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Polylactic acid (PLA) controlled delivery carriers for biomedical applications☆

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ABSTRACT

Polylactic acid (PLA) and its copolymers have a long history of safety in humans and an extensive range of applications. PLA is biocompatible, biodegradable by hydrolysis and enzymatic activity, has a large range of mechanical and physical properties that can be engineered appropriately to suit multiple applications, and has low immunogenicity. Formulations containing PLA have also been Food and Drug Administration (FDA)-approved for multiple applications making PLA suitable for expedited clinical translatability. These biomaterials can be fashioned into sutures, scaffolds, cell carriers, drug delivery systems, and a myriad of fabrications. PLA has been the focus of a multitude of preclinical and clinical testing. Three-dimensional printing has expanded the possibilities of biomedical engineering and has enabled the fabrication of a myriad of platforms for an extensive variety of applications. PLA has been widely used as temporary extracellular matrices in tissue engineering. At the other end of the spectrum, PLA's application as drug-loaded nanoparticle drug carriers, such as liposomes, polymeric nanoparticles, dendrimers, and micelles, can encapsulate otherwise toxic hydrophobic anti-tumor drugs and evade systemic toxicities. The clinical translation of these technologies from preclinical experimental settings is an ever-evolving field with incremental advancements. In this review, some of the biomedical applications of PLA and its copolymers are highlighted and briefly summarized.

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1. Introduction

Controlled drug delivery presents numerous advantages, as it reduces premature degradation, improves drug uptake, sustains drug concentrations within the therapeutic window, and reduces side effects. Over the past decade, recent advances in genomics and nanotechnologies have made it possible to effect drug delivery through the use of specifically designed nanoparticle carriers, particularly in the fields of anticancer therapy, vaccines, and theranostic imaging (Table 1). The benefits of nanoparticles include their large volume to surface area ratio, modifiable external shell, biodegradability, biocompatibility, low cytotoxicity, as well as targeting and stimulus-responsive capabilities [1]. They have also been found to improve the solubility of unmodified drug compounds [2]. These qualities make nanoparticles especially safe and effective for both encapsulating and delivering therapeutic agents to targeted diseased cells at an ad hoc controlled rate, thus bringing anticancer therapy closer to the ideal of personalized medicine [3,4].

Advanced drug delivery carriers based on biodegradable polyesters primarily use poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) matrices [5]. Due to their biocompatibility, low levels of immunogenicity, and toxicity, these polyesters can have their physicochemical and mechanical properties safely tailored via selection of polymer molecular weight, copolymerization, and functionalization [6,7]. These polymers have been approved by US Food and Drug Administration (FDA) for human use as sutures, bone implants, and screws, and in formulations for sustained drug delivery as well as vaccine antigens (proteins, peptides, and DNA).

The advantages of employing nanoparticles for antigen delivery have been widely demonstrated. Aside from the shown benefits of tailoring the degradation rate to ensure a controlled release of antigen/ligand, these particles not only protect the antigen load but also allow for the encapsulation of hydrophobic molecules. As new peptide, protein, and DNA-based drugs are developed in the biotechnology sector, the rise of commercial formulations for drug delivery, based on either PLGA or PLA matrices, is also expected to increase. This review discusses the current application of engineered PLA particles and the derivatization of these particles with other polymers or ligands within the biomedical field. We further discuss their comparative effectiveness in passive or active targeting and in controlled release strategies, alongside the corresponding disease target or envisaged application. We will also discuss the PLA bioresorbable matrices used as tissue engineering scaffolds as well as the development of PLA-derived drug delivery systems (DDS) with an emphasis on those systems that have reached clinical trials.

Table 1
Categorical overview of PLA biomedical applications.

Orthopedic
Peripheral nerve and spinal cord injury regeneration
Bioabsorbable screws
Meniscus repair
Guided bone regeneration
Cardiac
Chest wall reconstruction
Stent
Synergy DES
Biolimus-eluting stent
Hybrid stents
Dentistry
Guided tissue regeneration
Biocompatible space fillers
Plastic surgery
Suture
Reconstructive surgery
Dermal fillers
Skin graft
General surgery
Hernia mesh
Gynecology
Stress incontinence mesh
Radiology
Theranostic imaging
Oncology
Drug delivery
Intracranial delivery
Nanoparticles
Intranasal delivery
Micelles
Thermoresponsive hydrogels
Vaccines
Transdermal delivery

2. PLA—unique properties for biomedical applications

PLA was first discovered in the 1700s by a Swedish chemist, Scheele. Its first use for medical application was for the repair of mandibular fractures in dogs [8]. PLA is a hydrophobic aliphatic polyester and has a renewable source, making it affordable and available for biomedical applications [9]. Two optical forms of PLA exist: D-lactide and L-lactide. The physical properties and the biodegradability of PLA can be regulated by employing a hydroxyl acid comonomer component or by racemization of the D- and L-isomers [10]. A semi-crystalline polymer of poly-L-lactide (PLLA) is obtained from L-lactide and is a hard transparent polymer with a tensile strength of 45–70 MPa. Poly(DL-lactide) (PDLLA) is an amorphous polymer with no melting point and much lower tensile strength [10]. The rate of degradation of PLA is dependent upon the degree of crystallinity. The biodegradability of PLA can be tailored by

grafting. Polyethylene glycol (PEG) is the most popular hydrophilic polymer for surface modification and has been used to modify hydrophobic PLA to form amphiphilic copolymer PLA–PEG [11]. Another useful property of PLA is that it is moldable, allowing its applications to take on numerous shapes, including scaffolds, sutures, rods, films, nanoparticles, and micelles.

3. Orthopedic applications

3.1. Peripheral nerve and spinal cord injury regeneration/scaffolds

Peripheral nerve regeneration is limited in artificial conduits due to long lesion gaps, which are prone to the possibility of collapse, scar formation, and early resorption [12]. Synthetic conduits, made from PLA, and other biomaterials have been explored due to their flexibility of chemical and mechanical characteristics, lack of antigenicity, ease of availability, and bioabsorbable nature [13]. Gap lengths of 10 mm or larger in a rat sciatic nerve model have consistently shown regenerative failure with much research focused on this dilemma. The importance of an inner guidance structure for enhancing non-neuronal cell migration across the lesion gap to enhance nerve regeneration is critical. Cai et al. [13] demonstrated that highly permeable and degradable polymer conduits made from PLA induce axonal migration and maturation in a rat model. Permeable PLA conduits increased myelinated axon regeneration across lesion gaps and were significantly greater in combination with filament scaffolds. PLA conduits also supported axon myelination resulting in more myelin and qualitatively better myelin as compared to silicone conduits [13].

Similarly, PLA is utilized in spinal cord repair *in vivo* models. As in peripheral nerve injury, the gap lesion needs to be bridged and the development of glial scar must be limited. PDLLA scaffolds impregnated with brain-derived neurotrophic factor (BDNF) demonstrated tolerance for the implant and the BDNF promoted cell survival and angiogenesis [14]. However, the overall axonal regeneration response was low in this set of studies. Tubular PLA scaffolds have also delivered Schwann cells implanted into a transected rat thoracic spinal cord [15]. Tubes made from PDLLA, or PLA_{50}, or a high molecular weight, slower degrading mixture of PLA mixed with 10 wt% PLA oligomers, or $PLA_{100/10}$, were compared and both led to faster axonal regeneration as compared to controls. Unmyelinated axons and blood vessels were noted in the Schwann cell grafts as early as 2 weeks after implantation, with myelination following after 1 month. The generation response was greater in the Schwann cell filled $PLA_{100/10}$ tubes as compared to the PLA_{50} tubes with the PLA_{50} tube collapsing soon after implantation and the $PLA_{100/10}$ tube breaking into large pieces [15].

A hybrid polymer, which provides structural stability, mechanical integrity, and the ability to be seeded with and deliver cellular components or pharmacological treatment, is an attractive option. Artificial scaffolds made of synthetic biodegradable polymers such as polyglycolic acid (PGA), PLA, and their copolymers have shown potential in combination with neural stem/progenitor cell transplantation [16,17]. The PLA and poly(2-hydroxyethyl methacrylate) (PLA–b-PHEMA) block copolymer was tested in a thoracic spinal cord hemisection in rats and was shown to improve locomotion [18].

Biodegradable materials eliminate the need for a second operative procedure, in which permanent scaffolding is removed. At the same time, the degradation products of biodegradable materials need to be tailored to the environment. The degradation products cannot be cytotoxic or cause an inflammatory reaction, and the rate of polymer degradation must follow that of tissue regeneration [19]. Cell therapy, which can deliver Schwann cells, neural stem, or progenitor cells, can provide many of the factors required for a regenerative environment. Challenges exist, however, in maintaining cell viability, function, and differentiation [19]. The blood–spinal cord barrier is another concern to be managed and delivery strategies of neuroprotective or neuroregenerative molecules need to address these hurdles. Despite these many challenges, combination strategies of biomaterials, cells, and therapeutic molecules should facilitate functional repair to the injured spinal cord [19]. The polymer scaffold must also retain the appropriate mechanical, geometrical, and permeability properties over time to be beneficial to the regenerative process [14].

3.2. Bioabsorbable screws

Metal screws are frequently used at sites of bone fractures to restore mechanical properties and stability. These metallic implants, however, can lead to complications including bone atrophy and infections and upon removal can lead to increased weakening and re-fracture due to the presence of screw holes [20]. Additionally, 7% to 26% of internal bone fractures have been reported to re-fracture after implant removal due to screw cavities [20,21]. Bioresorbable PLA screws have been investigated by numerous groups that have examined shear and pull-out load retention, *in vitro* versus *in vivo* degradation kinetics, and decay products [22,23]. Composite formulations might be optimal to ensure appropriate degradation time as well as mechanical and pull-out strength [20].

3.3. Meniscus repair

Bioabsorbable meniscal repair approaches have been explored with multiple variations and improvements to enhance both the repair and replacement of damaged meniscus. The varying designs of these fasteners have included arrows, darts, screws, and staples. The meniscus has unique biochemical features as a shock absorber and a stabilizer. PLA has proven useful in biodegradable meniscus repair due to its wet-strength half-life of 6 months [24] and its tensile strength of 50 MPa with a modulus of 3.4 GPa [25].

A retrospective study evaluated the midterm healing rate and adverse events following meniscus repair with the BioStinger, a molded bioabsorbable PLLA construct, and showed a clinical success rate of 95% with few adverse events [26]. A comparison of six meniscal single suture repair techniques, including the BioStinger and the Meniscal Dart, a double-reversed barbed non-cannulated implant composed of PLLA, showed these PLA implants had significantly less failure rate and stiffness than two other types of repair techniques [27].

The meniscal arrow (Linvatec, Largo, Florida) is composed of PLLA, retains its strength for up to 1 year and takes another 2–3 years to reabsorb [28]. The FasT-Fix (Smith and Nephew) was then developed with absorbable PLLA anchors. Biomechanical studies have shown favorable results, and strength and load to failure characteristics have shown significant improvements as compared to earlier devices [29]. However the FasT-Fix takes 2 years or longer to reabsorb, which raises concern with regards to possible chondral damage [28]. A study by Kise et al. [30] demonstrated that the FasT-Fix was superior to the BioFix with significantly lower failure rates [30]. A recent study showed that the FasT-Fix was useful and effective in the pediatric population as well [31].

Baek et al. [32] utilized a method to layer aligned PLA electrospun (ES) scaffolds with human meniscus cells embedded in an extracellular matrix hydrogel [32]. This PLA ES scaffold was then tested *in vitro* for cell viability, cell morphology, and gene expression profiles. The PLA scaffold supported meniscus tissue formation; however, no difference in gene expression was seen between the random and the aligned PLA scaffolds [32]. A PLA/PGA scaffold was utilized to deliver human cartilage-derived morphogenetic protein-2 (hCDMP-2)-expressing canine myoblasts at the site of meniscal fibrocartilage injury to facilitate the repair of the injury in a canine model [33]. The PLA/PGA scaffold was fully degraded 8 weeks post-transplantation and was able to promote meniscal repair by fibrocartilage-like tissue regeneration.

3.4. Guided bone regeneration

Autogenous bone transplantation is the gold standard for treatment of bone defects; however, donor site discomfort, postoperative complications, and defined source limit has opened the pathway for new "osteobiologicals." Osteoinductive biomaterials can aid in the treatment of these large bone defects and can be incorporated with growth factors that can stimulate bone healing and regeneration. PLA's biodegradability and controlled degradation rates are beneficial for clinical applications. PLLA is preferred in orthopedic applications since its scaffolds have a porous architecture and mechanical strength [9]. Long PLA chains and their physical entanglements can act as the fixed phase, while polymer chains between the entanglements can be stretched to achieve a temporary shape. Shape memory properties of PLA such as recovery stress and strain may be improved by cross-linking, chemical modification, and the addition of copolymers [34–36]. PLA matrices can be filled with dispersed inorganic particles [37], which may act as an additional fixed phase. In applications for bone reconstruction, calcium-phosphate particles are being investigated. Poly lactic acid/hydroxyapatite (PLA/HA) 3D-scaffolds were found to withstand up to three compression-heating-compression cycles without delamination. It was shown that PLA/15% HA porous scaffolds obtained by 3D-printing with shape recovery of 98% may be used as a self-fitting implant for small bone defect replacement owing to shape memory effect [38].

A recent study by Li et al. [39] showed that bone morphogenetic protein-2 and protein-7 (BMP-2 and BMP-7) when released from a polylactide–poly(ethylene glycol)–polylactide (PELA) microcapsule-based scaffold significantly promoted osteogenesis as compared to a control group in a rat femoral defect model [39]. The scaffold then underwent degradation and was replaced by new bone within two months.

Peri-prosthesis osteolysis results in mechanical loosening, chronic inflammation, and bone resorption following total hip arthroplasty. In a study from 2003, human BMP-2 (rhBMP-2), produced by DNA recombination was combined with poly-D,L-lactic-acid-para-dioxanone-polyethyleneglycol block copolymer (PLA-DX-PEG) to treat peri-prosthesis osteolysis in a canine model [40]. During proximal bone defect repair, the prosthesis with the rhBMP-2 delivery system was implanted, and no loosening of the prosthesis was noted despite the compromised implant area. The rhBMP-2 initiated new bone formation, excessively in the highest percent loading group and then in a dose-dependent fashion. This indicated that a more refined design and release kinetic and pharmacokinetic profiles would be necessary before proceeding in humans [40]. This polymer can also be combined with hydroxyapatite and titanium for added tensile strength and stability.

4. Cardiac applications

4.1. Chest wall reconstruction

Synthetic meshes have been utilized for chest wall stability; however, they have disadvantages, including inciting inflammatory responses, incomplete incorporation with the surrounding tissues leading to erosion into underlying viscera, infection, and mandatory surgical removal [41]. Ideal characteristics of a prosthetic stabilization material are rigidity, inertness, malleability, and radiolucency [42]. The material also has to be able to undergo tension in all directions, and the location of the chest wall defect greatly influences this tension [41]. Synthetic meshes include polypropylene, polytetrafluoroethylene, polyglactin, and polypropylene mesh-methyl methacrylate composite but have the disadvantages of inflammation, poor incorporation into surrounding tissue, and need for surgical removal [41]. A retrospective study reviewed patients who had undergone chest wall stabilization with the bovine pericardial patches and PLA bars, either alone or in combination [41]. The study concluded that the combination of the patch and the PLA bars would be best indicated for infected sites due to the subsequent treatment with systemic antibiotics and that the product does not need to be removed with a second operative procedure. It would also be indicated for the treatment of lateral chest wall defects and small to moderate sternal defects. The use of PLA bars alone would be most suitable for primary and redo pectus repairs and single rib or double rib defects with sufficient overlying soft tissue [41]. Overall, it was determined that chest wall reconstruction with biomaterials was a promising and valuable option for the management of these patients.

4.2. Stents

Bioabsorbable stents have been utilized for percutaneous coronary intervention. In addition to providing mechanical support to the healing artery, these bioabsorbable stents deliver several advantages, including reduced vessel occlusion, limited restenosis, reduced late stent thrombosis, restoration of vasomotion, and improved lesion imaging [43]. Multiple companies have developed bioresorbable coronary scaffold devices for coronary artery disease. An additional advantage is that the material is broken down by the body and does not require physical or mechanical removal by a second surgical procedure. The first generation of drug-eluting stents was associated with variable rates of late and very late thrombosis. Delayed healing with incomplete intimal coverage and persistent inflammation and hypersensitivity were found to be common in these cases [44]. Hence, bioabsorbable and/or biodegradable stents have been developed for the treatment of coronary artery disease. Unlike biodegradable polymers, bioabsorbable polymers are designed and formulated to be absorbed in living cells, tissues, and/or organs. This unique characteristic provides significant advantages by enabling the device to remain flexible following degradation without mechanical removal.

The Synergy drug-eluting stent (Boston Scientific, USA) was the first coronary stent available in the United States that has a bioabsorbable polymer coating. The stent is made of a platinum chromium alloy that consists of platinum, chromium, iron, nickel, and molybdenum. The stent uses an ultra-thin bioabsorbable PLGA polymer and everolimus drug combination to create an abluminal coating. The drug is released over the first three months and the coating dissolves over several additional months, leaving only a bare metal stent in the vessel and thereby reducing the risk of very late stent thrombosis. In a porcine model, polymer reabsorption was complete within 4 months [45], and endothelialization was complete within 28 days [46]. The first human trial was the EVOLVE trial which evaluated two dose formulations of Synergy compared with the durable polymer Promus Element EES [47]. A total of 291 patients with de novo coronary artery disease were enrolled and assigned to one of the three groups: Promus Element, Synergy, or Synergy half dose. No stent thrombosis was reported in any group throughout the 6 months of the study and all groups were comparable. There was then a randomized trial with 1684 patients, which confirmed that the bioabsorbable polymer everolimus-eluting stent was non-inferior to the Promus Element Plus everolimus-eluting stent at 1 year follow-up [48]. These data support the safety and efficacy of this technology in a broad range of patients undergoing percutaneous coronary intervention in support of regulatory approval. Additionally, early healing assessment with optical coherence tomography of the Synergy bioabsorbable polymer drug-eluting stent system demonstrated a high degree of intimal coverage 3 months after implantation which continued to increase at 6 months post implantation [44]. This can have a significant effect on how long the patient has to be on dual antiplatelet therapy, an

important consideration for patients at risk for bleeding. The device was launched in the United States in October 2015.

The Biolimus-eluting stent is a PLA-based polymer that releases biolimus, a highly lipophilic semi-synthetic sirolimus analog. A meta-analysis examined 89 trials, including 85,490 patients, and at 1 year follow-up the bioabsorbable polymer-based biolimus-eluting stents were associated with lower rates of cardiac death and myocardial infarction, and target vessel revascularization than the bare-metal stents [49].

A hybrid stent comprised of a metallic wire, and a PLA fiber showed preservation of effective mechanical strength comparable with a PLA-only stent. It also was retrievable following PLA fiber degradation [50]. Other compounds and compound formulations also in development for release from implantable stents are everolimus, merilimus, and sirolimus/CD34 antibody. The CD34 antibody was incorporated into the stent with sirolimus to facilitate cell coverage by capturing endothelial cells and resulted in more coverage as compared to sirolimus-eluting stents alone [51]. The sirolimus/CD34-eluting stent has also demonstrated greater reduction in neointimal formation and inflammation while promoting endothelialization in a porcine artery model [51].

4.3. Dentistry

Biomaterials play a vital role in the restoration of both diseased and damaged teeth. New bone formation, occurring after dental surgery, is frequently compromised by the infiltration of fibroblasts from gingiva [52]. Strategies that have proven to protect the site from formation of new bone include providing a physiologically compatible barrier against fibroblast infiltration, delaying progenitor cell proliferation, and providing physical placement as a scaffold for bone regeneration [52]. Guided tissue regeneration refers to the use of a barrier membrane permeable to tissue fluids to aid in the restructuring of soft tissues during osseous fusion in the spine. Guided bone regeneration, a term used as a corollary to guided tissue regeneration, was coined in clinical dentistry to indicate the promotion of bone regeneration using a barrier membrane allowing for the repopulation of the osseous wound space [52]. Several non-resorbable products as well as biomaterials have been utilized with this goal in the field of dentistry, all with varying success. The advantages of implanting PLA and its copolymers include low rigidity, manageability, processabilty, controlled biodegradation, and drug encapsulation with subsequent drug delivery [52]. PLLA is characterized by thermal plasticity, suitable mechanical properties, and biocompatibility. The major disadvantage is its extended degradation time. To that end, various materials have been produced to increase the resorption rate. Products including Guidor, Vicryl Periodontal Mesh, and Atrisorb, among others, are currently utilized in dentistry as resorbable membranes with the limitation of resorption time and the effect of degradation products on bone formation. They typically consist of multiple membranes, with the goal of increasing tissue integration and nutrient permeation, recruiting fibroblasts and epithelial cells, and increasing bone and periodontal support by maintaining space around the tooth for bone development [53]. Drawbacks include capacity of space maintenance, early/late absorption, mechanical properties, and degradation products. Techniques in scaffold fabrication, including electrospinning, can weave human cells throughout the fibers increasing cell viability and mimicking the native extracellular matrix [53].

For successful dental implant placement and for long-term aesthetic and functional success, maintaining the original dimensions of the alveolar ridge is crucial. To reduce alveolar ridge resorption following tooth extraction, membranes, graft materials, and biodegradable space fillers can be utilized. Biocompatible PLA space fillers fabricated by fusing porous PLA particles loaded with drugs can help promote regeneration and maintain the original socket dimensions [54]. Fisiograft is a synthetic copolymer composed of PLA and PGA and used as a space filler during ridge preservation [55]. A study of 36 patients undergoing periodontal therapy included 26 patients who received Fisiograft following tooth extraction and who were evaluated 6 months later [56]. Biopsies revealed that the new bone that was formed was mineralized, mature, and well structured, indicating that alveolar bone resorption may be prevented or reduced by bioabsorbable synthetic sponges. Fisiograft in combination with a cellular dermal matrix allograft (Alloderm) also showed decreased dehiscence and osseous defects around immediate implants [57]. Controlled release of drugs in the tooth socket may help with healing of the socket as well.

Three-dimensional printing is a versatile technique that can be utilized in countless biomedical applications. The 3D printing of functionalized PLA scaffolds with surface coatings of polydopamine (PDA) have been tested to promote and regulate cell adhesion and proliferation and differentiation of human adipose-derived stem cells (hADSCs) [58]. The upregulation of angiogenic and osteogenic hADSCS as well as increased collagen I, cell cycle, and cell adhesions with a high PDA content were found. In dentistry, drug-loaded nanopharmaceuticals have been utilized extensively over the past few years. Research is focused on appropriate nanodelivery systems for efficient targeted delivery of drugs to the periodontal pocket. In this context, a few nanodelivery systems explored have included nanocomposite hydrogels, nanoparticles, and nanoemulsions. Polymers investigated as matrices for the delivery of drugs to the periodontal pocket include chitosan, poly lactic-co-glycolic acid copolymer, poly(ε-caprolactone), PLA, polypropylene, cellulose acetate propionate, and ethyl vinyl acetate [59].

5. Plastic surgery

5.1. Sutures

The application of PLA and PLGA as sutures was first determined and brought to the medical arena in the 1970s. Due to the fibers' low immunogenicity and toxicity, excellent biocompatibility, predictable biodegradation rates, and good mechanical properties, they were widely accepted and utilized [60]. This acceptance in the medical community led to relatively rapid testing of these biodegradable, bioabsorbable products in multiple biomedical applications over the years. Sutures have since been incorporated with antibiotics, bactericides, and antimicrobials all with varying results [61–63].

5.2. Reconstructive surgery

Historically, ligament injuries have been treated using biological grafts (autografts or allografts); however, some non-degradable synthetic braids or ropes have been conditionally approved by the FDA for ligament tissue repair [64]. Successful biodegradable grafts need to have the tensile and mechanical strength to stabilize the joint as well as facilitate tissue ingrowth. Its degradation rate must also be similar to the healing or rehabilitation rate of tissue recovery [65]. A polylactic acid and poly-caprolactone blend (PLA–PCL) material was investigated for mechanical behavior during degradation for future compatibility and applications.

In a study that explored the feasibility of using adipose-derived stem cells for engineered tendon repair *in vivo* in a rabbit Achilles tendon model, a composite tendon scaffold composed of an inner part of PGA unwoven fibers and an outer part of a net knitted with PGA/PLA fibers was used to provide mechanical strength [66]. The results showed that cell-free scaffolds did not form reasonable quality tendon tissue with fibril structure as compared to the cell-seeded PLA scaffolds.

5.3. Dermal fillers

PLLA is considered a semipermanent filler for soft tissue augmentation. It is biodegradable and resorbable. Injectable PLA (Sculptra, Dermik Laboratories, Berwyn, PA) consists of microparticles of PLA in a sodium

carboxymethyl cellulose gel. It is reconstituted with water prior to administration. It is injected into the subcutaneous plane and provides mechanical support, correction, and filling [67]. PLA microparticles gradually degrade and become surrounded by connective tissue consisting of connective tissue cells and inflammatory cells, such as macrophages, lymphocytes, mast cells, and foreign body giant cells [67]. Over time, this fibrous tissue response is thought to provide sustained correction.

Facial lipoatrophy is a problem suffered by HIV-infected patients undergoing highly active antiretroviral therapy. It is characterized by facial volume loss, affecting the facial contours of the cheeks, temples, and orbits and is associated with social stigma [68]. In 2004, PLLA, in the form of Sculptra, was the first FDA-approved treatment for lipoatrophy of the face in HIV-infected patients. Results at 12 weeks showed significant improvement in the visual analog scale score and improvement was maintained at 18 months [69]. Based on literature review, PLA is the only filler agent with a grade of recommendation of B. Other filler agents received a C or D [68].

5.4. Skin grafts

Bioengineered skin substitutes must restore the barrier function of skin, initiate or accelerate wound healing, reduce pain, and aid in correcting conditions throughout healing [70]. Although split thickness skin grafts, as allografts from the donor, remains the gold standard for resurfacing full thickness burns in the acute setting, dermal substitutes and tissue engineered products have remodeled the field of wound treatment [71]. Bioengineered skin must incorporate viable cells, such as multipotent stem cells and progenitor cells or adipose-derived stem/stromal cells [70]. The scaffold must have suitable physical and chemical properties that both provide a supportive structure that can serve as a template for constructing and restructuring new cells [70]. Suitable geometry, high porosity, and optimal pore size for cell accommodation and migration are also necessary for nutrient and gas exchange. Additionally, growth factors need to facilitate new skin growth and wound healing and therefore need to be included within the environment. Electrospun PLA scaffolds have been developed as artificial skin grafts for surgical repair of skin defects in plastic and reconstructive surgery. Sharma et al. [71] have developed a skin substitute made of a PLA scaffold with minced skin grafts. Skin cells were shown to migrate along the fibers of the scaffold and new collagen was formed. Epithelial and stromal cells were confirmed by immunohistochemistry and SEM [71]. PLGA has also been utilized in preclinical scaffold preparations for skin regeneration [72–74].

5.5. Hernia meshes

Two of the leading treatments for laparoscopic inguinal hernia repair are self-adhering mesh implants, one of which (Perietene Progrip, Covidien, France) is a self-gripping composite mesh, covered by a resorbable layer of micro grips made of PLA. Gruber-Blum et al. [75] showed that Progrip had good tissue integration, mild foreign body reaction, and was superior to the hydrogen fixation in an onlay model [75].

5.6. Urinary incontinence

Although the mainstay of treatment for stress urinary incontinence (SUI) and pelvic organ prolapse is a non-biodegradable polypropylene mesh that supports the urethra and counteracts sphincter weakness, the disadvantages of this implant include poor tissue integration, host immune attack, excessive fibrosis of the implant, erosion, pain, dysuria, and sexual dysfunction. Biomaterials under development include PLA, polyurethanes, and copolymers of the two [76]. An electrospun PLA mesh was tested *in vitro*. Polypropylene was shown to be stronger than the polyurethanes and the PLA; however, a scaffold of polyurethane containing PLA was weaker and stiffer than polyurethane but was significantly improved as compared to polyurethane scaffolds alone at supporting adipose-derived stem cells. Strategies being implemented to treat and correct SUI and pelvic organ prolapse should address natural tissue support in addition to correcting tissue defects with cell-based treatments. Adipose-derived stem cells have been seeded onto PLA scaffolds and may improve biomechanical properties and increase tissue strength [77]. The use of biomaterials with compounds that will help facilitate integration of new tissue and eventual replacement by infiltrating host cells is currently on the frontier of research.

5.7. Theranostic Imaging

Theranostics refers to individualized therapies combining diagnostic capacities and therapeutic administration in a single, efficient, and targeted agent. The development of innovative imaging systems combining biomaterials, contrast agents and imaging probes for improved diagnostic and theranostic applications is being intensely researched [78]. Nanoformulations can be used as MRI, optical imaging, and photoacoustic imaging contrast agents [79]. These nanoformulations can simultaneously be used as drug carriers, protecting their cargo from degradation, increasing circulation time, increasing tumor uptake through the enhanced permeability and retention effect as well as receptor-mediated endocytosis, and improving therapeutic benefit [79]. These innovations are expected to markedly enhance *in vivo* cell marking, early diagnosis of disease, and image-guided therapy [78]. A PLGA nanoparticle dually loaded with doxorubicin and indocyanine green demonstrated cellular uptake, subcellular localization, and cytotoxicity as compared to their free counterparts in ovarian carcinoma and uterine sarcoma cell lines [80]. Utilizing multifunctional nanoparticles that combine drug carriers and ultrasound imaging contrast agents, microbubbles can be formed *in vivo* that result in higher accumulation in tumor tissues, long-lasting ultrasound contrast within the tumor, and local on demand release of the therapeutic agent under the control of the ultrasound regimen [81].

Through encapsulation and chemical modification, PLA and its copolymers can produce finely tailored release kinetics, multiple mechanical properties, and include a vast array of shapes and manufacturing possibilities. In cancer imaging and treatment, a biomarker aberrantly expressed on the surface of a cancer cell can be targeted by probes and carriers on nanoplatforms that can co-deliver imaging functions [82]. These targeted nanoparticles can be used as tumor homing "devices," which result in targeting the site in question [82]. Multiple non-viral theranostic strategies are under current investigation with the advantages of enhanced stability, efficient intracellular delivery, biodegradability, low intrinsic toxicity, and enhanced release of payload. Paclitaxel was loaded into the core of PLA–poly(ethylene glycol)–poly(L-lysine)–diethylenetriamine pentaacetic acid (PLA–PEG–PLL–DTPA) and PLA–PEG–PLL–biotin micelles, and gadolinium ions were chelated to the CTPA moieties [83]. Biotinylated alpha-fetoprotein (AFP) antibodies were linked to the micelle surface by a biotin–avidin reaction to form targeted Gd/paclitaxel-loaded micelles (TGPM) [83]. These micelles were then tested for cytotoxicity, MR imaging capability, and tumor imaging intensity. *In vitro* and *in vivo* cytotoxicity was superior compared to free paclitaxel, and imaging intensity was increased by 3× and prolonged from 1 to 6 h [83].

Quantum dots are under investigation biologically as luminescent probes due to their unique optical and chemical properties. Quantum dots offer tunable emissions from visible to infrared wavelengths, resistance to photobleaching, photo stability, and broad excitation spectra because of high absorption coefficients; however, their use has been limited due to a high toxicity profile [84]. Encapsulation into polymeric particles has been investigated to take advantage of the quantum dots' unique imaging capabilities while decreasing biological toxicity. Pan et al. formulated PLA-vitamin E-TPGS/TPGS COOH nanoparticles and

demonstrated decreased *in vitro* cytotoxicity to both cancer and healthy cells. The combination of enhanced imaging techniques and multifaceted nanoplatforms should play a significant role in personalized medicine.

6. Oncology

6.1. Drug delivery

A promising approach to overcoming systemic toxicity is the application of drug-loaded nanosized drug carriers, such as liposomes, polymeric nanoparticles, dendrimers, and micelles. The incorporation of chemotherapeutic agents, frequently hydrophobic and otherwise administered intravenously with toxic solubilizing agents, into small drug carriers has several advantages compared to systemic chemotherapy [85]. Small nanosized drug carriers are passively targeted to tumors by the enhanced permeability and retention (EPR) effect, leading to a higher drug concentration at the tumor site and decreased toxicity compared with systemic administration [85]. These drugs with low molecular weight are rapidly eliminated by the liver and the kidneys and by loading them into nanoparticles, their bioavailability and subsequent payload and anti-tumor effect substantially increase.

6.2. Intracranial delivery

Since the majority of anticancer drugs have poor permeability through the blood–brain barrier, it has been necessary to develop implantable anticancer formulas with biodegradable polymers, which deliver sustained release profiles of these therapeutic drugs at the brain tumor site. The biodegradable, biocompatible polymer, [*bis*(*p*-carboxyphenoxy)] propane, and sebacic acid, in a 20:80 molar ratio releases the anti-tumor drug, carmustine [1, 3-*bis*(2-chloroethyl)-1-nitrosourea, or BCNU], a nitrosourea alkylating agent, when intracranially implanted at the site of tumor resection in patients with malignant glioma. It was the first FDA-approved polymer-based implant for the treatment of brain tumors. Multiple preclinical studies demonstrated the biocompatible implants' safety, biodistribution, and efficacy in rodent and non-human primate brain tumor models [86–89]. The first randomized, placebo-controlled prospective study was reported in 1995 [90]. The patients with recurrent high-grade glioma who received the Gliadel implant survived longer (31 weeks) as compared to the control group (23 weeks), $p < 0.006$ [90]. This was then followed by a multicenter trial including 240 patients in which the median survival was 13.9 months as compared to 11.6 month, $p = 0.03$ [91]. It has been determined that over 70% of the polymer is degraded within a period of 3 weeks. A recent meta-analysis of six studies including 513 patients who have received Gliadel wafers showed that carmustine-impregnated wafers play a significant role in improving survival in patients with newly diagnosed glioblastoma [92]. A second meta-analysis examined 62 publications, which reported data from 60 studies, and reviewed overall survival, median survival, and adverse events with the use of Gliadel [93]. For newly diagnosed patients with high-grade glioma, the 1-year overall survival percentage was 67% with carmustine wafers and 48% without; 2-year overall survival was 26% and 15%, respectively. For patients with recurrent high-grade glioma, 1-year overall survival was 37% with carmustine wafers and 34% without; 2-year overall survival was 15% and 12%, respectively [93].

PLGA has also been utilized to deliver anti-tumor agents to malignant gliomas. Systemically delivered camptothecin encapsulated into PLGA nanoparticles demonstrated increased tolerability of the normally toxic compound [94]. The tumor growth of intracranial mouse glioma was slowed and the median survival increased with the encapsulated treatment. Strohbehn et al. [95] formulated brain-penetrating PLGA nanoparticles and showed enhanced intracranial distribution when the nanoparticles were delivered via convection-enhanced delivery [95]. Superparamagnetic iron oxide (SPIO) was incorporated into brain-penetrating nanoparticles. Following convection-enhanced delivery, the distribution of particles was detected using MRI with the signal attenuation of the SPIO-loaded particles lasting over 1 month [95].

6.3. Nanoparticles

To discover and develop the next generation of sustained release formulas for anticancer drugs for therapeutic treatments, nanoparticles fabricated from PLA are potential biodegradable candidates. Nanoparticles are typically smooth and spherically shaped with a size in the range of 1–100 nm. They can be prepared in numerous ways with the emulsion solvent evaporation technique being one of the most utilized. PLA nanoparticles have been used to deliver a host of anti-tumor hydrophobic drugs in preclinical *in vitro* and *in vivo* cancer models [96–99]. PLA nanoparticles have been employed to deliver temozolomide to rodent glioma cells *in vitro*. The results indicate that the anti-tumor activity of temozolomide is sustained when delivered by nanoparticles [96]. PEGylated poly(D,L-lactide-co-glycolide) nanoparticles have been shown to deliver docetaxel (DTX) (an anticancer agent) to solid tumors [97]. DTX-loaded PEGylated nanoparticles increased the drug's half-life and provided substantial accumulation in solid tumors. BIND-014 is a targeted nanoparticle composed of a hydrophobic PLA polymeric core encapsulating docetaxel and a hydrophilic PEG corona with small molecule prostate-specific membrane antigens-targeting ligands [100]. The nanoparticles are designed to target and accumulate in prostate tumor tissue and release docetaxel in a measured controlled fashion. Preclinical studies showed that these docetaxel-loaded particles increased blood circulation half-life (approximately 20 h), minimal liver accumulation, and enhanced tumor accumulation and tumor growth suppression as compared to free docetaxel [101]. A Phase I clinical study examined two dosing regimens of BIND-014 in patients with advanced solid tumors, including cervical cancer, ampullary adenocarcinoma, non-small cell lung cancer, and breast and gastroesophageal cancer [100]. BIND-014 was well tolerated and displayed a dose-linear pharmacokinetic profile with prolonged persistence of docetaxel-encapsulated circulating nanoparticles [100]. BIND-014 is currently in Phase II clinical trials for KRAS-positive and squamous cell non-small cell lung cancer, advanced and metastatic cancer, and prostate cancer.

Tamoxifen, an estrogen receptor modulator, has good oral bioavailability but is associated with long-term toxicities. To increase tumor site concentrations and to avoid toxic side effects, polymeric nanoparticles have been used to encapsulate tamoxifen [102]. Tamoxifen-loaded PLGA nanoparticles demonstrated controlled sustained release over a prolonged period of time and were taken up well by the MCF-7 breast cancer cell line *in vitro* [103]. Localization of the nanoparticles was in the cytoplasm but not the nucleus of the MCF-7 breast cancer cells. Tamoxifen-loaded PLA nanoparticles showed decreased hepatotoxicity and nephrotoxicity and significantly reduced tumor size in a rat model of breast cancer [102]. Studies are also being conducted on co-loaded tamoxifen and topotecan PLGA nanoparticles. The dual-loaded particles have shown enhanced permeation of the topotecan and increased bioavilability in an *ex vivo* gut permeation study [104]. Encapsulation and delivery of these two toxic, yet effective, agents will need to be examined and optimized prior to clinical testing.

PLA nanoparticles have been investigated for use in the treatment of leukemia. Bovine seminal ribonuclease was attached to PLA via an adsorption method and demonstrated aspermatogenic and antiembryonal efficacy *in vivo* [105]. PLA nanofibers and tetraheptylammonium-capped FE_3O_4 magnetic nanoparticles showed preferential uptake in leukemia K562 cell lines [106]. This uptake facilitated the interaction of the leukemia cells with the anti-tumor compound daunorubicin and increased the permeation and that drug's uptake into the cancer cells. Similarly, nanocomposites made of PLA nanofibers and Au

nanoparticles conjugated with daunorubicin facilitated the cellular drug absorption of daunorubicin into drug-resistant leukemia cells [106]. Yadav et al. [107] developed PEGylated PLGA nanoparticles to deliver cytarabine, an antimetabolite to target leukemia [107]. Cytarabine is poorly absorbed from the gastrointestinal tract and has a short half-life, necessitating an intravenously administered multidose treatment regimen, which frequently results in necrosis of normal cells. PEGylated PLGA cytarabine nanoparticles were both internalized by L1210 mouse leukemia cells as well as in significantly higher concentration in the blood, bones, and brain as compared to the free drug [107].

The use of nanoparticles for metastatic cancer is particularly interesting due their possible wide allocation to a variety of tissues through systemic delivery. The innate tumor homing capabilities of some formulations of nanoparticles can be advantageous at targeting multiple tumor sites. For gastric cancer, a highly metastatic disease, copper-loaded PLA nanoparticles were prepared to aid in targeting the human copper transporter CTR-1 present in gastric mucosa and in the human gastric adenocarcinoma cell line related to CTR-1 [108]. CTR-1 plays a key role in the uptake of platinum drugs and reduced expression of this transporter results in tumor cell resistance [108]. The copper-loaded PLA nanoparticles had a cytotoxic effect on the gastric cancer cell line MKN-54 and showed increased apoptosis.

6.4. Nanoparticles for intranasal delivery

Nanoparticles have improved drug delivery and have increased the options for applications. Mucous-penetrating particles can aid in the delivery of compounds across mucous-covered epithelial surfaces such as the eye, orogastrointestinal tract, airways, vagina, and nasal passages for treatment of a multitude of health issues [109]. For example, intranasal delivery of therapies has been examined in multiple CNS conditions, such as stroke, Parkinson's disease, multiple sclerosis, Alzheimer's, epilepsy, and psychiatric disorders and have shown great promise [110]. In addition to providing a direct pathway to the CNS, intranasal drug delivery provides several advantages. First, it is non-invasive and easy to administer. Second, there is a large surface area which causes rapid absorption [110]. Finally, intranasal delivery avoids hepatic first-pass effects. Drugs can be encapsulated in carriers, such as cyclodextrins, microemulsions, and nanoparticles, to overcome these issues for intranasal delivery to the CNS [111]. Polymeric nanoparticles can offer several advantages due to their controlled and prolonged effects on drug release and intracellular uptake. Musumeci et al. [112] evaluated PLA, PLGA, and chitosan nanoparticles and evaluated uptake into olfactory ensheathing cells [112]. They showed that nanoparticles from PLGA showed a higher increase in uptake compared to nanoparticles from PLA and nanoparticles from chitosan.

6.5. Micelles

Micelles are colloidal particles within a size range of 5–100 nm. Polymer micelles are block copolymers with hydrophobic and hydrophilic units that possess a unique core-shell structure generated through the self-assembly in aqueous media, increasing the water solubility of the hydrophobic drug and allowing for delivery of higher doses than those achieved by the drug alone. PEG–b-PLA micelles have been tested extensively in humans in the incorporation and delivery of many hydrophobic anticancer compounds [113]. Although micelles have demonstrated enhanced tolerability compared to formulations based on low molecular weight surfactants, in some cases, their failure to retain their cargo following parenteral administration has hindered their capacity to target taxanes to solid tumors [114]. The loading efficiency of taxanes in polymeric micelles depends on several factors, including the physicochemical characteristics of the drug and core-forming polymer, the loading method, and the preparation parameters [114]. The length of the hydrophobic chain can also impact the release profile of paclitaxel from micelles. Increasing the length of the PLA segment delayed its release from PEG–b-PLA–b-PEG triblock and star-branched copolymer micelles [115]. Other factors, such as chemical composition of the core-forming polymer, polymer–drug compatibility as well as physical state of the micelle core, can substantially alter drug-loading and release kinetics [114]. While *in vitro* assays have not shown a significant benefit from paclitaxel-loaded polymeric micelles, *in vivo* tolerability was increased four-fold [116]. The micelle incorporation of toxic anticancer agents increases the plasma residence time to favor passive targeting to tumor tissues [114]; however, *in vivo* release kinetics remain to be characterized. Genexol-PM consists of 20–50 nm micelles formed by the self-assembly of polyethylene glycol and polylactide polymers with the core containing paclitaxel. A multicenter Phase II trial in women with metastatic breast cancer demonstrated a 58% response rate [117]. When combined with gemcitabine, Genexol-PM demonstrated favorable anti-tumor activity in non-small cell lung cancer patients in a Phase II trial of Cremorphor EL-free paclitaxel (Genexol-PM) and gemcitabine in patients with advanced non-small cell lung cancer [118].

Docetaxel-loaded micelles prepared from a thermosensitive copolymer (poly(*N*-isopropylacrylamide-co-acrylamide)-*b*-poly(D,L-lactide)) showed anti proliferative activity *in vitro* [119]. Cisplatin has been incorporated into polyethylene glycol (PEG)-poly(amino acid) block copolymer micelles and has had some promising results, both in preclinical studies and in clinical trials [120,121]. Another micelle has been formulated by covalently linking a platinum (IV) complex to the hydrophobic end of two methoxyl poly(ethylene glycol)-*b*-poly(D,L-lactide) (mPEG–PLA) copolymer chains, which could self-assemble in water into micelles [122]. *In vitro* release of the platinum (IV)-conjugated thermogel has shown platinum release up to two months with an *in vitro* cytotoxicity profile [122].

Co-delivery of drugs from micelles is also a possibility. Concurrent delivery of paclitaxel, 17-allylamino-17-demethoxygeldanamycin (17-AAG), and rapamycin (RAP) from poly(ethylene glycol)-*block*-poly(D,L-lactic acid) (PEG–b-PLA) micelles significantly increased the values of the area under the plasma concentration-time curves of PT and RAP in mice compared to the drugs delivered individually, while the pharmacokinetic parameters were the same for 17-AAG [123]. There was inter-drug PK interaction in that the 3-in-1 PEG–b-PLA micelles delivered the 3 drugs at modest doses, but the PK profile was altered when higher loading doses were attempted. This triple combination release, called Triolimus, has shown promise in preclinical *in vivo* breast cancer models [124] and was granted orphan drug status by the FDA for the treatment of angiosarcoma in 2015.

Multidrug resistance is being addressed through the utilization of micelles. A mixed micelle, including the PEG–PLA original vehicle for Genexol-PM and vitamin E-TPGS, a P-glycoprotein inhibitor, was tested against multi-drug-resistant cells *in vitro*. The mixed micelle showed a significantly improved drug-loading coefficient than the original paclitaxel-delivering Genexol-PM alone. The mixed micelle also had significant anti-tumor activity and enhanced cell uptake by overcoming multidrug resistance [125]. The usage of verapamil, one of the second-generation P-glycoprotein inhibitors, co-delivered in combination with either vincristine from PLGA nanoparticles or with paclitaxel in bi-functional micelles, restored vincristine, and paclitaxel toxicity in multi-drug-resistant tumor cells [126]. Similarly, a folate-modified pH-sensitive micelle system loaded with doxorubicin significantly increased the efficacy of doxorubicin and decreased systemic side effects in the treatment of a multi-drug-resistant tumor in mice [127]. Tariquidar, a third-generation P-glycoprotein inhibitor, was delivered in combination with paclitaxel from PLGA nanoparticles demonstrating significantly higher *in vitro* cytotoxicity than paclitaxel-loaded particles alone [128]. This may be due to the increased accumulation of paclitaxel in the drug-resistant tumor cells. Patel et al. also showed that biotin-functionalized particles encapsulated with tariquidar, and paclitaxel

had significantly higher inhibition of tumor growth in a mouse model of drug-resistant tumor.

6.6. Thermoresponsive hydrogels

Thermoresponsive gels are biodegradable, biocompatible gels that demonstrate reverse thermal gelation properties [129]. ReGel, a triblock copolymer comprised of PLGA and PEG with the basic structure of PLGA–PEG–PLGA, is water soluble at <15 °C and turns into a viscous gel at body temperature. It forms a water-insoluble gel once it is injected consistent with a hydrophobic-interacted gel state with no covalent cross-linking [129]. Preclinical studies of ReGel loaded with paclitaxel (OncoGel) demonstrated safety and efficacy using *in vivo* models for brain and esophageal cancers [130,131]. A Phase I clinical trial in patients with recurrent malignant glioma was terminated without conclusive results (NCT00479765). Another Phase I study performed on patients with inoperable solid tumors showed that the dose of OncoGel tested intralesionally was well tolerated and that paclitaxel remained localized at the injection site, confirming limited systemic exposure to the drug [130].

Similar to Triolimus is Triogel, a PLGA–b-PEG–b-PLGA hydrogel platform sol–gel that delivers paclitaxel, 17-AAG, and rapamycin [132]. This gel showed promise in an ES-2-luc ovarian cancer xenograft model by significantly reducing tumor burden and extending survival with no notable systemic toxicities. It has the dual functionality of being utilized for locoregional chemotherapy as well as being a barrier device via peritoneal surgery to prevent intra-abdominal lesions, typically observed following transperitoneal surgery [132].

6.7. Protein/peptide drug delivery for vaccine application

Protein and peptide therapies are FDA approved for use in the treatment of many diseases, including Alzheimers disease, cancer, diabetes, and melanoma, among others. The route of administration is most commonly parenteral; however, the requirement of frequent injections due to short *in vivo* half-life results in poor patient compliance [128]. Other drug delivery routes such as intranasal, transdermal, pulmonary, and oral offer several advantages; however, physicochemical properties and low permeability across biological membrane limit protein delivery via non-invasive routes [128]. Polymeric nanoparticles, among other delivery systems, may improve peptide absorption [128]. The microencapsulation of peptides and proteins in PLA/PLGA particles extends the biological half-life of the payload by protecting them from enzymatic degradation, and then can slowly release them yielding higher serum concentrations over a longer period of time. Variations in particle size, surface charge, surface chemistry, encapsulation efficiency, stability after preparation, and controlled release all need to be addressed in this ever changing and adaptive field [133]. Numerous preclinical studies have shown the benefits of particle delivery of peptides and proteins. To maintain drug bioactivity, Yeh et al. [134] demonstrated characteristics of insulin-loaded PLA microparticles *in vitro* and *in vivo* [134]. The study showed that by adding electrolytes like NaCl in the continuous phase, insulin could be efficiently trapped in PLA microparticles using the w/o/w emulsion solvent evaporation method. They also showed that glucose levels were significantly reduced following insulin-loaded PLA microparticles in a rabbit model. Furthermore, Ma et al. employed hydrophilic poly(lactide)-poly(ethylene glycol) (PELA) as a wall material for encapsulation in PLA/PLGA microspheres/microcapsules to increase the bioactivity of the protein drug [135]. These PELA microcapsules had a more uniform size and when loaded with the recombinant human growth hormone resulted in a higher drug concentration in blood over a 2 month period *in vivo* as compared to the PLA and PLGA microcapsules. Ma [135] also comments on the challenges of scaling up and maintaining predictable drug release of these formulations for clinical usage. PEG–PLA nanoparticles were applied for not only drug delivery but also for drug targeting chemotherapy in tumor neovasculature and tumor cells. Since fibronectin extra domain B (EDB) is expressed on both glioma neovasculature endothelial cells and glioma cells, EDB-targeted peptide APTEDB-modified PEG–PLA nanoparticles (APT-NP) were constructed with paclitaxel for treatments of tumor neovasculature and tumor cells [136]. Following intravenous injection APT-NP had higher and specific accumulation within the intracranial tumor as compared to unmodified nanoparticles and free taxol. This dual functioning therapy demonstrates the possibilities of targeting the tumor and its environment with these nanoparticles.

The delivery of the luteinizing hormone-releasing hormone (LHRH) agonist, leuprolide, has been extensively examined and FDA-approved with the Lupron Depot microspheres and *in situ* forming gels of Eligard. Lupron was FDA approved in 1989 and is utilized to treat multiple health issues, including prostate cancer, endometriosis, fibroids, and central precocious puberty. Zoladex is an implantable formulation that delivers another LHRH agonist, goserelin, through PLGA cylinders. Zoladex has a 3 month delivery duration and increases patient compliance, improves lifestyle, and improves outcomes [137].

Nanoparticle delivery has been potentiating antigen delivery for vaccine treatments. Nanoparticles can be uniquely tailored in size, shape, surface properties, and compositions and their size is similar to cellular components which allows them to enter cells through endocytosis and pinocytosis [138]. Nanoparticles for vaccine formulations allows for improved antigen stability and immunogenicity, as well as targeted delivery and controlled slow release [139]. A number of nanoparticle vaccines varying in formulations have been approved for human use with more candidates being tested currently [139]. Tetanus toxoid, a model antigen, was incorporated into PLA or PEG–PLA nanoparticles for nasal vaccine delivery and their formulations were characterized *in vitro* and *in vivo* [140]. The results showed that stability and aggregations of PLA nanoparticles were significantly improved by PEG coating. Furthermore, intranasal application of PEG–PLA nanoparticles showed significantly higher levels of antibody with long-lasting response. Similar to this, PLGA and PLA demonstrated significant advantage of antigen delivery for vaccine. PLA and PLGA can be tailored to degrade over a wide range of rates and they encapsulate hydrophobic molecules and may protect encapsulated antigens [141]. Both PLGA and PLA have been utilized as controlled release delivery systems for vaccines antigens. Encapsulated antigens or plasmid DNA can be protected from enzymatic degradation and released in a pulsatile fashion, mimicking conventional vaccines, as well as the passive or active targeting of antigen presenting cells [142].

6.8. Nanoparticles for transdermal delivery

Transdermal drug delivery has been developed as an alternative to pills and injections for slow transport into the body across the skin [143]. The skin's large surface area available for drug delivery, easy accessibility, and the advantage that dermal drug delivery can be potentially pain-free are all favorable reasons for pursuing transdermal delivery [144]. Transdermal polymeric delivery is often achieved through patches that are frequently made of polymer, contain a drug reservoir and adhesive layer, and provide steady controlled drug delivery [143]. Due to the barrier properties of the stratum corneum that permit transport of only small (<400 Da), oil soluble molecules, only a small subset of drugs can cross the skin in therapeutic doses [143]. The hair follicle canal of the pilosebaceous unit has been shown to accumulate micro-, submicron-, and nanosized substances demonstrating that the transfollicular pathway is important in the preferential penetration of these particles [145]. Particles that accrue in the hair follicle are not cleared by the stratum corneum and persist for days before they are cleared [146]. Because of this tendency, they have been proposed for site-specific drug delivery to pilosebaceous structures [147]. Rancan et al. [148] examined the penetration profiles of PLA particles (228 and

365 nm) in human skin explants and found that PLA particles penetrated into 50% of the vellus hair follicles reaching a maximal depth corresponding to the entry of sebaceous glands in 12–15% of all observed follicles [148]. PLA particles have shown promise for targeting hair follicle and sebaceuous glands [148]. Vijayan et al. [149] showed that PLA nanoparticles formed with Repaglinide, a blood glucose-lowering drug, and then loaded in Methocel transdermal patches maintained bioavailability by 75 fold, compared with orally dosed Repaglinide [149].

To further develop novel vaccine/drug delivery, microneedles have been developed as arrays of hollow or solid needles measuring microns that can painlessly pierce the skin to deliver drugs in a minimally invasive manner [150]. Park et al. fabricated polymer microneedles out of PLA, PGA, and PLGA because of their biocompatibility, cost effectiveness, and mechanical strength. The group looked at fabrication methods, resulting mechanical properties and their abilities to transport compounds across the skin [143]. Using mold-based fabrication methods that are relatively inexpensive and suitable for mass production, they showed that polymeric microneedles may have promise for drug delivery applications. Porous PLA microneedles, with a porosity of 75% lacked strength and were unable to penetrate the skin [144]. In a proof of principle set of studies, Gomaa et al. [151] encapsulated hydrophilic (rhodamine B) and hydrophobic (fluorescein isothiocyanate (FITC)), small- and medium-sized molecules into PLGA nanoparticles and then delivered these through porcine skin that had been pretreated with a microneedle array [151]. Skin permeation, dye flux, and solubility were measured, and confocal laser scanning microscopy imaging conducted. Skin permeation was affected by multiple factors, including the physicochemical characteristics of the nanoparticles, such as the nanoparticles' composition and attributes, as well as the solubility, particle size, hydrophilicity, and zeta potential of the encapsulated dye [151]. Successful molecular diffusion across skin layers will be dependent on synchronous optimization of the microneedle array, the nanoparticle carrier, and the agent being delivered [151]. A microneedle transdermal delivery system composed of embeddable chitosan microneedles and a PLA supporting array to deliver encapsulated antigens to the skin has been investigated [152] with ovalbumin used as a proof of principle antigen. The ovalbumin-loaded microneedles were embedded in rat skin *in vivo* and then examined histologically over time. Chen et al. [152] showed that compared to traditional intramuscular immunization, rats immunized by a single microneedle dose showed a significantly higher ovalbumin-specific antibody response lasting for 6 weeks. This promising antigen depot may provide sustained immune stimulation as well as improved immunogenicity. Vaccinations with microneedle PLA constructs have also been investigated for delivery of adenovirus vaccines in non-human primates [153]. PLA polymer microneedle patches were fabricated with replication-incompetent adenoviral serotype 5 vectors in a sucrose sugar–glass matrix and applied manually to macaque skin. Bioactivity was similar to that of a dose-matched aqueous solution and functional immunogenicity studies showed a strong cellular and humoral immunity with similar responses to that of traditional injections of adenoviral vaccine [153]. Possible advantages of microneedle usage in the clinical setting, i.e., self-administration, minimal invasiveness, and dermal delivery, are spurring on the development of this technology.

6.9. 3D printing techniques with PLA

The 3D printing techniques are constantly evolving, and with it, new applications for the end products are being developed. Tissue engineering, scaffolding for various applications, implantable medical devices, and anatomic simulation of 3D microarchitecture and printed scaffolds for patient-specific bone replacement are all currently under investigation. Solid free form fabrication allows for the design and fabrication of complex 3D structures. Some of which are patient specific. Through computer-aided design integration and advanced imaging techniques, solid free form fabrication allows for both macro and micro architecture to be created for biomedical devices [154]. The conformal printing of PLA on a rotating mandrel results in helical microstructures that have potential for various applications, including lab on a chip systems and microelectronics [155]. The costs of fabrication of these products vary as do resolution. Solvent-cast 3D printing includes the solvent-cast direct-write (SC-DW) fabrication method developed to fabricate 3D geometries of PLA at room temperature in a freeform fashion with dissolvable thermoplastic polymers. This method combines PLA, a renewable, low waste polymer, with the solvent, dichloromethane, which has fast evaporation and good dissolvability with PLA [156]. The SC-DW technique is low cost, highly flexible, and could lead to sustainable development due to its compatibility with recyclable and biodegradable products. Fabrication of 3D micro prosthetics, tissue engineering scaffolds, and cylindrical mesh are all currently being investigated.

7. Conclusion

Enormous strides have been made with the use of PLA and its copolymers in almost every medical specialty. Clinically impactful, FDA-approved PLA formulations will continue to be developed and engineered to deliver a wide range of therapeutic compounds. From oncology to orthopedics, from dentistry to skin grafting, the mechanical, chemical, and physical properties of PLA have been fabricated into numerous biomedical achievements. As more scientific data accrue in the various medical subspecialties, polymer formulations will be modified, encapsulation and delivery of compounds will be improved, and future applications will be limitless.

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