“Hard” ceramics for “Soft” tissue engineering: Paradox or opportunity?

“Hard” Ceramics for “Soft” Tissue Engineering: Paradox or Opportunity?

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Abstract

Tissue engineering provides great possibilities to manage tissue damages and injuries in modern medicine. The involvement of hard biocompatible materials in tissue engineering-based therapies for the healing of soft tissue defects has impressively increased over the last few years: in this regard, different types of bioceramics were developed, examined and applied either alone or in combination with polymers to produce composites. Bioactive glasses, carbon nanostructures, and hydroxyapatite nanoparticles are among the most widely-proposed hard materials for treating a broad range of soft tissue damages, from acute and chronic skin wounds to complex injuries of nervous and cardiopulmonary systems. Although being originally developed for use in contact with bone, these substances were also shown to offer excellent key features for repair and regeneration of wounds and "delicate" structures of the body, including improved cell proliferation and differentiation, enhanced angiogenesis, and antibacterial/anti-inflammatory activities. Furthermore, when embedded in a soft matrix, these hard materials can improve the mechanical properties of the implant. They could be applied in various forms and formulations such as fine powders, granules, and micro- or nanofibers. There are some pre-clinical trials in which bioceramics are being utilized for skin wounds; however, some crucial questions should still be addressed before the extensive and safe use of bioceramics in soft tissue healing. For example, defining optimal formulations, dosages, and administration routes remain to be fixed and summarized as standard guidelines in the clinic. This review paper aims at providing a comprehensive picture of the use and potential of bioceramics in treatment, reconstruction, and preservation of soft tissues (skin, cardiovascular and pulmonary systems, peripheral nervous system, gastrointestinal tract, skeletal muscles, and ophthalmic tissues) and critically discusses their pros and cons (e.g., the risk of calcification and ectopic bone formation as well as the local and systemic toxicity) in this regard.

Keywords: Bioceramics; Bioactive glasses; Hydroxyapatite; Carbon nanomaterials; Wound healing; Tissue repair

1. Introduction

The repair and regeneration of soft tissues are of great interest among researchers and scientists since they play critical roles in individuals' survival. Among different types of soft tissues, the skin, the cardiovascular and pulmonary systems, the peripheral nervous system, the gastrointestinal tract, the skeletal muscles, and the ophthalmic tissue form most parts of the human body. The extent of soft tissues put them at risk of various damages and defects from a simple dermal scratch to fatal burn injuries [1-3]. Prior studies have shown that all tissues possess a self-repairing ability; the healing process is fairly similar among various soft tissues including a series of basic and overlapping steps. These steps could be summarized as (1) hemostasis phase; (2) inflammatory phase; (3) cell proliferation and matrix deposition; and (4) remodeling phase [4]. However, the healing process commonly fails in the case of critical-size defects and needs to use natural and synthetic substitutes. The replacements used for the management of soft tissue damages must have necessary criteria including biocompatibility, biodegradability, and adequate mechanical strengths [5-8].

Regarding the criteria mentioned above, polymeric constructs seem to be a very suitable option to mimic the native structure of soft tissues; however, some additives (e.g., therapeutics) are commonly being included in the polymeric matrix to improve biological properties and thereby accelerate the wound healing process [9-12]. Among different types of additives, bioceramics (bioactive glasses (BGs), carbon nanostructures, and hydroxyapatite (HAp)) are identified appropriate materials for soft tissue repair and regeneration strategies due to their unique

properties [13-17]. Promoting cell growth and proliferation, inducing angiogenesis, and rendering anti-microbial activities are the main benefits of bioceramics for soft tissue healing applications [18-22]. For example, increased wettability and subsequent improved cell adhesion and growth were observed after adding BGs to polymeric scaffolds [23]. The possibility of co-delivery of therapeutics by specific types of bioceramics, for example, mesoporous BGs (MBGs), is also considered as a rational and smart approach for accelerated wound healing process [24]. MBGs are usually obtained during the sol-gel preparation in which hydrolysis and condensation of glass precursors (e.g., tetraethyl orthosilicate (TEOS)), drying, and stabilization happen respectively [25, 26]. While, obtaining MBGs with a highly well-ordered porous structure (pore sizes of 2–50 nm) is done by adding polymeric templates (e.g., P123) as mesostructure directing agents [27].

The results of *in vitro* and *in vivo* animal studies have previously shown the effectiveness of different types of bioceramics in managing various damages and injures of soft tissues including the skin, peripheral nerve, the heart, the lung, the skeletal muscle, the tendon, and the gastrointestinal tract [28-31]. Based on the literature, BGs have had more impact in treating soft tissue damages and injuries (e.g., skin wounds) and thereby received more attention in the field. This may be related to their unique features, like the ability of bonding with soft tissues and modulating cell activity via ion release [32]. Carbon nanostructures showed great promise in soft tissue regeneration as well: for example, the potential of carbon nanotubes (CNTs) and graphene have been well-documented in repairing large gaps in severed nerves [33, 34]. Moreover, researchers could easily incorporate HAp nano-sized particles into polymeric scaffolds (e.g.,

hydrogels and electrospun mats) to provide proper nanocomposite scaffolds for wound dressing applications [35, 36].

It should be pointed out that the use of bioceramics for soft tissue healing is relatively at the beginning steps and needs more research to reveal important details including ideal formulations and structures as well as optimal dosages to obtain better clinical outcomes. Moreover, the mismatch between the physico-mechanical properties of hard materials and those of soft tissues is one of the first and foremost issues that should be introduced and discussed. In this sense, it seems not possible to apply hard bioceramics as permanent replacements and they could just be used as temporary dressings or additives in polymeric substitutes for managing damaged soft tissues. Furthermore, determining their short-, mid-, and long-term effects in soft tissues is of great importance in order to forecast potential risks such as unwanted soft tissue calcification. For example, the healing process of skin wounds can last up to 14 days after the injury [37]; therefore, the degradation rate of bioceramics applied for skin regeneration should be carefully considered to somehow be compatible with this time period (ideally, the glass should resorb faster than soft tissue calcification occurs). Most of these critical points might be addressed to a large extent by tuning ceramics' forming elements as well as by mixing them to polymers to fabricate innovative three-dimensional (3D) composite scaffolds. For moving a step forward in the field, it seems necessary to evaluate the applicability of bioceramics in combination with technologies like 3D printing techniques to prepare precision substitutes for soft tissue defects. On this object, there are some scientific reports mentioning the beneficial effects of bioinks containing ceramics (e.g., CNTs) for 3D printing of soft tissues like vessel constructs [38].

In brief, according to their successful history in the field and relevant literature, the actual suitability of bioceramics is not far-fetched in treating various types of soft tissue damages and injuries. In the following sections, we will present a critical overview of the possible usage of different bioceramics in soft tissue healing and will discuss their pros and cons in the field.

2. Bioactive glasses and composites in soft tissue engineering

While BGs were first developed to treat hard tissue defects (e.g., repair of osseous defects in alveolar bone, the substitution of the middle ear small bones) [39], recent research shows their potential in soft tissue healing as well, either alone or in combination with other materials (e.g., bio-polymers) [40-42]. In fact, innovative formulations of BGs have led to such progress in the field of biomedical glasses. Compared to silicate-based BGs, other types of glasses, i.e., phosphate- and especially borate-based BGs, seem more suitable candidates for the management of the soft tissue healing process. Being easily shaped to fibers, fast degradation and consequent increase in local pH, as well as the ability to stimulate angiogenesis are respectively counted as benefits of phosphate- and borate-base BGs for soft tissue engineering applications (e.g., skin wound healing) [43, 44]. For instance, cotton-candy 13-93B3 borate BG ($53B_2O_3$-20CaO-$12K_2O$- $6Na_2O$-5MgO-$4P_2O_5$ wt.%) with the trade-name of "Dermafuse" (Mo-Sci Corporation (USA)) is one of the borate-based BGs products used to accelerate wound healing in veterinary medicine and showed promises in diabetic human patients suffering from chronic wounds.

The ability of bonding to soft tissues, enhancing the growth and proliferation of soft tissue-forming cells (e.g., fibroblasts), promoting the new vessel formation (angiogenesis), and delivering therapeutic cargoes are the most prominent features of BGs in soft tissue regeneration

approaches [45]. Some formulations of BGs can serve as anti-inflammatory agents to accelerate the wound healing at damaged sites; others can act against both Gram-positive and Gram-negative bacteria [46, 47]. Moreover, some BGs have been found to behave as hemostatic agents that could control the uncontrolled bleeding resulted from traumatic and surgical hemorrhage [48, 49]. Table 1 summarizes a list of metallic elements with the ability to improve wound healing, which can be easily incorporated into BG structure to take benefits for soft tissue engineering approaches. In the following subsections, we will explain and discuss various types of BGs as promising substances in the management of a wide range of soft tissue-related injuries and diseases (Table 2) to emphasize their capacity in this sense.

Table 1. A list of metallic therapeutic elements that can be incorporated into BGs for improving the soft tissue healing process.

Biological effects	Effector dissolution products	Ion concentration	Mechanisms	Ref (s)
Cell proliferation and differentiation	Si	50 and 100 µM	- Enhancing the proliferation and migration of fibroblasts as well as the synthesis of collagen type I	[50]
	Ca	0.03 to 2 mM	- Initiating multiple signaling cascades involving in skin tissue healing such as stimulating differentiation of keratinocytes and enhancing migration and proliferation of epidermal cells.	[51]
	B	2.5 mM and 5 mM	- Reducing DNA damages in cells and consequent improving the wound healing process	[52, 53]
		100 µg/ml	- Increasing the proliferation and migration rates of dermal cells through overexpressed genes of G-CSF, GM-CSF, and FGF-7, MMP-9	
	Cu	2 and 4mg/mL	- Improving the production of a series of molecules, growth factors, and enzymes involved in wound healing including PDGF, MMPs, tripeptide glycyl-l-histidyl-l-lysine (GHK), nerve growth factor (NGF), integrins, and lysyl oxidase	[54]
	Zn	200 ng/mL	- Modulating the TRIM protein Mitsugumin 53 (MG53) and subsequently promotes fibroblasts migration to the wound sites and trans-differentiation of fibroblasts into myofibroblasts resulting in ECM synthesis	[55, 56]
	Ce	270 mM	- Increasing the migration and proliferation of human keratinocytes and dermal fibroblasts via over-expression of genes involved in mitogenesis (CCNB1, CCND1, and CCNE1) - Stimulating the synthesis of collagen and non-collagen proteins in cardiac fibroblasts	[57]
Angiogenesis	Si	7 and 14 µg/mL	- Improving homing, migration, and proliferation of ECs - Promoting the secretion of angiogenic factors such as bFGF, FGF, VEGF, and eNOS	[58]
	Ca	0.5 to 4 mM	- Enhancing the proliferation of ECs - Increasing the production of bFGF, VEGF, EGF, PDGF, and IGF-I	[59]
	B	10, 20, and 40 mM	- Supporting the proliferation and migration of ECs - Promoting the secretion of TGF-b and VEGF/ TNF-α	[60]
	P	10 mM	- Improving the production of VEGF, MMP-2, bFGF, and FOXC2	[61]
	Cu	50 ppm	- Boosting the ECs' proliferation - Increasing the production of VEGF, bFGF, TNF- α, and IL-1 α	[62]
	Co	0.5 and 0.7 mM	- Improving ECs' proliferation - Overexpressing the HIF-1α and subsequent VEGF and bFGF	[63, 64]
	Mg	4 and 8 mM	- Enhancing the migration and sprouting of HUVECs - Increasing TGF- β	[65]
	Eu	1 and 10 µg/ml	- Improving ECs' proliferation - Enhancing the secretion of VEGF, CD31, PDGF, and MMP9	[66]
Anti-bacterial activity	Ag	Ranging from 0.1 to 50 mg/L based on microorganisms	- Blocking the respiration and electron transfer as well as collapse the proton motive force in bacteria - Causing the leakage of the massive proton through the bacteria cell membrane	[67]

	Cu	3.0 and 7.5 µg/ml	- Attaching to the bacteria plasma membrane and making lethal changes in the cell membrane, such as disruption of membrane integrity inevitably	[68]
	Ce	10, 100, and 200 mg/L	- Increasing the levels of ROS in the cerium-incubated bacteria cells, resulting in DNA, RNA, and protein damage	[69]
	Zn	Different concentrations (e.g., 0.1, 0.3, and 0.5 mg/mL) based on microorganisms	- Enhancing the production of ROS, and thereby cause DNA, RNA, and protein damage - Destabilization of bacterial membranes	[70]
	Ga	Ranging from 1 to 2,560 µM based on microorganisms	- Inhibiting essential biological reactions of bacteria	[71]
Anti-inflammatory activity	Ag	1 mmol/L	Suppressing the production of pro-inflammatory cytokines of TNF-α, IL-8 Inducing apoptosis in inflammatory cells and subsequent suppressed MMPs	[72]
	Li	10 mM and 20 mM	Inhibition of GSK-3β pathway and thereby suppressing of cyclooxygenase-2 expression, inhibiting of IL-1β and TNF-α production as well as IL-2 and IL-10 synthesis	[73, 74]
	Zn	Different concentrations (e.g,. 0.1, 0.5, and 1 mg/mL)	Decreasing the expression of TNF- α, IL-1 β, and VCAM by inhibition of NF- κB activation via A20 and PPAR- α pathways	[75, 76]
	Ce	10 nM, 100 nM, 1 µM, and 10 µM	Scavenging ROSs (e.g., over-produced NO) and thereby inhibiting inflammatory mediator production	[77]

2.1. BGs in cutaneous wound healing applications

The healing process of cutaneous wounds is stated as one of the most complex and challenging biological events, which needs medical interventions like tissue grafting [78]. Skin wounds are generally categorized into two distinct types including acute and chronic ones. The main cause of acute wounds is related to external damages such as surgical injuries, bites, cuts and abrasions, and burns; on the contrary, endogenous mechanisms including impaired arterial supply or impaired venous drainage and metabolic diseases like diabetes mellitus cause chronic wounds [79]. However, normal wound healing has an almost similar trend in various wounds in which a well-organized process of cell migration, proliferation, and subsequent deposition of extracellular matrix (ECM) occurs. All cellular and molecular events involved in the healing process could be classified into dynamic, continuous, and overlapping phases of inflammation, proliferation, maturation, and remodeling [80]. As previously stated, a few factors could be effective in the development of an optimal wound healing process in adults, especially efficient differentiation of stem cells, improved cell proliferation, enhanced angiogenesis, and accelerated re-epithelialization [81-83]. As an illustration, reduced production of vascular endothelial growth factor (VEGF) and thereby decreased angiogenesis can contribute to impaired wound healing in diabetic patients [84].

With respect to the inherent physico-chemical and biological characteristics of BGs including being easy to formulated to various forms, low network connectivity, the ability to bonding to soft tissues, the possibility to release therapeutic ions and bioactive molecules, and improving cell growth, proliferation, and migration [85-87], it seems that they could be useful tools to manage both acute and chronic skin wounds and to accelerate the healing [88-90]. Dealing with

this issue, a couple of review studies have recently been published to show the pros and cons of BGs in skin tissue engineering [28, 91]. In both studies, the main benefits of BGs for skin regeneration were summarized as the ability to bonding to the skin, providing a suitable substrate to cell adhesion, as well as inducing cells to grow, proliferate, and secret growth factors. While, the selection of glass composition and its optimized formulation, the risk of calcification and ectopic bone formation, and local toxicity (in some formulations) were reported as remaining critical barriers to wide usage of BGs in skin wound healing. In this regard, researchers are strongly suggested to design experiments by which molecular mechanisms resulted from the interactions of BGs with skin cells (keratinocytes) well defined. In addition, the combination of BGs and stem cells to achieve a scarless wound healing may be an interesting topic for future studies.

Among the first reports on the usability of BGs in wound healing, a research group under the supervision of Prof. Boccaccini could coat resorbable Vicryl® and non-resorbable Mersilk® surgical sutures by using silver-doped BGs through an aqueous slurry-dipping technique to impart antimicrobial and bactericidal properties to them [92]. Moreover, the study of interactions between BGs and skin fibroblasts is a critical item in providing details to enhance the chance of clinical success. It was reported that BGs encourage fibroblast cells to secrete growth factors and cytokines (collagen I, Fibronectin, α-SMA, bFGF, EGF, and VEGF) accelerating wound healing process [18]. Sol-gel derived 90S BG (90 SiO_2, 6 CaO, and 4 P_2O_5 mol%) was found to support the proliferation of normal human fibroblasts as well as up-regulate genes related to ECM molecules, such as collagen type I and III, fibronectin, and tenascin-C [93]. In addition to the effects on differentiated cells like fibroblasts, there is new evidence on the literature clarifying that ionic dissolution products of BGs could improve wound healing potential of undifferentiated

cells (stem cells) via enhancing the secretion of paracrine factors (collagen I, fibronectin, and α-SMA) (see Fig. 1) [93].

Doping with therapeutic metallic ions has been extensively studied for enhancing the intrinsic properties of BGs in the matter of skin tissue healing. For example, the synthesis of glasses with the ability to kill or inhibit both Gram-positive and Gram-negative bacteria is commonly being performed by adding cations like Ag^{+} and Cu^{2+} to BG structure [94-97]. In addition to the doping procedure, successful coating of BGs by anti-bacterial metals (silver) was also reported elsewhere [98]. Treating wounds by applying antibacterial materials is highly beneficial as the injured area may be prone to be easily infected by various pathogens, with additional problems to patients and an obvious delay of the wound closure process.

The use of doped BGs is being also evaluated for improving angiogenesis to accelerate skin wound healing. Improved proliferation and migration of fibroblasts and keratinocytes were observed after cell incubation with dissolution products of doped BGs [99]. Although there are a lot of studies using silicate-based glasses for skin wound healing [100, 101], different shapes and forms of phosphate and borate-based glasses (e.g., fibers and beads) have also been developed for dermal repair [102-104]. It was reported that BGs fibers show more angiogenic potential than glass beads due to their higher surface area and degradation rate which leads to enhanced release and elevated concentrations of angiogenic ions (e.g., borate and copper) [102]. For instance, 0-3% copper-doped borate 13-93B3 BG microfibers ($6Na_2O$, $8K_2O$, 8MgO, 22CaO, $54B_2O_3$, $2P_2O_5$; mol%) were used to prepare wound dressings for improving wound healing process in rodents via promotion of angiogenesis [104]. *In vivo* examinations revealed improved wound healing in skin defects treated with the glasses due to increasing the number of newly formed blood vessels (Fig. 2). Since re-epithelization is a critical step in wound healing in adult

mammals, the therapeutic potential of BGs to recover injured epidermis is of great interest in the field. However, there are few experimental studies in the literature concerning the effects of BGs on keratinocytes (the main cells involved in epithelialization); for instance, Vaseline ointment containing 18% BGs doped with gold (Au) nanoparticles were recently reported as a suitable formulation for nearly complete re-epithelization of an excisional injured skin of rats in 14 days post-treatment [105].

As a specific type of biocompatible glasses, MBGs either alone or in combination with polymers (composite material) can carry additional benefits in skin tissue engineering applications as regards their ability to deliver therapeutics to injured sites [106, 107]. Several formulations of these porous glasses have been synthesized and examined both *in vitro* and *in vivo*. However, there are few experimental studies in the literature concerning the use of MBGs in soft tissue healing [24, 106].

It is worth mentioning that nanocomposites made of BGs and polymers (natural and synthetic) are being used for treating skin defects [108-111]. To illustrate, Sghayyar et al. recently reported fish bio-waste gelatin-coated phosphate-BG fibers as suitable composites in wound-healing approaches [112]. Preparation of glass containing ointments should be also taken into account; the usability of BG-containing ointments in managing skin wounds has been previously well-documented [113, 114].

2.2. Bioactive glasses for cardiac and pulmonary tissue engineering

In comparison to other soft tissues (e.g., skin), less attention has been paid to the use of BGs in cardiac and pulmonary repair and regeneration. Theoretically, BGs could be safely used in heart and lung regeneration strategies as regard to their inherent characteristics such as bioactivity,

biocompatibility, and wound healing potential. Moreover, the dispersion of micro- or nano-sized BG particles in natural and synthetic polymers is a feasible approach to prepare reinforced constructs (patches) for cardiopulmonary applications [115]. However, it should be highlighted that there are some critical issues on administrating BGs in cardiac tissue regeneration including the risk of tissue calcification resulted from bioactivity as well as the non-conductive nature of glasses; therefore, more *in vitro* and *in vivo* studies should be performed to exactly reveal molecular interactions of different BGs and BG-incorporated scaffolds with the cellular composition of the heart (e.g., cardiomyocytes and cardiac stem cells). Moreover, it should be taken into account that some dopants (e.g., strontium) in glasses' composition may increase the risk of cardiovascular contraindications. Thus, primarily *in vitro* experiments on BGs composition and formulation would be indicative of the future of glasses in managing cardiac tissue engineering approaches.

In the case of the heart tissue, BG-containing polymeric constructs (e.g., hydrogels) were prepared to promote *in vitro* differentiation of various stem cells (e.g., embryonic stem cells (ESCs) to cardiomyocytes [116, 117]. For example, Chen et al. developed elastomeric composites made of poly(glycerol sebacate) (PGS) and nano-sized of Bioglass® particles to be used in the heart patch applications [117]. The increased pH values in the surrounding environment of the glasses are due to their partial dissolution and release of alkaline ions; very interestingly, the authors took benefit from this event to neutralize the acidity caused by the PGS degradation. Their results showed that 5 wt.% BG-containing PGS constructs improve cytocompatibility of mouse fibroblasts and human ESC derived cardiomyocytes in comparison to the counterparts without the BGs. The lack of functional vessels is one of the critical issues in

the myocardial tissue engineering; 45S5 Bioglass® (45 SiO_2, 24.5 CaO, 24.5 Na_2O, and 6 P_2O_5 wt.%) was added to gelatin-collagen (Gel/Col) hydrogels to improve angiogenesis [116]. The therapeutic effects of the prepared scaffolds were examined on human endometrial stromal cells (EnSCs) *in vitro*. The data obtained from molecular and cellular evaluations (real-time PCR and immunocytochemistry) clarified that the BG-containing hydrogels could enhance the expression of VEGF and differentiation of the cells toward endothelial lineage.

Although these primary studies are fully promising, there are a couple of concerns that should be addressed about the extensive use of BG-containing constructs in cardiac tissue regeneration. For example, when the heart is functioning it is necessary that electrical signals are transmitted over the tissue; however, BGs are electrical insulators and, accordingly, should be carefully used in combination with conductive polymers in cardiac tissue engineering applications. In addition, the risk of cardiac tissue calcification should be carefully considered and avoided as an apatite layer form upon the implantation of BGs at the interface between glass and tissues.

Previous reports have shown that the use of BGs has no adverse effects on cells derived from different parts of the human body (e.g., A549 lung carcinoma cells), and their resorption products could be cleared from the body without negative impacts on morphology and function of vital organs such as lungs and heart both in [118-121]. The usability of BGs in lung tissue engineering strategies was evaluated in a couple of experimental studies; Tan et al. showed scaffolds made of 58S (58 SiO_2- 36 CaO-6 P_2O_5 wt.%) could support the growth and proliferation of murine lung epithelial cells (MLE-12) either in bare or functionalized (with amine or mercaptan groups and/or laminin) forms [122]. These constructs showed a good cytocompatibility when exposed to human lung adenocarcinoma A549 cells [118].

Antibacterial BGs were also prepared through doping 2 mol% silver (Ag) into the samples and showed no toxic effect towards A549 cells *in vitro* [123]. The potential of poly(DL-lactic acid) (PDLLA)/45S5 Bioglass® porous composites was previously examined in the context of lung regeneration and the results clarified their cytocompatibility with A549 cells [124].

To date, the number of studies in which BGs have been proposed for lung tissue regeneration, both as alone and in the combination with other biomaterials (e.g., polymers), is still rare. As a suggestion, the activation and functional improvements of stem cells by BGs may be considered a useful approach before their transplantation *in vivo* animal studies.

2.3. BGs in peripheral nerve regeneration

A nerve cell, which is also known as a neuron, is comprised of three main parts including an axon, the dendrites, and a cell body and is considered as the basic compartment of the nervous tissue of the human body [125]. In the normal condition, neurons coated with a lipid-rich substance (i.e., myelin) come together in a cable-like shape and form the peripheral nerves. It has been well documented that the peripheral nerves have a limited potential for recovery of their native structure and function after mild injuries; however, the problems appear in the case of peripheral neuropathies that lead to the simultaneous loss of the fibers and membranes. Autoimmune diseases, diabetes, infections (viral or bacterial), tumors, and traumas are the main causes of peripheral neuropathies, which may result in cutting the nerve [126]. In these cases, the use of autografts and allografts could be a good choice; however, the shortage of donors, the risk of immune rejection, and the transfer of pathogens are the main barriers [127-129].

In the era of tissue engineering and regenerative medicine, huge numbers of attempts have been made to repair or even regenerate the injured and lost nerves, from simple conduits to 3D printed scaffolds [130, 131]. Biopolymers are mostly used as substrates of scaffolds designed for peripheral nerve regeneration due to the "soft" nature of the nerves. On this object, there are numerous successful studies applying various types (natural, synthetic, and relevant combinations) and shapes (e.g., tubular channels and 3D-printed scaffolds) of polymers to achieve the most efficient substitutes [132-134]. In this sense, nerve tubes made of collagen and poly(DL-lactide-ε-caprolactone) could recently get the FDA approval for peripheral nerve repair [135]. Researchers over the globe have tried to use other types of biomaterials to improve the nerve repair process; the applicability of different types of BGs including silicate-, phosphate-, and borosilicate-based glasses have been assessed through a series of experimental studies [136-139].

Generally, BGs could be utilized for nerve repair and regeneration in specific forms including glass tubes, glass powder/polymer composite tubes, and glass fibers/polymer composite warps [140]. To illustrate, Kim et al. showed the therapeutic capacity of phosphate glass fibers regarding neurite outgrowth and early regeneration of a peripheral nerve injury model (see Fig. 3) [141]. In another study, Marquardt et al. published a report on the therapeutic potential of borate-based BGs on peripheral nerve injury. They prepared melt-derived 13-93B3 glasses in different forms (rods (50–200 μm), microfibers (0.5–10 μm), and fibrin/BG scaffolds) and surveyed the neuron viability and neurite extension [142]. The obtained results proved that 13-93B3 rods and microfibers could enhance the percentage of living neurons *in vitro*, which may be attributed to the neuroprotective effect of the samples. The neurite extension measurements showed that fibrin scaffolds containing 35-70 mg/mL of the BG microfibers or aligned rod sheets

could improve neurite extension as similar as the fibrin scaffolds, suggesting the lack of a significant detrimental effect of the glasses on neuronal health. However, the aligned BG scaffolds guided neurite extension in an oriented manner, supporting directed axon growth. In order to achieve accelerated nerve regeneration, glasses doped with specific metals (e.g., zinc, yttrium, and cerium) were also evaluated along with promising outcomes [143, 144].

BG-incorporated polymeric cylindrical scaffolds were proposed as suitable substitutes in the regeneration of peripheral nerves [145-148]. In 2016, Souza et al. could successfully prepare a double-layered tubular nerve guide based on poly(ε-caprolactone) (PCL) and silicate-based BG fibers (SiO_2–Na_2O–K_2O–MgO–CaO–P_2O_5 system) [149]. The PCL was electrospun upon a layer of aligned BG fibers to make a two-layer bio-composite. The physico-chemical analyses showed that the prepared samples were permeable to water vapor, which is in favor of the exchange of cell metabolites between the inner portion of the nerve guide and the surrounding environment. Moreover, the presence of the BG fibers in the electrospun scaffolds resulted in a significant reduction of contact angle as well as an increase in mechanical properties. Recently, an *in vivo* study has reported the potential applicability of conductive polypyrrole/collagen/Sr-substituted nano-sized BG (PPY/Coll/n-Sr@BG) electrospun composites in sciatic nerve rejuvenation [150]. The electron micrographs of the prepared samples indicated that the mean distances across the pores in the nerve channels are between 2-15 mm, which is suitable for transportation of neuron nutrients and growth factors as well as for hindering lymphatic cell and fibroblast penetration. The implantation process of the samples was carried out in an animal model of sciatic nerve deformity in rats. The histological observations at 24 weeks post-implantation confirmed the effectiveness of the glass-containing scaffolds in the recovery of sciatic nerve filaments with a standard round shape and proper thickness [151].

The use of surface-modified BGs was also assessed to regenerate transected sciatic nerve; carbon nanotube (CNT)-interfaced phosphate glass microfibers were successfully prepared and placed into 3D poly(L/D-lactic acid) (PLDLA) tubular scaffolds [151]. The constructs showed proper physicochemical integrity along with good cell viability and neuronal interactions, leading to a significant increase in the maximal neurite length. The *in vivo* outcomes of the implantation of the samples into a 10-mm transected sciatic nerve for 16 weeks indicated successful tissue healing process in the CNT-modified group as regards the number of regenerating axons, the cross-sectional area of the re-innervated muscles and the electrophysiological functions.

Looking at the existing literature, it is worth noting that there are a couple of open issues in the context of BG-based therapies for the nervous system. First, it seems necessary to robustly compare the potential of silicate-, phosphate-, and borate-based glasses to select the best formulations for peripheral nerve regeneration. The preparation and evaluation of glasses doped with different metals should be performed to achieve more potent replacements; for example, magnesium is recognized as a neuroactive cation with the ability to improve the adhesion, proliferation, and neural-specific gene expression of stem cells, but just one study has been recently published in this regard [152]. More *in vivo* animal studies might be conducted to determine short and long term effects of glasses on neurogenesis as well as survey the final fate of glasses' by-products in the injured sites and other vital organs (e.g., liver). In this sense, evaluating varying particle sizes of BGs on neuron functions and other components of the nervous system may be an interesting topic for future studies. Moreover, the fabrication of 3D-printed structures containing BGs might be a step forward in the field. However, it should be mentioned that electrical insulation property of glasses may limit their extensive usage in nerve

tissue regeneration applications; combination with conductive polymers could be considered in the future.

2.4. BGs for repair and regeneration of gastrointestinal ulcers

The treatment of gastrointestinal (GI) ulcers is one of the most important issues in biomedicine due to the broad spreading of this disease [153]; biomaterials-based therapies offer great possibilities in this sense [154, 155]. Given the physico-mechanical and structural characteristics of the GI tract, polymeric constructs potentially meet the necessary criteria for the replacement of the injured or lost tissues. However, there are some promising signs of applicability of other types of biomaterials (e.g., bioceramics) for the repair of specific lesions of the GI, such as the peptic ulcer. As a pilot study, the therapeutic effects of 45S5 BG on intestinal epithelial restitution was confirmed through an *in vitro* co-culture model by Moosvi and Day in 2009 [156]. The authors seeded intestinal myofibroblasts onto the porous membrane of cell culture inserts coated with BG particles (2 μm in diameter). The BG/cell-loaded inserts were then placed into tissue culture plates seeded with a monolayer of epithelial cells to mimic *in vivo* conditions occurring during ulceration of superficial mucosa. The obtained data showed that the wound healing process improved in the co-culture systems containing the glasses (0.1 wt%) in comparison with the glass-free counterparts. This improvement was attributed to over-expressed levels of bFGF by myofibroblasts. Accordingly, the authors stated the efficacy of 45S5 BG regarding intestinal epithelial restitution. In another study, silica- and phosphate-based silver-doped nanoscale BGs showed proper compatibility with human gastric adenocarcinoma AGS cell line at a concentration of 100 $\mu g\ mL^{-1}$ at 24 h post-incubation [157].

In vivo experiments have also been conducted to show the protective effects of BGs in gastric ulcers; Ma et al. orally administrated 45S5 BG particles (20 μm) to rodents and compared the BG therapeutic efficacy on stress ulcers (in mice) and chronic ulcers (in rats) to two commonly-used drugs for gastric ulcers, i.e., omeprazole and hydrotalcite [158]. The various concentrations of 45S5 BG (0.001, 0.01, 0.1, and 1 % ionic dissolution) showed no significant inhibitory effects on GES-1 human gastric mucosa cells at 24, 48, or 72 h post-incubation, and the glass was then considered as a cytocompatible substance for this specific application. In contrast to both drugs, the oral absorption of the BG either in single or multi-gavage did not happen, which was confirmed by the ICP-OES assay of the animals' plasma for the Si contents presumably representing 45S5 BG. Single and multi-gavage (for 7 days) of the glasses provided significant protection against gastric erosions and prevented gastric ulcer recurrence by 50 %, which was comparable to the therapeutic effects of omeprazole and superior to those of hydrotalcite. The authors reported that continuous administrations of BGs (multi-gavage approach) have much better therapeutic effects on gastric ulcers than single gavage, exhibiting a dose-dependent trend. The lack of oral absorption was a unique property of BGs for this application due to the elimination of potential systemic toxicity or side effects. However, it should be emphasized that there is a highly heterogeneous distribution of pore sizes in native gastrointestinal mucus [159]: therefore, more research needs to be carried out to define transport of BGs at nano-scale sizes.

In 2018, Paliwal et al. reported 45S5 Bioglass® containing 1.3 mol% barium oxide (BaBG) as an effective substance in the acceleration of gastro-duodenal ulcer healing [160]. They first induced gastric and duodenal ulcers in rats and mice by using ethanol-, aspirin/pyloric ligation, and cysteamine, respectively. The administration of the BaBG at a concentration of 3 mg/kg could significantly reduce gastric ulcers in all the animals. The glass samples not only provided an

appropriate physical barrier over the gastro-duodenal epithelium cells but also significantly enhanced the gastric pH (due to the release of alkaline Ba^{2+} ions), thereby performing an antacid-like activity in the pyloric, ethanol and aspirin models. A notable increase in cell proliferation was recorded in the case of the BaBG exposed pyloric model. Antiulcer action of the glasses was associated with their activities as the formation of a protective physical barrier against harsh luminal factors, acid neutralization, and cell proliferation.

According to existing reports in the literature, it can be stated that the use of BGs in the treatment of ulcers related to the GI tract is in its beginning and more attempts should be made to assess their pros and cons in this regard. Given the harsh environment of most parts of the GI tract, it is suggested to use more durable BGs, like silicate-based glasses, for the treatment of various ulcers. Furthermore, the use of MBGs can be a worthwhile approach for repair and regeneration of the GI tract with respect to their excellent potential in the loading and delivery of different chemicals and drugs.

2.5. BGs for skeletal muscle tissue engineering

Considering the nature of skeletal muscle tissue, the use of polymeric based constructs has been the first option to manage injuries and diseases such as volumetric muscle loss (VML) [161]. Ideally, biomaterials designed for skeletal muscle tissue engineering should have the ability to increase the survival and function of skeletal muscle cells (myoblasts) and activate the differentiation of resident stem cells (satellite cells) [162]. Additionally, as there are complex vascular and neural networks inside the skeletal muscle, the repair and recovery of vasculature

and nerves seem necessary for muscle restoration [163]. Hence, promoting angiogenesis is also pursued as a critical parameter for the repair of skeletal muscle tissues [164].

Although BGs have just recently been applied for skeletal muscle tissue regeneration, their bonding potential to the muscle has been postulated a long time ago [32]. Moreover, it has been previously documented that BGs cause no adverse effects in contact with the skeletal muscle tissue [165]. More recently, Jia et al. reported the capacity of different formulations of silicate (45S5) and borate (8A3B and 13-93B3) glasses in the repair and regeneration of the VML [166]. The *in vitro* experiments were carried out on HUVECs and mouse muscle myoblast cells (C2C12s); the obtained data showed the ability of both glasses to enhance angiogenesis and stimulate myoblasts to secrete muscle-related growth factors (skeletal muscle insulin-like growth factor 1 (IGF-1), and connexin 43 (CX43)). The authors also implanted the glasses in a rat model of VML and the histology and immunohistological assessments indicated muscle regeneration in the animals treated with glass powders of 13-93B3 and 8A3B after 7 days of implantation. The number of muscle fibers was higher in the defects treated with borate glasses at 14 days post-implantation. In the case of the silicate glass, no or very few fibers were observed after 7 and 14 days of implantation respectively, which was comparable to control groups. The authors stated that 8A3B glass was the best option for muscle regeneration as respect to larger sizes of regenerated muscle fibers (~20 μm) as compared to those obtained by 13-93B3 BG (5-10 μm).

Although these primary results bring promises and open new horizons in the field of BG-based muscle tissue engineering, researchers should take some critical issues into account in future studies. For example, electrical stimulation could activate signaling pathways involved in skeletal muscle cell mechanotransductions and improve the healing process [167], while BGs are by nature electrical insulators [168]. Besides, the combination of BGs with a polymeric matrix

may be considered in upcoming research studies; the impact of BGs on mechanical properties of constructs should be fully examined [169]. Phosphate-based glasses also seem attractive substances in skeletal muscle tissue regeneration regarding their structure (they can be easily drawn in fibers) and resorbability that can be potentially tailored by ion doping to match the rate of tissue healing.

Table 2. Some of the most recent reports stating the usability of BGs in soft tissue engineering applications.

BG composition/Synthesis route	Applied construct	Therapeutics/ ions incorporated	Therapeutic target	Remarks	Ref (s)
45 SiO_2, 24.5 Na_2O, 24.5 CaO, and 6 P_2O_5 (mol.%) - Melt-derived method	BG particles (20 μm)	-	Full-thickness excisional skin wounds	- Accelerating the migration of ECs and fibroblasts - Enhancing capillary-like network formation of ECs - Increasing ECM's proteins deposition of fibroblasts - Reducing the inflammation during initial stages of wound healing by decreasing the numbers of neutrophils and increasing M2 macrophages in the wound sites	[100]
Silicate glass: 45 SiO2, 24.5 CaO, 24.5 Na_2O, 6 P_2O_5 (wt %) Borate glasses: 53 B_2O_3, 6 Na_2O, 20 CaO, 5 MgO, 12 K_2O, 4 P_2O_5 (wt%) 52.79 B_2O_3, 5.98 Na_2O, 19.92 CaO, 4.98 MgO, 11.95 K_2O, 3.98 P_2O_5, 0.40 CuO (wt%)- Melt-derived method	BG cotton-like microfibers	Cu	Chronic skin wounds	- Borate-based BGs containing Cu showed good biocompatibility after subcutaneous implantation in rats - Borate-based BGs containing Cu promoted extensive angiogenesis in comparison to the other groups	[103]
6 Na_2O, 8 K_2O, 8 MgO, 22 CaO, 54 B_2O_3, 2 P_2O_5; mol%) doped with 3.0 CuO (wt%)- Melt-derived method followed by blowing a high-pressure jet of gas	BG microfibers	Cu	Full-thickness skin defects	- Promoting the migration of HUVECs, tubule formation - Over-expressing angiogenic genes of VEGF, bFGF, and PDGF in the fibroblasts - Improving collagen deposition, maturity, and orientation after 14 days of implantation in rats	[104]
87 SiO_2,10.4 CaO, 2.6 Ag_2O (mol%)- Sol-gel method	Mesoporous BG powders	Ag	The 3D tissue-engineered infected skin model	- Exhibiting significant antibacterial effect against P. aeruginosa and S. aureus at a concentration of 1 mg/mL in the planktonic bacteria model - Lacking inhibition against *P. aeruginosa* in the 3D skin model	[106]
30.0 SiO_2, 27.0 CaO, 20.0 B_2O_3, 4.0 P_2O_5, 1.5 CuO, 1.0 ZnO, 3.0 K_2O, and 9.0 Na_2O (wt%)- Sol-gel method	Gelatin/chitosan electrospun nanofibrous membranes/ BGs	Cu	Infectious skin wounds	- Showing a high antibacterial activity against *A. Viscosus* and *E. coli* - Well-tolerated by the host tissue without causing any inflammation - Completely degradation at 4 weeks post-implantation	[109]
6 Na_2O-8 K_2O-8 MgO-22 CaO-	BGs/ PLGA	Cu- vitamin E	Incisional full-thickness	- Improving migration, tubule formation and VEGF secretion in	[110]

18 SiO_2-36 B_2O_3-2 P_2O_5-6 SrO (mol%) doped with 3.0 Cuo (wt%)- Sol-gel Method			skin defects	HUVECs *in vitro* - Improving in the epithelialization of wound closure and vessel sprouting and collagen remodeling *in vivo*	
80 SiO_2, 15 CaO, 5 P_2O_5 (mole %)- Sol-gel method	Electrospun fish collagen nanofibers/ BGs	-	Full-thickness skin defects	- Exhibiting antibacterial activity against *S. aureus* - Inducing keratinocyte proliferation and migration - Promoting the secretion of COL-I and VEGF in dermal fibroblasts - Stimulating the proliferation of HUVECs - Accelerating skin wound healing in rats	[111]
45 SiO_2-24.5 CaO-24.5 Na_2O-6 P_2O_5 (wt%) Melt-derived method	BGs/Gelatin-collagen hydrogels	-	Heart tissue via *in vitro* studies on EnSCs and L929 cells	- Stimulating the cells' differentiation into cardiomyocytes - Over-expressing VEGF	[116]
45 SiO_2, 24.5 CaO, 24.5 Na_2O, 6 P_2O_5 (wt%)- Melt-derived method	Poly(glycerol sebacate)	-	Heart tissue via *in vitro* studies on human ESC derived cardiomyocytes and fibroblasts	-Promoting cell differentiation -Showing no toxicity	[117]
8.4 Na_2O, 40 CaO-39.6 SiO_2, 12 P_2O_5 (wt%)- Sol-gel method	BG Particles	Fe	Lung tissue via *in vitro* studies on A549 cells	- Showing hyperthermic effect for possible application in lung cancer treatment	[120]
60 SiO_2, 35 CaO, 5 P_2O_5 (mol%)- Sol-gel method	BGs/ Gelatin-hyaluronic acid hydrogels	-	Lung tissue via oral administration to rats	- Exhibiting no remarkable change in the morphology of lung tissue	[121]
50 P_2O_5, 40 CaO, 5 Na_2O, 5 Fe_2O_3 (mol%)- Melt-derived method	Phosphate glass/ collagen scaffolds	-	Transected sciatic nerves of rats	- Stimulating neurite outgrowth along the fibers *in vitro* - Enhancing axons extending along the scaffold at 7 days post-surgery - Causing recovery of plantar muscle atrophy at 8 weeks post-implantation - No significant differences in case of the functional capacity between the experimental groups and controls (collagen- scaffolds lacking BGs) after 12 weeks of implantation	[141]
Silicate glass: 45.0 SiO_2, 24.5 Na_2O, 24.5 CaO, and 6.0 P_2O_5 (wt%) Borate glass: 53 SiO_2, 20 CaO, 6 Na2O, 4 P_2O_5, 12 K_2O, 5% MgO (wt%)- Melt-derived method	BGs/ Polyhydroxyalkanoate (PHA) composites	-	Nervous systems via *in vitro* studies on NG108-15 neuronal cells and in a co-culture along with RN22 Schwann cells	- Exhibiting good biocompatibility - Improving the mechanical properties needed for the regeneration of peripheral nerves - Supporting the growth and neuronal differentiation	[147]
50 P_2O_5, 40 CaO, 5 Na_2O, 5 Fe_2O_3 (mol%)- Melt-	Phosphate glass fiber–collagen scaffolds	Fe	Transected rat spinal cords	- Inducing axon growth from the proximal and distal stumps to the scaffold after 12 weeks implantation	[148]

derived method				- Recovering the locomotor and bladder functions at 8 weeks post-implantation - Increasing endogenous BDNF levels in the bladder at 12 weeks post-implantation	
45.0 SiO_2, 24.5 Na_2O, 24.5 CaO, and 6.0 P_2O_5 (wt%)- Melt-derived method	BG particles (20 µm)	-	Gastric ulcers	- Oral gavage of BGs protected stress ulcers in mice and chronic ulcers in rats - Showing a high efficacy in protecting the gastric against ulcers as comparable to omeprazole and superior to hydrotalcite	[158]
45.0 SiO_2, 24.5 Na_2O, 24.5 CaO, and 6.0 P_2O_5 doped with 1.3 BaO (mol%)- Melt-derived method	BG particles (~2.4 µm)	Ba	Gastric ulcers	- BG formed a physical protective barrier over the gastro-duodenal epithelium cell - Oral gavage of BGs resulted in a significant increase in gastric pH, indicating their antacid like activity. - BGs significantly enhanced cell proliferation in the pyloric ulcer model	[160]
45S5: 45.0 SiO_2, 24.5 Na_2O, 24.5 CaO, and 6.0 P_2O_5 (wt%) Borate 13-93B3: 56.7 B_2O_3, 5.5 Na_2O, 11.1 K_2O, 4.6 MgO, 18.4 CaO, 3.4 P_2O_5 (wt%) Aluminoborate, (8A3B): 50.7 B_2O_3, 10.8 Al_2O_3, 4.9 Na_2O, 9.9 K_2O, 4.1 MgO, 16.4 CaO, 3.2 P_2O_5(wt%)- Melt-derived method	BG particles (4 µm)	Al	Skeletal muscle	- Promoting angiogenesis and stimulating cells to secrete critical muscle-related growth factors - Borate-based BGs via activating of stem cells increase the regeneration of skeletal muscles in a rat volumetric muscle loss model	[166]

3. Carbon-based nanomaterials for soft tissue engineering applications

Carbon-based nanomaterials (CBNs), such as fullerenes, carbon dots (CDs) carbon nanotubes (CNTs), graphene (G), graphene oxide (GO), composite nanoparticles, and scaffolds have attracted much interest in soft tissue engineering. The CBNs have unique dimensions, mechanical, conductivity, and optical properties that present new options for soft tissue engineering. Thus far, many groups have developed various functionalization methods of CBNs to achieve biocompatibility, cell adhesion, and differentiation. Artificial scaffolds for soft tissue repair and regeneration are required to be similar to natural ECM in terms of physical properties, chemical composition, and mechanical properties. Furthermore, the electrical conductivity of CBN-based scaffolds can be used to offer an electrical signal to tissues. In this section, we review recent studies on the cell interactions with CBNs for soft tissue engineering applications, including neural, cartilage, skin, cardiac, and muscle tissues (as illustrated in Fig. 4 and summarized in Table 3**).**

3.1. Cardiac tissue

Over the last few decades, myocardial ischemia diseases cause major death worldwide. The regeneration of myocardial tissues occurs partially while the injury and damage tissues remain nearly permanent [170]. Cardiac tissue has unique physical properties including contractility related to the well-arranged microfiber architecture and electrical conductivity (0.005 S/m to 0.1 S/m) in the transverse and longitudinal direction. The CBNs nanomaterials have been used to stimulate the differentiation of stem cells towards cardiomyogenic cells [171-174]. CNTs stimulated cell division, proliferation, differentiation, and maturation in cardiomyocytes due to a

conductive property [174, 175]. The super-aligned CNT sheets (SA-CNTs) were shown to have the ability to guide cell morphology and to supply an electrical signal for cardiac repair [176]. The SA-CNTs were flexible and showed an aligned microfiber structure, providing an improved conductivity. The neonatal rat cardiomyocytes (CMs) cultured on the SA-CNTs exhibited elongated and aligned morphology at 3 days, and the electrophysiological actions of CMs recorded by cell patch-clamp method showed reduced cell-to-cell dispersion in repolarization, improved intercellular coupling, and matched natural beatings, thus, being useful for the recovery of heart failure and subsequent myocardial infarction (Fig. 5). Recently, 3D microporous polydimethylsiloxane (PDMS)/CNT composite scaffolds were reported for cardiac tissue engineering [177]. The 3D scaffolds showed electrical and mechanical properties comparable to the natural heart muscle, promoting viability, proliferation, and maturation of cardiomyocytes [177]. Kim et. al. reported that the G substrate could stimulate the cardiomyogenic differentiation of MSCs without the use of cardiomyogenic differentiation inducers [171]. The generation of ROS from GO was also reported to protect MSCs cells, enhancing angiogenesis and cardiomyogenic markers expression [172]. The combination of reduced GO (rGO) with MSC spheroids was shown to stimulate cell signaling molecules (paracrine factors and growth factors of angiogenesis) which are key factors for cardiac repair along the highly conductive rGO [173]. The 3D multilayer cardiac construct sheets and poly(L-lysine)-coated GO thin films were arranged on a substrate made of methacrylated gelatin (GelMA) hybrid hydrogels that incorporate rGO hydrogel. The GO improved the electrophysiological function, viability, cell adhesion and spreading, and mechanical integrity. In addition, 3D multilayer could enhance the cardiac cell organization, maturation, and cell-cell electrical coupling [178]. The CNTs added to photo-cross-linkable GelMA (GelMA-CNT)

enhanced modulus and conductive properties and provided microporous structural substrates to seeded cardiac cells, improving tissue morphogenesis, cardiac cell adhesion and maturation, and cell-cell electrical coupling [179]. GelMA-CNT was thus used as scaffolds to culture and electrically regulate the cardiac differentiation of mouse embryoid bodies [180].

In summary, the CBNs have the potential for cardiac tissue engineering applications owing to their unique properties such as conductivity and mechanical properties with biocompatibility. The cell-cell signaling coupling due to the electrical conductivity of CBNs and the improved cell adhesion can stimulate cell maturation and differentiation and functions for cardiac tissue regeneration. The research addressed to the improvement of conductivity stability and mechanical integrity in the long term deserves to be carried out in the future in order to further improve te suitability of CBNs for cardiac applications.

3.2. Neural tissue

The nervous system communicates signals to synchronize between the brain and other parts of the body. Human neural stem cells (NSCs) are self-renewing, multipotent [181, 182], and have the capacity to differentiate into neurons, oligodendrocytes, and astrocytes [183]. It is well known that NSCs are electrically active that respond to the electrically conductive nanomaterials and electrical stimuli. Therefore, the electrical fields (EFs) have been applied for stem cell differentiation and neurogenesis [33, 184, 185]. CNTs were used to culture neural cells. The effect of the length of CNT was observed with PC12 cells [186]. The long carboxylated CNTs were not effective in cell viability and morphology whereas short CNTs could stimulate PC12 cell differentiation by upregulated neuronal signaling pathway (TrkA/p75 and Pincher/Gap43/TH receptors). He et. al. [187] also reported the nanocomposite of CNT

improved neurite outgrowth and differentiation and maturation of the NSC-derived neurons. Recently, rGO was shown to potentially promote the NSC differentiation to neurons. Compared to GO, rGO has higher electrical properties owing to the elimination of most of the oxygen groups [188, 189]. Hong et. al. reported that the 2D G film showed enhanced differentiation of human NSCs into neurons rather than glial cells [190]. An interesting work showed the surface chemistry of GO affected the neural extension and branching [191]. The GO was modified with either amine ($-NH_2$), sulfonic acid ($-SO_3H$), or methoxyl-terminated ($-OCH_3$). The amine-GO (positively charged) was shown to be more helpful for the neural extension and branching than the other modified groups. In another work, the change in patterns of GO could affect the differentiation of human adipose-derived mesenchymal stem cells (hADMSCs) towards ectodermal neuronal cells. Approximately 30% conversion efficiency was observed on the grid patterns that mimic interconnected/elongated neuronal networks [192].

The 3D CBN scaffolds or hydrogels were also reported to enhance the differentiation of NSCs into neurons that mimicking the extracellular matrix microenvironments [193-195]. Hyun et al. [151] reported aminated CNTs onto the surface of aligned phosphate glass microfibers (PGFs), and the CNT-interfaced PGFs (CNT–PGFs) was used for the regeneration of transfected rat sciatic nerve [151]. The surface of the PGFs was first modified with CNTs and then the CNT-PGF was wrapped with poly(l/d-lactic acid) (PLDLA) nanofiber sheet and placed in a porous PLDLA cylindrical tube. The CNTs were shown to be coated homogeneously, and the electrical conductivity was increased due to the CNT. The DRG neurons cultured on CNT-PGF showed highly elongated neurites growth on the scaffold substrates. Furthermore, the 3D scaffolds (PGF and CNT-PGF) implanted in a completely transected sciatic nerve showed a higher number of SMI312-positive axons in the CNT-PGF group than the PGF group (Fig. 6). CNT-

PLGA composites membranes were shown to enhance human NSC differentiation under electrical stimulation. The CNT-PLGA nanofibers were conductive and biocompatible, supporting human NSC derived from an induced pluripotent stem cell (iPSC), and the nanofiber topography mimics the extracellular matrix for neuronal lineage expression [196]. The plasma-treated chitin CNT composite nanofibers were shown to enhance neuron adhesion and support of synaptic function of neurons [197]. Cho et. al. [198] developed 3D-conductive hyaluronic acid hydrogel composite with polypyrrole (PPy) and/or CNT to enhance the differentiation of iPSC derived neural progenitor cells and human NSC. The CNT scaffolds could stimulate the growth of immature neurons isolated from the neonatal rat spinal cord [199]. The spinal neurons cultured on conductive scaffolds were demonstrated to have promoted neuronal maturation markers and action potential generation. Serrano et. al. [200] reported that the rGO 3D-porous scaffolds implanted in spinal cord injury were able to guide neural growth and to stop extra damaging due to the presence of M2 macrophages at the injured place. The nanostructured rGO microfibers with light, flexible, mechanically strong, and cytocompatible properties were shown to regulate the NSCs differentiation toward neuronal phenotype acting as a functional nerve graft [201]. Recently, the fabrication of PCL / rGO conductive scaffold by 3D printing is considered a promising nerve guide conduits for the treatment of peripheral nerve injuries [202].

3.3. Cartilage tissue

The ECM of cartilage consists of collagen, noncollagenous proteins, and glycosaminoglycan (GAG). It is a strong elastic soft tissue and the chondrocytes are embedded in the ECM in a highly ordered manner [203]. The CBN-based biomaterials have been used for the repair of cartilage. Zhang et. al. [204] designed nanostructured biomatrix made

of polycaprolactone (PCL) poly-L-lysine coated carbon nanomaterials. The composite scaffolds showed enhanced mechanical strength and stimulated hMSC growth and functions for chondrogenic differentiation [204]. The scaffolds made of aligned pristine CNT were prepared as 2D sheets and 3D textiles. The 3D textile flexible scaffolds with tunable mechanical properties showed effective growth of chondrocytes that are implantable [205]. The aligned CNT bundles are considered to mimic the natural ECM collagen fibers in cartilage tissue. The effects of surface functionalization of CNTs were also investigated. CNTs were functionalized with -COOH or -PEG and then combined with agarose hydrogels. The composite hydrogels were shown to have improved mechanical properties and stimulated chondrocyte growth and repair of cartilage [206]. In particular, the *Col2a1* and *Fn* gene expressions those related to cell adhesion was stimulated only in –COOH functionalized CNT hydrogel (not in –PEG functionalized case), suggesting that the charged nature of the –COOH functionalization might promote the gene expression in this chondrocyte cultures. Furthermore, GO was used as both cell-adhesion substrate and protein (fibronectin) and growth factor (transforming growth factor-β3) delivery system for chondrogenic differentiation of human hADSCs [207]. Also, G, GO and porous-GO were shown to maintain pellet formation and chondrogenic differentiation of hMSCs [208]. Increasing concentration of G and porous-GO increased the degree of cell differentiation, and the porous-GO showed higher growth factor loading than GO, improving the cell differentiation. Recently, photopolymerizable poly-D, L-lactic acid/polyethylene glycol hydrogel with GO was developed for cartilage tissue engineering. With the integrated GO, the hybrid hydrogels showed higher modulus and enhanced chondrogenesis induction of human stem cells without exogenous chondro-inductive factor [209].

3.4. Skeletal muscle tissue

Recent studies have highlighted the importance of multi-scale cell-tissue interactions in skeletal muscle regeneration [43]. Among other candidate biomaterials, the CBN-based nanomaterials (CNT and graphene) have been widely used for the repair of skeletal muscle tissues [210-212]. A hybrid of poly(3,4-ethylenedioxythiophene) (PEDOT)/CNT provided a substrate for muscle cell C2C12 differentiation and myotube alignment. The electrical conductivity of the PEDOT/CNT substrate allowed a directional electrical response to C2C12 cells stimulating myogenic differentiation and myotube alignment [213]. The poly(lactic-co-glycolic acid) (PLGA)/CNT composite electrospun scaffolds were also prepared for muscle tube formation of C2C12 cells. The composite scaffolds enhanced the proliferation and differentiation of C2C12 cells due to the mechanical strength and conductivity [211]. The aligned electrospun gelatin-CNT composite scaffolds were also used for the proliferation and growth of myotube formation of C2C12 cells. The number of CNTs significantly enhanced myotubule formation. Under the electrical stimulation, the composite scaffolds enhanced the maturation and contraction of the myoblasts [214]. Graphene-based materials have improved cell spreading, proliferation, and myogenic differentiation of skeletal muscle cells [215]. The C2C12 cell adhesion and differentiation on r-GO films were enhanced compared with GO and glass-slide substrates [215]. Patterned G film showed better cellular alignment and myogenic differentiation of skeletal muscle cells [216], and the myogenic differentiation on G was further enhanced through the addition of growth factor IGF-1 [216]. Patterned G film also leads to the alignment of myotubes in response to electrical-pulse stimulations. Recently, Xing et. al. [217] reported conductive and elastic polydopamine (PDA)/rGO composite aerogel for skeletal muscle regeneration. With the external electrical field, the PDA/rGO aerogel promoted C2C12 myoblast differentiation and

myotube contraction *in vitro* and showed the capacity to treat the disused skeletal muscle atrophy [217]. The PDA/rGO composite showed electrical conductivity with the luminance of the LED bulb, and the aerogel revealed excellent compressibility. When cultured with myoblasts, the gene expressions (α-actinin, and MHC) were significantly upregulated on the composite, and the electrical stimulation (ES) further improved the differentiation, and the *in vivo* experiments showed improved gastrocnemius muscle weight of denervated muscles at 1 week or 3 weeks, implying the regeneration of nerves and the resultant muscle functions (Fig. 7). Moreover, the histological analysis of the implanted samples revealed the PDA/rGO is well biocompatible and induces mild inflammatory responses. Recently, a conductive, stretchable, and degradable composite of poly(citric acid-octane diol-polyethylene glycol) (PCE) with rGO was developed for the myoblasts proliferation, differentiation and *in vivo* skeletal muscle regeneration [218].

3.5. Skin tissue

Skin tissue repair needs wound closure with the proper growth of ECM. Many candidate scaffolds and biomaterials have been developed for this purpose [219], [220]. Because of the high surface area and growth factor loading property, carbon-based nanomaterials have also been used. The CNTs added to chitosan hydrogel at low concentration (1%) could improve wound healing whereas when the CNTs were added at high concentration (5%) more fibrosis was observed with stimulated pro-inflammatory cytokines [221]. The conductive cryogel (glycidyl methacrylate functionalized quaternized chitosan (QCSG) with CNT; QCSG/CNT) dressing was shown to improve wound healing compared with CNT-free cryogel dressing, and the effect was attributed to the physical electrical signals [222]. When treated in the skin wound for up to 15 days, the 4%CNT added QCSG cryogel showed significantly enhanced wound

contraction when compared with Tegaderm™ dressing and QCSG without CNT (Fig. 8). The antibacterial property and biocompatibility of carbon dots (CDs) were effective in improving the wound healing and pH monitoring of wounds at the same time [223]. Also, the CDs could change extra- and intracellular reactive oxygen species (ROS), improving the antioxidant effect on fibroblasts under oxidative stress and accelerating wound healing [224]. CDs have abundant surface reactive groups (hydroxyl and amine) which can transfer free electrons to the C–C backbone of CDs. Furthermore, CDs can be degraded by the release of acidic residues (carbonates and bicarbonates). In this way, CDs can scavenge free radicals. The polycaprolactone-gelatin scaffolds with CDs showed the antioxidant property and enhanced wound healing and complete regeneration with the stratified dermis and epithelial layer in three weeks [225]. Fullerenes nanomaterials exhibited interesting properties such as antioxidant and anti-inflammatory properties, scavenging ROS, and reactive nitrogen species for wound healing [226]. Recently, laser-mediated surface activation of GO was used to control antibacterial, antifungal, and fungal wound infection treatment using the near-infrared laser (NIR) [227]. The 3D graphene foam (3D-GF) scaffold loaded with MSCs could also enhance skin wound healing [228], with decreased scarring and increased vascularization [228]. Recently, Lu et. al. [229] reported that antioxidant and electroactive scaffolds (chitosan and silk fibroin; CS/SF) combined with polydopamine-rGO could enhance skin wound healing due to the stimulated cell growth and reduced ROS.

Table 3. Summary of CNB platform for soft tissue engineering applications.

Platform	Cell type	Tissue regeneration	Remarks	Ref.
G on coverslip	MSC	Cardiac	Graphene promoted cardiomyogenic differentiation	[171]
GO flakes	MSC	Cardiac	Prevention of ROS mediated death of implanted MSCs for cardiac repair	[172]
rGO flakes	MSC	Cardiac	Improves myocardial repair efficacy of MSCs by stimulating angiogenic growth factors and gap junction protein's	[173]
3D-PDMS-CNT scaffolds	Neonatal rat ventricular cardiomyocytes (NRVM)	Cardiac	To promote viability, proliferation, and maturation of cardiacmyocytes	[177]
PLL, GeIMA, rGO hydrogel	3T3 fibroblasts, MSCs, Neonatal rat ventricular cardiomyocyte	Cardiac	Enhanced the cardiomyocyte organization, maturation, and cell-cell electrical coupling in the presence of rGO	[178]
GeIMA-CNT hydrogels	Neonatal rat ventricular cardiomyocytes	Cardiac	Improve tissue morphogenesis, and improved cardiac cell adhesion and maturation, and cell-cell electrical coupling	[179]
Short and long length of carboxylated CNT	PC12	Neuronal	Short length CNT improved PC12 differentiation with neuronal signaling pathway (TrkA/p75 and Pincher/ Gap43/TH receptors)	[186]
Construction of CNT nanocomposite substrates	NSC	Neuronal	Improved neurite outgrowth, differentiation, and maturation of the NSC-derived neurons	[187]
GO and rGO films onto a quartz substrate	NSC	Neuronal	Promote NSC differentiation to neurons	[188-191]
Different functional groups of GO substrate	hADMSCs	Neuronal	The amine-GO (positively charged) has been more helpful for the neural extension and branching.	[192]
Aminated CNTs onto the surface of aligned phosphate glass microfibers	PC12 and dorsal root ganglion (DRG) cells	Neuronal and rat sciatic nerve model	Neurites of dorsal root ganglion outgrew actively along the aligned CNT–PGFs and that the CNT interfacing significantly increased the maximal neurite length	[151]

CNT-PLGA membranes	NSC	Neuronal	Enhance human NSC differentiation under electrical stimulation	[196]
rGO 3D-porous scaffolds	implanted for spinal cord injury	Neuronal	Capable to guide neural growth and the stoppage of extra damaging due to the presence of M2 macrophages at the injured place	[200]
rGO microfibers	NSC	Neuronal	NSCs differentiation toward a neuronal phenotype and form a just like a functional nerve graft surrounding the microfiber	[201]
PCL/CNT nanofibers	MSC	chondrogenic	Stimulate stem cell function for enhanced chondrogenic differentiation	[204]
scaffolds of aligned CNT; as 2D sheets and on 3D textiles	Primary canine chondrocytes (PCCs)	chondrogenic	3D textile flexible scaffolds show a very high affinity for the effective growth of chondrocyte.	[205]
CNT-agarose hydrogel	Primary chondrocytes	chondrogenic	Improved mechanical property for stimulates of chondrocyte growth, repair, and regeneration	[206]
GO substrate	hADSC	chondrogenic	Graphene oxide substrate served as a carrier for growth factor protein-delivery carrier for chondrogenic differentiation of adult stem cells	[207]
growth factor-loaded G / GO / porous-GO	MSCs	chondrogenic	The porous-GO has to permits a higher growth factor compared to the loading of GO and further improves the differentiation rate of the cells.	[208]
Photopolymerizable PDLLA hydrogel with GO scaffold	MSC	chondrogenic	Enhanced chondrogenesis induction of human stem cells without exogenous chondroinductive factor	[209]
PEDOT/CNT substrates	C2C12	skeletal muscle tissue	Substrate allowed directional electrical response between the substrate and C2C12 cells for cell C2C12 differentiation and myotube alignment	[213]
PLGA/CNT nanofibers scaffolds	C2C12	skeletal muscle tissue	Enhanced the proliferation and differentiation of C2C12 cells	[211]
Aligned electrospun gelatine-CNT scaffolds	C2C12	skeletal muscle tissue	Enhanced myoblasts formation by improving the physical properties such as electrical and mechanical properties	[214]
rGO films	C2C12	skeletal muscle tissue	Electrical stimulation on graphene films significantly enhanced myoblast cells differentiation	[215]
Patterned G film substrate	C2C12	skeletal muscle tissue	Growth cellular alignment and increased myogenic differentiation	[216]
PDA/rGO aerogel composite hydrogel	C2C12	skeletal muscle tissue	Promoted C2C12 myoblast differentiation and induce myotube contraction *in vitro*, and show the capable treatment for retarding the disused skeletal muscle atrophy	[217]

single and multiwall CNT with chitosan hydrogel	Dermal fibroblasts	Skin Wound Healing	Improved wound healing because CNT was increased pro-inflammatory cytokine release	[221]
conductive hydrogel (chitosan with CNT)	L929 cell and bacteria (E.coli and S. aureus) cell	Skin Wound Healing	Improved wound healing compared with CNT-free hydrogel dressing because the transfer of electric signals from conductive hydrogel dressing to the wound healing place	[222]
CDs and chitosan with CDs nanocomposites films	human cells (HFF & MG63) and RBCs	Skin Wound Healing	CDs were enhanced to accelerate wound healing due to radical scavenging potential.	[224]
GO	*Pathogenic Bacteria cells*	Skin Wound Healing	Controlling antibacterial, antifungal and fungal wound infection treatment using NIR light	[227]
3D-graphene foam	MSCs	Skin Wound Healing	Graphene foam guided the wound healing process in a faster way with decreased scarring effect	[228]
CS/SF with the integration of polydopamine-rGO Scaffolds	C2C12 and RAW 264.7 cells	Skin Wound Healing	To stimulate physical electrical conductive signal transmission for cell growth and reduce ROS oxidation for enhancing skin wound healing	[229]

4. Hydroxyapatite beyond bone applications

Hydroxyapatite has been used since decades in orthopedics for bone replacement and repair due to its compositional and crystallographic similarity with the hard mineral phase of bone [230]; furthermore, other calcium phosphates with tunable resorption rates (e.g. α- and β-tricalcium phosphates) have been proved suitable for similar purposes in non-load-bearing sites [231]. There are interesting clinical applications of hydroxyapatite in contact with soft tissues, too (Table 4), and some of them are in widespread use for many years.

4.1 Ophthalmic applications

Porous hydroxyapatite spheres are routinely used as orbital implants in ophthalmology, i.e. they are inserted in the patient's orbit after enucleation to restore the volume of the lost ocular globe. In fact, the 3D network of highly-interconnected macropores allows these ceramic implants to act as a passive framework for fibrovascular tissue in-growth, which carries a series of advantages including better anchorage of the implant to soft orbital tissues and lower risk of postoperative complications compared to their non-porous counterparts [232, 233]. Hydroxyapatite porous spheres deriving from bovine trabecular bone were used till the 1950s with long-term behavior since it was shown that small conjunctival damages (abrasion) due to the repetitive movements of the implant inside the orbit were prone to heal spontaneously. This favorable property was attributed to the high biocompatibility of the implanted material and the presence of blood supply (fibrovascularization) [234]. After being temporarily fallen in disuse owing to the advent of softer and more pliable polymeric implants, the bovine hydroxyapatite sphere was somehow reinvented in the 1970s [235-237] and is still used today under the tradename of "Molteno M-Sphere"; however, its diffusion is limited compared to the other

options due to the high brittleness caused by inherent high porosity (>80 vol.%), expensiveness and ethical/religious issue in some countries, where the use of animal-derived implants can be a matter of concern [238].

Coralline hydroxyapatite with porosity within 50-60 vol.% was introduced in the 1980s to substitute bovine bone apatite in ophthalmology [239]; today, this FDA-approved orbital implant is sold with the tradename of Bio-Eye sphere and is produced by converting the calcium carbonate phase of marine coral *Porites* into calcium phosphate by a hydrothermal process [240]. Issues related to disruption of marine life ecosystem due to harvesting of corals and high expensiveness of coralline material [241] led to the introduction of synthetic hydroxyapatite as an alternative implant material, the major commercial example being the FCI implant (currently in the third generation, FCI3).

Performance of coralline and synthetic hydroxyapatite in the orbit are similar and both allow central vascular in-growth, although some experimental works suggest that coral-derived implants significantly stimulate more rapid and homogenous vascularization than synthetic ones [242]. The clinical results of hydroxyapatite implants are generally good: as an example, Shield et al. [243] reported no cases of implant extrusion or migration and only one case of orbital infection in 250 enucleated patients over a mean follow-up of 23 months. However, it should be taken into account that these implants suffer from the high risk of inducing conjunctival abrasion due to their micro-rough surface with crystalline grains in the range of 1 to 5 μm. Therefore, hydroxyapatite implants should preferentially be wrapped within a sheet of smooth material before being used (e.g. autologous sclera, fascia lata or polymeric mesh) to facilitate attachment of the extraocular muscles and avoid conjunctival abrasion [244-246].

Application of a copper-doped MBG surface coating on the walls of hydroxyapatite porous spheres was proposed as a mean to promote angiogenesis (implant vascularization) and impart antibacterial properties due to the multifunctional effect of Cu^{2+} ions [247, 248].

4.2 Anticancer applications

Other emerging properties of hydroxyapatite concern its potential in anticancer applications followed by tissue regeneration, not necessarily limited to the field of hard tissues (orthopedics and dentistry). Al-Kattan et al. [249] showed that hybrid luminescent colloidal nanoparticles, obtained by combining Eu-doped nano-crystalline hydroxyapatite, a phospholipid moiety (2-aminoethylphosphate) and vitamin B9 (folic acid) acting as a cell-targeting agent, exhibited low cytotoxicity and pro-inflammatory potential as well as the capability of being internalized by ZR-75-1 breast cancer cells. These findings suggest promising applications of these composite nanoparticles in cancer diagnosis through intracellular imaging by luminescence. In the same study, pectin-hydroxyapatite composite microspheres were also proposed as potential drug carriers for cancer treatment [249].

Hydroxyapatite was often designed to act as a carrier for releasing a therapeutic agent that performs a desired biological function. In this regard, the adsorption of anticancer drugs (doxorubicin and methotrexate, an antifolate analog) and folic acid (used as a cell-targeting agent) on as-such and Fe-doped superparamagnetic hydroxyapatite nanoparticles was also investigated [250]. A higher adsorptive affinity was reported for the Fe-containing substrate compared to Fe-free one and, hence, a quicker release rate was observed from the latter. The anticancer properties of these biomaterials were also confirmed by *in vitro* tests using human

osteosarcoma (SaOS-2) cell line. Extension of these strategies to the field of soft tissue therapies would deserve investigation in the next future.

4.3 Applications in contact with blood

The research group led by Prof. Drouet reported interesting findings of the interaction between hydroxyapatite nanoparticles and blood. Adsorption of tranexamic acid, a clinically-used antifibrinolytic agent, on hydroxyapatite nanoparticles was proposed as a effictive strategy for obtaining bioceramics with hemostatic properties [251]. Drug delivery was fast during the first hours and the release kinetics were governed by a complex process involving both diffusions of the drug and hydroxyapatite dissolution. Early hemostasis tests using blood harvested from healthy adult dogs showed great promise and support the suitability of the prepared biomaterial formulation to intrinsically reduce bleeding in many surgical operations.

Very interestingly, hydroxyapatite nanoparticles were shown to play a role in the cryopreservation of red blood cells – which is crucial during the management of blood transfusions – in combinations with trehalose, a biocompatible cryoprotectant. Stefanic et al. [252] revealed that the addition of ceramic nanoparticles into the incubation medium significantly increased the red blood cell cryo-survival (91% vs. 42% in the absence of nanoparticles), achieving the standard values recommended by FDA in the cryoprotection protocol employing glycerol. The hydroxyapatite nanoparticles did not cross the lipid bilayer membrane of red blood cells but could modulate its physical status and promote the permeation of trehalose molecules (Fig. 9). Specifically, hydroxyapatite nanoparticles stabilized with 2-aminoethylphosphate and hexametaphosphate were shown to enhance the permeation of trehalose through the cell bilayer by locally interacting with the lipid bilayer. Trehalose

translocation into red blood cells was facilitated via an indirect mechanism due to nanoparticle-bilayer interactions rather than the direct formation of temporary pores in the cell membrane. As a result, hydroxyapatite nanoparticles could enable the translocation of trehalose by locally modifying the 3D organization of the lipids through transient breaching of the lipid bilayer. This approach represents a valuable, alternative strategy to the use of conventional but toxic glycerol for red blood cell cryopreservation, thus overcoming the need for cryopreservant removal before blood transfusion.

4.4 Wound repair and regeneration

Hydroxyapatite, alone or in combination with drugs or other biomaterials to form composites, was reported to play a role in accelerating wound healing.

Xu et al. [11] reported the antibacterial activity of a low-temperature photothermal therapy-assisted catalytic system comprising a polydopamine coating on gold-incorporating hydroxyapatite nanoparticles. This multi-material system produced hydroxyl radicals via catalysis of a small concentration of H_2O_2 to render bacteria in infected wounds more vulnerable to temperature change. After irradiation by 808 nm laser for 10 min, the bacterial inhibition against *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) was 96.8% and 95.2%, respectively, associated with a low photo-induced temperature of 45 °C that causes no damage to healthy tissues.

Given the stimulatory effect that silicon has on cell activity, Si-doped hydroxyapatite [253] and silica aerogel/hydroxyapatite composites [254] were found to improve the biocompatibility, proliferation and collagen secretion of fibroblasts in vitro.

Hydroxyapatite nanoparticles were also added to various "soft" organic matrices, including silk fibroin gel [255], keratin fibers [256], alginate-gelatin films [257] and chitosan gel [258], for improving the mechanical properties/thermal stability of the polymer – which could be easily applied/injected onto the injured site – and the fibroblast activity for potential application in wound dressing/burn treatment. Okabayashi et al. [255] also reported that using electrically-polarized hydroxyapatite microparticles (size < 74 μm) further promotes fibroblast maturation and re-epithelization of the skin wound area due to the beneficial effect of the charges stored in the gel.

Mesoporous hydroxyapatite was also proposed as a carrier for simvastatin, a potent pro-angiogenic drug that is insoluble in water [259]. In this regard, it was shown that an alginate hydrogel incorporating simvastatin-loaded mesoporous hydroxyapatite significantly enhanced new blood vessel formation and accelerated the re-epithelialization of cutaneous wounds.

4.5 Peripheral nerve regeneration

Some recent studies have suggested the potential suitability of hydroxyapatite in the context of peripheral nerve regeneration. The first report on this application was published in 2016 by Nawrotek et al. [260], who produced chitosan-based hydrogel hollow conduits incorporating hydroxyapatite nano-powders (size < 200 nm) by a patented electrodeposition method. The ceramic phase was added to (i) reinforce the polymer to match the stiffness of the nervous tissue and (ii) provide a source of calcium ions, which play a role in axonal regeneration. Results from physico-chemical and in vitro biological investigations showed promise and motivate further in vivo experiments, which are still to be reported.

The beneficial role of hydroxyapatite as a source of calcium ions was also pointed out by Salehi et al. [29] who prepared collagen type I hydrogels embedding hydroxyapatite nanoparticles (diameter around 212 nm). Schwann cells cultivated on this composite hydrogel showed higher proliferation compared to the ceramic-free control; these promising in vitro results were confirmed by in vivo experiments in rats through functional analysis (sciatic nerve functional index, hot plate latency, and compound muscle action potential amplitude measurement).

Liu et al. [261] reported that application of hydroxyapatite nanoparticles can be effective in the repair of mechanical stretch-induced nerve injury in rat spine. Specifically, it was observed that nano-hydroxyapatite can stop hemorrhage and edema triggered by high-rate mechanical stretch (60 mm/min); an explanation of this phenomenon, although not provided in that study, could rely on the inherent hemostatic properties of hydroxyapatite nanoparticles [262].

Table 4. Summary of studies dealing with the applications of hydroxyapatite in contact with soft tissues.

Form of application	Drug/ion incorporated	Therapeutic target	Remarks	Ref.
Hydroxyapatite porous sphere or ovoid	-	Eyeball replacement after enucleation	Bone-derived, coralline or synthetic hydroxyapatite are used for making commercially-available implants Coating with Cu-doped MBG was proposed to promote vascularization and elicit antibacterial properties	[226-238]
Eu-doped hydroxyapatite	Eu; folic acid	Cancer therapy	Eu imparts luminescent properties; folic agent is a cancer cell-targeting agent	[239]
Fe-doped hydroxyapatite	Fe; doxorubicin and methotrexate	Cancer therapy	The presence of Fe allows better adsorption of anticancer drugs.	[240]
Hydroxyapatite nanoparticles	Tranexamic acid	Hemostasis	Tranexamic acid was adsorbed on the surface of nanoparticles.	[241]
Hydroxyapatite nanoparticles	-	Cryopreservation of red blood cells	Combination with trehalose	[242]
Hydroxyapatite nanoparticles	Au; polydopamine coating	Wound healing	Photothermal therapy-assisted catalytic nanosystem eliciting antibacterial properties	[11]
Hydroxyapatite nanoparticles	Si	Wound healing	Doping with Si or incorporation in silica aerogel Stimulatory effect of Si on fibroblasts	[254]
Hydroxyapatite nanoparticles	-	Wound healing	Incorporation of nanoparticles in silk fibroin, keratin, alginate-gelatin and chitosan matrices for mechanical/thermal improvement	[256]
Mesoporous hydroxyapatite	Simvastatin	Wound healing	Pro-angiogenic effect	[259]
Hydroxyapatite nanoparticles	-	Peripheral nerve regeneration	Incorporation of nanoparticles in chitosan or collagen type I matrices Mechanical reinforcement, a beneficial effect of calcium ions	[260]

5. Other ceramics and composites

The use of other bioceramics has been less frequently reported in contact with soft tissues, including blood or endothelial cells for hemostatic, wound healing, or ophthalmic applications, as well as Schwann cells for neural regeneration, thus leaving room for future in-depth investigations.

5.1 Alumina

Alumina has been used for the production of load-bearing joint prosthetic implants in contact with bone since the 1970s due to its high biocompatibility and favorable mechanical properties [263]. Although orthopedics and dentistry are still the most popular fields of use for alumina and its composites with zirconia, there are some emerging applications in contact with soft tissues, too. It is worth underlining that alumina is a non-resorbable ceramic: this property is attractive for some specific applications, like orbital implants in ophthalmology where the main goal is lost eye volume restoration, but may be an apparent drawback for most applications where healthy tissue regeneration and recovery are the main goals, which usually require the implantation of a temporary construct. In the latter scenario, the most promising applications of alumina are addressed to wound healing.

Macroporous alumina spheres with total porosity around 75 vol.% and nominal pore size of 500 µm have been approved by FDA in 2000 for clinical use in enucleation and show great promise in overcoming the typical drawbacks of porous hydroxyapatite orbital implants. These orbital spheres, commercially marketed as “Bioceramic implant”, have a lower tendency to induce conjunctival abrasion over time due to the smoother surface with sub-micrometric crystals (less than 1 µm vs. 3-5 µm of hydroxyapatite implants) [264], which results in a reduced risk of

postoperative complications (e.g. implant exposure). This favorable behavior was demonstrated in a series of comparative studies in both animals (rabbits) [265] and human patients [266, 267] receiving alumina or hydroxyapatite orbital spheres. Another advantage of porous alumina is the low apparent density, which is only half that of a hydroxyapatite sphere of equal size: this reduces the pressure on the lower lid and thus decreases the risk of implant migration and sulcus deformity.

Mawn et al. [268] also reported an accurate comparison about the proliferation of human orbital fibroblasts *in vitro* after seeding on alumina, coralline, or synthetic hydroxyapatite, and porous polyethylene. The proliferation of fibroblasts was maximum on the alumina implant, which was attributed to its hydrophilic surface and finely crystalline microstructure, promoting cell attachment.

Wang et al. [269] reported that exposures of alumina implants occurred only after long-term follow-up and were preferentially associated with evisceration, pegging, and previous ocular surgeries, whereas no late side effects were found in enucleated eyes. Successful "salvage" treatments of exposures, without the need for implant removal, were performed by covering the exposed anterior area of alumina implants with biological patches deriving from autologous transplantation (e.g. retroauricular myoperiosteal graft containing myofibrovascularized tissue) [270, 271].

Alumina has also been proposed for use in other fields than ophthalmology. Recent advances in nanotechnology have allowed scientists to improve the conventional electrochemical procedures used for the anodization of Al, thus leading to the advent of nanoporous Al_2O_3 membranes for potential use in soft tissue engineering applications. The formation of regular pores on the surface of anodized aluminum oxide (AAO) can be easily controlled to modulate the pore size

from the micrometric scale to the nanoscale, in general, both types of pores can be generated through an electrochemically-driven process without the need for expensive equipment [272, 273]. The characteristics of nanopores can be tailored by acting on the process parameters, such as the nature and strength of the acid, the voltage applied, and the exposure time of the Al substrate to the electrolyte.

It was observed that the topography of the AAO membrane directly affects the basic functions of living cells, thus producing tunable biological responses. As the most popular use of alumina is in contact with osseous tissue, bone cells were first employed to test the *in vitro* biocompatibility of AAO. Some studies have shown the capability of AAO to promote the differentiation of bone marrow cells to osteoblasts [274]; furthermore, the small release of Al^{3+} ions from the nanoporous AAO membrane into the surrounding biological fluid (decrement of 0.03 wt.% of the initial sample mass after 9 days) supported the safe use of this material with minimal risk of aluminum-related toxicity [275].

Nanoporous AAO membranes were also investigated for possible use as a skin tissue engineering scaffold by Parkinson et al. [276]. Specifically, the nanoporous AAO membranes were initially seeded with human skin cells (keratinocytes and fibroblast epidermal cells) harvested from a patient. These cells were left to proliferate (Fig. 10) and to form a confluent layer, which was then either lifted from the AAO membrane and applied directly onto the wound bed or added with the AAO membrane facing out. An advantage of the latter strategy is that the exchange of gases/fluids through the alumina nano-channels is allowed but the colonization of the wound site by micrometric bacteria from outside is avoided due to size mismatch. Once the autologous cells have been incorporated into the wound bed, the outer AAO membrane can be safely removed. Being totally inorganic, the AAO membrane can be sterilized more easily than

polymeric wound-dressing products also by autoclaving or γ-irradiation. Furthermore, these AAO membranes (thickness 50-200 μm) are flexible and can be easily contoured to match the skin defect dimensions.

The biological responses of other soft tissue cells after seeding on AAO membranes were also reported in a quite limited number of studies. Hoess et al. [277] used AAO membranes as a substrate for the hepatocyte carcinoma cell line HepG2 and showed that these cells homogeneously attached and proliferated on the membrane. It was also found that larger pore diameters (230 nm) stimulated the seeded HepG2 cells to anchor to the membrane and favored fluid circulation to a higher extent compared to the smaller pores. This application could potentially disclose new opportunities in tissue engineering for the development of a bioartificial liver.

Karlsson et al. [278] found that AAO membranes with pore sizes ranging within 20-200 nm provide a favorable substrate for the proliferation of leukocytes and highlighted that the membrane pore size plays a key role in directing the biological response: in fact, adherent neutrophils on 20-nm pore-size membranes elicited much stronger initial oxygen free radical production and exhibited more extended pseudopodia compared to those grown on the surfaces with larger nanopores.

Alumina nano-powder was also proposed as a therapeutic agent for wound healing applications. Kirilova et al. [279] produced wound dressings by one-stage oxidation of Al nano-powder in water in the presence of acetylcellulose fibers; as a result, fibrous polymeric meshes (fiber diameter 1.5-3.0 μm) with adhered alumina nano-sheets were obtained. The antimicrobial properties of these materials were demonstrated by *in vitro* tests using both Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*)

bacterial strains. Although the antiseptic mechanism of action was not elucidated, these promising results were confirmed by *in vivo* experiments in both animals (male rats) and volunteer patients, where it was clearly shown a reduction of the wound healing period, an accelerated cleaning of the infected wound and an overall improvement of healthy tissue regeneration in the wound.

This attractive new property of nano-sized alumina powder was also exploited by Volodina et al. [280] in the fabrication of complex composite dressings for wound healing by using chlorhexidine digluconate as an antimicrobial agent, lidocaine as a painkiller, chymotrypsin as a necrolytic agent, and sol-gel alumina as an inherent wound healer. *In vivo* wound healing efficacy was assessed in a full-thickness excision wound model in Wistar rats: it was shown a marked decrease in scar size, which was 2.4 times smaller than that observed in the control group, and a complete re-epithelialization of the injured site after 15 ± 1 days, whereas the process was longer using an antiseptic solution alone (17 ± 1 days) or pure alumina gel alone (19 ± 1 days). Therefore, the synergistic combination of antiseptic drugs and sol-gel alumina as dressing material seems to provide a highly-promising therapeutic option for the treatment of skin injuries, wounds, and surface burns.

It is also worth mentioning the potential of, SiAlON-Al_2O_3 ceramics produced by direct nitridation, which were recently reported to exhibit good biocompatibility with human umbilical vein endothelial cells [281].

5.2 Calcium sulfate

Calcium sulfate is mainly used as a bone cement and is characterized by a fast resorption rate [282]. Its application as a hemostatic agent in contact with blood can be traced back, to some

extent, to the field of interactions with soft tissue. In this regard, Zhou et al. [283] prepared composite cements combining calcium sulfate with 2, 4, or 6 wt.% of hydroxypropyl methylcellulose or sodium alginate as an alternative to bone wax in blood transfusion treatments during cancellous bone injury. The cement could be solidified upon contact with an aqueous solution to form a physical barrier against bleeding with the additional supply of Ca^{2+} ions that further accelerate blood clotting. The incorporation of 2 wt.% sodium alginate seemed to provide the best properties in terms of setting time, compressive strength (5 MPa), stability, and fast blood-clotting capability (around 15 min) among all tested samples.

The capability of calcium sulfate to release high amounts of Ca^{2+} ions, which are known to play a role in dermal regeneration, would deserve further investigation in the future for other applications in contact with soft tissues, like wound dressing.

5.3 Titania and titanate-based ceramics

A colloidal solution of titania nanoparticles (size around 10 nm) produced by the sol-gel method displayed a clear trend to accelerate blood clotting, regardless of the addition of common anti-coagulation agents such as heparin [284]. *In vivo* studies in rats showed that the topical application of colloidal titania on thermally-induced burn sites resulted in a quicker reduction of the exposed wound area (Fig. 11), while the total duration of recovery was comparable to that of untreated wounds. Very interestingly, titania was apparently able to promote the restoration of the normal skin structure while discouraging the formation of scar tissue after healing of 2^{nd}-degree burns and improving the scar tissue appearance in the case of more severe burn damages

Many “traditional” bioceramics (e.g. BGs, hydroxyapatite, alumina) are electrical insulators, which means that they have some functional limitations in those applications where the

transmittance of electrical stimuli is a goal. Apart from CBNs, there is a limited set of bioceramics exhibiting conductivity properties, such as $CaTiO_3$ that belongs to the class of perovskites and exhibits a high dielectric constant and attractive conductivity properties [285]. A study published by Li et al. [286] suggested the incorporation of $CaTiO_3$ nanoparticles (110-220 nm) in chitosan scaffolds to promote the attachment, proliferation, and function of Schwann cells in vitro, thus showing promise for application in peripheral nerve repair. The mechanism behind the biological action of $CaTiO_3$ seems to strongly rely on the delivery of Ca^{2+} ions that stimulate neural cell proliferation [287] and affect the gating of nerve Na^+ channels involved in peripheral nerve conduction [288].

Another titanate material, $BaTiO_3$, was also tested for potential use in neuronal applications due to its piezoelectric properties. Specifically, poly(vinylidene fluoride-trifluoroethylene)/$BaTiO_3$ nanoparticle composite films were reported to promote, under ultrasound stimulation, Ca^{2+} transients as well as the differentiation of neuroblastoma cells via direct piezoelectric effect [289].

5.4 Akermanite

Akermanite powder ($Ca_2MgSi_2O_7$) was reported to increase re-epithelialization in mice affected by a dorsal thermally-induced burn [290]. The cellular mechanism for re-epithelialization was shown to involve improved proliferation, migration, and stemness of epidermal cells. Akermanite powder can activate theWnt/β-catenin signaling pathway in epidermal cells, which may be responsible for enhanced cellular stemness. Furthermore, the promotion of local

angiogenesis – which is key for the wound healing process – was induced by the local release of silicate, calcium and magnesium ions [291, 292].

5.5 Nanoceria

Cerium oxide nanoparticles (nanoceria) have attracted great interest in the biomaterials community over the last years due to their antioxidant, antibacterial, anti-inflammatory and pro-angiogenic properties. Use of nanoceria in tissue engineering has been primarily proposed in the field of bone repair, but some emerging applications for skin, peripheral nerve, cardiac, and ophthalmic regeneration, and have been reported as well. [293-296].

Furthermore, some recent experimental studies suggest the potential suitability of nanoceria in ameliorating brain diseases, such as cerebral ischemic stroke (CIS) that is one of the leading causes of severe disability – or even death – in the world. Kim et al. [297] showed that uniform 3 nm-sized PEGylated ceria nanoparticles can protect against CIS by scavenging ROS and reducing apoptosis in vitro. The antioxidant benefits and, especially, the neuroprotective potential of nanoceria towards focal CIS were emphasized and critically discussed by Zhou et al. in a valuable paper [298].

Following this highly promising early results, the effect of ceria nanoparticles (mean diameter 2.9 nm) was tested in an animal model of immunological and ROS-mediated injury leading to neurodegenerative disease [299]. It was shown that nanoceria, when administered intravenously to mice, could reduce ROS levels in the brain and alleviate the motor deficits in animals suffering from multiple sclerosis.

The great potential of nanoceria was further demonstrated by Park et al. [300], who showed the effectiveness of these nanoparticles in revascularizing critically-ischemic limbs in mice and restoring limb function. Histological analysis revealed stimulation of pro-angiogenic markers, maturation of blood vessels and remodeling of muscle tissue following injection of nanoceria (particle size 20-30 nm) since nanoceria could promote endothelial cell tubule formation via the Ref-1/APE1 signaling pathway.

6. Concluding remarks and future prospective

The main message of this article – also in order to provide a response to the question posed in the manuscript title – is that hard materials, i.e., bioceramics, are indeed a valuable resource for the novel, smart applications in contact with soft tissues.

In general, the use of hard ceramics in contact with the soft and delicate structures of the body requires some cautions. First, there is an obvious mismatch between the physico-mechanical properties of hard materials and those of soft tissues. Therefore, only in selected cases, bioceramics can be used alone as large-size products, like hydroxyapatite or alumina porous orbital implants. In most cases, they are produced in order to being somehow pliable and mouldable (e.g. the cotton-like 13-93B3 borate glass microfibers proposed for wound healing) or are incorporated in soft polymeric matrices to obtain a relatively flexible composite.

The second key aspect is that there is a variety of structures, morphologies, and related properties in soft tissues: therefore, one simple “ideal” choice does not exist but the type, shape, size, and dosage of hard materials should be carefully selected depending on the specific application. A similarity-based criterion can be followed: for example, fibers are obviously indicated for nerve and muscle regeneration considering the typical structure of these two types of tissues. In other

cases, micro- or nano-sized ceramic inclusions can be embedded in soft polymeric matrices (e.g. cardiac patches); the size and shape of these inclusions should be selected to tailor the topological and mechanical properties of the composites so that they match those of the native tissue. If the ceramic phase is resorbable, resorption kinetics and pH of the surrounding environment can also depend on its geometrical features apart from the composition.

Proper regeneration of soft tissues may require special functionalities, such as angiogenesis (e.g. in wound healing) and ability to transmit electrical stimuli (e.g. in cardiac, neural and muscle applications). Some hard materials, like BGs, were found to exhibit pro-angiogenic properties due to the release of therapeutic ions (basically silicate and calcium ions [301], and this property can be further potentiated by properly designing the glass composition. In fact, metallic dopants (e.g. copper) which are known to promote angiogenesis can be added to the glass formulation so that, once released during glass dissolution, they can elicit proangiogenic therapeutic effect. Furthermore, drugs and biomolecules can be incorporated in some special types of bioceramics, like MBGs, and then released to elicit targeted therapeutic actions to soft tissues.

CBNs are conductive, thus being appropriate options in those applications where innervation with a transmittance of electrical stimuli is a goal such as peripheral nerve conduits and cardiac patches. These examples suggest that only a wise combination of different hard materials can allow obtaining multiple extra-functionalities.

In this regard, we cannot ignore that the higher the complexity of multi-materials systems, the higher the barriers to clinical translations. In this regard, a better knowledge of the fine biomolecular mechanisms behind bioceramic-soft tissue interactions also in the long term is needed more than ever and will be possible only through a close collaboration between scientists with different expertise (chemists, bioengineers, clinicians); furthermore, involvement of

companies and stakeholders will be highly beneficial for the development of reliable and effective medical products. At present, there is a paucity of clinically-approved biomedical products incorporating bioceramics for application in contact with soft tissues. Perhaps the most famous example is the multifunctional 13-93B3 borate glass cotton-candy, which is pro-angiogenic/antibacterial and was cleared in 2010 for wound dressing in veterinarian applications under the tradename of "ReadiHeal™", Although FDA approval for widespread use in humans is still pending, this material has also been used under the name of Mirragen® (ETS Wound Care, MO, USA) in selected clinical cases suffering from diabetic ulcers with satisfactory therapeutic results.

The current literature proves and expands the exceptional versatility of bioceramics, and witnesses that there is a clear trend in the future, in which the applications of bioceramics will be extended from bone repair to the treatment of a number of soft tissue traumas and diseases in the body, and will continue to improve the quality of life of a myriad of patients worldwide.

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Figures' legends

Fig. 1. Schematic representation of the proposed molecular mechanisms by which 90S BGs can regulate the cellular behaviors of fibroblasts. Reproduced with permission from ref [93].

Fig. 2. (A) Micro-computed tomography (CT) images of the effects of 3% copper-doped BG microfibers (3Cu-BG) on the blood vessel formation in full-thickness skin defects after 14 days of implantation: (a) 3D reconstructed images of the neovascularization process; (b) and (c) morphometric analysis of the new blood vessel area and the number of blood vessels. Mean ± SD; n= 6. *$p < 0.05$ compared to control; %$p < 0.05$ compared to BG. (B) Images of Masson's trichrome stained samples of untreated and treated animals with BG and copper-doped B Masson's trichrome stained sections of the untreated defects (control) and the defects treated with the BG and 3Cu-BG after 7 and 14 days of implantation. Reproduced with permission from ref [104].

Fig. 3. (A) Composite scaffolds made of phosphate glass fibers (PGfs) and collagen for peripheral nerve reconstruction: (a) and (b) show to the manufacturing process of the 3D scaffold and its scanning microscopy photographs (SEM) (scale bar = 100 mm). (c) illustrates the surgery procedure of complete transection of the sciatic nerve to makes a gap of 3 mm in lengths with remaining neural sheath. (d) and (e) images are related to the implantation of the composites (0.8 mm diameter, 3 mm long) into the defect and suturing of the neural sheath with 10-0 nylon, respectively. (B) Representation of immunohistological staining of animals axons within the cross-section of: (a) intact sciatic nerve and (b) and (c) show cross-sections of scaffold collagen group and PGf/collagen group post 7 days of implantation, respectively. (d) and (e) show high magnification images of (c) yellow-lined boxes. (f) and (g) images represent magnified images of (c) white-lined boxes (white scale bar = 200 mm, yellow scale bar = 20 mm). Cross-sections 1mm distal from (h) collagen scaffolds; (i) PGf/collagen scaffolds post 8 weeks; and their counterparts, i.e., (j) and (k), after 12 weeks of implantation. (l) shows the number of axons at 1mm distal to scaffold in different groups post-implantation. DIC: differential interference contrast microscope (DIC). POW: postoperative week. Reproduced with permission from ref [141].

Fig. 4. Schematic representing the carbon-based nanomaterials developed for soft tissue repair and regeneration with their unique dimension, and the mechanical, optical, and electrical properties.

Fig. 5. SA-CNTs used for the myocardium patch. (a) The aligned arrangement of the myocardium. (b) Optical image of flexible multi-layer SA-CNTs. (c) SEM image of the SA-CNTs. (d) Cell morphology at 3 days on the cover glass and SA-CNTs. (e) Electrophysiological

behavior of CMs grown on control and SA-CNTs. Comparison of 30% action potential duration (APD_{30}) and APD_{90} dispersions between CMs grown on the control and SA-CNTs in the manner of beat-to-beat and cell-to-cell. Reproduced with permission from Ref. [7].

Fig. 6. CNT-PGF scaffolds used for peripheral nerve regeneration. (a) Schematic illustration showing the preparation method of scaffolds with aligned PGFs and interfaced CNTs. (b,c) SEM images. (d) Conductivity of samples. (e) Confocal images of DRG neuronal cell growth on the substrates for 3 days. (f-h) *In vivo* experiments in transacted rat sciatic nerve; (f) implantation of the scaffold, (g) Immuno-histochemical images of axons (green) in the transverse section at the proximal stump and (h) axons (SMI312, green), and Schwann cells (S100, red) in the sagittal section at the border between the scaffold and the distal stump of PGF or CNT-PGF scaffold-implanted sciatic nerve at 16 weeks post-implantation (yellow scale bar = 500 μm, white scale bar = 200 μm). Reproduced with permission from Elsevier from Ref. [28].

Fig. 7. rGO/PDA aerogel used for skeletal muscle regeneration. (a) Schematic representation showing the experimental design of PDA/rGO aerogel for skeletal muscle. (b) LED bulb lightening due to electrical conductivity. (c) C2C12 myoblast differentiation on a glass slide, gel, and gel + ES (electrical stimulation) at 7 days. F-actin (red), nucleus (blue), and MHC (green) in C2C12 myoblasts in different groups. Scale bars: 50 μm. (d) Differentiation index. (e) Muscle weight measured in the implanted samples in denervated muscles (DV) at 1 and 3 weeks. Reproduced with permission Ref. [50].

Fig. 8. QCSG / CNT cryogel used for skin regeneration. (a) Preparation of QCSG copolymer and (b) synthesis of QCSG/CNT cryogel. (c) SEM image of the cryogels without CNT (QCSG/CNT0) and with 4% CNT (QCSG/CNT4). (d) Electrical conductivity of the cryogels in the wet and dry state. (e,f) *In vivo* wound healing of the cryogels; (e) wound healing contraction, and (f) optical images of wounds healing at 5th, 10th, and 15th day for Tegaderm™ film, QCSG/CNT0, and QCSG/CNT4. Scale bar: 5 mm. Reproduced with permission from Nature publishing group from Ref. [55].

Fig. 9. Use of hydroxyapatite nanoparticles for improving red blood cell cryopreservation: schematic description of (a) aqueous colloidal suspension (1) and colloidal 2-aminoethylphosphate (AEP)/sodium hexametaphosphate (HMP)-stabilized nanoparticle (2); (b) general concept of improved trehalose permeation into red blood cells assisted by hydroxyapatite nanoparticles. Reproduced from ref [252].

Fig. 10. SEM images of keratinocytes on nanoporous AAO. Lamellipodia extending from the cell body have a similar size to the pores, lying across the surface of the substrate. Reproduced from ref [276].

Fig. 11. Effect of titania nanoparticles on wound healing in rats: top – quantification of wound surface reduction (Group 1, untreated 2^{nd}-degree burns; Group 2, 2^{nd}-degree burns treated with titania nanoparticles; Group 3, untreated 4^{th}-degree burns; Group 4, 4^{th}-degree burns treated with titania nanoparticles); bottom – the general appearance of the wounds through the healing process for one representative animal from each group. Reproduced from ref [284].