# Stem Cell & Regenerative Medicine

# Stem Cell Administration to Repair Torn Menisci

# Matthew J. Keagle and Vincent S. Gallicchio\*

Department of Biological Sciences, College of Science, Clemson University, Clemson, South Carolina, USA.

### \*Correspondence:

Dr. Vincent S. Gallicchio, 122 Long Hall, Department of Biological Sciences College of Science, Clemson University, Clemson, South Carolina, USA.

Received: 30 Apr 2023; Accepted: 28 May 2023; Published: 02 Jun 2023

Citation: Keagle MJ, Gallicchio VS. Stem Cell Administration to Repair Torn Menisci. Stem Cells Regen Med. 2023; 7(1): 1-29.

# ABSTRACT

The meniscus is a crescent-shaped, fibrocartilaginous padding in the knee that contains variable vascularization and histology. This structure enables proper loadbearing, knee movement, and protection of articular cartilage and bone of the tibiofemoral joint. The meniscus is subject to tears from acute injury and degenerative stresses. Many meniscal tears do not heal naturally due to poor vascularization and high stresses placed on the meniscus. These often result in pain and mechanical symptoms and are highly correlated to osteoarthritis (OA) development. While there are a wide variety of suggested treatments for meniscal tears, studies indicate common surgical interventions have little to no significant improvements in abating patient symptoms or limiting osteoarthritic progression, with high failure rates. Therefore, alternative treatments are being actively explored for meniscal tear repair. One of the most-researched treatment options is using mesenchymal stem cells (MSC), a type of adult multilineage progenitor cell capable of facilitating meniscal tissue regeneration. Many different types of MSCs and supplemental, cuttingedge techniques are being tested to maximize tear healing. MSCs hold great promise for regenerating meniscal tissue, limiting OA, and restoring joint functionality. However, more research is required to prove the significance of stem cell treatments in humans and define the conditions for their use.

### **Keywords**

Meniscal Tears Osteoarthritis, Mesenchymal Stem Cells, Meniscectomy, Tissue Engineering.

# Abbreviations

ACL: Anterior cruciate ligament, ANGPT-1: Angiopoietin, APM: Arthroscopic partial meniscectomy, ASC/AD-MSC: Adipose stem cells, bFGF: Basic fibroblast growth factor, BMI: Body mass index, CM: Conditioned media, COL1A1: Collagen type 1 A1, COMP: Cartilage oligomeric matrix protein, CSC: Cancer stem cells, CTGF: Connective tissue growth factor, ECM: Extracellular matrix, EGF: Endothelial growth factor, FGF: Fibroblast growth factor, FRI: Functional rating index, GAG: Glycosaminoglycan, GVHD: Graft vs. host disease, HA: Hyaluronic acid, HGF: Hepatocyte growth factor, HLA: Human leukocyte-associated, hMeSPCs: Human meniscus-derived stem/progenitor cells, IGF: Insulin-like growth factor, IKDC: International knee

documentation committee, iPS: Induced pluripotent stem cell, KOOS: Knee injury and osteoarthritis outcome score, LCL: Lateral collateral ligament, LIF: Leukemia inhibitory factor, LMPRT: Lateral meniscus posterior root tear, LMRT: Lateral meniscus root tear, MAT: Meniscus allograft transplantation, MC: Meniscus cell, MCI: Inner meniscus cell, MCL: Medial collateral ligament, MCO: Outer meniscus cell, MDM: Meniscus-derived matrix, miRNA: Micro ribonucleic acid, MMRT: Medial meniscus root tear, MMSC: Meniscus-derived MSCs, mRNA: Messenger ribonucleic acid, NEX: Matching excitation times, OA: Osteoarthritis, PCL: Posterior cruciate ligament, PCR: Polymerase chain reaction, PDGF-AB: Platelet-derived growth factor AB, PGF: Placental growth factor, PRP: Platelet-Rich plasma, PSC: Pluripotent stem cell, ROM: Range of motion, TE: Echo times, TGFβ-1: Transforming growth factor  $\beta$ , TR: Repetition times, VAS: Visual analog scale pain scoring, VEGF: Vascular endothelial growth factor, Wnt: Homologue of "wingless" in Drosophila.

### Introduction Meniscus Gross Anatomy

The meniscus is a fibrocartilaginous, crescent-shaped padding articulating with the femur and tibia intraarticularly in the knee joint [1]. The meniscus is divided into two asymmetrical components [2]. The medial meniscus articulates with the medial condyles of the femur and tibia, while the lateral meniscus articulates with the lateral condyles of the femur and tibia [1]. The medial meniscus is semicircular and covers 51% to 74% of the medial articular surface, while the lateral meniscus is shorter, more circular, and covers 75% to 93% of the lateral articular surface [3]. Both lobes contain anterior and posterior roots, anchoring the meniscus into the tibia [4,5]. The meniscus is also anchored to the tibial plateau with the coronary ligament, which attaches to the peripheral menisci, and the medial collateral ligament, which prevents translation of the medial meniscus [6]. The lateral meniscus is further connected

to the femur with the anterior and posterior meniscofemoral ligaments [7]. The lobes also contain an anterior horn, midbody, and posterior horn [8]. These have concave superior portions conforming to the femur, and flat inferior portions, which conform to the tibial plateau. The anterior lobes are connected through the transverse ligament [6].

The meniscus's normal functioning and health depend on the surrounding structures in the knee. The knee is a complex modified hinge joint, meaning it primarily facilitates flexion, extension, and some rotational movements [9]. The knee contains the tibiofemoral joint, where the meniscus enables proper articulation between the femur and tibia, and the patellofemoral articulation, where the patella moves against the femur [10]. The infrapatellar fat pad, adipose tissue below the patella, fills gaps between these joints [11]. Knee joint ligaments include the medial collateral



Figure 1: Pictures of the tibial plateau in a superior and posterior view. ACL, anterior cruciate ligament; LPRA, lateral meniscus posterior horn attachment; MPRA, medial meniscus posterior horn attachment; PCL, posterior cruciate ligament; SWF, shiny white fibers of the posterior horn of the medial meniscus [14].



Figure 2 (Left): Illustration depicting basic knee anatomy [15].

*Figure 3 (Right):* A. Radiographic image with outlined anterior and posterior meniscal horns regions. B. Illustration labeling regions of anterior and posterior meniscal horns, with dotted lines at the lateral and medial meniscus locations [6].



Figure 3: Illustration of the vascularization of the meniscus from the longitudinal and transverse planes [18].

ligament (MCL), lateral collateral ligament (LCL), anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), patellar ligament, and other smaller ligaments. These stabilize the knee, limiting extreme torsional or translational stresses that could damage structures like the meniscus. The ACL is suggested to provide 85% of knee stability. Muscles surrounding the knee joint act as secondary stabilizers and help facilitate motion [9]. The knee also contains four bursae, fluid-filled sacs between bones and other tissues. These limit friction and damage to soft tissue caused by joint movement [12]. A fibrous capsule surrounds the knee, containing the cells secreting joint-lubricating synovial fluid [13].

### **Meniscus Histology**

The meniscus is composed of 72% water, 22% collagen, 0.12% DNA, and 0.8% glycosaminoglycans (GAGs) by weight [16]. A cross-section of the meniscus reveals a triangular shape that can be subdivided into red-red, red-white, and white-white zones [14]. The red-red zone is the meniscus's most peripheral, fully vascularized portion. The red-white zone is intermediate and has some vascular supply. The white-white zone is interior and is avascular [6]. Blood is supplied by the perimeniscal capillary plexus generated from the lateral, medial, and middle genicular arteries [17].

The meniscus is divided into histological regions. The outer twothirds of the meniscus resemble fibrocartilage, the inner onethird is assembled more like traditional hyaline cartilage and the superficial region exhibits unique organization [19]. These regions are highly correlated with vascular supply.

The extracellular matrix of the meniscus includes hydrated proteoglycans and elastic fibers, which yield viscoelastic properties. This matrix also contains parallel, circumferentially oriented collagen bundles, which are more pronounced in the peripheral meniscus. These collagen fibers resist torsional stress [20]. This portion also contains tie-fibers, which largely protrude from the joint capsule radially into the meniscus. Blood vessels are oriented alongside and potentially protected by these tie fibers [21].

The outer section of the meniscus contains high concentrations of collagen type I and spindle-shaped fibroblast cells, which help renew the matrix [22]. These fibroblasts include two cell types: Outer, stellate cells with many cytoplasmic projections interacting with adjacent cells and the extracellular matrix; and inner cells with 1-2 projections that form a sheet-like conformation. These cells are linked with gap junctions, especially in the outer fibroblasts, providing greater stability and enabling chemical signal transmission [19,22]. Furthermore, the cells express CD34 on their surfaces enabling cellular adhesion [22].

The inner meniscus contains less uniform collagen organization, with small collagen type II fibers predominating [21]. The meniscal cells in this region are rounded with no projections, resembling chondrocytes, and lacking precise arrangement [16]. In addition, this region has higher GAG content, enabling greater fluid retention and less compressibility [23].

The superficial meniscus contains a fourth meniscal cell type, which is fusiform and lacks cytoplasmic projections [16]. These cells are arranged in a thin meshwork and are adept in healing, as they can increase actin expression enabling cellular migration to wound sites [24].

The menisci are innervated by the posterior tibial, obturator, and femoral nerves [1]. Meniscal mechanoreceptors include Ruffini endings and Pacinian corpuscles, which detect deep pressure [25]. These are found mainly in the meniscal horns. The meniscus largely contains free nerve endings in its vascularized regions [26]. Nociceptor free nerve endings are stimulated by tissue damage, while proprioceptors on the anterior and posterior horns are stimulated during knee movement, enabling the coordination of muscle tone [25,26]. Larger nerve fibers are oriented circumferentially in the peripheral zone, while smaller nerves run radially into the central meniscus. Most nerve fibers are associated with blood vessels [27].

Scanning electron microscopy revealed a series of canaliculi connecting the surface and interior of the meniscus. This structure has been suggested to aid in the diffusion of synovial fluid into the meniscus, which aids enables nutrient delivery to the avascular area [28].

While the meniscus is often associated with poor healing capabilities [29], it has been able to heal spontaneously, even in avascular zones. This mechanism likely involves mesenchymal stem cells (MSC) in the knee's synovial fluid [30]. This suggested mechanism involves synovial hyperplasia, chondrogenic differentiation, and the production of cartilage matrices by these cells [31]. In addition, the meniscus also contains clusters of natural progenitor cells identified by CD146+, which can promote healing [32]. These intrinsic progenitor cells have been demonstrated to migrate to the injury site with chemotaxis facilitated by alarmins and have chondrogenic potential [6,33].

## **Meniscus Development**

The meniscus is derived from the mesoderm germ layer, where mesenchymal cells differentiate into chondroblasts [34]. Meniscal embryonic development begins in the 7<sup>th</sup> week of gestation when the chondroblasts initially condense to form triangular precursors [35]. By weeks 8-10, the meniscal shape is completed. At this phase of embryology, the menisci are highly cellular and fully vascularized [25]. Further fetal development results in total decreased cellularity, increased collagen concentration, and reduced vascularization in the inner meniscus. Collagen assumes its circumferential arrangement due to movement and postnatal loadbearing [36].

# **Meniscus Function**

The meniscus has many vital purposes, including joint stability, preventing anterior tibial displacement, and improving weight distribution [17,37]. All these functions promote proper leg movement and protect the knee joint from damage. The knee transmits load via the four-spring model of the knee, where the outer springs are the menisci and articular cartilage separating the femur and tibia, and the inner springs are the articular cartilage between areas of direct femorotibial contact [15]. The histological regions of the meniscus uniquely enable resilience from weight forces and enable load transmission. Loadbearing causes meniscal compression between the femur and tibia. The histology of the interior aspects of the meniscal lobes enable resistance to compression, which results in radial expansion. This lateral growth puts tension on the peripheral circumferential collagen fibers, which have high tensile strength and are resilient to torsion [19].

The radial tie fibers limit damaging tension buildup and protect meniscal structure [38]. This circumferential tension reaches equilibrium with pressure on the femoral condyle, enabling load transmission. This process uniformly distributes pressure due to pore pressure uniformity in the fluid-saturated meniscus [21].

Total meniscectomy decreases contact area and increases contact pressure, causing average stress (load divided by contact area) to increase significantly [15,39]. These findings suggest that the menisci provide surface compliance necessary for load transmission across wider areas [40]. This function is especially present at higher forces, where the menisci become highly compressed, and in healthy knees, where osteoarthritic knees experience less meniscal load transmission [39,40].

The meniscus partially facilitates knee rotation and prevents hyperextension, although these functions are primarily governed by the condyles of the femur, cruciate ligaments, and knee capsule [15]. The menisci have widely been regarded as shock absorbers. Studies demonstrated total meniscectomy and partial meniscectomy decreased shock absorption capabilities [41]. However, recent anthropological findings and critique of existing literature disagree with this theory [42,43]. Therefore, this function is debatable.

The meniscus has also been suggested to play a role in joint lubrication. Due to the canaliculi system discussed above, meniscus compression associated with loadbearing causes a release of stored synovial fluids into the joint, which is suggested to lubricate the joint [36]. This mechanism can also provide nutrition to the articular cartilage [37].

# **Meniscus Tear Types**

There are many types of meniscus tears, each caused by stressors resulting in lesions impacting the fibrous structure of the meniscus. Traumatic meniscus tears are generally induced by acute forces between the femoral condyles and tibial plateau when the knee twists [44]. Therefore, damaging movements frequently involve rotation or inversion around a planted foot, jumping or landing, and significant external contact on the knee [45]. Degenerative meniscus tears are caused by gradual processes that wear down the meniscus and are often asymptomatic and untreated until the severe progression of osteoarthritis (OA) [44].

Molecular distinctions can also be drawn between these tear types, as differing gene expression patterns occur in traumatic tears relative to degenerative tears [46]. Increased chemokines in traumatic tears cause greater white blood cell recruitment and inflammation responses [47]. Increased matrix metalloprotease and decreased COL1A1 (Collagen type 1, A1) expression in traumatic tears are associated with chronic nonhealing due to increased collagen degradation and decreased collagen formation [48,49].

Meniscus tears also widely vary in morphology, with horizontal, longitudinal vertical, oblique, flap, radial, root, bucket handle, peripheral, and complex tears, each presenting different imaging

and pathologies [50,51]. Horizontal tears run parallel to the tibial plateau, longitudinal vertical tears run perpendicular to the tibial plateau and parallel to the meniscal long axis, and oblique tears run at a grade intermediate to the previous two tears. Radial tears run perpendicular to the tibial plateau, like vertical tears, but they originate centrally and extend peripherally, running perpendicular to the meniscal long axis. Flap tears occur when horizontal or oblique tears become displaced into the meniscal recess or intercondylar space. Root tears involve the meniscal tibial attachments and largely occur via avulsion or radial tears. Bucket handle tears are vertical tears where the interior aspect is displaced into the intercondylar space. Peripheral tears involve the peripheral horns of the meniscus. Finally, complex tears include combinations of multiple tear types [52,53]. Lateral root, horizontal, radial, and complex tears are associated with degenerative meniscus damage. In contrast, medial root, vertical longitudinal, and vertical bucket handle tears are more common in traumatic meniscus damage [51,54].

Meniscal extrusion or subluxation occurs when the meniscus protrudes outside the tibiofemoral compartment [55]. Extrusion can occur due to meniscus tears that impair meniscal rigidity when subjected to hoop stress, although it is more frequently associated with OA and joint space narrowing (JSN) [56]. Subluxation increases stress on all knee structures, especially tibial cartilage [55].



*Figure 5:* MRI imaging of common meniscus tear pathologies. 1. Radial tear of the medial meniscus (arrow) with MCL sprain (arrowheads); 2. The lateral meniscus has partial maceration and lateral extrusion (arrow), medial extrusion of the meniscus (arrowhead); 3. Horizontal, oblique tear of the posterior horn of the lateral meniscus; 4. Vertical tear on the posterior horn of medial meniscus; 5. Medial posterior root tear (arrow) with medial subluxation (arrowhead) [57].

Meniscus tears can also be graded based on morphology and severity. Grade I is less severe, globular, and does not extend to the surface, Grade II is intermediate, linear, and does not extend to the surface. Grade III is the most severe, linear, and extends to the superior and/or inferior surface [14]. Finally, meniscus tear location is essential. Meniscus tears occurring exclusively in the white-white avascular zone have significantly less chance of healing than those in the vascularized zones [58]. This finding is due to limited nutrient availability and less organized structures to facilitate cell migration in the white-white zone.

# Meniscus Tear Occurrence and Risk Factors

It is conservatively estimated that the incidence of meniscus tears is approximately 60 per 100,000 [59], but this estimate likely underestimates asymptomatic degenerative meniscus tears in adults [50].

Young athletes have an overall reported meniscus tear rate of 5.1 per 100,000 athletes, with 68% of reported tears occurring in males. However, in gender-comparable sports, females have higher rates of meniscal tears. 54% of these athletes also experienced additional knee injuries with meniscus tears. Therefore, athletics participation, specifically in contact sports, increases the risk of traumatic meniscus tears compared to control groups of peers [45].

Traumatic meniscus tears are highly correlated with other knee injuries, especially ACL tears and cartilage damage. Risk factors for having severe concomitant injuries with meniscal tears include maleness, elevated age, and surgical delays [60]. Demographic factors increasing the chance of meniscal tears include high BMI, increases in BMI, maleness, jobs with high amounts of kneeling, squatting, and stair-climbing, and age [61-64].

Finally, knee morphology can influence meniscus tear risk. Varus alignment and greater lateral posterior tibial slope is correlated with LMPRTs [54,61], while high posterior tibial slope increases the odds of ramp lesions [65]. ACL tears, which frequently generate meniscal trauma, are also influenced by knee morphology, including intercondylar notch stenosis, increased femoral condylar offset ratio, increased medial and lateral tibial slopes, and poor tibiofemoral congruity [66].

# Meniscus Tear Pathology Meniscus Degradation

Torn menisci can cause many adverse health effects, explaining why their treatment is important. A meniscus tear leads to accelerated meniscal degeneration. Damaged menisci decrease GAG production, limiting meniscal hydration and loadbearing capabilities. Damaged menisci have less organized structures, making them lose resiliency to hoop and shear stresses and more likely to experience wear and gross failure [67].

# Pain and Swelling

Meniscus injuries can cause extreme discomfort. Pain may originate from the meniscus, especially in peripheral tears, from the highly innervated synovium, or due to cytokine release [27,68]. Elevated pain is correlated with root tears. This tear type might cause greater pain due to their correlation with greater meniscal extrusion or accelerated cartilage damage [57]. While some patients experience pain, swelling, or a pop immediately after their tear, many patients with isolated meniscal tears do not report these occurring. Joint line pain and generalized knee pain can be reported by patients during exam. Damaged menisci can lead to synovitis or swelling, often experienced after an acute injury, or increasing activity level [37]. Pain in degenerative tears and latent acute tears was often correlated with twisting motions and walking upstairs [69].

#### **Mechanical Symptoms**

Meniscus tears are also frequently associated with mechanical symptoms, including popping, locking, catching, and buckling sensations [37]. Knee instability, which negatively affects biomechanics and quality of life, is a significant reason for intervention in meniscal tears. Peripheral tears are more likely to cause knee instability [33]. Other mechanical symptoms are more difficult to correlate with specific tear types. Mechanical symptoms, including clicking, popping, and catching, were found to insignificantly differ based on meniscal tear type [57], although flap tears were significantly correlated with catching sensations in another study [70]. These mechanical symptoms and pain can lead patients to lack confidence in their knees [69].

### Osteoarthritis

Approximately a third of osteoarthritic patients have radiographic meniscal damage [44]. Additionally, traumatic knee injury is among the strongest predictors of OA development [71,72]. Therefore, meniscus tears are highly correlated with osteoarthritis, a degenerative joint disease, and the primary cause of musculoskeletal disability in the developed world [44,73,74]. Knee OA involves articular cartilage damage, osteophyte generation, and subchondral bone sclerosis. OA-influencing factors include heredity, age, obesity, diabetes, inflammation, innate immunity, gena valgum ("knock-kneed") or gena varum ("bow-legged") alignment, and joint shape [74]. Meniscal damage is significantly correlated to joint space narrowing (JSN), which is also highly related to OA [75]. A 40% concomitant prevalence of osteoarthritis with symptomatic meniscus tear presentation has been suggested, possibly explaining the intersection of many of their pain and mechanical symptoms. OA risk is higher for meniscus injuries resulting in meniscal extrusion and osteochondral degeneration [76].

### **Meniscal Tear Treatments**



#### **Total Meniscectomy**

The meniscus was originally viewed as a vestigial structure with unimportant contributions to the structure and stability of the knee [6]. Furthermore, medical convention viewed tears in the semilunar cartilage of the meniscus as unable to heal due to low vascularization [29]. Therefore, total meniscectomy, involving the removal of both meniscal lobes, was the preferred procedure to treat prolonged locking, stiffness, and painful motion caused by meniscal tears [77]. Longitudinal studies following patients who underwent total meniscectomy as adolescents illustrated the detrimental effects of this surgical technique – these patients experienced radiological deterioration, OA, and total knee replacement at percentages far above their peers [78]. In fact, it is common to observe "Fairbank's changes" in the radiology of a totally meniscectomized knee, which include femoral condyle deformation (formation of ridge, flattening) and JSN [79].

#### **Partial Meniscectomy**

Open partial meniscectomy, which involves carefully removing only the damaged portions of the meniscus, has largely replaced total meniscectomy as its risks have become clear [80]. With the advancement in imaging technology, arthroscopic partial meniscectomy (APM) was developed, which provided greater latent results [81]. While AMP is currently used for degenerative tears, avascular tears, or tears associated with significant mechanical issues [82], many issues with partial meniscectomy remain. Possible complications include the failure to recognize concomitant ligamentous, articular cartilage, or meniscal injury; removing too much or too little meniscus; and continued knee locking [83]. Furthermore, excising any meniscal tissue can affect knee biomechanics [82]. However, the most common complication is osteoarthritis [84]. High percentages of knees with partial meniscectomies undergo accelerated degenerative changes [85,86], and radiographic signs of OA become significant on average 8-16 years after removal [87]. Despite the high correlation to articular cartilage damage and OA, partial meniscectomy continues to be widely used [85].

### **Meniscal Repair**

Meniscal repair involves suturing the meniscus using outsidein, inside-out, or all-inside suture techniques [88]. Candidates for this surgery typically have a better-preserved meniscus and tears located in more vascular regions with less degeneration or displacement. Meniscal repair largely has significantly better functional and radiographical results than meniscectomy and helps prevent early-onset OA [89,90]. However, meniscal repairs have relatively high failure rates of 12% between 0-1 years and 19% at 4-6 years, which can require surgical revision [91,92]. Over one-third of meniscus repair failures occur in the second year, and failure rates are relatively constant despite ACL status and tear morphology (not including degenerative, avascular, and root tears) [82].

#### Meniscus Allograft Transplantation (MAT)

Meniscus allograft transplantation (MAT) is a technique for harvesting meniscus grafts from cadavers to alleviate the symptoms of a meniscectomized knee [93,94]. This treatment option has many variables dictating success, including initial joint degeneration, graft processing, surgical technique, concomitant procedures, and outcome measures [79]. Some studies have found that these allografts protect articular cartilage [93], while others report transient (5-year) positive outcomes and no chondroprotective effects or osteoarthritic prevention [95,96].

MAT is often a prophylactic transplantation to prevent degenerative OA and early knee replacement. It is generally limited to young patients with symptomatic total meniscectomies correlated with early arthritis, ACL deficiency, or concomitant osteotomy [97,98]. While this technique may benefit these specific patients in protecting articular cartilage with low initial degeneration, it cannot be applied to most meniscal tear patients [93].

## **Meniscus Autography**

Autography replaces large portions of the meniscus with the patient's own tissue. Testing of autologous fat pad, tendon, cartilage, periosteum, synovial flap, and perichondrium tissue often returned poor results, with high rates of OA or graft failures [97]. While autography was shown to decrease cartilage degradation in animal models in the short-term, long-term results were better for non-operative meniscal tears than autograph-treated tears [99].

# **Meniscus Prothesis**

Meniscal prosthesis uses artificial materials to replace symptomatic partial and total meniscectomized knees [100]. Studies using numerous materials have generally found some cartilage protection and no improvements in biomechanical knee behavior [95,100,]. However, some studies have reported chondroprotective properties, limiting degeneration and pain, and similar responses to loading stress and relaxation compared to functional menisci [95,101,102]. Furthermore, drawing conclusions from result summaries is difficult due to the high variability of prosthetic materials. Future technological developments in prosthetic mirroring of meniscal physiological properties may yield greater successes and prove to be a viable prophylactic for patients with severe meniscal deformities, including totally meniscectomized knees [103]. However, this procedure has narrower applications compared to meniscal scaffolding.

# **Growth Factors**

Growth factors are biological signals stimulating cell proliferation, differentiation, and survival [104]. These can facilitate meniscus regeneration by enabling fibrochondrogenic cell recruitment, proliferation, and increased ECM production [34,105]. The most-studied growth factors for meniscal therapy include the transforming growth factor- $\beta$  (TGF $\beta$ ) superfamily, basic fibroblast growth factor (bFGF), and insulin-like growth factor-1 (IGF-1). Other growth factors, like connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and hepatocyte growth factor (HGF), have also been studied [105]. IGFs stimulate proteoglycan, collagen II, and integrin synthesis; these products inhibit ECM destruction [104,106]. TGF-β stimulates collagen II and GAG synthesis [105]. bFGFs increase meniscal cell proliferation [107]. VEGF promotes angiogenesis [107]. PDGF increases meniscal cell proliferation, migration, and proteoglycan production [106,108]. CTGF acts as a chemotactic and profibrogenic factor [109]. HGF exhibits

chemotactic and angiogenic properties [110].

Growth factors involved in stem cell differentiation and activity and growth factors upregulated by stem cells are discussed in **Stem Cells.** 

# Scaffolding

Scaffolding utilizes prosthetic or donor tissue to provide a framework for cell reconstruction. These scaffolds can transiently aid in tissue regeneration and the delivery of transfected cells, limit post-meniscectomy pain, and prevent the advancement of cartilage degeneration [111,112]. There is a lack of consensus on the ideal scaffold material or technique [113]. Materials include collagen, polymers, polycaprolactone/silk fibroin, meniscusderived matrix (MDM), and hydrogels [114-116]. Experiments have shown collagen scaffold implantation procedures have lower failure and reoperation rates, long-term improved clinical scores, and decreased cartilage degeneration compared to partial meniscectomy [111,114,117,118]. However, issues can arise with tailoring the size of the implant [111,117,118].

Polymer scaffolds also improve clinical scores [111]. Polycaprolactone/silk fibroin scaffolds can be intricately 3D printed and are often used to support cell additions in tissue engineering [119]. MDM scaffolds are derived from donor menisci, which contain native components of ECM promoting infiltration and remodeling of injured sites [115].

Scaffolds are often loaded with stem cells to promote healing; they will be discussed more in **Stem Cells:** 

## **Concurrent Treatments.** Platelet Concentrations

Platelet concentrates are transfusions that may stimulate healing. These concentrates are obtained by centrifuging autologous blood [120]. Platelet concentrates contain growth factors like PDGF-AB, TGF $\beta$ -1, and VEGF. These promote angiogenesis, cellular replication, and matrix remodeling [121]. Divisions of platelet products are based on the presence of fibrin and leukocytes; these include the pure platelet-rich plasma (P-PRP) family, leukocyteand platelet-rich plasma (L-PRP) family, pure platelet-rich fibrin (P-PRF) family, and leukocyte- and platelet-rich fibrin (L-PRF) family [122]. The pure families eliminate leukocytes, while fibrin families allow platelet concentration and fibrin matrix formation through an initial lack of anticoagulants after blood collection. PRP is easily produced and has minimal risks of adverse effects [121]. PRP has been used to augment meniscal regeneration, although its use is controversial [122]. Some studies report no statistically significant improvement in failure rate, pain, histology, or visible regeneration [120,122,123]. Other studies have shown significant platelet concentrate-induced improvements. Findings include PRP improving GAG synthesis, meniscal cell proliferation, meniscal healing rate, functional scores, and pain measures [124,125]. PRP is also generally correlated with reduced OA markers, lesser surgical swelling, and pain, accelerated soft tissue repair,

and transiently increased bone regeneration [121,126]. These diverse findings may be due to variable PRP generation methods, classifications, dosages, and timing; this therapy needs greater research and standardization [127].

### **Gene Therapy**

Gene therapy involves transforming meniscal cells with retroviral or adenoviral vectors [128]. This technique allows transient, advantageous changes in gene expression, which can be used to promote meniscal healing [3,128].

Gene therapy is used concurrently with stem cells; this topic will be discussed more in **Stem Cells:** 

## **Abrasion Therapy**

Abrasion therapy enables vascular meniscus tear healing by rasping or trephination of the damaged area. This procedure produces a new injury response, causing a fibrovascular scar promoting healing [105,129]. Abrasion therapy involves creating full-thickness channels adjacent to the injury site, which enables cellular migration and endogenous GF perfusion [130]. While there have been some experiments with greater meniscal healing after isolated abrasion therapy, problems with this procedure remain [131]. Issues with healing in non-immobile knees, the inability to reliably heal avascular regions, and the risk of creating more tears that don't heal limit the utilization of this technique [132-134].

### Fibrin Clot Meniscal Repair

Fibrin clot meniscal repair involves filling meniscal defects with exogenous fibrin clots, enabling fibrocartilaginous tissue to fill the defect [135]. It is posited that the fibrin clot releases GFs, facilitates migration of reparative cells to the site of the clot, and acts as a scaffold for healing [135-137]. This procedure predates PRP therapy, and its induced healing mechanism is similar [136]. Fibrin clotting was considered especially promising for healing avascular tears, as it was theorized that white-white meniscal healing was limited due to a lack of hematoma, which has chemotactic and scaffolding properties [137]. Studies have shown insignificant contributions to healing when isolated or concurrent with meniscal repair surgery [137,138], but its supplementation with abrasion therapy significantly increases its efficacy [139].

### **Surgical Repair Backlash**

There are growing suggestions that significant portions of surgical interventions for meniscus tears are "useless" [140]. Some reports suggest that meniscectomy and meniscal repair lead to no clinically relevant difference in pain (VAS, KOOS), Lysholm, or Tegner scores [117,141,142]. In fact, one study finds that placebo surgery and arthroscopic partial meniscectomy lead to no statistically significant differences in diagnostic findings after two years [143]. Long-term studies report an overall meniscus repair failure rate of nineteen percent [144], although procedures have become more advanced. It can also be argued that meniscal repair can improve mechanical symptoms [145]. While it can be reasoned that these procedures are performed too often, some symptoms warrant surgical intervention. High correlations with

OA and knee degeneration mean interest in developing meniscus repair mechanisms is still warranted.

# **Physical Therapy**

The alternative to surgical interventions for symptomatic meniscal damage often includes physical therapy, which aims to strengthen surrounding muscles and improve biomechanics to reduce symptoms and regain function. Physical therapy has been shown to perform similarly to partial meniscectomy and meniscal repair procedures in pain and physical function scoring in the short term [79,141,146]. However, it is notable that a significant portion of physical therapy patients (approximately 30%) eventually opt for surgery, leading to bias in data [79]. Furthermore, physical therapy success can vary based on patient compliance and timing after acute injury [147].

# Injections

Physicians can also delay surgery or limit symptoms with hyaluronic acid (HA) injections, analgesics, and nonsteroidal antiinflammatory drugs, or intraarticular injections of steroids [148]. HA is naturally found in the knees and is a glycosaminoglycan (GAG), forming an aggrecan structure with chondroitin (another GAG), which aids in meniscus hydration supporting compressive loads [23]. HA has anti-inflammatory therapeutic effects, possibly through the sequestration of inflammatory cytokines [148]. Furthermore, HA injection can also limit symptoms after arthroscopic surgery [149]. Steroidal injections can be effective for short-term symptom relief but often cannot provide long-term relief [142]. At low doses, corticosteroids increase cell growth and recovery and reduce inflammation [150,151]. Still, high doses can lead to chondrocyte toxicity, decreased synthesis of articular cartilage matrix components, gross cartilage damage, and accelerated OA [150-152]. Combined steroid and HA injections can further reduce pain [153].

### **Stem Cells**

Stem cells can divide to differentiate into numerous specialized cell types with the capacity for self-renewal and are classified by their differentiation capabilities. Totipotent stem cells can form all germ layers and the placenta in development, while pluripotent stem cells (PSCs) can form all germ layers [154]. Multipotent stem cells differentiate into numerous discrete cells; hematopoietic stem cells, which create the formed units of the blood, like erythrocytes, thrombocytes, and leukocytes, are examples of this cell type [155]. Oligopotent stem cells can only differentiate into a few closely related cell types; ocular stem cells, which can differentiate into corneal and goblet cells, are examples of this pathway [144]. Finally, unipotent cells have the least differentiation ability; germline stem cells, which only generate gametes, are examples of unipotent cells [156]. Stem cells can also be divided into embryonic and mature stem cells. Embryonic stem cells are pluripotent cells and can be obtained from blastocysts during in vitro fertilization. Mature stem cells are multipotent and are derived from body tissues, the umbilical cord, or the placenta after birth [157]. There are many different mature stem cell types, each specific to their niche.

While stem cells were originally isolated and cultured in 1981 [158], their use in the medical field was limited until recently due to their controversial nature. Embryonic stem cells, a form of PSC, were far more effective than adult stem cells in their differentiation and integration capabilities [159]. However, moral, and religious concerns were raised due to the requirement to harvest these cells from human embryos, which limited early stem cell research [160]. This issue was resolved with the advent of induced pluripotent stem cells (iPS), which enabled scientists to revert harvested adult stem cells to pluripotent stem cells with greater ability for differentiation [161]. These cells can be reprogrammed through retroviral or lentiviral transduction, plasmid integration, or direct delivery of mRNAs and proteins [162]. In addition, the iPS process enables autologous stem cell harvesting, which reduces immune rejection risk [163].

### Stem Cell Biology Stem Cell Niche

Asymmetric division is controlled by intrinsic and extrinsic factors [164]. The intrinsic mechanism is seen mainly in development, while the extrinsic mechanism is more pertinent to adult stem cells and meniscal repair [165]. This extrinsic mechanism is the stem cell niche. The niche is a discontinuous and dynamic microenvironment containing stem cells, stromal support cells, extracellular matrix (ECM) proteins, blood vessels, and neural inputs [166,167]. Stromal cells secrete adhesive signals, soluble factors, and the ECM, which functions in stem cell retention and facilitates differentiation [167,168]. The stem cell niche theory states that self-renewal signals, limited to specific microenvironments, are necessary to keep stem cells from differentiating. Therefore, if stem cells are located outside their niche, they will commence differentiation, and if they remain in their niche, they will retain self-renewal potential [168]. This mechanism leads to stem cell locations in specific portions of adult organs and the initiation of differentiation if stem cells are removed from their microenvironment [166,167]. Stem cell niches are highly dynamic, as they are required to respond to various physiological changes like inflammation, infection, malignancy, and signaling to maintain tissue homeostasis [166,168,169]. These stimuli can induce pathways leading to stem cell migration, changed division cycling rates, and alternate daughter cell production [169].

# Self-Renewal

Self-renewal is defined as the generation of at least one phenocopy daughter cell with a preserved undifferentiated stem cell state [170,171]. Self-renewal occurs via symmetric division generating daughter cells with the same fate or asymmetric division generating daughter cells with different fates [170]. Generally, symmetric division is observed in early embryonic stem cells, and asymmetric division is observed in other stem cells [172]. Stem cell division is encoded by proto-oncogenes supporting self-renewal, gatekeeping tumor suppressor genes restraining self-renewal, and caretaker tumor suppressor genes ensuring genomic integrity [173]. Transcription factors and epigenetic regulators activated by intrinsic mechanisms enable the activation or inhibition of these genes [174,175]. Extrinsic factors, like stem cell niche, cytokines, paracrine or nervous signaling, and GFs, regulate these intrinsic mechanisms [166,167,174,175]. When stem cells lose the balance between proto-oncogenes, gate-keeping tumor suppressors, and care-taking tumor suppressors, cancer stem cells (CSC), apoptosis, or a lack of renewal can be produced [173,174].

Numerous intracellular and extracellular processes mediate MSC self-renewal. *In vivo*, self-renewal is regulated by multiple factors, including leukemia inhibitory factor (LIF), fibroblast growth factors (FGF), BMPs, cytokines, hedgehog proteins, and homologs of "wingless" (Wnt) in *Drosophila* [171,186]. *In vitro*, division can be induced by cytokines and growth factors like FGF-2, PDGF-BB, and EGF [186].

# Differentiation

A similar mechanism controls stem cell differentiation, where generalized stem cells become more specialized. Differentiation of stem cells in their niche can be initiated by paracrine or neural signaling through Wnt/ $\beta$ -catenin, bone morphogenetic protein (BMP), Notch, Angiopoietin-1 (Ang-1), and growth factors [167]. Stem cells initially become transient amplifying cells, which divide rapidly and closely resemble parent cells but have a narrower multilineage potential. After a regulated number of divisions, these become progenitor cells, which can only differentiate into their target cell type [176]. Scientists can induce stem cell differentiation to specific cell types, arrest differentiation, or reverse differentiation to create iPS cells. These processes often involve adding signaling molecules to cultures or transcription factors to cells through transfection.

# Transdifferentiation

Transdifferentiation, or irreversibly converting one cell type to another, enables stem cells to change multilineage potentials when transfected to a different stem cell niche [177,178]. This mechanism enables the conversion of adult stem cells with limited plasticity to pluripotent stem cells capable of use in a wide variety of tissues [178]. For example, bone marrow-derived stem cells can produce epithelial cells of the liver, kidney, lung, skin, and GI [179]. This mechanism can expand the number of conditions that can be addressed by easily harvested stem cells.

# Mesenchymal Stem Cells

Mesenchymal stem cells are adult multilineage progenitor cells that can differentiate into mesoderm- and non-mesoderm-derived tissues [180,181]. MSCs have heterogeneous morphology, physiology, and cell surface antigens [182], leading to difficulty in identifying MSCs. This issue led to the creation of standards defining MSCs, which include plastic adherence; the ability to differentiate into osteoblasts, adipocytes, and chondroblasts; high population expression of CD105, CD73, and CD90; and low population expression of CD45, CD14/CD11b, CD79a/CD19, and HLA class II [183]. MSC colonies contain three types of cells with different multilineage differentiation potentials. The cells with the greatest plasticity could be isolated through unique cell surface proteins [182]. MSCs were initially discovered as fibroblast precursors in bone marrow [184,185]. However, MSCs have been

positively located in almost all organs, generally associated with connective tissues [184].

# Plasticity

The initial experimentation determining MSC plasticity discovered that multilineage potential is maintained during colony formation. These studies found MSCs could form adipocytes, chondrocytes, and osteocytes that produce bone or formed units of blood [187]. MSCs have more recently been identified that form myocytes, tendon fibers, and dental pulp [171,183,182]. Experiments have induced MSC differentiation into neuron-like and epithelial-like cells, although these were more controversial due to the difficulty of identifying specific MSC integration. However, studies have recently demonstrated BM-MSC fusion to neural progenitors, hepatocytes, and myocardial cells [183]. Through transdifferentiation, MSCs have the potential to form an even wider variety of tissue types [179]. Therefore, MSCs have a high degree of plasticity [182].

Chondrogenic differentiation of MSCs involves the activation of transcription factor genes like sox-9 and scleraxis, and ECM genes including collagen types II and IX, aggrecan, biglycan, decorin, and cartilage oligomeric matrix protein [171]. *In vitro*, chondrogenesis is often induced by applying TGF- $\beta$ 1, 2, or 3, and sometimes BMP2, 4, or 6 [188]. MSCs undergoing chondrogenesis can aid in the repair of articular cartilage in addition to the meniscus [189].

Other signals and pathways can lead MSCs to form different cell types [171]. Environmental factors can influence MSC differentiation. MSCs are more likely to undergo chondrogenesis with cyclic compressions. Adipocyte development is favored in microgravity or rounded cultures, while osteocytes are formed from MSCs subjected to shear stresses or sharp edges [190].

## MSC Benefits for Meniscal Repair Integration in Regenerated Tissue

MSCs are associated with natural pathways for tissue healing, as these cells mobilize to injury sites [191]. Intraarticularlyinjected MSCs have been proven to incorporate in regenerated tissue [192,193]. Undifferentiated MSCs may be more capable in this function, raising questions about the proper procedures in culturing MSCs for tissue repair [194-196]. Furthermore, some studies suggest that the role of MSC integration in healing promotion is limited, and other pathways are more important in tissue regeneration [197,198].

### **Extracellular Matrix Production**

MSCs activate ECM production, further enabling natural repair cells to migrate to meniscus tears [199-201]. ECM deposition raises the quantity of important tissue components like collagen, proteoglycans (GAG), and cartilage oligomeric matrix protein (COMP) [197,202-207]. This mechanism can improve regenerated tissue mechanical properties [208].

### Angiogenesis

MSCs are angiogenic. Their secretion of VEGF, TGF-β, HGF, PDGF, BFGF, placental growth factor (PGF), and other paracrine effectors promote tissue neovascularization [199,209]. In addition, their capability to differentiate into endothelial-like and pericyte-like cells potentially furthers angiogenesis [210,211]. This property can increase healing due to greater nutrient and healing factor perfusion at the site of injury [204,212].

# **Growth Factor Secretion**

MSC GF secretion also enables greater tissue repair [213]. Signals from supplemental MSCs can stimulate the proliferation and mobilization of fibroblasts, chondroblasts, and natural MSCs to the site of tissue damage [214,204]. This leads to greater integration of healing cells in repaired tissue, increasing its similarity to surrounding tissue [204,208].

## Immunomodulation

The MSC secretome, which includes signaling factors, extracellular proteins, and secreted mRNAs [215], is further correlated with immunomodulation [216-218]. They can suppress the production of inflammatory cytokines through direct and indirect cellular contact with T cells and macrophages [219,220]. MSCs limit B lymphocyte proliferation and differentiation, decreasing antibody production [218]. These stem cells also increase the secretion of anti-inflammatory, immune-suppressive signals like IL-6 and TGF-β1 [218,220]. MSCs upregulate regulatory T cell and B cell production, which check immune responses, and downregulate the production of matrix-degrading enzymes in arthritic patients [219]. In addition, MSCs secrete soluble mediators, which contain pro-inflammatory and anti-inflammatory cytokines [220,221]. These cytokines attract the upregulated regulatory T and B cells to the injury site, leading to greater immune cell infiltration while decreasing inflammation [204]. Finally, MSCs effectively reduce oxidative stress, tissue damage caused by an accumulation of oxygen-reactive species (ROS) in cells associated with injury [222,223]. Prevention of oxidative stress further facilitates proper healing mechanisms.

# **Trophic Effect**

MSC secretomes also have a trophic effect on injury sites, which limits apoptosis and promotes cell survival [184,224]. These effects are facilitated through MSC release of GF cytokines and their regulation of other signaling pathways, like nitric oxide, nuclear factor-kB, and indoleamine [225]. This action decreases the injury field, limits scarring, and promotes angiogenesis [184].

### **Better Prognosis**

Finally, MSC therapy is widely correlated with decreased reported pain and greater proportions of patients returning to normal activity [226-228]. In human trials, MSCs have proven effective at increasing regenerated meniscal volume [229]. More research is necessary to delineate the level of significance of these findings [230].

#### **Risks of Stem Cells Unregulated Stem Cells**

There are numerous risks involved with the use of stem cells. The rise of illegal or misleading marketing of stem cells by unlicensed clinics is problematic. The lack of oversight, training, and best practices by these clinics can lead to serious issues; case studies for stem-cell induced blindness, cancer, and multiorgan failure leading to death have all resulted from unregulated stem cell therapy [231-233].

# Tumorigenesis

Mutations can be introduced into stem cell lines from their resultant divisions or the method of pluripotency induction, although this risk has been diminished with improved transduction methods. Further, reprogramming factors can induce upregulation of oncogenes and unchecked growth [234]. Accordingly, stem cells carry the theoretical risk of malignant teratocarcinoma, a form of cancer originating from germ cells [172], or other cancers, although techniques have been demonstrated to reduce this already low risk [235-237]. An incredibly limited number patients have developed cancer caused by a meniscal therapy [233]. There have been no reported resultant cancers from knee intraarticular stem cell injections or from accredited and FDA-registered clinical stem cell trials, further highlighting the importance of steering clear of stem cell clinics [231,238,239].

## **Immune Rejection**

Immune rejection or graft vs. host disease (GVHD) risks can limit the therapeutic potential of stem cells and cause health issues, but this concern is limited by HLA- (human leukocyte-associated) matching or autologous donation. Stem cells also suppress elements of the immune system, limiting GVHD risk. In fact, stem cells can have potentially beneficial immunosuppressive and antiinflammatory effects [240].

# **Spreading to Other Structures**

Concerns about the potential for stem cells to spread to other structures have also been alleviated through experimentation. The specificity of MSC differentiation and advances in integration of MSCs at the site of injury can enable scientists to prevent MSC spread to healthy structures [200]. However, broader multilineage potential and general application can enable healing of other damaged structures in the event of concurrent injuries or OA [241,242]. Intraarticularly-injected fluorescently labeled MSCs were only observed inside the knee joint using imaging, histological assessments, and reverse transcription polymerase chain reaction (PCR) [243]. This result shows stem cells do not spread to other structures of the body when injected intraarticularly.

# **Failure to Improve Condition**

The most common risk of stem cell utilization is a failure to improve condition [192,244]. When MSC-assisted healing occurred, MSC-regenerated tissues showed reduced tensile strength, loadbearing, and resiliency to shear stresses when compared to healthy menisci [18,237,245,246]. This result may be due to histological differences and less order in repaired tissue [207,246,247]. Conversely,

MSCs improve regenerated tissue histology, organization, and cell morphology compared to untreated tears [18]. The poor mechanical properties of regenerated tissue or delicacy of MSC assimilation with tears sites could contribute to the success of short-term animal studies where the knees are immobilized, or the failures of studies where stem cells significantly improve short-term healing metrics but don't significantly improve long-term metrics [230,237]. Further studies could clarify which MSC types and techniques lead to regenerated tissue with the greatest similarity to natural meniscal tissue, leading to better mechanical properties and long-term results.

As seen in **Stem Cell Supporters**, there are many mechanisms used to improve the efficacy of stem cell treatments. However, some factors limiting stem cell-induced healing merit further consideration. For example, animal studies suggest obese, diabetic autologous stem cells have decreased healing and angiogenic capacity than stem cells from healthy donors [163].

The procedural aspect of stem cell injection carries its own risks, which are the most likely complications of this procedure. These include infection, bleeding, pain, tissue damage, nerve damage, and misplacement of stem cells.

# **MSC Sources**

The primary sources of MSCs for orthopedic use include bone marrow (BM-MSC), adipose (AD-MSC), synovial tissue (ST-MSC), peripheral blood-derived stem cells (PBSC), and the meniscus (MMSC). To a lesser extent, dental tissue, tendons, and the placenta (PL-MSC) have been considered for their orthopedic benefits [157,183,248,274].

### **Bone Marrow**

BM-MSCs are the originally discovered and most-studied MSC [210]. Autologous harvesting requires bone marrow biopsy, which often involves aspiration at the iliac crest or sternum and can be very painful and invasive [198]. BM-MSCs can be isolated from these bone marrow aspirations or bone marrow aspirate concentrate (BMAC), formed through centrifugation. BMAC also contains white blood cells and platelets in similar concentrations to PRP [249]. BMAC limits in vitro cellular manipulation and provides niche continuity, which has been suggested to increase MSC efficacy [250]. BMAC also contains some cellular secretome, which could increase its regenerative capacity [251]. An animal experiment showed BMAC increased healing and collagen II expression more than BM-MSCs, while BM-MSCs had higher collagen I expression [207]. However, BMAC can contain variable, low concentrations of BM-MSCs [252]. Difficulty in obtaining BM-MSCs through this method could limit its therapeutic effects, as research indicates optimal BM-MSC dosage as 106 cells/cm<sup>2</sup> [237]. More experiments in BMAC's orthopedic applications are merited, especially comparing results from BMAC vs. BM-MSCs with PRP or CM treatments.

Because of their frequent study, BM-MSCs have been highly correlated with positive outcomes and many benefits of MSCs

[247,253,254]. Chondrogenic differentiation potential is likely higher in BM-MSCs compared to ASCs [255]. BM-MSCs may not be ideal for meniscus repair due to their correlation to cartilage hypertrophy and osteogenesis [256]. However, cartilage hypertrophy can be limited through co-culturing BM-MSCs with meniscal cells [248,257]. Co-cultures with MCs have also been found to improve GAG, collagen types II and I, and positive gene expression (257-259). A very small percentage of bone marrow cells are MSCs, and BM-MSC yield, and quality can vary even from the same donor [260]. Furthermore, there is no cell membrane protein completely differentiating these MSCs from other bone marrow cells [260,261]. Finally, BM-MSCs have longer duplication periods and reach senescence earlier than other stem cells [261]. These factors have caused scientists to search for effective alternatives to BM-MSCs [262].

### **Adipose Tissue**

Another commonly used mesenchymal stem cell therapy in orthopedic surgery is Adipose Stem Cells (ASC or AD-MSC). These are capable of osteogenic, chondrogenic, adipogenic, and neurogenic differentiation [209,263,264]. ACSs can be autologously harvested using liposuction or subcutaneous adipose tissue sampling, which is a somewhat invasive procedure [179,263], and are easily expanded in vitro [209]. Isolation of ASCs involves the formation of a cell pellet with collagenase and centrifugation and culturing the cell pellet on plastic. Isolation can also be done through fluorescence-activated cell sorting using fluorescently tagged monoclonal antibodies binding to unique expressed CD markers [209,264]. ASCs can be chondrogenically induced through treatment with GF or conditioned media (CM), enabling the production of collagen II and proteoglycan [264]. Some studies have suggested that AD-MSCs are more effective at meniscus repair in autologous and allogenic purposes than BM-MSCs [265]. ASCs are potentially more potent suppressors of immune response than BM-MSCs [218,255]. Furthermore, AD-MSCs are found to be more supportive of hematopoiesis and angiogenesis than BM-MSCs [266]. Studies have confirmed the integration of AD-MSCs in repaired tissue [267,268].

### **Synovial Tissue**

ST-MSCs are promising for treating cartilage injuries, as they originate from common cells during the development of synovial joints [261]. These cells are capable of meniscal repair, as they show integration at the tissue repair site and high capabilities in enhancing collagen I and II deposition [200,206,242,269]. ST-MSCs can be derived from non-articular surfaces of synovial joints where synovial fluid is produced. However, due to the close association of synovium with fat tissues, sample contamination and attributing ASC properties to ST-MSCs could occur [183].

# **Peripheral Blood**

PBSCs are isolated through apheresis, arguably providing the safest and least invasive method for harvesting orthopedic stem cells [197]. These treatments have successfully produced proteoglycan and type II collagen; PBSCs have shown high success in cartilage repair [270]. Furthermore, peripheral blood-derived progenitor

# Meniscus

MMSCs are progenitor cells found in cartilage [273]. These cells can be treated to increase pluripotency, leading to their use in tissue engineering for avascular meniscus tear treatment [202,274,275]. MMSCs produce tissue mirroring hyaline cartilage more effectively than other methods and have higher collagen II expression than BM-MSCs [202,254,276]. MMSCs improve compressive properties and the gross morphology of regenerated tissue [254]. Labeled MMSCs have been shown at tissue repair sites, although their concentration decreased sharply over time in the animal study [254]. Harvesting autologous chondrocytes is highly invasive and requires removal of parts of the meniscus [275]. Therefore, allogenic biopsies are generally used. This method leads to an increased risk for immune rejection, although studies have repeatedly shown a lack of adverse immune reaction to these cells [248].

## **MSC-Associated Risks**

There are some downsides associated with MSCs. Researchers point to uncertainty in the properties of MSCs due to the difficulty in completely determining differentiation potential and isolation, which can introduce error [209]. Age, BMI, and gender can impact MSC proliferation, protein expression, angiogenesis, immunoregulation, and differentiation ability. The number of MSCs in niches and the healing potential of these MSCs decrease with age [260,277]. Obesity has been found to increase the risk of stem cell tumorigenesis [210,220]. MSCs often require expansion in vitro due to low natural frequency in specific niches in vivo, which is contrary to their natural behavior. This may introduce different cellular characteristics or lead to differentiation before application to an injured site, but advancements in culture methods help limit this risk [184]. More research needs to be conducted to determine if the effects of these factors merit allogenic donations for certain patients. Contradictory reports have also been filed, claiming MSCs exhibit tumorigenesis or tumor suppression [209,237]. However, current evidence suggests an extremely low probability of getting cancer from stem cells [237]. The use of allogenic ASCs induces antibody production in 19-34% of recipients. While MSCs largely suppress immune response, effects of this cellular response in meniscal repair are unknown [278].

# **Other Stem Cell Benefits**

While this paper is designed to review how stem cells can be utilized to heal torn menisci, intraarticular stem cell injection can also provide beneficial latent functions. Experiments have demonstrated MSC application to arthritic knees results in significantly reduced swelling, cartilage depletion, inflammatory exudate, and arthritic index [207,279]. Furthermore, MSCs can limit osteochondral lesions, osteophyte formation, and articular cartilage degradation [280-282]. Therefore, MSCs have been correlated with reduced OA progression, measured by decreased OA-associated signals, increased joint space, and decreased articular cartilage damage [197,202,254,283]. Conditioned media treatment might limit OA more than direct MSC treatments, though [282].

The healing of concomitant ligamentous injuries can also be aided by stem cell therapy, especially through its anti-inflammatory and matrix regenerative properties, although further human trials are necessary to confirm the positive results largely seen in animal models [279,284,285]. Stem cells have also been suggested to aid healing of wounds and decrease scarring response [286]. Therefore, patients that would normally be at risk for poor wound healing with arthroscopic or open meniscal procedures could additionally receive stem cells at their wound site for greater stimulation of healing. Risk factors of poor wound healing where patients could benefit from stem cell application include diabetes, hereditary healing disorders or a history of keloid formation, and an immunocompromised state [287].

#### **Environmental Conditions**

MSC environmental conditions during in vitro culturing can influence their properties. Their development in hypoxic conditions causes higher expression of angiogenic genes, potentially attenuating the effects that aging has on MSCs [210]. Cyclic compression of BM-MSCs has been suggested to improve mechanical properties, although it may concurrently decrease viability and adhesion to scaffolding [201,245]. Cell perfusion, involving a continuous change of culture medium providing new nutrients and removing wastes from the culture, has also been suggested to promote BM-MSC differentiation and protein synthesis, although results have been mixed [201,245]. Dynamic cultures in free-swelling conditions increase infiltration MSC and collagen deposition, while static cultures have greater GAG levels [288]. Co-culturing MSCs with meniscal cells (MCs) decreases hypertrophic effects on cartilage [248,257]. Other effects of coculturing include increased GAG matrix content, collagen II expression, and tissue generation [258,259]. Co-culturing with outer MCs (MCO) or inner MCs (MCI) can further change the properties of MSCs [259].

### **Tissue Engineering**

Tissue engineering treats meniscus injuries through the application of stem cells, signaling molecules, and potentially scaffolding [189]. As discussed in **current accepted treatments**, scaffolds have extremely variable composition. Studies are attempting to determine the most effective scaffolding material, porosity, and surface factors; more research in this area is especially needed due to recent scaffold advances [196]. Loading scaffolds with stem cells can increase its integration in healing menisci [247]. Tissue engineering can provide mechanical stability, enable cellular infiltration and stabilization to the injury site, increase key protein creation, and facilitate tissue repair [246,254,289,290]. Innovations recently included in some scaffolds include the incorporation of GFs in scaffold structure to stimulate healing; matrix degradation designed to enhance cell migration and tissue

Tissue engineering significantly increases tensile strength and resistance to shear stress compared to scaffold-only treatments [227]. The concurrent application of GF in tissue engineering can increase stem cell activity. Studies show TGF- $\beta$ 3 application in tissue engineering increases mature meniscus transcripts, indicating greater differentiation, and enables more significant GAG deposition [203,257]. TGF- $\beta$ 1 increases regenerated tissue compressive properties, while BMP2 increases the size of constructs without improving compressive properties [205]. Not all growth factors are effective; for example, IL-1 $\beta$  supplementation doesn't result in significant histological differences and decreases mRNA [258]. There have been failures in tissue engineering experiments, frequently due to issues with determining proper materials or creating scaffolds, which can survive the high-stress environment of the knee [208].

#### **Platelet Concentrates and Fibrin Clotting**

PRP can augment MSCs *in vitro* and *in vivo* through combination therapy. Stem cell cultures in PRP increased MSC proliferation in a dose-dependent manner and enhanced differentiation as measured by indicator protein production [292,294,295]. Combination therapy also enables greater stem cell potency and differentiation [293]. Finally, *in vivo* stem cell and PRP treatments lead to greater angiogenesis and tissue regeneration than isolated therapies [296]. These effects are potentially due to the GFs found in PRP, as culturing stem cells in isolated GF originally contained in PRP caused greater differentiation, division, and stem cell activity [295]. With a similar mechanism to PRP, MSC application concurrently with fibrin clotting significantly increases healing, angiogenesis, immune cell infiltrate, fibroblast proliferation, deposition of collagen fibers, and total bonding to surrounding tissues [204,208].

### **Conditioned Media**

Conditioned media (CM) is a regenerative therapy that can be used in concert with stem cells in vivo or in isolated applications. CM is obtained by collecting the cell secretome produced by cultured stem cells under specific protocols [297]. This secretome includes cytokines, chemokines, growth factors (TGF- $\alpha$ , TGF- $\beta$ , HGF, EGF, IGF-1, VEGF, angiopoietin (ANGPT-1), etc.), ECM proteins, exosomes, mRNA, and miRNA [215]. This therapy increases and prolongs the concentration of beneficial components of paracrine signaling found naturally in the body after injury [298]. CM provides all the non-cellular components of stem cells, which have been theorized to provide the main observed benefits in injury treatment [298,299]. However, studies indicate longterm healing is most achieved when CM is used concurrently with MSCs [282]. With these concomitant stem cell treatments, CM drives chemotaxis to the injury site and increases regeneration capabilities [196,297]. CM can be readily produced, sterilized, and stored [215]. More research is needed to determine the merits of CM and the proper methodology for its production.

Author(s), Year	Animal, Defect Model	Source Cell Number Method of Delivery	Control	Supplements	Outcome Measurements Timeline	Results
Shen et al. [202]	6 F rats with removed anterior half of medial menisci in both knees	6e6 human meniscus- derived stem/progenitor cells (hMeSPCs) Intraarticularly injected into R knee	Identical PBS volume injected in L knee	SDF-1/CXCR4 treatment	Harvesting 4 or 12 weeks post-surgery Flow cytometry determining multipotent differentiation potential. Oil Red O, Alkaline Phosphatase, and Safranin O staining for histology Area assay for macroscopic analysis Ink staining articular cartilage Meniscal morphology with TEM	High expression MSC markers, low expression hematopoietic markers Greater clonogenicity and higher collagen II expression than BMCs SDF-1/CXCR4 increases migration and adherence of hMeSPCs to injured meniscus, chemotactic effects limited by AMD3100 Intraarticular treatment increases tissue formation 4 weeks, reduces surface irregularities, decreases some OA markers Rat meniscus heals in control – require larger animal models
Masafumi et al. [197]	5 hemi- meniscectomized rat models	Rat MSCs or human BM-MSCs (2e6) intraarticularly injected into R knee	PBS injection into L knee	Activation or inhibition changing expression of Ihh, PTHLH, SAG, BMP2 in human MSCs Human dermal fibroblasts (HDF)	RT-PCR Collection of whole menisci 2,4,8 weeks Histology Immunochemistry	Increased expression collagen type II Inhibited OA expression pattern Low integration of hMSC Greater activation of chondrogenic genes Insignificant morphological changes
Pabbruwe et al. [196]	6 Ovine menisci fibrocartilage cylinders (histology) 6 Ovine whole menisci with incision (biomechanical)	Autologous BM- MSCs (.5e5 – 2.0e5 cells; undifferentiated or differentiated) in conditioned medium <b>Group 1:</b> Seeded scaffolds <b>Group 2:</b> Cells only <b>Group 3:</b> Scaffold only	<b>Group 4:</b> No intervention	Chondrogide, Ultrafoam Collagen Sponge, OSSIX PLUS scaffolds Conditioned media TGF-β1 (differentiation)	Histological analysis Biomechanical testing Cell migration assay	Greater integration of undifferentiated than differentiated stem cells in collagen membranes Significantly greater tensile strength of stem cell/ collagen-scaffold groups than others Highest integration in double-rough, porous collagenous Chondroglide and Ultrafoam Conditioned medium from meniscus drives chemotaxis regardless of vitality
Ferris et al. [299]	24 Horses with lameness from meniscal injuries, diagnosed by ultrasound 9 horses with meniscus score 1, 7 horses with meniscus score 2, 8 horses with meniscus score 3, 9 horses advanced joint disease	Autologous BM-MSCs injected intraarticularly 1.5e7 – 2e7 cells per joint 3-4 weeks after stifle arthroscopy surgery	Comparison with 2 published, peer reviewed studies describing return to function after routine stifle arthroscopy and treatment	None	Change in AAEP lameness score Graded severity of lesion Degree of return to previous level of work	Meniscus score 1: 56% return to previous level of work, 44% return to work. Meniscus score 2: 29% return to previous level of work, 29% returned to work, 42% fail to return to work. Meniscus score 3: 25% return to previous level of work, 37% return to work, 37% fail to return. Advanced joint disease: 45% return to previous level of work, 22% return to work, 33% fail to return. Significant differences for all conditions with returning to work

#### Table 1: Animal modeling data for meniscal repair experiments [300,301].

Ferris et al. [299]	12 mice with induced meniscal defects	Equine BM-MSC and fibrin glue-infused meniscal construct inserted	Fibrin glue- infused meniscal construct inserted	Equine fibrin forming fibrin glue Meniscal constructs from equine menisci	Harvesting constructs after 4 weeks Gross observations Histology	BM-MSC constructs have increased vascularization, decreased thickness of repair system, increased total bonding
Abdel-Hamid et al. [204]	8 dogs with inflicted longitudinal meniscal injury	Autologous BM-MSCs and clotted autologous bone marrow added to wound	Only autologous clotted bone marrow added to wound	Clotted bone marrow	After 3 weeks observe clinical signs for healing, remove meniscus after 12 weeks Histological and immunohistochemical studies Degree of healing	Statistically significant increase in complete healing, angiogenesis, immune cell infiltrate, fibroblast proliferation, deposition of collagen fibers in BM-MSC group
Nerurkar et al. [288]	Application of cells harvested from calves to scaffolds	1e7 BM-MSCs applied to both sides of scaffold Dynamic culture – incubated in orbital shaker, Transient dynamic culture – incubated in orbital shaker and free-swell	Application 1e7 cells to both sides of scaffold Static culture – incubated in free-swell,	Electrospun nanofibrous scaffold	Analysis at 12 weeks Mechanical testing Histology and quantification of infiltration	Dynamic culture has highest rate of infiltration, transient dynamic culture has most even infiltration GAG levels highest in static culture Dynamic culture has highest collagen production
Sanchez- Adams et al. [205]	Application to chondrogenic medium	Application of dermal stem cell micromasses from goats Adipogenic, osteogenic, or chondrogenic differentiation	None	TGF-β1, IGF-I, or BMP-2 Self-assembled tissue construct	qRT-PCR Gross morphology Histology and immunochemistry Biochemistry Compressive testing	Successful adipogenic, osteogenic, and chondrogenic differentiation Self-assembled tissue contructs upregulate collagen type II TGF-β1 increases compressive properties, BMP2 increases size
Ruiz-Ibán et al. [267]	Group 1 (12 rabbits): Short lesion anterior horn of meniscus, immediate suture Group 2 (8 rabbits): Short lesion anterior horn of meniscus, 3 week delayed suture Group 3 (12 rabbits): Larger, longitudinal lesion immediate suture Group 4 (8 rabbits): Larger, longitudinal lesion, 3 week delayed suture	1e5 ACSs harvested from rabbit fat pads put in gel and instilled in lesion	Matrigel with no ASCs instilled in lesion	None	Gross morphology Evaluation of repair with probe Histology	Significant increased healing in groups A, C indicating greater efficacy with less delay Significant healing of treatment vs. control No vascularization – lesions created in avascular zone Confirmed descendants of ASCs at healed area
Shen et al. [254]	9 rabbits with partial meniscectomy	Autologous BM-MSCs (6e6) intraarticularly injected into right knee 1 and 2 weeks post meniscectomy	PBS injected into left knee	TGF-β1 in vitro	Evaluation 4,8,12 weeks TEM Cell labelling and detection Histology Radiographic evaluation Immunohistochemistry RNA isolation and RT-PCR Biomechanical evaluation	Significant increase of neo-tissue, better defined shape, higher collagen II expression Resultant gross morphology from experimental group similar to normal menisci Labelled BM-MSCs contribute to regeneration, decrease sharply over time Greater compressibility than control Inhibit progression of OA by increasing joint space width and decreasing surface cartilage damage

Angele et al. [247]	18 rabbits with medial partial meniscectomy	18 Scaffold loaded with autologous BM-MSCs implanted (2.5e6 cells seeded)	12 Contralateral scaffolds without BMSCs 6 Untreated defects	Hyaluronan/gelatin composite scaffold TGF-β1	Harvesting 12 weeks Gross assessment of joint tissue morphology Histology Immunohistochemistry SEM	Extremely limited healing in untreated – generated tissue had no collagen II, limited fibrocartilage Total integration of implant with BM-MSCs, 54% empty scaffold integration Significant cartilage regeneration, greater cross- sectional width BM-MSC loaded scaffolds Histological structure less ordered than normal meniscal tissue
Zellner et al. [246]	66 rabbits, 4 mm longitudinal tears in avascular zone of pars intermedia	Group D: non- precultured BM-MSCs injected into scaffolds, implanted into meniscal tears Group E: precultured BMSCs injected into scaffolds, implanted into meniscal tears	Group A: Empty defect Group B: Meniscal suture Group C: PRP and unseeded scaffold	Hyaluronan/gelatin composite scaffold PRP	Harvesting 12 weeks Joint morphology Histology Immunochemistry Meniscus Scoring Biomechanical analysis	Group E significantly greater healing Group D cells don't significantly change healing Group E has higher collagen II expression 1.3 N dividing BM-MSC scaffold treatment menisci, 3 N for healthy meniscus
Yamasaki et al. [192]	30 rat meniscal scaffolds loaded with autologous cells	BM-MSCs (2e5) seeded into evacuated rat meniscal scaffolds	Scaffolds without cells cultured Normal menisci	None	Culture for 1,2,4 weeks Histology RT-PCR Measurement of stiffness	Integration of BM-MSC derived cells in healed area Similar Aggrecan, collagen X, GADPH gene expression to normal menisci, depressed collagen II gene expression Stiffness of culture approximates normal menisci after 2 weeks
Agung et al. [241]	32 rats with transverse ACL incisions and medial menisci	GFP-labelled rat BM-MSCs cultured in TGF-β3 and dexamethasone injected intraarticularly (1e6 and 1e7 concentrations)	GFP-labelled rat BM-MSCs not cultured in TGF-β3 and dexamethasone	TGF-β3	Analysis 4 weeks Gross morphology Fluorescent microscopic observation Immunohistochemical Histology RT-PCR	GFP shows mobilization of injected BM-MSCs to ACL at concentrations of 1e6 and greater, to menisci at concentrations of 1e7 and greater Scar tissue observed in 63% 1e7 knees, not in 1e6 ECM positivity around GFP cells indicates tissue regeneration
Hatsushika et al. [280]	16 rabbits with removal of anteromedial menisci	Intraarticular injection SMSCs (1e7)	Intraarticular injection PBS	BMP-7 TGF-β3	Harvesting 4,12,16,24 weeks Gross Morphology Histology	Significantly more uniform, organized healing of menisci with SMSCs Limits osteochondral lesions, better preserves articular cartilage SMSCs lead to faster recovery but not significant difference in size in 6 months
Osawa et al. [194]	12 rats given reproducible oblique medial meniscus tear	Group 1: 5e5 CD34+ cells Group 2: 5e5 CD146+ cells Group 3: 5e5 CD34- and CD146- cells	Group 4: PBS	None	Harvest 4 weeks Histology Immunofluorescence Chondrogenic, osteogenic, adipogenic assays	Naturally higher number of CD34/CD146 positive cells in peripheral menisci Fetal CD34 and CD146 positive cells recruited to meniscal repair sites, contribute to meniscal repair

Qi et al. [268]	18 rabbits with anteromedial partial meniscectomies	Group 1: Intraarticular injection autologous Superparamagnetic iron (SPIO) labelled ASCs (2e6) Group 2: Intraarticular injection autologous unlabeled ASCs (2e6)	Group 3: Intraarticular injection saline	None	Analysis 6,12 weeks MRI Gross observation Histology	Anterior meniscus histologically similar to normal tissue with good integration ASCs associated with regenerated tissue. Less tibial plateau damage, cartilage damage, and osteophyte development in ASC groups
Jülke et al. [282]	36 goats horizontal tear avascular zone of medial meniscus	Group 1: Single suture, wrapping collagen I/III membrane around tear Group 2: Single suture, wrapping collagen I/III membrane around tear with injected autologous articular chondrocytes	Control: Single suture	Porcine collagen I/III membrane wrapping	Sacrificed 3,6 months Gross inspection Histology	Highest OA scores collagen membrane only Collagen membrane has greater healing, cell response 3 months Collagen membrane and cells have greater healing, cell response 6 months
Ozeki et al. [242]	15 rat partial meniscectomy (anteromedial meniscus)	Tendon and MSC group: SMSC solution (1e6/ mL) applied to harvested autologous Achilles tissue grafted into defect. Tendon group: Harvested autologous Achilles tissue grafted into defect	Untreated groups: No cells or tendon grafting	Achilles tendon graft (labelled with Luciferase, LacZ, GFP)	Evaluation 2,4,8 weeks Macroscopic observation Histology Immunochemistry In Vivo Bioluminescent Imaging Detection LacZ Fluorescent examination Flow cytometry	Tendon seeded with SMSCs fully integrated after 8 weeks, still identifiable border Coarse synovial tissue fills defect in control Greater histological scores, type II collagen tendon with SMSCs No detection of cells in other regions
Nakagawa et al. [18]	15 micropigs Longitudinal tear lesion medial menisci	SMSC (2e7) suspension placed on meniscal lesion, sutured	Suture with no cell addition	None	Evaluation 2,4,12 weeks Macroscopic observation Histology Immunochemistry TEM MRI T1rho mapping Biomechanics Cell tracking	Full or partial healing SMSC, little healing control T1rho SMSC approaches that of meniscal cells More organization, similar cell morphology to normal meniscus Increased tensile strength, half of normal meniscus
Whitehouse et al. [237]	30 sheep with induced meniscal tear in avascular region	Group 1: 1e6 autologous BM-MSCs and scaffold with 48 hours incubation Group 2: Scaffold only Continuous perfusion and mechanical stimulation I group (1 time/day, 8 h/time), continuous perfusion and mechanical stimulation II group (4 time/day, 2 h/ time, 4 h rest)	Suture only group	Collagen meniscus scaffold Osteogenic or adipogenic supplements	Harvesting at 13,24 weeks Assessment histological analysis and histomorphometry	Significant better outcome with MSC and collagen scaffold after 13 weeks No animals experience complete healing after 24 weeks – early repair unable to survive loadbearing

 Table 2: Human data for meniscal repair experiments [300-302].

Author(s), Year	Test Subjects, Defect Model	Source Cell Number Method of Delivery	Control	Supplements	Outcome Measurements	Results
Pak et al. [226]	1 F, Grade II Meniscal Tear	Autologous AD-MCSs Injection medial inferior retropatellar joint	None	PRP, hyaluronic acid, CaCl <sup>2</sup>	MRI/3 months Symptom questionnaires at 6,12, 18 months	Visible meniscal healing; decreased FRI, VWI, extension VAS, flexion VAS; decreased extension degree, increased flexion degree
Centeno et al. [227]	1 M, degenerative joint disease	Autologous BM-MSCs 2.24e7 cells	None	PRP, containing PDGFs, TGFs, FGFs, IL, PL (given 0, 1, 2 weeks)	VAS questionnaires and FRI questionnaires before procedure, 1, 3 months Range of motion before procedure, 1, 3 months Imaging with NEX, TR, TE Image processing articular cartilage volume	Significant increased meniscal and femoral cartilage volume FRI and VAS steady decrease Slightly increased flexion and extension
Vangsness et al. [229]	55 patients with partial meniscectomy	Superolateral knee injection of allogenic MSCs Group A 5e7 cells Group B 1.5e8 cells	Sodium hyaluronate vehicle control	None	Sequential MRI imaging Sequential evaluations of clinical outcomes 2 year intervals	Significantly increased meniscus volume 24% Group A, 6% Group B, 0% control
Cui et al. [257]	Chondrogenic media pellets	BM-MSC co-cultured with mature MC at varying ratios (100:0, 75:25, 50:50, 0:100)	Total MSC control, Total MC control	Cultured with or without TGF-β3	Assessment 21 days Meniscal and hypertrophic gene expression Morphology Histology and immunochemistry of proteoglycan and collagen ECM	Co-culture MC MSC at 75:25 yields highest collagen type I and GAG production, lowest levels hypertrophic genes. Groups treated with TGF-β3 have greater GAG deposition
Mandal et al. [203]	Applied directly to silk scaffolds	8e5 BM-MSCs added to each of 3 scaffold layers	Non-seeded 3 scaffold layers	3D aqueous- derived silk scaffolds with pores TGF-β3	Biochemical assays for DNA, glycosaminoglycans, collagen Histology RT-PCR Conofocal and SEM imaging Mechanical testing	Histology indicates growth and differentiation Significant increase collagen and sGAG uniformly in scaffold Significant increase in mature meniscus transcripts TGF-β3
Saliken et al. [259]	4 human menisci harvested from total knee replacements Tissue removed from outer or inner regions of meniscus	BM-MSCs cultured with outer MC (MCO) or inner MC (MCI) in 1:3 ratio	Monocultures MCO, MCI, BM-MSC	Cultured with TGF-β1	Assessment 3 weeks qRT-PCR Biochemical analysis Histochemical analysis	Greater GAG matrix content and increased tissue for all samples No significant differences of DNA content throughout Collagen II expression increases throughout, significant with co-cultures of MCO:MSC Greatest Ihh and MMP-13 expression MCI:MSC
Chowdhury et al. [258]	Chondrogenic media pellets	Co-cultures of MCs and BM-MSCs microfuged forming pellet	Pure primary MCs or pure BM-MSCs microfuged forming pellet	Cultured with TGF-β3. Cultured with or without Interleukin-1β (IL-1β)	Assessment 17 days Histological, biochemical, RT-PCR for aggrecan, sox9, MMP-1, collagens I and II	IL-1β doesn't result in significant histological differences, decreases mRNA expression Co-culture increases GAG, collagen, and other positive gene expression
Whitehouse et al. [237]	4 M and 1 F with low energy, acute, isolated medial meniscal tears in avascular zone	Autologous BM-MSC + scaffold with 6 hours incubation after seeding, 1e6 cells	None	Collagen meniscus scaffold	Histological analysis and histomorphometry Tumorigenicity assessment Tegner and Lysholm scores, Range of Motion (ROM), IKDC	Optimal dosage BM-MSC 10 <sup>6</sup> cells per cm No indicators of tumorigenicity through anchorage-independent colony formation method Three patients required no further treatment. Two patients developed recurrent symptoms at 15 months posimplantation causing partial meniscectomy. Failure groups had slightly lower Tegner- Lysholm, ROM and same IKDC scores.

Mahajan et al. [228]	31 F with grade III tear of medial and lateral menisci, high- grade ACL tear	Intraarticularly injected autologous BM-MSCs (5e8 – 5e9) and AD- MSCs (1.6e9–4e8)	None	PRP derived from peripheral blood concomitantly injected	Follow-up 1 mo	Significant pain relief, improved range of motion, return to normal activity, improved grade of injury for meniscal tear
Olivos et al. [230]	17 patients with past meniscectomies 6 patients with concomitant ACL	Polyurethane scaffold group seeded with peripheral blood MSCs (2e7) with arthroscopic implantation	Acellular polyurethane scaffold group with arthroscopic implantation	Polyurethane meniscal scaffolds Locked knee brace 6 weeks removed 3-4x per day for range of motion exercise	MRI evaluation 3,6,9,12 mo postoperatively Clinical evaluation KOOS, IKDC, Lysholm scores	Insignificant increase in healing, meniscal tissue growth, articular cartilage preservation, and knee scores between groups MSC treatment more successful in short-term, negligible in long-term
Mandal et al. [203]	Silk scaffold in vitro testing	8e5 BM-MSCs added to 3 scaffold layers	Non-seeded 3 scaffold layers	3D aqueous- derived silk scaffolds with pores TGF-β3	Biochemical assays for DNA, glycosaminoglycans, collagen Histology RT-PCR Conofocal and SEM imaging Mechanical testing	Histology indicates growth and differentiation Significant increase collagen and sGAG uniformly in scaffold Presence of mature meniscus transcripts for TGF-β3 Greater compressive modulus for seeded scaffolds due to deposited ECM

## **Future Perspectives**

Stem cells are a promising therapy for meniscal repair. In animal studies, stem cell application can improve morphology [18,2 04,241,246,247,254,267,268,280,304], mechanical properties [196,254,304], histology [18,192,197,202,241,246,254,267,30 4], and limit OA progression [197,202,254,268,280]. However, drawing conclusions based on these findings is difficult, as the experiments vary widely with the type of animals, meniscal tears, stem cells, and supplements used. Furthermore, procedure variance and differences between animal and human knees can cause issues when projecting stem cell meniscal repair success for humans. In human studies, stem cells have also been correlated with improved morphology [226-229], mechanics [227,228], histology [202,293,257-259], and reduced pain and adverse symptoms [226-228]. However, these human studies are often limited in sample sizes and follow-up time with patients. Ultimately, more studies are required to find the optimal type of stem cell and procedure for meniscal tear repair and to prove statistically significant, long-term healing of the meniscus because of stem cell administration.

# References

- Farrell C. Anatomy, Bony Pelvis and Lower Limb, Medial Meniscus. StatPearls - NCBI Bookshelf. 2022; 19.
- 2. Liu Y, Du G, Liu J, et al. Meniscal anterior and posterior horn heights are associated with MRI-defined knee structural abnormalities in middle-aged and elderly patients with symptomatic knee osteoarthritis. BMC Musculoskeletal Disorders. 2022; 23: 218.
- Goto H, Shuler F. D, Lamsam C, et al. Transfer of LacZ Marker Gene to the Meniscus. Journal of Bone and Joint Surgery. 1999; 81: 918-925.
- Śmigielski R., Becker R, Zdanowicz U, et al. Medial meniscus anatomy—from basic science to treatment. Knee Surgery, Sports Traumatology, Arthroscopy. 2015; 23: 8-14.
- Chang P. R, Solon L. F, Lake S. P, et al. Mechanical and Microstructural Properties of Meniscus Roots Vary by Location. American Journal of Sports Medicine. 2022; 50: 2733-2739.

- 6. Brindle T, Nyland J, Johnson D. R, et al. The meniscus: review of basic principles with application to surgery and rehabilitation. Journal of Athletic Training. 2001; 36: 160-169.
- Bintoudi A, Natsis K, Tsitouridis I, et al. Anterior and Posterior Meniscofemoral Ligaments: MRI Evaluation. Anatomy Research International. 2012; 839724.
- Nishino K, Hashimoto Y, Tsumoto S, et al. Morphological Changes in the Residual Meniscus After Reshaping Surgery for a Discoid Lateral Meniscus. American Journal of Sports Medicine. 2021; 49: 3270-3278.
- Abulhasan J. F, Grey M. J, Anatomy and Physiology of Knee Stability. Journal of Functional Morphology and Kinesiology. 2017; 2: 34.
- Flandry F, Hommel G. Normal Anatomy and Biomechanics of the Knee. Sports Medicine and Arthroscopy Review. 2011; 19: 82-92.
- 11. Distel E, Cadoudal T, Durant S, et al. The infrapatellar fat pad in knee osteoarthritis: An important source of interleukin-6 and its soluble receptor. Arthritis & Rheumatism. 2009; 60: 3374-3377.
- 12. Meyler Z. Knee Anatomy. Arthritis-health. 2018.
- 13. Archer C. W, Dowthwaite G. P, Francis-West P, et al. Development of synovial joints. Teratology. 2003; 69: 144-155.
- 14. Fox A, Wanivenhaus F, Burge A. J, et al. The human meniscus: A review of anatomy, function, injury, and advances in treatment. Clinical Anatomy. 2015; 28: 269-287.
- 15. Seedhom, B. B. Transmission of the Load in the Knee Joint with Special Reference to the Role of the Menisci. Engineering in Medicine. 1979; 8: 207-219.
- 16. Herwig J, Egner E, Buddecke E, et al. Chemical changes of human knee joint menisci in various stages of degeneration. Annals of the Rheumatic Diseases. 1984; 43: 635-640.
- 17. Seedhom B. B, Dowson D, Wright V, et al. Proceedings:

Functions of the menisci. A preliminary study. Annals of the Rheumatic Diseases. 1974; 33: 111.

- Nakagawa Y, Muneta T, Kondo S, et al. Synovial mesenchymal stem cells promote healing after meniscal repair in microminipigs. Osteoarthritis and Cartilage. 2015; 23: 1007-1017.
- Graverand M. H. L, Ou Y, Schield-Yee T, et al. The cells of the rabbit meniscus: their arrangement, interrelationship, morphological variations and cytoarchitecture. Journal of Anatomy. 2000; 198: 525-535.
- 20. De Rosa M, Filippone G, Best T. M, et al. Mechanical properties of meniscal circumferential fibers using an inverse finite element analysis approach. Journal of the mechanical Behavior of Biomedical Materials. 2022; 126: 105073.
- 21. Andrews S, Adesida A. B, Abusara Z, et al. Current concepts on structure–function relationships in the menisci. Connective Tissue Research. 2017; 58: 271-281.
- 22. Sanchez-Adams J, Athanasiou K. A, The Knee Meniscus: A Complex Tissue of Diverse Cells. Cellular and Molecular Bioengineering. 2009; 2: 332-340.
- 23. Moyer J. H, Priest R, Bouman T, et al. Indentation properties and glycosaminoglycan content of human menisci in the deep zone. Acta Biomaterialia. 2013; 9: 6624-6629.
- 24. McDevitt C. A, Mukherjee S, Kambic H, et al. Emerging concepts of the cell biology of the meniscus. Current Opinion in Orthopaedics. 2002; 13: 345-350.
- 25. Chen S, Fu P, Wu H, et al. Meniscus, articular cartilage and nucleus pulposus: a comparative review of cartilage-like tissues in anatomy, development and function. Cell and Tissue Research. 2017; 370: 53-70.
- 26. Assimakopoulos A. P, Katonis P, Agapitos M. V, et al. The Innervation of the Human Meniscus. Clinical Orthopaedics and Related Research. 1992; 275: 232-236.
- 27. Mine T, Kimura M, Sakka A, et al. Innervation of nociceptors in the menisci of the knee joint: an immunohistochemical study. Archives of Orthopaedic and Trauma Surgery. 2000; 120: 201-204.
- 28. Bird M. K, Sweet M. A system of canals in semilunar menisci. Annals of the Rheumatic Diseases. 1987; 46: 670-673.
- 29. King D. THE HEALING OF SEMILUNAR CARTILAGES. Journal of Bone and Joint Surgery. 1936; 18: 333-342.
- Matsukura Y, Muneta T, Tsuji K, et al. Mesenchymal Stem Cells in Synovial Fluid Increase After Meniscus Injury. Clinical Orthopaedics and Related Research. 2014; 472: 1357-1364.
- Hiyama K, Muneta T, Koga H, et al. Meniscal regeneration after resection of the anterior half of the medial meniscus in mice. Journal of Orthopaedic Research. 2017; 35: 1958-1965.
- 32. Sun H, Wen X, Li H, et al. Single-cell RNA-seq analysis identifies meniscus progenitors and reveals the progression of meniscus degeneration. Annals of the Rheumatic Diseases. 2020; 79: 408-417.
- 33. Seol D, McCabe D. J, Choe H, et al. Chondrogenic progenitor

cells respond to cartilage injury. Arthritis & Rheumatism. 2012; 64: 3626-3637.

- 34. Glenister T. W, An embryological view of cartilage. Journal of Anatomy. 1976; 122: 323-330.
- 35. Hirohata K, Mizuno K, Matsubara T, et al. Trends in Research and Treatment of Joint Diseases, 2012.
- Fox A, Bedi A, Rodeo S. A, et al. The Basic Science of Human Knee Menisci. Sports Health: A Multidisciplinary Approach. 2012; 4: 340-351.
- Rath E, Richmond J. C. The menisci: basic science and advances in treatment. British Journal of Sports Medicine. 2000; 34: 252-257.
- Skaggs D. L, Warden W. H, Mow V. C, et al. Radial tie fibers influence the tensile properties of the bovine medial meniscus. Journal of Orthopaedic Research. 1994; 12: 176-185.
- Fukubayashi T, Kurosawa H. The Contact Area and Pressure Distribution Pattern of the Knee: A Study of Normal and Osteoarthrotic Knee Joints. Acta Orthopaedica Scandinavica. 1980; 51: 871-879.
- 40. Kurosawa H, Fukubayashi T, Nakajima H, et al. Load-bearing mode of the knee joint: physical behavior of the knee joint with or without menisci. Clinical Orthopaedics and Related Research. 1980; 149: 283-290.
- 41. Seitz A. M, Schwer J, De Roy L, et al. Knee Joint Menisci Are Shock Absorbers: A Biomechanical In-Vitro Study on Porcine Stifle Joints. Frontiers in Bioengineering and Biotechnology.2022; 10: 837554.
- 42. Gecelter R, Ilyaguyeva Y, Thompson N. E, The menisci are not shock absorbers: a biomechanical and comparative perspective. Anatomical Record-advances in Integrative Anatomy and Evolutionary Biology. 2021; 305: 1051-1064.
- 43. Andrews S, Shrive N. G, Ronsky J. L, The shocking truth about meniscus. Journal of Biomechanics. 2011; 44: 2737-2740.
- 44. Englund M, Roemer F. W, Hayashi D, et al. Meniscus pathology, osteoarthritis and the treatment controversy. Nature Reviews Rheumatology. 2012; 8: 412-419.
- 45. Mitchell J. D, Graham W, Best T. M, et al. Epidemiology of meniscal injuries in US high school athletes between 2007 and 2013. Knee Surgery, Sports Traumatology, Arthroscopy. 2016; 24: 715-722.
- Brophy R. H, Sandell L. J, Farooq M, et al. Traumatic and Degenerative Meniscus Tears Have Different Gene Expression Signatures. American Journal of Sports Medicine. 2017; 45: 114-120.
- 47. Hughes C. F, Nibbs R. J. B. A guide to chemokines and their receptors. FEBS Journal. 2018; 285: 2944-2971.
- 48. Caley M, Martins V. L. M, O'Toole E. A, et al. Metalloproteinases and Wound Healing. Advances in Wound Care. 2015; 4: 225-234.
- 49. Almeida L. R. S, Oliveira J, Guimarães L. H, et al. Wound healing genes and susceptibility to cutaneous leishmaniasis in

Brazil: Role of COL1A1. Infection, Genetics and Evolution. 2015; 30: 225-229.

- 50. Jarraya M, Roemer F. W, Englund M, et al. Meniscus morphology: Does tear type matter? A narrative review with focus on relevance for osteoarthritis research. Seminars in Arthritis and Rheumatism. 2017; 46: 552-561.
- Vaquero-Picado A, Rodríguez-Merchán E. C. Arthroscopic repair of the meniscus. EFORT Open Reviews, 2018; 3: 584-594.
- 52. Chahla J, Cinque M. E, Godin J. A, et al. Review of Arnoczky and Warren on the microvasculature of the human meniscus. Journal of ISAKOS. 2017; 2; 229-232.
- 53. https://www.ncbi.nlm.nih.gov/books/ NBK431067/#:~:text=Longitudinal%20(vertical)%20 tears%20run%20perpendicular,free%20edge%20of%20 the%20meniscus.
- Karpinski K, Forkel P, Häner M, et al. Etiology of posterior meniscus root tears: medial vs. lateral. Archives of Orthopaedic and Trauma Surgery. 2022; 143: 429-437.
- 55. Muzaffar N, Kirmani O, Ahsan M, et al. Meniscal Extrusion in the Knee: Should only 3 mm Extrusion be Considered Significant? An Assessment by MRI and Arthroscopy. Malaysian Orthopaedic Journal. 2015; 9: 17-20.
- 56. Gale D. P, Chaisson C. E, Totterman S, et al. Meniscal subluxation: association with osteoarthritis and joint space narrowing. Osteoarthritis and Cartilage. 1999; 7: 526-532.
- 57. MacFarlane L. A, Yang H. J, Collins J. G, et al. Associations among meniscal damage, meniscal symptoms and knee pain severity. Osteoarthritis and Cartilage. 2017; 25: 850-857.
- Bray R. A, Smith J, Eng M, et al. Vascular response of the meniscus to injury: Effects of immobilization. Journal of Orthopaedic Research. 2001; 19; 384-390.
- 59. Luvsannyam E, Jain M. S, Leitao A. R, et al. Meniscus Tear: Pathology, Incidence, and Management. Cureus. 2022; 14: e25121.
- Slauterbeck J. R, Kousa P, Clifton B. C, et al. Geographic Mapping of Meniscus and Cartilage Lesions Associated with Anterior Cruciate Ligament Injuries. Journal of Bone and Joint Surgery. 2009; 91: 2094-2103.
- 61. Wu M, Jiang J, Liu Z, et al. Age, male sex, higher posterior tibial slope, deep sulcus sign, bone bruises on the lateral femoral condyle, and concomitant medial meniscal tears are risk factors for lateral meniscal posterior root tears: a systematic review and meta-analysis. Knee Surgery, Sports Traumatology, Arthroscopy. 2022; 30: 4144-4155.
- 62. Farooq M, Patra D, Sandell L. J, et al. Transcriptome Analysis of Injured Human Meniscus Reveals a Distinct Phenotype of Meniscus Degeneration With Aging. Arthritis & Rheumatism. 2013; 65: 2090-2101.
- Snoeker B, Bakker E, Kegel C a. T, et al. Risk Factors for Meniscal Tears: A Systematic Review Including Metaanalysis. Journal of Orthopaedic & Sports Physical Therapy. 2013; 43: 352-367.

- Jiang J, Liu Z, Wang X, et al. Increased Posterior Tibial Slope and Meniscal Slope Could Be Risk Factors for Meniscal Injuries: A Systematic Review. Arthroscopy. 2022; 38: 2331-2341.
- 65. Bayer S, Meredith S. J, Wilson K. R, et al. Knee Morphological Risk Factors for Anterior Cruciate Ligament Injury. Journal of Bone and Joint Surgery. 2020; 102: 703-718.
- Howell R. H, Kumar N. S, Patel N. L, et al. Degenerative meniscus: Pathogenesis, diagnosis, and treatment options. World Journal of Orthopedics. 2014; 5: 597.
- 67. Kopf S, Beaufils P, Hirschmann M. T, et al. Management of traumatic meniscus tears: the 2019 ESSKA meniscus consensus. Knee Surgery, Sports Traumatology, Arthroscopy. 2020; 28: 1177-1194.
- 68. Hare K. B, Lohmander S, Kise N. J, et al. Middle-aged patients with an MRI-verified medial meniscal tear report symptoms commonly associated with knee osteoarthritis. Acta Orthopaedica. 2017; 88: 664-669.
- 69. Kamimura M, Umehara J, Takahashi A, et al. Medial meniscus tear morphology and related clinical symptoms in patients with medial knee osteoarthritis. Knee Surgery, Sports Traumatology, Arthroscopy. 2015; 23: 158-163.
- Muthuri S. G, McWilliams D. F, Doherty M, et al. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis and Cartilage. 2011; 19: 1286-1293.
- Poulsen E, Gonçalves G. H, Bricca A, et al. Knee osteoarthritis risk is increased 4-6 fold after knee injury – a systematic review and meta-analysis. British Journal of Sports Medicine. 2019; 53: 1454-1463.
- Lohmander S, Englund P. M, Dahl L, et al. The Long-term Consequence of Anterior Cruciate Ligament and Meniscus Injuries. American Journal of Sports Medicine. 2007; 35: 1756-1769.
- 73. Lespasio M. J, Piuzzi N. S, Me H, et al. Knee Osteoarthritis: A Primer. The Permanente Journal. 2017; 21: 16-183.
- 74. Chan W. P, Huang G, Hsu S, et al. Radiographic joint space narrowing in osteoarthritis of the knee: relationship to meniscal tears and duration of pain. Skeletal Radiology. 2008; 37: 917-922.
- Espregueira-Mendes J, Andrade R, Silva L. F, et al. Meniscus Subluxation Retensioning: "Autotransplant." Arthroscopy Techniques. 2019; 8: e335-e341.
- Duthie J, Macleod J. MENISCECTOMY IN SOLDIERS. The Lancet. 1944; 243: 182-183.
- Pengas I, Assiotis A, Nash W. A, et al. Total meniscectomy in adolescents. The Journal of Bone and Joint Surgery. 2012; 94: 1649-1654.
- Katz J. N, Brophy R. H, Chaisson C. E, et al. Surgery versus Physical Therapy for a Meniscal Tear and Osteoarthritis. The New England Journal of Medicine. 2013; 368: 1675-1684.
- 79. A Grana W, Connor S, Hollingsworth S, et al. Partial Arthroscopic Meniscectomy: A Preliminary Report. Clinical Orthopedics and Related Research. 1982; 164: 78-83.

- N Dandy D, Jackson R. Arthroscopic, open partial, and total meniscectomy. A comparative study. The Journal of Bone and Joint Surgery. 1983; 65: 400-404.
- Avila A, Vasavada K, Shankar D. S, et al. Current Controversies in Arthroscopic Partial Meniscectomy. Current Reviews in Musculoskeletal Medicine. 2022; 15: 336-343.
- Kinsella S. D, Carey J. R. Complications In Brief: Arthroscopic Partial Meniscectomy. Clinical Orthopaedics and Related Research. 2013; 471: 1427-1432.
- Buckwalter J. A, Saltzman C. L, Brown T. D, et al. The Impact of Osteoarthritis. Clinical Orthopaedics and Related Research. 2004; 427: S6-S15.
- 84. López-Vega M, Doménech-Fernández J, Peiró S, et al. Has Arthroscopic Meniscectomy Use Changed in Response to the Evidence? A Large-database Study From Spain. Clinical Orthopaedics and Related Research. 2022; 481: 7-16.
- 85. Jackson J. P. Degenerative changes in the knee after meniscectomy. BMJ. 1968; 2: 525-527.
- Petty C. A, Lubowitz, J. H. Does Arthroscopic Partial Meniscectomy Result in Knee Osteoarthritis? A Systematic Review With a Minimum of 8 Years' Follow-up. Arthroscopy. 2011; 27: 419-424.
- Wang Z, Xiong Y. Q, Tang, X et al., An arthroscopic repair technique for meniscal tear using a needle and suture: outsidein transfer all-inside repair. BMC Musculoskeletal Disorders. 2019; 20: 614.
- Lutz C, Dalmay F, Ehkirch F. P et al. Meniscectomy versus meniscal repair: 10years radiological and clinical results in vertical lesions in stable knee. Orthopaedics & Traumatology: Surgery & Research. 2014; 101: S327-S331.
- 89. Weber J. H, Koch M, Angele P, et al. The role of meniscal repair for prevention of early onset of osteoarthritis. Journal of Experimental Orthopaedics. 2018; 5:
- 90. Zachariah Gene Wing Ow, Michelle Shi Ni Law, Cheng Han Ng, et al. All-Cause Failure Rates Increase With Time Following Meniscal Repair Despite Favorable Outcomes: A Systematic Review and Meta-analysis. Arthroscopy. 2021; 37: 3518-3528.
- 91. Schweizer C, Hanreich C, Tscholl PM, et al. Nineteen percent of meniscus repairs are being revised and failures frequently occur after the second postoperative year: a systematic review and meta-analysis with a minimum follow-up of 5 years. Knee Surgery, Sports Traumatology, Arthroscopy. 2021; 30: 2267-2276.
- 92. Hergan D, Thut D, Sherman, et al. Meniscal Allograft Transplantation. Arthroscopy. 2011; 27: 101-112.
- 93. McNickle AG, Wang VM, Shewman E, et al. Performance of a Sterile Meniscal Allograft in an Ovine Model. Clinical Orthopaedics and Related Research. 2009; 467: 1868-1876.
- Vrancken A, Buma P, Van Tienen TG. Synthetic meniscus replacement: a review. International Orthopaedics. 2013; 37: 291-299.

- 95. Lubowitz JH, Verdonk P, Reid JL, et al. Meniscus allograft transplantation: a current concepts review. Knee Surgery, Sports Traumatology, Arthroscopy. 2007; 15: 476-492.
- Sekiya J, Ellington C. Meniscal Allograft Transplantation. Journal of the American Academy of Orthopaedic Surgeons. 2007; 14: 164-174.
- K Jon S, I Ellingson C. Meniscal Allograft Transplantation. Journal of the American Academy of Orthopaedic Surgeons. 2006; 14: 164-174.
- 98. Kelly BT, Potter HG, Deng X, et al. Meniscal Allograft Transplantation in the Sheep Knee. American Journal of Sports Medicine. 2006; 34: 1464-1477.
- 99. Sommerlath K, Gillquist J. The effect of a meniscal prosthesis on knee biomechanics and cartilage: An experimental study in rabbits. American Orthopedic Society for Sports Medicine. 1975; 20:
- 100. Kobayashi M, Chang Y, Oka M. A two year in vivo study of polyvinyl alcohol-hydrogel (PVA-H) artificial meniscus. Biomaterials. 2005; 26: 3243-3248.
- 101. Kobayashi M, Toguchida J, Oka M. Development of an artificial meniscus using polyvinyl alcohol-hydrogel for early return to, and continuance of, athletic life in sportspersons with severe meniscus injury. I: mechanical evaluation. Knee. 2003; 10: 47-51.
- Stone KH, Rodkey WG, Webber RL, et al. Future Directions. Clinical Orthopaedics and Related Research. 1990; 252: 129-135.
- Forriol F. Growth factors in cartilage and meniscus repair. Injury-International Journal of the Care of the Injured. 2009; 40: S12–S16.
- 104. Chen M, Guo W, Gao S, et al. Biochemical Stimulus-Based Strategies for Meniscus Tissue Engineering and Regeneration. BioMed Research International. 2018; 1-15.
- 105. Schmidt M, Chen E, Lynch S, et al. A review of the effects of insulin-like growth factor and platelet-derived growth factor on in vivo cartilage healing and repair. Osteoarthritis and Cartilage. 2006; 14: 403-412.
- 106. Ionescu L. C, Lee G, Huang K, et al. Growth factor supplementation improves native and engineered meniscus repair in vitro. Acta Biomaterialia. 2012; 8: 3687-3694.
- 107. Lee K, Olmer M, Baek J, et al. Platelet-derived growth factor-coated decellularized meniscus scaffold for integrative healing of meniscus tears. Acta Biomaterialia. 2018; 76: 126-134.
- 108. Tarafder S, Gulko J, Kim D. H, et al. Effect of dose and release rate of CTGF and TGF $\beta$ 3 on avascular meniscus healing. Journal of Orthopaedic Research. 2019; 37: 1555-1562.
- 109. Hidaka C, Ibarra C, Hannafin J. A, et al. Formation of Vascularized Meniscal Tissue by Combining Gene Therapy with Tissue Engineering. Tissue Engineering. 2002; 8: 93-105.

- Spencer S, Saithna A. C, Dhillon M. S, et al. Meniscal scaffolds: Early experience and review of the literature. Knee. 2012; 19: 760-765.
- 111. Hollister S. J. Scaffold Design and Manufacturing: From Concept to Clinic. Advanced Materials. 2009; 21: 3330-3342.
- 112. Smith B, Grande D. The current state of scaffolds for musculoskeletal regenerative applications. Nature Reviews Rheumatology. 2015; 11: 213-222.
- 113. Myers K, Sgaglione N. A, Kurzweil P. R, et al. A Current Update on Meniscal Scaffolds. Operative Techniques in Sports Medicine. 2013; 21: 75-81.
- 114. Abpeikar Z, Moradi L, Javdani M, et al. Characterization of Macroporous Polycaprolactone/Silk Fibroin/Gelatin/ Ascorbic Acid Composite Scaffolds and In Vivo Results in a Rabbit Model for Meniscus Cartilage Repair. Cartilage. 2021; 13: 1583S-1601S.
- 115. Ruprecht J. C, Waanders T. D, Rowland C, et al. Meniscus-Derived Matrix Scaffolds Promote the Integrative Repair of Meniscal Defects. Scientific Reports. 2019; 9: 8719.
- 116. Monllau J. C, Gelber P. E, Abat F, et al. Outcome After Partial Medial Meniscus Substitution With the Collagen Meniscal Implant at a Minimum of 10 Years' Follow-up. Arthroscopy. 2011; 27: 933-943.
- 117. Jungmann P. M, Gersing A. S, Baumann F, et al. Cartilage repair surgery prevents progression of knee degeneration. Knee Surgery, Sports Traumatology, Arthroscopy. 2019; 27: 3001-3013.
- 118. Li H, Liao Z, Yang Z, et al. 3D Printed Poly (ε-Caprolactone)/ Meniscus Extracellular Matrix Composite Scaffold Functionalized With Kartogenin-Releasing PLGA Microspheres for Meniscus Tissue Engineering. Frontiers in Bioengineering and Biotechnology. 2021; 9: 662381.
- Dai W, Zhang H, Lin Z, et al. Efficacy of platelet-rich plasma in arthroscopic repair for discoid lateral meniscus tears. BMC Musculoskeletal Disorders. 2019; 20: 113.
- 120. Ehrenfest D. M. D, Rasmusson L, Albrektsson T, et al. Classification of platelet concentrates: from pure plateletrich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends in Biotechnology. 2009; 27: 158-167.
- 121. Shin K, Lee H, Kang S, et al. Effect of Leukocyte-Rich and Platelet-Rich Plasma on Healing of a Horizontal Medial Meniscus Tear in a Rabbit Model. BioMed Research International. 2015; 1-7.
- 122. Griffin J. W, Hadeed M. M, Werner B. C, et al. Platelet-rich Plasma in Meniscal Repair: Does Augmentation Improve Surgical Outcomes? Clinical Orthopaedics and Related Research. 2015; 473: 1665-1672.
- 123. Ishida K, Kuroda R, Miwa M, et al. The Regenerative Effects of Platelet-Rich Plasma on Meniscal CellsIn Vitroand ItsIn VivoApplication with Biodegradable Gelatin Hydrogel. Tissue engineering. 2007; 13: 1103-1112.
- 124. Kaminski R. M, Kulinski, K, Kozar-Kaminska K, et al. A

Prospective, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Meniscal Healing, Clinical Outcomes, and Safety in Patients Undergoing Meniscal Repair of Unstable, Complete Vertical Meniscal Tears (Bucket Handle) Augmented with Platelet-Rich Plasma. BioMed Research International. 2018; 1-9.

- 125. Chirichella P. S, Jow, S, Iacono S. A, et al. Treatment of Knee Meniscus Pathology: Rehabilitation, Surgery, and Orthobiologics. Pm&R. 2019; 11: 292-308.
- 126. Magalon J, Chateau A, Bertrand B, et al. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. BMJ Open Sport and Exercise Medicine. 2016; 2: e000060.
- 127. Kawamura S, Lotito K, Rodeo S. A, et al. Biomechanics and healing response of the meniscus. Operative Techniques in Sports Medicine. 2003; 11; 68-76.
- 128. Arnoczky S. P, Warren R. F. The microvasculature of the meniscus and its response to injury. American Journal of Sports Medicine. 1983; 11: 131-141.
- 129. Ochi M, Uchio Y, Okuda K, et al. Expression of cytokines after meniscal rasping to promote meniscal healing. Arthroscopy. 2001; 17; 724-731.
- Okuda K, Ochi M, Shu N, et al. Meniscal Rasping for Repair of Meniscal Tear in the Avascular Zone. Arthroscopy. 1999; 15: 281-286.
- Gershuni D. H, Mj S, Danzig L. A, et al. Experimental models to promote healing of tears in the avascular segment of canine knee menisci. Journal of Bone and Joint Surgery.1969; 71: 363-1370.
- 132. Nakhostine M, Gershuni D. H, Anderson R, et al. Effects of abrasion therapy on tears in the avascular region of sheep menisci. Arthroscopy. 1990; 6: 280-287.
- 133. Longo U. G, Campi S, Romeo G, et al. Biological Strategies to Enhance Healing of the Avascular Area of the Meniscus. Stem Cells International. 2012; 1-7.
- 134. Arnoczky S. P, Warren R. B, Spivak J. M, et al. Meniscal repair using an exogenous fibrin clot. An experimental study in dogs. Journal of Bone and Joint Surgery. 1988; 70: 1209-1217.
- 135. Jang S, Lou X. W. D, Lee D. H, et al. Fibrin Clot Delivery System for Meniscal Repair. Knee Surgery & Related Research. 2011; 23: 180-183.
- 136. Illingworth K. D, Musahl V, Lorenz S, et al. Use of Fibrin Clot in the Knee. Operative Techniques in Orthopaedics. 2010; 20: 90-97.
- 137. Port J, Jackson D. N, Lee T. Q, et al. Meniscal Repair Supplemented With Exogenous Fibrin Clot and Autogenous Cultured Marrow Cells in the Goat Model. American Journal of Sports Medicine. 1996; 24: 547-555.
- 138. Henning C. A, Lynch M. E, Yearout K. M, et al. Arthroscopic Meniscal Repair Using an Exogenous Fibrin Clot. Clinical Orthopaedics and Related Research. 1990; 252: 64-72.

- 139. https://www.nytimes.com/2016/08/04/upshot/the-right-toknow-that-an-operation-is-next-to-useless.html
- 140. Kise N. J, Risberg M. A, Stensrud S, et al. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ. 2016; 354: i3740.
- 141. Vermesan D, Prejbeanu R, Laitin S, et al. Arthroscopic debridement compared to intra-articular steroids in treating degenerative medial meniscal tears. European Review for Medical and Pharmacological Sciences. 2013; 17: 3192-3196.
- 142. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial. Annals of the Rheumatic Diseases. 2018; 77: 188-195.
- 143. Schweizer C, Hanreich C, Tscholl P. M, et al. Nineteen percent of meniscus repairs are being revised and failures frequently occur after the second postoperative year: a systematic review and meta-analysis with a minimum follow-up of 5 years. Knee Surgery, Sports Traumatology, Arthroscopy. 2021; 30: 2267-2276.
- 144. Monk P, Roberts P. G, Palmer A. W, et al. The Urgent Need for Evidence in Arthroscopic Meniscal Surgery: A Systematic Review of the Evidence for Operative Management of Meniscal Tears. American Journal of Sports Medicine. 2017; 45: 965-973.
- 145. Van De Graaf V. A, Noorduyn J. C. A, Willigenburg N. W, et al. Effect of Early Surgery vs Physical Therapy on Knee Function Among Patients With Nonobstructive Meniscal Tears. JAMA. 2018; 320: 1328.
- 146. Sluijs E, Kok G, Van Der Zee J. S, et al. Correlates of Exercise Compliance in Physical Therapy. Physical Therapy. 1993; 73: 771-782.
- 147. J Minguell J, Erices A, Conget P, et al. Mesenchymal Stem Cells. Experimental Biology and Medicine. 2001; 226: 507-520.
- 148. Westrich G. H, Schaefer S, Walcott-Sapp S, et al. Randomized prospective evaluation of adjuvant hyaluronic acid therapy administered after knee arthroscopy. The American Journal of Orthopedics. 2009; 38: 612-616.
- 149. Wernecke C, Braun H. J, Dragoo J. L, et al. The Effect of Intraarticular Corticosteroids on Articular Cartilage. Orthopaedic Journal of Sports Medicine. 2015; 3: 232596711558116.
- 150. Hauser R. The Deterioration of Articular Cartilage in Osteoarthritis by Corticosteroid Injections. Journal of Prolotherapy. 1996; 1: 107-123.
- 151. Kompel A. J, Roemer F. W, Murakami A, et al. Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought? Radiology. 2019; 293: 656-663.
- 152. Smith C, Patel R, Vannabouathong C, et al. Combined intra-articular injection of corticosteroid and hyaluronic acid reduces pain compared to hyaluronic acid alone in the treatment of knee osteoarthritis. Knee Surgery, Sports Traumatology, Arthroscopy. 2019; 27: 1974-1983.

- 154. Tabansky I, Stern J. N. H. Basics of Stem Cell Biology as Applied to the Brain. Research and Perspectives in Endocrine Interactions. 2016; 11-24.
- 155. Ko K, Araúzo-Bravo M. J, Kim J, et al. Conversion of adult mouse unipotent germline stem cells into pluripotent stem cells. Nature Protocols. 2010; 5: 921-928.
- 156. Akpancar S, Tatar O, Turgut H, et al. The Current Perspectives of Stem Cell Therapy in Orthopedic Surgery. Archives of Trauma Research. 2016; 5: e37976.
- Evans M, Kaufman M. J. Establishment in culture of pluripotential cells from mouse embryos. Nature. 1981; 292: 154-156.
- 158. Rossant J, Nagy A. In search of the tabula rasa of human cells. Nature Biotechnology. 1999; 17: 23-4.
- 159. Mukhopadhyay C. S, Tokas J, Mathur P. D, et al. Prospects and Ethical Concerns of Embryonic Stem Cells Research-A Review. Veterinary World. 2011; 4: 281-286.
- 160. Takahashi K, Yamanaka S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Cell. 2006; 126: 663-676.
- 161. Kumar D, Talluri T. R, Anand T, et al. Induced pluripotent stem cells: Mechanisms, achievements and perspectives in farm animals. World Journal of Stem Cells. 2015; 7: 315.
- 162. Gorecka J, Kostiuk V, Fereydooni A, et al. The potential and limitations of induced pluripotent stem cells to achieve wound healing. Stem Cell Research & Therapy. 2019; 10: 87.
- 163. Berika M. Y, Elgayyar M. E, El-Hashash A. H, et al. Asymmetric cell division of stem cells in the lung and other systems. Frontiers in Cell and Developmental Biology. 2014; 2: 33.
- 164. Knoblich J. A. Mechanisms of Asymmetric Stem Cell Division. Cell. 2008; 132: 583-597.
- Voog J. C, Jones D. Stem Cells and the Niche: A Dynamic Duo. Cell Stem Cell. 2010; 6: 103-115.
- 166. Ferraro F, Lo Celso C, Scadden D. T, et al. Adult Stem Cels and Their Niches. Springer eBooks. 2010; 695: 155-168.
- 167. Pennings S, Liu K. P, Qian H, et al. The Stem Cell Niche: Interactions between Stem Cells and Their Environment. Stem Cells International. 2018; 1-3.
- 168. Batsivari A, Haltalli M. L. R, Passaro D, et al. Dynamic responses of the haematopoietic stem cell niche to diverse stresses. Nature Cell Biology. 2020; 22: 7-17.
- Majumdar S, Liu S. Cell division symmetry control and cancer stem cells. AIMS Molecular Science. 2020; 7: 82-101.
- 170. Kolf C. M, Cho E, Tuan R. S, et al. Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. Arthritis Research & Therapy. 2007; 9: 204.

- 171. Lanza R, Atala A. Essentials of Stem Cell Biology. 2013.
- 172. Herreros-Pomares A. Identification, Culture and Targeting of Cancer Stem Cells. Life. 2022; 12: 184.
- 173. He S, Nakada D, Morrison S. J, et al. Mechanisms of Stem Cell Self-Renewal. Annual Review of Cell and Developmental Biology. 2009; 25: 377-406.
- 174. Chen G, Yin S, Zeng H, et al. Regulation of Embryonic Stem Cell Self-Renewal. Life. 2022; 12: 1151.
- 175. Deininger P. L. Genetic instability in cancer: caretaker and gatekeeper genes. The Ochsner Journal. 1999; 1: 206-209.
- 176. Dua H. S, Joseph A. J, Shanmuganathan V. A, et al. Stem cell differentiation and the effects of deficiency. Eye. 2003; 17: 877-885.
- 177. Shen C, Burke Z. D, Tosh D, et al. Transdifferentiation, Metaplasia and Tissue Regeneration. Organogenesis. 2004; 1: 36-44.
- 178. Herzog E. L, Chai L, Krause D. S, et al. Plasticity of marrowderived stem cells. Blood. 2003; 102: 3483-3493.
- 179. Williams A. J, Hare J. M. Mesenchymal Stem Cells. Circulation Research. 2011; 109: 923-940.
- 180. Beane O. S, Darling E. M. Isolation, Characterization, and Differentiation of Stem Cells for Cartilage Regeneration. Annals of Biomedical Engineering. 2012; 40: 2079-2097.
- 181. Bobis S, Jarocha D, Majka M, et al. Mesenchymal stem cells: characteristics and clinical applications. Folia Histochemica Et Cytobiologica. 2006; 44: 215-230.
- Zhao R. C. Essentials of Mesenchymal Stem Cell Biology and Its Clinical Translation. 2013.
- 183. Da Silva Meirelles L, Caplan A. I, Nardi N. B, et al. In Search of the In Vivo Identity of Mesenchymal Stem Cells. Stem Cells. 2008; 26: 2287-2299.
- Caplan A. I. Mesenchymal stem cells. Journal of Orthopaedic Research. 1991; 9: 641-650.
- 185. Gharibi B, Ghuman M. S, Hughes F. M, et al. Akt- and Erk-mediated regulation of proliferation and differentiation during PDGFRβ-induced MSC self-renewal. Journal of Cellular and Molecular Medicine. 2012; 16: 2789-2801.
- 186. Pittenger M. F, Mackay A. M, Beck S. D, et al. Multilineage Potential of Adult Human Mesenchymal Stem Cells. Science. 1999; 284: 143-147.
- 187. Glennon-Alty L, Williams R, Dixon S, et al. Induction of mesenchymal stem cell chondrogenesis by polyacrylate substrates. Acta Biomaterialia. 2013; 9: 6041-6051.
- 188. Solchaga L. A, Penick K, Welter J. F, et al. Chondrogenic Differentiation of Bone Marrow-Derived Mesenchymal Stem Cells: Tips and Tricks. 2011; 698: 253-278.
- 189. Huang C. C, Dai J, Zhang X, et al. Environmental, physical cues determine the lineage specification of mesenchymal stem cells. Biochimica Et Biophysica Acta - General Subjects. 2015; 1850; 1261-1266.
- 190. Fong E. L. S, Chan C. K, Goodman S. B, et al. Stem cell

homing in musculoskeletal injury. Biomaterials. 2011; 32: 395-409.

- 191. Yamasaki T, Deie M, Shinomiya R, et al. Meniscal regeneration using tissue engineering with a scaffold derived from a rat meniscus and mesenchymal stromal cells derived from rat bone marrow. Journal of Biomedical Materials Research Part A. 2005; 75: 23-30.
- 192. Howell R. H, Kumar N. S, Patel N. L, et al. Degenerative meniscus: Pathogenesis, diagnosis, and treatment options. World Journal of Orthopedics. 2014; 5: 597.
- 193. Osawa A, Harner C. D, Gharaibeh B, et al. The Use of Blood Vessel–Derived Stem Cells for Meniscal Regeneration and Repair. Medicine and Science in Sports and Exercise. 2013; 45: 813-823.
- 194. Dai T, Pan Z, Yin F, et al. In Vivo Studies of Mesenchymal Stem Cells in the Treatment of Meniscus Injury. Orthopaedic Surgery. 2021; 13: 2185-2195.
- 195. Pabbruwe M. B, Kafienah W, Tarlton J. F, et al. Repair of meniscal cartilage white zone tears using a stem cell/collagen-scaffold implant. Biomaterials. 2010; 31: 2583-2591.
- 196. Horie M, Choi H. H. F, Lee R. W, 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. Osteoarthritis and Cartilage. 2012; 20: 1197-1207.
- 197. Hjortholm N, Jaddini E, Hałaburda K, et al. Strategies of pain reduction during the bone marrow biopsy. Annals of Hematology. 2013; 92: 145-149.
- 198. Watt S. M, Gullo F, Van Der Garde M, et al. The angiogenic properties of mesenchymal stem/stromal cells and their therapeutic potential. British Medical Bulletin. 2013; 108: 25-53.
- 199. 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; 27: 878-887.
- 200. Petri M, Ufer K, Toma I, et al. Effects of perfusion and cyclic compression on in vitro tissue engineered meniscus implants. Knee Surgery, Sports Traumatology, Arthroscopy. 2012; 20: 223-231.
- 201. Shen W, Chen J, Zhu T, et al. Intra-Articular Injection of Human Meniscus Stem/Progenitor Cells Promotes Meniscus Regeneration and Ameliorates Osteoarthritis Through Stromal Cell-Derived Factor-1/CXCR4-Mediated Homing. Stem Cells Translational Medicine. 2014; 3: 387-394.
- 202. Mandal B. B, Park S, Gil E. S, et al. Stem Cell-Based Meniscus Tissue Engineering. Tissue Engineering Part A. 2011; 17: 2749-2761.
- 203. Abdel-Hamid M. E, Hussein M. A, Ahmad A, et al. Enhancement of the repair of meniscal wounds in the redwhite zone (middle third) by the injection of bone marrow cells in canine animal model. International Journal of Experimental Pathology. 2005; 86: 117-123.

- 204. Sanchez-Adams J, Athanasiou, K. A. Dermis isolated adult stem cells for cartilage tissue engineering. Biomaterials. 2012; 33: 109-119.
- 205. Fang P, Leng P, Zhang J, et al. Enhanced Meniscal Repair by Overexpression of hIGF-1 in a Full-thickness Model. Clinical Orthopaedics and Related Research. 2009; 467: 3165-3174.
- 206. 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 Engineering Part C-Methods. 2016; 22: 608-619.
- 207. Baker B. M, Mauck R. L. The effect of nanofiber alignment on the maturation of engineered meniscus constructs. Biomaterials. 2007; 28: 1967-1977.
- 208. Gir P, Oni G, Brown S, et al. Human Adipose Stem Cells. Plastic and Reconstructive Surgery. 2012; 129: 1277-1290.
- 209. De Barros S. G, Dehez S, Arnaud E, et al. Aging-related Decrease of Human ASC Angiogenic Potential Is Reversed by Hypoxia Preconditioning Through ROS Production. Molecular Therapy. 2013; 21: 399-408.
- 210. Rautiainen S, Laaksonen T, Koivuniemi R, et al. Angiogenic Effects and Crosstalk of Adipose-Derived Mesenchymal Stem/Stromal Cells and Their Extracellular Vesicles with Endothelial Cells. International Journal of Molecular Sciences. 2021; 22: 10890.
- 211. Petersen W, Pufe T, Stärke C, et al. Locally applied angiogenic factors--a new therapeutic tool for meniscal repair. Annals of Anatomy-anatomischer Anzeiger. 2005; 187: 509-519.
- 212. Tsuji W, Rubin J. P, Marra K. G, et al. Adipose-derived stem cells: Implications in tissue regeneration. World Journal of Stem Cells. 2014; 6: 312.
- 213. Maxson S. A, Lopez E, Yoo D, et al. Concise Review: Role of Mesenchymal Stem Cells in Wound Repair. Stem Cells Translational Medicine. 2012; 1: 142-149.
- 214. Andia I, Maffulli N. Biological Therapies in Regenerative Sports Medicine. Sports Medicine. 2017; 47: 807-828.
- 215. Han Y, Yang J, Fang J, et al. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Signal Transduction and Targeted Therapy. 2022; 7: 92.
- Blanc K. L, Ringdén O. Immunomodulation by mesenchymal stem cells and clinical experience. Journal of Internal Medicine. 2007; 262: 509-525.
- 217. Ceccarelli S, Pontecorvi P, Anastasiadou E, et al. Immunomodulatory Effect of Adipose-Derived Stem Cells: The Cutting Edge of Clinical Application. Frontiers in Cell and Developmental Biology. 2020; 8: 236.
- 218. Gonzalez-Rey E, Gonzalez M. A, Varela N, et al. Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010; 69: 241-248.

- 219. Al-Ghadban S, Bunnell B. A. Adipose Tissue-Derived Stem Cells: Immunomodulatory Effects and Therapeutic Potential. Physiology. 2020; 35: 125-133.
- 220. Salari V, Mengoni F, Del Gallo F, et al. The Anti-Inflammatory Properties of Mesenchymal Stem Cells in Epilepsy: Possible Treatments and Future Perspectives. International Journal of Molecular Sciences. 2020; 21: 9683.
- 221. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. Oxidative Medicine and Cellular Longevity. 2017; 1-13.
- 222. Lee K. H, Tseng W, Yang C, et al. The Anti-Inflammatory, Anti-Oxidative, and Anti-Apoptotic Benefits of Stem Cells in Acute Ischemic Kidney Injury. International Journal of Molecular Sciences. 2019; 20: 3529.
- 223. Calissano P, Amadoro G, Matrone C, et al. Does the term 'trophic' actually mean anti-amyloidogenic? The case of NGF. Cell Death & Differentiation.2010; 17: 1126-1133.
- 224. Hofer H, Tuan R. S. Secreted trophic factors of mesenchymal stem cells support neurovascular and musculoskeletal therapies. Stem Cell Research & Therapy. 2016; 7: 131.
- 225. Pak J, Lee J. P, Lee S. Y, et al. Regenerative Repair of Damaged Meniscus with Autologous Adipose Tissue-Derived Stem Cells. BioMed Research International. 2014; 436029.
- 226. Centeno C. J, Busse D, Kisiday J. D, et al. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain Physician. 2008; 11: 343-353.
- 227. Mahajan P. V, Subramanian S, Parab S. C, et al. Autologous Minimally Invasive Cell-Based Therapy for Meniscal and Anterior Cruciate Ligament Regeneration. Case reports in orthopedics. 2021; 6614232.
- 228. Vangsness C. T, Farr J, Boyd J. L, et al. Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy. Journal of Bone and Joint Surgery. 2014; 96: 90-98.
- 229. Olivos-Meza A, Pérez Jiménez F. J, Granados-Montiel J, et al. First Clinical Application of Polyurethane Meniscal Scaffolds with Mesenchymal Stem Cells and Assessment of Cartilage Quality with T2 Mapping at 12 Months. Cartilage. 2021; 13: 197S-207S.
- 230. https://www.theatlantic.com/science/archive/2017/10/stem-cell-eye/541299/
- 231. Večerić-Haler Ž, Borštnar Š, Luzar B, et al. Multiorgan failure with fatal outcome after stem cell tourism. European Journal of Medical Research, 2021; 26: 5.
- 232. Woodworth C. F, Jenkins G. D, Barron J, et al. Intramedullary cervical spinal mass after stem cell transplantation using an olfactory mucosal cell autograft. Canadian Medical Association Journal. 2019; 191: E761-E764.
- 233. Kumar D, Anand T, Kues, W. A, et al. Clinical potential of human induced pluripotent stem cells. Cell Biology and Toxicology. 2017; 33: 99-112.

- 234. Rong Z, Fu X, Wang M, et al. A Scalable Approach to Prevent Teratoma Formation of Human Embryonic Stem Cells. Journal of Biological Chemistry. 2012; 287: 32338-32345.
- 235. Wuputra K, Ku C, Wu D, et al. Prevention of tumor risk associated with the reprogramming of human pluripotent stem cells. Journal of Experimental & Clinical Cancer Research. 2020; 39: 100.
- 236. Whitehouse M. R, Howells N. R, Parry M. C, et al. Repair of Torn Avascular Meniscal Cartilage Using Undifferentiated Autologous Mesenchymal Stem Cells: From In Vitro Optimization to a First-in-Human Study. Stem cells translational medicine. 2017; 6, 1237-1248.
- 237. https://understandlipogems.com/the-truth-about-stem-cells/
- 238. https://www.fda.gov/consumers/consumer-updates/fdawarns-about-stem-cell-therapies
- 239. Herberts C. A, Kwa M. S. G, Hermsen H, et al. Risk factors in the development of stem cell therapy. Journal of Translational Medicine. 2011; 9: 29.
- 240. 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, Sports Traumatology, Arthroscopy. 2006; 14: 1307-1314.
- 241. Ozeki N, Muneta T, Matsuta S, et al. Synovial Mesenchymal Stem Cells Promote Meniscus Regeneration Augmented by an Autologous Achilles Tendon Graft in a Rat Partial Meniscus Defect Model. Stem Cells. 2015; 33: 1927-1938.
- 242. Ikuta Y, Kamei N, Ishikawa M, et al. In VivoKinetics of Mesenchymal Stem Cells Transplanted into the Knee Joint in a Rat Model Using a Novel Magnetic Method of Localization. Clinical and Translational Science. 2015; 8: 467-474.
- 243. Sekiya I, Koga H, Katano H, et al. Second-look arthroscopy after meniscus repair and synovial mesenchymal stem cell transplantation to treat degenerative flaps and radial tears of the medial meniscus: A case report. Journal of orthopaedic science: Official Journal of the Japanese Orthopaedic Association. 2022; 27: 821-834.
- 244. Liu C, Abedian R, Meister R, et al. Influence of perfusion and compression on the proliferation and differentiation of bone mesenchymal stromal cells seeded on polyurethane scaffolds. Biomaterials. 2012; 33: 1052-1064.
- 245. Zellner J, Hierl K, Mueller M. D, et al. Stem cell-based tissue-engineering for treatment of meniscal tears in the avascular zone. Journal of Biomedical Materials Research Part B. 2013; 101: 1133-1142.
- 246. Angele P, Johnstone B, Kujat R, et al. Stem cell based tissue engineering for meniscus repair. Journal of Biomedical Materials Research Part A. 2008; 85: 445-455.
- 247. Bilgen B, Jayasuriya C. T, Owens B. D, et al. Current Concepts in Meniscus Tissue Engineering and Repair. Advanced Healthcare Materials. 2018; 7: 1701407.

- 248. Holton J. M, Imam M. A, Ward J. M, et al. The basic science of bone marrow aspirate concentrate in chondral injuries. Orthopedic Reviews. 2016; 8: 6659.
- 249. Lana J. F. S. D, Da Fonseca L. F, Da Rocha Macedo R, et al. Platelet-rich plasma vs bone marrow aspirate concentrate: An overview of mechanisms of action and orthobiologic synergistic effects. World Journal of Stem Cells. 2021; 13: 155-167.
- 250. Lana J. F. S. D, Da Fonseca L. F, Azzini G. O. M, et al. Bone Marrow Aspirate Matrix: A Convenient Ally in Regenerative Medicine. International Journal of Molecular Sciences. 2021; 22: 2762.
- 251. Brozovich A, Sinicrope B. J, Bauza G, et al. High Variability of Mesenchymal Stem Cells Obtained via Bone Marrow Aspirate Concentrate Compared With Traditional Bone Marrow Aspiration Technique. Orthopaedic Journal of Sports Medicine. 2021; 9: 232596712110584.
- 252. Fu X, Liu G, Halim A, et al. Mesenchymal Stem Cell Migration and Tissue Repair. Cells. 2019; 8: 784.
- 253. Shen W, Chen J, Zhu T, et al. Osteoarthritis Prevention Through Meniscal Regeneration Induced by Intra-Articular Injection of Meniscus Stem Cells. Stem Cells and Development. 2013; 22: 2071-2082.
- 254. Waldner M, Zhang W, James I. B, et al. Characteristics and Immunomodulating Functions of Adipose-Derived and Bone Marrow-Derived Mesenchymal Stem Cells Across Defined Human Leukocyte Antigen Barriers. Frontiers in Immunology. 2018; 9: 1642.
- 255. Ding Z, Huang H. Mesenchymal stem cells in rabbit meniscus and bone marrow exhibit a similar feature but a heterogeneous multi-differentiation potential: superiority of meniscus as a cell source for meniscus repair. BMC Musculoskeletal Disorders. 2015; 16: 65.
- 256. Cui X, Hasegawa A, Lotz M, et al. Structured three-dimensional co-culture of mesenchymal stem cells with meniscus cells promotes meniscal phenotype without hypertrophy. Biotechnology and Bioengineering. 2012; 109: 2369-2380.
- 257. Chowdhury A, Bezuidenhout L. W, Mulet-Sierra A, et al. Effect of interleukin-1β treatment on co-cultures of human meniscus cells and bone marrow mesenchymal stromal cells. BMC Musculoskeletal Disorders. 20136; 14: 216.
- 258. TerHuurneM,SchelbergenR,BlattesR,etal.Antiinflammatory and chondroprotective effects of intraarticular injection of adipose-derived stem cells in experimental osteoarthritis. Arthritis & Rheumatism. 2012; 64: 3604-3613.
- 259. Sakaguchi Y, Sekiya I, Yagishita K, et al. Comparison of human stem cells derived from various mesenchymal tissues: Superiority of synovium as a cell source. Arthritis & Rheumatism. 2005; 52: 2521-2529.
- 260. Berebichez-Fridman R, Montero-Olvera P. R. Sources and Clinical Applications of Mesenchymal Stem Cells: State-ofthe-art review. Sultan Qaboos University Medical Journal. 2018; 18: 264.

- 261. Makris E, Hadidi P, Athanasiou K. A, et al. The knee meniscus: Structure–function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials. 2011; 32: 7411-7431.
- 262. Lindroos B, Suuronen R, Miettinen S, et al. The Potential of Adipose Stem Cells in Regenerative Medicine. Stem Cell Reviews and Reports. 2011; 7: 269-291.
- 263. Zuk P. A, Zhu M, Ashjian P, et al. Human Adipose Tissue Is a Source of Multipotent Stem Cells. Molecular Biology of the Cell. 2002; 13: 4279-4295.
- 264. Mazini L, Rochette L, Amine M, et al. Regenerative Capacity of Adipose Derived Stem Cells (ADSCs), Comparison with Mesenchymal Stem Cells (MSCs). International Journal of Molecular Sciences. 2019; 20: 2523.
- 265. Strioga M, Viswanathan S, Darinskas A, et al. Same or Not the Same? Comparison of Adipose Tissue-Derived Versus Bone Marrow-Derived Mesenchymal Stem and Stromal Cells. Stem Cells and Development. 2012; 21: 2724-2752.
- 266. Ruiz-Ibán M. Á, Díaz-Heredia J, Garcia-Gomez I, et al. The Effect of the Addition of Adipose-Derived Mesenchymal Stem Cells to a Meniscal Repair in the Avascular Zone: An Experimental Study in Rabbits. Arthroscopy. 2011; 27: 1688-1696.
- 267. Qi Y, Yang Z, Ding Q, et al. Targeted transplantation of iron oxide-labeled, adipose-derived mesenchymal stem cells in promoting meniscus regeneration following a rabbit massive meniscal defect. Experimental and Therapeutic Medicine. 2016; 11: 458-466.
- 268. Sekiya I, Muneta T, Horie M, et al. Arthroscopic Transplantation of Synovial Stem Cells Improves Clinical Outcomes in Knees With Cartilage Defects. Clinical Orthopaedics and Related Research. 2015; 473: 2316-2326.
- 269. Saw K, Anz A. W, Jee C. S, et al. High Tibial Osteotomy in Combination With Chondrogenesis After Stem Cell Therapy: A Histologic Report of 8 Cases. Arthroscopy. 2015; 31: 1909-1920.
- 270. Chen Y, Yan X, Yuan F, et al. The Use of Peripheral Blood-Derived Stem Cells for Cartilage Repair and Regeneration In Vivo: A Review. Frontiers in Pharmacology. 2020; 11: 404.
- 271. Sloan S. R. Chapter 19 Peripheral-Blood-Derived Hematopoietic Progenitor Cells. In Handbook of Transfusion Medicine. 2001; 161-170.
- 272. Chondrocytes. J Clin Pathol Suppl (R Coll Pathol). 1978; 31: 7-13.
- 273. Weinand C, Peretti G. M, Adams S. B, et al. Healing potential of transplanted allogeneic chondrocytes of three different sources in lesions of the avascular zone of the meniscus: a pilot study. Archives of Orthopaedic and Trauma Surgery. 2006; 126: 599-605.
- 274. Peretti G. M, Caruso E, Randolph M, et al. Meniscal repair using engineered tissue. Journal of Orthopaedic Research. 2001; 19: 278-285.

- 275. Marsano A, Millward-Sadler S. J, Salter D, et al. Differential cartilaginous tissue formation by human synovial membrane, fat pad, meniscus cells and articular chondrocytes. Osteoarthritis and Cartilage. 2007; 15: 48-58.
- 276. Yang Y. H. K, Ogando C. R, See C. W, et al. Changes in phenotype and differentiation potential of human mesenchymal stem cells aging in vitro. Stem Cell Research & Therapy. 2018; 9: 131.
- 277. Toyserkani N. M, Jørgensen M. R. V, Tabatabaeifar S, et al. Concise Review: A Safety Assessment of Adipose-Derived Cell Therapy in Clinical Trials: A Systematic Review of Reported Adverse Events. Stem Cells Translational Medicine. 2017; 6: 1786-1794.
- 278. Lu V. M, Tennyson M, Zhang J. J, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles in Tendon and Ligament Repair—A Systematic Review of In Vivo Studies. Cells. 2021; 10: 2553.
- 279. Hatsushika D, Muneta T, Horie, M, et al. Intraarticular injection of synovial stem cells promotes meniscal regeneration in a rabbit massive meniscal defect model. Journal of Orthopaedic Research. 2013; 31: 1354-1359.
- 280. Kondo S, Muneta T, Nakagawa Y, et al. Transplantation of autologous synovial mesenchymal stem cells promotes meniscus regeneration in aged primates. Journal of Orthopaedic Research. 2017; 35: 1274-1282.
- Jülke H, Mainil-Varlet P, Jakob R. P, et al. The Role of Cells in Meniscal Guided Tissue Regeneration. Cartilage. 2015; 6: 20-29.
- 282. Faqeh H. A, Hamdan B, Chen H. S, et al. The potential of intra-articular injection of chondrogenic-induced bone marrow stem cells to retard the progression of osteoarthritis in a sheep model. Experimental Gerontology. 2012; 47: 458-464.
- 283. Ruipeng G, Gao L, Xu B, et al. Current Evidence of Adult Stem Cells to Enhance Anterior Cruciate Ligament Treatment: A Systematic Review of Animal Trials. Arthroscopy. 2018; 34: 331-340.
- 284. Hevesi M, LaPrade M. D, Saris D. B, et al. Stem Cell Treatment for Ligament Repair and Reconstruction. Current Reviews in Musculoskeletal Medicine. 2019; 12: 446-450.
- 285. Jones R. E, Foster D. S, Hu M. S, et al. Wound healing and fibrosis: current stem cell therapies. Transfusion. 2019; 59: 884-892.
- 286. Guo S, DiPietro L. A. Factors Affecting Wound Healing. Journal of Dental Research. 2010; 89: 219-229.
- 287. Nerurkar N. L, Sen S, Baker B. M, et al. Dynamic culture enhances stem cell infiltration and modulates extracellular matrix production on aligned electrospun nanofibrous scaffolds. Acta Biomaterialia. 2011; 7: 485-491.
- 288. Liu Z, Tang M, Zhao J, et al. Looking into the Future: Toward Advanced 3D Biomaterials for Stem-Cell-Based Regenerative Medicine. Advanced Materials. 2018; 30: 1705388.

- 289. Kwon H, Brown W. J, Lee C. A, et al. Surgical and tissue engineering strategies for articular cartilage and meniscus repair. Nature Reviews Rheumatology. 2019; 15: 550-570.
- 290. Mauck R. L, Burdick J. A. From Repair to Regeneration: Biomaterials to Reprogram the Meniscus Wound Microenvironment. Annals of Biomedical Engineering. 2015; 43: 529-542.
- 291. Liebig B. E, Kisiday J. D, Bahney C. S, et al. The plateletrich plasma and mesenchymal stem cell milieu: A review of therapeutic effects on bone healing. Journal of Orthopaedic Research. 2020; 38: 2539-2550.
- 292. Tobita M, Tajima S, Mizuno H, et al. Adipose tissue-derived mesenchymal stem cells and platelet-rich plasma: stem cell transplantation methods that enhance stemness. Stem Cell Research & Therapy. 2015; 6: 215.
- 293. Lai F, Kakudo N, Morimoto N, et al. Platelet-rich plasma enhances the proliferation of human adipose stem cells through multiple signaling pathways. Stem Cell Research & Therapy. 2018; 9: 107.
- 294. Qian Y, Han Q, Chen W, et al. Platelet-Rich Plasma Derived Growth Factors Contribute to Stem Cell Differentiation in Musculoskeletal Regeneration. Frontiers in Chemistry. 2017; 5: 89.
- 295. Fernandes G, Yang S. Application of platelet-rich plasma

with stem cells in bone and periodontal tissue engineering. Bone Research. 2016; 4: 16036.

- 296. Osugi M, Katagiri W, Yoshimi R, et al. Conditioned Media from Mesenchymal Stem Cells Enhanced Bone Regeneration in Rat Calvarial Bone Defects. Tissue Engineering Part A. 2012; 18: 1479-1489.
- 297. Gunawardena T. N, Rahman M. M, Abdullah B. J. J, et al. Conditioned media derived from mesenchymal stem cell cultures: The next generation for regenerative medicine. Journal of Tissue Engineering and Regenerative Medicine. 2019; 13: 569-586.
- 298. Ferris D. J, Frisbie D. D, Kisiday J. D, et al. Clinical Outcome After Intra-Articular Administration of Bone Marrow Derived Mesenchymal Stem Cells in 33 Horses With Stifle Injury. Veterinary Surgery. 2014; 43: 255-265.
- 299. Yu H, Adesida A. B, Jomha N. M, et al. Meniscus repair using mesenchymal stem cells – a comprehensive review. Stem Cell Research & Therapy. 2015; 6: 86.
- 300. Jacob G. P, Shimomura K, Krych A. J, et al. The Meniscus Tear: A Review of Stem Cell Therapies. Cells. 2019; 9: 92.
- 301. Bian Y, Wang H, Zhao X, et al. Meniscus repair: up-to-date advances in stem cell-based therapy. Stem cell research & therapy. 2022; 13: 207.

© 2023 Keagle MJ, et al. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License