Biological augmentation to promote meniscus repair: from basic science to clinic application—state of the art

Courtney R Carlson Strother,1 Daniel B F Saris,1 Peter Verdonk,2 Norimasa Nakamura,3 Aaron J Krych1

ABSTRACT
Meniscus tears range from acute tears during physical activity to chronic degenerative tears. The role of the meniscus in knee stability, load distribution, knee proprioception and arthritis prevention has been well established, and successful repair of meniscus tears has better clinical outcomes and protection from increased degenerative changes. Advancements in surgical techniques have demonstrated meniscus repair is possible in tears previously deemed unsalvageable. In addition, the use of biological augmentation has improved rates of meniscal healing, and the use of biologics is an active area of investigation. In this article, we review current methods of biological augmentation to promote meniscal healing, including biological injections, concomitant procedures and biological membranes.

INTRODUCTION
Meniscus tears are an increasingly common problem worldwide, affecting approximately 0.7 and 2 out of every 1000 people per year in Denmark and the Netherlands, respectively.1 2 A recent study in the USA found the number of meniscus repairs has doubled over a 7-year epidemiology study, making them one of the most common orthopaedic surgeries in the country.3 Menisci are semi-lunar fibrocartilage structures that have a peripheral vascular and central avascular zone (figure 1). The peripheral vascular zone contains fibroblastic cells and type-I collagen fibres, with a low concentration of proteoglycans.4 The geniculate arteries supply this zone, which is approximately 10%–25% of the meniscus.1 4 6 The avascular central zone contains mainly fibrochondrocytes, type-II collagen and proteoglycans.4 Diffusion and mechanical pumping provide nutrients to cells in the avascular zone.7 Neural elements are located in the periphery of menisci,8 and the anterior and posterior horns contain mechanoreceptors thought to contribute to proprioception of the knee.7

Biomechanical studies have shown the role of the meniscus in knee stability, load distribution and knee proprioception.9 10 17 The collagen fibre orientation converts axial loads at the knee to hoop stresses,10 thus allowing for load distribution and shock absorption.16 Baratz et al19 demonstrated that medial meniscectomy resulted in a loss of 75% contact area and a 235% increase in peak local contact stresses of the knee. These increased forces across the joint are thought to contribute to histological and biochemical changes at the knee associated with osteoarthritis, but at an accelerated rate.20 Meniscus tears range from acute, often sports-related, injuries in young adults to degenerative tears commonly seen in older adults.21–23 Supraphysiologic forces applied to the meniscus create an acute, traumatic meniscus tear. Conversely, degenerative tears develop from repetitive physiological forces applied to an ageing meniscus.7 11 24 Tears are often classified by their pattern and include vertical longitudinal, oblique, radial, horizontal and complex (including degenerative). Patients typically present with joint line pain, effusions and mechanical symptoms such as locking in the knee.7 While a successful meniscus repair has shown favourable long-term clinical and radiological outcomes,25 treatment decision-making often revolves around predictors of successful meniscus healing, particularly the limited healing capability of meniscus tears in the avascular zone.11 21 However, recent surgical and biological augmentation methods have improved the healing capacity in meniscus tears previously considered unsalvageable,26 and development of these methods continues to be an active area of investigation. The purpose of this article is to provide an up-to-date review of the current methods of biological augmentation to promote meniscus healing following injury, including both acute and degenerative meniscus tears. Procedures examined in this review include biological injections, concomitant surgeries and the use of biological membranes (figure 2).

BODY
Hyaluronic acid
Hyaluronic acid (HA) is a major component of synovial fluid and cartilage extracellular matrix thought to provide lubrication and shock absorption in the knee, and its use has been largely studied in the treatment of osteoarthritis.27 28 In an animal study examining meniscus tears, Forriol et al did not see any evidence of meniscus healing 8 weeks following trephination and HA injection into the defect.29 Additionally, in a clinical study by Vangsness et al, no meniscus growth occurred 2 years after injection of HA following partial meniscectomy.30 Therefore, evidence is lacking on the efficacy of HA in treatment of meniscus defects.

Growth factor injections
A multitude of preclinical studies have examined the efficacy of various growth factors in promoting
meniscus healing for their effects in cell proliferation, differentiation and angiogenesis. Platelet-derived growth factor (PDGF) is a potent stimulator of cell proliferation, extracellular matrix formation and angiogenesis, and Bhargava et al demonstrated new organised collagen at the sites of meniscus defects 4 weeks after gel application of PDGF in vitro. Similar meniscus regeneration has been revealed in preclinical studies of fibroblast growth factor, insulin-like growth factor I and transforming growth factor beta (TGFβ). Stimulating angiogenesis with the use of vascular endothelial growth factor in the avascular zone of meniscus tears did not show an increase in meniscus healing or angiogenesis in separate animal studies by Kopf et al and Petersen et al.

Following meniscus injury, increased levels of inflammatory cytokines such as interleukin-1 (IL-1) are hypothesised to activate matrix metalloproteinases (MMPs), enzymes linked to collagen degradation. Meniscus repairs exposed to IL-1 significantly increased MMP activity and were associated with decreased repair strength and cell accumulation at the repair site in an in vitro study by Wilusz et al. Conversely, broad-spectrum inhibition of MMPs in an in vitro meniscus tear model demonstrated increased shear strength and tissue repair in a study by McNulty et al. In a study by Stone et al, degenerative menisci harvested from vervet monkey knees secreted significantly increased levels of MMPs compared with healthy, younger menisci. In addition, synovial fluid analysis of the knees of 16 patients with known meniscus tears found a 25-fold increase in MMP levels when compared with control knees. Unfortunately, a randomised control trial of an oral MMP inhibitor produced significant musculoskeletal toxicity in subjects, without evidence of significant improvement in their knee osteoarthritis. To our knowledge, no further clinical studies have examined the effects of meniscus augmentation using growth factors, though local administration may provide an avenue for effective treatment while minimising toxicities.

Marrow stimulation derived from concomitant anterior cruciate ligament (ACL) repair
Long-term studies have shown significantly improved clinical outcomes and reduced reoperation rates in meniscus repairs with concomitant ACL reconstruction. Furthermore, inside-out techniques have reduced reoperations compared with all-inside repairs in patients with concurrent ACL repair. One theory for improved outcomes in meniscus repair performed with an ACL reconstruction is the notion that biological healing factors are stimulated with bony tunnel drilling. This concept lead to the development of bone marrow stimulation as a method to augment meniscus healing in isolated repairs. Howarth et al demonstrated significantly improved meniscus healing in animals with meniscus repair in conjunction with microfracture compared with those without. In addition, intercondylar notch marrow venting with isolated meniscus repair produced similar clinical outcomes and failure rates as meniscus repair with concomitant ACL repair at 2-year minimum follow-up in a study by Dean et al. Bone marrow aspirates have also been studied as a potential source of meniscus augmentation derived from bone marrow stimulation. In a preclinical study by Zhang et al, meniscus defects injected with bone marrow aspirates showed significant meniscus regeneration compared with a cell-free gel injection. This regeneration was further enhanced with cells transfected with human insulin-like growth factor 1. Further studies are needed on the safety and efficacy of bone marrow stimulation, but early studies show promising results.
State of the art review

Table 1 Biological augmentation tools to promote meniscus repair

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Author</th>
<th>Year</th>
<th>Stage of disease</th>
<th>Design</th>
<th>Clinical outcome</th>
<th>Biological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet-rich plasma</td>
<td>Zellner et al</td>
<td>2013</td>
<td>Meniscus tear</td>
<td>In vivo: rabbit</td>
<td>–</td>
<td>No regeneration</td>
</tr>
<tr>
<td></td>
<td>Pujol et al</td>
<td>2015</td>
<td>Meniscus tear</td>
<td>Case control</td>
<td>Improved</td>
<td>Healing on MRI</td>
</tr>
<tr>
<td></td>
<td>Griffen et al</td>
<td>2015</td>
<td>Meniscus tear</td>
<td>Retrospective review</td>
<td>No difference</td>
<td>–</td>
</tr>
<tr>
<td>Fibrin clot</td>
<td>Jang et al</td>
<td>2011</td>
<td>Meniscus tear</td>
<td>Cohort</td>
<td>–</td>
<td>Healing on MRI or second look arthroscopy</td>
</tr>
<tr>
<td></td>
<td>Nakayama et al</td>
<td>2019</td>
<td>Meniscus tear</td>
<td>Cohort</td>
<td>Improved</td>
<td>Healing on MRI</td>
</tr>
<tr>
<td></td>
<td>Ra et al</td>
<td>2013</td>
<td>Radial tear</td>
<td>Cohort</td>
<td>Improved</td>
<td>Healing on MRI or second look arthroscopy</td>
</tr>
<tr>
<td>Hyaluronic Acid</td>
<td>Forriol et al</td>
<td>2015</td>
<td>Meniscus tear</td>
<td>In vivo: sheep</td>
<td>–</td>
<td>No regeneration</td>
</tr>
<tr>
<td></td>
<td>Vangsness et al</td>
<td>2014</td>
<td>Partial meniscectomy</td>
<td>Randomised control trial</td>
<td>Improved</td>
<td>No regeneration on MRI</td>
</tr>
<tr>
<td>Concomitant ACL repair</td>
<td>Melton et al</td>
<td>2011</td>
<td>Meniscus tear</td>
<td>Retrospective review</td>
<td>Improved</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Wassertein et al</td>
<td>2013</td>
<td>Meniscus tear</td>
<td>Cohort</td>
<td>Improved</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Westermann et al</td>
<td>2014</td>
<td>Meniscus tear</td>
<td>Prospective cohort</td>
<td>Low reoperation rate at 6 year follow-up</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Westermann et al</td>
<td>2017</td>
<td>Meniscus tear</td>
<td>Meta-regression analysis</td>
<td>Inside-out repair showed reduced failure rates than all-inside repair</td>
<td>–</td>
</tr>
<tr>
<td>Marrow stimulation</td>
<td>Howarth et al</td>
<td>2016</td>
<td>Meniscus tear</td>
<td>In vivo: goat</td>
<td>Improved healing</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Dean et al</td>
<td>2017</td>
<td>Meniscus tear</td>
<td>Cohort</td>
<td>Similar outcomes as meniscus repair with concomitant ACL repair</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Zhang et al</td>
<td>2009</td>
<td>Meniscus defect</td>
<td>In vivo: goat</td>
<td>Meniscus regeneration with bone marrow aspirate injection</td>
<td>–</td>
</tr>
<tr>
<td>Stem cell therapy</td>
<td>Hatsushika et al</td>
<td>2014</td>
<td>Partial meniscectomy</td>
<td>In vivo: swine</td>
<td>–</td>
<td>Meniscus regeneration and articular cartilage protection</td>
</tr>
<tr>
<td></td>
<td>Horie et al</td>
<td>2012</td>
<td>Meniscus defect</td>
<td>In vivo: rabbit</td>
<td>–</td>
<td>Increase in quality meniscus tissue</td>
</tr>
<tr>
<td></td>
<td>Desando et al</td>
<td>2013</td>
<td>Meniscus tear</td>
<td>In vivo: rabbit</td>
<td>–</td>
<td>Meniscus regeneration and articular cartilage protection</td>
</tr>
<tr>
<td></td>
<td>Vangsness et al</td>
<td>2014</td>
<td>Partial meniscectomy</td>
<td>Randomised control trial</td>
<td>Improved</td>
<td>Increased meniscus volume</td>
</tr>
<tr>
<td>Growth factor Injections</td>
<td>Bhargava et al</td>
<td>2005</td>
<td>Meniscus defect</td>
<td>In vitro</td>
<td>–</td>
<td>Meniscus regeneration</td>
</tr>
<tr>
<td></td>
<td>Narita et al</td>
<td>2012</td>
<td>Meniscus tear</td>
<td>In vivo: rabbit</td>
<td>–</td>
<td>Meniscus healing</td>
</tr>
<tr>
<td></td>
<td>Tumia NS, Johnstone AJ</td>
<td>2004</td>
<td>Meniscus tear</td>
<td>In vitro</td>
<td>–</td>
<td>Meniscus regeneration</td>
</tr>
<tr>
<td></td>
<td>McNulty AL, Guilak F</td>
<td>2008</td>
<td>Meniscus tear</td>
<td>In vitro</td>
<td>–</td>
<td>Enhanced meniscus repair</td>
</tr>
<tr>
<td></td>
<td>Riera et al</td>
<td>2011</td>
<td>Meniscus tear</td>
<td>In vitro</td>
<td>–</td>
<td>Meniscus cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Kopf et al</td>
<td>2010</td>
<td>Meniscus tear</td>
<td>In vivo: sheep</td>
<td>–</td>
<td>No angiogenesis or meniscus healing</td>
</tr>
<tr>
<td></td>
<td>Petersen et al</td>
<td>2007</td>
<td>Meniscus tear</td>
<td>In vivo: sheep</td>
<td>–</td>
<td>No meniscus healing</td>
</tr>
<tr>
<td></td>
<td>McNulty et al</td>
<td>2009</td>
<td>Meniscus tear</td>
<td>In vitro</td>
<td>–</td>
<td>Meniscus healing</td>
</tr>
<tr>
<td></td>
<td>Krzeski et al</td>
<td>2007</td>
<td>Knee osteoarthritis</td>
<td>Randomised control trial</td>
<td>Significantly increased musculoskeletal toxicity</td>
<td>No significant improvement in joint space narrowing on radiographs</td>
</tr>
</tbody>
</table>

Platelet-rich plasma

Platelet-rich plasma (PRP) has been used since the 1970s for its increased concentrations of autologous growth factors thought to promote tissue growth and differentiation. This was derived from in vitro studies establishing the ability of PDGF, a major component in PRP, to increase soft tissue cell activity and stimulate repair. In an animal study by Zellner et al, repairing meniscus defects with collagen-based scaffolds filled with PRP resulted in poor tear filling without evidence of regeneration after 3 months. However, clinical studies of PRP have demonstrated benefits in treating rotator cuff tears, Achilles tendon repairs and lateral epicondylitis. Despite these findings, PRP remains controversial in orthopaedics given the lack of high-quality clinical evidence. In a case–control study of 34 patients, Pujol et al found injecting PRP into a meniscus lesion immediately following open repair produced better clinical outcomes and evidence of healing on MRI than standard open meniscus repair alone. Conversely, Griffin et al found no difference in clinical outcomes in a retrospective review comparing arthroscopic meniscus repair with and without intraoperative...
PRP augmentation. Further investigation is needed on the role of PRP in meniscus tear augmentation.

**Fibrin clot**

Fibrin clots have similar healing components as PRP, and it acts as a scaffold to fill meniscus defects. They can be prepared with autologous blood in a shorter time period and are less expensive than PRP, making fibrin clots an area of interest for meniscus repair augmentation. Jang et al. reported a 95% success rate of meniscus repair using fibrin clots by second-look arthroscopy at a mean of 8.3 months after surgery, and Nakayama et al. found 75% of degenerative meniscus tears repaired using a fibrin clot showed clinical signs and MRI evidence of healing at 2-year follow-up. Ra et al. demonstrated complete healing on MRI and improved clinical scores in 11 of 12 patients treated with arthroscopic inside-out technique with a fibrin clot. To our knowledge, there are no comparative studies demonstrating the advantage of fibrin clot augmentation in meniscus repairs.

**Stem cell therapy**

Mesenchymal stem cells (MSCs) can differentiate in vitro into various cells including osteoblasts, chondrocytes, myocytes and connective tissue. The cells can be harvested from bone marrow, synovium, muscle and adipose tissue, and they are an exciting potential source of regenerating connective tissue such as the meniscus. However, in vivo, MSCs are pericytes that behave as medicinal signalling cells. They provide beneficial immune-modulatory and trophic effects to create a regenerative micro-environment. Clinical trials have established the safety and efficacy of the use of allogenic MSC in knee cartilage regeneration. Multiple animal studies demonstrated improved quantity and quality of meniscus tissue regeneration following

---

**Table 2** Biological membranes used to promote meniscal healing

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Scaffold</th>
<th>Author</th>
<th>Year</th>
<th>Stage of disease</th>
<th>Design</th>
<th>Clinical outcome</th>
<th>Biological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrochondrocytes</td>
<td>Nanofibrous</td>
<td>Shimomura et al.</td>
<td>2015</td>
<td>Meniscus tear</td>
<td>In vitro</td>
<td>—</td>
<td>Partial healing, improved mechanical strength</td>
</tr>
<tr>
<td>Fibrochondrocytes</td>
<td>PLDLA/PCL-T</td>
<td>Esposito et al.</td>
<td>2013</td>
<td>Menisectomy</td>
<td>In vivo: rabbit</td>
<td>—</td>
<td>Fibrocartilage tissue formation and articular cartilage protection</td>
</tr>
<tr>
<td>Fibrochondrocytes</td>
<td>PHBV</td>
<td>Lu et al.</td>
<td>2011</td>
<td>Menisectomy</td>
<td>In vivo: rabbit</td>
<td>—</td>
<td>Fibrocartilage tissue formation, articular cartilage protection</td>
</tr>
<tr>
<td>Chondrocytes</td>
<td>Hyaluronic acid</td>
<td>Kon et al.</td>
<td>2012</td>
<td>Menisectomy</td>
<td>In vivo: sheep</td>
<td>—</td>
<td>Cartilaginous tissue formation</td>
</tr>
<tr>
<td>Myoblasts</td>
<td>PLA/PGA</td>
<td>Gu et al.</td>
<td>2012</td>
<td>Meniscal defect</td>
<td>In vivo: canine</td>
<td>—</td>
<td>Meniscus-like fibrocartilage formation</td>
</tr>
<tr>
<td>Myoblasts</td>
<td>PLA/PGA</td>
<td>Zhu et al.</td>
<td>2014</td>
<td>Meniscus tear</td>
<td>In vivo: canine</td>
<td>—</td>
<td>Meniscus-like fibrocartilage formation</td>
</tr>
<tr>
<td>MSC</td>
<td>Nanofibrous</td>
<td>Shimomura et al.</td>
<td>2015</td>
<td>Meniscus tear</td>
<td>In vitro</td>
<td>—</td>
<td>Meniscus healing, improved mechanical strength</td>
</tr>
<tr>
<td>MSC</td>
<td>Hyaluronic collagen</td>
<td>Zellner et al.</td>
<td>2013</td>
<td>Meniscus tear</td>
<td>In vivo: rabbit</td>
<td>—</td>
<td>Meniscus healing, improved biomechanical properties</td>
</tr>
<tr>
<td>Bone marrow aspirate</td>
<td>Collagen matrix</td>
<td>Piontek et al.</td>
<td>2016</td>
<td>Meniscus tear</td>
<td>Case series</td>
<td>Improved</td>
<td>Healing on MRI</td>
</tr>
<tr>
<td>CMI</td>
<td>Warth RJ, Rodkey WG</td>
<td>2015</td>
<td>Meniscus defect</td>
<td>Systematic review</td>
<td>Satisfactory clinical outcomes</td>
<td>Healing on MRI, meniscus-like tissue at second look arthroscopy, integration of new tissue on biopsy by histology</td>
<td></td>
</tr>
<tr>
<td>Autologous meniscus/ MSC</td>
<td>CMI</td>
<td>Hagmeijer et al.</td>
<td>2018</td>
<td>Meniscus defect</td>
<td>In vivo: cadaver</td>
<td>—</td>
<td>Satisfactory cell number and distribution through the scaffold</td>
</tr>
<tr>
<td>CMI</td>
<td>Zaffagnini et al.</td>
<td>2011</td>
<td>Meniscus defect</td>
<td>Cohort</td>
<td>Improved</td>
<td>No significant joint space narrowing on radiographs. Meniscus degenerative signal on follow-up MRI</td>
<td></td>
</tr>
<tr>
<td>Synthetic scaffold</td>
<td>Tienen et al.</td>
<td>2006</td>
<td>Meniscectomy</td>
<td>In vivo: canine</td>
<td>—</td>
<td>Meniscus-like tissue infiltration into the scaffold</td>
<td></td>
</tr>
<tr>
<td>Synthetic scaffold</td>
<td>Schuttler et al.</td>
<td>2013</td>
<td>Meniscus defect</td>
<td>Case series</td>
<td>Improved</td>
<td>Scaffolding extrusion and abnormal signal on MRI</td>
<td></td>
</tr>
<tr>
<td>Synthetic scaffold</td>
<td>Leroy et al.</td>
<td>2017</td>
<td>Meniscus defect</td>
<td>Case series</td>
<td>Improved. 62% survivorship at 5 years</td>
<td>Reduced size on MRI</td>
<td></td>
</tr>
<tr>
<td>Synthetic scaffold</td>
<td>Dhillander et al.</td>
<td>2016</td>
<td>Meniscus defect</td>
<td>Case series</td>
<td>Improved. 62% survivorship at 5 years</td>
<td>Abnormal signal and reduced implant size on MRI</td>
<td></td>
</tr>
<tr>
<td>Synthetic scaffold</td>
<td>Bulgheroni et al.</td>
<td>2013</td>
<td>Meniscus defect</td>
<td>Case series</td>
<td>Improved</td>
<td>Increases signal on MRI. Irregular morphology and reduced size in second look arthroscopy</td>
<td></td>
</tr>
<tr>
<td>CMI &amp; Synthetic scaffold</td>
<td>Bulgheroni et al.</td>
<td>2016</td>
<td>Meniscus defect</td>
<td>Cohort</td>
<td>Improved clinical outcomes. No evidence of superiority</td>
<td>No progression of arthritis on MRI. Histological evidence of tissue growth in both scaffold types</td>
<td></td>
</tr>
</tbody>
</table>

CMI, collagen meniscus implant; MSC, mesenchymal stem cells; PHBV, poly-(3-hydroxybutyrate-co-3-hydroxyvalerate); PLA/PGA, polyactic acid/polyglycolic acid; PLDLA/PCL-T, poly(LD,L-lactic acid/poly(caprolactone-tri-ol)].
In addition, MSC provided articular cartilage protection in animals with meniscus defects. In a double-blind, randomised control trial by Vagnness et al, patients with a partial medial meniscectomy had a significantly increased meniscus volume 12 months postoperatively when treated with allogenic MSC injection compared with HA injections. Furthermore, patients with osteoarthritic changes at the time of injection demonstrated significantly improved Visual Analogue Score pain scores 2 years after stem cell treatment when compared with controls. The authors concluded MSCs provide a safe and potentially effective augmentation to meniscus tears, though further research on clinical outcomes was recommended.

### Box 1: Key Articles on meniscus repair biological augmentation


### Box 2: Validated outcome measures and classifications

- Second-look arthroscopy
- MRI
- Biopsy and histology
- Cartilage degeneration
- Surgical failure/revision rate
- Pain and functional scores
  - International Knee Documentation Committee examination score
  - Knee Injury and Osteoarthritis Outcome Score
  - Visual Analogue Score
  - Tegner activity level
  - Lysholm Knee Scoring Scale
  - Western Ontario and McMaster Universities Osteoarthritis Index
  - Short Form-12 or Short Form-36

### Box 3: Key issues for patient selection

- **Meniscus tear**
  - Tears with a concomitant ACL injury heal better than isolated tears.
  - Vertical tears are more likely to heal than horizontal, radial and multi-planar tears.
  - Tears in the vascular zone have greater healing potential than tears in the avascular zone.
  - Degenerative tears are often present with osteoarthritic changes to the knee and have worse outcomes with meniscus repair.
diffusional shift and synovial fluid catabolic activity, and, consequently, can lead to tissue degeneration.25 37 64 In a clinical series, SynchroMed SI, a 62% survival of implants at 5 years follow-up.74 This series reported 13 adverse events prior biologic treatment. National governing bodies will largely determine what is clinically available for biologic options, and future developments will be determined by national and local regulatory pathways for approval. In this review, stem cell therapy and biological membranes demonstrate encouraging preclinical results, and we anticipate sophistication of treatment techniques will produce further strides in this field. Prospective randomised control trials are needed to determine the safety and efficacy of biological augmentation in a clinical setting. In this field of rapid development, it is imperative surgeons treating meniscus tears remain up to date with advancement in surgical

Box 4 Major pitfalls

1. There is a wide variety of biological augmentation methods.
2. The literature on each method of biological augmentation has a significant amount of heterogeneity, making comparison challenging.
3. No biological method has demonstrated a clear efficacy and/or superiority over meniscus repair alone in clinical trials.
4. While clinical trials have demonstrated the safety of biologics, the ambiguity in the literature of the efficacy could lead to unnecessary surgeries and excessive costs to patients and healthcare systems.
5. National governing bodies determine what is clinically available for biological options.

Box 5 Future perspectives

1. Future preclinical studies may demonstrate a superior method of biological augmentation compared with the many other options.
2. Clinical trials will be needed to demonstrate the safety and surgical feasibility of biological augmentation methods in meniscus repair.
3. Randomised control trials will then be necessary to evaluate the efficacy of biologics compared with meniscus repair alone, and head-to-head clinical trials will provide comparison between the various biological augmentation methods.
techniques and evolving use of biological augmentation in order to provide the best care for patients.

Contributors NN and AJK had the idea for this article. CCS performed literature review and drafting of the manuscript. NN and AJK performed literature review and revision of the manuscript. DBFS and PV provided review of the manuscript and contribution to literature review. AJK is the guarantor for this article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CCS and NN have nothing to disclose. AK reports grants and personal fees from Arthrex, Inc, personal fees from Vericel, and personal fees from JRF Ortho outside the submitted work. PV reports grants and personal fees from Active Implants, Cartiheal, CONMED Linvatec, and DePuy outside the submitted work. DS reports grants and personal fees from JRF Ortho, Smith & Nephew outside the submitted work.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

REFERENCES


61 Caplan AI. Mesenchymal stem cells: time to change the name! *Stem Cells Transl Med* 2013;2:1445–51.


64 de Windt TS, Vonk LA, Slaper-Cortenbach ICM, et al. Allogeneic mesenchymal stem cells stimulate cartilage regeneration and are safe for single-stage cartilage repair in humans upon mixture with recycled autologous Chondrons. *Stem Cells* 2017;35:256–64.


