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# Novel Approaches in Meniscal Repair Utilizing Mesenchymal Stem Cells, New Generation Bioscaffolds and Biological Adhesives as Cell Delivery Vehicles

*James Melrose*

## Abstract

Mesenchymal stem cells (MSCs) have been widely applied in the repair of the knee-joint menisci which have a limited ability to undergo spontaneous repair. The menisci stabilise the knee-joint and are weight-bearing structures subjected to considerable tensional and compressive forces during flexion-extension and torsional loading of the knee. Traumatic loading of the knee-joint menisci can generate a number of lesions in the inner avascular meniscal regions. These have a limited capability of intrinsic repair and predispose the underlying articular cartilages to premature osteoarthritis. A number of strategies have therefore been developed for meniscal repair employing MSCs, bioscaffolds, hydrogels, biological glue cell delivery systems and agents which promote cell proliferation/matrix synthesis. Meniscal implants have also been developed in combination with the above procedures. It is important that meniscal defects be repaired not only to maintain knee-joint stability but also to prevent further degenerative changes in other knee joint tissues. Degenerative menisci contribute degradative proteinases and inflammatory mediators to the total synovial degradative proteinase pool. Partial or total surgical removal of the menisci is not a solution since this leads to premature osteoarthritis. Meniscal integrity needs to be maintained or repair strategies implemented in a timely manner to maintain knee joint function.

**Keywords:** meniscal repair, mesenchymal stem cell, bioscaffolds, biological glues, meniscal implants/allografts

## 1. Introduction

### 1.1 Meniscal structure: function

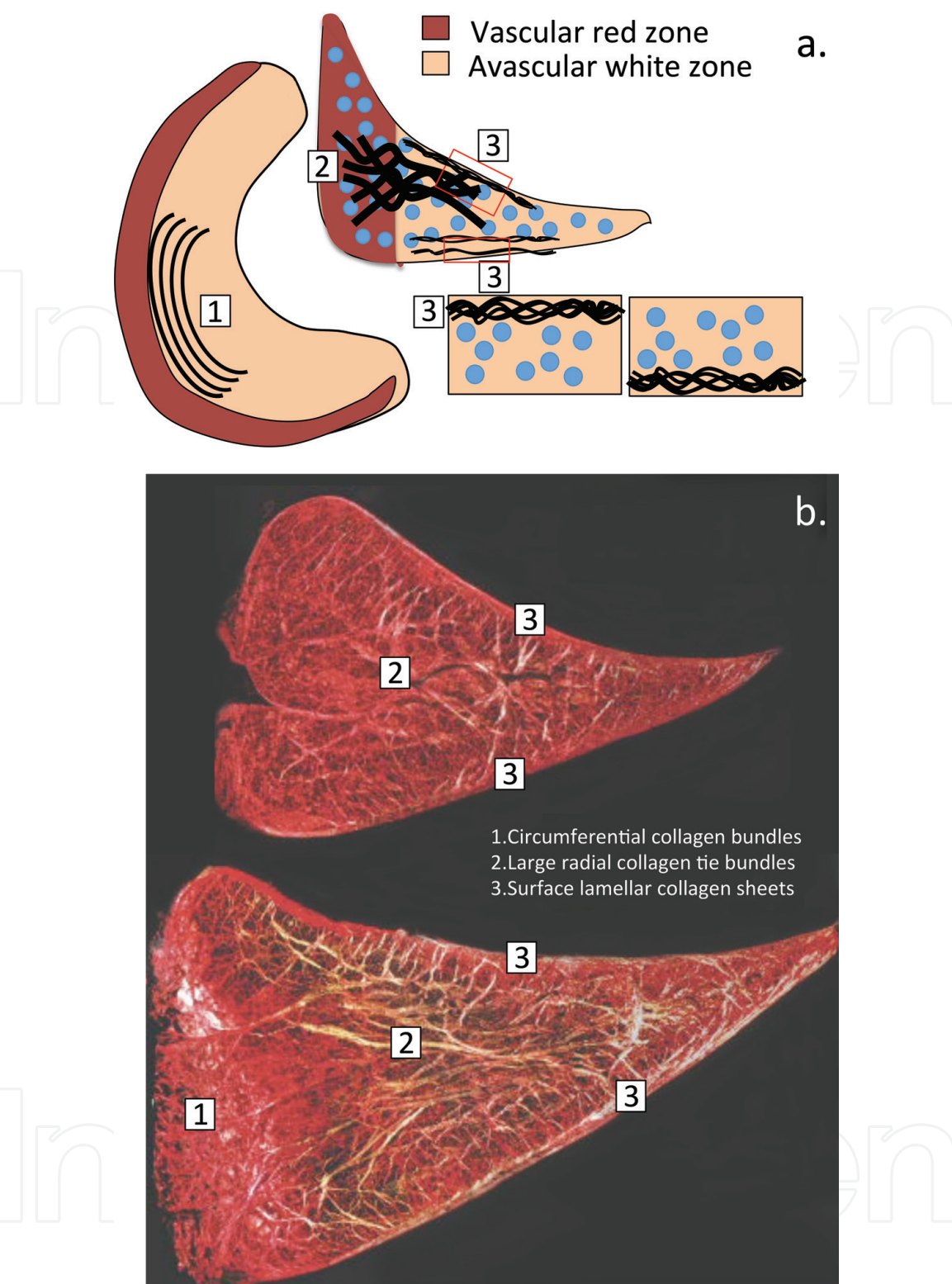
The knee joint menisci provide joint stability during weight bearing, the curved superior meniscal surfaces provide congruity between the curved femoral condyle and flat tibial articular cartilages [1]. The menisci act as shock absorbers and protect

the weight bearing articular tissues from excessive point loading [2] transferring forces between the femoral and tibial joint surfaces, transmitting 50–90% of the total knee joint load during weight-bearing [3, 4]. The structural organisation of the meniscus is designed to withstand circumferential hoop stresses which are generated within the meniscal tissue to dissipate tensile stresses which are transferred along the circumferential meniscal collagen fibre networks counteracting the tendency of the menisci to be extruded peripherally when the knee joint is subjected to compressive loading [5]. Energy is absorbed into the collagen fibres by the dynamic expulsion of joint fluid from the aggrecan-hyaluronan macro-aggregate networks entrapped within the meniscal collagenous networks. The menisci are fibre reinforced structures stiffening and protecting them from damage by excessive deformation during compressive loading [6] (**Figure 1a and b**).

The contribution of intact menisci in knee load-bearing is emphasised from the increase in contact forces in the underlying articular cartilages of up to 350% following partial or total meniscectomy where as little as 16–34% of the intact meniscus may be removed [1, 3, 7]. Radial meniscal tears which extend to its periphery may result in significant contact forces being transmitted to the underlying articular cartilages which can damage these tissues [8].

Water (~70% wet weight) and collagen, (mainly type I, and lower amounts of type II, III and VI collagen constitute 60–70% of the meniscal dry weight) are major meniscal components [9–15]. Proteoglycans (aggrecan, decorin, biglycan, versican, fibromodulin, lumican, keratocan) and elastic microfibrillar glycoproteins are quantitatively minor meniscal extracellular matrix (ECM) components but convey essential functional properties [14–16]. The meniscus is a complex fibre-reinforced structure designed to withstand multidirectional tensional and compressive forces (**Figure 1a and b**). The outer third of the meniscus (red zone) is served by a fine capillary network. Defects in this region of the meniscus have the ability to undergo spontaneous repair however the inner two thirds of the meniscus (white zone) is avascular and has a limited ability to undergo repair (**Figure 2a**). The outer zone of the meniscus is a collagen rich fibrocartilaginous tissue while the inner zone contains higher proteoglycan levels and is cartilaginous (**Figure 2b**). Immunolocalisation of perlecan, HSPG2, a large modular HS multifunctional proteoglycan demonstrates a strong localisation pattern in this inner region. Perlecan is marker of chondrogenesis [17–20].

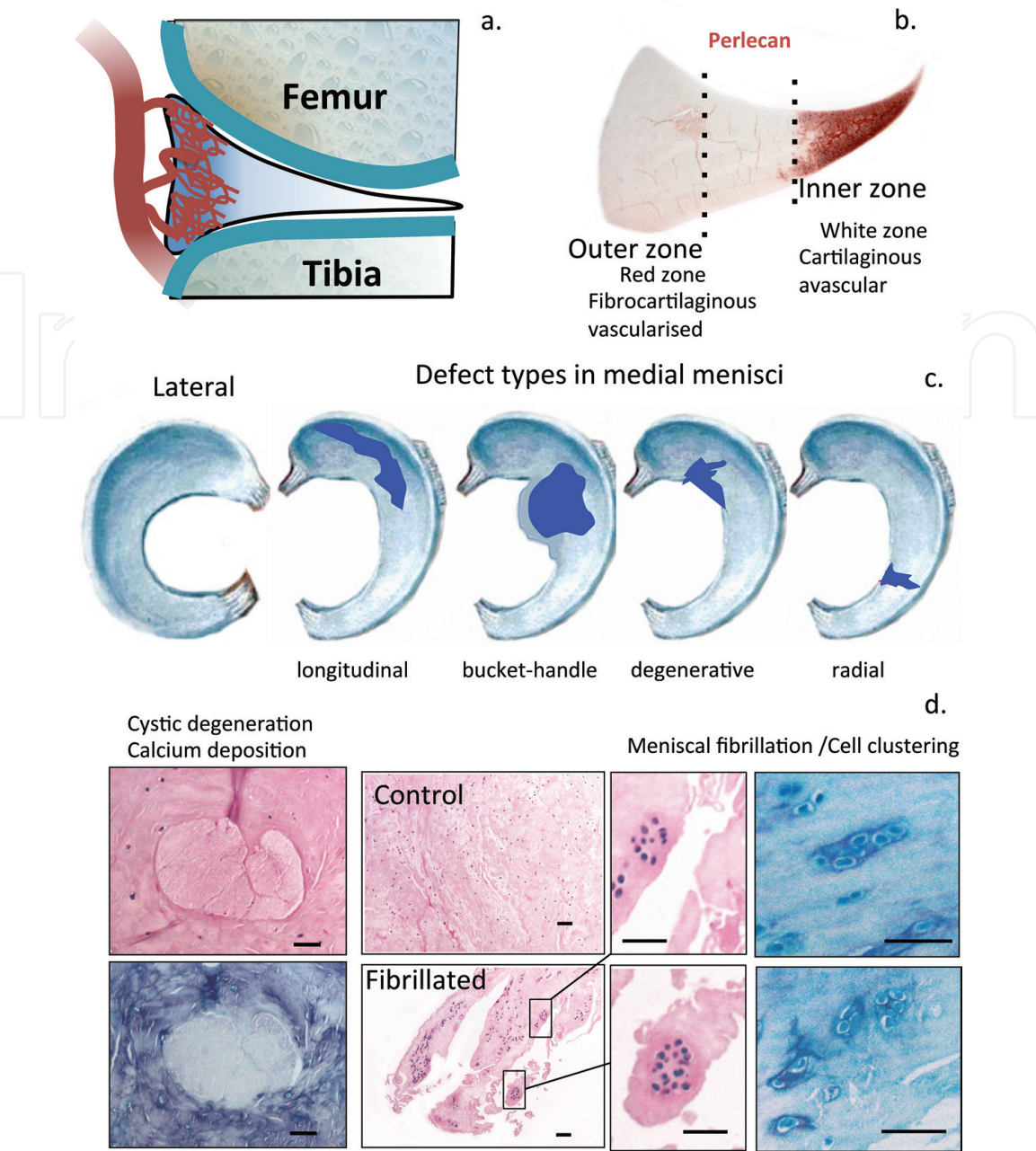
Supraphysiological overload of the menisci may generate defects in the inner meniscus diminishing its weight bearing capability and ability to resist tensional stresses and it becomes less able to dissipate such forces to prevent overloading of the underlying articular cartilage. A number of characteristic tears (bucket-handle, degenerate) occur in the inner meniscal region. Longitudinal and radial tears can also affect the outer meniscus (**Figure 2c**). This can also damage the underlying articular cartilages formerly protected by the menisci leading to degenerative changes and impacting on the knee's ability to act efficiently as an articulating weight bearing structure. Development of premature osteoarthritis (OA) may also result in such circumstances [21, 22]. Menisci in OA knees are also subject to ectopic focal depositions of calcium in cyst like structures (**Figure 2d**). Fibrillation of the inner meniscal region is also a common degenerative feature in OA. Meniscal cell clustering adjacent to such fibrillations is also common and may indicate endogenous adult stem cell activity in response to altered biomechanics/nutrition in this region. Cell clustering has also been observed adjacent to surface fibrillations in OA articular cartilage and adjacent to lesions in the annulus fibrosus of the degenerate intervertebral disc [23–29]. Such cell clustering may be indicative of an incomplete frustrated repair response by resident adult stem cells.



**Figure 1.**  
*Diagrammatic representation of the collagenous organisation in a meniscus. (i) The meniscus contains a complex arrangement of radial collagen fibre bundles in the outer meniscus, (ii) thick radial tie bundles internally as well as (iii) finer collagen fibre bundles of collagen in lamellar sheets in the inferior and superior meniscal surfaces. Notice that the inferior lamina is significantly thicker than the superior lamina. Vertical radial sections through 2 year old lateral and medial ovine menisci stained with picrosirius red and viewed under polarised light depicting collagen bundles which are highly refractile due to their ordered collagenous structure appearing as bright rod-like structures (b). Picrosirius red predominantly visualises the major fibrillar meniscal collagen, type I collagen. Methodology for Picrosirius red staining is as described earlier [78].*

Many strategies have consequently been developed to effect meniscal repair using a number of cell types including mesenchymal stem cells (MSCs) sourced from a number of tissues (**Table 1**), and combinations of bioscaffolds, hydrogels,





**Figure 2.** Structural features evident in the normal and degenerate meniscus. Diagrammatic representation of the vascularisation of a vertically sectioned meniscus showing the extensive capillary network in the outer meniscal red zone and lack of a blood supply to the inner two thirds of the meniscus (a). The inner meniscus is a cartilage like tissue which is well delineated in a newborn meniscus by immunolocalisation of perlecan, HSPG2, a chondrogenic marker proteoglycan (b). Menisci are subject to a number of structural defects which are summarised diagrammatically (c). Histochemical visualisation (H & E) and toluidine blue staining, of some features of degenerate menisci (d). Focal deposition of small calcium deposits in a cyst like formation in the outer meniscus zone in a 53 year old human meniscus. Fibrillation of the inner meniscal zone and cell cluster formation. In the normal meniscus single cells are distributed throughout the meniscus with no clustering.

bioadhesive cell delivery systems and bioactive agents which stimulate the resident and exogenous cells applied for therapeutic purposes (Tables 2 and 3).

In-vitro experiments have shown that co-culture of bone marrow derived stromal stem cells with meniscal cells increases cell proliferation and matrix synthesis [30]. Type I and type II collagen and aggrecan mRNA expression were elevated and ECM protein levels increased (Figure 3a and b). Significantly, meniscal cells stimulated with FGF-2 or FGF-18 in 3D pellet culture also produced elevated levels of these ECM components (Figure 3c and d). MSCs are believed to act both through transfer of material directly to resident cell populations through cell-cell contact

MSC source	Lesion or study type	References
Intra-articular injection synovial MSCs	Avascular tear	[143]
Rabbit meniscal MSCs	Central meniscal defect	[155]
Synovium derived MSCs	Longitudinal tears and punch holes	[142, 144, 145]
Targeted intra-articularly delivered super-paramagnetic FeO labelled adipose MSCs	Massive lesions encompassing the avascular zone	[146]
Bone marrow, adipose, synovium, meniscus derived MSC delivery to tears in fibrin glue/gel/clot, scaffold	Literature Review of MSCs used in meniscal repair in multiple animal models	[44, 45]
Bone marrow and meniscal derived MSCs	In vitro cell culture	[148]
Blood vessel derived MSCs	Avascular tears	[151]
Bone marrow derived MSCs and fibrin glue	Closure of meniscal tears	[149]
Collagen membrane wrapped meniscal defects injected with MSCs	Tears in avascular zone	[156]
Co-cultured synovial stem cell-meniscal cell cultures	In-vitro demonstration of superior cell proliferation with co-culture compared to monoculture	[43]
Systematic review of the use of MSCs in meniscal repair	Promising results in human meniscal repair	[152]
Comparison of autologous MSCs and meniscal cells for meniscal repair	Rabbit meniscal model punch defect, successful repair of meniscal defects in OARSI grade 3.1 early OA tissues by both cell types	[46–48]
hMSCs delivery in a decellularized ECM to meniscal defects in a nude rat model	Delivery system appropriate for repair purposes	[158]
Review of hMSCs in human meniscal repair	Autologous adipose tissue-derived stem cells or culture-expanded bone marrow-derived stem cells were both suitable for meniscal repair	[153]
Prospective, open-label first-in-human safety clinical trial of hMSCs delivered in collagen scaffold in patients with an avascular meniscal tear	Repair of torn avascular meniscal cartilage by undifferentiated hMSCs harvested from iliac crest bone marrow biopsy. Significant clinical improvement over 2 years, no recurrence of meniscal tears	[157]
3D co-culture meniscal cell: equine MSCs in collagen type I tissue derived small intestinal ECM bioscaffold	Favourable in-vitro results obtained with cells of meniscal cellular morphology attained by MSCs and expression of type I, II collagen	[160]
Allogeneic adipose derived stem cells in scaffold free tissue engineered construct	Rabbit model using 1.5 mm circular defects in anterior horn of medial menisci filled with MSCs in bioscaffold gave positive results	[147]
A review of cell based approaches in meniscal repair	An assessment of mono and co-culture approaches with meniscal cells and MSCs in bioscaffolds and scaffold free approaches	[154]
3D MSC: meniscal fibrochondrocyte co-cultures for meniscal repair	Change in MSC morphology to a fibrochondrocytic phenotype is conducive to meniscal repair	[159]

**Table 1.**  
*Mesenchymal stem cell (MSC) sources used in therapeutic approaches for meniscal repair.*

Method/polymer	Details of technique	References
Regen Menaflex™ collagen meniscal implant	Resorbable meniscal implant, however the FDA removed approval for device in 2013	[87]
Actifit synthetic meniscal substitute to stabilise knee	Post meniscectomy allogeneic implant with cell infiltration into implant from meniscal wall	[88]
Medial meniscus allograft transplantation (MAT) using a modified bone plug	Meniscal allograft harvested using an arthroscopic bone plug technique	[100]
Anatomically shaped polycarbonate-urethane meniscal implant	Artificial meniscal implant designed for the preservation of articular cartilage	[93]
Polycarbonate-urethane implant	Meniscal replacement	[91]
Thermoplastic polyurethane implant	Meniscal replacement	[98, 219]
Salt modified crosslinked PVA hydrogel meniscus cell implant	Meniscal shaped flexible implants for meniscal replacement	[95]
Polycaprolactone supplemented with slow release microbeads containing CTGF and TGF-β3	3D printed meniscus	[103, 106]
Interpenetrating network gels of poly(2-acrylamido-2-methylpropanesulfonate) and polyacrylamide	3D printed meniscal replacement	[104]

**Table 2.**  
*Meniscal allografts and implants used for meniscal repair and replacement.*

Scaffolds	Lesion and study type	References
Myoblast loaded PLGA mesh scaffold	Avascular tears	[172]
HYADD4® HA hydrogel cell delivery	Radial-longitudinal tears	[173]
Electro spun type I collagen scaffolds and vascular/avascular region meniscal cells	Avascular meniscal tears	[174]
Radio opaque electro spun scaffold	Meniscal regrowth	[176]
Wrapping of meniscal defects with collagen membrane and injection of MSCs	Tears in avascular zone	[156]
Aligned electro spun nano fibrous scaffold	Radial tear	[178]
Collagen gel scaffold or HA hydrogel delivery of meniscal, synovial and adipose cells	Bucket handle tear	[177]
Type I collagen scaffold/ infrapatellar fat pad	Anterior 2 mm round holes	[179]
Chondrocyte + PLGA mesh scaffold + PRP	Chondrocytes evaluated	[180]
Meniscal cells in fibre reinforced collagen-GAG scaffold + PRP	Gene profiling study	[168]

Scaffolds	Lesion and study type	References
Juvenile meniscus fragments	Avascular tears	[181]
A review of biomaterials used in meniscal repair	An assessment of state of the art materials currently in use in meniscal repair	[197]
Tissue derived ECM scaffolds	Biological scaffolds derived from cell and tissue-derived ECM have shown great promise in tissue engineering maintaining the biological and biomechanical properties, structure, and function of the native meniscus	[198]
A comprehensive review of hydrogels used in meniscal repair	A number of hydrogels exhibiting high water regain provide a 3D microenvironment with variable topographical properties typical of meniscal tissue and useful platforms for cellular colonisation. Controlled delivery of bioactive molecules has been built into the design of some of these scaffolds to enhance repair processes	[200]
Decellularised, micronized ECM scaffolds for improved meniscal repair	Decellularised menisci cryoground into a powder was cytocompatible with meniscal fibrochondrocytes, synoviocytes. Cellular infiltration and proliferation demonstrated the ability of this scaffold to promote cellular survival, migration, and proliferation and meniscal repair	[198]
Rapidly dissociation of autologous meniscal cells enhances their healing properties	Bovine meniscal cells were isolated by rapid dissociation using collagenase and applied in a fibrin gel to a radial meniscal tear. This procedure enhanced the healing properties of the seeded cells inserted into the meniscal defect	[199]
<i>Bioactive supplements added to scaffolds</i>		
Multiple injection of leukoreduced PRP	ACL and meniscal repair	[165]
10% human serum, 5% PRP, 5% autologous plasma	Non-vascular meniscal lesions	[166]
Human chondrocyte-seeded PLGA scaffold + PRP	Testing of biocompatibility of bio scaffold in nude mice	[170, 197]
PRP plasma for anterior cruciate ligament and meniscal repair	A review of clinical and basic science strategies aimed at biological augmentation of the healing response	[120]
Platelet-rich plasma for open meniscal repair in young patients	Effective treatment of horizontal tears extending into the avascular zone	[171]
Platelet-rich fibrin for meniscal repair	PRP-fibrin promotes rabbit meniscus repair by meniscocyte Proliferation, migration, and ECM synthesis	[220]
Fibrin clot augmentation	Fibrin clot augments meniscal repair	[221]
Platelet rich fibrin clot	Repair of horizontal meniscal defects	[222]
Platelet rich plasma for meniscal repair	Prospective, randomized, double-blind, placebo-controlled study evaluating healing of unstable complete vertical bucket handle meniscal healing, of unstable, complete vertical meniscal tears (Bucket Handle)	[169]



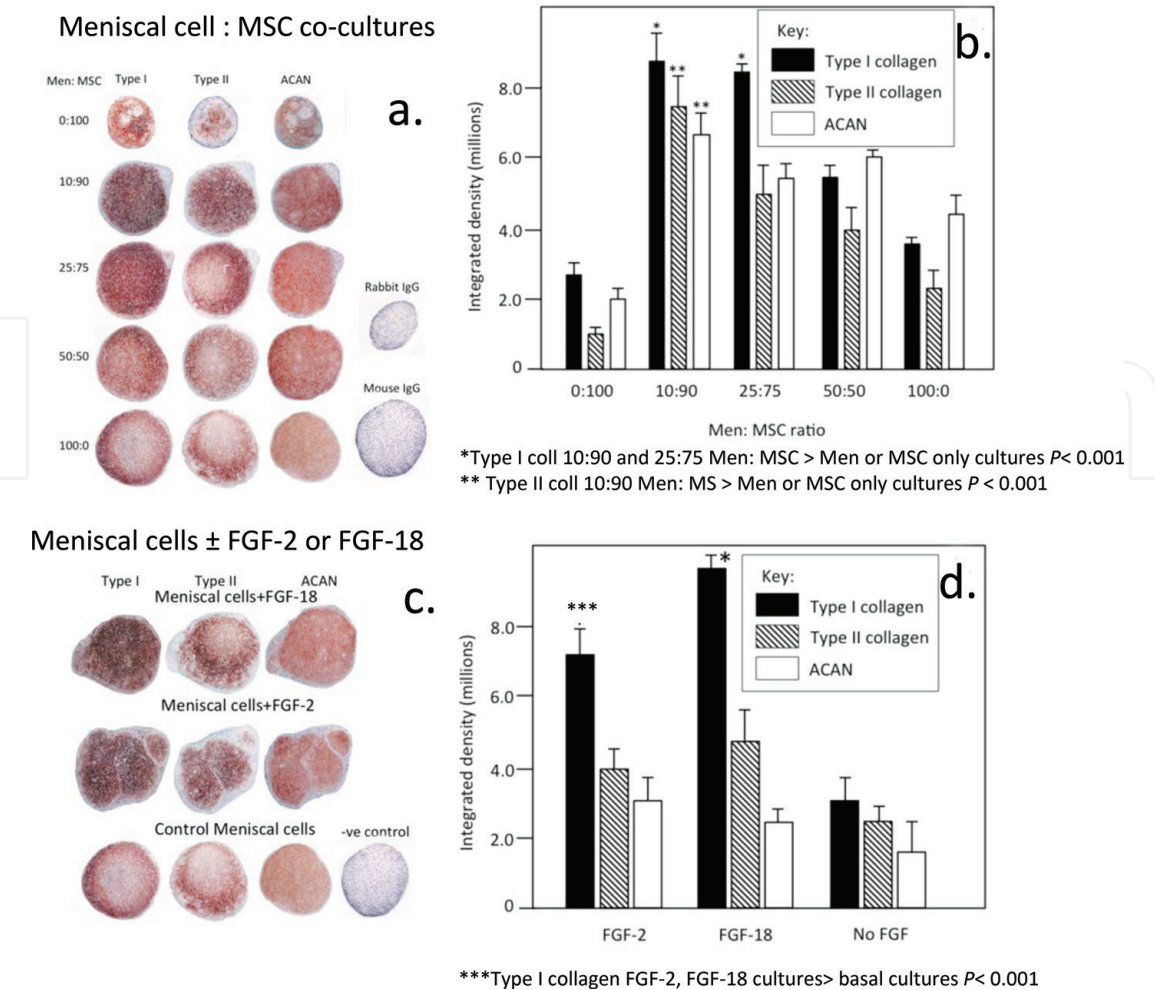
Scaffolds	Lesion and study type	References
Administration of an EGF inhibitor in a customised collagen bio scaffold	Meniscal regeneration in a rabbit model	[223]
Administration of Simvastatin in meniscal repair	Repair of avascular defects in a rabbit meniscal defect model	[224]
Overexpression of TGF- $\beta$ via rAAV-mediated gene transfer	Healing of human meniscal lesions	[183]
rAAV overexpression of TGF- $\beta$	Complex meniscal tears	[183]
Transduced IGF-1 over-expressing meniscal cells	Avascular tears	[184]
Liposome gene transfer IGF-1 meniscal cells	Avascular tears	[185]
Chondrocyte, VEGF, BMP-7, matrigel, HA cultures	Inner avascular tears	[186]
Intra-articular injection of microRNA-210	Avascular tears	[187]
Fibrin-CTGF stimulates meniscal cell to repair inner zone meniscal defects	Avascular tears	[188]
Serum, HA, TGF- $\beta$ 3 supplemented scaffold directed repair of meniscal tears	Directed repair of meniscal tears	[182]
Non-viral gene transfer to meniscal cells and FGF-2 overexpressing meniscal cells	FGF-2 transduced meniscal cells in alginate beads	[190, 191]
VEGF stimulation of resident meniscal cells	Avascular tears	[194]
TGF- $\beta$ 1 induction of meniscal cell proliferation and migration to a meniscal defect	Micro wound assay system	[195]
OP-1 putty in punch biopsy meniscal holes	2 mm holes—inner meniscus	[196]
Gelatin hydrogel + FGF-2	Horizontal tears	[192]
HA-collagen composite + PRP	2 mm holes, implant	[47, 193]
Type I collagen scaffold and infrapatellar fat pad	Repair of 2mm meniscal defects	[179]
Intra-articular injection of micro RNA 210	Promotes angiogenesis and repair of avascular meniscal defects	[187]
Use of BMP-7 for meniscal repair	healing of circular defects in avascular region by OP-1 putty	[186]
VEGF, BMP-7, Matrigel™, hyaluronic acid, in vitro cultured chondrocytes for meniscal repair	Healing of defects in the inner two thirds of the meniscus	[186]
Electro spun gelatin/poly(lactic acid-co-glycolic acid) bilayered nanofiber scaffolds for meniscal repair	PLGA nanofibre reinforced scaffolds have useful properties and are compatible as a substrate for meniscal repair	[175]

Scaffolds	Lesion and study type	References
HYADD4 based hydrogel for meniscal repair	Intra-articular administration of HYADD4 hydrogel to human knees containing degenerative meniscal tears improved VAS pain clinical indices and improved knee functionality based on WOMAC scores	[173]
Electro spun collagen bio scaffolds for meniscal repair	Electro spun collagen type I scaffolds seeded with human meniscal cells placed in longitudinal avascular meniscal defects stimulated meniscal repair as assessed by histology, immunohistochemistry, mechanical testing, and MRI	[174]
Aligned electro spun nano fibrous scaffolds for meniscal repair	Repair of meniscal radial tears using aligned electro spun Nano fibrous scaffolds seeded with meniscal fibrochondrocytes	[178]
Non-viral gene transfer systems of possible application in meniscal repair	A comparison of 18 non-viral gene transfer systems to identify an efficient transfection system for primary cultures of juvenile and adult human meniscal fibrochondrocytes. Overexpression of FGF-2 following transfection with FGF-2 increased meniscal fibrochondrocyte proliferation but not GAG synthesis	[190, 191]
<i>Bio adhesives</i>		
Pre-treatment of meniscal surfaces with collagenase and TGF- $\beta$ 3 prior to use of bio adhesives for meniscal repair	Enzymatic pre-treatment improves effectiveness of bio adhesives	[225]
Biodegradable hyper-branched adhesives for meniscal repair	Sealing of meniscal tears	[211]
CS-bone marrow tissue adhesive	Novel bone marrow derived CS adhesive suitable for securing repair tissue interfaces	[214]
3D PGA-HA bio scaffold stabilized with fibrin	ECM repair by meniscal cells	[189]
New generation meniscal adhesives	Inner avascular lesions	[211]
Re-attachment of horizontal meniscal tears	Fibrin re-attachment	[215]
Mussel based bio adhesives	bio adhesives containing bactericidal and fungicidal activity and improved wet strength for reattachment of surgical incisions	[216, 217]

*Abbreviations: PRP, platelet rich plasma; rAAV, recombinant Adeno-Associated Virus; PGA, polyglycolic acid; HYADD4®, hyaluronan derivative; PLGA, polylactic-co-glycolic acid, CTGF, connective tissue growth factor; VEGF, vascular endothelial cell growth factor; OP-1, osteogenic protein-1; CS, chondroitin sulphate; FGF-2, fibroblast growth factor-2; TGF- $\beta$ , transforming growth factor- $\beta$ .*

**Table 3.**  
*Meniscal repair using bio scaffolds, bioactive substances and bio adhesives.*

and also by secretion of trophic factors which both stimulate tissue regenerative processes [31–42]. Co-cultures of synovial stem cells [43] and MSCs [44–48] with meniscal cells have been evaluated in a number of biomatrices for meniscal repair purposes (**Table 1**).



**Figure 3.** Co-culture of meniscal cells and bone marrow derived mesenchymal stromal cells induces cell proliferation and ECM production and is recapitulated to some degree by treatment of meniscal cells with FGF-2 and FGF-18. Immunolocalisation of meniscal matrix components in micro-mass pellet culture. Immunolocalisation of type I collagen, type II collagen and aggrecan (ACAN) in meniscal-MSC micro-mass pellet co-cultures (a). Negative controls of pellets using rabbit IgG (MSC pellet) and mouse IgG (meniscal cell pellet) for immunolocalisation in the absence of primary antibody. Anti-type I collagen (clone I-8H5) and anti-type II collagen (clone II-4CII) were from MP Biomedicals, Ohio, USA. A rabbit polyclonal antibody (pAb) # 2194 to aggrecan G1 domain was a gift from Dr. J Mort Joint Diseases laboratory, Shriners, Hospital for Children, McGill University, Montreal, QC, Canada [218]. PAb 2194 was raised against a mixture of four aggrecan specific G1 peptide-ovalbumin conjugates including HDNSLSVSIPQPSGGC, RVLLGTSLTIPCYFIDPMHPVTTAPS, TEGRRVRVNSAYQDKGGC and SSRYDAICYTG (single letter amino acid code). Morphometric image analysis of meniscal matrix components produced in pellet culture. Quantitation of type I and type II collagen and aggrecan immunolocalisation levels in meniscal: MSC co-cultures using Adobe Photoshop CS4 morphometric image analysis software as integrated pixel density. Mean values  $\pm$  SD for 3 pellet sections is shown (b). Immunolocalisation of matrix components produced by meniscal cells in pellet cultures stimulated with FGF-2 and FGF-18. Immunolocalisation of Type I and Type II collagen and aggrecan (ACAN) in meniscal cell micromass pellet cultures stimulated with FGF-2 and FGF-18 (a-c) for 21 days (c). Morphometric image analysis of meniscal matrix components using Adobe Photoshop CS4 morphometric image analysis software (d).

## 2. Meniscus preserving therapies

### 2.1 Why it is important to preserve the knee joint meniscus? A historical perspective

The meniscus was historically considered a vestigial muscle remnant and little importance was attributed to this structure for knee joint function. Consequently, radical surgery and total removal of the meniscus were common surgical practice in the 1980s with serious long-term consequences for the meniscectomised knee. It should have been obvious from meniscectomy studies used to induce OA

experimentally in animals that surgical removal of the menisci from knee joints was not a benign procedure [49–74]. However it took time for these animal findings to be translated to human studies [59–61, 65, 67, 70, 72] and for these experimental findings to be fed through to human clinical practice and the importance of the meniscus in entirety in knee joint articulation, weight bearing and load distribution became established. Even so, publications were still appearing as late as 2016 emphasising the importance of the preservation of the knee joint menisci to ensure optimal knee joint function three decades after meniscal removal had been shown to induce degenerative changes in other knee joint tissues [75].

Currently, the consensus in the surgical treatment of meniscal tears is to preserve as much functional meniscal tissue as possible to preserve knee joint function [76].

The menisci play critical protective roles for the knee joint articular cartilages through shock absorption and load distribution and also have important roles to play in proprioception and balance [5]. The ESSKA (European Society for Sports Traumatology, Knee Surgery and Arthroscopy) MENISCUS CONSENSUS INITIATIVE was initiated in 2014 to find a European consensus on the treatment of meniscus pathologies [76].

Further studies in animals [73, 77–79] established a more direct contribution from meniscal degeneration to joint structures globally during degenerative conditions such as OA and RA. During the development of arthritic conditions in animals [73, 77, 79] and humans [80] tissue proteoglycans become fragmented through proteolytic degradation and this reduces the weight bearing and articular properties of the articular cartilages and menisci and may even impact on subchondral bone [80]. Matrix metalloproteases (MMPs), ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs)-4 and ADAMTS-5 produced by articular chondrocytes have a major impact on aggrecan and other cartilage proteoglycans reducing the weight bearing properties of the knee joint articular cartilages. The increase in synovial degradative protease pool during OA and RA was previously attributed to the articular chondrocytes which respond to inflammatory cytokines in the arthritic joint by producing these degradative proteases. Recent in-vitro studies have however now shown that meniscal fibrochondrocytes also potentially respond to interleukin-1 and tumour necrosis factor- $\alpha$  by producing significant levels of MMPs (MMP-1, 2, 3, 9, 13), ADAMTS-4 and ADAMTS-5 and are a major cellular source of these components in the total global degradative enzyme pool present in synovial fluid [81–83]. Meniscal cells actually produce higher levels of these degradative components than articular chondrocytes, thus represent a previously unidentified therapeutic target in the treatment of OA and RA.

## 2.2 Meniscal implants

Partial or total meniscal replacement by collagen or synthetic allografts following meniscectomy have yielded mixed results (**Table 2**) [84, 85]. Implants fall into two categories, (i) porous, resorbable implants which stimulate tissue regeneration and (ii) solid, non-resorbable implants which physically replace the meniscus [86]. The Regen Menaflex™ collagen total meniscal implant (CMI®, Ivy Sports Medicine) is a resorbable implant. A review of the CMI® by Hansen et al. in a 10 year follow up confirmed good clinical outcomes, solid integration of the CMI® with host tissue and it was concluded that the CMI® held promise for meniscal repair [87]. After a protracted series of re-reviews of experimental data, technical issues and protocols the FDA rescinded approval for the Menaflex® device in 2013. The Actifit® polymeric polyurethane partial implant (ORTEQ Sports Medicine) is a honeycomb scaffold that enables blood-flow through it providing a route for cellular in-growth as the body's natural healing process takes place. Once the damaged section of the



meniscus surgically removed the implant is attached to an area of the remaining meniscus with a good blood supply [86]. This has improved knee joint function and reduced knee pain in patients for up to 5 years after implantation and a stable cartilage profile was achieved in 46.7% of patients but a relatively high failure rate was also reported [88–90].

An artificial Polycarbonate-urethane implant has been developed for replacement of the medial meniscus [91–93]. NUsurface<sup>®</sup> have developed a polyethylene reinforced polycarbonate urethane total meniscal implant, approved for use in Europe since 2008 and in Israel since 2011 [94]. The safety and long-term performance of the NUsurface implant is currently under evaluation in SUN (Safety Using NUsurface<sup>®</sup>) and VENUS (Verifying the Effectiveness of the NUsurface<sup>®</sup> System) clinical trials in the USA.

Salt modified cross-linked PVA based hydrogels seeded with meniscal cells have been evaluated for meniscal repair [95] as have polyglycolic acid implants seeded with chondrocytes [96] and (poly-(3-hydroxybutyrate-co-3-hydroxyvalerate) meniscal implants seeded with fibrochondrocytes [97].

Biodegradable thermoplastic polyurethane Estane<sup>®</sup> polymer (Lubrizol Corp, USA) porous implants have been evaluated in dogs as a meniscal replacement [98]. Colonisation of the implant by resident meniscal synovial cells from the peripheral attachments, laying down of matrix components within the implant and the biointegration of the implant to the peripheral meniscal attachment tissues were evaluated 3–6 month post implantation. This demonstrated that the implant filled completely with meniscal tissue as demonstrated by toluidine blue staining for proteoglycan, and for type II collagen and I by immunolocalisations using specific collagen antibodies. Histological evaluation of the tibia and femoral articular cartilages confirmed these tissues did not degenerate in the experimental period employed for this study.

A number of critical reviews on the performance of meniscal implants [86, 87, 99–101] generally acknowledge that despite initial promising findings long-term and randomised controlled studies still need to be undertaken to confirm implant performance and reliability for meniscal repair and that the development of a meniscal replacement tissue of comparable performance to native tissue has yet to be achieved.

### **2.3 3D printing of knee joint menisci**

Polycaprolactone has been used as a scaffolding material to form an exact meniscal replica using a 3D printer [102–105]. MRI scans of the meniscus are converted into a 3D image, data from this image is then used to drive a 3D printer, which produces a scaffold in the exact shape of the meniscus, down to a resolution of 10  $\mu\text{m}$ . Differential release of CTGF and TGF- $\beta$ 3 to drive formation initially of the outer collagenous meniscal region then the more cartilaginous inner meniscus is achieved by slow release microspheres containing CTGF and TGF- $\beta$ 3 in the printed meniscus. These attract meniscal progenitor cells into the scaffold which lay down tissue gradients to form the collagenous outer and cartilaginous inner regions of the meniscus. In sheep this takes between 4 and 6 weeks to achieve meniscal replacement and the scaffolding material then slowly redissolves to be eliminated by normal resorptive processes.

Interpenetrating networks of poly(2-acrylamido-2-methylpropanesulfonate) and polyacrylamide can be prepared by varying the ratio of polyacrylamide to cross-linker, to yield a gel with compression strength and elastic modulus of 61.9 and 0.44 MPa. This gel has maximum compressive and tensile strengths of 93.5 and 1.4 MPa respectively. This can be used in a 3D printer to prepare replacement

menisci from a patients X-ray computed tomography image of a meniscus [104]. Slow release of CTGF and TGF- $\beta$ 3 from a 3D printed meniscus stimulated endogenous stem/progenitor cells to undertake meniscal regeneration [106].

### 3. Meniscus regenerative therapies

#### 3.1 Therapeutic use of mesenchymal stem cells in tissue repair

Mesenchymal stem cells (MSCs) have been the subject of intense investigation since their discovery in the 1960s due to their remarkable efficacy in tissue repair. MSCs were originally considered to migrate into sites of injury, where they engrafted, and differentiated into functional cells, resulting in regeneration of damaged or diseased connective tissue [107]. Findings from several hundred animal studies and many human clinical trials have challenged this mode of action. MSCs certainly exhibit a remarkable ability to repair diseased tissues, but it has become increasingly apparent that they do not engraft in enough numbers or for sufficient durations in tissue defects to provide tissue repair and clinical benefit directly. Additional modes of action for MSCs have therefore been proposed based on their ability to enhance resident cell viability and/or proliferation, reduce cell apoptosis [108, 109], and, in some cases, modulate immune responses [110–114]. These are due to paracrine effects due to secreted growth factors, cytokines, and hormones by the MSCs and cell-cell interactions mediated through communicating nanotubes, which convey extracellular vesicles containing reparative peptides/proteins, mRNA, and microRNAs [107]. Caplan (2017) has proposed that stem cells should be renamed *Medicinal Signalling Cells* to more accurately reflect how they home in on injured or diseased tissue sites secreting bioactive factors with immunomodulatory and trophic properties which direct the resident cells to undertake the tissue repair process, this may happen long after the MSCs have disappeared from the defect site [115].

MSCs have gained popularity for tissue repair with good reason [32, 116], and several applications have been developed for their use in the repair of connective tissues including the meniscus [117–125].

##### 3.1.1 How do MSCs effect tissue repair?

Despite their widespread use in therapeutic applications the precise mode of action of MSCs remains elusive [126–130]. MSCs undergo engraftment in a defect site and differentiate to an appropriate cell lineage conducive to tissue repair [131] where they act as in-situ reservoirs of trophic factors [132] which direct resident cell populations to effect tissue repair [33, 40, 133–135]. It is un-resolved whether cell-cell contact is essential for MSC action in tissue repair [33, 117, 131]. The pluripotency of MSCs facilitates the differentiation of the engrafted cells to effect tissue repair [33, 133]. However, some evidence shows that only a small proportion of the MSCs actually integrate and survive in the host tissues and the predominant mechanism by which MSCs participate in tissue repair appears to reside in their paracrine activity through the production of a multitude of growth factors and cytokines [33, 132]. Lipid micro vesicles released by MSCs have also been shown to be an important means of cellular communication and occurs alongside the mediators secreted by the MSCs. Nano vesicles/exosomes transfer proteins, lipids and small RNAs to neighbouring cells, and through these mediate a variety of biological responses in addition to those mediated by soluble trophic factors supplied by the MSCs [35, 136, 137].

### **3.2 Use of MSCs and chondrocytes for meniscal repair**

The use of meniscal, chondrocytes or MSCs [138] in tissue engineering [139] using synthetic and biological scaffolds [101] containing bioactive factors [140] hold promise in the repair of the meniscus. Direct intra-synovial injections of MSCs have also been employed and meniscal regeneration and resolution of pain recorded [135, 141]. MSCs sourced from a number of tissues including synovial tissues [142–145], adipose [146, 147], bone marrow [45, 148–150] and blood vessels [151] have been applied in a number of applications to promote meniscal repair [44–48, 152–158] (**Table 1**). Co-cultures of meniscal cells and MSCs have also been examined in meniscal repair strategies [43, 159, 160]. Furthermore, a diverse range of bio scaffolds have been developed containing CS have been developed to promote MSC differentiation in-vivo for varied applications in repair biology [161] (**Table 3**). These scaffolds are also appropriate for strategies aimed at meniscal repair but have yet to be applied in this area.

### **3.3 Co-culture of MSCs/meniscal cells and in-vitro stimulation with FGF-2/FGF-18**

MSCs hold tremendous promise in regenerative medicine however their mode of action remains to be precisely established. Direct cell-cell transfer of stem cell material to resident cells has been shown to promote tissue repair processes, while soluble trophic factors secreted by the stem cells can also stimulate repair. In order to examine these possibilities further in the meniscus, bone marrow MSCs and meniscal cells have been co-cultured in micro-mass pellet cultures (**Figure 3a and b**). The influence of FGF-2 and FGF-18 on meniscal pellet cultures have also been assessed to mimic the action of soluble trophic factors (**Figure 3c and d**). Immunolocalisation of the extracellular matrix (ECM) components type I and II collagen and aggrecan (ACAN) have been used to assess the response of the meniscal cells to these treatments. Meniscal cell proliferation is significantly elevated by MSC co-culture, and deposition of type I collagen and type II collagen and ACAN elevated. FGF-2 and FGF-18 also increase these ECM components in pellet culture. Cross-talk between meniscal cells and MSCs (and FGF-2 and FGF-18 to a lesser extent) thus positively influence cell proliferation and matrix production conducive to tissue replenishment and repair which would be expected to be re-capitulated in-vivo upon administration of stem cells to meniscal defects. Thus direct cell-cell contact and soluble trophic factors both stimulate meniscal repair processes.

### **3.4 Bioscaffolds, bioactive substances and bioadhesives and meniscal repair**

The outer and inner meniscus have widely differing repair capability correlating with their relative blood supply [162, 163] (**Figure 1a**). The inner meniscus has the poorest blood supply and consequently the weakest repair response. Many strategies have focussed on the development of measures to improve repair of the inner meniscus and they fall into three broad categories: (i) mesenchymal stem cells administered by direct intra-articular injection; (ii) bioscaffold, hydrogel or bioadhesive cell delivery vehicles for the delivery of chondrocytes, meniscal cells or MSCs into meniscal defects; and (iii) meniscal implants and allografts for total or partial meniscal replacement. These procedures are often undertaken with bioactive substances in the scaffold, hydrogel or bioadhesive delivery system which stimulate repair processes in therapeutic and resident cell populations (**Table 3**). An alternative approach is the co-culture of MSCs with chondrocytes or meniscal cells to pre-condition these or expand cell numbers prior to their incorporation



into bioscaffolds, hydrogels or bioadhesives prior to administration to the meniscal defect [159, 164] (**Figure 3a** and **b**). Platelet rich plasma or platelet rich fibrin clots have been used to enhance meniscal repair in bioscaffolds [120, 165–171].

Myoblast loaded PLGA scaffolds have been evaluated for the repair of inner meniscal defects [172]. A derivatised HA, HYADD4<sup>®</sup> hydrogel cell delivery system has been used for the repair of radial-longitudinal tears in a randomised controlled study [173]. Electrospun type I collagen and gelatin-PLGA bilayered nanofibre reinforced scaffolds seeded with meniscal cells isolated from outer and inner regions have been used in the repair of lesions in the inner meniscus [174, 175] and radio-opaque collagen scaffolds have been used in order to observe the action of therapeutic cells including MSCs on meniscal repair [176]. Meniscal defects wrapped in collagen membranes prior to injection of autologous chondrocytes for repair have been evaluated for the repair of the avascular meniscus [156]. Collagen gel scaffolds containing meniscal, synovial and adipose stem cells have been employed for meniscal repair [177] or in electrospun nanofibrous scaffolds [178]. The use of a type I collagen scaffold and infrapatellar fat pad for meniscal repair has been evaluated in rabbits [179]. PLGA mesh and fibre reinforced collagen-GAG scaffolds seeded with chondrocytes [180] or meniscal cells [168] supplemented with PRP have been evaluated for meniscal repair. Minced juvenile menisci sandwiched with meniscal explants from inner meniscal regions have been evaluated for their reparative potential on tears of the inner meniscal regions [181]. A number of bioactive factors have been evaluated for their reparative properties on meniscal defects. These include multiple injections of leuko-reduced PRP [165], 10% human serum, 5% PRP, 5% autologous plasma [182]. Over expression of TGF- $\beta$  induced by a rAAV vector, stimulated matrix production and cell proliferation in human meniscal explants consistent with active repair [183]. IGF-I over-expressing meniscal cells induced by transfection of the hIGF-I gene [184] or by liposome Fugene 6 transfer of hIGF-I, stimulated ECM production, proliferation and differentiation of cultured meniscal cells and explants from the inner meniscus [185]. VEGF, BMP-7 and HA stimulated chondrocytes have been implanted into meniscal defects to undertake repair in-vitro [186]. Intra-articular injection of microRNA 210 stimulated mitochondrial activity and angiogenesis promoting repair of avascular meniscal defects by upregulation of anabolic matrix genes by resident meniscal cells, VEGF and FGF-2 production [187]. Fibrin-CTGF administration into avascular defects stimulated repair by the resident meniscal cells [188] as did HA, TGF- $\beta$ 3, platelet concentrates and serum supplemented scaffolds [166, 182, 189]. FGF-2 over-expressing meniscal cells [190, 191] and gelatin-FGF-2 scaffolds [192] also stimulated repair of inner meniscal defects. HA-collagen-PRP composites [47, 193], VEGF [194], TGF- $\beta$ 1 [195] and OP-1 [196] also stimulated meniscal cells and MSCs to undertake repair of inner meniscal defects or punch biopsy wounds in menisci. The bioscaffolds used in meniscal repair or regenerative strategies have been extensively reviewed [197–200].

### 3.5 Bioadhesives and meniscal repair

First generation fibrin sealant/glue formulations (Tisseel<sup>®</sup> (Baxter International Inc.), Tissucol<sup>®</sup> (Baxter Healthcare SA), Beriplast<sup>®</sup> (CSL Behring GmbH), Hemaseel<sup>®</sup> (Haemacure Corp)) were originally based on bovine fibrinogen, thrombin and aprotinin isolated from pooled bovine donors. With the discovery of bovine spongiform encephalitis and the technical difficulty of removing prions from bovine protein products, second generation fibrin glues were developed using human proteins and in-house methodologies for the isolation of autologous platelet plasma. Vitagel<sup>®</sup> (Orthovita Inc.)/Costasis<sup>®</sup> (Angiotech Pharmaceuticals Inc.) is a fibrin sealant variant containing bovine collagen and thrombin and human



plasma. To minimise transmission of viral components, second generation fibrin sealants/glues utilise heat-treated human fibrinogen, autologous platelet plasma and virally incapacitated human thrombin. Autologous fibrin sealants based on platelet rich plasma (PRP), or platelet poor plasma (PPP) with added calcium and thrombin, produce a platelet gel which promotes haemostasis and wound healing aided by the release of platelet growth factors (especially TGF- $\beta$ 1 and TGF- $\beta$ 2) and cytokines. Autologous fibrin sealants suffer inconsistency due to variation in patient plasma protein profiles. Commercial FDA approved second generation fibrin sealants such as Quixil<sup>®</sup> (OMRIX Biopharmaceuticals SA)/Crosseal<sup>™</sup> (OMRIX Biopharmaceuticals) have controlled levels of fibrinogen and thrombin with aprotinin replaced by the anti-fibrinolytic, tranexamic acid. Concerns over the use of tranexamic acid subsequently led to it being dropped from the formulation in the product Evicel<sup>®</sup> (Ethicon HCP). Formulations of fibrin sealants/glues have been developed as aerosol administered foams and collagen films based on equine collagen and combinations of animal (Tachocomb<sup>®</sup> (Baxter Healthcare Corp)) and human fibrinogen/thrombin (Tachocomb H<sup>®</sup>, TachoSil<sup>®</sup> (Baxter Healthcare Corp)). While fibrin sealants/glues were originally developed to minimise surgical blood loss and to aid in wound repair they have now been applied as autologous cell delivery vehicles for osteochondral repair in autologous chondrocyte implantation (ACI) whereby chondrocyte numbers are expanded in-vitro then loaded into cartilage defects and are contained within this site using a periosteal or collagen membrane sutured over the defect site and sealed along its margins using fibrin sealants/glues. This technique was subsequently modified using the matrix assisted chondrocyte implantation (MACI) procedure where chondrocytes seeded into a matrix material were placed into the chondral defect and sealed in place with fibrin sealant/glue obviating the use of sutures. A modification of this procedure (fibrin ACI) where fibrin sealants were used as scaffolds for cell delivery has also been developed. The fibrin ACI methodology has been applied to the repair of meniscal tears [201–203] using a number of bioactive supplements to improve cell proliferation and matrix synthesis to promote meniscal repair.

An interesting novel bio-glue has been discovered in the Australian frog genus *Notaden bennetti*. During the mating season the female frog expresses an adhesive exudate from the dorsal skin which ensures sexual union with the male for an extended period to ensure effective fertilisation. This exudate has been harvested from frog skin by electro-stimulation and characterised. Examination of the toxicity and biocompatibility of this biological glue [204], its molecular composition and mechanism of action [205] has shown that this protein based adhesive [206] is non-immunogenic, biocompatible, displays elastomeric properties similar to elastin and the strength of its adhesive properties is several fold that of fibrin glue. This frog glue has been used in combination with suturing of infraspinatus tendon to the bone interface in rotator cuff operations and significantly increased the strength of these attachments [207]. The frog glue also outperformed fibrin glue for the re-attachment of the cut surfaces of a longitudinal bucket handle meniscal tear in an in-vitro comparison [208, 209]. Marine sources of biological glues from the New Zealand green lipped mussel and barnacle are known and have appropriate strong adhesive properties for orthopaedic applications, these await commercialisation [210–213].

CS-bone marrow tissue adhesive [214], fibrin stabilised PGA scaffolds [189] have both found application in meniscal repair. New generation bio-glues has been used as cell delivery vehicles and as bioadhesives in meniscal repair [210, 211] and in the re-attachment of horizontal meniscal defects [215]. Mussel based bioadhesives containing antibiotics and fungicides with improved wet strength properties for use in the closure of surgical incisions have even been developed [216, 217].

## 4. Conclusions

- i. Direct MSC-meniscal cell contact and soluble trophic factors both stimulate meniscal repair processes by the resident meniscal cell populations.
- ii. The bioscaffolds, hydrogel and bioadhesive cell delivery described in this review provide not only protective matrices for MSC and other administered cells but provide a matrix for attachment of migrating cells at the defect site and physical stabilisation of the defect site to prevent further damage while the repair process ensues. MSCs have impressive therapeutic credentials.
- iii. Bioscaffolds and cell delivery systems have undergone significant advances in the last few years facilitating the localisation of MSCs in tissues for reparative purposes, and hold considerable therapeutic promise in the treatment of problematic lesions in the inner meniscus zone.
- iv. Many biomaterials have been examined in the quest for potential meniscal implants but none have displayed as efficient properties as the native menisci of the human knee.
- v. Clinical trials of partial/total replacement menisci are enrolled and their results are eagerly awaited. Despite promising results, scaffold and implant properties still need optimisation.
- vi. Advanced degeneration of menisci and mechanical damage result in a significant loss of meniscal tissue and there is a clear need for a replacement material either for a portion of the meniscus or the meniscus in entirety.
- vii. Significant in-roads have been made in the development of new biopolymers for use in 3D printing and slow release biofactors which direct meniscal regeneration.
- viii. Developments in bioadhesive design offers improved adhesive properties for surgical applications. These can also be used as cell delivery vehicles to promote meniscal regeneration.

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## Author details

James Melrose<sup>1,2,3,4\*</sup>

1 Raymond Purves Bone and Joint Research Laboratory, Kolling Institute, Northern Sydney Local Health District, St. Leonards, NSW, Australia


2 Sydney Medical School, Northern, The University of Sydney, Australia

3 Faculty of Medicine and Health, University of Sydney, Royal North Shore Hospital, St. Leonards, NSW, Australia

4 Graduate School of Biomedical Engineering, University of New South Wales, Sydney, NSW, Australia

\*Address all correspondence to: james.melrose@sydney.edu.au

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## References

- [1] Mow V, Ratcliffe A, Chen KY, Kelly MA. Structure and function relationships of the menisci of the knee. In: Mow VC, Arnoczky SP, Jackson DW, editors. *Knee Meniscus: Basic and Clinical Foundations*. New York: Raven Press; 1992. pp. 37-57
- [2] Fithian DC, Kelly MA, Mow VC. Material properties and structure-function relationships in the menisci. *Clinical Orthopaedics and Related Research*. 1990;**252**:19-31
- [3] Ahmed AM, Burke DL. In-vitro measurement of static pressure distribution in synovial joints—part I: Tibial surface of the knee. *Journal of Biomechanical Engineering*. 1983;**105**:216-225
- [4] Walker PS, Erkman MJ. The role of the menisci in force transmission across the knee. *Clinical Orthopaedics and Related Research*. 1975;**109**:184-192
- [5] Tissakht M, Ahmed AM. Tensile stress-strain characteristics of the human meniscal material. *Journal of Biomechanics*. 1995;**28**:411-422
- [6] Storm C, Pastore JJ, MacKintosh FC, Lubensky TC, Janmey PA. Nonlinear elasticity in biological gels. *Nature*. 2005;**435**:191-194
- [7] Makris EA, Hadidi P, Athanasiou KA. The knee meniscus: Structure-function, pathophysiology, current repair techniques, and prospects for regeneration. *Biomaterials*. 2011;**32**:7411-7431
- [8] Lee SJ, Aadalén KJ, Malaviya P, Lorenz EP, Hayden JK, Farr J, Kang RW, Cole BJ. Tibiofemoral contact mechanics after serial medial meniscectomies in the human cadaveric knee. *The American Journal of Sports Medicine*. 2006;**34**:1334-1344
- [9] Cheung HS. Distribution of type I, II, III and V in the pepsin solubilized collagens in bovine menisci. *Connective Tissue Research*. 1987;**16**:343-356
- [10] Gao J. Immunolocalization of types I, II, and X collagen in the tibial insertion sites of the medial meniscus. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2000;**8**:61-65
- [11] Wildev GM, Billett AC, Matyas JR, Adams ME, McDevitt CA. Absolute concentrations of mRNA for type I and type VI collagen in the canine meniscus in normal and ACL-deficient knee joints obtained by RNase protection assay. *Journal of Orthopaedic Research*. 2001;**19**:650-658
- [12] Eyre DR, Wu JJ. Collagen of fibrocartilage: A distinctive molecular phenotype in bovine meniscus. *FEBS Letters*. 1983;**158**:265-270
- [13] Peterson W, Tillmann B. Collagenous fibril texture of the human knee joint menisci. *Anal Embryol*. 1998;**197**:317-324
- [14] Nakano T, Dodd CM, Scott PG. Glycosaminoglycans and proteoglycans from different zones of the porcine knee meniscus. *Journal of Orthopaedic Research*. 1997;**15**:213-220
- [15] Scott PG, Nakano T, Dodd CM. Isolation and characterization of small proteoglycans from different zones of the porcine knee meniscus. *Biochimica et Biophysica Acta*. 1997;**1336**:254-262
- [16] McAlinden A, Dudhia J, Bolton MC, Lorenzo P, Heinegard D, Bayliss MT. Age-related changes in the synthesis and mRNA expression of decorin and aggrecan in human meniscus and articular cartilage. *Osteoarthritis and Cartilage*. 2001;**9**:33-41



- [17] French MM, Gomes RR Jr, Timpl R, Hook M, Czymmek K, Farach-Carson MC, Carson DD. Chondrogenic activity of the heparan sulfate proteoglycan perlecan maps to the N-terminal domain I. *Journal of Bone and Mineral Research*. 2002;**17**:48-55
- [18] Gomes RR Jr, Farach-Carson MC, Carson DD. Perlecan functions in chondrogenesis: Insights from in vitro and in vivo models. *Cells, Tissues, Organs*. 2004;**176**:79-86
- [19] Yang W, Gomes RR, Brown AJ, Burdett AR, Alicknavitch M, Farach-Carson MC, Carson DD. Chondrogenic differentiation on perlecan domain I, collagen II, and bone morphogenetic protein-2-based matrices. *Tissue Engineering*. 2006;**12**:2009-2024
- [20] Smith SM, Shu C, Melrose J. Comparative immunolocalisation of perlecan with collagen II and aggrecan in human foetal, newborn and adult ovine joint tissues demonstrates perlecan as an early developmental chondrogenic marker. *Histochemistry and Cell Biology*. 2010;**134**:251-263
- [21] Englund M, Guermazi A, Lohmander LS. The meniscus in knee osteoarthritis. *Rheumatic Diseases Clinics of North America*. 2009;**35**:579-590
- [22] Englund M, Guermazi A, Lohmander SL. The role of the meniscus in knee osteoarthritis: A cause or consequence? *Radiologic Clinics of North America*. 2009;**47**:703-712
- [23] Brown S, Matta A, Erwin M, Roberts S, Gruber HE, Hanley EN Jr, Little CB, Melrose J. Cell clusters are indicative of stem cell activity in the degenerate intervertebral disc: Can their properties be manipulated to improve intrinsic repair of the disc? *Stem Cells and Development*. 2018;**27**:147-165
- [24] Jayasuriya CT, Hu N, Li J, Lemme N, Terek R, Ehrlich MG, Chen Q. Molecular characterization of mesenchymal stem cells in human osteoarthritis cartilage reveals contribution to the OA phenotype. *Scientific Reports*. 2018;**8**:7044
- [25] McGonagle D, Baboolal TG, Jones E. Native joint-resident mesenchymal stem cells for cartilage repair in osteoarthritis. *Nature Reviews Rheumatology*. 2017;**13**:719-730
- [26] Tesche F, Miosge N. Perlecan in late stages of osteoarthritis of the human knee joint. *Osteoarthritis and Cartilage*. 2004;**12**:852-862
- [27] Tesche F, Miosge N. New aspects of the pathogenesis of osteoarthritis: The role of fibroblast-like chondrocytes in late stages of the disease. *Histology and Histopathology*. 2005;**20**:329-337
- [28] Turner S, Balain B, Caterson B, Morgan C, Roberts S. Viability, growth kinetics and stem cell markers of single and clustered cells in human intervertebral discs: Implications for regenerative therapies. *European Spine Journal*. 2014;**23**:2462-2472
- [29] Franceschetti T, De Bari C. The potential role of adult stem cells in the management of the rheumatic diseases. *Therapeutic Advances in Musculoskeletal Disease*. 2017;**9**:165-179
- [30] Shu C, Fuller E, Melrose J. Co-culture of mesenchymal stromal stem and meniscal cells upregulates type I and type II collagen and aggrecan production conducive to meniscal repair. *Current Topics in Biotechnology*. 2018;**9**:11-20
- [31] Caplan AI. Mesenchymal stem cells. *Journal of Orthopaedic Research*. 1991;**9**:641-650
- [32] Caplan AI. Review: Mesenchymal stem cells: Cell-based reconstructive therapy in orthopedics. *Tissue Engineering*. 2005;**11**:1198-1211

- [33] Caplan AI. Why are MSCs therapeutic? New data: New insight. *Journal of Pathology*. 2009;**217**:318-324
- [34] Caplan AI. MSCs: The sentinel and safe-guards of injury. *Journal of Cellular Physiology*. 2016;**231**:1413-1416
- [35] Baglio SR, Pegtel DM, Baldini N. Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. *Frontiers in Physiology*. 2012;**3**:359
- [36] Bobis-Wozowicz S, Kmiotek K, Sekula M, Kedracka-Krok S, Kamycka E, Adamiak M, Jankowska U, Madetko-Talowska A, Sarna M, Bik-Multanowski M, Kolcz J, Boruckiowski D, Madeja Z, Dawn B, Zuba-Surma EK. Human induced pluripotent stem cell-derived microvesicles transmit RNAs and proteins to recipient mature heart cells modulating cell fate and behavior. *Stem Cells*. 2015;**33**:2748-2761
- [37] Boomsma RA, Geenen DL. Evidence for transfer of membranes from mesenchymal stem cells to HL-1 cardiac cells. *Stem Cells International*. 2014;**2014**:653734
- [38] Choi HY, Moon SJ, Ratliff BB, Ahn SH, Jung A, Lee M, Lee S, Lim BJ, Kim BS, Plotkin MD, Ha SK, Park HC. Microparticles from kidney-derived mesenchymal stem cells act as carriers of proangiogenic signals and contribute to recovery from acute kidney injury. *PLoS One*. 2014;**9**:e87853
- [39] da Silva Meirelles L, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. *Stem Cells*. 2008;**26**:2287-2299
- [40] Devine SM, Peter S, Martin BJ, Barry F, McIntosh KR. Mesenchymal stem cells: Stealth and suppression. *Cancer Journal*. 2001;**7**(Suppl 2):S76-S82
- [41] Gao Y, Lu Z, Chen C, Cui X, Liu Y, Zheng T, Jiang X, Zeng C, Quan D, Wang Q. Mesenchymal stem cells and endothelial progenitor cells accelerate intra-aneurysmal tissue organization after treatment with SDF-1alpha-coated coils. *Neurological Research*. 2016;**38**:1-9
- [42] Melrose J. Strategies in regenerative medicine for intervertebral disc repair using mesenchymal stem cells and bioscaffolds. *Regenerative Medicine*. 2016;**11**:705-724
- [43] Xie X, Zhu J, Hu X, Dai L, Fu X, Zhang J, Duan X, Ao Y. A co-culture system of rat synovial stem cells and meniscus cells promotes cell proliferation and differentiation as compared to mono-culture. *Scientific Reports*. 2018;**8**:7693
- [44] Angele P, Kujat R, Koch M, Zellner J. Role of mesenchymal stem cells in meniscal repair. *Journal of Experimental Orthopaedics*. 2014;**1**:12
- [45] Yu H, Adesida AB, Jomha NM. Meniscus repair using mesenchymal stem cells—A comprehensive review. *Stem Cell Research & Therapy*. 2015;**6**:86
- [46] Zellner J, Hierl K, Mueller M, Pfeifer C, Berner A, Dienstknecht T, Krutsch W, Geis S, Gehmert S, Kujat R, Dendorfer S, Prantl L, Nerlich M, Angele P. Stem cell-based tissue-engineering for treatment of meniscal tears in the avascular zone. *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*. 2013;**101**:1133-1142
- [47] Zellner J, Mueller M, Berner A, Dienstknecht T, Kujat R, Nerlich M, Hennemann B, Koller M, Prantl L, Angele M, Angele P. Role of mesenchymal stem cells in tissue engineering of meniscus. *Journal of Biomedical Materials Research. Part A*. 2010;**94**:1150-1161
- [48] Zellner J, Pattappa G, Koch M, Lang S, Weber J, Pfeifer CG, Mueller MB, Kujat R, Nerlich M, Angele P.

Autologous mesenchymal stem cells or meniscal cells: What is the best cell source for regenerative meniscus treatment in an early osteoarthritis situation? *Stem Cell Research & Therapy*. 2017;**8**:225

[49] Appleyard RC, Burkhardt D, Ghosh P, Read R, Cake M, Swain MV, Murrell GA. Topographical analysis of the structural, biochemical and dynamic biomechanical properties of cartilage in an ovine model of osteoarthritis. *Osteoarthritis and Cartilage*. 2003;**11**:65-77

[50] Appleyard RC, Ghosh P, Swain MV. Biomechanical, histological and immunohistological studies of patellar cartilage in an ovine model of osteoarthritis induced by lateral meniscectomy. *Osteoarthritis and Cartilage*. 1999;**7**:281-294

[51] Armstrong S, Read R, Ghosh P. The effects of intraarticular hyaluronan on cartilage and subchondral bone changes in an ovine model of early osteoarthritis. *The Journal of Rheumatology*. 1994;**21**:680-688

[52] Bulgheroni P, Bulgheroni E, Regazzola G, Mazzola C. Polyurethane scaffold for the treatment of partial meniscal tears. Clinical results with a minimum two-year follow-up. *Joints*. 2013;**1**:161-166

[53] Burkhardt D, Hwa SY, Ghosh P. A novel microassay for the quantitation of the sulfated glycosaminoglycan content of histological sections: Its application to determine the effects of Diacerhein on cartilage in an ovine model of osteoarthritis. *Osteoarthritis and Cartilage*. 2001;**9**:238-247

[54] Cake M, Read R, Edwards S, Smith MM, Burkhardt D, Little C, Ghosh P. Changes in gait after bilateral meniscectomy in sheep: Effect of two hyaluronan preparations. *Journal of Orthopaedic Science*. 2008;**13**:514-523

[55] Cake MA, Read RA, Appleyard RC, Hwa SY, Ghosh P. The nitric oxide donor glyceryl trinitrate increases subchondral bone sclerosis and cartilage degeneration following ovine meniscectomy. *Osteoarthritis and Cartilage*. 2004;**12**:974-981

[56] Cake MA, Read RA, Corfield G, Daniel A, Burkhardt D, Smith MM, Little CB. Comparison of gait and pathology outcomes of three meniscal procedures for induction of knee osteoarthritis in sheep. *Osteoarthritis and Cartilage*. 2013;**21**:226-236

[57] Cake MA, Read RA, Guillou B, Ghosh P. Modification of articular cartilage and subchondral bone pathology in an ovine meniscectomy model of osteoarthritis by avocado and soya unsaponifiables (ASU). *Osteoarthritis and Cartilage*. 2000;**8**:404-411

[58] Cake MA, Smith MM, Young AA, Smith SM, Ghosh P, Read RA. Synovial pathology in an ovine model of osteoarthritis: Effect of intraarticular hyaluronan (Hyalgan). *Clinical and Experimental Rheumatology*. 2008;**26**:561-567

[59] Chatain F, Robinson AH, Adeleine P, Chambat P, Neyret P. The natural history of the knee following arthroscopic medial meniscectomy. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2001;**9**:15-18

[60] Englund M. The role of the meniscus in osteoarthritis genesis. *Rheumatic Diseases Clinics of North America*. 2008;**34**:573-579

[61] Englund M. The role of the meniscus in osteoarthritis genesis. *The Medical Clinics of North America*. 2009;**93**:37-43

[62] Ghosh P, Holbert C, Read R, Armstrong S. Hyaluronic acid (hyaluronan) in experimental osteoarthritis. *The Journal of*



Rheumatology. Supplement.  
 1995;**43**:155-157

[63] Ghosh P, Read R, Numata Y, Smith S, Armstrong S, Wilson D. The effects of intraarticular administration of hyaluronan in a model of early osteoarthritis in sheep. II. Cartilage composition and proteoglycan metabolism. *Seminars in Arthritis and Rheumatism*. 1993;**22**:31-42

[64] Hwa SY, Burkhardt D, Little C, Ghosh P. The effects of orally administered diacerein on cartilage and subchondral bone in an ovine model of osteoarthritis. *The Journal of Rheumatology*. 2001;**28**:825-834

[65] Jarraya M, Roemer FW, Englund M, Crema MD, Gale HI, Hayashi D, Katz JN, Guermazi A. Meniscus morphology: Does tear type matter? A narrative review with focus on relevance for osteoarthritis research. *Seminars in Arthritis and Rheumatism*. 2017;**46**:552-561

[66] Little C, Smith S, Ghosh P, Bellenger C. Histomorphological and immunohistochemical evaluation of joint changes in a model of osteoarthritis induced by lateral meniscectomy in sheep. *The Journal of Rheumatology*. 1997;**24**:2199-2209

[67] McDaniel D, Tilton E, Dominick K, Flory K, Ernest T, Johnson JC, Main DC, Kondrashov P. Histological characteristics of knee menisci in patients with osteoarthritis. *Clinical Anatomy*. 2017;**30**:805-810

[68] Oakley SP, Lassere MN, Portek I, Szomor Z, Ghosh P, Kirkham BW, Murrell GA, Wulf S, Appleyard RC. Biomechanical, histologic and macroscopic assessment of articular cartilage in a sheep model of osteoarthritis. *Osteoarthritis and Cartilage*. 2004;**12**:667-679

[69] Oakley SP, Portek I, Szomor Z, Appleyard RC, Ghosh P,

Kirkham BW, Murrell GA, Lassere MN. Arthroscopy—A potential “gold standard” for the diagnosis of the chondropathy of early osteoarthritis. *Osteoarthritis and Cartilage*. 2005;**13**:368-378

[70] Shakespeare DT, Rigby HS. The bucket-handle tear of the meniscus. A clinical and arthrographic study. *Journal of Bone and Joint Surgery*. 1983;**65**:383-387

[71] Smith MM, Cake MA, Ghosh P, Schiavinato A, Read RA, Little CB. Significant synovial pathology in a meniscectomy model of osteoarthritis: Modification by intra-articular hyaluronan therapy. *Rheumatology (Oxford, England)*. 2008;**47**:1172-1178

[72] Tasker T, Waugh W. Articular changes associated with internal derangement of the knee. *Journal of Bone and Joint Surgery. British Volume (London)*. 1982;**64**:486-488

[73] Young AA, Smith MM, Smith SM, Cake MA, Ghosh P, Read RA, Melrose J, Sonnabend DH, Roughley PJ, Little CB. Regional assessment of articular cartilage gene expression and small proteoglycan metabolism in an animal model of osteoarthritis. *Arthritis Research & Therapy*. 2005;**7**:R852-R861

[74] Ghosh P, Read R, Armstrong S, Wilson D, Marshall R, McNair P. The effects of intraarticular administration of hyaluronan in a model of early osteoarthritis in sheep. I. Gait analysis and radiological and morphological studies. *Seminars in Arthritis and Rheumatism*. 1993;**22**:18-30

[75] Seil R, Becker R. Time for a paradigm change in meniscal repair: Save the meniscus! *Knee Surgery, Sports Traumatology, Arthroscopy*. 2016;**24**:1421-1423

[76] Beaufils P, Becker R, Kopf S, Englund M, Verdonk R, Ollivier M, Seil R.



- Surgical management of degenerative meniscus lesions: The 2016 ESSKA meniscus consensus. *Joints*. 2017;**5**:59-69
- [77] Little CB, Ghosh P, Bellenger CR. Topographic variation in biglycan and decorin synthesis by articular cartilage in the early stages of osteoarthritis: An experimental study in sheep. *Journal of Orthopaedic Research*. 1996;**14**:433-444
- [78] Melrose J, Smith S, Cake M, Read R, Whitelock J. Comparative spatial and temporal localisation of perlecan, aggrecan and type I, II and IV collagen in the ovine meniscus: An ageing study. *Histochemistry and Cell Biology*. 2005;**124**:225-235
- [79] Young AA, McLennan S, Smith MM, Smith SM, Cake MA, Read RA, Melrose J, Sonnabend DH, Flannery CR, Little CB. Proteoglycan 4 downregulation in a sheep meniscectomy model of early osteoarthritis. *Arthritis Research & Therapy*. 2006;**8**:R41
- [80] Melrose J, Fuller ES, Roughley PJ, Smith MM, Kerr B, Hughes CE, Caterson B, Little CB. Fragmentation of decorin, biglycan, lumican and keratocan is elevated in degenerate human meniscus, knee and hip articular cartilages compared with age-matched macroscopically normal and control tissues. *Arthritis Research & Therapy*. 2008;**10**:R79
- [81] Fuller E, Little CB, Melrose J. Interleukin-1 $\alpha$  induces focal degradation of biglycan and tissue degeneration in an in-vitro ovine meniscal model. *Experimental and Molecular Pathology*. 2016;**101**:214-220
- [82] Fuller ES, Smith MM, Little CB, Melrose J. Zonal differences in meniscus matrix turnover and cytokine response. *Osteoarthritis and Cartilage*. 2012;**20**:49-59
- [83] Melrose J, Fuller EM, Little CB. The biology of meniscal pathology in osteoarthritis and its contribution to joint disease: Beyond simple mechanics. *Connective Tissue Research*. 2016, 2017;**58**(3-4):282-294
- [84] Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, Holsten D, Bulgheroni P, Monllau JC, Berbig R, Lagae K, Crespo R, Marcacci M. Two-year clinical results of lateral collagen meniscus implant: A multicenter study. *Arthroscopy*. 2015;**31**:1269-1278
- [85] Bouyarmine H, Beaufils P, Pujol N, Bellemans J, Roberts S, Spalding T, Zaffagnini S, Marcacci M, Verdonk P, Womack M, Verdonk R. Polyurethane scaffold in lateral meniscus segmental defects: Clinical outcomes at 24 months follow-up. *Orthopaedics & Traumatology, Surgery & Research*. 2014;**100**:153-157
- [86] Vrancken AC, Buma P, van Tienen TG. Synthetic meniscus replacement: A review. *International Orthopaedics*. 2013;**37**:291-299
- [87] Hansen R, Choi G, Bryk E, Vigorita V. The human knee meniscus: A review with special focus on the collagen meniscal implant. *Journal of Long-Term Effects of Medical Implants*. 2011;**21**:321-337
- [88] Baynat C, Andro C, Vincent JP, Schiele P, Buisson P, Dubrana F, Gunepin FX. Actifit synthetic meniscal substitute: Experience with 18 patients in Brest, France. *Orthopaedics & Traumatology: Surgery & Research*. 2014;**100**:S385-S389
- [89] Dhollander A, Verdonk P, Verdonk R. Treatment of painful, irreparable partial meniscal defects with a polyurethane scaffold: Midterm clinical outcomes and survival analysis. *The American Journal of Sports Medicine*. 2016;**44**:2615-2621
- [90] Schuttler KF, Haberhauer F, Gesslein M, Heyse TJ, Figiel J, Lorbach O, Efe T, Roessler PP. Midterm follow-up after implantation of a polyurethane

meniscal scaffold for segmental medial meniscus loss: Maintenance of good clinical and MRI outcome. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2016;**24**:1478-1484

[91] De Coninck T, Elsner JJ, Linder-Ganz E, Cromheecke M, Shemesh M, Huyse W, Verdonk R, Verstraete K, Verdonk P. In-vivo evaluation of the kinematic behavior of an artificial medial meniscus implant: A pilot study using open-MRI. *Clinical Biomechanics (Bristol, Avon)*. 2014;**29**:898-905

[92] Elsner JJ, Portnoy S, Zur G, Guilak F, Shterling A, Linder-Ganz E. Design of a free-floating polycarbonate-urethane meniscal implant using finite element modeling and experimental validation. *Journal of Biomechanical Engineering*. 2010;**132**:095001

[93] Zur G, Linder-Ganz E, Elsner JJ, Shani J, Brenner O, Agar G, Hershman EB, Arnoczky SP, Guilak F, Shterling A. Chondroprotective effects of a polycarbonate-urethane meniscal implant: Histopathological results in a sheep model. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2011;**19**:255-263

[94] Kaleka CC, Debieux P, da Costa Astur D, Arliani GG, Cohen M. Updates in biological therapies for knee injuries: Menisci. *Current Reviews in Musculoskeletal Medicine*. 2014;**7**:247-255

[95] Hayes JC, Curley C, Tierney P, Kennedy JE. Biomechanical analysis of a salt-modified polyvinyl alcohol hydrogel for knee meniscus applications, including comparison with human donor samples. *Journal of the Mechanical Behavior of Biomedical Materials*. 2016;**56**:156-164

[96] Yoo JJ, Bichara DA, Zhao X, Randolph MA, Gill TJ. Implant-assisted meniscal repair in vivo using a chondrocyte-seeded flexible PLGA scaffold. *Journal of*

*Biomedical Materials Research. Part A*. 2011;**99**:102-108

[97] Lu HD, Cai DZ, Wu G, Wang K, Shi DH. Whole meniscus regeneration using polymer scaffolds loaded with fibrochondrocytes. *Chinese Journal of Traumatology*. 2011;**14**:195-204

[98] Tienen TG, Heijkants RG, de Groot JH, Pennings AJ, Schouten AJ, Veth RP, Buma P. Replacement of the knee meniscus by a porous polymer implant: A study in dogs. *The American Journal of Sports Medicine*. 2006;**34**:64-71

[99] Buma P, van Tienen T, Veth R. The collagen meniscus implant. *Expert Review of Medical Devices*. 2007;**4**:507-516

[100] Frank RM, Cole BJ. Meniscus transplantation. *Current Reviews in Musculoskeletal Medicine*. 2015;**8**:443-450

[101] Lin DD, Picardo NE, Adesida A, Khan WS. Clinical studies using biological and synthetic materials for meniscus replacement. *Current Stem Cell Research & Therapy*. 2016;**12**:348-353

[102] Bakarich SE, Gorkin R 3rd, In Het Panhuis M, Spinks GM. Three-dimensional printing fiber reinforced hydrogel composites. *ACS Applied Materials & Interfaces*. 2014;**6**:15998-16006

[103] Szoika A, Lalh K, Andrews SHJ, Jomha NM, Osswald M, Adesida AB. Biomimetic 3D printed scaffolds for meniscus tissue engineering. *Bioprinting*. 2017;**8**:1-7

[104] Yang F, Tadapelli V, Wiley BJ. 3D printing of a double network hydrogel with a compression strength and elastic Modulus greater than those of cartilage. *ACS. Biomaterials*. 2017;**3**:863-869

[105] Zhang ZZ, Wang SJ, Zhang JY, Jiang WB, Huang AB, Qi YS, Ding JX,

- Chen XS, Jiang D, Yu JK. 3D-printed poly(epsilon-caprolactone) scaffold augmented with mesenchymal stem cells for total meniscal substitution: A 12- and 24-week animal study in a rabbit model. *The American Journal of Sports Medicine*. 2017;**45**:1497-1511
- [106] Lee CH, Rodeo SA, Fortier LA, Lu C, Eriskien C, Mao JJ. Protein-releasing polymeric scaffolds induce fibrochondrocytic differentiation of endogenous cells for knee meniscus regeneration in sheep. *Science Translational Medicine*. 2014;**6**:266ra171
- [107] Spees JL, Lee RH, Gregory CA. Mechanisms of mesenchymal stem/stromal cell function. *Stem Cell Research & Therapy*. 2016;**7**:125
- [108] Shi X, Liu J, Yang T, Zhang Y, Li T, Chen J. TLR2/NFkappaB signalling regulates endogenous IL-6 release from marrow-derived mesenchymal stromal cells to suppress the apoptosis of PC12 cells injured by oxygen and glucose deprivation. *Molecular Medicine Reports*. 2016;**13**:5358-5364
- [109] Song YS, Joo HW, Park IH, Shen GY, Lee Y, Shin JH, Kim H, Kim KS. Bone marrow mesenchymal stem cell-derived vascular endothelial growth factor attenuates cardiac apoptosis via regulation of cardiac miRNA-23a and miRNA-92a in a rat model of myocardial infarction. *PLoS One*. 2017;**12**:e0179972
- [110] Bifari F, Lisi V, Mimiola E, Pasini A, Krampera M. Immune modulation by mesenchymal stem cells. *Transfusion Medicine and Hemotherapy*. 2008;**35**:194-204
- [111] Bruno S, Deregibus MC, Camussi G. The secretome of mesenchymal stromal cells: Role of extracellular vesicles in immunomodulation. *Immunology Letters*. 2015;**168**:154-158
- [112] Caplan AI, Sorrell JM. The MSC curtain that stops the immune system. *Immunology Letters*. 2015;**168**:136-139
- [113] Fibbe WE, Nauta AJ, Roelofs H. Modulation of immune responses by mesenchymal stem cells. *Annals of the New York Academy of Sciences*. 2007;**1106**:272-278
- [114] Rasmusson I. Immune modulation by mesenchymal stem cells. *Experimental Cell Research*. 2006;**312**:2169-2179
- [115] Caplan AI. Mesenchymal stem cells: Time to change the name! *Stem Cells Translational Medicine*. 2017;**6**:1445-1451
- [116] Trounson A, McDonald C. Stem cell therapies in clinical trials: Progress and challenges. *Cell Stem Cell*. 2015;**17**:11-22
- [117] Barry F, Murphy JM, O'Brien T, Mahon B. Mesenchymal stem cell transplantation for tissue repair. *Seminars in Plastic Surgery*. 2005;**19**:229-239
- [118] Ansari S, Chen C, Xu X, Annabi N, Zadeh HH, Wu BM, Khademhosseini A, Shi S, Moshaverinia A. Muscle tissue engineering using gingival mesenchymal stem cells encapsulated in alginate hydrogels containing multiple growth factors. *Annals of Biomedical Engineering*. 2016;**44**:1908-1920
- [119] Hellstrom M, Moreno-Moya JM, Bandstein S, Bom E, Akouri RR, Miyazaki K, Maruyama T, Brannstrom M. Bioengineered uterine tissue supports pregnancy in a rat model. *Fertility and Sterility*. 2016;**106**:487-496
- [120] Hutchinson ID, Rodeo SA, Perrone GS, Murray MM. Can platelet-rich plasma enhance anterior cruciate ligament and meniscal repair? *The Journal of Knee Surgery*. 2015;**28**:19-28
- [121] Murphy M, Barry F. Cellular chondroplasty: A new technology for joint regeneration. *The Journal of Knee Surgery*. 2015;**28**:45-50
- [122] Ozpur MA, Guneren E, Canter HI, Karaaltin MV, Ovali E, Yogun FN,



Baygol EG, Kaplan S. Generation of skin tissue using adipose tissue-derived stem cells. *Plastic and Reconstructive Surgery*. 2016;**137**:134-143

[123] Pantcheva P, Reyes S, Hoover J, Kaelber S, Borlongan CV. Treating non-motor symptoms of Parkinson's disease with transplantation of stem cells. *Expert Review of Neurotherapeutics*. 2015;**15**:1231-1240

[124] Saini JS, Temple S, Stern JH. Human retinal pigment epithelium stem cell (RPESC). *Advances in Experimental Medicine and Biology*. 2016;**854**:557-562

[125] Tilokee EL, Latham N, Jackson R, Mayfield AE, Ye B, Mount S, Lam BK, Suuronen EJ, Ruel M, Stewart DJ, Davis DR. Paracrine engineering of human explant-derived cardiac stem cells to over-express stromal-cell derived factor 1alpha enhances myocardial repair. *Stem Cells*. 2016;**34**:1826-1835

[126] Abumaree M, Al Jumah M, Pace RA, Kalionis B. Immunosuppressive properties of mesenchymal stem cells. *Stem Cell Reviews*. 2012;**8**:375-392

[127] Dimarino AM, Caplan AI, Bonfield TL. Mesenchymal stem cells in tissue repair. *Frontiers in Immunology*. 2013;**4**:201

[128] Parekkadan B, Milwid JM. Mesenchymal stem cells as therapeutics. *Annual Review of Biomedical Engineering*. 2010;**12**:87-117

[129] Prockop DJ, Oh JY. Mesenchymal stem/stromal cells (MSCs): Role as guardians of inflammation. *Molecular Therapy*. 2012;**20**:14-20

[130] Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal stem cell secretome: Toward cell-free therapeutic strategies in regenerative medicine. *International Journal of Molecular Sciences*. 2017;**18**. pii: E1852

[131] Ansboro S, Greiser U, Barry F, Murphy M. Strategies for improved targeting of therapeutic cells: Implications for tissue repair. *European Cells & Materials*. 2012;**23**:310-318 discussion 318-319

[132] Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. *Journal of Cellular Biochemistry*. 2006;**98**:1076-1084

[133] Caplan AI. Mesenchymal stem cells: The past, the present, the future. *Cartilage*. 2010;**1**:6-9

[134] Caplan AI. Adult mesenchymal stem cells: When, where, and how. *Stem Cells International*. 2015;**2015**:628767

[135] Barry F, Murphy M. Mesenchymal stem cells in joint disease and repair. *Nature Reviews Rheumatology*. 2013;**9**:584-594

[136] Guescini M, Guidolin D, Vallorani L, Casadei L, Gioacchini AM, Tibollo P, Battistelli M, Falcieri E, Battistin L, Agnati LF, Stocchi V. C2C12 myoblasts release micro-vesicles containing mtDNA and proteins involved in signal transduction. *Experimental Cell Research*. 2010;**316**:1977-1984

[137] Yang J, Liu XX, Fan H, Tang Q, Shou ZX, Zuo DM, Zou Z, Xu M, Chen QY, Peng Y, Deng SJ, Liu YJ. Extracellular vesicles derived from bone marrow mesenchymal stem cells protect against experimental colitis via attenuating colon inflammation, oxidative stress and apoptosis. *PLoS One*. 2015;**10**:e0140551

[138] Ong E, Chimutengwende-Gordon M, Khan W. Stem cell therapy for knee ligament, articular cartilage and meniscal injuries. *Current Stem Cell Research & Therapy*. 2013;**8**:422-428

[139] Pereira H, Frias AM, Oliveira JM, Espregueira-Mendes J, Reis RL. Tissue engineering and regenerative medicine



strategies in meniscus lesions.  
*Arthroscopy*. 2011;**27**:1706-1719

[140] Scordino LE, Deberardino TM. Biologic enhancement of meniscus repair. *Clinics in Sports Medicine*. 2012;**31**:91-100

[141] Vangsness CT Jr, Farr J 2nd, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: A randomized, double-blind, controlled study. *The Journal of Bone and Joint Surgery. American Volume*. 2014;**96**:90-98

[142] Horie M, Driscoll MD, Sampson HW, Sekiya I, Caroom CT, Prockop DJ, Thomas DB. Implantation of allogenic synovial stem cells promotes meniscal regeneration in a rabbit meniscal defect model. *The Journal of Bone and Joint Surgery. American Volume*. 2012;**94**:701-712

[143] Horie M, Sekiya I, Muneta T, Ichinose S, Matsumoto K, Saito H, Murakami T, Kobayashi E. Intra-articular injected synovial stem cells differentiate into meniscal cells directly and promote meniscal regeneration without mobilization to distant organs in rat massive meniscal defect. *Stem Cells*. 2009;**27**:878-887

[144] Moriguchi Y, Tateishi K, Ando W, Shimomura K, Yonetani Y, Tanaka Y, Kita K, Hart DA, Gobbi A, Shino K, Yoshikawa H, Nakamura N. Repair of meniscal lesions using a scaffold-free tissue-engineered construct derived from allogenic synovial MSCs in a miniature swine model. *Biomaterials*. 2013;**34**:2185-2193

[145] Nakagawa Y, Muneta T, Kondo S, Mizuno M, Takakuda K, Ichinose S, Tabuchi T, Koga H, Tsuji K, Sekiya I. Synovial mesenchymal stem cells promote healing after meniscal repair in microminipigs. *Osteoarthritis and Cartilage*. 2015;**23**:1007-1017

[146] Qi Y, Yang Z, Ding Q, Zhao T, Huang Z, Feng G. Targeted transplantation of iron oxide-labeled, adipose-derived mesenchymal stem cells in promoting meniscus regeneration following a rabbit massive meniscal defect. *Experimental and Therapeutic Medicine*. 2016;**11**:458-466

[147] Toratani T, Nakase J, Numata H, Oshima T, Takata Y, Nakayama K, Tsuchiya H. Scaffold-free tissue-engineered allogenic adipose-derived stem cells promote meniscus healing. *Arthroscopy*. 2017;**33**:346-354

[148] Ding Z, Huang H. Mesenchymal stem cells in rabbit meniscus and bone marrow exhibit a similar feature but a heterogeneous multi-differentiation potential: Superiority of meniscus as a cell source for meniscus repair. *BMC Musculoskeletal Disorders*. 2015;**16**:65

[149] Ferris D, Frisbie D, Kisiday J, McIlwraith CW. In vivo healing of meniscal lacerations using bone marrow-derived mesenchymal stem cells and fibrin glue. *Stem Cells International*. 2012;**2012**:691605

[150] Yoo JU, Barthel TS, Nishimura K, Solchaga L, Caplan AI, Goldberg VM, Johnstone B. The chondrogenic potential of human bone-marrow-derived mesenchymal progenitor cells. *The Journal of Bone and Joint Surgery. American Volume*. 1998;**80**:1745-1757

[151] Osawa A, Harner CD, Gharaibeh B, Matsumoto T, Mifune Y, Kopf S, Ingham SJ, Schreiber V, Usas A, Huard J. The use of blood vessel-derived stem cells for meniscal regeneration and repair. *Medicine and Science in Sports and Exercise*. 2013;**45**:813-823

[152] Chew E, Prakash R, Khan W. Mesenchymal stem cells in human meniscal regeneration: A systematic review. *Annals of Medicine and Surgery*. 2017;**24**:3-7

[153] Pak J, Lee JH, Park KS, Jeon JH, Lee SH. Potential use of mesenchymal stem

cells in human meniscal repair: Current insights. *Open Access Journal of Sports Medicine*. 2017;**8**:33-38

[154] Niu W, Guo W, Han S, Zhu Y, Liu S, Guo Q. Cell-based strategies for meniscus tissue engineering. *Stem Cells International*. 2016;**2016**:4717184

[155] Huang H, Wang S, Gui J, Shen H. A study to identify and characterize the stem/progenitor cell in rabbit meniscus. *Cytotechnology*. 2016;**68**:2083-2103

[156] Julke H, Mainil-Varlet P, Jakob RP, Brehm W, Schafer B, Nesic D. The role of cells in meniscal guided tissue regeneration: A proof of concept study in a goat model. *Cartilage*. 2015;**6**:20-29

[157] Whitehouse MR, Howells NR, Parry MC, Austin E, Kafienah W, Brady K, Goodship AE, Eldridge JD, Blom AW, Hollander AP. Repair of torn avascular meniscal cartilage using undifferentiated autologous mesenchymal stem cells: From in vitro optimization to a first-in-human study. *Stem Cells Translational Medicine*. 2017;**6**:1237-1248

[158] Yuan X, Wei Y, Villasante A, Ng JJD, Arkonac DE, Chao PG, Vunjak-Novakovic G. Stem cell delivery in tissue-specific hydrogel enabled meniscal repair in an orthotopic rat model. *Biomaterials*. 2017;**132**:59-71

[159] McCorry MC, Puetzer JL, Bonassar LJ. Characterization of mesenchymal stem cells and fibrochondrocytes in three-dimensional co-culture: Analysis of cell shape, matrix production, and mechanical performance. *Stem Cell Research & Therapy*. 2016;**7**:39

[160] Kremer A, Ribitsch I, Reboredo J, Durr J, Egerbacher M, Jenner F, Walles H. Three-dimensional coculture of meniscal cells and mesenchymal stem cells in collagen type I hydrogel on a small intestinal matrix—A pilot study toward equine meniscus tissue engineering. *Tissue Engineering. Part A*. 2017;**23**:390-402

[161] Farrugia BL, Lord MS, Whitelock JM, Melrose J. Harnessing chondroitin sulphate in composite scaffolds to direct progenitor and stem cell function for tissue repair. *Biomaterials Science*. 2018;**6**:947-957

[162] Arnoczky SP, Warren RF. Microvasculature of the human meniscus. *The American Journal of Sports Medicine*. 1982;**10**:90-95

[163] Kobayashi K, Fujimoto E, Deie M, Sumen Y, Ikuta Y, Ochi M. Regional differences in the healing potential of the meniscus—an organ culture model to eliminate the influence of microvasculature and the synovium. *The Knee*. 2004;**11**:271-278

[164] Cui X, Hasegawa A, Lotz M, D'Lima D. Structured three-dimensional co-culture of mesenchymal stem cells with meniscus cells promotes meniscal phenotype without hypertrophy. *Biotechnology and Bioengineering*. 2012;**109**:2369-2380

[165] Cook JL, Smith PA, Bozynski CC, Kuroki K, Cook CR, Stoker AM, Pfeiffer FM. Multiple injections of leukoreduced platelet rich plasma reduce pain and functional impairment in a canine model of ACL and meniscal deficiency. *Journal of Orthopaedic Research*. 2016;**34**:607-615

[166] Freymann U, Metzlauff S, Kruger JP, Hirsh G, Endres M, Petersen W, Kaps C. Effect of human serum and 2 different types of platelet concentrates on human meniscus cell migration, proliferation, and matrix formation. *Arthroscopy*. 2016;**32**:1106-1116

[167] Griffin JW, Hadeed MM, Werner BC, Diduch DR, Carson EW, Miller MD. Platelet-rich plasma in meniscal repair: Does augmentation improve surgical outcomes? *Clinical Orthopaedics and Related Research*. 2015;**473**:1665-1672

[168] Howard D, Shepherd JH, Kew SJ, Hernandez P, Ghose S, Wardale JA,

- Rushton N. Release of growth factors from a reinforced collagen GAG matrix supplemented with platelet rich plasma: Influence on cultured human meniscal cells. *Journal of Orthopaedic Research*. 2014;**32**:273-278
- [169] Kaminski R, Kulinski K, Kozar-Kaminska K, Wielgus M, Langner M, Wasko MK, Kowalczewski J, Pomianowski S. A prospective, randomized, double-blind, parallel-group, placebo-controlled study evaluating meniscal healing, clinical outcomes, and safety in patients undergoing meniscal repair of unstable, complete vertical meniscal tears (bucket handle) augmented with platelet-rich plasma. *BioMed Research International*. 2018;**2018**:9315815
- [170] Kwak HS, Nam J, Lee JH, Kim HJ, Yoo JJ. Meniscal repair in vivo using human chondrocyte-seeded PLGA mesh scaffold pretreated with platelet-rich plasma. *Journal of Tissue Engineering and Regenerative Medicine*. 2017;**11**:471-480
- [171] Pujol N, Salle De Chou E, Boisrenoult P, Beaufils P. Platelet-rich plasma for open meniscal repair in young patients: Any benefit? *Knee Surgery, Sports Traumatology, Arthroscopy*. 2015;**23**:51-58
- [172] Gu Y, Zhu W, Hao Y, Lu L, Chen Y, Wang Y. Repair of meniscal defect using an induced myoblast-loaded polyglycolic acid mesh in a canine model. *Experimental and Therapeutic Medicine*. 2012;**3**:293-298
- [173] Zorzi C, Rigotti S, Screpis D, Giordan N, Piovan G. A new hydrogel for the conservative treatment of meniscal lesions: A randomized controlled study. *Joints*. 2015;**3**:136-145
- [174] Baek J, Sovani S, Glembotski NE, Du J, Jin S, Grogan SP, D'Lima DD. Repair of avascular meniscus tears with electrospun collagen scaffolds seeded with human cells. *Tissue Engineering. Part A*. 2016;**22**:436-448
- [175] Li P, Zhang W, Yu H, Zheng L, Yang L, Liu G, Sheng C, Gui H, Ni S, Shi F. Applying electrospun gelatin/poly(lactic acid-co-glycolic acid) bilayered nanofibers to fabrication of meniscal tissue engineering scaffold. *Journal of Nanoscience and Nanotechnology*. 2016;**16**:4718-4726
- [176] Martin JT, Milby AH, Ikuta K, Poudel S, Pfeifer CG, Elliott DM, Smith HE, Mauck RL. A radiopaque electrospun scaffold for engineering fibrous musculoskeletal tissues: Scaffold characterization and in vivo applications. *Acta Biomaterialia*. 2015;**26**:97-104
- [177] Schwartz JA, Wang W, Goldstein T, Grande DA. Tissue engineered meniscus repair: Influence of cell passage number, tissue origin, and biomaterial carrier. *Cartilage*. 2014;**5**:165-171
- [178] Shimomura K, Bean AC, Lin H, Nakamura N, Tuan RS. In vitro repair of meniscal radial tear using aligned electrospun nanofibrous scaffold. *Tissue Engineering. Part A*. 2015;**21**:2066-2075
- [179] Oda S, Otsuki S, Kurokawa Y, Hoshiyama Y, Nakajima M, Neo M. A new method for meniscus repair using type I collagen scaffold and infrapatellar fat pad. *Journal of Biomaterials Applications*. 2015;**29**:1439-1448
- [180] Kwak HS, Nam J, Lee JH, Kim HJ, Yoo JJ. Meniscal repair in vivo using human chondrocyte-seeded PLGA mesh scaffold pretreated with platelet-rich plasma. *Journal of Tissue Engineering and Regenerative Medicine*. 2014;**11**:471-480
- [181] Dai Z, Li K, Chen Z, Liao Y, Yang L, Liu C, Ding W. Repair of avascular meniscal injuries using juvenile meniscal fragments: An in vitro organ culture study. *Journal of Orthopaedic Research*. 2013;**31**:1514-1519



- [182] Freymann U, Endres M, Goldmann U, Sittlinger M, Kaps C. Toward scaffold-based meniscus repair: Effect of human serum, hyaluronic acid and TGF- $\alpha$ 3 on cell recruitment and re-differentiation. *Osteoarthritis and Cartilage*. 2013;**21**:773-781
- [183] Cucchiaroni M, Schmidt K, Frisch J, Kohn D, Madry H. Promotes the healing of human meniscal lesions ex vivo on explanted menisci. *The American Journal of Sports Medicine*. 2015;**43**:1197-1205
- [184] Zhang H, Leng P, Zhang J. Enhanced meniscal repair by overexpression of hIGF-1 in a full-thickness model. *Clinical Orthopaedics and Related Research*. 2009;**467**:3165-3174
- [185] Zhang HN, Leng P, Wang YZ, Zhang J. Treating human meniscal fibrochondrocytes with hIGF-1 gene by liposome. *Clinical Orthopaedics and Related Research*. 2009;**467**:3175-3182
- [186] Forriol F, Longo UG, Duarte J, Ripalda P, Vaquero J, Loppini M, Romeo G, Campi S, Khan WS, Muda AO, Denaro V. VEGF, BMP-7, Matrigel(TM), hyaluronic acid, in vitro cultured chondrocytes and trephination for healing of the avascular portion of the meniscus. An experimental study in sheep. *Current Stem Cell Research & Therapy*. 2014;**10**:69-76
- [187] Kawanishi Y, Nakasa T, Shoji T, Hamanishi M, Shimizu R, Kamei N, Usman MA, Ochi M. Intra-articular injection of synthetic microRNA-210 accelerates avascular meniscal healing in rat medial meniscal injured model. *Arthritis Research & Therapy*. 2014;**16**:488
- [188] He W, Liu YJ, Wang ZG, Guo ZK, Wang MX, Wang N. Enhancement of meniscal repair in the avascular zone using connective tissue growth factor in a rabbit model. *Chinese Medical Journal*. 2011;**124**:3968-3975
- [189] Freymann U, Endres M, Neumann K, Scholman HJ, Morawietz L, Kaps C. Expanded human meniscus-derived cells in 3-D polymer-hyaluronan scaffolds for meniscus repair. *Acta Biomaterialia*. 2012;**8**:677-685
- [190] Lee HP, Kaul G, Cucchiaroni M, Madry H. Nonviral gene transfer to human meniscal cells. Part I: Transfection analyses and cell transplantation to meniscus explants. *International Orthopaedics*. 2014;**38**:1923-1930
- [191] Lee HP, Rey-Rico A, Cucchiaroni M, Madry H. Nonviral gene transfer into human meniscal cells. Part II: Effect of three-dimensional environment and overexpression of human fibroblast growth factor 2. *International Orthopaedics*. 2014;**38**:1931-1936
- [192] Narita A, Takahara M, Sato D, Ogino T, Fukushima S, Kimura Y, Tabata Y. Biodegradable gelatin hydrogels incorporating fibroblast growth factor 2 promote healing of horizontal tears in rabbit meniscus. *Arthroscopy*. 2012;**28**:255-263
- [193] Pabbruwe MB, Kafienah W, Tarlton JF, Mistry S, Fox DJ, Hollander AP. Repair of meniscal cartilage white zone tears using a stem cell/collagen-scaffold implant. *Biomaterials*. 2010;**31**:2583-2591
- [194] Kopf S, Birkenfeld F, Becker R, Petersen W, Starke C, Wruck CJ, Tohidnezhad M, Varoga D, Pufe T. Local treatment of meniscal lesions with vascular endothelial growth factor. *The Journal of Bone and Joint Surgery. American Volume*. 2010;**92**:2682-2691
- [195] Riera KM, Rothfus NE, Wilusz RE, Weinberg JB, Guilak F, McNulty AL. Interleukin-1, tumor necrosis factor- $\alpha$ , and transforming growth factor- $\beta$  1 and integrative meniscal repair: Influences on meniscal cell



proliferation and migration. *Arthritis Research & Therapy*. 2011;**13**:R187

[196] Forriol F, Ripalda P, Duart J, Esparza R, Gortazar AR. Meniscal repair possibilities using bone morphogenetic protein-7. *Injury*. 2014;**45**(Suppl 4):S15-S21

[197] Kean CO, Brown RJ, Chapman J. The role of biomaterials in the treatment of meniscal tears. *PeerJ*. 2017;**5**:e4076

[198] Monibi FA, Cook JL. Tissue-derived extracellular matrix bioscaffolds: Emerging applications in cartilage and meniscus repair. *Tissue Engineering. Part B, Reviews*. 2017;**23**:386-398

[199] Numpaisal PO, Rothrauff BB, Gottardi R, Chien CL, Tuan RS. Rapidly dissociated autologous meniscus tissue enhances meniscus healing: An in vitro study. *Connective Tissue Research*. 2017;**58**:355-365

[200] Rey-Rico A, Cucchiaroni M, Madry H. Hydrogels for precision meniscus tissue engineering: A comprehensive review. *Connective Tissue Research*. 2017;**58**:317-328

[201] Ishimura M, Ohgushi H, Habata T, Tamai S, Fujisawa Y. Arthroscopic meniscal repair using fibrin glue. Part II: Clinical applications. *Arthroscopy*. 1997;**13**:558-563

[202] Ishimura M, Ohgushi H, Habata T, Tamai S, Fujisawa Y. Arthroscopic meniscal repair using fibrin glue. Part I: Experimental study. *Arthroscopy*. 1997;**13**:551-557

[203] Patel S, Rodriguez-Merchan EC, Haddad FS. The use of fibrin glue in surgery of the knee. *Journal of Bone and Joint Surgery. British Volume (London)*. 2010;**92**:1325-1331

[204] Graham LD, Danon SJ, Johnson G, Braybrook C, Hart NK, Varley RJ, Evans MD, McFarland GA, Tyler

MJ, Werkmeister JA, Ramshaw JA. Biocompatibility and modification of the protein-based adhesive secreted by the Australian frog *Notaden bennetti*. *Journal of Biomedical Materials Research. Part A*. 2010;**93**:429-441

[205] Graham LD, Glattauer V, Huson MG, Maxwell JM, Knott RB, White JW, Vaughan PR, Peng Y, Tyler MJ, Werkmeister JA, Ramshaw JA. Characterization of a protein-based adhesive elastomer secreted by the Australian frog *Notaden bennetti*. *Biomacromolecules*. 2005;**6**:3300-3312

[206] Graham LD, Glattauer V, Li D, Tyler MJ, Ramshaw JA. The adhesive skin exudate of *Notaden bennetti* frogs (Anura: Limnodynastidae) has similarities to the prey capture glue of *Euperipatoides* sp. velvet worms (Onychophora: Peripatopsidae). *Comparative Biochemistry and Physiology. Part B, Biochemistry & Molecular Biology*. 2013;**165**:250-259

[207] Millar NL, Bradley TA, Walsh NA, Appleyard RC, Tyler MJ, Murrell GA. Frog glue enhances rotator cuff repair in a laboratory cadaveric model. *Journal of Shoulder and Elbow Surgery*. 2009;**18**:639-645

[208] Nowak R. Frog glue repairs damaged cartilage. *New Scientist*. 5 October 2004

[209] Szomor Z, Murrell GAC, Appleyard RC. Use of *Notaden bennetti* frog-glue for meniscal repair. *Techniques in Knee Surgery*. 2008;**7**:261-265

[210] Bochynska AI, Hannink G, Grijpma DW, Buma P. Tissue adhesives for meniscus tear repair: An overview of current advances and prospects for future clinical solutions. *Journal of Materials Science. Materials in Medicine*. 2016;**27**:85

[211] Bochynska AI, Van Tienen TG, Hannink G, Buma P, Grijpma

DW. Development of biodegradable hyper-branched tissue adhesives for the repair of meniscus tears. *Acta Biomaterialia*. 2016;**32**:1-9

[212] Brubaker CE, Messersmith PB. The present and future of biologically inspired adhesive interfaces and materials. *Langmuir*. 2012;**28**:2200-2205

[213] Shao H, Bachus KN, Stewart RJ. A water-borne adhesive modeled after the sandcastle glue of *P. californica*. *Macromolecular Bioscience*. 2009;**9**:464-471

[214] Simson JA, Strehin IA, Allen BW, Elisseeff JH. Bonding and fusion of meniscus fibrocartilage using a novel chondroitin sulfate bone marrow tissue adhesive. *Tissue Engineering. Part A*. 2013;**19**:1843-1851

[215] Kamimura T, Kimura M. Meniscal repair of degenerative horizontal cleavage tears using fibrin clots: Clinical and arthroscopic outcomes in 10 cases. *Orthopaedic Journal of Sports Medicine*. 2014;**2**:2325967114555678

[216] Guo J, Wang W, Hu J, Xie D, Gerhard E, Nisic M, Shan D, Qian G, Zheng S, Yang J. Synthesis and characterization of anti-bacterial and anti-fungal citrate-based mussel-inspired bioadhesives. *Biomaterials*. 2016;**85**:204-217

[217] Mehdizadeh M, Weng H, Gyawali D, Tang L, Yang J. Injectable citrate-based mussel-inspired tissue bioadhesives with high wet strength for sutureless wound closure. *Biomaterials*. 2012;**33**:7972-7983

[218] Weir C, Morel-Kopp MC, Gill A, Tinworth K, Ladd L, Hunyor SN, Ward C. Mesenchymal stem cells: Isolation, characterisation and in vivo fluorescent dye tracking. *Heart, Lung & Circulation*. 2008;**17**:395-403

[219] Tienen TG, Heijkants RG, de Groot JH, Schouten AJ, Pennings AJ, Veth RP,

Buma P. Meniscal replacement in dogs. Tissue regeneration in two different materials with similar properties. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2006;**76**:389-396

[220] Wong CC, Kuo TF, Yang TL, Tsuang YH, Lin MF, Chang CH, Lin YH, Chan WP. Platelet-rich fibrin facilitates rabbit meniscal repair by promoting Meniscocytes proliferation, migration, and extracellular matrix synthesis. *International Journal of Molecular Sciences*. 2017;**18**. pii: E1722

[221] Chahla J, Kennedy NI, Geeslin AG, Moatshe G, Cinque ME, DePhillipo NN, LaPrade RF. Meniscal repair with fibrin clot augmentation. *Arthroscopy Techniques*. 2017;**6**:e2065-e2069

[222] Kowalski C, Gallo RA. Platelet-rich fibrin clot-augmented repair of horizontal cleavage meniscal tear. *Arthroscopy Techniques*. 2017;**6**:e2047-e2051

[223] Pan Z, Wu Y, Zhang X, Fu Q, Li J, Yang Y, Yu D, Xu Y, Lu X, Sun H, Heng BC, Bunpetch V, Zhang S, Ouyang H. Delivery of epidermal growth factor receptor inhibitor via a customized collagen scaffold promotes meniscal defect regeneration in a rabbit model. *Acta Biomaterialia*. 2017;**62**:210-221

[224] Zhang S, Matsushita T, Kuroda R, Nishida K, Matsuzaki T, Matsumoto T, Takayama K, Nagai K, Oka S, Tabata Y, Nagamune K, Kurosaka M. Local administration of simvastatin stimulates healing of an avascular meniscus in a rabbit model of a meniscal defect. *The American Journal of Sports Medicine*. 2016;**44**:1735-1743

[225] Bochynska AI, Hannink G, Verhoeven R, Grijpma DW, Buma P. The effect of tissue surface modification with collagenase and addition of TGF-beta3 on the healing potential of meniscal tears repaired with tissue glues in vitro. *Journal of Materials Science. Materials in Medicine*. 2017;**28**:22