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Narrative Review

The biology of mesenchymal stem/stromal cells in the treatment of osteoarthritis

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ABSTRACT

Introduction: Osteoarthritis affects the whole joint and is usually treated using pain relief for many years followed by arthroplasty. Mesenchymal stem/stromal cells have the potential to form cartilage and bone and have been investigated for their capacity to repair these tissues, but until recently there has been no strong rationale for their use in the treatment of age-related, idiopathic osteoarthritis.

Objectives: The aim of this review is to explore the origins of cell therapy for joint diseases and how the early work in cartilage repair has built toward the possibility of an injectable mesenchymal cell approach for osteoarthritis.

Methods: A broad selection of publications has been identified relating to cartilage repair, mesenchymal cell biology, meniscal cartilage repair, and osteoarthritis therapeutics. Primary studies as well as several systematic reviews and meta-analyses have been included.

Results: Cell therapies for cartilage lesions have been shown to be successful for traumatic injury but will be difficult to adapt for the treatment of idiopathic osteoarthritis. However the biological understanding of mesenchymal cells as a reservoir for trophic factors has led to their use as an injectable therapy. These studies have provided good evidence that sustained pain reduction can be achieved by injecting mesenchymal cells into the osteoarthritic joint, with some evidence also for functional improvement. Exosomes derived from mesenchymal may provide a scalable alternative to the cell therapy approach in future.

Conclusions: Mesenchymal cells have potential as a possible injectable cell therapy for idiopathic osteoarthritis and should be further explored through larger-scale, carefully designed clinical trials.

Background

Osteoarthritis (OA) is a disease affecting the whole diarthrodial joint. The primary signs and symptoms have been well described and include increased subchondral bone density (subchondral sclerosis), osteophyte formation (osteophytosis), cartilage erosion leading to joint space narrowing (JSN), chronic pain, and loss of joint function.[1-5] However the relationship between these different components of the disease is by no means simple. For example, in a community-based study of 167 OA patients,[6] joint pain measured using a validated Visual Analogue Scale (VAS) was only weakly associated with JSN and osteophytosis, but strongly, and significantly associated with subchondral sclerosis. On the other hand, loss of joint function, measured using the function sub-scale of the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, was only associated with JSN and had no relationship with

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subchondral sclerosis or osteophytosis. These observations implied a bone-origin for pain and a cartilage-erosion origin for the loss of joint function. Others studies have also emphasized the complexity of identifying the origins of pain in the OA joint.[7] This apparent differential origin of pain and functional change may underly the huge challenge there has been in developing disease-modifying drugs for OA.[8] In the absence of a single drug entity acting through a defined molecular pathway, an alternative approach may be to develop a biological or cell-based therapeutic acting through multiple mechanisms. In this review we describe the concept of mesenchymal stem/stromal cells (MSCs) and trace the origins of cell therapy options for idiopathic, age-related OA, from the use of chondrocytes to repair cartilage, through tissue engineering strategies, meniscal repair as a means of preventing secondary OA, leading on to clinical trials of intra-articular MSC injections as a potential therapy for idiopathic disease.

Definition of MSCs

MSCs were first isolated from bone marrow and characterized in the mid-20th Century.[9-12] Whilst they were initially shown to have osteogenic properties, their multi-potential differentiation profile became gradually clear,[13-19] with a particular focus on their chondrogenic potential.[19-25] Subsequent work demonstrated similar or equivalent cells that could be isolated from adipose, umbilical cord, and synovial membrane.[26-29] Some studies have attempted to demonstrate a more primitive stem cell phenotype for MSCs. The Verfaillie group published evidence of MSC pluripotency,[30] however substantial errors in the data were identified, and corrected,[31] leading to doubts about the conclusions reached. More recently, a perivascular origin for MSC precursors has been proposed.[25,32,33] But the more widely accepted view is that MSCs do not display all the necessary characteristics of pluripotent cells and indeed there remains doubt as to whether they should be considered as stem cells at all, with Mesenchymal Stromal Cells becoming the more widely used name for these cells.[34-37] Yet despite these uncertainties, it remains the case that MSCs are being used for a wide range of clinical investigations for tissue regeneration (eg, bone and cartilage; cardiovascular disease) as well as for disease modification, including hematological disease, graft-versus-host disease, and inflammatory diseases.[38]

The International Society for Cellular Therapy (ISCT) has attempted to standardize the definition of MSCs[39,40] using the following criteria: the cells must be plastic-adherent in standard culture conditions; they must express CD105, CD73, and CD90 and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and human leucocyte antigen-DR surface molecules; and they must differentiate to osteoblasts, adipocytes, and chondroblasts in vitro. These criteria have gone some way to improving the comparative approaches of different studies, yet even a cursory review of the literature would suggest that heterogeneity of approach remains. Recognizing the on-going problem, an International Consensus group has developed the "DOSES" tool as a transparent communication method for any description of MSC-based therapies.[41,42] DOSES recommends that all such reports include information on *D*onor, *O*rigin of tissue, *S*eparation method, *E*xhibited cell characteristics and *S*ite of delivery. Whilst helpful in driving best practice in research/product communication, DOSES does not solve the problem of how best to define what an MSC is and how its identity and activity should be defined.

It has recently been proposed that MSCs should be defined by markers of their intended mode of action[43] as well as by the various methods outlined using the DOSES tool. This proposal recognizes that the "stem cell" terminology is limiting in that it implies the capacity to engraft and differentiate and therefore that this is the intended mode of action.[44] However there is a growing body of evidence that MSCs can orchestrate trophic repair through their capacity to release growth factors, cytokines and other signaling molecules that can influence host cells to synthesize neotissue and to suppress inflammation and immune responses.[25,45-55] It follows that the development of MSCs for therapeutic purposes should be based on a clear decision as to which mode of action (stem cell engraftment or trophic repair) is being exploited.[43]

Cell implantation and tissue engineering for repair of cartilage lesions

Consideration of a cell therapy for cartilage repair dates back to a large body of research and clinical work on autologous chondrocyte implantation (ACI) starting in the 1980s, led by a generation of cell biologists and orthopedic surgeons, including Mats Brittberg, Daniel Grande, Anders Lindahl, Tom Minas, Stefan Nehrer, Lars Peterson, James Richardson, and Sally Roberts.[56-68] The first patient was treated by Brittberg and Peterson in October 1987 and reported 7 years later in their seminal paper.[63] Since then, thousands of patients around the world have been treated with ACI or using matrix-assisted ACI (MACI) where the implanted cells are supported with a bio-scaffold.[69] Clear evidence for the benefit of ACI/MACI over more conventional approaches were provided by a randomized control trial of ACI versus microfracture.[70] However this technique was designed for the treatment of focal traumatic cartilage lesions and cannot be used to intervene in the more diffuse cartilage damage observed in OA joints.

Tissue engineering of cartilage takes the concept of ACI and MACI a stage further as it envisages in vitro culture of cells on bio-scaffolds to allow the maturation of a neocartilage prior to implantation.[71-73] In principle, this should enable the treatment of larger, more diffuse lesions because the engineered cartilage will have some capacity to bear load soon after implantation. In exploratory studies, the Langer group, engineered cartilage in a bioreactor using immature calf chondrocytes, which had a much higher potential for chondrocyte formation than adult articular chondrocytes.[74,75] However for human translational work an alternative cell source would be required if tissue engineering was to be of any practical value. This led to the investigation of bovine nasal chondrocytes as a cell source, based on the observation that nasal septum cartilage has a much higher level of metabolic activity than articular cartilage. Those studies showed the superiority of nasal versus articular chondrocytes for 3-dimensional cartilage tissue engineering in vitro,[76] and the advantage of pre-cultivation of tissue engineered cartilage when used for the treatment of chondral lesions in a goat model.[77,78] A first in human trail of cartilage engineered using autologous nasal septum chondrocytes provided clear evidence of feasibility.[79]

At the same time, MSCs were being explored as an alternative cell source for cartilage engineering. It was reasoned that even with nasal septum chondrocytes, generating enough autologous cells for large, diffuse lesions would be challenging, whereas MSCs should have greater replicative potential. Several groups were able to demonstrate effective cartilage formation using human bone marrow MSCs, comparable in quality to cartilage engineered using bovine nasal chondrocytes.[22-25,80-90] However there remained serious doubts as to whether a tissue engineering approach to resurfacing denuded OA cartilage would be viable, despite a ready cell source, given the large lesion areas and complexity of the tissue organization as well as the challenge of integrating a mature cartilage sheet with sclerotic sub-chondral bone and survival under day to day mechanical forces.[91,92]

MSCs for meniscal repair in the prevention of secondary OA

The menisci are fibrocartilage structures in the knee that are commonly torn as a resulted of trauma during sport and other activities, usually requiring partial meniscectomy with the attendant increased risk of OA due to loss of meniscal tissue.[93-95] In a landmark study, Murphy et al[96] tested the effects of injecting 10 million MSCs into the knees of goats following meniscal/ligament injury, and ligament resection. The injury model led to the development of OA in controls that were injected with Hyaluronic acid (HA). However in animals injected with MSCs in HA, there was clear evidence for partial regeneration of the damaged meniscus, and for inhibition of the development of OA. A subsequent series of pre-clinical studies by other research groups, in rats, pigs and rabbits, added further evidence in support of the approach.[97-100] This body of work led to the first randomized, double-blind, controlled study of injected MSCs following partial medial meniscectomy.[101,102] The study compared 2 doses of MSCs (50×10^6 and 150×10^6) with HA control and the patients were followed for up to 2 years. The most important outcome from the study was clear evidence for a sustained reduction in pain, whereas meniscal regeneration, measured as meniscal volume on MRI, was only observed in a subset of treated patients and was mostly not sustained for the 2 years of the study. These results are important as they highlight the powerful trophic effects of MSCs, that may be independent of their regenerative capacity.

An alternative to treating the symptoms of OA that develop after meniscectomy would be to avoid meniscectomy all together by repairing avascular tears. This was the basis of a new approach combining a collagen scaffold with undifferentiated autologous MSCs that was implanted into the torn meniscus at the time of surgical repair.[50,103,104] In a proof of concept first in human study, 5 patients with fresh avascular meniscal tears were repaired rather than the injured meniscus being removed. Three of the 5 patients remained asymptomatic with no re-tear after 2 years follow-up.[50] Since the implanted cells were undifferentiated, it was considered possible that any therapeutic effect was a result of trophic repair rather than engraftment, and differentiation.

MSCs for the treatment of primary, idiopathic OA

The emergence of ACI as a surgical treatment option for focal injuries opened up the idea of cell therapies for primary OA, although the greater challenge of this age-related disease was well recognized from early on.[105] These techniques were designed for focal lesions in patients with traumatic injuries whereas patients with primary OA are normally excluded from treatment with cells because of the well described disease complexities. Furthermore, when considering a cell therapy approach to OA, it is necessary to deal with not only the challenges of achieving regeneration in a complex pathologic environment (both local and systemic) but also the health economic aspects. A successful therapy should be relatively cheap, easy to apply, and feasible in multiple joints. Nevertheless, there has been growing interest in the use of MSCs to treat primary OA. The first report of injection of MSCs into an OA knee was from Centeno et al. in 2008, with a single patient showing encouraging outcomes.[106] A second study of 4 patients, reported in 2011 also showed some benefit but with a more modest outcome.[107] A series of subsequent studies using either bone marrow-derived or adipose-derived MSCs have been reported for knees, thumb, and shoulder OA.[108-114] These pioneering, small-scale studies have been followed by an array of clinical trials of varying design and quality, that have been described in a series of systematic reviews and meta-analyses.[115-119] All except the oldest of the 5 meta-analyses concluded that there is a significant improvement in pain scores following MSC injection and 2 of them also found a significant improvement in joint function.[115,119] None of the systematic reviews identified any significant safety concerns and there was anecdotal evidence from imaging data in some studies of increased cartilage volume or decreased JSN following MSC injection. These independent analyses provide substantial confidence that MSC injections can be of therapeutic value and therefore closer examination of the findings from the highest quality trials is warranted. In the most recent meta-analysis,[115] Ma et al. identified ten clinical trials for the treatment of knee OA that were considered to be of high enough quality to evaluate: 5 using autologous MSCs[120-124] and 5 using allogeneic MSCs.[125-129] Some key findings and observations from these ten studies are summarized in Table and outlined below.

Patients were followed for up to 12 months in the majority of studies, though 3 studies only followed up for 6 months, and 1 extended to 4 years.[123] Pain was significantly reduced in the MSC treatment group in 8 of the ten studies and there was no apparent difference when comparing studies using autologous or allogeneic cells or tissue origin of the cells (adipose, bone marrow or placenta/umbilical cord). Knee function was significantly improved in the MSC treatment group in 8 out of ten studies and once again there was no apparent difference when comparing studies using autologous or allogeneic cells or tissue origin of the cells. Radiological assessment of cartilage thickness and/or cartilage lesion size was assessed in 8 of the ten studies with evidence of improvement in the MSC treatment group in 4 of the 8 studies and partial improvement in a further 2 studies. Six of the ten studies were testing a proprietary cell therapy product, however there was no apparent difference in outcome between the commercially-based and non–commercial investigations. Two of the studies were classed as Phase 2b,[120,121] whilst all the other studies were classed as Phase 1/2 or pilot investigations. Both of the Phase 2b studies found significant reduction in pain following MSC treatment compared with controls and some evidence of radiological improvement, though only one of them showed evidence for improved

Table
Summary of data from ten clinical trials of intra-articular MSCs.

Study	Cell source	Trial design	Dosage	Pain and Function*	Radiology
Lu et al[120]	Autologous adipose derived MSCs Proprietary product: *Re*-join Cellular biomedicine Group (CBMG)	• MSCs in both knees (n = 26) v HA in both knees (n = 26) • 6- and 12-mo follow-up • Double blind • Phase 2b	• 50×10^6 per knee at d 0 and 3 wk	• VAS/significant improvement • SF-36 - significant improvement; WOMAC – no significant difference	• Significant increase in cartilage volume (after 2 doses)
Lee et al[121]	Autologous adipose derived MSCs Proprietary product: Jointstem R-Bio Co Ltd (Biostar)	• MSCs (n = 12) v saline (n = 12) • 6-mo follow-up • Double blind • Phase 2b	• 100×10^6 per knee at d 0	• VAS – Significant improvement • WOMAC – significant improvement; KOOS -significant improvement	• No significant difference in cartilage thickness; Stable lesion size v significant increase in lesion size in control group
Emadedin et al[122]	Autologous BMSCs	• BMSCs (n = 19) v Saline+2%HSA (n = 24) • 3- and 6-mo follow-up • Double blind • Phase 1/2	• 40×10^6 per knee at d 0	• VAS – no significant difference; Painless walking distance and standing time – significant improvement • WOMAC – significant improvement	• Not assessed
Lamo-Espinosa et al[123]	Autologous BMSCs	• BMSCs at 2 doses + HA (n = 8 and n = 8) v HA (n = 9) • 4 y follow-up • Double blind • Phase 1/2	• 10×10^6 or 100×10^6 per knee at d 0	• VAS – significant improvement • WOMAC – significant improvement	• Not assessed
Freitag et al[124]	Autologous adipose derived MSCs Proprietary product: Magellan Advanced Treatment Magellan Stem Cells	• MSCs at 2 doses in saline (n = 10 and n = 10) v Conventional management with no injection (n = 10) • 12 mo follow-up • Unblinded • Pilot study	• 100×10^6 per knee at d 0 or at BOTH d 0 and 6 mo	• Pain score – significant improvement at both doses • WOMAC – significant improvement; KOOS – significant improvement at both doses for all components • No significant differences between the single and double dosage regime	• Significant improvement or lack of progression after 2 dose but not significant after 1 dose (though a trend in positive direction)
Khalifeh Soltani et al[125]	Allogeneic placenta derived MSCs	• MSCs (n = 10) v saline (n = 10) • 2-, 8-, and 24-wk follow-up • Double blind • Pilot study	• 50 - 60×10^6 per knee at d 0 • Three patients per placenta	• VAS – no significant difference • ROM – significant improvement; KOOS – significant improvement at 2 and 8 wk but not after 24 wk	• Significant increase in cartilage thickness after 24 wk
Kuah et al[126]	Allogeneic adipose derived MSCs Proprietary product: Progenza Regeneus Ltd	• MSCs at 2 doses in conditioned medium (n = 8 and n = 8) v conditioned medium a placebo (n = 4) • Double blind • 3-, 6-, 9-, and 12-mo follow-up Phase 1/2	• 3.9×10^6 or 6.7×10^6 per knee at d 0 • One donor	• VAS – significant improvement at both doses • WOMAC – no significant difference between treatment and placebo but significant improvement within treatment groups	• Significant improvement in cartilage volume v placebo (treatment groups remained stable, placebo cartilage became thinner)
Vega et al[127]	Allogeneic BMSCs	• BMSCs (n = 15) v HA (n = 15) • Double blind • 8 d, 3-, 6-, and 12-mo follow-up • Phase 1/2	• 40×10^6 per knee at d 0 • Three donors (all being treated with autologous MSCs)	• VAS – significant improvement; Pain score – significant improvement • WOMAC – significant improvement; LEQUESNE – significant improvement	• Significant improvement in T2 relaxation time for lesion areas
Matas et al[128]	Allogeneic umbilical cord-derived MSCs Proprietary product: Cellistem OA Cell for Cell	• MSCs at 1 or 2 time points (n = 9 and n = 9) v HA (n = 8) • Triple blind • 12-mo follow-up • Phase 1/2	• 20×10^6 per knee at d 0 or d 0 and 6 mo • Three placenta donors	• VAS - significant improvement in the repat dose group • WOMAC - significant improvement in the repeat dose group	• No significant difference in structural appearance
Gupta et al[129]	Allogeneic BMSCs Proprietary product: Stempeucel Stempeutics	• BMSCs at 4 doses + subsequent HA (n = 10 at each dose) v Plasma + subsequent HA (n = 20) • Double-blind • 12-mo follow-up • Phase 2	• 25×10^6, 50×10^6, 75×10^6 or 150×10^6 per knee • Pooled stem cell bank from multiple donors	• VAS – significant reduction but only at lowest dose of cells • WOMAC – no significant difference but trend to reduction greatest for lowest dose of cells	• No significant difference in structural appearance

* VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; LEQEUSNE, Lequesne index of severity for osteoarthritis; SF-36, Short Form-36 general health questionnaire; KOOS, Knee injury and Osteoarthritis Outcome Score; ROM, Range of Motion.

knee function. Cell dose varied widely from one study to the other. The range of doses used was from 3.9×10^6 up to 150×10^6, given either once on day 0 or, in some cases, repeated a second time after 3 weeks or 6 months. There was no clear evidence of a dose-response effect, with some positive outcomes seen even at the lowest doses, although in 2 of the studies there was a tendency for a weaker efficacy at the highest doses. This unusual finding is consistent with the meta-analysis by Kabat et al. of MSC dosage when used for a variety of pathologies, in which they identified a minimal effective dose range for intra-articular MSCs of $50–100 \times 10^6$ cells/patient, with lack of efficacy above or below that range.[130]

Taken together, the clinical trials outlined above and the systematic reviews and meta-analyses of their outcomes, provide a growing body of evidence that MSCs may provide a new approach to the treatment of primary, idiopathic OA. Of particular importance is the evidence for a sustained reduction in pain 12 months after administration of the MSCs and remarkably, in 1 case, even at 4 years follow-up.[123] Serious side-effects were rare and more likely at the highest cell doses or after repeat dosing over a short (3-week interval) time-frame. The degree of functional improvement and/or cartilage regeneration remains unclear, despite the positive data from the most recent meta-analysis.[115] The variability in these outcomes between trials may depend on dosing, cohort size or on the methodology used for clinical, and radiological evaluation. Carefully designed Phase 3 trials will be needed to establish the full potential of intra-articular MSCs in the treatment of OA.

Future perspectives

At present, OA is generally managed through the use of pain control for a decade or more,[131] until end-stage disease, when arthroplasty is usually the most effective choice.[7,132-135] However there are also a range of options for intra-articular administration of therapeutics to control flare-ups in pain in single joints, including corticosteroids (CS),[136] HA[137] and Platelet-Rich Plasma (PRP),[138,139] some of which may also have disease-modifying activity.[8,140-142] MSCs and disease-modifying biologicals such as PRP are likely to act through similar mechanisms, involving the activation and inhibition of cytokine and growth factor networks in the joints[143] and some evidence has also been provided to suggest that PRP implanted into cartilage lesions may recruit chondro-progenitor cells.[144]

More recently, a new option for an MSC-based therapy has been proposed based on the isolation and purification of MSC exosomes, which are thought to be involved in the paracrine secretion of trophic factors from MSCs.[145-147] They are 1 of 3 types of extracellular vesicle, along with apoptotic bodies and micro-vesicles, and they are thought to play an important role in cell migration, proliferation, differentiation, and extracellular matrix formation.[146] Interestingly, exosomes can also be derived from PRP and both PRP-derived and MSC-derived exosomes were found to have efficacy in the treatment of muscle strain in rats.[148] The biology of exosomes is complex, has not been well described, and clearly overlaps with extracellular vesicles more generally and the whole MSC secretome.[149,150] Furthermore, whilst the in vitro profile of extracellular vesicles, exosomes and MSC secretome is of growing interest, it is too early to know if they will have the specificity and potency needed to act as a therapeutic alternative to MSCs. In the meantime, further work on injectable MSC clinical trials will determine if the cells themselves can replace more conventional treatments for this hard to manage age-related disease. Ultimately, even if a good efficacy, and safety profile of MSCs can be shown, there will also need to be a clear advantage over these existing therapeutic options if these cells are to become a first line treatment option, especially given the likely higher cost of production relative to more traditional drugs.

Authorship contributions

Both authors reviewed the published literature, drafted the manuscript, and edited the final version.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Some of the published data mentioned in this review relate to a patent filed by The University of Liverpool, UK on which A.P.H. is a named inventor and to the work of Azellon Ltd, a spin-out company in which A.P.H. holds founder equity.

References

1. Altman RD, Block DA, Brandt KD, et al. Osteoarthritis: definitions and criteria. *Ann Rheum Dis*. 1990;49:201.
2. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the american rheumatism association. *Arthritis Rheum*. 1986;29:1039–1049.
3. Casscells SW. Gross pathological changes in the knee joint of the aged individual. *Clin. Orthop. Relat. Res*. 1978;132:225–232.
4. Spector TD, Cooper C, Cushnaghan J, Hart DJ, Dieppe PA. *A Radiographic Atlas of Knee Osteoarthritis*. London: Springer; 1992.
5. Martel-Pelletier J, Barr AJ, Cicuttini FM, et al. Osteoarthritis. *Nat Rev Dis Primers*. 2016;2:16072.
6. Szebenyi B, Hollander AP, Dieppe P, et al. Associations between pain, function, and radiographic features in osteoarthritis of the knee. *Arthritis Rheum*. 2006;54:230–235.
7. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet*. 2005;365:965–973.
8. Oo WM, Yu SP, Daniel MS, Hunter DJ. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. *Expert Opin Emerg Drugs*. 2018;23:331–347.
9. Friedenstein AJ, Piatetzky II S, Petrakova KV. Osteogenesis in transplants of bone marrow cells. *J Embryol Exp Morphol*. 1966;16:381–390.
10. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow.Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation*. 1968;6:230–247.
11. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet*. 1970;3:393–403.

12. Bruder SP, Jaiswal N, Haynesworth SE. Growth kinetics, self-renewal, and the osteogenic potential of purified human mesenchymal stem cells during extensive subcultivation and following cryopreservation. *J Cell Biochem*. 1997;64:278–294.
13. Caplan AI. Mesenchymal stem cells. *J Orthop Res*. 1991;9:641–650.
14. Lennon DP, Haynesworth SE, Young RG, Dennis JE, Caplan AI. A chemically defined medium supports in vitro proliferation and maintains the osteochondral potential of rat marrow-derived mesenchymal stem cells. *Exp Cell Res*. 1995;219:211–222.
15. Haynesworth SE, Baber MA, Caplan AI. Cytokine expression by human marrow-derived mesenchymal progenitor cells in vitro: effects of dexamethasone and IL-1 alpha. *J Cell Physiol*. 1996;166:585–592.
16. Allay JA, Dennis JE, Haynesworth SE, et al. LacZ and interleukin-3 expression in vivo after retroviral transduction of marrow-derived human osteogenic mesenchymal progenitors. *Hum Gene Ther*. 1997;8:1417–1427.
17. Caplan AI, Elyaderani M, Mochizuki Y, Wakitini S, Goldberg VM. Principles of cartilage repair and regeneration. *Clin. Orthop. Relat. Res.*. 1997;342:254–269.
18. Johnstone B, Hering TM, Caplan AI, Goldberg VM, Yoo JU. In vitro chondrogenesis of bone marrow-derived mesenchymal progenitor cells. *Exp Cell Res*. 1998;238:265–272.
19. Yoo JU, Barthel TS, Nishimura K, et al. The chondrogenic potential of human bone-marrow-derived mesenchymal progenitor cells. *J Bone Joint Surg Am*. 1998;80:1745–1757.
20. Berry L, Grant ME, McClure J, Rooney P. Bone-marrow-derived chondrogenesis in vitro. *J Cell Sci*. 1992;101(Pt 2):333–342.
21. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284:143–147.
22. Kafienah W, Mistry S, Williams C, Hollander AP. Nucleostemin is a marker of proliferating stromal stem cells in adult human bone marrow. *Stem Cells*. 2006;24:1113–1120.
23. Kafienah W, Mistry S, Dickinson S, et al. Three-dimensional cartilage tissue engineering using adult stem cells from osteoarthritis patients. *Arthritis Rheum*. 2007;56:177–187.
24. Kafienah W, Mistry S, Perry MJ, Politopoulou G, Hollander AP. Pharmacological regulation of adult stem cells: chondrogenesis can be induced using a synthetic inhibitor of the retinoic acid receptor. *Stem Cells*. 2007;25:2460–2468.
25. Dickinson SC, Sutton CA, Brady K, et al. The Wnt5a receptor, receptor tyrosine kinase-like orphan receptor 2, is a predictive cell surface marker of human mesenchymal stem cells with an enhanced capacity for chondrogenic differentiation. *Stem Cells*. 2017;35:2280–2291.
26. De Bari C, Dell'Accio F, Tylzanowski P, Luyten FP. Multipotent mesenchymal stem cells from adult human synovial membrane. *Arthritis Rheum*. 2001;44:1928–1942.
27. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell- based therapies. *Tissue Eng*. 2001;7:211–228.
28. Kern S, Eichler H, Stoeve J, Kluter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells*. 2006;24:1294–1301.
29. SY Lee, Nakagawa T, Reddi AH. Mesenchymal progenitor cells derived from synovium and infrapatellar fat pad as a source for superficial zone cartilage tissue engineering: analysis of superficial zone protein/lubricin expression. *Tissue Eng Part A*. 2009;16:317–325.
30. Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature*. 2002;418:41–49.
31. Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Erratum: pluripotency of mesenchymal stem cells derived from adult marrow. *Nature*. 2007;447:880–881.
32. James AW, Zara JN, Zhang X, et al. Perivascular stem cells: a prospectively purified mesenchymal stem cell population for bone tissue engineering. *Stem Cells Transl Med*. 2012;1:510–519.
33. Crisan M, Yap S, Casteilla L, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell*. 2008;3:301–313.
34. Kuroda Y, Kitada M, Wakao S, Dezawa M. Bone marrow mesenchymal cells: how do they contribute to tissue repair and are they really stem cells? *Arch. Immunol. Ther. Exp. (Warsz.)*. 2011.
35. Sipp D, Robey PG, Turner L. Clear up this stem-cell mess. *Nature*. 2018;561:455–457.
36. Caplan AI. Mesenchymal stem cells: time to change the name!. *Stem Cells Transl Med*. 2017;6:1445–1451.
37. Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell Stem Cell*. 2008;2:313–319.
38. Squillaro T, Peluso G, Galderisi U. Clinical Trials With Mesenchymal Stem Cells: an Update. *Cell Transplant*. 2016;25:829–848.
39. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. *Cytotherapy*. 2006;8:315–317.
40. Horwitz EM, Le Blanc K, Dominici M, et al. Clarification of the nomenclature for MSC: the international society for cellular therapy position statement. *Cytotherapy*. 2005;7:393–395.
41. Murray IR, Chahla J, Safran MR, et al. International expert consensus on a cell therapy communication tool: DOSES. *J Bone Joint Surg Am*. 2019;101:904–911.
42. Rodeo SA. A call for standardization in cell therapy studies: commentary on an article by Iain R. Murray, BMedSci(Hons), MRCS, MFSEM, PhD, et al.: "international expert consensus on a cell therapy communication tool: DOSES". *J Bone Joint Surg Am*. 2019;101:e47.
43. Salerno A, Brady K, Rikkers M, et al. MMP13 and TIMP1 are functional markers for two different potential modes of action by mesenchymal stem/stromal cells when treating osteoarthritis. *Stem Cells*. 2020;38:1438–1453.
44. Liechty KW, MacKenzie TC, Shaaban AF, et al. Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. *Nat Med*. 2000;6:1282–1286.
45. Tolar J, Le Blanc K, Keating A, Blazar BR. Concise review: hitting the right spot with mesenchymal stromal cells. *Stem Cells*. 2010;28:1446–1455.
46. Prockop DJ. Repair of tissues by adult stem/progenitor cells (MSCs): controversies, myths, and changing paradigms. *Mol Ther*. 2009;17:939–946.
47. Caplan AI, Correa D. The MSC: an injury drugstore. *Cell Stem Cell*. 2011;9:11–15.
48. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. *J Cell Biochem*. 2006;98:1076–1084.
49. Prockop DJ. "Stemness" does not explain the repair of many tissues by mesenchymal stem/multipotent stromal cells (MSCs). *Clin Pharmacol Ther*. 2007;82:241–243.
50. Whitehouse MR, Howells NR, Parry MC, 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 Transl Med*. 2017;6:1237–1248.
51. Pabbruwe MB, Kafienah W, Tarlton JF, et al. Repair of meniscal cartilage white zone tears using a stem cell/collagen-scaffold implant. *Biomaterials*. 2010;31:2583–2591.
52. Uccelli A, Pistoia V, Moretta L. Mesenchymal stem cells: a new strategy for immunosuppression? *Trends Immunol*. 2007;28:219–226.
53. Uccelli A, Moretta L, Pistoia V. Immunoregulatory function of mesenchymal stem cells. *Eur. J. Immunol.*. 2006;36:2566–2573.
54. Spaggiari GM, Capobianco A, Abdelrazik H, et al. Mesenchymal stem cells inhibit natural killer cell proliferation, cytotoxicity and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. *Blood*. 2008;111:1327–1333.
55. Keating A. Mesenchymal stromal cells: new directions. *Cell Stem Cell*. 2012;10:709–716.
56. Shortkroff S, Barone L, Hsu H-P, et al. Healing of chondral and osteochondral defects in a canine model: the role of cultured chondrocytes in regeneration of articular cartilage. *Biomaterials*. 1996;17:147–154.
57. Brittberg M. Autologous chondrocyte transplantation. *Clin Orthop*. 1999(367 Suppl):S147–S155.
58. Richardson JB, Caterson B, Evans EH, Ashton BA, Roberts S. Repair of human articular cartilage after implantation of autologous chondrocytes. *J Bone Joint Surg Br*. 1999;81:1064–1068.
59. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop*. 1999:149–162.
60. Minas T. Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. *Am J Orthop*. 1998;27:739–744.
61. Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. *Clin Sports Med*. 1999;18:13–44.
62. Minas T, Nehrer S. Current concepts in the treatment of articular cartilage defects. *Orthopedics*. 1997;20:525–538.
63. Brittberg M, Lindahl A, Nilsson A, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331:889–895.

64. Peterson L, Minas T, Brittberg M, et al. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop*. 2000;374:212–234.
65. Brittberg M, Tallheden T, Sjogren-Jansson B, Lindahl A, Peterson L. Autologous chondrocytes used for articular cartilage repair: an update. *Clin Orthop*. 2001(391 Suppl):S337–S348.
66. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin Orthop*. 2001(391 Suppl):S349–S361.
67. Brittberg M, Nilsson A, Lindahl A, Ohlsson C, Peterson L. Rabbit articular cartilage defects treated with autologous cultured chondrocytes. *Clin Orthop*. 1996:270–283.
68. Grande DA, Pitman MI, Peterson L, Menche D, Klein M. The repair of experimentally produced defects in rabbit articular cartilage by autologous chondrocyte transplantation. *J Orthop Res*. 1989;7:208–218.
69. Trattnig S, Ba-Ssalamah A, Pinker K, et al. Matrix-based autologous chondrocyte implantation for cartilage repair: noninvasive monitoring by high-resolution magnetic resonance imaging. *Magn Reson Imaging*. 2005;23:779–787.
70. Van Assche D, Staes F, Van Caspel D, et al. Autologous chondrocyte implantation versus microfracture for knee cartilage injury: a prospective randomized trial, with 2-year follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2009.
71. Berthiaume F, Maguire TJ, Yarmush ML. Tissue engineering and regenerative medicine: history, progress, and challenges. *Annu Rev Chem Biomol Eng*. 2011;2:403–430.
72. Langer R, Vacanti JP. Tissue engineering. *Science*. 1993;260:920–926.
73. Ashiku SK, Randolph MA, Vacanti CA. Tissue engineered cartilage. *Materials Science Forum*. 1997;250:129–150.
74. Freed LE, Hollander AP, Martin I, et al. Chondrogenesis in a cell-polymer bioreactor system. *Exp. Cell Res.*. 1998;240:58–65.
75. Riesle J, Hollander AP, Langer R, Freed LE, Vunjak-Novakovic G. Collagen in tissue engineered cartilage; types, structure and crosslinks. *J. Cell. Biochem.*. 1998;71:313–327.
76. Kafienah W, Jakob M, Demarteau O, et al. Three dimensional tissue engineering of hyaline cartilage: comparison of adult nasal and articular chondrocytes. *Tissue Eng.*. 2002;8:817–826.
77. Miot S, Brehm W, Dickinson S, et al. Influence of in vitro maturation of engineered cartilage on the outcome of osteochondral repair in a goat model. *Eur Cell Mater*. 2012;23:222–236.
78. Farhadi J, Fulco I, Miot S, et al. Precultivation of engineered human nasal cartilage enhances the mechanical properties relevant for use in facial reconstructive surgery. *Ann. Surg.*. 2006;244:978–985.
79. Mumme M, Barbero A, Miot S, et al. Nasal chondrocyte-based engineered autologous cartilage tissue for repair of articular cartilage defects: an observational first-in-human trial. *Lancet*. 2016;388:1985–1994.
80. Armstrong JPK, Shakur R, Horne JP, et al. Artificial membrane-binding proteins stimulate oxygenation of stem cells during engineering of large cartilage tissue. *Nat Commun*. 2015;6:7405.
81. Raghunath J, Salacinski HJ, Sales KM, Butler PE, Seifalian AM. Advancing cartilage tissue engineering: the application of stem cell technology. *Curr Opin Biotechnol*. 2005;16:503–509.
82. Caplan AI. Review: mesenchymal stem cells: cell-based reconstructive therapy in orthopedics. *Tissue Eng*. 2005;11:1198–1211.
83. Stevens MM, Marini RP, Schaefer D, et al. In vivo engineering of organs: the bone bioreactor. *Proc Natl Acad Sci U S A*. 2005;102:11450–11455.
84. Li WJ, Tuli R, Okafor C, et al. A three-dimensional nanofibrous scaffold for cartilage tissue engineering using human mesenchymal stem cells. *Biomaterials*. 2005;26:599–609.
85. Uematsu K, Hattori K, Ishimoto Y, et al. Cartilage regeneration using mesenchymal stem cells and a three-dimensional poly-lactic-glycolic acid (PLGA) scaffold. *Biomaterials*. 2005;26:4273–4279.
86. Ochoa ER, Vacanti JP. An overview of the pathology and approaches to tissue engineering. *Ann N Y Acad Sci*. 2002;979:10–26.
87. Solchaga LA, Dennis JE, Goldberg VM, Caplan AI. Hyaluronic acid-based polymers as cell carriers for tissue-engineered repair of bone and cartilage. *J Orthop Res*. 1999;17:205–213.
88. Caterson EJ, Li WJ, Nesti LJ, et al. Polymer/alginate amalgam for cartilage-tissue engineering. *Ann N Y Acad Sci*. 2002;961:134–138.
89. Radice M, Brun P, Cortivo R, et al. Hyaluronan-based biopolymers as delivery vehicles for bone-marrow- derived mesenchymal progenitors. *J Biomed Mater Res*. 2000;50:101–109.
90. Mason JM, Breitbart AS, Barcia M, et al. Cartilage and bone regeneration using gene-enhanced tissue engineering. *Clin Orthop*. 2000(379 Suppl):S171–S178.
91. Hollander AP, Dickinson SC, Kafienah W. Stem cells and cartilage development: complexities of a simple tissue. *Stem Cells*. 2010;28:1992–1996.
92. Zhang L, Hu J, Athanasiou KA. The role of tissue engineering in articular cartilage repair and regeneration. *Crit Rev Biomed Eng*. 2009;37:1–57.
93. Clayton RA, Court-Brown CM. The epidemiology of musculoskeletal tendinous and ligamentous injuries. *Injury*. 2008;39:1338–1344.
94. Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. *Osteoarthritis Cartilage*. 2011;19:1286–1293.
95. Kimura M, Shirakura K, Hasegawa A, Kobuna Y, Niijima M. Second look arthroscopy after meniscal repair. Factors affecting the healing rate. *Clin Orthop Relat Res*. 1995:185–191.
96. Murphy JM, Fink DJ, Hunziker EB, Barry FP. Stem cell therapy in a caprine model of osteoarthritis. *Arthritis Rheum*. 2003;48:3464–3474.
97. Horie M, Driscoll MD, Sampson HW, et al. Implantation of allogenic synovial stem cells promotes meniscal regeneration in a rabbit meniscal defect model. *J Bone Joint Surg Am*. 2012;94:701–712.
98. Ruiz-Iban MA, Diaz-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.
99. Dutton AQ, Choong PF, Goh JC, Lee EH, Hui JH. Enhancement of meniscal repair in the avascular zone using mesenchymal stem cells in a porcine model. *J Bone Joint Surg Br*. 2010;92:169–175.
100. 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.
101. Vangsness Jr CT, Farr 2nd J, Boyd J, et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. *J Bone Joint Surg Am*. 2014;96:90–98.
102. Ellis HB. Can a meniscus really regenerate so easily? A Level-I study says it can but not for everyone: commentary on an article by C. Thomas Vangsness Jr., MD, et al.: Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. *J Bone Joint Surg Am*. 2014;96:e14.
103. Pabbruwe MB, Kafienah W, Tarlton JF, et al. Repair of meniscal cartilage white zone tears using a stem cell/collagen-scaffold implant. *Biomaterials*. 2010;31:2583–2591.
104. Pabbruwe MB, Esfandiari E, Kafienah W, Tarlton JF, Hollander AP. Induction of cartilage integration by a chondrocyte/collagen-scaffold implant. *Biomaterials*. 2009;30:4277–4286.
105. LaPrade RF, Swiontkowski MF. New horizons in the treatment of osteoarthritis of the knee. *JAMA*. 1999;281:876–878.
106. Centeno CJ, Busse D, Kisiday J, et al. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician*. 2008;11:343–353.
107. 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;14:211–215.
108. Centeno CJ, Freeman MD. Percutaneous injection of autologous, culture-expanded mesenchymal stem cells into carpometacarpal hand joints: a case series with an untreated comparison group. *Wien Med Wochenschr*. 2014;164:83–87.
109. Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman MD. A prospective multi-site registry study of a specific protocol of autologous bone marrow concentrate for the treatment of shoulder rotator cuff tears and osteoarthritis. *J Pain Res*. 2015;8:269–276.

110. Emadedin M, Aghdami N, Taghiyar L, et al. Intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis. *Arch Iran Med*. 2012;15:422–428.
111. Jo CH, Lee YG, Shin WH, 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;32:1254–1266.
112. Koh YG, Jo SB, Kwon OR, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy*. 2013;29:748–755.
113. Soler R, Orozco L, Munar A, et al. Final results of a phase I-II trial using ex vivo expanded autologous mesenchymal stromal cells for the treatment of osteoarthritis of the knee confirming safety and suggesting cartilage regeneration. *Knee*. 2016;23:647–654.
114. Orozco L, Munar A, Soler R, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. *Transplantation*. 2013;95:1535–1541.
115. Ma W, Liu C, Wang S, et al. Efficacy and safety of intra-articular injection of mesenchymal stem cells in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99:e23343.
116. Xia P, Wang X, Lin Q, Li X. Efficacy of mesenchymal stem cells injection for the management of knee osteoarthritis: a systematic review and meta-analysis. *Int Orthop*. 2015;39:2363–2372.
117. Kim SH, Ha CW, Park YB, et al. 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;139:971–980.
118. Kim SH, Djaja YP, Park YB, et al. Intra-articular injection of culture-expanded mesenchymal stem cells without adjuvant surgery in knee osteoarthritis: a systematic review and meta-analysis. *Am J Sports Med*. 2020;48:2839–2849.
119. Yubo M, Yanyan L, Li L, et al. Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: a meta-analysis. *PLoS ONE*. 2017;12.
120. Lu L, Dai C, Zhang Z, et al. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. *Stem Cell Res Ther*. 2019;10:143.
121. Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase iib, randomized, placebo-controlled clinical trial. *Stem Cells Transl Med*. 2019;8:504–511.
122. Emadedin M, Labibzadeh N, Liastani MG, et al. Intra-articular implantation of autologous bone marrow-derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. *Cytotherapy*. 2018;20:1238–1246.
123. Lamo-Espinosa JM, Mora G, Blanco JF, 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;14:246.
124. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *Regen Med*. 2019;14:213–230.
125. Khalifeh Soltani S, Forogh B, Ahmadbeigi N, et al. Safety and efficacy of allogenic placental mesenchymal stem cells for treating knee osteoarthritis: a pilot study. *Cytotherapy*. 2019;21:54–63.
126. Kuah D, Sivell S, Longworth T, et al. Safety, tolerability and efficacy of intra-articular Progenza in knee osteoarthritis: a randomized double-blind placebo-controlled single ascending dose study. *J Transl Med*. 2018;16:49.
127. Vega A, Martin-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation*. 2015;99:1681–1690.
128. Matas J, Orrego M, Amenabar D, et al. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. *Stem Cells Transl Med*. 2019;8:215–224.
129. Gupta PK, Chullikana A, Rengasamy M, et al. Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel(R)): preclinical and clinical trial in osteoarthritis of the knee joint. *Arthritis Res Ther*. 2016;18:301.
130. Kabat M, Bobkov I, Kumar S, Grumet M. Trends in mesenchymal stem cell clinical trials 2004-2018: is efficacy optimal in a narrow dose range? *Stem Cells Transl Med*. 2020;9:17–27.
131. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. *Arthritis Care Res (Hoboken)*. 2015;67:203–215.
132. Creamer P. Osteoarthritis pain and its treatment. *Curr Opin Rheumatol*. 2000;12:450–455.
133. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. *JAMA*. 2000;284:1247–1255.
134. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American college of rheumatology subcommittee on osteoarthritis guidelines. *Arthritis Rheum*. 2000;43:1905–1915.
135. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89:780–785.
136. Singh H, Knapik DM, Polce EM, et al. Relative Efficacy of intra-articular injections in the treatment of knee osteoarthritis: a systematic review and network meta-analysis. *Am J Sports Med*. 2021.
137. Creamer P, Sharif M, George E, et al. Intra-articular hyaluronic acid in osteoarthritis of the knee: an investigation into mechanisms of action. *Osteoarthritis Cartilage*. 1994;2:133–140.
138. Tucker JD, Goetz LL, Duncan MB, et al. Randomized, placebo-controlled analysis of the knee synovial environment following platelet-rich plasma treatment for knee osteoarthritis. *PMR*. 2021;13:707–719.
139. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2011;19:528–535.
140. Chevalier X, Sheehan B, Whittington C, et al. Efficacy and safety of hylan G-F 20 versus intra-articular corticosteroids in people with knee osteoarthritis: a systematic review and network meta-analysis. *Clin Med Insights Arthritis Musculoskelet Disord*. 2020;13.
141. Zhao D, Pan JK, Yang WY, et al. Intra-articular injections of platelet-rich plasma, adipose mesenchymal stem cells, and bone marrow mesenchymal stem cells associated with better outcomes than hyaluronic acid and saline in knee osteoarthritis: a systematic review and network meta-analysis. *Arthroscopy*. 2021;37 pp. 2298-314 e10.
142. Garg N, Perry L, Deodhar A. Intra-articular and soft tissue injections, a systematic review of relative efficacy of various corticosteroids. *Clin Rheumatol*. 2014;33:1695–1706.
143. Collins T, Alexander D, Barkatali B. Platelet-rich plasma: a narrative review. *EFORT Open Rev*. 2021;6:225–235.
144. Kruger JP, Hondke S, Endres M, et al. Human platelet-rich plasma stimulates migration and chondrogenic differentiation of human subchondral progenitor cells. *J Orthop Res*. 2012;30:845–852.
145. Kim YG, Choi J, Kim K. Mesenchymal stem cell-derived exosomes for effective cartilage tissue repair and treatment of osteoarthritis. *Biotechnol J*. 2020;15.
146. Mianehsaz E, Mirzaei HR, Mahjoubin-Tehran M, et al. Mesenchymal stem cell-derived exosomes: a new therapeutic approach to osteoarthritis? *Stem Cell Res Ther*. 2019;10:340.
147. Joo HS, Suh JH, Lee HJ, Bang ES, Lee JM. Current knowledge and future perspectives on mesenchymal stem cell-derived exosomes as a new therapeutic agent. *Int J Mol Sci*. 2020;21:727–748.
148. Iyer SR, Scheiber AL, Yarowsky P, et al. Exosomes isolated from platelet-rich plasma and mesenchymal stem cells promote recovery of function after muscle injury. *Am J Sports Med*. 2020;48:2277–2286.
149. Harrell CR, Fellabaum C, Jovicic N, et al. Molecular mechanisms responsible for therapeutic potential of mesenchymal stem cell-derived secretome. *Cells*. 2019;8:467–500.
150. Harrell CR, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Mesenchymal stem cell-derived exosomes and other extracellular vesicles as new remedies in the therapy of inflammatory diseases. *Cells*. 2019;8:1605–1626.