orbital bone fractures should exhibit pore size in the 100-600  $\mu\text{m}$  range, as recommended for BG-based bone tissue engineering scaffolds.<sup>103</sup> Pores within 300-700  $\mu\text{m}$  should be achieved in the case of BG porous orbital implants, taking the pore characteristics of the commonly used devices (HA, PE and alumina porous spheres<sup>17,32,104</sup>) as a starting point. Pore diameter ranging from 50 to 150  $\mu\text{m}$ <sup>105</sup> is adequate to allow keratocytes invasion and proliferation within a BG keratoprosthesis. As to the solubility after contact with biological fluids, *in vivo* resorption can be desirable in the case of orbital floor grafts (the BG implant progressively dissolves and is replaced by newly formed bone tissue) but it should be avoided for orbital implants and artificial cornea.

BG composition has to be designed by carefully selecting the amount and ratio of the different constituent oxides. This is a crucial stage as BG formulation affects the physico-chemical and biological properties of the final material. If a soluble material is pursued (as in the case of orbital floor grafts), phosphate glasses can be chosen, otherwise silicate BGs with high SiO<sub>2</sub> content (typically above 50 mol.%) should be considered. Additional metal oxides can be introduced in small amounts into the BG to finely tune its bioactive properties upon the release of appropriate ions: for instance, CuO can be considered in the case of orbital implants as Cu<sup>2+</sup> is known to have an angiogenic effect and could stimulate implant fibrovascularization, as suggested by Ye et al.<sup>46</sup> The most appropriate technique for implant fabrication has to be chosen/developed on the basis of the properties required for each specific application (e.g. adequate pore size allowing relevant cells to colonize the implant, as mentioned above). Dense BG plates matching the size of bone orbital fractures can be produced by simple melting-casting route.<sup>37-41</sup> If porous BG implants are pursued, a number of methods involving the use of pore-forming agents, surfactant-assisted sol-gel methods (in the case of MBGs) and rapid prototyping techniques are at the researchers' disposal. Sintering of relatively large glass particles (250-500 μm) without the use of pore formers can be performed (the final porosity derives from the interparticle void spaces among the original glass particles).<sup>61</sup> The deposition of a thin BG coating on a substrate ocular device with adequate morpho-structural characteristics in order to impart it a specific added value (e.g. antibacterial effect<sup>46,94</sup>) is a valuable strategy. BGs can be also produced in a nanoporous form, i.e. sol-gel glasses, characterized by an intrinsic nanoporosity left by the condensation of the network, or MBGs, in which the ordered mesoporosity is due to the use a surfactant. In general, nanoporous BGs have a higher apatite forming ability upon contact with biological fluids compared to melt-derived BGs due to the higher exposed surface available for ion-exchange processes: this could be an important added values if BGs are addressed top orbital bone repair. Mesopores could be also exploited for the uptake and subsequent local release of drugs and biomolecules, which could be an interesting extra-functionality for all the three applications considered in this review.

## Testing and validation

The morphology, surface features and pores characteristics of the BG-derived implant can be assessed by SEM and X-ray micro-CT; XPS and SIMS can be exploited to investigate the surface chemistry, and EDS for elemental analysis. The material microstructure should be analysed by wide-angle X-ray diffraction (XRD) to assess the presence of crystalline phases developed during the thermal treatments applied for implant manufacturing. If MBGs are employed, small-angle XRD, TEM and probe molecules sorption techniques (e.g. N<sub>2</sub> sorption) are useful to assess the mesopores characteristics. Assessment of the surface roughness, which can be performed by profilometry or atomic force microscopy (AFM), is particularly important in the case of BG/BGC orbital implants, that after implantation could erode the patient's conjunctiva.

*In vitro* tests without cells for preliminary assessment of BG solubility and ion release kinetics in appropriate media (e.g. artificial aqueous humour<sup>60</sup>), as well as BG-induced pH variations, are of utmost importance to validate the materials in the light of the implant specifications. As BGs and BGCs are, formally, non-crystalline or partially crystalline ceramics, the standard ISO 10993-14 on *in vitro* testing of bioceramics<sup>59</sup> can be used as a valuable guideline.<sup>58</sup> Dissolution studies at different pH values can provide useful data to mimic what happens during implant infections.<sup>106</sup> In the case of BGs/BGCs for orbital floor repair, where the formation of a surface apatite layer after contact with biological fluids is a key goal, FT-IR, XRD, SEM and EDS are all valuable techniques to assess the presence of this new phase. If the ocular implant comprises MBGs hosting therapeutic agents into the mesopores, drug uptake and release tests should be performed.

*In vitro* cytotoxicity testing with appropriate cell types should be commonly recognized as a key eliminatory criterion in the selection of BGs/BGCs for ocular applications. Such tests are useful because they avoid unnecessary, time-consuming and expensive animal experiments. In this regard, Sandeman et al.<sup>107</sup> proposed a series of *in vitro* screening assays for the preliminary selection of

(polymeric) biomaterials to be used in the fabrication of artificial corneas. Useful indications for the *in vitro* screening of orbital implant biomaterials were provided by Mawn et al.<sup>108</sup> who proposed the use of orbital fibroblasts. From a general viewpoint, the standard ISO 10993-5 can be followed for *in vitro* biological tests.<sup>109</sup> Advanced studies could be also considered; for example, Tan et al.<sup>110</sup> reported the use of AFM in contact mode to assess the adhesion strength of keratocytes seeded on biomaterials for artificial cornea. Antibacterial tests can be performed if the antiseptic effect is one of the implant goals.<sup>46</sup>

Mechanical testing of BG-based ocular implants is very important, especially considering that BGs and BGCs are brittle materials and, therefore, problems of integrity could occur both during implantation and in the postoperative follow-up. A consensus should be achieved on what mechanical characteristics to assess and testing methods to apply/adapt; at least the compressive strength and elastic modulus should be determined.<sup>60</sup> Some authors suggested the use of *ex vivo* (animal) eyes for a preliminary evaluation of the mechanical compatibility between experimental keratoprosthetic skirt and corneal tissue.<sup>111</sup> From a general viewpoint, it cannot be ignored that BGs and BGCs can have a generally good mechanical compatibility with the orbital bone but are remarkably stiffer, even if produced in a porous form, than the ocular and intraorbital tissues (Table III)<sup>75,112-115</sup>. Therefore, future research directions could be addressed to the development of more compliant ocular biomaterials, such as BG/polymer constructs that have already been successfully experimented in ophthalmic surgery<sup>14,19,30,51</sup>.

According to the majority of scientists, after extensive *in vitro* tests with cells there is no recognized alternative to pre-clinical animal trials in order to progress the development of biomedical implants towards the final stage of clinical trials (human patients). It is worth underlining that the ideal implantation site for ophthalmic biomaterials is the eye with its unique physiological and microenvironmental characteristics; however, this requires the expertise and availability of an ophthalmic surgeon to perform operation, which can represent an additional difficulty in building interdisciplinary research teams. In order to simplify the experiments, some authors proposed a

rabbit skin subcutaneous model to investigate the *in vivo* suitability of new keratoprosthesis biomaterials.<sup>116</sup> Special care should be dedicated to the development of methods to correlate and interpret the results deriving from different *in vivo* studies, the selection of the most appropriate animal models and the sequence to follow in performing the experiments. CT scanning and MRI are useful to assess tissue in-growth within the implanted porous BG-based ocular devices.

Finally, sterilization is a crucial issue in view of implant commercialization and safe clinical use. In principle, BG-derived ocular implants could be easily sterilized by  $\gamma$ - and  $\beta$ -irradiation, exposition to ethylene oxide or UV irradiation without undergoing degradation. Problems with sterilization by autoclaving can occur if the BG is susceptible to moisture, like in the case of phosphate glasses that are prone to dissolution in aqueous media. Persistence of original properties after sterilization by irradiation or autoclaving might be a problem for polymer/BG composites.<sup>44,45,60</sup>

## CONCLUSIONS

The main message of this article – also in order to answer the question posed in the manuscript title – is that BGs can be indeed useful and valuable materials for smart applications in ophthalmology. At present, however, this potential is still underestimated and the research on such a topic is growing very slowly, probably also due to the difficulty of building highly interdisciplinary research groups involving the collaboration amongst biomaterials researchers, glass chemists, bioengineers, biologists and ophthalmic/maxillofacial surgeons. In general, while BGs and BGCs have been extensively investigated for bone and dental repair, there has been relatively little research on their application in other medical areas, including ophthalmology. In this regard, it is instructive to look at the modern story of biomaterials science: we need to remember that only 40 years ago the concept of a material that would be able to actively stimulate tissue regeneration seemed impossible; this dream became reality with the invention of 45S5 Bioglass<sup>®</sup> by Prof. Larry Hench's group, but none of the high-impact future applications were forecast when the research

began. BGs and BGCs could further improve the performance of ocular implants imparting them valuable extra-functionalities. BGs and BGCs can bond to bone promoting new tissue growth, which is a key added value for implants devoted to the repair of orbital floor fractures. Through the release of appropriate ionic dissolution products, porous BGs and BGCs could stimulate fibrovascular in-growth, which is a fundamental characteristic to ensure an adequate motility of orbital implants and to reduce the risk of postoperative infections. Porous BGs have been also shown to allow and even stimulate keratocytes adhesion and proliferation, which make them promising candidates for the development of a new class of skirt keratoprostheses. Looking at the future, novel perspectives for eye surgery could raise from the development of BGs with tailorable mesoporosity for intraocular/intraorbital drug release, magnetic and radioactive BGs and BGCs for eye cancer treatment and BG-based implants whose ion dissolution products can elicit angiogenic and antibacterial effects.

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### Figure legends

**FIGURE 1.** Implantation of an orbital floor graft via the transantral approach through maxillary bone: (a) the graft is introduced under endoscopic guidance; (b) repaired orbital floor. (Legend: 1 = maxillary access; 2 = orbital floor fracture; 3 = implanted material repairing the fracture).

**FIGURE 2.** Sagittal section of a human orbit after enucleation surgery followed by placement of a spherical implant that replaces the volume deficit created by eye removal. In this picture the extraocular muscles are sutured directly to the implant, which is a common practice in the case of malleable polymeric implants (e.g. porous PE); on the contrary, ceramic orbital implant (e.g. HA, alumina), being hard and having a rough surface (especially for porous HA), are usually wrapped with donor sclera or other natural/synthetic polymeric materials, that are useful for the anchorage of the extraocular muscles, make easier the insertion into the anophthalmic socket and limit, acting as a physical protective barrier, the risk of postoperative erosion of the patient's conjunctiva. The ocular prosthesis is designed to fit in between the eyelids and the conjunctiva/implant in order to mimic the normal appearance of a healthy eye. The optional placement of a peg in the frontal part of the orbital implant, that must be drilled after some months from primary surgery, allows direct connection with the ocular prosthesis: Use of pegged implants leads to a greater transmission of movement of the implant to the artificial aesthetic eye, giving it a more life-like appearance.

**FIGURE 3.** Schematic perspective view of conventional OOKP (vertical orientation: top - front of the eye; bottom - back of the eye).

**FIGURE 4.** Use of BG plates for the repair of orbital floor defect: (a) CT scan taken 2 years after orbital floor reconstruction with a 25 mm × 2 mm S53P4 glass implant (arrow); (b) photograph of a BG plate harvested from the orbit in revision surgery after 2 years from primary operation (slight resorption of the original margins of the plate was assessed). (Images adapted from Peltola et al.<sup>40</sup>).

**FIGURE 5.** MBG-coated porous HA scaffolds for possible use as orbital implants: (a) optical image showing the outward appearance of the HA devices before and after undergoing different MBG coating (MBG coating with 0, 2 and 5 mol.% of Cu were produced); (b) surface morphology of porous HA coated with 5 mol.% Cu-doped MBG and (c) detail of the HA/MBG interface. (Images adapted from Ye et al.<sup>46</sup>).

**FIGURE 6.** Use of BGs for the production of experimental synthetic OOKP: (a); detail of the porous disk of glass-reinforced HA (the porosity of about 22 vol.% was obtained by adding 30 vol.% poly(vinyl alcohol) as a porogen) (image adapted from Santos et al.<sup>58</sup>); (b) and (c) PMMA/BG composite skirt around the optical PMMA cylinder (images adapted from Laattala et al.<sup>60</sup>).

**TABLE I. Overview of the BG and BGC Implants That Have Been Clinically Used or Suggested as Experimental Biomaterials in Ocular Surgery.**

Application	Material and type of implants	Recipient <sup>a</sup>	Remarks	References
Eye orbit floor repair	Cast curved plates of S53P4 glass	HP	Slowly resorbable.	37-41
Orbital implants	Porous glass-ceramic sphere (unknown glass-ceramic compositions)	AM, HP	Experimented in rabbits and humans.	42,43
	BG/PE porous sphere	AM, HP	Experimented in rabbits and humans. Apparently, no significant improvement in implant fibrovascularization was observed with respect to porous PE. Studies involving a higher number of patients are necessary for a more exhaustive assessment. Optimization of bioactive glass composition could be necessary.	44,45
	Cu-containing mesoporous BG coating on porous hydroxyapatite implants	IV	Encouraging antibacterial results against <i>S. Aureus</i> and <i>E. Coli</i> .	46
	BG filler for peg tracts	HP	Successful repair and re-pegging of porous hydroxyapatite implants.	50
Keratoprostheses	“Ceravital”-based implants	HP	Concerns about material resorbability caused discontinuance of experiments.	52-55

## Bioactive glasses in ocular surgery

	Bioverit <sup>®</sup> I and II	AM	Experimented in rabbits as materials for the porous skirt.	<sup>56</sup>
	Bioactive A/W glass-ceramic coating on titanium	AM	Used to coat the titanium flange that anchored the prosthesis to the host corneal tissue. Experimented in rabbits.	<sup>57</sup>
	Glass-reinforced HA porous composites (intended use for the keratoprosthesis skirt)	IV	Encouraging results with human dermal fibroblasts. Degradation studies in biological media at different pH were carried out.	<sup>58</sup>
	BG/PMMA composite skirts	-	No biological tests with cells have been carried out yet. Decrease of mechanical properties due to glass particles dissolution is an issue to be taken onto account.	<sup>60</sup>
	BG porous skirts (1-98 and 28-04 glasses)	IV	Encouraging results with keratocytes.	<sup>61</sup>
	BGC disk (intended use for the keratoprosthesis skirt)	AM	Experimented in rabbits. The material was found unsuitable.	<sup>62</sup>

<sup>a</sup> HP = human patients; AM = animal model only; IV = *in vitro* tests only.

**TABLE II. Main Added Values That Can Be Provided by BG/BGC Ocular Implants With Respect to Existing Solutions.**

Feature	Provided by currently-used materials? <sup>a</sup>	Improvement provided by BGs/BGCs
Biocompatibility	Yes, at present it is recognized as a pre-condition for clinical applications.	BGs and BGCs are biocompatible and well-tolerated by the body under appropriate design of glass composition.
Ease of processing/shaping	Yes; a number of implant shapes/sizes are available on the marketplace. Problems of brittleness can occur with porous HA plates for OF.	In principle, BGs and BGCs have the same problems of brittleness of ceramics. They have higher versatility with respect to crystalline ceramics such as HA and alumina: for instance, BGs can be produced by melting-casting. Furthermore, porous BG scaffolds are usually mechanically stronger than porous HA (better sintering), which can help to easily shape and contour the implant at the time of surgery, if necessary.
Open porosity	Yes	Yes. Besides an interconnected macroporosity, a nano-scale porosity (e.g. sol-gel glasses, mesoporous BG) can be introduced by using appropriate synthesis routes to impart extra-functionalities to the implant (e.g. drug uptake/release).
Solubility	Usually not, except for the absorbable polymeric implants sometimes used for OF. Absorption of the autologous skirt in the case of Strampelli's OOKP is an undesired event. Note that solubility can be a desired option in the case of OF, but should be avoided for OI and KP.	BGs and BGCs with different solubility can be produced depending on the oxide formulation.

## Bioactive glasses in ocular surgery

Bone in-growth (for OF only)	It depends on the used materials; for instance, yes in the case of porous HA, not in the case of porous PE (only vascular in-growth is allowed).	Yes. Glass bioactivity can be further enhanced by the presence of a nano-scale porosity (sol-gel and mesoporous BGs).
Fibrovascularization (for OI only)	Yes, it is allowed in porous implants (“angioconductive” ability).	Angioinduction could be obtained if the glass is doped with appropriate metal ions (e.g. Cu <sup>2+</sup> ).
Keratocytes colonization (for KP only)	It is allowed, but it can be difficult in some cases.	Yes, early results are promising.
Antibacterial properties	Not.	Yes, if the glass is doped with appropriate metal ions (e.g. Ag <sup>+</sup> ).
Structural integrity	Usually yes; some problems with porous HA plates for OF (upon implantation).	Yes, the mechanical strength can be properly tailored acting on glass composition.

<sup>a</sup> Just to provide the reader a very short overview, the most routinely used materials in ocular surgery for orbital floor repair (OF), orbital implants (OI) and keratoprotheses (KP) are the following: autologous bone, porous HA, a number of permanent/absorbable porous/non-porous polymers (including the widely-used porous PE), titanium meshes are used for OF<sup>16</sup>; porous HA, PE and alumina spheres, silicone and PMMA solid spheres, and other PMMA implants of more complex design are used for OI<sup>17,31</sup>; in the case of KP, PMMA (more rarely a transparent hydrogel) is used for the optical core whereas the skirt is made of porous polymers or autologous tooth/bone laminate (Strampelli’s OOKP)<sup>19</sup>.

**TABLE III. Comparison Between the Mechanical Properties of Selected Ocular Tissues and Those of BGs (45S5 Bioglass<sup>®</sup> Was Chosen as a Representative Material).**

Material/tissue	Compressive strength (MPa)	Tensile strength (MPa)	Elastic modulus (MPa)	References
45S5 Bioglass <sup>®</sup>	500	42	35000	112
Porous 45S5 Bioglass <sup>®</sup> (85-90 vol.% porosity)	0.2-0.4	0.01-0.02	1570	75,113,114
Human cortical bone	130-180	50-150	12000-18000	112
Human cancellous bone	4-12	-	100-500	112
Human cornea	-	3.8	0.2-20	115
Human sclera	-	-	2-11	115

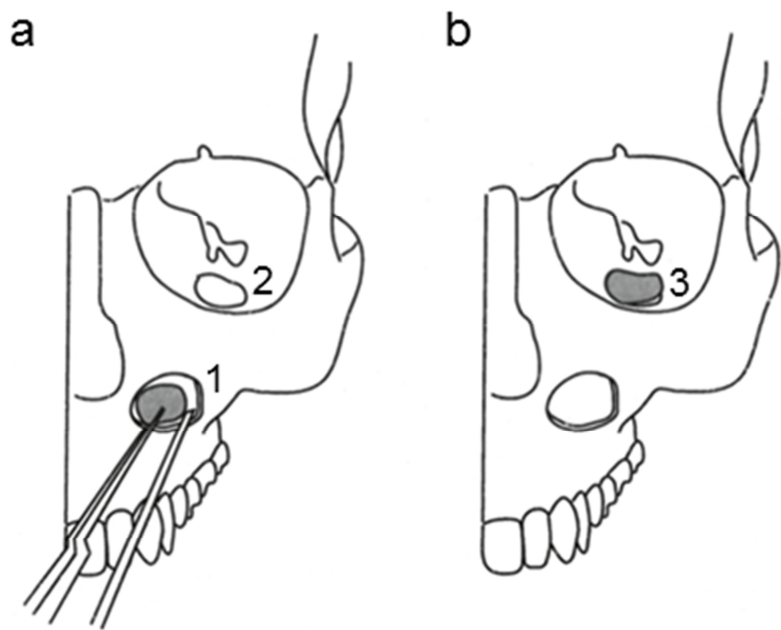


Fig. 1

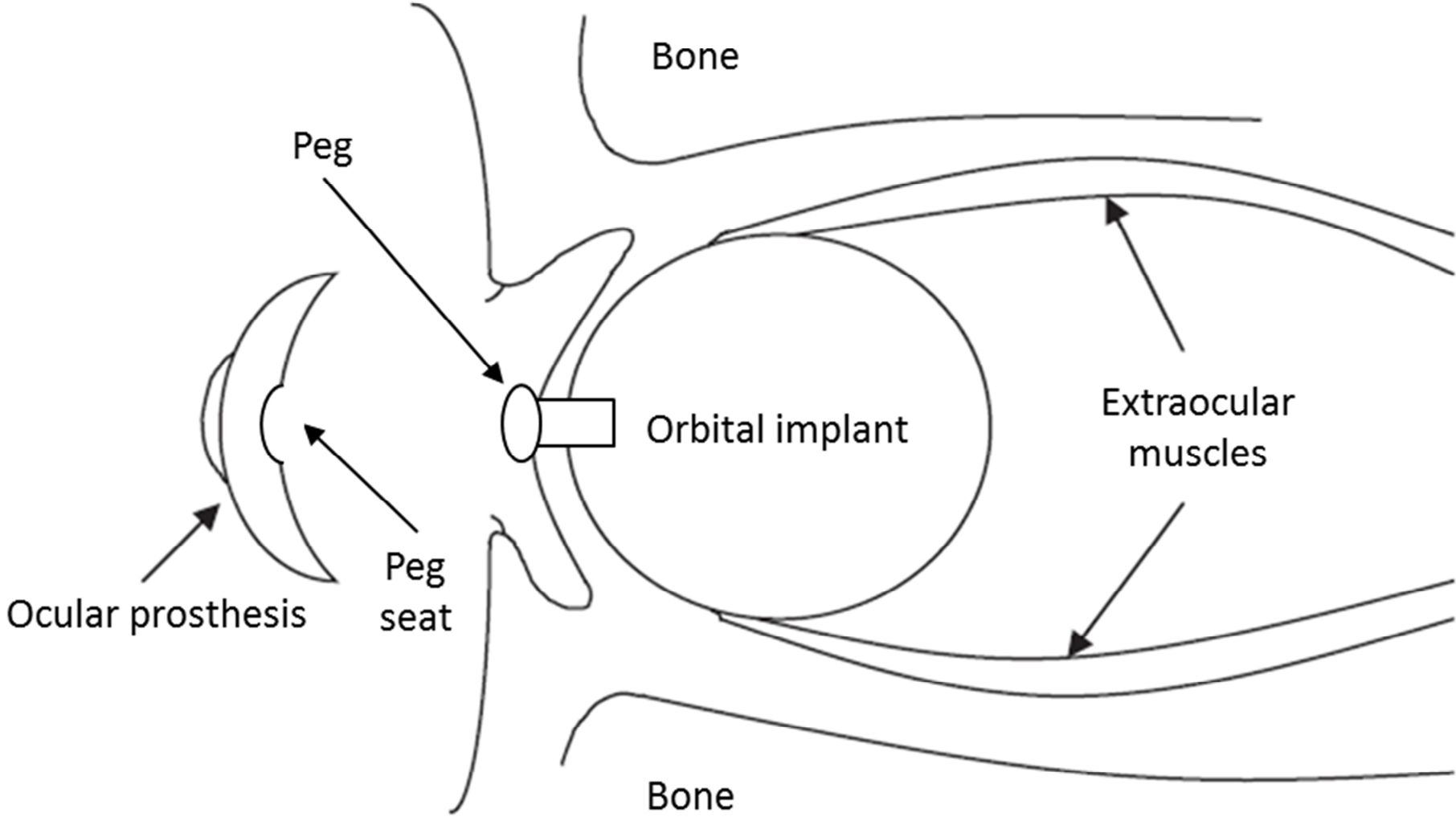


Fig. 2

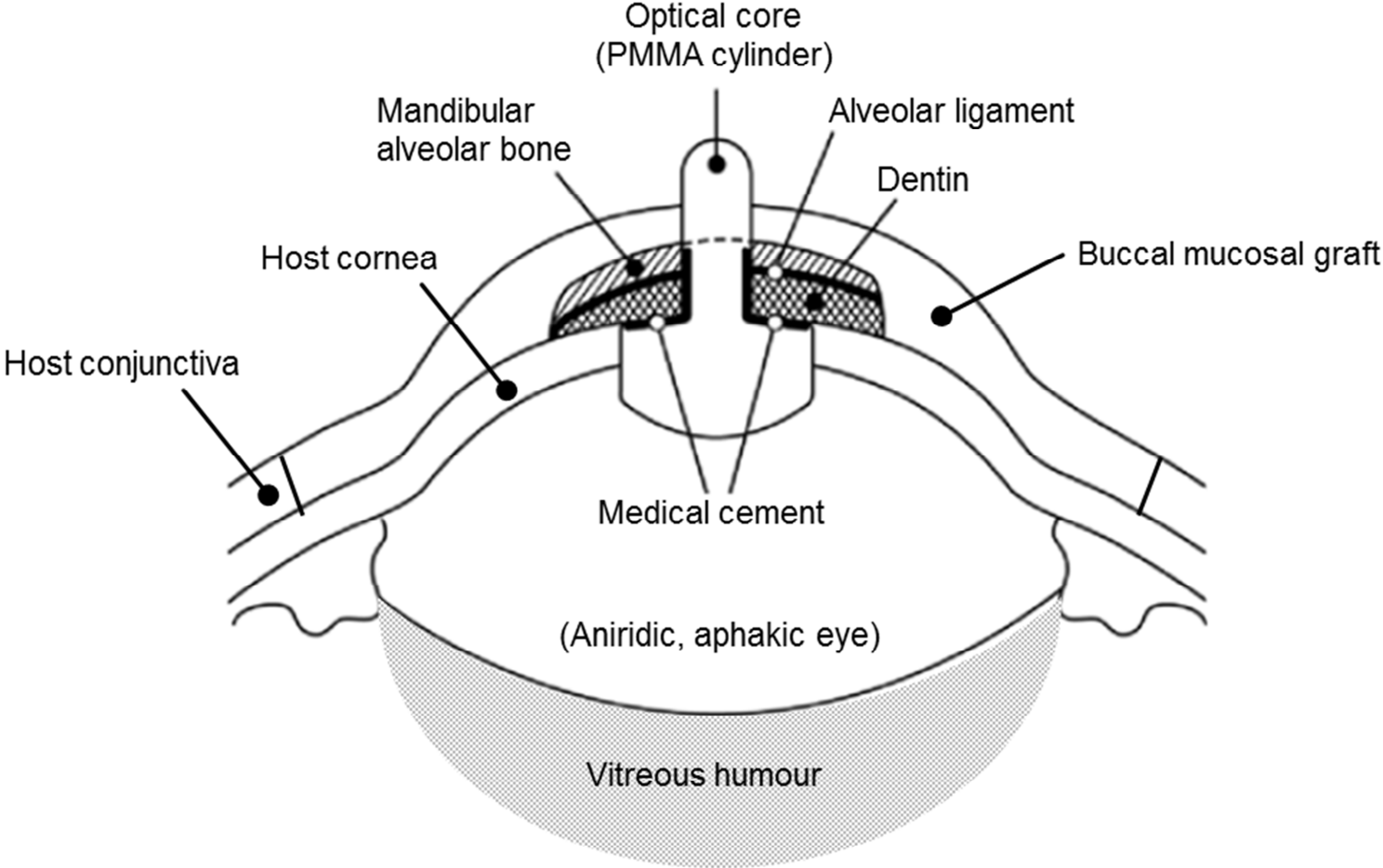


Fig. 3

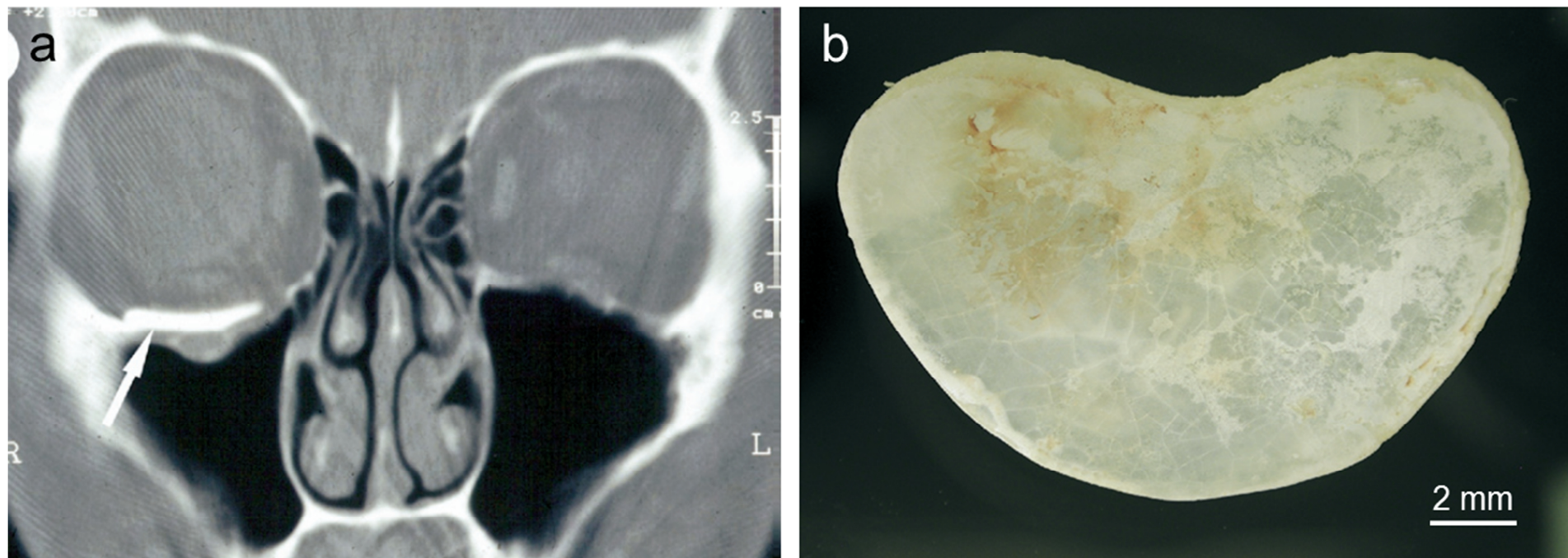


Fig. 4

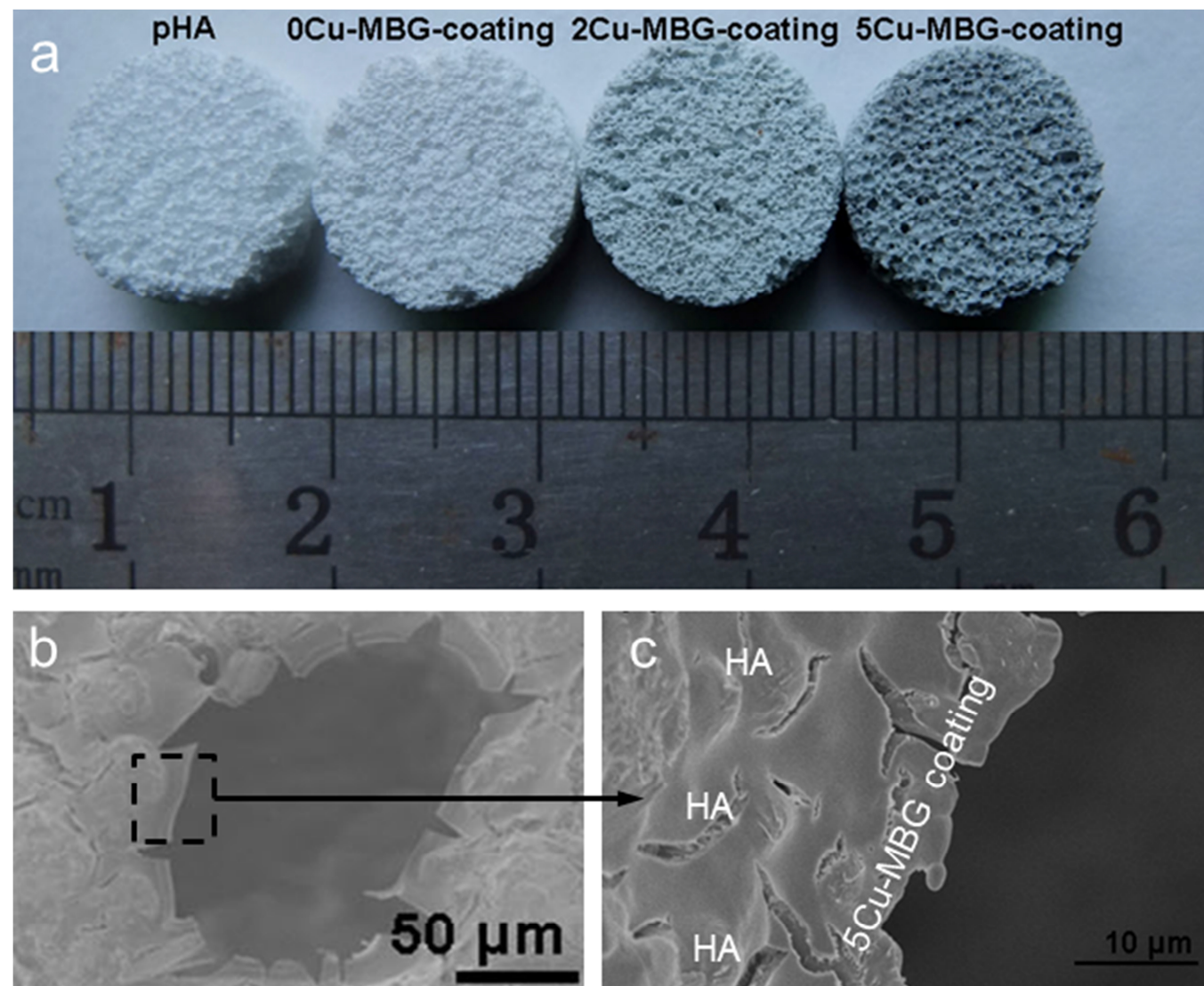


Fig. 5

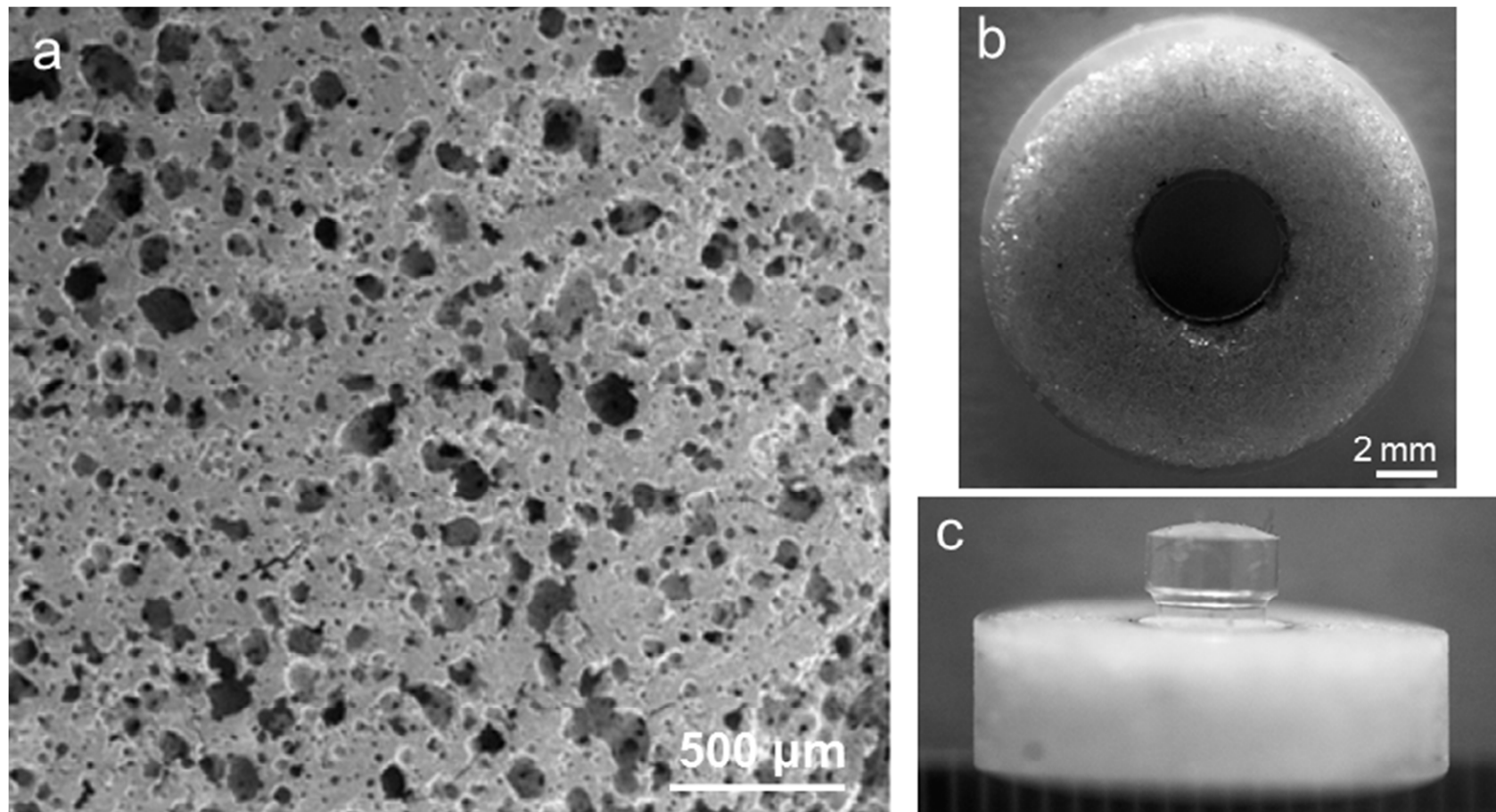


Fig. 6