
**UNIVERSITI PUTRA MALAYSIA**

# *REGENERATIVE POTENTIAL OF SECRETOME DERIVED FROM HUMAN EXFOLIATED DECIDUOUS TEETH STEM CELL ON OSTEOARTHRITIC CHONDROCYTES*

**SULEIMAN ALHAJI MUHAMMAD**

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By

**SULEIMAN ALHAJI MUHAMMAD**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy**

**April 2019**

**DEDICATION**

This thesis is dedicated to my treasured mother, father and to my entire household.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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**Chairman : Associate Professor Sharida Fakurazi, PhD**
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Osteoarthritis (OA) is a degenerative joint disease that remains a major clinical challenge due to limited intrinsic healing capacity of articular cartilage. The current therapies are only effective in symptoms or pain relief and offer short-term benefits. Recent studies utilising mesenchymal stem cells (MSCs) for the treatment of osteoarthritis have shown promising results. However, emerging evidence suggests that the therapeutic benefits of MSCs are mediated through paracrine mechanism due to multiple secreted factors that modulate the defective tissue to evoke reparative and regenerative processes. Thus, the objective of this thesis was to investigate the regenerative potential of the secretome of stem cells from human exfoliated deciduous teeth (SHED) for the treatment of osteoarthritis. To realise this objective, viable chondrocytes were isolated from cartilage using enzymatic digestion and characterised for the expression of the cartilage-specific phenotype. Secretome prepared from SHED was used to treat interleukin-1β (IL-1β)-stimulated chondrocytes as the OA *in vitro* model. The level of interleukin-10 (IL-10), transforming growth factor-β1 (TGF-β1) and interleukin-6 (IL-6) were assessed in stimulated chondrocytes incubated with secretome. Furthermore, the expression of aggrecan, collagen type 2, a disintegrin metalloproteinase with thrombospondin motifs 4 (ADAMTS4), matrix metalloproteinase-13 (MMP-13) and nuclear factor-kB (NF-kB) were also evaluated. Results showed that the number of viable chondrocytes yield per gram of cartilage was significantly higher in collagenase type II as compared with trypsin. Aggrecan and collagen type 2 were highly expressed in the isolated chondrocytes, indicating that the cells retained cartilage-specific phenotype. SHED highly expressed MSC markers (CD44, CD73, CD90, and CD105), but were negative for haematopoietic markers. SHED also showed protein expression of NANOG, OCT4 and SOX2 with differential subcellular localisation. Interestingly, the results also revealed that secretome significantly decreased ($p$<0.05) IL-6 level in osteoarthritic chondrocytes compared to serum-free medium (SFM) control group. The level of TGF-β1 was higher in cells

treated with secretome compared to stimulated cells incubated in SFM. Meanwhile, the level of IL-10 was significantly lowered in stimulated cells treated with secretome compared to stimulated cells incubated in SFM. However, IL-10 level in IL-1β-stimulated cells treated with secretome was similar to non-stimulated cells. Furthermore, the expression of MMP-13 and NF-kB was significantly downregulated in stimulated cells incubated with secretome when compared with stimulated cells incubated in SFM. Similarly, a decrease mRNA expression of ADAMTS4 was observed in osteoarthritic chondrocytes incubated with secretome compared to SFM. Secretome also increased the expression of aggrecan and collagen type 2 when compared with stimulated cells incubated in SFM. Thus, secretome may act to regenerate extracellular matrix proteins and modulate proteinases and inflammatory activities through inhibition of NF-kB. The results highlighted the potential use of secretome for cartilage repair and regeneration.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**POTENSI PENJANAAN SEMULA KONDROSIT OSTEOARTRITIS OLEH SEKRETOM DARIPADA SEL STEM GIGI SUSU MANUSIA**

Oleh

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Osteoartritis (OA) adalah penyakit sendi degeneratif yang masih kekal sebagai cabaran klinikal yang besar disebabkan oleh keupayaan penyembuhan intrinsik rawan artikular yang terhad. Terapi-terapi terkini hanya berkesan dalam meredakan simptom atau kesakitan dan hanya memberi manfaat jangka pendek. Kajian terbaru menggunakan sel stem mesenkimal (MSCs) untuk rawatan osteoartritis telah menunjukkan hasil yang memberangsangkan. Walau bagaimanapun, bukti-bukti kajian yang ditemui menunjukkan bahawa manfaat terapeutik MSCs adalah dipengaruhi oleh mekanisme parakrin yang disebabkan oleh perembesan pelbagai faktor yang memodulasikan tisu yang rosak untuk membangkitkan proses pembaikan dan penjanaan semula tisu baru. Oleh itu, objektif tesis ini adalah untuk mengkaji potensi penjanaan semula sel oleh sekretom dari sel stem gigi susu manusia (SHED) untuk rawatan osteoartritis. Untuk merealisasikan objektif ini, kondrosit yang berdaya hidup dipencilkan daripada tulang rawan menggunakan kaedah penghadaman enzim dan dicirikan untuk mengekspreskan fenotip- khusus tulang rawan. Sekretom disediakan daripada SHED untuk rawatan kondrosit yang telah dirangsang oleh interleukin-1β (IL-1β) sebagai model *in vitro* untuk OA. Paras interleukin-10 (IL-10), transforming growth factor -β1 (TGF-β1) dan interleukin-6 (IL-6) dinilai dalam kondrosit yang telah dirangsangkan dan dieramkan dengan sekretom. Tambahan pula, pengekspresan aggrecan, kolagen jenis 2, metalloproteinase disintegrin with thrombospondin motif 4 (ADAMTS4), matrix metalloproteinase-13 (MMP-13) dan nuklear factor-kB (NF-kB) juga turut dianalisa. Keputusan ujian menunjukkan bahawa bilangan kondrosit berdaya hidup yang dihasilkan daripada satu gram tulang rawan adalah jauh lebih tinggi dari kondrosit yang dihasilkan menggunakan kolagenase jenis II berbanding trypsin. Aggrecan dan kolagen jenis 2 diekspres pada kadar yang tinggi di dalam kondrosit terpencil, menunjukkan bahawa sel-sel tersebut mengekalkan fenotip-khusus tulang rawan. SHED mengekspreskan penanda MSC (CD44, CD73, CD90 dan CD105) pada kadar yang tinggi, tetapi tidak mengekspreskan penanda hematopoietik. SHED juga menunjukkan pengekspresan

NANOG, OCT4 dan SOX2 dengan pembezaan lokalisasi subsel. Menariknya, keputusan ujian juga menunjukkan sekretom menurunkan paras IL-6 ($p < 0.05$) dengan ketara dalam kondrosit osteoartritis berbanding dalam kumpulan kawalan media tanpa serum (SFM). Paras TGF-β1 adalah lebih tinggi dalam sel-sel yang dirawat dengan secretome berbanding sel-sel yang dirangsang yang dieram dalam SFM. Manakala, paras IL-10 berkurangan dengan ketara dalam sel-sel yang dirwat dengan sekretom berbanding sel-sel yang dirangsang yang dieram dalam SFM. Walau bagaimanapun, paras IL-10 dalam sel-sel yang telah dirangsang dengan IL-1β dan dirawat dengan sekretom adalah sama dengan kumpulan sel-sel yang tidak dirangsang dengan IL-1β. Tambahan pula, pengekspresan MMP-13 dan NF-kB telah menurun dengan ketara dalam sel-sel yang dirangsang yang dieram dengan secretome apabila dibandingkan dengan sel-sel yang dirangsang yang dieram dalam SFM. Begitu juga, penurunan pengekspresan mRNA daripada ADAMTS4 diperhatikan dalam kondrosit osteoartritis yang dieram dengan sekretom berbanding SFM. Sekretom juga meningkatkan pengekspresan aggrecan dan kolagen jenis 2 apabila dibandingkan dengan sel yang dirangsang yang dieram dalam SFM. Oleh itu, sekretom berkemungkinan bertindak untuk menjanakan semula protein matriks ekstrasel dan memodulasi proteinase dan aktiviti inflamasi melalui perencatan NF-kB. Hasil kajian ini menunjukkan potensi kegunaan sekretom dalam proses pembaikkan dan penjanaan semula tulang rawan.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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| | |
|---|---|
| ACAN | Aggrecan |
| ADAMTS | A disintegrin-metalloproteinase with thrombospondin motifs |
| ADP | Adenosine monophosphate |
| ADSC | Adipose-derived stem cell |
| ATP | Adenosine triphosphate |
| BMSC | Bone marrow mesenchymal stem cell |
| BSA | Bovine serum albumin |
| CCM | Complete culture medium |
| CD | Cluster of differentiation |
| Col II | Collagenase type II |
| COL1 | Collagen type 1 |
| COL 2 | Collagen type II |
| COX2 | Cyclooxygenase 2 |
| DPSCs | Dental pulp stem cells |
| DNA | Deoxyribonucleic acid |
| DNMT1 | DNA methyltransferase 1 |
| ECM | Extracellular matrix |
| ESC | Embryonic stem cell |
| EV | Extracellular vesicle |
| FGF | Fibroblast growth factor |
| GAG | Glycosaminoglycan |
| HGF | Hepatocyte growth factor |
| HMG | High mobility group |
| IDO | Indoleamine 2,3-dioxygenase |

| | |
|---|---|
| IGF | Insulin growth factor |
| IL | Interleukin |
| IL-1ra | Interleukin-1 receptor antagonist |
| iPSC | Induced-pluripotent stem cell |
| JNK | Jun N-terminal kinase |
| KLF4 | Kruppel-like factor |
| MAPK | Mitogen-activated protein kinase |
| MHCII | Major histocompatibility complex II |
| MMP-13 | Metalloproteinase-13 |
| NES | Nuclear export signal |
| NF-kB | Nuclear factor- kappa beta |
| NLS | Nuclear localisation signal |
| NO | Nitric oxide |
| OA | Osteoarthritis |
| OCT4 | Octamer-binding transcription factor 4 |
| PGE2 | Prostaglandin E2 |
| PHA | Phytohaemagglutinin |
| POU | Pit-Oct-Unc |
| PPAR-γ | Peroxisome proliferator-activated receptor-gamma |
| RNA | Ribonucleic acid |
| S48 | Secretome collected after 48 h of incubation |
| S72 | Secretome collected after 72 h of incubation |
| SHED | Stem cells from human exfoliated deciduous teeth |
| SFM | Serum-free medium |
| sHLA-G | Soluble human leucocyte antigen G |
| SOX | SRY (Sex-determining region Y)-box |

| | |
|---|---|
| SSEA | Stage-specific embryonic antigen |
| STAT3 | Signal transducer and activator of transcription 3 |
| TGF-β | Transforming growth factor-beta |
| TIMP | Tissue inhibitor of metalloproteinase |
| TKA | Total knee arthroplasty |
| TNF-α | Tumour necrosis factor alpha |
| TNFR | Tumour necrosis factor receptor |
| TSG-6 | Tumour factor-inducible gene 6 protein |
| VCAM-1-VLA | Vascular adhesion molecule 1-very late antigen |
| VEGF | Vascular endothelial growth factor |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the Study

Osteoarthritis (OA) is a musculoskeletal degenerative joint disease which is one of the prevailing causes of disability worldwide (Neogi, 2013). The disease is characterised by degeneration of cartilage, subchondral bone sclerosis and synovitis accompanied by pain and activity limitation (Burr & Gallant, 2012; de Lange-Brokaar et al., 2012; Muratovic et al., 2015). Osteoarthritis affects all weight-bearing joints that are often under mechanical stress (Buckwalter & Martin, 2006). The most common symptoms of osteoarthritis are swelling, stiffness and pain in the affected joint due to the damaged of articular cartilage (Madry et al., 2012).

It is well-established facts that the aetiology of osteoarthritis is multifactorial, with metabolic, mechanical and inflammatory factors being the major causes. Ageing, genetic predisposition, obesity, mechanical injury and joint trauma are the various contributing factors that have been implicated in osteoarthritis (Dahaghin et al., 2009; Haq et al., 2010). Cartilage and chondrocytes are the major components that are actively involved in the degeneration process coupled with inflammatory factors in osteoarthritis (Maldonado & Nam, 2013). Inflammatory factors cause imbalances between synthesis and degradation of extracellular matrix in favour of degradation that altered the biomechanical milieu of the chondrocytes (Maldonado & Nam, 2013).

In osteoarthritis, the activity of matrix metalloproteinase-13 (MMP-13) is increased which is capable of depleting collagen type 2 as well as proteoglycans, collagen type IV, collagen type IX, perlecan and osteonectin in articular cartilage (Wang et al., 2013). Spontaneous OA-like articular cartilage destruction has also been reported in transgenic mice overexpressing collagen type X and MMP-13 (Wu et al., 2008), suggesting a direct relationship between increased MMP-13 and articular cartilage destruction. These findings show that MMPs, catabolic enzymes play a key role in the development and progression of OA. Therefore, the development of therapeutic strategies targeting these enzymes could reduce the articular cartilage degradation in OA.

Traditionally, OA is associated with older age and is considered degenerative arthritis. However, with the increasing number of younger populations presenting with symptoms of osteoarthritis and the involvement of inflammatory mediators in aggravating the disease that can lead to joint failure, hence the term ‘degenerative disease of wear and tear’ may be misleading (Ackerman et al., 2017; Sutton & Holloway, 2013). Athletes and younger individuals who engage most of their time in recreational and occupational activities are more susceptible to joint injuries and are at higher risk of developing OA (Amoako & Pujalte, 2014). Sports that involve repetitive exposure of joint to high levels of impact and loading increase the likelihood

of degeneration of articular cartilage, leading to a clinical manifestation of OA (Buckwalter & Lane, 1997). The impact of OA on younger people is the ability to work and retain a job. Individuals with arthritis are at increased risk of not being part of the labour force. As such, it could result in short- and longer-term economic consequences. Among the work-related impacts of osteoarthritis include considerable workplace limitations, increased likelihood of sick leave and a greater chance of job loss as a result of illness or disability (Ackerman et al., 2017).

The initial management of the disease is non-surgical strategy such as patient education, weight loss, exercise, nutraceuticals, analgesic and non-steroidal anti-inflammatory drugs as well as intra-articular injections (Mushtaq et al., 2011; Sutton & Holloway, 2013). Unfortunately, these measures often offer inadequate and short-term benefit. Due to the lack of effective treatments, total knee arthroplasty is often recommended as the last resort in end-stage OA patients (Kristjánsson & Honsawek, 2014). In younger patients, total knee arthroplasty is associated with a greater risk of early failure that may require revision surgery (Sutton & Holloway, 2013). Therefore, it is imperative to search for a treatment strategy that could overcome these limitations. It has been shown that the rates of implant failure resulting in revision surgery in younger patients are higher compared to older patients (Paxton et al., 2010). Furthermore, the rates of revision surgery in younger patients would increase due to a higher risk of total knee arthroplasty (TKA) failure and the longer life expectancy in this age population (Losina & Katz, 2012). Postoperative complications such as infections, arthrofibrosis, heterotrophic ossifications culminate to stiffness for which a revision surgery might be required (Schiavone et al., 2009).

At present, there are no effective treatment strategies that reverse damaged tissue integrity (Mobasheri et al., 2014). Cellular treatment, such as autologous chondrocyte implantation has been introduced into the clinical domain which is capable of repairing and restoring cartilage, but often leads to poor outcome due to insufficient self-renewal and regenerative capability of chondrocytes (Vasiliadis & Wasiak, 2010). Taken together, non-invasive therapeutic strategy capable of repairing and regenerating damaged articular cartilage would in no doubt reduce the socio-economic burden of OA.

*In vitro* model of osteoarthritis is important as it would provide the basis for the advancement of research into the mechanism underlying the origins of the disease for testing of potential therapeutics (Johnson et al., 2016). Since there is a shift towards refining, reducing and replacing (3R) the use of animals in preclinical studies has made *in vitro* models of OA desirable (Johnson et al., 2016; Madden et al., 2012).

Stem cells from human exfoliated deciduous teeth (SHED) are multipotent cells present in the dental pulp, a soft connective tissue within the teeth. Dental pulp is an attractive source of mesenchymal stem cells due to the presence of a large number of cells with high proliferation rate and less invasive methods of isolation compared to bone marrow aspiration (Gronthos et al. 2000; Xin et al., 2013).

Mesenchymal stem cells (MSCs) have been under investigation as a treatment option in cartilage regeneration because of their differentiation and self-renewal capabilities. Intra-articular injection of MSCs to the affected joint only sometimes differentiate into chondrocytes to produce extracellular matrix (van Buul et al., 2012). This suggests that different mechanisms other than differentiation are involved in the repair of damaged cartilage caused by OA. A number of bioactive factors secreted by the MSCs such as transforming growth factor-beta (TGF-β), interleukin 10 (IL-10), indoleamine 2,3-dioxygenase (IDO), hepatocyte growth factor (HGF) and insulin growth factor (IGF) have been reported to participate in immune regulation (van Buul et al., 2012). Similarly, MMPs and tissue inhibitors of metalloproteinases (TIMPs) have been suggested to modulate and participate in extracellular turnover (Lozito & Tuan, 2011).

Secretome (conditioned medium) is a cell culture supernatant that contains secreted factors of stem cells that are produced by preconditioning the cells to serum-free medium, hypoxic condition, genetic manipulation or pharmacological treatment. The beneficial effects of secretome from stem cells without cell engraftment suggest that secreted factors may be involved in tissue regeneration (Vishnubhatla et al., 2014; Yang et al., 2013). Studies have reported that apart from soluble factors, stem cells release extracellular vesicles (microvesicles and exosomes) which produce comparable biological activity to the stem cells (Chen et al., 2017; Lai et al., 2015; Xin et al., 2013). These secreted factors play an essential role in cell to cell communication and are capable of altering the activity of target cells through surface receptor interactions (Akyurekli et al., 2015; Vishnubhatla et al., 2014). Dental pulp stem cells (DPSC) and SHED reside in the cell-rich zone of the dental pulp, which is a very good source to generate a large volume of secretome due to high proliferation capacity. A remarkable feature of secretome from DPSC/SHED is high proportions of secreted factors when compared with secretome from bone marrow stem cells and adipose-derived stem cells (Ahmed et al., 2016; Yamaguchi et al., 2015).

This study was designed to explore the therapeutic benefit of secretome from SHED in osteoarthritic chondrocytes. To realise this objective, chondrocytes were stimulated with interleukin 1β (IL-1β) and then treated with secretome derived from SHED. To depict possible mechanism(s) of crosstalk between catabolic and anabolic factors in modulating tissue regeneration, the expression of collagen type 2, aggrecan, a disintegrin, and metalloproteinase with thrombospondin motifs 4 (ADAMTS4), MMP 13, as well as nuclear factor-kappaB (NF-kB) were evaluated.

## 1.2 Problem Statement

Osteoarthritis, a degenerative disease of the joint that involves cartilage deterioration is one of the leading causes of pain and disability worldwide. The disease is among the most challenging diseases of the joint due to the inadequate intrinsic healing capacity of articular cartilage. Despite a global increase in the incidence and morbidity associated with osteoarthritis, there is no cure for it. The available pharmacological therapies are only effective in pain and symptom reliefs. Cell-based therapies such as autologous chondrocytes implantation (ACI) and MSC implantation have shown

promising outcomes in preclinical and some clinical studies (Borakati et al., 2018; Wang et al., 2017; Xia et al., 2015). However, these treatments are not without drawbacks. The limitations of ACI include the necessity for extra surgery, availability of adequate chondrocytes for implantation, and maintenance of chondrocytes phenotype during monolayer culture expansion. On the other hand, MSC therapy has its own challenges, ranging from the paucity of standardised functional characterisation that hinders large-scale production of MSCs with consistent biological activities for clinical trials (Lee & Wang., 2017). Selection of appropriate cell dose for implantation to give desirable outcome is also another challenge, as large variations in dosage exist between studies. Furthermore, emerging evidence suggests that the therapeutic efficacy of MSCs is attributed to the paracrine actions of their secretions. Exploring the mechanisms that allow these bioactive factors to modulate the microenvironment and extracellular matrix turnover for tissue regeneration could be effective and less invasive therapeutic strategies to combat osteoarthritis.

## 1.3 Justification of the Study

Osteoarthritis is the fourth leading cause of pain and disability worldwide (Fransen et al., 2011). It is estimated that about 15% of the world population suffers from the disease and 65 % of them are aged 60 years and older (Alekseeva & Nasonov, 2013). OA is fast becoming a significant economic and medical burden to the society due to increase in the ageing population and the costs of treatment. The affected individuals experience activity limitations that have a consequential burden in quality of life and economy. With increasing incidence of OA in the younger population and number of ageing population, new and less invasive treatment strategies that would be affordable are crucial to reducing the socioeconomic burden of osteoarthritis. Reports indicate that secretome from bone marrow, adipose and embryonic tissues derived MSC have been shown to possess therapeutic benefit in OA (Platas et al., 2013; van Buul et al., 2012; Wang et al., 2017). SHED represents ideal stem cells due to high proliferative capacity for the production of secretome for cartilage regeneration. Thus, secretome is a potential alternative strategy to stem cell treatment that merits investigating the mechanism of its actions for tissue regeneration. Due to increasing evidence of the role of secreted factors as a therapeutic efficacy of stem cells, this project sought to investigate the regenerative potential of the secretome of stem cells from human deciduous teeth in osteoarthritic chondrocytes.

## 1.4 General Objective

To determine the regenerative potential of secretome from stem cells of human exfoliated deciduous teeth in osteoarthritic chondrocytes.

The specific objectives were:

- to isolate and characterise chondrocytes from human articular cartilage,
- to characterise SHED and determine the level of cytokines in SHED-derived secretome and
- to study the effect of SHED-derived secretome in regulating the extracellular matrix proteins and proteinases in osteoarthritic chondrocytes.

## 1.5 Hypotheses

**Ho:** SHED secretome will not contain a significant amount of secreted factors to regenerate cartilage-specific phenotype in osteoarthritic chondrocytes
**Ha:** SHED secretome will contain a significant amount of secreted factors to regenerate cartilage-specific phenotype in osteoarthritic chondrocytes.

## REFERENCES


Abdullah, M. F., Abdullah, S. F., Omar, N. S., Mahmood, Z., Fazliah Mohd Noor, S. N., Kannan, T. P., & Mokhtar, K. I. (2014). Proliferation rate of stem cells derived from human dental pulp and identification of differentially expressed genes. *Cell Biology International*, 38(5),582–590.

Abedin, M., & King, N. (2010). Diverse evolutionary paths to cell adhesion. *Trends in Cell Biology*, 20(12),734–742.

Ackerman, I., Kemp, J.L., Crossley, K.M., Culvenor, A.G., & Hinman, R.S. (2017). Hip and knee osteoarthritis affects younger people too. *Journal of Orthopaedic and Sports Physical Therap,* 47(2), 67–79.

Ahmed, N.E.B., Murakami, M., Hirose, Y., & Nakashima, M. (2016). Therapeutic potential of dental pulp stem cell secretome for Alzheimer's disease treatment: An in vitro study. *Stem Cells International*, 2016,1–11.

Aida, Y., Maeno, M., Suzuki, N., Shiratsuchi, H., Motohashi, M., & Matsumura, H. (2005). The effect of IL-1beta on the expression of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in human chondrocytes. *Life Sciences*, *77*(25),3210–3221.

Akgun, I., Unlu, M. C., Erdal, O. A., Ogut, T., Erturk, M., Ovali, E., Kantarci, E., Caliskan, G., & Akgun, Y. (2015). Matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous chondrocyte implantation in the treatment of chondral defects of the knee: a 2-year randomized study. *Archives of Orthopaedic and Trauma Surgery*, 135(2), 251–263.

Akiyama, H. (2008). Control of chondrogenesis by the transcription factor Sox9. *Modern Rheumatology*, 18(3),213–219.

Akiyama, S. K. (1996). Integrins in cell adhesion and signaling. *Human Cell*, 9(3),181–186.

Akkiraju, H., & Nohe, A. (2015). Role of chondrocytes in cartilage formation, progression of osteoarthritis and cartilage regeneration. *Journal of Developmental Biology*. 3(4),177–192.

Akpinar, G., Kasap, M., Aksoy, A., Duruksu, G., Gacar, G., & Karaoz, E. (2014). Phenotypic and proteomic characteristics of human dental pulp derived mesenchymal stem cells from a natal, an exfoliated deciduous, and an impacted third molar tooth. *Stem Cells International*, 2014,457059.

Akyurekli, C., Le, Y., Richardson, R. B., Fergusson, D., Tay, J., & Allan, D. S. (2015). A systematic review of preclinical studies on the therapeutic potential of mesenchymal stromal cell-derived microvesicles. *Stem Cell Reviews*, 11(1), 150–160.

Alekseeva, L.I., & Nasonov, E.L. (2013). Osteoarthritis and comorbidities. *Medicographia*, 35, 152-157

Alford, J. W., & Cole, B. J. (2005). Cartilage restoration, part 1: basic science, historical perspective, patient evaluation, and treatment options. *The American Journal of Sports Medicine*, 33(2), 295–306.

Alkaisi, A., Ismail, A. R., Mutum, S. S., Ahmad, Z.A.R., Masudi, S., & Abd Razak, N. H. (2013). Transplantation of human dental pulp stem cells: enhance bone consolidation in mandibular distraction osteogenesis. *Journal of Oral and Maxillofacial Surgery, 71*(10), 1758.e1-13.

Alleman, M., Low, E., Truong, K., Huang, E., Hill, C. K., Chen, T. Y., Deaton, M., & Kingsley, K. (2013). Dental pulp-derived stem cells (DPSC) differentiation in vitro into odontoblast and neuronal progenitors during cell passaging is associated with alterations in cell survival and viability. *International Journal of Medicine and Biomedical Research*, *2*(2), 133–141.

Allickson, J. G., Sanchez, A., Yefimenko, N., Borlongan, C. V., & Sanberg, P. R. (2011). Recent Studies Assessing the Proliferative Capability of a Novel Adult Stem Cell Identified in Menstrual Blood. *The Open Stem Cell Journal,* 3 (2011), 4–10.

Amoako, A.O., & Pujalte, G.G.A. (2014). Osteoarthritis in young, active, and athletic individuals. Clinical Medicine Insights: *Arthritis and Musculoskeletal Disorders,* 7, 27-32.

Ando, Y., Matsubara, K., Ishikawa, J., Fujio, M., Shohara, R., Hibi, H., Ueda, M., & Yamamoto, A. (2014). Stem cell-conditioned medium accelerates distraction osteogenesis through multiple regenerative mechanisms. *Bone*, *61*, 82–90.

Annibali, S., Cristalli, M. P., Tonoli, F., & Polimeni, A. (2014). Stem cells derived from human exfoliated deciduous teeth: a narrative synthesis of literature. *European Review for Medical and Pharmacological Sciences*, 18(19), 2863–2881.

Atlasi, Y., Mowla, S. J., Ziaee, S.A.M., Gokhale, P.J., & Andrews, P. W. (2008). OCT4 spliced variants are differentially expressed in human pluripotent and nonpluripotent cells. *Stem Cells,* 26(12), 3068–3074.

Attur, M., Yang, Q., Shimada, K., Tachida, Y., Nagase, H., Mignatti, P., Statman, L., Palmer, G., Kirsch, T., Beier, F., & Abramson, S. B. (2015). Elevated expression of periostin in human osteoarthritic cartilage and its potential role in matrix degradation via matrix metalloproteinase-13. *The FASEB Journal*, 29(10), 4107–4121.

Avilion, A.A., Nicolis, S. K., Pevny, L. H., Perez, L., Vivian, N., & Lovell-Badge, R. (2003). Multipotent cell lineages in early mouse development depend on SOX2 function. *Genes and Development*, 17(1), 126–140.

Babaei, P., Soltani Tehrani, B.,& Alizadeh, A. (2012). Transplanted bone marrow mesenchymal stem cells improve memory in rat models of Alzheimer's disease. *Stem Cells International*, 2012, 369417

Baghaban E.M., Taghiyar, L., & Falahi, F. (2009). Quantitative analysis of the proliferation and differentiation of rat articular chondrocytes in alginate 3D culture. *Iranian Biomedical Journal*, 13(3), 153–160.

Baillie, R., Itinteang, T., Yu, H.H., Brasch, H.D., Davis, P.F., & Tan, S. T. (2016). Cancer stem cells in moderately differentiated oral tongue squamous cell carcinoma. *Journal of Clinical Pathology*, 69(8), 742–744.

Baker-LePain, J. C., Nakamura, M.C., & Lane, N. E. (2011). Effects of inflammation on bone: an update. *Current Opinion in Rheumatology*, 23(4), 389–395.

Baltus, G. A., Kowalski, M. P., Zhai, H., Tutter, A. V., Quinn, D., Wall, D., & Kadam, S. (2009). Acetylation of Sox2 induces its nuclear export in embryonic stem cells. *Stem Cells*, 27(9), 2175–2184.

Baraniak, P.R., & McDevitt, T.C. (2010). Stem cell paracrine actions and tissue regeneration. *Regenerative Medicine*, 5(1), 121–143.

Barrachina, L., Remacha, A. R., Romero, A., Vázquez, F. J., Albareda, J., Prades, M., Ranera, B., Zaragoza, P., Martin-Burriel, I., & Rodellar, C. (2016). Effect of inflammatory environment on equine bone marrow derived mesenchymal stem cells immunogenicity and immunomodulatory properties. *Veterinary Immunology and Immunopathology*, 171, 57–65.

Baugé, C., Girard, N., Lhuissier, E., Bazille, C., & Boumediene, K. (2013). Regulation and role of TGFβ signaling pathway in aging and osteoarthritis joints. *Aging and Disease*, 5(6), 394–405.

Benam, K. H., Dauth, S., Hassell, B., Herland, A., Jain, A., Jang, K.J., Karalis, K., Kim, H.J., MacQueen, L., Mahmoodian, R., Musah, S., Torisawa, Y.S., & Ingber, D. E. (2015). Engineered in vitro disease models. *Annual Review of Pathology*, 10, 195–262.

Benelli, R., Lorusso, G., Albini, A. and Noonan, D. M. (2006). Cytokines and chemokines as regulators of angiogenesis in health and disease. *Current Pharmaceutical Design*, 12(24), 3101–3115.

Benito, M. J., Veale, D. J., FitzGerald, O., van den Berg, W. B. and Bresnihan, B. (2005). Synovial tissue inflammation in early and late osteoarthritis. *Annals of the Rheumatic Diseases*. 64(9), 1263–1267.

Bhang, S.H., Lee, S., Shin, J.Y., Lee, T.J., Jang, H.K., & Kim, B.S. (2014). Efficacious and clinically relevant conditioned medium of human adipose-derived stem cells for therapeutic angiogenesis. *Molecular Therapy*, 22(4), 862–872.

Bianco, P. (2014). "Mesenchymal" stem cells. *Annual Review of Cell and Developmental Biology*, 30, 677–704.

Blanco, F. J., Geng, Y., & Lotz, M. (1995). Differentiation-dependent effects of IL-1 and TGF-beta on human articular chondrocyte proliferation are related to inducible nitric oxide synthase expression. *The Journal of Immunology*, 154(8), 4018–4026.

Botelho, J., Cavacas, M. A., Machado, V., & Mendes, J. J. (2017). Dental stem cells: recent progresses in tissue engineering and regenerative medicine. *Annals of Medicine*, 49(8), 644–651.

Boyer, L. A., Lee, T. I., Cole, M. F., Johnstone, S. E., Levine, S. S., Zucker, J. P., Guenther, M.G., Kumar, R.M., Murray, H.L., Jenner, R.G., Gifford, D.K., Melton, D.A., Jaenisch, R., & Young, R. A. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell*, 122(6), 947–956.

Borakati, A., Mafi, R., Mafi, P., & Khan, W.S. (2018). A systematic review and meta-analysis of clinical trials of mesenchymal stem cell therapy for cartilage repair. *Current Stem Cell Research and Therapy*, 13(3), 215–225.

Bruno, S., Grange, C., Collino, F., Deregibus, M. C., Cantaluppi, V., Biancone, L., Tetta, C., & Camussi, G. (2012). Microvesicles derived from mesenchymal stem cells enhance survival in a lethal model of acute kidney injury. *PloS One*, 7(3), e33115.

Buckwalter, J.A., & Lane, N.E. (1997). Athletics and osteoarthritis. *American Journal of Sports Medicine,* 25, 873-881.

Buckwalter, J. A., & Martin, J. A. (2006). Osteoarthritis. *Advanced Drug Delivery Reviews*, *58*(2), 150–167.

Burr, D.B., & Gallant, M.A. (2012). Bone remodelling in osteoarthritis. *Nature Reviews in Rheumatology*, 8(11), 665-673

Burrage, P. S., Mix, K.S., & Brinckerhoff, C. E. (2006). Matrix metalloproteinases: role in arthritis. *Frontiers in Bioscience,* 11, 529–543.

Butcher, E. C., & Picker, L. J. (1996). Lymphocyte homing and homeostasis. *Science,* 272(5258), 60–66.

Cai, J., Li, W., Su, H., Qin, D., Yang, J., Zhu, F., Xu, J., He, W., Guo, X., Labuda, K., Peterbauer, A., Wolbank, S., Zhong, M., Li, Z., Wu, W., So, KF, Redi, H., Zheng, L., Esteban, M.A., & Pei, D. (2010). Generation of human induced pluripotent stem cells from umbilical cord matrix and amniotic membrane mesenchymal cells. *The Journal of Biological Chemistry*, 285(15), 11227–11234.

Campo, G. M., Avenoso, A., D'Ascola, A., Scuruchi, M., Prestipino, V., Calatroni, A., & Campo, S. (2012). Hyaluronan in part mediates IL-1beta-induced inflammation in mouse chondrocytes by up-regulating CD44 receptors. *Gene*, *494*(1), 24–35.

Carlin, R., Davis, D., Weiss, M., Schultz, B., & Troyer, D. (2006). Expression of early transcription factors Oct-4, Sox-2 and Nanog by porcine umbilical cord (PUC) matrix cells. *Reproductive Biology and Endocrinology*, 4, 8.

Cauffman, G., Liebaers, I., Van Steirteghem, A., & Van de Velde, H. (2006). POU5F1 isoforms show different expression patterns in human embryonic stem cells and preimplantation embryos. *Stem Cells,* 24(12), 2685–2691.

Centola, M., Tonnarelli, B., Hendriks, J., van den Doel, M., Feliciano, S., Papadimitropoulos, A.,Piccinini, E., Geurts, J., Martin, I., & Barbero, A. (2015). An improved cartilage digestion method for research and clinical applications. *Tissue Engineering Part C: Methods*, 21(4), 394–403.

Chabane, N., Zayed, N., Benderdour, M., Martel-Pelletier, J., Pelletier, J.-P., Duval, N., & Fahmi, H. (2009). Human articular chondrocytes express 15-lipoxygenase-1 and -2: potential role in osteoarthritis. *Arthritis Research and Therapy*, *11*(2), R44.

Chan, C.K., Wu, K.H., Lee, Y.S., Hwang, S.M., Lee, M.S., Liao, S.K., Cheng, E.H., See, L.C., Tsai, C.N., Kuo, M.L., & Huang, J.L. (2012). The comparison of interleukin 6-associated immunosuppressive effects of human ESCs, fetal-type MSCs, and adult-type MSCs. *Transplantation*, 94(2), 132–138.

Chang, D. F., Tsai, S. C., Wang, X. C., Xia, P., Senadheera, D., & Lutzko, C. (2009). Molecular characterization of the human NANOG protein. *Stem Cells,* 27(4), 812–821.

Charo, I.F., & Ransohoff, R. M. (2006). The many roles of chemokines and chemokine receptors in inflammation. *The New England Journal of Medicine*, 354(6), 610–621.

Chen, B., Li, Q., Zhao, B., & Wang, Y. (2017). Stem cell-derived extracellular vesicles as a novel potential therapeutic tool for tissue repair. *Stem Cells Translational Medicine*, 6(9), 1753–1758.

Chen, D., Fu, W., Zhuang, W., Lv, C., Li, F., & Wang, X. (2017). Therapeutic effects of intranigral transplantation of mesenchymal stem cells in rat models of Parkinson's disease. *Journal of Neuroscience Research*, 95(3), 907–917.

Chen, K., Xiong, H., Xu, N., Shen, Y., Huang, Y., & Liu, C. (2014). Chondrogenic potential of stem cells from human exfoliated deciduous teeth in vitro and in vivo. *Acta Odontologica Scandinavica*, 72(8), 664–672.

Chen, X., Shao, H., Zhi, Y., Xiao, Q., Su, C., Dong, L., Liu, X., Li, X., & Zhang, X. (2016). CD73 pathway contributes to the immunosuppressive ability of mesenchymal stem cells in intraocular autoimmune responses. *Stem Cells and Development*, *25*(4), 337–346.

Chimal-Monroy, J., Rodriguez-Leon, J., Montero, J. A., Gañan, Y., Macias, D., Merino, R.., & Hurle, J. M. (2003). Analysis of the molecular cascade responsible for mesodermal limb chondrogenesis: Sox genes and BMP signaling. *Developmental Biology*, *257*(2), 292–301.

Chung, C., Mesa, J., Miller, G.J., Randolph, M. A., Gill, T.J., & Burdick, J.A. (2006). Effects of auricular chondrocyte expansion on neocartilage formation in photocrosslinked hyaluronic acid networks. *Tissue Engineering*, *12*(9), 2665–2673.

Chung, L., Dinakarpandian, D., Yoshida, N., Lauer-Fields, J. L., Fields, G.B., Visse, R., & Nagase, H. (2004). Collagenase unwinds triple-helical collagen prior to peptide bond hydrolysis. *The EMBO Journal*, 23(15), 3020–3030.

Civinini, R., Nistri, L., Martini, C., Redl, B., Ristori, G., & Innocenti, M. (2013). Growth factors in the treatment of early osteoarthritis. *Clinical Cases in Mineral and Bone Metabolism*, 10(1), 26–29.

Clements, D.N., Carter, S. D., Innes, J. F., Ollier, W. E. and Day, P. J. (2006). Analysis of normal and osteoarthritic canine cartilage mRNA expression by quantitative polymerase chain reaction. *Arthritis Research and Therapy*, 8(6), R158.

Cooper, C., Dennison, E., Edwards, M., & Litwic, A. (2013). Epidemiology of osteoarthritis. *Medicographia*. 35, 145-151

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., Bridgett, L., William, S., Guillemin, F., Hill, C.L., Laslett, L.L., Jones, G., Cicuttini, F., Osborne, R., Vos, T., Buchbinder, R., Woolf, A., & March, L. (2014). The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, 73(7), 1323-1330

Dahaghin, S., Tehrani-Banihashemi, S.A., Faezi, S.T., Jamshidi, A.R., & Davatchi, F. (2009). Squatting, sitting on the floor, or cycling: are life-long daily activities risk factors for clinical knee osteoarthritis? Stage III results of a community-based study. *Arthritis and Rheumatism*, 61(10), 1337–1342.

Daheshia, M., & Yao, J. Q. (2008). The interleukin 1beta pathway in the pathogenesis of osteoarthritis. *The Journal of Rheumatology,* 35(12), 2306–2312.

Daltoe, F.P., Mendonca, P.P., Mantesso, A., & Deboni, M.C.Z. (2014). Can SHED or DPSCs be used to rpair/regenerate non-dental tissues? A systematic review of in vivo studies. *Brazilian Oral Research,* 28 (1), 1-7

Darling, E.M. & Athanasiou, K. A. (2005). Rapid phenotypic changes in passaged articular chondrocyte subpopulations. *Journal of Orthopaedic Research*. 23(2), 425–432.

Darr, H., Mayshar, Y., & Benvenisty, N. (2006). Overexpression of NANOG in human ES cells enables feeder-free growth while inducing primitive ectoderm features. *Development,* 133(6), 1193–1201.

Davidson, E. N. B., Vitters, E. L., van der Kraan, P.M., & van den Berg, W. B. (2006). Expression of transforming growth factor- β (TGFβ) and the TGFβ signalling molecule SMAD- 2P in spontaneous and instability- induced osteoarthritis: role in cartilage degradation, chondrogenesis and osteophyte formation. *Annals of the Rheumatic Diseases*, 65(11), 1414–1421.

De Becker, A., & Riet, I. V. (2016). Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy? *World Journal of Stem Cells*, 8(3), 73–87.

de Hooge, A. S. K., van de Loo, F. A. J., Bennink, M. B., Arntz, O. J., de Hooge, P., & van den Berg, W. B. (2005). Male IL-6 gene knock out mice developed more advanced osteoarthritis upon aging. *Osteoarthritis and Cartilage*, 13(1), 66–73.

de Lange-Brokaar, B. J. E., Ioan-Facsinay, A., van Osch, G. J. V. M., Zuurmond, A.-M., Schoones, J., Toes, R.E.M., Huizinga, T.W., & Kloppenburg, M. (2012). Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. *Osteoarthritis and Cartilage*, 20(12), 1484–1499.

de Oliveira Bravo, M., Carvalho, J.L., & Saldanha-Araujo, F. (2016). Adenosine production: a common path for mesenchymal stem-cell and regulatory T-cell-mediated immunosuppression. *Purinergic Signalling*, 12(4), 595–609.

Deasy, B. M., Gharaibeh, B. M., Pollett, J. B., Jones, M. M., Lucas, M. A., Kanda, Y., & Huard, J. (2005). Long-term self-renewal of postnatal muscle-derived stem cells. *Molecular Biology of the Cell*, 16(7), 3323–3333.

Delon, I., & Brown, N. H. (2009). The integrin adhesion complex changes its composition and function during morphogenesis of an epithelium. *Journal of Cell Science*, 122(23), 4363–4374.

Diaz-Romero, J., Nesic, D., Grogan, S.P., Heini, P., & Mainil-Varlet, P. (2008). Immunophenotypic changes of human articular chondrocytes during monolayer culture reflect bona fide dedifferentiation rather than amplification of progenitor cells. *Journal of Cellular Physiology*, 214(1), 75–83.

Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D.I., & Horwitz, E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy,* 8(4), 315–317.

Dreier, R. (2010). Hypertrophic differentiation of chondrocytes in osteoarthritis: the developmental aspect of degenerative joint disorders. *Arthritis Research and Therapy*. 12(5), 216.

Du, L., Lv, R., Yang, X., Cheng, S., Ma, T., & Xu, J. (2016). Hypoxic conditioned medium of placenta-derived mesenchymal stem cells protects against scar formation. *Life Sciences*, *149*, 51–57.

Duelen, R., & Sampaolesi, M. (2017). Stem cell technology in cardiac regeneration: A pluripotent stem cell promise. *EBioMedicine*, 16, 30–40.

Eirin, A., Zhu, X.-Y., Puranik, A. S., Woollard, J. R., Tang, H., Dasari, S., Lerman, A., van Wijnen, A.J., & Lerman, L.O. (2016). Comparative proteomic analysis of extracellular vesicles isolated from porcine adipose tissue-derived mesenchymal stem/stromal cells. *Scientific Reports,* 6, 36120.

El-Hefnawy, T., Raja, S., Kelly, L., Bigbee, W. L., Kirkwood, J.M., Luketich, J.D., & Godfrey, T. E. (2004). Characterization of amplifiable, circulating RNA in plasma and its potential as a tool for cancer diagnostics. *Clinical Chemistry*. 50(3), 564–573.

Ellman, M. B., An, H. S., Muddasani, P., & Im, H.-J. (2008). Biological impact of the fibroblast growth factor family on articular cartilage and intervertebral disc homeostasis. *Gene*, 420(1), 82–89.

El Mansouri, F.E., Chabane, N., Zayed, N., Kapoor, M., Benderdour, M., Martel-Pelletier, J. Pelletier, J.P., Duval, N., & Fahmi, H. (2011). Contribution of H3K4 methylation by SET-1A to interleukin-1-induced cyclooxygenase 2 and inducible nitric oxide synthase expression in human osteoarthritis chondrocytes. *Arthritis and Rheumatism*, *63*(1). 168-179.

Enomoto, H., Furuichi, T., Zanma, A., Yamana, K., Yoshida, C., Sumitani, S., Yamamoto, H., Enomoto-Iwamoto, M. Iwamoto, M., & Komori, T. (2004). Runx2 deficiency in chondrocytes causes adipogenic changes in vitro. *Journal of Cell Science*, 117(3), 417–425.

Erices, A. A., Allers, C. I., Conget, P. A., Rojas, C.V., & Minguell, J. J. (2003). Human cord blood-derived mesenchymal stem cells home and survive in the marrow of immunodeficient mice after systemic infusion. *Cell Transplantation*, 12(6), 555–561.

Ezeh, U.I., Turek, P.J., Reijo, R.A., & Clark, A. T. (2005). Human embryonic stem cell genes OCT4, NANOG, STELLAR, and GDF3 are expressed in both seminoma and breast carcinoma. *Cancer*, 104(10), 2255–2265.

Famian, M. H., Saheb, S.M., & Montaseri, A. (2017). Conditioned medium of wharton's jelly derived stem cells can enhance the cartilage specific genes expression by chondrocytes in monolayer and mass culture systems. *Advanced Pharmaceutical Bulletin*, 7(1), 123.

Fan, J., Gong, Y., Ren, L., Varshney, R.R., Cai, D., & Wang, D.A. (2010). In vitro engineered cartilage using synovium-derived mesenchymal stem cells with injectable gellan hydrogels. *Acta Biomaterialia*, *6*(3), 1178–1185.

Fan, W., Li, J., Wang, Y., Pan, J., Li, S., Zhu, L., Guo, C., & Yan, Z. (2016). CD105 promotes chondrogenesis of synovium-derived mesenchymal stem cells through Smad2 signaling. *Biochemical and Biophysical Research Communications*, *474*(2), 338–344.

Farmer, S.R. (2005). Regulation of PPARgamma activity during adipogenesis. *International Journal of Obesity,* 29, S13-16.

Feng, R., & Wen, J. (2015). Overview of the roles of Sox2 in stem cell and development. *Biological Chemistry*, *396*(8), 883–891.

Ferro, F., Spelat, R., D'Aurizio, F., Puppato, E., Pandolfi, M., Beltrami, A.P., Cesseli, D, Falini, G., Beltrami, C.A., & Curcio, F. (2012). Dental pulp stem cells differentiation reveals new insights in Oct4A dynamics. *Plos One*, 7(7), e41774.

Findlay, D.M. (2010). If good things come from above, do bad things come from below? *Arthritis Research and Therapy*, 12(3), 119.

Finnson, K.W., Chi, Y., Bou-Gharios, G., Leask, A., & Philip, A. (2012). TGF-b signaling in cartilage homeostasis and osteoarthritis. *Frontiers in Bioscience, 4,* 251–268.

Foldager, C.B., Gomoll, A.H., Lind, M. & Spector, M. (2012). Cell seeding densities in autologous chondrocyte implantation techniques for cartilage repair. *Cartilage,* 3, 108–117.

Fong, H., Hohenstein, K.A., & Donovan, P. J. (2008). Regulation of self-renewal and pluripotency by Sox2 in human embryonic stem cells. *Stem Cells.* 26(8), 1931–1938.

Fonsatti, E., Sigalotti, L., Arslan, P., Altomonte, M., & Maio, M. (2003). Emerging role of endoglin (CD105) as a marker of angiogenesis with clinical potential in human malignancies. *Current Cancer Drug Targets*, 3(6), 427–432.

Fortier, L. A., Mohammed, H. O., Lust, G., & Nixon, A. J. (2002). Insulin-like growth factor-I enhances cell-based repair of articular cartilage. *The Journal of Bone and Joint Surgery,* 84(2), 276–288.

Fortier, Lisa A., Barker, J. U., Strauss, E. J., McCarrel, T.M., & Cole, B. J. (2011). The Role of growth factors in cartilage repair. *Clinical Orthopaedics and Related Research*, 469(10), 2706–2715.

Fox, A.J.S., Bedi, A., & Rodeo, S.A. (2009). The basic science of articular cartilage: structure, composition and function. *Sports Health,* 1(6), 461-468.

Fransen, M., Bridgett, L., March, L., Hoy, D., Penserga, E., & Brooks, P. (2011). The epidemiology of osteoarthritis in Asia. *International Journal of Rheumatic Diseases*, 14(2), 113–121.

Frantz, C., Stewart, K.M., & Weaver, V. M. (2010). The extracellular matrix at a glance. *Journal of Cell Science*, 123(24), 4195–4200.

Friel, N.A., & Chu, C.R. (2013). The role of ACL injury in the development of posttraumatic knee steoarthritis. *Clinics in Sports Medicine*, 32(1), 1–12.

Fujita, T., Azuma, Y., Fukuyama, R., Hattori, Y., Yoshida, C., Koida, M., Ogita, K., &Komori, T. (2004). Runx2 induces osteoblast and chondrocyte differentiation and enhances their migration by coupling with PI3K-Akt signaling. *The Journal of Cell Biology*, 166(1), 85–95.

Fülber, J., Maria, D. A., Silva, L. C. L. C. da, Massoco, C. O., Agreste, F., & Baccarin, R. Y. A. (2016). Comparative study of equine mesenchymal stem cells from healthy and injured synovial tissues: an in vitro assessment. *Stem Cell Research and Therapy*, *7*, 35.

Gao, X., Shen, Z., Guan, M., Huang, Q., Chen, L., Qin, W., Ge, X., Chen, H., Xiao, Y., & Lin, Z. (2018). Immunomodulatory role of stem cells from human exfoliated deciduous teeth on periodontal regeneration. *Tissue Engineering Part A*, https://doi.org/10.1089/ten.TEA.2018.0016.

Gao, Y., Liu, S., Huang, J., Guo, W., Chen, J., Zhang, L., Zhao, B., Peng, J., Wang, A., Wang, Y., Xu, W., Lu, S., Yuan, M., & Guo, Q. (2014). The ECM-cell interaction of cartilage extracellular matrix on chondrocytes. *BioMed Research International*, 2014, 1-8.

García-Carvajal, Z.Y., Garciadiego-Cázares, D., Parra-Cid, C., Aguilar-Gaytán, R., Velasquillo, C., Ibara, C., & Carmona, J.S.C. (2013). Cartilage Tissue Engineering: The role of extracellular matrix (ECM) and novel strategies. In: Andrades JA, ed. Regenerative medicine and tissue engineering. Croatia: InTech, pp. 365–97

Gatti, S., Bruno, S., Deregibus, M. C., Sordi, A., Cantaluppi, V., Tetta, C., & Camussi, G. (2011). Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia–reperfusion-induced acute and chronic kidney injury. *Nephrology Dialysis Transplantation*, 26(5), 1474–1483.

Gazarian, K.G., & Ramírez-García, L.R. (2017). Human deciduous teeth stem cells (SHED) display neural crest signature characters. *Plos One*, 12(1), e0170321.

Ge, X.P., Gan, Y.H., Zhang, C.G., Zhou, C.Y., Ma, K.T., Meng, J.H., & Ma, X.C. (2011). Requirement of the NF-κB pathway for induction of Wnt-5A by interleukin-1β in condylar chondrocytes of the temporomandibular joint: functional crosstalk between the Wnt-5A and NF-κB signaling pathways. *Osteoarthritis and Cartilage*, 19(1), 111–117.

Gelse, K., Pöschl, E., & Aigner, T. (2003). Collagens--structure, function, and biosynthesis. *Advanced Drug Delivery Reviews*, 55(12), 1531–1546.

Gentili, C., & Cancedda, R. (2009). Cartilage and bone extracellular matrix. *Current Pharmaceutical Design*, 15(12), 1334–1348.

Gerber, H. P., Dixit, V., & Ferrara, N. (1998). Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. *The Journal of Biological Chemistry*, 273(21), 13313–13316.

Gerber, H. P., Vu, T.H., Ryan, A.M., Kowalski, J., Werb, Z., & Ferrara, N. (1999). VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nature Medicine*, 5(6), 623–628.

Ginani, F., Soares, D. M., Rabêlo, L. M., Rocha, H.A.O., de Souza, L.B., & Barboza, C.A.G. (2016). Effect of a cryopreservation protocol on the proliferation of stem cells from human exfoliated deciduous teeth. *Acta Odontologica Scandinavica*, 74(8), 598–604.

Glenn, J.D. and Whartenby, K.A. (2014). Mesenchymal stem cells: Emerging mechanisms of immunomodulation and therapy. *World Journal of Stem Cells*. 6(5), 526–539.

Goldring, M. B. (2012). Articular cartilage degradation in osteoarthritis. *HSS Journal*. 8(1), 7–9.

Goldring, M.B., & Goldring, S. R. (2010). Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Annals of the New York Academy of Sciences*. 1192(1), 230–237.

Goldring, S.R., & Goldring, M.B. (2007). Eating bone or adding it: the Wnt pathway decides. *Nature Medicine*, *13*(2), 133–134.

Goodrich, L.R., Hidaka, C., Robbins, P.D., Evans, C.H., & Nixon, A.J. (2007). Genetic modification of chondrocytes with insulin-like growth factor-1 enhances cartilage healing in an equine model. *The Journal of Bone and Joint Surgery.* 89(5), 672–685.

Gordon, M.K., & Hahn, R.A. (2010). Collagens. *Cell and Tissue Research*, 339(1), 247–257.

Gottardi, R., Hansen, U., Raiteri, R., Loparic, M., Düggelin, M., Mathys, D., Frieder, N.F., Bruckner, P., & Stolz, M. (2016). Supramolecular organization of collagen fibrils in healthy and osteoarthritic human knee and hip joint cartilage. *PLos One,* 11(10). e0163552.

Govindasamy, V., Abdullah, A. N., Ronald, V. S., Musa, S., Ab Aziz, Z.A.C., Zain, R.B., Totey, S., Bhonde, R.R., & Abu Kasim, N.H. (2010). Inherent differential propensity of dental pulp stem cells derived from human deciduous and permanent teeth. *Journal of Endodontics*, 36(9), 1504–1515.

Gregory, C.A., Singh, H., Perry, A.S., & Prockop, D.J. (2003). The Wnt signaling inhibitor Dickkopf-1 is required for reentry into the cell cycle of human adult stem cells from bone marrow. *Journal of Biological Chemistry*, *278*(30), 28067–28078.

Gronthos, S., Mankani, M., Brahim, J., Robey, P.G., & Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proceedings of the National Academy of Sciences of the United States of America,* 97(25), 13625–13630.

Gronthos, S., Arthur, A., Bartold, P.M., & Shi, S. (2011). A method to isolate and culture expand human dental pulp stem cells. In: Vemuri M., Chase L., Rao M. (Eds) *Mesenchymal Stem Cell Assays and Applications*. *Methods in Molecular Biology*. Humana Press, pp.107-121.

Grotle, M., Hagen, K.B., Natvig, B., Dahl, F.A., & Kvien, T.K. (2008). Obesity and osteoarthritis in knee, hip and/or hand: An epidemiological study in the general population with 10 years follow-up. *BMC Musculoskeletal Disorders*, *9*, 132.

Grover, A.K., & Samson, S. E. (2016). Benefits of antioxidant supplements for knee osteoarthritis: rationale and reality. *Nutrition Journal*, *15*, 1.

Gu, T.T., Liu, S.Y., & Zheng, P.S. (2012). Cytoplasmic NANOG-positive stromal cells promote human cervical cancer progression. *The American Journal of Pathology*, 181(2), 652–661.

Guo, Y., Liu, S., Wang, P., Zhao, S., Wang, F., Bing, L., Zhang, Y., Ling, E.A., Gao, J., & Hao, A. (2011). Expression profile of embryonic stem cell-associated genes Oct4, Sox2 and Nanog in human gliomas. *Histopathology*, 59(4), 763–775.

Halkos, M.E., Zhao, Z.Q., Kerendi, F., Wang, N.P., Jiang, R., Schmarkey, L.S., Martin, B.J., Ouyyumi, A.A., Few, W.L., Kin, H., Guyton, R.A., & Vinten-Johansen, J. (2008). Intravenous infusion of mesenchymal stem cells enhances regional perfusion and improves ventricular function in a porcine model of myocardial infarction. *Basic Research in Cardiology*, 103(6), 525–536.

Han, S.M., Han, S.H., Coh, Y.R., Jang, G., Ra, J. C., Kang, S.K., Lee, H.W. and Youn, H.Y. (2014). Enhanced proliferation and differentiation of Oct4- and Sox2-overexpressing human adipose tissue mesenchymal stem cells. *Experimental and Molecular Medicine*, 46(6), e101.

Haq, S. A., Davatchi, F., Dahaghin, S., Islam, N., Ghose, A., Darmawan, J., Chopra A., yu, ZO., Dans, L.F., & Rasker, J.J. (2010). Development of a questionnaire for identification of the risk factors for osteoarthritis of the knees in developing countries. A pilot study in Iran and Bangladesh. An ILAR-COPCORD phase III study. *International Journal of Rheumatic Diseases*, *13*(3), 203–214.

Haque, N., & Abu Kasim, N.H. (2017). Pooled human serum increases regenerative potential of in vitro expanded stem cells from human extracted deciduous teeth. *Advances in Experimental Medicine and Biology*, doi: 10.1007/5584_2017_74.

Hauser RA. (2010). The acceleration of articular cartilage degeneration in osteoarthritis by nonsteroidal anti-inflammatory drugs. *Journal of Prolotherapy*, 2(1), 305–322.

Hegde, S., Pahne, J., & Smola-Hess, S. (2004). Novel immunosuppressive properties of interleukin-6 in dendritic cells: inhibition of NF-kappaB binding activity and CCR7 expression. *FASEB Journal,* 18(12), 1439–1441.

Hirata, M., Ishigami, M., Matsushita, Y., Ito, T., Hattori, H., Hibi, H.,Goto, H., Ueda, M., & Yamamoto, A. (2016). Multifaceted therapeutic benefits of factors derived from dental pulp stem cells for mouse liver fibrosis. *Stem Cells Translational Medicine*, 5(10), 1416–1424.

Hofer, H.R., & Tuan, R.S. (2016). Secreted trophic factors of mesenchymal stem cells support neurovascular and musculoskeletal therapies. *Stem Cell Research & Therapy*, 7(1).131

Hoff, P., Buttgereit, F., Burmester, G.R., Jakstadt, M., Gaber, T., Andreas, K., Matziolis, G., Perka, C., & Röhner, E. (2012). Osteoarthritis synovial fluid activates pro-inflammatory cytokines in primary human chondrocytes. *International Orthopaedics*, 37(1), 145–151.

Horie, M., Choi, H., Lee, R.H., Reger, R.L., Ylostalo, J., Muneta, T., Sekiya, I., & Prockop, D.J. (2012). Intra-articular injection of human mesenchymal stem cells (MSCs) promote rat meniscal regeneration by being activated to express Indian hedgehog that enhances expression of type II collagen. *Osteoarthritis and Cartilage,* 20(10), 1197–1207.

Houard, X., Goldring, M.B., & Berenbaum, F. (2013). Homeostatic Mechanisms in Articular Cartilage and Role of Inflammation in Osteoarthritis. *Current Rheumatology Reports*, 15(11), 375.

Huang, G.T.J., Sonoyama, W., Chen, J., & Park, S.H. (2006). In vitro characterization of human dental pulp cells: various isolation methods and culturing environments. *Cell and Tissue Research*, 324(2), 225–236.

Huang, H.L., Hsing, H.W., Lai, T.C., Chen, Y.W., Lee, T.R., Chan, H.T., Lyu, P.C., Wu, C.L., Lu, Y.C., Lin, S.T., Lin, C.W., Lai, C.H., Chang, H.T., Chou, H.C., & Chan, H.L. (2010). Trypsin-induced proteome alteration during cell subculture in mammalian cells. *Journal of Biomedical Science*, *17*(1), 36.

Hulejová, H., Baresová, V., Klézl, Z., Polanská, M., Adam, M., & Senolt, L. (2007). Increased level of cytokines and matrix metalloproteinases in osteoarthritic subchondral bone. *Cytokine*, 38(3), 151–156.

Hunziker, E.B., Quinn, T.M., & Häuselmann, H.J. (2002). Quantitative structural organization of normal adult human articular cartilage. *Osteoarthritis and Cartilage*, 10(7), 564–572.

Hwang, H.S., & Kim, H.A. (2015). Chondrocyte Apoptosis in the Pathogenesis of Osteoarthritis. *International Journal of Molecular Sciences*, 16(11), 26035–26054.

Iannone, F., De Bari, C., Dell'Accio, F., Covelli, M., Cantatore, F.P., Patella, V., Lo Bianco, G., & Lapadula, G. (2001). Interleukin-10 and interleukin-10 receptor in human osteoarthritic and healthy chondrocytes. *Clinical and Experimental Rheumatology*, 19(2), 139–145.

Idrus, R.B.H., Hui, C.K., Ibrahim, F.W., Hussein, F.N., & Saim, A.B. (2007). The expansion potential of human nasal septum chondrocytes for the formation of engineered cartilage. *ScienceAsia*, *33*(2), 145–152.

Igura, K., Zhang, X., Takahashi, K., Mitsuru, A., Yamaguchi, S., & Takashi, T.A. (2004). Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. *Cytotherapy*, 6(6), 543–553.

Ilić, D., Almeida, E.A.C., Schlaepfer, D.D., Dazin, P., Aizawa, S., & Damsky, C.H. (1998). Extracellular matrix survival signals transduced by focal adhesion kinase suppress p53-mediated apoptosis. *The Journal of Cell Biology*, 143(2), 547–560.

Inoue, T., Sugiyama, M., Hattori, H., Wakita, H., Wakabayashi, T., & Ueda, M. (2013). Stem cells from human exfoliated deciduous tooth-derived conditioned medium enhance recovery of focal cerebral ischemia in rats. *Tissue Engineering Part A*, 19(1–2), 24–29.

Inukai, T., Katagiri, W., Yoshimi, R., Osugi, M., Kawai, T., Hibi, H., & Ueda, M. (2013). Novel application of stem cell-derived factors for periodontal regeneration. *Biochemical and Biophysical Research Communications*, 430(2), 763–768.

Ivanova-Todorova, E., Bochev, I., Mourdjeva, M., Dimitrov, R., Bukarev, D., Kyurkchiev, S., Tivchev, P., Altunkova, I., & Kyurkchiev, D.S. (2009). Adipose tissue-derived mesenchymal stem cells are more potent suppressors of dendritic cells differentiation compared to bone marrow-derived mesenchymal stem cells. *Immunology Letters*, 126(1–2), 37–42.

Jakob, M., Démarteau, O., Schäfer, D., Stumm, M., Heberer, M., & Martin, I. (2003). Enzymatic digestion of adult human articular cartilage yields a small fraction of the total available cells. *Connective Tissue Research*, 44(3–4), 173–180.

Jansen, N.W.D., Roosendaal, G., Hooiveld, M.J.J., Bijlsma, J.W.J., van Roon, J.A.G., Theobald, M., & Lafeber, F.P.J.G. (2008). Interleukin-10 protects against blood-induced joint damage. *British Journal of Haematology*, 142(6), 953–961.

Jarvinen, L., Badri, L., Wettlaufer, S., Ohtsuka, T., Standiford, T. J., Toews, G.B., Pinsky, D.J., Peters-Golden, M., & Lama, V.N. (2008). Lung resident mesenchymal stem cells isolated from human lung allografts inhibit T cell proliferation via a soluble mediator. *Journal of Immunology,* 181(6), 4389–4396.

Jeong, C.H., Cho, Y.Y., Kim, M.O., Kim, S.H., Cho, E.J., Lee, S.Y., Jeon, Y.J., Lee, K.Y., Yao, K., Keum, Y.S. Bode, A.M. & Dong, Z. (2010). Phosphorylation of Sox2 cooperates in reprogramming to pluripotent stem cells. *Stem Cells,*28(12), 2141-2150.

Jeter, C.R., Yang, T., Wang, J., Chao, H.P., & Tang, D. G. (2015). NANOG in cancer stem cells and tumor development: An update and outstanding questions. *Stem Cells*, 33(8), 2381–2390.

Jiang, Z. L., Fletcher, N. M., Diamond, M. P., Abu-Soud, H. M., & Saed, G. M. (2009). Hypoxia regulates iNOS expression in human normal peritoneal and adhesion fibroblasts through nuclear factor kappa B activation mechanism. *Fertility and Sterility*, 91(2), 616–621.

John, T., Müller, R. D., Oberholzer, A., Zreiqat, H., Kohl, B., Ertel, W., Hostmann, A., Tschoeke, S.K., & Schulze-Tanzil, G. (2007). Interleukin-10 modulates pro-apoptotic effects of TNF-α in human articular chondrocytes in vitro. *Cytokine*, 40(3), 226–234.

Johnson, C.I., Argyle, D.J., & Clements, D.N. (2016). In vitro models for the study of osteoarthritis. *The Veterinary Journal*, *209*, 40–49.

Johnson, V.L., & Hunter, D.J. (2014). The epidemiology of osteoarthritis. *Best Practice and Research: Clinical Rheumatology*, 28(1), 5–15.

Joos, H., Wildner, A., Hogrefe, C., Reichel, H., & Brenner, R. E. (2013). Interleukin-1 beta and tumor necrosis factor alpha inhibit migration activity of chondrogenic progenitor cells from non-fibrillated osteoarthritic cartilage. *Arthritis Research and Therapy*. 15(5), R119.

Jung, Y.K., Kim, G.W., Park, H.R., Lee, E.J., Choi, J.Y., Beier, F., & Han, S.W. (2013). Role of interleukin-10 in endochondral bone formation in mice: anabolic effect via the bone morphogenetic protein/Smad pathway. *Arthritis and Rheumatism*, *65*(12), 3153–3164.

Kadler, K. E. (2017). Fell Muir Lecture: Collagen fibril formation in vitro and in vivo. *International Journal of Experimental Pathology*, 98(1), 4–16.

Kafri, M., Metzl-Raz, E., Jona, G., & Barkai, N. (2015). The cost of protein production. *Cell Reports*, *14*(1), 22–31.

Kano, F., Matsubara, K., Ueda, M., Hibi, H., & Yamamoto, A. (2017). Secreted ectodomain of sialic acid-binding Ig-like lectin-9 and MCP-1 synergistically regenerate transected rat peripheral nerves by altering macrophage polarity. *Stem Cells,* 35(3),641-653.

Karamzadeh, R., Baghaban Eslaminejad, M., & Sharifi-Zarchi, A. (2017). Comparative in vitro evaluation of human dental pulp and follicle stem cell commitment. *Cell Journal,* 18(4), 609–618.

Kashyap, R. (2015). SHED - Basic structure for stem cell research. *Journal of Clinical and Diagnostic Research,* 9(3), ZE07–ZE09.

Kastelowitz, N., & Yin, H. (2014). Exosomes and microvesicles: identification and targeting by particle size and lipid chemical probes. *Chembiochem: A European Journal of Chemical Biology*, 15(7), 923–928.

Kay, A. G., Long, G., Tyler, G., Stefan, A., Broadfoot, S. J., Piccinini, A.M., Middleton, J., & Kehoe, O. (2017). Mesenchymal stem cell-conditioned medium reduces disease severity and immune responses in inflammatory arthritis. *Scientific Reports*, 7(1), 18019.

Kerkis, I., Kerkis, A., Dozortsev, D., Stukart-Parsons, G.C., Gomes Massironi, S.M., Pereira, L.V., Caplan, A.I., & Cerruti, H.F. (2006). Isolation and characterization of a population of immature dental pulp stem cells expressing OCT-4 and other embryonic stem cell markers. *Cells, Tissues, Organs*,184(3–4), 105–116.

Khan, L. (2008). Ethics analysis of the human embryonic stem cell research debate. *Online Journal of Health Ethics*, 5(2), 1-12.

Kim, J.H., Jee, M.K., Lee, S.Y., Han, T.H., Kim, B.S., Kang, K.S., Kang, S.K. (2009). Regulation of adipose tissue stromal cells behaviors by endogenic OCT4 expression control. *Plos One,* 4, e7166.

King, L. K., March, L., & Anandacoomarasamy, A. (2013). Obesity & osteoarthritis. *The Indian Journal of Medical Research*, 138(2), 185–193.

Kobayashi, M., Squires, G. R., Mousa, A., Tanzer, M., Zukor, D. J., Antoniou, J., Feige, U., & Poole, A.R. (2005). Role of interleukin-1 and tumor necrosis factor alpha in matrix degradation of human osteoarthritic cartilage. *Arthritis and Rheumatism*, 52(1), 128–135.

Koç, O. N., Peters, C., Aubourg, P., Raghavan, S., Dyhouse, S., DeGasperi, R., Kolodny, E.H., Yoseph, Y.B., Gerson, S.L., Lazarus, H.M., Caplan, A.I., Watkins, P.A., & Krivit, W. (1999). Bone marrow-derived mesenchymal stem cells remain host-derived despite successful hematopoietic engraftment after allogeneic transplantation in patients with lysosomal and peroxisomal storage diseases. *Experimental Hematology*, 27(11), 1675–1681.

Kon, E., Filardo, G., Martino, A. D., & Marcacci, M. (2012). ACI and MACI. *The Journal of Knee Surgery*, 25(01), 017–022.

Konala, V.B.R., Mamidi, M.K., Bhonde, R., Das, A.K., Pochampally, R., & Pal, R. (2016). The current landscape of the mesenchymal stromal cell secretome: A new paradigm for cell-free regeneration. *Cytotherapy*, 18(1), 13–24.

Krampera, M., Pasini, A., Rigo, A., Scupoli, M. T., Tecchio, C., Malpeli, G., Scarpa, A., Dazzi, F., Pzzolo, G., Vinante, F. (2005). HB-EGF/HER-1 signaling in bone marrow mesenchymal stem cells: inducing cell expansion and reversibly preventing multilineage differentiation. *Blood*, 106(1), 59–66.

Krasnokutsky, S., Belitskaya-Lévy, I., Bencardino, J., Samuels, J., Attur, M., Regatte, R., Rosenthal, P., Greenberg, J., Schweitzer, M., Abramson, S.B., & Rybak, L. (2011). Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. *Arthritis and Rheumatism*, 63(10), 2983–2991.

Kristjánsson, B., & Honsawek, S. (2014). Current perspectives in mesenchymal stem cell therapies for osteoarthritis. *Stem Cells International*, *2014*, 194318.

Kronsteiner, B., Peterbauer-Scherb, A., Grillari-Voglauer, R., Redl, H., Gabriel, C., van Griensven, M., & Wolbank, S. (2011). Human mesenchymal stem cells and renal tubular epithelial cells differentially influence monocyte-derived dendritic cell differentiation and maturation. *Cellular Immunology*, *267*(1), 30–38.

Kühn, K., Hashimoto, S., & Lotz, M. (2000). IL-1β protects human chondrocytes from CD95- induced apoptosis. *Journal of Immunology,* 164 (4), 2233-2239.

Kumasaka, A., Kanazawa, K., Ohke, H., Miura, I., & Miura, Y. (2017). Post-ischemic intravenous administration of allogeneic dental pulp-derived neurosphere cells ameliorated outcomes of severe forebrain ischemia in rats. *Neurocritical Care*, 26(1),133-142.

Kurth, T., Hedbom, E., Shintani, N., Sugimoto, M., Chen, F. H., Haspl, M., Martinovic, S., & Hunziker, E.B. (2007). Chondrogenic potential of human synovial mesenchymal stem cells in alginate. *Osteoarthritis and Cartilage*, 15(10), 1178–1189.

Kusindarta, D.L., Wihadmadyatami, H., Fibrianto, Y.H., Nugroho, W.S., Susetya, H., Musana, D.K., Wijayanto, H., Prihatna, S.A., & Wahyuni, A.E. (2016). Human umbilical mesenchymal stem cells conditioned medium promote primary wound healing regeneration. *Veterinary World*, 9(6), 605–610.

Kyurkchiev, D., Bochev, I., Ivanova-Todorova, E., Mourdjeva, M., Oreshkova, T., Belemezova, K., & Kyurkchiev, S. (2014). Secretion of immunoregulatory cytokines by mesenchymal stem cells. *World Journal of Stem Cells*, 6(5), 552–570.

Lai, R.C., Yeo, R.W.Y., & Lim, S.K. (2015). Mesenchymal stem cell exosomes. *Seminars in Cell and Developmental Biology*, 40, 82–88.

Larsson, S., Englund, M., Struglics, A., & Lohmander, L.S. (2015). Interleukin-6 and tumor necrosis factor alpha in synovial fluid are associated with progression of radiographic knee osteoarthritis in subjects with previous meniscectomy. *Osteoarthritis and Cartilage,* 23(11), 1906-1911.

Lee, J., Lee, J.Y., Chae, B.C., Jang, J., Lee, E., Son, Y. (2017). Fully Dedifferentiated chondrocytes expanded in specific mesenchymal stem cell growth medium with FGF2 obtains mesenchymal stem cell phenotype in vitro but retains chondrocyte phenotype in vivo. *Cell Transplantation*, *26*(10), 1673–1687.

Lee, J., Kim, H.K., Rho, J.Y., Han, Y.M., & Kim, J. (2006). The human OCT-4 isoforms differ in their ability to confer self-renewal. *The Journal of Biological Chemistry*, 281(44), 33554–33565.

Lee, M.J., Kim, J., Lee, K.I., Shin, J.M., Chae, J.I., & Chung, H.M. (2011). Enhancement of wound healing by secretory factors of endothelial precursor cells derived from human embryonic stem cells. *Cytotherapy*, 13(2), 165–178.

Lee, W. Y., & Wang, B. (2017). Cartilage repair by mesenchymal stem cells: Clinical trial update and perspectives. *Journal of Orthopaedic Translation*, 9, 76–88.

Lefebvre, J., Ancot, F., Leroy, C., Muharram, G., Lemière, A., & Tulasne, D. (2012). Met degradation: more than one stone to shoot a receptor down. *The FASEB Journal*, 26(4), 1387–1399.

Lengner, C. J., Camargo, F. D., Hochedlinger, K., Welstead, G. G., Zaidi, S., Gokhale, S., Scholer, H.R., Tomilin, A., & Jaenisch, R. (2007). Oct4 expression is not required for mouse somatic stem cell self-renewal. *Cell Stem Cell*, *1*(4), 403–415.

Leong, D.J., Choudhury, M., Hirsh, D.M., Hardin, J.A., Cobelli, N.J., & Sun, H.B. (2013). Nutraceuticals: potential for chondroprotection and molecular targeting of osteoarthritis. *International Journal of Molecular Scences,* 14, 23063–23085

Lewis, J. S., Hembree, W. C., Furman, B. D., Tippets, L., Cattel, D., Huebner, J.L., Little, D., DeFrate, L.E., Kraus, V.B., Guilak, F., & Olson, S. A. (2011). Acute joint pathology and synovial inflammation is associated with increased intra-articular fracture severity in the mouse knee. *Osteoarthritis and Cartilage*, 19(7), 864–873.

Levi, B., Wan, D. C., Glotzbach, J. P., Hyun, J., Januszyk, M., Montoro, D., Sorkin, M., James, A.W., Nelson, E.R, Li, S., Quarto, N., Lee, M., Gurtner, G.C., & Longaker, M. T. (2011). CD105 protein depletion enhances human adipose-derived stromal cell osteogenesis through reduction of transforming growth factor β1 (TGF-β1) signaling. *The Journal of Biological Chemistry*, *286*(45), 39497–39509.

Li, C.Y., Wu, X.Y., Tong, J.B., Yang, X.X., Zhao, J.L., Zheng, Q.F., Zhao, G.B., & Ma, Z.J. (2015). Comparative analysis of human mesenchymal stem cells from bone marrow and adipose tissue under xeno-free conditions for cell therapy. *Stem Cell Research and Therapy*, 6, 55.

Li, H., Wang, D., Yuan, Y., & Min, J. (2017). New insights on the MMP-13 regulatory network in the pathogenesis of early osteoarthritis. *Arthritis Research and Therapy*, 19(1), 248.

Li, J.F., Duan, H.F., Wu, C.T., Zhang, D.J., Deng, Y., Yin, H.L., Han, B., Gong, H.C., Wang, H.W., & Wang, Y.L. (2013). HGF accelerates wound healing by promoting the dedifferentiation of epidermal cells through-integrin/ILK pathway. *BioMed Research International*. *2013*, e470418.

Li, Q., Zhang, S., Zheng, Y., Wen, H., Han, X., Zhang, M., & Guan, W. (2017). Differentiation potential of neural stem cells derived from fetal sheep. *Animal Cells and Systems,* 21(4), 233-240.

Li, X., Zhao, S., & Wang, L. (2018). Therapeutic effect of adipose‐derived stem cell transplantation on optic nerve injury in rats. *Molecular Medicine Reports*, 17(2), 2529–2534.

Li, Y., Yang, Y.Y., Ren, J.L., Xu, F., Chen, F.M., & Li, A. (2017). Exosomes secreted by stem cells from human exfoliated deciduous teeth contribute to functional recovery after traumatic brain injury by shifting microglia M1/M2 polarization in rats. *Stem Cell Research and Therapy*, 8, 198.

Li, Z., Liu, C., Xie, Z., Song, P., Zhao, R. C. H., Guo, L., Liu, Z., & Wu, Y. (2011). Epigenetic dysregulation in mesenchymal stem cell aging and spontaneous differentiation. *Plos One,* 6(6), e20526.

Liang, B., Song, Z., Wu, B., Gardner, D., Shealy, D., Song, X.Y., & Wooley, P.H. (2009). Evaluation of anti-IL-6 monoclonal antibody therapy using murine type II collagen-induced arthritis. *Journal of Inflammation,* 6, 10.

Liang, C., Chen, S.L., Wang, M., Zhai, W.J., Zhou, Z., Pang, A.M., Feng, S.Z., & Han, M. (2013). Synergistic immunomodulatory effects of interferon-gamma and bone marrow mesenchymal stem cells. *Zhonghua Xue Ye Xue Za Zhi, 34(*3), 213–216.

Liang, Q., Wang, X., & Chen, T. (2014). Resveratrol protects rabbit articular chondrocyte against sodium nitroprusside-induced apoptosis via scavenging ROS. *Apoptosis*. 19(9), 1354–1363.

Liao, S. M. (2005). Rescuing human embryonic stem cell research: the blastocyst transfer method. *The American Journal of Bioethic,.* 5(6), 8–16.

Lin, L., & Du, L. (2018). The role of secreted factors in stem cells-mediated immune regulation. *Cellular Immunology*, 326, 24–32.

Lin, Z., Fitzgerald, J.B., Xu, J., Willers, C., Wood, D., Grodzinsky, A. J., & Zheng, M.H. (2008). Gene expression profiles of human chondrocytes during passaged monolayer cultivation. *Journal of Orthopaedic Research,* 26(9), 1230–1237.

Lin, Z., Willers, C., Xu, J. & Zheng, M.H. (2006). The chondrocyte: biology and clinical application. *Tissue Engineering*, 12(7), 1971–1984.

Litwic, A., Edwards, M., Dennison, E., & Cooper, C. (2013). Epidemiology and Burden of Osteoarthritis. *British Medical Bulletin*, 105, 185–199.

Liu, A., Yu, X., & Liu, S. (2013). Pluripotency transcription factors and cancer stem cells: small genes make a big difference. *Chinese Journal of Cancer*, 32(9), 483–487.

Liu, L., Wei, X., Ling, J., Wu, L., & Xiao, Y. (2011). Expression pattern of Oct-4, Sox2, and c-Myc in the primary culture of human dental pulp derived cells. *Journal of Endodontics*, 37(4), 466–472.

Liu, S., Jia, Y., Yuan, M., Guo, W., Huang, J., Zhao, B., peng, J., Xu, W., Lu, S., & Guo, Q. (2017). Repair of osteochondral defects using human umbilical cord Wharton's jelly-derived mesenchymal stem cells in a rabbit model. *BioMed Research International*, 2017, 1-12.

Liu, T. M., Lee, E. H., Lim, B., & Shyh-Chang, N. (2016). Concise review: balancing stem cell self-renewal and differentiation with PLZF. *Stem Cells*, 34(2), 277–287.

Livshits, G., Zhai, G., Hart, D.J., Kato, B.S., Wang, H., Williams, F.M.K., & Spector, T.D. (2009). Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford Study. *Arthritis and Rheumatism*, 60(7), 2037–2045.

Lo, B. and Parham, L. (2009). Ethical issues in stem cell research. *Endocrine Reviews*, 30(3), 204–213.

Loeser, R.F. (2010). Age-related changes in the musculoskeletal system and the development of osteoarthritis. *Clinics in Geriatric Medicine*, *26*(3), 371–386.

Lohmander, L.S. (2013). Knee replacement for osteoarthritis: facts, hopes, and fears. *Medicographia*. 35,181-188

Longobardi, L., O'Rear, L., Aakula, S., Johnstone, B., Shimer, K., Chytil, A., Horton, W.A., Moses, H.L., & Spagnoli, A. (2006). Effect of IGF-I in the chondrogenesis of bone marrow mesenchymal stem cells in the presence or absence of TGF-beta signaling. *Journal of Bone and Mineral Research,* 21(4), 626–636.

López-Armada, M. J., Caramés, B., Lires-Deán, M., Cillero-Pastor, B., Ruiz-Romero, C., Galdo, F., & Blanco, F.J. (2006a). Cytokines, tumor necrosis factor-α and interleukin-1β, differentially regulate apoptosis in osteoarthritis cultured human chondrocytes. *Osteoarthritis and Cartilage*. 14(7), 660–669.

López-Armada, M. J., Caramés, B., Martín, M. A., Cillero-Pastor, B., Lires-Dean, M., Fuentes-Boquete, I., Arenas, J., & Blanco, F. J. (2006b). Mitochondrial activity is modulated by TNFα and IL-1β in normal human chondrocyte cells. *Osteoarthritis and Cartilage*, 14(10), 1011–1022.

Losina, E., & Katz, J.N. (2012). Total knee arthroplasty on the rise in younger patients: are we sure that past performance will guarantee future success? *Arthritis and Rheumatisim,* 64(2),339-341.

Lotz, M., Rosen, F., McCabe, G., Quach, J., Blanco, F., Dudler, J., Solan, J., Goding, J., Seegmiller, J.E., & Terkeltaub, R. (1995). Interleukin 1 beta suppresses transforming growth factor-induced inorganic pyrophosphate (PPi) production and expression of the PPi-generating enzyme PC-1 in human chondrocytes. *Proceedings of the National Academy of Sciences of the United States of America*, 92(22), 10364–10368.

Lozito, T.P., & Tuan, R.S. (2011). Mesenchymal stem cells inhibit both endogenous and exogenous MMPs via secreted TIMPs. *Journal of Cellular Physiology*, 226(2), 385–396.

Lu, W., Wang, L., Wo, C., & Yao, J. (2016). Ketamine attenuates osteoarthritis of the knee via modulation of inflammatory responses in a rabbit model. *Molecular Medicine Reports,* 13, (6), 5013–5020.

Luo, J., Chen, J., Deng, Z.L., Luo, X., Song, W.X., Sharff, K.A., Tang, N., Haydon, R.C., Luu, H.H., & He, T.C. (2007). Wnt signaling and human diseases: what are the therapeutic implications? *Laboratory Investigation,* 87(2), 97–103.

Ma, B., Zhou, P. H., Xie, T., Shi, L., Qiu, B., & Wang, Q. (2015). Inhibition of interleukin-1beta-stimulated dedifferentiation of chondrocytes via controlled release of CrmA from hyaluronic acid-chitosan microspheres. *BMC Musculoskeletal Disorders*, *16*(1), 61.

Ma, L., Makino, Y., Yamaza, H., Akiyama, K., Hoshino, Y., Song, G., Kukita, T., Nonak, K., Shi, S., & Yamaza, T. (2012). Cryopreserved dental pulp tissues of exfoliated deciduous teeth is a feasible stem cell resource for regenerative medicine. *PloS One*, 7(12), e51777.

Ma, S., Xie, N., Li, W., Yuan, B., Shi, Y., & Wang, Y. (2014). Immunobiology of mesenchymal stem cells. *Cell Death & Differentiation*, 21(2), 216–225.

Madden, J.C., Hewitt, M., Przybylak, K., Vandebriel, R.J., Piersma, A.H., & Cronin, M. T. (2012). Strategies for the optimisation of in vivo experiments in accordance with the 3Rs philosophy. *Regulatory Toxicology & Pharmacology,* 63(1), 140–154.

Madrigal, M., Rao, K.S., & Riordan, N. H. (2014). A review of therapeutic effects of mesenchymal stem cell secretions and induction of secretory modification by different culture methods. *Journal of Translational Medicine*, 12, 260.

Madry, H., Luyten, F.P., & Facchini, A. (2012). Biological aspects of early osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*, 20(3), 407-422.

Maggini, J., Mirkin, G., Bognanni, I., Holmberg, J., Piazzón, I.M., Nepomnaschy, I., Costa, H., Canones, C., Raiden, S., Vermeulen, M., & Geffner, J.R. (2010). Mouse bone marrow-derived mesenchymal stromal cells turn activated macrophages into a regulatory-like profile. *Plos One*, 5(2), e9252.

Maguire, G. (2013). Stem cell therapy without the cells. *Communicative and Integrative Biology*, 6(6), e26631.

Makhani, K., Ali1, S.M., Yousuf1, S., & Siddiqui, S. (2015). Therapeutic potential of totipotent, pluripotent and multipotent stem cells. *MOJ Cell Science and Report*, 2(5), 1–6.

Maldonado, M., & Nam, J. (2013). The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. *BioMed Research International*, 2013, 284873.

Man, G., & Mologhianu, G. (2014). Osteoarthritis pathogenesis – a complex process that involves the entire joint. *Journal of Medicine and Life*, *7*(1), 37–41.

Marcu, K.B., Otero, M., Olivotto, E., Borzi, R.M., & Goldring, M.B. (2010). NF-κB signaling: multiple angles to target OA. *Current Drug Targets*, 11(5), 599–613.

Martinez Saez, D., Sasaki, R.T., Neves, A.D., & da Silva, M.C. (2016). Stem cells from human exfoliated deciduous teeth: a growing literature. *Cells, Tissues, Organs*, 202(5–6), 269–280.

Matsubara, K., Matsushita, Y., Sakai, K., Kano, F., Kondo, M., Noda, M., Hashimoto, N., Imagama, S., Ishiquro, N, Suzumura, A., Ueda, M., & Yamamoto, A. (2015). Secreted ectodomain of sialic acid-binding Ig-like lectin-9 and monocyte chemoattractant protein-1 promote recovery after rat spinal cord injury by altering macrophage polarity. *The Journal of Neuroscience,* 35(6), 2452–2464.

Matsushita, Y., Ishigami, M., Matsubara, K., Kondo, M., Wakayama, H., Goto, H., Ueda, M., & Yamamoto, A. (2017). Multifaceted therapeutic benefits of factors derived from stem cells from human exfoliated deciduous teeth for acute liver failure in rats. *Journal of Tissue Engineering and Regenerative Medicine,* 11(6),1888-1896

McBride, K. M., Banninger, G., McDonald, C., & Reich, N. C. (2002). Regulated nuclear import of the STAT1 transcription factor by direct binding of importin-α. *The EMBO Journal*, 21(7), 1754–1763.

Mehrabani, D., Mahdiyar, P., Torabi, K., Robati, R., Zare, S., Dianatpour, M., & Tamadon, A. (2017). Growth kinetics and characterization of human dental pulp stem cells: Comparison between third molar and first premolar teeth. *Journal of Clinical and Experimental Dentistry*, 9(2), e172–e177.

Meirelles, L.daS., Fontes, A.M., Covas, D.T., & Caplan, A.I. (2009). Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine and Growth Factor Reviews*, 20(5–6), 419–427.

Messier, S.P., Legault, C., Mihalko, S., Miller, G.D., Loeser, R.F., DeVita, P.,Lyles, M., Eckstein, F., Hunter, D.J., Williamson, J.D., & Nicklas, B. J. (2009). The intensive diet and exercise for arthritis (IDEA) trial: design and rationale. *BMC Musculoskeletal Disorders*, 10, 93.

Meszaros, E., & Malemud, C.J. (2012). Prospects for treating osteoarthritis. *Therapeutic Advances in Chronic Disease*, 3(5), 219–229.

Minegishi, Y., Hosokawa, K., & Tsumaki, N. (2013). Time-lapse observation of the dedifferentiation process in mouse chondrocytes using chondrocyte-specific reporters. *Osteoarthritis and Cartilage*, 21(12), 1968–1975.

Mirabella, T., Cilli, M., Carlone, S., Cancedda, R., & Genttili., C. (2011). Amniotic liquid derived stem cells as reservoir of secreted angiogenic factors capable of stimulating neo-arteriogenesis in an ischemic model. *Biomaterials*, 32(15), 3689–3699.

Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L.W., Robey, P.G., & Shi, S. (2003). SHED: stem cells from human exfoliated deciduous teeth. *Proceedings of the National Academy of Sciences*, 100(10), 5807–5812.

Mobasheri, A., Kalamegam, G., Musumeci, G., & Batt, M.E. (2014). Chondrocyte and mesenchymal stem cell-based therapies for cartilage repair in osteoarthritis and related orthopaedic conditions. *Maturitas*, 78(3), 188–198.

Morad, G., Kheiri, L., & Khojasteh, A. (2013). Dental pulp stem cells for in vivo bone regeneration: a systematic review of literature. *Archives of Oral Biology*, 58(12), 1818–1827.

Moraes, D.A., Sibov, T.T., Pavon, L.F., Alvim, P.Q., Bonadio, R. S., Da Silva, J.R., Pic-Taylor, A., Toledo, O.A. Marti, L.C., Azevedo, R.B., & Oliveira, D.M. (2016). A reduction in CD90 (THY-1) expression results in increased differentiation of mesenchymal stromal cells. *Stem Cell Research and Therapy*, 7(1), 97.

Müller, R.D., John, T., Kohl, B., Oberholzer, A., Gust, T., Hostmann, A., Hellmuth, D., LaFace, D., Hutchins, B., Laube, G., Veh, R.W., Tschoeke, S.K., Ertel, W., & Schulze-Tanzil, G. (2008). IL-10 overexpression differentially affects cartilage matrix gene expression in response to TNF-alpha in human articular chondrocytes in vitro. *Cytokine*, 44(3), 377–385.

Müller, S., Acevedo, L., Wang, X., Karim, M. Z., Matta, A., Mehrkens, A. Schaerens, S., Felciano, S., Jakob, M., Martin, I., Barbero, A., & Erwin, W.M. (2016). Notochordal cell conditioned medium (NCCM) regenerates end-stage human osteoarthritic articular chondrocytes and promotes a healthy phenotype. *Arthritis Research and Therapy*, 18 (1), 125.

Munro, M. J., Wickremesekera, S. K., Peng, L., Tan, S.T., & Itinteang, T. (2018). Cancer stem cells in colorectal cancer: a review. *Journal of Clinical Pathology*, 71(2), 110–116.

Muratovic, D., Cicuttini, F., Wluka, A., Findlay, D., Wang, Y., Otto, S., Taylor, D., Humphries, J., Lee, Y., Labrinidis, A., Williams, R., & Kuliwaba, J. (2015). Bone marrow lesions detected by specific combination of MRI sequences are associated with severity of osteochondral degeneration. *Arthritis Research and Therapy*, 18, 54.

Murray, C.J.L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., … Memish, Z.A. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380(9859), 2197–2223.

Mushtaq, S., Choudhary, R., & Scanzello, C. R. (2011). Non-surgical treatment of osteoarthritis-related pain in the elderly. *Current Reviews in Musculoskeletal Medicine*, 4(3),113–122.

Musumeci, G., Castrogiovanni, P., Leonardi, R., Trovato, F.M., Szychlinska, M.A., Di Giunta, A., Loreto, C., & Castorina, S. (2014). New perspectives for articular cartilage repair treatment through tissue engineering: A contemporary review. *World Journal of Orthopedics*, 5(2), 80–88.

Nam, J., Perera, P., Liu, J., Rath, B., Deschner, J., Gassner, R., Butterfield, T.A., &Agarwal, S. (2011). Sequential alterations in catabolic and anabolic gene expression parallel pathological changes during progression of monoiodoacetate-induced arthritis. *Plos One,* 6(9), e24320.

Namba, A., Aida, Y., Suzuki, N., Watanabe, Y., Kawato, T., Motohashi, M., Maeno, M., Matsumura, H., & Matsumoto, M. (2007). Effects of IL-6 and soluble IL-6 receptor on the expression of cartilage matrix proteins in human chondrocytes. *Connective Tissue Research,* 48(5), 263–270.

Naranda, J., Gradišnik, L., Gorenjak, M., Vogrin, M., & Maver, U. (2017). Isolation and characterization of human articular chondrocytes from surgical waste after total knee arthroplasty (TKA). *PeerJ*, 5.e3079.

Nelson, A.E., Braga, L., Renner, J.B., Atashili, J., Woodard, J., Hochberg, M.C., Helmick, C.G., & Jordan, J.M. (2010). Characterization of individual radiographic features of hip osteoarthritis in African American and White women and men: the Johnston County Osteoarthritis Project. *Arthritis Care and Research*, 62(2), 190–197.

Németh, K., Leelahavanichkul, A., Yuen, P. S. T., Mayer, B., Parmelee, A., Doi, K., Robey, P.G., leelahavanichkul, K. Koller, B.H. Brown, J.M. Hu, X., Jelinek, I. Star, R.A., & Mezey, E. (2009). Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nature Medicine*. 15(1), 42–49.

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage,* 21(9), 1145–1153.

Newton, P.T., Staines, K.A., Spevak, L., Boskey, A.L., Teixeira, C.C., Macrae, V.E., Canfield, A.E., & Farquharson, C. (2012). Chondrogenic ATDC5 cells: An optimised model for rapid and physiological matrix mineralisation. *International Journal of Molecular Medicine,* 30(5), 1187–1193.

Niwa, H., Miyazaki, J., & Smith, A.G. (2000). Quantitative expression of Oct-3/4 defines differentiation, dedifferentiation or self-renewal of ES cells. *Nature Genetics*. 24(4), 372–376.

Novakofski, K.D., Torre, C.J., & Fortier, L.A. (2012). Interleukin-1α, -6, and -8 decrease Cdc42 activity resulting in loss of articular chondrocyte phenotype. *Journal of Orthopaedic Research*, 30(2), 246–251.

Oeckinghaus, A., & Ghosh, S. (2009). The NF-κB family of transcription factors and its regulation. *Cold Spring Harbor Perspectives in Biology*, *1*(4). a000034.

Oka, M., Moriyama, T., Asally, M., Kawakami, K., & Yoneda, Y. (2013). Differential role for transcription factor Oct4 nucleocytoplasmic dynamics in somatic cell reprogramming and self-renewal of embryonic stem cells. *The Journal of Biological Chemistry*, 288(21), 15085–15097.

Olivotto, E., Otero, M., Marcu, K. B., & Goldring, M. B. (2015). Pathophysiology of osteoarthritis: canonical NF-κB/IKKβ-dependent and kinase-independent effects of IKKα in cartilage degradation and chondrocyte differentiation. *RMD Open*, 1(Suppl 1), e000061.

Olsen, J. V., Ong, S.-E. and Mann, M. (2004). Trypsin cleaves exclusively C-terminal to arginine and lysine residues. *Molecular & Cellular Proteomics.* 3(6), 608–614.

Opal, S.M., & DePalo, V.A. (2000). Anti-inflammatory cytokines. *Chest*, 117(4), 1162– 1172.

Oseni, A.O., Butler, P.E., & Seifalian, A.M. (2013). Optimization of chondrocyte isolation and characterization for large-scale cartilage tissue engineering. *Journal of Surgical Research*, 181(1), 41–48.

Otabe, K., Muneta, T., Kawashima, N., Suda, H., Tsuji, K., & Sekiya, I. (2012). Comparison of gingiva, dental pulp, and periodontal ligament cells from the standpoint of mesenchymal stem cell properties. *Cell Medicine*, 4(1), 13–21.

Pan, G., Qin, B., Liu, N., Schöler, H. R. and Pei, D. (2004). Identification of a nuclear localization signal in OCT4 and generation of a dominant negative mutant by its ablation. *Journal of Biological Chemistry*. 279(35), 37013–37020.

Panagiotou, N., Wayne Davies, R., Selman, C., & Shiels, P. G. (2016). Microvesicles as vehicles for tissue regeneration: changing of the guards. *Current Pathobiology Reports*, 4(4), 181–187.

Pankajakshan, D., & Agrawal, D.K. (2014). Mesenchymal stem cell paracrine factors in vascular repair and regeneration. *Journal of Biomedical Technology and Research*. 1(1). 1-21.

Pawitan, J. A. (2014). Prospect of stem cell conditioned medium in regenerative medicine. *Biomed Research International*, 2014, 1-14.

Paxton, E.W., Namba, R.S., Maletis, G.B., Khatod, M., Yue, E.J., Davies, M., Low, R.B.,Wyatt, R.W., Inacio, M.C., & Funahashi, T.T. (2010). A prospective study of 80,000 total joint and 5000 anterior cruciate ligament reconstruction procedures in a community-based registry in the United States. *Journal of Bone Joint Surgery American,* 92 (S2):117–32.

Pearle, A.D., Warren, R.F., & Rodeo, S.A. (2005). Basic science of articular cartilage and osteoarthritis. *Clinics in Sports Medicine,* 24(1),1-12.

Pei, D. (2009). Regulation of pluripotency and reprogramming by transcription factors. *The Journal of Biological Chemistry*, 284(6), 3365–3369.

Petchdee, S., Suphamungm, W., & Bootcha, R. (2016). Therapeutic benefit of intra-articular administration of deciduous teeth stem cells in rabbit model of osteoarthritis. *Asian Journal of Animal and Veterinary Advances*, 11(6), 363–370.

Petersen, A.M., & Pedersen, B.K. (2006). The role of IL-6 in mediating the anti-inflammatory effects of exercise. *Journal of Physiology and Pharmacology,* 57(10), 43-51.

Pierantozzi, E., Gava, B., Manini, I., Roviello, F., Marotta, G., Chiavarelli, M., & Sorrentino, V. (2011). Pluripotency regulators in human mesenchymal stem cells: expression of NANOG but not of OCT-4 and SOX-2. *Stem Cells and Development*, 20(5), 915–923.

Platas, J., Guillén, M.I., del Caz, M.D.P., Gomar, F., Mirabet, V., & Alcaraz, M.J. (2013). Conditioned media from adipose-tissue-derived mesenchymal stem cells downregulate degradative mediators induced by interleukin-1β in osteoarthritic chondrocytes. *Mediators of Inflammation*, 2013. 1-10.

Popova, A.P., Bozyk, P.D., Goldsmith, A.M., Linn, M.J., Lei, J., Bentley, J.K., & Hershenson, M.B. (2010). Autocrine production of TGF-β1 promotes myofibroblastic differentiation of neonatal lung mesenchymal stem cells. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 298(6), L735–L743.

Porée, B., Kypriotou, M., Chadjichristos, C., Beauchef, G., Renard, E., Legendre, F., Melin, M. Gueret, S., Hartmann, D.J., Mallein-Gerin, F., Pujol, J.P., Boumediene, K., & Galéra, P. (2008). Interleukin-6 (IL-6) and/or soluble IL-6 receptor down-regulation of human type II collagen gene expression in articular chondrocytes requires a decrease of Sp1.Sp3 ratio and of the binding activity of both factors to the COL2A1 promoter. *The Journal of Biological Chemistry*, 283(8), 4850–4865.

Potdar, P.D., Deshpande, S.S. (2013). Mesenchymal stem cell transplantation: new avenues for stem cell therapies. *Journal of Transplantation Technologies and Research*. 3, 22..

Potdar, P.D., & Jethmalani, Y.D. (2015). Human dental pulp stem cells: Applications in future regenerative medicine. *World Journal of Stem Cells*, 7(5), 839–851.

Rajendran, R., Gopal, S., Masood, H., Vivek, P., & Deb, K. (2013). Regenerative potential of dental pulp mesenchymal stem cells harvested from high caries patient's teeth. *Journal of Stem Cells*, *8*(1), 25–41.

Ramasamy, R., Tong, C.K., Seow, H.F., Vidyadaran, S., & Dazzi, F. (2008). The immunosuppressive effects of human bone marrow-derived mesenchymal stem cells target T cell proliferation but not its effector function. *Cellular Immunology,* 251, 131-136.

Rasmusson, I., Ringden, O., Sundberg, B., & Le Blanc, K. (2003). Mesenchymal stem cells inhibit the formation of cytotoxic T lymphocytes, but not activated cytotoxic T lymphocytes or natural killer cells. *Transplantation*, 76(8), 1208–1213.

Rastegar, F., Shenaq, D., Huang, J., Zhang, W., Zhang, B.Q., He, B.C., Chen, L., Zuo, G.W., Luo, Q., Shi, Q., Wagner, E.R., Huang, E., Gao, Y., Goa, J.L. Kim, S.H., Zhou, J.Z., Bi, Y., Su, Y., Zhu, G., Luo, J., Luo, X., Qin, J., Reid, R.R., Luu, H.H., Haydon, R.C., Deng, Z.L., & He, T.C. (2010). Mesenchymal stem cells: molecular characteristics and clinical applications. *World Journal of Stem Cells, 2*(4), 67–80. Rigoglou, S., & Papavassiliou, A.G. (2013). The NF-κB signalling pathway in osteoarthritis. *The International Journal of Biochemistry and Cell Biology*, 45(11), 2580–2584.

Ringdén, O., Brazauskas, R., Wang, Z., Ahmed, I., Atsuta, Y., Buchbinder, D., Burns, L.J., Cahn, J.Y., Duncan, C., Hale, G.A., Halter, J., Hayashi, R.J., Hsu, J.W., Jacobsohn, D.A., Kamble, R.T., Kamani, N.R., Kasow, K.A., Khera, N., Lazarus, H.M., Loren, A.W., Marks, D.I., Myers, K.C., Ramanathan, M., Saber, W., Savani, B.N., Schouten, H.C., Socie, G., Sorror, M.L., Steinberg, A., Popat, U., Wingard, J.R., Mattsson, J., & Majhail, N. S. (2014). Second solid cancers after allogeneic hematopoietic cell transplantation using reduced-intensity conditioning. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, 20(11), 1777–1784.

Rizzo, J.D., Curtis, R.E., Socié, G., Sobocinski, K.A., Gilbert, E., Landgren, O., Travis, W.D., Flowers, M.E., Friedman, D.L., Horowitz, M.W., Wingard, J.R., & Deeg, H. J. (2009). Solid cancers after allogeneic hematopoietic cell transplantation. *Blood*, 113(5), 1175–1183.

Rodda, D.J., Chew, J.L., Lim, L.H., Loh, Y.H., Wang, B., Ng, H.H., & Robson, P. (2005). Transcriptional regulation of nanog by OCT4 and SOX2. *The Journal of Biological Chemistry*, *280*(26), 24731–24737.

Rose, B.J., & Kooyman, D.L. (2016). A tale of two joints: the role of matrix metalloproteases in cartilage biology. *Disease Markers*, 2016, 1-7.

Rosen, E.D., & Spiegelman, B.M. (2000). Molecular regulation of adipogenesis. *Annual Review of Cell & Developmental Biology*, 16, 145–171.

Rosenzweig, D.H., Matmati, M., Khayat, G., Chaudhry, S., Hinz, B., & Quinn, T.M. (2012). Culture of primary bovine chondrocytes on a continuously expanding surface inhibits dedifferentiation. *Tissue Engineering Part A*, 18(23–24), 2466–2476.

Rosner, M.H., Vigano, M.A., Ozato, K., Timmons, P.M., Poirier, F., Rigby, P.W., & Staudt, L.M. (1990). A POU-domain transcription factor in early stem cells and germ cells of the mammalian embryo. *Nature,* 345(6277), 686–692.

Rozario, T., & DeSimone, D.W. (2010). The extracellular matrix in development and morphogenesis: a dynamic view. *Developmental Biology*, *341*(1), 126–140.

Ryu, J.H., Shin, Y., Huh, Y.H., Yang, S., Chun, C.H., & Chun, J.S. (2012). Hypoxia-inducible factor-2α regulates Fas-mediated chondrocyte apoptosis during osteoarthritic cartilage destruction. *Cell Death & Differentiation*, 19(3), 440–450.

Sadat, S., Gehmert, S., Song, Y.-H., Yen, Y., Bai, X., Gaiser, S., Klein, H., & Alt, E. (2007). The cardioprotective effect of mesenchymal stem cells is mediated by IGF-I and VEGF. *Biochemical and Biophysical Research Communications*, 363(3), 674–679.

Sah, R.L., Chen, A.C., Grodzinsky, A.J., & Trippel, S.B. (1994). Differential effects of bFGF and IGF-I on matrix metabolism in calf and adult bovine cartilage explants. *Archives of Biochemistry and Biophysics*, *308*(1), 137–147.

Saito, T., & Tanaka, S. (2017). Molecular mechanisms underlying osteoarthritis development: Notch and NF-κB. *Arthritis Research and Therapy*, *19*(1), 94.

Sakata, R., Iwakura, T., & Reddi, A.H. (2015). Regeneration of articular cartilage surface: morphogens, cells, and extracellular matrix scaffolds. *Tissue Engineering Part B, Reviews*, 21(5), 461–473.

Scanzello, C.R., McKeon, B., Swaim, B. H., DiCarlo, E., Asomugha, E. U., Kanda, V., Nair, A., Lee, D.M., Richmond, J.C., Katz, J.N., Crow, M.K., & Goldring, S.R. (2011). Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular characterization and relationship to symptoms. *Arthritis and Rheumatism,* 63( 2), 391–400.

Scanzello, C.R., Umoh, E., Pessler, F., Diaz-Torne, C., Miles, T., Dicarlo, E., Potter, H.G., Mandi, L., Marx, R., Rodeo, S., Goldring, S.R., & Crow, M.K. (2009). Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. *Osteoarthritis and Cartilage*, 17(8), 1040–1048.

Scheller, J., Chalaris, A., Schmidt-Arras, D., & Rose-John, S. (2011). The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica Biophysica Acta*, 1813(5), 878–888.

Schiavone Panni, A., Cerciello, S., Vasso, M., & Tartarone, M. (2009). Stiffness in total knee arthroplasty. *Journal of Orthopaedics and Traumatology,* 10(3), 111–118.

Schöler, H.R., Ruppert, S., Suzuki, N., Chowdhury, K., & Gruss, P. (1990). New type of POU domain in germ line-specific protein Oct-4. *Nature*, 344(6265), 435–439.

Schrobback, K., Klein, T.J., Schuetz, M., Upton, Z., Leavesley, D.I., & Malda, J. (2011). Adult human articular chondrocytes in a microcarrier-based culture system: expansion and redifferentiation. *Journal of Orthopaedic Research,* 29(4), 539–546.

Schubert, R., Strohmeyer, N., Bharadwaj, M., Ramanathan, S. P., Krieg, M., Friedrichs, J., Franz, C.M., & Muller, D.J. (2014). Assay for characterizing the recovery of vertebrate cells for adhesion measurements by single-cell force spectroscopy. *FEBS Letters*, 588(19), 3639–3648.

Schulze-Tanzil, G., Souza, P. de, Castrejon, H. V., John, T., Merker, H.-J., Scheid, A., & Shakibaei, M. (2002). Redifferentiation of dedifferentiated human chondrocytes in high-density cultures. *Cell and Tissue Research*, 308(3), 371–379.

Segers, V. F. M., Van Riet, I., Andries, L. J., Lemmens, K., Demolder, M.J., De Becker, A.J., Kockx, M.M., & De Keulenaer, G.W. (2006). Mesenchymal stem cell adhesion to cardiac microvascular endothelium: activators and mechanisms. *American Journal of Physiology. Heart and Circulatory Physiology*, 290(4), H1370-1377.

Séguin, C.A., & Bernier, S.M. (2003). TNFalpha suppresses link protein and type II collagen expression in chondrocytes: role of MEK1/2 and NF-kappaB signaling pathways. *Journal of Cellular Physiology*, 197(3), 356–369.

Seifrtová, M., Havelek, R., Cmielová, J., Jiroutová, A., Soukup, T., Brůčková, L., Mokry, J., English, D., & Rezáčová, M. (2012). The response of human ectomesenchymal dental pulp stem cells to cisplatin treatment. *International Endodontic Journal*, 45(5), 401–412.

Seo, B. M., Sonoyama, W., Yamaza, T., Coppe, C., Kikuiri, T., Akiyama, K., Lee, J.S., & Shi, S. (2008). SHED repair critical-size calvarial defects in mice. *Oral Diseases*, 14(5), 428–434.

Shan, J., Shen, J., Liu, L., Xia, F., Xu, C., Duan, G., Xu, Y., Ma, Q., Yang, Z., Zhang, Q., Ma, L., Liu, J., Xu, S., Yan, X., Bie, P., Cui, Y., Bian, X.W., & Qian, C. (2012). Nanog regulates self-renewal of cancer stem cells through the insulin-like growth factor pathway in human hepatocellular carcinoma. *Hepatology,* 56(3), 1004–1014.

Shen, B., Wei, A., Tao, H., Diwan, A.D., & Ma, D.D.F. (2009). BMP-2 enhances TGF-beta3-mediated chondrogenic differentiation of human bone marrow multipotent mesenchymal stromal cells in alginate bead culture. *Tissue Engineering Part A*,15(6), 1311–1320.

Shimojima, C., Takeuchi, H., Jin, S., Parajuli, B., Hattori, H., Suzumura, A., Hibi, H., Ueda, M., & Yamamoto, A. (2016). Conditioned medium from the stem cells of human exfoliated deciduous teeth ameliorates experimental autoimmune encephalomyelitis. *Journal of Immunology,* 196(10), 4164–4171.

Silacci, P., Dayer, J. M., Desgeorges, A., Peter, R., Manueddu, C., & Guerne, P.A. (1998). Interleukin (IL)-6 and its soluble receptor induce TIMP-1 expression in synoviocytes and chondrocytes, and block IL-1-induced collagenolytic activity. *The Journal of Biological Chemistry*, 273(22), 13625–13629.

Silva, F.de S., Ramos, R.N., de Almeida, D.C., Bassi, E. J., Gonzales, R.P., Miyagi, S.P., Maranduba, C.P., Sant'Anna, O.A., Marques, M.M., Barbuto, J.A., Camara, N.O., & da Costa Maranduba, C.M. (2014). Mesenchymal stem cells derived from human exfoliated deciduous teeth (SHEDs) induce immune modulatory profile in monocyte-derived dendritic cells. *Plos One,* 9(5), e98050.

Sohn, D.H., Sokolove, J., Sharpe, O., Erhart, J.C., Chandra, P.E., Lahey, L.J., Lindstrom, T.M., Hwang, I., Boyer, K.A., Andriacchi, T.P., & Robinson, W.H. (2012). Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. *Arthritis Research and Therapy*, 14(1), R7.

Solchaga, L. A., Penick, K. J., & Welter, J. F. (2011). Chondrogenic Differentiation of Bone Marrow-Derived Mesenchymal Stem Cells: Tips and Tricks. *Methods in Molecular Biology*, *698*, 253–278.

Sophia Fox, A. J., Bedi, A., & Rodeo, S. A. (2009). The Basic Science of Articular Cartilage. *Sports Health*, 1(6), 461–468.

Srikanth, V.K., Fryer, J. L., Zhai, G., Winzenberg, T. M., Hosmer, D., & Jones, G. (2005). A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis and Cartilage*, 13(9), 769–781.

Stall, N.M., Kagoma, Y. K., Bondy, J. N., & Naudie, D. (2013). Surgical waste audit of 5 total knee arthroplasties. *Canadian Journal of Surgery*, 56(2), 97–102.

Suchánek, J., Visek, B., Soukup, T., El-Din Mohamed, S.K., Ivancaková, R., Mokrỳ, J., Abdoul-Ezz, E.H., & Omran, A. (2010). Stem cells from human exfoliated deciduous teeth--isolation, long term cultivation and phenotypical analysis. *Acta Medica (Hradec kralove),* 53(2), 93–99.

Sutton, P.M., & Holloway, E.S. (2013). The young osteoarthritic knee: dilemmas in management. *BMC Medicine*, 11:14

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 126(4), 663–676.

Takeda, J., Seino, S., & Bell, G.I. (1992). Human Oct3 gene family: cDNA sequences, alternative splicing, gene organization, chromosomal location, and expression at low levels in adult tissues. *Nucleic Acids Research*, 20(17), 4613–4620.

Tang, J., Cui, W., Song, F., Zhai, C., Hu, H., Zuo, Q., & Fan, W. (2015). Effect of mesenchymal stem cells on interleukin-1β-treated chondrocytes and cartlage in a rat osteoarthritic model. *Molecular Medicine Reports,* 12(2),1753-1760

Tang, Y. L., Zhao, Q., Zhang, Y. C., Cheng, L., Liu, M., Shi, J., Yang, Y.Z., Pan, C., Ge, J. & Phillips, M. I. (2004). Autologous mesenchymal stem cell transplantation induce VEGF and neovascularization in ischemic myocardium. *Regulatory Peptides*, 117(1), 3–10.

Tew, S.R., Murdoch, A.D., Rauchenberg, R.P., & Hardingham, T.E. (2008). Cellular methods in cartilage research: primary human chondrocytes in culture and chondrogenesis in human bone marrow stem cells. *Methods*, 45(1), 2–9.

Tilg, H., Trehu, E., Atkins, M.B., Dinarello, C.A., & Mier, J.W. (1994). Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood*, 83(1), 113–118.

Timmers, L., Lim, S.K., Hoefer, I.E., Arslan, F., Lai, R.C., van Oorschot, A.A. Goumans, M.J., Strider, C., Sze, S.K., Choo, A., Piek, J.J., Doevendans, P.A., Pasterkamp., de Kleijn, D.P. (2011). Human mesenchymal stem cell-conditioned medium improves cardiac function following myocardial infarction. *Stem Cell Research*, 6(3), 206–214.

Tofiño-Vian, M., Guillén, M. I., Pérez Del Caz, M. D., Silvestre, A., & Alcaraz, M. J. (2018). Microvesicles from human adipose tissue-derived mesenchymal stem cells as a new protective strategy in osteoarthritic chondrocytes. *Cellular Physiology and Biochemistry,* 47(1), 11–25.

Torrero, J., &Martínez, C. (2015). New developments in the treatment of osteoarthritis-focus on biologic agents. *Open Access Rheumatology: Research and Reviews,* 2015(7), 33-43

Tsai, C.C., & Hung, S.C. (2012). Functional roles of pluripotency transcription factors in mesenchymal stem cells. *Cell Cycle*, 11(20), 3711–3712.

Tsai, C.C., Su, P.F., Huang, Y.F., Yew, T.L., & Hung, S.C. (2012). Oct4 and Nanog directly regulate Dnmt1 to maintain self-renewal and undifferentiated state in mesenchymal stem cells. *Molecular Cell*, 47(2), 169–182.

Tsai, C.L., Chuang, P.C., Kuo, H.K., Chen, Y.H., Su, W.H., Wu, P.C. (2015). Differentiation of stem cells from human exfoliated deciduous teeth toward a phenotype of corneal epithelium in vitro. *Cornea*, *34*(11), 1471–1477.

Tsuchida, A. I., Beekhuizen, M., Rutgers, M., van Osch, G. J., Bekkers, J.E., Bot, A.G., Geurts, B., Dhert, W.J., Saris, D.B., & Creemers, L.B. (2012). Interleukin-6 is elevated in synovial fluid of patients with focal cartilage defects and stimulates cartilage matrix production in an in vitro regeneration model. *Arthritis Research and Therapy*, 14(6), R262.

Tsuchiya, H., Kitoh, H., Sugiura, F., & Ishiguro, N. (2003). Chondrogenesis enhanced by overexpression of sox9 gene in mouse bone marrow-derived mesenchymal stem cells. *Biochemical and Biophysical Research Communications*, 301(2), 338–343.

Tyler, J.A. (1989). Insulin-like growth factor 1 can decrease degradation and promote synthesis of proteoglycan in cartilage exposed to cytokines. *Biochemical Journal*, 260(2), 543–548.

Udgata, S. (2014). Osteoarthritis: an overview. *Journal of Pharmacy and Biological Sciences*, 9(5), 7-15

Ullah, I., Subbarao, R.B., Kim, E.J., Bharti, D., Jang, S.J., Park, J.S., Shivakumar, S.B., Lee, S.L., Kang, D., Byun, J.H., Park, B.W., & Rho, G.-J. (2016). In vitro comparative analysis of human dental stem cells from a single donor and its neuronal differentiation potential evaluated by electrophysiology. *Life Sciences*, 154, 39–51.

Umulis, D., O'Connor, M. B., & Blair, S.S. (2009). The extracellular regulation of bone morphogenetic protein signaling. *Development,* 136(22), 3715–3728.

van Buul, G. M., Villafuertes, E., Bos, P.K., Waarsing, J. H., Kops, N., Narcisi, R., Weinans, H., Verhaar, J.A., Bernsen, M.R., & van Osch, G.J. (2012). Mesenchymal stem cells secrete factors that inhibit inflammatory processes in short-term osteoarthritic synovium and cartilage explant culture. *Osteoarthritis and Cartilage*, 20(10), 1186–1196.

van der Kraan, P. M., Blaney Davidson, E. N., Blom, A., & van den Berg, W. B. (2009). TGF-beta signaling in chondrocyte terminal differentiation and osteoarthritis: modulation and integration of signaling pathways through receptor-Smads. *Osteoarthritis and Cartilage*, 17(12), 1539–1545.

van Roon, J.A., van Roy, J.L., Gmelig-Meyling, F.H., Lafeber, F.P., & Bijlsma, J.W. (1996). Prevention and reversal of cartilage degradation in rheumatoid arthritis by interleukin-10 and interleukin-4. *Arthritis and Rheumatism*, 39(5), 829–835.

van Schaijik, B., Davis, P.F., Wickremesekera, A.C., Tan, S. T., & Itinteang, T. (2018). Subcellular localisation of the stem cell markers OCT4, SOX2, NANOG, KLF4 and c-MYC in cancer: a review. *Journal of Clinical Pathology*, 71(1), 88–91.

Vasiliadis, H.S., & Wasiak, J. (2010). Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. *The Cochrane Database of Systematic Reviews*, 10, CD003323.

Vedicherla, S., & Buckley, C.T. (2017). Rapid chondrocyte isolation for tissue engineering applications: the effect of enzyme concentration and temporal exposure on the matrix forming capacity of nasal derived chondrocytes. *BioMed Research International*. 2017, e2395138.

Verma, P., & Dalal, K. (2011). ADAMTS-4 and ADAMTS-5: key enzymes in osteoarthritis. *Journal of Cellular Biochemistry*, 112(12), 3507–3514.

Verma, R.P., & Hansch, C. (2007). Matrix metalloproteinases (MMPs): chemical-biological functions and (Q)SARs. *Bioorganic and Medicinal Chemistry*, 15(6), 2223–2268.

Vishnubhatla, I., Corteling, R., Stevanato, L., Hicks, C., & Sinden, J. (2014). The development of stem cell-derived exosomes as a cell-free regenerative medicine. *Journal of Circulating Biomarkers*. 3, 2.

Vishwanath, V.R., Nadig, R.R., Nadig, R., Prasanna, J.S., Karthik, J., & Pai, V.S. (2013). Differentiation of isolated and characterized human dental pulp stem cells and stem cells from human exfoliated deciduous teeth: An in vitro study. *Journal of Conservative Dentistry,* 16(5), 423–428.

Vizoso, F. J., Eiro, N., Cid, S., Schneider, J., & Perez-Fernandez, R. (2017). Mesenchymal stem cell secretome: toward cell-free therapeutic strategies in regenerative medicine. *International Journal of Molecular Sciences*, 18(9), 1852.

Vos, T., Flaxman, A.D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., … Memish, Z. A. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet,* 380(9859), 2163–2196.

Wakayama, H., Hashimoto, N., Matsushita, Y., Matsubara, K., Yamamoto, N., Hasegawa, Y., Ueda, M., & Yamamoto, A. (2015). Factors secreted from dental pulp stem cells show mutifaceted benefits for treating acute lung injury in mice. *Cytotherapy*, 17(18), 1119-1129

Wakitani, S., Imoto, K., Kimura, T., Ochi, T., Matsumoto, K., & Nakamura, T. (1997). Hepatocyte growth factor facilitates cartilage repair. Full thickness articular cartilage defect studied in rabbit knees. *Acta Orthopaedica Scandinavica*, 68(5), 474–480.

Wakitani, S., Okabe, T., Horibe, S., Mitsuoka, T., Saito, M., Koyama, T., Nawata, M., Tensho, K., Kato, H., Uematsu, K., Kuroda, R., Kurosaka, M., Yoshiya., S. & Ohgushi, H. (2011). Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. *Journal of Tissue Engineering and Regenerative Medicine*, 5(2), 146–150.

Wang, L., Gai, P., Xu, R., Zheng, Y., Lv, S., Li, Y., & Liu, S. (2015). Shikonin protects chondrocytes from interleukin-1beta-induced apoptosis by regulating PI3K/Akt signaling pathway. *International Journal of Clinical and Experimental Pathology*, 8(1), 298–308.

Wang, M., Sampson, E.R., Jin, H., Li, J., Ke, Q.H., Im, H.J., & Chen, D. (2013). MMP13 is a critical target gene during the progression of osteoarthritis. *Arthritis Research and Therapy*, *15*, R5.

Wang, X., Zhao, Y., Xiao, Z., Chen, B., Wei, Z., Wang, B., Zhang, J., Han, J., Gao, Y., Li, L., Zhao, H., Zhao, W., Lin, H., & Dai, J. (2009). Alternative translation of OCT4 by an internal ribosome entry site and its novel function in stress response. *Stem Cell,* 27(6), 1265–1275.

Wang, Y., & Lou, S. (2001). Direct protective effect of interleukin-10 on articular chondrocytes in vitro. *Chinese Medical Journal*. 114(7), 723–725.

Wang, Y, Yu, D., Liu, Z., Zhou, F., Dai, J., Wu, B., Zhou, J., Heng, B.C., Zou, X.H., Ouyang, H., & Liu, H. (2017). Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. *Stem Cell Research and Therapy*, 8(1), 189.

Weber, G.F., Bjerke, M.A., & DeSimone, D.W. (2011). Integrins and cadherins join forces to form adhesive networks. *Journal of Cell Science*. 124(8), 1183–1193.

Wei, X., Yang, X., Han, Z., Qu, F., Shao, L. and Shi, Y. (2013). Mesenchymal stem cells: a new trend for cell therapy. *Acta Pharmacologica Sinica*, 34(6), 747–754.

Wilusz, R.E., Sanchez-Adams, J., & Guilak, F. (2014). The structure and function of the pericellular matrix of articular cartilage. *Matrix Biology,* 39, 25–32.

Wojdasiewicz, P., Poniatowski, Ł.A., & Szukiewicz, D. (2014). The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. *Mediators of Inflammation*, 2014, 1-19.

Woolf, A.D., & Pfleger, B. (2003). Burden of major musculoskeletal conditions. *Bulletin of the World Health Organization*, 81(9), 646–656.

Wu, L., Leijten, J. C. H., Georgi, N., Post, J. N., van Blitterswijk, C. A., & Karperien, M. (2011). Trophic effects of mesenchymal stem cells increase chondrocyte proliferation and matrix formation. *Tissue Engineering. Part A*, 17(9–10), 1425–1436.

Wu, L., Prins, H.J., Helder, M.N., van Blitterswijk, C.A., & Karperien, M. (2012). Trophic effects of mesenchymal stem cells in chondrocyte co-cultures are independent of culture conditions and cell sources. *Tissue Engineering Part A*, 18(15–16), 1542–1551.

Wu, Q., Kim, K.O., Sampson, E.R., Chen, D., Awad, H., O'Brien, T., Puzas, J.E., Drissi, H., Schwarz, E.M., O'Keefe, R.J., Zuscik, M.J., & Rosier, R.N. (2008). Induction of an osteoarthritis-like phenotype and degradation of phosphorylated Smad3 by Smurf2 in transgenic mice. *Arthritis and Rheumatism*, 58(10), 3132–3144.

Xia, P., Wang, X., Lin, Q., & Li, X. (2015). Efficacy of mesenchymal stem cells injection for the management of knee osteoarthritis: a systematic review and meta-analysis. *International Orthopaedics*, 39(12), 2363–2372.

Xin, H., Li, Y., Liu, Z., Wang, X., Shang, X., Cui, Y., Zhang, Z.G., & Chopp, M. (2013). MiR-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells in rats via transfer of exosome-enriched extracellular particles. *Stem Cells,* 31(12), 2737–2746.

Xin, L.Z., Govindasamy, V., Musa, S., & Abu Kasim, N.H. (2013). Dental stem cells as an alternative source for cardiac regeneration. *Medical Hypotheses*, 81(4), 704–706.

Xue, H., Tu, Y., Ma, T., Liu, X., Wen, T., Cai, M., Xia, Z., & Mei, J. (2015). Lactoferrin inhibits IL-1β-induced chondrocyte apoptosis through AKT1-induced CREB1 activation. *Cellular Physiology and Biochemistry*, 36(6), 2456–2465.

Xue, J., Wang, J., Liu, Q., & Luo, A. (2013). Tumor necrosis factor-α induces ADAMTS-4 expression in human osteoarthritis chondrocytes. *Molecular Medicine Reports*, 8(6), 1755–1760.

Yamagata, M., Yamamoto, A., Kako, E., Kaneko, N., Matsubara, K., Sakai, K., Sawamoto, K., & Ueda, M. (2013). Human dental pulp-derived stem cells protect against hypoxic-ischemic brain injury in neonatal mice. *Stroke*, 44(2), 551–554.

Yamaguchi, S., Shibata, R., Yamamoto, N., Nishikawa, M., Hibi, H., Tanigawa, T., Ueda, M., Murohara, T., & Yamamoto, A. (2015). Dental pulp-derived stem cell conditioned medium reduces cardiac injury following ischemia-reperfusion. *Scientific Reports*, 5, 16295.

Yamashita, A., Nishikawa, S., & Rancourt, D.E. (2010). Identification of five developmental processes during chondrogenic differentiation of embryonic stem cells. *Plos One, 5*(6), e10998.

Yamaza, T., Kentaro, A., Chen, C., Liu, Y., Shi, Y., Gronthos, S., Wang, S., & Shi, S. (2010). Immunomodulatory properties of stem cells from human exfoliated deciduous teeth. *Stem Cell Research and Therapy*, 1(1), 5.

Yang, B., Kang, X., Xing, Y., Dou, C., Kang, F., Li, J., Quan, Y., & Dong, S. (2014). Effect of microRNA-145 on IL-1β-induced cartilage degradation in human chondrocytes. *FEBS Letters*, 588(14), 2344–2352.

Yang, C.C., Lin, C.Y., Wang, H.S., & Lyu, S.R. (2013). Matrix metalloproteases and tissue inhibitors of metalloproteinases in medial plica and Pannus-like tissue contribute to knee osteoarthritis progression. *PLos One*, 8(11), e79662.

Yang, D., Wang, W., Li, L., Peng, Y., Chen, P., Huang, H., Guo, Y., Xia, X., Wang, Y., Wang, H., Wang, W.E., & Zeng, C. (2013). The relative contribution of paracine effect versus direct differentiation on adipose-derived stem cell transplantation mediated cardiac repair. *PLos One,* 8(3), e59020.

Yang, G., Li, S., Li, B., Cheng, L., Jiang, P., Tian, Z., & Sun, S. (2017). Protective effects of garlic-derived S-allylmercaptocysteine on IL-1 $\beta$ -stimulated chondrocytes by regulation of MMPs/TIMP-1 ratio and type II collagen expression via suppression of NF- $\kappa$ B pathway. *BioMed Research International*, 2017, 1–10.

Yang, K.G.A., Saris, D.B.F., Geuze, R.E., van Rijen, M.H.P., van der Helm, Y.J.M., Verbout, A.J., Creemers, L.B., & Dhert, W.J.A. (2006). Altered in vitro chondrogenic properties of chondrocytes harvested from unaffected cartilage in osteoarthritic joints. *Osteoarthritis and Cartilage*, 14(6), 561–570.

Yang, S., Li, W., Liu, W., Gao, C., Zhou, B., Li, S., Li, Y., & Kong, Y. (2006). IL-10 gene modified dendritic cells induced antigen-specific tolerance in experimental autoimmune myocarditis. *Clinical Immunology,* 121(1), 63–73.

Yang, X., Zhu, T.Y., Wen, L.C., Cao, Y.P., Liu, C., Cui, Y.P., Meng, Z.C., & Liu, H. (2015). Intraarticular injection of allogenic mesenchymal stem cells has a protective role for the osteoarthritis. *Chinese Medical Journal*, 128(18), 2516–2523.

Yang, Z., Mo, X., Gong, Q., Pan, Q., Yang, X., Cai, W., Li, C., Ma, J.X., He, Y., & Gao, G. (2008). Critical effect of VEGF in the process of endothelial cell apoptosis induced by high glucose. *Apoptosis,* 13(11), 1331–1343.

Ye, Z., Chen, Y., Zhang, R., Dai, H., Zeng, C., Zeng, H., Feng, H., Du, G., Fang, H., &Cai, D. (2013). c-Jun N-terminal kinase–c-Jun pathway transactivates Bim to promote osteoarthritis. *Canadian Journal of Physiology and Pharmacology*, 92(2), 132–139.

Yoo, S.W., Chang, D.Y., Lee, H.S., Kim, G.H., Park, J.S., Ryu, B.Y., Joe, E.H., Lee, Y.D., Kim, S.S. & Suh-Kim, H. (2013). Immune following suppression mesenchymal stem cell transplantation in the ischemic brain is mediated by TGF-β. *Neurobiology of Disease*, *58*, 249–257.

Yoon, D.S., Kim, Y.H., Jung, H.S., Paik, S., & Lee, J.W. (2011). Importance of Sox2 in maintenance of cell proliferation and multipotency of mesenchymal stem cells in low- density culture. *Cell Proliferation*, 44(5), 428–440.

Yoon, H. J., Kim, S. B., Somaiya, D., Noh, M. J., Choi, K.B., Lim, C.L., Lee, H.Y., Lee, Y.J., Yi, Y., & Lee, K. H. (2015). Type II collagen and glycosaminoglycan expression induction in primary human chondrocyte by TGF-β1. *BMC Musculoskeletal Disorders*, 16, 141.

Young, J.C., Major, A.T., Miyamoto, Y., Loveland, K.L., & Jans, D.A. (2011). Distinct effects of importin α2 and α4 on Oct3/4 localization and expression in mouse embryonic stem cells. *FASEB Journal,* 25(11), 3958–3965.

Youssef, A., Aboalola, D., & Han, V.K.M. (2017). The roles of insulin-like growth factors in mesenchymal stem cell niche. *Stem Cells International*, 2017, 1-12.

Yubo, M., Yanyan, L., Li, L., Tao, S., Bo, L., & Lin, C. (2017). Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: A meta-analysis. *Plos One*, 12(4), e0175449

Yu, H.H., Featherston, T., Tan, S.T., Chibnall, A.M., Brasch, H.D., Davis, P.F. & Itinteang, T. (2016). Characterization of cancer stem cells in moderately differentiated buccal mucosal squamous cell carcinoma. *Frontiers in Surgery*, 3, 46.

Yu, J., Vodyanik, M.A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J.L., Tians, S., Nie, J., Jonsdottir, G.A., Ruotti, V., Stewart, R., Slukvin. I.I., & Thomson, J. A. (2007). Induced pluripotent stem cell lines derived from human somatic cells. *Science,* 318(5858), 1917–1920.

Yu, S., Diao, S., Wang, J., Ding, G., Yang, D., & Fan, Z. (2014). Comparative analysis of proliferation and differentiation potentials of stem cells from inflamed pulp of deciduous teeth and stem cells from exfoliated deciduous teeth. *BioMed Research International,* 2014, 930907.

Zangrossi, S., Marabese, M., Broggini, M., Giordano, R., D'Erasmo, M., Montelatici, E., Intini, D., Neri, A., & Lazzari, L. (2007). Oct-4 expression in adult human differentiated cells challenges its role as a pure stem cell marker. *Stem Cells, 25*(7), 1675–1680.

Zhang, Q.Z., Su, W.R., Shi, S-H., Wilder-Smith, P., Xiang, A.P., Wong, A., Nguyen, A.L., Kwon, C.W., & Le, A.D. (2010). Human gingiva-derived mesenchymal stem cells elicit polarization of m2 macrophages and enhance cutaneous wound healing. *Stem Cell,* 28(10), 1856–1868.

Zhang, S., Chu, W.C., Lai, R. C., Lim, S.K., Hui, J.H.P., & Toh, W.S. (2016). Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. *Osteoarthritis and Cartilage*, *24*(12), 2135–2140.

Zhang, S., & Cui, W. (2014). Sox2, a key factor in the regulation of pluripotency and neural differentiation. *World Journal of Stem Cells*, 6(3), 305–311.

Zhang, W., Ouyang, H., Dass, C.R., & Xu, J. (2016). Current research on pharmacologic and regenerative therapies for osteoarthritis. *Bone Research*, 4, 15040.

Zhang, X., Zhu, Y., Chen, X., Zhang, Y., Zhang, Y., Jia, Y., Wang, H., Liu, Y., & Xiao, L. (2014). Baicalein ameliorates inflammatory-related apoptotic and catabolic phenotypes in human chondrocytes. *International Immunopharmacology*, 21(2), 301–308.

Zhang, Y., Hunter, D. J., Nevitt, M. C., Xu, L., Niu, J., Lui, L.Y., Yu, W., Aliabadi, P., & Felson, D.T. (2004). Association of squatting with increased prevalence of radiographic tibiofemoral knee osteoarthritis: The Beijing Osteoarthritis Study. *Arthritis and Rheumatism*, 50(4), 1187–1192.

Zhu, Y, Song, X., Wang, J., Li, Y., Yang, Y., Yang, T., Ma, H., Wang, L., Zhang, G., Cho, W.C., Liu, X., & Wei, J. (2015). Placental mesenchymal stem cells of fetal origin deposit epigenetic alterations during long-term culture under serum-free condition. *Expert Opinion on Biological Therapy*, 15(2), 163–180.

Zhu, Y, Wang, Y., Zhao, B., Niu, X., Hu, B., Li, Q., Zhang, J., Ding, J., Chen, Y. and Wang, Y. (2017). Comparison of exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells and synovial membrane-derived mesenchymal stem cells for the treatment of osteoarthritis. *Stem Cell Research and Therapy*, 8(1), 64.

Zwickl, H., Niculescu-Morzsa, E., Halbwirth, F., Bauer, C., Jeyakumar, V., Reutterer, A., Berger, A., Nehrer, S. (2016). Correlation analysis of SOX9, -5, and -6 as well as COL2A1 and aggrecan gene expression of collagen I implant–derived and osteoarthritic chondrocytes. *Cartilage*, 7(2), 185–192.