Materials Science & Engineering C 94 (2019) 1083–1101

Contents lists available at ScienceDirect

Materials Science & Engineering C

journal homepage: www.elsevier.com/locate/msec

Review

Polylactide-based materials science strategies to improve tissue-material interface without the use of growth factors or other biological molecules

Lukas Gritsch[a,b,*], Gioacchino Conoscenti[c], Vincenzo La Carrubba[c,d,e], Patcharakamon Nooeaid[f], Aldo R. Boccaccini[a]

[a] Institute of Biomaterials, University of Erlangen-Nuremberg, Cauerstraße 6, 91058 Erlangen, Germany
[b] Lucideon Ltd., Queens Road, Penkhull, Stoke-on-Trent, Staffordshire, ST4 7LQ, UK
[c] Department of Civil, Environmental, Aerospace and Materials Engineering (DICAM), University of Palermo, Viale delle Scienze building 6, 90128 Palermo, Italy
[d] Consorzio Interuniversitario di Scienza e Tecnologia dei Materiali (INSTM) – University of Palermo Research Unit, Viale delle Scienze Building 6, 90128 Palermo, Italy
[e] ATeN Center, University of Palermo, Viale delle Scienze building 18, 90128 Palermo, Italy
[f] Division of Polymer Materials Technology, Faculty of Agricultural Product Innovation and Technology, Srinakharinwirot University, Rangsit-Nakhon Nayok road, 12160 Nakhon Nayok, Thailand

ARTICLE INFO

Keywords:
Polylactic acid
Tissue-material interface
Bioactivity
Extracellular matrix
Tissue engineering
Scaffold
Composites

ABSTRACT

In a large number of medical devices, a key feature of a biomaterial is the ability to successfully bond to living tissues by means of engineered mechanisms such as the enhancement of biomineralization on a bone tissue engineering scaffold or the mimicking of the natural structure of the extracellular matrix (ECM). This ability is commonly referred to as “bioactivity”. Materials sciences started to grow interest in it since the development of bioactive glasses by Larry Hench five decades ago. As the main goal in applications of biomedical devices and tissue scaffolds is to obtain a seamless tissue-material interface, achieving optimal bioactivity is essential for the success of most biomaterial-based tissue replacement and regenerative approaches. Polymers derived from lactic acid are largely adopted in the biomedical field, they are versatile, FDA approved and relatively cost-effective. However, as for many other widespread biomedical polymers, they are hydrophobic and lack the intrinsic ability of positively interacting with surrounding tissues. In the last decades scientists have studied many solutions to exploit the positive characteristics of polylactide-based materials overcoming this bottleneck at the same time. The efforts of this research fruitfully produced many effective tissue engineering technologies based on PLA and related biopolymers.

This review aims to give an overview on the latest and most promising strategies to improve the bioactivity of lactic acid-based materials, especially focusing on biomolecule-free bulk approaches such as blending, copolymerization or composite fabrication. Avenues for future research to tackle current needs in the field are identified and discussed.

1. Introduction

1.1. Tissue-material interfaces and the concept of bioactivity

The outcome of the majority of medical devices which are in contact with a biological environment depends on an effective interaction between the host organism and the graft or implant. In ideal terms, this interaction should minimize foreign body reactions (e.g. fibrosis), control post-implant inflammation and eventually lead to the formation of a seamless interface between the two parts and thus to complete embedding of the device within healthy human tissues. General approaches used to overcome foreign body response and subsequent in vivo instability have been reported. These include coating with biocompatible materials and using anti-inflammatory and angiogenic drugs [1]. In practice, a successful biomaterial should be designed in such a way that the ability of its interface to interact with the biological system is significantly improved, in terms of cell migration, extracellular matrix (ECM) deposition and vascularization, towards the ideal seamless state. Generally speaking, a material that is able to address this issue and that is characterized by the ability of positively interact with tissues is labelled “bioactive”. Bioactivity is broadly defined as the ability of a material to successfully interact with a targeted living tissue [2–5]. However, since biological tissues have very diverse characteristics (e.g. composition of the ECM), also the specific features of a

* Corresponding author.
E-mail address: lukas.gritsch@fau.de (L. Gritsch).

https://doi.org/10.1016/j.msec.2018.09.038
Received 29 January 2018; Received in revised form 14 August 2018; Accepted 11 September 2018
Available online 13 September 2018
0928-4931/

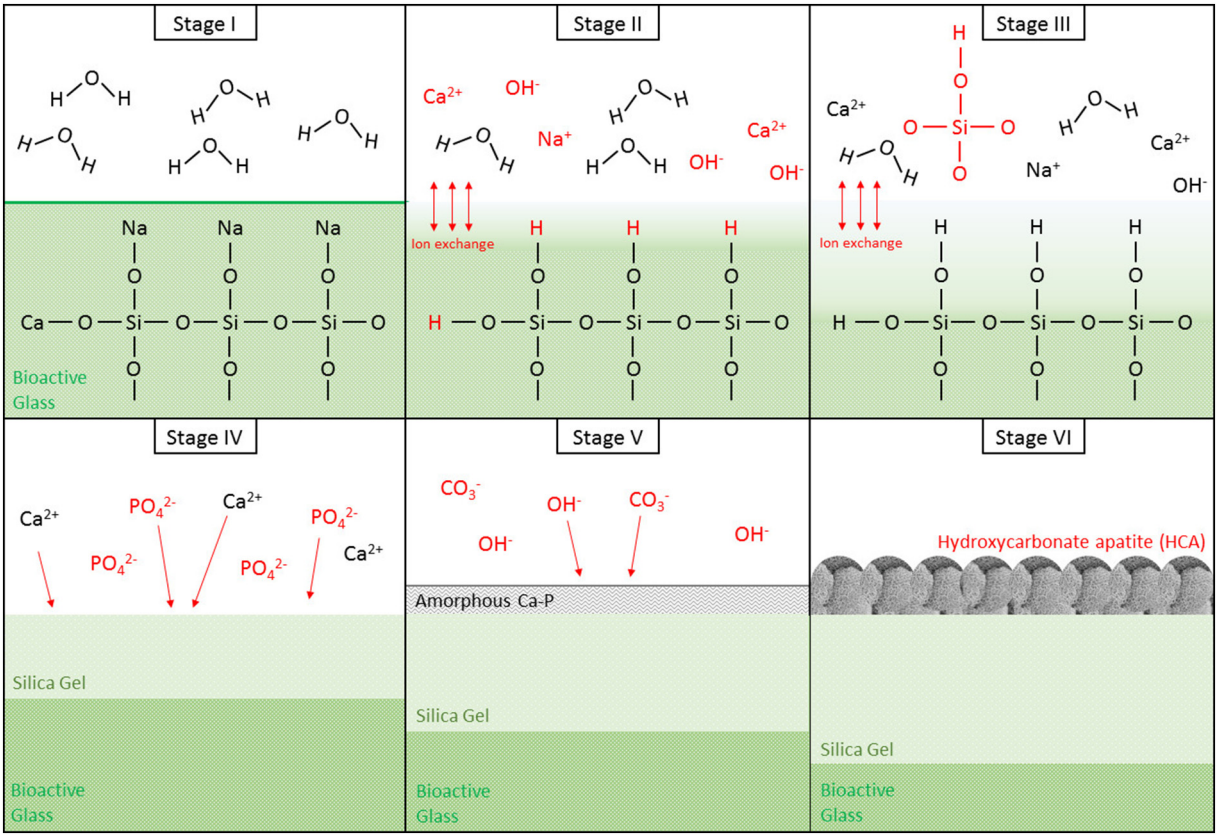

Fig. 1. Illustration of the mechanism of hydroxycarbonate apatite (HCA) formation on the surface of a bioactive glass in contact with body fluids: the surface modifies into an open-structured silica gel exchanging ions with body fluids (Stages I to III). Calcium and phosphate ions arrange into an amorphous calcium phosphate layer (Stage IV). Then the CaP layer incorporates hydroxyl and carbonate ions, determining the crystallization of HCA (stage V).

bioactive material will highly depend on the tissue it is targeted for. For instance, the term bioactivity is often associated with bone regeneration and, more specifically, with biomineralization, the process of deposition of hydroxyapatite crystals on the surface of biomaterials in order to achieve the attachment of bone cells and the formation of mature bone [6,7]. This link between bioactivity and bone gradually developed when the adjective *bioactive* started to be strongly associated with the family of SiO_2-Na_2O-CaO-P_2O_5 glasses discovered by Larry Hench in the late sixties [8] and to a few other bone-bonding glass-ceramic materials [2,9]. In this context, a device will be called bioactive if it is able, once in contact with living bone tissue or a simulated body fluid (SBF) [10], to specifically guide the crystallization of calcium phosphate salts towards hydroxyapatite, thus promoting the link between artificial and natural components. For instance, Fig. 1 shows the mechanism of bioactive mineralization for biosilicates [11].

This trend of linking bioactivity exclusively with bone tissue is clued by the significantly higher amount of publications that feature the terms “bioactivity” and “bone” compared to other tissues (source: PubMed and Scopus). Nevertheless, it is in fact conflicting with the actual definition of bioactivity as the property of enhancing the tissue-medical device interface.

Specifically referring to biomaterials and tissue engineering (TE), a bioactive scaffold or other TE device can be defined as a structure with an integrated biological functionality that supports and modulates cell growth and the subsequent regeneration of tissue. In other words, a bioactive tissue engineering scaffold will positively regulate cell and tissue response, determining a more effective communication and integration with the host organism, regardless of the type of tissue [3]. The entity of this bond between the material and the targeted tissue can be quantified by the bioactivity index (I_B), introduced by Hench in 1988 and defined as follows, where $t_{0.5\ bb}$ is the time required for > 50% of the interface to be bonded:

$$I_B = \frac{1}{t_{0.5\ bb}}$$

Contrary to expectations, the bioactivity index of bioactive glasses and glass-ceramics is reported to present a threshold level (i.e. $I_B > 8$) beyond which this class of materials bonds with soft tissues as well (Fig. 2). This suggests that, even though the contribution of studies that investigate bioactivity as enhancement of mineralization is fundamental, two main conclusions can be drawn. Firstly, that scientific literature has primarily focused on bioactivity towards inorganic materials for bone. We believe this is a consequence of the raise of the concept of *bioactive material* within Hench's study on bone regeneration. Secondly, there is a vast less explored area of bioactive materials meant to target soft tissues. As a matter of fact, latest research on bioactive glasses is branching from the traditional bone tissue engineering path to novel and innovative applications targeting soft tissues, such as nerves and skin, and to the investigation of the effect of bioactive glasses (BGs) on angiogenesis [13,14].

There is an interesting branch of the biomedical field investigating the optimization of tissue-material interface (i.e. bioactivity) of polymer-based systems for diverse tissue engineering applications [15,16]. However, no review paper has been found to report on the strategies used to improve the host/implant interface performance of one of the most used materials for biomedical applications: polylactic acid (PLA). Polymers derived from lactic acid have been largely adopted in the biomedical field, since they are versatile, tunable and relatively low-cost, however they lack intrinsic bioactivity (as per the definition above) and they necessitate the development of tailored technologies to improve their bond to tissues.

In this review we present an overview on the latest and most

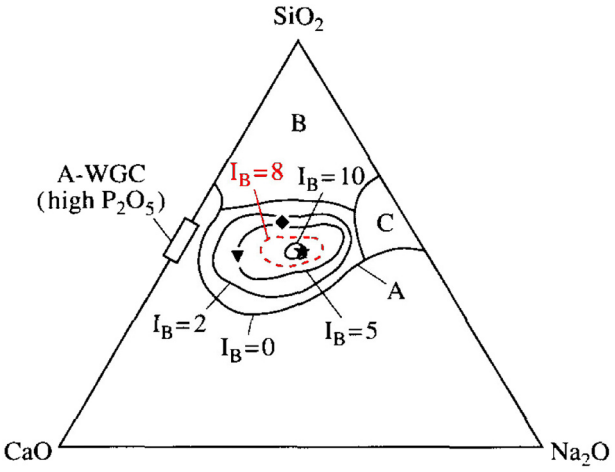

Fig. 2. Compositional dependence (in weight percent) of bone bonding and soft-tissue bonding of bioactive glasses and glass-ceramics. The region highlighted in red is the soft-tissue bonding region, where $I_B > 8$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Adapted from reference [12]. Reproduced with permission of John Wiley and Sons.

promising strategies to improve the bond between tissue and material of lactic acid-based tissue engineering devices. In particular, whenever possible, we have covered literature beyond bone and cartilage, focusing on a broader definition of bioactivity and identifying those applications in which polylactic acid is modified in order to enhance the interaction with any kind of tissue (both soft and hard). We will principally discuss studies that conducted analyses with the intent of achieving bond improvement (e.g. bioactivity testing, collagen deposition, histologies). Moreover, since bioactivity is generally defined as an intrinsic property of a material we intend to sum up approaches that can be defined as "bulk strategies": therefore this review will avoid describing more pharmaceutical-based approaches such as surface modifications with biomolecules or other species, addition of growth factors (GF) and drug delivery devices. These topics are already discussed in-depth in recent reviews [17,18].

2. PLA synthesis and properties

2.1. PLA: biocompatible, bioresorbable and not bioactive

In the past fifty years PLA has attracted considerable attention as a structural material for biomedical applications thanks to its biocompatibility, biodegradability, mechanical properties and versatility. However, when PLA was first synthesized in 1932 by Wallace Carothers (renowned for the development of nylon), it was initially considered a failure because of its lack of long term stability and especially because of its extremely high production costs [19]. PLA was then abandoned until 1954, when DuPont patented the synthesis process and started to commercially synthesize the polymer [19]. In the sixties PLA started to raise interest as a candidate material for medical applications such as sutures and bone implants [20], but the wide production of PLA was still unsuitable due to elevated fabrication costs. From then on the advances in the fermentation of glucose to produce lactic acid together with the development of manufacturing techniques that exploit renewable agronomic resources (e.g. sugar cane, corn starch) determined an exponential growth in industrial interests towards PLA. Its degradability, which at first was considered a disadvantage, gradually turned into its most interesting property for broad consumption (e.g. disposable packaging, hygiene products, diapers and even clothing) as well as for high-tech biomedical devices. Particularly relevant was the work of Langer and Vacanti, who started investigating the suitability of PLA as base material for the fabrication of tissue engineering scaffolds [21]. In the same years Vert and coworkers conducted an in-depth investigation of the degradation behavior of PLA and other similar aliphatic polyesters, highly contributing to the explanation of the phenomenon [22–24]. For instance they are responsible for the description of the commonly accepted model, based on diffusion-reaction phenomena combined with autocatalytic effect, which explains how and why massive PLA devices often incur failure [23].

Currently, the worldwide production of PLA peaks at > 300k tons per year, mostly coming from a few major manufacturers.

As schematized by Xiao et al. [25], there are five main advantages that favor the growth of polylactic acid-based technologies within the biomedical field: (i) unlikely many other biomaterials, several products have been approved by the FDA for direct contact with biological fluids already in the 1970s; (ii) nowadays PLA is obtained from renewable resources at relatively low costs; (iii) PLA is easily thermally processable compared to other similar polymers (typical forming processes involved are film casting, foaming, extrusion and fiber spinning); (iv) PLA needs low energy consumption during its production; (v) PLA is biocompatible and not toxic both in solid form and when degraded.

However, with these many positive characteristics some drawbacks come along. The principal disadvantages of polylactic acid are that (i) its hydrolysis degradation rate is too low for numerous applications, both industrial and biomedical, and (ii) it is usually brittle. However, to overcome these limitations the neat polymer can be modified by adding or blending other species. A major drawback is the fact that (iii) PLA is strongly hydrophobic, potentially eliciting inflammatory response when implanted because of scarce interaction with the cells. Moreover, the acidic byproducts of degradation can also intervene in the setting of an inflammation. Altogether, PLA can be considered a non-bioactive polymer. In PLA-based biomedical devices additional bioactivity has to be provided by other components since the base polymer does not effectively promote the link with the tissue by itself. This goal can be achieved via diverse strategies that must be tailored depending on the specific target tissue. Some relevant approaches are blending [26], fabrication of composites, including nanocomposites [27,28], surface bio-functionalization [29,30], and plasma treatments [31].

2.2. Synthesis of PLA

PLA is a biodegradable thermoplastic aliphatic polyester. Its precursors (i.e. lactic acid monomers or lactides) are routinely produced by fermentation of renewable agricultural sources; therefore, they can be produced at relative competitive cost and energy expense compared to other similar materials. Lactic acid is a small 2-hydroxycarboxylic acid. It has a chiral carbon atom and exists in two stereoisomers: L-lactic acid and D-lactic acid enantiomers (S and R respectively), as shown in Fig. 3.

The lactic acid is industrially synthetized by hydrolysis of lactonitrile, generally formed by the addition reaction of acetaldehyde and hydrogen cyanide. As a function of the lactic unit, different lactide can be obtained (Fig. 4). The typical way to produce the lactide is by

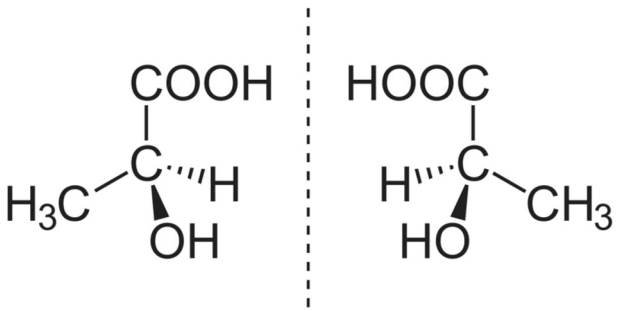

Fig. 3. Stereoisomers of lactic acid. Respectively (S)-(+)-lactic acid on the left and (R)-(−)-lactic acid on the right.

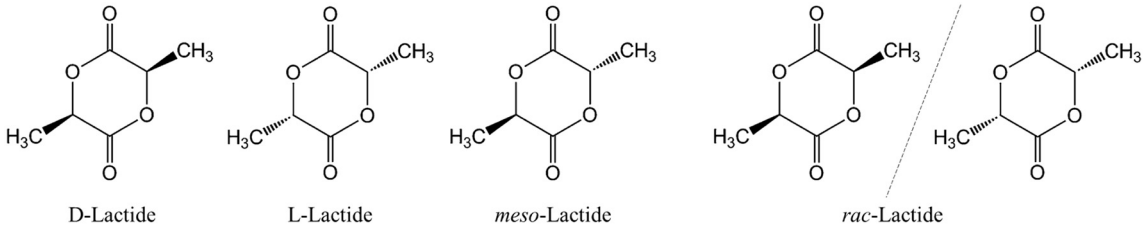

Fig. 4. Stereoisomers of lactides.

depolymerization of the corresponding oligo(lactic acid) (OLLA) obtained by polycondensation of the lactic acid. This reaction is catalyzed by metal compounds of Sn, Zn, Al, etc. Then, the crude lactide is purified by melt crystallization or recrystallization from solution.

There are two main synthetic routes to produce PLA: (I) Direct polycondensation of lactic acid and (II) Ring-opening polymerization (ROP) of lactide. The first process was established by Mitsui Chemicals Co. (Japan) in 1995, wherein lactic acid and catalyst are azeotropically dehydrated in a refluxing, high boiling point, aprotic solvent such as diphenyl ether. To obtain very high weight-average molecular weight PLA the process is conducted under reduced pressure in order to decrease the amount of water of PLA in the polycondensation [32]. This method is especially effective for the co-polycondensation of L-lactic acid (PLLA) with other monomers (hydroxyl-acids and diol/dicarboxylic acid combinations). The ring opening polymerization method is mostly used for high throughput industrial production. It is convenient for controlling the molecular weight of PLLA and achieving a high molecular weight polymer (Mw > 10^6). NatureWorks LLC (USA) or Hisun (China), for instance, produce PLA by this synthetic route. Fig. 5 reports the stereoisomers of the polymer starting from D-lactide and L-lactide.

The polymerization of pure L- or D-lactides gives isotactic homopolymers of, respectively, PLLA and PDLA. This phenomenon gives several possibilities of tuning the properties of the polymer depending on its final application [33]. If the starting compound is pure, L or D stereoisomer, the final product is semicrystalline and it shows a melting temperature around 180 °C. A decrease of the purity of L- and D-lactide means a reduction of crystallinity and T_m. If the reagents are rac- and meso-lactides the resulting polymer is called PDLLA, which is a racemic, atactic sequence of D and L monomers. PDLLA has no crystalline component and it is completely amorphous. Following the ROP route many copolymers can be produced starting from PLLA or PDLA. The synthesis of stereoregular PLA is a novel and effective strategy to tailor its properties even more precisely [34]. The stereo-regularity of D- and L-monomers can be finely controlled unit by unit. In this way, by changing the chain length and/or the block succession, it is possible to tune the mechanical and physical properties (degradation rate, crystallinity, melting temperature).

One of the most important features in food or liquid packaging polymers is their permeability to gases, water vapor and aroma molecules. This is also true for polymers used to fabricate scaffolds. Bao et al. [35] studied the properties of PLA (L/D ratio of 98.7/1.3) in terms of gas permeation and activation energy of N_2 (nitrogen), O_2 (oxygen) and CO_2 (carbon dioxide) at 30 °C. The authors reported permeation values that are lower than other similar materials, highlighting a possible optimization pathway for PLA based materials.

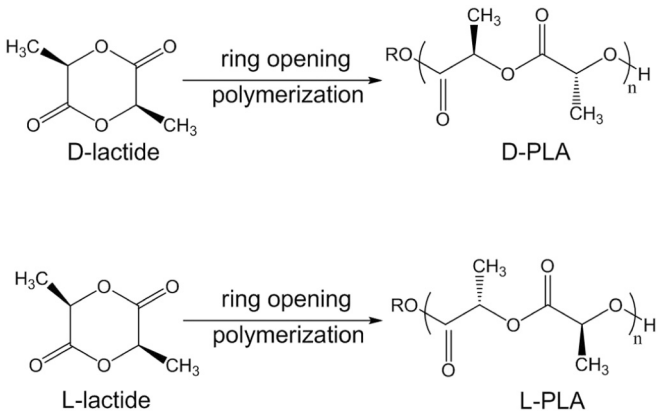

Fig. 5. Stereoisomers of the polymer starting from different lactides.

2.3. Degradation of PLA

The possibility to finely tune the degradation behavior of PLA is a key feature in the development of effective biomedical devices. For this reason, during the years the degradation behavior of this family of polymers was thoroughly investigated and rich literature is available on the topic [22–24,36–40]. It is now commonly accepted that the phenomenon that leads to degradation of PLAs is simple proton catalyzed (i.e. the degradation is a strong function of pH [39]) hydrolytic chain-scission. Other parameters affecting degradation are temperature, molecular weight, chain ending groups and chain stereo-configuration among others [39,40]. According to Zhang et al. [40], a main variable affecting the kinetics of PLA degradation is the purity of the polymer. Briefly, while PLAs characterized by low purity and the presence of low molecular weight compounds follow first order kinetics, the degradation of polymers subjected to purification treatments is characterized by the presence of an initial lag phase and by third order kinetics. Furthermore, the crystallinity degree determines degradation rate and autocatalysis, being the latter a major degradation phenomenon of amorphous domains [36]. In parallel with hydrolytic degradation, there seems to be a contribution to degradation by enzymes when PLAs are subjected to a biological environment. However, it is not clear yet if enzymes are directly responsible for an increase in degradation rate or if they only indirectly contribute to it by enhancing the removal of by-products [36].

3. PLA applications

Poly(α-hydroxy acids), and in particular PLA, have shown large potential for biomedical and pharmaceutical applications in the last decades [36,41]. Various studies ~~have~~ investigated in-depth the mechanical and degradation properties of PLA, exploiting its characteristic of degrading into species that can be eliminated via the normal Krebs cycle to develop a vast amount of biomedical technologies [42–45]. Different techniques have been used to process PLA, with various enantiomer compositions, into porous biodegradable scaffolds: among others particulate leaching [46], phase separation [47–50], electrospinning [51] and 3D micro-printing [52]. Moreover, polylactic acid, especially in combination with polyglycolic acid, was studied as a drug delivery carrier [53]. It was adopted as a carrier for many species such as bovine serum albumin (BSA) [54], triclosan [55], lysozyme [56], leuprolide [57], insulin [58,59], ketoprofen [60]. PLGA copolymers are especially suitable for drug delivery since the addition of glycolic monomers speeds up the degradation. The general rule states that the degradation rate and the glycolic acid monomers content are directly

proportional with the exception of 50:50 PLGA, which shows the fastest degradation time (i.e. circa 1–2 months) [61,62]. PLA has been processed into fibers [60], films [44], microparticles or microspheres [63], micelles [53] and hydrogels [64]. The possibility of combining it to form copolymers was also studied: several works presented copolymers: PLA-polyethylene glycol [53,65], PLA-polyglycolic acid [52], PLA-polycaprolactone [66,67] and more.

In this review we chose to illustrate the principal applicative strategies that aim to enhance the tissue-material interface properties (i.e. bioactivity) of PLAs following a well-known materials science dichotomy: inorganic (ceramic) and organic (polymers) materials. For clarity, inorganics and organics will be further classified into well-known categories (e.g., bioactive glasses, metal oxides, and so on). Selected case studies that distinguish themselves for outstanding performances in optimizing the bond between tissue and device will be presented and discussed.

3.1. Combination of PLA with inorganic materials

Manufacturing micro or nanocomposite materials for tissue engineering by combining the bioactivity and mechanical proprieties of ceramics (as fillers) with the high processability and flexibility of polymers (as matrix) is probably one of the most widespread and explored route to produce synthetic scaffolds that successfully support tissue regeneration [68–70]. Indeed the composite approach is one of the most known and effective techniques to enhance bioactivity, as defined in Section 1.1. Practically, every kind of inorganic material that could have a bioactive effect was already studied as filler. And since polylactic acids are a well-known class of polymers, FDA approved for several applications in direct contact with biological fluids, many of these studies have considered PDLLA, PLLA, PLGA or similar polymers as the matrix phases. Due to the rigid mechanical nature of most ceramics, these technologies are mostly (but not exclusively) suitable for bone tissue regeneration. The use of inorganic fillers in a polymeric matrix has mainly three goals: (i) triggering biomineralization as a phenomenon that helps the successful bond between bone tissue and material, (ii) enhancement of the original mechanical properties of the polymeric phase and, (iii) fine tuning of the degradation of the scaffold. The release of ions such as Ca, Mg and Si could stimulate osteoblast proliferation and differentiation, as already discussed in the introductive section of this article. Furthermore, the addition of an inorganic phase to a biodegradable polymer may alter the in vitro and in vivo degradation rates of the polymer phase, providing additional tuning properties. For instance, the dispersion of alkaline ions in water from a ceramic phase such as wollastonite or bioactive glass can determine a local pH buffering effect that reduces the rate of hydrolysis of the matrix polymer and, in the case of PLA, consequently reduces the risk of inflammation that could occur due to excessive pH reduction [71]. The inorganic materials used to improve the bioactivity of PLA can be mainly divided into four categories: calcium-based, bioactive glasses, carbon nanostructures and metal oxides.

3.1.1. Calcium-based inorganic fillers

In this review we define a calcium (Ca)-based class of ceramic fillers that give bioactive characteristics to PLA based matrices. Ca-based PLA fillers reported in literature are mainly formulations of calcium-phosphate (CaP) salts (e.g. hydroxyapatite and β-tricalcium phosphates) [72–75], calcium silicates [76] such as wollastonite ($CaSiO_3$ mineral containing also small quantities of iron, magnesium, and manganese) [77,78] and diopside ($MgCaSi_2O_6$) [79,80] (Table 1). Okada et al. [78] presented a study that highlights the efficacy of the combination of the high processability of PLA with the ability of wollastonite to induce the precipitation of ECM mineral phase. The group prepared and tested three different protocols – casting, spin coating and hot pressing methods – to combine the polyester with $CaSiO_3$ particles in order to obtain the same level of bioactivity reducing the amount of filler as much as possible. The bioactivity was evaluated by incubation in SBF for 14 days and subsequently a morphological scanning electron microscopy (SEM) study was performed in order to identify characteristic hydroxycarbonate apatite (HCA) structures. Ca, P and Si ion release assays were also performed. The results showed an increase of bioactivity from casting to spin coating to hot pressing method. The composite scaffolds prepared via hot pressing method showed the fastest rate of apatite formation compared to the other methods probably due to the direct exposure of $CaSiO_3$ particles on the surface of the composites to the SBF fluid [78]. In addition to the aforementioned fabrication techniques, PLA can be processed in several other ways. A popular technique among tissue engineering applications is electrospinning, a method that allows the production of non-woven fibrous mats that were proven to be a very promising substrate for cell growth. For instance, Dong et al. [76] reported an effective fabrication of composite nanofibers of PLA with another type of calcium silicate (i.e. belite, Ca_2SiO_4) via electrospinning. The results of the characterization on scaffolds produced with this approach proved that, compared to bare PLA fibers, composite structures favor cell activity and the formation of new ECM. Successful formation of HA crystals occurred while cell proliferation and alkaline phosphatase (ALP) secretion increased (Fig. 6). In particular, the secretion of ALP is an important sign of osteoblast activity and thus a sign of the activation of cells towards an effective bonding of the material with new, mineralized ECM.

In a similar recent study, a nanofibrous PLA mat was coated with a calcium silicate powder suspended in a chitosan slurry. When cultured on these composite mats, mesenchymal stem cells responded with increased secretion of collagen type I and fibronectin compared to polylactide-only mats. In addition to this, genes that correlate with hard tissue formation (alkaline phosphatase, ALP) and osteogenic differentiation (osteopontin, OPN and osteocalcin, OC) were overexpressed in comparison with control PLA samples [81].

Similarly to calcium silicates, diopside (DP), a pyroxene mineral with chemical composition $MgCaSi_2O_6$, is adopted in bone and periodontal tissue engineering for their excellent osteogenesis/cementogenesis [79,80]. Composite PLLA/diopside scaffolds were fabricated via solvent casting and particulate leaching, using an inorganic phase with average pore size of 400–500 μm at 20% and 40% wt/wt DP/PLLA ratios [79]. In vitro degradability, bioactivity and in vivo osteogenesis of the scaffolds were investigated. White rabbits with an induced defect in the left leg were chosen for the in vivo investigation. The results showed that the addition of DP into PLLA improved the in vitro degradability and biomineralization according to the concentration. The composite scaffold also enhanced ALP activity of osteoblast cells in vitro and, coherently, the formation of new bone in vivo. Overall, the results of the studies on PLA/DP composites show that this approach can improve the bioactivity and the tissue/material interface compared to the bare polymer not only in vitro, but also and more interestingly in an in vivo experimental set-up.

Among other Ca-based materials, calcium phosphates (CaP) are highly interesting because of their affinity with the natural components of bone matrix and because of their excellent osteoconductivity [82]. CaPs are biocompatible and present high affinity for proteins able to stimulate proliferation and differentiation of osteoprogenitor cells, such as BMP-2 [83], thus promoting the integration of the medical device with the surrounding tissues. As a function of the ratio between calcium and phosphate (Ca/P) it is possible to distinguish several compounds: (I) hydroxyapatite (HA), chemical composition $Ca_5(PO_4)_3(OH)$ and $Ca/P = 1.67$; (II) β-TCP, chemical composition $Ca_3(PO_4)_2$ and a $Ca/P = 1.5$, and (III) biphasic calcium phosphate (BCP), which refers to blends of HA and β-TCP without specific ratio. CaPs ceramics can be combined with polymers to create composites with or without chemical surface modifications [84]. When CaPs are combined into a composite scaffold usually their degradation rate is slower than the one of the polymer, this allows an optimal balance between cell proliferation and infiltration, new tissue formation, biomineralization and the

Table 1
Selected strategies to enhance PLA bioactivity using Ca-based fillers.

Filler	Type of polymer	Technique	Applications	Advantages	References
CaP	PDLLA	Monolithic composite with TCP microsphere	Bone tissue regeneration	Better bone-to-implant contact in a rabbit model	Shin [87]
	PDLLA	Monolithic composite ——— Coating	Bone graft substitutes	Beneficial effect of CaP towards osteogenic differentiation of hMSCs	Tahmasebi Birgani [73]
	PLLA	Particulate leaching	Bone tissue engineering	Increase in bioactivity and mechanical properties	Kang [72] Lou [75]
	PLLA	Electrospinning	Bone regeneration mats	Optimal stem cells differentiation	D'Angelo [74]
	PLGA	Brushite composite with polymeric micro-extruded fibers	Load bearing bone cement	Improved mechanical properties that stimulate bone formation in vivo	Maenz [89]
Wollastonite ($CaSiO_3$)	PDLLA	Solvent casting	Bioactive films	Improved bioactivity and mechanical properties	Ye [77]
	PDLLA	Solvent casting ——— Spin coating ——— Hot pressing	Scaffolds for TE	Bioactive with minimal amounts of filler	Okada [78]
Belite (Ca_2SiO_4)	PLLA	Electrospinning	Bone tissue engineering	Increased ALP activity and expression of ALP, BSP and OCN genes	Dong [76]
Diopside ($CaMgSi_2O_6$)	PLLA	Solvent casting ——— Particulate leaching	Bone tissue engineering	Increasing of degradability and bioactivity	Liu [79]
Amorphous calcium silicates	PDLLA	Electrospinning ——— Coating	Bone regeneration	Increased secretion of collagen I and fibronectin. Increased expression of ALP, OPN and OC genes	Su [81]
	PDLLA	Particulate leaching	Bone tissue engineering	Expression of osteogenic genes (collagen type I, OPN, OC and ALP)	Jin [174]

simultaneous resorption of the implant [85]. Furthermore CaPs release degradation products tend to precipitate as carbonated apatite, a substance with similar composition and chemical structure to the mineral phase of physiological bone tissue [86]. The beneficial effects of the degradation of CaPs was evaluated in vivo by Shin et al. [87] in a recent publication. The study reports the results of a 16 weeks implantation in a rabbit femoral model, showing enhanced bone-to-implant contact ratio using a composite of TCP microspheres and PLA compared to a commercially available TCP-based bone filler. The authors claim that this increase in tissue-material interface is a consequence of the pores generated near the surface during the degradation of the composites [87].

There are numerous studies investigating the bioactivity of composites of polylactides and CaP [73,87–89]. As an example, Kang et al. [72] performed in vitro test in dynamic SBF fluid to test the effect on bioactivity of β-TCP/PLLA composites. Scaffolds made combining β-TCP and PLLA were fabricated via particulate leaching and had an average porosity of 200–400 μm [72]. Two set of bioreactor-aided in vitro tests were performed. These experimental set-ups allow in vitro experiments with conditions that are closer to a real biological environment. In one case the scaffolds were immerse in a dynamic flow chamber of SBF at 37 °C and a flow rate of 2 ml/100 ml min, a value close to the physiological blood flow rate in bone tissue; in the second case a dynamic loading of 0.6 Hz and 0.1 MPa was also added. The experiments in both cases lasted 6 weeks and the outcomes were characterized in terms of morphology, weight loss and compressive strength. The results showed a good formation of apatite in all conditions with an increase of biodegradation rate on the scaffold with mechanical loading [72].

An unusual, but yet effective approach for the fabrication of bone tissue engineering scaffolds was recently proposed as a valid alternative to popular calcium phosphates based technologies. PLA can be combined with naturally occurring calcium carbonates from the shell of various mussels. These calcium carbonates can be either isolated from natural sources [90] or synthetized *ex novo* [91]. In a case study by Liu et al. [90] three compositions have been investigated: PLLA combined with nacre, aragonite and vaterite. Freeze-dried PLA foams with microparticles of calcium carbonates (~50 μm) were obtained from nacre of different species of shells. The results showed that both aragonite and nacre (but not vaterite) increased the proliferation and ALP activity of osteoblasts at competitive levels compared to more established calcium phosphate technologies. This result, together with the documented enhancing ability of nacre towards biomineralization [92], confirms that nacre can be a promising filler of biodegradable polyesters to develop osteoconductive composite scaffolds for bone regeneration.

3.1.2. Bioactive glasses (BGs)

Bioactive glasses (BGs) have been investigated in many studies as solution for tissue engineering challenges thanks to their ability to induce the expression of genes that regulate osteogenesis, angiogenesis [93,94] and to enhance the production of relevant growth factors (GFs) for the repair of tissues [95,96]. The strongest advantage of BGs is that they have a particularly strong and established way of eliciting a positive biological response towards the formation of new, well-connected tissue in the absence of growth supplements [97].

The first bioactive glass, produced in the late 1960s, is the so called 45S5, characterized by a chemical composition of 45% SiO_2, 24.5% Na_2O, 25.4% CaO and 6% P_2O_5 (wt%) [9] (see Section 1.1). In the last five decades, in order to increase its processing characteristics maintaining optimal bioactivity, several other BG compositions have been developed. For instance "1393" and "6P53B" glasses with K_2O and MgO, 58SBG with a higher amount of CaO or boron containing compositions such as 1393B1 and 1393B3 [98]. Apart from the main composition of the vitreous structure, which leads to silicate, phosphate and borate BGs, an effective strategy to produce optimal bioactive glasses is by doping with small quantities of biologically active metal ions with therapeutic effects (e.g. osteogenesis, angiogenesis, antibacterial activity) [99]. The most common field of application of BGs in tissue engineering is in bone and tooth repair and regeneration, exploiting their ability of enhancing biomineralization, osteoconduction and osteostimulation [100–102]. Nevertheless in recent years the use of BGs as filler in polymeric network raised increasing attention also in the regeneration of soft tissues [13,103]. Wilson et al. [104] first studied

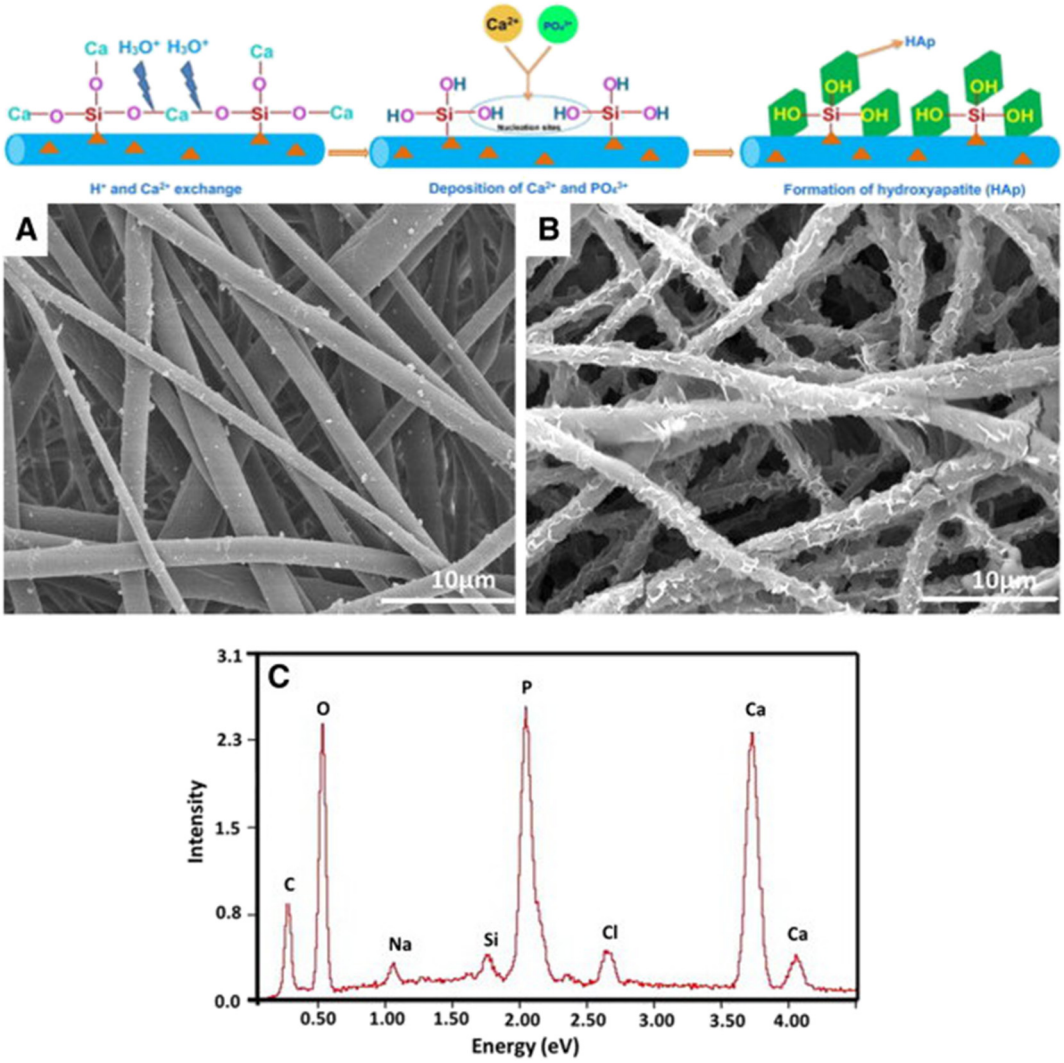

Fig. 6. Schematic representation of the formation of hydroxyapatite on PLLA/Ca_2SiO_4 electrospun fibers (top). SEM micrographs of the fibers before and after immersion in SBF (middle) and EDX spectrum of the scaffolds showing high peaks for calcium and phosphorus (bottom).
Adapted from reference [76]. Reproduced with permission of Elsevier.

the possibility of bonding between BGs and soft connective tissues. Interestingly, the hydroxycarbonate apatite (HCA) crystallites formed on BG surfaces can bond to chondral interface metabolites and specific ion dissolution products can promote and regulate angiogenesis. In more recent years other publications reported the positive effects of BGs on the formation of healthy fibroconnective tissue. For instance, Bi et al. [98] assessed the performance of an array of bioactive glasses (45S5, 1393, 1393B1 and 1393B3) in vivo in terms of bone regeneration, angiogenesis and hydroxyapatite conversion. Their results concluded that 45S5 was characterized by the highest pro-angiogenic effect while the best bone formation performance was the one of 1393B1. Similarly, Arkudas et al. [94] recently published an in vivo study showing the pro vascularization potential of 45S5 Bioglass®. Angiogenesis is a key feature and one of the main bottlenecks in the achievement of successful bond between scaffold and the surrounding biological environment. In an innovative sol-gel approach, organically modified glass (Ormoglass) and PLGA were blended in trifluoroethanol (TFE) and electrospun into nanofibrous mats for guided regeneration [105]. The degradation behavior of these mats leads to the leaching of essential ions, first of all calcium, which in turn locally regulate and enhance angiogenesis [105–107]. The pro-angiogenic potential of BGs could come in handy to overcome the problem and take tissue engineering to a new level. Two reviews on soft tissue engineering applications of BGs, have been published, listing achievements and possible future trends [13,103]. In parallel also reviews summing up the countless applications of BGs in bone tissue engineering are available. In particular we would like to highlight recent comprehensive literature reviews of bioactive glass scaffolds for bone tissue engineering [108–110] and polymer/BGs composites [110–112].

Bioactive glasses have been extensively combined with PLA [113–117] (Table 2). Different strategies have been adopted to integrate BG fillers into PLA to enhance the bioactivity and tissue-material bond of the pure polymer, including: freeze-extraction techniques [118], modified phase separation protocols [48], previous treatment of BG with 3-aminopropyltrimethoxysilane (APS) or polydopamine [119] to increase the bond polymer/filler [120], blend of PLA/PCL [121], BG-coated PLA/chitosan [122] and combination of BG with TiO_2 [123], among others. Blaker et al. [117] for instance reported, in a series of publications, their studies on the integration of BGs into porous PDLLA matrices fabricated via Thermally Induced Phase Separation (TIPS). Composite samples were fabricated with different concentrations of BG from 5% to 40%. An in-depth investigation on these scaffolds was carried out in order to validate their performance as bone tissue engineering devices, which included investigation of bioactivity [117,124], cell cultures with human osteosarcoma cells [116,117] and human bone marrow cells [125], in vitro degradation [124,126],

Table 2
Selected strategies to enhance PLA bioactivity using bioactive glass fillers.

Filler	Type of lactide	Technique	Applications	Advantages	References
BG	PLGA	Salt leaching	Regeneration of bone defects	Increase of collagen secretion Enhancement and modulation of osteogenesis in vitro depending on the composition of the glass Induction of ectopic bone formation in vivo	Filipowska [175,176] Pamula [177]
	PDLLA	Thermally Induced Phase Separation (TIPS)	Scaffolds for TE	Tuning of degradability, mechanical properties, biodegradation and cell viability Increase in bioactivity	Blaker [113,115,117] Maquet [124] Verrier [116] Yang [125]
	PDLLA	Solvent casting	Membranes	Spatial distribution of filler	Leal [127]
	PLA/PCL 50:50 (v/v)	Electrospinning	Membranes	Production of submicron fibrous BBG-containing membranes	Rowe [121]
	PLGA 75:25 (v/v)	Immersion precipitation	Nerve guidance conduits	Peripheral nerve regeneration and protection Therapeutic ions release	Zhang [178–181]
	PCL/PDLLA 70:30	Salt leaching	Soft and hard tissue engineering	No inflammation Formation of healthy connective tissue Ectopic bone formation	Meretoja [128]
Ormoglass	PLDLLA 70/30 L-lactide/DL-lactide	Sol gel blend electrospinning	Vascularized tissue engineering	Ideal pH and Ca^{2+} release for the stimulation of angiogenesis	Sachot [105]
BG/TiO_2	PDLLA	Solvent casting	Films	Increasing of bioactivity	Wei [123]
BG treated with APS	PLLA	TIPS	Scaffolds for TE	Increasing of the bond polymer/filler	Zhang [120]
Mesoporous BG treated with dopamine	PLLA	Selective laser sintering	Soft and hard tissue engineering	Improved hydrophilicity and bioactivity Increased cell adhesion, proliferation and ALP activity	Xu [119]

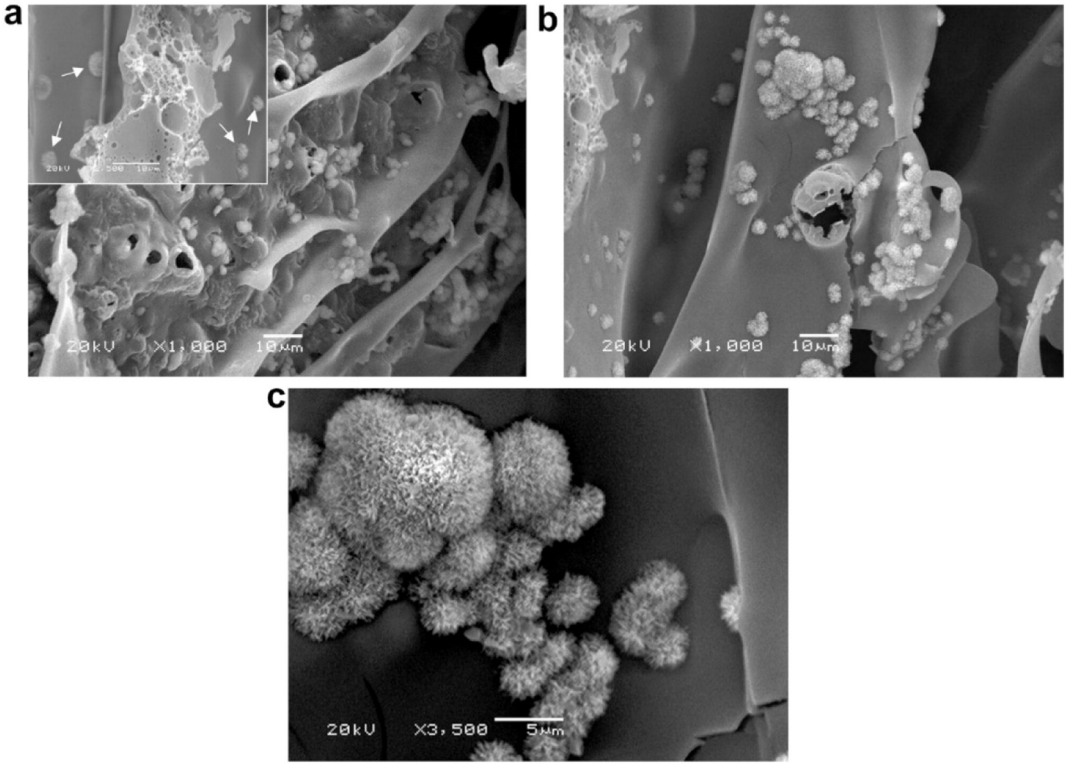

Fig. 7. SEM micrographs of PDLLA foams with 30% of Bioglass® after 600 days in SBF. (a) Evidence of severe blistering on the surface of the pore walls. The blistering appears both distal and proximal to the HA particles. A section of the pore wall is shown at high magnification (inset), revealing the HA particles on the pore wall (arrowed). (b) Transverse section, showing HA particles proximal to blister formation. (c) HA particles shown at high magnification.
Reproduced from reference [113] with permission of Elsevier.

porosity assessment [124], thermogravimetric analysis [115], mechanical testing [115] and long term in vitro degradation (up to 600 days) [113] (Fig. 7). Regarding the investigation on the bond between scaffold and tissue, SBF tests were carried out up to 28 days and specimens analyzed via SEM, XRD and Raman spectroscopy: the analyses confirmed the ability of the scaffolds to trigger the deposition of HA on their surfaces. In particular, as expected, after 28 days a continuous HA layer of 7 µm in thickness was found on the specimens containing the highest amount of BG (i.e. 40%). A similar PLA/BG composite was also used to produce membranes for tissue engineering [97]. Asymmetric membranes (PDLLA/BG), in terms of different distribution of BG on the two sides of the membrane, were produced via

solvent casting [127]. One side of the membrane is richer in BG, specifically developed to be in contact with the tissue defect and stimulate its regeneration thanks to ion leaching. The other side has less BG and acts as a barrier from the external environment (i.e. other tissues). Bioactivity tests after 21 days showed an asymmetric distribution of the HCA layer on two sides of the membranes, regular coating on the BG richer side and a smooth surface on the BG-free layer. Another form of PLA/BG composite scaffolds has been recently reported by Goh et al. [122]. Electrospun PLA/chitosan blended fibers were dip-coated with BG. After immersion in SBF solution for 7 days, apatite was formed and fully covered the entire surface of fiber mat, indicating an enhancement of bioactivity of polymer by an incorporation of BG. A further enhancement of the fabrication of composites of PLA and BG is the modification of one of the two components (usually BG) with 3-aminopropyltrimethoxysilane (APS), a molecule capable of bonding both the organic and inorganic phase of the composite and thus improving the interface between the phases [120]. Similarly, the interface between a mesoporous bioactive glass (mBG) and PLLA was improved by crosslinking dopamine on the surface of the mBG [119]. The improvement of the interface between the two phases of the composite was identified as a key feature in order to tailor the long term degradation behavior of the polymer [113]. These findings suggest that PLA/BG composites, thanks to their tunable degradation and optimal enhancement of biomineralization, are structures characterized by optimal bioactivity and interface properties in bone tissue engineering applications. These beneficial properties of BGs and their composites are well-established and make them very promising candidates for tissue engineering. However, there is still a lot of room for improvement. Especially, as already mentioned, BGs can improve the development of soft tissues. In this direction, polyester-based (i.e. copolymers of PLA and PCL) scaffolds with a particulate bioactive glass filler (particle size $< 45\,\mu m$) were implanted subcutaneously in a rat model to evaluate the entity of the bond development with surrounding tissues, both soft and hard, in an in vivo set-up. Results after 4 weeks of implantation revealed no major inflammatory response, minor host response and overall good biocompatibility. Moreover, the scaffolds, especially the ones with BGs, where characterized by optimal cell and ECM infiltration that determined the formation of new, well-vascularized connective or bony tissue. Specifically concerning bone tissue, the biomineralization after 12 weeks in scaffolds with BGs increased sevenfold. These results suggest that PLA/BG scaffolds are candidates to achieve an optimal bond between material and tissues, being the latter both soft and hard [128]. In particular, some authors propose the application of these systems in areas where the device must bond both to soft and hard tissue at the same time (e.g. middle ear and articulation implants) [13,128].

3.1.3. Carbon nanotubes and fibers

PLA-based polymers have been reported to give promising results when used to fabricate tissue engineering structures in combination with carbon nanotubes (CNTs) and fibers. This combination is reported to be particularly effective: specific interactions occur between couples of enantiomers and promote an optimal dispersion and self-networking of the CNTs [129]. The suitability of the PLA/nanotubes pair targeting various tissues has been investigated [130–136]. Once again, the highest amount of reports on the topic concern bone tissue engineering [131,132,135,136]. Some exemplary cases of the synergic combination of PLA and carbon nanotubes to optimize the bond of scaffolds with the target tissue are discussed below.

Mikael et al. [132] presented an effective way to produce composite scaffolds from PLGA microspheres and multi-walled carbon nanotubes (MWCTs) with various surface modifications. The scaffolds generally showed excellent in vitro cell adhesion, cell proliferation and mineralization, first clues of a positive bond with tissue. On the other hand, the in vivo studies gave less univocal results and, depending on the composition, a strong inflammatory response occurred. This result showed once again the difference between the outcomes of in vivo and in vitro testing. However, the positive outcome of in vitro characterization still motivates to perform further investigations. A similar approach to the one described above was also tested and validated with single walled carbon nanotubes (SWCTs) for muscoskeletal tissue engineering: the combination with SWCTs resulted in better cell proliferation and gene expression compared to pristine PLGA scaffolds, showing that the seeded cells were organizing to form new muscular tissue. The authors believe that this phenomenon is a consequence of the upregulation of integrin receptors expression caused by the topographical features of SWCTs and that it can be a key element for a better interaction of the polymeric scaffold with biological components [131].

The possibility of combining PLA and CNTs with electrospinning was also explored [137,138]. In particular Magiera et al. [137] reported on a ternary system of nanotubes, PLA and gelatin which exhibited optimized hydrophilicity and protein adsorption compared to pure PLA. These improved properties, in turn, determine a more favorable cell response [137,139].

Carbon fibers (CFs) have been also used as fillers in PLA matrices [134]. CFs were modified via high temperature processing in order to give them a highly porous structure and subsequently blended into salt leached PLGA foams. The PLGA composite with activated CFs has high adsorption capability (making it suitable as a drug delivery carrier) and showed optimal tissue bonding without significant inflammatory response when implanted subcutaneously in a rat. Carbon nanotubes can be exploited to modify the thermal and electrical properties of polylactic acid [129,136]. This approach has a number of different applications and can be used to enhance the response of cells seeded on the polymer via electrical stimulation, thus improving the tissue regeneration on the long-term [140]. Further research needs to be carried out in this direction in order to fully understand how the functionalities introduced by the CNTs (e.g. chemical, topographical and electrical stimuli) influence cell response. Lastly, it is important to recall that nanostructures of carbon still raise significant concerns regarding their safe use as constituents of biomedical devices. Many aspects of this possible threat must be addressed in the future, such as the possible carcinogenicity of CNTs or the full understanding of the risk of accumulation of degradation products in the human body [141,142].

3.1.4. Metal oxides

The categories listed above are the most studied strategies to increase the bioactivity of PLA and related polymers. However, many other approaches have been proposed. For instance some PLA/metal oxide systems have been investigated: among them zinc oxide (ZnO) [143–145], magnesium oxide (MgO) [146–148] and iron oxides (Fe_3O_4 or γFe_2O_3) [149,150]. Each one of these metal oxides has specific properties ideal for various tissue engineering applications. ZnO, for instance, has proven to inhibit bacterial attachment and to drive cell differentiation towards the myocyte phenotype. When integrated into a composite system based on PLLA, ZnO (as nanorods of ~40 nm) slowly releases zinc ions in the surrounding environment. Moreover, it has also been found that the nanorods act as catalytic nuclei and slightly enhance the degradation of the polymer. This is a key phenomenon that allows the oxide to be exposed on the surface and thus improves the desired myodifferentiation and bond between newly differentiated myocytes and the scaffold [143]. Alternatively, magnesium oxide is applied, similarly to bioactive glass, to improve biomineralization and slow down the degradation of PLA [148]. MgO particles embedded in the polymer matrix buffer the surrounding pH, reducing the hydrolysis rate of PLA, especially reducing the characteristic autocatalytic effect of the polymer [148]. In a recent relevant study Brown et al. [146] fabricated a porous PLGA/MgO composite that aims to improve the current state of the art in dental bone grafting. The group reported increased compressive strength and Young's modulus, steady degradation rate, in vitro bone marrow stromal cell proliferation and, most important, novel bone formation and cell infiltration in vivo in a canine model.

Compared to clinically-used pristine PLGA these composite constructs could decrease inflammation and at the same time improve osteogenesis and osteointegration. Among other metal oxides, the oxides of iron offer a mostly unique property that can be exploited in order to improve the tissue/biomaterial connection: superparamagnetism [149–151]. The use of superparamagnetic iron oxide nanoparticles (SPIONs), particularly studied in targeted cancer treatment and a number of other drug delivery systems, is an emerging trend also in the field of regenerative medicine technologies. Some authors reported the inclusion of superparamagnetic iron oxide nanoparticles (both magnetite and maghemite) into a polylactide matrix and the subsequent application of a static magnetic field (SMF) to the construct during cell culture. Two major results were reported: both the magnetic stimulation and the nanoparticles taken alone slightly promote the differentiation of osteoblasts. The proposed explanations for the phenomena are that stimulation via SMF, due to the diamagnetic properties of the cell membrane, alters the ion flux through the membrane, on the other hand, iron oxide NPs diminish the intracellular H_2O_2 production through intrinsic peroxidase-like activity, thus accelerating cell cycle progression. Moreover, the two stimuli act synergistically leading to massively enhanced cell proliferation, differentiation and ECM secretion, thus promoting the bond between tissue and material [149].

3.2. Combination of PLA with other polymers

3.2.1. Natural polymers and compounds

Natural polymers have always been an intuitive choice for tissue engineering purposes: they mimic the composition of ECM and usually are non-toxic and characterized by competitive bioresorbability, bioadhesion [152] and, generally, biocompatibility. However, natural polymers tend to be both less available and reproducible than synthetic ones and could raise concerns regarding their immunogenicity due to their origin: collagen, for instance, is characterized by a number of antigens that can trigger a dangerous immune response in the host organism [153,154]. Still natural polymers remain very good candidates in a number of applications. Mainly natural polymers can be divided following two criteria: their origin or their chemical nature (see Fig. 8).

Given the capacity of many natural polymers to efficiently bond to natural tissue, together with their ability of stimulating cells to produce new matrix, several papers reported the combination of members of the PLA family with natural polymers with the specific aim of improving the lack of bioactivity of the former. Many strategies, such as blending, covalent coupling and various composite approaches were explored using various materials (e.g. gelatin, collagen, chitosan, dextran among others). Some relevant examples are described below and summarized in Table 3.

Cai et al. [155] investigated the biomineralization of electrospun scaffolds fabricated by blending PLLA and gelatin in 2,2,2-trifluoroethanol (TFE). The group used supersaturated simulated body fluid (5xSBF) as system to both quickly predict the bioactivity of the scaffold and coat the same with a convenient layer of hydroxyapatite that could further enhance its positive response in vivo. The comparison of results after 24 h of immersion in SBF proved how gelatin has a clear accelerating effect on the bioactivity of bare PLLA. The increase of hydrophilicity caused by the addition of gelatin triggered a higher adsorption of ions on the surface of blended samples. This in turn caused further adsorption of ions of opposite charge and then, eventually, the formation of calcium phosphates occurred [155]. Moreover, PLLA/gelatin blends, compared to pure PLLA, showed a higher precipitation of dicalcium phosphate dehydrate (DCPD), a salt that is believed to be the precursor of hydroxyapatite, as well as a better crystal morphology compared to control. These results suggest that PLLA/gelatin blends are more likely to develop a successful bond with bone than pure PLLA.

Another commonly investigated and promising natural polymer for tissue engineering is chitosan. In addition to biocompatibility, antimicrobial activity and non-toxicity, chitosan can be degraded in vivo via interaction with cellular lysozymes [156]. Based on the hypothesis that chitosan's physicochemical, antimicrobial and biological properties could positively increase the outcome of PLA-based tissue engineering scaffolds, Duarte et al. [157] prepared and characterized PLLA/chitosan blended foams by supercritical assisted phase-inversion. Different PLLA/chitosan ratios were compared to understand how the composition would change the morphology and how the two polymers distribute within the matrix. The feasibility of the preparation of chitosan-blended PLLA scaffolds for bone tissue engineering was demonstrated. Nevertheless further analyses are needed to assess and confirm the hypothesis that chitosan can actually bring significant improvements to bare PLLA matrices, especially in terms of bioactivity. The better mineralization on specimens with chitosan can be possibly explained as a consequence of the chelation ability of the polysaccharide: chitosan could be able to entrap calcium ions and trigger the deposition of CaP on the samples. For instance, a precalcification treatment was demonstrated to be an effective approach in improving the biomineralization and bioactivity of chitosan coated PLLA foams [158]. Porous scaffolds based on PLA, chitosan and keratin blends have been biologically evaluated using MG63 osteoblast-like cells as reported by Tanase et al. In vitro cell culture at day 7 showed that the PLA/chitosan/keratin (2–4 wt%) scaffolds supported cell adhesion and proliferation as well as PLA/chitosan scaffolds without the presence of keratin. This preliminary result did not show influence of keratin on bone cell response, while keratin had an impact on the mechanical properties. The authors suggested that keratin contents should be further tailored to enhance bone cell response [156].

Blending is not the only technique investigated to combine PLA with chitosan. There is a number of studies where chitosan proved to have positive effects on PLA matrices produced with other approaches. For example, the ability of chitosan of enhancing the bond with new forming tissue was investigated by Zhu et al. [159]. In their studies, chitosan was covalently bonded to the polyester matrix via chemical crosslinking and then used as polycationic part in the formation of a polycomplex with heparin. The molecules of heparin stabilize and regulate the expression of growth factors and enhance both the proliferation of cells and the production of new ECM in vivo, eventually providing a healthy bond between tissue and host material [160]. The authors claim that the same strategy could be applied not only to heparin, but also to many other molecules (e.g. other glycosaminoglycans). PLA/chitosan/heparin complexes showed inhibition of platelet adhesion and activation coupled with increased cell adhesion. These findings suggest this material can be a good candidate to engineer the growth of the endothelium [160].

Another proposed system that combines a polysaccharide with PLA, specifically in its copolymeric form with polyglycolic acid (PGA), PLGA, was reported by Pan et al. [161]. Blended PLGA/dextran was fabricated in order to design a scaffold/patch for dermal tissue regeneration and wound healing. In this context, PLGA was chosen over other forms of PLA because of its more suitable mechanical properties (i.e. lower Young's modulus, flexibility). Dextran was blended with PLGA, then electrospun and photo-crosslinked. Cell assays were performed using dermal fibroblasts and cell morphology, attachment, distribution, viability, proliferation, migration, cytoskeleton organization, contractility, ECM deposition and gene expression were investigated (Fig. 9). The results showed that cells interacted favorably with the scaffold, migrated into the matrix of the scaffold and organized themselves into multi-layered physiological-like dermal structures. The presence of the scaffold also enhanced gel contraction and did not cause alteration in gene expression. These findings suggest that blending PLGA with dextran improves the bioactivity of the bare polyester when tested with dermal fibroblasts. Therefore this strategy could potentially be useful in enhancing the healing of chronic or trauma wounds and in other skin regenerative medicine applications. PLA copolymerized with polyethylene glycol (PEG)-based scaffolds have been developed and

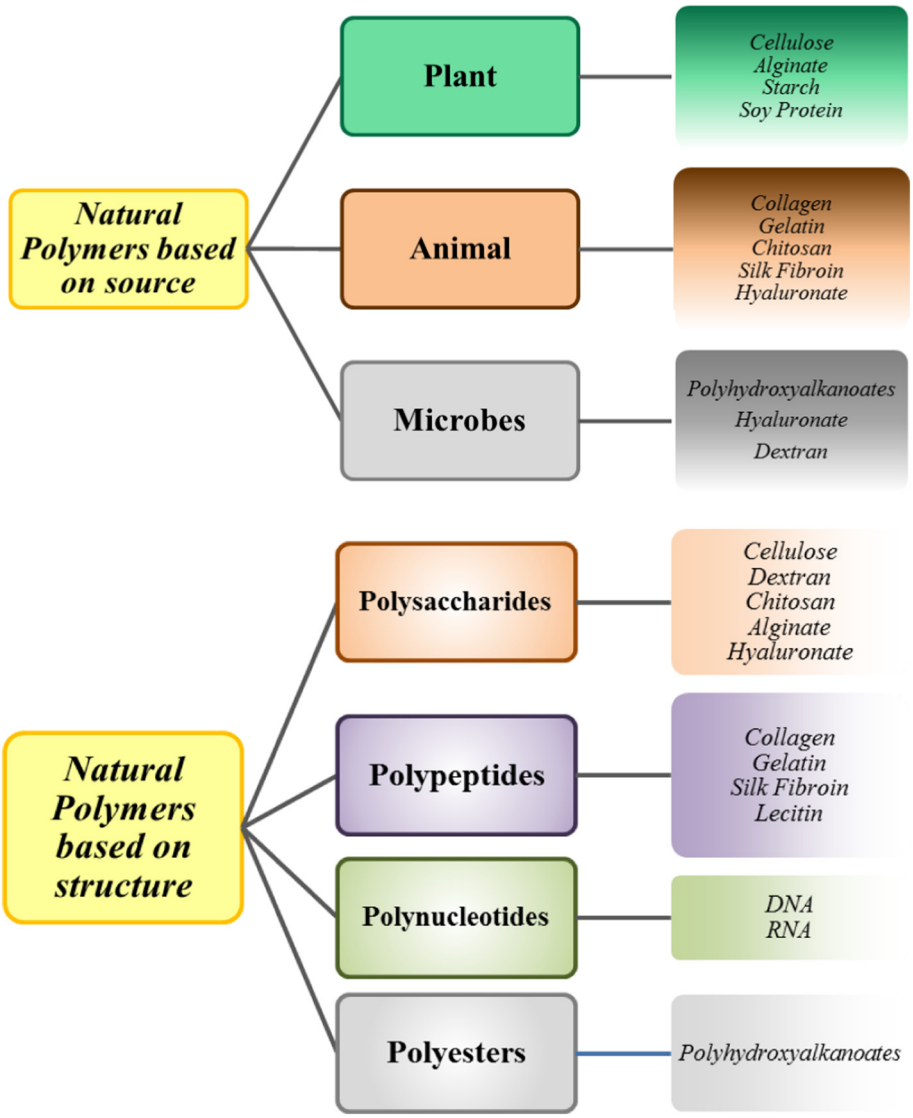

Fig. 8. Classification of natural polymers depending on their source (top), or their chemical structure (bottom).

incorporated with bacteria cellulose (BC) nanofibers for soft tissue engineering applications (i.e. muscle, bladder, skin and blood vessels) [156]. BC nanofibers were found to improve the mechanical properties of the scaffolds, including their elasticity and toughness, and also their biocompatibility.

In cartilage tissue engineering, the combination of PLA and PLGA has been developed in form of three-dimensional electrospun fibrous scaffolds to grow chondrocytes for cartilage regeneration. The study of Armed et al. [156] developed collagen blended PLA/PLGA fibers by electrospinning. By this approach, synthetic PLA and PLGA enhanced the mechanical properties of collagen and simultaneously collagen improved the biological properties of synthetic polyesters. Collagen/PLA/PLGA scaffolds showed an outstanding biological performance in terms of proliferation, extracellular matrix production and cartilage-specific gene expression of ATDC5 chondrogenic cell line. It was also found that cells retained their correct phenotype in long-term culture. This characteristic is crucial for chondral repair due to an occurrence of cell de-differentiation that generally leads to failure in cartilage regeneration. Thus, the study indicated that blending synthetic polyesters (PLA and PLGA) with natural polymers like collagen provided both mechanical and bioactive properties suitable for cartilage tissue engineering.

The combination of collagen and PLA is particularly promising. In a recent publication by Barrientos et al. [162] the two polymers were blended in hexafluoropropanol and electrospun. The presence of collagen in the blended mats resulted in a reduction of fiber diameter and in increased hydrophilicity and modulation of drug release. Especially in the applicative context of antibacterial scaffolds, the collagen/PLA mats showed outstanding performance against both relevant Gram-positive and Gram-negative strains (i.e., *Escherichia coli* and *Staphylococcus aureus*).

3.2.2. Synthetic polymers and compounds

Among the possible combinations between members of the polylactic acid family (Table 4) and other synthetic polymers, one pair that raised a significant interest because of its superior enhancement of tissue-material interface is the one with poly(glycerol sebacate) (PGS). In recent years, many studies reported the blending of PGS with various forms of PLA, especially PLLA. Due to its elastomeric nature, PGS was found to be a perfect material to be blended with PLLA, combining the high stiffness of polylactic acid with the tailored properties for soft tissues of polyglycerol sebacate [163]. With this strategy a material with intermediate properties can be obtained. For instance Frydrych et al. [163] worked on 73:27 PGS/PLLA blends fabricated via freeze-drying. These structures, compared to pristine PLLA produced with the same technique, showed more suitable porous microstructure,

Table 3
Selected strategies to enhance PLA bioactivity using natural polymers.

Material	Type of lactide	Technique	Applications	Advantages	References
Chitosan	PLLA	Blending	Scaffolds for TE	Fine tuning and improvement of properties	Duarte [157]
	PDLLA			Antibacterial properties	Grande [182]
	PDLLA	X-linking	Various TE substrates	Chitosan enhances bioactivity and allows further modifications (e.g. polycomplexation)	Zhu [159]
	PLLA	Composite	Bone TE scaffolds	Improved initial mechanical strength and biomineralization	Mano [158]
	PLLA			Enhanced bioactivity	Wang [183]
Collagen	PDLLA	Electrospinning	Antibacterial TE scaffolds Hernia repair	Better hydrophilicity and drug release	Barrientos [162,184]
	PDLLA	3D printing Freeze-drying	Multi-tissue regeneration platforms	Tailorable mechanical properties and ECM mimicking ability	Mozdzen [185]
	PLGA	Composite	Nano fibrous membranes for drug delivery	Better fibroblast response Possibility of carrying species	Chen [186]
	PLGA		Core/shell fibrous scaffolds	Ameliorated ALP activity And osteoblasts response	Wei [187]
	PLGA	Surface adsorption	Urinary bladder reconstruction	Increased cellular response	Salem [188]
Dextran	PLGA	Solvent blend	Skin scaffolds and wound healing	Good cell viability, migration and formation of derma-like structures Enhanced collagen formation	Pan [161]
	PLGA	Composite	Drug release devices and bone TE scaffolds	Sustained dextran release	Wei [187]
Gelatin	PLLA	Blend	Bone TE scaffolds	Accelerated biomineralization	Cai [155]
	PDLLA	Composite	TE scaffolds	Better osteoconductivity	Magiera [137]

hydrophilicity, mechanical properties and, most important, collagen deposition (Fig. 10).

The suitability of PGS/PLLA scaffolds for adipose tissue engineering and their increased bioactivity (i.e. bonding between the scaffold and the newly produced ECM) was demonstrated by improved cell penetration and tissue in-growth. In a recent study by Xu et al. [164], the same polymers have been also combined via core/shell electrospinning, producing an interesting nanocomposite structure characterized by transversally anisotropic fibers (i.e. PGS core and PLLA shell) with a nanoporous surface caused by ~~a~~ fast evaporation of the solvent

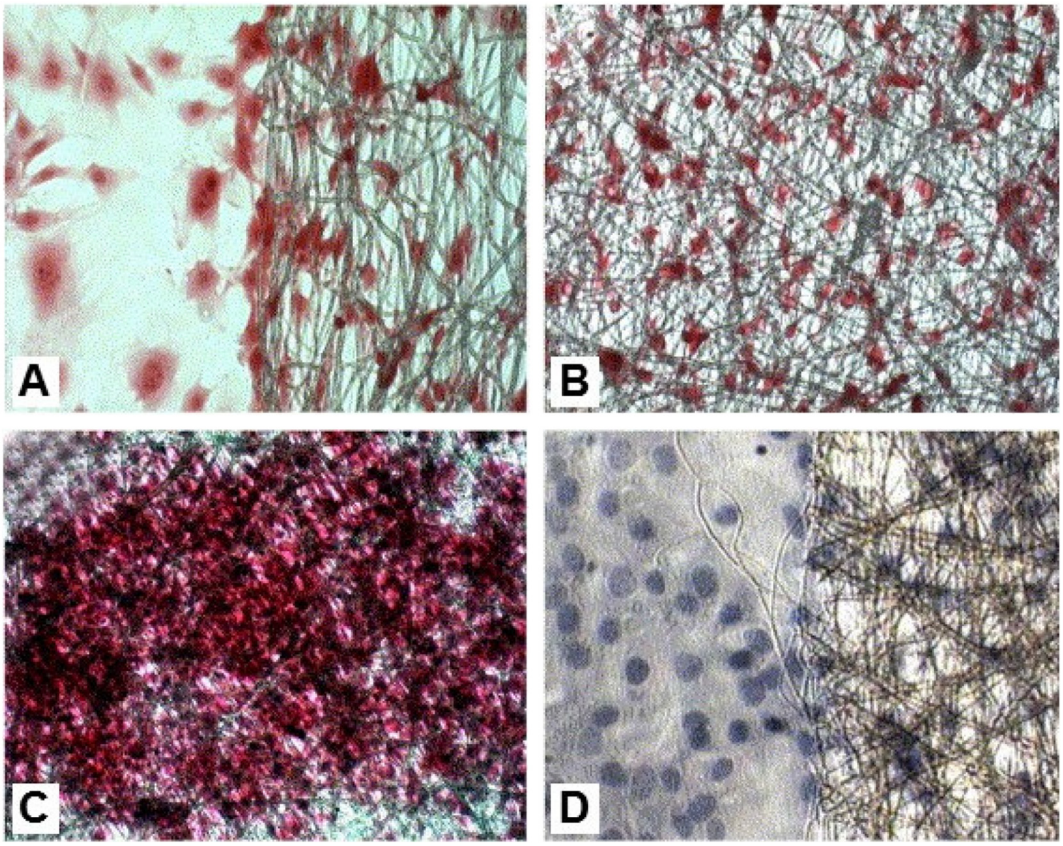

Fig. 9. Fibroblasts deposition of ECM proteins in Dextran/PLGA scaffold fabricated by Pan et al. Figures from A to C report collagen production respectively at days 1, 3 and 5. Authors claim that increasing collagen production can be recognized by day 3 and day 5. Fig. D shows how the elastin production of the cells at day 1 was the same in the scaffold (right) and on the control (left). All images shown have a 20× magnification.
Reproduced from reference [161] with permission of Elsevier.

Table 4
Selected strategies to enhance PLA bioactivity using synthetic polymers.

Material	Type of lactide	Technique	Applications	Advantages	References
Poly(glycerol sebacate) (PGS)	PLLA	Blend	Adipose TE	Enhanced material properties Enhanced tissue in-growth	Frydrych [163]
	PLLA/PDLLA (70:30)		Myocardial patches	Physiological-like cell growth	Kenar [189,190]
	PDLLA		Bone TE	Improved biomineralization	Shi [191]
	PLLA	Core/shell composite	Soft tissues exposed to cyclic deformations	Tailored non-linear mechanical properties Complex topography	Xu [164,192]
Poly(trimethylene carbonate) (PTMC)	PLLA	Blend	Neural TE (nerve guidance channel)	Tailored rubber-like mechanical properties Possibility of carrying drugs	Wach [165]
Polyaniline	PLLA	Electrospun blend	Cardiomyocytes-based bioactuators	Spontaneous beating with regular contraction patterns after 21 days of culturing	Wang [193]
	PLA	Blend	Biomedical conductive substrates	Tailorable resistivity	Shah [194]
	PDLLA	Electrospun blend	Wound dressing	Enhanced cell growth, antimicrobial and electrical conductive	Gizdavic-Nikolaidis [167]
	PLGA	Electrospun blend	Cardiac grafts	Synchronized beat of cardiomyocytes	Hsiao [166]
Poly(3-hexylthiophene)	PDLLA	Composite	Tissue engineering	Combination of contact guidance cues with the spatial electric signals	Sun [169]
	PLGA	Electrospun blends	Tissue engineering scaffolds	well-organized tissue structure and collagen deposition	Subramanian [168]
Maleic anhydride + hexanediamine	PDLLA	Covalent coupling	Tissue engineering and drug delivery	More side chain reactive groups Degradation related acidification controlled	Pan [172]

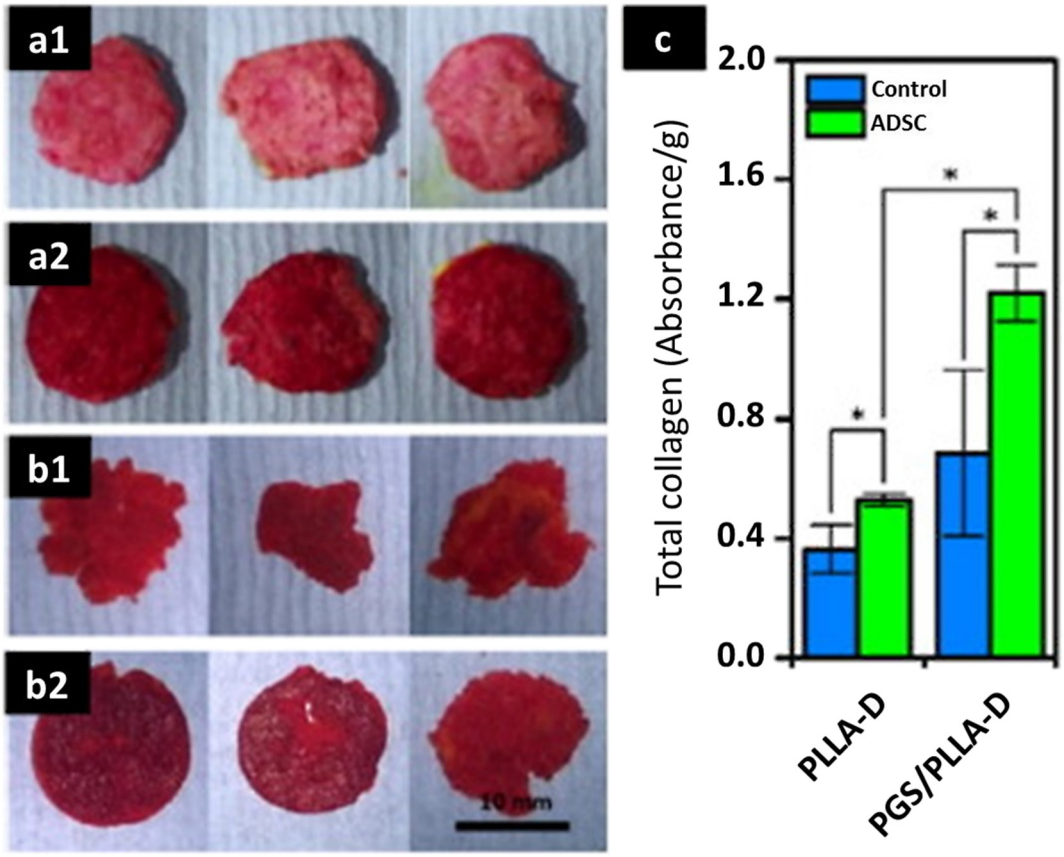

Fig. 10. Evaluation of ECM deposition of human adipose-derived stem cells (ADSCs) in PLLA-D and PGS/PLLA-D scaffolds after 21 days culture in DMEM (staining with Sirius red). (a1) PLLA-D cell free control; (a2) PLLA-D with ADSCs; (b1) cell free PGS/PLLA-D control samples; (b2) PGS/PLLA-D with ADSCs. (c) Total collagen amounts reported as mean ± standard deviation ($n = 3$; $^*P < 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Reproduced from reference [163] with permission of Elsevier.

from the surface. The combination of nanofibrous and nanoporous structures offers a complex array of topographical stimuli together with non-linear mechanical properties that can match the needs of targeted host tissues such as ligaments, tendons, cardiac muscles, smooth muscles and guts. Especially considering the intestinal environment (e.g. colon patch), ex vivo and in vivo trials were performed and they confirmed that the scaffold supports and fosters the growth of enteric neural crest (ENC) progenitor cells. The complex physico-mechanical properties of the PLLA/PGS system are a direct consequence of the material choice, their combination and the specific fabrication technique, confirming once again how the most effective strategies in tissue engineering come from a smart mixture of factors.

A similar approach of combining the mechanical strength of PLLA with a rubber-like polymer was reported, using in-house synthetized poly(trimethylene carbonate) (PTMC) as elastomeric component. Considering that PTMC is soft and tacky at physiological temperature (i.e. 37 °C), PLLA can enhance the load bearing capacity of the blend and the resulting material can offer a tailored environment for cells to grow optimally. In the attempt to regenerate broken peripheral nerves sufficient mechanical strength combined with high elasticity of the guidance tubes are crucial in order to provide a favorable interaction between regenerating tissue and supporting material. In a reported case study, Wach et al. [165] proposed the fabrication of PLLA/PTMC nerve conducts combining dip coating, phase separation and electron beam sterilization (i.e. radiation-induced crosslinking of PTMC). Cell viability assays performed using L929 murine fibroblasts confirmed the cytocompatibility of the constructs; however the cell behavior on a pristine PLLA control has not been assessed. New tests have to be performed specifically addressing this topic to confirm that PLLA/PTMC nerve conducts have significantly superior properties. Furthermore, the biological properties of polyurethane (PU)/PLLA composite scaffolds were evaluated for bone regeneration and reported by Lui et al. By incorporating an elastomeric PU, the flexibility of brittle PLLA was enhanced. In vitro results of the PU/PLLA scaffolds showed an improvement of osteoblast-like cells' adhesion and proliferation. Furthermore, the scaffolds provided a stable contact with surrounding bones, forming a tight interface between material and bone as confirmed by the in vivo tests in a critical-sized defect of a rabbit [156].

Polylactic acid-based polymers were also combined with conductive polymers, such as polyaniline [166,167] or polyhexylthiophene (PHT) [168,169], with the goal of creating scaffolds provided with cues for spatial distributed electric stimulation that could control the proliferation and the osteogenic differentiation of cells. Various morphologies have been proposed such as nanofibrous scaffolds [167] or tubular constructs [169] depending on the target tissue. Electrospun blended scaffolds of PLGA and PHT were also tested in vivo and their biocompatibility verified in a rat model. The combination of the two polymers enhanced the bond between the structure of the scaffold and the murine tissues, as determined from the assessed well-organized tissue structure and newly formed ECM deposition [168].

A main bottleneck in the optimization of the tissue-PLAs bond is the possible local pH dropping as a consequence of hydrolytic degradation when the PLA device is beyond its critical mass. For instance, devices that exceed this critical mass are PLA orthopedic aids, such as bioresorbable fixation devices. Clinical reports showed how these devices can often cause chronic inflammation and implant failure [170,171]. The same risk could also occur, with a lower probability, for PLA scaffolds [170]. To overcome this limitation an effective bulk modification of polylactic acid using maleic anhydride (MA) and hexanediamine (HAD) was reported [172]. The grafting of side chains rich in carboxyl and amino groups enhances the reactivity of PLA and also opens a number of possible further grafting and/or crosslinking options with other bioactive species. Even though the grafting is surely an effective and versatile strategy, an interesting result that the group reported is achieved by the MA/HAD-modified polymer per se: the modification with hexanediamine contributed to settle the pH. When samples were incubated in phosphate buffer saline for up to 12 weeks, the pH value of the solution for PLA and MA-modified PLA samples decreased to below 2.0 within 7 weeks, whereas the pH of the MA/HAD-modified PLA remained higher than 6.0 throughout the whole experiment. The authors did not propose an explanation for this phenomenon. Probably the diamine modification either buffers the environment or slows down the degradation. Further studies have to be performed to investigate these findings [172].

4. Conclusions

An overview of the most recent bulk technologies designed to address the intrinsic lack of bioactivity (i.e. the ability of successfully interact with a targeted living tissue) of polylactic acid has been presented in this paper. Both organic and inorganic-based approaches were discussed as possible routes to improve the naturally low ability of PLA-based tissue engineering devices to successfully favor the development of a seamless tissue-material interface. Polylactic acid is certainly a very versatile and popular polymer in biomedical applications, from orthopedics to controlled drug delivery, from biosensors to regenerative medicine. In the decades since its first development countless studies have been published and many combinations have been tested. Nevertheless, there is still vast room for improving the bioactive characteristics of this class of polymers. At least three main promising trends in the development of bioactive PLA-based novel technologies for tissue engineering can be highlighted: (I) the investigation towards new ways to stimulate the bond between tissue and material, (II) the development of therapeutic ions based technologies and (III) the exploitation of bioactive glasses in combination with PLA for novel soft tissue engineering applications. Since the start of interest in nanotechnologies applied to biomaterials, polylactic acid was used as matrix in the development of nanocomposites. Future research could explore this field and provide new bioactive functionalities to biomaterials that go beyond the well-known improvement of biomineralization and mechanical properties. The stimulation of cells is a multi-faceted and complex topic in which many different chemical and physical phenomena take part [173]. When designing new bioactive PLA-based materials this complexity should be addressed and engineered. Magnetic stimulation via superparamagnetic iron oxide nanoparticles or electric stimulation via carbon nanotubes are just two examples being proposed to enhance the interaction between tissue and material, taking this issue to a new level, exploring the physical side of cell stimulation. The two (or more) components should work synergistically and create a system where the positive characteristics of all its constituents are maintained and the downsides balanced out.

Simultaneously, the engineering of new chemical stimuli is currently addressed and should be further investigated. Strong research efforts are put towards the design of polylactides functionalized with various biomolecules (e.g. growth factors, recombinant proteins) that enhance the bioactivity of the polymer exposing more reactive groups on the outer surface. These groups achieve a better material-cell communication than the hydrophobic, inert, bare polymer. However, these biomolecules are expensive and potentially dangerous (e.g. undesired immune response), therefore alternative technologies should be developed. An emerging and promising approach in this regard is therapeutic ion release. Many metal ions have a fundamental role in physiological pathways and appear to be very effective in the regulation of tissue growth even in a small quantity. Doped bioactive glasses are one of the most studied carriers for these ions since they are finely tunable and easy to synthetize. They work perfectly when combined with PLA because of the complementary degradation products of the two species (acidic for PLA and alkaline for BG), that contribute to maintain a buffered state around the construct. Recent literature on BGs indicates that their application should not be limited to the skeletal system [13,103]. Therefore, we anticipate that future research efforts on PLA/BG systems should specifically address soft tissue engineering

applications, especially exploiting the angiogenesis regulation and gene expression abilities of ion-doped BGs.

These approaches to increase the bioactivity of polylactic acid based materials will help research move towards creating tissue engineering approaches that take full advantage of the many benefits of PLA, such as its relative low costs and ease of processing, maximizing at the same time the outcomes of the interaction and bonding between tissue and host construct.

Acknowledgements

This work has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie actions (HyMedPoly project, Grant Agreement No. 643050). We thank the HyMedPoly consortium for its support. The authors would also like to thank Mr. Nathan G Atkinson for his help in the revision of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] J.M. Morais, F. Papadimitrakopoulos, D.J. Burgess, Biomaterials/tissue interactions: possible solutions to overcome foreign body response, AAPS J. 12 (2010) 188–196, https://doi.org/10.1208/s12248-010-9175-3.
[2] W. Cao, L.L. Hench, Bioactive materials, Ceram. Int. 22 (1996) 493–507, https://doi.org/10.1016/0272-8842(95)00126-3.
[3] S. Hofmann, M. Garcia-Fuentes, Bioactive scaffolds for the controlled formation of complex skeletal tissues, Regen. Med. Tissue Eng. Cells Biomater. (2011) 393–432.
[4] L.L. Hench, Bioactive materials: the potential for tissue regeneration, J. Biomed. Mater. Res. 41 (1998) 511–518, https://doi.org/10.1002/(SICI)1097-4636(19980915)41:4<511::AID-JBM1>3.0.CO;2-F.
[5] L.L. Hench, Bioactive ceramics, Ann. N. Y. Acad. Sci. 523 (1988) 54–71, https://doi.org/10.1111/j.1749-6632.1988.tb38500.x.
[6] J.P. Gorski, Biomineralization of bone: a fresh view of the roles of non-collagenous proteins, Front. Biosci. (Landmark Ed.) 16 (2011) 2598–2621 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431766/.
[7] H. Ozawa, K. Hoshi, N. Amizuka, Current concepts of bone biomineralization, J. Oral Biosci. 50 (2008) 1–14, https://doi.org/10.1016/S1349-0079(08)80014-X.
[8] L.L. Hench, R.J. Splinter, W.C. Allen, T.K. Greenlee, Bonding mechanisms at the interface of ceramic prosthetic materials, J. Biomed. Mater. Res. 5 (1971) 117–141, https://doi.org/10.1002/jbm.820050611.
[9] L.L. Hench, The story of Bioglass®, J. Mater. Sci. Mater. Med. 17 (2006) 967–978, https://doi.org/10.1007/s10856-006-0432-z.
[10] T. Kokubo, H. Takadama, How useful is SBF in predicting in vivo bone bioactivity? Biomaterials 27 (2006) 2907–2915, https://doi.org/10.1016/j.biomaterials.2006.01.017.
[11] A.C.M. Renno, P.S. Bossini, M.C. Crovace, A.C.M. Rodrigues, E.D. Zanotto, N.A. Parizotto, Characterization and in vivo biological performance of biosilicate, Biomed. Res. Int. 2013 (2013), https://doi.org/10.1155/2013/141427.
[12] L.L. Hench, Bioceramics, J. Am. Ceram. Soc. 81 (2005) 1705–1728, https://doi.org/10.1111/j.1151-2916.1998.tb02540.x.
[13] V. Miguez-Pacheco, L.L. Hench, A.R. Boccaccini, Bioactive glasses beyond bone and teeth: emerging applications in contact with soft tissues, Acta Biomater. 13 (2015) 1–15, https://doi.org/10.1016/j.actbio.2014.11.004.
[14] A.A. Gorustovich, J.A. Roether, A.R. Boccaccini, Effect of bioactive glasses on angiogenesis: a review of in vitro and in vivo evidences, Tissue Eng. B Rev. 16 (2010) 199–207, https://doi.org/10.1089/ten.TEB.2009.0416.
[15] P.K. Suresh, Physicochemical properties, biomolecular corona, bioactivity, and pharmacology-based issues of biopolymers: a brief overview: letter in response to an opinion article published in Trends in Biotechnology: Wang, C. and Dong, L. (2015) Exploring “New” Bioac, Trends Biotechnol. 34 (2016) 85–86, https://doi.org/10.1016/j.tibtech.2015.12.003.
[16] M.R. Abdullah, A. Goharian, M.R. Abdul Kadir, M.U. Wahit, Biomechanical and bioactivity concepts of polyetheretherketone composites for use in orthopedic implants-a review, J. Biomed. Mater. Res. A 103 (2015) 3689–3702, https://doi.org/10.1002/jbm.a.35480.
[17] D.N. Kapoor, A. Bhatia, R. Kaur, R. Sharma, G. Kaur, S. Dhawan, PLGA: a unique polymer for drug delivery, Ther. Deliv. 6 (2015) 41–58, https://doi.org/10.4155/tde.14.91.
[18] B. Tyler, D. Gullotti, A. Mangraviti, T. Utsuki, H. Brem, Polylactic acid (PLA) controlled delivery carriers for biomedical applications, Adv. Drug Deliv. Rev. 107 (2016) 163–175, https://doi.org/10.1016/j.addr.2016.06.018.
[19] R.A. Auras, L.-T. Lim, S.E.M. Selke, H. Tsuji, Poly(Lactic Acid): Synthesis, Structures, Properties, Processing, and Applications, (2010).
[20] R.K. Kulkarni, E.G. Moore, A.F. Hegyeli, F. Leonard, Biodegradable Poly(Lactic Acid) Polymers, 5 (1971), pp. 169–181.
[21] C.A. Vacanti, R. Langer, B. Schloo, J.P. Vacanti, Synthetic polymers seeded with chondrocytes provide a template for new cartilage formation, Plast. Reconstr. Surg. 88 (1991) 753–759.
[22] M. Vert, S. Li, H. Garreau, More about the degradation of LA/GA-derived matrices in aqueous media, J. Control. Release 16 (1991) 15–26, https://doi.org/10.1016/0168-3659(91)90027-B.
[23] M. Vert, J. Mauduit, S. Li, Biodegradation of PLA/GA polymers: increasing complexity, Biomaterials 15 (1994) 1209–1213, https://doi.org/10.1016/0142-9612(94)90271-2.
[24] I. Grizzi, H. Garreau, S. Li, M. Vert, Hydrolytic degradation of devices based on poly(DL-lactide acid) size-dependence, Biomaterials 16 (1994) 305–311, https://doi.org/10.1016/0142-9612(95)93258-F.
[25] L. Xiao, Bo Wang, Guang Yang, Mario Gauthier, Poly(lactic-acid)-based biomaterials: synthesis, modification and applications, Biomed. Sci. Eng. Technol. 902 (2012), https://doi.org/10.5772/23927.
[26] J.-B. Zeng, K.-A. Li, A.-K. Du, Compatibilization strategies in poly(lactic acid)-based blends, RSC Adv. 5 (2015) 32546–32565, https://doi.org/10.1039/c5ra01655j.
[27] R.L. Simpson, S.N. Nazhat, J.J. Blaker, A. Bismarck, R. Hill, A.R. Boccaccini, U.N. Hansen, A.A. Amis, A comparative study of the effects of different bioactive fillers in PLGA matrix composites and their suitability as bone substitute materials: a thermo-mechanical and in vitro investigation, J. Mech. Behav. Biomed. Mater. 50 (2015) 277–289, https://doi.org/10.1016/j.jmbbm.2015.06.008.
[28] D. Meng, A.R. Boccaccini, Nanostructured biocomposites for tissue engineering scaffolds, Biomed. Compos. (2009) 509–546, https://doi.org/10.1533/9781845697372.4.509.
[29] M.A. Mateos-Timoneda, R. Levato, X. Punet, I. Cano, O. Castano, E. Engel, Biofunctionalization of polymeric surfaces, Proc. Ann. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS (2015) 1745–1748, https://doi.org/10.1109/EMBC.2015.7318715 2015–Novem.
[30] J. Seras-Franzoso, C. Steurer, M. Roldán, M. Vendrell, C. Vidaurre-Agut, A. Tarruella, L. Saldaña, N. Vilaboa, M. Parera, E. Elizondo, I. Ratera, N. Ventosa, J. Veciana, A.J. Campillo-Fernández, E. García-Fruitós, E. Vázquez, A. Villaverde, Functionalization of 3D scaffolds with protein-releasing biomaterials for intracellular delivery, J. Control. Release 171 (2013) 63–72, https://doi.org/10.1016/j.jconrel.2013.06.034.
[31] A. Jordá-Vilaplana, V. Fombuena, D. García-García, M.D. Samper, L. Sánchez-Nácher, Surface modification of polylactic acid (PLA) by air atmospheric plasma treatment, Eur. Polym. J. 58 (2014) 23–33, https://doi.org/10.1016/j.eurpolymj.2014.06.002.
[32] Y. Kimura, Molecular, structural, and material design of bio-based polymers, Polym. J. 41 (2009) 797–807, https://doi.org/10.1295/polymj.PJ2009154.
[33] J.R. Dorgan, H. Lehermeier, M. Mang, Thermal and rheological properties of commercial-grade poly(lactic acid)s, J. Polym. Environ. 8 (2000) 1–9, https://doi.org/10.1023/A:1010185910301.
[34] K. Fukushima, Y. Kimura, Stereocomplexed polylactides (neo-PLA) as high-performance bio-based polymers: their formation, properties, and application, Polym. Int. 55 (2006) 626–642, https://doi.org/10.1002/pi.2010.
[35] L. Bao, J.R. Dorgan, D. Knauss, S. Hait, N.S. Oliveira, I.M. Maruccho, Gas permeation properties of poly(lactic acid) revisited, J. Memb. Sci. 285 (2006) 166–172, https://doi.org/10.1016/j.memsci.2006.08.021.
[36] M. Vert, S.M. Li, G. Spenlehauer, P. Guerin, Bioresorbability and biocompatibility of aliphatic polyesters, J. Mater. Sci. Mater. Med. 3 (1992) 432–446, https://doi.org/10.1007/BF00701240.
[37] M. Agarwal, K.W. Koelling, J.J. Chalmers, Characterization of the degradation of polylactic acid polymer in a solid substrate environment, Biotechnol. Prog. 14 (1998) 517–526, https://doi.org/10.1021/bp980015p.
[38] S.J. de Jong, E.R. Arias, D.T.S. Rijkers, C.F. van Nostrum, J.J. Kettenes-van den Bosch, W.E. Hennink, New insights into the hydrolytic degradation of poly(lactic acid): participation of the alcohol terminus, Polymer (Guildf.) 42 (2001) 2795–2802 https://doi.org/10.1016/S0032-3861(00)00646-7.
[39] F. Codari, S. Lazzari, M. Soos, G. Storti, M. Morbidelli, D. Moscatelli, Kinetics of the hydrolytic degradation of poly(lactic acid), Polym. Degrad. Stab. 97 (2012) 2460–2466, https://doi.org/10.1016/j.polymdegradstab.2012.06.026.
[40] X. Zhang, U.P. Wyss, D. Pichora, M.F.A. Goosen, An investigation of poly(lactic acid) degradation, J. Bioact. Compat. Polym. 9 (1994) 80–100, https://doi.org/10.1177/088391159400900105.
[41] R. Zhang, P.X. Ma, Poly(a-hydroxyl acids)/hydroxyapatite porous composites for bone-tissue engineering. I. Preparation and morphology, J. Biomed. Mater. Res. 44 (1999) 446–455, https://doi.org/10.1002/(SICI)1097-4636(19990315)44:4<446::AID-JBM11>3.0.CO;2-F.
[42] F. Carfì Pavia, V. La Carrubba, V. Brucato, Polymeric scaffolds based on blends of poly-l-lactic acid (PLLA) with poly-D-L-lactic acid (PLA) prepared via thermally induced phase separation (TIPS): demixing conditions and morphology, Polym. Bull. 70 (2013) 563–578, https://doi.org/10.1007/s00289-012-0861-4.
[43] D. Ishii, T.H. Ying, T. Yamaoka, T. Iwata, Characterization and biocompatibility of biopolyester nanofibers, Materials (Basel) 2 (2009) 1520–1546, https://doi.org/10.3390/ma2041520.
[44] V. Langlois, K. Vallee-Rehel, J.J. Peron, A. le Borgne, M. Walls, P. Guerin, Synthesis and hydrolytic degradation of graft copolymers containing poly(lactic acid) side chains: in vitro release studies of bioactive molecules, Polym. Degrad. Stab. 76 (2002) 411–417.
[45] F. Carfì Pavia, V. La Carrubba, V. Brucato, Tuning of biodegradation rate of PLLA scaffolds via blending with PLA, Int. J. Mater. Form. 2 (2009) 713–716, https://doi.org/10.1007/s12289-009-0574-x.

[46] D. Narayan, S.S. Venkatraman, Effect of pore size and interpore distance on endothelial cell growth on polymers, J. Biomed. Mater. Res. A 87 (2008) 710–718, https://doi.org/10.1002/jbm.a.31749.
[47] G.A. Mannella, G. Conoscenti, F. Carfì Pavia, V. La Carrubba, V. Brucato, Preparation of polymeric foams with a pore size gradient via Thermally Induced Phase Separation (TIPS), Mater. Lett. 160 (2015) 31–33, https://doi.org/10.1016/j.matlet.2015.07.055.
[48] F.C. Pavia, V. La Carrubba, G. Ghersi, V. Brucato, Poly-left-lactic acid tubular scaffolds via diffusion induced phase separation: control of morphology, Polym. Eng. Sci. 53 (2013) 431–442, https://doi.org/10.1002/pen.23273.
[49] F.C. Pavia, V. La Carrubba, V. Brucato, Morphology and thermal properties of foams prepared via thermally induced phase separation based on polylactic acid blends, J. Cell. Plast. 48 (2012) 399–407, https://doi.org/10.1177/0021955X12452180.
[50] F.C. Pavia, V. La Carrubba, S. Piccarolo, V. Brucato, Polymeric scaffolds prepared via thermally induced phase separation: tuning of structure and morphology, J. Biomed. Mater. Res. A 86A (2008) 459–466, https://doi.org/10.1002/jbm.a.31621.
[51] X. Xu, X. Chen, Z. Wang, X. Jing, Ultrafine PEG-PLA fibers loaded with both paclitaxel and doxorubicin hydrochloride and their in vitro cytotoxicity, Eur. J. Pharm. Biopharm. 72 (2009) 18–25, https://doi.org/10.1016/j.ejpb.2008.10.015.
[52] T. Serra, M. Ortiz-Hernandez, E. Engel, J. a Planell, M. Navarro, Relevance of PEG in PLA-based blends for tissue engineering 3D-printed scaffolds, Mater. Sci. Eng. C Mater. Biol. Appl. 38 (2014) 55–62, https://doi.org/10.1016/j.msec.2014.01.003.
[53] H. Danafar, K. Rostamizadeh, S. Davaran, M. Hamidi, PLA-PEG-PLA copolymer-based polymersomes as nanocarriers for delivery of hydrophilic and hydrophobic drugs: preparation and evaluation with atorvastatin and lisinopril, Drug Dev. Ind. Pharm. 40 (2014) 1411–1420, https://doi.org/10.3109/03639045.2013.828223.
[54] C.-F. Kuo, N. Tsao, H.-H. Chou, Y.-L. Liu, W.-C. Hsieh, Release of FITC-BSA from poly(L-lactic acid) microspheres analysis using flow cytometry, Colloids Surf. B Biointerfaces 89 (2012) 271–276, https://doi.org/10.1016/j.colsurfb.2011.09.032.
[55] E. Llorens, L.J. del Valle, J. Puiggalí, Multifunctional ternary drug-loaded electrospun scaffolds, J. Appl. Polym. Sci. 133 (2016), https://doi.org/10.1002/app.42751 (n/a-n/a).
[56] K. Al-Tahami, A. Meyer, J. Singh, Poly lactic acid based injectable delivery systems for controlled release of a model protein, lysozyme, Pharm. Dev. Technol. 11 (2006) 79–86, https://doi.org/10.1080/10837450500464040.
[57] S. Singh, J. Singh, Phase-sensitive polymer-based controlled delivery systems of leuprolide acetate: in vitro release, biocompatibility, and in vivo absorption in rabbits, Int. J. Pharm. 328 (2007) 42–48, https://doi.org/10.1016/j.ijpharm.2006.07.051.
[58] R. Sheshala, K.K. Peh, Y. Darwis, Preparation, characterization, and in vivo evaluation of insulin-loaded PLA-PEG microspheres for controlled parenteral drug delivery, Drug Dev. Ind. Pharm. 35 (2009) 1364–1374, https://doi.org/10.3109/03639040902939213.
[59] R. Hashide, K. Yoshida, Y. Hasebe, S. Takahashi, K. Sato, J.I. Anzai, Insulin-containing layer-by-layer films deposited on poly(lactic acid) microbeads for pH-controlled release of insulin, Colloids Surf. B Biointerfaces. 89 (2012) 242–247, https://doi.org/10.1016/j.colsurfb.2011.09.023.
[60] J.Y. Park, I.H. Lee, Controlled release of ketoprofen from electrospun porous polylactic acid (PLA) nanofibers, J. Polym. Res. 18 (2011) 1287–1291, https://doi.org/10.1007/s10965-010-9531-0.
[61] H.K. Makadia, S.J. Siegel, Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier, Polymers (Basel) 3 (2011) 1377–1397, https://doi.org/10.3390/polym3031377.
[62] P. Gentile, V. Chiono, I. Carmagnola, P.V. Hatton, An overview of poly(lactic-co-glycolic) acid (PLGA)-based biomaterials for bone tissue engineering, Int. J. Mol. Sci. 15 (2014) 3640–3659, https://doi.org/10.3390/ijms15033640.
[63] V. Lassalle, M.L. Ferreira, PLA nano- and microparticles for drug delivery: an overview of the methods of preparation, Macromol. Biosci. 7 (2007) 767–783, https://doi.org/10.1002/mabi.200700022.
[64] J. Yanpeng, L. Zonghua, Z. Changren, Fabrication and characterization of PLLA–chitosan hybrid scaffolds with improved cell compatibility, J. Biomed. Mater. Res. A 80 (2007) 820–825, https://doi.org/10.1002/jbm.a.
[65] T. Phaechamud, S. Chitrattha, Pore formation mechanism of porous poly(DL-lactic acid) matrix membrane, Mater. Sci. Eng. C 61 (2016) 744–752, https://doi.org/10.1016/j.msec.2016.01.014.
[66] M.H. Huang, J. Coudane, S. Li, M. Vert, Methylated and pegylated PLA-PCL-PLA block copolymers via the chemical modification of di-hydroxy PCL combined with the ring opening polymerization of lactide, J. Polym. Sci. A Polym. Chem. 43 (2005) 4196–4205, https://doi.org/10.1002/pola.20870.
[67] a.C. Vieira, J.C. Vieira, R.M. Guedes, a.T. Marques, Degradation and viscoelastic properties of PLA-PCL, PGA-PCL, PDO and PGA Fibres, Mater. Sci. Forum 636–637 (2010) 825–832, https://doi.org/10.4028/www.scientific.net/MSF.636-637.825.
[68] Y.-J. Seol, D.Y. Park, J.Y. Park, S.W. Kim, S.J. Park, D.-W. Cho, A new method of fabricating robust freeform 3D ceramic scaffolds for bone tissue regeneration, Biotechnol. Bioeng. 110 (2013) 1444–1455, https://doi.org/10.1002/bit.24794.
[69] S. Izwan, A. Razak, N. Fadzliana, A. Sharif, W. Aizan, W. Abdul, Biodegradable polymers and their bone applications: a review, Int. J. Basic Appl. Sci. 12 (2012) 31–49.
[70] E. Nejati, V. Firouzdor, M.B. Eslaminejad, F. Bagheri, Needle-like nano hydroxyapatite/poly(L-lactide acid) composite scaffold for bone tissue engineering application, Mater. Sci. Eng. C. 29 (2009) 942–949, https://doi.org/10.1016/j.msec.2008.07.038.
[71] H. Li, J. Chang, In vitro degradation of porous degradable and bioactive PHBV/wollastonite composite scaffolds, Polym. Degrad. Stab. 87 (2005) 301–307, https://doi.org/10.1016/j.polymdegradstab.2004.09.001.
[72] Y. Kang, Y. Yao, G. Yin, Z. Huang, X. Liao, X. Xu, G. Zhao, A study on the in vitro degradation properties of poly(L-lactic acid)/β-tricalcuim phosphate(PLLA/β-TCP) scaffold under dynamic loading, Med. Eng. Phys. 31 (2009) 589–594, https://doi.org/10.1016/j.medengphy.2008.11.014.
[73] Z. Tahmasebi Birgani, C.A. van Blitterswijk, P. Habibovic, Monolithic calcium phosphate/poly(lactic acid) composite versus calcium phosphate-coated poly (lactic acid) for support of osteogenic differentiation of human mesenchymal stromal cells, J. Mater. Sci. Mater. Med. 27 (2016) 54, , https://doi.org/10.1007/s10856-016-5666-9.
[74] F. D'Angelo, I. Armentano, I. Cacciotti, R. Tiribuzi, M. Quattrocelli, C. Del Gaudio, E. Fortunati, E. Saino, A. Caraffa, G.G. Cerulli, L. Visai, J.M. Kenny, M. Sampaolesi, A. Bianco, S. Martino, A. Orlacchio, Tuning multi/pluri-potent stem cell fate by electrospun poly(L-lactic acid)-calcium-deficient hydroxyapatite nanocomposite mats, Biomacromolecules 13 (2012) 1350–1360, https://doi.org/10.1021/bm3000716.
[75] T. Lou, X. Wang, G. Song, Z. Gu, Z. Yang, Fabrication of PLLA/??-TCP nanocomposite scaffolds with hierarchical porosity for bone tissue engineering, Int. J. Biol. Macromol. 69 (2014) 464–470, https://doi.org/10.1016/j.ijbiomac.2014.06.004.
[76] S. Dong, J. Sun, Y. Li, J. Li, W. Cui, B. Li, Electrospun nanofibrous scaffolds of poly (L-lactic acid)-dicalcium silicate composite via ultrasonic-aging technique for bone regeneration, Mater. Sci. Eng. C 35 (2014) 426–433, https://doi.org/10.1016/j.msec.2013.11.027.
[77] L. Ye, J. Chang, C. Ning, K. Lin, Fabrication of poly-(DL-lactic acid)—wollastonite composite films with surface modified {beta}-$CaSiO_3$ particles, J. Biomater. Appl. 22 (2008) 465–480, https://doi.org/10.1177/0885328207079670.
[78] K. Okada, F. Hasegawa, Y. Kameshima, A. Nakajima, Bioactivity of $CaSiO_3$/poly-lactic acid (PLA) composites prepared by various surface loading methods of $CaSiO_3$ powder, J. Mater. Sci. Mater. Med. 18 (2007) 1605–1612, https://doi.org/10.1007/s10856-007-3059-9.
[79] Z. Liu, J. Ji, S. Tang, J. Qian, Y. Yan, B. Yu, J. Su, J. Wei, Biocompatibility, degradability, bioactivity and osteogenesis of mesoporous/macroporous scaffolds of mesoporous diopside/poly(L-lactide) composite, J. R. Soc. Interface 12 (2015) 20150507, , https://doi.org/10.1098/rsif.2015.0507.
[80] C. Wu, Y. Ramaswamy, H. Zreiqat, Porous diopside ($CaMgSi_2O_6$) scaffold: a promising bioactive material for bone tissue engineering, Acta Biomater. 6 (2010) 2237–2245, https://doi.org/10.1016/j.actbio.2009.12.022.
[81] C.-J. Su, M.-G. Tu, L.-J. Wei, T.-T. Hsu, C.-T. Kao, T.-H. Chen, T.-H. Huang, Calcium silicate/chitosan-coated electrospun poly (lactic acid) fibers for bone tissue engineering, Materials (Basel) 10 (2017) 501, https://doi.org/10.3390/ma10050501.
[82] R.Z. LeGeros, Properties of osteoconductive biomaterials: calcium phosphates, Clin. Orthop. Relat. Res. (2002) 81–98.
[83] H.C. Kroese-Deutman, P.Q. Ruhé, P.H.M. Spauwen, J.A. Jansen, Bone inductive properties of rhBMP-2 loaded porous calcium phosphate cement implants inserted at an ectopic site in rabbits, Biomaterials 26 (2005) 1131–1138, https://doi.org/10.1016/j.biomaterials.2004.04.021.
[84] K.A. Hing, Bioceramic bone graft substitutes: influence of porosity and chemistry, Int. J. Appl. Ceram. Technol. 2 (2005) 184–199, https://doi.org/10.1111/j.1744-7402.2005.02020.x.
[85] A.R. Amini, C.T. Laurencin, S.P. Nukavarapu, Bone tissue engineering: recent advances and challenges, Crit. Rev. Biomed. Eng. 40 (2012) 363–408, https://doi.org/10.1615/CritRevBiomedEng.v40.i5.10.
[86] B.K.B. Tay, V.V. Patel, D.S. Bradford, Calcium sulfate– and calcium phosphate—based bone substitutes, Orthop. Clin. North Am. 30 (1999) 615–623, https://doi.org/10.1016/S0030-5898(05)70114-0.
[87] D.Y. Shin, M.-H. Kang, I.-G. Kang, H.-E. Kim, S.-H. Jeong, In vitro and in vivo evaluation of polylactic acid-based composite with tricalcium phosphate microsphere for enhanced biodegradability and osseointegration, J. Biomater. Appl. 32 (2018) 1360–1370, https://doi.org/10.1177/0885328218763660.
[88] C.B. Danoux, D. Barbieri, H. Yuan, J.D. de Bruijn, C.A. van Blitterswijk, P. Habibovic, In vitro and in vivo bioactivity assessment of a polylactic acid/hydroxyapatite composite for bone regeneration, Biomatter 4 (2014) e27664, , https://doi.org/10.4161/biom.27664.
[89] S. Maenz, O. Brinkmann, E. Kunisch, V. Horbert, F. Gunnella, S. Bischoff, H. Schubert, A. Sachse, L. Xin, J. Günster, B. Illerhaus, K.D. Jandt, J. Bossert, R.W. Kinne, M. Bungartz, Enhanced bone formation in sheep vertebral bodies after minimally invasive treatment with a novel, PLGA fiber-reinforced brushite cement, Spine J. 17 (2017) 709–719, https://doi.org/10.1016/j.spinee.2016.11.006.
[90] Y. Liu, Q. Huang, Q. Feng, 3D scaffold of PLLA/pearl and PLLA/nacre powder for bone regeneration, Biomed. Mater. 8 (2013) 65001, , https://doi.org/10.1088/1748-6041/8/6/065001.
[91] H. Maeda, V. Maquet, T. Kasuga, Q.Z. Chen, J.A. Roether, A.R. Boccaccini, Vaterite deposition on biodegradable polymer foam scaffolds for inducing bone-like hydroxycarbonate apatite coatings, J. Mater. Sci. Mater. Med. 18 (2007) 2269–2273, https://doi.org/10.1007/s10856-007-3108-4.
[92] H. Liao, H. Mutvei, M. Sjöström, L. Hammarström, J. Li, Tissue responses to natural aragonite (*Margaritifera* shell) implants in vivo, Biomaterials 21 (2000) 457–468, https://doi.org/10.1016/S0142-9612(99)00184-2.
[93] A. Arkudas, J.P. Beier, A.R. Boccaccini, R.E. Horch, Characterisation of vascularisation of scaffolds for tissue engineering, Mater. Sci. Technol. 31 (2015) 180–187, https://doi.org/10.1179/1743284714Y.0000000611.
[94] A. Arkudas, A. Balzer, G. Buehrer, I. Arnold, A. Hoppe, R. Detsch, P. Newby,

T. Fey, P. Greil, R.E. Horch, A.R. Boccaccini, U. Kneser, Evaluation of angiogenesis of bioactive glass in the arteriovenous loop model, Tissue Eng. C Methods 19 (2013) 479–486, https://doi.org/10.1089/ten.TEC.2012.0572.
[95] G. Kaur, O.P. Pandey, K. Singh, D. Homa, B. Scott, G. Pickrell, A review of bioactive glasses: their structure, properties, fabrication and apatite formation, J. Biomed. Mater. Res. A 102 (2014) 254–274, https://doi.org/10.1002/jbm.a.34690.
[96] M.N. Rahaman, D.E. Day, B. Sonny Bal, Q. Fu, S.B. Jung, L.F. Bonewald, A.P. Tomsia, Bioactive glass in tissue engineering, Acta Biomater. 7 (2011) 2355–2373, https://doi.org/10.1016/j.actbio.2011.03.016.
[97] O. Tsigkou, L.L. Hench, A.R. Boccaccini, J.M. Polak, M.M. Stevens, Enhanced differentiation and mineralization of human fetal osteoblasts on PDLLA containing Bioglass composite films in the absence of osteogenic supplements, J. Biomed. Mater. Res. A 80 (2007) 837–851, https://doi.org/10.1002/jbm.a.30910.
[98] L. Bi, S. Jung, D. Day, K. Neidig, V. Dusevich, D. Eick, L.F. Bonewald, Evaluation of bone regeneration, angiogenesis, and hydroxyapatite conversion in critical-sized rat calvarial defects implanted with bioactive glass scaffolds, J. Biomed. Mater. Res. A 100 (A) (2012) 3267–3275, https://doi.org/10.1002/jbm.a.34272.
[99] V. Mouriño, J.P. Cattalini, a.R. Boccaccini, Metallic ions as therapeutic agents in tissue engineering scaffolds: an overview of their biological applications and strategies for new developments, J. R. Soc. Interface 9 (2012) 401–419, https://doi.org/10.1098/rsif.2011.0611.
[100] J.R. Jones, Review of bioactive glass: from Hench to hybrids, Acta Biomater. 9 (2013) 4457–4486, https://doi.org/10.1016/j.actbio.2012.08.023.
[101] Q. Fu, E. Saiz, M.N. Rahaman, A.P. Tomsia, Bioactive glass scaffolds for bone tissue engineering: state of the art and future perspectives, Mater. Sci. Eng. C Mater. Biol. Appl. 31 (2011) 1245–1256, https://doi.org/10.1016/j.msec.2011.04.022.
[102] W.J.E.M. Habraken, J.G.C. Wolke, J.A. Jansen, Ceramic composites as matrices and scaffolds for drug delivery in tissue engineering, Adv. Drug Deliv. Rev. 59 (2007) 234–248, https://doi.org/10.1016/j.addr.2007.03.011.
[103] F. Baino, G. Novajra, V. Miguez-Pacheco, A.R. Boccaccini, C. Vitale-Brovarone, Bioactive glasses: special applications outside the skeletal system, J. Non-Cryst. Solids 432 (2016) 15–30, https://doi.org/10.1016/j.jnoncrysol.2015.02.015 Part.
[104] J. Wilson, G.H. Pigott, F.J. Schoen, L.L. Hench, Toxicology and biocompatibility of bioglasses, J. Biomed. Mater. Res. 15 (1981) 805–817, https://doi.org/10.1002/jbm.820150605.
[105] N. Sachot, A. Roguska, J.A. Planell, M. Lewandowska, E. Engel, O. Castaño, Fast-degrading PLA/ORMOGLASS fibrous composite scaffold leads to a calcium-rich angiogenic environment, Int. J. Nanomedicine 12 (2017) 4901–4919, https://doi.org/10.2147/IJN.S135806.
[106] H. Oliveira, S. Catros, C. Boiziau, R. Siadous, J. Marti-Munoz, R. Bareille, S. Rey, O. Castano, J. Planell, J. Amédée, E. Engel, The proangiogenic potential of a novel calcium releasing biomaterial: impact on cell recruitment, Acta Biomater. 29 (2016) 435–445, https://doi.org/10.1016/j.actbio.2015.10.003.
[107] F. Baino, S. Fiorilli, C. Vitale-Brovarone, Bioactive glass-based materials with hierarchical porosity for medical applications: review of recent advances, Acta Biomater. 42 (2016) 18–32, https://doi.org/10.1016/j.actbio.2016.06.033.
[108] J. Will, L.-C. Gerhardt, A.R. Boccaccini, Bioactive glass-based scaffolds for bone tissue engineering, Adv. Biochem. Eng. Biotechnol. 126 (2012) 195–226, https://doi.org/10.1007/10_2011_106.
[109] L.-C. Gerhardt, A.R. Boccaccini, Bioactive glass and glass-ceramic scaffolds for bone tissue engineering, Materials 3 (2010), https://doi.org/10.3390/ma3073867.
[110] Q.Z. Chen, J.A. Roether, A.R. Boccaccini, Tissue engineering scaffolds from bioactive glass and composite materials, Top. Tissue Eng. 4 (2008) 1–27, https://doi.org/10.1586/17434440.2.3.303.
[111] A.R. Boccaccini, M. Erol, W.J. Stark, D. Mohn, Z. Hong, J.F. Mano, Polymer/bioactive glass nanocomposites for biomedical applications: a review, Compos. Sci. Technol. 70 (2010) 1764–1776, https://doi.org/10.1016/j.compscitech.2010.06.002.
[112] K. Rezwan, Q.Z. Chen, J.J. Blaker, A.R. Boccaccini, Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering, Biomaterials 27 (2006) 3413–3431, https://doi.org/10.1016/j.biomaterials.2006.01.039.
[113] J.J. Blaker, S.N. Nazhat, V. Maquet, A.R. Boccaccini, Long-term in vitro degradation of PDLLA/Bioglass bone scaffolds in acellular simulated body fluid, Acta Biomater. 7 (2011) 829–840, https://doi.org/10.1016/j.actbio.2010.09.013.
[114] W. Helen, C.L.R. Merry, J.J. Blaker, J.E. Gough, Three-dimensional culture of annulus fibrosus cells within PDLLA/Bioglass® composite foam scaffolds: assessment of cell attachment, proliferation and extracellular matrix production, Biomaterials 28 (2007) 2010–2020, https://doi.org/10.1016/j.biomaterials.2007.01.011.
[115] J.J. Blaker, V. Maquet, R. Jérôme, A.R. Boccaccini, S.N. Nazhat, Mechanical properties of highly porous PDLLA/Bioglass® composite foams as scaffolds for bone tissue engineering, Acta Biomater. 1 (2005) 643–652, https://doi.org/10.1016/j.actbio.2005.07.003.
[116] S. Verrier, J.J. Blaker, V. Maquet, L.L. Hench, A.R. Boccaccini, PDLLA/Bioglass® composites for soft-tissue and hard-tissue engineering: an in vitro cell biology assessment, Biomaterials 25 (2004) 3013–3021, https://doi.org/10.1016/j.biomaterials.2003.09.081.
[117] J.J. Blaker, J.E. Gough, V. Maquet, I. Notingher, A.R. Boccaccini, In vitro evaluation of novel bioactive composites based on Bioglass-filled polylactide foams for bone tissue engineering scaffolds, J. Biomed. Mater. Res. A 67 (2003) 1401–1411, https://doi.org/10.1002/jbm.a.20055.
[118] A.M. El-Kady, E.A. Saad, B.M.A. El-Hady, M.M. Farag, Synthesis of silicate glass/poly(l-lactide) composite scaffolds by freeze-extraction technique: characterization and in vitro bioactivity evaluation, Ceram. Int. 36 (2010) 995–1009, https://doi.org/10.1016/j.ceramint.2009.11.012.
[119] Y. Xu, P. Wu, P. Feng, W. Guo, W. Yang, C. Shuai, Interfacial reinforcement in a poly-l-lactic acid/mesoporous bioactive glass scaffold via polydopamine, Colloids Surf. B Biointerfaces 170 (2018) 45–53, https://doi.org/10.1016/j.colsurfb.2018.05.065.
[120] K. Zhang, Y. Wang, M.a. Hillmyer, L.F. Francis, Processing and properties of porous poly(L-lactide)/bioactive glass composites, Biomaterials 25 (2004) 2489–2500, https://doi.org/10.1016/j.biomaterials.2003.09.033.
[121] M.J. Rowe, K. Kamocki, D. Pankajakshan, D. Li, A. Bruzzaniti, V. Thomas, S.B. Blanchard, M.C. Bottino, Dimensionally stable and bioactive membrane for guided bone regeneration: an in vitro study, J. Biomed. Mater. Res. B Appl. Biomater. (2015) 594–605, https://doi.org/10.1002/jbm.b.33430.
[122] Y. fan Goh, M. Akram, A. Alshemary, R. Hussain, Antibacterial polylactic acid/chitosan nanofibers decorated with bioactive glass, Appl. Surf. Sci. 387 (2016) 1–7, https://doi.org/10.1016/j.apsusc.2016.06.054.
[123] J. Wei, Q.Z. Chen, M.M. Stevens, J.A. Roether, A.R. Boccaccini, Biocompatibility and bioactivity of PDLLA/TiO_2 and PDLLA/TiO_2/Bioglass nanocomposites, Mater. Sci. Eng. C 28 (2008) 1–10, https://doi.org/10.1016/j.msec.2007.01.004.
[124] V. Maquet, A.R. Boccaccini, L. Pravata, I. Notingher, R. Jérôme, Preparation, characterization, and in vitro degradation of bioresorbable and bioactive composites based on Bioglass®-filled polylactide foams, Biomed. Mater. Res. A 66A (2003) 335–346, https://doi.org/10.1002/jbm.a.10587.
[125] X.B. Yang, D. Webb, J.J. Blaker, A.R. Boccaccini, V. Maquet, C. Cooper, R.O.C. Oreffo, Evaluation of human bone marrow stromal cell growth on biodegradable polymer/Bioglass® composites, Biochem. Biophys. Res. Commun. 342 (2006) 1098–1107, https://doi.org/10.1016/j.bbrc.2006.02.021.
[126] S.G. Kazarian, K.L. Andrew Chan, V. Maquet, A.R. Boccaccini, Characterisation of bioactive and resorbable polylactide/Bioglass® composites by FTIR spectroscopic imaging, Biomaterials 25 (2004) 3931–3938, https://doi.org/10.1016/j.biomaterials.2003.10.099.
[127] A.I. Leal, S.G. Caridade, J. Ma, N. Yu, M.E. Gomes, R.L. Reis, J.A. Jansen, X.F. Walboomers, J.F. Mano, Asymmetric PDLLA membranes containing Bioglass® for guided tissue regeneration: characterization and in vitro biological behavior, Dent. Mater. 29 (2013) 427–436, https://doi.org/10.1016/j.dental.2013.01.009.
[128] V.V. Meretoja, T. Tirri, M. Malin, J.V. Seppala, T.O. Narhi, Ectopic bone formation in and soft-tissue response to P(CL/DLLA)/bioactive glass composite scaffolds, Clin. Oral Implants Res. 25 (2014) 159–164, https://doi.org/10.1111/clr.12051.
[129] D. Zhang, X. Liu, G. Wu, Forming CNT-guided stereocomplex networks in polylactide-based nanocomposites, Compos. Sci. Technol. 128 (2016) 8–16, https://doi.org/10.1016/j.compscitech.2016.03.003.
[130] H.-S. Ahn, J.-Y. Hwang, M.S. Kim, J.-Y. Lee, J.-W. Kim, H.-S. Kim, U.S. Shin, J.C. Knowles, H.-W. Kim, J.K. Hyun, Carbon-nanotube-interfaced glass fiber scaffold for regeneration of transected sciatic nerve, Acta Biomater. 13 (2015) 324–334, https://doi.org/10.1016/j.actbio.2014.11.026.
[131] A. Gupta, B.J. Main, B.L. Taylor, M. Gupta, C.A. Whitworth, C. Cady, J.W. Freeman, S.F. El-Amin 3rd, In vitro evaluation of three-dimensional single-walled carbon nanotube composites for bone tissue engineering, J. Biomed. Mater. Res. A 102 (2014) 4118–4126, https://doi.org/10.1002/jbm.a.35088.
[132] P.E. Mikael, A.R. Amini, J. Basu, M. Josefina Arellano-Jimenez, C.T. Laurencin, M.M. Sanders, C. Barry Carter, S.P. Nukavarapu, Functionalized carbon nanotube reinforced scaffolds for bone regenerative engineering: fabrication, in vitro and in vivo evaluation, Biomed. Mater. 9 (2014) 35001, , https://doi.org/10.1088/1748-6041/9/3/035001.
[133] S. Poonsawat, S. Phattanarudee, Physical properties of maleated poly(lactic acid) composites containing different functionalized multiwalled carbon nanotubes, J. Nanosci. Nanotechnol. 14 (2014) 3239–3246.
[134] Y. Shi, H. Han, H. Quan, Y. Zang, N. Wang, G. Ren, M. Xing, Q. Wu, Activated carbon fibers/poly(lactic-co-glycolic) acid composite scaffolds: preparation and characterizations, Mater. Sci. Eng. C 43 (2014) 102–108, https://doi.org/10.1016/j.msec.2014.07.007.
[135] I.A.W.B. Siqueira, M.A.F. Corat, B.N. das Cavalcanti, W.A. Ribeiro Neto, A.A. Martin, R.E.S. Bretas, F.R. Marciano, A.O. Lobo, In vitro and in vivo studies of novel poly(D,L-lactic acid), superhydrophilic carbon nanotubes, and nanohydroxyapatite scaffolds for bone regeneration, ACS Appl. Mater. Interfaces 7 (2015) 9385–9398, https://doi.org/10.1021/acsami.5b01066.
[136] Q. Cheng, K. Rutledge, E. Jabbarzadeh, Carbon nanotube-poly(lactide-co-glycolide) composite scaffolds for bone tissue engineering applications, Ann. Biomed. Eng. 41 (2013) 904–916, https://doi.org/10.1007/s10439-012-0728-8.
[137] A. Magiera, J. Markowski, E. Menaszek, J. Pilch, S. Blazewicz, PLA-based hybrid and composite electrospun fibrous scaffolds as potential materials for tissue engineering, J. Nanomater. 2017 (2017) 1–11, https://doi.org/10.1155/2017/9246802.
[138] L.Y. Yeo, J.R. Friend, Electrospinning carbon nanotube polymer composite nanofibers, J. Exp. Nanosci. 1 (2006) 177–209, https://doi.org/10.1080/17458080600670015.
[139] T. Kaur, S. Kulanthaivel, A. Thirugnanam, I. Banerjee, K. Pramanik, Biological and mechanical evaluation of poly(lactic-co-glycolic acid)-based composites reinforced with 1D, 2D and 3D carbon biomaterials for bone tissue regeneration, Biomed. Mater. 12 (2017), https://doi.org/10.1088/1748-605X/aa5f76.
[140] D. Meng, S.N. Rath, N. Mordan, V. Salih, U. Kneser, A.R. Boccaccini, In vitro evaluation of 45S5 Bioglass®-derived glass-ceramic scaffolds coated with carbon nanotubes, J. Biomed. Mater. Res. A 99 A (2011) 435–444, https://doi.org/10.1002/jbm.a.33185.
[141] J. Zhao, V. Castranova, Toxicology of nanomaterials used in nanomedicine, J.

Toxicol. Environ. Health B Crit. Rev. 14 (2011) 593–632, https://doi.org/10.1080/10937404.2011.615113.
[142] M.L. Etheridge, S.A. Campbell, A.G. Erdman, C.L. Haynes, S.M. Wolf, J. McCullough, The big picture on nanomedicine: the state of investigational and approved nanomedicine products, Nanomedicine 9 (2013) 1–14, https://doi.org/10.1016/j.nano.2012.05.013.
[143] S. Trujillo, E. Lizundia, J.L. Vilas, M. Salmeron-Sanchez, PLLA/ZnO nanocomposites: dynamic surfaces to harness cell differentiation, Colloids Surf. B Biointerfaces 144 (2016) 152–160, https://doi.org/10.1016/j.colsurfb.2016.04.007.
[144] J. Ahmed, Y.A. Arfat, E. Castro-Aguirre, R. Auras, Mechanical, structural and thermal properties of Ag–Cu and ZnO reinforced polylactide nanocomposite films, Int. J. Biol. Macromol. 86 (2016) 885–892, https://doi.org/10.1016/j.ijbiomac.2016.02.034.
[145] P. Kanmani, J.-W. Rhim, Properties and characterization of bionanocomposite films prepared with various biopolymers and ZnO nanoparticles, Carbohydr. Polym. 106 (2014) 190–199, https://doi.org/10.1016/j.carbpol.2014.02.007.
[146] A. Brown, S. Zaky, H.J. Ray, C. Sfeir, Porous magnesium/PLGA composite scaffolds for enhanced bone regeneration following tooth extraction, Acta Biomater. 11 (2015) 543–553, https://doi.org/10.1016/j.actbio.2014.09.008.
[147] X. Li, C.L. Chu, L. Liu, X.K. Liu, J. Bai, C. Guo, F. Xue, P.H. Lin, P.K. Chu, Biodegradable poly-lactic acid based-composite reinforced unidirectionally with high-strength magnesium alloy wires, Biomaterials 49 (2015) 135–144, https://doi.org/10.1016/j.biomaterials.2015.01.060.
[148] S.C. Cifuentes, R. Gavilan, M. Lieblich, R. Benavente, J.L. Gonzalez-Carrasco, In vitro degradation of biodegradable polylactic acid/magnesium composites: relevance of Mg particle shape, Acta Biomater. 32 (2016) 348–357, https://doi.org/10.1016/j.actbio.2015.12.037.
[149] J. Meng, Y. Zhang, X. Qi, H. Kong, C. Wang, Z. Xu, S. Xie, N. Gu, H. Xu, Paramagnetic nanofibrous composite films enhance the osteogenic responses of pre-osteoblast cells, Nanoscale 2 (2010) 2565–2569, https://doi.org/10.1039/c0nr00178c.
[150] Q. Cai, Y. Shi, D. Shan, W. Jia, S. Duan, X. Deng, X. Yang, Osteogenic differentiation of MC3T3-E1 cells on poly(l-lactide)/Fe_3O_4 nanofibers with static magnetic field exposure, Mater. Sci. Eng. C 55 (2015) 166–173 https://doi.org/10.1016/j.msec.2015.05.002.
[151] W. Montha, W. Maneeprakorn, N. Buatong, I. Tang, W. Pon-on, Synthesis of doxorubicin-PLGA loading on chitosan stabilized (Mn, Zn)Fe_2O_4 nanoparticles: biological activity and pH-responsive drug release studies, Mater. Sci. Eng. C (2015), https://doi.org/10.1016/j.msec.2015.09.098.
[152] M.L.B. Palacio, B. Bhushan, Bioadhesion: a review of concepts and applications, Philos. Trans. R. Soc. Lond. A Math. Phys. Eng. Sci. 370 (2012) 2321–2347 http://rsta.royalsocietypublishing.org/content/370/1967/2321.abstract.
[153] F.J.O. Brien, Biomaterials & scaffolds for tissue engineering, Mater. Today 14 (2011) 88–95, https://doi.org/10.1016/S1369-7021(11)70058-X.
[154] D.G. Brocks, H.P. Neubauer, H. Strecker, Type IV collagen antigens in serum of diabetic rats: a marker for basement membrane collagen biosynthesis, Diabetologia 28 (1985) 928–932.
[155] Q. Cai, Q. Xu, Q. Feng, X. Cao, X. Yang, X. Deng, Biomineralization of electrospun poly(L-lactic acid)/gelatin composite fibrous scaffold by using a supersaturated simulated body fluid with continuous CO_2 bubbling, Appl. Surf. Sci. 257 (2011) 10109–10118, https://doi.org/10.1016/j.apsusc.2011.06.157.
[156] C.E. Tanase, I. Spiridon, PLA/chitosan/keratin composites for biomedical applications, Mater. Sci. Eng. C 40 (2014) 242–247, https://doi.org/10.1016/j.msec.2014.03.054.
[157] A.R.C. Duarte, J.F. Mano, R.L. Reis, Novel 3D scaffolds of chitosan-PLLA blends for tissue engineering applications: preparation and characterization, J. Supercrit. Fluids 54 (2010) 282–289, https://doi.org/10.1016/j.supflu.2010.05.017.
[158] J.F. Mano, G. Hungerford, J.L. Gómez Ribelles, Bioactive poly(L-lactic acid)-chitosan hybrid scaffolds, Mater. Sci. Eng. C 28 (2008) 1356–1365, https://doi.org/10.1016/j.msec.2008.03.005.
[159] A. Zhu, M. Zhang, J. Wu, J. Shen, Covalent immobilization of chitosan/heparin complex with a photosensitive hetero-bifunctional crosslinking reagent on PLA surface, Biomaterials 23 (2002) 4657–4665.
[160] B. Mulloy, J. Hogwood, E. Gray, R. Lever, C.P. Page, Pharmacology of heparin and related drugs, Pharmacol. Rev. 68 (2016) 76–141, https://doi.org/10.1124/pr.115.011247.
[161] H. Pan, H. Jiang, W. Chen, Interaction of dermal fibroblasts with electrospun composite polymer scaffolds prepared from dextran and poly lactide-co-glycolide, Biomaterials 27 (2006) 3209–3220, https://doi.org/10.1016/j.biomaterials.2006.01.032.
[162] I.J. Hall Barrientos, E. Paladino, P. Szabó, S. Brozio, P.J. Hall, C.I. Oseghale, M.K. Passarelli, S.J. Moug, R.A. Black, C.G. Wilson, R. Zelkó, D.A. Lamprou, Electrospun collagen-based nanofibres: a sustainable material for improved antibiotic utilisation in tissue engineering applications, Int. J. Pharm. 531 (2017) 67–79, https://doi.org/10.1016/j.ijpharm.2017.08.071.
[163] M. Frydrych, S. Román, S. Macneil, B. Chen, Biomimetic poly(glycerol sebacate)/poly(L-lactic acid) blend scaffolds for adipose tissue engineering, Acta Biomater. 18 (2015) 40–49, https://doi.org/10.1016/j.actbio.2015.03.004.
[164] B. Xu, B. Rollo, L.A. Stamp, D. Zhang, X. Fang, D.F. Newgreen, Q. Chen, Non-linear elasticity of core/shell spun PGS/PLLA fibres and their effect on cell proliferation, Biomaterials 34 (2013) 6306–6317, https://doi.org/10.1016/j.biomaterials.2013.05.009.
[165] R.A. Wach, A. Adamus, A.K. Olejnik, J. Dzierzawska, J.M. Rosiak, Nerve guidance channels based on PLLA-PTMC biomaterial, J. Appl. Polym. Sci. 127 (2013) 2259–2268, https://doi.org/10.1002/app.37932.
[166] C.-W. Hsiao, M.-Y. Bai, Y. Chang, M.-F. Chung, T.-Y. Lee, C.-T. Wu, B. Maiti, Z.-X. Liao, R.-K. Li, H.-W. Sung, Electrical coupling of isolated cardiomyocyte clusters grown on aligned conductive nanofibrous meshes for their synchronized beating, Biomaterials 34 (2013) 1063–1072, https://doi.org/10.1016/j.biomaterials.2012.10.065.
[167] M. Gizdavic-Nikolaidis, S. Ray, J.R. Bennett, A.J. Easteal, R.P. Cooney, Electrospun functionalized polyaniline copolymer-based nanofibers with potential application in tissue engineering, Macromol. Biosci. 10 (2010) 1424–1431, https://doi.org/10.1002/mabi.201000237.
[168] A. Subramanian, U.M. Krishnan, S. Sethuraman, In vivo biocompatibility of PLGA-polyhexylthiophene nanofiber scaffolds in a rat model, Biomed. Res. Int. 2013 (2013) 390518, https://doi.org/10.1155/2013/390518.
[169] Y. Sun, H. Li, Y. Lin, L. Niu, Q. Wang, Integration of poly(3-hexylthiophene) conductive stripe patterns with 3D tubular structures for tissue engineering applications, RSC Adv. 6 (2016) 72519–72524, https://doi.org/10.1039/c6ra14109a.
[170] P. Debieux, C.E.S. Franciozi, M. Lenza, M.J. Tamaoki, R.A. Magnussen, F. Faloppa, J.C. Belloti, Bioabsorbable versus metallic interference screws for graft fixation in anterior cruciate ligament reconstruction, Cochrane Database Syst. Rev. 7 (2016) CD009772, , https://doi.org/10.1002/14651858.CD009772.pub2.
[171] R. Gutwald, H. Pistner, J. Reuther, J. Mühling, Biodegradation and tissue-reaction in a long-term implantation study of poly(L-lactide), J. Mater. Sci. Mater. Med. 5 (1994) 485–490, https://doi.org/10.1007/BF00058988.
[172] J. Pan, Y. Wang, S. Qin, B. Zhang, Y. Luo, Grafting reaction of poly(D,L)lactic acid with maleic anhydride and hexanediamine to introduce more reactive groups in its bulk, J. Biomed. Mater. Res. B. Appl. Biomater. 74 (2005) 476–480, https://doi.org/10.1002/jbm.b.30208.
[173] E. Santos, G. Orive, R. Hernández, J. Pedraz, Cell-biomaterial interaction: strategies to mimic the extracellular matrix, On Biomimetics (2009) 529–558, https://doi.org/10.5772/21634.
[174] G.Z. Jin, H.W. Kim, Nanocomposite bioactive polymeric scaffold promotes adhesion, proliferation and osteogenesis of rat bone marrow stromal cells, Tissue Eng. Regen. Med. 11 (2014) 284–290, https://doi.org/10.1007/s13770-014-0033-8.
[175] J. Filipowska, K. Cholewa-Kowalska, J. Wieczorek, D. Semik, Z. Dabrowski, M. Łaczka, A.M. Osyczka, Ectopic bone formation by gel-derived bioactive glass-poly-L-lactide-co-glycolide composites in a rabbit muscle model, Biomed. Mater. 12 (2017), https://doi.org/10.1088/1748-605X/aa4eb7.
[176] J. Filipowska, J. Pawlik, K. Cholewa-Kowalska, G. Tylko, E. Pamula, L. Niedzwiedzki, M. Szuta, M. Laczka, A.M. Osyczka, Incorporation of sol-gel bioactive glass into PLGA improves mechanical properties and bioactivity of composite scaffolds and results in their osteoinductive properties, Biomed. Mater. 9 (2014), https://doi.org/10.1088/1748-6041/9/6/065001.
[177] E. Pamula, J. Kokoszka, K. Cholewa-Kowalska, M. Laczka, L. Kantor, L. Niedzwiedzki, G.C. Reilly, J. Filipowska, W. Madej, M. Kolodziejczyk, G. Tylko, A.M. Osyczka, Degradation, bioactivity, and osteogenic potential of composites made of PLGA and two different sol–gel bioactive glasses, Ann. Biomed. Eng. 39 (2011) 2114–2129, https://doi.org/10.1007/s10439-011-0307-4.
[178] S. Kehoe, X.F. Zhang, D. Boyd, Composition–property relationships for an experimental composite nerve guidance conduit: evaluating cytotoxicity and initial tensile strength, J. Mater. Sci. Mater. Med. 22 (2011) 945–959, https://doi.org/10.1007/s10856-011-4263-1.
[179] X.F. Zhang, A. Coughlan, H. O'Shea, M.R. Towler, S. Kehoe, D. Boyd, Experimental composite guidance conduits for peripheral nerve repair: an evaluation of ion release, Mater. Sci. Eng. C 32 (2012) 1654–1663, https://doi.org/10.1016/j.msec.2012.04.058.
[180] X.F. Zhang, S. Kehoe, S.K. Adhi, T.G. Ajithkumar, S. Moane, H. O'Shea, D. Boyd, Composition–structure–property (Zn2+ and Ca2+ ion release) evaluation of Si–Na–Ca–Zn–Ce glasses: potential components for nerve guidance conduits, Mater. Sci. Eng. C 31 (2011) 669–676, https://doi.org/10.1016/j.msec.2010.12.016.
[181] X.F. Zhang, H. O'Shea, S. Kehoe, D. Boyd, Time-dependent evaluation of mechanical properties and in vitro cytocompatibility of experimental composite-based nerve guidance conduits, J. Mech. Behav. Biomed. Mater. 4 (2011) 1266–1274, https://doi.org/10.1016/j.jmbbm.2011.04.013.
[182] R. Grande, L.A. Pessan, A.J.F. Carvalho, Ternary melt blends of poly(lactic acid)/poly(vinyl alcohol)-chitosan, Ind. Crop. Prod. 72 (2015) 159–165, https://doi.org/10.1016/j.indcrop.2014.12.041.
[183] J. Wang, L. Qu, X. Meng, J. Gao, H. Li, G. Wen, Preparation and biological properties of PLLA/beta-TCP composites reinforced by chitosan fibers, Biomed. Mater. 3 (2008) 25004, , https://doi.org/10.1088/1748-6041/3/2/025004.
[184] I.J. Hall Barrientos, E. Paladino, S. Brozio, M.K. Passarelli, S. Moug, R.A. Black, C.G. Wilson, D.A. Lamprou, Fabrication and characterisation of drug-loaded electrospun polymeric nanofibers for controlled release in hernia repair, Int. J. Pharm. 517 (2017) 329–337, https://doi.org/10.1016/j.ijpharm.2016.12.022.
[185] L.C. Mozdzen, A. Vucetic, B.A.C. Harley, Modifying the strength and strain concentration profile within collagen scaffolds using customizable arrays of polylactic acid fibers, J. Mech. Behav. Biomed. Mater. 66 (2017) 28–36, https://doi.org/10.1016/j.jmbbm.2016.10.017.
[186] D.W. Chen, Y.H. Hsu, J.Y. Liao, S.J. Liu, J.K. Chen, S.W.N. Ueng, Sustainable release of vancomycin, gentamicin and lidocaine from novel electrospun sandwich-structured PLGA/collagen nanofibrous membranes, Int. J. Pharm. 430 (2012) 335–341, https://doi.org/10.1016/j.ijpharm.2012.04.010.
[187] K. Wei, Y. Li, H. Mugishima, A. Teramoto, K. Abe, Fabrication of core-sheath structured fibers for model drug release and tissue engineering by emulsion electrospinning, Biotechnol. J. 7 (2012) 677–685, https://doi.org/10.1002/biot.201000473.

[188] S.A. Salem, N.M. Hwei, A. Bin Saim, C.C.K. Ho, I. Sagap, R. Singh, M.R. Yusof, Z. Md Zainuddin, R.Bt.H.J. Idrus, Polylactic-co-glycolic acid mesh coated with fibrin or collagen and biological adhesive substance as a prefabricated, degradable, biocompatible, and functional scaffold for regeneration of the urinary bladder wall, J. Biomed. Mater. Res. A 101 A (2013) 2237–2247, https://doi.org/10.1002/jbm.a.34518.
[189] H. Kenar, G.T. Kose, M. Toner, D.L. Kaplan, V. Hasirci, A 3D aligned microfibrous myocardial tissue construct cultured under transient perfusion, Biomaterials 32 (2011) 5320–5329, https://doi.org/10.1016/j.biomaterials.2011.04.025.
[190] H. Kenar, G.T. Kose, V. Hasirci, Design of a 3D aligned myocardial tissue construct from biodegradable polyesters, J. Mater. Sci. Mater. Med. 21 (2010) 989–997, https://doi.org/10.1007/s10856-009-3917-8.
[191] H. Shi, Q. Gan, X. Liu, Y. Ma, J. Hu, Y. Yuan, C. Liu, Poly(glycerol sebacate)-modified polylactic acid scaffolds with improved hydrophilicity, mechanical strength and bioactivity for bone tissue regeneration, RSC Adv. 5 (2015) 79703–79714, https://doi.org/10.1039/C5RA13334C.
[192] B. Xu, Y. Li, X. Fang, G.A. Thouas, W.D. Cook, D.F. Newgreen, Q. Chen, Mechanically tissue-like elastomeric polymers and their potential as a vehicle to deliver functional cardiomyocytes, J. Mech. Behav. Biomed. Mater. 28 (2013) 354–365, https://doi.org/10.1016/j.jmbbm.2013.06.005.
[193] L. Wang, Y. Wu, T. Hu, B. Guo, P.X. Ma, Electrospun conductive nanofibrous scaffolds for engineering cardiac tissue and 3D bioactuators, Acta Biomater. 59 (2017) 68–81, https://doi.org/10.1016/j.actbio.2017.06.036.
[194] A.M. Shah, M.R.A. Kadir, S.I.A. Razak, Novel PLA-based conductive polymer composites for biomedical applications, JOM 69 (2017) 2838–2843, https://doi.org/10.1007/s11837-017-2577-2.