



Current Non-Surgical Curative Regenerative Therapies for Knee Osteoarthritis

Ali Bahari Golamkaboudi¹ · Elham Vojoudi¹ · Kosar Babaeian Roshani² · Pejman Porouhan³ · David Houshang⁴ · Zahra Barabadi⁵ 

Accepted: 26 July 2024 / Published online: 15 August 2024

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2024

Abstract

Osteoarthritis (OA) is a prevalent musculoskeletal disease affecting middle-aged and elderly individuals, with knee pain as a common complaint. Standard therapy approaches generally attempt to alleviate pain and inflammation, using various pharmacological and non-pharmacological options. However, the efficacy of these therapies in long-term tissue repair remains debated. As an alternative, regenerative medicine offers a promising strategy, with decreased adverse event rates and increasing evidence of safety and efficacy. This review will outline current advances in regenerative medicine for knee OA, emphasizing outpatient clinic-based therapies that use orthobiological and non-biological products. Different strategies based on orthobiologics are discussed as potential regenerative options for the management of knee OA. Cell-free therapies including platelet-rich plasma, autologous anti-inflammatories, exosomes, human placenta extract, and mitochondrial transplantation are discussed, focusing on their potential for cartilage regeneration. Additionally, cell-based therapies with regenerative properties including bone marrow aspirate concentrate, adipose stromal vascular fraction, microfat, nanofat, stem cell therapy, and genetically modified cells as part of orthobiologics, are being investigated. Also, this study is looking into non-biological approaches such as using gold-induced cytokines, extracorporeal shockwave therapy, and ozone therapy. The mechanisms of action, effectiveness, and clinical applications of each therapy are being explored, providing insights into their role in the management of knee OA.

Keywords Osteoarthritis · Orthobiologics · Regenerative medicine · Platelet rich plasma · Human placenta extract · Adipose stromal vascular fraction

Introduction

Osteoarthritis (OA) is a common musculoskeletal disease that mainly affects middle-aged and elderly individuals [1]. As the population continues to age and obesity rates rise, there is a predicted increase in the occurrence of OA in the future. According to projections, by the year 2040, approximately one in four adults aged 18 years and older will be diagnosed with arthritis by a medical professional [1]. Knee pain is one of the most common complaints that patients seek help for, and the most common cause of pain is OA [2]. OA has no cure, despite being highly prevalent and significantly impacting the quality of life for those affected [3]. A history of prior knee trauma (increases the risk of knee OA by 3.86 times), advancing age (significant risk factor), being female, having excess weight or obesity, engaging in repetitive joint use, bone density, muscle weakness, and joint laxity all contribute significantly to the development of knee

Ali Bahari Golamkaboudi and Elham Vojoudi contributed equally to this work.

✉ Zahra Barabadi
z.barabadi@umsha.ac.ir

¹ School of Medicine, Regenerative Medicine, Organ Procurement and Transplantation Multi- Disciplinary Center, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

² Department of Medicine, Guilan University of Medical Sciences, Rasht, Iran

³ Department of Radiation Oncology, Vasee Hospital, Sabzevar University of Medical Sciences, Sabzevar, Iran

⁴ Department of Biomedical Engineering, University of Houston, Houston, United States

⁵ Department of Tissue Engineering and Biomaterials, School of Advanced Medical Sciences and Technologies, Hamadan University of Medical Sciences, Hamadan, Iran

OA [4, 5]. Standard treatment modalities act by stopping/minimizing pain levels or reducing the inflammatory process to facilitate endogenous repair mechanisms. There are two types of treatment for knee OA: nonsurgical and surgical. Nonsurgical treatment consists of non-pharmacological as well as pharmacological treatment, and non-pharmacological treatment is the core first-line treatment for patients with OA, which includes education, self-management, exercise, and weight loss. Walking canes, braces, and orthotics are other primary non-pharmacological treatments for OA.

Standard pharmacological treatments for musculoskeletal conditions typically include paracetamol, oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular corticosteroids. While these medications are commonly recommended for managing acute and chronic musculoskeletal pain, recent Cochrane Database Systematic Reviews have highlighted a lack of robust evidence supporting their efficacy in promoting long-term tissue healing [4, 5]. In fact, NSAIDs may even hinder the healing process [6, 7]. Studies comparing intra-articular steroid injections to saline injections for knee OA treatment have not consistently shown improvements in pain relief, with some evidence suggesting accelerated OA progression in patients receiving steroid injections [8]. Moreover, the use of standard local steroid injections has been associated with detrimental effects on chondrocytes, both in experimental models and clinical settings [9, 10]. In early-stage management, alternative therapies such as glucosamine/chondroitin supplements [11], hyaluronic acid injections [12], and destructive modalities like radiofrequency ablation and botulinum toxin injections [13] are sometimes employed, although their effectiveness remains a topic of debate.

In addition to symptomatic treatments, interventions aimed at promoting cell-based repair are being increasingly explored. Techniques such as abrasion arthroplasty [14], debridement [15], and microfracture [16] are utilized to stimulate the migration of stem cells from the bone marrow to facilitate tissue repair. Restorative procedures like mosaicplasty [17], and autologous chondrocyte implantation (ACI) involve harvesting patient-derived chondrocytes from non-load-bearing regions, expanding them in culture, and implanting them into the damaged area. Matrix-assisted autologous chondrocyte implantation (MACI), which utilizes a collagen scaffold to support implanted cells, represents an innovative FDA-approved approach that leverages tissue engineering principles to enhance cartilage repair. Following these techniques, the expanded chondrocytes are returned to the surgeon about six to eight weeks after they are obtained. In all of these methods, the conditions of the arthroscopic operating room as well as GMP grade facilities are necessary, which may not be possible in all clinics. Therefore, we will not discuss them in this article. Total knee arthroplasty is a preferred surgical option for severe OA by

some surgeons, as it has been shown to be the most effective procedure for end-stage knee OA. However, recent meta-analyses have cast doubt on the efficacy of many standard orthopedic surgeries [18], such as arthroscopic surgery for knee arthritis and meniscal tears in older patients, suggesting that they may not be superior to sham surgery or conservative treatments and could potentially accelerate degeneration in affected knee joints [19]. On the other hand, regenerative medicine treatments have shown promising results with lower rates of adverse events compared to traditional allopathic options [20], as evidenced by a growing body of statistically significant medical literature [21]. The field of Tissue Engineering and Regenerative Medicine (TERM) aims to create three-dimensional cell/biomaterial complexes that mimic living tissues or organs to repair or regenerate damaged tissues. TERM strategies typically involve cell/biomaterial/growth factor complexes [22]; cell-based therapies like stem cell transplantation, immunotherapy, and gene therapy [23–25]; as well as biomaterial systems that integrate into tissues when implanted in the body [26]. While scaffold-based products require open surgery for placement in the knee, this review focuses on injectable products that can be used in clinical settings.

Tissue Engineering and Regenerative Medicine (TERM) offers various strategies for the treatment of knee OA, which can be categorized into two groups: orthobiological and non-biological products. Orthobiologics are biologically augmented substances derived from a human source, either from the patient or a donor, used to promote the healing of musculoskeletal injuries. However, the terminology used to describe orthobiologic therapies can be confusing due to the variation in their contents and mechanisms of action [27].

Prolotherapy is one mechanism by which orthobiologics exert their effect, involving the injection of a natural irritant, such as high-concentration dextrose, into the soft tissue of an injured joint to stimulate the body's healing response. This leads to a temporary, low-grade inflammation at the injection site, which activates fibroblasts and promotes the production of mature collagen, strengthening connective tissue. Some experts consider Platelet-Rich Plasma (PRP) as a form of prolotherapy treatment due to its similar mechanism of action [28].

Therapies Based on Orthobiological Products

The evolution of regenerative therapies for OA (OA) initially centered around the concept of using administered cells to integrate into damaged areas and differentiate into chondrocytes [29]. However, in recent years, there has been a shift towards utilizing intra-articular injectable 'orthobiologics' as a means to alleviate symptoms and potentially slow

down or prevent disease progression without resorting to joint replacement. Extensive research has been conducted to investigate the efficacy and outcomes of these treatments. Given the absence of a vascular network in articular cartilage [30], intra-articular injections, particularly orthobiological agents, have emerged as a preferred approach for enhancing cartilage regeneration. The biological agents used in the treatment of knee OA can be broadly classified into two main categories: cell-based therapies and cell-free therapies.

Cell-Free Therapies

Table 1 summarizes various cell-free therapies studies in the treatment of knee Osteoarthritis, including the therapy methods, study types, sample size, outcome measures, duration of follow-up, and adverse effects.

Platelet Rich Plasma

Platelet-rich plasma (PRP) is a prevalent orthobiologic therapy that can be readily obtained by centrifuging or filtering the blood of patients. PRP consists of platelets and plasma, with platelets being non-nucleated cells containing vesicles carrying bioactive factors [31]. Plasma contains bioactive molecules and chemokines that aid in the mobilization of mesenchymal stem cells (MSCs) from their perivascular niches, along with mitogens that promote MSC proliferation [32]. PRP is also able to alleviate inflammation, which makes PRP one of the most extensively studied non-invasive interventions for cartilage regeneration in the context of OA. There are a number of factors that can affect the effectiveness of PRP, including individual patient factors, platelet levels, different procurement methods, and different concentrating mechanisms [33]. There is significant variation in the concentration of platelets in PRP preparations, and there is no consensus regarding the optimal concentration range that should be used for optimal results in PRP preparations [34].

Numerous studies have indicated that an effective concentration of platelet-rich plasma (PRP) consists of approximately 1,000,000 platelets per microliter (μL) in a 5 mL plasma volume, which has been correlated with enhanced clinical outcomes [35]. PRP formulations are commonly categorized based on the presence of low levels of white blood cells (referred to as leukocyte-poor PRP) or high levels of white blood cells (known as leukocyte-rich PRP). There are commercially available PRP systems, which offer options such as Leukocyte-Rich PRP (LR-PRP) and Leukocyte-Poor PRP (LP-PRP) [36]. Additionally, the incorporation of exogenous factors, such as thrombin, is becoming an increasingly viable strategy as a way to enhance the activation of platelets within PRP formulations [37]. Despite promising findings, ongoing research continually refines our

understanding of the optimal PRP formulations and concentrations for maximizing the effectiveness of cartilage repair and OA treatment.

Autologous Anti-Inflammatories (AAIs)

There is no doubt that inflammation plays a key role in the pathophysiology of OA. Proinflammatory cytokines as well as matrix metalloproteinases (MMP) exhibit upregulation in both the synovial fluid and tissues of patients with OA [38]. In addition, the presence of elevated levels of interleukin-1 (IL-1) receptors on the surface of chondrocytes and synovial fibroblasts further emphasize the presence of an inflammatory environment in OA patients [39].

In light of the fact that a significant portion of the anti-inflammatory agents in blood are derived from white blood cells rather than platelets, research has been conducted to develop strategies that specifically target white blood cells or the anti-inflammatory factors they release. One such strategy involves the utilization of autologous conditioned serum (ACS), which is a cell-free serum containing anti-inflammatory factors released from activated white blood cells [40]. Additionally, autologous protein solution (APS) is generated by processing platelet-rich plasma (PRP) with a high concentration of white blood cells, aiming to replicate the release and concentration of anti-inflammatory factors [41]. Several studies have demonstrated that ACS is a highly effective treatment for OA, and attributed its ability to reduce inflammation primarily due to its interaction with the interleukin-1 receptor antagonist (IL-1Ra), a compound that effectively inhibits the production of IL-1 in OA patients [42]. In the late 1990s, Orthokine, the first commercially available ACS product, obtained from ACS processing, represented an important step forward [43]. As a result of incubating blood with glass beads for 24 h at 37°C, it was discovered that macrophages, monocytes, and platelets were able to produce IL-1Ra rapidly [44]. It has been shown that intra-articular injections of ACS have demonstrated a significant reduction in symptoms associated with knee OA, an improvement in range of motion (ROM), and an overall improvement in quality of life for individuals with knee OA [45]. Despite the apparent efficacy of ACS (Orthokine) as a treatment option for knee OA, it is important to mention that this product has not yet received approval from the United States Food and Drug Administration (FDA). To be able to fully integrate ACS into mainstream treatment approaches for OA, further research and regulatory considerations are required.

Exosomes

A relatively new treatment approach for knee OA is to inject exosomes into the knee joint [46]. Exosomes are

Table 1 A summary of the studies investigating cell-free therapies for osteoarthritis

Type of Therapy	Treatment Procedures	Study Type	Sample Size	Outcome Measures	Duration of Follow-Up	Adverse Effects
Platelet Rich Plasma (PRP)	5 mL of 5% concentrate PRP was injected every week, three times into the knee joint [68]	Clinical Trial, prospective study	153 patients	Pain reduction; stiffness, functional score, and quality of life improvement	6 months	No adverse event was observed
	Patients randomly received either PRP (10 billion platelets) or hyaluronic acid (HA; 4 ml) [69]	Randomized controlled trial	4 patients	Pain reduction; stiffness and physical function improvement; composite score were significantly better in PRP group versus HA group; no increase in cartilage thickness on MRI in either group; significant decrease of inflammatory cytokines of the synovial fluid at one month in PRP group versus HA group	12 months	Mild transient adverse events like pain, stiffness and synovitis in both groups
Autologous Anti-Inflammatories (AAIs)	Patients received single injection of either AAIs, APS (Autologous Protein Solution) (31 patients) or saline (15 patients) [70]	Randomized controlled trial	46 Patients	65% improvement in WOMAC pain score in the AAIs, APS group versus 41% in the saline group; significant improvement in bone marrow lesion size on MRI and osteophytes in the central zone of the lateral femoral condyle in the APS group rather than control group	12 months	Safe, with no significant differences in frequency and severity of adverse events between groups
	Patients received single intra-articular injection of APS [71]	Nonrandomized, prospective study		Pain reduction; stiffness and physical function improvement	12 months	Minor transient adverse events like arthralgia /musculoskeletal discomfort

Table 1 (continued)

Type of Therapy	Treatment Procedures	Study Type	Sample Size	Outcome Measures	Duration of Follow-Up	Adverse Effects
Exosomes	Single 2 mL exosomes from bone marrow mesenchymal stem/stromal cells (ExoFlo) intra-articular injection [72] 10 μ L of TGF- β 1-induced BMSC-derived exosomes were administered intra-articularly to ACLT mice. (1×10^{11} exosome particles/mL) [52]	Prospective, open-label, non-randomized trial In Vivo – Mouse model of knee OA	58 knee-injected patients	Pain reduction, improved function Reduction of OA pain behaviors; reduction of cartilage damage; suppressed calcification of the cartilage zone; inhibition of osteoclastogenesis and abnormal angiogenesis in subchondral bone	6 months 6 months	Mild transient pain Not applicable (animal studies)
Human Placenta Extract (HPE)	8 mL HPE was injected weekly into acupuncture points for five weeks [73] 14 days post-OA induction, HPE was administered intra-articularly once a day for 14 days [74]	Nonrandomized prospective study In-vitro; In Vivo – Rat model of knee OA	52 patients	Pain reduction, improvements in joint swelling, and productive time Attenuation of swelling by all doses of HPE; limping reduction by higher doses of HPE; attenuation of cartilage degeneration	5 weeks 28 days	Not indicated Not applicable (animal studies)
Mitochondrial Transplantation	No mitochondrial transplantation conducted for human OA, but a study on rats has shown that mitochondrial transplantation can be effective for the treatment of this condition [67]	In Vivo (animal study)—Preclinical trial	10 rats	The intervention improves mitochondrial function, enhances the synthesis of ATP, the consumption of oxygen, and the viability of cells, leading to tissue regeneration	Up to 6 months (in animals)	Not applicable (animal studies)

extracellular vesicles that are released by a variety of cell types, such as stem cells from adipose tissue or bone marrow, as part of their metabolism. Exosomes contain a variety of molecules including proteins, lipids, and nucleic acids that can play a role in the repair and regeneration of tissues [47]. There is evidence that exosomes have the potential to influence the behavior and function of different cell types involved in knee OA, including chondrocytes, synovioocytes, and immune cells. They are capable of stimulating chondrocytes to produce collagen and proteoglycans, which are essential components in cartilage tissue [48]. Moreover, exosomes can modulate the immune response in the joint, promoting an anti-inflammatory environment and reducing tissue damage as well as controlling the activity of synovioocytes [49]. Exosomes are injected directly into the knee joint under ultrasound or fluoroscopy guidance to stimulate the regeneration of damaged cartilage and reduce inflammation in the joint [50, 51].

Studies have demonstrated that exosomes derived from mesenchymal stem cells (MSCs) contain various anti-inflammatory factors, including interleukin-10 (IL-10), transforming growth factor-beta (TGF-beta) [52], and indoleamine 2,3-dioxygenase (IDO) [53]. These exosomes have been found to suppress inflammatory responses within joints and also contain growth factors [54], such as insulin-like growth factor 1 (IGF-1) [55], hepatocyte growth factor (HGF) [56], and vascular endothelial growth factor (VEGF) [57], which promote the proliferation of chondrocytes and the synthesis of the extracellular matrix. These growth factors facilitate chondrocyte proliferation and extracellular matrix synthesis. Furthermore, exosomes can inhibit the activation of immune cells, particularly macrophages, and reduce the production of pro-inflammatory cytokines, thereby mitigating inflammation associated with knee OA. Although research on the application of exosomes as a treatment for knee OA is still in its nascent stages, initial studies and reports have yielded promising outcomes. Patients have reported decreased pain, improved joint function, and enhanced mobility following exosome injections for knee OA. However, it is important to note that the cost of this treatment can be substantial, and insurance coverage may vary based on individual circumstances. Additional research is required to establish exosome therapy's safety, efficacy, and long-term advantages for knee OA.

Human Placenta Extract (HPE)

Human placental extract (HPE) is a substance derived from the placenta of humans. It contains a variety of growth factors, cytokines, and other bioactive molecules that have potential therapeutic effects due to their biological activities [57].

Previous studies have proposed that intra-articular injections of HPE may offer benefits in terms of pain reduction, improved function, and enhanced quality of life for patients afflicted with knee OA [58]. Moreover, HPE exhibits immunomodulatory properties, enabling it to regulate and suppress aberrant immune responses that contribute to the pathogenesis and progression of knee OA [59]. HPE contains various growth factors, including epidermal growth factor, fibroblast growth factor, and vascular endothelial growth factor, which have demonstrated the ability to facilitate tissue healing and regeneration [60]. As HPE stimulates the formation of new cells and tissues inside the knee joint, it may be able to repair cartilage and reduce the pain and stiffness associated with OA in addition to improving joint function [61]. The process of angiogenesis is often elevated in osteoarthritic joints. Since HPE has angiogenic effects, as it has been demonstrated by its potential to form blood vessels, it can help the formation of new blood vessels in the knee joint and reduce inflammation. However, HPE is not yet widely accepted or endorsed by established medical organizations as a treatment for knee OA, and more research is needed to assess its safety and efficacy in these patients [62] [63].

Mitochondrial Transplantation

There are several favorable characteristics of mitochondrial transplantation that make it a promising strategy for treating OA. There is evidence that mitochondria, intricate organelles which play a crucial role in maintaining cellular homeostasis by producing energy, are dysfunctional in chondrocytes suffering from OA [64]. Mitochondrial dysfunctions include impaired mitochondrial respiratory chain enzyme activities, altered membrane potentials, and reduced ATP production, which result in cartilage degeneration through oxidative stress, calcium homeostasis disruption, and mitochondrial DNA mutation [65]. As OA's impact on chondrocytes, matrix anabolism and catabolism are unbalanced, resulting in reduced mitochondrial activity. Autophagy, a cellular mechanism that eliminates unwanted components, is diminished in the presence of OA due to increased reactive oxygen species (ROS) levels, which inhibits the progression of autophagy in lysosomes. These dysfunctional mitochondria and lysosomes contribute to autophagosome accumulation and OA progression [66]. The transplantation of mitochondria may be viewed as a potential therapeutic strategy for the treatment of mitochondrial dysfunction seen in a variety of diseases. The intervention enhances the synthesis of ATP, the consumption of oxygen, and the viability of cells, positively affecting the system as a whole [67]. There are no human studies currently being conducted on mitochondrial transplantation for OA, but a study conducted on rats has shown that mitochondrial transplantation can be effective for the treatment of this condition.

Cell-Based Therapies

Table 2 summarizes the studies conducted on various cell-based therapies in the treatment of osteoarthritis.

Bone Marrow Aspirate Concentrate (BMAC)

Bone marrow aspirate and concentrate (BMAC) constitute a heterogeneous mixture of mixed connective tissue progenitor cells that have demonstrated the ability to expedite bone repair and exert immunomodulatory effects [75]. BMAC is obtained from bone marrow aspirates and promptly processed for immediate use [76]. The procedure for bone marrow aspiration is typically executed percutaneously and is characterized by its rapidity, safety, and relatively low level of donor site morbidity [77]. The aspirate is obtained in the form of a single-cell suspension, allowing for immediate processing and utilization with minimal manipulation, thereby obviating the need for extensive clinical trials for regulatory approval. Depending on the technique employed and the patient's age, various potential sites for bone marrow harvest exist, including the iliac crest (the most common), sternum, calcaneus, tibia (particularly when the iliac crest is inaccessible or unsuitable), and vertebrae. The iliac crest exhibits a higher concentration of osteoblastic progenitor cells compared to the tibia, calcaneus, or other anatomical regions [78, 79]. Since fibroblast colony forming units (CFU-F) diminish with age, this could have an impact on the efficacy of stem cell transplantation in the elderly population [80]. There are many mesenchymal stem cells (MSCs) in BMAC, which play a key role in cartilage regeneration after injury [81]. MSCs have the potential to differentiate into various cell types, including cartilage cells. After injection, they can migrate to the damaged cartilage and promote the repair and regeneration [82]. Also, by stimulating the surrounding cells, MSCs can stimulate new cartilage to grow and help repair the damaged area [83]. Additionally, MSCs have anti-inflammatory properties, capable of modulating the immune response within the joint by interfering with immune cells, like T-cells, which help to slow the progression of OA and possibly slow down the degeneration of the joints as well [84].

In a systematic review conducted by Keeling et al., the efficacy of isolated Bone Marrow Aspirate Concentrate (BMAC) injection for OA treatment in the knee joint was evaluated using data from eight studies. The analysis revealed significant improvements in patient-reported outcomes, with 34 out of 36 patients showing notable enhancement from baseline to the latest follow-up assessment. The researchers concluded that BMAC injection effectively alleviates pain and enhances patient-reported outcomes within short- to midterm follow-up periods. However, BMAC did

not exhibit superiority over other commonly used biologic therapies such as Platelet-Rich Plasma (PRP) and Microfragmented Adipose Tissue (MFAT) in the context of OA treatment [85].

Adipose Stromal Vascular Fraction (SVF)

Stromal vascular fraction (SVF), also referred to as adipose-derived stromal vascular fraction injection, is a form of regenerative therapy utilized in the management of knee OA [86]. SVF is derived from adipose tissue, which contains a diverse array of components including stem cells, immune cells, growth factors, and other bioactive factors. Recently, autologous SVF has emerged as a promising source for delivering adipose-derived mesenchymal stem cells effectively [87]. SVF can be conveniently prepared on-site using a small volume of lipoaspirate, requiring minimal training. This can be achieved through manual protocols or automated devices, such as integrated equipment, following standardized commercial procedures [88]. Injection of concentrated SVF into the knee joint is believed to work by promoting the repair of tissues, reducing inflammation, and possibly slowing the progression of OA. From a medical perspective, it's important for SVF to contain plenty of mesenchymal stem cells (MSCs), endothelial progenitor cells, and M2 macrophages [89]. The stem cells in SVF can differentiate into diverse cell types and contribute to repairing and regenerating damaged tissues. There's evidence from a case report showing that bone regeneration can be enhanced by utilizing adipose-derived cells and growth factors [90, 91]. Also, the immune cells and growth factors present within SVF have the ability to modulate the inflammation response and speed up the healing process [92].

There is ongoing debate regarding the comparative therapeutic potential of adipose-derived stromal/stem cells versus bone marrow stromal/stem cells across various clinical applications. Adipose tissue is believed to contain significantly more mesenchymal stem cells (MSCs) compared to bone marrow, with a less invasive and painful extraction process [93, 94]. Conversely, bone marrow MSCs are typically obtained through iliac crest puncture, which poses risks such as potential long-term impairment of blood cell regeneration due to the removal of a large number of bone marrow cells [95]. The characteristics of SVF, including nucleated cell count, cell viability, and flow cytometry results, appear to be consistent regardless of individual factors like age, gender, BMI, or ethnicity [96]. Studies have shown that SVF injections can offer benefits to patients with knee OA, leading to reduced pain levels and improved functional outcomes.

A systematic review by Shanmugasundaram et al. examined 11 studies on SVF injection for knee OA, revealing

Table 2 A summary of the studies investigating cell-based therapies for osteoarthritis

Type of Therapy	Treatment Procedures	Study Type	Sample Size	Outcome Measures	Duration of Follow-Up	Adverse Effects
Bone Marrow Aspirate Concentrate (BMAC)	Single intra-articular BMAC injection into one knee, the contralateral knee was injected with saline as placebo (15ml each) [135]	Randomized, placebo controlled trial	25 patients	Pain reduction in both groups, improvement of life quality, significant improvement in activity level, no cartilage regenerative benefit, no superiority to saline injection	12-month	Not indicated
	7 cc of the autologous bone marrow derived mesenchymal stem cells and 10 cc of adipose tissues were injected into the each knee joint [136]	Nonrandomized, prospective study	41 patients (75 knees)	Pain reduction, improvement of the knee functional scales; poor relief of pain and functional recovery in the group of K–L grade IV	Mean follow-up period of 8.7 months; ranging from 6 to 19 months	Pain and swelling, rheumatoid arthritis
Adipose Stromal Vascular Fraction (SVF)	One SVF injection (average cell count of 5×10^7 to 1.15×10^7) with 3-ml PRP; followed by monthly injection of PRP for 4 months [137]	Case series study	4 patients (7 knees)	Pain and quality of life improvement; functional performance recovery to normal range	12 months	Not indicated
	Single SVF injection with 3 ml of CaCl ₂ activated PRP [138]	Nonrandomized, prospective study	21 patients	Pain reduction after 3 months; increase of cartilage thickness in MRI after 6 months; improvement of quality of life; significant improvements in joint function	6 months	No side-effects or complications related to the procedure
Micro-fat and Nano-fat	Single intra-articular autologous MFAT injection [101]	Prospective case series study	64 patients	Therapeutic response rate (TRR%) of 64% at 3 months and 45% at 12 months for bone marrow lesions, pain reduction, improvement of daily activity performance	12 months	Inflammatory reaction (pain, swelling, or stiffness); subjective knee instability; muscle aching in the calves
	Single articular injection of 6 ml concentrated autologous Nanofat [100]	In vivo study- OA rat model & Clinical retrospective study	18 knee, OA patients	Pain relief; disappearing the bone marrow edema, decrease of the joint effusion, repair of the articular cartilage and meniscus damages	9 months	Transient marked pain with swelling after the injection in one patient

Table 2 (continued)

Type of Therapy	Treatment Procedures	Study Type	Sample Size	Outcome Measures	Duration of Follow-Up	Adverse Effects
Multi Lineage – Differentiating Stress-Enduring Cells (Muse Cells)	A MSC spheroid composed of 50,000 either Muse or non-Muse MSCs was placed in the induced osteochondral defect area [139]	In-vitro & In vivo study (OA model in immunocompromised mice)	21 mice	Higher chondrogenic differentiation potential of Muse cells versus Non-Muse MSCs; good repair of osteochondral lesions in both groups, without significant difference between MSC groups	8 weeks	Not applicable (animal studies)
Very Small Embryonic-like Stem Cells (V CELLS)	hVSEL cells isolated from blood by apheresis following G-CSF mobilization were enriched by elutriation and loaded into collagen sponge scaffolds containing 2,000–30,000 hVSEL cells were implanted into cranial defects generated in SCID mice [140]	In vivo –female SCID mice	5 groups consisting of 10–13 mice per group	Bone formation in the defect site, presence of circulating human osteocalcin within the serum of the animals treated by hVSEL	16 weeks	Not applicable (animal studies)

Table 2 (continued)

Type of Therapy	Treatment Procedures	Study Type	Sample Size	Outcome Measures	Duration of Follow-Up	Adverse Effects
Stem Cell Therapy	Patients received an ultrasound-guided intra-articular injection of BM-MSCs. Three groups of patients received either of 1×10^6, 10×10^6, and 50×10^6 BM-MSCs in 6.5 ± 1.5 mL of excipient [141] Treatment groups received different treatment dosing regimens of autologous ADMSCs of: 1- a single intra-articular injection of 100×10^6 ADMSCs 2- two intra-articular injections of 100×10^6 ADMSCs (baseline and 6 months) [142]	Nonrandomized, open-label, dose-escalation phase I/II clinical trial	12 patients	Significant improvement in pain, quality of life, and stiffness relative to baseline, no significant changes of cartilage morphology in MRI; the 50 million BM-MSC dose demonstrated a better outcome	12 months	Minor local transient adverse events (pain and/or swelling at the site of injection)
		Randomized, clinical trial	30 patients	Significant pain reduction and functional improvement against control group, no significant difference between the two treatment groups of single and two injections; improvement of activities of daily living and quality of life; the two-injection group was the only group to show improvement in cartilage loss in MRI	12 months	Mild discomfort and/or swelling post ADMSC therapy
Genetically Modified Cells	Treatment group received one intra-articular injection (3.5 ml) of 1.8×10^7 of genetically engineered chondrocytes expressing TGF- β 1 (TissueGene-C) [143]	Placebo-controlled randomized trial	54 patients	Significant improvements in pain, function and quality of life	24 weeks	Transient adverse events localized to the injection site. One subject experienced a transient anaphylactic reaction

positive outcomes in terms of pain relief, range of motion, and functional scores. The authors concluded that SVF injection is a safe and effective treatment option for knee OA patients who have not responded to conservative or arthroscopic interventions [97].

While the use of adipose SVF injections shows promise in knee OA management, regulatory approval from bodies like the FDA is still pending. Further clinical trials are necessary to establish optimal dosing, quality standards, injectate characterization, cost-effectiveness, potential adverse events, and long-term effects of SVF therapy [98].

Microfat and Nanofat

Nanofat and microfat are products from the SVF process in liposuction, possessing regenerative properties but with slight differences. Liposuction fat undergoes physical breakdown, initially becoming microfat with a 0.2–0.8 mm size. Upon further breakdown, it transforms into nanofat. In nanofat, we almost have no adipose cells, while microfat retains some adipose cells [99]. Both products, nanofat and microfat, are likely usable for treating knee OA through intra-articular injection. For this purpose, studies have been conducted on both nanofat [100] and microfat [101].

Stem Cell Therapy

Cell-based therapies have gained significant attention as a potential treatment strategy for musculoskeletal disorders, with stem cells likened to seeds in the garden of regenerative medicine. Stem cells are crucial players in this field, with a limited presence in circulating blood. The primary types of stem cells utilized in therapeutic applications include pluripotent stem cells (embryonic stem cells and induced pluripotent stem cells) and multipotent stem cells (mesenchymal stem cells and hematopoietic stem cells). Here, we will review the various types of stem cells utilized in treating knee OA.

Induced Pluripotent Stem Cells (iPS CELLS)

Induced pluripotent stem cells (iPSCs) are generated by reprogramming adult cells to assume an embryonic stem cell-like state [102]. This process involves activating genes and factors essential for maintaining the characteristics of embryonic stem cells, typically achieved through viral vectors or enzymatic methods [103]. iPSCs exhibit similarities to embryonic stem cells regarding pluripotency, cellular structure, gene expression, and proliferation capacity. Notably, iPSCs are patient-specific, reducing the risk of immune responses and positioning them as an ideal cell source for cell-based therapies [104]. However, it is crucial to consider that iPSCs have the potential to develop into cancerous cells

[105]. The ability of iPSCs to differentiate into chondrocytes and their utility in disease modeling have been demonstrated in various studies [106–108]. For instance, Diekmann et al. established an in vitro model of cartilage defects to investigate the regenerative potential of iPSC-derived chondrocytes. These chondrocytes, derived from iPSCs, were able to produce cartilage matrix within a week of seeding, indicating their reparative capabilities.

In a recent study by Rim et al. [109], the therapeutic efficacy of iPSC-derived chondrocytes was validated through a single intra-articular injection in a rat model with osteochondral defects. After eight weeks post-transplantation, the injected iPSC-derived chondrocytes exhibited robust recovery abilities, forming lacunae in vivo. Further research is needed to assess the clinical applicability of these cells and their potential for treating knee OA.

Multilineage-Differentiating Stress-Enduring Cells (MUSE CELL)

The Muse cells, found in adipose or bone marrow tissue, can be isolated by subjecting it to rigorous stress conditions, including exposure to collagenase enzyme, serum deprivation, low temperatures, and oxygen deprivation. This method allows for the extraction of a pure population of Muse-AT cells without the requirement of cell sorting techniques. Unlike other adult stem cells, these cells are believed to possess pluripotent characteristics and exhibit a high survival rate when transplanted into different areas of the body [110]. Notably, unlike embryonic cells, they do not demonstrate tumor formation capabilities [111]. Moreover, Muse-AT cells display remarkable resistance to adverse conditions such as hypoxia, acidosis, temperature fluctuations, and toxic environments [112]. Given their ability to withstand harsh conditions, they appear to be well-suited for application in joint-related treatments [113]. Currently, adipose tissue seems to be the most favorable source for harvesting Muse cells, as it offers ease of extraction and relatively high yield [114]. They are easy to harvest with a relatively high yield.

Very Small Embryonic-Like Stem Cells (V CELLS)

The scientific community is increasingly recognizing the significance of Very Small Embryonic-Like Stem Cells (V Cells). These cells were initially discovered in 2006 by Ratajczak and colleagues in bone marrow aspirate, displaying distinct characteristics [115]. Notably, V cells exhibit pluripotent markers such as SSEA-1, Oct-4, Nanog, and Rex-1, along with an open chromatin structure and a high nucleus-to-cytoplasm ratio [116]. Moreover, V cells demonstrate elevated levels of telomerase activity, indicating relatively well-preserved DNA. In their inactive state, these smaller-than-average cells circulate in the blood and are

triggered by physiological stress. To activate V cells in a clinical setting, they are kept in a hypoxic environment at a temperature of four degrees centigrade for approximately 12 h. Various methods are employed to enhance the release of V cells into the bloodstream from the bone marrow. Vitamin A and intravenous CoQ-10 have been identified as stimulants for these cells, and they can be administered via intravenous or intra-articular routes. Additionally, V cells possess a specific marker for parathyroid hormone (PTH) on their cell membrane [117]. Studies have indicated that PTH can promote the release of stem cells from the bone marrow. PTH delivery can be achieved through a patch or in oral homeopathic form. Intravenous administration of PTH has shown potential for extending the telomeres of immune system cells, further contributing to the growing acceptance of these cells over time. The precise role of V cells in joint regeneration is still under investigation. Typically, around 200 CCs of blood yield approximately 30 CCs of the final cell solution, which is primarily administered intravenously and occasionally intra-articularly [2].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are increasingly being utilized in therapeutic applications due to their ability to migrate to sites of inflammation or tissue injury and secrete a variety of bioactive agents [118]. In response to injury, MSCs exhibit immunomodulatory properties that impact various components of the immune system, such as T-cells, regulatory T cells (Treg cells), and dendritic cells. Additionally, MSCs possess trophic effects, including angiogenic, mitotic, antiapoptotic, chemoattractive, and regenerative properties. When administered to an injured area, MSCs may not necessarily survive long-term but can create a supportive environment for other cells to carry out their functions effectively. Furthermore, MSCs have been found to exhibit antibacterial properties through the production of a compound known as LL-37 or human cathelicidin antimicrobial peptide, which helps prevent infections in joints during MSC-based therapies [119]. MSCs can differentiate into two distinct types depending on the inflammatory environment they encounter [120]. Type II MSCs, which predominate in an inflammatory milieu, are involved in immune modulation, promotion of T_{reg} cell production, inhibition of T-cell activity, and release of growth factors essential for tissue regeneration. On the other hand, type I MSCs can activate M1 macrophages and T-cells, potentially contributing to autoimmune diseases. In regenerative medicine applications, type II MSCs are generally preferred.

MSCs can be sourced from various tissues, with bone marrow aspirate and adipose tissue being the primary sources for medical purposes. While the number of MSCs in bone marrow decreases with age, adipose tissue provides

a more consistent supply of MSCs that remains relatively stable over time. Adipose tissue-derived stem cells (ASCs) have the capacity to differentiate into different cell types originating from the three primary germ layers [121]. One challenge associated with utilizing MSCs from adipose tissue is the isolation process. While free fat grafts can yield MSCs and Muse cells, breaking down adipose tissue is necessary to obtain a higher concentration of stem cells per volume. This process typically involves a liposuction technique similar to that used in plastic surgery, utilizing enzymatic and mechanical methods to break down the fat tissue effectively. Mechanical methods may involve specialized equipment designed to disintegrate adipose tissue into its constituent components [122].

MSCs, serving as precursors to mesodermal tissues, exhibit the ability to differentiate into various lineages, such as bone, cartilage, fat, muscle, tendon/ligament, and more. The induction of chondrogenic differentiation in MSCs involves cultivating them in a serum-free nutrient medium within a three-dimensional culture, supplemented with a member of the transforming growth factor (TGF)- β superfamily [123]. This process has positioned MSCs as promising candidates for therapeutic applications, especially in conditions like OA. OA, often associated with degenerative changes in the absence of adequate repair mechanisms, has been identified as a potential target for MSC-based therapy. The dysfunction in the MSC population might contribute to the development of OA, making MSCs a plausible option for intervention [123]. Using the regenerative capacity of MSCs, there is a prospect of repairing damaged tissues and replenishing lost cells in OA-affected joints [124]. A systematic review conducted by Shoukrie et al. [125] demonstrated the safety and efficacy of injecting mesenchymal stem cells into human knee joints for the treatment of OA. The findings emphasize that MSC injections are not only safe but also effective in improving the condition of osteoarthritic joints, with minimal side effects. This research emphasized the potential of MSC-based therapies as a viable and well-tolerated approach for addressing OA-related issues.

Genetically Modified Cells

The Food and Drug Administration (FDA) defines Gene Therapy as the use of nucleic acids, viruses, or genetically modified microbes to transfer genetic material into host cells, either directly in vivo or ex vivo. In the context of OA treatment, allogenic cartilage-derived chondrocytes are often utilized for gene therapy [126]. These chondrocytes are modified in vitro to deliver anti-inflammatory genes (IL-1Ra) or growth factors (TGF-1) before being injected into the patient's joint. IL-1 is a key target for gene therapy due to its role in inflammation, pain, and cartilage loss [127]. Transgenes are delivered to the joint cells to induce sustained

local synthesis of their products. TissueGene-C (TG-C) is an example of a gene therapy involving human allogenic chondrocytes modified to overexpress TGF-β1. Animal studies and clinical trials have shown promising results with TG-C, including improved joint structure and pain relief [128, 129]. It has been shown in several clinical trials that TG-C improves the International Knee Documentation Committee (IKDC) and Visual Analog Scale (VAS) scores in patients with chronic degenerative knee OA [130, 131].

CRISPR/Cas9 technology offers precise genome editing of mammalian cells with minimal off-target effects. By using this technology, researchers aim to improve OA therapy by addressing inflammatory responses that may impact cell transplantation success. For instance, targeting genes associated with inflammation, such as IL-1β receptor (IL-1R1) and TAK1, has shown potential in reducing cytokine stimulation and inflammatory factor secretion in transplanted cartilage [132]. This highlights the importance of CRISPR/Cas9 in advancing precision medicine approaches for joint-related conditions [133]. CRISPR/Cas9 technology is demonstrating the potential to mitigate the inflammatory responses associated with treatment for OA [134], highlighting its importance in the advancement of precision medicine approaches for treating joint-related conditions.

A recent outcome registry by Drs. Rogers, Malanga, and Bowen covers a wide range of regenerative medicine treatments, including PRP, hyaluronic acid, bone marrow, adipose-derived mesenchymal cells, and other regenerative medicine treatments. PRP was found to be the most commonly used orthobiologic treatment in the registry, followed by adipose and BMAC [2].

Non-Biological Therapies

Table 3 summarizes non-biological ttherapies studies in the treatment of osteoarthritis.

Gold Induced Cytokines

This unique regenerative therapy, known as GOLDIC®, or "Gold Induced Cytokines" is an all-natural solution to induce the healing potential of conditioned serum rich in cytokines (Gold-IC), and is achieved through the interaction of gold particles with the patient's own blood. Various in vitro studies have revealed that gold particles have an inhibitory effect on catabolic factors such as nitric oxide (NO), as well as an increase in both anticatabolic and anabolic factors. Despite the fact that the exact mechanism of GOLDIC® is still unclear, in vitro studies have shown an increase in plasma gelsolin levels in autologous serum, as well as in synovial fluid after intra-articular injection of GOLDIC® [144].

Table 3 A summary of the studies investigating non-biological treatments for osteoarthritis

Type of Therapy	Treatment Procedures	Study Type	Sample Size	Outcome Measures	Duration of Follow-Up	Adverse Effects
Gold Induced Cytokines (GOLDIC)	Four ultrasound-guided intra-articular knee injections of preconditioning autologous blood with gold particles (GOLDIC) at three to six-day intervals [159]	Phase 2a, open-label trial	64 patients (89 knees)	Significant improvement in WOMAC and KOOS scores for up to four years	4 years	No severe adverse events; mild pain and swelling in some patients
Extracorporeal Shockwave Therapy (ESWT)	Evaluation of short-term effectiveness of ESWT on bone mineral density (BMD) in postmenopausal osteoporotic patients. The patients were randomized into three groups, receiving low-energy or high-energy ESWT or serving as controls [160]	Prospective, randomized, placebo-controlled study	64 patients	Significant improvement in BMD in the treated bone area	12 months	No significant complications; mild skin swelling and redness in some patients
Ozone Therapy	20 ml ozone-oxygen mixture gas concentration of 20 µg/ml was injected into knee articular cavity, for six weeks, twice a week [161]	Nonrandomized, prospective study	76 patients	Significant decrease of pain intensity in patients with mild to moderate Knee Osteoarthritis (KOA); improvement of functional status	6 weeks	Not indicated

With its documented benefits in animal studies, GOLDIC® therapy is emerging as a promising avenue for treating degenerative joint diseases in humans. Patients suffering from OA of the knee who have received GOLDIC® therapy have shown encouraging early clinical results, with a statistically significant improvement in their WOMAC scores and a noticeable reduction in their pain levels. It has been shown that GOLDIC® demonstrated a favorable safety profile, with patients expressing a willingness to recommend GOLDIC® to others based on their own experience [145, 146].

The Extracorporeal Shockwave Therapy (ESWT)

ESWT uses powerful shockwaves to help heal various musculoskeletal disorders by promoting regenerative effects through growth factors and molecules. These shockwaves are generated through electrohydraulic, electromagnetic, and piezoelectric sources [147]. The therapy has been successful in treating conditions like plantar fasciitis, tendinopathies, fractures, and diabetic foot ulcers [148–150]. In cases of knee OA, ESWT has shown promising results in preserving cartilage and improving the microstructure of subchondral bone. It works by stimulating growth factors such as TGF- β 1 and VEGF, which help reduce cartilage degradation and promote the synthesis of ECM components for cartilage repair [151]. ESWT also enhances anabolic processes in the subchondral bone and by modulating nerve endings reduces pain markers, leading to pain relief and improved joint function [152]. Patients who undergo this therapy experience a significant improvement in their quality of life.

Ozone Therapy

Ozone has been demonstrated to possess analgesic, anti-inflammatory, immunomodulatory, and trophic properties [153, 154]. In the treatment of OA, a series of intra-articular injections are typically administered once a week for approximately 6 to 7 weeks. Each injection involves the introduction of 10–20 CCs of ozone (O₃) into the affected joint. The concentration of ozone is variable according to various studies and is in the range of 10–40 μ g/ml [155]. Ozone exerts various effects on the joint, including the inhibition of PGE₂ synthesis of nitric oxide (NO), suppression of pro-inflammatory cytokines (such as IL-1, TNF, IFN) [154], stimulation of anti-inflammatory cytokines (such as IL-4, IL-10, IL-13), and promotion of growth factors like TGF-beta and IGF-1 [156]. Although ozone therapy shows promise, further clinical trials are needed to establish its efficacy. Consequently, it could be considered a valuable adjunct in regenerative therapies.

Supplements to Increase Success

Supplements play a crucial role in regenerative medicine, with several options available for this purpose. One notable supplement is Neo-40, which has been shown to boost nitric oxide (NO) levels in the body. This increase in NO has a similar effect to hyperbaric oxygen therapy, leading to an enhanced output of stem cells [28]. Another supplement, UltraCur, is a highly potent form of curcumin that offers greater bioavailability compared to standard curcumin products. By inhibiting interleukin 1, UltraCur effectively reduces inflammation in the extracellular matrix. StemXCell is yet another supplement that has been found to stimulate the release of stem cells from the bone marrow, similar to the effects of GCSF [157]. Lastly, CH-Alpha is a supplement that provides collagen for repair purposes [158]. Alongside these supplements, maintaining hormonal balance and taking multivitamins are also crucial factors for success in the field of regenerative medicine.

Conclusion

Regenerative therapies for OA have evolved from the concept of administered cells engrafting to lesion sites to the use of intra-articular injectable orthobiologics aimed at relieving symptoms, slowing disease progression, and potentially preventing joint replacement. These therapies fall into two main categories: cell-based and cell-free treatments. Cell-free therapies like PRP and AAI have shown promise in alleviating inflammation and promoting cartilage regeneration. Exosomes, derived from stem cells, have demonstrated the ability to stimulate cartilage repair and modulate the immune response in the joint. HPE and mitochondrial transplantation offer potential benefits in reducing pain, improving joint function, and regulating immune responses.

Cell based therapy, whether derived from bone marrow or adipose tissue, offers the potential for tissue repair and regeneration through the differentiation of stem cells into various cell types involved in cartilage and bone repair. Additionally, stem cells exhibit immunomodulatory properties that can mitigate inflammation and slow down the progression of OA. Furthermore, emerging technologies such as CRISPR/Cas9 hold promise for enhancing the effectiveness of cell-based therapies by targeting specific genes associated with inflammation, thereby improving the outcomes of treatment for OA.

Non-biological treatments such as GOLDIC®, Extracorporeal Shockwave therapy, Ozone therapy, and supplements are showing promising results in the field of regenerative medicine for treating degenerative joint diseases, particularly knee OA. These therapies offer regenerative benefits, reduce cartilage degradation, promote the synthesis of

essential extracellular matrix components specific to cartilage, modulate nerve endings to decrease pain-related markers, and improve overall joint function and quality of life for patients.

In conclusion, the field of orthobiological treatments for OA is diverse, with various therapies showing promise in reducing inflammation, promoting tissue repair, and improving joint function. Further research is needed to establish the safety, efficacy, and long-term benefits of these treatments, as well as to optimize their formulations and concentrations for maximizing effectiveness in cartilage repair and OA management.

Acknowledgements Authors would like to acknowledge Omolbani Kheirkhah from Malaria and vector research group (MVRG), Biotechnology research center (BRC), Pasteur Institute, Tehran, Iran, for her collaboration on graphical abstract drawing.

Authors' Contributions Zahra Barabadi had the idea for the article, Ali Bahari Golamkaboudi and Elham Vojoudi performed the literature search, all authors drafted the manuscript and Zahra Barabadi critically revised the work. Pejman Porouhan made substantial contribution to the revision of the final draft. All authors reviewed and approved the final version of the manuscript.

Funding No funding was received for conducting this study.

Data Availability No additional data and materials are associated with this manuscript.

Code Availability Not applicable.

Declarations

Conflicts of Interest/Competing Interests The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

References

- Hootman, J. M., Helmick, C. G., Barbour, K. E., Theis, K. A., & Boring, M. A. (2016). Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015–2040. *Arthritis & Rheumatology*, 68(7), 1582–1587. <https://doi.org/10.1002/art.39692>
- Y, E. M. (2022). *Musculoskeletal Ultrasound-Guided Regenerative Medicine*. Springer Nature (prevajalec, Trans.).
- Schmitz, C., Alt, C., Pearce, D. A., Furia, J. P., Maffulli, N., Alt, E. U. (2022). Methodological flaws in meta-analyses of clinical studies on the management of knee osteoarthritis with stem cells: A Systematic Review. *Cells*, 11(6). <https://doi.org/10.3390/cells11060965>
- Pattanittum, P., Turner, T., Green, S., Buchbinder, R. (2013). Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database of Systematic Reviews*, 2013(5), Cd003686. <https://doi.org/10.1002/14651858.CD003686.pub2>
- McLauchlan, G. J., Handoll, H. H. (2001). Interventions for treating acute and chronic Achilles tendinitis. *Cochrane Database of Systematic Reviews* (2), Cd000232. <https://doi.org/10.1002/14651858.Cd000232>
- Global regenerative medicines market—analysis and forecast (2017–2025) (Focus on therapy, a., market share analysis, 22 country analysis, and competitive landscape). Market Research, Business Wire. Available at: www.reportlinker.com/p05292525/Global-Regenerative-MedicinesMarket-Analysis-and-Forecast-Focus-on-TherapyApplications-Market-Share-Analysis-22-CountryAnalysis-and-Competitive-Landscape.html. Accessed 12 Oct 2020
- www.mohawkcollege.ca/employees/occupational-healthtolerability/ergonomics/musculoskeletal-disordermsd-signs-and-symptoms. Accessed 12 Oct 2020.
- McAlindon, T. E., LaValley, M. P., Harvey, W. F., Price, L. L., Driban, J. B., Zhang, M., & Ward, R. J. (2017). Effect of Intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: A randomized clinical trial. *Jama*, 317(19), 1967–1975. <https://doi.org/10.1001/jama.2017.5283>
- Farkas, B., Kvell, K., Czömpöly, T., Illés, T., & Bárdos, T. (2010). Increased chondrocyte death after steroid and local anesthetic combination. *Clinical Orthopaedics and Related Research*, 468(11), 3112–3120. <https://doi.org/10.1007/s11999-010-1443-0>
- Dragoo, J. L., Dhanial, C. M., Braun, H. J., Pouliot, M. A., & Kim, H. J. (2012). The chondrotoxicity of single-dose corticosteroids. *Knee Surgery, Sports Traumatology, Arthroscopy*, 20(9), 1809–1814. <https://doi.org/10.1007/s00167-011-1820-6>
- Ogata, T., Ideno, Y., Akai, M., Seichi, A., Hagino, H., Iwaya, T., ... Hayashi, K. (2018). Effects of glucosamine in patients with osteoarthritis of the knee: a systematic review and meta-analysis. *Clinical Rheumatology*, 37(9), 2479–2487. <https://doi.org/10.1007/s10067-018-4106-2>
- Aggarwal, A., & Sempowski, I. P. (2004). Hyaluronic acid injections for knee osteoarthritis. Systematic review of the literature. *Canadian Family Physician*, 50, 249–256.
- Salari, M., Sharma, S., Jog, M. S. (2018). Botulinum toxin induced atrophy: An uncharted territory. *Toxins (Basel)*, 10(8). <https://doi.org/10.3390/toxins10080313>
- Johnson, L. L. (2001). Arthroscopic abrasion arthroplasty: a review. *Clinical Orthopaedics and Related Research*, 391(Suppl), S306–317.
- Insall, J. (1974). The Pridie debridement operation for osteoarthritis of the knee. *Clinical Orthopaedics and Related Research*, 101, 61–67.
- Mithoefer, K., Williams, R. J., 3rd, Warren, R. F., Potter, H. G., Spock, C. R., Jones, E. C., ... Marx, R. G. (2006). Chondral resurfacing of articular cartilage defects in the knee with the microfracture technique. Surgical technique. *The Journal of bone and joint surgery American*, 88 Suppl 1 Pt 2, 294–304. <https://doi.org/10.2106/jbjs.F.00292>
- Bentley, G., Biant, L. C., Vijayan, S., Macmull, S., Skinner, J. A., & Carrington, R. W. (2012). Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. *The Journal of Bone and Joint Surgery*, 94(4), 504–509. <https://doi.org/10.1302/0301-620x.94b4.27495>
- Kan, H., Chan, P., Chiu, K., Yan, C., Yeung, S., Ng, Y., ... Ho, T. (2019). Non-surgical treatment of knee osteoarthritis. *Hong Kong Med J*, 25(2):127–33. <https://doi.org/10.12809/hkmj187600>
- Siemieniuk, R. A. C., Harris, I. A., Agoritsas, T., Poolman, R. W., Brignardello-Petersen, R., Van de Velde, S., ... Kristiansen, A. (2017). Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *Bmj*, 357, j1982. <https://doi.org/10.1136/bmj.j1982>
- Singh, J. A., Kundukulam, J., Riddle, D. L., Strand, V., & Tugwell, P. (2011). Early postoperative mortality following joint arthroplasty: a

- systematic review. *The Journal of Rheumatology*, 38(7), 1507–1513. <https://doi.org/10.3899/jrheum.110280>
21. Hernigou, P., Auregan, J. C., Dubory, A., Flouzat-Lachaniette, C. H., Chevallier, N., & Rouard, H. (2018). Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee. *International Orthopaedics*, 42(11), 2563–2571. <https://doi.org/10.1007/s00264-018-3916-9>
 22. Narimanpour, Z., Nazm Bojnordi, M., Somayeh, E.-B., Elham, V., Jamileh, S., & Ghasemi, H. H. (2022). Silk nanofibrous electrospun acaffold amplifies proliferation and stemness profile of mouse spermatogonial stem cells. *Regenerative Engineering and Translational Medicine*, 8(1), 86–93. <https://doi.org/10.1007/s40883-020-00189-5>
 23. Ashoobi, M. T., Hemmati, H., Aghayan, H. R., Zarei-Behjani, Z., Keshavarz, S., Babaloo, H., . . . Vojoudi, E. (2023). Wharton's jelly mesenchymal stem cells transplantation for critical limb ischemia in patients with type 2 diabetes mellitus: a preliminary report of phase I clinical trial. *Cell and Tissue Research*. <https://doi.org/10.1007/s00441-023-03854-7>
 24. Keshavarz, S., Wall, J. R., Keshavarz, S., Vojoudi, E., & Jafari-Shakib, R. (2023). Breast cancer immunotherapy: a comprehensive review. *Clinical and Experimental Medicine*, 23(8), 4431–4447. <https://doi.org/10.1007/s10238-023-01177-z>
 25. Grol, M. W. (2024). The evolving landscape of gene therapy strategies for the treatment of osteoarthritis. *Osteoarthritis Cartilage*. <https://doi.org/10.1016/j.joca.2023.12.009>
 26. Vojoudi, E., & Babaloo, H. (2023). Application of electrospun nanofiber as drug delivery systems: A review. *Pharmaceutical Nanotechnology*, 11(1), 10–24. <https://doi.org/10.2174/2211738510666220928161957>
 27. Dhillon, M. S., Behera, P., Patel, S., & Shetty, V. (2014). Orthobiologics and platelet rich plasma. *Indian Journal of Orthopaedics*, 48(1), 1–9. <https://doi.org/10.4103/0019-5413.125477>
 28. Purita, J. (2022). The Nuts and bolts of regenerative medicine as it pertains to the joint (prevajalec, Trans.). *V musculoskeletal ultrasound-guided regenerative medicine* (str. 35–55). Springer.
 29. Im, G. I., Kim, T. K. (2020). Regenerative therapy for osteoarthritis: A perspective. *International Journal of Stem Cells*, 13(2), 177–181. <https://doi.org/10.15283/ijsc20069>
 30. Jackson, A., & Gu, W. (2009). Transport properties of cartilaginous tissues. *Current Rheumatology Reviews*, 5(1), 40. <https://doi.org/10.2174/157339709787315320>
 31. Murrell, W. D., Anz, A. W., Badsha, H., Bennett, W. F., Boykin, R. E., & Caplan, A. I. (2015). Regenerative treatments to enhance orthopedic surgical outcome. *PM&R*, 7(4 Suppl), S41–s52. <https://doi.org/10.1016/j.pmrj.2015.01.015>
 32. Haynesworth SE, G. V., Caplan AI. (1994). *Diminution of the number of mesenchymal stem cells as a cause for skeletal aging*. In: *Musculoskeletal soft-tissue aging: impact on mobility* (prevajalec, Trans.). American Academy of Orthopaedic Surgeons, Publishers.
 33. Arnoczky, S. P. (2011). Platelet-rich plasma augmentation of rotator cuff repair: letter. *The American Journal of Sports Medicine*, 39(6), NP8–9; author reply NP9–11. <https://doi.org/10.1177/0363546511410381>
 34. Mazzocca, A. D., McCarthy, M. B., Chowanec, D. M., Cote, M. P., Romeo, A. A., Bradley, J. P., . . . Beitzel, K. (2012). Platelet-rich plasma differs according to preparation method and human variability. *Journal of Bone and Joint Surgery*, 94(4), 308–316. <https://doi.org/10.2106/jbjs.K.00430>
 35. Marx, R. E. (2001). Platelet-rich plasma (PRP): What is PRP and what is not PRP? *Implant Dentistry*, 10(4), 225–228. <https://doi.org/10.1097/00008505-200110000-00002>
 36. DeLong, J. M., Russell, R. P., & Mazzocca, A. D. (2012). Platelet-rich plasma: The PAW classification system. *Arthroscopy*, 28(7), 998–1009. <https://doi.org/10.1016/j.arthro.2012.04.148>
 37. Pensato, R., Al-Amer, R., & La Padula, S. (2023). Protocol for obtaining Platelet-Rich Plasma (PRP), Platelet-Poor Plasma (PPP), and thrombin for autologous use. *Aesthetic Plastic Surgery*. <https://doi.org/10.1007/s00266-023-03470-4>
 38. Wassilew, G. I., Lehnigk, U., Duda, G. N., Taylor, W. R., Matziolis, G., & Dynybil, C. (2010). The expression of proinflammatory cytokines and matrix metalloproteinases in the synovial membranes of patients with osteoarthritis compared with traumatic knee disorders. *Arthroscopy*, 26(8), 1096–1104. <https://doi.org/10.1016/j.arthro.2009.12.018>
 39. Martel-Pelletier, J., McCollum, R., DiBattista, J., Faure, M. P., Chin, J. A., Fournier, S., . . . Pelletier, J. P. (1992). The interleukin-1 receptor in normal and osteoarthritic human articular chondrocytes. Identification as the type I receptor and analysis of binding kinetics and biologic function. *Arthritis & Rheumatism*, 35(5), 530–540. <https://doi.org/10.1002/art.1780350507>
 40. Evans, C. H., Chevalier, X., & Wehling, P. (2016). Autologous conditioned serum. *Physical Medicine and Rehabilitation Clinics*, 27(4), 893–908.
 41. Kon, E., Engebretsen, L., Verdonk, P., Nehrer, S., & Filardo, G. (2020). Autologous protein solution injections for the treatment of knee osteoarthritis: 3-year results. *The American Journal of Sports Medicine*, 48(11), 2703–2710.
 42. Sawyere, D. M., Lanz, O. I., Dahlgren, L. A., Barry, S. L., Nichols, A. C., & Werre, S. R. (2016). Cytokine and growth factor concentrations in canine autologous conditioned serum. *Veterinary Surgery*, 45(5), 582–586.
 43. Dinarello, C. A. (1984). Interleukin-1. *Reviews of Infectious Diseases*, 6(1), 51–95. <https://doi.org/10.1093/clinids/6.1.51>
 44. Frisbie, D. D., Kawcak, C. E., Werp, N. M., Park, R. D., & McIlwraith, C. W. (2007). Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. *American Journal of Veterinary Research*, 68(3), 290–296. <https://doi.org/10.2460/ajvr.68.3.290>
 45. Tassara, M., De Ponti, A., Barzizza, L., Zambelli, M., Parisi, C., Milani, R., & Santoleri, L. (2018). Autologous conditioned serum (ACS) for intra-articular treatment in Osteoarthritis: Retrospective report of 28 cases. *Transfusion and Apheresis Science*, 57(4), 573–577. <https://doi.org/10.1016/j.transci.2018.07.021>
 46. Miao, C., Zhou, W., Wang, X., & Fang, J. (2021). The research progress of exosomes in osteoarthritis, with particular emphasis on the mediating roles of miRNAs and lncRNAs. *Frontiers in Pharmacology*, 12, 685623.
 47. Maas, S. L. N., Breakefield, X. O., & Weaver, A. M. (2017). Extracellular vesicles: Unique intercellular delivery vehicles. *Trends in Cell Biology*, 27(3), 172–188. <https://doi.org/10.1016/j.tcb.2016.11.003>
 48. Jiang, K., Jiang, T., Chen, Y., & Mao, X. (2021). Mesenchymal stem cell-derived exosomes modulate chondrocyte glutamine metabolism to alleviate osteoarthritis progression. *Mediators of Inflammation*, 2021(1), 2979124. <https://doi.org/10.1155/2021/2979124>
 49. Qi, H., Liu, D. P., Xiao, D. W., Tian, D. C., Su, Y. W., & Jin, S. F. (2019). Exosomes derived from mesenchymal stem cells inhibit mitochondrial dysfunction-induced apoptosis of chondrocytes via p38, ERK, and Akt pathways. *In Vitro Cellular & Developmental Biology - Animal*, 55(3), 203–210. <https://doi.org/10.1007/s11626-019-00330-x>
 50. Tang, Y., Wu, Z., Guo, R., Huang, J., Rong, X., Zhu, B., . . . Qiu, L. (2022). Ultrasound-augmented anti-inflammatory exosomes for targeted therapy in rheumatoid arthritis. *Journal of Materials Chemistry B*, 10(38), 7862–7874.
 51. Phillips, A., Wong, A., Chen, G., & Kuo, J. (2021). One month safety study of ExoFlo injection for the treatment of lumbar or cervical radiculopathy in the epidural space. *International Journal of Science and Research Archive*, 4(1), 119–124.

52. Wang, R., & Xu, B. (2022). TGF β 1-modified MSC-derived exosome attenuates osteoarthritis by inhibiting PDGF-BB secretion and H-type vessel activity in the subchondral bone. *Acta Histochemica*, 124(7), 151933.
53. Bianco, N. R., Kim, S. H., Ruffner, M. A., & Robbins, P. D. (2009). Therapeutic effect of exosomes from indoleamine 2, 3-dioxygenase-positive dendritic cells in collagen-induced arthritis and delayed-type hypersensitivity disease models. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 60(2), 380–389.
54. Yoo, K. H., Thapa, N., Chwae, Y. J., Yoon, S. H., Kim, B. J., Lee, J. O., . . . Kim, J. (2022). Transforming growth factor- β family and stem cell-derived exosome therapeutic treatment in osteoarthritis. *International journal of molecular medicine*, 49(5), 1–11.
55. Fan, Y., Li, Z., & He, Y. (2022). Exosomes in the pathogenesis, progression, and treatment of osteoarthritis. *Bioengineering*, 9(3), 99.
56. Wang, H., Zheng, R., Chen, Q., Shao, J., Yu, J., & Hu, S. (2017). Mesenchymal stem cells microvesicles stabilize endothelial barrier function partly mediated by hepatocyte growth factor (HGF). *Stem Cell Research & Therapy*, 8(1), 211. <https://doi.org/10.1186/s13287-017-0662-7>
57. Liu, Y., Zeng, Y., Si, H.-B., Tang, L., Xie, H.-Q., & Shen, B. (2022). Exosomes derived from human urine-derived stem cells overexpressing miR-140-5p alleviate knee osteoarthritis through downregulation of VEGFA in a rat model. *The American Journal of Sports Medicine*, 50(4), 1088–1105.
58. McIntyre, J. A., Jones, I. A., Danilkovich, A., & Vangsness, C. T., Jr. (2018). The placenta: applications in orthopaedic sports medicine. *The American Journal of Sports Medicine*, 46(1), 234–247.
59. Ghoneum, M., & El-Gerbed, M. S. (2021). Human placental extract ameliorates methotrexate-induced hepatotoxicity in rats via regulating antioxidative and anti-inflammatory responses. *Cancer Chemotherapy and Pharmacology*, 88, 961–971.
60. Jazayeri, M. H., Barzaman, K., Nedaeinia, R., Aghaie, T., & Motallebnezhad, M. (2020). Human placental extract attenuates neurological symptoms in the experimental autoimmune encephalomyelitis model of multiple sclerosis—a putative approach in MS disease? *Autoimmunity Highlights*, 11, 1–9.
61. Abumaree, M., Abomaray, F., Alshabibi, M., AlAskar, A., & Kalionis, B. (2017). Immunomodulatory properties of human placental mesenchymal stem/stromal cells. *Placenta*, 59, 87–95.
62. Seifi, S., Shamloo, A., Tavoosi, S. N., Almasi-Jaf, A., Shaygani, H., & Sayah, M. R. (2023). A novel multifunctional chitosan-gelatin/carboxymethyl cellulose-alginate bilayer hydrogel containing human placenta extract for accelerating full-thickness wound healing. *International Journal of Biological Macromolecules*, 253, 126929.
63. Kim, J.-K., Kim, T.-H., Park, S.-W., Kim, H.-Y., Hoon Kim, S., Youl Lee, S., & Lee, S.-M. (2010). Protective effects of human placenta extract on cartilage degradation in experimental osteoarthritis. *Biological and Pharmaceutical Bulletin*, 33(6), 1004–1010.
64. Liu, H., Li, Z., Cao, Y., Cui, Y., Yang, X., Meng, Z., & Wang, R. (2019). Effect of chondrocyte mitochondrial dysfunction on cartilage degeneration: A possible pathway for osteoarthritis pathology at the subcellular level. *Molecular Medicine Reports*, 20(4), 3308–3316. <https://doi.org/10.3892/mmr.2019.10559>
65. Ansari, M. Y., Ahmad, N., Voleti, S., Wase, S. J., Novak, K., Haqqi, T. M. (2020). Mitochondrial dysfunction triggers a catabolic response in chondrocytes via ROS-mediated activation of the JNK/AP1 pathway. *Journal of Cell Science*, 133(22). <https://doi.org/10.1242/jcs.247353>
66. Ansari, M. Y., Ball, H. C., Wase, S. J., Novak, K., & Haqqi, T. M. (2021). Lysosomal dysfunction in osteoarthritis and aged cartilage triggers apoptosis in chondrocytes through BAX mediated release of Cytochrome c. *Osteoarthritis and Cartilage*, 29(1), 100–112.
67. Hwang, J. W., Lee, M. J., Chung, T. N., Lee, H. A. R., Lee, J. H., Choi, S. Y., . . . Kim, S. H. (2021). The immune modulatory effects of mitochondrial transplantation on cecal slurry model in rat. *Critical Care*, 25(1), 1–12.
68. Moretti, L., Maccagnano, G., Coviello, M., Cassano, G. D., Franchini, A., Laneve, A., & Moretti, B. (2022). Platelet rich plasma injections for knee osteoarthritis treatment: a prospective clinical study. *Journal of Clinical Medicine*, 11(9), 2640.
69. Bansal, H., Leon, J., Pont, J. L., Wilson, D. A., Bansal, A., Agarwal, D., & Preteasa, I. (2021). Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. *Scientific Reports*, 11(1), 3971. <https://doi.org/10.1038/s41598-021-83025-2>
70. Kon, E., Engebretsen, L., Verdonk, P., Nehrer, S., & Filardo, G. (2018). Clinical outcomes of knee osteoarthritis treated with an autologous protein solution injection: A 1-Year pilot double-blinded randomized controlled trial. *The American Journal of Sports Medicine*, 46(1), 171–180. <https://doi.org/10.1177/0363546517732734>
71. Hix, J., Klaassen, M., Foreman, R., Cullen, E., Toler, K., King, W., & Woodell-May, J. (2017). An autologous anti-inflammatory protein solution yielded a favorable safety profile and significant pain relief in an open-label pilot study of patients with osteoarthritis. *BioResearch Open Access*, 6(1), 151–158. <https://doi.org/10.1089/biores.2017.0027>
72. Johnny East, D., Trace Alexander, D., & Dordevic, M. (2020). IRB approved pilot safety study of extracellular vesicle isolate product evaluating the treatment of osteoarthritis in combat-related injuries. *Stem Cell Res*, 1(2), 1–10.
73. Park, K. M., & Cho, T. H. (2017). Therapeutic effect of acupuncture point injection with placental extract in knee osteoarthritis. *Journal of Integrative Medicine*, 15(2), 135–141. [https://doi.org/10.1016/s2095-4964\(17\)60316-9](https://doi.org/10.1016/s2095-4964(17)60316-9)
74. Kim, J., Kim, T.-H., Park, S.-W., Kim, H.-Y., Kim, S., Lee, S., & Lee, S.-M. (2010). Protective effects of human placenta extract on cartilage degradation in experimental osteoarthritis. *Biological & Pharmaceutical Bulletin*, 33, 1004–1010. <https://doi.org/10.1248/bpb.33.1004>
75. Kim, G. B., Seo, M. S., Park, W. T., Lee, G. W. (2020). Bone marrow aspirate concentrate: Its uses in osteoarthritis. *International Journal of Molecular Sciences*, 21(9). <https://doi.org/10.3390/ijms21093224>
76. Gaul, F., Bugbee, W. D., Hoenecke, H. R., Jr., & D’Lima, D. D. (2019). A review of commercially available point-of-care devices to concentrate bone marrow for the treatment of osteoarthritis and focal cartilage lesions. *Cartilage*, 10(4), 387–394.
77. Hernigou, P., Mathieu, G., Poignard, A., Manicom, O., Beaujean, F., & Rouard, H. (2006). Percutaneous autologous bone-marrow grafting for nonunions: surgical technique. *JBJS*, 88(1), 322–327.
78. Pierini, M., Di Bella, C., Dozza, B., Frisoni, T., Martella, E., Bellotti, C., . . . Donati, D. (2013). The posterior iliac crest outperforms the anterior iliac crest when obtaining mesenchymal stem cells from bone marrow. *The Journal of bone and joint surgery American*, 95(12), 1101–1107. <https://doi.org/10.2106/jbjs.L.00429>
79. Oliver, K. S., Bayes, M., Crane, D., & Pathikonda, C. (2015). Clinical outcome of bone marrow concentrate in knee osteoarthritis. *Journal of Prolotherapy*, 7, 937–946.
80. Goldenberg, A., Kelley, P., Ibrahim, S., Sen, F., & Liu, C. (2005). Influence of age and needle gauge on bone marrow biopsy specimen adequacy. *Blood*, 106(11), 5581–5581. <https://doi.org/10.1182/blood.V106.11.5581.5581>
81. Brozovich, A., Sinicrope, B. J., Bauza, G., Niclot, F. B., Lintner, D., Taraballi, F., & McCulloch, P. C. (2021). High variability of mesenchymal stem cells obtained via bone marrow aspirate concentrate compared with traditional bone marrow

- aspiration technique. *Orthopaedic Journal of Sports Medicine*, 9(12), 23259671211058460. <https://doi.org/10.1177/23259671211058460>
82. Zhu, C., Wu, W., & Qu, X. (2021). Mesenchymal stem cells in osteoarthritis therapy: a review. *American Journal of Translational Research*, 13(2), 448–461.
 83. Le, H., Xu, W., Zhuang, X., Chang, F., Wang, Y., & Ding, J. (2020). Mesenchymal stem cells for cartilage regeneration. *Journal of Tissue Engineering*, 11, 2041731420943839. <https://doi.org/10.1177/2041731420943839>
 84. Najar, M., Martel-Pelletier, J., Pelletier, J.-P., & Fahmi, H. (2020). Mesenchymal stromal cell immunology for efficient and safe treatment of osteoarthritis. *Frontiers in Cell and Developmental Biology*, 8, 567813.
 85. Keeling, L. E., Belk, J. W., Kraeutler, M. J., Kallner, A. C., Lindsay, A., McCarty, E. C., & Postma, W. F. (2022). Bone marrow aspirate concentrate for the treatment of knee osteoarthritis: A systematic review. *The American Journal of Sports Medicine*, 50(8), 2315–2323. <https://doi.org/10.1177/03635465211018837>
 86. Lana, J., Lana, A., da Fonseca, L. F., Coelho, M. A., Marques, G. G., Mosaner, T., ... de Andrade, M. A. P. (2022). Stromal vascular fraction for knee osteoarthritis - An update. *Journal of Stem Cells and Regenerative Medicine*, 18(1), 11–20. <https://doi.org/10.46582/jstrm.1801003>
 87. Hirose, Y., Funahashi, Y., Matsukawa, Y., Majima, T., Yamaguchi, M., Kawabata, S., ... Yamamoto, T. (2018). Comparison of trophic factors secreted from human adipose-derived stromal vascular fraction with those from adipose-derived stromal/stem cells in the same individuals. *Cytotherapy*, 20(4), 589–591.
 88. Condé-Green, A., Kotamarti, V. S., Sherman, L. S., Keith, J. D., Lee, E. S., Granick, M. S., Rameshwar, P. (2016). Shift toward mechanical isolation of adipose-derived stromal vascular fraction: Review of upcoming techniques. *Plastic and Reconstructive Surgery – Global Open*, 4(9), e1017 <https://doi.org/10.1097/gox.0000000000001017>
 89. Schmitz, C., Alt, C., Würfel, T., Milz, S., Dinzey, J., Hill, A., ... Alt, E. U. (2024). New, biomechanically sound tendon tissue after injection of uncultured, autologous, adipose derived regenerative cells in partial Achilles tendon defects in rabbits. Preprint retrieved from <https://www.biorxiv.org/content/https://doi.org/10.1101/2024.02.18.580890v1>. <https://doi.org/10.1101/2024.02.18.580890>
 90. Bourin, P., Bunnell, B. A., Casteilla, L., Dominici, M., Katz, A. J., March, K. L., ... Gimble, J. M. (2013). Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: A joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). *Cytotherapy*, 15(6), 641–648.
 91. Solakoglu, Ö., Götz, W., Kiessling, M. C., Alt, C., Schmitz, C., & Alt, E. U. (2019). Improved guided bone regeneration by combined application of unmodified, fresh autologous adipose derived regenerative cells and plasma rich in growth factors: A first-in-human case report and literature review. *World Journal of Stem Cells*, 11(2), 124–146. <https://doi.org/10.4252/wjsc.v11.i2.124>
 92. Ude, C. C., Shah, S., Ogueri, K. S., Nair, L. S., & Laurencin, C. T. (2022). Stromal vascular fraction for osteoarthritis of the knee regenerative engineering. *Regenerative Engineering and Translational Medicine*, 8(2), 210–224.
 93. Hass, R., Kasper, C., Böhm, S., & Jacobs, R. (2011). Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. *Cell Communication and Signaling*, 9, 12. <https://doi.org/10.1186/1478-811x-9-12>
 94. Lundeen, M., Hurd, J. L., Hayes, M., Hayes, M., Facile, T. R., Furia, J. P., ... Pearce, D. A. (2023). Management of partial-thickness rotator cuff tears with autologous adipose-derived regenerative cells is safe and more effective than injection of corticosteroid. *Scientific Reports*, 13(1), 19348. <https://doi.org/10.1038/s41598-023-46653-4>
 95. Rotherl, R., Tomelden, J., Alt, E. U. (2023). Safety and efficacy of autologous stem cell treatment for facetogenic chronic back pain. *Journal of Personalized Medicine*, 13(3). <https://doi.org/10.3390/jpm13030436>
 96. Schmitz, C., Alt, C., Azares, A. R., Pearce, D. A., Facile, T. R., Furia, J. P., ... Alt, E. U. (2022). The composition of adipose-derived regenerative cells isolated from lipoaspirate using a point of care system does not depend on the subject's individual age, sex, body mass index and ethnicity. *Cells*, 12(1). <https://doi.org/10.3390/cells12010030>
 97. Shanmugasundaram, S., Vaish, A., Chavada, V., Murrell, W. D., & Vaishya, R. (2021). Assessment of safety and efficacy of intra-articular injection of stromal vascular fraction for the treatment of knee osteoarthritis-a systematic review. *International Orthopaedics*, 45(3), 615–625. <https://doi.org/10.1007/s00264-020-04926-x>
 98. Marenah, M., Li, J., Kumar, A., & Murrell, W. (2019). Quality assurance and adverse event management in regenerative medicine for knee osteoarthritis: Current concepts. *Journal of Clinical Orthopaedics and Trauma*, 10(1), 53–58. <https://doi.org/10.1016/j.jcot.2018.09.005>
 99. Rihani, J. (2019). Microfat and nanofat: When and where these treatments work. *Facial Plastic Surgery Clinics of North America*, 27(3), 321–330. <https://doi.org/10.1016/j.fsc.2019.03.004>
 100. Chen, Z., Ge, Y., Zhou, L., Li, T., Yan, B., Chen, J., ... Shan, L. (2021). Pain relief and cartilage repair by Nanofat against osteoarthritis: preclinical and clinical evidence. *Stem Cell Research & Therapy*, 12(1), 477. <https://doi.org/10.1186/s13287-021-02538-9>
 101. Van Genechten, W., Vuylsteke, K., Martinez, P. R., Swinnen, L., Sas, K., Verdonk, P. (2021). Autologous micro-fragmented adipose tissue (MFAT) to treat symptomatic knee osteoarthritis: Early outcomes of a consecutive case series. *Journal of Clinical Medicine*, 10(11). <https://doi.org/10.3390/jcm10112231>
 102. Lach, M. S., Rosochowicz, M. A., Richter, M., Jagiello, I., Suchorska, W. M., Trzeciak, T. (2022). The induced pluripotent stem cells in articular cartilage regeneration and disease modeling: Are we ready for their clinical use? *Cells*, 11(3). <https://doi.org/10.3390/cells11030529>
 103. Murphy, C., Mobasher, A., Tancos, Z., Kobolák, J., & Dinnyés, A. (2018). The potency of induced pluripotent stem cells in cartilage regeneration and osteoarthritis treatment. *Advances in Experimental Medicine and Biology*, 1079, 55–68. https://doi.org/10.1007/5584_2017_141
 104. Csobonyei, M., Polak, S., Nicodemou, A., Zamborsky, R., Danisovic, L. (2021). iPSCs in modeling and therapy of osteoarthritis. *Biomedicines*, 9(2). <https://doi.org/10.3390/biomedicines9020186>
 105. Furia, J. P., Lundeen, M. A., Hurd, J. L., Pearce, D. A., Alt, C., Alt, E. U., ... Maffulli, N. (2022). Why and how to use the body's own stem cells for regeneration in musculoskeletal disorders: a primer. *Journal of Orthopaedic Surgery and Research*, 17(1), 36. <https://doi.org/10.1186/s13018-022-02918-8>
 106. Zhu, Y., Wu, X., Liang, Y., Gu, H., Song, K., Zou, X., & Zhou, G. (2016). Repair of cartilage defects in osteoarthritis rats with induced pluripotent stem cell derived chondrocytes. *BMC Biotechnology*, 16(1), 78. <https://doi.org/10.1186/s12896-016-0306-5>
 107. Yamashita, A., Morioka, M., Yahara, Y., Okada, M., Kobayashi, T., Kuriyama, S., ... Tsumaki, N. (2015). Generation of scaffoldless hyaline cartilaginous tissue from human iPSCs. *Stem Cell Reports*, 4(3), 404–418. <https://doi.org/10.1016/j.stemcr.2015.01.016>

108. Xu, M., Stattin, E. L., Shaw, G., Heinegård, D., Sullivan, G., Wilmut, I., . . . Barry, F. (2016). Chondrocytes derived from mesenchymal stromal cells and induced pluripotent cells of patients with familial osteochondritis dissecans exhibit an endoplasmic reticulum stress response and defective matrix assembly. *Stem Cells Translational Medicine*, 5(9), 1171–1181. <https://doi.org/10.5966/sctm.2015-0384>
109. Rim, Y. A., Nam, Y., Park, N., Lee, J., Park, S. H., & Ju, J. H. (2018). Repair potential of nonsurgically delivered induced pluripotent stem cell-derived chondrocytes in a rat osteochondral defect model. *Journal of Tissue Engineering and Regenerative Medicine*, 12(8), 1843–1855. <https://doi.org/10.1002/term.2705>
110. Alanazi, R. F., Alhwity, B. S., Almahlawi, R. M., Alatawi, B. D., Albalawi, S. A., Albalawi, R. A., . . . Elsherbiny, N. (2023). Multilineage differentiating stress enduring (Muse) cells: A new era of stem cell-based therapy. *Cells*, 12(13). <https://doi.org/10.3390/cells12131676>
111. Fisch, S. C., Gimeno, M. L., Phan, J. D., Simerman, A. A., Dumesic, D. A., Perone, M. J., & Chazenbalk, G. D. (2017). Pluripotent nontumorigenic multilineage differentiating stress enduring cells (Muse cells): a seven-year retrospective. *Stem cell research & therapy*, 8(1), 1–9.
112. Velasco, M. G., Satué, K., Chicharro, D., Martins, E., Torres-Torrillas, M., Peláez, P., . . . Rubio, M. (2023). Multilineage-differentiating stress-enduring cells (Muse Cells): The future of human and veterinary regenerative medicine. *Biomedicine*, 11(2). <https://doi.org/10.3390/biomedicine11020636>
113. Toyoda, E., Sato, M., Takahashi, T., Maehara, M., Nakamura, Y., Mitani, G., . . . Watanabe, M. (2019). Multilineage-differentiating stress-enduring (Muse)-like cells exist in synovial tissue. *Regenerative Therapy*, 10, 17–26.
114. Wang, S., Wang, P., & Zhang, R. (2023). Adipose tissue-derived Muse cells promote autophagy and oxidative stress tolerance in human epidermal melanocytes. *Cell and Tissue Banking*, 24(1), 253–264.
115. Kucia, M., Reca, R., Campbell, F., Zuba-Surma, E., Majka, M., Ratajczak, J., & Ratajczak, M. (2006). A population of very small embryonic-like (VSEL) CXCR4+ SSEA-1+ Oct-4+ stem cells identified in adult bone marrow. *Leukemia*, 20(5), 857–869.
116. Kassmer, S. H., & Krause, D. S. (2013). Very small embryonic-like cells: Biology and function of these potential endogenous pluripotent stem cells in adult tissues. *Molecular reproduction and development*, 80(8), 677–690.
117. Sampson, E. R., Hilton, M. J., Tian, Y., Chen, D., Schwarz, E. M., Mooney, R. A., . . . Zuscik, M. J. (2011). Teriparatide as a chondroregenerative therapy for injury-induced osteoarthritis. *Science Translational Medicine*, 3(101), 101ra193. <https://doi.org/10.1126/scitranslmed.3002214>
118. Chacón-Martínez, C. A., Koester, J., Wickström, S. A. (2018). Signaling in the stem cell niche: regulating cell fate, function and plasticity. *Development*, 145(15). <https://doi.org/10.1242/dev.165399>
119. Krasnodembskaya, A., Song, Y., Fang, X., Gupta, N., Serikov, V., Lee, J. W., & Matthey, M. A. (2010). Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells*, 28(12), 2229–2238. <https://doi.org/10.1002/stem.544>
120. Caplan, A. I. (2017). Mesenchymal stem cells: Time to change the name! *Stem Cells Translational Medicine*, 6(6), 1445–1451. <https://doi.org/10.1002/sctm.17-0051>
121. Karimi, T., Pan, Z., Potaman, V. N., Alt, E. U. (2023). Conversion of unmodified stem cells to pacemaker cells by overexpression of key developmental genes. *Cells*, 12(10). <https://doi.org/10.3390/cells12101381>
122. Alexander, R. (2012). Understanding adipose-derived stromal vascular fraction (AD-SVF) cell biology and use on the basis of cellular, chemical, structural and paracrine components: a concise review. *J Prolother*, 4(1), e855–869.
123. Barry, F. P., & Murphy, J. M. (2004). Mesenchymal stem cells: clinical applications and biological characterization. *The International Journal of Biochemistry & Cell Biology*, 36(4), 568–584. <https://doi.org/10.1016/j.biocel.2003.11.001>
124. Kong, L., Zheng, L. Z., Qin, L., & Ho, K. K. W. (2017). Role of mesenchymal stem cells in osteoarthritis treatment. *Journal of Orthopaedic Translation*, 9, 89–103. <https://doi.org/10.1016/j.jot.2017.03.006>
125. Shoukrie, S. I., Venugopal, S., Dhanoa, R. K., Selvaraj, R., Selvamani, T. Y., Zahra, A., . . . Hamid, P. F. (2022). Safety and efficacy of injecting mesenchymal stem cells into a human knee joint to treat osteoarthritis: A systematic review. *Cureus*, 14(5), e24823. <https://doi.org/10.7759/cureus.24823>
126. Wirth, T., Parker, N., & Ylä-Herttuala, S. (2013). History of gene therapy. *Gene*, 525(2), 162–169. <https://doi.org/10.1016/j.gene.2013.03.137>
127. Li, K. C., & Hu, Y. C. (2015). Cartilage tissue engineering: recent advances and perspectives from gene regulation/therapy. *Advanced Healthcare Materials*, 4(7), 948–968. <https://doi.org/10.1002/adhm.201400773>
128. Lee, B., Parvizi, J., Bramlet, D., Romness, D. W., Guermazi, A., Noh, M., . . . Mont, M. A. (2020). Results of a Phase II study to determine the efficacy and safety of genetically engineered allogeneic human chondrocytes expressing TGF-β1. *Journal of Knee Surgery*, 33(2), 167–172. <https://doi.org/10.1055/s-0038-1676803>
129. Lee, H., Kim, H., Seo, J., Choi, K., Lee, Y., Park, K., . . . Choi, H. (2020). TissueGene-C promotes an anti-inflammatory micro-environment in a rat monoiodoacetate model of osteoarthritis via polarization of M2 macrophages leading to pain relief and structural improvement. *Inflammopharmacology*, 28. <https://doi.org/10.1007/s10787-020-00738-y>
130. Lee, M. C., Ha, C. W., Elmallah, R. K., Cherian, J. J., Cho, J. J., Kim, T. W., . . . Mont, M. A. (2015). A placebo-controlled randomised trial to assess the effect of TGF-β1-expressing chondrocytes in patients with arthritis of the knee. *The Bone & Joint Journal*, 97-b(7), 924–932. <https://doi.org/10.1302/0301-620x.97b7.35852>
131. Ha, C. W., Cho, J. J., Elmallah, R. K., Cherian, J. J., Kim, T. W., Lee, M. C., & Mont, M. A. (2015). A multicenter, single-blind, Phase IIa clinical trial to evaluate the efficacy and safety of a cell-mediated gene therapy in degenerative knee arthritis patients. *Human Gene Therapy Clinical Development*, 26(2), 125–130. <https://doi.org/10.1089/humc.2014.145>
132. Zhang, F., Wen, Y., & Guo, X. (2014). CRISPR/Cas9 for genome editing: progress, implications and challenges. *Human Molecular Genetics*, 23(R1), R40–46. <https://doi.org/10.1093/hmg/ddu125>
133. Karlsen, T., Fernández Pernas, P., Staerk, J., Caglayan, S., Brinchmann, J. (2016). Generation of IL1β-resistant chondrocytes using CRISPR-CAS genome editing (prevajalec, Trans.; št. 24). <https://doi.org/10.1016/j.joca.2016.01.581>
134. Bonato, A., Fisch, P., Ponta, S., Fercher, D., Manninen, M., Weber, D., . . . Zenobi-Wong, M. (2023). Engineering inflammation-resistant cartilage: Bridging gene therapy and tissue engineering. *Advanced Healthcare Materials*, 12(17), 2202271. <https://doi.org/10.1002/adhm.202202271>
135. Shapiro, S. A., Arthurs, J. R., Heckman, M. G., Bestic, J. M., Kazmerchak, S. E., Diehl, N. N., . . . O'Connor, M. I. (2019). Quantitative T2 MRI mapping and 12-month follow-up in a randomized, blinded, placebo controlled trial of bone marrow aspiration and concentration for osteoarthritis of the knees. *Cartilage*, 10(4), 432–443. <https://doi.org/10.1177/1947603518796142>

136. Kim, J. D., Lee, G. W., Jung, G. H., Kim, C. K., Kim, T., Park, J. H., . . . You, Y. B. (2014). Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee. *European Journal of Orthopaedic Surgery & Traumatology*, 24(8), 1505–1511. <https://doi.org/10.1007/s00590-013-1393-9>
137. Gibbs, N., Diamond, R., Sekyere, E. O., & Thomas, W. D. (2015). Management of knee osteoarthritis by combined stromal vascular fraction cell therapy, platelet-rich plasma, and musculoskeletal exercises: a case series. *Journal of Pain Research*, 8, 799–806. <https://doi.org/10.2147/jpr.S92090>
138. Van Pham, P., Bui, K. H.-T., Duong, T. D., Nguyen, N. T., Nguyen, T. D., Le, V. T., . . . Ngoc, N. K. (2014). Symptomatic knee osteoarthritis treatment using autologous adipose derived stem cells and platelet-rich plasma: a clinical study. *Biomedical Research and Therapy*, 1(1), 2. <https://doi.org/10.7603/s40730-014-0002-9>
139. Watanabe, S., Hosokawa, H., Sakamoto, T., Horii, M., Ono, Y., Kimura, S., . . . Sasho, T. Investigating the potential of multi-lineage differentiating stress-enduring cells for osteochondral healing. *Cartilage*, 0(0), 19476035241262020. <https://doi.org/10.1177/19476035241262020>
140. Havens, A. M., Shiozawa, Y., Jung, Y., Sun, H., Wang, J., McGee, S., . . . Taichman, R. S. (2013). Human very small embryonic-like cells generate skeletal structures, in vivo. *Stem Cells and Development*, 22(4), 622–630. <https://doi.org/10.1089/scd.2012.0327>
141. Chahal, J., Gómez-Aristizábal, A., Shestopaloff, K., Bhatt, S., Chaboureaud, A., Fazio, A., . . . Viswanathan, S. (2019). Bone marrow mesenchymal Stromal cell treatment in patients with osteoarthritis results in overall improvement in pain and symptoms and reduces synovial inflammation. *Stem Cells Translational Medicine*, 8(8), 746–757. <https://doi.org/10.1002/sctm.18-0183>
142. Freitag, J., Bates, D., Wickham, J., Shah, K., Huguenin, L., Tenen, A., . . . Boyd, R. (2019). Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: A randomized controlled trial. *Regenerative Medicine*, 14(3), 213–230. <https://doi.org/10.2217/rme-2018-0161>
143. Lee, M., Ha, C., Elmallah, R., Cherian, J., Cho, J., Kim, T., . . . Mont, M. (2015). A placebo-controlled randomised trial to assess the effect of TGF- β 1-expressing chondrocytes in patients with arthritis of the knee. *The bone & joint journal*, 97(7), 924–932.
144. DiNubile, M. J. (2008). Plasma gelsolin as a biomarker of inflammation. *Arthritis Research & Therapy*, 10(6), 124. <https://doi.org/10.1186/ar2547>
145. Tulpule, S., Jeyaraman, M., Jayakumar, T., Jeyaraman, N., Bapat, A., & Yadav, S. (2023). Gold-induced cytokine (GOLDIC®) Therapy in the management of knee osteoarthritis: An observational study. *Cureus*, 15(9), e46231. <https://doi.org/10.7759/cureus.46231>
146. Schneider, U., Lotzof, K., Murrell, W., Wachter, E., Hollands, P. (2021). Safety and efficacy of systemically administered autologous Gold-Induced Cytokines (GOLDIC®). *Cellr4*, 9. https://doi.org/10.32113/cellr4_20214_3132
147. Wang, C. J. (2012). Extracorporeal shockwave therapy in musculoskeletal disorders. *Journal of Orthopaedic Surgery and Research*, 7, 11. <https://doi.org/10.1186/1749-799x-7-11>
148. Stasinopoulos, D., & Johnson, M. I. (2005). Effectiveness of extracorporeal shock wave therapy for tennis elbow (lateral epicondylitis). *British Journal of Sports Medicine*, 39(3), 132–136. <https://doi.org/10.1136/bjsm.2004.015545>
149. Jeong, D., Lee, J. H., Lee, G. B., Shin, K. H., Hwang, J., Jang, S. Y., . . . Jang, W. Y. (2023). Application of extracorporeal shock-wave therapy to improve microcirculation in diabetic foot ulcers: A prospective study. *Medicine (Baltimore)*, 102(11), e33310. <https://doi.org/10.1097/md.0000000000003310>
150. Cacchio, A., Giordano, L., Colafarina, O., Rompe, J. D., Tavernese, E., Ioppolo, F., . . . Santilli, V. (2009). Extracorporeal shock-wave therapy compared with surgery for hypertrophic long-bone non-unions. *The Journal of Bone and Joint Surgery American*, 91(11), 2589–2597. <https://doi.org/10.2106/jbjs.H.00841>
151. Chen, Y. J., Wurtz, T., Wang, C. J., Kuo, Y. R., Yang, K. D., Huang, H. C., & Wang, F. S. (2004). Recruitment of mesenchymal stem cells and expression of TGF- β 1 and VEGF in the early stage of shock wave-promoted bone regeneration of segmental defect in rats. *Journal of Orthopaedic Research*, 22(3), 526–534. <https://doi.org/10.1016/j.orthres.2003.10.005>
152. Wess, O. J. (2008). A neural model for chronic pain and pain relief by extracorporeal shock wave treatment. *Urological research*, 36, 327–334.
153. Baranova, I. V., Bezsmertnyi, Y. A., Bezsmertnaya, H. V., Postovitenko, K. P., Iliuk, I. A., Gumeniuk, A. F., . . . Postovitenko, K. (2020). Analgetic effect of ozone therapy: myths of reality? *Polish Annals of Medicine*, 27(1), 62–67.
154. Tartari, A. P. S., Moreira, F. F., Pereira, M. C. D. S., Carraro, E., Cidral-Filho, F. J., Salgado, A. I., & Kerppers, I. I. (2020). Anti-inflammatory effect of ozone therapy in an experimental model of rheumatoid arthritis. *Inflammation*, 43(3), 985–993.
155. Sconza, C., Respizzi, S., Virelli, L., Vandenbulcke, F., Iacono, F., Kon, E., Di Matteo, B. (2020). Oxygen–ozone therapy for the treatment of knee osteoarthritis: A systematic review of randomized controlled trials. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, 36(1), 277–286.
156. Fernández-Cuadros, M. E., Pérez-Moro, O. S., Albaladejo-Florín, M. J., Tobar-Izquierdo, M. M., Magaña-Sánchez, A., Jiménez-Cuevas, P., Rodríguez-de-Cía, J. (2022). Intra articular ozone modulates inflammation and has anabolic effect on knee osteoarthritis: IL-6 and IGF-1 as pro-inflammatory and anabolic biomarkers. *Processes*, 10(1), 138.
157. Csaki, C., Mobasheri, A., & Shakibaei, M. (2009). Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1 β -induced NF- κ B-mediated inflammation and apoptosis. *Arthritis Research & Therapy*, 11, 1–17.
158. Clark, K. L., Sebastianelli, W., Flechsenhar, K. R., Aukermann, D. F., Meza, F., Millard, R. L., . . . Albert, A. (2008). 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain. *Current medical research and opinion*, 24(5), 1485–1496.
159. Schneider, U., Kumar, A., Murrell, W., Ezekwesili, A., Yurdi, N. A., & Maffulli, N. (2021). Intra-articular gold induced cytokine (GOLDIC®) injection therapy in patients with osteoarthritis of knee joint: a clinical study. *International Orthopaedics*, 45, 497–507.
160. Shi, L., Gao, F., Sun, W., Wang, B., Guo, W., Cheng, L., . . . Wang, W. (2017). Short-term effects of extracorporeal shock wave therapy on bone mineral density in postmenopausal osteoporotic patients. *Osteoporosis International*, 28, 2945–2953.
161. Feng, X., Beiping, L. (2017). Therapeutic Efficacy of Ozone Injection into the Knee for the Osteoarthritis Patient along with Oral Celecoxib and Glucosamine. *Journal of Clinical and Diagnostic Research*, 11(9), Uc01-uc03. <https://doi.org/10.7860/jcdr/2017/26065.10533>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.