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POLY(LACTIC ACID) NANOFIBROUS SCAFFOLDS FOR TISSUE ENGINEERING

Marco Santoro[#a], **Sarita R. Shah**[#b], **Jennifer L. Walker**[b], and **Antonios G. Mikos**[a,b,*]

[a]Department of Chemical and Biomolecular Engineering, Rice University, Houston, TX 77005

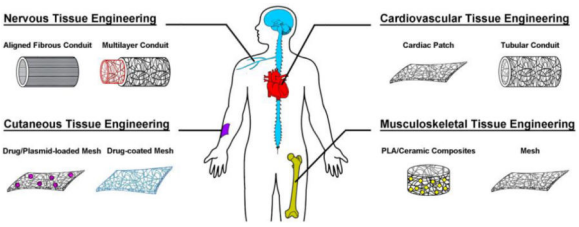
[b]Department of Bioengineering, Rice University, Houston, TX 77030

[#] These authors contributed equally to this work.

Abstract

Poly(lactic acid) (PLA) is a synthetic polyester that has shown extensive utility in tissue engineering. Synthesized either by ring opening polymerization or polycondensation, PLA hydrolytically degrades into lactic acid, a metabolic byproduct, making it suitable for medical applications. Specifically, PLA nanofibers have widened the possible uses of PLA scaffolds for regenerative medicine and drug delivery applications. The use of nanofibrous scaffolds imparts a host of desirable properties, including high surface area, biomimicry of native extracellular matrix architecture, and tuning of mechanical properties, all of which are important facets of designing scaffolds for a particular organ system. Additionally, nanofibrous PLA scaffolds hold great promise as drug delivery carriers, where fabrication parameters and drug-PLA compatibility greatly affect the drug release kinetics. In this review, we present the latest advances in the use of PLA nanofibrous scaffolds for musculoskeletal, nervous, cardiovascular, and cutaneous tissue engineering and offer perspectives on their future use.

Graphical abstract



Keywords

PLA; scaffolds; nanofibers; tissue engineering; drug delivery

[*]To whom correspondence may be addressed: Antonios G. Mikos, PhD, Department of Bioengineering, MS-142, BioScience Research Collaborative, Rice University, 6500 Main Street, Houston, TX 77030, mikos@rice.edu, Tel: (713) 348-5355, Fax: (713) 348-4244.

1. Introduction

Poly(lactic acid) (PLA) is one of the most widely used synthetic polymers in the biomedical field [1, 2]. First synthesized by Carothers in 1932, PLA is produced from polycondensation of lactic acid or by ring opening polymerization of the cyclic dimer lactide [3, 4]. Like other polyesters, PLA degrades by non-enzymatic hydrolysis, and its byproducts are eliminated through normal cell metabolism [5]. The cytocompatibility and biodegradability of PLA make it an ideal candidate for implantable devices [5, 6].

The regulation of PLA-based devices by the Food and Drug Administration has raised further interest in the use of PLA in the field of tissue engineering. Tissue engineering aims to restore, sustain, or improve tissue function through the combination of three components: scaffolds, bioactive molecules, and/or cells [7]. Although not all tissue engineering approaches involve the use of all three components, the presence of a biocompatible scaffold is essential to provide the architectural cues crucial for the regeneration of large defects [8]. PLA has been widely employed to fulfill this requirement, not only for its intrinsic cytocompatibility and biodegradability, but also because the chirality of lactic acid (L- and D-lactic acid) can be leveraged to synthesize PLA with different stereoregularities. Stereoregularity influences the physicochemical properties of the material, such as mechanical and thermal properties and degradation characteristics [9]. These aspects are critical in many tissue engineering strategies, as scaffolds that can be engineered to match the mechanical properties of the native tissue are likely to be successful. Consequently, PLA has been widely used in tissue engineering applications, both as scaffolds and as drug delivery systems [4, 9, 10].

Electrospinning and thermally-induced phase separation (TIPS) are the most common techniques used in the recent literature for the fabrication of fibrous scaffolds. Electrospinning is an established technique used to fabricate fibrous scaffolds whose properties (such as porosity, pore size, fiber size) can be easily tuned [11]. Fabrication parameters such as polymer solvent, polymer concentration, voltage, and collector distance can be varied to modify fiber and scaffold properties. However, varying these fabrication parameters globally influences the resulting scaffold, and individual properties cannot be independently tuned. A typical example is the increasing pore size with the increasing fiber size [11, 12]. Another less common technology used to fabricate PLA scaffolds is TIPS [13]. TIPS has been used for fabricating nanofibrous poly(L-lactic acid) (PLLA) scaffolds that mimic the structure of fibrillar collagen while maintaining macropores that can facilitate nutrient exchange and cell migration [13]. TIPS is based on the phase separation of a homogeneous polymer solution into a polymer-rich and a solvent-rich phase, typically induced by either cooling the solution or adding an immiscible solvent [13, 14]. Although the detailed physical mechanism of TIPS is still not fully understood, during this process the polymer crystallizes into nanofiber bundles that mimic the structure of native ECM [14].

Nanofibrous PLA materials find wide applicability not only as scaffolds for tissue regeneration but also as drug delivery vehicles, especially when fabricated via electrospinning. The simplest method for drug-loading is direct adsorption of drug to the surface of nanofibers, which leverages the intrinsic large surface area of nanoscale materials

[15]. Direct adsorption relies on non-covalent chemical interactions, such as electrostatic and van der Waals interactions, between the drug and the polymer to facilitate binding of the drug to the scaffold. Drug diffusion from the polymer surface is facilitated due to the high porosity and surface area offered by the use of nanofibers, often times leading to a high initial release of drug upon contact with release medium, referred to as “burst release.” This method is particularly desirable for drugs and gene constructs that may be sensitive to the organic solvents or high voltage used in electrospinning [16].

Hydrophobic drugs that are soluble in organic solvents can be directly mixed into solution of PLA for electrospinning with homogeneous distribution in the fibers. Hydrophilic water-soluble drugs can be incorporated into PLA through water/oil emulsification, allowing for a simple and cost-effective method to electrospin drug-loaded nanofibrous scaffolds with drug loading and encapsulation efficiency higher than other delivery carriers, such as hydrogels and liposomes [17, 18]. This method entraps drug within the polymer matrix as well as retaining some drug at the polymer surface, taking advantage of the degradability of PLA and leading in general to sustained release kinetics with an early burst. The release profile depends on the drug distribution within the fiber section, which is partly dictated by interactions between PLA and the drug of choice. In particular, hydrophilic drugs may undergo phase separation when mixed with hydrophobic polymers like PLA, resulting in a burst release of drug due to a high fraction of drug at the fiber surface [19].

To address this issue, coaxial electrospinning has emerged as a way to spin fibers with a core-shell morphology, where the drug is dissolved in a compatible material in the core while the outer PLA layer determines the release kinetics and protects the drug from the surrounding environment [20, 21]. This approach, together with the more recently developed emulsion electrospinning [18], is now pursued to encapsulate sensitive growth factors and plasmids and to minimize the interaction between the drug and the PLA solvent that may denature the biomolecule/genetic material [22–24]. In the case of drugs that demonstrate slow release rates due to the low wettability of PLA, such as the model protein cytochrome C, the hydrophobic PLA nanofibers can be blended with hydrophilic nanofibers (e.g. polyethylenimine or poly(L-lysine)) to tune the wettability of the overall scaffold, resulting in increased penetration of water into the mat and increasing the release of drug [25]. Another less common method of drug loading includes immobilization of drug onto the polymer surface through methods such as layer-by-layer deposition. This strategy is particularly useful for charged entities such as negatively changed DNA for gene delivery applications, where a positively charged macromolecule such as polyethylenimine can be used as a countercharge [16, 26].

Release kinetics are an important consideration when designing drug-loaded scaffolds, and choice of polymer, loading method, and scaffold parameters largely determine the final mechanisms of release. In general, there are three major mechanisms of release from electrospun nanofiber PLA membranes: desorption, diffusion, and degradation. PLA nanofibers loaded by mixing typically exhibit an initial burst release followed by a reservoir-type release [27]. The initial burst release is due to desorption of drug from the outermost surface fibers, usually followed by diffusion-mediated release. Using ibuprofen as a model drug, it has been shown that altering scaffold parameters such as spinning time can affect the

fiber density within the membrane, consequently affecting the penetration of water into the membrane as well as the porosity of the membrane [27]. Membranes with lower fiber density have high porosity and allow free penetration of water and release of drug, while higher fiber densities have lower porosity and pack drug molecules closer together, restraining drug delivery. In general, drug-loaded electrospun PLA nanofiber mats demonstrate solution-diffusion kinetics, and time-scale can be tuned through a variety of processing parameters, such a fabrication method, drug choice and ionization state, and uniaxial/coaxial electrospinning [28].

Coaxial electrospinning can remove desorption from the PLA surface as a major release mechanism, as the drug is encapsulated within the core. Entrapment of drug in a core within a porous PLA sheath can result in diffusion-dominated release kinetics [29], while entrapment within a solid PLA sheath can promote degradation as the driving mechanism for release [30]. However, it is important to note that the kinetics for coaxial spun fibers can be highly dependent on processing parameters and may still show desorption-diffusion release kinetics [31]. Scaffolds produced by electrostatic layer-by-layer deposition or adsorption utilize competitive binding of serum proteins to drive release of the charged complexes from the scaffold [26, 32].

Despite its many desirable properties, the main concern with the use of PLA lies in its degradation products. PLA degrades into lactic acid, a relatively strong acid that can elicit an inflammatory response [1]. This effect is further exacerbated by the fact that PLA-based devices commonly undergo bulk erosion. As a result, the accumulation of acidic products within the bulk of the material accelerates its degradation, leading eventually to a sudden loss of its mechanical integrity and a delayed inflammatory response [1, 10]. However, PLA is still a preferred material for scaffold fabrication because of the reduced concentration of degradation products with increased porosity. Consequently, several approaches have been proposed to mitigate the shortcomings of this synthetic polymer including preparation of lactic acid copolymers and PLA-based composites [33–36].

In this review, we discuss advances with PLA scaffolds for tissue engineering applications during the last five years. Specifically, we focus on the use of lactic acid homopolymers for the fabrication of scaffolds and drug delivery systems for tissue engineering.

2. PLA Scaffolds for Musculoskeletal Tissue Engineering

Musculoskeletal defects are common and can result from a variety of etiologies, including trauma, infection, or underlying pathology. Failure to adequately address defects in bone, muscle, or tendon may lead to significant loss of function and lower quality of life for those affected. In light of the significant role of PLA in the orthopedic field, it is not surprising that PLA continues to play a central role in many musculoskeletal tissue engineering strategies [37]. Scaffolds for bone tissue engineering are typically fabricated with low surface area to volume ratio geometries, usually cylinders, which provide mechanical stability and an environment conducive to bone regeneration [33, 38]. To this end, mechanical properties and degradation kinetics of PLA-based scaffolds can be tuned by varying the racemic mixture of lactic acids composing the polymer chains [10].

Among the techniques used to process PLA, TIPS has been leveraged to fabricate PLLA scaffolds with nanoscale features [14]. Cylindrical PLLA nanofibrous scaffolds fabricated using with TIPS have demonstrated significantly greater surface area than raw PLLA material, which consequently leads to higher protein adsorption but also faster degradation. This shortcoming can be mitigated by using a dual TIPS process to form a chitosan network within a PLLA network. The addition of chitosan slows the PLLA degradation kinetics and makes the resulting scaffold more biomimetic, as shown by *in vitro* cell viability tests with mesenchymal stem cells [13].

In an attempt to design scaffolds suitable for load-bearing applications, a common strategy to improve PLA mechanical properties for bone applications involves the use of ceramics, rather than the more common metal implants [39, 40]. For example, TIPS and salt leaching have been used together to produce nanocomposite scaffolds made of PLLA and β-tricalcium phosphate (β-TCP) [41]. While the PLLA provides macropores to facilitate *in vivo* neovascularization and nutrient exchange, β-TCP nanoparticles mimic native bone microarchitecture and strengthen the resulting composite. Compressive modulus and cell viability increased in a β-TCP-dependent fashion, with little effect on scaffold overall porosity [41]. Similar results were found when using hydroxyapatite (HA) modified with silane groups to improve the ceramic/PLLA interactions [42]. By increasing HA hydrophobicity, the ceramic was better dispersed in the PLLA phase, further improving the mechanical properties of the resulting scaffold [42].

While PLA found the greatest applicability in bone repair and regeneration, it has been recently used to engineer other musculoskeletal tissues. Several investigations attempted to fabricate 2-dimensional scaffolds, usually sheets or films, with nano- and micro-features that resemble the properties of collagen fibers, a key component of connective tissues like bone, but also cartilage, ligaments, and tendons [13, 38, 43, 44]. Phase separation micromolding has been used to fabricate PLLA sheets for muscle applications, in which a PLLA solution was casted on a patterned substrate and then exposed to a non-solvent to induce phase separation, producing a nanofibrous scaffold [43]. By optimizing parameters such as PLLA molecular weight and weight fraction, and pattern design, it was possible to produce highly porous fibrous scaffolds with interconnected porosity that increased cell-cell contact in progenitor myoblasts [43].

Poly(L-*co*-D,L lactic acid) (PLDLA) has also been employed to engineer the anterior cruciate ligament (ACL), with the objective of producing a scaffold that matches native collagen fibrous architecture and mechanical properties [44]. Specifically, electrospun PLDLA fibers were exposed to a water solution at a temperature higher than the PLDLA glass transition temperature. The thermally induced stress within the polymer network was exploited to produce crimp-like fibers and to alter the mechanical properties of the scaffold. Scaffolds fabricated via this method exhibited a compressive modulus close to that of native ACL. Additionally, the crimp-like pattern promoted ECM deposition by fibroblasts and the formation of fascicles, a distinctive architectural feature of the ECM of native ACL [44].

Musculoskeletal tissue engineering has harnessed the chemical and mechanical properties of PLA to engineer both hard and soft tissues [2, 39, 45, 46]. The combination of L- and D-

lactic acid offers the possibility to tune polymer crystallinity, mechanical properties, and degradation kinetics [1, 2, 10, 47]. Additionally, PLLA has been blended with poly(D-lactic acid) (PDLA), resulting in a fibrous scaffold with higher compressive and tensile strength than scaffolds made of pure PLLA or PDLA [47]. Nevertheless, a major challenge in bone tissue engineering involves the development of mechanically strong scaffolds that are highly porous enabling vascularization [37]. Future research with PLA will likely focus on the design of L/D-lactic acid copolymers to develop new materials suitable for load-bearing applications. Additionally, the incorporation of ceramics will continue being a valuable strategy to improve the mechanical properties of PLA [36].

3. PLA Scaffolds for Nervous Tissue Engineering

The destruction of peripheral nerves due to injury, pathology, or surgical intervention can cause severe functional and aesthetic deficits. The current gold standard for nerve repair is autologous nerve grafting. However, this process has several drawbacks, including donor site morbidity, limited donor tissue, need for a second surgical site, and mismatch between donor and recipient nerves [48]. Scaffolds for nerve tissue engineering are typically either hollow or filled tubes designed to be biocompatible, degradable, and mechanically matched to nerves to support cells, growth factor release, or a combination of both [48]. In addition, variations in topography, conduit design, and functionalization have become increasingly popular modes of optimizing scaffold design [49]. Because of these design criteria, PLA and its composites have been utilized in the development of degradable nerve guidance conduits.

The fabrication of nerve conduits from PLA fibers has advanced significantly beyond simple tubes, and in recent years, many researchers have focused on variations in the alignment, topography, and mechanical properties of PLA fibrous scaffolds to assist in the support of nerve regeneration. For instance, the mechanical strength of PLA sutures can be enhanced by rotor-twisting into filaments and microbraiding into single or multilayer tubes [50]. When evaluated by subcutaneous implantation in rats, it was demonstrated that these conduits maintained lumen and wall integrity, which can be of concern with polymers that swell significantly or degrade too quickly [50]. Furthermore, implantation of the conduits into a 10 mm defect in rat sciatic nerve resulted in nerve regeneration in all animals, with histologically visible axon-Schwann cell regeneration units and minimal inflammation [50]. Recent investigations have also sought to combine microscale and nanoscale features by fabricating nanofibrous conduit scaffolds with single or multiple microchannels [51, 52]. *In vitro* results have shown that PLA nanofibrous conduits fabricated by injection molding/TIPS had more than three orders of magnitude greater surface area than solid wall tubes, thus impacting protein adsorption and cell adhesion [51]. Results from this study showed increased adhesion of rat PC12 cells and rabbit patellar fibroblasts to PLA nanofibrous scaffolds compared to solid wall scaffolds [51]. This strategy has been widely applied in tissue engineering to several biomaterials, including PLA and PCL, to modify the surface topography of the scaffold and ultimately influence cell phenotype and long-term differentiation [52]. The dominant effects on cellular growth are likely due to the orientation of fibers. However, synthetic biomaterials can vary greatly in terms of mechanical properties and degradation time, two parameters that affect further development of these scaffolds as gene or drug delivery vehicles [53, 54].

While many studies have evaluated the adhesion of differentiated cells to PLA scaffolds, other researchers have explored these scaffolds as substrates to support the differentiation of stem cells. Nanofibrous mats of PLLA functionalized with the peptide sequence YIGSR through click-chemistry significantly impacted the differentiation of mouse embryonic stem cells [55]. Electrospun mats of aligned or random PLLA nanofibers were fabricated and were either functionalized or left untreated. Evaluation of neuron-specific class III β-tubulin, neurite extension, and gene expression for neural markers showed that aligned and functionalized PLLA nanofibrous scaffolds increased the proportion of embryonic stem cells that demonstrated markers of neural differentiation compared to mats of either random or untreated fibers [55]. Similarly, coaxial electrospinning was used to fabricate PLLA/gelatin composites for neuronal stem cell differentiation [56]. These composite scaffolds incorporated controlled release of retinoic acid and purmorphamine from the gelatin fibers [56]. Contrary to most coaxially spun composites of PLLA, drug-loaded cross-linked gelatin comprised the outer sheath with an interior core of PLLA. This configuration allows for early quick release of drug while using PLLA nanofibers to comprise the structural integrity of the scaffold. Drug release demonstrated an attenuated burst release at higher gelatin cross-linking, as expected [56]. Engineered neural stem-like cells cultured on scaffolds loaded with retinoic acid and purmorphamine were able to differentiate toward a neuronal lineage, and neurite length was greatest on fibers with these instructive cues [56]. Coaxial electrospun nanofibrous scaffolds comprising a silk fibroin core with a PLA sheath have been investigated for the delivery of nerve growth factor to support differentiation of neuronal stem cells [24]. Nerve growth factor was incorporated into the silk fibroin core to preserve bioactivity and attenuate burst release. These scaffolds were also plasma treated in order to increase wettability and attachment of PC12 neuronal stem cells [24]. Neurite extension was shown to be enhanced on air plasma treated coaxial nanofibrous scaffolds eluting nerve growth factor when PC12 cells were cultured in differentiation medium without the growth factor [24]. Embryonic E9 chick dorsal root ganglion cells and rat Schwann cells cultured on highly aligned PLA nanofibrous scaffolds promoted neurite extension parallel to fibers, as well as aligned Schwann attachment and cell growth [57]. This investigation clearly demonstrated the importance of fiber alignment by showing that the presence of transverse fibers had the ability to divert or even stop neurite extension [57].

Recent research on PLA nanofibrous nerve conduits has focused on the optimization of fiber design and surface topography for cell survival, proliferation, and/or differentiation. Though some results have indicated that the incorporation of microchannels or microgrooves to the surface of conduits can improve vascularity [58], the final utility of this improvement is currently unclear, and focus has shifted towards the use of nanofibrous scaffolds to promote nerve regeneration. Recent research has also demonstrated that the increase in surface area from utilizing nanofibers and the fabrication of highly aligned fiber geometry scaffolds, mimicking the fiber alignment of nerves, improves the suitability of scaffolds for cell growth [55, 57].

4. PLA Scaffolds for Cardiovascular Tissue Engineering

Cardiovascular disease is the leading cause of death worldwide, warranting a serious look at tissue engineering strategies to replace cardiovascular tissues [59]. There is large-scale need

for scaffolds that support the regeneration of heart and blood vessels, leading to the use of PLA nanofibrous scaffolds for these applications. More in-depth reviews of the physiology behind the need for tissue engineering strategies to address cardiovascular problems are available elsewhere in the literature [59–61]. In recent years, PLA nanofibrous scaffolds have been most commonly used for the purpose of vascular tissue engineering, although there are instances where PLA nanofibrous patches are fabricated for cardiac muscle repair [62]. Similar to nerve conduit scaffolds, the design of PLA fibrous vascular scaffolds requires a tube with hollow lumen that is biocompatible, degradable, and mechanically compliant with the graft site.

PLA nanofibrous tubes have emerged as a popular scaffold type for vascular tissue engineering, and researchers have attempted to improve scaffold biomimicry by developing a bilayered electrospun scaffold comprising a nano- to micro-scale PLA fibrous outer layer and silk fibroin-gelatin nanofibrous inner layer [63]. The outer PLA fibrous layer was shown to support the growth and proliferation of 3T3 mouse fibroblasts, while the inner silk fibroin-gelatin layer supported the attachment and growth of human umbilical vein endothelial cells [63]. Subcutaneous implantation of the scaffold demonstrated minimal inflammatory response, and at 3 months, the authors reported the formation of a connective vascular network coinciding with degradation of the implant [63]. Another study evaluated PLA nanofibrous scaffolds fabricated via phase separation and seeded with adult primary human aortic smooth muscle cells, demonstrating that cells cultured on nanofibrous scaffolds upregulated gene expression of smooth muscle myosin heavy chain compared to cells on flat films, though there was no difference in expression of smoothelin or myoCD genes [64]. Subcutaneous implantation of scaffolds into nude mice 24 h after cell seeding revealed significant deposition of collagen into the pores of the scaffold and maintenance of human primary aortic smooth muscle cells within the scaffold 2 weeks post-implantation [64]. The PLA nanofibrous scaffold used in this study supported the growth of contractile cells and also confirmed integration into the host tissue [64]. Moreover, the use of a composite scaffold of PLA/gelatin with aligned fibers demonstrated that cells on aligned fibers oriented and elongated with the direction of the fibers, and the presence of gelatin caused an increase in human umbilical vein endothelial cell and smooth muscle cell attachment, likely due to the presence of adhesion sites normally absent on PLA alone [65]. Conduits for vascular tissue engineering are often limited by the tendency for the lumen to clot, especially in small diameter vessels, preventing blood flow from occurring. However, small diameter PLA nanofibrous conduits have been shown to remain patent after 12 months of implantation in the infrarenal aorta of a mouse [66]. In addition, histological and polymerase chain reaction analyses supported the presence of smooth muscle cells, collagen I and III, matrix metalloproteinases-2 and -9, and a macrophage marker, indicating that the conduit was undergoing remodeling [66].

Much of the recent work utilizing PLA nanofibrous scaffolds for cardiovascular tissue engineering has focused on characterizing scaffolds and introducing porosity to improve mass transport of nutrients, metabolic wastes, and degradation products. *In vitro* work has shown that these scaffolds can support the proliferation of cells contributing to vessel development and growth, and *in vivo* implantation in subcutaneous pockets has

demonstrated biocompatibility. However, PLA nanofibrous scaffolds will require additional functional testing in animal models before any clinical translation.

5. PLA Scaffolds for Cutaneous Tissue Engineering

The healing of cutaneous wounds is of immense importance to every field, especially tissue engineering. As the body's primary protection against the outside environment, failure of the skin barrier leads to a host of issues with infection, hydration, and thermoregulation. PLA nanofibrous mats are particularly well suited to address cutaneous healing. Nanofibrous meshes mimic the native topography of the dermal bed and assist in protecting the wound bed, preventing loss of moisture and proteins, and removal of exudate [67]. The large surface area-to-volume ratio of nanofibrous meshes also encourages the attachment and proliferation of cells, promoting the closure of large wounds. Informative reviews of skin anatomy and the use of scaffolds for skin tissue engineering can be found in the literature [67].

In the area of skin regeneration, PLA is particularly useful because nanofibrous mats can be leveraged as drug delivery vehicles as well as providing a hydrophobic barrier against water loss and the environment. Electrospun PLA has been used to entrap and deliver drugs that promote wound healing, especially anti-inflammatory and anti-oxidant molecules, and to facilitate non-viral nucleic acid delivery. Drugs such as alkannin, shikonin, curcumin, and ibuprofen have been loaded into electrospun PLA scaffolds to promote cutaneous wound healing [68–70]. It has been shown that curcumin, a plant extract with anti-inflammatory, anti-oxidant, and wound healing properties, loaded into PLA nanofibrous meshes increased the rate of healing of a cutaneous wound in mice compared to either PLA meshes alone or no treatment [69]. Similarly, ibuprofen-loaded PLA nanofibrous scaffolds support the attachment and proliferation of human epidermal keratinocytes and human dermal fibroblasts [70]. It was also demonstrated in an *in vivo* full thickness mouse skin incision model that cell-seeded ibuprofen-loaded PLA bandages rescued wound contracture and increased blood vessel formation compared to acellular ibuprofen-loaded PLA bandages [70].

PLA nanofibrous scaffolds are ideally suited for local drug delivery to infected cutaneous wounds due to their ability to load a variety of antibacterial drugs [71]. Although uniaxial loading of antibiotics was popular in the past, this strategy has been replaced by more sophisticated methods to gain increased control over release kinetics [71]. For example, in a study comparing the release of gentamicin from uniaxial PLA nanofibers, uniaxial collagen nanofibers, or coaxial nanofibers with a collagen core and a PLA sheath, it was found that collagen fibers release all drug in a burst fashion, while PLA fibers released surface adsorbed drug as a burst but then retained drug within the polymer matrix [31]. The coaxial spun nanofibrous scaffolds showed an intermediate release profile between the uniaxial collagen and PLA release profiles, indicating that gentamicin was not completely entrapped within the collagen core and some drug remained adsorbed to the surface of the PLA [31]. When all three gentamicin-releasing constructs were cultured with MG-63 osteoblasts, no difference in cell viability was noted in comparison to a construct of PLA without gentamicin [31]. Other antibiotics have been incorporated into PLA or PLA composite nanofibrous cutaneous wound dressings, such as mupirocin [72] and tetracycline [73]. In

addition to conventional antibiotics, the antimicrobial peptide bacteriocin has been incorporated into blends of PDLLA and poly(ethylene oxide) (PEO) in an attempt to offer an alternative solution to antibiotic-resistance [74]. As expected, cumulative drug release increased as the ratio of PEO:PDLLA increased, and bacteriocin maintained the majority of its antimicrobial activity [74]. The antimicrobial peptide nisin has also been electrospun into a nanofibrous PEO:PDLLA (50:50) wound dressing and tested against a full-thickness wound infected with *Staphylococus aureus* in a mouse model [75]. Drug-eluting nanofibrous wound dressing significantly reduced the bacterial burden present in the wound, but did not appear to improve wound healing compared to non-loaded nanofibrous wound dressing [75]. While the ideal cutaneous wound dressing would prevent and/or treat infection in conjunction with improving healing, resolution of infection is a minimum requirement for any further therapies to succeed and thus this type of therapy remains useful for cutaneous wound healing. PLA nanofibrous wound dressings have also been doped with silver microparticles and nanoparticles to evaluate the composite mesh as an antibacterial wound dressing [76]. When evaluated in a 3-dimensional co-culture of keratinocytes and *S. aureus*, silver was shown to decrease both *S. aureus* and keratinocyte proliferation [76]. Interestingly, the cell-seeded wound dressings inhibited bacterial growth as much as the presence of silver particles, indicating that a scaffold that is more conducive to cell growth will be more resistant to *S. aureus* infection [76].

In addition to traditional drug delivery, non-viral delivery of plasmids encoding for keratinocyte growth factor via PLA nanofibrous scaffolds has been shown to improve the healing of full thickness cutaneous wounds in mice [77]. Furthermore, higher levels of plasmid-derived keratinocyte growth factor in the wound area correlated to more mature skin tissue with less inflammation and decreased unhealed epithelial wound size [77].

While most applications of cutaneous scaffolds are concerned with the attachment and growth of cells, their use in hypertrophic scarring is more nuanced, requiring modulation of the appropriate balance of cells, inflammation, and extracellular matrix since hypertrophic scarring is a disorder of dermal fibroproliferation [78]. PLA fibrous mats with nano- and micro-fibers can be leveraged to deliver the drug ginsenoside-Rg3 over 3 months and have been shown to reduce the formation of hypertrophic scars in rabbits [78].

PLA nanofibrous mats serve many roles in the healing of cutaneous wounds, including occlusive dressings, mechanical scaffolds, anti-infective devices, and drug delivery vehicles. Research in this area has focused primarily on drug delivery, with results indicating that PLA nanofibrous scaffolds promote cell attachment and skin regeneration without significant inflammation. In addition, cutaneous applications offer additional opportunities to address disorders beyond the classic “critical size defect,” including infection and disorders of normal healing such as hypertrophic scarring.

6. Conclusions

PLA nanofibrous scaffolds have shown themselves to be a versatile tool for tissue engineering, as a 3-dimensional topographical surface for cell attachment, a depot for drug delivery, and a substrate for bio-functionalization. Electrospinning and thermally-induced

phase separation are widely used techniques for the production of nanofibrous scaffolds, and recent refinements upon these processes have enabled the creation of designer scaffolds addressing the needs of specific tissues, such as having fiber alignment and incorporating of bioactive molecules. While many PLA nanofibrous scaffolds have been characterized and evaluated *in vitro*, translation of these scaffolds into human use will require more testing in appropriate animal models. The future of PLA likely lies in its combination with other biomaterials in order to leverage its strengths and mitigate its weaknesses, a potent strategy for the engineering of complex tissues.

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Abbreviations

ACL	Anterior cruciate ligament
β-TCP	β-tricalcium phosphate
BMP-2	Bone morphogenetic protein-2
HA	Hydroxyapatite
PLA	Poly(lactic acid) (if the stereoregularity is not specified)
PDLA	Poly(D-lactic acid)
PLLA	Poly(L-lactic acid)
PDLLA	Poly(D,L-lactic acid)
PLDLA	Poly(L-*co*-D,L lactic acid)
TIPS	Thermally-induced phase separation
PEO	Poly(ethylene oxide)

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Table 1

PLA scaffolds for Musculoskeletal Tissue Engineering.

Scaffold type	Application	Reference
Cylindrical composite of PLLA/chitosan nanofibers via TIPS	*In vitro* culture with mesenchymal stem cells for bone repair	[13]
PLLA/β-TCP nanocomposite disc via TIPS and salt leaching	Scaffold with hierarchical porosity for bone ingrowth	[41]
PLLA/silanized HA nanocomposite via TIPS	Scaffold with improved ceramic/polymer interactions	[42]
PLLA nanofibrous sheet via phase separation micromolding	*In vitro* culture with mouse progenitor myoblasts	[43]
Thermally stressed electrospun PLDLA nanofibrous sheet	*In vitro* testing of scaffold with bovine fibroblasts for anterior cruciate ligament repair	[44]

Table 2

PLA Scaffolds for Nervous Tissue Engineering.

Scaffold type	Application	Reference
Multi-layer microbraided PLA suture conduit	Subcutaneous implantation in a rat	[50]
Multichannel nanofibrous PLLA conduit	*In vitro* cytocompatibility of neuroblasts and fibroblasts	[51]
Peptide-functionalized PLLA nanofibrous scaffold	*In vitro* differentiation of mouse embryonic stem cells	[55]
Drug-releasing coaxial electrospun PLLA/gelatin composite nanofibrous scaffold	*In vitro* neuronal stem cell differentiation and controlled release of neurogenic drugs	[56]
Growth-factor-releasing coaxial electrospun PLA/silk fibroin composite nanofibrous scaffold	*In vitro* release of nerve growth factor and PC12 neuronal stem cell differentiation and neurite extension	[24]
Aligned PLLA nanofibrous scaffold	*In vitro* culture of dorsal root ganglion cells and Schwann cells; neurite formation and extension	[57]

Table 3

PLA Scaffolds for Cardiovascular Tissue Engineering.

Scaffold type	Application	Reference
Nanofibrous PLA patch via rotary jet-spinning	Seeding with neonatal rat ventricular cardiomyocytes as cardiac patch precursor	[62]
Nanofibrous and microfibrous bilayered electrospun PLA/silk fibroin/gelatin scaffold	*In vitro* culture of fibroblasts and endothelial cells; *in vivo* testing in a rat subcutaneous model	[63]
Nanofibrous tubular scaffold via phase separation in sugar template	*In vitro* culture with human aortic smooth muscle cells; subsequent *in vivo* subcutaneous implantation in nude mice	[64]
Nanofibrous tubular scaffold of PLLA/gelatin aligned fibers	*In vitro* culture with human umbilical cord-derived endothelial cells and smooth muscle cells	[65]
Nanofibrous PLA conduit	Infrarenal aortic graft implantation in nude mice	[66]

Table 4

PLA Scaffolds for Cutaneous Tissue Engineering.

Scaffold type	Application	Reference
Drug-loaded electrospun nanofibrous PLLA mesh	*In vitro* drug delivery of wound-healing agents alkannin and shikonin	[68]
Drug-loaded electrospun nanofibrous PLA patch	*In vitro* cytotoxicity of wound-healing agent curcumin on mouse myoblasts; *in vivo* implantation in a full thickness skin defect in mice	[69]
Drug-loaded electrospun nanofibrous PLA scaffold	*In vitro* cytotoxicity test of ibuprofen on human dermal keratinocytes and fibroblasts; *in vivo* implantation in a full thickness mouse skin incision model	[70]
Electrospun nanofibrous PLA scaffold coated with plasmid/poly(ethylenimine)	*In vitro* plasmid deliver and transfection of 3T3 cells; *in vivo* wound healing repair in a mouse dorsal full thickness defect	[77]
Drug-loaded uniaxial PLA, uniaxial collagen, and coaxial collagen core/PLA sheath electrospun nanofiber wound dressing	*In vitro* release of gentamicin, susceptibility testing against pathogenic bacteria, and culture with MG-63 osteoblasts	[31]
Drug-loaded PLA/PEO blend nanofibrous wound dressing	*In vitro* release of antimicrobial peptide bacteriocin and susceptibility testing against pathogenic bacteria	[74]
Drug-loaded PLA/PEO blend nanofibrous wound dressing	*In vitro* testing of antimicrobial peptide nisin against *S. aureus* and *in vivo* evaluation of nanofibrous wound dressing in an infected full-thickness murine cutaneous wound	[75]
Electrospun nanofibrous PLA wound dressing doped with silver nano/microparticles	*In vitro* drug delivery of silver in human dermal keratinocyte culture and antimicrobial effect on *S. aureus*	[76]
Drug-loaded electrospun PLA nano/microfiber wound dressing	*In vivo* delivery of anti-scarring agent 20(R)-ginsenoside Rg3 in a rabbit ear model of hypertrophic scarring	[78]