Title	The past, present and future in scaffold-based tendon treatments
Author(s)	Lomas, A.J.; Ryan, C.N.M.; Sorushanova, A.; Shologu, N.; Sideri, A.I.; Tsioli, V.; Fthenakis, G.C.; Tzora, A.; Skoufos, I.; Quinlan, Leo R.; Ó Laighin, Gearóid; Mullen, A.M.; Kelly, A.M.; Kearns, J.L.; Biggs, S.; Pandit, Abhay; Zeugolis, Dimitrios I.
Publication Date	2015-04
Publication Information	Lomas, A. J., Ryan, C. N. M., Sorushanova, A., Shologu, N., Sideri, A. I., Tsioli, V. Fthenakis, G. C., Tzora, A., Skoufos, I., Quinlan, L. R., O'Laighin, G., Mullen, A. M., Kelly, J. L., Kearns, S., Biggs, M., Pandit, A. , Zeugolis, D. I. (2015). The past, present and future in scaffold-based tendon treatments. Advanced Drug Delivery Reviews, 84, 257-277. doi: https://doi.org/10.1016/j.addr.2014.11.022
Publisher	Elsevier
Link to publisher's version	https://doi.org/10.1016/j.addr.2014.11.022
Item record	http://hdl.handle.net/10379/7113
DOI	http://dx.doi.org/10.1016/j.addr.2014.11.022

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The past, present and future in scaffold-based tendon treatments

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Abbreviations:

ACL, anterior cruciate ligament; ADSC adipose derived stem cell; bFGF, basic fibroblast growth factor; BMSC, bone marrow stem cell; BMP, bone morphogenic protein; DNA, deoxyribonucleic acid; ECM, extracellular matrix; EGR, early growth response protein; GAG, glycosaminoglycan; GDF, growth differentiation factor; HA, hyaluronic acid; IGF, insulin-like growth factor; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NSAIDs, non-steroidal anti-inflammatory drugs; NO, nitric oxide; Oct 4, octamer-binding transcription factor 4; PDGF, platelet-derived growth factor; PCL, poly-ε-caprolactone; PLGA, poly(lactic-co-glycolic acid); PRP, platelet rich plasma; PG, proteoglycan; SSARD, slow acting anti-rheumatic drugs; SSEA-4, stage-specific embryonic antigen-4; TGF-β, transforming growth factor-β; TC, tenocyte; TSC, tendon stem cells; VEGF, vascular endothelial growth factor

Abstract

Tendon injuries represent a significant clinical burden on healthcare systems worldwide. As the human population ages and the life expectancy increases, tendon injuries will become more prevalent, especially among young individuals with long life ahead of them. Advancements in engineering, chemistry and biology have made available an array of three-dimensional scaffold-based intervention strategies, natural or synthetic in origin. Further, functionalisation strategies, based on biophysical, biochemical and biological cues, offer control over cellular functions; localisation and sustained release of therapeutics / biologics; and the ability to positively interact with the host to promote repair and regeneration. Herein, we critically discuss current therapies and emerging technologies that aim to transform tendon treatments in the years to come.

Keywords

Human and equine tendon injury; Tendon cellular and extracellular composition; Tendon healing; Tissue grafts; Biomaterials; Sustained and localised delivery of therapeutics / biologics

Contents

1. Introduction

Tendon injuries constitute an unmet clinical need for both human and equine patients. Over 30 million human tendon-related procedures take place annually worldwide with an estimated healthcare expenditure in excess of €140 billion per year [1]. As the human population ages and life expectancy increases, it is estimated that 25% of all adults will suffer a tendon related condition that will put a further physical and financial strain on healthcare systems [2, 3]. Proportional is the situation with equine patients: 46% of the racehorses will suffer a tendon-related injury that will negatively impact the industry, which is valued at €400 billion worldwide [4, 5].

Subject to the severity of the injury, from a small sprain to a complete rupture, numerous therapeutic strategies of variable efficacy are currently available (**Table 1**). Unfortunately, preclinical and clinical data to-date indicate, regardless of injury severity, no current therapies have achieved complete pre-injury state recovery [6]. Further, severe injuries are often associated with compromised function, joint instability and long-term pain and disabilities, due to the inherent poor regeneration capacity of tendon [7].

These findings impose the need for the development of functional therapies for injured tendon tissues. However, for successful tissue engineered therapies, it is important to understand epidemiological data of the different injuries, the function of cellular and extracellular components in tendon physiology and healing, and pioneered technologies that have become available in recent years. Upon this knowledge, it is likely to revolutionise functional tendon treatments in the years to come.

2. Epidemiology and clinical description of human tendon injuries

The most frequently injured tendons are the shoulder rotator cuff, the forearm extensor, the hand flexor, the Achilles, the tibialis posterior and the patellar [8, 9], while the anterior cruciate ligament (ACL) is one of the most painful and debilitating of knee injuries [8, 9]. Previously, the tendon research community recognised inflammation as the underlying cause of tendon injury, however, with advancements in imaging technologies and understanding of histopathology, it is widely accepted that tendon injuries are more degenerative in nature [10-14]. These degenerative conditions, referred to as tendinopathies, comprise of typical pathological changes, including islands of high cellularity and initial tissue disorganisation in mild degeneration, whilst in severe degeneration is accompanied by chondrocyte appearance [15]. Macroscopically, degenerative tissue appears to be yellow / brown due to mucoid degeneration and the loss of the highly organised appearance of collagen fibre bundles [14, 16]. Further, microscopic changes occur within the collagen structure itself and fibrosis and neovascularisation are evident [17-19]. In addition, current data suggest that the formation of additional blood vessels is responsible for the pain prevalent in tendinopathies [20, 21], and not inflammatory infiltration, as previously suspected [22, 23].

16% of the general population, 21% of elderly people and 80% of individuals older than 80 years sustain rotator cuff injuries [10], with full or partial tears affecting 27% and 37% of the general population respectively, with high recurrence rate, despite surgical repair [11, 12]. Rotator cuff tears impair shoulder function, cause pain and lead to degenerative changes in the glenohumeral joint. Partial tears are customarily treated through means of physiotherapy. Surgical treatments include arthroscopic cuff decompression and repair and, in severe cases, open surgery [13, 14]. Debridement is undertaken when <50% of the rotator cuff is torn; in cases where >50% of the tendon is torn, partial or complete repair, usually with substitutes and various tendon transfers, is utilised [15, 16]. Graft augmentation is employed for long-standing tears of medium to large extent [17, 18]. Unfortunately, graft augmentation is associated with high tear recurrence (94%), subject to the size of the initial tear, the degree of muscular atrophy, the fatty infiltration, the tendon quality and the post-surgical rehabilitation protocol [19-21].

Hand flexor tendon injuries are more frequently encountered in younger patients [22]. Clinical presentation is characterised by pain, tenderness, swelling and erythema of the affected tendons [23]. Surgery treatment strategies for the tendon and the sheath are based on suturing, followed by active motion post-surgery [24]. However, reoperation following flexor tendon repair is necessary in as high as 17% of cases [24-26], with unsatisfactory outcomes reported by up to 20% of patients [27]. It has also been reported that reoperation is required more often in older patients [28]. Rupture of the Achilles tendon is a common sport-related injury, with degeneration occurring in an estimated 11% of runners [29], with the highest incidence of rupture seen in 30- to 50- years old

males [25]. Clinical diagnosis is based on palpation of the gap and a positive Thompson test, with ultrasonography and/or magnetic resonance imaging (MRI) used to confirm the diagnosis [25, 26]. Surgical treatment is necessary in one-third of the patients [27] and includes minimally invasive, percutaneous or open repair strategies, subject to the extent of the injury. Unfortunately, future complications and treatment failures are common [28-30]. Injury of the tibialis posterior tendon occurs more commonly in middle-aged women, with clinical features including pain in the medial foot, loss of function and flatfoot deformity with no history of pre-existing trauma [31]. Therapeutic approaches include surgical tendon reconstruction (debridement of the tendon or tendon transfer), calcaneal osteotomy and arthrodesis [32]. Patellar tendon injury usually occurs in active adults younger than 40 years and jumping sport athletes. Clinical diagnosis is based on presence of pain, difficulty to stand and palpation of a subcutaneous depression at the region. X-ray, ultrasonography and/or MRI methods are used to confirm the diagnosis and are particularly useful in patients with long-standing, mild clinical signs [33]. Primary repair is the treatment of choice in recent years, whilst chronic injuries necessitate graft augmentation. ACL injury occurs predominantly in the male population due to increased exposure to physical tasks and involvement in sports; however females have been identified to be at higher risk of injury [30]. Patients experience joint instability and knee pain following non-surgical treatments [31-33] and risk further injury within the knee, when the ACL is working at insufficient functional capacity [34]. Reconstructive surgery is usually performed instead of partial repairs, due to the poor healing capability of the ligament [35]. The most successful reconstructions implement biological tissue grafts, due to joint integration and optimal remodelling [36]. However, preclinical studies have shown that the biomechanical properties, including load to failure and stiffness, of new ligaments are mechanically deficient compared to normal by up to a quarter within a year following surgery [37-39].

3. Epidemiology and clinical description of equine tendon injuries

In sporting horses, energy-storing tendons often stretch close to failure strain limit, especially during jumping at high-speed locomotion, which explains why tendons, such as the superficial digital flexor, are more prone to strain injuries [40]. In contrast, tendons not subjected to such increased forces, such as the deep digital flexor, show a significantly smaller incidence of strain injuries [41]. Intrinsic (e.g. age, bodyweight, organ fatigue) and external (e.g. track surfaces) reasons have been described as predisposing factors [42]. Regardless of the cause, all equine tendon injuries heal slowly and improperly due to the formation of permanent disordered scar tissue [43]. Upon healing, the repaired tendon increases in size and becomes structurally strong with increased stiffness [44]. Restrictive adhesions develop within the synovial sheath of the tendon, leading to impaired functionality in daily activity and, ultimately, to reduced performance of the animal and increased risk for re-rupture [45].

The majority of equine mild strain injuries occur to the forelimb tendons, with the superficial digital flexor tendon being involved in up to 90% of incidents [46]. Such injuries usually occur at the mid-metacarpal region, in the central part of the tendon. Mild injuries of the superficial digital flexor tendon are clinically manifested initially with severe lameness, which although may resolve rapidly, it will remain as an on-going problem. Careful palpation of the affected limb at the metacarpal area would elicit a pain response from the animal and reveal an oedematous region. Ultrasonography imaging is essential for confirmation of the clinical diagnosis, as well as for the identification of the exact location and the severity of the injury. Upon diagnosis, treatment should start immediately to avoid further damage [47]. Therapeutic options include a conservative approach (general rest, support bandaging and reduced activity over an extended period of time), as well as surgical proximal check desmotomy and/or tendon splitting. Transection of the proximal check ligament increases the elastic limit of the tendon by allowing the muscle to contribute to the overall elasticity; however this may be compromised by the formation of the scar tissue [48, 49]. Tendon splitting should be performed soon after the injury occurs, in order to minimise damage by proteolytic enzymes released [50]. Injuries of the deep digital flexor tendon are rare, affecting mainly the tendon within the digital sheath. Should it occur, brought about lameness is severe and persists for a long period of time, with oedematous appearance of the region and pain reaction present during clinical examination. Ultrasonography and MRI are used for confirmation of diagnosis [51]. Bursoscopy may also be used diagnostically, with the added advantage of facilitating surgical management of the lesions. Conservative treatment, such as box rest, can also be applied, but in general, prognosis for return to exercise is guarded [52].

Although tendon lacerations are usually the result of cuts by sharp objects, they can also occur during sporting events [47]. Careful examination of the limb conformation during weight bearing

and ambulation provides useful information regarding tendons involved. When the superficial digital flexor tendon is lacerated, a significant hyperextension of the metatarsophalangeal joint is evidenced. When the deep digital flexor tendon is compromised, the distal interphalangeal joint is hyperextended, resulting in the toe being elevated from the ground. Concurrent laceration of the above two tendons and the suspensory ligament result in the pastern resting on the ground and the toe being elevated [53]. Management of lacerations in non-sheathed zones of the tendon(s) aims to reduce gap and adhesion formation and preserve the intrinsic healing process. Tenorrhaphy is usually performed, preferably by the three-loop pulley technique [54]. When lacerations at the sheathed zone of the tendon have occurred, adhesions and septic tenosynovitis are common complications; tenorrhaphy within the sheathed zones is not recommended, as it cannot prevent gap creation between tendon ends or formation of adhesions [55, 56]. Lacerations of the digital extensor tendons are common, both in the fore- and hind- limbs. In such cases, lameness is minimal and treatment requires debridement of the wound. For these injuries, suturing of the tendon is usually not required [50]. Laceration of the long and lateral digital extensor tendons may not elicit any gait abnormalities, whereas transection may lead to abnormalities in protraction of the limb and knuckling of the toe. Tendon end suturing is performed only in recent, clean and sharp lacerations in the non-sheathed zones of the tendons; in all other cases, second intention healing (debridement, lavage, drainage) is preferred [57].

4. The cellular and extracellular composition of tendon tissue

4.1 The cellular composition of tendon tissues

Human and equine tendons are comprised of various cell populations (**Figure 1** and **Table 2**), with similar characteristics between species [58, 59]. Around 90-95% of the cells present in tendon are elongated specialised fibroblasts, termed tenocytes (TC), and their precursor cells, termed tenoblasts. In embryonic and juvenile tendons, TCs are numerous and found within close proximity to the developing collagen fibres. In mature tendons, TCs reduce in number and flatten, with cytoplasmic processes shortening and diminishing in number [60]. They form a network of cellular protrusions, allowing them to react cohesively to external forces and enabling the tissue to react best to mechanical demands [61]. Tenoblasts vary in size and shape ranging from round, spherical or cuboid to spindle star like morphologies of between 20 and 70μm in length and 8 to 20μm in width and have been considered to be the major cell type responsible for tissue remodelling [62]. Upon maturation into TCs, they become elongated with up to 300μm length and less metabolically active [63], suggesting that they play different role in tendon physiology than tenoblasts. Commonly used markers include collagen type I, collagen type III, decorin, scleraxis, tenascin C, tenomodulin and thrombospondin 4. However, specific markers to distinguish tenoblasts from TCs are yet to be identified.

The remaining 10% of cells present in tendon are a combination of progenitor cells (tendon stem cells; TSCs), chondrocytes (found towards the bone junction), vascular endothelial cells (found in surrounding vascular network), synovial cells (found in the tendon sheath) and smooth muscle cells (found toward the musculotendon junction) [58, 64]. TSCs are a recently discovered population of cells resident in tendon that have the capacity to differentiate into bone, cartilage and fat [65]. In addition to this multi-lineage potential, rabbit TSCs have been found to express the stem cells markers octamer-binding transcription factor 4 (Oct 4) and stage-specific embryonic antigen-4 (SSEA-4) and to have significantly longer population doubling times to TCs isolated from the same tendon source [66]. The concentration of TSCs has been found to vary with age, position and species, with tendons from younger specimens containing higher numbers [67]. Perivascular cells are found in the walls of internal and external tendon capillaries and have been identified as cells that could have a regenerative capacity. They are expressing both mature tendon and stem cell related markers, after being isolated and cultured *in vitro* [68, 69]. Further small populations of mesenchymal stem cells (MSC) have also been identified to be present in both equine and human tendons, although they are generally not recognised as a site for potential stem cell source, due to their poor availability [70]. Fat pads not only aid tendon mechanical function [71], but also provide a source of adipose derived stem cells (ADSCs), with regenerative potential [72].

4.2. The extracellular composition of tendon tissues

Collagens, elastin, glycosaminoglycans (GAGs) and proteoglycans (PGs) make up the load bearing structures of human and equine tendon tissues (**Figure 1**), with slight variations in their concentration between tendons found in different parts of the body. In tendon, collagen type I is the major constituent, making up around 80-90% of the tendon dry mass [58]. Collagen fibres perform several functions, including maintenance of tissue architecture, transmission and absorption loads and prevention against mechanical failure [73, 74]. The base unit of collagen I is a triple helical hetero-polymer consisting of two α1(I) chains and one α2(I) chain [75]. To form this structure, each left handed helical α-chain is staggered by one residue relative to each other to coil about a central axis, forming a right-handed super-helix [76, 77]. The helix is stabilised by hydrogen bonds between adjacent glycine domains and between the hydroxyl groups of hydroxyproline residues. If the positioning of these molecules is incorrect, or the molecules are not present, the collagen will degrade rapidly [78]. Collagen triple helices spontaneously self-assemble in the extracellular space, following or during secretion, to form quarter staggered fibrils with a characteristic 67nm periodicity (D banding) created by the alternating overlap and gap regions [79-81]. Subsequent cross-linking takes place that provides collagen fibrils with high degree of axial alignment and enhances tissue integrity and mechanical resilience. It has been proposed that intermolecular cross-linking occurs in two ways; firstly longitudinal cross-linking of the end-overlapped molecules, and secondly by the interaction of these cross-links between two molecules in parallel [82].

Other, less abundant collagen molecules (e.g. collagen types III, V, XII, XIV) are particularly important when examining tendon aging and pathophysiologies [83, 84]. In healthy tendon, type III collagen is found predominantly in the endotenon and epitenon layers surrounding the collagen type I fibrils [85]. Aging and tissue damage reduces its content, resulting in reduction in tendon elasticity [86, 87]. Type V collagen is found at the centre of the collagen fibrils and mediates fibril development and diameter growth. This process ensures that a collection of many small collagen I fibres are formed, rather than one large structure [88, 89]. Collagens XII and XIV are also present in tendons in small quantities [90, 91]. These collagens act as supplementary molecules in the force transition process, aiding collagen I bundles to glide over each other when a force is applied by decreasing interactions between fibres and thus preventing potential tendon injury [92].

Elastin is present in tendon in the form of elastic fibres and makes up between 1 and 2% of the total dry mass [58]. Elastin molecules are composed of alternating hydrophobic and lysine-rich cross-linking domains, which are critical for molecular structural assembly and elastic function [93]. During structural assembly, the lysine side chains oxidise, via the enzyme lysyl oxidase, allowing the formation of covalent cross-links with neighbouring molecules [94, 95]. The elastic properties are created by the hydrophobic regions, which adopt a random coil configuration following

extension [96]. Overextension is prevented by covalent cross-links that provide tendon tissues with a high degree of flexibility, ensuring complete recovery of the wavy configuration of the surrounding attached collagen fibres, after muscle contraction and tendon stretch [97].

GAGs and PGs, although encountered in miniscule amounts in tissues, are involved in many physiological processes, including collagen fibril formation, growth factor interaction, cell-cell interactions and cell regulation [98, 99]. In addition, GAGs and PGs are highly polar molecules that attract water and therefore play key role as lubricants and shock absorbers. This water absorption capacity allows fibrils to slip over each other during mechanical deformation, preventing breakage. Further, GAGs and PGs provide several cell adhesion sites [100]. The PG composition of tendons depends on both its location and role in the body. Compression bearing tendons, such as the supraspinatus tendon found in the shoulder, have a significantly higher PG content than tension tendons, such as the biceps (3.5% versus 0.2% of total tendon dry weight) [101]. In highly active tendons, such as the equine super digital flexor tendon, PG content within the tendon can be much higher than in non-stressed tendons, with several studies concluding that PG content is directly related to the load bearing capacity of the tendon [102]. The most common encountered PGs in tendon are decorin, versican and aggrecan and can be grouped based on the nature of their GAG chains. Specifically, decorin is commonly associated with dermatan sulphate [103], aggrecan with a combination of dermatan sulphate and keratan sulphate [104] and versican with chondroitin sulphate [103]. In tendon, dermatan sulphate is thought to provide a mechanism of the limitation growth of collagen fibrils, preventing the diameter of individual fibrils becoming too large and maintaining the hierarchical structure seen in connective tissues, thus helping to maintain their physical properties, while chondroitin sulphate plays a vital role in maintaining the amount of water retained by the tissue and controlling the organisation of the collagen present, specifically void space and overall tissue stiffness [105]. The location of the tendon and the specific area of the tendon denominates which PG is most prevalent. Decorin, for example, is the major PG in the central load bearing tendon regions, whilst versican is identified in areas of bone insertion and where compressive forces are prevalent [106].

5. Tendon healing

The wound healing process in tendons occurs in three overlapping phases (**Figure 2**), which are regulated by various growth factors, cytokines and cell types. In the first (inflammation) phase, inflammatory cells migrate into the injury site and phagocytise necrotic tissue and clot. In the second (repair) phase, fibroblasts proliferate in the injury site and synthesise and deposit extracellular matrix (ECM) components. In the third and final (remodelling) phase, the newly produced collagen fibres are aligned along the longitudinal axis of the tendon and eventually become capable of sustaining loads [107]. Over the years, two healing mechanisms have been proposed, subject to the cell populations participating. Intrinsic healing is predominantly controlled by resident TCs, whilst the extrinsic is controlled by cells migrating from the external surrounding tissues [108]. Due to the low activity / reparative capacity of the resident cells [1, 109-112], the extrinsic healing mechanism is activated. In reality, it is likely that a combination of both mechanisms occurs, with different injuries and injury sites determining which mechanism is the overriding one [113].

A by-product of the extrinsic healing process is that extensive amounts of disorganised collagen are deposited, resulting in scar tissue formation and adhesions between the neotissue formed and surrounding tissues. Scar tissue has reduced overall mechanical properties and is associated with an increased chance of re-rupture in later life [114]. Further, increased concentration of collagen type III, remained at the wound site during healing, could also lead to reduced mechanical properties [115]. The presence and arrangement of non-collagenous macromolecules is also altered during tendon healing, even after long periods of recovery [116] and has been found to be dependent on the healing stage. Biglycan expression, for example, is upregulated in the early phases of tendon regeneration, whilst decorin expression is increased during the remodelling phase [117]. The influx of extrinsic cells into a wound area results in increased number of cell populations (e.g. vascular endothelial cells, fibroblasts and stem cells) not usually seen in healthy tendons [107]. These cells could dominate endogenous TCs, especially with respect to cellular secretome, resulting in compromised functionality [118] and adhesion formation that are associated with pain and locomotion issues [119]. As a result of these changes, mechanical, structural, biochemical and biological properties of the healed tendon never match those of the tissue prior to injury [64]. Thus, it has been proposed that tendon therapies, based on injectable systems or implantable devices, should enhance the intrinsic and suppress the extrinsic healing mode, in order to better restore tendon function [120].

6. Minimally invasive strategies for small tendon injuries

Injectable systems allow localisation of the cargo and its sustained release at the side of injury, increasing that way the effectiveness of the treatment. Among the natural biopolymers, collagen type I and fibrin are the most widely used [121, 122], although the use of hyaluronic acid (HA) has also been advocated as it allows tissue integration and prevents adhesions to surrounding tissues [123]. The attractiveness of collagen type I is based on the fact that constitutes the major component of tendon and is removed from the body through physiological enzymatic processes, as a function of the extent of cross-linking and functionalisation [105, 124-127]. Clinically, injectable collagen hydrogels have been utilised as carriers for biological and pharmaceutical agents [128]. Collagen peptides have also been used, with preclinical data demonstrating increased collagen synthesis [129], maintenance of homeostasis [130] and improved healing, as judged by mean average diameter, distribution of fibrils and GAG composition [131]. The utilisation of fibrin has been advocated based on its high cytocompatibility, biodegradability, controllable cross-linking, carrier capacity and presence of several ECM proteins, such as fibronectin, that enhance cell adhesion and proliferation [132-134]. Preclinical analysis revealed that fibrin glue around the suture site enabled rabbit flexor tendon healing with smooth gliding surface and without formation of adhesions [119]. In a rat supraspinatus tendon defect model, although fibrin clot improved collagen organisation and mechanical properties over time and reduced cellularity, the biomechanical properties did not reach the properties of the healthy tissue by week 12 post-implantation [135]. In a ruptured Achilles tendon model, biomechanical and histological analysis revealed comparable characteristics between fibrin- and suture-based repairs [136, 137]. Clinical data also advocate the use of fibrin; in an Achilles tendon repair situation, although complete restoration of healthy tendon properties was not achieved, functional and cosmetic results were significantly improved [138, 139]. To-date, injectable systems, loaded with pharmaceutical agents, biological molecules and viable cell populations are under intense research and development in the quest of recapitulating native tendon function following injury.

6.1 Delivery of pharmaceutical agents

Anti-inflammatory molecules, such as slow acting anti-rheumatic drugs (SAARDs) or non-steroidal anti-inflammatory drugs (NSAIDs), are extensively used in tendinopathy [140]. Data to-date demonstrate reduction in inflammation observed during the early stages of tendinopathy and maintenance of tendon structural integrity and mechanical properties [141]. However, the effective window of SAARDs is limited to the very early stages (at most 2 years after degeneration has begun) of tendon damage [142]. Similarly, NSAIDs have a beneficial effect on injured tendons, should they injected soon after the injury occurs (a few days); however, patient response to the treatment varies widely, side effects associated with prolonged use and their detrimental effect on cell proliferation and PG synthesis further compromise their use [143-145]. The use of glucocorticoids, as inflammation suppressive drugs, has also been advocated in tendon field [59], however *in vitro* studies demonstrate suppression in PG production, which may hinder regenerative processes [146].

Given nitric oxide (NO) is normally expressed in healthy tendon, albeit at low levels, and is diminished in fibrous tendon scar tissue, its use following tendon injury and in tendinopathy has been advocated [147, 148]. Topical gels and slow release patches have been used as delivery vehicles [147, 149]. Clinical findings using topical gels show improved early stage healing and pain reduction, and long term improvements in functionality [150], however, natural tolerance can occur in long term treatments leading to reduced therapeutic benefit and side effects, such as headaches, have been reported in some cases, limiting the use of NO to specific tendon conditions [151].

HA has been utilised in tendon therapy for several years in both equine [152] and human patients [153]. Long term follow up studies on athletes with patellar tendon injuries demonstrated that HA injections directly into the tendon and surrounding areas have a beneficial effect on tendon healing, as assessed by scoring methods [154]. Further studies investigating repeated HA injections to hand damaged flexor tendons indicated reduction in adhesions with surrounding tissues [155]. Similar small animal model studies have identified reduction in adhesion formation as the primary mode of action of HA in tendon healing [156].

Intra-tissue injections are the preferred delivery mode of pharmaceuticals for both human and equine patients. The cost-benefit of pharmaceuticals to treat tendon injuries, especially the use of corticosteroid, is under severe scrutiny with respect to their efficacy and associated side effects [157-160]. Given there is currently no sufficiently effective pharmaceutical-based therapy, the use of more potent biological molecules was proposed as an alternative strategy.

6.2 Delivery of biological molecules – Growth factors

Growth factors, natural functional molecules that stimulate cellular processes [161], have been extensively studied as means to recapitulate native tendon function following injury [162-164], given their role in tendon physiology and healing, through cell recruitment at the site of injury and stimulation of ECM synthesis [165-168]. For example, vascular endothelial growth factor (VEGF) increases revascularisation of repairing tendon tissue, improving overall healing [169]; platelet-derived growth factor (PDGF) has beneficial effects on the functional repair of tendon tissue in the canine model, increasing tendon glide, but not mechanical properties, over a 42 day period [170]; basic fibroblast growth factor (bFGF) stimulates both MSC proliferation and differentiation towards tenogenic lineage, leading to increased expression of tendon specific ECM proteins and increased collagen production from cells [171]; bone morphogenic protein 12 (BMP-12), also referred to as growth differentiation factor 7 (GDF-7) induces both *in vitro* and *in vivo* tenogenesis of MSCs in both human and equine cells [172-174]; BMP-13 (GDF-6) induces an increase in the expression of tendon specific proteins in rat MSCs along with increasing the characteristic wave like pattern found in tendon histological samples after 14 days implantation in a rat Achilles defect model [175]; BMP-14 (GDF-5) reduces adhesion formation between tendons and surrounding tissues, improving overall function and recovery [176]; early growth response protein 1 (EGR1) directs tendon differentiation in rat MSCs and improve tendon healing in a rat Achilles tendon injury model [177]; and transforming growth factor-β (TGF-β) is highly influential in the recruitment and maintenance of TC progenitor cells during injury [178]. While these growth factors have demonstrated efficacy, as assessed by increased cellular migration, matrix production and matrix mechanical properties over a short period of time (up to around 8 weeks), little difference has been documented in long term tissue integration, matrix composition and overall tissue strength over control groups [177, 178]. To this end, the use of single growth factor injections [179] or cocktails of thereof [180] at different healing stages has been proposed [181]. However, single or combinatory growth factor injectable therapies have not reached clinical use.

Despite the promising preliminary results achieved, the literally infinite number of growth factor combinations, dose regimes and injection time, makes the identification of a suitable therapy elusive. To this end, platelet rich plasma (PRP), a natural concentrate of many growth factors [182-184], is under intense investigation. PRP has been proposed as a therapy for the treatment of equine tendon injuries, with data demonstrating development and maturation of a healing tendon tissue, based on improved metabolic activity, increased failure strength and elastic modulus of the repairing tissues and increased neovascularisation, over the saline injected counterparts in an equine superficial digital flexor tendon model [185-188]. In a clinical setting, PRP injections have been used under various identifying names for decades [189, 190]; however long-term, large and blinded

studies have yet to be reported, with current data contradicting each other. Pilot studies, for example, have demonstrated safety of either PRP alone or in conjunction with other therapies including surgical suturing techniques and physiotherapy [191-194]. On the other hand, the use of PRP injections is opposed based on data demonstrating no added value in patients received anterior cruciate ligament (ACL) allograft replacement and PRP injections [195] and on data revealing tendon thickening, pain and reduction in mechanical properties, following PRP injections [196-198]. Primary limitations of this approach include the lack of standardisation for PRP potency, preparation and dosing. It is well recognised that PRP preparations used clinically depend upon their human source and preparation methods and that age, health indices and genetics comprise part of the complex matrix that determines PRP potency. Many of the inconsistencies and variables in the PRP literature result from a widely varying PRP product applied for healing purposes [182, 189, 190, 194]. For example, it is necessary for PRP to be clotted for delivery to the target site, thus traditionally bovine thrombin is implemented; however, this adds the risk of coagulopathies due to the induction of the production of antibodies to clotting factors [199]. To this end, other clotting agents, such as fibrin and collagen I, have been studied [200, 201], which make comparison between studies even more complicated. It has been suggested that PRP products should be derived from the patient's blood, given that platelet concentrations vary between individuals and even between samples taken from the same patient under different conditions [202], making commercialisation of such technology even more complicated.

6.3 Delivery of biological molecules – Genes

Gene delivery systems, which utilise the action of transfecting mRNA sequences into cells to genetically alter their DNA and induce expression, upregulation or downregulation of proteins, have also been proposed as injectable tendon therapy systems [203]. Preclinical studies have demonstrated the potential for gene therapy in tendon and ligament repair. Collagen hydrogels loaded with TGF-β adenovirus have been shown to transduce invading endogenous cells in both *in vitro* and *in vivo* models over a 21 day period, with transduced cells found up to 6mm from the hydrogel / tissue junction, demonstrating its potential for use in the clinic [204]. TGF-β has been used to transduce rat muscle cells for use in the repair of induced tendon injuries, with gene-treated cell grafts leading to almost normal histological appearance, greater mechanical strength and higher presence of collagen I over an 8 week study period, again demonstrating its potential effectiveness for clinical use [205]. Fibromodulin plasmid with micro-bubbles were injected into the Achilles tendon of wild type and fibromodulin deficient mutant mice and burst *in situ* using high intensity ultrasound. High transfection efficiency was achieved up to 19 days and gene expression was detectable for over 100 days. Further, the collagen fibril diameter in mutant mice was comparable to that of wild type mice, demonstrating the method's potential effectiveness for delivering gene therapies for degenerative tendon disease treatment [206]. However, mechanical analysis of recovered tendon was not performed to demonstrate therapeutic efficacy. Recent work investigating the use of injectable poly(lactic-co-glycolic acid) (PLGA) nanoparticles to transfect intrinsic cells *in vivo* with TGF-β in a chicken foot induced defect model demonstrated sustained delivery for over a 4 week period, leading to a small, but significant reduction in adhesion formation. However a large significant reduction in tendon mechanical properties was recorded [207], demonstrating that while some aspects of tendon healing can be improved by using this method, further work is needed to enable overall therapeutic benefits. Although gene therapy has great potential in difficult to cure injuries and degenerative conditions (e.g. spinal cord injury, Alzheimer's disease, arthritis), gene transfer is associated with potent host inflammatory and immune responses [208, 209] and therefore its clinical potential for small, non-life threating tendon injuries (e.g. tennis elbow) is questionable [210].

6.4 Delivery of viable cell populations

The limited regenerative capacity of tendons has been attributed to the low activity and low reparative potential of the resident cells [1, 109, 110, 112]. Further, permanently differentiated and stem cell populations act as a *biological factory* [1] of a spectrum of bioactive and biotrophic molecules that regulate several physiological processes [211-213]. Thus, delivery of cells is clearly more beneficial than any single or even dual biological molecule delivery strategy, which has little chance of commercialisation, given the complexity of the system. To this end, direct cell injections were pioneered, with positive results in equine patients [44, 214], even with low number of cells [215-217]. However, direct cell injections have failed to deliver in a consistent manner in humans due to poor cell localisation [218-221], triggering an extensive investigation into the optimal cell carrier for tendon repair [1]. The ideal carrier system should prevent cell membrane rupture during the injection process; create increased tissue integration through fast *in situ* self-assembly; facilitate long-term cell survival and functionality maintenance; and allow spatiotemporal release of the cargo [222-231]. Preclinical data using either collagen [232] or fibrin [233] hydrogels have demonstrated improved mechanical properties, histological scores, tissue integration and restored functionality using TCs and various stem cell populations [234, 235], however clinical use of injectable cell/hydrogel systems is still to be realised.

Biologically informed advancements in chemistry have made available stimuli responsive polymers that can controllably react to environmental stimuli, such as temperature, pH, enzymes, affinity ligands, oxidative stress, magnetic / electric fields, mechanical loading [236, 237] and release their cargo. Matrix metalloproteinase (MMP) [238-240] or mechanical stimuli [241] responsive polymers are expected to pioneer tendon therapies in the years to come due to their sensitivity / specificity to the local tissue microenvironment. For example, MMP activity is increased in tendon rupture and overuse [242-244] and therefore can be used as a trigger for the stimuli-responsive carrier to release its cargo.

7. Surgical approaches for large tendon injuries

When tendon injuries are associated with large defects, implantable devices with sufficient mechanical resilience are required to bridge the gap. To this end, tissue grafts and three-dimensional natural or synthetic in origin scaffolds, that closely imitate native tendon architecture, are at the forefront of scientific and technological research and development. Before though we are in position to develop a suitable implantable device with adequate mechanical properties, it is essential to understand the mechanical properties of the native tissue.

7.1 Mechanical properties of tendon tissue

The primary function of tendons is linking and transmitting forces generated by muscle to bone, in order to mobilise and stabilise the joints that they cross. Tendons exhibit viscoelastic and plastic properties, both essential in transmitting muscle-contraction-induced tensile strains into movements, whilst maintaining structural integrity [245-247]. The collagenous network is considered to be the main load-bearing structure, through intra- and inter- molecular cross-links between the adjacent helical molecules [248-252]. Non-collagenous macromolecules are also important, but to a lesser extent [253, 254]. For example, the viscoelastic properties of elastin and presence of proteoglycans allow tendons withstanding compressive and tensile forces [255, 256].

The deformation mechanism of tendons is similar to those of crystalline polymers that yield and undergo plastic flow [257-265]. The yielding mechanism involves some form of flow, such as inter-fibrillar slippage, which is crucial in the tensile deformation of tendons [266, 267]. During loading of collagen molecules, fibrils, and fibril bundles deform and finally fail by a process termed defibrillation. Up to a strain of 2% (toe region), stretching of the triple helix is the predominant mechanism of deformation [268-271] and corresponds to the gradual removal of a macroscopic crimp in the collagen fibrils [272-281]. This macroscopic crimp has been characterised as the shock absorber of tendons that permits non-damaging longitudinal elongation of fibrils within the tissue [261, 282]. At strains beyond 2% strain, the low modulus of the toe region gives rise to the non-linear heel region, during which reorientation and un-crimping of the collagen fibrils and stretching of the triple helix, the non-helical ends and the cross-links takes place [269, 271, 283]. When collagen is stretched beyond the heel region, no further extension is possible [259, 270, 284, 285], the wavy pattern is now straightened and cross-links and fibrils start breaking [261]. To-date, advances in chemistry and engineering have made available numerous polymers, cross-linking systems and scaffold fabrication technologies that closely imitate the biomechanical properties of native tendons (**Table 3**).

7.2 Tissue grafts – The top-down approach for tendon repair

The current gold standard in clinical practice for large tendon defects is autologous, allogeneic or xenogeneic in nature tissue grafts [2, 3]. The choice of the site from which an autograft will be harvested depends on tissue accessibility and availability; on the physical dimensions and mechanical properties of the donor tissue; and on the extent of site morbidity that will be induced [286, 287]. The use of autografts in clinical setting has been strongly supported by superior functional results [288, 289]. Nonetheless, availability issues and the unavoidable site morbidity that will only partially improve the properties of the originally injured tendon tissue [290-293] pushed the field towards allogeneic [294-298] alternatives. Clinical data indicated no functional difference between autograft and allograft intervention in ACL repair [299-301]; however MRI analysis favoured the autograft, as allograft intervention brought about a less mature neotissue [302]. The use of autografts in ACL reconstruction has been further reinforced with recent data indicating that allografts are almost 6.7 times more likely to fail, when compared to autografts [303]. Further, it has been suggested that mismatch in age, activity and body weight between donor and recipient may be crucial factors in the failure of allografts for ACL reconstruction [304]. In addition, the use of allografts is further limited by their higher overall surgical costs; approximately US$ 1,000 extra per clinical case [305, 306]. For these reasons, the use of xenografts took off, with numerous products currently available [307, 308]. Although positive functional scores and improved movement as early as 6 months post-operation have been reported [309], many studies have demonstrated high failure rates and tearing incidents [310-313], which may be attributed to processing conditions (e.g. decellularisation, cross-linking, sterilisation) employed to battle immune rejection, which remains the major obstacle for both allogeneic [314, 315] and xenogeneic [316] approaches.

Significant advancements in chemistry and biology, combined with the inherent capacity of tissue grafts to closely imitate the native tissue composition and architecture, it is likely to yield a functional therapy in years to come. For example, in a canine model, HA functionalised allografts demonstrated significant reduction in adhesions, without any negative effect in cellularity and mechanical properties [317, 318], whilst HA pre-treatment in a rabbit ACL model demonstrated mechanical integrity maintenance and improved healing [319]. Separate studies investigating the effect of the addition of HA molecules to the surface of allografts in canine models found that adhesions to surrounding tissue, were reduced when HA was used 6 weeks post-surgery, and that HA had no effect on the cellularity of tissues after removal or overall tissue mechanical properties [317, 318]. This has been confirmed in the rabbit model [319]. Gene delivery has also been investigated using GDF-5 (BMP-14) loaded freeze dried allograft tissues, finding that adhesions can

be reduced and fibril alignment improved in a murine Achilles model over control tendon grafts [320], however gene functionalised grafts have not been translated to the clinic as yet.

Functionalisation of allografts with autologous cells has also reached preclinical assessment. *In vitro* studies demonstrate that tendon grafts support the growth of human ADSCs for up to 14 days in culture, resulting in increased tensile strength and collagen density [297]. Further studies demonstrated that mechanical stimulation of TC recellularised rabbit flexor tendons resulted in increased ultimate tensile strength and elastic modulus of the graft tissues after 4 weeks *in vivo* [321]. Sectioned canine decellularised tendons stacked into layers and loaded with bone marrow stem cells (BMSCs) increased expression of tendon specific markers [322]. However the mechanical properties of these structures were not influenced by the addition of cells, possibly due to the static conditions the graft composites were cultured in.

Studies assessing the recellularisation potential of BMSCs, ADSCs, TCs and sheath fibroblasts indicated that prolonged culture time (6 weeks) was required for recellularisation of tissue grafts [323]. Indeed, harsh cross-linking methods, employed to control the immunogenicity of the device, create a compact structure and are often associated with foreign body response, compromising healing. Thus, biomaterial-based approaches are under investigation, as they provide the opportunity to treat tendon injuries, whilst avoiding morbidity and availability issues encountered with autografts and potential disease transmission associated with allografts and xenografts.

7.3 Sutures and screws

Absorbable sutures are too weak to provide sufficient mechanical resilience [324]; thus non-absorbable suture are the primary surgical repair option for tendon repair [325] and are the only option in cases involving the flexor tendons of the hand [326]. To-date, numerous suture techniques have been adopted for tendon repair, including lateral trap, end-wave, locking, grasping, Bunnell, Mason-Allen and modified Kessler [324, 326, 327], with the modified Kessler being the most popular. Commonly used materials for suturing tendons include stainless steel, catgut, polypropylene, polyethylene, polyesters, nylon, silicone, silk and collagen coated versions of some of them. These materials are produced either in mono- or multi-filament versions and may or may not be braided [326]. Traditional sutures involve end-to-end repair to bridge the gap at rupture [327]. Multi-strand (primarily four-strand [328]) locking configuration are extensively used in clinical practice. Although locking loops prevent sutures from pulling, they are often associated with suture breakage and tendon rupture due to pulling of the suture at the sutured site [329]. Given that knots adversely affect gliding and locking configurations negatively impact on vascularity, barbed sutures have gained more attention as they ensure equal distribution of load throughout the intratendinous suture length [330-334]. Despite the significant work in the field, there is still no gold standard.

Suitable tendon healing will not occur for gaps greater that 5 mm [335, 336]. To this end, improvements in the fixation methods are at the forefront of clinical research to reduce the bone tunnel enlargement for tendon [337, 338] and ligament [339, 340]. Interferential screws, bioabsorbable or metalling in origin [341], are considered as the gold standard for tendon-to-bone fixation and for ligament reconstruction [342-344]. However, recent data demonstrate viscoelastic deformation, which causes widening of the bone tunnel into which the tendon is inserted, resulting in slippage of the tendon [345]. Primary fixation is employed to act as an interlock between the screw and the graft [346]. Recent data demonstrate improved strength fixation by as much as 30% by simply ensuring that the screw is shorter than the graft [337, 347]. Nonetheless, numerous complications and adverse effects have been reported in clinical setting (e.g. intra-operative fracture, intra-articular complications, extra-articular abscesses) [348], clearly indicating that further research is necessary to elucidate the underlying mechanisms of tendon-to-bone healing and to translate safe and therapeutic interventions [349].

7.4 Bottom-up approached for tendon repair based on natural in origin scaffolds

To-date, numerous biopolymers have been assessed for tendon repair, with variable degree of efficacy. Among them, collagen-based devices, in many physical forms (e.g. sponges, films, fibres), appear to be the favourite raw material [124, 127]. Advancements in engineering, chemistry and biology have made available numerous technologies that allow fabrication of hierarchical three-dimensional scaffolds that closely imitate native tendon architectural features and mechanical properties, whilst enabling localised and sustained delivery of therapeutics [350]. Collagen sponges, for example, with or without aligned tracks and loaded with GAGs, growth factors and various cell populations have demonstrated enhanced cell motility and phenotype maintenance *in vitro* and increased collagen expression levels in small animal models [351-355]. However, such scaffold conformations cannot provide adequate mechanical resistance, in such a high mechanical demand environment [356]. Using a wet extrusion system, micro-scale collagen fibres (**Figure 3**) were first produced in late 1970's and since then numerous papers have demonstrated that this process gives rise to fibres with ultrastructure characteristics, physical and mechanical properties similar to native tendon [257, 259, 357-359]. Further *in vitro* analysis demonstrated that such materials, largely attributed to their surface features, not only facilitate bidirectional cell alignment, but also maintain tenogenic phenotype *in vitro* [360]. Further, preclinical experimentation in peripheral nerve repair and in tendon small and large animal models enhanced the clinical potential of these fibres, as judged by improved structural alignment and biomechanics [361-363]. Using an isoelectric focusing setup, aligned collagen fibres have been produced with ultrastructural characteristics and physical properties similar to native tendon [364, 365]. Of significant importance are *in vitro* data that have been obtained using these materials. When their potential for spinal cord injuries was assessed, it became apparent that such materials not only promote directional neurite guidance, but also overcome inhibition by myelin associated glycoprotein [366]. In a tendon setting, these collagen fibres have been shown to promote bidirectional alignment and migration of tendon derived cells and to differentiate human BMSCs towards tenogenic lineage, even in the absence of biological signals [367, 368]. Combinations of fibrous scaffolds that offer mechanical resilience and hydrogels systems that offer cell retention capacity have demonstrated improved biomechanics and functionality in preclinical models [369, 370]. Whether such systems will reach the clinic, remains to be seen, given the notable lack of extensive *in vivo* data. Further, appropriate regulatory framework should be implemented to allow such systems to enter the clinic.

Silk-based sutures have been extensively used to treat ruptured tendon due to their high mechanical properties and excellent biodegradability [371-375]. *In vitro* data have demonstrated that silk-based scaffolds support adherence, expansion and differentiation of human BMSCs towards tenogenic lineage, as assessed by the expression levels of collagen types I and III and tenascin-C [376]. Silk

fibres functionalised with peptide moieties [377], HA [378] and chondroitin sulphate / collagen [379] have been shown to maintain tendon function *in vitro*, to increase blood vessel formation and cellular infiltration, to promote formation for dense collagen fibres and to encourage overall tendon healing over control counterparts in a canine patellar tendon defect model and to a rabbit cruciate ligament defect model. Mechanical loading of aligned silk scaffolds loaded with BMSCs resulted in increased production of collagen type I, collagen type III and tenascin C, when compared to not aligned and not mechanically stimulated counterparts [380]. Further large animal model studies have demonstrated that silk / BMSCs composites induced functional ACL replacement, with silk degrading in a similar rate as the neotissue was formed [381]. However, complete replacement based on silk did not yield a functional therapy [382], which, in addition to the concerns of allergic reaction, have restricted its use in regenerative medicine [373]. To a smaller extent, chitosan / alginate composites have been assessed for tendon repair, with *in vitro* data demonstrating adherence of rabbit tendon fibroblast and increased collagen type I expression and mechanical properties [383]. Preclinical data of chitosan and chitosan / HA scaffolds have demonstrated enhanced tissue-specific ECM production and improved mechanical strength, as compared to the control treatments [384-387]. Polyhydroxyalkanoates, natural polymers produced by bacteria, have also shown great potential in tissue engineering [388]. Specifically to tendon repair, such materials have shown improved mechanical properties, improved functionality and minimal inflammatory response in small animal studies over 40 days implantation in an Achilles defect model [389]. The batch-to-batch variability of natural biomaterials and their susceptibility to various sterilisation methods [390] have triggered investigation into the potential of synthetic biomaterials for tendon repair and regeneration.

7.5 Bottom-up approached for tendon repair based on synthetic in origin scaffolds

Absorbable and not absorbable synthetic materials are used extensively in tendon repair, as they can be produced reproducibly with structural, physical and mechanical properties similar to the tissue to be replaced [391]. Unfortunately, non-degradable devices have failed to deliver functional repair. A polyester-based device, for example, although it has been used extensively in clinical practice, clinical data demonstrate inferior to tissue grafts repair that is often associated with laxity in joints, engraftment tunnel enlarging and, in some cases, complete rupture [392-394]. Similarly, although polypropylene-based devices have demonstrated superior mechanical properties to control treatments, histological evaluation revealed poor tissue integration, evidenced by the formation of a disordered fibrous capsule [395]. Dacron (polyethylene terephthalate) prosthesis, although it has demonstrated acceptable mechanical properties, functional regeneration and neotissue formation was not achieved [396, 397]; however HA / chitosan coating demonstrated good histological scores in a rabbit articular tendon model [398]. Carbon fibres have exhibited clinically acceptable mechanical and structural properties, promoted extrinsic and intrinsic cellular activity and ultimately a functional neotissue formation, leading to long-term tissue integration and healing [399, 400]. However, the potential side effects of carbon have limited their further development [401-403]. These results gave rise to degradable-based substitutes for tendon repair.

Among the manifold polymers, PLGA based scaffolds have been extensively assessed in tendon repair. With respect to fabrication methods, electro-spinning (**Figure 4**) appears to be the method of choice, as aligned nano- to micro-fibrous scaffolds can be produced with mechanical and structural features similar to the tissue to be replaced and with ability to control permanently differentiated and stem cell fate *in vitro*; to locally deliver in a controlled manner pharmacological agents, biological molecules and cells at the side of injury; and to enhance directional neotissue formation [404-409]. Although electro-spun collagen scaffolds have demonstrated improved neotissue alignment and mechanical properties, over control counterparts in a rabbit Achilles tendon model [410] the realisation that the use of fluoro-alcohols denatures the triple helical confirmation of collagen [411, 412] has reduced further investigations.

Although tendon-like tissues have been generated *in vitro* using TCs grown on PLGA electro-spun fibres, the *de novo* formed tissue was found to be significantly thinner and weaker than a natural tendon control [413]. However, mechanical stimulation of human foetal extensor tendon TCs loaded on electro-spun PLGA fibres promoted collagen alignment, produced a more mature collagen structure and created a stronger *de novo* tissue [414], suggesting that mechanical stimulation might be an optimal *in vitro* niche for engineering functional tendon equivalents *ex vivo*. Porcine dermal fibroblasts and TCs loaded on PLGA electro-spun fibres have been shown to promote tenogenic function *in vitro* and improved healing, as evidenced by improved gross

morphology, histological analysis and biomechanical properties, *in vivo* [413-416]. In conjugation with BMSCs, electro-spun PLGA scaffolds have demonstrated suppression of lymphocytes *in vitro* and improved biomechanical properties and acceptable integration into the native tendon tissue [417]. GDF-5 loaded PLGA electro-spun scaffolds supported growth and promoted tenogenic differentiation of rat ADSCs [418]. Further *in vitro* studies using bFGF loaded PLGA electro-spun scaffolds have demonstrated enhanced BMSC proliferation and tendon differentiation, as evidenced by increased expression collagen type I and tenascin-C [419], whilst *in vivo* studies have shown greater vascularisation, higher histological scores and superior mechanical properties to naturally healed and non-functionalised counterparts [420]. A more complex approach based on PLGA electro-spun scaffold and a fibrin gel loaded with ADSCs and PDGF-*ββ* demonstrated improved healing over standard controls [421]. Electro-spun poly-*ε*-caprolactone (PCL) scaffolds coated with tendon-derived ECM promoted ADSC attachment, homogeneous distribution within the scaffolds and expression of tendon specific markers [422]. Functionalisation using HA has enabled integration of PCL electro-spun scaffolds into a chicken foot tendon model, whilst preventing post-surgical adhesions [423].

Lithography-based technologies have also been used as means to produce anisotropic substrates for tendon repair (**Figure 5**). Such micro-grooved substrates have been shown to maintain TC phenotype *in vitro*, as indicated by collagen type I and tenomodulin expression; most importantly, these micro-grooved substrates were shown to recapitulate the lost tenogenic phenotype of TCs [424]. Given the literally unlimited number of possible topographies, a recent study developed imprinted substrates using tendon slices as template; the produced substrates, following collagen type I coating, supported tenogenic differentiation of BMSCs [425]. To-date, there is no *in vivo* work of such substrates in a tendon model.

Despite the huge progress that has been achieved to-date, synthetic materials are yet to meet the requirements for functional tendon tissue remodelling [426]. The use of PLGA and PCL has been problematic, with *in vitro* data showing poor tendon cell adhesion, reduced proliferation rate and phenotypic drift [360, 427]; with preclinical *in vivo* data showing poor cellular infiltration and mechanical properties compared to controls [428]; and with clinical evaluations showing problems with cell lysis, anchor failure, macrophage stimulation and allergic responses [429, 430]. This high failure rate has been attributed to their hydrophobic nature and their lack of cell recognition signals that prevents cell attachment [391, 431-434]. To this end, scaffold-free therapies based on the principles of tissue engineering by self-assembly / cell-sheet technology are slowly, but surely, gaining more scientific and technological interest.

7.6 Tissue engineering by self-assembly therapies

Tissue engineering by self-assembly or cell-sheet tissue engineering has been extensively studied over the years for various clinical targets [435-439]. The rationale of this approach is based on the fact that cells can create their own tissue-specific ECM, bypassing the need for artificial devices and their shortfalls. The first *in vitro* study demonstrated that such cellular assemblies resemble the nonlinear behaviour of immature tendons [440]. Using rat TSCs, a neotendon tissue was formed that after eight weeks in a rat patellar tendon defect model showed marked improvement in histological scores, tissue alignment and mechanical properties, as compared to naturally healed control [441]. Unfortunately, such technologies require prolonged culture time to develop an implantable device with sufficient strength, which is often associated with phenotypic drift and cellular senescence [442]. To this end, the use of cell-sheets combined with biodegradable meshes [443] or tissue grafts [444] has been advocated as means to create a mechanically stable implantable device, with the latter showing better results than the graft or the cells alone intervention in a rabbit model. An alternative strategy that bypasses the use of the carrier systems and their limitations is based on the principles of macromolecular crowding [445-448]. Indeed, the addition of negatively charged macromolecules in the culture media (**Figure 6**), by imitating the naturally crowded *in vivo* context, dramatically accelerates the conversion of procollagen to collagen, resulting in a 30- to 80-fold increase in tissue-specific ECM deposition. Using human TCs, a rich in ECM and cohesive cell-sheet was produced with intact cell-cell and cell-ECM junctions as early as 6 days in culture, without any negative effects in TC functions [449]. Despite these advancements, a complete three-dimensional tendon-equivalent has yet to be developed.

8. Conclusions

It is undeniable that recent advancements in engineering, chemistry and biology have made available numerous technologies that can be utilised for tendon repair and regeneration. Two- and three-dimensional fabrication technologies have realised tissue facsimiles that closely imitate the properties of native tendon tissue, control cellular fate *in vitro* and promote directional neotissue formation *in vivo*. Improved processing, decellularisation and recellularisation strategies reinstate the potential of allogeneic and xenogeneic tissue grafts. Novel chemistries allow for localised and sustained delivery of pharmaceuticals, biologics and cells at the side of injury.

However, none of the current therapies restores tendon function to the state prior to injury, as every single therapy has its distinct failure modes, and all fail to closely match the native tendon biomechanics over prolonged period of time *in vivo*. Further, knot improving and stress relieving mounting strategies should be developed to enhance functional regeneration. Strategies that provide continuous and sufficient mechanical properties and gradients of stress distributions from bone attachment surfaces, seen in native ligaments, will likely offer decreased failure rates.

It is also imperative to understand the *in vivo* milieu prior to injury and the biological events that take place thereafter. Only then we will be in position to develop clinically relevant carrier systems loaded with efficacious pharmaceuticals / biologics and sufficient density of suitable viable cells that will effectively interact with the host and promote functional tendon repair, remodelling and regeneration, avoiding scar and foreign body responses are also likely to succeed.

Overall, systems that will provide sufficient mechanical integrity, biological / biochemical cues and suitable cell types will continue to be at the forefront of academic, industrial and clinical research, promising to deliver functional regeneration through rehabilitation in the years to come.

9. Acknowledgements

The authors would like to thank Maciek Doczyk for the preparation of the graphical abstract, Figure 1 and Figure 5. This work is supported by the: EU FP7/2007-2013, Marie Curie, IAPP award, part of the People programme, Tendon Regeneration Project (Grant Agreement Number: 251385) to D.Z.; EU FP7/2007-2013, NMP award, Green Nano Mesh Project (Grant Agreement Number: 263289) to D.Z.; Science Foundation Ireland (Project Number: SFI_09-RFP-ENM2483) to D.Z.; Health Research Board, Health Research Awards Programme, under the grant agreement number HRA_POR/2011/84 to D.Z.; Enterprise Ireland, Collaborative Centre for Applied Nanotechnology (Project No: CCIRP-2007-CCAN-0509), under the Irish Government's National Development Plan 2007-2013 to D.Z.; Teagasc, Department of Agriculture, Food and Marine, FIRM / RSF / CoFORD (Project Number: 11-F-043) to D.Z. We thank NW Tex Net for hosting C.N.M.R and Vornia Biomaterials for hosting D.Z.

10. Tables

Table 1: Common injuries presented in human and equine subjects, provided along with current treatment strategies and respective limitations.

Species	Tendon Injury	Treatment	Limitation	Ref
Human	Hand extensor / flexor tendon	Immobilisation (splint)	Scar tissue leads to loss / reduction of motion. Joint stiffness is often experienced.	[28, 450, 451]
		Steroid injection	Serious doubts over effectiveness.	
		Open Surgery: Kessler stitch	Re-rupture rate following surgery is as high as 4 to 18% worldwide.	
	Achilles tendon (rupture)	Cast immobilisation	Susceptible to re-rupture at a rate of about 11%.	[23, 452, 453]
		Functional cast	Low re-rupture rate of 1-2%, but high complication rate of 12.5%.	
		Open Surgery: Kessler stitch	High re-rupture rate of 8% and nerve injury of 13%.	
		Tissue grafts	Failures seen at tissue intersect points.	
		Biomaterial repair	Inadequate mechanical strength and foreign body response.	
	Rotator cuff (tear)	Steroid injection	Up to 40% failure rates have been reported.	[2, 454-458]

		Open surgery: Decompression and debridement	Often associated with deltoid dysfunction and postoperative pain.	
		Biomaterial repair	Inadequate mechanical strength and foreign body response.	
	Patellar tendon (tear)	End-to-end suture	10 out of the 13 repairs are effective.	[459]
		Tissue grafts	Limited availability, pain at donor site.	
	ACL (rupture)	Tissue grafts	Up to 13% re-rupture rate.	[460]
Equine	Superficial digital flexor tendon injury	Cold therapy & compression bandaging	23 to 67% will re-injure their tendons within 2 years of the original injury.	[43, 46]
		Immobilisation (splint)	Associated with stiffness and fibrosis.	
		Autologous cell therapy	Questionable cell survival / localisation.	[44, 461, 462]
	Deep digital flexor tendon injury	Conservative treatment (rest and reduced activity)	Return to exercise is not recommended.	[51, 52]
	Digital extensor tendon laceration	Three-loop pulley tenorrhaphy technique	Adhesions and septic tenosynovitis are common complications.	[54]
	Suspensory ligament	Conservative treatment (rest and reduced activity)	Return to exercise is not recommended for several months.	[463, 464]

		Shock wave therapy	Evidence of disorganised tissue. Not suitable in severe cases.	[465, 466]
		PRP treatment	No standardised treatment protocol.	[467-469]

Table 2: Cellular composition and characteristics of tendon tissue.

Healing Mechanism	Cell Population	Location	Morphology	Dimensions (μm)	Ref
Intrinsic Healing	**Tenocytes**	Throughout tendon, surrounding collagen fibrils	Elongated, spindle shape	Width: 8 – 20 Length: < 300	[470]
	Tenoblasts	Throughout tendon, surrounding collagen fibrils	Polygonal	Width: 8 – 20 Length: 20 – 70	[62]
	Tendon stem cells	Throughout tendon	Species, tendon, development stage dependent morphology (e.g. cobblestone, square, round, spindle)	Width: 20 – 30 Length: 20 – 30	[65, 66, 471]
Extrinsic Healing	**Chondrocytes**	Close to bone junction	Polygonal	Width: 10 – 15 Length: 10 – 15	[472]
	Vascular endothelial cells	Surrounding vascular network	Cobblestone / square	Width: 8 – 12 Length: 8 – 12	[473]
	Synovial cells	Tendon sheath	Elongated, with extended cytoplasmic projections	Width: 10 – 50 Length: ≤ 200	[474, 475]
	Smooth muscle cells	Musculotendon junction, internal and external tendon capillaries	Cobblestone / square	Width: 20 – 30 Length: 20 – 30	[64, 476]
	Perivascular cells	In the walls of internal and external tendon capillaries	Elongated, spindle shape	Width: ≤ 50 Length: ≤ 300	[68, 69]
	Mesenchymal stem	Migrate from surrounding tissues,	Elongated, spindle shape	Width: 10 – 20	[70, 477]

	cells	especially bone marrow		Length: 100 – 300	
	Adipose derived stem cells	Surrounding fat pads	Elongated, spindle shape	Width: 10 – 20 Length: 100 – 300	[72]

Table 3: Mechanical properties of native tendon tissues and tendon substitutes

Tissue / Biomaterial	Stress (MPa)	Strain (%)	Modulus (MPa)	Reference
Equine digital flexor / extensor	65 – 160	12 – 22	613 – 1220	[478-480]
Human Achilles	29 – 86	4 – 22	1.9 – 822	[481-483]
Human rotator	14 – 45	1 – 11	14 – 629	[484-486]
Human patellar	5 – 65	5 – 15	1500 – 1800	[487, 488]
Human Achilles graft	16	1	201	[489]
Human patellar graft	26 – 95	13 – 31	191 – 660	[490]
Human tibialis graft	81 – 105	13 – 40	1 – 905	[491-493]
Collagen-based materials	1 – 355	1 – 60	3 – 4272	[257, 359, 494-497]
Silk-based materials	500 – 972	4 – 20		[373]
Synthetic micro-fibres	435 – 840	22 – 45		[498]
Synthetic nano-fibres	1 – 474	1 – 11	2 – 14	[171, 410, 422, 499-502]

11. Figures

Graphical Abstract: Injectable systems, anisotropic materials and tissue engineering by self-assembly therapies for human and equine injuries.

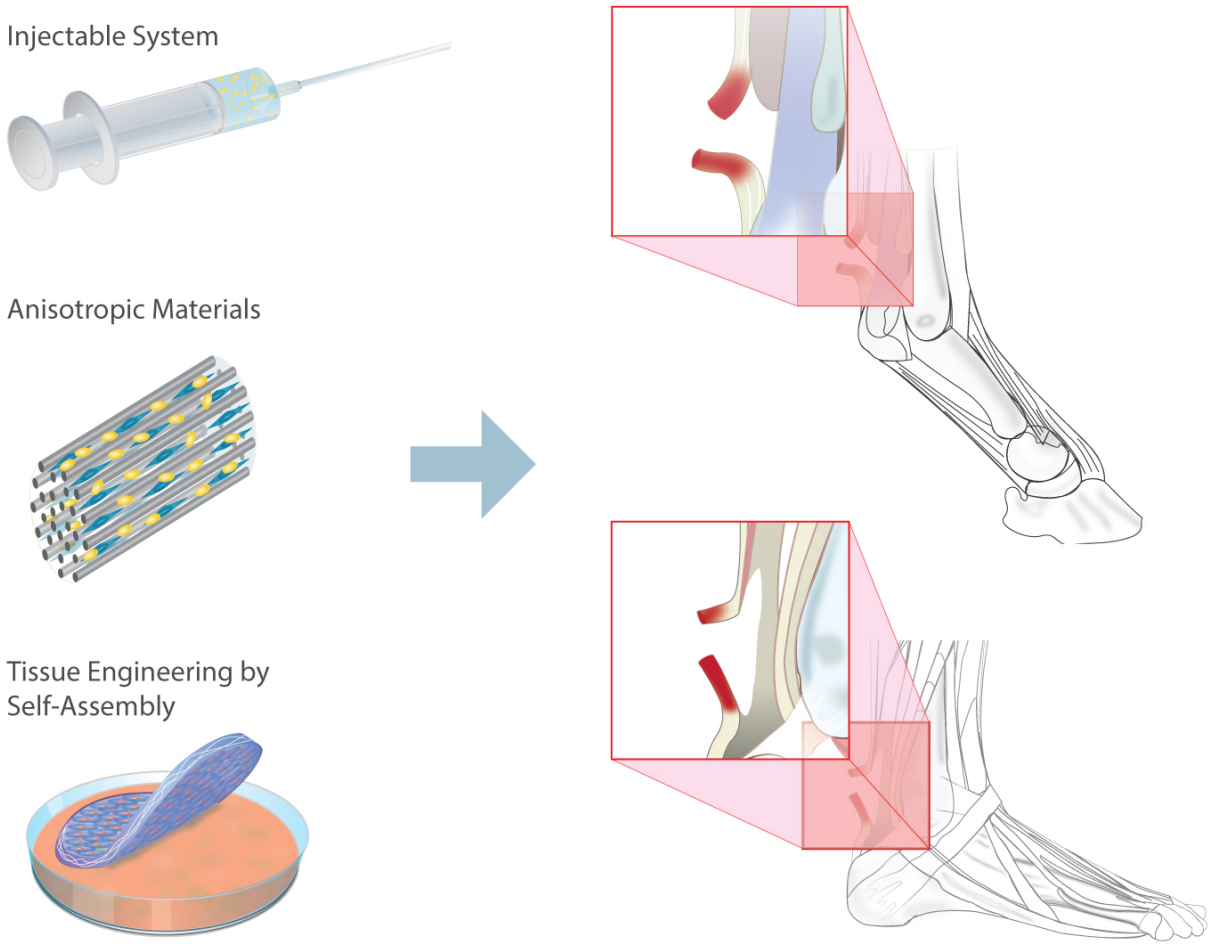


Figure 1: Spatial distribution of cellular and matrix components in tendons.

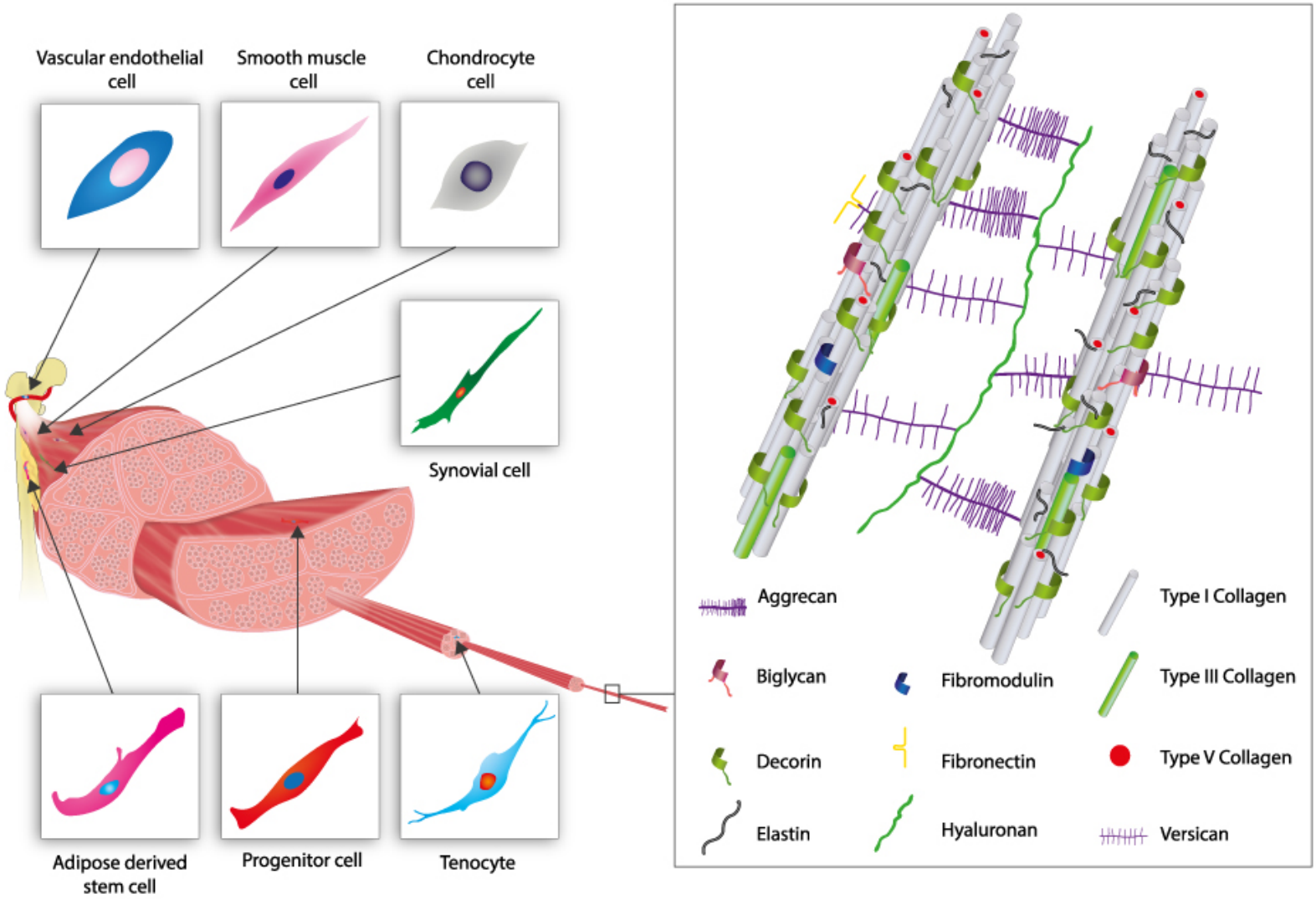


Figure 2: The three phases of tendon healing (inflammation, repair, remodelling) and associated events, as a function of time, and the respective functional performance of the tendon. The repaired tendon will never achieve complete recovery to the state prior to injury.

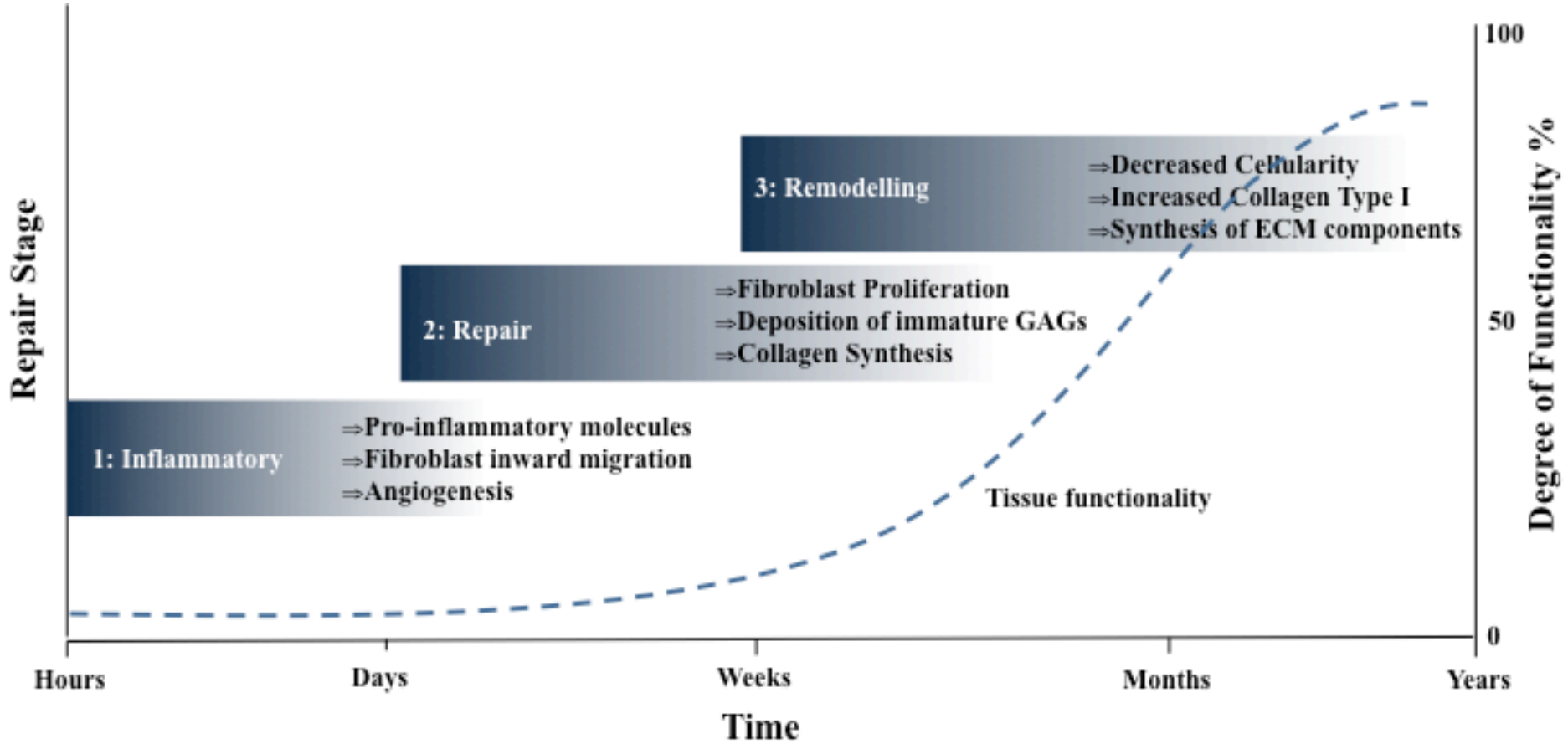


Figure 3: Transmission electron microscopy revealed that extruded collagen fibres exhibit the characteristic quarter-staggered periodicity of collagen, in addition to a high order axial alignment, parallel to the fibre axis (a). This axial alignment is responsible for undulation and crevices that run parallel to the longitudinal axis of the fibre (b). These surface characteristics induce parallel to the fibre axis tenocyte elongation as early as 24h in culture (c). A fibre bundle, suitable for tendon repair, is formed, when several fibres are put together (d).

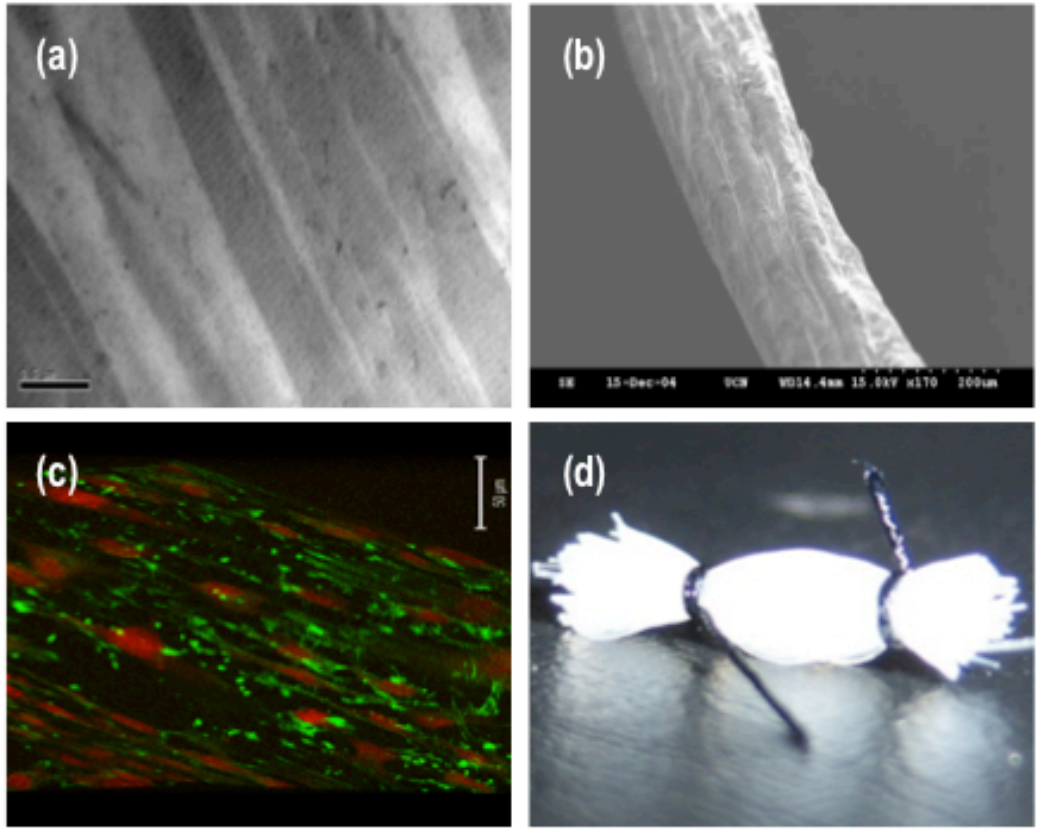


Figure 4: Using a rotating collector, aligned electro-spun fibres can be produced (a). This anisotropic topography maintains the physiological elongated tenocyte morphology in culture (b). Such materials can be used as tendon sheaths (c) or, when rolled, as a full tendon replacement device.

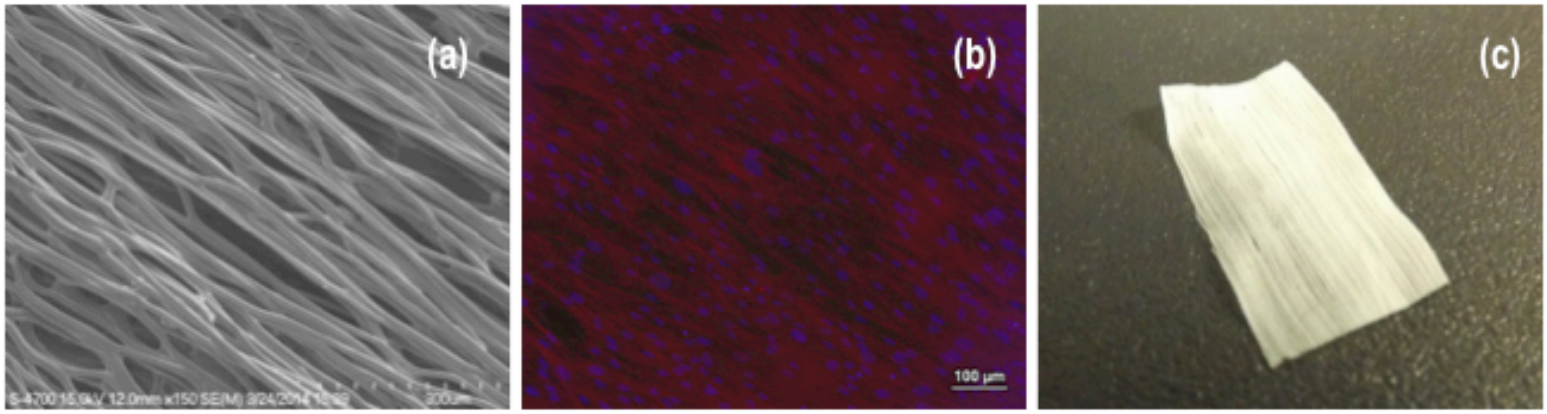


Figure 5: Using imprinting technologies, substrates with precise topographical features, ranging from nano- to micro level, can be created (a and b). Among them, anisotropic substrates (c) have been shown to maintain physiological TC morphology (d).

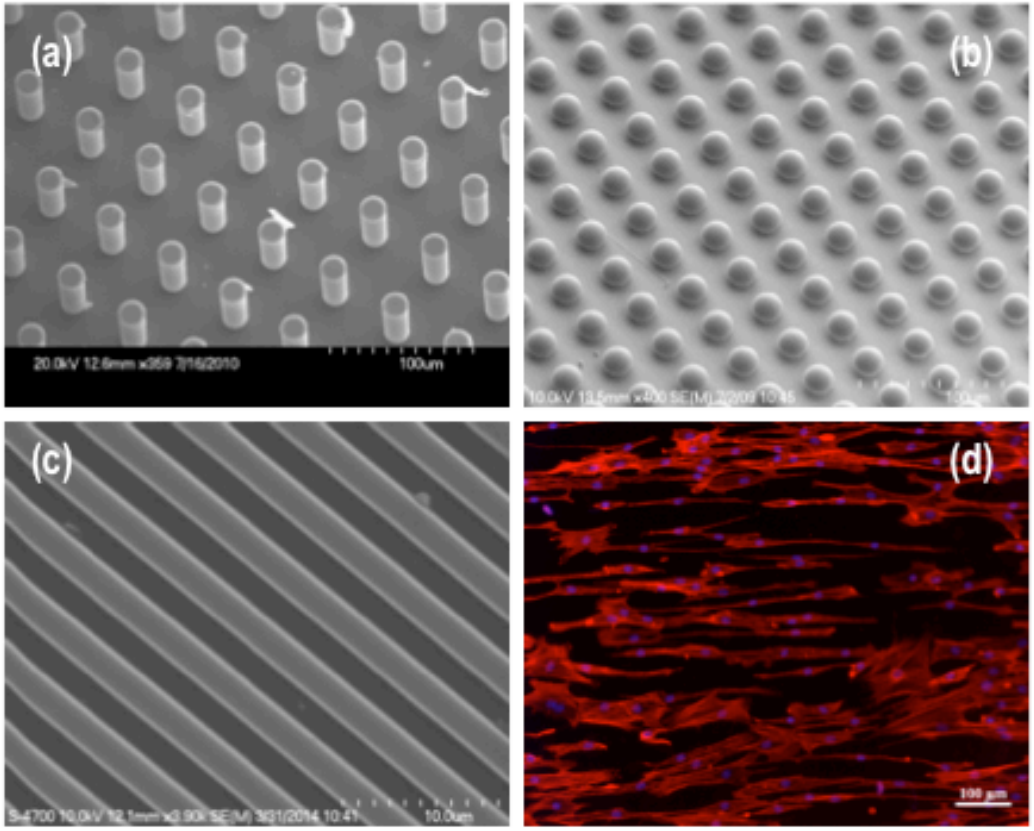
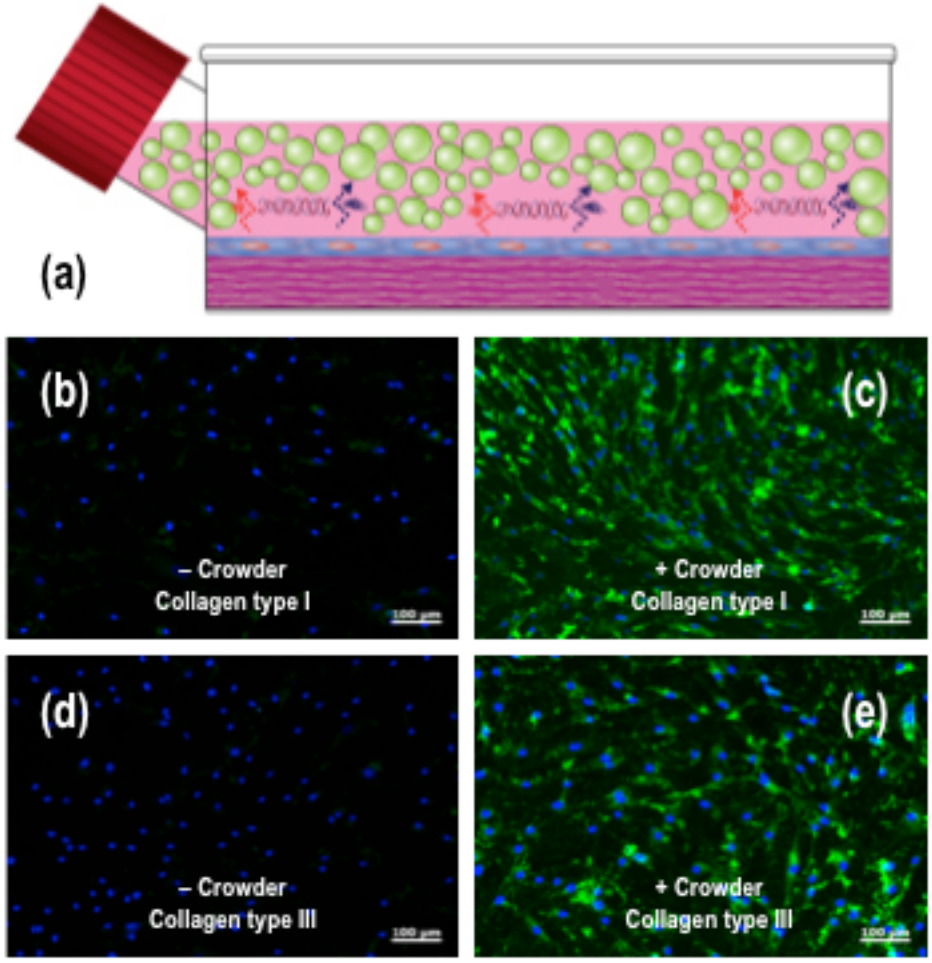


Figure 6: Macromolecular crowding, the addition of inert macromolecules in the culture media, dramatically accelerates the conversion of procollagen to collagen and the production of a rich in ECM cell layer (a). In tenocyte culture, among others, significant increase in collagen type I (c) and collagen type III (e) deposition has been observed, as compared to the non-crowded counterparts (b and d respectively).



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