HHS Public Access

Author manuscript

Clin Sports Med. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Clin Sports Med. 2020 January ; 39(1): 125–163. doi:10.1016/j.csm.2019.08.003.

Meniscus repair and regeneration: A systematic review from a basic and translational science perspective

John Twomey-Kozak, B.S.[1], **Chathuraka Jayasuriya, Ph.D.**[1,*]

[1.]Department of Orthopaedics, Brown University/Rhode Island Hospital, Box G-A1, Providence, Rhode Island, 02912, USA

Abstract

Meniscus injuries are among the most common athletic injuries and result in functional impairment in the knee. Repair is crucial for pain relief and prevention of degenerative joint diseases like osteoarthritis. Current treatments, however, do not produce long-term improvements. Thus, recent research has been investigating new therapeutic options for regenerating injured meniscal tissue. This review comprehensively details the current methodologies being explored in the basic sciences to stimulate better meniscus injury repair. Furthermore, it describes how these pre-clinical strategies may improve current paradigms of how meniscal injuries are clinically treated through a unique and alternative perspective to traditional clinical methodology.

Keywords

Meniscus; stem cell; tissue engineering; scaffolds; regenerative medicine

INTRODUCTION

The meniscal injury is a major cause of functional impairment in the knee joint. This fibrocartilaginous tissue was once considered to be an unnecessary, vestigial appendage that could be sacrificed with minimal consideration[1,2]. This total meniscectomy technique, though common in the past, has largely been abandoned as long-term results after major meniscectomy reported disappointing and adverse effects such as the degradation of underlying articular cartilage and subsequent development of early osteoarthritis[1,3,4,5]. As clinical medicine and basic science has evolved, we now properly recognize the meniscus as a necessary structure in the knee joint that is vital for biomechanical and anatomical purposes[6]. Namely, the menisci are key for knee stability, distributing axial load, shock absorption between the articular cartilage of the tibia and femur, and nutrient distribution for protection of the underlying articular cartilage[1,6,7].

[*]Send correspondence to: chathuraka_jayasuriya@brown.edu.

NO Disclosures

Biochemical Composition:

The meniscus is composed of a dense extracellular matrix (ECM) that consists of 72% water, 22% collagen and 0.8% glycosaminoglycans (GAGs)[8,9]. The remaining dry weight is made up of proteins, glycoproteins and interspersed cells within the meniscus. These cells are referred to as *fibrochondrocytes*, as they have a marked resemblance to both fibroblasts and chondrocytes and synthesize the ECM and meniscal tissue [10,9,11]. Type I collagen is expressed abundantly throughout the meniscus, while Type II collagen is detected in the inner region. The interactions of these collagens, GAGs and proteins likely account for the compressive load resistance, lubrication and semi-elastic deformation properties of the meniscus[9,12].

Biomechanics and Gross Anatomy:

The knee joint capsule houses the menisci, which are smooth, lubricated, crescent-shaped discs composed of fibrocartilaginous tissue with a medial and lateral component. These menisci sit on the natural contours of the tibial plateau between the femoral condyle and tibia of the knee. Joint motion and the biomechanical stressors associated with physical activity are important factors in determining the orientation of the collagen fibers that provide meniscal structure. There are two types of structural fibers that make up the meniscus: Type I and Type II collagen. These fibers are typically oriented based on the layers of the meniscus from surface to core: **superficial** (random orientation), **lamellar** (more organized radially at anterior and posterior horns) and **deep** (oriented circumferentially with some radial fibers) and allow the meniscus to expand under compressive forces to increase contact area of the joint[6,13].

A capillary network that originates in the synovium provides a direct blood supply to the meniscus--but only in certain “zones” of the meniscus. These zones are named based on the extent of vascularization of each respective region. The peripheral, outer third of the meniscus is known as the “red-red” zone, which has an excellent prognosis for repair as the blood supply is directly provided here[14,15]. The intermediate “red-white” zone receives a limited blood supply and usually has a fair prognosis, as long as it is at the border of the vascular zone. The inner “white-white” zone of the meniscus, however, is completely avascular and presents a poor prognosis for recovery, regeneration and healing[15]. The lack of blood supply in this region confers difficulties for lesion/injury repair and regeneration of injured meniscus tissue. Current clinical reparative capacity seems to be restricted mainly to the peripheral, “red-red” vascular region of the meniscus, where there is a sufficient blood supply to promote healing. Biological tissue engineering and cell-based therapies constitute pre-clinical meniscus repair/regeneration strategies that offer much promise for the future[8,16].

Injury Prevalence and Call For Repair

With a combination of axial loading and rotational forces that generate a shear force, the meniscus is subject to both acute and degenerative injury making it arguably the most commonly injured tissue in the knee[17]. The epidemiological data for the incidence and prevalence of meniscus injuries and clinical repair is limited, but seems to be rising every year. Logerstedt et al., Hede et al., Jones et al. reported that the incidence rate of meniscus

injury was 0.33 and 0.61 per 1000 person-years, with a prevalence of 12–14%[18–20]. In the United States, of the estimated 850,000–1,000,000 cases per year in 2010, 10–20% of orthopaedic surgeries involved surgical repair of the meniscus[21,22].

Clinicians and scientists alike agree that meniscal injury is considered an essential predictor of the subsequent development of degenerative joint disease, and specifically strongly correlated with the development of early osteoarthritis[23–25]. Therefore, considering the high incidence rate and increased risk of osteoarthritis development, it is critical to develop an ideal method for the prevention, repair and treatment of injured meniscus tissue. Recent efforts have been directed towards regeneration of native meniscus tissue rather than meniscal resection. Although surgical techniques for mending damaged meniscus tissue have been extensively explored in the clinical setting, these repair attempts continue to fail for various reasons (i.e. lack of longevity, tissue avascularity, etc.). Thus, it seems ideal to reframe this problem through an alternative perspective from the lens of basic science and regenerative medicine. This avenue, rather than meniscectomy or resection, has become an intriguing idea for addressing meniscal injuries in pre-clinical models. This review comprehensively details the current methodologies that are being explored in the basic sciences to stimulate better meniscus injury repair. Furthermore, it describes how these pre-clinical strategies may stand to improve current paradigms of how meniscal injuries are clinically treated through a unique and alternative perspective to traditional clinical methodology.

CURRENT CLINICAL PARADIGM

When clinicians come across an irreparable tear in the meniscus or with patients who have undergone a total or subtotal meniscectomy, meniscal allograft transplantation (MAT) may be considered as a preferred modality for knee joint restoration[26]. However, the indications for MAT remain controversial, as meniscal transplantation has been demonstrated to produce unsatisfactory results in the knee including issues with graft size mismatching, donor incompatibility and sterilization, transplant remodeling and stability, and long-term chondroprotection[27–29].

With an increasing incidence rate of meniscal injury, the urgent need for an innovative and efficacious repair strategy has become evident. Due to the aforementioned limitations, MAT cannot serve as a “fix-all” model. Because of this, the development of acellular biological scaffolds emerged as an interesting alternative to MAT. The primary goal of using these scaffolds is to use a minimally immunogenic 3D tissue-replacement that stimulates migration, proliferation, and integration of endogenous/native cells into the scaffold for the purpose of restoring meniscus function with a secondary goal of chondroprotection with respect to joint-loading function[30].

Collagen Meniscus Implant (CMI)

Currently in the United States, there is only one FDA-approved cell-free scaffold for meniscus replacement: the Collagen Meniscus Implant (CMI). This scaffold was the first regenerative technique specifically invented and used for meniscus replacement in the clinical setting[31–33]. The CMI is composed primarily of type I collagen fibers and GAGs

isolated from bovine achilles tendon that are sterilized via gamma-irradiation[34]. This scaffold is perforated and porous to allow for ideal cell infiltration for better tissue integration purposes; clinical studies have indeed reported this native cell integration into the CMI[35]. In theory, this scaffold appears to be a better replacement than MAT, as it is less destructive to the joint, it's shape can be custom-fit and it is composed of biological tissue--thus virtually eliminating the risk of an immunologic response from donor mismatch[36]. However, there has been debated controversy in terms of efficacy of the CMI. In 1999, Rodkey et al reported that 8 patients who underwent arthroscopic replacement with the CMI at short-term follow-up demonstrated tissue regeneration, no degenerative progression and chondroprotection of the joint surface[37]. These results were confirmed by radiographs and the histological grading confirmed new fibrocartilage formation. Further, a medium-term follow-up study was done by Bulgheroni et al in 2010, with 34 patients who underwent CMI implantation[38]. These patients were evaluated 2–5 years later and showed good to excellent results with chondroprotection, no further degradation of the joint surface and some newly synthesized tissue that appeared healthy[38]. However, the CMI had rescinded in size, and was presenting some clinical challenges. Long-term follow-up studies have demonstrated similar adverse results, as the implant significantly shrank in size after 5–6 years--possibly due to degradation--and led to decreased biomechanical function[39]. The dangers of a potential size mismatch in the joint post-implantation of the CMI would change the mechanical environment of the knee and decrease the chondroprotection of the underlying cartilage, resulting in further joint damage and likely further the progression of osteoarthritis[40,41].

Platelet-Rich Plasma/Fibrin (PRP/PRF)

Within the field of orthopaedics, the use of platelet rich plasma (PRP) as a clinical therapeutic technique has seen a rapid increase in popularity. In the United States alone, it is estimated that 86,000 athletes are treated with PRP annually[42]. PRP is an autologous blood product containing numerous growth factors and cytokines that is being implemented as a clinical intervention for musculoskeletal defects including meniscus injuries[43]. The increased concentration of platelets and growth factors are purported to aid in the native wound-healing process through the stimulation of meniscus cell proliferation and migration, angiogenesis and matrix synthesis[42,43]. Despite its growing popularity both in medicine and in the mainstream media, the efficacy and usage of this biological treatment remains controversial.

Pujol et al. attempted to augment repair and promote meniscal healing through the use of PRP treatment for horizontal meniscal tears[44]. At a minimum of 24 months postoperatively, they reported a slight improvement in functional outcome and MRI-documented healing during midterm follow-up in young patients[44]. Further, Blanke et al. treated 10 patients with grade II meniscal lesions with percutaneous injections of PRP in seven-day intervals. Four of ten patients showed a decrease of the meniscal lesion and relief of pain in a follow-up MRI and pain score after 6 months[45]. In addition to slight pain relief and improved functional outcomes, certain groups have demonstrated the growth factor and immunologic response associated with PRP treatment. Wasterlain et al. found that serum growth factors were significantly elevated after PRP injection, which may contribute to a better repair

response[42]. It is believed that PRP may augment healing by increasing the levels of growth factors and cytokines localized to the injury site[46–48].

Although these groups have demonstrated positive results, there are also many others that report either (1) no significant improvements using PRP treatment or (2) adverse outcomes associated with PRP treatment. For example, one study conducted at the University of Virginia performed 35 isolated arthroscopic meniscal repairs with and without PRP augmentation and reported no clinical advantage of using PRP over non-PRP after a minimum follow-up of 2 years[48]. Further, Zellner et al. 2010, Zellner et al. 2013 reported that implantation of a composite matrix loaded with PRP failed to improve meniscal healing in the avascular zone[49,50]. This was characterized by poor tear filling without meniscal regeneration after a 3-month period. Available *in vitro* data reporting on the efficacy of PRP treatment for meniscal tears appears to be mixed as well, with groups finding contrasting results[47,48,51–53]. It should be noted that recent studies have found some success by using various mesenchymal stem cell sources supplemented with PRP for meniscus repair[49]-- however, this field is still being investigated and needs more published data.

Although some studies have demonstrated the benefits of PRP as a therapeutic for meniscal regeneration and healing, the clinical efficacy and results seem to be mixed and unclear. More clinical studies with larger sample sizes and medium to long-term follow-ups with measurable outcomes such as histological analysis and functional grading of meniscus repair are needed to determine the true efficacy of PRP.

ACELLULAR MENISCUS REGENERATION AND REPAIR TECHNIQUES IN BASIC/TRANSLATIONAL SCIENCE

Decellularized Scaffold and Growth Factors

As an alternative method for a biomimetic cell-free scaffold, some have suggested utilizing the process of decellularization of intact, native meniscus tissue in order to preserve the native structure and fiber-level organization. This is a significant advantage compared to other scaffolds since these retain the naturally occurring collagen networks present in the healthy meniscus. Further, this type of scaffold would have a much lower risk of an adverse immunogenic reaction. However, one major challenge associated with using decellularized tissue is the low infiltration of cells into these scaffolds, due to their dense extracellular matrix (ECM) structure as well as improper fitting and mismatch sizing issues in the joint.

In response to this, some groups have suggested using biomimetic, biosynthetic scaffolds coupled with chemotactic agents such as growth factors to stimulate native cell migration and infiltration to enhance integration into the scaffold. These growth factors that are used usually play a significant role in limb development. Local delivery or supplementation of growth factors may create a beneficial microenvironment to promote endogenic repair and integration for engineered tissue-scaffolds[54]. Growth factors act on target cells to stimulate cellular growth, proliferation, healing, and cellular differentiation. This effect is achieved usually through a receptor-mediated mechanism; whereby a growth factor will bind to its

respective receptor and trigger a secondary system of signals or messengers to activate nuclear genes that control different cellular processes[54,55].

Certain growth factors have been demonstrated to play a key role in the metabolic activity of meniscal fibrochondrocytes: regulating development, homeostasis, cell rejuvenation and regeneration. With this idea in mind, there have been a myriad of different growth factor delivery methods to treat native fibrochondrocytes in both *in vivo* and *in vitro* experimental studies with the ultimate goal of optimizing meniscus tissue-engineering and repair[56–58]. Specifically, this review focuses on the supplementation of growth factors to meniscal fibrochondrocytes (the native cell of the meniscus) or direct addition of growth factors to meniscal tissue. The most commonly used growth factors for treating meniscal tissue or meniscal fibrochondrocytes seem to be Basic Fibroblast Growth Factor (bFGF), Transforming Growth Factor Beta 1 and 3 (TGFB1, TGFB3) and Insulin-Like Growth Factor-1 IGF-1, with others being used less frequently. (Table 1)

bFGF—Fibroblast growth factor-basic (bFGF) is a bioactive protein that acts as both a growth factor and signaling protein that possesses broad mitogenic and cell survival activities, which play a primary role in angiogenesis, mitogenesis of fibroblasts, tyrosine activation and inhibition of bone morphogenetic proteins (BMPs). When culturing meniscal fibrochondrocytes in monolayer, Hiraide et al. and Kasemkijwattan et al. found that addition of bFGF resulted in enhanced cell proliferation[59,60]. Further *in vitro* studies have demonstrated that bFGF addition resulted in enhanced native tissue integration into various scaffold models and improved meniscus repair[54,61].

TGF-Beta—The multifunctional cytokine superfamily that is transforming growth factor beta (TGFB) is involved in a receptor kinase mechanism that initiates a signaling cascade, which activates many downstream substrates and proteins. The role of TGFB isoforms TGFB1 and TGFB3 have in the regulation of differentiation, chemotaxis, cell proliferation and the immune response has been studied extensively in orthopaedic research. *In vitro* supplementation of TGFB1 and TGFB3 to meniscal fibrochondrocytes in monolayer, synthetic scaffolds and explant tissue culture models have generally yielded positive results. These include increased GAG and proteoglycan synthesis by native cells, enhanced native cell proliferation, regeneration of articular cartilage, and targeted homing of endogenous cells[54,62–68].

IGF-1—Insulin Growth-Factor 1 (IGF-1) is a member of the insulin-related peptide family that plays an important role in childhood growth with continued anabolic effects in adults. IGF-1 is a primary mediator of the effects of growth hormone (GH), which stimulates systemic body growth and is of key interest in the orthopaedic research field for musculoskeletal purposes. Addition of IGF-1 to meniscal fibrochondrocytes in monolayer, scaffold culture and explant culture in vitro resulted in enhanced cell proliferation, increased GAG and proteoglycan production, and better homing of cells[69–72].

CELL-BASED MENISCAL REGNERATION AND AUGMENTATION TECHNIQUES IN BASIC/TRANSLATIONAL SCIENCE

The cell-based therapeutic potential of human multipotent mesenchymal stem cells (MSC) has long been investigated in the field of meniscal tissue healing and regenerative medicine. This tissue engineering strategy is closer to translation than some might think, and there are even some clinical trials currently underway (ClinicalTrials.gov Identifier: []). Currently, groups are investigating several promising cell types and isolation methods to identify ideal MSC sources for meniscus repair. This exploration has produced encouraging but mixed results that are likely due to varying experimental conditions used in each individual investigation. This has made it difficult to directly compare efficacious outcomes in the field of tissue engineering and regeneration. With an aim to alleviate these difficulties, in 2006, the International Society for Cellular Therapy (ISCT) published a minimal criteria to define human MSCs[78]. First, the MSCs must adhere to tissue culture plastic when maintained in standard culture conditions. Second, the phenotypic profile and epitope expression of MSCs must be at the very minimum: CD105+, CD73+, CD90+ while being CD45-, CD34-. CD14-, CD11b-, CD79a- or CD19-[78]. Third, MSCs must demonstrate trilineage potential, meaning that they can be differentiated into osteoblasts, adipocytes and chondroblasts *in vitro*[78]. In addition, it is believed that these stem cells must be self-renewing and have a high proliferation capacity in the sense that they can perpetually divide/replicate while maintaining an undifferentiated state[79].

Therefore, this review will focus exclusively on what we, in accordance with the ISCT minimal criterion, consider the mesenchymal stem cell sources most widely used and most-promising in the basic and translational science research setting for cell-based meniscus regeneration: Bone-Marrow derived mesenchymal stem cells (BM-MSCs), Adipose-derived stem cells (ADSCs), Synovium-derived stem cells (SDSCs), Native meniscal fibrochondrocytes and progenitor cells, Articular cartilage-derived progenitor cells (CPCs).

In the following paragraphs, we will report on preclinical, *in vivo* studies with data on meniscal tear augmentation using various cell-based therapies. This data focuses TABLE 2, which provides the cell type and quantity used, the animal model that was used, the length of time of the study, the measurements of successful treatment outcomes (histology, MRI, macroscopic, formation of neo-meniscal tissue, presence of fibrochondrocytes, etc.) and finally the limitations for each cell type.

CELL TYPES AND THEIR PRECLINICAL RESULTS

Bone-Marrow Mesenchymal Stem Cells (BM-MSCs)—Cell-based meniscal regeneration strategies using various mesenchymal stem cell sources have been well documented in the literature. There is still no true consensus as to which cell source is best for meniscus repair. However, bone-marrow derived mesenchymal stem cells (BM-MSCs) are often considered the ‘gold standard’ in the field of cell-based regenerative medicine since they are used so frequently and have been thoroughly investigated since they were first discovered by Friedenstein et al. in 1968[30,80,81]. These cells are capable of multipotency and

exhibit a phenotypic marker profile that is characteristic of mesenchymal stem cells: CD44+, CD45-, CD54-, CD90+,, CD105+, CD166+, CD271+[78,82].

In 1999, Pittenger et al proposed a method of isolating BM-MSCs autologously from marrow aspirants during minimally invasive surgery that is still used today[83]. While these cells are relatively easy to collect, they only make up .0017%--.0201% of bone marrow cells[84]. It has been widely reported that BM-MSCs tend to demonstrate a robust chondrogenic response with elevated COL2A1 and matrix synthesis levels that seem beneficial for meniscus repair. However, these cells also have a harmful tendency to exhibit a hypertrophic phenotype[85–87]. This hypertrophic state has been illustrated specifically in meniscus co-culture studies[88]. The propensity of BM-MSCs for hypertrophic differentiation could be detrimental for tissue regeneration and engineering purposes. Currently, the need to address this limitation of the current cell sources used for meniscus repair seems to center on (1) finding a novel and ideal cell source that is more resistant to cellular hypertrophy or (2) modulating BM-MSCs in such a way to dampen hypertrophy. An ideal cell source would be capable of maintaining multipotency while resisting hypertrophy and terminal differentiation in cell-based meniscal tissue engineering applications.

Preclinical Applications of BM-MSCs Results: Bone marrow mesenchymal stem cells are the most thoroughly investigated and most frequently used cell source for meniscal repair in the field of regenerative medicine. These cells have been used in many preclinical meniscal repair studies. They have been utilized for the repair of meniscal tears[89–93] and various types of meniscal defects[49] as well as meniscus transections[94,95]. These studies use anywhere form $.1 \times 10^6$ -- 30×10^6 BM-MSCs for cell-based treatment depending on the animal model and size of the meniscus injury, and range from 3 weeks to 24 months. Further, since BM-MSCs have been widely utilized for this type of repair, there are many published findings that demonstrate both the advantages and limitations for using BM-MSCs in many small and larger animal models (TABLE 2).

Ferris et al. demonstrated in a horse model that intra-articular injection of $15–20 \times 10^6$ BM-MSCs postoperatively for meniscal lesions resulted in 75% return to some level of work compared to control groups after 24 months[96]. While this large animal model is beneficial as it is a good emulator of a human meniscus model, the outcome measurement of “returning to some level of work” is very limited. Further, it is difficult to assess the efficacy of BM-MSC mediated repair without histological data, mechanical testing, or MRI analysis. In another larger animal model, Desando et al. performed a unilateral medial meniscectomy in sheep and treated the injury with a Hyaff(®)-11 (HA) construct seeded with either autologous BM-MSCs (6×10^6 cells) or bone marrow concentrate (BMC)[97]. After 12 weeks post-op, minor joint healing and anti-inflammatory effects were noticed for both groups, however the BMC group actually allowed for the best meniscus regeneration[97]. Zellner et al. conducted a study where they created a defect in the avascular zone of a rabbit meniscus and treated the injury with an HA/collagen matrix scaffold that housed $.1 \times 10^6$ autologous BM-MSCs or a cell-free HA/collagen matrix scaffold alone[50]. After 12 weeks, the BM-MSC matrix constructs initiated some fibrocartilage-like tissue repair and exhibited better integration and biomechanical properties than the control group[50]. In two more recent studies, Zhang et al. and Koch et al. both performed meniscectomies in rabbits and used two different types of

scaffolds seeded with BM-MSCs for tissue regeneration and repair[98,99]. Zhang et al. used a PCL scaffold either cell-free or seeded with BM-MSCs and showed that after 24 weeks, the BM-MSC seeded scaffold group had a better gross meniscus appearance with higher expression of type I, II and III collagen and proteoglycan production found in native fibrochondrocytes with less cartilage degradation than any control group as well as better tensile and compressive properties[98]. In comparison, Koch et al. used a cell-free polyurethane Actifit scaffold as a control, or the Actifit implant seeded with BM-MSCs; each implant was sutured in place during the operation[99]. After 12 weeks, the results showed that both the cell-free and BM-MSC-loaded scaffolds led to well-integrated and stable meniscus-like repair tissue and dense vascularization[99]. The only difference between the groups was that the BM-MSC groups seemed to accelerate the healing response. Yuan et al. created a radial cut in a rat meniscus and treated it intra-articularly with human BM-MSCs housed in an injectable, decellularized extracellular matrix (ECM) cus ECM hydrogel were retained and contributed to tissue regeneration and protection from osteoarthritis development as evidenced by macroscopic and microscopic images. Perhaps their most significant findings, however, was that the injured tissue that received the ECM hydrogel + BM-MSC treatment did not demonstrate histological evidence of mineralization and was moderately negative for type X collagen staining[100]. This study is especially interesting as hypertrophy, senescence and evidence of adverse terminal differentiation to bone in BM-MSCs has been reported extensively both *in vitro* and *in vivo*[87,100,101]. These reports place emphasis on increased type X collagen expression, which has been detected in senescent and degenerative osteoarthritic menisci[102,103]. The limitations with this study, however, include a short length of follow-up time that may not allow for possible hypertrophic development or terminal differentiation to occur; both challenges that naturally arise with using BM-MSCs for meniscus repair. Further, the authors list the small sample size of rats and a lack of a larger animal model such as a rabbit, pig or sheep as major limitations that should be addressed in future work[100].

There have been many studies done to date using different and innovative delivery methods of BM-MSCs for meniscal repair, different quantities of cells, for different time period and different culturing conditions all aiming to treat different types of meniscus injury and regenerate damaged tissue in various animal models. However, the challenge of hypertrophy and mineralization always tends to arise when discussing the use of BM-MSCs as a cell source for meniscus repair. As mentioned before, high expression of hypertrophy and ossification markers generally correlate to calcification and a poor healing response *in vivo*[104–106] and represent a major challenge with using BM-MSCs for tissue engineering given their high expression of COL10A1 and other hypertrophic markers[107]. Currently, the need to address this limitation in meniscal tissue engineering and regeneration is evident and may focus on finding conditions that can better prevent hypertrophy in BM-MSCs themselves, or through the discovery of a new cell source that is more resistant to hypertrophy altogether.

Adipose-derived Stem Cells (ADSCs)—Adipose-derived stem cells (ADSCs) from the infrapatellar fat pad of the knee are considered to be a promising alternative cell source for cartilage and meniscus repair strategies. Zuk et al. first introduced ADSCs in 2002, when the

group isolated this multipotent, undifferentiated, self-renewing progenitor cell population from digested adipose tissue[108,109]. This heterogeneous population of cells was derived from the embryonic mesenchyme that contained an easily-isolated stroma[108]. Zuk et al. isolated these cells and coined the term 'processed lipoaspirate (PLA) cells'; demonstrating that they can be readily accessed from human adipose tissue. Further, Zuk et al. demonstrated that PLA cells expressed a phenotypic profile (CD marker antigens) and genotypic profile (mRNA levels and protein analysis) that resembled that of well-defined MSCs[108,109]. This CD marker profile was CD90+, CD105+, CD73+, CD44+ and CD166+. However, these ADSCs were negative for the hematopoietic markers CD45 and CD34[110]. Histological analysis using established staining methods have demonstrated the trilineage potential and multipotency of this cell source[108].

Although these cells are isolated from fatty tissue, they do possess the capability to undergo chondrogenic differentiation to produce proteoglycans and type II collagen. However, studies have demonstrated the limited chondrogenic potential of ADSCs in comparison to BM-MSCs[85,111]. Hamid et al. sought to induce chondrogenesis and characterize their capacity[112]. This group found that after one week in culture, the expression of chondrogenic genes (collagen type II, ACAN, COMP, ELASTIN and collagen type XI) was reduced significantly[112]. This dampened chondrogenic capacity may limit their consideration for meniscal and cartilaginous tissue repair. Further, Hamid et al. showed that there was a high expression of hypertrophy marker, type X collagen, after 3 weeks of chondrogenic induction[112]. This suggests that repeated induction of ADSCs may confer a hypertrophic state that is characterized by increased bone matrix synthesis and a suppressed chondrogenic program. This would be detrimental in the repair of the fibrocartilaginous meniscus tissue. With the exception of a few studies, it appears to be well-demonstrated that BM-MSCs have an enhanced potential for chondrogenesis as compared to ADSCs by measures of glycosaminoglycans (GAG) production, type II collagen gene expression and deposition, and pellet size[85,113,114].

Preclinical Applications of ADSCs Results: ADSCs extracted from the fat pad represent a bioavailable cell type that has been used for various types of tissue repair and regeneration strategies. It has only been within the last decade that ADSCs have been used specifically for meniscal tissue injury and regeneration. Most of the *in vivo* data currently available focuses on meniscus injury in smaller animal models like rabbit[115–117], with a few groups using larger models like equine and bovine (See TABLE 2). These studies range from 12-weeks to a maximum of 12 months in follow-up length after surgical injury and use a range of 0.1×10^6 to 20×10^6 ADSCs for therapeutic cell treatment. Ruiz-Iban et al. used sutures to close a meniscal lesion in the vascular zone of a rabbit and treated the site with ADSCs suspended in a hydrogel[115]. Although they demonstrated neo-meniscal tissue formation and reported that the ADSC-treated meniscus group had slight cellularity increase compared with normal tissue, their study is limited as there was no power analysis performed due to the small number of animals that were used per group and since the length of the study was only 12 weeks, longer-term studies are called for. In another study, Qi et al. labeled ADSCs with superparamagnetic iron-oxide (SPIO) and used magnets to target specific homing to the injured tissue site after meniscectomy in rabbits[116]. They reported that after 12 weeks there

was minimal neo-meniscal tissue present that integrated with the host meniscus (confirmed through histological data), but this tissue was abnormally shaped. Further, the targeting efficiency of the SPIO-labeled ADSCs was admittedly not high, as these cells migrated to other non-targeted tissue[116]. In a short-medium term study (7 months) Moradi et al. performed a complete meniscectomy in a rabbit and completely replaced the meniscus with a Polyvinyl alcohol/Chitosan (PVA/Ch) scaffold seeded with ADSCs[118]. They found no significant contribution in the healing process for the scaffold-seeded ADSC group, and even found a decreased chondrogenic response with lower Col II, ACAN and Col I mRNA expression levels present. This is a typical characteristic of ADSCs, and one that may be a hindrance for meniscal repair. To date, Gonzalez-Ferndandez et al. have been the only group to use a large-animal equine model for ADSC-mediated meniscal repair and regeneration[119]. In their study, they created a defect in the medial meniscus of an adult horse and filled it with autologous ADSCs. After 12 months post-op, their results were mixed with some defects appearing to be filled with fibrocartilaginous-like tissue, while others remained completely unfilled[119]. Since the application of ADSCs for meniscus repair and regeneration has been a recent phenomenon, current studies that are present in the literature lack significant larger animal data and longer-term follow up data. Additional studies should, therefore, include longer time points as well as biomechanical and biochemical analysis of the regenerated meniscal tissue to investigate the true efficacy of using ADSCs for meniscal repair and regeneration.

Synovium-Derived Stem Cells (SDSCs)—Synovium-derived stem cells (SDSCs) are a relatively newly utilized and promising cell source that are garnering a lot of attention in the field of meniscus repair. These are colony-forming cells that can be derived from the synovium of the knee during a simple arthroscopic procedure[23,120]. However, contrary to popular belief, the synovium only contains a small population of multipotent cells that can form colonies[23,121]. Nevertheless, these cells exhibit multipotent capability as well as surface epitope CD markers in accordance with the ISCT-established MSC marker criteria[122,123]. Namely, these ADSCs express CD90, CD166, CD44, CD105 and CD147[124].

This cell population has been shown to increase in number following injuries to the meniscus[122,125]. This suggests that this population may be an important cell source for meniscal repair. In multiple characterization studies comparing SDSCs to BM-MSCs, it has been demonstrated that SDSCs have greater chondrogenic capacity and adipogenic capacity than BM-MSCs[126–128]. Sakaguchi et al. also compared the osteogenic capacities of these cell types and found comparably high mineralization levels in BM-MSCs and SDSCs using Alizarin red-positive staining[126]. Further, RT-PCR results indicated high mRNA expression levels of osteogenic markers RUNX2 and BGLAP in cells derived from the knee synovium (SDSCs)[124,126]. Another study done by Pei et al. demonstrated that addition of TGF-B3 for chondrogenic induction *in vitro* resulted in an upregulation of COL10A1 and ALPL in porcine SCSC pellets compared to TBGF-B1[129]. While these studies illustrate the aforementioned favorable multipotency of SDSCs, it also points out a potential problem with using these cells to repair the fibrocartilaginous tissue of the meniscus: a high osteogenic capacity may be detrimental for repair in the long term. Stem cell induced mineralization and calcification of the meniscus could theoretically lead to ineffective repair as these cells

become hypertrophic and may potentially serve as a preamble to further joint disease such as osteoarthritis in the long-term. Therefore, it is ideal that cells used in meniscal repair and tissue regeneration exhibits high chondrogenic capacity, while simultaneously exhibiting low osteogenic and hypertrophy markers. As it stands now, long-term studies are required to fully explore the efficacy of SCSCs in meniscus tissue repair.

Preclinical Applications of SDSCs Results: Similar to ADSCs, synovium derived mesenchymal stem cells (SDSCs) are a new and promising cell source for meniscal repair. Although this source can be obtained from the synovium during a simple arthroscopic surgery, SDSCs have limited bioavailability since there is only a small population of these colony-forming cells present. Recently, the use of SDSCs for meniscus tissue engineering and repair strategies have been advocated for and investigated heavily[1,130,131]. The literature indicates that groups investigating this cell type for therapeutic repair have been conducting both small and larger animal model studies (TABLE 2). These studies range from 4 weeks to 6-month duration post-operation and use anywhere from $.20 \times 10^6$ to 50×10^6 SDSCs for cell treatment quantity. Hatsushika et al. investigated whether intra-articular injection of 10×10^6 SDSCs could enhance meniscal regeneration in a rabbit meniscal defect model[132]. The SDSC and control groups were compared macroscopically and histologically at various time points (1, 3, 4 and 6 months) and showed mixed results. While the histological score of the meniscus and chondroprotection was better in the SDSC group, the overall size and macroscopic view of the meniscus between groups was insignificant. As an alternative cell-delivery model to intra-articular injection, Katagiri et al. prepared SDSC aggregates in an effort to develop a more practical clinical solution for future human use[133]. They engineered aggregates consisting of $.25 \times 10^6$ SDSCs, placed them on a meniscal defect created in a rat and found regenerated meniscal tissue that had histological scores similar to normal menisci after 12 weeks[133]. In addition to small animal studies, the use of SDSCs for meniscus repair in large animals has been investigated with moderate success[134–136]. To comparatively investigate the efficacy of two different cell types for repairing a massive meniscal defect, Horie et al. injected either 5×10^6 dual luciferase Luc/LacZ+ SDSCs or 5×10^6 BM-MSCs into massive meniscectomized knees of wild-type rats[137]. After 12 weeks, the regenerated meniscal tissue in the SDSC group produced more type II collagen, proliferated at a higher rate than control or BM-MSC group and appeared macroscopically superior to the control group, but looked identical to the BM-MSC group. However, there were no noticeable differences of regenerated meniscus in morphology or histological scoring between the SDSC and BM-MSC groups.

While these studies have demonstrated that SDSCs and BM-MSCs are comparable in term of their repair capacity in both small and larger animal models, none of them have measured Collagen X or any other markers of cellular hypertrophy or osteoarthritic markers like MMPs either pre- or post-treatment. Moreover, since SDSCs are a fairly new cell source that is being used for meniscus repair, more studies in general are needed to better support the findings thus far. Further, the longest time period allowed for in the aforementioned studies was 6 months, which may not be enough time to evaluate proper repair capacity or possible longer-term effects of SDSCs for meniscus repair.

Native Meniscal Fibrochondrocytes (MFCs) + Meniscus-Derived Stem Cells— One of the most recent developments in cell-based meniscus repair/regeneration are meniscus-derived stem cells (MDSCs) or meniscal fibrochondrocytes (MFCs). The cellular component of the meniscus consists of a population of fibrochondrocytes living within the extracellular matrix[138]. Webber et al. first coined the term 'fibrochondrocytes' to describe these unique cells that they isolated from the menisci of New Zealand white rabbits in their 1985 study[139]. Moon et al. and Upton et al. suggested that location-specific MFCs respond to changing mechanical environments as the periphery of the meniscus contains cells that better resemble fibroblasts, while the inner rim of the meniscus behaves more like chondrocytes[140,141]. Biomechanically, the periphery of the meniscus is primarily responsible for shock absorption and tensile forces, while the inner meniscus acts as a direct point of contact for the femoral condyle, and is subject to compressive forces[140–142]. These meniscal fibrochondrocytes (MFCs) display properties of both fibroblasts and chondrocytes, regulating the crucial process of extracellular matrix synthesis and deposition in response to the mechanical stimuli present in the joint[138,142,143]. Depending on their position in the meniscus (inner zone vs. periphery), MFCs/MDSCs exhibit different morphologies and biochemical properties. For example, MFCs/MDSCs from the inner avascular region have a rounded morphology that resemble articular chondrocytes and are spaced out within extracellular matrix[105,144,106]. Conversely, MFCs/MDSCs isolated from the outer fibrous region are spindle-shaped and form gap junctions many other neighboring cells[105,106,144].

These MDSCs are reported to be highly adherent to tissue culture plastic, like all mesenchymal stem cells. Further these individual cells that migrate out of the tissue and adhere to the plastic tend to exhibit high colony-forming efficiency, exhibit trilineage potential and express common mesenchymal stem cell markers including CD44, CD90 and Nanog[23].

A significant challenge associated with using autologous MDSCs/MFCs for meniscus regeneration and repair is their extremely sparse population in the meniscus[144–147]. Perhaps an even larger problem, however, is the counterintuitive and invasive surgical technique that is required to isolate and extract this cell type. A piece of meniscus tissue would need to be excised from an intact meniscus, diced into small pieces, digested with a protease such as Collagenase or Pronase, expanded in monolayer culture and then collected for application. This is a lengthy and fairly common process, but more importantly one that involves injuring a healthy meniscus. This may mechanically compromise the tissue, thus decreasing tibiofemoral contact area and increasing the stress on the underlying cartilage which may further damage the joint[144,148,149].

Cartilage-derived progenitor cells (CPCs)—Similar to the tissue-derived mesenchymal cell types listed already, normal (non-arthritic) human articular cartilage also contains a tissue-specific mesenchymal stem/progenitor cell population that has been proposed for use in tissue repair applications[150,151]. These cells are often referred to as cartilage-derived chondrogenic progenitor cells (CPCs). It has been demonstrated that CPCs from healthy human articular cartilage samples can be effectively isolated using a differential adhesion assay to fibronectin[107,150,151]. The trilineage ability of CPCs to differentiate into osteogenic, adipogenic and chondrogenic tissue has also been

demonstrated *in vitro*[107,152,153] and *in ovo*[150]. These cells express mesenchymal stem cell surface markers CD44, CD49e, CD90, CD105, CD146 and CD166[154]. Furthermore, Williams et al. demonstrated the high telomerase activity and maintenance of telomere length in clonally isolated populations CPCs, which is a prototypical characteristic of a mesenchymal stem cell population[151,153]. CPCs from cartilage appear morphologically fibrochondrocyte-like and exhibit high colony-forming efficiency, expression of Notch1 gene and high chondrogenic potential[82,107,154–156].

The use of CPCs for meniscus repair and regeneration may confer benefits that expanded mature chondrocytes lack; including no terminal differentiation or de-differentiation, improved cell quality and enhanced potency[155]. The existence of this population within articular cartilage coupled with it's phenotypic profile, reduced propensity for hypertrophy and enhanced chondrogenic capacity suggests that CPCs may have the biological repertoire necessary for cell-based regeneration and repair of the meniscus.

As is the case with BM-MSCs and SDSCs, a major challenge for utilizing these cells for meniscus regeneration and repair is their sparse bioavailability. CPCs have been reported to compose about 1.47 +/− .16% of all cells from normal healthy human articular cartilage[157]. Despite their small population in cartilage, their high colony-forming capacity and proliferation rate is crucial for effective, therapeutic cell-based meniscus application. Although a current clinical model does not exist for deriving cartilage CPCs, there is the already established method of autologous chondrocyte implantation (ACI) where healthy chondrocytes are transferred from a non-load bearing region of cartilage to a tissue defect[158]. Hypothetically, it should be possible to mimic this ACI method to expand and relocate CPCs isolated from non-loadbearing regions for autologous cell-based delivery for meniscal repair. This cell source is still quite new for the purposes of meniscus repair, so ongoing research is being conducted with CPCs. However, based on CPCs phenotypic and genetic profile, coupled with their hypertrophy resistance and high chondrogenic capacity, we believe this stem cell source could represent ideal cell source for cell-based meniscal repair and regeneration.

Preclinical Applications of CPCs Results: Notably the newest cell type being used in the field of meniscus repair is a mesenchymal stem cell population derived from cartilage known as CPCs. As mentioned before, these cells are reported to be highly proliferative and possess beneficial multipotentiality[159]. Perhaps most importantly, they have a high chondrogenic potential and are resistant to terminal differentiation and hypertrophy with decreased levels of hypertrophy marker, COL10A1[107]. To date, only one study has been published using CPCs for meniscus repair. Jayasuriya et al. demonstrate how CPCs may be more suitable than BM-MSCs to mediate bridging and reintegration of fibrocartilage tissue tears in the meniscus using an *ex vivo* rat model[107]. In this study, a radial tear was created in the inner anterior horn of a rat meniscus, and co-cultured the torn menisci with 1×10^5 BM-MSCs, CPCs or no cells for 20 days. Results showed that the CPCs were able to initiate reintegration of a meniscus tissue tear in an explant culture, and demonstrated for the first time that CPCs produce a paracrine effect that improves the rate of meniscal fibrochondrocyte proliferation that was similar, if not better, than BM-MSCs. This was confirmed by histology, microscopic visualization and RT-PCR. Further, CPC-treated

menisci had significantly lower expression of hypertrophic marker COL10A1 mRNA levels, in comparison to the BM-MSC group. These findings suggest that CPCs from healthy human cartilage resist cellular hypertrophy and maintain high chondrogenic capacity, which are conducive for successful meniscus repair. However, since this is the only study of its kind thus far, the results are limited and it is clear that more research needs to be done in an *in vivo* animal model with longer-term results.

MESENCHYMAL STEM CELL DELIVERY METHOD

Biomaterial scaffolds for meniscus tissue engineering tend to vary significantly in terms of their material composition, biomimetic properties and 3D structure. With meniscal research expanding due to new biological advances in the basic science field, novel approaches and robust solutions for treating meniscal tears are emerging more frequently than ever. To this end, biomaterials that can be seeded or pre-treated with cells and successfully retain these cells in the scaffold appear to confer the best advantages for repair. Since these biomaterials must be able to beneficially interact with the surrounding tissue (biomimetic properties), the hope is that these different meniscus scaffolds will be able to improve or replace the anatomical defect. Ideally, an effective cell-based scaffold would (1) allow for a more robust repair response through the use of a mesenchymal stem cell source, and (2) enhance stimulate migration and integration of native meniscus fibrochondrocytes into the scaffold. Various cell populations have been investigated for this role (TABLE 2), with BM-MSCs being used most frequently as ideal choices for biomaterial engineering. Typically, this process of tissue-engineering a biomimetic scaffold involves the isolation of mesenchymal stem cells, which are then seeded into a biocompatible matrix or cell-carrier material that resembles the native ECM. This matrix should be able to securely house the cells to ensure that they stay in their desired and localized area when implanted into the joint. The most commonly used natural materials are type I and type II collagen-based scaffolds[160]. There are also many synthetic materials being designed such as polyglycolic acid, poly-L-lactic acid, polycaprolactone (PCL) and other composite mixtures[160,161]. Thus, an ideal meniscal biomaterial must promote anabolic activity; namely endogenous tissue repair and regeneration through a biomimetic scaffold that allows for cellular attachment and growth to promote ideal tissue-scaffold integration, while resisting terminal differentiation and hypertrophy.

References

1. Scotti C, Hirschmann MT, Antinolfi P, Martin I, Peretti GM. Meniscus repair and regeneration: Review on current methods and research potential. Eur Cells Mater 2013. doi:10.22203/eCM.v026a11.
2. Sutton J Ligaments: Their Nature and Morphology. Bristol Medico-Chirurgical J 1897;15(58):344.
3. Huckell JR Is meniscectomy a benign procedure? A long term follow up study. Can J Surg 1965;8:254–260.
4. Appel H Late results after meniscectomy in the knee joint: a clinical and roentgenologic follow up investigation. Acta Orthop Scand Suppl 1970;133:1–111. [PubMed: 5271191]
5. Allen PR, Denham R a, Swan a V. Late degenerative changes after meniscectomy. Factors affecting the knee after operation. J Bone Joint Surg Br 1984.

6. Makris EA, Hadidi P, Athanasiou KA. The knee meniscus: Structure-function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 2011. doi:10.1016/j.biomaterials.2011.06.037.
7. Seedhom BB, Hargreaves DJ. Transmission of the load in the knee joint with special reference to the role of the menisci. Part II: Experimental results, discussion and conclusions. Eng Med 1979. doi:10.1243/emed_jour_1979_008_051_02.
8. Tan GK, Cooper-White JJ. Interactions of meniscal cells with extracellular matrix molecules: Towards the generation of tissue engineered menisci. Cell Adhes Migr 2011. doi:10.4161/cam.5.3.14463.
9. Fox AJS, Bedi A, Rodeo SA. The Basic Science of Human Knee Menisci: Structure, Composition, and Function. Sports Health. 2012. doi:10.1177/1941738111429419.
10. McDevitt C, Miller R, Sprindler K. The cells and cell matrix interaction of the meniscus In: Mow V, Arnoczky S, Jackson D, eds. Knee Meniscus: Basic and Clinical Foundations. Raven Press; 1992:29–36.
11. Webber RJ, Norby DP, Malemud CJ, Goldberg VM, Moskowitz RW. Characterization of newly synthesized proteoglycans from rabbit menisci in organ culture. Biochem J 1984. doi:10.1042/bj2210875.
12. FITHIAN DC, KELLY MA, MOW VC. Material Properties and Structure-Function Relationships in the Menisci. Clin Orthop Relat Res 1990. doi:10.1097/00003086-199003000-00004.
13. Athanasiou KA, Sanchez-Adams J. Engineering the Knee Meniscus. Synth Lect Tissue Eng 2009. doi:10.2200/S00186ED1V01Y200903TIS001.
14. Beaufils P, Becker R, Kopf S, Matthieu O, Pujol N. The knee meniscus: management of traumatic tears and degenerative lesions. EFORT Open Rev 2017. doi:10.1302/2058-5241.2.160056.
15. Mordecai SC. Treatment of meniscal tears: An evidence based approach. World J Orthop 2014. doi:10.5312/wjo.v5.i3.233.
16. Jarraya M, Roemer FW, Englund M, et al. Meniscus morphology: Does tear type matter? A narrative review with focus on relevance for osteoarthritis research. Semin Arthritis Rheum 2017. doi:10.1016/j.semarthrit.2016.11.005.
17. Fox AJS, Wanivenhaus F, Burge AJ, Warren RF, Rodeo SA. The human meniscus: A review of anatomy, function, injury, and advances in treatment. Clin Anat 2015. doi:10.1002/ca.22456.
18. Baker BE, Peckham AC, Pupparo F, Sanborn JC. Review of meniscal injury and associated sports. Am J Sports Med 1985. doi:10.1177/036354658501300101.
19. Lauder TD, Baker SP, Smith GS, Lincoln AE. Sports and physical training injury hospitalizations in the Army. Am J Prev Med 2000. doi:10.1016/S0749-3797(99)00174-9.
20. Jones JC, Burks R, Owens BD, Sturdivant RX, Svoboda SJ, Cameron KL. Incidence and risk factors associated with meniscal injuries among active-duty US Military service members. J Athl Train 2012. doi:10.4085/1062-6050-47.1.67.
21. Logerstedt DS, Snyder-Mackler L, Ritter RC, Axe MJ, Godges J. Knee Pain and Mobility Impairments: Meniscal and Articular Cartilage Lesions. J Orthop Sport Phys Ther 2010. doi:10.2519/jospt.2010.0304.
22. Hede A, Jensen DB, Blyme P, Sonne-Holm S. Epidemiology of meniscal lesions in the knee: 1,215 open operations in copenhagen 1982–84. Acta Orthop 1990. doi:10.3109/17453679008993557.
23. Korpershoek JV, De Windt TS, Hagmeijer MH, Vonk LA, Saris DBF. Cell-based meniscus repair and regeneration: At the brink of clinical translation?: A systematic review of preclinical studies. Orthop J Sport Med 2017. doi:10.1177/2325967117690131.
24. Englund M, Roemer FW, Hayashi D, Crema MD, Guermazi A. Meniscus pathology, osteoarthritis and the treatment controversy. Nat Rev Rheumatol 2012. doi:10.1038/nrrheum.2012.69.
25. McDermott ID, Amis AA. The consequences of meniscectomy. J Bone Jt Surg - Br Vol 2006. doi:10.1302/0301-620X.88B12.18140.
26. Lee SR, Kim JG, Nam SW. The tips and pitfalls of meniscus allograft transplantation. Knee Surg Relat Res 2012. doi:10.5792/ksrr.2012.24.3.137.
27. De Bruycker M, Verdonk PCM, Verdonk RC. Meniscal allograft transplantation: a meta-analysis. SICOT-J 2017. doi:10.1051/sicotj/2017016.

28. Noyes FR, Barber-Westin SD. Long-term survivorship and function of meniscus transplantation. Am J Sports Med 2016. doi:10.1177/0363546516646375.
29. Rosso F, Bisicchia S, Bonasia DE, Amendola A. Meniscal allograft transplantation: A systematic review. Am J Sports Med 2015. doi:10.1177/0363546514536021.
30. Guo W, Xu W, Wang Z, Chen M, Hao C, Zheng X, Huang J, Sui X, Yuan 1, Zhang Y, Wang M, Li X, Wang Z, Peng J, Wang A, Wang Y, Liu S, Lu SGQ Cell-Free Strategies for Repair and Regeneration of Meniscus Injuries through the Recruitment of Endogenous Stem/Progenitor Cells. Stem Cells Int 2018.
31. Stone KR, Rodkey WG, Webber R, McKinney L, Steadman JR. Meniscal regeneration with copolymeric collagen scaffolds. In vitro and in vivo studies evaluated clinically, histologically, and biochemically. In: American Journal of Sports Medicine.; 1992. doi: 10.1177/036354659202000202.
32. Stone KR, Steadman JR, Rodkey WG, Li ST. Regeneration of meniscal cartilage with use of a collagen scaffold. Analysis of preliminary data. J Bone Joint Surg Am 1997. doi:10.1042/bj1970385.
33. Zaffagnini S, Giordano G, Vascellari A, et al. Arthroscopic collagen meniscus implant results at 6 to 8 years follow up. Knee Surgery, Sport Traumatol Arthrosc 2007. doi:10.1007/s00167-006-0144-4.
34. Tucker B Tissue Engineering for the Meniscus: A Review of the Literature. Open Orthop J 2012. doi:10.2174/1874325001206010348.
35. Hansen R, Choi G, Bryk E, Vigorita V. The human knee meniscus: a review with special focus on the collagen meniscal implant. J Long Term Eff Med Implants 2011. doi:10.1615/JLongTermEffMedImplants.v21.i4.60.
36. Vaquero J Meniscus tear surgery and meniscus replacement. Muscles Ligaments Tendons J 2016. doi:10.11138/mltj/2016.6.1.071.
37. Rodkey WG, Steadman JR, Li ST. A clinical study of collagen meniscus implants to restore the injured meniscus. In: Clinical Orthopaedics and Related Research.; 1999. doi: 10.1097/00003086-199910001-00027.
38. Bulgheroni P, Murena L, Ratti C, Bulgheroni E, Ronga M, Cherubino P. Follow-up of collagen meniscus implant patients: Clinical, radiological, and magnetic resonance imaging results at 5years. Knee. 2010. doi:10.1016/j.knee.2009.08.011.
39. Steadman JR, Rodkey WG. Tissue-engineered collagen meniscus implants: 5- To 6-year feasibility study results. Arthrosc - J Arthrosc Relat Surg 2005. doi:10.1016/j.arthro.2005.01.006.
40. Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, et al. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: A minimum 10-year follow-up study. Am J Sports Med 2011. doi:10.1177/0363546510391179.
41. Zaffagnini S, Marcheggiani Muccioli GM, Bulgheroni P, et al. Arthroscopic collagen meniscus implantation for partial lateral meniscal defects: A 2-year minimum follow-up study. Am J Sports Med 2012. doi:10.1177/0363546512456835.
42. Wasterlain AS, Braun HJ, Harris AHS, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. Am J Sports Med 2013. doi:10.1177/0363546512466383.
43. Zhang JY, Fabricant PD, Ishmael CR, Wang JC, Petrigliano FA, Jones KJ. Utilization of Platelet-Rich Plasma for Musculoskeletal Injuries: An Analysis of Current Treatment Trends in the United States. Orthop J Sport Med 2016. doi:10.1177/2325967116676241.
44. Pujol N, Salle De Chou E, Boisrenoult P, Beaufils P. Platelet-rich plasma for open meniscal repair in young patients: Any benefit? Knee Surgery, Sport Traumatol Arthrosc 2014. doi:10.1007/s00167-014-3417-3.
45. Blanke F, Vavken P, Haenle M, von Wehren L, Pagenstert G, Majewski M. Percutaneous injections of Platelet rich plasma for treatment of intrasubstance meniscal lesions. Muscles Ligaments Tendons J 2015. doi:10.11138/mltj/2015.5.3.162.
46. Hutchinson ID, Rodeo SA, Perrone GS, Murray MM. Can platelet-rich plasma enhance anterior cruciate ligament and meniscal repair? J Knee Surg 2015. doi:10.1055/s-0034-1387166.

47. Ishida K, Kuroda R, Miwa M, et al. The Regenerative Effects of Platelet-Rich Plasma on Meniscal Cells In Vitro and Its In Vivo Application with Biodegradable Gelatin Hydrogel. Tissue Eng 2007. doi:10.1089/ten.2006.0193.
48. Griffin JW, Hadeed MM, Werner BC, Diduch DR, Carson EW, Miller MD. Platelet-rich Plasma in Meniscal Repair: Does Augmentation Improve Surgical Outcomes? Clin Orthop Relat Res 2015. doi:10.1007/s11999-015-4170-8.
49. Zellner J, Mueller M, Berner A, et al. Role of mesenchymal stem cells in tissue engineering of meniscus. J Biomed Mater Res - Part A 2010. doi:10.1002/jbm.a.32796.
50. Zellner J, Hierl K, Mueller M, et al. Stem cell-based tissue-engineering for treatment of meniscal tears in the avascular zone. J Biomed Mater Res - Part B Appl Biomater 2013. doi:10.1002/jbm.b.32922.
51. 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. J Tissue Eng Regen Med 2017. doi:10.1002/term.1938.
52. Zellner J, Taeger CD, Schaffer M, et al. Are Applied Growth Factors Able to Mimic the Positive Effects of Mesenchymal Stem Cells on the Regeneration of Meniscus in the Avascular Zone? Biomed Res Int 2014. doi:10.1155/2014/537686.
53. Sheth U, Simunovic N, Klein G, et al. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: A meta-analysis. J Bone Jt Surg - Ser A 2012. doi:10.2106/JBJS.K.00154.
54. Ionescu LC, Lee GC, Huang KL, Mauck RL. Growth factor supplementation improves native and engineered meniscus repair in vitro. Acta Biomater 2012. doi:10.1016/j.actbio.2012.06.005.
55. Forriol F Growth factors in cartilage and meniscus repair. Injury 2009. doi:10.1016/S0020-1383(09)70005-1.
56. Font Tellado S, Balmayor ER, Van Griensven M. Strategies to engineer tendon/ligament-to-bone interface: Biomaterials, cells and growth factors. Adv Drug Deliv Rev 2015. doi:10.1016/j.addr.2015.03.004.
57. Bhardwaj N, Devi D, Mandal BB. Tissue-engineered cartilage: The crossroads of biomaterials, cells and stimulating factors. Macromol Biosci 2015. doi:10.1002/mabi.201400335.
58. Fortier LA, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The role of growth factors in cartilage repair. In: Clinical Orthopaedics and Related Research. ; 2011. doi:10.1007/s11999-011-1857-3.
59. Hiraide A, Yokoo N, Xin K-Q, et al. Repair of Articular Cartilage Defect by Intraarticular Administration of Basic Fibroblast Growth Factor Gene, Using Adeno-Associated Virus Vector. Hum Gene Ther 2005. doi:10.1089/hum.2005.16.1413.
60. Kasemkijwattana C, Menetrey J, Goto H, Niyibizi C, Fu FH, Huard J. The use of growth factors, gene therapy and tissue engineering to improve meniscal healing. Mater Sci Eng C 2000. doi:10.1016/S0928-4931(00)00172-7.
61. Stewart K, Pabbruwe M, Dickinson S, Sims T, Hollander AP, Chaudhuri JB. The Effect of Growth Factor Treatment on Meniscal Chondrocyte Proliferation and Differentiation on Polyglycolic Acid Scaffolds. Tissue Eng 2007. doi:10.1089/ten.2006.0242.
62. Bochyńska AI, Hannink G, Verhoeven R, Grijpma DW, Buma P. The effect of tissue surface modification with collagenase and addition of TGF-β3 on the healing potential of meniscal tears repaired with tissue glues in vitro. J Mater Sci Mater Med 2017. doi:10.1007/s10856-016-5832-0.
63. Tarafder S, Gulko J, Sim KH, Yang J, Cook JL, Lee CH. Engineered Healing of Avascular Meniscus Tears by Stem Cell Recruitment. Sci Rep 2018. doi:10.1038/s41598-018-26545-8.
64. Tanaka T, Fujii K, Kumagae Y. Comparison of biochemical characteristics of cultured fibrochondrocytes isolated from the inner and outer regions of human meniscus. Knee Surgery, Sport Traumatol Arthrosc 1999. doi:10.1007/s001670050125.
65. Pangborn CA, Athanasiou KA. Effects of Growth Factors on Meniscal Fibrochondrocytes. Tissue Eng 2005. doi:10.1089/ten.2005.11.1141.
66. Imler SM, Doshi AN, Levenston ME. Combined effects of growth factors and static mechanical compression on meniscus explant biosynthesis. Osteoarthr Cartil 2004. doi:10.1016/j.joca.2004.05.007.

67. Marsano A, Millward-Sadler SJ, Salter DM, et al. Differential cartilaginous tissue formation by human synovial membrane, fat pad, meniscus cells and articular chondrocytes. Osteoarthr Cartil 2007. doi:10.1016/j.joca.2006.06.009.
68. De Mulder ELW, Hannink G, Giele M, Verdonschot N, Buma P. Proliferation of meniscal fibrochondrocytes cultured on a new polyurethane scaffold is stimulated by TGF-β. J Biomater Appl 2013. doi:10.1177/0885328211417317.
69. Tumia NS, Johnstone AJ. Regional regenerative potential of meniscal cartilage exposed to recombinant insulin-like growth factor-I <I>in vitro</I> J Bone Jt Surg 2004. doi: 10.1302/0301-620X.86B7.13747.
70. Puetzer JL, Brown BN, Ballyns JJ, Bonassar LJ. The Effect of IGF-I on Anatomically Shaped Tissue-Engineered Menisci. Tissue Eng Part A. 2013. doi:10.1089/ten.tea.2012.0645.
71. Bhargava MM, Attia ET, Murrell GAC, Dolan MM, Warren RF, Hannafin JA. The effect of cytokines on the proliferation and migration of bovine meniscal cells. Am J Sports Med 1999. doi: 10.1177/03635465990270051601.
72. Acosta CA, Forriol F, Izal I, Ripalda P. In Vitro Healing of Avascular Meniscal Injuries with Fresh and Frozen Plugs Treated with TGF-beta1 and IGF-1 in Sheep. Int J Clin Exp Pathol 2008 doi:PMC2480574.
73. Forriol F, Ripalda P, Duart J, Esparza R, Gortazar AR. Meniscal repair possibilities using bone morphogenetic protein-7. Injury 2014. doi:10.1016/S0020-1383(14)70005-1.
74. Petersen W, Pufe T, Stärke C, et al. The effec t of locally applied vascular endothelial growth factor on meniscus healing: Gross and histological findings. Arch Orthop Trauma Surg 2007. doi: 10.1007/s00402-005-0024-2.
75. Hidaka C, Ibarra C, Hannafin JA, et al. Formation of Vascularized Meniscal Tissue by Combining Gene Therapy with Tissue Engineering. Tissue Eng 2002. doi:10.1089/107632702753503090.
76. Nishida T, Kubota S, Kojima S, et al. Regeneration of defects in articular cartilage in rat knee joints by CCN2 (connective tissue growth factor). J Bone Miner Res 2004. doi:10.1359/JBMR.040322.
77. Tumia NS, Johnstone AJ. Platelet derived growth factor-AB enhances knee meniscal cell activity in vitro. Knee 2009. doi:10.1016/j.knee.2008.08.008.
78. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006. doi:10.1080/14653240600855905.
79. He S, Nakada D, Morrison S. Mechanisms of stem cell self-renewal. Annu Rev Cell Dev Biol 2009;25:377–406. [PubMed: 19575646]
80. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. J Embryol Exp Morphol 1966;16(3):381–390. [PubMed: 5336210]
81. Friedenstein AJ, Ivanov-Smolenski AA, Chajlakjan RK, et al. Origin of bone marrow stromal mechanocytes in radiochimeras and heterotopic transplants. Exp Hematol 1978.
82. Bilgen B, Jayasuriya CT, Owens BD. Current Concepts in Meniscus Tissue Engineering and Repair. Adv Healthc Mater 2018. doi:10.1515/text.1.1983.3.3.299.
83. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science (80−). 1999. doi:10.1126/science.284.5411.143.
84. Alvarez-Viejo M, Menendez-Menendez Y, Blanco-Gelaz MA, et al. Quantifying mesenchymal stem cells in the mononuclear cell fraction of bone marrow samples obtained for cell therapy. Transplant Proc 2013. doi:10.1016/j.transproceed.2012.05.091.
85. Diekman BO, Rowland CR, Lennon DP, Caplan AI, Guilak F. Chondrogenesis of Adult Stem Cells from Adipose Tissue and Bone Marrow: Induction by Growth Factors and Cartilage-Derived Matrix. Tissue Eng Part A. 2010. doi:10.1089/ten.tea.2009.0398.
86. Mueller MB, Tuan RS. Functional characterization of hypertrophy in chondrogenesis of human mesenchymal stem cells. Arthritis Rheum 2008. doi:10.1002/art.23370.
87. Pelttari K, Winter A, Steck E, et al. Premature induction of hypertrophy during in vitro chondrogenesis of human mesenchymal stem cells correlates with calcification and vascular invasion after ectopic transplantation in SCID mice. Arthritis Rheum 2006. doi:10.1002/art.22136.

88. Chowdhury A, Bezuidenhout LW, Mulet-Sierra A, Jomha NM, Adesida AB. Effect of interleukin-1β treatment on co-cultures of human meniscus cells and bone marrow mesenchymal stromal cells. BMC Musculoskelet Disord 2013. doi:10.1186/1471-2474-14-216.
89. Agung M, Ochi M, Yanada S, et al. Mobilization of bone marrow-derived mesenchymal stem cells into the injured tissues after intraarticular injection and their contribution to tissue regeneration. Knee Surgery, Sport Traumatol Arthrosc 2006. doi:10.1007/s00167-006-0124-8.
90. Al Faqeh H, Nor Hamdan BMY, Chen HC, Aminuddin BS, Ruszymah BHI. The potential of intra-articular injection of chondrogenic-induced bone marrow stem cells to retard the progression of osteoarthritis in a sheep model. Exp Gerontol 2012. doi:10.1016/j.exger.2012.03.018.
91. Caminal M, Fonseca C, Peris D, et al. Use of a chronic model of articular cartilage and meniscal injury for the assessment of long-term effects after autologous mesenchymal stromal cell treatment in sheep. N Biotechnol 2014. doi:10.1016/j.nbt.2014.07.004.
92. Hong J, Park J-I, Kim K-H, Kim Y-M, Joo Y-B, Jeon Y-S. Repair of the complete radial tear of the anterior horn of the medial meniscus in rabbits: a comparison between simple pullout repair and pullout repair with human bone marrow stem cell implantation. Knee Surg Relat Res 2011;23:164–175. [PubMed: 22570829]
93. Zhang H, Leng P, Zhang J. Enhanced meniscal repair by overexpression of hIGF-1 in a full-thickness model. In: Clinical Orthopaedics and Related Research.; 2009. doi:10.1007/s11999-009-0921-8.
94. Horie M, Choi H, Lee RH, et al. Intra-articular injection of human mesenchymal stem cells (MSCs) promote rat meniscal regeneration by being activated to express Indian hedgehog that enhances expression of type II collagen. Osteoarthr Cartil 2012. doi:10.1016/j.joca.2012.06.002.
95. Walsh CJ, Goodman D, Caplan AI, Goldberg VM. Meniscus Regeneration in a Rabbit Partial Meniscectomy Model. Tissue Eng 1999. doi:10.1089/ten.1999.5.327.
96. Ferris DJ, Frisbie DD, Kisiday JD, et al. Clinical outcome after intra-articular administration of bone marrow derived mesenchymal stem cells in 33 horses with stifle injury. Vet Surg 2014. doi:10.1111/j.1532-950X.2014.12100.x.
97. Desando G, Giavaresi G, Cavallo C, et al. Autologous Bone Marrow Concentrate in a Sheep Model of Osteoarthritis: New Perspectives for Cartilage and Meniscus Repair. Tissue Eng Part C Methods. 2016. doi:10.1089/ten.tec.2016.0033.
98. Zhang ZZ, Wang SJ, Zhang JY, et al. 3D-Printed Poly(∈-caprolactone) Scaffold Augmented with Mesenchymal Stem Cells for Total Meniscal Substitution: A 12- and 24-Week Animal Study in a Rabbit Model. Am J Sports Med 2017. doi:10.1177/0363546517691513.
99. Koch M, Achatz FP, Lang S, et al. Tissue Engineering of Large Full-Size Meniscus Defects by a Polyurethane Scaffold: Accelerated Regeneration by Mesenchymal Stromal Cells. Stem Cells Int 2018. doi:10.1155/2018/8207071.
100. Yuan X, Wei Y, Villasante A, et al. Stem cell delivery in tissue-specific hydrogel enabled meniscal repair in an orthotopic rat model. Biomaterials. 2017. doi:10.1016/j.biomaterials.2017.04.004.
101. Johnstone B, Hering TM, Caplan AI, Goldberg VM, Yoo JU. In vitro chondrogenesis of bone marrow-derived mesenchymal progenitor cells. Exp Cell Res 1998. doi:10.1006/excr.1997.3858.
102. Eerola I, Salminen H, Lammi P, et al. Type X collagen, a natural component of mouse articular cartilage: Association with growth, aging, and osteoarthritis. Arthritis Rheum 1998. doi:10.1002/1529-0131(199807)41:7<1287::AID-ART20>3.0.CO;2-D.
103. Bluteau G, Labourdette L, Ronzière MC, et al. Type X collagen in rabbit and human meniscus. Osteoarthr Cartil 1999. doi:10.1053/joca.1999.0245.
104. Gao J Immunolocalization of types I, II, and X collagen in the tibial insertion sites of the medial meniscus. Knee Surgery, Sport Traumatol Arthrosc 2000. doi:10.1007/s001670050013.
105. Le Graverand MPH, Ou YC, Schield-Yee T, et al. The cells of the rabbit meniscus: Their arrangement, interrelationship, morphological variations and cytoarchitecture. J Anat 2001. doi:10.1017/S0021878201007671.
106. Le Graverand MPH, Sciore P, Eggerer J, et al. Formation and phenotype of cell clusters in osteoarthritic meniscus. Arthritis Rheum 2001. doi:10.1002/1529-0131(200108)44:8<1808::AID-ART318>3.0.CO;2-B.

107. Jayasuriya CT, Twomey-Kozak J, Newberry J, et al. Human Cartilage-Derived Progenitors Resist Terminal Differentiation and Require CXCR4 Activation to Successfully Bridge Meniscus Tissue Tears. Stem Cells. 2018.
108. Zuk P, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13:4279–4295. [PubMed: 12475952]
109. Frese L, Dijkman PE, Hoerstrup SP. Adipose Tissue-Derived Stem Cells in Regenerative Medicine. Transfus Med Hemotherapy. 2016;43(4):268–274.
110. Bourin P, Bunnell BA, Casteilla L, et al. Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: A joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International So. Cytotherapy. 2013. doi:10.1016/j.jcyt.2013.02.006.
111. Diekman BO, Christoforou N, Willard VP, et al. Cartilage tissue engineering using differentiated and purified induced pluripotent stem cells. Proc Natl Acad Sci 2012. doi:10.1073/pnas.1210422109.
112. Hamid A, Idrus R, Saim A, Sathappan S, Chua K. Characterization of human adipose-derived stem cells and expression of chondrogenic genes during induction of cartilage differentiation. Clinics 2012. doi:10.6061/clinics/2012(02)03.
113. Huang JI, Kazmi N, Durbhakula MM, Hering TM, Yoo JU, Johnstone B. Chondrogenic potential of progenitor cells derived from human bone marrow and adipose tissue: A patient-matched comparison. J Orthop Res 2005. doi:10.1016/j.orthres.2005.03.018.
114. Im G Il, Shin YW, Lee KB. Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells? Osteoarthr Cartil 2005. doi:10.1016/j.joca.2005.05.005.
115. Ruiz-Ibán MN, Díaz-Heredia J, García-Gómez I, Gonzalez-Lizán F, Elías-Martín E, Abraira V. The ffect of the addition of adipose-derived mesenchymal stem cells to a meniscal repair in the avascular zone: An experimental study in rabbits. Arthrosc - J Arthrosc Relat Surg 2011. doi:10.1016/j.arthro.2011.06.041.
116. 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. Exp Ther Med 2016. doi:10.3892/etm.2015.2944.
117. Toratani T, Nakase J, Numata H, et al. Scaffold-Free Tissue-Engineered Allogenic Adipose-Derived Stem Cells Promote Meniscus Healing. Arthrosc - J Arthrosc Relat Surg 2017. doi:10.1016/j.arthro.2016.07.015.
118. Moradi L, Vasei M, Dehghan MM, Majidi M, Farzad Mohajeri S, Bonakdar S. Regeneration of meniscus tissue using adipose mesenchymal stem cells-chondrocytes co-culture on a hybrid scaffold: In vivo study. Biomaterials 2017. doi:10.1016/j.biomaterials.2017.02.022.
119. González-Fernández ML, Pérez-Castrillo S, Sánchez-Lázaro JA, et al. Assessment of regeneration ni meniscal lesions by use of mesenchymal stem cells derived from equine bone marrow and adipose tissue. Am J Vet Res 2016. doi:10.2460/ajvr.77.7.779.
120. Morito T, Muneta T, Hara K, et al. Synovial fluid-derived mesenchymal stem cells increase after intra-articular ligament injury in humans. Rheumatology 2008. doi:10.1093/rheumatology/ken114.
121. De Bari C, Dell'Accio F, Tylzanowski P, Luyten FP. Multipotent mesenchymal stem cells from adult human synovial membrane. Arthritis Rheum 2001. doi:10.1002/1529-0131(200108)44:8<1928::AID-ART331>3.0.CO;2-P.
122. Matsukura Y, Muneta T, Tsuji K, Koga H, Sekiya I. Mesenchymal stem cells in synovial fluid increase after meniscus injury. Clin Orthop Relat Res 2014. doi:10.1007/s11999-013-3418-4.
123. Xie X, Zhu J, Hu X, et al. A co-culture system of rat synovial stem cells and meniscus cells promotes cell proliferation and differentiation as compared to mono-culture. Sci Rep 2018;8(1).
124. Hatakeyama A, Uchida S, Utsunomiya H, et al. Isolation and Characterization of Synovial Mesenchymal Stem Cell Derived from Hip Joints: A Comparative Analysis with a Matched Control Knee Group. Stem Cells Int 2017. doi:10.1155/2017/9312329.

125. Zellner J, Pattappa G, Koch M, et al. Autologous mesenchymal stem cells or meniscal cells: What is the best cell source for regenerative meniscus treatment in an early osteoarthritis situation? Stem Cell Res Ther 2017. doi:10.1186/s13287-017-0678-z.

126. Sakaguchi Y, Sekiya I, Yagishita K, Muneta T. Comparison of human stem cells derived from various mesenchymal tissues: Superiority of synovium as a cell source. Arthritis Rheum 2005. doi:10.1002/art.21212.

127. Yamazaki K, Tachibana Y. Vascularized synovial flap promoting regeneration of the cryopreserved meniscal allograft: Experimental study in rabbits. J Orthop Sci 2003. doi:10.1007/s007760300010.

128. Liu H, Wei X, Ding X, et al. Comparison of cellular responses of mesenchymal stem cells derived from bone marrow and synovium on combined silk scaffolds. J Biomed Mater Res - Part A. 2015. doi:10.1002/jbm.a.35154.

129. Pei M, He F, Li J, Tidwell JE, Jones AC, McDonough EB. Repair of Large Animal Partial-Thickness Cartilage Defects Through Intraarticular Injection of Matrix-Rejuvenated Synovium-Derived Stem Cells. Tissue Eng Part A. 2013. doi:10.1089/ten.tea.2012.0351.

130. Koay E, Athanasiou K. Development of serum-free, chemically defined conditions for human embryonic stem cell-derived fibrochondrogenesis. Tissue Eng Part A. 2009;15(8):2249–2257. [PubMed: 19231974]

131. Hoben GM, Koay EJ, Athanasiou KA. Fibrochondrogenesis in two embryonic stem cell lines: effects of differentiation timelines. Stem Cells 2008. doi:10.1634/stemcells.2007-0641.

132. Hatsushika D, Muneta T, Horie M, Koga H, Tsuji K, Sekiya I. Intraarticular injection of synovial stem cells promotes meniscal regeneration in a rabbit massive meniscal defect model. J Orthop Res 2013. doi:10.1002/jor.22370.

133. Katagiri H, Muneta T, Tsuji K, et al. Transplantation of aggregates of synovial mesenchymal stem cells regenerates meniscus more effectively in a rat massive meniscal defect. Biochem Biophys Res Commun 2013. doi:10.1016/j.bbrc.2013.05.026.

134. Hatsushika D, Muneta T, Nakamura T, et al. Repetitive allogeneic intraarticular injections of synovial mesenchymal stem cells promote meniscus regeneration in a porcine massive meniscus defect model. Osteoarthr Cartil 2014. doi:10.1016/j.joca.2014.04.028.

135. Nakagawa Y, Muneta T, Kondo S, et al. Synovial mesenchymal stem cells promote healing after meniscal repair in microminipigs. Osteoarthr Cartil 2015. doi:10.1016/j.joca.2015.02.008.

136. Moriguchi Y, Tateishi K, Ando W, et al. Repair of meniscal lesions using a scaffold-free tissue-engineered construct derived from allogenic synovial MSCs in a miniature swine model. Biomaterials 2013. doi:10.1016/j.biomaterials.2012.11.039.

137. Horie M, Sekiya I, Muneta T, et al. 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. doi:10.1634/stemcells.2008-0616.

138. Brindle T, Nyland J, Johnson DL. The Meniscus: Review of Basic Principles with Application to Surgery and Rehabilitation. J Athl Train 2001. doi:10.1093/acprof.

139. Webber RJ, Harris MG, Hough AJ. Cell culture of rabbit meniscal fibrochondrocytes: Proliferative and synthetic response to growth factors and ascorbate. J Orthop Res 1985. doi:10.1002/jor.1100030104.

140. Moon MS, Kim JM, Ok IY. The normal and regenerated meniscus in rabbits. Morphologic and histologic studies. Clin Orthop Relat Res 1984.

141. Upton ML, Chen J, Guilak F, Setton LA. Differential effects of static and dynamic compression on meniscal cell gene expression. J Orthop Res 2003. doi:10.1016/S0736-0266(03)00063–9.

142. Sweigart MA, Aufderheide AC, Athanasiou KA. Fibrochondrocytes and their Use in Tissue Engineering of the Meniscus. Tissue Eng 2003. doi:DOI 10.1016/j.ceramint.2013.05.084.

143. Mow V Structure and function relationships of the meniscus in the knee In: VC M, SP A, DW J, eds. Knee Meniscus: Basic and Clinical Foundations Raven Press; 1992:37–58.

144. Mauck RL, Martinez-Diaz GJ, Yuan X, Tuan RS. Regional multilineage differentiation potential of meniscal fibrochondrocytes: Implications for meniscus repair. Anat Rec 2007. doi:10.1002/ar.20419.

145. Mcdevitt CA, Webber RJ. The ultrastructure and biochemistry of meniscal cartilage. Clin Orthop Relat Res 1989. doi:10.1097/NCN.0b013e31823ea54e.

146. Adams Hukins DWL. ME The extracellular matrix of the meniscus In: Mow V, Arnoczky S, Jackson D, eds. “Knee Meniscus: Basic and Clinical Foundations” Raven Press; 1992:15–28.

147. Setton LA, Guilak F, Hsu EW, Vail TP. Biomechanical factors in tissue engineered meniscal repair. In: Clinical Orthopaedics and Related Research ; 1999. doi: 10.1097/00003086-199910001-00025.

148. Baratz ME, Fu FH, Mengato R. Meniscal tears: The effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. Am J Sports Med 1986. doi:10.1177/036354658601400405.

149. Rath E, Richmond JC. The menisci: Basic science and advances in treatment. Br J Sports Med 2000. doi:10.1136/bjsm.34.4.252.

150. Dowthwaite G, Bishop J, Redman S, et al. The surface of articular cartilage contains a progenitor cell population. J Cell Sci 2004;117(6):889–897. [PubMed: 14762107]

151. Williams R, Khan IM, Richardson K, et al. Identification and clonal characterisation of a progenitor cell sub-population in normal human articular cartilage. PLoS One 2010. doi:10.1371/journal.pone.0013246.

152. Thornemo M, Tallheden T, Sjögren Jansson E, et al. Clonal populations of chondrocytes with progenitor properties identified within human articular cartilage. Cells Tissues Organs 2005. doi: 10.1159/000088242.

153. Khan IM, Bishop JC, Gilbert S, Archer CW. Clonal chondroprogenitors maintain telomerase activity and Sox9 expression during extended monolayer culture and retain chondrogenic potential. Osteoarthr Cartil 2009. doi:10.1016/j.joca.2008.08.002.

154. Jayasuriya CT, Chen Q. Potential benefits and limitations of utilizing chondroprogenitors in cell-based cartilage therapy. Connect Tissue Res 2015. doi:10.3109/03008207.2015.1040547.

155. Marcus P, De Bari C, Dell’Accio F, Archer CW. Articular Chondroprogenitor Cells Maintain Chondrogenic Potential but Fail to Form a Functional Matrix When Implanted Into Muscles of SCID Mice. Cartilage 2014. doi:10.1177/1947603514541274.

156. Koelling S, Kruegel J, Irmer M, et al. Migratory Chondrogenic Progenitor Cells from Repair Tissue during the Later Stages of Human Osteoarthritis. Cell Stem Cell 2009. doi:10.1016/j.stem.2009.01.015.

157. Fellows CR, Williams R, Davies IR, et al. Characterisation of a divergent progenitor cell sub-populations in human osteoarthritic cartilage: The role of telomere erosion and replicative senescence. Sci Rep 2017. doi:10.1038/srep41421.

158. D’Angelo M, Pacifici M. Articular chondrocytes produce factors that inhibit maturation of sternal chondrocytes in serum-free agarose cultures: A TGF-β independent process. J Bone Miner Res 1997. doi:10.1359/jbmr.1997.12.9.1368.

159. DeShazo R, Mather P, Grant W, et al. Evaluation of patients with local reactions to insulin with skin tests and in vitro techniques. Diabetes Care 1987;10(3):330–336. [PubMed: 2954799]

160. Kean CO, Brown RJ, Chapman J. The role of biomaterials in the treatment of meniscal tears. PeerJ 2017. doi:10.7717/peerj.4076.

161. Chen JP, Cheng TH. Thermo-responsive chitosan-graft-poly(N-isopropylacrylamide) injectable hydrogel for cultivation of chondrocytes and meniscus cells. Macromol Biosci 2006. doi: 10.1002/mabi.200600142.

162. Ude CC, Sulaiman SB, Min-Hwei N, et al. Cartilage regeneration by chondrogenic induced adult stem cells in osteoarthritic sheep model. PLoS One 2014. doi:10.1371/journal.pone.0098770.

163. Pak J, Lee JH, Lee SH. Regenerative repair of damaged meniscus with autologous adipose tissue-derived stem cells. Biomed Res Int 2014. doi:10.1155/2014/436029.

164. Sasaki H, Rothrauff BB, Alexander PG, et al. In Vitro Repair of Meniscal Radial Tear With Hydrogels Seeded With Adipose Stem Cells and TGF-β3. Am J Sports Med 2018. doi: 10.1177/0363546518782973.

165. Kondo S, Muneta T, Nakagawa Y, et al. Transplantation of autologous synovial mesenchymal stem cells promotes meniscus regeneration in aged primates. J Orthop Res 2017. doi:10.1002/jor.23211.

166. Okuno M, Muneta T, Koga H, et al. Meniscus regeneration by syngeneic, minor mismatched, and major mismatched transplantation of synovial mesenchymal stem cells in a rat model. J Orthop Res 2014. doi:10.1002/jor.22614.

167. Horie M, Driscoll MD, Sampson HW, et al. Implantation of allogenic synovial stem cells promotes meniscal regeneration in a rabbit meniscal defect model. J Bone Jt Surg - Ser A. 2012. doi:10.2106/JBJS.K.00176.

168. Mizuno K, Muneta T, Morito T, et al. Exogenous synovial stem cells adhere to defect of meniscus and differentiate into cartilage cells. J Med Dent Sci 2008.

169. Dutton AQ, Choong PF, Goh JC-H, Lee EH, Hui JHP. Enhancement of meniscal repair in the avascular zone using mesenchymal stem cells in a porcine model. J Bone Jt Surg - Br Vol 2010. doi:10.1302/0301-620X.92B1.22629.

170. Angele P, Johnstone B, Kujat R, et al. Stem cell based tissue engineering for meniscus repair. J Biomed Mater Res - Part A. 2008. doi:10.1002/jbm.a.31480.

171. Ishimura M, Ohgushi H, Habata T, Tamai S, Fujisawa Y. Arthroscopic meniscal repair using fibrin glue. Part I: Experimental study. Arthroscopy 1997. doi:10.1016/S0749-8063(97)90179–1.

172. 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 Evolutionary developmental biology and morphology. BMC Musculoskelet Disord 2015. doi:10.1186/s12891-015-0511-8.

173. 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 Int 2012. doi: 10.1155/2012/691605.

174. Murphy JM, Fink DJ, Hunziker EB, Barry FP. Stem Cell Therapy in a Caprine Model of Osteoarthritis. Arthritis Rheum 2003. doi:10.1002/art.11365.

175. Qi Y, Chen G, Feng G. Osteoarthritis prevention and meniscus regeneration induced by transplantation of mesenchymal stem cell sheet in a rat meniscal defect model. Exp Ther Med 2016. doi:10.3892/etm.2016.3325.

176. Yamasaki T, Deie M, Shinomiya R, Yasunaga Y, Yanada S, Ochi M. Transplantation of meniscus regenerated by tissue engineering with a scaffold derived from a rat meniscus and mesenchymal stromal cells derived from rat bone marrow. Artif Organs 2008. doi:10.1111/j. 1525-1594.2008.00580.x.

177. Izuta Y, Ochi M, Adachi N, Deie M, Yamasaki T, Shinomiya R. Meniscal repair using bone marrow-derived mesenchymal stem cells: Experimental study using green fluorescent protein transgenic rats. Knee 2005. doi:10.1016/j.knee.2001.06.001.

Key Points:

- Meniscus injury is one of the most common athletic injuries
- Current reparative techniques fail to produce long-term improvements and thus alternative regenerative medicine applications are being investigated in the meniscus field
- Acellular and cellular therapies as well as their delivery methods are being investigated for repair and regeneration of meniscus tissue
- Various progenitor/stem cell types are being investigated as optimal cell sources to help stimulate native tissue regeneration of the meniscus

TABLE 1:

Effect of Different Growth Factor Supplementation on Meniscal Fibrochondrocytes

Citation Source	Growth Factor Used	Cell Source	Results/Effects	In vitro/In vivo
Ionescu et al 2012[54]	bFGF	None (Tissue Scaffold)	Short-term delivery enhanced integration strength of native tissue with scaffold	In vitro explant--Scaffold (Bovine)
Hiraide et al 2005[59]	bFGF	Meniscal Fibrochondrocytes	Enhanced cell proliferation	In vitro--Monolayer
Kasemkijwattana et al 2000[60]	bFGF	Meniscal Fibrochondrocytes	Enhanced cell proliferation	In vitro--Monolayer
Stewart et al 2007[61]	bFGF	Meniscal Fibrochondrocytes	Enhanced cell proliferation	In vitro--PGA Scaffold culture
Ionescu et al 2012[54]	bFGF + TGFB3	None (Scaffold)	Improved scaffold/tissue integration and enhanced meniscus repair	In vitro--Electrospun PCL Scaffold
Ionescu et al 2012[54]	TGFB3	None (Tissue Scaffold)	Sustained delivery enhanced integration strength of native tissue with scaffold and increased proteoglycan content	In vitro explant--Scaffold (Bovine)
Bochynska et al 2017[62]	TGFB3	None (Scaffold)	Regeneration of articular cartilage underlying meniscus by homing of endogenous cells	In vivo--PCLHA scaffold (Rabbit)
Tarafder et al 2018[63]	CTGF + TGFB3	None (Tissue Scaffold)	Remodeling of fibrous matrix into fibrocartilaginous matrix by TGFB3 mechanism, induced recruitment of synovial mesenchymal cells/ progenitor cells and meniscal tissue integration through CTGF application..	In vitro--loaded fibrin glue scaffold (Bovine)
Tanaka et al. 1999[64]	TGFB1	Meniscal Fibrochondrocytes	Increased Collagen and GAG synthesis	In vitro--Monolayer
Pangborn and Athanasiou 2005[65]	TGFB1	Meniscal Fibrochondrocytes	Increased Collagen and GAG synthesis	In vitro--PGA scaffold
Imler et al 2004[66]	TGFB1	Meniscal Fibrochondrocytes	Increased Collagen and GAG synthesis	In vitro--Meniscus explant culture
Marsano et al 2007[67]	TGFB1	Meniscal Fibrochondrocytes	Enhanced cell proliferation	In vitro--Monolayer
De Mulder et al 2013[68]	TGFB1	Meniscal Fibrochondrocytes	Enhanced cell proliferation	In vitro--PU scaffold
Forriol et al 2014[73]	BMP-7	None	Filled meniscal defect with cellular fibrous tissue	In vivo--Intraarticular injection (Sheep)
Bhargava et al 1999[71]	BMP-7 (OP-1)	Meniscal Fibrochondrocytes	Enhanced cell migration/proliferation	In vitro
Tumia and Johnstone 2004[69]	IGF-1	Meniscal Fibrochondrocytes	Enhanced cell proliferation, synthesis of proteoglycans and ECM while inhibiting destruction of matrix	In vitro--monolayer culture
Puetzer et al 2013[70]	IGF-1	Meniscal Fibrochondrocytes	Increased levels of collagen and GAG synthesis	In vitro--scaffold culture
Bhargava et al 1999[71]	IGF-1	Meniscal Fibrochondrocytes	Enhanced cell migration/homing of cells	In vitro--Explant culture
Izal et al 2008[72]	IGF-1 + TGFB1	None (Tissue Scaffold)	Enhanced repair of avascular (white-white) zone of meniscus	In vitro--Explant culture

Citation Source	Growth Factor Used	Cell Source	Results/Effects	In vitro/In vivo
Petersen et al 2007[74]	VEGF	None (Suture Coating)	Failure to enhance repair or cell migration	In vivo--VEGFcoated sutures (Sheep)
Hidaka et al 2002[75]	HGF	Meniscal Fibrochondrocytes	Increased angiogenesis to promote healing response	In vivo--PGA scaffold (Mice)
Nishida et al 2004[76]	CTGF	None (Scaffold)	Enhanced articular cartilage regeneration	In vivo--Hydrogel Collagen scaffold (Rat)
Tumia and Johnstone 2009[77]	PDGF-AB	Meniscal Fibrochondrocytes	Increased cell proliferation rate and matrix synthesis/formation	In vitro--monolayer culture
Marsano et al 2007[67]	FGF-2	Meniscal Fibrochondrocytes/Tissue	Enhanced cell proliferation	In vitro--Monolayer culture
Pangborn and Athanasiou 2005[65]	FGF-2	Meniscal Fibrochondrocytes/Tissue	Enhanced collagen synthesis	In vitro--scaffold culture

TABLE 2:

Various Mesenchymal Stem Cell Sources Used for Meniscus Repair/Regeneration and Their Preclinical Application

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
SPIO-labeled ADSCs	2×10^6	Rabbit	½ anterior meniscectomy of medial meniscus	Superparamagnetic iron oxide (SPIO) –labeled ADSCs	Saline OR Unlabeled ADSCs	12 weeks: Targeted ADSC delivery promoted meniscal regeneration + protective effects from OA damage	Qi et al 2015[116]
Allogeneic Rabbit ADSCs	$.1 \times 10^6$	Rabbit	Longitudinal lesion in avascular zone	Suture + ADSCs suspended in Matrigel	Suture + Matrigel only	12 weeks: Improved healing rate in avascular zone for acute lesions that received suture + ADSCs	Ruiz-Iban et al 2011[115]
Autologous Sheep ADSCs	20×10^6	Sheep	Medial meniscectomy (and ACL resection)	Autologous chongrogenicallyinduced ADSCs	Culture medium	6 weeks: Regenerated de novo cartilage underlying meniscus	Ude et al 2014[162]
Autologous Human ADSCs	16×10^6	Human	Grade II Meniscal tear	Autologous hADSCs + PRP and Hyaluronic Acid injections	PRP + Hyaluronic Acid Injections	3 months: Reduced pain and minimal regeneration of meniscus tissue	Pak et al 2014[163]
Autologous Equine ADSCs	--	Equine	Medial Meniscus Defect	Autologous ADSCs	Autologous BM-MSCs	12 months: Some defects appeared to fill in with fibrocartilaginous tissue, others did not heal or fill in	Gonzalez-Fernandez et al 2016[119]
Human ADSCs	--	Bovine (explant in vitro)	Radial tear on cylindrical explant punch biopsy from inner avascular region of meniscus	Photo-crosslinked Hydrogel loaded with ADSCs + TGFB3	TGFB3 only	4 weeks and 8 weeks: Increased matrix-sulfated proteoglycan deposition and some healing of meniscus	Sasaki et al 2018[164]
Allogeneic Rabbit ADSCs	--	Rabbit	Complete meniscectomy of medial meniscus	Polyvinyl alcohol/ Chitosan (PVA/Ch) scaffold seeded with ADSCs	Scaffold seeded with Articular chondrocytes OR Cell-free scaffold	7 months: Minor meniscus regeneration for Articular Chondrocyte group (ADSCs had no significant contribution in healing process and lower Col II, Aggrecan and Col 1)	Moradi et al 2017[118]
Allogeneic Rabbit ADSCs	5×10^4 cells/ spheroid (400–500 spheroids)	Rabbit	Partial meniscectomy of the medial meniscus	High-density ADSC Spheroid Construct (3D culture)	No cells	2, 4, 8 and 12 weeks: Mixed results; Some rabbits showed beneficial healing effect in the avascular zone of the meniscus	Toratani et al 2017[117]
Autologous SDSCs	$.25 \times 10^6$	Primate	Partial meniscectomy of medial meniscus + insertional ligament of medial meniscus transection	Autologous SDSC aggregate	Intra-articular SDSC injection	8 weeks and 16 weeks: Apparent meniscus regeneration in aggregate and control group; SDSC aggregate group had better articular cartilage histology scores *No statistical analysis	Kondo et al 2017[165]

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
Allogeneic SDSCs	20×10^6	Microminipig	Longitudinal tear lesion in medial menisci	Injection of SDSC suspension + Suture	Suture only	12 weeks: Meniscal healing in SDSC group reported to be significantly better than control group with collagen fibrils present in SDSC group only	Nakagawa et al 2015[135]
Allogeneic SDSCs	50×10^6	Pig	Partial meniscectomy of medial menisci	Intra-articular injection of SDSCs at 0. 2 and 4 weeks	Intra-articular injection of PBS	2, 4, 8, 12 and 16 weeks: Resected meniscus regeneration enhanced in SDSC group based on histology and MRI + better articular cartilage protection	Hatsushika et al 2014[134]
Syngeneic and Allogeneic SDSC	5×10^6	Rat	Partial meniscectomy of medial meniscus	Intra-articular injection of syngeneic SDCSs, minor immune mismatch model cell transplantation, major immune mismatch model cell transplantation (For Histocompatability)	Intra-articular injection of PBS	4 weeks: Regenerated area of meniscus was larger in Minor Mismatch and Syngeneic SDSC groups than Major Mismatch group with more cells present (indicated by immunofluorescence)	Okuno et al 2014[166]
Autologous SDSCs	10×10^6	Rabbit	Partial meniscectomy of medial meniscus	Intra-articular injection of autologous SDSCs in PBS	No cells	1, 3, 4 and 6 months: Meniscus size was larger in SDSC-treated group initially, but at months 4 and 6 there was no difference; SDSCs adhered to local area of defect; and articular cartilage appeared thicker in SDSC group than control (better histological scoring)	Hatsushika et al 2013[132]
SDSCs	$.25 \times 10^5$	Rat	Partial meniscectomy	SDSC Aggreg	Intra-articular injection of 5×10^6 cell suspension in PBS AND $.25 \times 10^5$ cell suspension in PBS	12 weeks: Larger meniscal area and better histological scores for aggregate groups	Katagiri et al 2013[133]
Allogeneic SDSCs	$.2 \times 10^6$ cells cultured for 3 weeks to make 3D construct	Pig	4 mm cylindrical defect in medial meniscus	Cultured SDSC 3D cell/ matrix tissue construct (scaffold-free)	No treatment	6 months: SDSC 3D construct group filled meniscal defect and showed improved tissue integration compared to control	Moriguchi et al 2013[136]
Allogeneic SDSCs	2×10^6	Rabbit	1.5 mm cylindrical defect in avascular zone of medial meniscus	Allogeneic SDSCs suspended in PBS	PBS only	4, 12 and 24 weeks: Mixed results: Quantity of regenerated tissue significant ONLY at 4 and 12 weeks. Quality of repair scores significant at 12 and 24 weeks. Cells expressed type-I and type-II collagen at 24 weeks	Horie et al 2012[167]
Allogeneic SDSCs	5×10^6	Rat	Partial meniscectomy of medial meniscus	Intra-articular injection of Luc/LacZ+ SDSCs AND BM-MSCs	PBS only	12 weeks: Some meniscal regeneration in SDSC group that were LacZ+; SDSCs reportedly differentiated	Horie et al 2009[137]

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
						into meniscal cells and promoted regeneration of tissue	
Allogeneic/ Exogenous SDSCs	--	Rat	Cylindrical defect created in meniscus	Intra-articular injection of GFP positive SDSCs	PBS only	1 day, 2, 4, 8 and 12 weeks: SDSC group expressed type II collagen, attached to the defect site and seemed to have improved histological scores at week 12, BUT there was NO statistically significant difference between groups	Mizuno et al 2008[168]
Allogeneic SDSCs	--	Rabbits	Full-thickness longitudinal incision on medial meniscus	Fibrin gel loaded with SDSCs + CTGF and TBGFB3	Fibrin alone OR Fibrin + CTGF	6 weeks: Fibrocartilaginous tissue integration demonstrated by H&E and Saf-O fast green stain; Tensile testing revealed enhanced biomechanical properties	Tarafder et al 2018[63]
Autologous BMMSCs	6×10^6	Sheep	Unilateral medial meniscectomy	Autologous BM-MSCs from iliac crest in Hyaff(®)-11 (HA) construct	Bone marrow Concentrate (BMC) in HA construct	12 weeks: BMC in HA construct allowed for better tissue regeneratio than BM-MSCs n and this group seemed to inhibit OA progression with a reduction in cartilage and meniscus inflammation. BUT subchondral bone thickness was decreased in both BM-MSC and MSC groups	Desando et al 2016[97]
Autologous BMMSCs	$15–20 \times 10^6$	Horse	Meniscal tear	Intra-Articular Injection of Autologous, expanded BM-MSCs into the joint	Surgery only, NO treatment	24 months: 75% of horses returned to some level of work post-treatment of meniscal injury with BM-MSCs	Ferris et al 2014[96]
Autologous BMMSCs	$.1 \times 10^6$	Rabbit	4-mm longitudinal tear in avascular zone of medial meniscus	Implantation of autologous BM-MSCs cultured and embedded in Hyaluronan/collagen matrix	Suture only, cell-free matrix construct, or PRP	6 and 12 weeks: BM-MSC matrix constructs initiated fibrocartilage-like repair tissue and demonstrated better integration and biomechanical properties than any control group.	Zelllner et al 2013[50]
Human BM-MSCs and Rat BM-MSCs	2×10^6	Rats	Partial meniscectomy	Intra-articular injection of Human BM-MSCs or Rat BM-MSCs	PBS only	2, 4 and 8 weeks: Human BM-MSCs rapidly decreased in number over time, but enhanced meniscal regeneration similar to Rat BMMSCs. Human BM-MSCs increased local expression of Col II and Indian hedgehog (Ihh), with a subset that activated local expression of, PTHLH and BMP2.	Horie et al 2012[94]
Human BM-MSCs	2×10^6	Rabbit	Complete radial tear of medial meniscus at	Pull-out surgical repair + Human BM-MSCs embedded in a matrix gel scaffold	Pull-out surgical repair (NO cells)	2, 4 and 8 weeks: n=20/25 rabbits survived postoperation. Of these, there was no significant	Hong et al 2011[92]

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
			the anterior tibial attachment site			difference in regenerative healing or fibrocartilage-like tissue formation between BM-MSC treatment and no cell control group	
Autologous BM-MSCs	1.5×10^6	Rabbit	2-mm meniscal tissue punch defect in avascular zone	Hyaluronan-collagen composite matrices loaded with autologous BM-MSCs	PRP loaded in matrices OR Autologous bone marrow loaded in matrices OR Cell-free matrices	12 weeks: Neither bone marrow nor PRP loaded in matrices produced improvements in healing compared with cell-free implants; BM-MSCs loaded in collagen matrix resulted in fibrocartilagelike tissue repair that only partially integrated with the native meniscus	Zellner et al 2010[49]
Autologous BMMSCs	$1–2 \times 10^6$	Pig	Radial tear in the avascular zone of the meniscus	Autologous BM-MSCs + sutures and fibrin glue	No treatment OR Sutures and fibrin glue alone	8 weeks: No complete healing in the no treatment group or with sutures and fibrin glue alone; Complete healing was seen in 3 animals and incomplete healing was seen in 5 of the animals in the BMMSC treated group	Dutton et al 2010[169]
Autologous BMMSCs	30×10^6 cells/mL	Goat	Full-thickness meniscal defect in white-white area of meniscus	BM-MSCs transfected with hIGF-1 + calcium alginate gel	Non-transfected BM-MSCs OR Calcium alginate gel alone OR No treatment	4, 8 and 16 weeks: Defects were filled with fibrocartilage-like tissue composed of cells embedded in matrix spaces of meniscal fibers with enhanced proteoglycan levels in hIGF-1 overexpressed BM-MSCs	Zhang et al 2009[93]
Autologous BM-MSCs	2.5×10^6 then 14 days in culture	Rabbit	Partial meniscectomy of middle ½of meniscus	Autologous BM-MSCs (cultured for 14 days in chondrogenic conditions) loaded into a hyaluronan/gelatin scaffold	Cell-free scaffold OR No treatment	12 weeks: Untreated defects showed no healing; Cell-free scaffolds showed some repair of fibrocartilaginous tissue; BMMSC-loaded scaffold had significantly enhanced fibrocartilage repair compared to either control	Angele et al 2008[170]
BM-MSCs	$.5 \times 10^6$ /mL	Rabbit	Partial meniscectomy of medial meniscus	Type I collagen sponge loaded with Autologous BM-MSCs	Cell-free collagen sponge OR Periosteal Autograft OR No treatment	24 weeks: Periosteal autograft differentiated into a bone-like composite that is harmful for meniscus repair; Collagen sponge alone supported a fibrous repair response; Collagen sponge loaded with BMMSCs produced fibrocartilaginous tissue similar to native tissue, but the biomechanical function of the meniscus was NOT restored	Walsh et al 1999[95]
BM-MSCs	~1×10^6 cells (from	Rabbit	1.5-mm full-thickness defect in	BM-MSCs suspended in fibrin glue	Fibrin glue alone OR No treatment	1, 3, 6 and 12 weeks: Defects were smaller in the Fibrin glue alone	Ishimura et al 1997[171]

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
	bone marrow aspirant)		avascular zone of meniscus			group and the fibrin glue + BM-MSC group; Healing response was faster in the Fibrin glue + BM-MSC group	
Allogeneic BM-MSCs	.3 × 10^6	Rabbit and Rat	Explant culture	Allogeneic rabbit BMMSCs or rabbit Meniscal-Derived Stem Cells (MDSC) housed in Matrigel	-	3 weeks: BM-MSCs had a high propensity for cartilage hypertrophy and bone formation. MDSCs exhibited greater chondrogenic potential than BM-MSCs	Ding and Huang2015[172]
Allogenic Horse BM-MSCs	.2 × 10^6	Nude Mice	Equine meniscal sections	Allogeneic horse BMMSCs + Fibrin Glue subcutaneously implanted into rat	PBS OR Fibrin glue alone	BM-MSC group showed increased vascularization with increased total bonding of repair and native tissue	Ferris et al 2012[173]
Autologous BM-MSCs	11–12 × 10^6	Sheep	Meniscal tear of medial meniscus	Intra-articular injection of BM-MSC suspension	Intra-articular injection of suspension medium (NO cells)	6–12 months: BM-MSC injection group showed no adverse immunologic effects, and meniscus regeneration was demonstrated through histology and macroscopic parameters, BUT these instances were limited and case-dependent	Caminal et al 2014[91]
Autologous BM-MSCs	10 × 10^6	Sheep	Complete meniscectomy of the medial meniscus + ACL excision	Intra-articular injection of chondrogenicallyinduced BM-MSCs OR Intra-articular injection of basal-culture medium BM-MSCs	Intra-articular injection of basal medium (NO cells)	6 weeks:: Control group had severe OA and meniscus damage; No significant ICRS scoring was detected between the two BM-MSC groups; Chondrogenicallyinduced BM-MSC group displayed better meniscus regeneration than basal BMMSCs and significantly better than the control group	Al Faqeh et al 2012[90]
Allogeneic BM-MSCs	1 × 10^6 Vs. 10 × 10^6	Rats	Meniscal tear + ACL tear + Articular cartilage defect	Intra-articular injection of Allogeneic GFP positive BM-MSCs	Sham operation OR Saline	4 weeks: GFP positive BM-MSCs mobilized to the injury site and contributed to tissue regeneration compared to control groups	Agung et al 2006[89]
Autologous BM-MSCs	10 × 10^6	Goat	OA induction through complete meniscectomy of the medial meniscus	Intra-articular injection of Autologous BM-MSCs expressing eGFP (retrovirus) suspended in sodium hyaluronan	Sodium hyaluronan alone (NO cells)	26 weeks: BM-MSC treatment group displayed meniscus regeneration, with eGFP fluorescent cells located in the newly-formed tissue; Degeneration of cartilage and the OA phenotype was reduced in the BM-MSC group compared to the control group	Murphy et al 2003[174]
Human BM-MSCs	30 × 10 cells/mL	Rat	Radial cut of the medial meniscus (2 mm x 2 mm excision)	Human BM-MSCs encapsulated in decellularized extracellular matrix hydrogel	PBS	8 weeks: Significant tissue regeneration in BM-MSC group with higher GAG, type I and type II collagen than control group; some	Yuan et a 2017[100]

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
						tissue regeneration in control animals	
Autologous BM-MSCs	--	Rabbit	Total meniscectomy	BM-MSC seeded PCL scaffold meniscus replacement	Cell-free scaffold, sham operation and Total Meniscectomy alone	12 and 24 weeks: BM-MSC seeded PCL scaffold group had a better gross meniscus appearance with higher expression of type I, II and III collagen and proteoglycan production found in native fibrochondrocytes + less cartilage degradation than any control group + better tensile and compressive properties in cellseeded implant	Zhang et al 2017[98]
Allogeneic BM-MSCs	~4.8 × 10^6	Rat	Partial meniscectomy (1/2) resection) of the medial meniscus	Allogeneic BM-MSCs cultured in a cell "sheet" from monolayer culture	No treatment	4 weeks and 8 weeks: Histological evaluation revealed regenerated tissue "similar" to native tissue with some collagen bridging as a measure of tissue integration with some alleviation of degenerative cartilage damage compared to the control group	Qi et al 2016[175]
Allogeneic BM-MSCs	--	Rat	Meniscal Defect	Allogeneic Rat-derived BM-MSCs were seeded into a scaffold and cultured for 4 weeks then implanted	Cell-free scaffold OR Meniscectomy	4 weeks and 8 weeks: Expression of extracellular matrices was observed in transplanted tissue 4 weeks postsurgery. Articular cartilage was better protected/less damaged in MSC scaffold group than either control group.	Yamasaki et al 2008[176]
Allogeneic Human BM-MSCs	--	Rat	Meniscal Defect	Allogeneic Human GFP-positive BM-MSCs cultured in monolayer then embedded in fibrin glue and transplanted to injury defect	No treatment OR Fibrin glue only (NO cells)	8 weeks: GFP-positive BM-MSCs survived and proliferated in the meniscal defects while producing extracellular matrix	Izuta et al 2005[177]
Autologous BM-MSCs	--	Rabbit	Partial meniscectomy of white-red zone	Autologous BM-MSCs loaded in a polyurethane scaffold (Actifit) and sutured into the defect	Polyurethane scaffold alone (Actifit) (NO cells)	6 and 12 weeks: Both cell-free and BM-MSC loaded scaffolds led to well-integrated and stable meniscus-like repair tissue with dense vascularization; Accelerated healing was achieved by the BMMSC loaded scaffold.	Koch et al 2018[99]
CPCs	.1 × 10^6	Rat (Ex vivo)	Radial tear in inner anterior horn	C-PC Line 3 + SDF-1 pre-treatment OR ' Primary C-PCs + SDF-1 pre-treatment	BM-MSCs OR No cell treatment	3, 5, 10, 17 and 20 days: Chondroprogenitors (CPCs) promoted meniscal fibrochondorcyte proliferation and native tissue integration of torn meniscal tissue through progressive; SDF-1/ CXCR4 axis is required	Jayasuriya et al 2018[107]

Cell Source	Number of Cells Used	Animal Model	Meniscus Injury Model	Experimental Treatment	Control	Outcome/Results	Reference
						to successfully fill meniscus tissue tears	