**Current Strategies in Meniscal Regeneration**

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**Abstract**

The meniscus plays an important role in the biomechanics and tribology of the knee joint. Damage to or disease of the meniscus is now recognised to predispose to the development of osteoarthritis. Treatment of meniscal injury through arthroscopic surgery has become one of the most common orthopaedic surgical procedures, and in the United States this can represent 10-20% of procedures related to the knee. The meniscus has a limited healing capacity constrained to the vascularised periphery and therefore, surgical repair of the avascular regions is not always feasible. Replacement and repair of the meniscus to treat injuries is being investigated using tissue engineering strategies. Promising as these approaches may be, there are, however, major barriers to overcome before translation to the clinic.

**Keywords:** Meniscus, Scaffolds, Regenerative medicine, Tissue engineering

**Introduction**

The menisci are a pair of semi-lunar fibrocartilaginous structures found between the femoral condyles and tibial plateau in the knee joint (Fig. 1). They play a central role in the knee including joint stabilization, shock absorption and load transmission.1-3 Meniscal injury from both athletic events and activities of daily living is common and often requires surgical intervention. Treatment of meniscal injury through arthroscopic surgery has become one of the most common orthopaedic surgical procedures in the United States, and can represent 10-20% of all procedures.4 Until recently total meniscectomy was used to treat meniscal injury. However, understanding that this results in supra-physiological stress on the articular cartilage, which can lead to knee damage and osteoarthritis, has led to efforts in devising alternative treatments that avoid meniscectomy.5,6 The meniscus does have an inherent ability to heal itself, but this is limited to the vascularised periphery.7 Any damage suffered to the internal avascular regions is not repaired intrinsically, leading to further deterioration over time. Therefore, alternative approaches are needed to facilitate meniscal repair and/or replacement. Tissue engineering strategies which aim to regenerate menisci offer a potential solution, however there has been limited progress in this field in comparison to other orthopaedic tissues. The aim of this review is to provide an overview of the meniscus and outline the challenges faced by those investigating potential therapies for meniscal regeneration.

**Meniscus Structure and Function**

Like other tissues, the most abundant component of the menisci is water, constituting 70% of the total wet weight,8 with the remaining 30% composed of organic matter. Of this collagen accounts for 75% with proteoglycans, cells and adhesion glycoproteins forming the other 25%.2,9,10 Approximately 90% of the collagen present in the menisci is collagen Type I.11 A major Type II collagen network is also present in the menisci; however this network is not as extensive as the hybrid network found in articular cartilage that incorporates the proteoglycan aggrecan.12,13 Types III, IV, V and VI collagen have also been shown to be present in the menisci but are minor components.12,13

The collagen in the meniscus is organized into three distinct layers: superficial, lamellar and deep (Fig. 2), and is covered in a thin layer of synovium. The collagen matrix in these layers is highly structured and imparts the necessary characteristics required to aid the menisci in withstanding the forces acting on them. Fibers in the superficial layer show no specific orientation and this is also true for fibers in the lamellar layer, noting the exception of radially oriented fibers in the anterior and posterior sections.14-16 The fibers in the bulk of the meniscus in the outer deep portion mainly exhibit a circumferential orientation14,17 along with a few radial fibers which begin at the periphery of the meniscus and travel into the central portion.2,16,18 The inner region is composed mainly of collagen II and has a high GAG content compared to the rest of the meniscus. This region most resembles hyaline cartilage, mainly dealing with compressive forces. The outer portion is more fibrous and composed almost entirely of continuous collagen I fibers attached at the meniscal horns to the tibial plateau. The circumferentially oriented collagen fibers convert axial load into hoop stresses, dissipating it through the meniscus.19 The meniscus has attachments to the tibial plateau at the meniscal horns, anchoring it in place and resisting radial displacement. The continuous circumferential collagen fibers extend into the tibial plateau through the cartilage layer terminating in the bone to form a dense enthesis.

The first clue to the function of the menisci can be found in their geometry. The wedge shaped structures provide congruity between the tibial plateau and femoral condyles allowing stable articulation and low contact pressures. It has been shown that ~50% of the load through the knee is transmitted through the menisci. The highly organized extracellular matrix imparts the necessary characteristics to deal with these stresses. As ~70% of a meniscus is composed of water, with cells and extracellular matrix constituting the remaining 30%, the menisci are considered as biphasic tissues.20,21 Zhu et al. (1994) demonstrated that it is the interactions between the collagen fibers, negatively charged proteoglycans and water that imparts the biphasic (manifested through time-dependent viscoelastic) properties to the menisci.22 As load is applied to the meniscus, frictional drag forces help limit water flow as water is forced from the extracellular matrix absorbing some of the initial shock.21 Once the load is released the negatively charged sulphate and carboxyl groups on the GAGs attract water back in to rehydrate the tissue.2 Finite element analysis has also revealed that the fluid phase initially appears to support a significant portion of the load23 due to the hydrostatic pressure developed, before further loading leads to transfer of the load from the fluid to the solid phase.21

The meniscus has been described as an anisotropic tissue due to the directional variation in its material properties.2,24 The compressive modulus, a measure of stiffness, and the permeability, a measure of the ease at which fluid flows through a material, are the two properties most reported in the literature. Regional variations exist between the compressive modulus of the anterior, central and posterior regions, with the anterior region exhibiting 58% greater modulus than the posterior.25,26 Values of the order of 0.1 - 0.4 MPa were obtained for the mean aggregate modulus.25-28 Values obtained for the permeability range from 0.8 - 5.6 x 10-15 m4N-1s-1.26,28 Disparity in the results may be due to differing test methods as well as the use of in silico models rather than experimental determination of the permeability (Table 1). Data on the tensile properties of the meniscus is also as variable (Table 2). Again, this may be explained by different test methods being used. Sample geometries used have varied from the typical dumbbell shape, which some argue has no rationale in meniscal testing due the presence of non-continuous collagen fibers in the wider regions,21 to uniform width rectangular specimens. Sample geometry has been shown to play a significant role in the determination of tensile properties due to the heterogeneous nature of the ECM and collagen fibers present in the sample. Again, regional variations exist with the anterior portion exhibiting a higher tensile modulus when compared to central and posterior regions.2,29-33

As mentioned previously, the meniscus is largely avascular. The level of vascularisation decreases with age, in neonates the menisci are completely vascularised and this gradually decreases to ~20% in adulthood. In the adult, the vasculature extends into the meniscus radially from the perimeniscal capillary plexus forming three zones describing the differing levels of vascularisation: red, red-white and white. The hyaline-like inner region, known as the white zone, is avascular; the outer portion is known as the red zone and is vascularised, with the transition zone in between these regions known as the red-white zone. The level of vascularisation determines the healing potential of these regions within the meniscus.

Four morphologically different stromal cell types have been identified in the menisci. In the outer vascularised margin, consisting mainly of fibrocartilage, cells have been shown to have a stellate appearance and numerous long thin cytoplasmic projections.34 Cells present in the deeper fibrocartilaginous region, which is less extensively vascularised, have been shown to have fewer projections, at most one or two and the projections join cells from both these regions into sheets.34 In the avascular hyaline-like region of the menisci, cells have a more rounded morphology and are said to be chondrocyte-like, with no projections.34 The cells in the superficial and lamellar regions have been found to be fibroblast-like with fusiform morphology.34

**Meniscal Injury and Degeneration**

Normal menisci are semi-lunar, fibrocartilage structures. Deviations from this can occur due to disease, degeneration, traumatic injury or abnormal development. It is known that degeneration renders the menisci more prone to injury.35 Osteoarthritis leads to degenerative changes in the menisci as well as the surrounding cartilage, and has been implicated in ~75% of all meniscal tears and extrusions.36,37 Osteoarthritis affects the geometry of menisci, causing thickening of the medial posterior and lateral anterior horns. This in turn can affect the biomechanics of the tissue leading to injury.38 Adams et al. (1983) assessed the glycosaminoglycan (GAG) content of menisci in a beagle model of osteoarthritis.39 One week after induction of osteoarthritis the water content increased as the GAG content decreased. After 15 months the water content had returned to normal and the GAG content had reached elevated levels, suggesting stiffening of the tissue. Radial displacement/extrusion of the meniscus as a result of osteoarthritis leads to joint space narrowing.40

**Injury**

The most common form of meniscal injury is mechanical failure of the tissue due to degeneration or trauma resulting in a tear. Meniscal tears can be categorised into the following types: longitudinal, horizontal, radial, oblique and complex (Fig. 5).41-44 Longitudinal tears occur in a vertical direction and can vary in length from ~1mm to the length of the meniscus (Fig. 5.1).42 A variation of a longitudinal tear is known as the bucket handle tear and these occur when the tear spans the entire thickness of the meniscus, splitting a section mediolaterally (Fig. 5.2).42,43 Horizontal tears develop due to shear stresses generated by inferior and superior sections of the meniscus and are more common in elderly patients (Fig. 5.3).42 Radial tears begin at the inner edge however radial tears extend radially towards the periphery and disrupt the meniscus’ ability to contain hoop stresses (Fig. 5.4).41,42 Oblique tears are similar to radial tears in that they also start at the inner edge of the meniscus however these tears slant inwards (Fig. 5.5), and along with longitudinal tears have been shown to make up 81% of all tears.42 Complex tears are composed of several different tears (Fig. 5.6), associated with degeneration and their incidence has been shown to increase with age.41,42

Meniscal tears can reveal themselves through various symptoms. Common symptoms include pain, a catching sensation, “giving way” and effusion.45 The incidence of meniscal tears has been shown to be approximately 60-70 per 100,000 with 70-80% of tears occurring in males.42,46 Campbell et al. (2001) showed that tears occurred almost twice as often in the medial meniscus compared to the lateral meniscus, with 66% and 34%, respectively.47 The majority of medial meniscal tears have been found to be longitudinal (75%) with horizontal tears (23%) second most common,46 whereas longitudinal tears constituted a smaller proportion of tears in the lateral meniscus (54%) and, oblique (15%) and complex (15%) tears represented similarly large proportions.46 The normal function of the meniscus is reliant on the ligaments of the knee and there is an increase in meniscal injury with ACL deficiency.42,48,49 Although the ACL plays the most important role in stabilising the knee joint, the menisci act as secondary stabilisers.50 Levy et al. (1982) showed that although meniscectomy has no significant impact on stabilisation of normal knee joints, in ACL deficient knees the medial meniscus restricts displacement of the tibia, stabilising the knee joint. It was also suggested that when the ACL is disrupted, displacement of the tibia wedges the medial meniscal horn between the bones and prevents further displacement. Further work on meniscal stabilisation after ACL resection has shown that there is an increase of 197% in the forces within the medial meniscus.48 Moglo and Shirazi-Adl (2002) showed that through to 30° of flexion the medial meniscus is subjected to higher loads and stresses in an ACL-deficient knee,51 indicating that the meniscus is heavily reliant on the ligaments of the knee to function properly and remain healthy.

**Meniscectomy**

Repair of the meniscus has only been popular since it was described that meniscectomy was “not totally innocuous”.52 Previous to that, total meniscectomy was used widely to treat meniscal injuries and defects.52-54 In a study by Perey et al. (1962) it was shown that total meniscectomy produced clinically good results up to 10 years after surgery.54 It was later discovered that meniscectomy causes joint space narrowing, lowers the rate of regeneration, leads to an increase in the degenerative changes in the surrounding cartilage, and hence a higher incidence of osteoarthritis.52,53,55-60 This understanding facilitated a switch to partial meniscectomy as the chosen form of treatment as well as surgical repair and implantation.8,52,58 Partial meniscectomy is one of the most commonly performed arthroscopic procedures and preserves the load distribution characteristics of the meniscus.58,61 Several studies have shown that the amount of degeneration that takes place after partial meniscectomy is proportional to the amount of tissue resected during the procedure.56,61-63 Partial meniscectomy has also been shown to produce favourable results when compared to total meniscectomy, with 88 to 95% positive outcomes.60,61 Given that degeneration still proceeds even when partial meniscectomy is performed, restoration of meniscal tissue to its native state is most desirable. One way in which to achieve this is by facilitating the healing process.

**Repair**

Surgery related to the meniscus accounts for around one million procedures a year in the United States of America alone.64,65 Therefore it is obvious that these procedures are a massive drain on health services in terms of time, expenditure and resources. As the meniscus is not a homogeneous tissue, its capacity for healing is limited. As only the outer periphery is vascularised, general prognosis for healing is excellent in this area.8 Healing is poorest in the innermost avascular zone as there is no access to a blood supply or source of reparative cells.7,8 Current repair techniques are effective in the vascularised zone of the meniscus but fail to encourage healing in the avascular zone.66 Several methods have been devised to aid the healing of the meniscus, ranging from the creation of channels to introduce blood and reparative cells to tears; to suturing and resorbable scaffolds.18,67-71 Trephination is one such method and involves the creation of a channel from the vascularised zone to the tear.70 Use of this method has resulted in very good results with Fox et al. (1993) reporting good results in 90% of cases67 and Zhang et al. (1988) showing that trephination led to healing of all tears, either partially or fully,69 with an improved healing rate compared to suturing alone.70 Suturing may stabilise a tear, however it does not encourage healing due to the lack of a blood supply.71 Other ways of introducing a blood supply and/or reparative cells to the site of injury are using a vascularised synovial flap or a fibrin clot.9,18,68,72 Ghadially et al. (1986) created bucket-handle tears in the avascular zone of ovine menisci and repaired them using only suturing or by introducing a flap of synovium to the tear.18 Menisci that were sutured did not display any indication of healing; whereas the menisci repaired using synovium showed some healing. These results are supported by another study in which 11 of 35 menisci repaired using a free synovium flap were healed as opposed to none in the control groups.72 The use of a fibrin clot in meniscal lesion repair has shown that it is possible to repair tears in the avascular zone using this method.9 Surgical techniques range from arthroscopic to open repair.73 There are various alternatives to suturing available that work on the same premise including the Meniscus Arrow (Bionx, Blue Bell, Pennsylvania), the Meniscal Dart (Arthrex, Naples, Florida), the T-Fix Suture Bar (Smith & Nephew, Endoscopy Division, Andover, Massachusetts) and the Clearfix Meniscal Screw (Johnson & Johnson).73,74 Repair devices are usually produced from poly L-lactic acid (PLLA), however these are not often resorbed and so remain in place indefinitely.

The nature of the repaired tissue must also be considered when critiquing a technique. Repair tissue that is as similar to native meniscal tissue histologically, morphologically and biomechanically is most desirable. It has been shown that calcification increases with meniscal injury and may be a secondary symptom of degeneration.75 Repair tissue produced using the fibrin clot method was found to be similar to normal meniscal repair tissue; however it was dissimilar to normal meniscal tissue.9 The strength of meniscal repair tissue has been studied after repair by suturing or fibrin glue.76 After 6 weeks, the tissue had regained 26% and 42.5% of its original strength for the suture and fibrin glue techniques, respectively. A secondary area of weakness was also found in the peri-scar tissue in the line of the scar and this reduced in size after 12 weeks of healing.76

**Replacement**

Replacement of the meniscus is a more favourable approach than repair as it has a greater potential to protect the joint surfaces. Transplantation using autologous77 or allogeneic tissue is an option when patients have suffered degenerative changes to the joint due to previous meniscectomy or when an irreparable tear is encountered. Allogeneic transplants are grafts taken from cadaveric donors. These have been available in various forms including fresh, frozen, lyophilised, and cryopreserved. Fresh allografts are not readily available and have limitations of storage and immunogenicity.78,79 Allografts may be stored frozen however the freezing process kills all donor cells potentially leading to matrix degradation upon implantation. Lyophilisation removes all water from the allograft, devitalising donor cells and may cause matrix disruption. Lyophilised menisci have been shown to shrink considerably once implanted.80 Menisci that are cryopreserved retain the greatest cell viability81 however their use is limited by availability and cost of the process. Advantages of allogeneic compared to autologous meniscal transplants are that there is no donor site morbidity and less time is spent in surgery as there is no need to harvest from the recipient. There are also no size limitations therefore replacements can be tailored to individuals.81 As the donated tissue is not genetically identical, there may be problems with immune rejection, particularly with the use of fresh allografts.78,79 However, the cells that survive transplantation and remain viable can potentially continue to synthesise extracellular matrix helping to maintain the tissue. Verdonk (1997) showed using DNA fingerprinting that donor cells were localised in meniscal allografts 2 years post transplantation.82,83 Allotransplantation has been shown to be most successful in patients without knee instability and malalignment or with concomitant procedures to correct these. However, it is likely that patients undergoing allotransplantation will progress to revision surgery to treat a meniscal tear. Due to the lack of available good quality tissue allotransplantation is not ideal. Autogenous transplantation refers to transplantation of tissue originating within the individual to whom it is to be applied. Tissue has been sourced from a variety of locations including the patellar tendon85,86 and quadriceps.87 The advantage of autogenous transplants is lack of immune rejection. Disadvantages include size limitations, longer time in surgery and cosmetic issues due to harvesting of tissue, and donor site morbidity. In order to assess the viability of autogenous transplantation, as well as provide a premise for allogeneic transplantation, Stone et al. (1995) carried out autogenous transplantation of meniscal cartilage in dogs representing a theoretically ideal replacement, where the meniscus was excised and replanted.88 Gross healing occurred in 50% of cases. Limping was noted in 79%, with collagen abnormalities at the healing interface and within the tissue noted. Degenerative joint disease in the form of joint space narrowing and osteophyte formation was also seen in 50% of dogs. These results may have been improved with fixation using bone plugs as even though the replacement tissue was fresh and ideally sized it has been shown that fixation using bone plugs yields improved results compared to soft-tissue fixation.89,90 Although the basis for autogenous transplantation is good, evidence indicates that this does not translate clinically. Problems arise with the biomechanics of the grafted tissue as it is less able to withstand the forces encountered in the knee. This may be due to insufficient remodelling and vascularisation, and in some cases shrinkage of the graft leading to exposure of cartilage surfaces resulting in continued degeneration.

Due to a potentially unlimited source of tissue, the idea of xenogeneic transplantation is gaining popularity. Porcine menisci are the closest match to human menisci in terms of size. However, there are a number of issues that may prevent xenotransplantation translating to the clinic. These include ethical, legal and religious concerns, potential for transmission of zoonoses91 and hyperacute rejection. Hyperacute rejection has been shown to be a major problem for pig to primate organ transplantation.92,93 This is due to the galactosyl-α(1,3)galactose (α-gal) epitope present on cell membrane glycolipids and glycoproteins of lower mammals. The α-gal epitope is not present in humans or Old World monkeys due to mutations of α1,3-galctosyltransferase, the enzyme responsible for producing α-gal. Hyperacute rejection occurs due to the fact that humans naturally produce high titres of antibodies to α-gal, possibly due to constant exposure to intestinal bacteria with epitopes which cross-react with α-gal. These antibodies mediate hyperacute rejection via complement and antibody dependent cellular cytotoxic mechanisms.92

**Tissue Engineering**

A tissue engineered substitute conforming to the biological and biomechanical characteristics of native menisci would reduce the burden on health services and improve patients’ lives as it would prevent degeneration of the joint eradicating the need for further surgery or treatment. Many attempts have been made to tissue engineer a meniscus with limited success so far (Tables 3 - 6). The highly organized nature of the meniscus and heterogeneous cell population make it very challenging to recapitulate. The replacement has to be biocompatible, integrate with the surrounding tissue, allow ingrowth of vasculature, remodel in a timely manner whilst maintaining biomechanical and lubrication properties until regeneration has occurred and neo-tissue is able to withstand the biomechanical forces acting through the meniscus preventing degeneration of cartilage surfaces. Ultimately, there are two strategies for engineering a meniscal replacement: a cell-based method in which scaffolds are seeded with cells before implantation or a cell-free method in which acellular scaffolds are designed to promote and support regeneration once implanted through the infiltration of endogenous cells from the surrounding tissue. A variation of the cell-based method that is currently gaining momentum is the scaffold-free approach in which stem cells or native meniscal cell types are cultured under specific conditions to produce meniscus-like ECM. This approach aims to eradicate the issues associated with the use of scaffolds such as adverse host responses, interference with cell-cell interactions and ECM alignment. In a study in which articular chondrocytes and fibrochondrocytes were co-cultured in a meniscus-shaped mould, a biomechanically anisotropic tissue was developed with collagen I, II and GAG deposition.94 The ideal approach for meniscal replacement has, however yet to be determined, with each method showing merit and impetus for further investigation.

The mechanical environment within the knee also needs to be considered when developing a tissue engineering strategy. The implanted material, whether comprised of cells plus scaffold/ECM or scaffold alone must be able to function under load without deforming or failing and provide the correct environment for cells to adhere and interact. It has already been shown that certain cell types exhibit material-specific interactions dependent on material modulus, with mesenchymal stem cells, a cell source widely investigated in meniscal tissue engineering, shown to commit to specific lineages dependent on matrix stiffness.95

**Scaffold Based**

Scaffold based approaches include the use of synthetic materials, naturally derived materials and acellular biological tissues. Synthetic materials are attractive options as they are easily processed, offer minimal batch to batch variability compared to naturally derived materials, and their mechanical and chemical properties can be tailored. However, they lack the signalling cues present in naturally derived materials and can cause inflammation. Synthetic scaffolds for meniscal repair and replacement were initially investigated extensively however interest in their use has declined. This may be due to evidence of adverse host responses96-99 and failure to provide suitable environments for cellular ingrowth and matrix synthesis.98,99 More recent studies, however, have shown some promise, possibly due to advances in biomaterials science and there are now approaches based on the use of materials such as PLLA, poly p-dioxanone (PPD), polycaprolactone (PCL), and polyurethane, that are more biocompatible than polymers previously used. Acellular PLLA-PPD and PLLA scaffolds have been shown to regenerate surgically created meniscal defects in animal models with integration to the native tissue with some collagen alignment100 and protection of cartilage surfaces from damage.101 Even so, synthetic materials will always induce a foreign body reaction and if unchecked fibrotic scar tissue can isolate the implant from the surrounding milieu preventing the infiltration of cells and regeneration. To counteract these effects scaffolds produced from synthetic polymers have been coated in natural ECM components such as hyaluronan.102 The degradation rate can also be controlled to reduce the concentrations of inflammatory degradation products released by the scaffold.

There is much interest in using natural scaffolds for tissue engineering the meniscus. Collagen, decellularised menisci and small intestinal submucosa (SIS) have all been investigated in an attempt to address meniscal regeneration.103-106 Porcine small intestinal submucosa has been used in animal models of Achilles tendon repair to promote a regenerative response rather than a healing response where scar-tissue is formed.107 It acts as a temporary scaffold that degrades by 8 weeks after implantation while remodelling into functional tissue.107-109 It has been shown to improve limb function and reduce cartilage damage when used in repair of meniscal defects in dogs.64 In studies in which SIS was used to treat avascular meniscal defects it was shown to integrate well, produce an organized collagen matrix, and improve clinical function,104 however the Poisson’s ratio, permeability and shear modulus of tissue formed were not significantly different to the tissue formed when no treatment was applied.110 In one study in which SIS was used to fill meniscal defects in a leporine model it was found that there was increased degeneration in the grafted areas with unorganized matrix formation.103 Currently SIS has been licensed as a clinical treatment for several applications other than meniscal repair.

Collagen, in the form of a collagen meniscal implant, or CMI® (ReGen Biologics, Hackensack, NJ, USA), has been used to stimulate meniscal tissue ingrowth. Using collagen is advantageous as there are no storage or handling issues,111 and there is no antigenicity due to the fact collagen has maintained a highly preserved structure through evolution.112 Porosity, pore size, permeability, shape and mechanical properties can also be adjusted *in vitro*.111 Studies in animal models have shown that the CMI® promoted the in-growth of fibrochondrocytes and preserved the cartilage surfaces.105,113 However, it has also been shown that an unorganized and biomechanically unstable matrix is produced in patients using CMI® and it is therefore a poor substitute.114 Limited success has been achieved using decellularised menisci and SIS,110,115 whereas more progress has been made *in vivo* using collagen implants.113 Current materials under investigation as possible meniscal replacement or repair materials include collagen and collagen-GAG composites, hyaluronan, and decellularised or devitalized meniscus. These have shown varying degrees of success with evidence of stem cell differentiation and ECM deposition *in vitro*, and integration and regeneration of defects *in vivo*. The use of decellularised porcine or human menisci as a natural scaffold has been gaining momentum in recent years.116,117 The aims of decellularisation are to remove all immunogenic constituents of the tissue and provide an ideal structural framework for recellularisation either *in vitro* or *in vivo*. Further work is required in this area to demonstrate practical feasibility.

**Cell Based**

The majority of methodologies under *in vitro* investigation combine both a scaffold composed of either a natural, synthetic or combination biomaterial coupled with a cell population. In some cases this maybe in order to ascertain the biocompatibility of the chosen scaffold and its ability to direct cell interaction and expression, however it is evident from preclinical studies that a cellularised scaffold integrates much more readily to the native tissue with more extensive ECM deposition and organization.118,119 This may occur due to the hastening of the remodelling response as cells producing ECM are already present and so do not need to migrate into the scaffold.118 Polyglycolic acid (PGA) remains the most propitious synthetic material under investigation as a synthetic scaffold for tissue engineering the meniscus and has been shown to be biocompatible and non-toxic when it degrades. PGA scaffolds have been shown to be more effective than agarose scaffolds at supporting cell proliferation, collagen synthesis and GAG production.120 A study by Kang et al. (2006) using a meniscus-shaped PGA scaffold seeded with fibrochondrocytes before implantation demonstrated significant regeneration of fibrocartilage as well as zonal production of collagen I and II as seen in native menisci.121

Collagen based scaffolds have been shown to allow recellularisation and matrix production, with growth factors allowing these properties to be enhanced.122 Cell behaviour has also been shown to be sensitive to collagen-GAG composites, with a collagen II-GAG composite promoting increased production of matrix components and reduced shrinkage as opposed to a collagen I-GAG composite.123 Hyaluronan has also shown promise as it can be used to produce bi-zonal tissue similar to meniscal tissue.124

Fibrochondrocytes have been heavily investigated as a cell source for meniscal tissue engineering.120,125-129 Chondrocytes have also been well characterised and have been induced to produce meniscus-like ECM through manipulation of the culture conditions. Other more readily available and easily procured cells have also been assessed for suitability in meniscal tissue engineering. These include various sources of stem cells130-133 which are yet to be understood in this application, as well as meniscal fibrochondrocytes or chondrocytes. However, stem cells have shown promise in producing a meniscus-like ECM. Bone marrow derived mesenchymal stem cells have been shown to produce dense ECM containing type II collagen when seeded onto hyaluronan-gelatin composite scaffolds.132 Synovium-derived stem cells have been utilised in an injectable system for meniscal repair and have been shown to develop a gene expression profile which was more similar to meniscal cells than when bone marrow derived mesenchymal stem cells were used.130 Investigations which have focussed upon the use of cells in combination with scaffolds or in self-assembly approaches (Table 5) have, however, failed to articulate how the approach can be readily translated to routine clinical use.

Whether a scaffold-only or scaffold seeded with cells approach is successfully translated to the clinic in the future will be very much dependent upon practical and regulatory considerations. A scaffold-only approach might represent an ideal solution if a scaffold that had the appropriate mechanical properties to fulfil the load bearing and biotribological function of the meniscus immediately upon implantation could be engineered that also promoted rapid infiltration of host cells to initiate healing and integration. This approach could provide a low cost, off-the-shelf class III medical device that has the potential to be translated to the clinic within a relatively short time frame. Such a device could be used in the treatment of a wide range of patients.

On the other hand, solutions for meniscal repair and regeneration which encompass a living cell population might give rise to improved healing and remodelling within a shorter frame. However, the use of living cells in the clinical application would require harvesting of autologous cells, in order to avoid immuno-incompatibility, necessitating two interventions and potential donor site morbidity, to produce a personalised implant. Approaches based upon the use of cultured living cells would also require subsequent culture expansion of the cells to obtain sufficient numbers, and manipulation of cells in culture or a bioreactor system. This approach would inevitably entail substantially higher costs to the patient and/or health service and would not be readily available to the majority of patients.

It is possible that a compromise could be reached in which a population of cells is sourced during surgery and used in conjunction with a scaffold without further ex vivo manipulation to enhance the regenerative properties of the implanted scaffold. This approach would still be regulated as a low cost class III medical device, ensuring the therapy was accessible to a large number of patients

**Conclusion**

Tissue engineering aims to create functional tissue with the potential for regeneration and growth. The choice of scaffold for this purpose is crucial. The ideal scaffold should be biocompatible, biomechanically and geometrically suited to resist forces within the knee as healing progresses, non-immunogenic, and, if acellular, allow for endogenous cell population and vascularisation. Although different materials have been investigated, an ideal conduit is yet to be developed. Promising results have been obtained using both natural and synthetic materials. Approaches which use a combination of cells and scaffold materials to recapitulate the meniscus prior to implantation are at a much earlier stage of development and there is little consideration of how these approaches might be translated to the clinic in the literature.

**Figures**

Figure 1: The right knee joint, illustrating the anatomical location of the menisci

Figure 2: Meniscus collagen organization. Fibers are oriented randomly in the superficial (1) and lamellar (2) layers. Circumferential fibers are present in the outer (3) and inner (4) deep portions with radial tie-fibers interspersed.

Figure 3: Meniscus (right knee) under loading. Arrows represent the distribution of load through the meniscus.

Figure 4: Vascularisation of the meniscus

Figure 5: Types of meniscal tear. 1) Longitudinal 2) Bucket-handle 3) Horizontal 4) Radial 5) Oblique 6) Complex

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