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Clinical Applications of Naturally Derived Biopolymer-Based Scaffolds for Regenerative Medicine

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Abstract

Naturally derived polymeric biomaterials, such as collagens, silks, elastins, alginates, and fibrins are utilized in tissue engineering due to their biocompatibility, bioactivity, and tunable mechanical and degradation kinetics. The use of these natural biopolymers in biomedical applications is advantageous because they do not release cytotoxic degradation products, are often processed using environmentally-friendly aqueous-based methods, and their degradation rates within biological systems can be manipulated by modifying the starting formulation or processing conditions. For these reasons, many recent *in vivo* investigations and FDA-approval of new biomaterials for clinical use have utilized natural biopolymers as matrices for cell delivery and as scaffolds for cell-free support of native tissues. This review highlights biopolymer-based scaffolds used in clinical applications for the regeneration and repair of native tissues, with a focus on bone, skeletal muscle, peripheral nerve, cardiac muscle, and cornea substitutes.

Keywords

Biopolymers; Scaffolds; Regenerative medicine

INTRODUCTION

Beginning in the mid 1970s, investigators explored the use of materials for biological and medical applications, leading to rapid growth in the field of biomaterials and their applications in tissue engineering.[16,120,250] Successful tissue engineering strategies attempt to recreate or mimic the conditions present in healthy tissue *in vivo*. However, positive *in vitro* results have yielded limited translational success with *in vivo* models as well as in the clinic due to the simplified culture conditions, lack of cell retention *in vivo*, unknown biological factors, such as long-term immune response, which are difficult to predict or determine *in vitro*. A constant influx of new information from biological and medical

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research as well as improvements in *in vitro* experimental models will continue to guide methodologies and product development. Due to continued advancements in the fields of developmental biology, optics, and assay development, biomedical research continues to progress rapidly building from these improvements in the fundamental building blocks to generate better *in vitro* systems that more accurately recapitulate the *in vivo* environment (e.g., evaluation, utilization, and application of extracellular matrix composition, co-culture, and immunomodulation). Key components of this progress involve the careful selection and preparation of scaffold materials and use of physical, chemical, and/or electrical stimuli to direct delivered cell behavior to ultimately mimic the characteristic profile of the desired native tissue.

The Role of Biomaterials in Translational Medicine

Two traditional groups of biomaterials are available: synthetic polymers (Table 1) and natural biopolymers (Table 2). Since each group possesses distinct advantages and limitations, a wide variety of composite materials and interpenetrating networks have been utilized to achieve desired results. These include composites of natural materials, such as silk and collagen[31,233] or chitosan and alginate,[48,78,201,216,243,264,287] as well as blends of natural and synthetic systems, such as alginate, polyacrylamide, and poly(ε-caprolactone) interpenetrating networks.[135] In addition, hybrid variants of these materials have emerged through synthetic designs and genetic engineering of peptide-based biopolymers.[8,18,36,203]

Synthetic Materials—Synthetic polymer-based materials are widely used as biomaterials for tissue engineering and regenerative medicine due to their well-defined chemical and structural characteristics, as well as the flexibility they afford in allowing the researcher to control and fine-tune the final properties of their scaffold. Thus, a diverse spectrum of synthetic polymers has been explored for use in virtually all tissue engineering applications. These polymers can be designed to be either non-degradable (e.g., polyethylene terephthalate/Dacron™) or degradable (e.g., poly(glycerol sebacate)). Non-biodegradable materials are advantageous in biological systems that experience high mechanical loading demands since the non-degradable materials can maintain their structural integrity over time. In contrast, fibrotic response to an inert, non-degradable scaffold due to inability to integrate within the native tissue or adverse inflammatory response can result in long-term implant failures or secondary complications. For example, the use of Dacron™ or PTFE for repair of congenital heart defects in children can lead to secondary complications such as aneurism or fatal arrhythmia.[98,102,241] Biodegradable synthetic materials are advantageous because their chemical formulation can be tuned to obtain specific degradation properties (e.g., chemical hydrolysis or surface erosion). Unfortunately, cell-based degradation or natural deterioration may result in the release of cytotoxic or inflammatory small molecules, prompting the need to determine tissue-specific degradation rates, local dose–response sensitivity, and metabolic response of neighboring cells to these byproducts (See Refs.[219,253] for a more detailed review). Commonly used synthetic biomaterials for tissue engineering are listed in Table 1. While Table 1 does not cover all possible synthetic materials, the polymers listed highlight novel structures and formulations utilized in current and emerging technologies as well as standard clinical products that represent areas in need of improvement.

Natural Materials—For the purpose of this review, we will define natural biomaterials as those found in nature, originating from a plant-based or tissue-based origin. Once properly purified for *in vivo* applications, these materials generally do not elicit an unwanted or unexpected immune response, leading to biocompatible and often bioactive matrices that can integrate with surrounding native tissue.[132,204,214,267] In addition, the degradation products are generally more biocompatible, metabolically accessible, and less toxic when compared to their synthetic counterparts. A disadvantage of naturally derived biomaterials is their chemical heterogeneity and high dispersity, leading to variability in mechanical properties, structure, and performance, including variations in local degradation rates.[132] Despite this variability, biopolymer scaffold materials have successfully advanced to the clinic for the repair of soft tissues, such as skin and muscle, and hard tissues, such as bone. Commonly investigated biopolymers and their benefits *in vivo* are listed in Table 2.

Natural materials can be further classified based on their origin and the processing methods used to obtain the material. Simple biopolymers are derived from a natural origin, such as rat-tail or bovine tendon for the isolation of collagen. These methods first require the removal of all cellular material and then the subsequent dissolution of the biopolymer in acidic medium to yield a semi-clear solution that has been purified to contain a specific protein (e.g., collagen type I).[207] Alternatively, natural materials for scaffold fabrication can also be obtained from the decellularization of complex tissues. For example, collagen-based scaffolds can also arise from the decellularization of porcine dermis or pericardium. In some cases, such as in the use of demineralized (DMB) or decellularized (DCB) bone, the 3D architecture of the native tissue is maintained and utilized as the skeletal architecture of the scaffold. Both biopolymer-based scaffolds and decellularized matrices have achieved some clinical success, especially in the field of wound healing and skin regeneration. This review will discuss the use of biopolymer-based scaffolds for tissue repair and regeneration, with a focus on *in vivo* and clinical application (Table 3) to highlight the hurdles that still exist in the bench-to-bedside clinical transition.

BIOPOLYMERS FOR BONE REPLACEMENT

The rising age of the population coupled with the increasing incidence of age-related conditions such as osteoarthritis and osteoporosis has produced an overwhelming market for bone replacement materials (Fig. 1).[61] Despite modest success in the development of bone fillers, surgeons must still resort to autografts or allografts for critical sized defect repair. Over the past several decades, research has turned to tissue engineering as a strategy for functional bone repair. However, attempts to produce high-strength, porous scaffolds for bone regeneration have been limited by the intrinsic weakness associated with high porosity materials. Moreover, many formulations of natural or synthetic polymeric materials fail to promote adequate vascularization, innervation, and maturation of osteogenic cells.[24,220] This section of the review addresses the critical role that biopolymers play in the repair of bone tissue, and highlights the clinical translation of these natural materials to the clinic.

Design Criteria for Bone Replacement

From an engineering perspective, bone tissue is a composite, anisotropic material built to preferentially withstand mechanical forces in one direction (Fig. 1a).[13] Due to the unique organic–inorganic composite structure of osseous tissue, design strategies *in vitro* aim to mimic natural mineralization processes. For example, mineralization can be induced *via* phosphorylation of collagen or the incorporation of bioactive agents (e.g., hydroxyapatite, bioactive glass particles).[140,151–154] Additionally, mineralization can be achieved *via* the hybridization of collagenous biomaterial constructs with non-collagenous recombinant proteins, such as INFUSE®.[234] Clinical success of peptide-based mineralization has been limited by the high cost of the peptides, as well as deleterious side effects (e.g., breathing difficulty, hematomas, swelling) caused by secondary inflammation near the site of implantation.[96] The secondary inflammation can be caused by an unwanted immune response to the non-native peptides introduced for mineralization.[234] For example, INFUSE® delivers recombinant bone morphogenic protein-2 (rhBMP-2) *via* a collagen sponge. Clinical results demonstrated that the desired inflammatory response at the treatment site may spread to adjacent critical structures, leading to increased postoperative morbidity.[234]

Despite the challenges tissue engineers face in achieving collagen scaffold mineralization *in vivo*, collagen-based biomaterials continue to be one of the most highly investigated natural materials for bone regeneration (Table 3). The implantation of pre-mineralized collagen matrices or pre-seeding with osteogenic cell lines remains the primary focus of *in vivo* collagen-based bone repair. The application of collagen hydrogels in particular has received much attention for bone repair. Implantation of a collagen hydrogel in a critical-sized rabbit segmental diaphyseal defect model resulted in supporting pre-seeded osteosarcoma cells,[254] while collagen hydrogels with a collagen fibril density equivalent to native tissues (i.e., 10–15%) maintained structural stability up to 5 weeks post-implantation.[177] These studies, among others, demonstrate the necessity of effective strategies for *in vivo* mineralization for successful graft integration and defect regeneration.

Silk—Silk protein has been widely used as a scaffolding material for tissue development and cell-based remodeling both *in vitro* and *in vivo*.[20,57,150,165,192,261] Due to its robust mechanical profile, ability to be mineralized, controllable degradation, and excellent osteoconductive and osteoinductive properties, extensive research has been conducted on the use of silk for bone repair. The biocompatibility of silk has also been thoroughly investigated in the trabecular bone of sheep tibia and humerus defects.[261] Despite the ability of silk scaffolds to deliver small molecules and growth factors while maintaining biocompatibility, silk exhibits a low compressive strength, thereby limiting its use in non-load-bearing bone regeneration. Within the past few years, however, several strategies have been implemented to overcome this mechanical limitation. Mandal *et al.* addressed the need for a stronger and stiffer natural polymeric matrix using a solvent-processed silk sponge scaffold reinforced with micron-sized silk fibers.[150] Alternative strategies to improve the compressive strength of silk scaffolds utilize the addition of hydroxyapatite or bioglass particles, or *in situ* crystallization of calcium phosphate on the scaffold surface. Silk scaffolds have also been evaluated for the effect of pore size in bone repair in an *in vivo* model.[165] Collectively, these

studies demonstrate the potential of a natural silk material for bone tissue regeneration, and provide evidence for the utilization of silk or silk-based composites in clinical bone repair.

Alginate—The use of alginate-based materials for load bearing bone repair in critical-sized defects has been limited by the poor mechanical profile of alginate and the lack of cell-based degradation mechanisms, which can delay native tissue ingrowth into an alginate implant. However, despite these limitations, alginate-based materials and composites have been studied in orthopedic research for promoting osteogenesis, improving osteogenic differentiation, and delivering cells and growth factors to bone defect sites.[265] One such study investigated the ability of an alginate/nanofiber mesh composites scaffold loaded with rhBMP-2 to enhance the repair of critically sized segmental bone defects in a rat model. Implantation with controlled release of rhBMP-2 resulted in consistent bony bridging within the defect, demonstrating the promise of these composites for growth factor delivery to repair of critically sized bone defects.[126]

Natural Materials as Bone Fillers and Cements—The rapidly rising demand for orthopedic tissue engineering products to repair spinal damage, musculoskeletal defects, or bone fractures has led to the development of several FDA-approved bone cements and filler materials. Calcium phosphates (CaP), particularly hydroxyapatite (HA), remain a focus for orthopedic applications due to their semblance to the mineral phase and crystalline structure of bone.[59] A majority of bone filler materials are comprised of calcium phosphate cements (CPCs) (Table 4). In an aqueous environment, CPCs undergo rapid sedimentation and precipitation to apatite, hardening within minutes at body temperature. These reactive CPCs are optimal for on-site surgical filling of a bone gap, due to their moldability and rapid setting. Clinically, they are used in periodontal repair, cranio-maxillofacial surgery, and augmentation of an autograft or allograft. Once set, CPCs are very brittle and are therefore not applicable in the repair of load bearing critical-sized defects, where connection to the host vasculature, nervous, and muscular systems are paramount for clinical success.[24,220] Overall, CPCs, especially when formulated using natural, non-toxic processing materials such as silk,[165] represent a current clinical success story for research driven material design for clinical applications.

Clinical Translation and Commercialization

Cell-free bone cements and putties represent the state of the art in repair of small bone defects. However, secondary limitations, such as the lack of vascularization and organized structure of these cements, restrict their clinical potential. Given the recent progress in directing differentiation of human induced pluripotent stem (hiPS) cells towards osteoblast and osteoclast lineages[50] in combination with improved material design, the development of successful cell-based therapies for repair of damaged or diseased bone is within reach.[7] Progress towards clinical application of functional, critically sized bone grafts is underway, but current and future work must still address the combination of mineralized bone with other tissue structures such as bone marrow. In addition, connection of the new structure to the host system *via* vascularization/angiogenesis, innervation, and lymphangiogenesis has not been sufficiently addressed.[7,24,43,106,114,129,220] Integration of a construct with the host

tissue *via* these factors must be addressed in order to achieve long-term improvements in patient prognosis,.

BIOPOLYMERS FOR SKELETAL MUSCLE AND NERVE TISSUE REGENERATION

Skeletal muscle tissue has the innate ability to repair and regenerate following acute injury, as evidenced by the successful increase in organized and functional muscle tissue following prolonged and repeated periods of exercise. Exercise induces small tears in the muscle fibers, which the body is able to not only repair, but also respond to, *via* increase in skeletal muscle volume. However, some of the most important parameters in dictating clinical success include the maintenance and growth of vascular and neural network architectures within the new muscle. In critically sized defects, such as those caused by volumetric muscle loss following of trauma,[41,42,147] vasculature and neural networks are not maintained. Regeneration of these connections *in vivo*, specifically for the nerve (i.e., the neuromuscular junction (NMJ)), is paramount for functional muscle recovery resulting in controllable contractile function. Consequently, there is still an unmet need for the development of critically sized tissue replacements comprised of aligned, functional muscle containing nerve conduits with functional neuromuscular junctions.

Design Criteria for Critically Sized Skeletal Muscle Defects

Skeletal Muscle—Like bone tissue, the structure of skeletal muscle dictates its function. Muscle is composed of bundles of muscle fibers surrounded by connective tissue, with each muscle fiber representing a single, often multinucleated, muscle cell. Individual cells or fibers are bundled together into small groups called fascicle, which are surrounded by a thin layer of connective tissue. Multiple fascicle will make up a given skeletal muscle. The tubular structure formed by the fascicle is vascularized and innervated such that the vessels and nerve conduits run parallel to the bundled muscle fibers (Fig. 2).[242]

During development, changes in gene expression, structural alignment, and chemical cues facilitate the maturation of muscle progenitor cells into mature myoblasts or fibers, which are also key parameters in activating muscle progenitor or satellite cells in adult tissue.[35,41,218,255,258,266,290] Many skeletal muscle engineering strategies have leveraged bulk alignment within the scaffold architecture, nanotopographical cues, and either passive tension or stretch applied by a bioreactor in order to mimic the native muscle structure.[41,42,147,194]

Engineering Skeletal Muscle with functional Neuromuscular Junctions (NMJs)

Apart from bulk alignment and cell–cell coupling, innervation of skeletal muscle is necessary for proper functioning of a critically sized muscle graft. Engineering the neuromuscular junction (NMJ) has proven extremely challenging due to the complexity required for proper cell-to-cell interactions that result in directed muscle movement.[75,258] The neuromuscular junction develops in a complex multistep process involving both inter and extracellular signaling pathways, leading to the formation of synaptic contact between the terminal branches of the motor neuron and a specialized area of the muscle cell

sarcolemma (i.e., plasma membrane) called the motor end-plate.[281] To properly regenerate and build NMJs, interactions between motor neurons, skeletal muscle fibers, and glial cells must be tightly regulated through both time and space. As such, a thorough understanding how these cells interact and how to properly co-culture them is required before the development of critically sized constructs that achieve functional results will be successful.[95,137,281] To further complicate the engineering problem, it is well known that improper cell-to-cell interaction and unorganized muscle-nerve interaction can lead to disease states such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy, and muscular dystrophy.[245]

In Vivo Accomplishments for Muscle and Nerve Tissue Regeneration

Many recent *in vitro* studies have demonstrated the potential use of natural biomaterial systems to guide skeletal and smooth muscle and nerve development, and further establish the functional connection between these two tissues.[75,258] Current research aims to translate these successes to *in vivo* studies, further validating the use of natural materials for engineering critically sized muscle constructs. *In vitro* analyses suggest that constructs formed by the co-culture of two or more cell types may lead to better vascularization and innervation *in vivo*.[75,258,281] By incorporating a mixed muscle progenitor cell population cultured on an aligned decellularized bladder matrix in the repair of volumetric muscle loss in rodents, the *in vivo* functional capacity of injured musculature improved 2.3-fold with the addition of a mixed cell population promoting the generation of functional skeletal muscle fibers. Additionally, a rodent model was used to demonstrate that innervation of rat skeletal muscle seeded fibrin gels prior to implantation significantly increased force generation and NMJ development *in vivo*.[55] Addition of agrin, a large proteoglycan important for NMJ development, significantly increased the formation of acetylcholine receptor clusters on differentiated C2C12 mouse myoblasts *in vitro*.[125] Pre-fabrication of acetylcholine receptor clusters on differentiated C2C12s in fibrin gels prior to implantation also accelerated innervation *in vivo* in a male nude rat model.[125] These recent results demonstrate the potential for engineering the NMJ *in vivo*, while also elucidating current limitations in scaffold design, such as lack of control over cell-to-cell contacts, and physiologically inaccurate 3D geometries preventing proper NMJ development on aligned muscle fibers, all of which must be addressed in future designs.

Clinical Translation and Commercialization

While the clinical realization of innervated skeletal muscle constructs has yet to be achieved, clinical success in the repair of short nerve defects within muscle tissue has been demonstrated. Materials for nerve repair are commercially available and focus on guiding nerve growth using artificial conduits. Stryker® (Kalamazoo, MI) developed type I collagen-based biomaterials for peripheral nerve and soft tissue repair. Their products, NeuorMatrix™, NeuroFlex™, and NeuroMend™ all use type I collagen as a wrap or tube to repair peripheral nerve injuries (Fig. 2b). In addition, TissueMend™ (Stryker®, Kalamazoo, MI) acellular collagen scaffolds are designed to augment repair and provide mechanical reinforcement for damaged tissues. While these materials are FDA-approved, they do not meet many of the design criteria described above. For example, type I collagen-based materials do not provide bulk alignment, support NMJ formation, or promote differentiation of local progenitor cells into functional nerve or muscle tissue.

Similarly, both natural and synthetic materials have been utilized for form aligned skeletal muscle fibers using a variety of formats including scaffolds, films, and limited success has been demonstrated in animal models (see Ref. 279 for recent review).[41,42] Overall, bridging the gap from promising *in vivo* animal studies to human trials and commercialization has proven difficult due to the multiple tissues that must integrate fully to provide functional recovery. However, as further progress is made using stem or progenitor cells, these remain a promising avenue for the repair of critically sized muscle defects.[26]

BIOPOLYMERS FOR CARDIAC TISSUE REGENERATION

Heart disease is the leading cause of death in both men and women, costing the United States $108.9 billion each year in health care services, medication, and loss of productivity.[30] In adult patients, complications from heart disease often result in heart failure, but in children, heart failure is frequently caused by congenital malformations of the heart (e.g., birth defects), weakened heart muscle, or damaged tissue not specifically due to heart disease. Currently, the only clinically available treatments for congenital birth defects and end-stage heart failure include left ventricular assist devices (LVADs), total heart transplantation, and surgical reconstruction.[225,282] Despite some success in heart repair and regeneration in small animal models, regeneration of electromechanically integrated human myocardium has yet to succeed, driving the need for new ideas and alternative engineering approaches for the repair and restoration of proper heart function.

Design Criteria for Cardiac Tissue Replacement

Scaffolds designed for cardiac tissue engineering must provide equivalent functionalities of physiological cardiac muscle, offering mechanical and electrical support for the native or encapsulated cardiomyocytes. Like skeletal muscle, cardiac muscle is striated. Therefore, alignment of scaffold architecture, whether achieved through passive stretch or tension, constant strain, or structural patterning, has shown to significantly improve cardiomyocyte function (Fig. 3a).[21,170,174] Whether acellular or cell-seeded, scaffolds must demonstrate a high degree of elasticity, promote cellular remodeling, maintain cell viability, support stem cell differentiation, and eventually sustain cardiomyocyte hypertrophy. In a cell-delivery approach, the scaffold design must yield integration of the provided cells (e.g., stem cells) with the host tissue and electromechanically couple these cells with the native heart muscle through both host cell ingrowth and delivered cell outgrowth (Fig. 3a). Mechanical considerations depend on many factors, including the age of the patient and the presence of injury or disease, and therefore, the modulus of scaffolds for cardiac tissue engineering should range between 5 and 50 kPa with pore sizes ranging from 20 to 40 μm.[204,225] Additionally, delivery of growth factors such as insulin-like growth factor-1 (IGF-1), human growth factor (HGF), vascular endothelial growth factor (VEGF), and stromal cell-derived factor-1 (SDF-1) have improved cardiac function and tissue integration following trauma.[257,282] As designs for cardiac tissue engineering move forward, the use of time-dependent and slow-release delivery systems will be necessary to achieve the desired paracrine signaling profiles *in vivo*.

In Vivo Accomplishments for Cardiac Tissue Replacement

Recent *in vitro* and rodent-based *in vivo* data support the use of both cellular and acellular approaches for repairing and restoring heart tissue in both children and adults, yet clinical realization of these strategies has proven difficult.[26,128] These therapies include the use of hydrogels or decellularized extracellular matrix solutions that are injected into or onto the heart,[226] the implantation of scaffolds or matrices, or the implantation of films or cell sheets.[160] Treatments are aimed at either restoring heart wall thickness and strengthening the muscle or minimizing scar tissue accumulation in the area and replacing it with electromechanically coupled tissue.

Alginate and Chitosan—Polysaccharides, such as alginate and chitosan, have been widely utilized for cardiac tissue engineering due to their biocompatibility and ease of use.[239] Currently, liquid alginate solutions (Sodium Alginate and Calcium Gluconate, NCT01226563 and Algisyl-LVR™ intramyocardial injections of alginate hydrogel, NCT01311791) are undergoing thorough investigation in human clinical trials. However, a three-dimensional, pre-formed alginate-based cardiac patch has not yet reached the clinic despite promising *in vitro* results.[239] The development of a cardiac patch from one or both of these materials is extremely challenging due to the limitations in electrical conductivity. Gold nanowires, gold nanoparticles, and carbon nanotubes have been incorporated into polysaccharide-based hydrogels to improve electrical coupling between adjacent cardiac cells *in vitro*. As with all critically sized constructs, vascularization is paramount to the success of a cardiac construct. One approach is to add pro-angiogenic growth factors to the matrix to improve host infiltration. Recent efforts using these polysaccharide based biopolymers have led to the successful delivery or growth factors and small molecules *in vivo*.[133,262]

Gelatin and Elastin—Use of collagen alone to repair heart defects is challenging since the protein itself causes stiffening of the heart tissue and induces reprogramming of cardiac fibroblasts. Instead, gelatin and elastin based scaffolds serve as sufficient alternatives for cardiac tissue engineering due to their rapid cellular degradation and bulk elasticity. Gelatin-based sheets for the fabrication of cardiac patches are currently under investigation in clinical trials (e.g., AutoLogous Human CArdiac-Derived stem cell to treat Ischemic cArdiomyopathy (ALCADIA), NCT00981006). Novel composites formed by methacrylating biopolymers, such as GelMa (methacrylated gelatin[236]) and MeTro (methacrylated tropoelastin[10]), have also been studied extensively *in vitro*. These biopolymers also lack electrical conductivity, which has prompted the *in vivo* investigation of composite materials containing single walled carbon nanotubes (SWNTs) for left ventricle repair following myocardial infarction. The implantation of these devices *in vivo* resulted in significantly increased fractional shortening and ejection fraction compared to untreated hearts, partially due to enhanced the expression of intercellular adhesive junctions and electrochemical junctions in rats who received SWCT-based implants.[294] Overall, SWCT-based scaffolds integrated into infarct myocardium exerted beneficial effects on myocardial regeneration and remodeling in the infarct areas, resulting in the improvement of heart functions in rats.[294] *In vitro*, the addition of the SWCTs enhanced spontaneous electrical activity in seeded cell constructs as well as cardiomyocyte connectivity, as

demonstrated by the ability of SWCT-containing constructs to beat regionally after 2–3 days and contract synchronously at day 8, which was not observed in SWCT-free materials.[294] SWNT-based materials supported the contractile properties of engineered cardiac tissue through enhancement of the formation of gap junctions and promotion of the excitation–contraction coupling of cardiomyocytes.[294] However, the long-term biocompatibility of SWCTs *in vivo* raises concern for the translation of these scaffolds to human clinical trials.

Fibrin—Fibrin-based scaffolds show exciting promise for cardiac repair given the elastic nature of the scaffold and the rapid degradation and cellular remodeling potential afforded by the chemical structure.[89] Initial work with this biopolymer demonstrated modulation of gelation rates by adjusting the fibrinogen to thrombin ratio to achieve an injectable material capable of delivering cells or growth factors to a damaged heart surface.[39,178] Initial *in vitro* investigations of fibrin for cardiac repair established potential therapy to regenerate post-myocardial infarction cardiac tissue using 3D functional fibrin-based myocardial equivalent grafts formed *in vitro*. Results indicated that the aligned fibrin scaffolds demonstrated a significant increase in twitch force compared to the isotropic constructs.[21] Parameters that could be modulated to tailor these construct properties prior to implantation include regulating the magnitude of stretch used to induce alignment, preconditioning the scaffold to stretch in a bioreactor, or pre-seeding the graft with cardiomyocytes prior to implantation.[173–176,285,292]

Clinical Translation and Future Directions

Current research on cardiac patch biomaterials is promising, yet full realization of the potential of these therapies remains elusive. Unless a patient is undergoing open-heart surgery, such as a valve replacement, surgical access to the outer left ventricle wall is limited. Regeneration strategies have instead focused on delivering cells or injectable gels at the damaged site by a catheter.[226] Additionally, natural biopolymer-based cardiac patches may provide solutions to complex cardiac reconstruction in young patients with complex congenital heart defects. Natural-based cardiac patches have allowed engineers to overcome the limitations of current synthetic patches, which do not promote cellular remodeling, do not grow as the child grows, and often require reoperation (Fig. 3b).[102] Furthermore, in young patients, both extracellular matrix composition and cardiomyocyte metabolism differ greatly from mature, adult tissue, necessitating a careful analysis of design criteria and biomaterial selection for cardiac graft fabrication.[276,282] These results present two major implications for the future of cardiac tissue regeneration and remodeling: (1) repair in younger patients may be more successful due a greater percentage of proliferating cells and circulating progenitors and (2) the fetal environment (e.g., matrix composition, tissue density, tissue mechanics) may represent improved design criteria for repair and regeneration in the adult heart.

BIOPOLYMERS FOR CORNEAL TISSUE REPLACEMENT

The human cornea is a transparent, avascular, connective tissue that provides an optical interface with substantial refractive power, while protecting the eye from mechanical injury and potential infection. This organ is comprised of three distinct cellular layers: corneal

epithelium, stroma, and endothelium, which are separated by two acellular collagenous interfaces known as the Bowman's Layer and Descemet's membrane (Fig. 4).[214] Improper corneal development, damage to the cornea and limbal cells, or nerve injury resulting from infection or trauma can result in loss of corneal transparency, leading to either partial or complete loss of vision. Approximately 10 million people worldwide suffer from corneal vision loss, prompting the need for an effective corneal transplant therapy. These transplants can be categorized into two main repair options: allogenic and synthetic materials. Although allogenic materials from human donors are preferred, a shortage of quality donor graft material has limited the broad applicability of this clinical option. Alternatively, synthetic homologs to donor corneal grafts are primarily used as temporary replacements until suitable donor tissue becomes available. The use of a synthetic homolog for long-term repair is limited by intrinsic risks of corneal melting, bacterial endophthalmitis, and retinal detachment resulting in graft failure.

Design Criteria for Cornea Tissue Replacement

The main functions of the cornea necessitate three major design requirements: protection, transparency, and an effective optical interface. In addition, a corneal replacement device must also be biocompatible in the human body and ideally bioactive such that the graft material can integrate within the surrounding host tissue (Fig. 4). Efforts to regenerate the cornea have focused on the *in vitro* regeneration of the epithelium, stroma, and endothelium strata, followed by the promotion of neural and vascular interfaces. Natural biopolymers have been used extensively to mimic the corneal epithelium layer. In particular, reconstituted and chemically cross-linked type I collagen or silk hydrogels have been used as substrates for human epithelial cell growth and functional tissue organization.[138,169] Reconstruction of the corneal stroma has proven challenging due to the complex structure, mechanical strength requirements, and need for optical transparency. Therefore, corneal stroma engineering has focused on the development of functional corneal stroma substrates through chemical, morphological, and mechanical cues.[88,131,277] In the particular context of the corneal stroma, type I collagen has been used extensively due to its dominant content in the native corneal tissue as well as its standardized processability.[84] Alternatively, silk films have been optimized to support corneal stromal cell growth and organization in both 2D and 3D environments, in which topography, surface chemistry, porosity, degradation profiles, and transparency were controlled.[87,229]

In Vivo Accomplishments for Corneal Tissue Replacement

In order to study the integration of an implanted biomaterial within corneal native tissue, *in vivo* implantation of acellular corneal tissue equivalents has been investigated.[139,205] Studies have focused on recapitulating the three-layer structure of the cornea (epithelium, stroma, and endothelium).[2,91] Recent efforts have used decellularized biological material, such as amniotic membranes and animal-derived cornea. However, the results of an acellular porcine cornea in combination with amniotic epithelial cells in a rabbit lamellar keratoplasty resulted in degradation of the tissue-engineered cornea due to host rejection.[143] Decellularized amniotic membrane was clinically evaluated in combination with human corneal endothelial cells in a lamellar keratoplasty model. The endothelium and part of the Descemet's membrane were removed, and the construct was able to function as a corneal endothelium

equivalent.[73] In all cases, complications due to foreign material host response and material performance limitations such as lack in transparency, degradability, and mismatch in mechanical and permeability properties hindered success in the reported animal studies.

Clinical Translation and Commercialization

Anterior partial keratoplasty performed in humans using biosynthetic corneas made from cross-linking recombinant human collagen type III showed that these naturally derived collagen scaffolds provide effective tissue regeneration by promoting endogenous tissue growth and innervation without signs of vascularization for up to two years. However, a delay in epithelial closure and a fibrotic response were observed, likely caused by surgical sutures.[68] A 4-year follow up showed a stably integrated implant, although a more robust material with better shape retention may improve visual acuity.[69] Partial or full-thickness engineered corneal tissues have been developed for *in vitro* preclinical cornea tissue repair models to reduce animal testing for commercial products for eye irritancy tests.[45] A multi-layer collagen hydrogel scaffold was developed and evaluated using primary corneal endothelial, stromal, and epithelial cells.[209] The commercially available products mainly referred to engineered epithelium based on trans-well permeable membrane architecture, as in the case of Clonetics™ Human Corneal Epithelial Culture Model (Lonza, Hopkinton, MA), LabCyte Cornea-Model (Japan Tissue Engineering Co., Ltd., Gamagori City, Aichi, Japan), and EpiOcular™ (MatTek Corporation, Ashland, MA).

THE FUTURE OF BIOPOLYMERS: A FOCUS ON CLINICAL TRANSLATION

Given the wide range of products available on the market today, there still exists a pressing need for further product development to repair full thickness wounds. The path to clinical translation and commercialization of wound healing products presents a case where academics, start-up companies, and venture capitalists can reflect on both the successes and failures of product implementation in the medical field. A major lesson learned is that there is no “one-size-fits-all” solution such that a single product or biomaterial will not meet the design criteria and patient need for every clinical application. For instance, wound healing is more complex and takes longer in diabetic patients compared to healthy patients, as these patients often suffer from ischemia and neuropathy in their extremities. Thus, challenges with cost-to-patient-benefit analysis, proper doctor recommendation and utilization, long times between initial development and FDA approval, and other unforeseen challenges have impeded the clinical translation of many promising biopolymer-based products.[107]

A fundamental understanding of native tissue structure and organization, as well as physical, and biochemical properties is essential for the successful design of biomaterial scaffold systems to produce effective tissue replacement therapies. The goal of this review was to provide an overview of recent efforts based on natural polymers to mimic *in vivo* structures for tissue types including bone, muscle, peripheral nerve, cardiac, and cornea, and to highlight the progression of these systems from animal models into clinical settings. Despite major recent advancements in the tissue engineering field, significant challenges such as lack of vascularization, fine control of biomaterial degradation rate and byproducts, and construct re-innervation in critical-size grafts are limiting factors in the translation of tissue

engineered products to clinical scenarios. Thus, there remains a significant opportunity to develop new methods and techniques for the generation of pre-vascularized and re-innervated tissues to promote angiogenesis and neovascularization, lymphangiogenesis, and innervation in order to create fully functioning tissues.

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REFERENCES

1. Abou Neel EA, Bozec L, Knowles JC, Syed O, Mudera V, Day R, and Hyun JK. Collagen—emerging collagen based therapies hit the patient. Adv. Drug Deliv. Rev 65:429–456, 2013. [PubMed: 22960357]
2. Alaminos M, Sánchez-Quevedo MDC, Muñoz-Ávila JI, Serrano D, Medialdea S, Carreras I, and Campos A. Construction of a complete rabbit cornea substitute using a fibrin-agarose scaffold. Investig. Ophthalmol. Vis. Sci 47:3311–3317, 2006. [PubMed: 16877396]
3. Allen RA, Wu W, Yao M, Dutta D, Duan X, Bachman TN, Champion HC, Stolz DB, Robertson AM, and Kim K. Nerve regeneration and elastin formation within poly (glycerol sebacate)-based synthetic arterial grafts one-year post-implantation in a rat model. Biomaterials 35:165–173, 2014. [PubMed: 24119457]
4. Alluin O, Wittmann C, Marqueste T, Chabas J-F, Garcia S, Lavaut M-N, Guinard D, Feron F, and Decherchi P. Functional recovery after peripheral nerve injury and implantation of a collagen guide. Biomaterials 30:363–373, 2009. [PubMed: 18929405]
5. Almine JF, Bax DV, Mithieux SM, Nivison-Smith L, Rnjak J, Waterhouse A, Wise SG, and Weiss AS. Elastin-based materials. Chem. Soc. Rev 39:3371–3379, 2010. [PubMed: 20449520]
6. Altman GH, Diaz F, Jakuba C, Calabro T, Horan RL, Chen J, Lu H, Richmond J, and Kaplan DL. Silk-based biomaterials. Biomaterials 24:401–416, 2003. [PubMed: 12423595]
7. Amini AR, Laurencin CT, and Nukavarapu SP. Bone tissue engineering: recent advances and challenges. Crit. Rev. Biomed. Eng 40:363–408, 2012. [PubMed: 23339648]
8. An B, DesRochers TM, Qin GK, Xia XX, Thiagarajan G, Brodsky B, and Kaplan DL. The influence of specific binding of collagen-silk chimeras to silk biomaterials on hMSC behavior. Biomaterials 34:402–412, 2013. [PubMed: 23088839]
9. Anitua E, Andia I, Ardanza B, Nurden P, and Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb. Haemost 91:4–15, 2004. [PubMed: 14691563]
10. Annabi N, Tsang K, Mithieux SM, Nikkhah M, Ameri A, Khademhosseini A, and Weiss AS. Highly elastic micropatterned hydrogel for engineering functional cardiac tissue. Adv. Funct. Mater 23:4950–4959, 2013.
11. Astete CE, and Sabliov CM. Synthesis and characterization of plga nanoparticles. J. Biomater. Sci. Polym. Ed 17:247–289, 2012.
12. Athanasiou KA, Niederauer GG, and Agrawal C. Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers. Biomaterials 17:93–102, 1996. [PubMed: 8624401]
13. Athanasiou KA, Zhu CF, Lanctot DR, Agrawal CM, and Wang X. Fundamentals of biomechanics in tissue engineering of bone. Tissue Eng. 6:361–381, 2000. [PubMed: 10992433]
14. Baldock C, Oberhauser AF, Ma L, Lammie D, Siegler V, Mithieux SM, Tu Y, Chow JY, Suleman F, Malfois M, Rogers S, Guo L, Irving TC, Wess TJ, and Weiss AS. Shape of tropoelastin, the highly extensible protein that controls human tissue elasticity. Proc. Natl. Acad. Sci. USA 108:4322–4327, 2011. [PubMed: 21368178]
15. Bartus C, William Hanke C, and Daro-Kaftan E. A decade of experience with injectable poly-l-lactic acid: a focus on safety. Dermatol. Surg 39:698–705, 2013. [PubMed: 23379657]

16. Bell E, Ivarsson B, and Merrill C. Production of a tissue-like structure by contraction of collagen lattices by human fibroblasts of different proliferative potential in vitro. Proc. Natl. Acad. Sci 76:1274–1278, 1979. [PubMed: 286310]
17. Bellas E, Panilaitis BJB, Glettig DL, Kirker-Head CA, Yoo JJ, Marra KG, Rubin JP, and Kaplan DL. Sustained volume retention in vivo with adipocyte and lipoaspirate seeded silk scaffolds. Biomaterials 34:2960–2968, 2013. [PubMed: 23374707]
18. Beun LH, Storm IM, Werten MW, de Wolf FA, Cohen Stuart MA, and de Vries R. From micelles to fibers: balancing self-assembling and random coiling domains in ph-responsive silk-collagen-like protein-based polymers. Biomacromolecules 15:3349–3357, 2014. [PubMed: 25133990]
19. Bhola M, Sanchez S, and Kolhatkar S. Use of an extracellular matrix membrane for root coverage: case series and review of the literature. Clin. Adv. Periodontics 3:16–21, 2013.
20. Bhumiratana S, Grayson WL, Castaneda A, Rockwood DN, Gil ES, Kaplan DL, and Vunjak-Novakovic G. Nucleation and growth of mineralized bone matrix on silk-hydroxyapatite composite scaffolds. Biomaterials 32:2812–2820, 2011. [PubMed: 21262535]
21. Black LD III, Meyers JD, Weinbaum JS, Shvelidze YA, and Tranquillo RT. Cell-induced alignment augments twitch force in fibrin gel–based engineered myocardium via gap junction modification. Tissue Eng. Part A 15:3099–3108, 2009. [PubMed: 19338433]
22. Bond E, Barrett S, Pragnell J, and Victoria R. Successful treatment of nonhealing wounds with xelma®. Br. J. Nursing 18:1404–1409, 2009.
23. Borrelli M, Reichl S, Feng Y, Schargus M, Schrader S, and Geerling G. In vitro characterization and ex vivo surgical evaluation of human hair keratin films in ocular surface reconstruction after sterilization processing. J. Mater. Sci. Mater. Med 24:221–230, 2013. [PubMed: 23015265]
24. Bose S, Roy M, and Bandyopadhyay A. Recent advances in bone tissue engineering scaffolds. Trends Biotechnol. 30:546–554, 2012. [PubMed: 22939815]
25. Boublik J, Park H, Radisic M, Tognana E, Chen F, Pei M, Vunjak-Novakovic G, and Freed LE. Mechanical properties and remodeling of hybrid cardiac constructs made from heart cells, fibrin, and biodegradable, elastomeric knitted fabric. Tissue Eng. 11:1122–1132, 2005. [PubMed: 16144448]
26. Burdick JA, Mauck RL, Gorman JH, and Gorman RC. Acellular biomaterials: an evolving alternative to cell-based therapies. Sci. Transl. Med 5:176ps4, 2013.
27. Buskens E, Meijboom MJ, Kooijman H, and Van Hout BA. The use of a surgical sealant (coseal) in cardiac and vascular reconstructive surgery: an economic analysis. J. Cardiovasc. Surg 47:161–170, 2006.
28. Cannata A, Taglieri C, Russo CF, Bruschi G, and Martinelli L. Use of coseal in a patient with a left ventricular assist device. Ann. Thorac. Surg 87:1956–1958, 2009. [PubMed: 19463640]
29. Carlson M, Faria K, Shamis Y, Leman J, Ronfard V, and Garlick J. Epidermal stem cells are preserved during commercial-scale manufacture of a bilayered, living cellular construct (apligraf®). Tissue Eng. Part A 17:487–493, 2010. [PubMed: 20849380]
30. Centers for Disease Control and Prevention. Heart disease fact sheet. Atlanta, GA: US Department of Health and Human Services, 2014.
31. Chen JL, Yin Z, Shen WL, Chen X, Heng BC, Zou XH, and Ouyang HW. Efficacy of hESC-MSCs in knitted silk-collagen scaffold for tendon tissue engineering and their roles. Biomaterials 31:9438–9451, 2010. [PubMed: 20870282]
32. Chen Q-Z, Ishii H, Thouas GA, Lyon AR, Wright JS, Blaker JJ, Chrzanowski W, Boccaccini AR, Ali NN, Knowles JC, and Harding SE. An elastomeric patch derived from poly(glycerol sebacate) for delivery of embryonic stem cells to the heart. Biomaterials 31:3885–3893, 2010. [PubMed: 20153041]
33. Chicatun F, Pedraza CE, Ghezzi CE, Marelli B, Kaartinen MT, McKee MD, and Nazhat SN. Osteoid-mimicking dense collagen/chitosan hybrid gels. Biomacromolecules 12:2946–2956, 2011. [PubMed: 21661759]
34. Chicatun F, Pedraza CE, Muja N, Ghezzi CE, McKee MD, and Nazhat SN. Effect of chitosan incorporation and scaffold geometry on chondrocyte function in dense collagen type I hydrogels. Tissue Eng. Part A 19:2553–2564, 2013. [PubMed: 23859275]

35. Cho OH, Mallappa C, Hernandez-Hernandez JM, Rivera-Perez JA, and Imbalzano AN. Contrasting roles for myod in organizing myogenic promoter structures during embryonic skeletal muscle development. Dev. Dyn 2014. doi:10.1002/dvdy.24217.
36. Chow D, Nunalee ML, Lim DW, Simnick AJ, and Chilkoti A. Peptide-based biopolymers in biomedicine and biotechnology. Mater. Sci. Eng. R 62:125–155, 2008.
37. Choy DKS, Nga VDW, Lim J, Lu J, Chou N, Yeo TT, and Teoh S-H. Brain tissue interaction with three-dimensional, honeycomb polycaprolactone-based scaffolds designed for cranial reconstruction following traumatic brain injury. Tissue Eng. Part A 19:2382–2389, 2013. [PubMed: 23691928]
38. Christman KL, Fok HH, Sievers RE, Fang Q, and Lee RJ. Fibrin glue alone and skeletal myoblasts in a fibrin scaffold preserve cardiac function after myocardial infarction. Tissue Eng. 10:403–409, 2004. [PubMed: 15165457]
39. Christman KL, Vardanian AJ, Fang Q, Sievers RE, Fok HH, and Lee RJ. Injectable fibrin scaffold improves cell transplant survival, reduces infarct expansion, and induces neovasculature formation in ischemic myocardium. J. Am. Coll. Cardiol 44:654–660, 2004. [PubMed: 15358036]
40. Cormio L, Perrone A, Di Fino G, Ruocco N, De Siati M, de la Rosette J, and Carrieri G. Tachosil® sealed tubeless percutaneous nephrolithotomy to reduce urine leakage and bleeding: outcome of a randomized controlled study. J. Urol 188:145–150, 2012. [PubMed: 22591964]
41. Corona BT, Machingal MA, Criswell T, Vadhavkar M, Dannahower AC, Bergman C, Zhao W, and Christ GJ. Further development of a tissue engineered muscle repair construct in vitro for enhanced functional recovery following implantation in vivo in a murine model of volumetric muscle loss injury. Tissue Eng. Part A 18:1213–1228, 2012. [PubMed: 22439962]
42. Corona BT, Ward CL, Baker HB, Walters TJ, and Christ GJ. Implantation of in vitro tissue engineered muscle repair constructs and bladder acellular matrices partially restore in vivo skeletal muscle function in a rat model of volumetric muscle loss injury. Tissue Eng. Part A 20:705–715, 2013. [PubMed: 24066899]
43. Corpas Ldos S, Lambrichts I, Quirynen M, Collaert B, Politis C, Vrielinck L, Martens W, Struys T, and Jacobs R. Peri-implant bone innervation: histological findings in humans. Eur. J. Oral Implantol 7:283–292, 2014. [PubMed: 25237672]
44. Curran MP, and Plosker GL. Bilayered bioengineered skin substitute (apligraf®). BioDrugs 16:439–455, 2002. [PubMed: 12463767]
45. Curren RD, and Harbell JW. Ocular safety: a silent (in vitro) success story. Altern. Lab. Anim 30(Suppl 2):69–74, 2002.
46. Dahl SLM, Kypson AP, Lawson JH, Blum JL, Strader JT, Li Y, Manson RJ, Tente WE, DiBernardo L, Hensley MT, Carter R, Williams TP, Prichard HL, Dey MS, Begelman KG, and Niklason LE. Readily available tissue-engineered vascular grafts. Sci. Transl. Med 3:68ra9, 2011.
47. Dan H, Vaquette C, Fisher AG, Hamlet SM, Xiao Y, Hutmacher DW, and Ivanovski S. The influence of cellular source on periodontal regeneration using calcium phosphate coated polycaprolactone scaffold supported cell sheets. Biomaterials 35:113–122, 2014. [PubMed: 24120045]
48. De la Riva B, Nowak C, Sanchez E, Hernandez A, Schulz-Siegmund M, Pec MK, Delgado A, and Evora C. VEGF-controlled release within a bone defect from alginate/chitosan/PLA-H scaffolds. Eur. J. Pharm. Biopharm 73:50–58, 2009. [PubMed: 19442724]
49. De Luca AC, Stevens JS, Schroeder SLM, Guilbaud JB, Saiani A, Downes S, and Terenghi G. Immobilization of cell-binding peptides on poly-ε-caprolactone film surface to biomimic the peripheral nervous system. J. Biomed. Mater. Res. Part A 101:491–501, 2013.
50. de Peppo GM, Marcos-Campos I, Kahler DJ, Alsalman D, Shang L, Vunjak-Novakovic G, and Marolt D. Engineering bone tissue substitutes from human induced pluripotent stem cells. Proc. Natl. Acad. Sci. USA 110:8680–8685, 2013. [PubMed: 23653480]
51. de Valence S, Tille J-C, Mugnai D, Mrowczynski W, Gurny R, Möller M, and Walpoth BH. Long term performance of polycaprolactone vascular grafts in a rat abdominal aorta replacement model. Biomaterials 33:38–47, 2012. [PubMed: 21940044]
52. Deal DN, Griffin JW, and Hogan MV. Nerve conduits for nerve repair or reconstruction. J. Am. Acad. Orthop. Surg 20:63–68, 2012. [PubMed: 22302443]

53. Deng Y, Bi X, Zhou H, You Z, Wang Y, Gu P, and Fan X. Repair of critical-sized bone defects with anti-mir-31-expressing bone marrow stromal stem cells and poly (glycerol sebacate) scaffolds. Eur. Cells Mater 27:13, 2014.
54. Dhanraj P A clinical study comparing helicoll with scarlet red and opsite in the treatment of split thickness skin graft donor sites—a randomized controlled trial. Indian J. Surg 2013. doi:10.1007/s12262-013-0850-3.
55. Dhawan V, Lytle IF, Dow DE, Huang Y-C, and Brown DL. Neurotization improves contractile forces of tissue-engineered skeletal muscle. Tissue Eng. 13:2813–2821, 2007. [PubMed: 17822360]
56. Di Martino A, Sittinger M, and Risbud MV. Chitosan: a versatile biopolymer for orthopaedic tissue-engineering. Biomaterials 26:5983–5990, 2005. [PubMed: 15894370]
57. Diab T, Pritchard EM, Uhrig BA, Boerckel JD, Kaplan DL, and Guldberg RE. A silk hydrogel-based delivery system of bone morphogenetic protein for the treatment of large bone defects. J. Mech. Behav. Biomed. Mater 11:123–131, 2012. [PubMed: 22658161]
58. Dornseifer U, Lonic D, Gerstung TI, Herter F, Fichter AM, Holm C, Schuster T, and Ninkovic M. The ideal split-thickness skin graft donor-site dressing: a clinical comparative trial of a modified polyurethane dressing and aquacel. Plast. Reconstr. Surg 128:918–924, 2011. [PubMed: 21681125]
59. Dorozhkin SV Calcium orthophosphate-based biocomposites and hybrid biomaterials. J. Mater. Sci 44:2343–2387, 2009.
60. Downie F, and Gannon R. Opsite flexifix gentle: preventing skin breakdown in vulnerable skin. Br. J. Nurs 22:698–700, 2013.
61. Driscoll P Tissue engineering, cell therapy, and transplantation: products, technologies, and market opportunities worldwide: 2009–2018. Tissue Eng. Cell Ther 2010. http://www.mediligence.com/rpt/rpt-s520.htm.
62. Dvir T, Timko BP, Brigham MD, Naik SR, Karajanagi SS, Levy O, Jin H, Parker KK, Langer R, and Kohane DS. Nanowired three-dimensional cardiac patches. Nat. Nanotechnol 6:720–725, 2011. [PubMed: 21946708]
63. Eaglstein WH, and Falanga V. Tissue engineering and the development of apligraf®, a human skin equivalent. Clin. Ther 19:894–905, 1997. [PubMed: 9385478]
64. Ellis CN Outcomes with the use of bioprosthetic grafts to reinforce the ligation of the intersphincteric fistula tract (biolift procedure) for the management of complex anal fistulas. Dis. Colon Rectum 53:1361–1364, 2010. [PubMed: 20847616]
65. Engelmayr Jr., Cheng GC,M, Bettinger CJ, Borenstein JT, Langer R, and Freed LE. Accordion-like honeycombs for tissue engineering of cardiac anisotropy. Nat. Mater 7:1003–1010, 2008. [PubMed: 18978786]
66. Erb MA, Claus T, Hartrumpf M, Bachmann S, and Albes JM. The use of tachosil® surgical patch or fibrin glue in coronary artery surgery does not affect quality of anastomosis or provoke postoperative adhesions in pigs. Eur. J. Cardiothorac. Surg 36:703–707, 2009. [PubMed: 19699105]
67. Etienne O, Schneider A, Kluge JA, Bellemin-Laponnaz C, Polidori C, Leisk GG, Kaplan DL, Garlick JA, and Egles C. Soft tissue augmentation using silk gels: an in vitro and in vivo study. J. Periodontol 80:1852–1858, 2009. [PubMed: 19905955]
68. Fagerholm P, Lagali NS, Merrett K, Jackson WB, Munger R, Liu Y, Polarek JW, Soderqvist M, and Griffith M. A biosynthetic alternative to human donor tissue for inducing corneal regeneration: 24-month follow-up of a phase 1 clinical study. Sci. Transl. Med 2:46ra61, 2010.
69. Fagerholm P, Lagali NS, Ong JA, Merrett K, Jackson WB, Polarek JW, Suuronen EJ, Liu Y, Brunette I, and Griffith M. Stable corneal regeneration four years after implantation of a cell-free recombinant human collagen scaffold. Biomaterials 35:2420–2427, 2014. [PubMed: 24374070]
70. Falabella AF, Schachner LA, Valencia IC, and Eaglstein WH. The use of tissue-engineered skin (apligraf) to treat a newborn with epidermolysis bullosa. Arch. Dermatol 135:1219–1222, 1999. [PubMed: 10522669]

71. Falabella AF, Valencia IC, Eaglstein WH, and Schachner LA. Tissue-engineered skin (apligraf) in the healing of patients with epidermolysis bullosa wounds. Arch. Dermatol 136:1225–1230, 2000. [PubMed: 11030768]
72. Falanga V, and Sabolinski M. A bilayered living skin construct (apligraf®) accelerates complete closure of hard-to-heal venous ulcers. Wound Repair Regen. 7:201–207, 1999. [PubMed: 10781211]
73. Fan T, Ma X, Zhao J, Wen Q, Hu X, Yu H, and Shi W. Transplantation of tissue-engineered human corneal endothelium in cat models. Mol. Vis 19:400–407, 2013. [PubMed: 23441111]
74. Ferreira AM, Gentile P, Chiono V, and Ciardelli G. Collagen for bone tissue regeneration. Acta Biomater. 8:3191–3200, 2012. [PubMed: 22705634]
75. Fishman JM, Tyraskis A, Maghsoudlou P, Urbani L, Totonelli G, Birchall MA, and De Coppi P. Skeletal muscle tissue engineering: which cell to use? Tissue Eng. Part B 19:503–515, 2013.
76. Fivenson D, and Scherschun L. Clinical and economic impact of apligraf® for the treatment of nonhealing venous leg ulcers. Int. J. Dermatol 42:960–965, 2003. [PubMed: 14636194]
77. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, and Rodeo SA. Platelet-rich plasma from basic science to clinical applications. Am. J. Sports Med 37:2259–2272, 2009. [PubMed: 19875361]
78. Francis NL, Hunger PM, Donius AE, Riblett BW, Zavaliangos A, Wegst UGK, and Wheatley MA. An ice-templated, linearly aligned chitosan-alginate scaffold for neural tissue engineering. J. Biomed. Mater. Res. Part A 101:3493–3503, 2013.
79. Garkavenko O, Wynyard S, Nathu D, Quane T, Durbin K, Denner J, and Elliott R. The first clinical xenotransplantation trial in new zealand: efficacy and safety. Xenotransplantation 19:6, 2012.
80. Gentzkow GD, Iwasaki SD, Hershon KS, Mengel M, Prendergast JJ, Ricotta JJ, Steed DP, and Lipkin S. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes Care 19:350–354, 1996. [PubMed: 8729158]
81. Geuze RE, Theyse LF, Kempen DH, Hazewinkel HA, Kraak HY, Oner FC, Dhert WJ, and Alblas J. A differential effect of bone morphogenetic protein-2 and vascular endothelial growth factor release timing on osteogenesis at ectopic and orthotopic sites in a large-animal model. Tissue Eng. Part A 18:2052–2062, 2012. [PubMed: 22563713]
82. Ghezzi CE, Marelli B, Muja N, Hirota N, Martin JG, Barralet JE, Alessandrino A, Freddi G, and Nazhat SN. Mesenchymal stem cell-seeded multilayered dense collagen-silk fibroin hybrid for tissue engineering applications. Biotechnol. J 6:1198–1207, 2011. [PubMed: 21751393]
83. Ghezzi CE, Marelli B, Muja N, and Nazhat SN. Immediate production of a tubular dense collagen construct with bioinspired mechanical properties. Acta Biomater. 8:1813–1825, 2012. [PubMed: 22326787]
84. Ghezzi CE, Muja N, Marelli B, and Nazhat SN. Real time responses of fibroblasts to plastically compressed fibrillar collagen hydrogels. Biomaterials 32:4761–4772, 2011. [PubMed: 21514662]
85. Ghezzi CE, Risse PA, Marelli B, Muja N, Barralet JE, Martin JG, and Nazhat SN. An airway smooth muscle cell niche under physiological pulsatile flow culture using a tubular dense collagen construct. Biomaterials 34:1954–1966, 2013. [PubMed: 23257180]
86. Ghezzi CE, Rnjak-Kovacina J, Weiss AS, and Kaplan DL. Multifunctional silk-tropoelastin biomaterial systems. Isr. J. Chem 53:777–786, 2013. [PubMed: 26005219]
87. Gil ES, Mandal BB, Park SH, Marchant JK, Omenetto FG, and Kaplan DL. Helicoidal multi-lamellar features of RGD-functionalized silk biomaterials for corneal tissue engineering. Biomaterials 31:8953–8963, 2010. [PubMed: 20801503]
88. Gil ES, Park SH, Marchant J, Omenetto F, and Kaplan DL. Response of human corneal fibroblasts on silk film surface patterns. Macromol. Biosci 10:664–673, 2010. [PubMed: 20301120]
89. Grassl ED, Oegema TR, and Tranquillo RT. Fibrin as an alternative biopolymer to type-I collagen for the fabrication of a media equivalent. J. Biomed. Mater. Res 60:607–612, 2002. [PubMed: 11948519]
90. Grau AE, and Durán JA. Treatment of a large corneal perforation with a multilayer of amniotic membrane and tachosil. Cornea 31:98–100, 2012. [PubMed: 21963863]

91. Griffith M, Osborne R, Munger R, Xiong X, Doillon CJ, Laycock NL, Hakim M, Song Y, and Watsky MA. Functional human corneal equivalents constructed from cell lines. Science 286:2169–2172, 1999. [PubMed: 10591651]
92. Griffiths M, Ojeh N, Livingstone R, Price R, and Navsaria H. Survival of apligraf in acute human wounds. Tissue Eng. 10:1180–1195, 2004. [PubMed: 15363174]
93. Gu X, Ding F, and Williams DF. Neural tissue engineering options for peripheral nerve regeneration. Biomaterials 35:6143–6156, 2014. [PubMed: 24818883]
94. Guan L, Ge H, Tang X, Su S, Tian P, Xiao N, Zhang H, Zhang L, and Liu P. Use of a silk fibroin-chitosan scaffold to construct a tissue-engineered corneal stroma. Cells Tissues Organs 198:190–197, 2013. [PubMed: 24247045]
95. Guo X, Das M, Rumsey J, Gonzalez M, Stancescu M, and Hickman J. Neuromuscular junction formation between human stem-cell-derived motoneurons and rat skeletal muscle in a defined system. Tissue Eng. Part C 16:1347–1355, 2010.
96. Guyer RD, Tromanhauser SG, and Regan JJ. An economic model of one-level lumbar arthroplasty versus fusion. Spine J. Off. J. N. Am. Spine Soc 7:558–562, 2007.
97. Hall KK, Gattás-Asfura KM, and Stabler CL. Microencapsulation of islets within alginate/poly(ethylene glycol) gels cross-linked via staudinger ligation. Acta Biomater 7:614–624, 2011. [PubMed: 20654745]
98. Hallab NJ Hypersensitivity to implant debris. Degrad. Implant Mater 2012:329–345, 2012.
99. Han J, Lazarovici P, Pomerantz C, Chen X, Wei Y, and Lelkes PI. Co-electrospun blends of plga, gelatin, and elastin as potential nonthrombogenic scaffolds for vascular tissue engineering. Biomacromolecules 12:399–408, 2010. [PubMed: 21182235]
100. Hansbrough JF, Mozingo DW, Kealey GP, Davis M, Gidner A, and Gentzkow GD. Clinical trials of a biosynthetic temporary skin replacement, dermagraft-transitional covering, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. J. Burn Care Res 18:43–51, 1997.
101. Hart CE, Loewen-Rodriguez A, and Lessem J. Dermagraft: use in the treatment of chronic wounds. Adv. Wound Care 1:138–141, 2012.
102. Hauser M, Eicken A, Kuehn A, Hess J, Fratz S, Ewert P, and Kaemmerer H. Managing the right ventricular outflow tract for pulmonary regurgitation after tetralogy of fallot repair. Heart Asia 5:106–111, 2013. [PubMed: 27326099]
103. Hayabuchi Y, Mori K, Kitagawa T, Sakata M, and Kagami S. Polytetrafluoroethylene graft calcification in patients with surgically repaired congenital heart disease: evaluation using multidetector-row computed tomography. Am. Heart J 153:806.e1–806.e8, 2007. [PubMed: 17452157]
104. Herrmann JB, Kelly RJ, and Higgins GA. Polyglycolic acid sutures: laboratory and clinical evaluation of a new absorbable suture material. Arch. Surg 100:486–490, 1970. [PubMed: 5417172]
105. Hoffman AS Stimuli-responsive polymers: biomedical applications and challenges for clinical translation. Adv. Drug Deliv. Rev 65:10–16, 2013. [PubMed: 23246762]
106. Hofmann S, Hilbe M, Fajardo RJ, Hagenmueller H, Nuss K, Arras M, Mueller R, von Rechenberg B, Kaplan DL, Merkle HP, and Meinel L. Remodeling of tissue-engineered bone structures in vivo. Eur. J. Pharm. Biopharm 85:119–129, 2013. [PubMed: 23958323]
107. Holzapfel BM, Reichert JC, Schantz J-T, Gbureck U, Rackwitz L, Noeth U, Jakob F, Rudert M, Groll J, and Hutmacher DW. How smart do biomaterials need to be? A translational science and clinical point of view. Adv. Drug Deliv. Rev 65:581–603, 2013. [PubMed: 22820527]
108. Hong Y, Huber A, Takanari K, Amoroso NJ, Hashizume R, Badylak SF, and Wagner WR. Mechanical properties and in vivo behavior of a biodegradable synthetic polymer microfiber–extracellular matrix hydrogel biohybrid scaffold. Biomaterials 32:3387–3394, 2011. [PubMed: 21303718]
109. Hu S, Kirsner RS, Falanga V, Phillips T, and Eaglstein WH. Evaluation of apligraf® persistence and basement membrane restoration in donor site wounds: a pilot study. Wound Repair Regen. 14:427–433, 2006. [PubMed: 16939570]

110. Hu X, Wang X, Rnjak J, Weiss AS, and Kaplan DL. Biomaterials derived from silk-tropoelastin protein systems. Biomaterials 31:8121–8131, 2010. [PubMed: 20674969]
111. Huang AH, and Niklason LE. Engineering biological-based vascular grafts using a pulsatile bioreactor. J. Vis. Exp 2011. doi:10.3791/2646.
112. Ilic D Industry update: latest developments in the field of stem cell research and regenerative medicine compiled from publicly available information and press releases from nonacademic institutions from 1 November 2013 until 31 December 2013. Regen. Med 9:137–143, 2014.
113. Japan Tissue Engineering Company. Labcyte cornea model product page. 2014. http://www.jpte.co.jp/english/business/LabCyte/CORNEAmodel.html.
114. Jell G, Kerjaschki D, Revell P, and Al-Saffar N. Lymphangiogenesis in the bone-implant interface of orthopedic implants: importance and consequence. J. Biomed. Mater. Res. A 77:119–127, 2006. [PubMed: 16392126]
115. Kaiser D, Hafner J, Mayer D, French LE, and Lauchli S. Alginate dressing and polyurethane film versus paraffin gauze in the treatment of split-thickness skin graft donor sites: a randomized controlled pilot study. Adv. Skin Wound Care 26:67–73, 2013. [PubMed: 23337646]
116. Kanjickal D, Lopina S, Evancho-Chapman MM, Schmidt S, and Donovan D. Effects of sterilization on poly(ethylene glycol) hydrogels. J. Biomed. Mater. Res. Part A 87A:608–617, 2008.
117. Karr JC Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (primatrix) and a bilayered living cell therapy (apligraf). Adv. Skin Wound Care 24:119–125, 2011. [PubMed: 21326023]
118. Kawazoe N, Inoue C, Tateishi T, and Chen G. A cell leakproof PLGA-collagen hybrid scaffold for cartilage tissue engineering. Biotechnol. Prog 26:819–826, 2010. [PubMed: 20039440]
119. Kehoe S, Zhang XF, and Boyd D. FDA approved guidance conduits and wraps for peripheral nerve injury: a review of materials and efficacy. Injury 43:553–572, 2012. [PubMed: 21269624]
120. Kierstan M, and Bucke C. The immobilization of microbial cells, subcellular organelles, and enzymes in calcium alginate gels. Biotechnol. Bioeng 19:387–397, 1977. [PubMed: 321046]
121. Kim DM, Nevins M, Camelo M, Schupbach P, Kim S-W, Camelo JM, Al Hezaimi K, and Nevins ML. The feasibility of demineralized bone matrix and cancellous bone chips in conjunction with an extracellular matrix membrane for alveolar ridge preservation: a case series. Int. J. Periodontics Restor. Dent 31:39–47, 2011.
122. Kim J, McBride S, Tellis B, Alvarez-Urena P, Song Y-H, Dean DD, Sylvia VL, Elgendy H, Ong J, and Hollinger JO. Rapid-prototyped PLGA/beta-TCP/hydroxyapatite nanocomposite scaffolds in a rabbit femoral defect model. Biofabrication 4:025003, 2012. [PubMed: 22427485]
123. Kirsner RS The use of apligraf in acute wounds. J. Dermatol 25:805–811, 1998. [PubMed: 9990773]
124. Knoll LD Use of porcine small intestinal submucosal graft in the surgical management of peyronie's disease. Urology 57:753–757, 2001. [PubMed: 11306396]
125. Ko IK, Lee B-K, Lee SJ, Andersson K-E, Atala A, and Yoo JJ. The effect of in vitro formation of acetylcholine receptor (ACHR) clusters in engineered muscle fibers on subsequent innervation of constructs in vivo. Biomaterials 34:3246–3255, 2013. [PubMed: 23391495]
126. Kolambkar YM, Dupont KM, Boerckel JD, Huebsch N, Mooney DJ, Hutmacher DW, and Guldberg RE. An alginate-based hybrid system for growth factor delivery in the functional repair of large bone defects. Biomaterials 32:65–74, 2011. [PubMed: 20864165]
127. Komura M, Komura H, Kanamori Y, Tanaka Y, Suzuki K, Sugiyama M, Nakahara S, Kawashima H, Hatanaka A, Hoshi K, Ikada Y, Tabata Y, and Iwanaka T. An animal model study for tissue-engineered trachea fabricated from a biodegradable scaffold using chondrocytes to augment repair of tracheal stenosis. J. Pediatr. Surg 43:2141–2146, 2008. [PubMed: 19040922]
128. Kreutziger KL, and Murry CE. Engineered human cardiac tissue. Pediatr. Cardiol 32:334–341, 2011. [PubMed: 21293854]
129. Krishnan L, Willett N, and Guldberg R. Vascularization strategies for bone regeneration. Ann. Biomed. Eng 42:432–444, 2014. [PubMed: 24468975]

130. Kwon H, Sun L, Cairns DM, Rainbow RS, Preda RC, Kaplan DL, and Zeng L. The influence of scaffold material on chondrocytes under inflammatory conditions. Acta Biomater. 9:6563–6575, 2013. [PubMed: 23333441]

131. Lawrence BD, Marchant JK, Pindrus MA, Omenetto FG, and Kaplan DL. Silk film biomaterials for cornea tissue engineering. Biomaterials 30:1299–1308, 2009. [PubMed: 19059642]

132. Lee E, Kasper FK, and Mikos A. Biomaterials for tissue engineering. Ann. Biomed. Eng 42:323–337, 2014. [PubMed: 23820768]

133. Lee KY, and Mooney DJ. Alginate: properties and biomedical applications. Prog. Polym. Sci 37:106–126, 2012. [PubMed: 22125349]

134. Leslie-Barbick JE, Saik JE, Gould DJ, Dickinson ME, and West JL. The promotion of microvasculature formation in poly(ethylene glycol) diacrylate hydrogels by an immobilized VEGF-mimetic peptide. Biomaterials 32:5782–5789, 2011. [PubMed: 21612821]

135. Liao IC, Moutos FT, Estes BT, Zhao X, and Guilak F. Composite three-dimensional woven scaffolds with interpenetrating network hydrogels to create functional synthetic articular cartilage. Adv. Funct. Mater 23:5833–5839, 2013. [PubMed: 24578679]

136. Lin CC, and Anseth KS. Glucagon-like peptide-1 functionalized PEG hydrogels promote survival and function of encapsulated pancreatic beta-cells. Biomacromolecules 10:2460–2467, 2009. [PubMed: 19586041]

137. Lin W, Burgess RW, Dominguez B, Pfaff SL, Sanes JR, and Lee KF. Distinct roles of nerve and muscle in postsynaptic differentiation of the neuromuscular synapse. Nature 410:1057–1064, 2001. [PubMed: 11323662]

138. Liu J, Lawrence BD, Liu A, Schwab IR, Oliveira LA, and Rosenblatt MI. Silk fibroin as a biomaterial substrate for corneal epithelial cell sheet generation. Investig. Ophthalmol. Vis. Sci 53:4130–4138, 2012. [PubMed: 22661480]

139. Liu W, Merrett K, Griffith M, Fagerholm P, Dravida S, Heyne B, Scaiano JC, Watsky MA, Shinozaki N, Lagali N, Munger R, and Li F. Recombinant human collagen for tissue engineered corneal substitutes. Biomaterials 29:1147–1158, 2008. [PubMed: 18076983]

140. Liu Y, Li N, Qi Y-P, Dai L, Bryan TE, Mao J, Pashley DH, and Tay FR. Intrafibrillar collagen mineralization produced by biomimetic hierarchical nanoapatite assembly. Adv. Mater 23:975–980, 2011. [PubMed: 21341310]

141. Living Cell Technologies. Diabecell product page. 2014. http://www.lctglobal.com/products/diabecell.

142. Living Cell Technologies. Ntcell product page. 2014. http://www.lctglobal.com/products/ntcell.

143. Luo H, Lu Y, Wu T, Zhang M, Zhang Y, and Jin Y. Construction of tissue-engineered cornea composed of amniotic epithelial cells and acellular porcine cornea for treating corneal alkali burn. Biomaterials 34:6748–6759, 2013. [PubMed: 23764112]

144. Luvizuto ER, Tangl S, Zanoni G, Okamoto T, Sonoda CK, Gruber R, and Okamoto R. The effect of bmp-2 on the osteoconductive properties of [beta]-tricalcium phosphate in rat calvaria defects. Biomaterials 32:3855–3861, 2011. [PubMed: 21376389]

145. Ma HY, Hu JA, and Ma PX. Polymer scaffolds for small-diameter vascular tissue engineering. Adv. Funct. Mater 20:2833–2841, 2010. [PubMed: 24501590]

146. Ma L, Gao C, Mao Z, Zhou J, Shen J, Hu X, and Han C. Collagen/chitosan porous scaffolds with improved biostability for skin tissue engineering. Biomaterials 24:4833–4841, 2003. [PubMed: 14530080]

147. Machingal MA, Corona BT, Walters TJ, Kesireddy V, Koval CN, Dannahower A, Zhao W, Yoo JJ, and Christ GJ. A tissue-engineered muscle repair construct for functional restoration of an irrecoverable muscle injury in a murine model. Tissue Eng. Part A 17:2291–2303, 2011. [PubMed: 21548710]

148. Mackinnon SE, and Dellon AL. Clinical nerve reconstruction with a bioabsorbable polyglycolic acid tube. Plast. Reconstr. Surg 85:419–424, 1990. [PubMed: 2154831]

149. Maisano F, Kjærgård HK, Bauernschmitt R, Pavie A, Rábago G, Laskar M, Marstein JP, and Falk V. Tachosil surgical patch versus conventional haemostatic fleece material for control of bleeding in cardiovascular surgery: a randomised controlled trial. Eur. J. Cardiothorac. Surg 36:708–714, 2009. [PubMed: 19595605]

150. Mandal BB, Grinberg A, Gil ES, Panilaitis B, and Kaplan DL. High-strength silk protein scaffolds for bone repair. Proc. Natl. Acad. Sci. USA 109:7699–7704, 2012. [PubMed: 22552231]
151. Marelli B, Ghezzi CE, Alessandrino A, Barralet JE, Freddi G, and Nazhat SN. Silk fibroin derived polypeptide-induced biomineralization of collagen. Biomaterials 33:102–108, 2012. [PubMed: 21982293]
152. Marelli B, Ghezzi CE, Barralet JE, Boccaccini AR, and Nazhat SN. Three-dimensional mineralization of dense nanofibrillar collagen-bioglass hybrid scaffolds. Biomacromolecules 11:1470–1479, 2010. [PubMed: 20443577]
153. Marelli B, Ghezzi CE, Barralet JE, and Nazhat SN. Collagen gel fibrillar density dictates the extent of mineralization in vitro. Soft Matter 7:9898–9907, 2011.
154. Marelli B, Ghezzi CE, Mohn D, Stark WJ, Barralet JE, Boccaccini AR, and Nazhat SN. Accelerated mineralization of dense collagen-nano bioactive glass hybrid gels increases scaffold stiffness and regulates osteoblastic function. Biomaterials 32:8915–8926, 2011. [PubMed: 21889796]
155. Marston WA Dermagraft®, a bioengineered human dermal equivalent for the treatment of chronic nonhealing diabetic foot ulcer. Expert Rev. Med. Devices 1:21–31, 2004. [PubMed: 16293007]
156. Marston WA, Hanft J, Norwood P, and Pollak R. The efficacy and safety of dermagraft in improving the healing of chronic diabetic foot ulcers results of a prospective randomized trial. Diabetes Care 26:1701–1705, 2003. [PubMed: 12766097]
157. Marta GM, Facciolo F, Ladegaard L, Dienemann H, Csekeo A, Rea F, Dango S, Spaggiari L, Tetens V, and Klepetko W. Efficacy and safety of tachosil® versus standard treatment of air leakage after pulmonary lobectomy. Eur. J. Cardiothorac. Surg 38:683–689, 2010. [PubMed: 20541949]
158. Martino MM, Tortelli F, Mochizuki M, Traub S, Ben-David D, Kuhn GA, Müller R, Livne E, Eming SA, and Hubbell JA. Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. Sci. Transl. Med 3:100ra89, 2011.
159. Martins AM, Eng G, Caridade SG, Mano JF, Reis RL, and Vunjak-Novakovic G. Electrically conductive chitosan/carbon scaffolds for cardiac tissue engineering. Biomacromolecules 15:635–643, 2014. [PubMed: 24417502]
160. Matsuura K, Haraguchi Y, Shimizu T, and Okano T. Cell sheet transplantation for heart tissue repair. J. Controlled Release 169:336–340, 2013.
161. MatTekCorporation. Mattek corporation: *In vitro* tissue models, Ashland, MA. 2014. http://www.mattek.com/.
162. McCarty LP, Buss DD, Datta MW, Freehill MQ, and Giveans MR. Complications observed following labral or rotator cuff repair with use of poly-l-lactic acid implants. J. Bone Jt. Surg 95:507–511, 2013.
163. McHugh KJ, Tao SL, and Saint-Geniez M. Porous poly (ε-caprolactone) scaffolds for retinal pigment epithelium transplantation. Investig. Ophthalmol. Vis. Sci 55:1754–1762, 2014. [PubMed: 24550370]
164. McInnes A Consensus statement on the use of xelma in diabetic foot ulcers. Diabetic Foot 13:148–151, 2010.
165. McNamara SL, Rnjak-Kovacina J, Schmidt DF, Lo TJ, and Kaplan DL. Silk as a biocohesive sacrificial binder in the fabrication of hydroxyapatite load bearing scaffolds. Biomaterials 35:6941–6953, 2014. [PubMed: 24881027]
166. Meek MF, and Coert JH. US food and drug administration/conformit Europe-approved absorbable nerve conduits for clinical repair of peripheral and cranial nerves. Ann. Plast. Surg 60:110–116, 2008. [PubMed: 18281807]
167. Meek MF, and Coert JH. Recovery of two-point discrimination function after digital nerve repair in the hand using resorbable FDA- and CE-approved nerve conduits. J. Plast. Reconstr. Aesthet. Surg 66:1307–1315, 2013. [PubMed: 23827446]
168. Meinel L, Hofmann S, Karageorgiou V, Kirker-Head C, McCool J, Gronowicz G, Zichner L, Langer R, Vunjak-Novakovic G, and Kaplan DL. The inflammatory responses to silk films in vitro and in vivo. Biomaterials 26:147–155, 2005. [PubMed: 15207461]

169. Mi SL, Chen B, Wright B, and Connon CJ. Ex vivo construction of an artificial ocular surface by combination of corneal limbal epithelial cells and a compressed collagen scaffold containing keratocytes. Tissue Eng. Part A 16:2091–2100, 2010. [PubMed: 20109018]

170. Miklas JW, Nunes SS, Sofla A, Reis LA, Pahnke A, Xiao Y, Laschinger C, and Radisic M. Bioreactor for modulation of cardiac microtissue phenotype by combined static stretch and electrical stimulation. Biofabrication 6:024113, 2014. [PubMed: 24876342]

171. Mirza D, Millar AJW, Sharif K, Vilca-Melendez H, Rela M, and Heaton N. The use of tachosil in children undergoing liver resection with or without segmental liver transplantation. Eur. J. Pediatr. Surg 21:111–115, 2011. [PubMed: 21494994]

172. Mithieux SM, Wise SG, and Weiss AS. Tropoelastin—a multifaceted naturally smart material. Adv. Drug Deliv. Rev 65:421–428, 2013. [PubMed: 22784558]

173. Morgan KY, and Black LD III. It's all in the timing: modeling isovolumic contraction through development and disease with a dynamic dual electromechanical bioreactor system. Organogenesis 10:1, 2014. [PubMed: 24281142]

174. Morgan KY, and Black LD III. Mimicking isovolumic contraction with combined electromechanical stimulation improves the development of engineered cardiac constructs. Tissue Eng. Part A 20:1654–1667, 2014. [PubMed: 24410342]

175. Morgan KY, and Black LD III. Creation of a bioreactor for the application of variable amplitude mechanical stimulation of fibrin gel-based engineered cardiac tissue. Methods Mol. Biol 1181:177–187, 2014. [PubMed: 25070337]

176. Morgan KY, and Black LD III. Investigation into the effects of varying frequency of mechanical stimulation in a cycle-by-cycle manner on engineered cardiac construct function. J. Tissue Eng. Regen. Med 2014. doi:10.1002/term.1915.

177. Mudera V, Morgan M, Cheema U, Nazhat SN, and Brown RA. Ultra-rapid engineered collagen constructs tested in an in vivo nursery site. J. Tissue Eng. Regen. Med 1:192–198, 2007. [PubMed: 18038411]

178. Nakamuta JS, Danoviz ME, Marques FLN, Dos Santos L, Becker C, Gonçalves GA, Vassallo PF, Schettert IT, Tucci PJF, and Krieger JE. Cell therapy attenuates cardiac dysfunction post myocardial infarction: effect of timing, routes of injection and a fibrin scaffold. PLoS ONE 4:e6005, 2009. [PubMed: 19547700]

179. Napoleone CP, Oppido G, Angeli E, and Gargiulo G. Resternotomy in pediatric cardiac surgery: Coseal® initial experience. Interact. Cardiovasc. Thorac. Surg 6:21–23, 2007. [PubMed: 17669759]

180. Napoleone CP, Valori A, Crupi G, Ocello S, Santoro F, Vouhé P, Weerasena N, and Gargiulo G. An observational study of coseal® for the prevention of adhesions in pediatric cardiac surgery. Interact. Cardiovasc. Thorac. Surg 9:978–982, 2009. [PubMed: 19767304]

181. Neal RA, Jean A, Park H, Wu PB, Hsiao J, Engelmayr GC Jr., Langer R, and Freed LE. Three-dimensional elastomeric scaffolds designed with cardiac-mimetic structural and mechanical features. Tissue Eng. Part A 19:793–807, 2013. [PubMed: 23190320]

182. Neuenschwander P Scaffolds for artificial heart valves and vascular structures, Eidgenössische Technische Hochschule Zürich. 2007.

183. Nevins M, Nevins ML, Camelo M, Camelo JM, Schupbach P, and Kim DM. The clinical efficacy of dynamatrix extracellular membrane in augmenting keratinized tissue. Int. J. Periodontics Restor. Dent 30:151–161, 2010.

184. Nguyen LH, Kudva AK, Guckert NL, Linse KD, and Roy K. Unique biomaterial compositions direct bone marrow stem cells into specific chondrocytic phenotypes corresponding to the various zones of articular cartilage. Biomaterials 32:1327–1338, 2011. [PubMed: 21067807]

185. Nishio S, Kosuga K, Igaki K, Okada M, Kyo E, Tsuji T, Takeuchi E, Inuzuka Y, Takeda S, and Hata T. Long-term (>10 years) clinical outcomes of first-in-human biodegradable poly-l-lactic acid coronary stents Igaki-Tamai stents. Circulation 125:2343–2353, 2012. [PubMed: 22508795]

186. O'Brien G, Buckley K, Vanwalleghem G, Vanrenterghem D, Dharma H, Winter RL, and Douglass J. A multi-centre, prospective, clinical in-market evaluation to assess the performance of opsite™ post-op visible dressings. Int. Wound J 7:329–337, 2010. [PubMed: 20636341]

187. Omar AA, Mavor AID, Jones AM, and Homer-Vanniasinkam S. Treatment of venous leg ulcers with dermagraft®. Eur. J. Vasc. Endovasc. Surg 27:666–672, 2004. [PubMed: 15121121]

188. Ouasti S, Donno R, Cellesi F, Sherratt MJ, Terenghi G, and Tirelli N. Network connectivity, mechanical properties and cell adhesion for hyaluronic acid/PEG hydrogels. Biomaterials 32:6456–6470, 2011. [PubMed: 21680016]

189. Ozcelik B, Brown KD, Blencowe A, Daniell M, Stevens GW, and Qiao GG. Ultrathin chitosan-poly(ethylene glycol) hydrogel films for corneal tissue engineering. Acta Biomater. 9:6594–6605, 2013. [PubMed: 23376126]

190. Parenteau-Bareil R, Gauvin R, and Berthod F. Collagen-based biomaterials for tissue engineering applications. Materials 3:1863–1887, 2010.

191. Park H, Larson BL, Kolewe ME, Vunjak-Novakovic G, and Freed LE. Biomimetic scaffold combined with electrical stimulation and growth factor promotes tissue engineered cardiac development. Exp. Cell Res 321:297–306, 2014. [PubMed: 24240126]

192. Partlow BP, Hanna CW, Rnjak-Kovacina J, Moreau JE, Applegate MB, Burke KA, Marelli B, Mitropoulos AN, Omenetto FG, and Kaplan DL. Highly tunable elastomeric silk biomaterials. Adv. Funct. Mater 24:4615–4624, 2014. [PubMed: 25395921]

193. Pellenc D, Berry H, and Gallet O. Adsorption-induced fibronectin aggregation and fibrillogenesis. J. Colloid Interface Sci 298:132–144, 2006. [PubMed: 16375913]

194. Pennisi CP, Olesen CG, De Zee M, Rasmussen J, and Zachar V. Uniaxial cyclic strain drives assembly and differentiation of skeletal myocytes. Tissue Eng. Part A 17:2543–2550, 2011. [PubMed: 21609183]

195. Pocar M, Passolunghi D, Bregasi A, and Donatelli F. Tachosil® for postinfarction ventricular free wall rupture. Inter. Cardiovasc. Thorac. Surg 14:866–867, 2012.

196. Pok S, Benavides OM, Hallal PA, and Jacot J. Use of myocardial matrix in a chitosan-based full thickness heart patch. Tissue Eng. 20:1877–1887, 2014.

197. Preda RC, Leisk G, Omenetto F, and Kaplan DL. Bioengineered silk proteins to control cell and tissue functions. Methods Mol. Biol. (Clifton, N.J.) 996:19–41, 2013.

198. Pryor HI II, O'Doherty E, Hart A, Owens G, Hoganson D, Vacanti JP, Masiakos PT, and Sundback CA. Poly(glycerol sebacate) films prevent postoperative adhesions and allow laparoscopic placement. Surgery 146:490–497, 2009. [PubMed: 19715806]

199. Purdue GF, Hunt JL, Still JM Jr., Law EJ, Herndon DN, Goldfarb IW, Schiller WR, Hansbrough JF, Hickerson WL, and Himel HN. A multicenter clinical trial of a biosynthetic skin replacement, dermagraft-TC, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. J. Burn Care Res 18:52–57, 1997.

200. Qi M, Strand BL, Morch Y, Lacik I, Wang Y, Salehi P, Barbaro B, Gangemi A, Kuechle J, Romagnoli T, Hansen MA, Rodriguez LA, Benedetti E, Hunkeler D, Skjak-Braek G, and Oberholzer J. Encapsulation of human islets in novel inhomogeneous alginate-Ca^{2+}/Ba^{2+} microbeads: in vitro and in vivo function. Artif. Cells Blood Substit. Biotechnol 36:403–420, 2008.

201. Qiao P, Wang J, Xie Q, Li F, Dong L, and Xu T. Injectable calcium phosphate-alginate-chitosan microencapsulated mc3t3-e1 cell paste for bone tissue engineering in vivo. Mater. Sci. Eng. C 33:4633–4639, 2013.

202. Quintessenza J 2011, Bicuspid vascular valve and methods for making and implanting same, Google Patents.

203. Rabotyagova OS, Cebe P, and Kaplan DL. Protein-based block copolymers. Biomacromolecules 12:269–289, 2011. [PubMed: 21235251]

204. Radisic M, and Christman KL. Materials science and tissue engineering: repairing the heart. Mayo Clin. Proc 88:884–898, 2013. [PubMed: 23910415]

205. Rafat M, Li F, Fagerholm P, Lagali NS, Watsky MA, Munger R, Matsuura T, and Griffith M. PEG-stabilized carbodiimide crosslinked collagen-chitosan hydrogels for corneal tissue engineering. Biomaterials 29:3960–3972, 2008. [PubMed: 18639928]

206. Rai R, Tallawi M, Grigore A, and Boccaccini AR. Synthesis, properties and biomedical applications of poly(glycerol sebacate) (PGS): a review. Prog. Polym. Sci 37:1051–1078, 2012.

207. Rajan N, Habermehl J, Coté MF, Doillon CJ, and Mantovani D. Preparation of ready-to-use, storable and reconstituted type I collagen from rat tail tendon for tissue engineering applications. Nat. Protoc 1:2753–2758, 2007.
208. Redekop WK, McDonnell J, Verboom P, Lovas K, and Kalo Z. The cost effectiveness of apligraf® treatment of diabetic foot ulcers. Pharmacoeconomics 21:1171–1183, 2003. [PubMed: 14594438]
209. Reichl S, Bednarz J, and Muller-Goymann CC. Human corneal equivalent as cell culture model for in vitro drug permeation studies. Br. J. Ophthalmol 88:560–565, 2004. [PubMed: 15031177]
210. Richter JR, de Guzman RC, and Van Dyke ME. Mechanisms of hepatocyte attachment to keratin biomaterials. Biomaterials 32:7555–7561, 2011. [PubMed: 21782237]
211. Rnjak-Kovacina J, Wray LS, Golinski JM, and Kaplan DL. Arrayed hollow channels in silk-based scaffolds provide functional outcomes for engineering critically sized tissue constructs. Adv. Funct. Mater 24:2188–2196, 2014. [PubMed: 25395920]
212. Rockwood DN, Preda RC, Yucel T, Wang X, Lovett ML, and Kaplan DL. Materials fabrication from *Bombyx mori* silk fibroin. Nat. Protoc 6:1612–1631, 2011. [PubMed: 21959241]
213. Rouse JG, and Van Dyke ME. A review of keratin-based biomaterials for biomedical applications. Materials 3:999–1014, 2010.
214. Ruberti JW, Roy AS, and Roberts CJ. Corneal biomechanics and biomaterials. Annu. Rev. Biomed. Eng 13:269–295, 2011. [PubMed: 21568714]
215. Saffer EM, Tew GN, and Bhatia SR. Poly(lactic acid)-poly(ethylene oxide) block copolymers: new directions in self-assembly and biomedical applications. Curr. Med. Chem 18:5676–5686, 2011. [PubMed: 22172072]
216. Sajesh KM, Jayakumar R, Nair SV, and Chennazhi KP. Biocompatible conducting chitosan/polypyrrole–alginate composite scaffold for bone tissue engineering. Int. J. Biol. Macromol 62:465–471, 2013. [PubMed: 24080452]
217. Samal SK, Dash M, Van Vlierberghe S, Kaplan DL, Chiellini E, van Blitterswijk C, Moroni L, and Dubruel P. Cationic polymers and their therapeutic potential. Chem. Soc. Rev 41:7147–7194, 2012. [PubMed: 22885409]
218. Sambasivan R, Yao R, Kissenpfennig A, Van Wittenberghe L, Paldi A, Gayraud-Morel B, Guenou H, Malissen B, Tajbakhsh S, and Galy A. Pax7-expressing satellite cells are indispensable for adult skeletal muscle regeneration. Development 138:3647–3656, 2011. [PubMed: 21828093]
219. Santerre JP, Woodhouse K, Laroche G, and Labow RS. Understanding the biodegradation of polyurethanes: from classical implants to tissue engineering materials. Biomaterials 26:7457–7470, 2005. [PubMed: 16024077]
220. Santos MI, and Reis RL. Vascularization in bone tissue engineering: physiology, current strategies, major hurdles and future challenges. Macromol. Biosci 10:12–27, 2010. [PubMed: 19688722]
221. Sasson L, Houri S, Raucher Sternfeld A, Cohen I, Lenczner O, Bove EL, Kapusta L, and Tamir A. Right ventricular outflow tract strategies for repair of tetralogy of fallot: effect of monocusp valve reconstruction. Eur. J. Cardiothorac. Surg 43:743–751, 2013. [PubMed: 23024233]
222. Schaaf S, Shibamiya A, Mewe M, Eder A, Stoehr A, Hirt MN, Rau T, Zimmermann W-H, Conradi L, Eschenhagen T, and Hansen A. Human engineered heart tissue as a versatile tool in basic research and preclinical toxicology. Plos One 6:e26397, 2011. [PubMed: 22028871]
223. Schneider S, Feilen PJ, Brunnenmeier F, Minnemann T, Zimmermann H, Zimmermann U, and Weber MM. Long-term graft function of adult rat and human islets encapsulated in novel alginate-based microcapsules after transplantation in immunocompetent diabetic mice. Diabetes 54:687–693, 2005. [PubMed: 15734844]
224. Schonfeld WH, Villa KF, Fastenau JM, Mazonson PD, and Falanga V. An economic assessment of apligraf® (graftskin) for the treatment of hard-to-heal venous leg ulcers. Wound Repair Regen. 8:251–257, 2000. [PubMed: 11013015]
225. Seif-Naraghi SB, and Christman KL. Tissue engineering and the role of biomaterial scaffolds: the evolution of cardiac tissue engineering. In: Resident Stem Cells and Regenerative Therapy, edited by Goldenberg RCS and de Carvalho ACC. Elsevier, 2013, pp. 43–67. http://www.sciencedirect.com/science/book/9780124160125.

226. Seif-Naraghi SB, Singelyn JM, Salvatore MA, Osborn KG, Wang JJ, Sampat U, Kwan OL, Strachan GM, Wong J, Schup-Magoffin PJ, Braden RL, Bartels K, DeQuach JA, Preul M, Kinsey AM, DeMaria AN, Dib N, and Christman KL. Safety and efficacy of an injectable extracellular matrix hydrogel for treating myocardial infarction. Sci. Transl. Med 5:10, 2013.
227. Shachar M, Tsur-Gang O, Dvir T, Leor J, and Cohen S. The effect of immobilized RGD peptide in alginate scaffolds on cardiac tissue engineering. Acta Biomater. 7:152–162, 2011. [PubMed: 20688198]
228. Shafei S, Sharifudin MA, Ismail MS, Ab Rahman S, and Sadagatullah AN. A comparative study of Tualang honey spray versus film spray (opsite®) as post-long bone fracture fixation wound dressing. In: Kelantan Research Day 2013. Rural Transformation Centre (RTC), Terminal Agribisnes Negara (TEMAN), Kota Bharu. 2013. http://irep.iium.edu.my/32605/.
229. Shang K, Rnjak-Kovacina J, Lin Y, Hayden R, Tao H, and Kaplan D. Accelerated in vitro degradation of optically clear low beta-sheet silk films by enzyme mediated pretreatment. Trans. Vis. Sci. Technol 2:2, 2013.
230. Shapiro AMJ, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson P, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DER, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, and Lakey JRT. International trial of the Edmonton protocol for islet transplantation. N. Engl. J. Med 355:1318–1330, 2006. [PubMed: 17005949]
231. Sharifpoor S, Simmons CA, Labow RS, and Santerre JP. A study of vascular smooth muscle cell function under cyclic mechanical loading in a polyurethane scaffold with optimized porosity. Acta Biomater. 6:4218–4228, 2010. [PubMed: 20601230]
232. Sharifpoor S, Simmons CA, Labow RS, and Santerre JP. Functional characterization of human coronary artery smooth muscle cells under cyclic mechanical strain in a degradable polyurethane scaffold. Biomaterials 32:4816–4829, 2011. [PubMed: 21463894]
233. Shen W, Chen X, Hu Y, Yin Z, Zhu T, Hu J, Chen J, Zheng Z, Zhang W, Ran J, Heng BC, Ji J, Chen W, and Ouyang HW. Long-term effects of knitted silk-collagen sponge scaffold on anterior cruciate ligament reconstruction and osteoarthritis prevention. Biomaterials 35:8154–8163, 2014. [PubMed: 24974007]
234. Shields LBE, Raque GH, Glassman SD, Campbell M, Vitaz T, Harpring J, and Shields CB. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. Spine 31:542–547, 2006. doi: 10.1097/01.brs.0000201424.27509.72. [PubMed: 16508549]
235. Shimizu T, Yamato M, Kikuchi A, and Okano T. Cell sheet engineering for myocardial tissue reconstruction. Biomaterials 24:2309–2316, 2003. [PubMed: 12699668]
236. Shin SR, Jung SM, Zalabany M, Kim K, Zorlutuna P, Kim Sb, Nikkhah M, Khabiry M, Azize M, Kong J, Wan K-t, Palacios T, Dokmeci MR, Bae H, Tang X, and Khademhosseini A. Carbon-nanotube-embedded hydrogel sheets for engineering cardiac constructs and bioactuators. ACS Nano 7:2369–2380, 2013. [PubMed: 23363247]
237. Sicchieri LG, Crippa GE, de Oliveira PT, Beloti MM, and Rosa AL. Pore size regulates cell and tissue interactions with PLGA-cap scaffolds used for bone engineering. J. Tissue Eng. Regen. Med 6:155–162, 2012. [PubMed: 21446054]
238. Sierpinski P, Garrett J, Ma J, Apel P, Klorig D, Smith T, Koman LA, Atala A, and Van Dyke M. The use of keratin biomaterials derived from human hair for the promotion of rapid regeneration of peripheral nerves. Biomaterials 29:118–128, 2008. [PubMed: 17919720]
239. Silva AKA, Juenet M, Meddahi-Pellé A, and Letourneur D. Polysaccharide-based strategies for heart tissue engineering. Carbohydr. Polym 116:267–277, 2014. [PubMed: 25458300]
240. Siti-Ismail N, Bishop AE, Polak JM, and Mantalaris A. The benefit of human embryonic stem cell encapsulation for prolonged feeder-free maintenance. Biomaterials 29:3946–3952, 2008. [PubMed: 18639332]
241. Skulstad H, Erikssen G, Estensen ME, and Lindberg HL. Insufficient long term follow up and risk for aneurism in patients operated with dacron patch for coarctatio aortae. Eur. Heart J 34:P2117, 2013.

242. Sosa H, Popp D, Ouyang G, and Huxley HE. Ultrastructure of skeletal muscle fibers studied by a plunge quick freezing method: myofilament lengths. Biophys. J 67:283–292, 1994. [PubMed: 7918996]

243. Sowjanya JA, Singh J, Mohita T, Sarvanan S, Moorthi A, Srinivasan N, and Selvamurugan N. Biocomposite scaffolds containing chitosan/alginate/nano-silica for bone tissue engineering. Colloids Surf. B 109:294–300, 2013.

244. Spotnitz WD Fibrin sealant: past, present, and future: a brief review. World J. Surg 34:632–634, 2010. [PubMed: 19820991]

245. Stavarachi M, Apostol P, Toma M, Cimponeriu D, and Gavrila L. Spinal muscular atrophy disease: a literature review for therapeutic strategies. J. Med. Life 3:3, 2010. [PubMed: 20302191]

246. Steinberg JS, Edmonds M, Hurley DP Jr., and King WN. Confirmatory data from eu study supports apligraf for the treatment of neuropathic diabetic foot ulcers. J. Am. Podiatr. Med. Assoc 100:73–77, 2010. [PubMed: 20093548]

247. Stoppel WL, White JC, Horava SD, Bhatia SR, and Roberts SC. Transport of biological molecules in surfactant-alginate composite hydrogels. Acta Biomater. 7:3988–3998, 2011. [PubMed: 21798381]

248. Stoppel WL, White JC, Horava SD, Henry AC, Roberts SC, and Bhatia SR. Terminal sterilization of alginate hydrogels: efficacy and impact on mechanical properties. J. Biomed. Mater. Res. Part B 102:877–884, 2013.

249. Streit M, and Braathen LR. Apligraf–a living human skin equivalent for the treatment of chronic wounds. Int. J. Artif. Organs 23:831–833, 2000. [PubMed: 11197742]

250. Takata I, Tosa T, and Chibata I. Screening of matrix suitable for immobilization of microbial cells. J. Solid-Phase Biochem 2:225–236, 1977.

251. Tan C, Utley M, Paschalides C, Pilling J, Robb JD, Harrison-Phipps KM, Lang-Lazdunski L, and Treasure T. A prospective randomized controlled study to assess the effectiveness of coseal® to seal air leaks in lung surgery. Eur. J. Cardiothorac. Surg 40:304–308, 2011. [PubMed: 21288733]

252. Tan PLJ Company profile: tissue regeneration for diabetes and neurological diseases at living cell technologies. Regen. Med 5:181–187, 2010. [PubMed: 20210578]

253. Taylor MS, Daniels AU, Andriano KP, and Heller J. Six bioabsorbable polymers: in vitro acute toxicity of accumulated degradation products. J. Appl. Biomater 5:151–157, 1994. [PubMed: 10147175]

254. Themistocleous GS, Katopodis HA, Khaldi L, Papalois A, Doillon C, Sourla A, Soucacos PN, and Koutsilieris M. Implants of type I collagen gel containing mg-63 osteoblast-like cells can act as stable scaffolds stimulating the bone healing process at the sites of the surgically-produced segmental diaphyseal defects in male rabbits. In Vivo 21:69–76, 2007. [PubMed: 17354616]

255. Tonami K, Hata S, Ojima K, Ono Y, Kurihara Y, Amano T, Sato T, Kawamura Y, Kurihara H, and Sorimachi H. Calpain-6 deficiency promotes skeletal muscle development and regeneration. PLoS Genet. 9:e1003668, 2013. [PubMed: 23935533]

256. Trent JF, and Kirsner RS. Tissue engineered skin: apligraf, a bi-layered living skin equivalent. Int. J. Clin. Pract 52:408–413, 1998. [PubMed: 9894378]

257. Troncoso R, Ibarra C, Vicencio JM, Jaimovich E, and Lavandero S. New insights into IGF-1 signaling in the heart. Trends Endocrinol. Metab 25:128–137, 2014. [PubMed: 24380833]

258. Turner NJ, Keane TJ, and Badylak SF. Lessons from developmental biology for regenerative medicine. Birth Defects Res. Part C 99:149–159, 2013.

259. Turrentine MW, McCarthy RP, Vijay P, McConnell KW, and Brown JW. PTFE monocusp valve reconstruction of the right ventricular outflow tract. Ann. Thorac. Surg 73:871–880, 2002. [PubMed: 11899194]

260. Twardowski R, and Black LD III. Cardiac fibroblasts support endothelial cell proliferation and sprout formation but not the development of multicellular sprouts in a fibrin gel co-culture model. Ann. Biomed. Eng 42:1074–1084, 2014. [PubMed: 24435656]

261. Uebersax L, Apfel T, Nuss KMR, Vogt R, Kim HY, Meinel L, Kaplan DL, Auer JA, Merkle HP, and von Rechenberg B. Biocompatibility and osteoconduction of macroporous silk fibroin

implants in cortical defects in sheep. Eur. J. Pharm. Biopharm 85:107–118, 2013. [PubMed: 23958322]

262. Ungerleider JL, and Christman KL. Concise review: Injectable biomaterials for the treatment of myocardial infarction and peripheral artery disease: translational challenges and progress. Stem Cells Transl. Med 3:1090–1099, 2014. [PubMed: 25015641]
263. Van Goethem F, Adriaens E, Alepee N, Straube F, De Wever B, Cappadoro M, Catoire S, Hansen E, Wolf A, and Vanparys P. Prevalidation of a new in vitro reconstituted human cornea model to assess the eye irritating potential of chemicals. Toxicol. In Vitro 20:1–17, 2006. [PubMed: 16019187]
264. Venkatesan J, Bhatnagar I, and Kim S-K. Chitosan-alginate biocomposite containing fucoidan for bone tissue engineering. Mar. Drugs 12:300–316, 2014. [PubMed: 24441614]
265. Venkatesan J, Bhatnagar I, Manivasagan P, Kang K-H, and Kim S-K. Alginate composites for bone tissue engineering: a review. Int. J. Biol. Macromol 72C:269–281, 2014.
266. von Maltzahn J, Jones AE, Parks RJ, and Rudnicki MA. Pax7 is critical for the normal function of satellite cells in adult skeletal muscle. Proc. Natl. Acad. Sci. USA 110:16474–16479, 2013. [PubMed: 24065826]
267. Vorndran C Recent us patents on extracellular matrix in tissue engineering and regenerative medicine. Recent Patents Regen. Med 4:34–39, 2014.
268. Vowden K, McGowan J, Pilcher M, D'Arcy A, Renton C, Warner V, Megson J, and Vowden P. Experience with the use of an amelogenin-based extracellular matrix substitute (xelma®) in the management of a variety of complex hard-to-heal chronic wounds. In: European Wound Management Association Conference Abstracts, May 2007, Glasgow, Scotland. Oral presentation #91.
269. Vowden P, Romanelli M, Peter R,Boström Å, Josefsson A, and Stege H. The effect of amelogenins (xelma™) on hard-to-heal venous leg ulcers. Wound Repair Regen. 14:240–246, 2006. [PubMed: 16808801]
270. Wang X, Wang W, Ma J, Guo X, Yu X, and Ma X. Proliferation and differentiation of mouse embryonic stem cells in apa microcapsule: a model for studying the interaction between stem cells and their niche. Biotechnol. Prog 22:791–800, 2006. [PubMed: 16739963]
271. Wang Y, Kim YM, and Langer R. In vivo degradation characteristics of poly(glycerol sebacate). J. Biomed. Mater. Res. Part A 66A:192–197, 2003.
272. Wang Z, Cui Y, Wang J, Yang X, Wu Y, Wang K, Gao X, Li D, Li Y, Zheng X-L, Zhu Y, Kong D, and Zhao Q. The effect of thick fibers and large pores of electrospun poly(*ε*-caprolactone) vascular grafts on macro-phage polarization and arterial regeneration. Biomaterials 35:5700–5710, 2014. [PubMed: 24746961]
273. Waterhouse A, Wise SG, Ng MKC, and Weiss AS. Elastin as a nonthrombogenic biomaterial. Tissue Eng. Part B 17:93–99, 2011.
274. Weber RA, Breidenbach WC, Brown RE, Jabaley ME, and Mass DP. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. Plast. Reconstr. Surg 106:1036–1045, 2000. [PubMed: 11039375]
275. White ES, and Muro AF. Fibronectin splice variants: understanding their multiple roles in health and disease using engineered mouse models. IUBMB Life 63:538–546, 2011. [PubMed: 21698758]
276. Williams C, Quinn KP, Georgakoudi I, and Black III LD. Young developmental age cardiac extracellular matrix promotes the expansion of neonatal cardiomyocytes in vitro. Acta Biomater. 10:194–204, 2014. [PubMed: 24012606]
277. Wilson SL, Wimpenny I, Ahearne M, Rauz S, El Haj AJ, and Yang Y. Chemical and topographical effects on cell differentiation and matrix elasticity in a corneal stromal layer model. Adv. Funct. Mater 22:3641–3649, 2012.
278. Wise AK, Fallon JB, Neil AJ, Pettingill LN, Geaney MS, Skinner SJ, and Shepherd RK. Combining cell-based therapies and neural prostheses to promote neural survival. Neurotherapeutics 8:774–787, 2011. [PubMed: 21904788]

279. Wolf MT, Dearth CL, Sonnenberg SB, Loboa EG, and Badylak SF. Naturally derived and synthetic scaffolds for skeletal muscle reconstruction. Adv. Drug Deliv. Rev 2014. doi:10.1016/j.addr.2014.08.011.

280. Wray LS, Rnjak-Kovacina J, Mandal BB, Schmidt DF, Gil ES, and Kaplan DL. A silk-based scaffold platform with tunable architecture for engineering critically-sized tissue constructs. Biomaterials 33:9214–9224, 2012. [PubMed: 23036961]

281. Wu H, Xiong WC, and Mei L. To build a synapse: signaling pathways in neuromuscular junction assembly. Development 137:1017–1033, 2010. [PubMed: 20215342]

282. Xin M, Olson EN, and Bassel-Duby R. Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair. Nat. Rev. Mol. Cell Biol 14:529–541, 2013. [PubMed: 23839576]

283. Xu ZC, Zhang WJ, Li H, Cui L, Cen L, Zhou GD, Liu W, and Cao Y. Engineering of an elastic large muscular vessel wall with pulsatile stimulation in bioreactor. Biomaterials 29:1464–1472, 2008. [PubMed: 18155136]

284. Yamato M, and Okano T. Cell sheet engineering. Mater. Today 7:42–47, 2004.

285. Ye KY, Sullivan KE, and Black LD III. Encapsulation of cardiomyocytes in a fibrin hydrogel for cardiac tissue engineering. J. Vis. Exp 2011. doi:10.3791/3251.

286. Yin H, Gong C, Shi S, Liu X, Wei Y, and Qian Z. Toxicity evaluation of biodegradable and thermosensitive PEG-PCL-PEG hydrogel as a potential in situ sustained ophthalmic drug delivery system. J. Biomed. Mater. Res. B 92B:129–137, 2010.

287. Yu C-C, Chang J-J, Lee Y-H, Lin Y-C, Wu M-H, Yang M-C, and Chien C-T. Electrospun scaffolds composing of alginate, chitosan, collagen and hydroxyapatite for applying in bone tissue engineering. Mater. Lett 93:133–136, 2013.

288. Yuvarani I, Kumar SS, Venkatesan J, Kim S-K, and Sudha PN. Preparation and characterization of curcumin coated chitosan-alginate blend for wound dressing application. J. Biomater. Tissue Eng 2:54–60, 2012.

289. Zaky SH, Lee K-W, Gao J, Jensen A, Close J, Wang Y, Almarza AJ, and Sfeir C. Poly (glycerol sebacate) elastomer: a novel material for mechanically loaded bone regeneration. Tissue Eng. Part A 20:45–53, 2013. [PubMed: 24020497]

290. Zammit PS, Relaix F, Nagata Y, Ruiz AP, Collins CA, Partridge TA, and Beauchamp JR. Pax7 and myogenic progression in skeletal muscle satellite cells. J. Cell Sci 119:1824–1832, 2006. [PubMed: 16608873]

291. Zaulyanov L, and Kirsner RS. A review of a bi-layered living cell treatment (apligraf®) in the treatment of venous leg ulcers and diabetic foot ulcers. Clin. Interv. Aging 2:93, 2007. [PubMed: 18044080]

292. Zhang D, Shadrin IY, Lam J, Xian H-Q, Snodgrass HR, and Bursac N. Tissue-engineered cardiac patch for advanced functional maturation of human esc-derived cardiomyocytes. Biomaterials 34:5813–5820, 2013. [PubMed: 23642535]

293. Zhang X, Zhu L, Lv H, Cao Y, Liu Y, Xu Y, Ye W, and Wang J. Repair of rabbit femoral condyle bone defects with injectable nanohydroxyapatite/chitosan composites. J. Mater. Sci. Mater. Med 23:1941–1949, 2012. [PubMed: 22555503]

294. Zhou J, Chen J, Sun H, Qiu X, Mou Y, Liu Z, Zhao Y, Li X, Han Y, Duan C, Tang R, Wang C, Zhong W, Liu J, Luo Y, Xing MM, and Wang C. Engineering the heart: Evaluation of conductive nanomaterials for improving implant integration and cardiac function. Sci. Rep 4:1–11, 2014.

295. Zimmermann H, Shirley S, and Zimmermann U. Alginate-based encapsulation of cells: past, present, and future. Curr. Diab.Rep 7:314–320, 2007. [PubMed: 17686410]

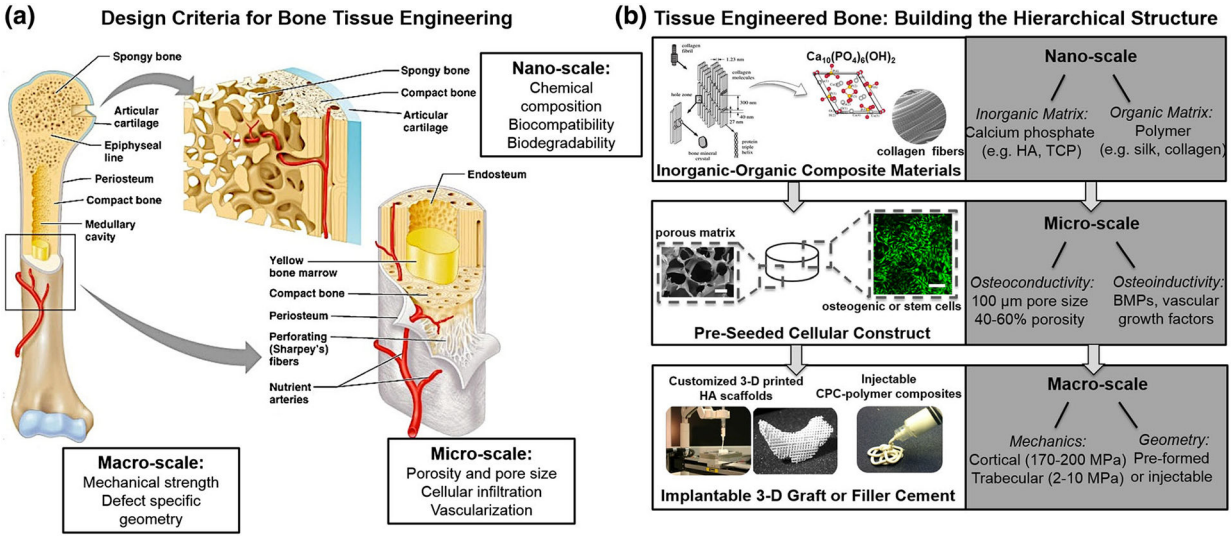

FIGURE 1.

Bone tissue replacement. (a) Overview of the anatomical structure of human bone tissue and essential design criteria at the macro, micro, and nano-scales. (b) Building a functional bone graft or bone substitute material from a bottom-up approach involves careful selection of natural biocompatible and biodegradable materials to mimic the inorganic–organic structure of native bone. Calcium phosphates, such as hydroxyapatite (HA) and tricalcium phosphate (TCP), are frequently complexed with polymeric materials, such as collagen or silk, to form a composite structure. At a micro-scale, osteoconductivity of the composite scaffold is supported by porosity (40–60%) and pore size (>100 μm), and osteoinductivity to promote osteogenesis *in vivo* is accomplished by release of bone morphogenic proteins (BMPs) or vascular growth factors. On a macro-scale, scaffolds must withstand physiologic loading forces (2–10 MPa in trabecular bone and 170–200 MPa in cortical bone) and should be defect specific. This can be achieved with various methods including 3-D printing of patient-specific grafts or the use of an injectable, self-setting calcium phosphate cement (CPC)-polymeric fillers.

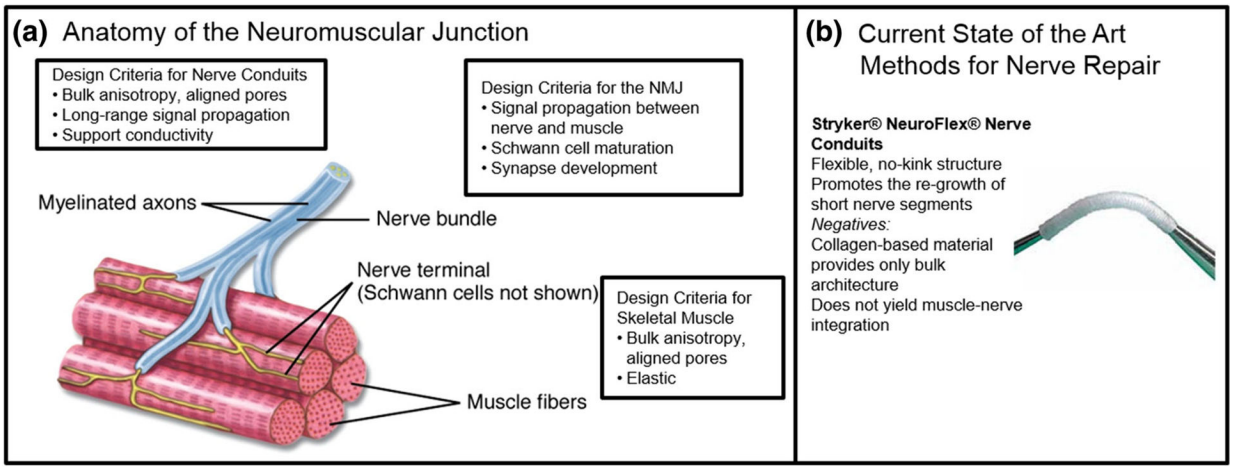

FIGURE 2.

Engineering the neuromuscular junction (NMJ). (a) Anatomy of the neuromuscular junction showing myelinated axons of the nerve bundle interfacing with the striated muscle fibers at the nerve terminal. Design criteria for nerve conduits and skeletal muscle-NMJ interface include bulk alignment, elasticity, long-range signal propagation, and conductivity as well as efficient signal transmission to the sarcomere to elicit muscular response. (b) Commercially available scaffolds for nerve repair, such as Stryker NeuroFlex, are clinically available for implantation to promote the re-growth of short nerve segments. However, these conduits are only able to address nerve injuries or gaps of less than a critical size of 2.5 cm, nor can they provide effective muscle-nerve connectivity, which is essential for the regeneration of traumatic skeletal muscle and nerve injuries.

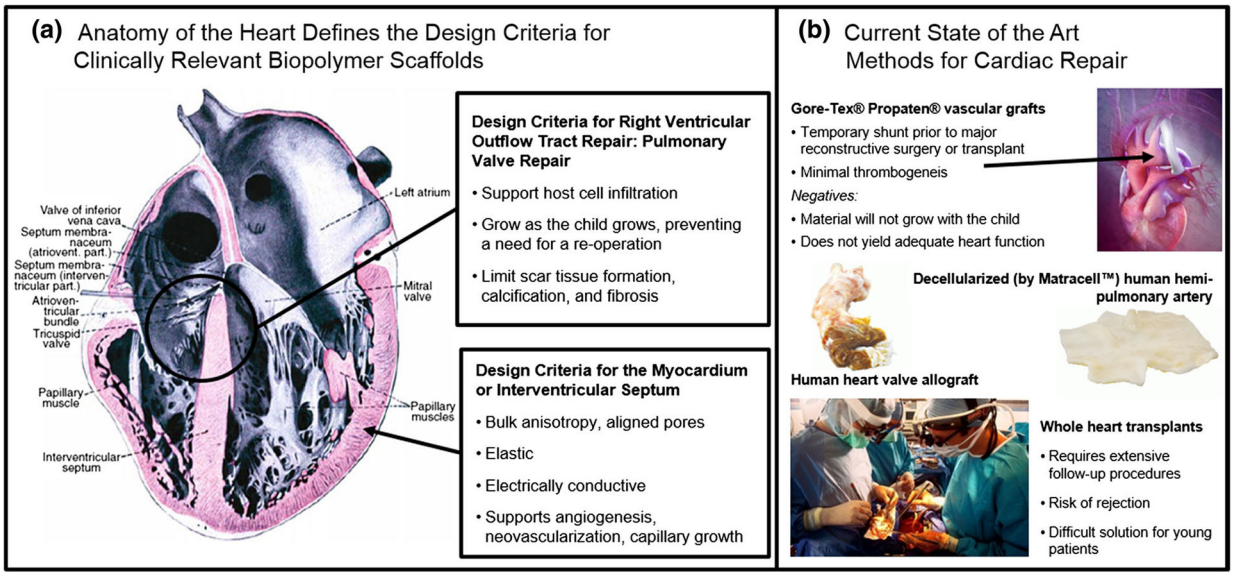

FIGURE 3.

Cardiac tissue replacement. (a) Anatomy of the heart showing the striated alignment of cardiac muscle. Design criteria for cardiac tissue engineering include high elasticity, aligned porosity, support of vascular and capillary network growth, and methods for integration into the host tissue both mechanically and electrically. (b) A variety of materials are commercially available for temporary repair of cardiac defects, but most are made from non-degradable plastics, which do not grow with the patient or integrate with the tissue, leading to the risk of fatal arrhythmias. Some disadvantages of clinically available vascularized grafts or decellularized matrices are thrombosis or a lack of tissue integration and growth within the patient. Decellularized grafts represent an allogenic approach to repairing damaged tissue, but patients run the risk of rejection, infection, and fibrosis.

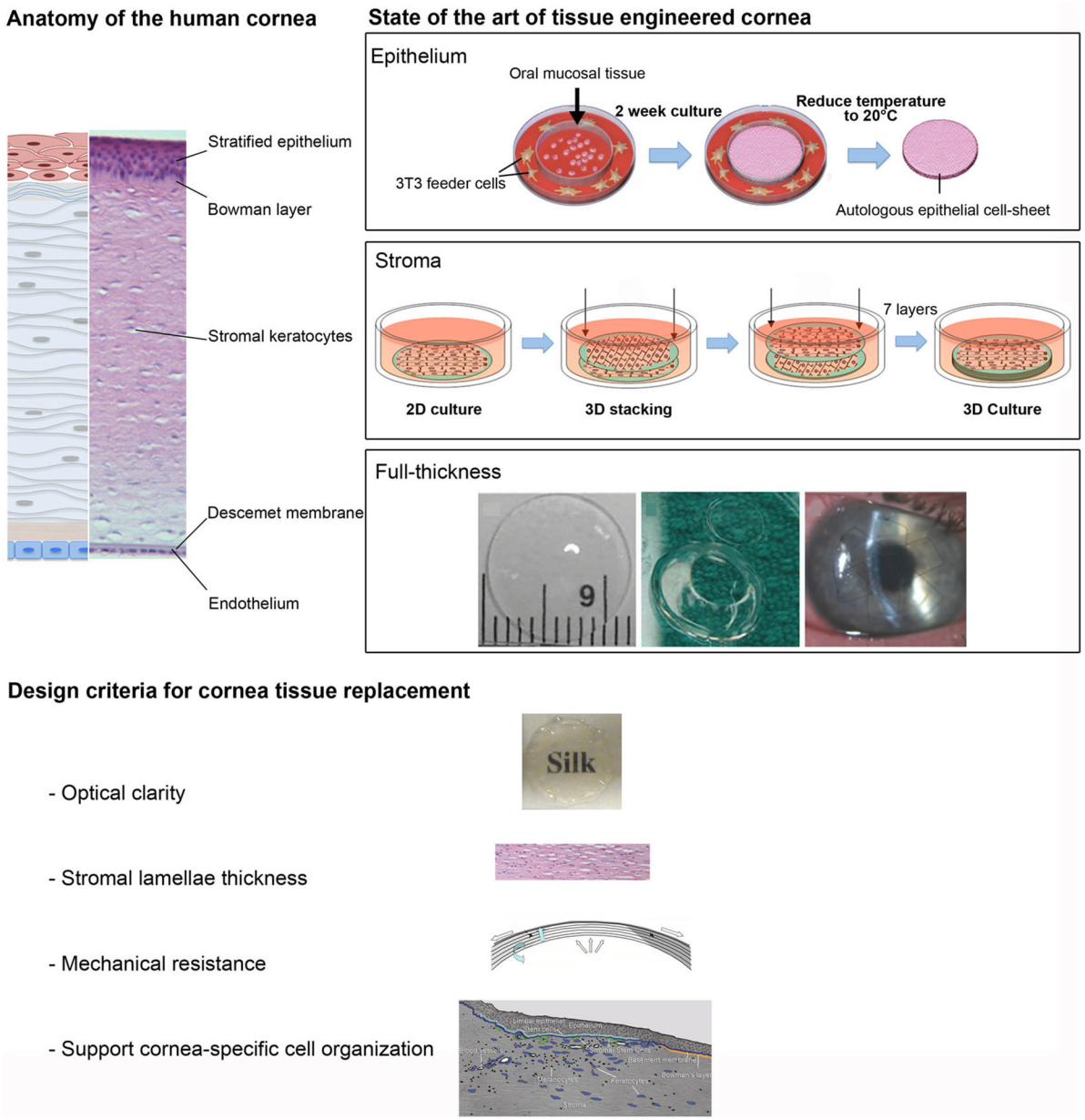

FIGURE 4.

Cornea tissue replacement. (a) Anatomy of the human cornea: schematic and histological images of human cornea layers: the corneal stratified squamous epithelium with underlying the Bowman's layer, the stroma with keratocytes for the maintenance and production of extracellular matrix, the Descemet's membrane, and, the single-layer endothelium. State of the art of tissue engineered cornea: *Epithelium* Human epithelial cell sheet obtained from oral epithelial cells after removal of the cell sheet from the thermoresponsive surface; *Stroma* Assembly diagram for 3D silk film corneal constructs seeded with human corneal fibroblasts; *Full-thickness* Synthetically crosslinked collagen, molded into an implantable,

full-thickness corneal substitute. Transparent samples were trephined to prepare a button for corneal implantation and then held in place by sutures in the patient eye.

TABLE 1.

Common synthetic polymers used for tissue engineering and clinical applications.

Synthetic polymer	Selective *in vitro* applications, clinical translation and commercialization	Refs.
Poly(L-lactic acid) (PLA or PLLA)	Composite materials, 2D gels, thin films Stent coatings, orthopedic applications, wound healing, soft tissue reconstruction	15,48,62,130,144,162,185,215
Poly(glycolic acid) (PGA)	2D and 3D mesh and scaffolding Sutures, soft tissue reconstruction, nerve conduits	12,46,104,111,127,148,274,283
Poly(ethylene glycol) (PEG)	Composite materials, backbone for chemical modification, 2D gels and surfaces, easily modified, well-controlled structure Wound healing, soft tissue reconstruction	27,28,97,116,134,136,179,180,184,188,205,251,286
Poly(lactic-*co*-glycolic acid) (PLGA)	Nanoparticles, composites, electrospun scaffolds Drug delivery, cartilage tissue repair, bone scaffolds, vascular reconstruction, soft tissue engineering	11,81,99,118,122,237
Polyurethane	Wound healing, cardiac tissue engineering, skin grafting	54,58,60,108,115,186,228,231,232
Polytetrafluoroethylene (PTFE)	Cell free, non-modifiable structure with minimal degradation for 2D surfaces and implants Cardiac repair, vascular grafts	103,145,202,221,259
Poly(*N*-isopropylacrylamide) (poly(NIPAAm))	Thermo-reversible; 2D cell sheets, thin tissue layers (≤600 μm), injectable gels Cartilage tissue engineering, cell sheet technology, soft tissue repair	105,235,284
Polycaprolactone (PCL)	Electrospun scaffolds, thin films, honeycomb architectures Cardiac tissue engineering, vascular grafts, cranial reconstruction	37,47,49,51,163,196,272,286
Poly(glycerol sebacate) (PGS)	3D scaffolds and films; major focus is cardiac and bone Wound healing, nerve conduits, soft tissue reconstruction, bone scaffolding	3,32,53,65,181,182,191,198,206,271,289

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TABLE 2.

Common natural biopolymers used for tissue engineering and clinical applications.

Biopolymer	Structure	Biological interactions	Applications and references
Alginate	1 → 4 linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues G residues function with divalent cations to form ionic crosslinks	Variations in local mechanical properties controlled by concentration of calcium ions Form soft gels, composite materials, interpenetrating networks Electrospun fibers with improved mechanical integrity	Wound healing, drug delivery, soft tissue engineering, cell delivery, *in vitro* stem cell maintenance[48,78,79,112,126,135,141,142,200,201,216,223,230,240,243,247,248,252,264,265,270,287,295]
Chitosan	Linear polysaccharide from deacetylation of chitin (main component in the exoskeletons of crustaceans) Randomly distributed β-(1–4)-linked D-glucosamine and *N*-acetyl-D-glucosamine	Soluble, cationic in acidic conditions and insoluble in neutral and basic conditions	Wound healing, orthopedics, cardiac repair, neural tissue engineering, cornea repair, drug and gene delivery[34,56,94,146,159,189,196,205,217,288,293]
Collagen	monomeric and crosslinked 3D triple helical structures Many types, type I consists of two identical α1 chains and one α2 chain Utilized *in vitro* in fibrous and hydrogel formats Content measured by quantifying hydroxyproline content Gelatin is a commonly used animal-based collagen product for gels	Easily remodeled and degraded by cells Chemical crosslinking decreases degradation and improves long-term Mechanical properties Many types available, which are specific to different tissue types Collagen IV primarily found in the basal lamina, secreted by epithelial cells, collagen I is the main component in scar tissue, cartilage, bone, tendon, and other connective tissues and muscles Improper expression or mutation leads to disease	Wound healing, skin grafts, muscle repair, nerve regeneration, anti-aging[1,33,74,82–85,152–154,190]
Elastin	Elastic component in soft tissues that allows tissue to return to normal shape following stretch or pinch Crosslinking smaller tropoelastin polymers using lysyl oxidase to form mesh-like structures	Small tropoelastin polymers can be used to form composite materials Can form films, gels, scaffolds, and electrospun fibers Easily remodeled by cells	Cardiac stent coatings, soft tissue reconstruction, orthopedics[5,10,14,86,110,172,273]
Fibrin	Formed when thrombin cleaves fibrinogen, generating soft gels Gelation kinetics controlled by ratio of thrombin to fibrinogen, calcium concentration, temperature	Fibrinolytic inhibitors, like aprotinin or aminocaproic acid, reduce *in vitro* degradation rates	Wound healing, cardiac repair, *in vivo* cell delivery[25,38,178,222,244,260,285,292]
Fibronectin	Glycoprotein secreted by fibroblasts Binds integrins, transmits mechanical cues from the environment to the cell binds other ECM proteins such as collagen and fibrin	Improper regulation of expression leads to diseases such as cancer, fibrosis Fibronectin can be grafted onto 2D and 3D surfaces to improve biocompatibility Many sites for cell-based protein degradation	Wound healing, stem cell differentiation, cardiac repair, bone regeneration[158,193,227,275]
Keratin	Bundles form intermediate filaments that make up hair (α-keratins) and nails (β-keratins)	Structure attributed to disulfide bridges; more bridges yields lower elasticity	Cornea tissue engineering, wound healing, skin regeneration, cardiac repair, drug delivery, nerve repair[23,210,213,238]

Biopolymer	Structure	Biological interactions	Applications and references
	Tough, insoluble polymer found in non-mineralized tissues Monomers form stable left-handed superhelical structures to form filaments	Classified as neutral-basic or acidic, dictating *in vivo* occurrence	
Silk	Extracted from the cocoons of *Bombyx mon* silkworm Foams, sponges, films and hydrogels are formed from silk solution	*In vivo* degradation rate controlled by crystallinity (β-sheet content) Mechanics tailored by modifying concentration, crystallization, molecular weight, and scaffold format	Muscle repair and regeneration, bone tissue engineering, cornea repair, drug delivery[6,8,17,67,86,110,165,168,192,197,211,212,280]

TABLE 3.

Examples of commercially available biopolymer systems for various types of tissue repair.

Manufacturer	Product	Application	Product description	Refs.
Baxter International, Inc. (Deerfield, IL)	TachoSil®	Cardiac Wound Sealant	Contains human fibrinogen and human thrombin to form a fibrin sealant Fibrinogen and thrombin formed on surface of an equine collagen patch Extensive literature on use for many applications other than FDA approved use	40,66,90,149,157,171,195
Collagen Matrix, Inc. (Franklin Lakes, NJ) sold by Stryker® (Kalamazoo, MI)	NeuroFlex®	Nerve Repair and Regrowth	Type I Collagen mesh Flexible tube, kink-resistant	4,52,93,119,166,167
Collagen Matrix, Inc. (Franklin Lakes, NJ) sold by Stryker® (Kalamazoo, MI)	NeuroMatrix®	Nerve repair and regrowth	Type I Collagen mesh Flexible tube	4,52,93,119,166,167
Collagen Matrix, Inc. (Franklin Lakes, NJ) sold by Stryker® (Kalamazoo, MI)	NeuroMend®	Nerve Repair and Regrowth	Type I Collagen mesh Designed to wrap injured nerves for a range of injuries	4,52,93,119,166,167
Cook Biotech, Inc. (West Lafayette, IN)	Dynamatrix®	Wound healing Soft Tissue Reconstruction	Acellular graft containing collagen (types I, III, VI), glycosaminoglycans (hyaluronic acid, chondroitin sulfate A and B, heparin, and heparan sulfate), proteoglycans, growth factors, and fibronectin	19,121,183
Cook Biotech, Inc. (West Lafayette, IN)	BioDesign® Grafts	Brain Surgery Abdominal Reconstruction Wound Healing Cardiac Surgery	Acellular scaffold, non-cross-linked, non-dermis-based graft Forms water tight seal so fluid cannot leak from the closed wound	64,124
Japan Tissue Engineering Co., Ltd. (Gamagori City, Aichi, Japan)	LabCyte Cornea-Model	Corneal epithelium	Trans-well permeable membrane seeded with primary human corneal epithelial cells Epidermal model also available	113
Living Cell Technologies™ (Manukau, Auckland, New Zealand)	DIABECELL®	Type 1 Diabetes	Alginate-based porcine-derived islet of Langerhans cell product	79,112,141,252
Living Cell Technologies™ (Manukau, Auckland, New Zealand)	NTCELL®	Parkinson's Disease T reatment	Alginate-based choroid plexus cell product	142,252,278
MatTek Corporation[a] (Ashland, MA)	EpiOcular™	Corneal epithelium	Fully biological scaffold containing human-derived epidermal keratinocytes	161
Medtronic Sofamor Danek (Minneapolis, MN)	INFUSE®	Bone Repair	Absorbable collagen sponge in a metal Delivers recombinant bone morphogenetic protein-2	96,234
Mölnlyke Health Care (Norcross, GA)	Xelma	Ulcers Wound Healing	Extracellular matrix proteins mixed with propylene glycol and alginate	22,164,268,269

Manufacturer	Product	Application	Product description	Refs.
Musculoskeletal Transplant Foundation™ (Edison, NJ)	CASCADE® Autologous Platelet System	Soft Tissue Repair Bone Defects	Autologous platelet delivery system using a fibrin gel Arthroscopic delivery, followed by suturing in place	9,77
Organogenesis, Inc. (Canton, MA)	Apligraft®	Skin Ulcers Wound Healing	Cellular material comprised of foreskin-derived neonatal fibroblasts cultured *in vitro*, combined with bovine type I collagen coated in cultured neonatal keratinocytes First biomaterial with living cells to get FDA approval Achieves complete wound closure in chronic foot ulcers Initial production was not cost effective Shipping affected product reliability 10+ years to make profits	29,44,63,70–72,76,92,109,117,123,208,224,246,249,256,291
Organogenesis, Inc. (Canton, MA)	Dermagraft®	Skin Ulcers Wound Healing	Cellular material comprised of human neonatal fibroblasts seeded on bioabsorbable polyglactin mesh scaffold Cells are cultured over time on the mesh to allow for ECM production on the mesh	80,100,101,155,156,187,199
Skin Ethic Laboratories (Lyon, France)	HCE	Corneal epithelium repair	Permeable polycarbonate substrate seeded with immortalized human corneal epithelial cells	263

[a] MatTek Corporation offers a variety of similar products for in vitro analysis.[161]

TABLE 4.

Commonly used synthetic bone filler materials on the US market.

Product	Manufacturer	Composition	Forms
BonePlast	Interpore-Cross Intl.	Calcium sulfate	Injectable paste
PeoOsteon	Interpore-Cross Intl.	Coralline HA	Granules/blocks
Vitoss	Orthovita	β-tricalcium phosphate	Granules/blocks
α-BSM	Depuy Synthes	Calcium phosphate cement	Injectable paste
β-BSM	Depuy Synthes	Calcium phosphate cement	Injectable paste
γ-BSM	Depuy Synthes	Calcium phosphate cement	Moldable putty
Norian SRS	Depuy Synthes	Calcium phosphate cement	Injectable paste
Calceon6	Depuy Synthes	Calcium sulfate	Pellets
CalStrux	Stryker Biotech	TCP with carboxymethycellulose	Moldable putty
BoneSource	Stryker Biotech	Calcium phosphate cement	Paste
HydroSet	Stryker Biotech	Calcium phosphate cement	Injectable paste
Collagraft	Zimmer/NeuColl	HA/TCP granules w/collagen gel	Strips
Cellplex	Wright Medical Inc.	Tricalcium phosphate	Granules
MIIG X3	Wright Medical Inc.	Calcium sulfate	Pellets
OsteoSet	Wright Medical Inc.	Calcium sulfate	Pellets
Actifuse	Baxter International, Inc.	Silicate-substituted calcium phosphate ceramic	Injectable

Most filler materials are calcium-based ceramics that can be mixed or cross-linked with polymeric materials to form composite scaffolds.

These bone fillers come in a variety of forms including injectable paste, powder/granules, pellets, and blocks.

HA, hydroxyapatite; TCP, β-tricalcium phosphate.