Chapter

Structural Design, Fabrication and Evaluation of Resorbable Fiber-Based Tissue Engineering Scaffolds

Martin W. King, Jiyang Chen, Monica Deshpande, Ting He, Harshini Ramakrishna, Yu Xie, Fan Zhang and Fan Zhao

Abstract

The use of tissue engineering to regenerate viable tissue relies on selecting the appropriate cell line, developing a resorbable scaffold and optimizing the culture conditions including the use of biomolecular cues and sometimes mechanical stimulation. This review of the literature focuses on the required scaffold properties, including the polymer material, the structural design, the total porosity, pore size distribution, mechanical performance, physical integrity in multiphase structures as well as surface morphology, rate of resorption and biocompatibility. The chapter will explain the unique advantages of using textile technologies for tissue engineering scaffold fabrication, and will delineate the differences in design, fabrication and performance of woven, warp and weft knitted, braided, nonwoven and electrospun scaffolds. In addition, it will explain how different types of tissues can be regenerated by each textile technology for a particular clinical application. The use of different synthetic and natural resorbable polymer fibers will be discussed, as well as the need for specialized finishing techniques such as heat setting, cross linking, coating and impregnation, depending on the tissue engineering application.

Keywords: resorbable polymer, tissue engineering scaffold, biocompatibility, cell culture, porosity, braiding, knitting, weaving, nonwoven web

1. Introduction

The field of tissue engineering and regenerative medicine was conceptualized about 35 years ago by Robert S. Langer, Institute Professor at Massachusetts Institute of Technology, together with Joseph P. Vacanti, MD a pediatric and transplantation surgeon-scientist at Massachusetts General Hospital and Harvard Medical School [1]. They recognized that in all fields of reconstructive surgery less than 30% of patients needing an organ transplant were able to obtain one [2], and that an alternative approach of engineering viable tissues and organs using cell culture techniques was needed to address this limited supply [3]. As a result, "an interdisciplinary field of research that applies the principles of engineering and the life sciences towards the development of biological substitutes that restore, maintain or improve tissue function" has been created with the ultimate goal of repairing injured and diseased organs [1].

Originally, the concept of tissue engineering required a triad of cells, scaffolds and signaling molecules. The cells, preferably derived autologously from the patient, can be stem cells, progenitor cells or mature cells. After expansion, they are seeded on a porous and resorbable scaffold and cultured in the presence of signaling molecules such as growth factors, specific metabolites, morphogens and adhesins [4]. Today, it is known that additional conditions are required so as to obtain the desired tissue. Depending on the type of tissue and the application, it may be necessary to add mechanical [5] and/or bioelectrical stimulation [6, 7], or increase the oxygen levels during cell culture in the bioreactor [8].

The focus of this chapter is to describe the different types of scaffolds used for tissue engineering with a particular emphasis on fiber-based scaffolds that are mostly fabricated on textile processing equipment. The desirable properties of the various types of scaffolds will be enumerated and the specific advantages of using fiber-based structures will be explained.

2. Specifications for tissue engineering scaffolds

Figure 1 represents the desired structural, mechanical and chemical properties that every tissue engineering scaffold should possess. The structure needs to have open pores that facilitate the passage of nutrients and waste products to and from the cells in the interior of the scaffold. The average pore size and pore size distribution are critical so as to ensure that cells, which may measure 10–50 μm in size, can infiltrate into the interior of the scaffold. This is particularly crucial for endothelial cells that are responsible for the formation of vasa vasorum and internal vascularization of the scaffold tissue.

The surface properties of the scaffold should be suitable from both chemical and topographical points of view so as to enable cell attachment and proliferation. To this end surfaces are often coated or modified with extra cellular matrix proteins, such as collagen or fibronectin, to promote cellular interaction. It is assumed that all surfaces are biocompatible so as elicit cell interaction and avoid a cytotoxic response.

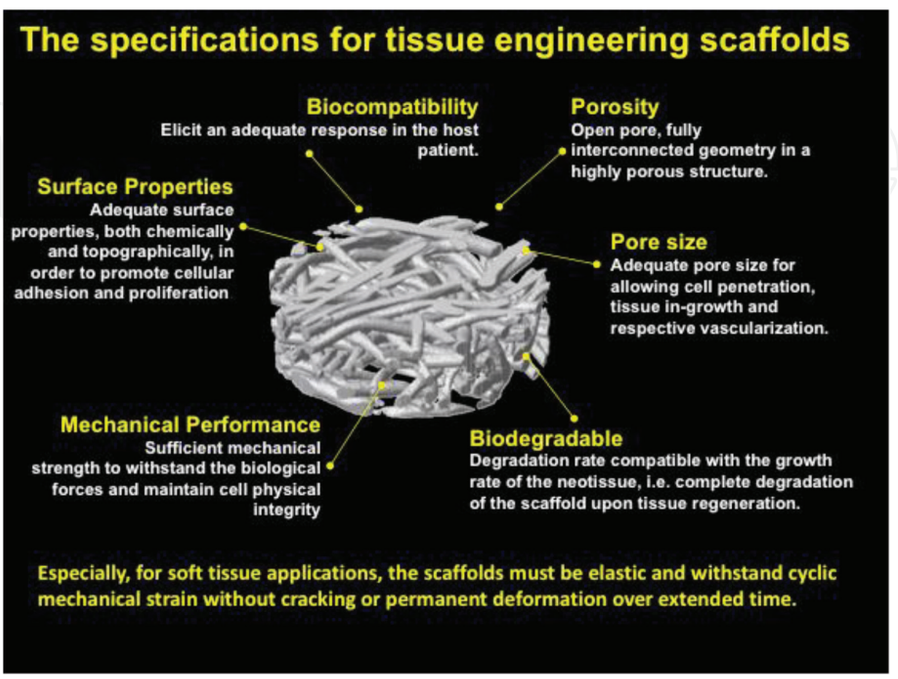

Figure 1.
Required properties of tissue engineering scaffolds.

3. Types of nonfiber-based tissue engineering scaffolds

The scaffold structures fabricated by a number of conventional methods, such as solvent casting, particulate leaching, gas foaming, phase separation and freeze drying are illustrated in **Figure 2**. The porous structures are inconsistent and there are limited processing options to alter the average pore size and the pore size distribution. Hence the mechanical performance in any direction is limited, especially for scaffolds that need to support mechanical loading during cell culture. In addition, a number of the polymer materials require the use of toxic organic solvents that increases the risk of cytotoxic effects during cell culture.

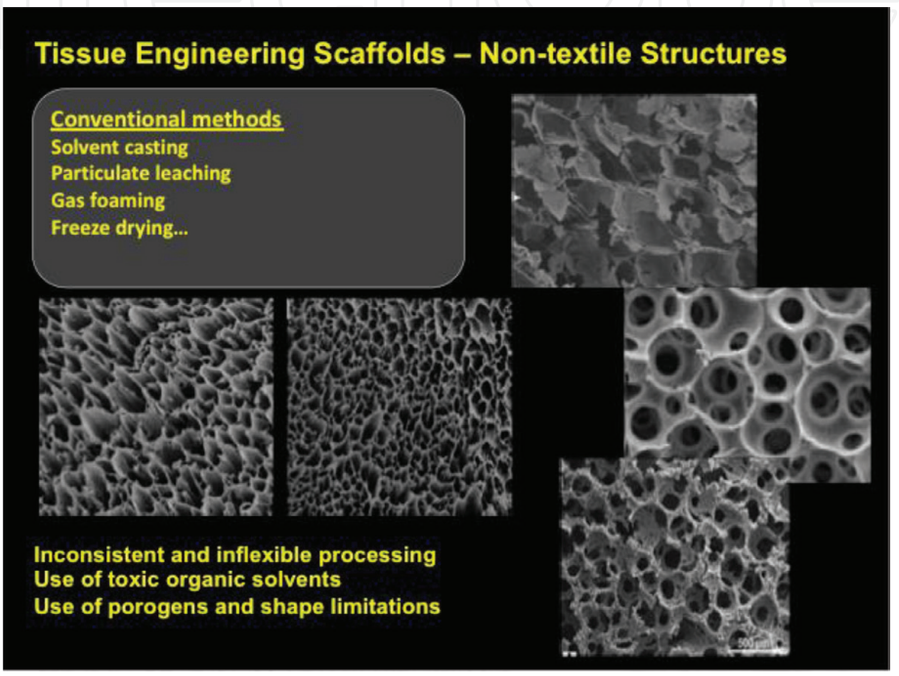

Figure 2.
Porous structures of non-textile tissue engineered scaffolds.

4. Types of fiber-based tissue engineering scaffolds

As seen in **Figure 3**, there a number of textile technologies that can and have been used to fabricate tissue engineering scaffolds. They include weaving, weft knitting, warp knitting, braiding, nonwoven production and electrospinning. Each of these technologies is described in the following sections, which discuss both the concepts and principles as well as examples of their application.

4.1 Woven scaffolds

Weaving is a conventional textile fabrication technology that is widely used in tissue engineering applications, because it enables a 3D scaffold to be fabricated that can imitate the mechanical and biological features of native human tissues. Woven structures are basically formed by interlacing two sets of yarns, namely, warp and weft yarns. With various interlacing and pattern designs, woven fabrics are categorized as plain, twill and satin weaves (**Figure 4**). Compared with knitted and braided structures, woven fabrics have better mechanical strength and structural stability [9]. The properties of woven fabrics, such as thickness, porosity and strength, can be easily adjusted and modified by woven design selection and the density of the warp and weft yarns [10].

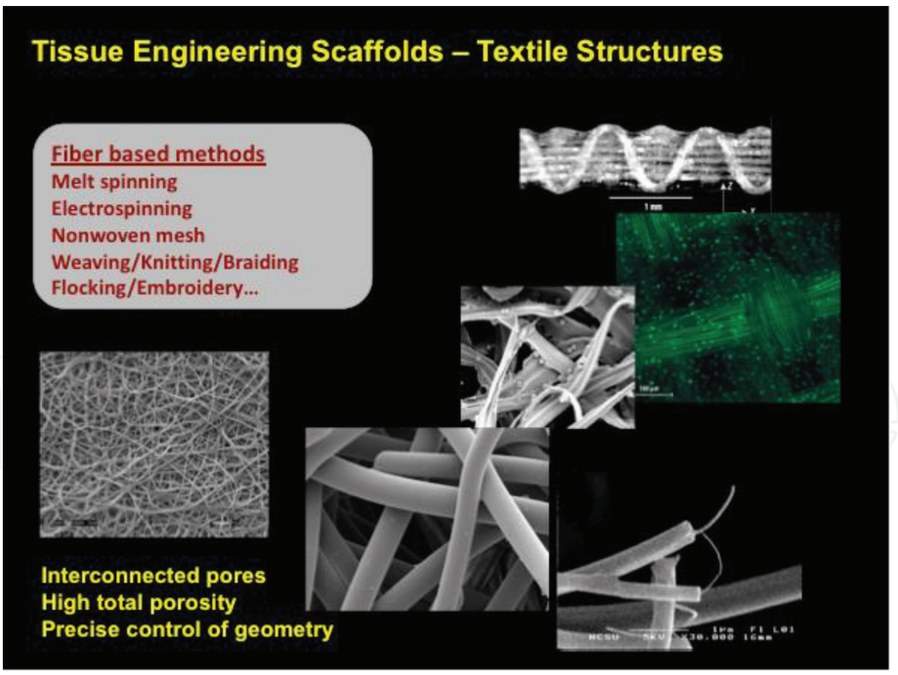

Figure 3.
Porous structures of fiber-based tissue engineered scaffolds.

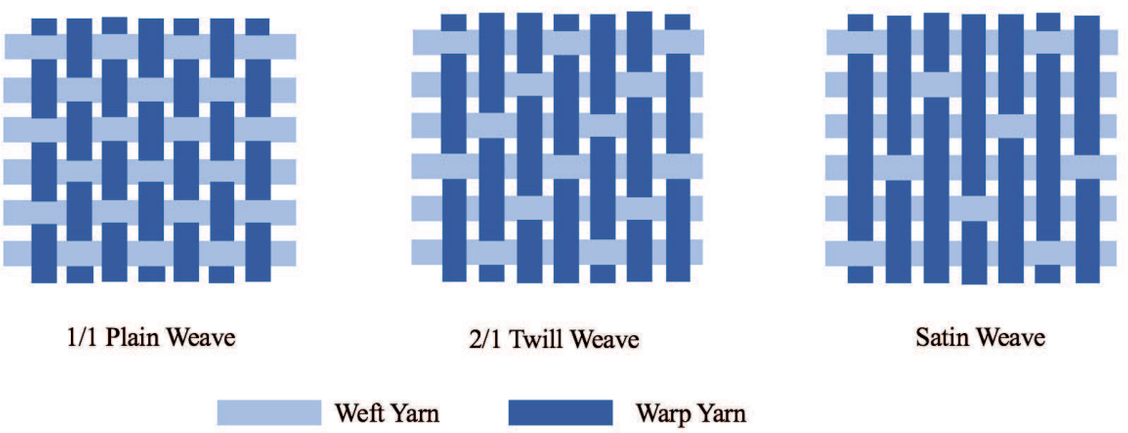

Figure 4.
Woven designs showing plain, twill and satin weaves [10].

4.1.1 Woven tendon bridging and reinforcement

A tendon is a crucial linkage between a muscle and bone, and it plays an important role in the movement of the joints, such as the rotator cuff tendon which allows shoulder movement. When a tendon ruptures or tears, it causes dysfunction of the joint. The complex multilayered avascular structure limits the rate and potential for healing [11–13]. Tissue engineered scaffolds not only need to have excellent mechanical properties such as high tensile stress and modulus, but also should have excellent biological properties to promote rapid host cell growth and tissue regeneration.

Commercial woven scaffolds, such as X-Repair (Synthasome, CA, USA) and Biofiber™ CM (Tornier, MN, USA) made from biodegradable polymers, are already used clinically for tendon repair. Derwin et al. reported using the woven poly-L-lactic acid (PLLA) X-Repair patch to provide bridging reinforcement for a shoulder tendon in a canine model. Post-operatively the augmented and repaired tendon was 23% significantly stronger, and after 12 weeks the patch reinforcement

showed less tendon retraction and significantly greater stiffness (26%), and ultimate load (35%) compared to those animals that were repaired without a patch [14]. For the first time in 2014, Proctor successfully used the X-Repair woven patch with an arthroscopic approach to repair a series of patients who presented with a large-to-massive rotator cuff tear. He reported that the surgery provided substantial functional improvement for 83% of patients after 12 months and 78% of the patients after 42 months [15]. Ratcliffe et al. compared the mechanical properties of a number of commercially available synthetic and extracellular matrix (ECM) scaffolds, and found that only the X-Repair was able to provide a similar stress-strain curve to a human or canine infraspinatus rotator cuff tendon with a short toe region and high strength (**Figure 5**) [16].

More recently, a woven structure has been used together with non-woven layers to assemble a laminated multilayered scaffold (**Figure 6A**) to closely match the mechanical properties of a human rotator cuff tendon and provide nanofiber *in vitro* and *in vivo* bioactivity [17]. Wu et al. combined the nanofibers with a woven structure by weaving the nanofiber yarn directly into the scaffold. With dynamic conditioning, the scaffold can promote significant collagen secretion and tenogenic differentiation of the tri-culture of derived mesenchymal stem cells, human tenocytes, and human umbilical vein endothelial cells [18].

Islam et al. manually wove plied and crosslinked electrochemically aligned collagen threads (ELACs) using pins into a scaffold for rotator cuff tendon repair

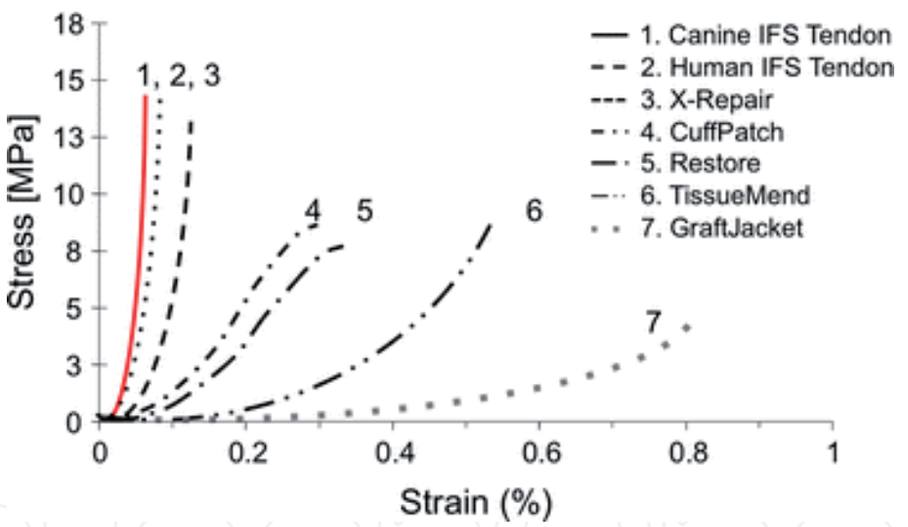

Figure 5.
Stress–strain curves for the human and canine infraspinatus rotator cuff tendon, and for the products used in the repair of rotator cuff injuries [16].

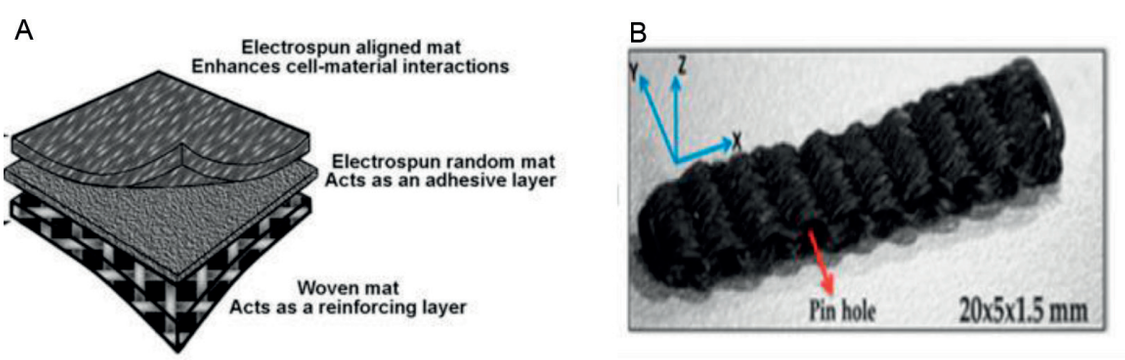

Figure 6.
Recent woven scaffold innovations for tendon repair applications. (A) Composite multilayer woven and electrospun scaffold [17]. (B) Pin woven scaffold made from novel electrochemically aligned collagen threads [19].

(**Figure 6B**) [19]. The scaffold has approximately 60% of the functional strength of a comparable sized native rabbit infraspinatus tendon, a stiffness close to that of a native tendon and the ability to initiate tenogenic differentiation of human mesenchymal stem cells [20].

4.1.2 Bone and cartilage regeneration

Human bone has a complex hierarchical and lamella structure of mineralized collagen fibrils which makes it difficult to replicate the complex ECM structure for better cell growth and bone regeneration [21]. By adjusting the pore size and structure of the woven fabric a potential scaffold candidate can address the required mechanical and biological features of an ideal tissue engineering bone scaffold [22]. Recently, a three dimensional (3D) woven structure has shown potential for bone regeneration.

Polylactic acid (PLA) and silk fibroin were combined and electrospun into nanofibers and fabricated into a woven multilayer fabric with subsequent mineralization using simulated body fluid. This approach significantly improved the scaffold's compression resistance and enhanced cell proliferation by promoting osteogenic differentiation of mesenchymal stem cells (MSC) [21]. This stem cell differentiation was also confirmed by Persson et al. who seeded cells onto a 2.4 mm thick 3D woven scaffold made from wet spun PLA and hydroxyapatite (HA) composite fibers (**Figure 7**) [23]. A 3D engineered woven poly(ϵ-caprolactone) (PCL) scaffold was created for the purpose of assisting deposition of cartilaginous and mineralized matrix from marrow-derived human bone for repairing chondral or osteochondral defects [24]. By using subchondral bone anchor in a porcine *in vivo* model, a 3D PCL woven scaffold has the potential to be used for long-term repair of chondral defects [25], and with an MSC-seeded hydrogel layer, the PCL woven scaffold could provide a microenvironment for stem cell chondrogenesis [26]. Other degradable polymers have also been investigated to fabricate 3D woven scaffolds for bone regeneration, such as poly-L-lactic acid (PLLA) [27].

4.1.3 Aortic heart valve replacement

With the problems of aortic valve insufficiency and stenosis, patients need heart valve replacement surgery to regulate blood flow between the left ventricle and the aorta [10]. The ideal scaffold should be able to simulate the native valve in terms of an active change of shape, size and stiffness of the cusp, annulus, sinus, and sinotubular junction during the cardiac cycle [28]. Textiles have been used to fabricate

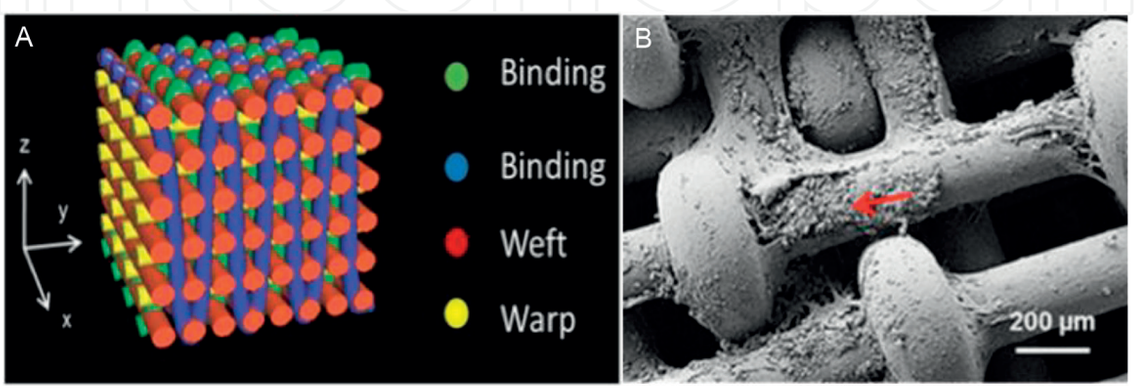

Figure 7.
(A) Schematic view of a 3D orthogonal woven scaffold, the PLA/HA 3D woven scaffold has five warp layers (x-direction) and six weft layers (y-direction), bound together by a warp set through-the-thickness (z-direction) and (B) cell mineralization (arrow) occurred on PLA/HA 3D woven scaffold after 35-days of culture in osteogenic induction medium [23].

heart valves because of their unique structural and mechanical characteristics that enable the production of unique anisotropic properties [10].

Wu et al. proposed a novel engineered valve design of combining a woven fabric with a hydrogel to mimic the heterogeneous and anisotropic features of native heart valves [29]. The scaffold was composed of a polyacrylonitrile (PAN) electrospun weft yarn and a multifilament PAN warp yarn with a methacrylated hyaluronic acid (Me-HA) or methacrylate gelatin (Me-Gel) layer for encapsulation of human aortic valve interstitial cells. The composite scaffold showed a similar initial toe, transient, and peak tangent regions in a stress-strain curve under load, similar to that of native aortic valve leaflets. High cell viability and layered cell penetration through the fibrous network were obtained after 14-days of *in vitro* culture. The woven fabric structure of the composite was able to promote the alignment and natural proliferation of normal cells, promote ECM remodeling, increase cell proliferation on the Me-HA/Me-Gel hydrogels and reduce the extent of shrinkage. Moreover, the composite scaffolds were able to suppress the trans-differentiation of diseased cells. This concept has suggested the possibility of woven structures being applied to heart valve regeneration if combined with the appropriate selection of a degradable polymer, such as PCL [10].

4.1.4 Vascular substitution and reconstruction

When patients suffer from atherosclerosis or an aneurysm, they may need an arterial prosthesis or stent-graft to replace or bypass the occluded or dilated vessel. Woven textiles have a long history of being used to fabricate arterial protheses with non-degradable synthetic polymer yarns, such as polyester, for long-term therapy of large caliber vessels. For tissue engineered vascular grafts, woven structures are less frequently used compared to other textile structures with more flexibility, such as electrospun non-woven webs and knitted structures [30–34]. However, weaving technology is capable of producing complex branched tubular structure for vascular application, such as seamless bifurcated or trifurcated endovascular prostheses [35].

Yokota has proposed a small diameter vascular graft with inner diameter equal to 4 mm, fabricated by combining a collagen microsponge with a plain-woven tube made from sheath-core yarns, namely, polyglycolic acid (PGA) as the sheath and poly-L-lactic acid (PLLA) as the core (**Figure 8A**) [36].

After 12 months of implantation in a canine carotid animal model, the graft showed no evidence of thrombogenic activity or aneurysm formation. Instead there was evidence of excellent in situ tissue regeneration [36]. The same group then examined the reconstruction potential of the vessel wall by implanting a woven patch into the canine pulmonary artery (**Figure 8B** and **C**). Similarly, no aneurysm and thrombus formation were observed after 6 months but a monolayer of

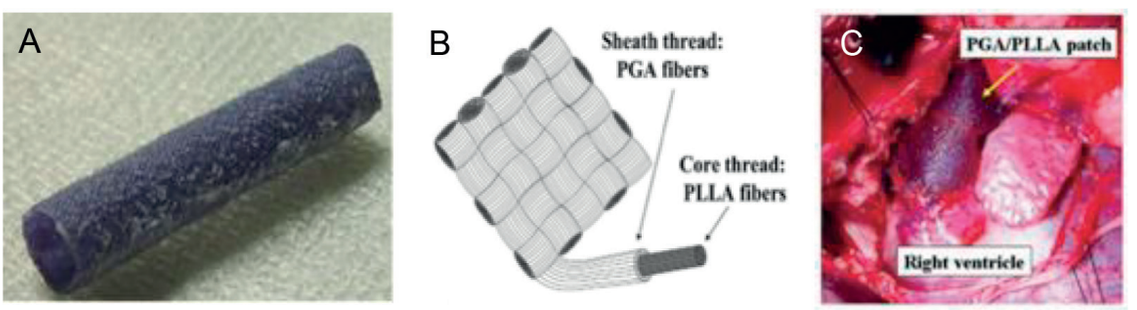

Figure 8.
(A) The small diameter vascular graft with plain weave fabricated from bicomponent yarn with PLLA core fibers and PGA sheath fibers [36]; (B) woven scaffold design with PGA/PLLA sheath-core yarns; and (C) intraoperative view of patch (arrow) implanted in the canine pulmonary artery [37].

endothelial cells and layers of smooth muscle cells were presented [37]. The ability to promote *in situ* autologous vascular regeneration with a tissue engineered PLA woven/PGA knitted/collagen-microsponge composite scaffold was also confirmed by using a porcine descending aorta model for a 6-month implantation study [38].

4.2 Weft knitted scaffolds

Weft knitting technology dates back to the sixteenth century when the Reverend William Lee in England invented a knitting frame to produce woolen hosiery. Weft knitted fabrics can include three main types of stitches: jersey, rib and interlock structures, which can be fabricated from a single yarn [39].

Compared with weaving and warp knitting, weft knitting has superior compliance and flexibility of design. When used with advanced biodegradable materials, such as poly-L-lactic acid (PLLA), polyglycolic acid (PGA) and polyurethanes (PU), their mechanical performance is predictable whether or not they serve as the reinforcing component of a tissue engineering scaffold [40, 41]. Structural instability and fabric permeability are the two main concerns relating to the performance of weft knitted fabrics. The use of advanced coatings and immersion techniques compensate for these limitations, and the combined scaffolds provide improvements in device function [42, 43]. To date, various implantable scaffolds have been fabricated as weft knitted structures, including a cardiac support device (CSD), aortic valves, vascular prostheses and nerve guides [42].

4.2.1 Cardiac support device

In the event of a heart attack or myocardial infarction (MI), the muscle wall of the left ventricle will experience a remodeling process [44]. Today, the major challenge is how to provide the mechanical support for the left ventricle and deliver stem cells to the target area where the infarct occurred. For this application, the scaffold needs to be extensible and match the different compliances of the left ventricle in the radial and longitudinal directions [45].

Until now, Boublick et al. developed a knitted cardiac patch that has been developed and assessed by *in vitro* and *in vivo* tests for its mechanical support and its ability to reverse the remodeling process [46]. This cardiac patch was knitted from hyaluronan benzyl ester (HBE) sutures (Hyaff-11®) and seeded with rat cardiac cells mixed with fibrin (**Figure 9**). This knitted, biodegradable construct exhibited excellent

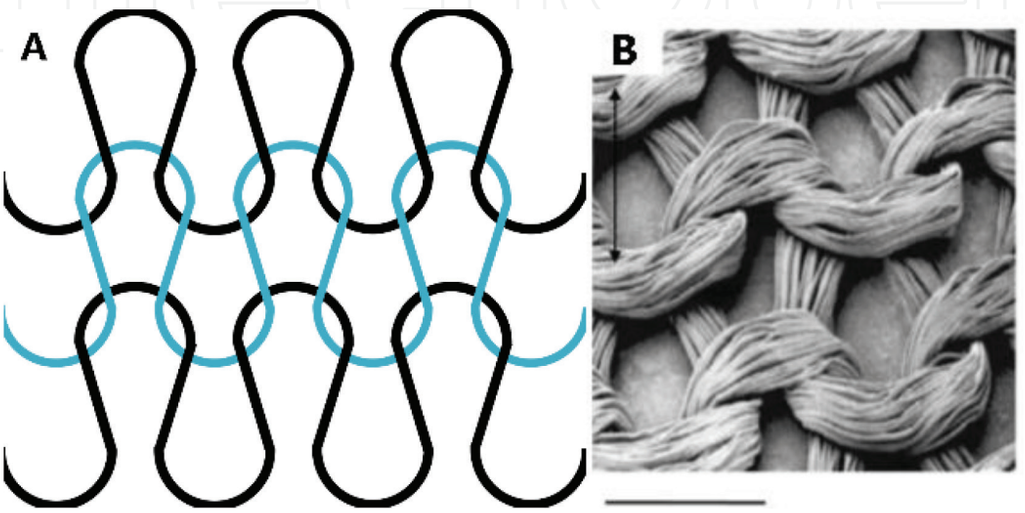

Figure 9.
(A) Three courses of weft knitted loop structure and (B) SEM image of knitted heart patch. Scale bar: 500 μm [46].

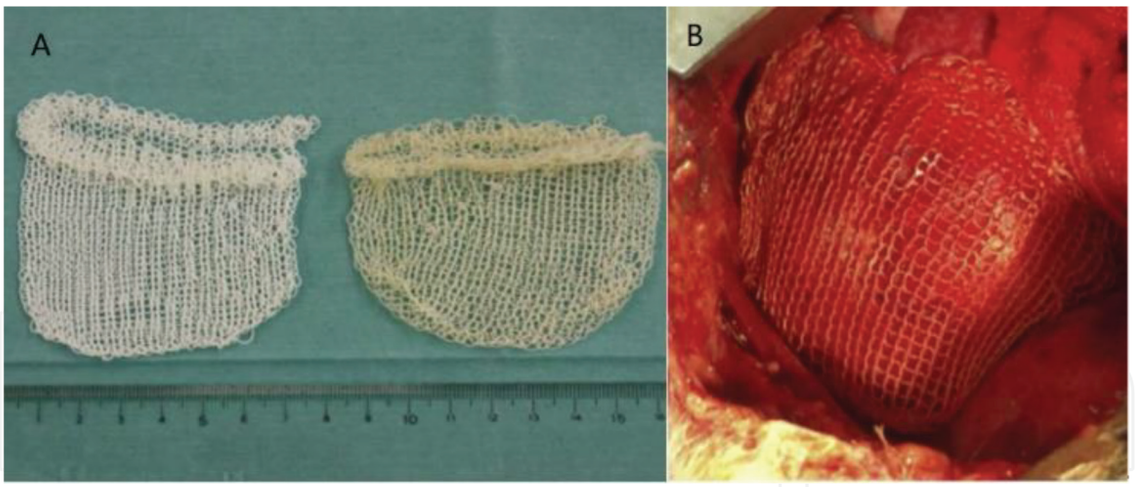

Figure 10.
Knitted cardiac support devices. (A) Non-degradable PET knitted device (left) and a degradable PGA knitted device (right) and (B) The implanted device after implantation around the ventricles of the canine heart [48].

mechanical matching with the native rat myocardium, and it was able to successfully repair the mechanical defect and malfunction of the rat heart. Chen et al. has also fabricated a PLA cardiac patch with rib stitch structure to deliver cardiosphere-derived cells (CDCs) to the ventricular wall. The *in vitro* tests indicated that (1) the mechanical properties of the rib stitch patch structure matched those of native tissues, and (2) the CDCs were able to attach to and proliferate on the patch [47].

Related to the heart patch concept, a biodegradable knitted heart cap has proven to have a beneficial effect when used in a canine heart failure model (**Figure 10**). After comparing the healing response of a biodegradable (PGA) heart cap with that of a non-degradable (PET) heart cap in a canine cardiac model, Kitahara et al. pointed out that the failure of the CorCap™ cardiac support device was that it was knitted from a non-degradable material, which was polyester (polyethylene terephthalate) (PET) yarns. The improved heart function of using biodegradable PGA in a canine model has supported this conclusion, which is consistent with the clinical data for the CorCap™ device [48, 49].

4.2.2 Aortic valve

Surgical aortic valve replacement (AVR) is conducted on patients with aortic valve stenosis [50]. The expectancy of the replacement valve to continue to function is from 10 years to a lifetime, which requires the implanted valves to have excellent durability and biocompatibility. The most challenging aspect of the surgery is the risk of post-surgical paravalvular leak, increasing the risk of the heart failure and other severe complications [51, 52]. Lieshout et al. developed a knitted scaffold for the aortic valve from polycaprolactone yarn. The fabric was knitted into a rectangular patch with three leaflets (**Figure 11**).

During valve opening and closing, the knitted leaflets performed well with complete coaptation and no collison with the aortic wall. In an *in vitro* durability fatigue test, the knitted valve experienced 10 million cycles without tearing and failing. A 3 layer coating of fibrin gel was applied to improved the biocompatibility [53]. It exhibited excellent durability and structural stability in a long-term *in vitro* fatigue study. In the future, PCL may be a good choice to regenerate heart valve leaflets in a bioreactor using native cells and extracellular matrix. This approach is likely to be more reliable than the permanent synthetic implants on the market [54].

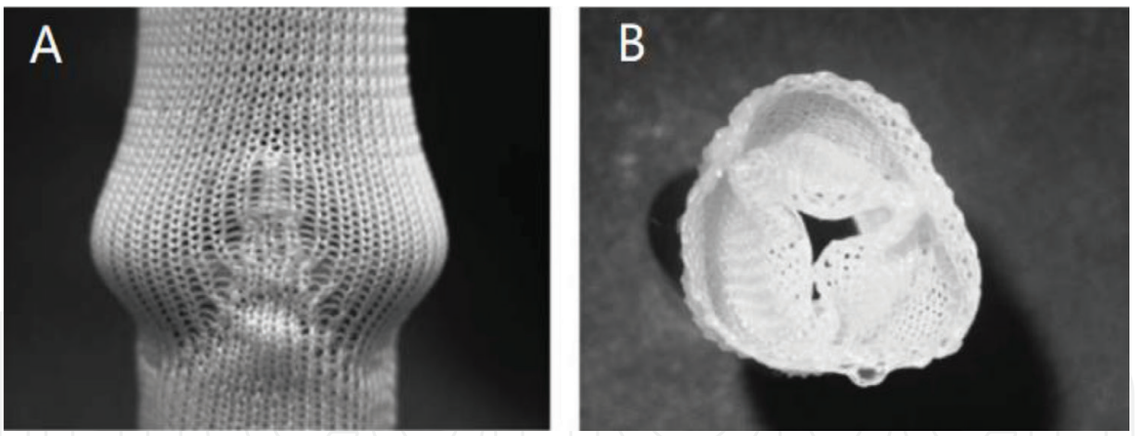

Figure 11.
The appearance of a weft knitted heart valve. (A) External lateral view and (B) top view of heart valve after application of fibrin gel layers [53].

4.2.3 Vascular prosthesis

A vascular graft is a common and useful therapy to rebuild small diameter blood vessels and treat the symptoms of atherosclerotic vascular disease [55]. However, to date only yarns spun form permanent or non-degradable polymers have been used to fabricate commercial large caliber prostheses.

With the objective of developing a resorbable small diameter vascular prosthesis, Xie et al. designed a weft knitted/electrospun PLA/PLCL tube with comparable compliance to a human saphenous vein [33]. Zhang et al. has also fabricated a small diameter vascular scaffold by weft knitting electrochemically aligned collagen (ELAC) yarns into a tubular structure on a circular weft knitting machine (**Figure 12**).

The tube serves as the backbone of the scaffold and provides sufficient mechanical support and structural integrity. Also, by utilizing collagen as the material, the scaffold has demonstrated advanced endothelial cell adhesion [56, 57]. Although a common complaint of weft knitted structures has been their poor dimensional stability and their tendency to unravel from the unsecured end, these are surmountable issues that can be controlled by knitting a backloop binding-off structure or sewing a reinforcing edge seam along the cut edge.

Figure 12.
The circular knitting machine for weft knitting tubular fabric.

4.2.4 Nerve guide

A novel approach to fabricating a nerve guide is to combine weft knitting technology with freeze drying to form a high porosity scaffold. After being injured, the distal stump of the peripheral nerve is unable to repair the gap between neurons. So to bridge this gap, a nerve guide with good compliance can be used to evaluate the neural signals and promote axonal growth [58]. Wang et al. designed and fabricated a chitosan scaffold for nerve tissue engineering. The knitted chitosan tubular fabric was fitted onto a mandrel and immersed in a chitosan solution. Acupuncture needles were then inserted into the hollow chitosan tube to create inner pores for guiding neural growth and proliferation. Following the immersion process, the scaffolds were freeze dried to form interconnected micropores in both the outer wall and inner matrix. The knitted scaffold provided sufficient compressive resistance and recovery to serve as a nerve guide scaffold. A porous microstructure improved the axonal elongation and migration of the neural cells [59]. *In vitro* evaluation of this knitted, freeze dried scaffold confirmed that it had suitable mechanical properties, and it provided good cell affinity, porosity and rate of biodegradation for neural tissue engineering [60].

4.3 Warp knitted scaffolds

Warp knitted fabrics are formed by wales which are vertical columns of yarns looped in the warp or machine direction. Warp knitted fabrics gain popularity in many medical applications due to the superior structural stability, the avoidance of yarn raveling after cutting to size, and higher suture retention strength in comparison with weft knitted fabrics.

The knitting productivity of warp knitted fabrics is usually much higher than for weft knitted fabrics. However, the yarn preparation for warp knitting is more challenging due to yarn beam preparation. There are fewer design pattern options for warp knitted fabrics than for weft knits because the warp knitted design is limited by the pattern drum on the machine, which is more difficult to create complex structures [61]. Two dimensional (2D) warp knitted fabrics have been widely adopted for biomedical applications due to their superior structural stability and durability. For example, most permanent hernia repair meshes are warp knitted so as to provide high tear resistance and bursting strength, reliable stabilization of the fascial tissue in the abdominal wall, no raveling when cut to size and limited contraction during healing [62]. Other permanent applications involve commercial arterial prostheses, aortic valve rings [53] and artificial skin [63].

On the other hand, only a few resorbable warp knitted fabrics are being developed as tissue engineering scaffolds. Secant Medical LLC (Telford, PA, USA) is developing a warp knitted fabric using degradable yarns for a tissue engineering application [64]. In order for a tissue engineering scaffold to mimic the volume and complexity of natural tissue a 3D warp knitted structure is required, and for this application, a warp knitted spacer fabric is the preferred structure. Spacer fabrics are defined as a 3 layer sandwich structure with two outer layers of fabric, each knitted on its own row of needles, and a third inner spacer layer as shown in **Figure 13A**. In addition to having the advantages of a warp knitted fabric, such as high bursting strength, high elongation, high porosity and low Young's modulus, the 3D spacer fabric is a one piece multi-layered structure with high volume to weight ratio, softness, breathability, moisture permeability, compression resistance and excellent recovery properties [65, 66].

The spacer yarn that lies in the thickness direction provides the mechanical support and the high total porosity needed for a tissue engineering scaffold. The yarns ensure

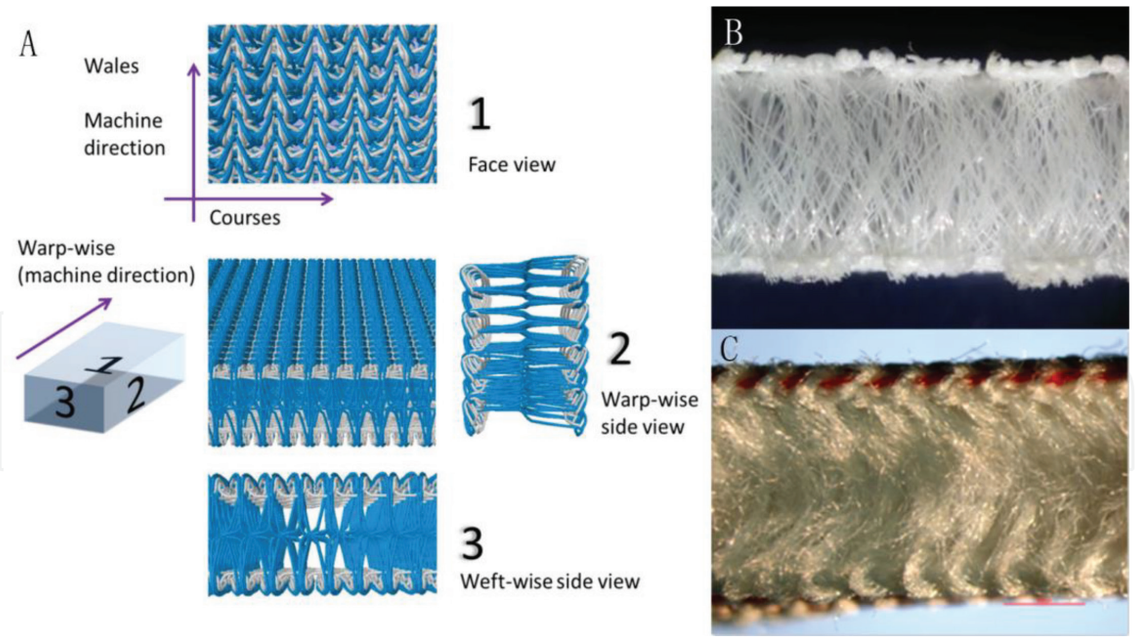

Figure 13.
ProCAD warp knit simulation of a 3D warp knitted spacer fabric (A); a spacer fabric knitted with monofilament yarns (B) and multifilament yarn (C) in the middle spacer layer [67].

a high surface area for cell attachment and proliferation, and the porous structure is highly interconnected which allow fluids carrying nutrients and waste by-products to flow through the entire structure [67]. The technical face, back and spacer layers are all knitted independently. So distinct characteristics can be designed and incorporated into the same fabric by means of changing the yarns and the construction in each layer. The distance between the two needle beds, also known as the void volume or "total porosity", can be altered by the knitting pattern in the spacer layer, which defines the macro level. At the same time, the size, twist and texture of the filament yarns, and their individual cross-sectional shape defines the micro level. The unique spacer layer determines the thickness of the scaffold, ranging from about 100 μm to several centimeters. Space fabrics are knitted from monofilament or multifilament yarns as shown in **Figure 13B** and **C**. A monofilament yarn consists of one thick filament per yarn so the yarn stiffness is higher and the fabric compression resistance is higher than a multifilament spacer fabric. Multi-filament yarns have several filaments per yarn, sometimes there can be hundreds of filaments. The higher the filament count, the finer each fiber. So multifilament spacer fabrics have extraordinary surface areas with high porosity [61].

Warp knitting is a promising technology to fabricate basic and complex scaffolds for tissue engineering applications. Warp knitted scaffolds have a high potential for commercial success because they can adapt to FDA-compliant materials without sacrificing their property requirements. The warp knitted fabric has great structural stability and suture retention performance, which is crucial in any clinical application. The unique type of 3D warp knitted spacer fabric, has proven to be biocompatible in lab trials with excellent cell attachment and tissue penetration into the 3D scaffold network. It is also an attractive candidate in complex tissue engineering applications such as at muscle-tendon junctions.

4.4 Braided scaffolds

Braiding technology, developed in the 1800s [68], is the process of interlacing three or more yarns obliquely to form either tubular or flat fabrics. In order to braid a tube one needs to use an even number of yarns, half rotating clockwise,

and the other half rotating counter-clockwise. If a flat braid is needed, then one needs to use an odd number of ends. By increasing the number of sets of yarns or the thickness of the yarns, one can obtain a thicker or wider product with superior mechanical performance [69]. These designs can be a hollow or solid construction with either a uniform or variable cross-sectional shape [69]. Braiding technology has traditionally been used to fabricate textile structures such as ropes, but it is gradually gaining attention in biomedical applications, such as sutures, stents and in tissue engineering (TE) scaffolds for the repair of connective tissues, nerve guides and vascular prostheses.

4.4.1 Design of braided structure

Braiding angle, the most important geometrical parameter of braided structures, is defined as the angle between the braided yarns and the longitudinal direction. Braiding angles can range from 0° to 90° while they are usually between 30° and 80°. In comparison with a woven structure, the yarns in a braid are able to rotate and slide at the crossing points when under an external force. This offers braided structures with superior flexibility [70].

Tubular braids or ropes are mainly used in medical applications, which are manufactured with an even number of yarns arranged around a circle. The two common structures that have been developed are the diamond braided structure with each yarn crossing above and below the other yarns (1/1) and the regular braided structure with each yarn crossing over two of the other yarns (2/2) (**Figure 14**). In addition, other braided structures can be developed. For example, axial yarns can be introduced in the longitudinal direction to form a tri-axial braided structure [71].

4.4.2 Fabrication of braided scaffolds

The most widely used braiding machine for fabricating tubular braids has two sets of bobbins mounted on spindles moving along two tracks. One set of bobbins revolves in the clockwise direction and the other set revolves in the counter-clockwise direction, in order to form the braided pattern (**Figure 15**) [68, 72].

Yarns wrapped on the bobbins are pulled continuously and interlaced with each other at the braiding point. The braided yarns are then wound up on a scroll or take-up package. By adjusting the ratio of the braiding velocity and the take-up velocity, different braiding angles can be obtained which significantly affect the performance of the braided product.

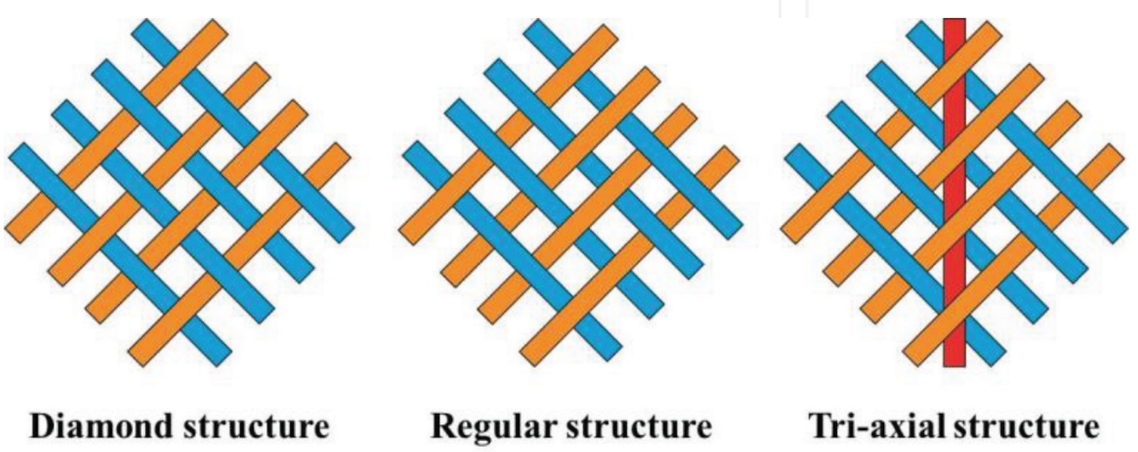

Figure 14.
Three types of braided structure.

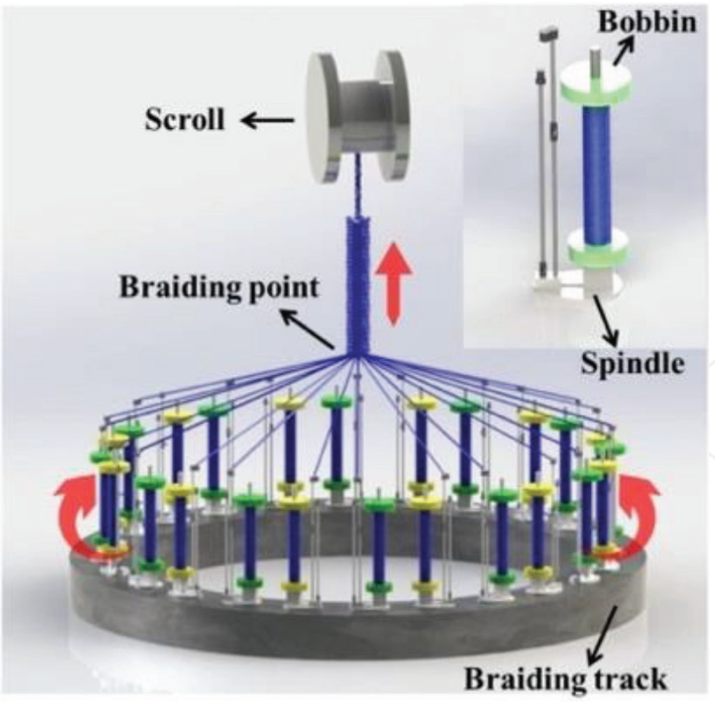

Figure 15.
Schematic diagram of braiding machine.

4.4.3 Evaluation of braided scaffolds

Braided scaffolds have frequently been used for tubular or rope-like tissue engineering scaffolds because of their precise and predictable porous structure and adjustable performance to mimic natural structures and properties [73, 74]. Extensive tissue ingrowth and mechanical characteristics that match natural tissues can be achieved with the appropriate selection of materials, braiding parameters and suitable pore size [75]. First, the mechanical and physical performance are considered as the most important criteria for designing a braided tissue engineering scaffold, followed by the question of biocompatibility.

4.4.3.1 Physical properties of braided scaffold

For rope-like braided scaffolds, the braiding angle is the key to affect their mechanical properties. The cover factor, combined with the braiding angle, needs to be measured in order to evaluate the physical properties of the tubular braided scaffold. The easiest way to measure braiding angle (θ) is by using a microscope and angle measurement software, as shown in **Figure 16**.

For tubular braided scaffolds, the cover factor is defined as the percentage of the mandrel's surface covered by yarns and calculated with Eq. (1) [76]:

$$\textit{Cover factor}: \quad = \quad 1 - \left(1 - \frac{W_y \; N_c}{4\pi R \cos\theta}\right)^2 \tag{1}$$

where W_y is the width of braiding yarns; N_c represents the number of bobbins; R is the outer radius of mandrel (mm) and θ is the braiding angle.

4.4.3.2 Mechanical properties of braided scaffold

Radial compression, tensile and bending measurements are commonly used to evaluate the mechanical properties of braided scaffolds, especially tubular braided scaffolds.

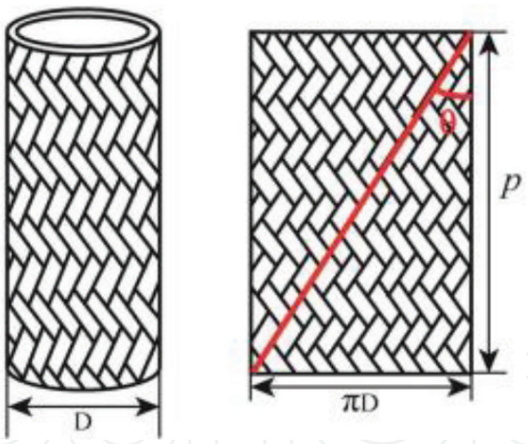

Figure 16.
Diagram of braiding angle. D: outer diameter of braided scaffold; p: axial distance of braiding yarn in one spiral.

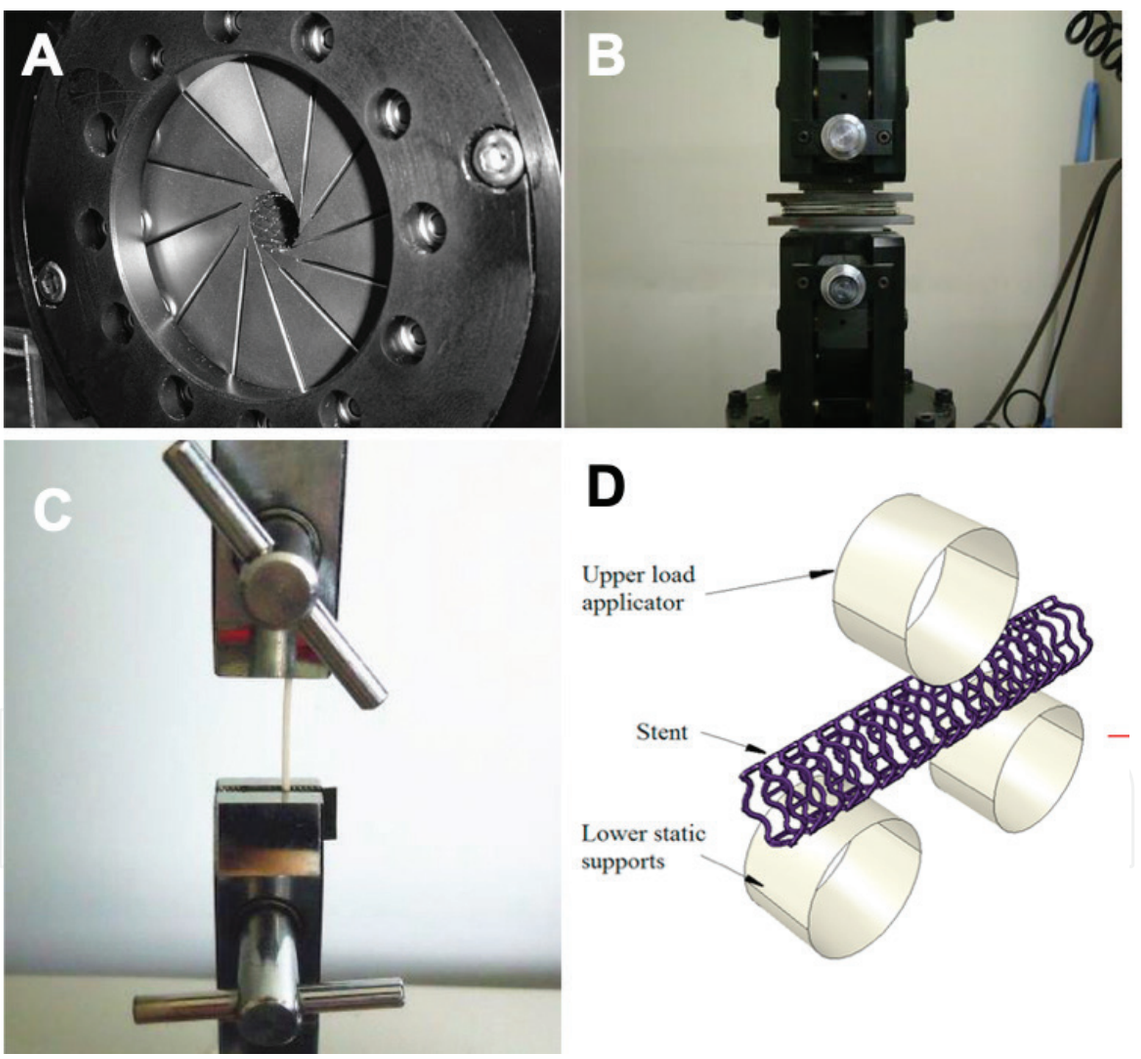

Figure 17.
(A) Radial compression machine; (B) parallel plate compression tester; (C) uniaxial tensile measurement; (D) diagram of three-point bending measurement.

According to ISO 25539-2012 [77], the radial force test with a radial compression machine and the crush resistance test with a parallel plate tester are highly recommended to evaluate the radial compressional properties of tubular braided scaffolds (**Figure 17A** and **B**) [78, 79]. A uniaxial tensile test (**Figure 17C**) [75, 80] and a three-point bending test (**Figure 17D**) [81] are measurements used to evaluate the tensile strength and bending stiffness of braided scaffolds, respectively.

4.4.4 Tissue engineering applications of braided scaffolds

For tissue engineering applications, braided scaffolds are required to have good cell adhesion and cell proliferation. At present, different biomaterials are used to fabricate various braided scaffolds for tissue engineering applications such as tendon/ligament reconstruction, cartilage, bone, vascular grafts and nerve regeneration.

Barber et al. [82] and Rothrauff et al. [83] reported that they had braided nanofibrous scaffolds (BNFSs) for tissue engineering tendons and ligaments. Several bundles of electrospun nanofibers were braided into rope-like scaffolds. Human mesenchymal stem cells (hMSCs) showed good adhesion and orientation after seeding and culturing on the BNFSs, and were also reported to promote hMSCs proliferation and key pluripotency gene expression. Cooper et al. [84] and Freeman et al. [85] developed braided scaffolds made with synthetic poly(L-lactic acid) for anterior cruciate ligament repair. The scaffolds mimicked the morphology and mechanical properties of the native ligament tissue and when tested in rabbits showed excellent healing and regeneration. In another study, Fang et al. developed a braided scaffold using antheraea pernyi silk fibroin for tissue engineering a tendon [86]. The scaffold was investigated *in vitro* and *in vivo* using tenocytes and a rabbit animal model. It was found that the scaffolds integrated with the native tissue and formed tendon tissue in rabbits.

Sun et al. fabricated a gene-modified scaffold by lyophilizing the CHS mixture with braided silk cables for fibrocartilage application [87]. The scaffold, seeded with mesenchymal stem cells (MSCs), showed vigorous cell proliferation and differentiation to reconstruct the cartilage. Fujihara et al. successfully developed a braided carbon/PEEK composite to be used as a bone plate [88]. The bending properties of the braided composite were comparable with natural bone. In another study, Evans et al. developed a tubular braid to improve the efficiency of bone fracture treatment [89]. It was shown that changing the braid angle and the thickness of the tubular cast produced a stiffness similar to that of native bone. Ichihara et al. braided PLLA and PGA yarns coated with collagen to form a novel nerve guide tube for nerve regeneration [90]. The animal experiment showed fast recovery and good regeneration by using the scaffold, which suggested the potential for nerve gap repair. Zhang et al. designed a tri-layer graft from electrospun silk fibroin (SF) and poly(L-lactide-co-ε-caprolactone) (PLCL) and braided layers of silk yarns, to mimic the tri-layer structure of the intima, media, and adventitia of native blood vessels [91]. It was demonstrated that the braided outer layer significantly improved the mechanical properties of the construct. Besides good mechanical properties, and biocompatibility the prototype sample also exhibited appropriate anticoagulation properties as a result of the heparin coating.

4.5 Nonwoven scaffolds

Nonwoven textiles can be distinguished from traditional textiles based on the fact that nonwoven textiles are manufactured directly from staple fibers or filaments and do not involve the intermediate yarn manufacturing process [92].

Various definitions of nonwoven textiles are used by various nonwoven organizations. One of the most widely used definition is the one defined by the Association of Nonwoven Fabrics Industry (INDA), which is "A sheet, web, or batt of natural and/or man-made fibers or filaments, excluding paper, that have not been converted into yarns, and that are bonded to each other by any of several means" [93].

Thus, nonwoven textiles essentially are characterized by those fabrics which are converted directly from fibers. As opposed to conventional textile manufacturing

of woven or knitted fabrics, nonwoven manufacturing processes are characterized by cost effective and high productivity due to elimination of the yarn manufacturing step. The ability to process a wide range of raw materials from staple fibers to continuous polymer filaments adds to a versatility in the range of products that can be obtained from nonwoven textile processing [94].

4.5.1 Nonwoven fabrication process

Nonwoven fabric manufacturing consists of three main steps: (1) selection of raw material fiber or polymer, (2) web formation, and (3) web consolidation and finishing [95]. Selection of the raw material or type of fiber is generally based on the requirement of specific properties for the end use application. Raw material for nonwoven fabrics includes staple fibers or polymers, binders for thermal or chemical web consolidation and finishing agents such as softeners, flame retardants, antimicrobials [95]. On the basis of web formation, nonwovens can be classified into two main categories, web formation from staple fiber and web formation from polymers. Staple-fiber-based web formation is further divided into two categories: dry laid webs and wet laid webs.

Dry laid web formation includes opening and mixing of staple fibers and the formation of a thin layer of web of randomly laid or oriented individual fibers by air laying or a conventional carding machine. The single layered web is then laid into its final web structure by going through cross lapping or parallel laying to get a stable structural integrity. The orientation of fibers in the machine or cross direction can be engineered through these processes, depending upon the properties required in the final product [95]. Wet laid web formation includes initial mixing of the staple fibers in chemicals and water and then deposition of the mixture into a thin layer of web consisting of randomly laid fibers. The advantage of wet laid web formation is that fibers with very short staple length can be easily converted into a web [95]. Polymer based web formation is further divided into spunbonded and melt blown web formation. Both the processes include melting of the polymer into a dope which is then spun into fine filaments or microfibers and directly collected on a collection plate in the form of a web which can then be further processed for producing a hybrid nonwoven structure or can be finished into a final product [95]. Variables such as fiber type, fiber processing, type of web formation, web weight, uniformity and the presence of binder can impact the characteristics and properties of the final fabric [94].

Web consolidation or web bonding processes are classified into three main types, which are mechanical, chemical and thermal bonding. Different types of web consolidation processes impart specific properties to the nonwoven fabric. Mechanical web bonding consists of two types: needle punching and hydroentangling. In both the processes a randomly laid or carded web goes through penetration with either barbed needles or high-speed water jets resulting in interlocking and bonding of the web in the form of a fabric with strength and stability. The properties of the scaffold such as thickness, total porosity, air permeability can be engineered by various machine variables such as the intensity and depth of penetration of the needles, the number of entanglements per specific surface area [94]. In chemical bonding, the adhesion of fibers in the web is achieved with the help of binders such as polyvinyl acid derived resins. The characteristics and amount of binder used determines the properties of the nonwoven fabric (**Figure 18**).

For example, increasing the amount of binder results in increased strength and stiffness, but reduced softness and flexibility. Chemical bonding can be achieved by various methods such as saturation, foam, spray, and print bonding [94]. Thermal bonding involves binding the web using thermoplastic binders, such as fibers or powders. Thermal bonding techniques include hot calendering, air thermal

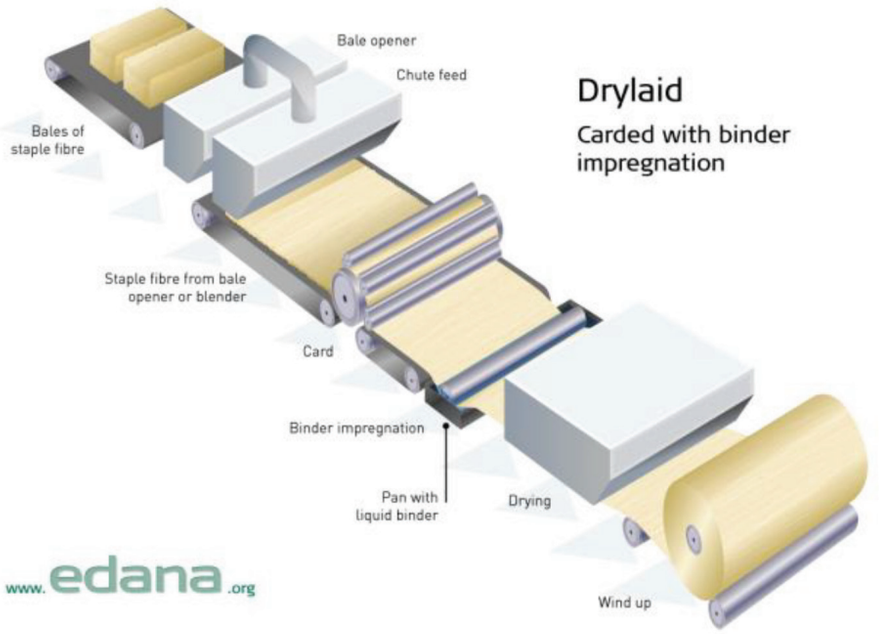

Figure 18.
Schematic diagram of nonwoven web formation using a carded drylaid web and bonding with liquid chemical binder impregnation and drying.

bonding, ultrasonic, and radiant heat bonding. In thermal bonding, various surface characteristics can be introduced using calender bonding of different profiles including area bonding, point bonding, embossing and grid bonding [94].

Finishing of nonwovens includes various mechanical and chemical finishes such as calendering, heat setting, shearing, singeing, and applying antimicrobial and antistatic agents. The chemical finishes can be applied through processes such as padding, coating, laminating and newer finishing techniques such as plasma and microencapsulation [94].

4.5.2 Nonwoven fabrics as scaffolds

Nonwoven fabrics are characterized by properties such as high surface area and high porosity, which encourages researchers to study various types of nonwoven fabrics for applications in tissue engineering. Though currently there is no commercial product available, various studies have been conducted on nonwoven fabrics as tissue engineering scaffolds for *in vitro* tissue regeneration [96–102]. Needle punched nonwoven scaffolds have been studied for cell attachment and proliferation of cell types including mesenchymal stromal cells, mouse fibroblasts and hepatocytes using different types of fibers such as polyvinylidene fluoride (PVDF), polyester, polypropylene and nylon fibers [96–98]. Polyester melt blown nonwoven scaffolds have also been studied for osteogenic differentiation using mesenchymal stem cells [99]. Another study incorporating nonwoven scaffolds included poly(vinyl alcohol) (PVA) bonded to a wet-laid chitosan nonwoven scaffold characterized by high porosity and a narrow pore size distribution. These scaffold properties are recommended for soft tissue regeneration, such as cartilage tissue [100]. Polymer impregnated Lyocell fiber nonwoven biomaterials were seeded with chondrocytes to study their ability to regenerate cartilage tissue [101]. Conductive scaffolds have also been fabricated by coating poly-L-lactide (PLLA) spunbond biomaterials with conductive poly(3,4-ethylenedioxythiophene) (PEDOT), and human dermal fibroblasts have been cultured to evaluate on the biocompatibility of the coated scaffold [102].

4.6 Electrospun scaffolds

Electrospinning is one of the most popular techniques for fabricating tissue engineering scaffolds. Its widespread use is accredited to its ease of manipulation, cheap and accessible equipment needs, and its versatility. The technique can be applied to various materials, ranging from synthetic polymers such as PLA [103], PGA [104], PCL [105, 106], PU [107, 108], and their copolymers [109], to natural polymers such as collagen [110, 111], elastin [112], gelatin [113] and chitosan [114]. Electrospun scaffolds have been applied in various tissue engineering applications, such as skin [115], bone [107, 116], cartilage [113, 117], tendon [118, 119], ligament [118], nerve [105, 120], blood vessel [121], cardiac tissue [122], and aortic valve [108].

Electrospinning is a fiber-forming method by injecting a conductive polymer solution or melt through a high-voltage field, and the fiber is stretched by the attenuating electrical force and collected on a grounded collector (**Figure 19**). It has a unique advantage in fabricating micro and nano-fibers that mimic the structure of the extra cellular matrix (ECM), such as the basement membrane of blood vessels. Hackett et al. [105], Zhang et al. [91] and our studies [57] have all demonstrated that an electrospun layer attached to the luminal surface of a vascular scaffold is able to reduce the pore size and facilitate endothelial cell proliferation. The nanofiber web provides an ideal scaffold surface for endothelial cells that require a flat surface with nano-sized pores to form a monolayer on the vascular intima.

Another advantage of electrospinning is that it is able to adapt to a wide range of materials. In order to fabricate a scaffold that mimicks the native ECM both structurally and biochemically, one can apply natural polymers such as collagen, elastin, and cellular components to the scaffold's surface. Collagen, as the predominant protein in native ECM, has been reported by many researchers to be an attractive scaffold coating that leads to advanced cell adhesion, proliferation, and migration [123, 124]. Furthermore, the addition of cellular components to the electrospinning solution has also been described. Venugopal et al. [125] reported preparing an electrospun scaffold from a blend of gelatin and phytochemical components, such as hexadecanoic acid (HDA), octadecanoic acid (ODA) and

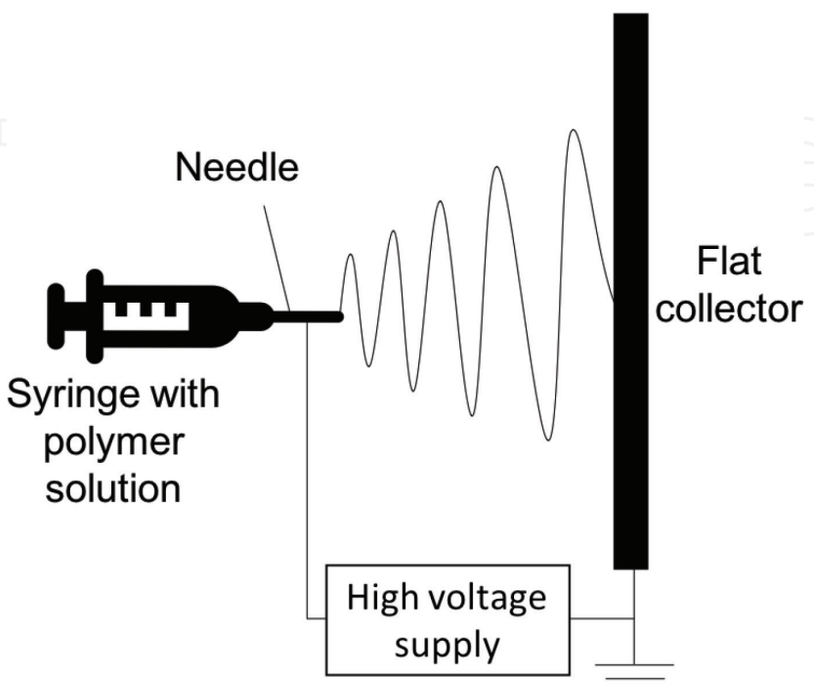

Figure 19.
Typical experimental electrospinning setup.

N,N-diisopropyl(2,2,3,3,3-pentafluoropropyl)amine (DPA), which is able to promote primary human meniscus cells and human MG63 osteoblast-like cells to attach and proliferate for bone and cartilage tissue regeneration.

On the other hand, its micro- or nanoscale structure turns out to be its limitation in fabricating a 3-dimentional scaffold. The small pore size prevents cell infiltration through its thickness, and so it does not regenerate bulk tissue with any thickness [108]. In addition, its mechanical weakness limits its translational ability. Thus, a composite scaffold by combining electrospinning with other textile technologies is an attractive strategy to take advantage of the different properties of different textile structures, and in this way promote the development of the novel and advanced tissue engineering scaffolds.

5. Conclusions

This chapter has demonstrated the use of a number of textile fiber-based technologies that can be used to prepare resorbable scaffolds for a wide variety of tissue engineering applications. Each textile fabrication technique has its particular advantages in being able to control its physical dimensions (e.g. average pore size and pore size distribution), its surface topography and its mechanical properties, whether they be related to supporting tensile, compression, bending and shear forces, within a precise and predictable range.

Few experimental prototype tissue engineering structures have been accepted clinically, and fewer still have been approved by the US regulatory agency for commercial production, distribution and use. Additional work is needed in order to understand the complex biomaterial-cell-tissue interactions that occur at the scaffold interface. It is hoped that by describing in this chapter the success of using fiber-based scaffolds that more efforts and collaborations among interdisciplinary research teams will be able to overcome these challenges.

Conflict of interest

None of the authors of this chapter have a 'conflict of interest' to declare.

Author details

Martin W. King[1,2*], Jiyang Chen[1], Monica Deshpande[1], Ting He[1,3], Harshini Ramakrishna[1], Yu Xie[1], Fan Zhang[1] and Fan Zhao[1,2]

1 North Carolina State University, Raleigh, USA

2 Donghua University, Shanghai, China

3 The Lycra Company, Wilmington, DE, USA

*Address all correspondence to: mwking2@ncsu.edu

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