The Current Role of Stem Cell Therapy and iPS Cells

15

George Jacob, Kazunori Shimomura, David A. Hart, and Norimasa Nakamura

15.1 Introduction

Over the last decade, there has been a great deal of interest in mesenchymal stem cells (MSCs) and their potential role to play in the treatment of osteoarthritis (OA). The burden of OA has seen an exponential increase, with the World Health Organization reporting 10% of men and 18% of women over the age of 60 years suffering from symptoms of OA [1]. This burden is expected to increase with the universal rising geriatric population [2–4]. The exact aetiology of OA remains uncertain, but literature has revealed age, obesity, trauma, genetics, infection and primary orthopaedic pathologies, together have a multifactorial role in contributing to the biochemical and biomechanical alterations in joint homeostasis to initiate or progress to OA [5, 6]. In the past, OA treatment strategies consisted of pain alleviation with drugs or interventions such as platelet-rich plasma [7], corticosteroid injections, viscosupplementation [8] and finally surgical interventions such as microfracture [9, 10], osteotomies [11] and finally arthroplasty [12, 13]. Recently, with further clarity on the pathophysiology of OA, research has shown numerous cytokines and free radicals having a significant role in increasing pro-inflammatory pathways leading to matrix degradation and onset of OA [14]. This has resulted in a keen interest in biological approaches for treatments using stem cells such as mesenchymal stem cells (MSCs), which have proven immunomodulatory and anti-inflammatory roles [15–18]. It has been suggested that some of these roles are fulfilled by paracrine signalling by employment of exosomes shed from MSCs, allowing for the regeneration and upregulation of endogenous chondrocytes [19, 20]. Recent studies also indicate that there may be subsets of MSCs that perform different functions [21]; MSC may, therefore, have multiple roles to play in cartilage repair. In the past, the most commonly used source of MSCs was bone marrow, but over time, literature has revealed that this source contributes inadequate cell numbers and is inferior when compared to other sources such as adipose and synovium [22–25]. Another source of stem cell is embryonic stem cells (ESCs), which are known to be superior in pluripotency but pose many ethical issues regarding their clinical and experimental

G. Jacob · K. Shimomura
Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan
e-mail: kazunori-shimomura@umin.net

D. A. Hart
McCaig Institute for Bone and Joint Health, University of Calgary, Calgary, AB, Canada

N. Nakamura (✉)
Institute for Medical Science in Sports, Osaka Health Science University, Osaka, Japan

Global Centre for Medical Engineering and Informatics, Osaka University, Osaka, Japan
e-mail: norimasa.nakamura@ohsu.ac.jpk

C. Lattermann et al. (eds.), *Early Osteoarthritis*, https://doi.org/10.1007/978-3-030-79485-9_15

use [26]. A more recent breakthrough cell source was discovered by Yamanaka et al. [27], where these authors were able to reprogramme mouse and human adult fibroblasts to become pluripotent cells, which exhibited embryonic stem cell morphology and growth properties [28]. These induced pluripotent stem (iPS) cells showed differentiation capacities into all three germ cell layers similar to ESCs, making them an additional potential cell source for all regenerative cell therapies. Table 15.1 summarizes the major differences between MSCs, ESCs and iPS cells, with modifications from a table compiled by Lin et al. [35].

Clinical improvement with the use of stem cell therapies has been shown in a number of pre-clinical trials, but the objective outcome data have not been consistent, and this limitation remains a limitation for clinical trials [36–39]. Overall, with the use of MSC therapies being deemed safe in either autologous or allogeneic form, much research has been focused on identifying cell based therapies to retard OA progression and reverse the disease-associated catabolic pathways [40–42]. In this chapter, we discuss the current roles of stem cells and the current research on iPS cells in OA management.

15.2 Mesenchymal Stem Cells in OA

As mentioned above, various types of stem cells exist, and depending on their tissue of origin, they possess different advantages and disadvantages. MSCs may be harvested from bone marrow [43], synovium, adipose [44], dental pulp [45], umbilical cord blood [46], peripheral blood [43, 46], placenta [47], muscle [48], skin [49] and periosteum [50]. Figure 15.1 illustrates a few of the many sources of MSCs in the human body. MSCs are characterized by their fibroblast-like shape, adherence to plastic, trilineage differentiation capacity, and immunophenotypes [51]. At present, there remains no consensus on the ideal cell source for MSCs, and considerations include harvest cell number, donor site, differentiation capacity, and proliferative potential. MSCs have been applied for chondral repair as they have the potential to differentiate into chondral, adipose, and bone tissue [51, 52]. Due to their lack of human leukocyte antigen class II, these cells exhibit low immunogenicity making allogeneic cell use possible [53]. MSCs have been postulated to function by either acting as a precursor to chondrocytes or to mediate joint regeneration via enhanced secretion of trophic factors by endogenous cells [54], thus supporting the possibility of multiple subsets [21]. The paracrine effects of MSCs, mediated by the shedding of exosomes and secretion of bioactive molecules, have been identified to be a key feature allowing for immunomodulation and facilitated tissue regeneration [19, 54–56]. These trophic factors increase cellular migration and differentiation while regulating prostaglandin and inflammatory molecule production [57].

Table 15.1 Comparing the major differences and similarities between MSCs, iPSCs and ESCs

	Morphology	Differentiation/ proliferative potential	Phenotype	Clinical application	Tumourgenicity	Ethical issues
MSCs	Fibroblastic-like	Mesodermal/Finite [29]	CD29+, CD44+, CD73+, CD90+, CD105+, CD166+, CD14−, CD31−, CD45−, CD34− [30]	Induction not necessary	−	−
IPSCs	Embryonic stem cell-like	All three germ layers/infinite [27, 31]	OCT4+, NANOG+, SOX2+, SSEA1+, SSEA3+, SSEA4+, TRA1-60+, TRA1-81+, ALP+ [32]	Requires induction	+	+
ESCs	Embryonic stem cell-like	All three germ layers + extraembryonic tissue/infinite [33]	SSEA-1,3,4+, CD324,90,117,326,9,24,59,133,31,49f, TRA-160,1-81+, AP+, Fzd 1-10, TDGF-1+ [34]	Requires induction	+	+

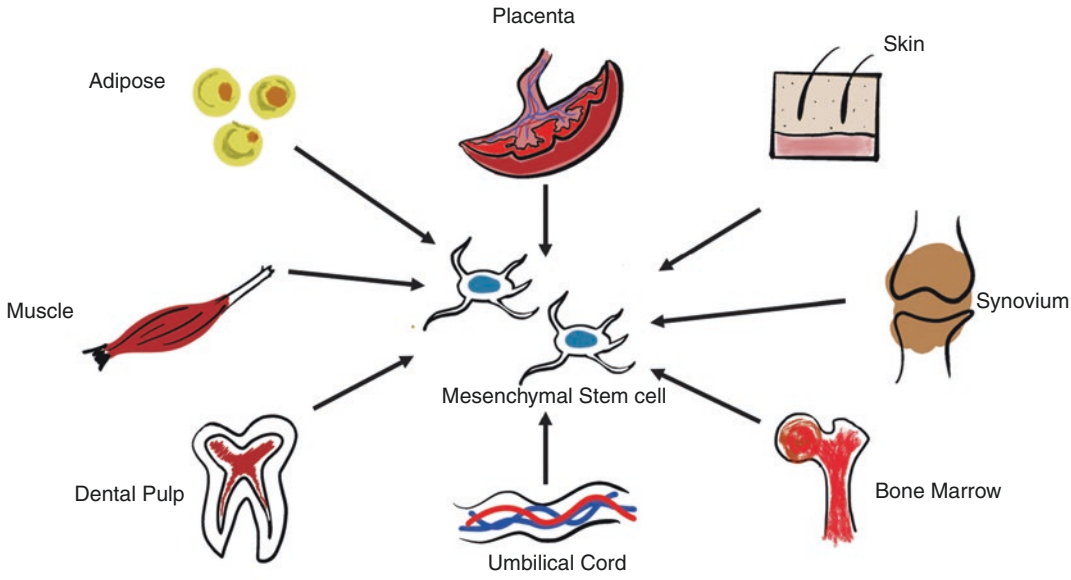

Fig. 15.1 Illustrating a few of the various sources of mesenchymal stem cells in the human body

MSC-based OA therapies have been investigated in both pre-clinical studies and clinical trials environments with cells from different tissue sources and various formulations. They are commonly isolated and expanded in culture before administration through direct intra-articular injection, or in combination with a tissue engineering strategy on a scaffold. One step injection protocols have been popular, with the earliest being simple bone marrow aspirate injections, although yields contained low MSC numbers [58]. Newer injections protocols have now been developed, such as using a stromal vascular fraction (SVF) [59–61] derived from adipose tissue and micro-fragmented adipose tissue [62]. These newer approaches utilizing adipose tissue have shown to yield higher number of MSCs [60, 63]. However, expansion of MSCs in vitro before administration as a treatment is not possible in many clinical settings due to regulatory restrictions imposed by government agencies.

15.3 Embryonic Stem Cells in OA

ESCs originate from the embryo, more specifically from the inner cell mass of the blastocyst depicted in Fig. 15.2. These cells are totipotent with the ability to differentiate into any cell type that would make up a fully developed human. ESCs are also highly proliferative and do not undergo differentiation like other cells. The fact that these cells are extremely young and possess the ability for self-renewal and differentiation into ectodermal, endodermal and mesodermal cells theoretically makes them the most superior stem cell source available for stem cell therapies. However, experiments with these cells have demonstrated teratoma formation, a finding that raises concerns about the use of ESCs in clinical cell therapies. The main challenges with ESCs have been related to ethical approvals and regulations, which do not allow for the harvest of the cells from the blastocyst. Therefore, despite the many positive reports on the potential of ESCs, the efficacy of such treatments and more importantly safety are yet to be determined.

15.4 Induced Pluripotent Stem Cells in OA

iPS cells were first generated using murine fibroblasts [27], soon after which they were created using human fibroblasts [28, 31]. In the murine models, the fibroblast cells were transduced

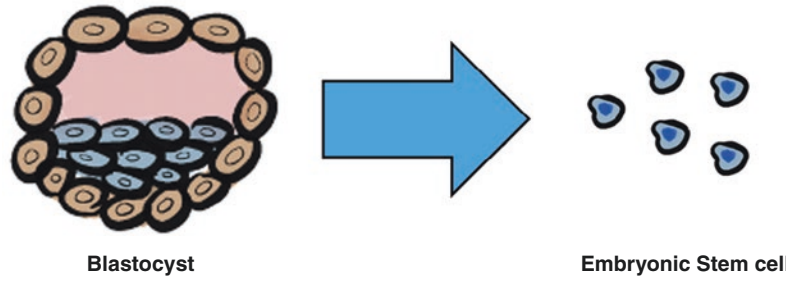

Fig. 15.2 Embryonic stem cells are harvested from the inner cell mass of the blastocyst

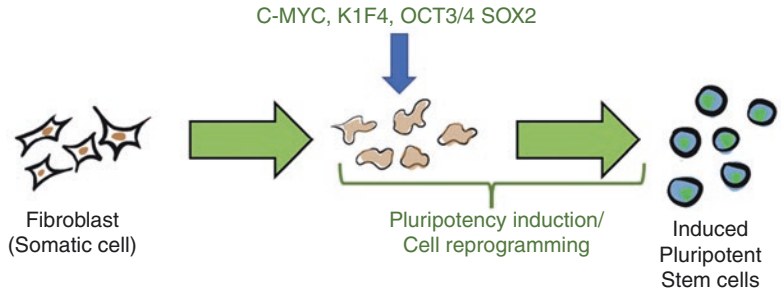

Fig. 15.3 Somatic cells are reprogrammed using four factors; c-Myc, K1f4, Oct3/4 and Sox2, which result in the production of induced pluripotent cells

using four factors; c-Myc, K1f4, Oct3/4, and Sox2, allowing for somatic cell reprogramming [27] illustrated in Fig. 15.3. These cells formed teratomas when transplanted into immunodeficient mice, where the production of hyaline cartilage was also noted [64]. iPS cells have been used in a variety of regenerative modalities with the hope of possible disease modification. Owing to their indefinite proliferative potential, ability to become any desired cell type, and abundance, iPS cells eliminate many shortcomings associated with the previously discussed stem cell therapies, making them an attractive option in current experimental trials [65]. Previous ethical concerns prevented the use of embryonic cells in such trials; however, iPS cells do not evoke such concerns. Another important advantage of iPS cells over bone marrow MSCs (BMMSCs) is that in vitro BMMSCs are primed towards endochondral ossification [66–68] resulting in the tissue produced being hypertrophic, expressing large amounts of collagen I and markers of calcifying cartilage [66, 69]. iPS cells could also allow for larger amounts of in vitro hyaline cartilage generation [68]. With respect to cartilage regeneration and OA, the use of iPS cells would allow for the generation of autologous cells with just the use of a skin fragment and initial dermal fibroblast cultures. After which, the cells can be induced to form iPS cells and then subsequently subjected to chondrogenic differentiation [70, 71]. Four induction methods have been studied for the conversion of iPS cells to chondrocytes [72, 73]. The first is with primary chondrocyte co-culture, where various secretory factors from the chondrocytes can stimulate the iPS cells towards chondrogenic differentiation. The second study method involves the use of growth factors for chondrocyte differentiation. A third method employing chondrogenic supplementation can be used similar to the method used for MSC chondrocyte differentiation. Finally, differentiation can be regulated by specific media changes mimicking that of normal developmental cell differentiation processes. This latter method appears to be the most successful method for the production of stable hyaline cartilage [74–76].

iPS cell therapies do have some challenges to overcome, and making them available for cell-based therapies is a major hurdle at this point in time. Although any cell can be reprogrammed to form an iPS cell, all cells appear to undergo some element of genetic mutation during their lifetime.

This risk could affect the reprogrammed cells negatively and enhance the potential for tumourigenicity [77]. Using embryonic cells from cord blood for iPS cell generation is, therefore, preferred in view of their low genetic modification rate [78, 79], but this option is not available in many cases. Cord blood banking has been a popular trend in recent times, but generating iPS cells from cord blood cells and subsequently banking them for a large population is an extensive and difficult task. Therefore, an allogeneic system may be more practical, and much research has been focused on making this a reality through iPS cell banks [80, 81]. Another concern is the unlimited proliferative potential of iPS cells, while being one of their major initial advantages, upon implantation, they theoretically could proliferate indeterminately and result in tumours. In view of such concerns, iPS cells cannot be implanted without prior differentiation, and exclusion of all iPS non-differentiated cells must be confirmed prior to the initiation of the therapy [68]. Numerous strategies to decrease such risks have been proposed, including the inclusion of suicide genes to destroy the cells in the event of an adverse effect [82]. There is no doubt regarding the value and potential of these universal cell sources to eliminate the shortcomings of previous cell-based therapies, especially with regard to the field of cartilage regeneration.

Clinical trials have not begun for cartilage repair treatments with iPS cells, but the ongoing pre-clinical research appears positive, along with the development of iPS cell banks. Pre-clinical studies aim to identify the safety of iPS cell treatments, including the ideal sources of these cells and optimal culture conditions. Yamashita et al. [74] performed a study with cultured human iPS cells in a chondrogenic medium containing specific growth factors resulting in chondrocytes, which were then transplanted into immunodeficient mice and mini-pigs. They found the presence of bone morphogenic protein 2 (BMP2), transforming growth factor b1 (TGF-b1), and GDF5 to be essential for chondrogenic differentiation of human iPS cells. They reported that transplantation of the cells into mice and mini-pigs showed good integration with the surrounding native cartilage. This is a positive finding, as when mature chondrocytes have been transplanted they do not exhibit such good integration. iPS cells being in very early phases of differentiation can mimic the normal developmental pathway allowing for better chondral maturation and, therefore, improved integration with the mature native cartilage tissue. These authors also did not report any teratomas or tumour formation in the in vivo studies, a major concern with the use of iPS cells. Various other studies have also used growth factors for chondrogenic differentiation of iPS cells and reported encouraging results [83, 84]. Other protocols to stimulate chondrogenic differentiation have involved MSC-like populations [70, 85], chondrocyte co-cultures [86], and embryoid body formation [87]. The progenitor cell for iPS cells has also been a topic of study, and neural crest cells were thought to be a good candidate given their ability to differentiate into osteochondral tissues. iPS cells derived from neural crest cells have been studied and shown to have good chondrogenic differentiation capacity under in vitro conditions; however, the cells did not achieve adequate defect filling when implanted to in vivo chondral defect sites. Again, there was no teratoma formation or tumour growth detected [88]. Other progenitor cell sources from which iPS cells have been derived and studied for differentiation into chondrocytes include umbilical cord blood [89], peripheral blood, [90, 91] and dermal fibroblasts [92]. Research is still experimenting with the ideal cell source and methods leading to chondrogenesis concerning iPS cells. For some, peripheral blood and umbilical cord blood have become preferred sources of iPS cells because of easy harvest and effective reprogramming [93]. Optimal methods for induction of chondrogenesis are under investigation, with each protocol having its own advantages. Suchorska et al. recently suggested the most direct, fast, and cost-effective methods to be monolayer cultures with growth factors or a medium conditioned with human chondrocytes [92]. These pre-clinical studies should lead to movement in the direction of further in vivo studies, and in time, clinical trials once they have achieved more efficient cell reprogramming and chondrogenesis protocols.

15.5 Review of Clinical Trials Using MSCs in OA

Several clinical trials have been reported using varying numbers of MSCs from different sources. These studies also report on different delivery modalities ranging from intra-articular injections to tissue engineered approaches. These variable approaches are discussed in the sub-sections that follow.

15.5.1 Intra-articular Injections

A systematic review conducted by Chahla et al. [94] investigated the use MSCs in the treatment of OA and concluded that they were unable to perform a meta-analysis due to the high heterogenicity between trials. Their review included 6 studies, of which 3 focused on MSC therapies in OA across 124 knees. Of the three studies reporting on OA, two utilized autologous adipose derived mesenchymal stem cells (ADMSCs) and one BMMSCs, which were expanded to passage 3. They noted overall positive clinical improvement in the selected studies and reported the therapies to be safe, but could not rule out a placebo effect. They concluded that literature quality is poor owing to lack of blinded trials, cell population definition, standardization, and quantitative metrics to define cell populations.

Kim et al. [95] analysed five randomized control trials (RCTs) (level II), where four trials employed BMMSCs and one ADMSCs. Their cumulative pain score assessment revealed significant improvement in clinical outcome scores [96–99]; however, the MRI evaluations from three of the selected studies showed no evidence for improvement [96–98]. They too concluded that the optimal cell concentration needed to be determined, along with better standardized trials and that, currently, despite the encouraging results, MSC injections in OA should be investigational based on the available literature.

A larger systematic review was performed by Ha et al. [100], where 17 level I–III studies were included. Their mean follow-up was to 28 months, and cell study sources included bone marrow, adipose, SVF, and umbilical cord blood. Of the 17 studies, all but 2 reported clinical improvement. Only seven studies compared the experimental arm to a control group, where four reported significantly better results in the MSC treated group [97–99, 101]. Eleven of 17 studies reported MRI evaluation, of which only two reported no change in cartilage status [96, 102]. The last two assessed outcomes were second look arthroscopy and histology. Of six studies, one reported no improvement at arthroscopy, [102] and out of four studies, one demonstrated osteoarthritic chondrocytes [102]. Their principal finding was similar to other reports in that they concluded there is limited evidence for the use of MSCs in knee osteoarthritis. Although several studies reported clinical benefit, the RCTs reported controversial results.

Jevotovsky et al. [103] performed a review to evaluate MSC use in OA, in relation to study quality and procedural specifics. Their conclusion was similar to the other discussed reviews in that MSC therapies alleviated symptoms of OA, but due to inconsistencies in study methodology, MSC preparations and protocol design, it is difficult to draw definite conclusions regarding the therapeutic benefits of MSC treatments. Most reviews regarding intra-articular therapies have reported MSC injections to be safe overall; however, a few adverse effects such as synovitis [96], pain and swelling have been reported, but such reactions were also found in study control groups, indicating that they could be associated with any injection [101]. The literature also remains inconclusive regarding the optimal MSC cell count in the intervention, as well as the number of doses, with some studies reporting higher cell number and multiple doses being more beneficial [39, 99, 104, 105].

15.5.2 Tissue Engineering Approaches

Tissue engineering utilizing cell-based strategies has aimed to take things further than simple injections, by programming the stem cells to differentiate towards specific target tissues [106, 107]. Studies have employed specific growth fac-

tors and scaffolds made of various biomaterials, all to provide the cells with an effective microenvironment to promote differentiation into chondral tissue [108]. Most clinical studies in this area have used MSCs in combination with a scaffold or an adjunct technique such as autologous chondrocyte implantation or microfracture. The most popular tissue source for clinical MSC tissue engineering treatments has been bone marrow, usually in the form of an autologous bone marrow aspirate concentrate. However, several of the other above-mentioned sources have also been used. MSCs have been combined as an adjunct to existing techniques such as augmented autologous matrix-induced chondrogenesis [109], as well as to microfracture [110], to improve the outcomes of already utilized techniques. MSCs have also been combined with scaffolds such as a collagen matrix [111–114], polyglycolic acid [115], polylactic acid, [116] and hyaluronan [117]. These studies have mostly reported clinical improvement and reasonable chondral defect fill; however, the quality of the repair tissue has been at best hyaline-like cartilage, which is still imperfect. MSCs appear to improve tissue quality and outcomes, but further research is required to generate repair tissue that is actual tissue regeneration. Isolation and quality control of MSCs remains the major challenge as, currently, the resultant cell populations are very heterogeneous with regard to proliferation, lineage differentiation, and molecular response patterns. This can lead to variable results in terms of chondrogenic differentiation efficiency [118]. Recently, a scaffold-free tissue engineering technique has been introduced using synovial MSCs in a high-density monolayer culture, which results in the formation of a three-dimensional tissue engineered construct (TEC) [119]. TEC implantation has shown favourable pre-clinical results demonstrating hyaline cartilage repair, which has both biological and mechanical properties similar to that of native cartilage [120]. With the excellent pre-clinical data, a clinical study was conducted using TEC in five patients with knee chondral defects. At 24-month follow up, patients had significantly improved clinical outcome scores, second-look arthroscopy demonstrated complete defect fill, and histology of a repair tissue biopsy showed the presence of hyaline cartilage [121]. The same group is currently performing a randomized control trial. Table 15.2 summarizes the results with each MSC tissue source and the resultant clinical outcomes.

Table 15.2 Summary of the differentiation capacities of bone marrow, adipose and synovium tissue and the clinical results for each MSC source

MSC sources	Differentiation capacity			Clinical applicability	Clinical results
	Osteogenic	Chondrogenic	Adipogenic		
Bone marrow	+++	+++	++	Harvest under L/A, ↓cell yield, painful	Direct use of bone marrow without cell expansion results in very low MSC yield despite concentration (0.01–0.02% of TCV) [122]. BMMSC therapies appear to improve clinical symptoms and are safe. Despite defect fill being adequate on MRI and second look arthroscopy, histology has shown a hyaline-like regenerate at best [58].
Adipose	+	+	+++	↑cell yield, ↑tissue requirement	Adipose tissue harvest results in a high number of MSCs (1 g tissue = 2000–20,000 ASCs) [59, 63]. This can overcome the need for cell expansion which results in loss of stem cell homing effects [123]. ASC and SVF therapies have shown significant clinical improvements and radiological outcomes along with good defect fill when compared to patients who did not undergo any treatment [124].

(continued)

Table 15.2 (continued)

MSC sources	Differentiation capacity			Clinical applicability	Clinical results
	Osteogenic	Chondrogenic	Adipogenic		
Synovium	+++	+++	+++	Painless, staged surgery, cell expansion required. Minimal tissue requirement	Synovial cells have demonstrated good proliferative potential and superior differentiation capacity, however, require expansion [22]. TEC have exhibited excellent chondral repair tissue quality, as well as having other favourable features such as adhesion and malleability without the need for additional fixation. Clinical histological trials have shown excellent clinical results. Second look arthroscopy and biopsy have shown complete defect filling and hyaline cartilage repair [121]. The regenerate has also demonstrated mechanical properties similar to that of normal cartilage tissue [119].

L/A local anaesthesia, *MSC* mesenchymal stem cell, *TCV* total cell volume, *BMMSC* bone marrow mesenchymal stem cell, *MRI* magnetic resonance imaging, *ASC* adipose-derived stem cell, *SVF* stromal vascular fraction, *TEC* tissue engineered construct

15.6 Conclusion

Currently, available literature on MSC therapies in osteoarthritis is voluminous, and despite this, it is difficult to deduce precise inferences regarding the effects of MSC therapies for OA treatment and chondral regeneration. The heterogeneity and inferior quality of clinical trials have instigated misperceptions and unregulated non-standardized use of what may be a valuable clinical solution for OA. The iPS cell has in pre-clinical studies shown immense potential and superiority over MSC treatments but has also exhibited possible tumourigenic risks. Without extensive pre-clinical studies and steps to mitigate such risks, as well as ascertain the detailed behaviour of these cells, clinical trials should be delayed. It is hoped that with the introduction of MSC therapy definitions, and the development of superior isolation and quality control protocols, better standardized clinical trials and indications will be published allowing for higher quality analysis of level I data. At present, stem cell therapies for OA should be investigational, and clinicians using them should be encouraged to collect outcome data in the form of high-quality RCTs defining their cell source and specifics of preparation so as to contribute to the standardization of protocols and evaluation of optimized procedures.

References

1. Gao SG, Li KH, Zeng KB, Tu M, Xu M, Lei GH. Elevated osteopontin level of synovial fluid and articular cartilage is associated with disease severity in knee osteoarthritis patients. Osteoarthr Cartil. 2010;18(1):82–7.
2. Richardson SM, Kalamegam G, Pushparaj PN, Matta C, Memic A, Khademhosseini A, et al. Mesenchymal stem cells in regenerative medicine: focus on articular cartilage and intervertebral disc regeneration. Methods. 2016;99:69–80.
3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010;26(3):355–69.
4. Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. Rheumatology. 2005;44(12):1531–7.
5. Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet. 2015;3886(9991):376–87.
6. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther. 2009;11(3):227.
7. Kydd ASR, Hart DA. Efficacy and safety of platelet-rich plasma injections for osteoarthritis. Curr Treat Options Rheumatol. 2020;6:87–98.
8. Rutjes AWS, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteo-

arthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012;157(3):180–91.
9. Erggelet C, Vavken P. Microfracture for the treatment of cartilage defects in the knee joint—a golden standard? J Clin Orthop Trauma. 2016;7(3):145–52.
10. Medvedeva EV, Grebenik EA, Gornostaeva SN, Telpuhov VI, Lychagin AV, Timashev PS, et al. Repair of damaged articular cartilage: current approaches and future directions. Int J Mol Sci. 2018;19(8):2366.
11. Brouwer RW, Huizinga MR, Duivenvoorden T, van Raaij TM, Verhagen AP, Bierma-Zeinstra SMA, et al. Osteotomy for treating knee osteoarthritis. Cochrane Database Syst Rev. 2014;(12):CD004019.
12. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum. 2014;43(6):701–12.
13. Bruyère O, Cooper C, Pelletier JP, Maheu E, Rannou F, Branco J, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis-from evidence-based medicine to the real-life setting. Semin Arthritis Rheum. 2016;45(4):S3–11.
14. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis. 2013;5(2):77–94.
15. van Buul GM, Villafuertes E, Bos PK, Waarsing JH, Kops N, Narcisi R, et al. Mesenchymal stem cells secrete factors that inhibit inflammatory processes in short-term osteoarthritic synovium and cartilage explant culture. Osteoarthr Cartil. 2012;20(10):1186–96.
16. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011;9(1):11–5.
17. Caplan AI. Mesenchymal stem cells. J Orthop Res. 1991;9(5):641–50.
18. Li H, Shen S, Fu H, Wang Z, Li X, Sui X, et al. Immunomodulatory functions of mesenchymal stem cells in tissue engineering. Stem Cells Int. 2019;2019:9671206.
19. Mianehsaz E, Mirzaei HR, Mahjoubin-Tehran M, Rezaee A, Sahebnasagh R, Pourhanifeh MH, et al. Mesenchymal stem cell-derived exosomes: a new therapeutic approach to osteoarthritis? Stem Cell Res Ther. 2019;10(1):340.
20. Caplan AI. Why are MSCs therapeutic? New data: new insight. J Pathol. 2009;217(2):318–24.
21. Affan A, Al-Jezani N, Railton P, Powell JN, Krawetz RJ. Multiple mesenchymal progenitor cell subtypes with distinct functional potential are present within the intimal layer of the hip synovium. BMC Musculoskelet Disord. 2019;20(1):125.
22. Sakaguchi Y, Sekiya I, Yagishita K, Muneta T. Comparison of human stem cells derived from various mesenchymal tissues: superiority of synovium as a cell source. Arthritis Rheum. 2005;52(8):2521–9.
23. Jacob G, Shimomura K, Krych AJ, Nakamura N. The meniscus tear: a review of stem cell therapies. Cell. 2020;9(1):92.
24. Fan J, Varshney RR, Ren L, Cai D, Wang DA. Synovium-derived mesenchymal stem cells: a new cell source for musculoskeletal regeneration. Tissue Eng Part B Rev. 2009;15(1):75–86.
25. Yoshimura H, Muneta T, Nimura A, Yokoyama A, Koga H, Sekiya I. Comparison of rat mesenchymal stem cells derived from bone marrow, synovium, periosteum, adipose tissue, and muscle. Cell Tissue Res. 2007;327(3):449–62.
26. Lo B, Parham L. Ethical issues in stem cell research. Endocr Rev. 2009;30(3):204–13.
27. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–76.
28. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–72.
29. Sachs PC, Francis MP, Zhao M, Brumelle J, Rao RR, Elmore LW, et al. Defining essential stem cell characteristics in adipose-derived stromal cells extracted from distinct anatomical sites. Cell Tissue Res. 2012;349(2):505–15.
30. Dey D, Evans GRD. Generation of induced pluripotent stem (iPS) cells by nuclear reprogramming. Stem Cells Int. 2011;2011:619583.
31. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318(5858):1917–20.
32. Scheper WCS. The molecular mechanism of induced pluripotency: a two-stage switch. Stem Cell Rev Rep. 2009;5(3):204–23.
33. Bernardo AS, Faial T, Gardner L, Niakan KK, Ortmann D, Senner CE, Callery EM, Trotter MW, Hemberger M, Smith JC, Bardwell L. BRACHYURY and CDX2 mediate BMP-induced differentiation of human and mouse pluripotent stem cells into embryonic and extraembryonic lineages. Cell Stem Cell. 2011;9(2):144–55.
34. Zhao W, Ji X, Zhang F, Li L, Ma L. Embryonic stem cell markers. Molecules. 2012;17(6):6196–236.
35. Lin HT, Otsu M, Nakauchi H. Stem cell therapy: an exercise in patience and prudence. Philos Trans R Soc B Biol Sci. 2013;368(1609):20110334.
36. Black LL, Gaynor J, Adams C, Dhupa S, Sams AE, Taylor R, et al. Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. Vet Ther. 2008;9(3):192.
37. Van Buul GM, Siebelt M, Leijs MJC, Bos PK, Waarsing JH, Kops N, et al. Mesenchymal stem cells reduce pain but not degenerative changes in a mono-

iodoacetate rat model of osteoarthritis. J Orthop Res. 2014;32(9):1167–74.
38. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells, platelet lysate and dexamethasone. Am J Case Rep. 2008;9(3):246–51.
39. Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells. 2014;32(5):1254–66.
40. Iijima H, Isho T, Kuroki H, Takahashi M, Aoyama T. Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation. Regen Med. 2018;3(1):1–3.
41. Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials in critical care. PLoS One. 2012;7(10):e47559.
42. Peeters CMM, Leijs MJC, Reijman M, van Osch GJVM, Bos PK. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review. Osteoarthr Cartil. 2013;21(10):1465–73.
43. Mafi R. Sources of adult mesenchymal stem cells applicable for musculoskeletal applications—a systematic review of the literature. Open Orthop J. 2011;5:242.
44. Berebichez-Fridman R, Gómez-García R, Granados-Montiel J, Berebichez-Fastlicht E, Olivos-Meza A, Granados J, et al. The holy grail of orthopedic surgery: mesenchymal stem cells—their current uses and potential applications. Stem Cells Int. 2017;2017:2638305.
45. Pierdomenico L, Bonsi L, Calvitti M, Rondelli D, Arpinati M, Chirumbolo G, et al. Multipotent mesenchymal stem cells with immunosuppressive activity can be easily isolated from dental pulp. Transplantation. 2005;80(6):836–42.
46. Tondreau T, Meuleman N, Delforge A, Dejeneffe M, Leroy R, Massy M, et al. Mesenchymal stem cells derived from CD133-positive cells in mobilized peripheral blood and cord blood: proliferation, Oct4 expression, and plasticity. Stem Cells. 2005;23(8):1105–12.
47. Pipino C, Shangaris P, Resca E, Zia S, Deprest J, Sebire NJ, et al. Placenta as a reservoir of stem cells: an underutilized resource? Br Med Bull. 2013;105(1):43–67.
48. Jackson WM, Nesti LJ, Tuan RS. Potential therapeutic applications of muscle-derived mesenchymal stem and progenitor cells. Expert Opin Biol Ther. 2010;10(4):505–17.
49. Vaculik C, Schuster C, Bauer W, Iram N, Pfisterer K, Kramer G, et al. Human dermis harbors distinct mesenchymal stromal cell subsets. J Invest Dermatol. 2012;132(3):563–74.
50. de Mara CS, Sartori AR, Duarte AS, Andrade ALL, Pedro MAC, Coimbra IB. Periosteum as a source of mesenchymal stem cells: the effects of TGF-β3 on chondrogenesis. Clinics. 2011;66(3):487–92.
51. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315–7.
52. Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, et al. Clarification of the nomenclature for MSC: the International Society for Cellular Therapy position statement. Cytotherapy. 2005;7(5):393–5.
53. Jacobs SA, Roobrouck VD, Verfaillie CM, Van Gool SW. Immunological characteristics of human mesenchymal stem cells and multipotent adult progenitor cells. Immunol Cell Biol. 2013;91(1):32–9.
54. Toh WS, Foldager CB, Pei M, Hui JHP. Advances in mesenchymal stem cell-based strategies for cartilage repair and regeneration. Stem Cell Rev Rep. 2014;10(5):686–96.
55. Li JJ, Hosseini-Beheshti E, Grau GE, Zreiqat H, Little CB. Stem cell-derived extracellular vesicles for treating joint injury and osteoarthritis. Nanomaterials. 2019;9(2):261.
56. Shabbir A, Zisa D, Suzuki G, Lee T. Heart failure therapy mediated by the trophic activities of bone marrow mesenchymal stem cells: a noninvasive therapeutic regimen. Am J Physiol Heart Circ Physiol. 2009;296(6):H1888–97.
57. Yi T, Song SU. Immunomodulatory properties of mesenchymal stem cells and their therapeutic applications. Arch Pharm Res. 2012;35(2):213–21.
58. Cotter EJ, Wang KC, Yanke AB, Chubinskaya S. Bone marrow aspirate concentrate for cartilage defects of the knee: from bench to bedside evidence. Cartilage. 2018;9(2):161–70.
59. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13(12):4279–95.
60. Pak J, Lee JH, Park KS, Park M, Kang LW, Lee SH. Current use of autologous adipose tissue-derived stromal vascular fraction cells for orthopedic applications. J Biomed Sci. 2017;24(1):9.
61. Yokota N, Yamakawa M, Shirata T, Kimura T, Kaneshima H. Clinical results following intra-articular injection of adipose-derived stromal vascular fraction cells in patients with osteoarthritis of the knee. Regen Ther. 2017;6:108–12.
62. Tremolada C, Colombo V, Ventura C. Adipose tissue and mesenchymal stem cells: state of the art and Lipogems® technology development. Curr Stem Cell Rep. 2016;2(3):304–12.
63. Baer PC, Geiger H. Adipose-derived mesenchymal stromal/stem cells: tissue localization, characterization, and heterogeneity. Stem Cells Int. 2012;2012:812693.

64. Tsumaki N, Okada M, Yamashita A. iPS cell technologies and cartilage regeneration. Bone. 2015;70:48–54.
65. Shi Y, Inoue H, Wu JC, Yamanaka S. Induced pluripotent stem cell technology: a decade of progress. Nat Rev Drug Discov. 2017;16(2):115–30.
66. Pelttari K, Winter A, Steck E, Goetzke K, Hennig T, Ochs BG, et al. Premature induction of hypertrophy during in vitro chondrogenesis of human mesenchymal stem cells correlates with calcification and vascular invasion after ectopic transplantation in SCID mice. Arthritis Rheum. 2006;54(10):3254–66.
67. Janicki P, Kasten P, Kleinschmidt K, Luginbuehl R, Richter W. Chondrogenic pre-induction of human mesenchymal stem cells on β-TCP: enhanced bone quality by endochondral heterotopic bone formation. Acta Biomater. 2010;6(8):3292–301.
68. Diederichs S, Richter W. Induced pluripotent stem cells and cartilage regeneration. In: Cartilage. Cham: Springer; 2017. p. 73–93.
69. Dickhut A, Dexheimer V, Martin K, Lauinger R, Heisel C, Richter W. Chondrogenesis of human mesenchymal stem cells by local transforming growth factor-beta delivery in a biphasic resorbable carrier. Tissue Eng Part A. 2010;16(2):453–64.
70. Koyama N, Miura M, Nakao K, Kondo E, Fujii T, Taura D, et al. Human induced pluripotent stem cells differentiated into chondrogenic lineage via generation of mesenchymal progenitor cells. Stem Cells Dev. 2013;22(1):102–13.
71. Medvedev SP, Grigor'Eva EV, Shevchenko AI, Malakhova AA, Dementyeva EV, Shilov AA, et al. Human induced pluripotent stem cells derived from fetal neural stem cells successfully undergo directed differentiation into cartilage. Stem Cells Dev. 2011;20(6):1099–112.
72. Park S, Im G-I. Embryonic stem cells and induced pluripotent stem cells for skeletal regeneration. Tissue Eng Part B Rev. 2014;20(5):381–91.
73. Oldershaw RA. Cell sources for the regeneration of articular cartilage: the past, the horizon and the future. Int J Exp Pathol. 2012;93(6):389–400.
74. Yamashita A, Morioka M, Yahara Y, Okada M, Kobayashi T, Kuriyama S, et al. Generation of scaffoldless hyaline cartilaginous tissue from human iPSCs. Stem Cell Rep. 2015;4(3):404–18.
75. Wu L, Bluguermann C, Kyupelyan L, Latour B, Gonzalez S, Shah S, et al. Human developmental chondrogenesis as a basis for engineering chondrocytes from pluripotent stem cells. Stem Cell Rep. 2013;1(6):575–89.
76. Umeda K, Zhao J, Simmons P, Stanley E, Elefanty A, Nakayama N. Human chondrogenic paraxial mesoderm, directed specification and prospective isolation from pluripotent stem cells. Sci Rep. 2012;2(1):1–1.
77. Gore A, Li Z, Fung HL, Young JE, Agarwal S, Antosiewicz-Bourget J, et al. Somatic coding mutations in human induced pluripotent stem cells. Nature. 2011;471(7336):63–7.
78. Haase A, Olmer R, Schwanke K, Wunderlich S, Merkert S, Hess C, et al. Generation of induced pluripotent stem cells from human cord blood. Cell Stem Cell. 2009;5(4):434–41.
79. Giorgetti A, Montserrat N, Aasen T, Gonzalez F, Rodríguez-Pizà I, Vassena R, et al. Generation of induced pluripotent stem cells from human cord blood using OCT4 and SOX2. Vol. 5. Cell Stem Cell. 2009;5(4):353–7.
80. Turner M, Leslie S, Martin NG, Peschanski M, Rao M, Taylor CJ, et al. Toward the development of a global induced pluripotent stem cell library. Cell Stem Cell. 2013;13(4):382–4.
81. Taylor CJ, Peacock S, Chaudhry AN, Bradley JA, Bolton EM. Generating an iPSC bank for HLA-matched tissue transplantation based on known donor and recipient HLA types. Cell Stem Cell. 2012;11(2):147–52.
82. Di Stasi A, Tey SK, Dotti G, Fujita Y, Kennedy-Nasser A, Martinez C, et al. Inducible apoptosis as a safety switch for adoptive cell therapy. N Engl J Med. 2011;365(18):1673–83.
83. Cheng A, Kapacee Z, Peng J, Lu S, Lucas RJ, Hardingham TE, et al. Cartilage repair using human embryonic stem cell-derived chondroprogenitors. Stem Cells Transl Med. 2014;3(11):1287–94.
84. Boreström C, Simonsson S, Enochson L, Bigdeli N, Brantsing C, Ellerström C, et al. Footprint-free human induced pluripotent stem cells from articular cartilage with redifferentiation capacity: a first step toward a clinical-grade cell source. Stem Cells Transl Med. 2014;3(4):433–47.
85. Villa-Diaz LG, Brown SE, Liu Y, Ross AM, Lahann J, Parent JM, et al. Derivation of mesenchymal stem cells from human induced pluripotent stem cells cultured on synthetic substrates. Stem Cells. 2012;30(6):1174–81.
86. Qu C, Puttonen KA, Lindeberg H, Ruponen M, Hovatta O, Koistinaho J, et al. Chondrogenic differentiation of human pluripotent stem cells in chondrocyte co-culture. Int J Biochem Cell Biol. 2013;45(8):1802–12.
87. Craft AM, Rockel JS, Nartiss Y, Kandel RA, Alman BA, Keller GM. Generation of articular chondrocytes from human pluripotent stem cells. Nat Biotechnol. 2015;33(6):638–45.
88. Chijimatsu R, Ikeya M, Yasui Y, Ikeda Y, Ebina K, Moriguchi Y, et al. Characterization of mesenchymal stem cell-like cells derived from human iPSCs via neural crest development and their application for osteochondral repair. Stem Cells Int. 2017;2017:1960965.
89. Nam Y, Rim YA, Jung SM, Ju JH. Cord blood cell-derived iPSCs as a new candidate for chondrogenic differentiation and cartilage regeneration. Stem Cell Res Ther. 2017;8(1):16.
90. Li Y, Hai Y, Chen J, Liu T. Differentiating chondrocytes from peripheral blood-derived human induced pluripotent stem cells. J Vis Exp. 2017;125:e55722.

91. Li Y, Liu T, Van Halm-Lutterodt N, Chen JY, Su Q, Hai Y. Reprogramming of blood cells into induced pluripotent stem cells as a new cell source for cartilage repair. Stem Cell Res Ther. 2016;7(1):31.
92. Suchorska WM, Augustyniak E, Richter M, Trzeciak T. Comparison of four protocols to generate chondrocyte-like cells from human induced pluripotent stem cells (hiPSCs). Stem Cell Rev Rep. 2017;13(2):299–308.
93. Zhang XB. Cellular reprogramming of human peripheral blood cells. Genomics Proteomics Bioinform. 2013;11(5):264–74.
94. Chahla J, Piuzzi NS, Mitchell JJ, Dean CS, Pascual-Garrido C, LaPrade RF, et al. Intra-articular cellular therapy for osteoarthritis and focal cartilage defects of the knee: a systematic review of the literature and study quality analysis. J Bone Joint Surg Am. 2016;98(18):1511–21.
95. Kim SH, Ha CW, Park YB, Nam E, Lee JE, Lee HJ. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg. 2019;139(7):971–80.
96. Gupta PK, Chullikana A, Rengasamy M, Shetty N, Pandey V, Agarwal V, et al. Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel®): preclinical and clinical trial in osteoarthritis of the knee joint. Arthritis Res Ther. 2016;18(1):301.
97. Lamo-Espinosa JM, Mora G, Blanco JF, Granero-Moltó F, Nuñez-Córdoba JM, Sánchez-Echenique C, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). J Transl Med. 2016;14(1):246.
98. Wong KL, Lee KBL, Tai BC, Law P, Lee EH, Hui JHP. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy. 2013;29(12):2020–8.
99. Koh YG, Kwon OR, Kim YS, Choi YJ. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study. Arthroscopy. 2014;30(11):1453–60.
100. Ha CW, Park YB, Kim SH, Lee HJ. Intra-articular mesenchymal stem cells in osteoarthritis of the knee: a systematic review of clinical outcomes and evidence of cartilage repair. Arthroscopy. 2019;35(1):277–88.
101. Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation. 2015;99(8):1681–90.
102. Pers Y-M, Rackwitz L, Ferreira R, Pullig O, Delfour C, Barry F, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: a phase I dose-escalation trial. Stem Cells Transl Med. 2016;5(7):847–56.
103. Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES. Osteoarthritis and stem cell therapy in humans: a systematic review. Osteoarthr Cartil. 2018;26(6):711–29.
104. Emadedin M, Aghdami N, Taghiyar L, Fazeli R, Moghadasali R, Jahangir S, et al. Intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis. Arch Iran Med. 2012;15(7):422–8.
105. Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. Int J Rheum Dis. 2011;14(2):211–5.
106. Jung Y, Bauer G, Nolta JA. Concise review: induced pluripotent stem cell-derived mesenchymal stem cells: progress toward safe clinical products. Stem Cells. 2012;30(1):42–7.
107. de Peppo GM, Marolt D. Modulating the biochemical and biophysical culture environment to enhance osteogenic differentiation and maturation of human pluripotent stem cell-derived mesenchymal progenitors. Stem Cell Res Ther. 2013;4(5):106.
108. Grässel S, Lorenz J. Tissue-engineering strategies to repair chondral and osteochondral tissue in osteoarthritis: use of mesenchymal stem cells. Curr Rheumatol Rep. 2014;16(10):452.
109. Gigante A, Calcagno S, Cecconi S, Ramazzotti D, Manzotti S, Enea D. Use of collagen scaffold and autologous bone marrow concentrate as a one-step cartilage repair in the knee: histological results of second-look biopsies at 1 year follow-up. Int J Immunopathol Pharmacol. 2011;24(1_Suppl 2):69–72.
110. Gigante A, Cecconi S, Calcagno S, Busilacchi A, Enea D. Arthroscopic knee cartilage repair with covered microfracture and bone marrow concentrate. Arthrosc Tech. 2012;1(2):e175–80.
111. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. Cartilage. 2011;2(3):286–99.
112. Gobbi A, Georgios Karnatzikos SRS. One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. Am J Sports Med. 2014;42(3):648–57.
113. Skowroński J, Skowroński R, Rutka M. Large cartilage lesions of the knee treated with bone marrow concentrate and collagen membrane—results. Ortop Traumatol Rehabil. 2013;15(1):69–76.
114. Kuroda R, Ishida K, Matsumoto T, Akisue T, Fujioka H, Mizuno K, et al. Treatment of a full-thickness articular cartilage defect in the femoral condyle of an

athlete with autologous bone-marrow stromal cells. Osteoarthr Cartil. 2007;15(2):226–31.
115. Enea D, Cecconi S, Calcagno S, Busilacchi A, Manzotti S, Kaps C, et al. Single-stage cartilage repair in the knee with microfracture covered with a resorbable polymer-based matrix and autologous bone marrow concentrate. Knee. 2013;20(6):562–9.
116. Wakitani S, Nawata M, Tensho K, Okabe T, Machida H, Ohgushi H. Repair of articular cartilage defects in the patello-femoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees. J Tissue Eng Regen Med. 2007;1(1):74–9.
117. Gobbi A, Whyte GP. Long-term clinical outcomes of one-stage cartilage repair in the knee with hyaluronic acid–based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate. Am J Sports Med. 2019;47(7):1621–8.
118. Lam AT, Reuveny S, Oh SK-W. Human mesenchymal stem cell therapy for cartilage repair: Review on isolation, expansion, and constructs. Stem Cell Res. 2020;44:101738.
119. Ando W, Tateishi K, Katakai D, Hart DA, Higuchi C, Nakata K, et al. In vitro generation of a scaffold-free tissue-engineered construct (TEC) derived from human synovial mesenchymal stem cells: biological and mechanical properties and further chondrogenic potential. Tissue Eng Part A. 2008;14(12):2041–9.
120. Shimomura K, Ando W, Moriguchi Y, Sugita N, Yasui Y, Koizumi K, et al. Next generation mesenchymal stem cell (MSC)–based cartilage repair using scaffold-free tissue engineered constructs generated with synovial mesenchymal stem cells. Cartilage. 2015;6(2_Suppl):13S–29S.
121. Shimomura K, Yasui Y, Koizumi K, Chijimatsu R, Hart DA, Yonetani Y, et al. First-in-human pilot study of implantation of a scaffold-free tissue-engineered construct generated from autologous synovial mesenchymal stem cells for repair of knee chondral lesions. Am J Sports Med. 2018;46(10):2384–93.
122. Chahla J, Dean CS, Moatshe G, Pascual-Garrido C, Serra Cruz R, LaPrade RF. Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: a systematic review of outcomes. Orthop J Sport Med. 2016;4(1):2325967115625481.
123. Sohni A, Verfaillie CM. Mesenchymal stem cells migration homing and tracking. Stem Cells Int. 2013;2013:130763.
124. Roato I, Belisario DC, Compagno M, Lena A, Bistolfi A, Maccari L, et al. Concentrated adipose tissue infusion for the treatment of knee osteoarthritis: clinical and histological observations. Int Orthop. 2019;43(1):15–23.