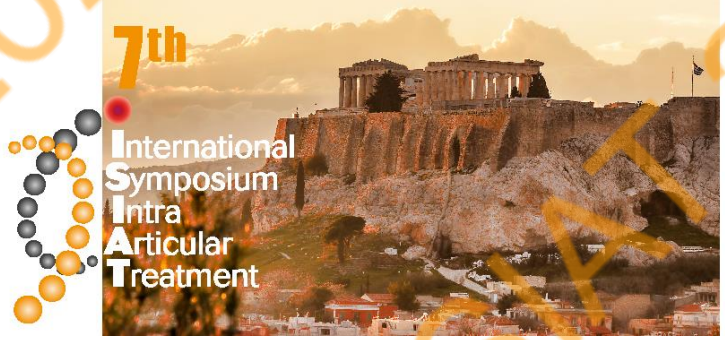

Athens

5-7 October 2023

Should we implant or inject the stem cells ?

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Disclosures

- Funding: Chugai, Amgen, Novartis
- Expert committee: Pfizer, Abbvie, Novartis
- Communications: Medac, BMS, Abbvie

Introduction

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Bijlsma JWJ et al. Lancet 2011

Introduction

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

OA is COMMON & GROWING

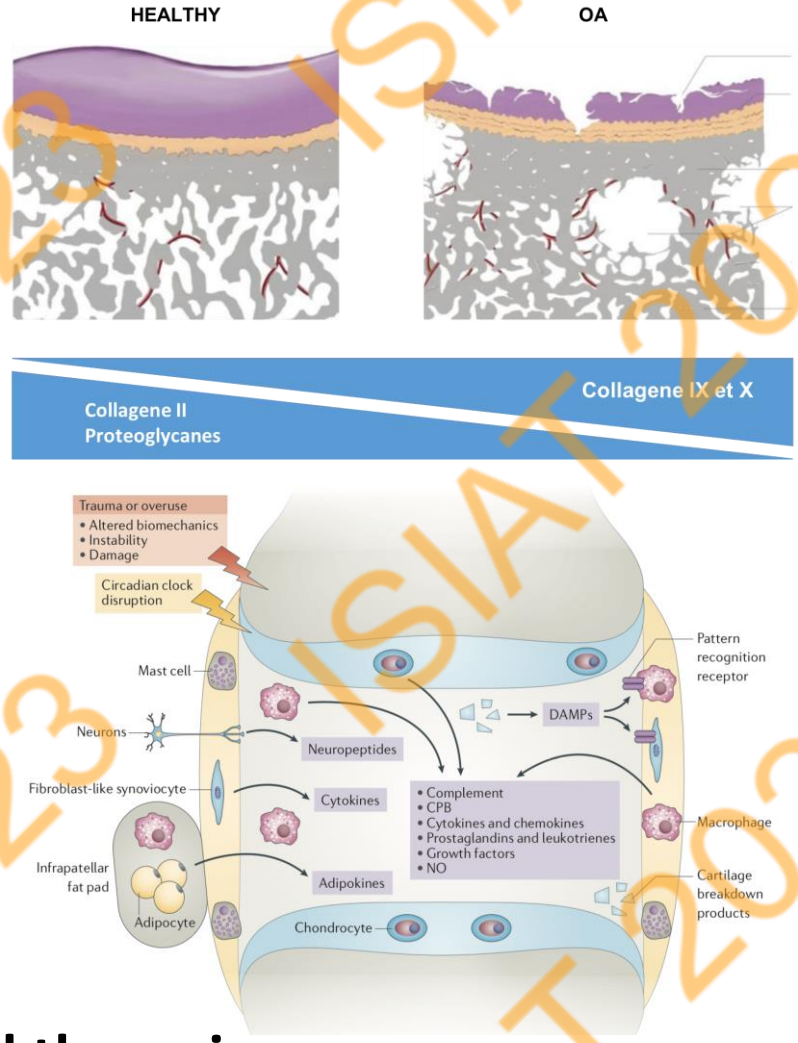
Affects
240 million
people worldwide

2x more women than men

Bijlsma JWJ et al. Lancet 2011

Introduction

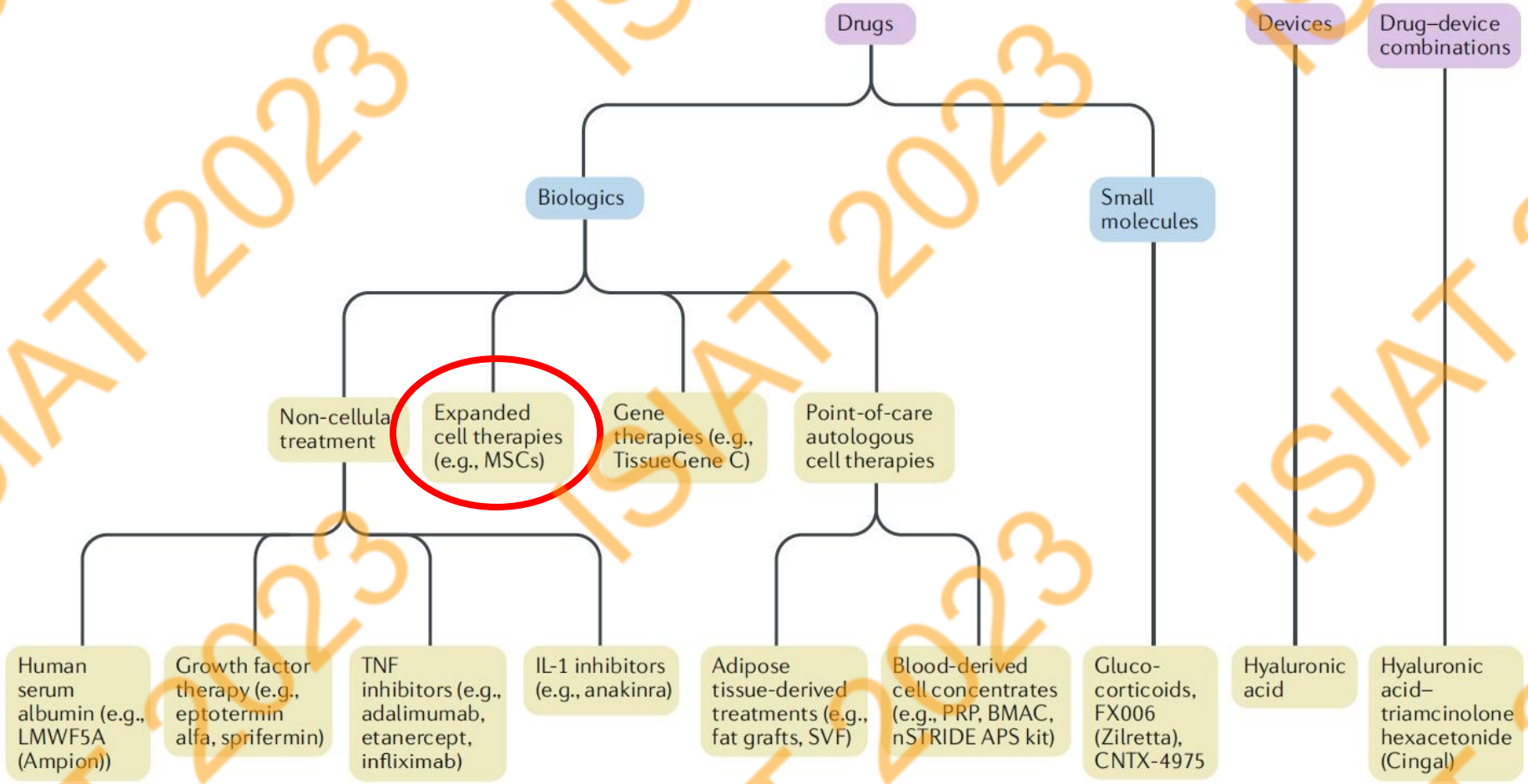
- All the components of the joint are involved in the process
  - Cartilage ≈ chondrocytes + ECM
  - Subchondral bone ≈ OC/OB
  - Synovial ≈ inflammation
  - Muscles, ligaments
- Therapeutic background
  - No curative or chondro-protective treatment
  - Moderate pain efficacy:
    - Poor tolerance on high-risk subjects
    - Moderate effectiveness: NSAIDs improve less than 50% of the WOMAC score



Need to explore new targets and therapies

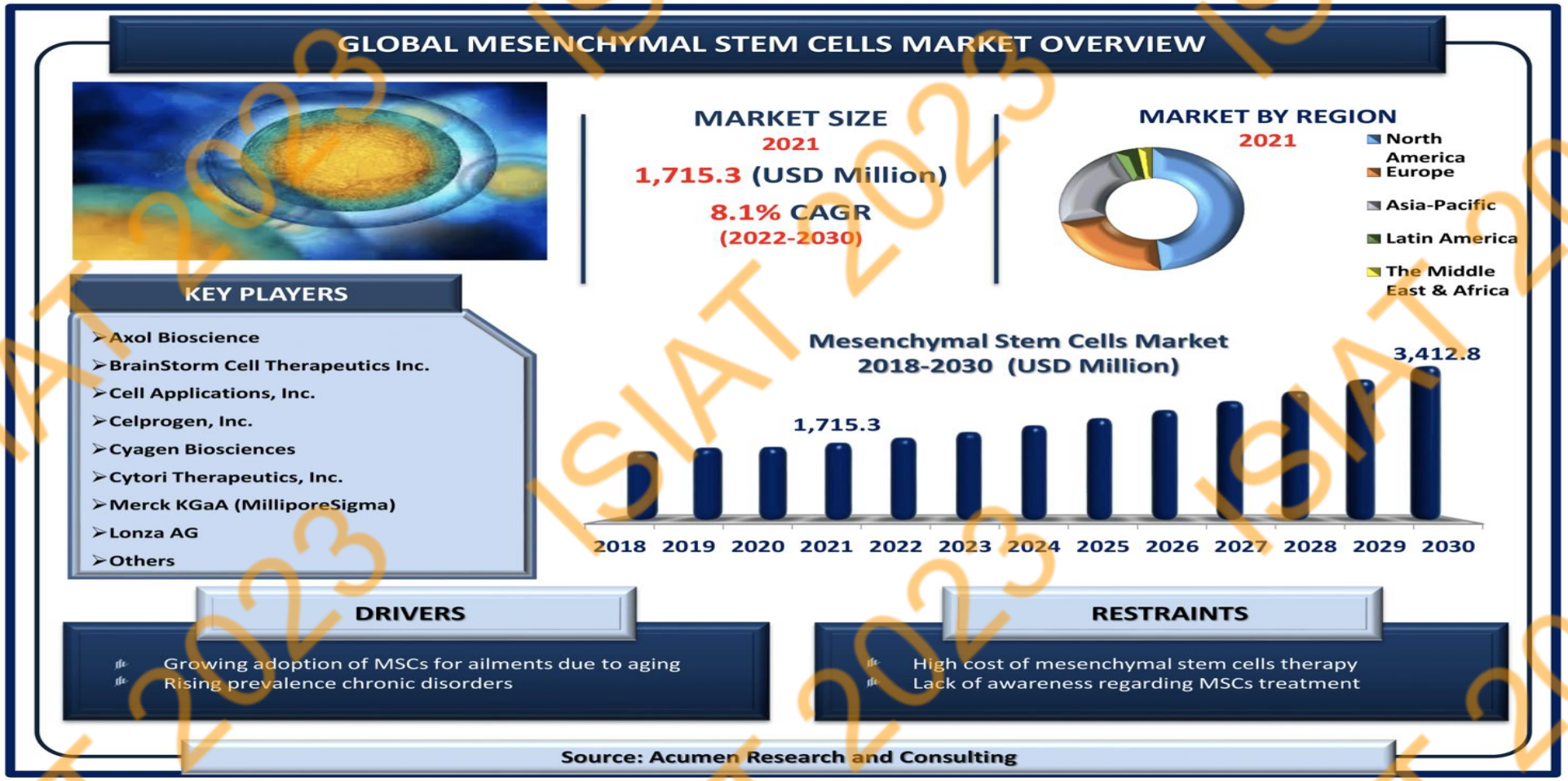
Robinson et al. Nat Rev Rheumatol 2016

Intra-articular treatment in OA



Jones IA. Nature Rev Rheum. 2018

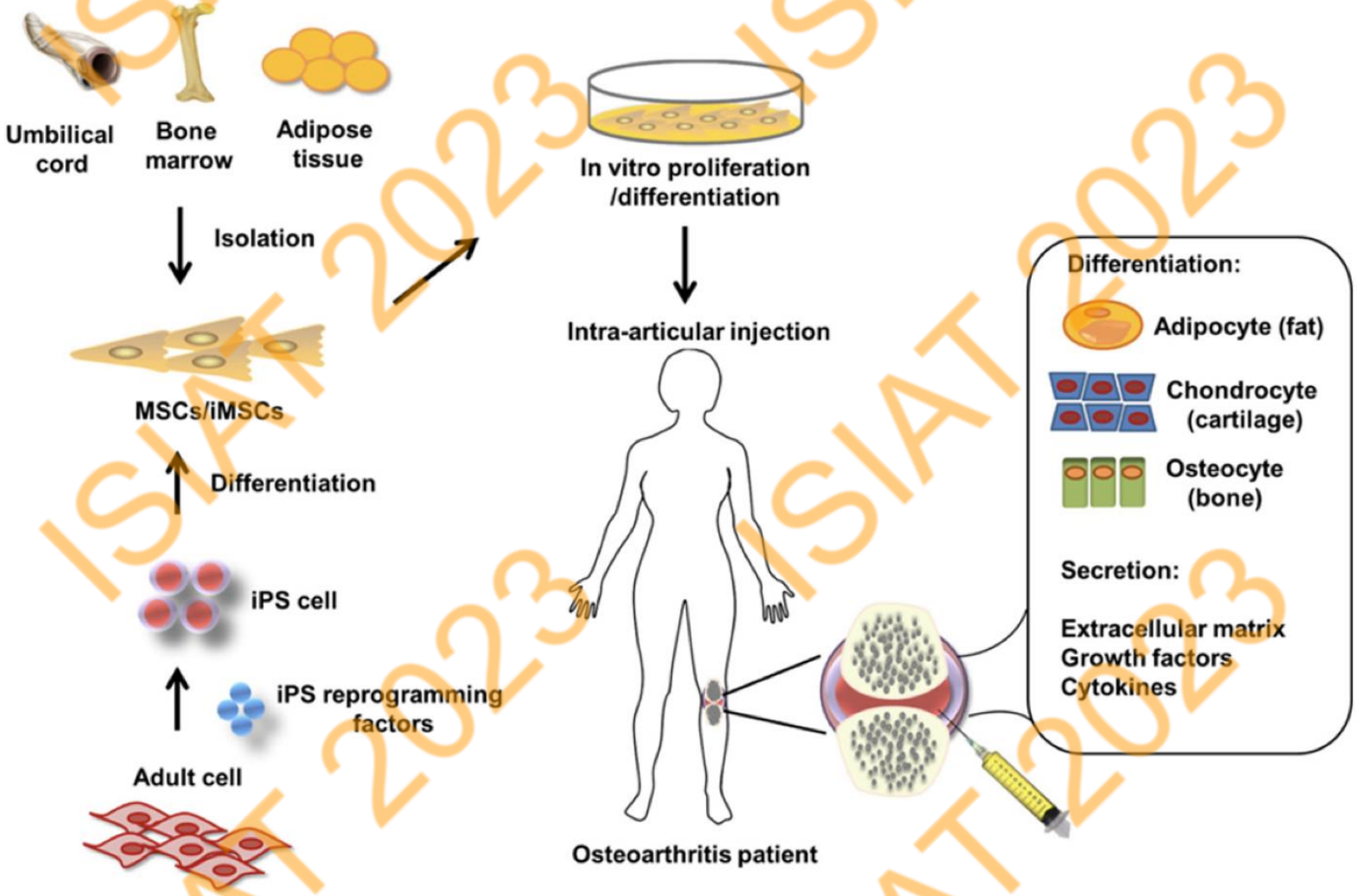
Global mesenchymal stem cell market expected to double in less than 10 years !



Mesenchymal Stem Cells Market Size - Global Industry, Share, Analysis, Trends and Forecast 2022 – 2030. Healthcare and Pharmaceuticals. https://www.acumenresearchandconsulting.com/mesenchymal-stem-cells-market. Published 2022

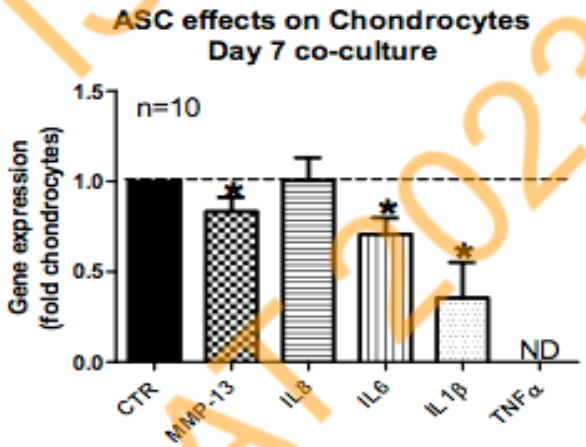
Why stem cell therapy makes sense in OA ?

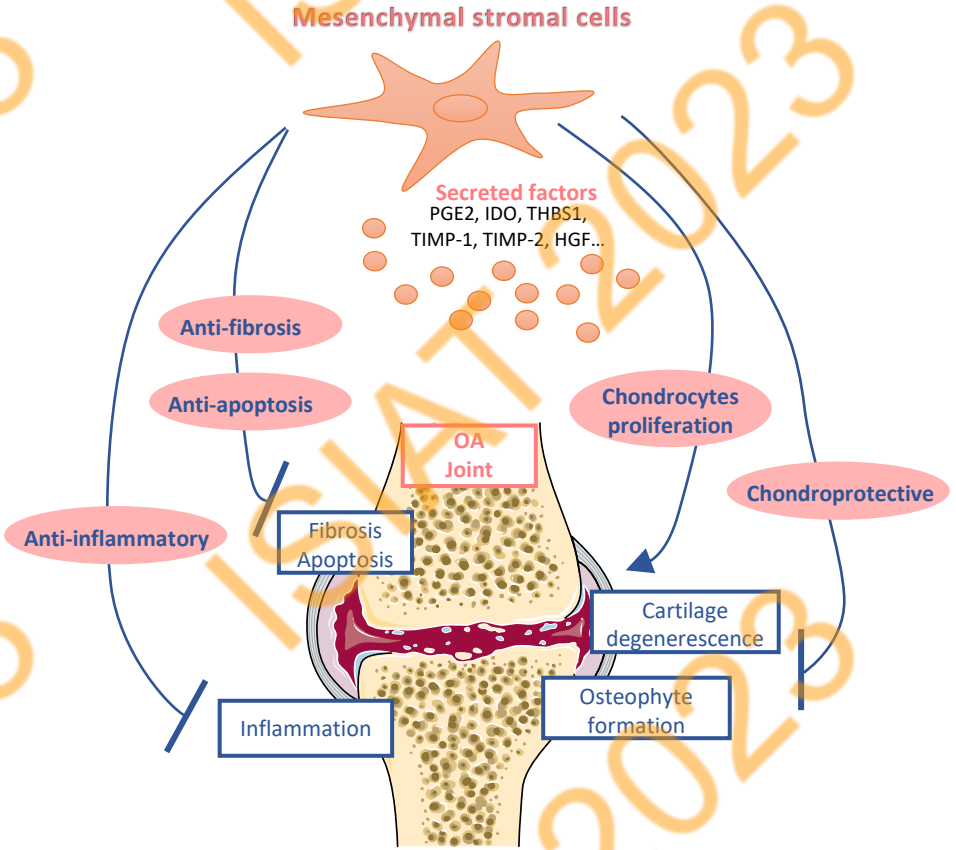
- MSC > Chondrocytes
- Sources available
- Cell differentiation
- Allo > autologous

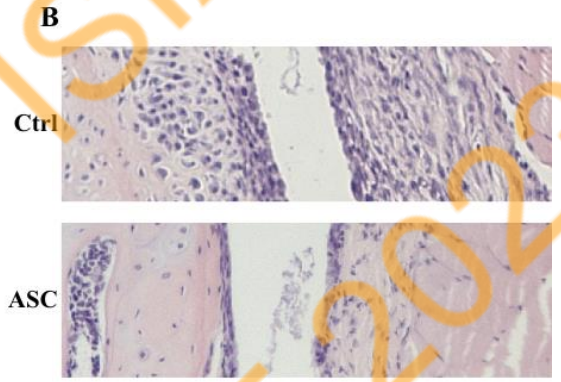


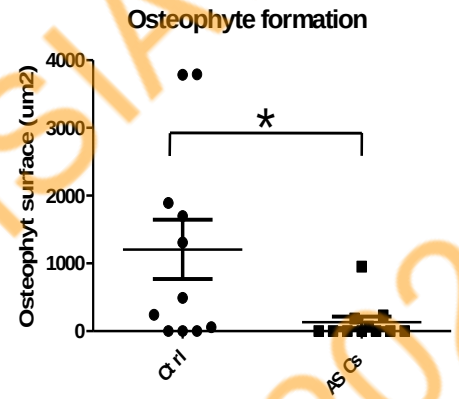
Zhu C et al. Am J Transl Res 2021

Why stem cell therapy makes sense in OA ?



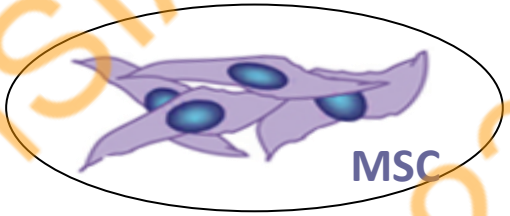




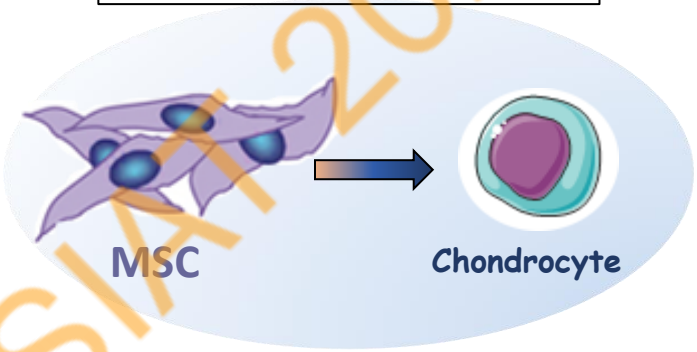


Maumus M, Pers YM et al. Med Sciences 2019
Ter Huurne and Van Lent P et al. Arthritis and Rheumatol. 2012
Manferdini et al. Arthritis and Rheumatol. 2013

When MSC may be useful for cartilage damage ?



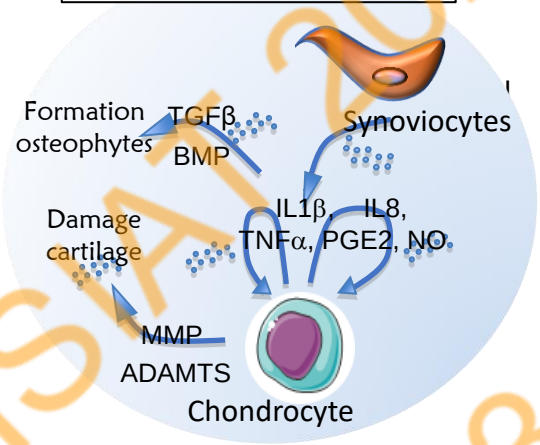
Differentiation capacities



Differentiation in chondrocytes using biomaterials

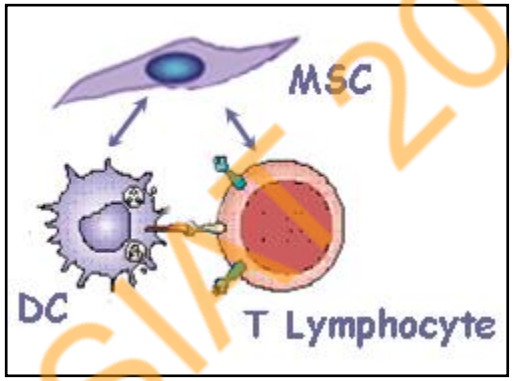
Tissue engineering: Repair of focal defects

Trophic functions



Chondroprotection and stimulation of endogenous repair

Immunoregulatory functions



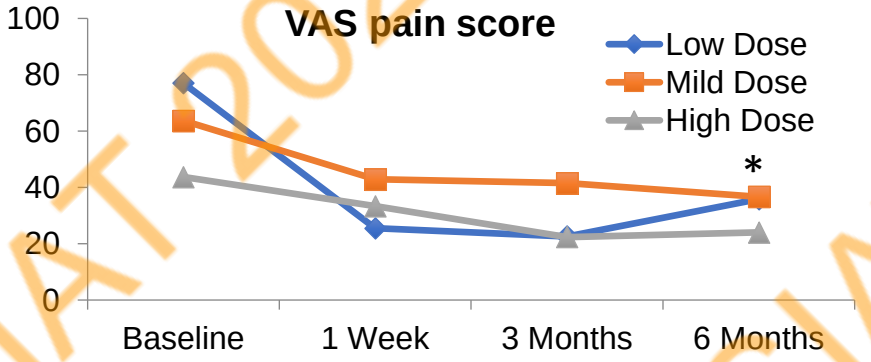
To block inflammation

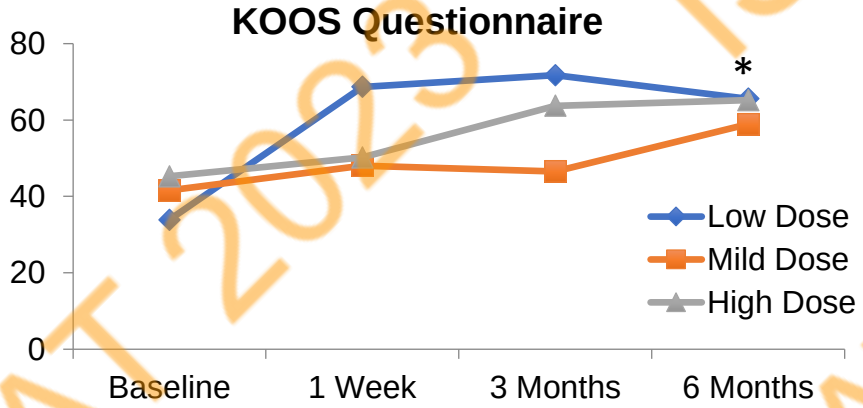
Anti-inflammatory cell therapies

Application to osteoarthritis

ADIPOA1 clinical study

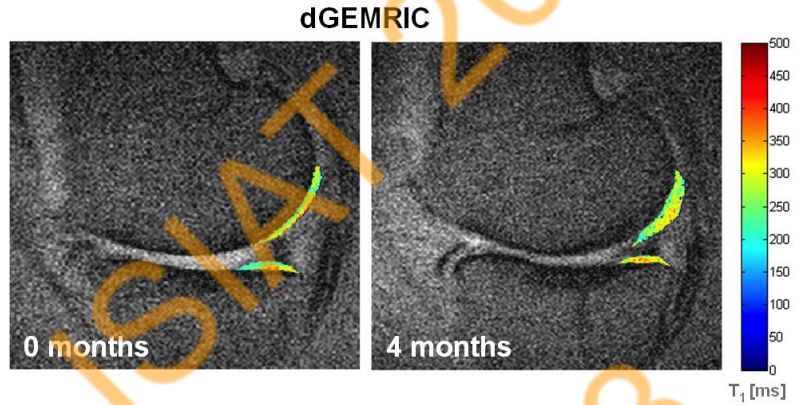
- Excellent safety: 4 local joint effusion during the first month
- Histological analysis at 3 months: no cell or ectopic proliferation
- TKR occurs for 18% of patients at 1 year and 55% at 4 years

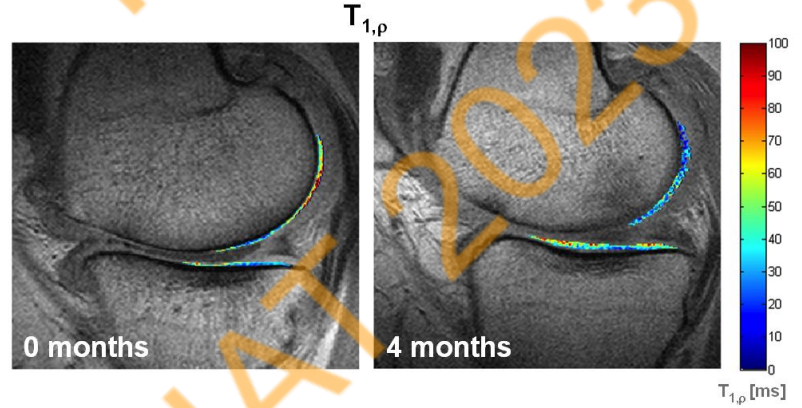




Pers YM et al. Stem Cells Translational Medicine 2016

- MRI with dGEMRIC (GAG) sequences
- 3 patients improved
- Possible structural effect?





MSC clinical results in OA

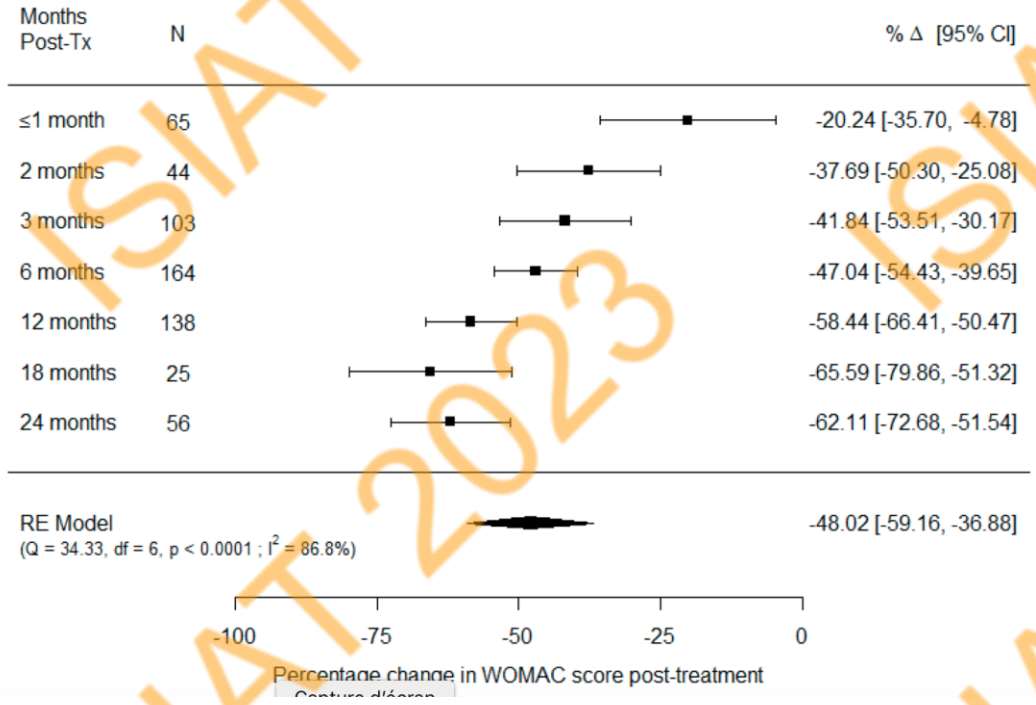
cells

MDPI

Systematic Review

Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis

Nikhil Agarwal [1], Christopher Mak [2], Christine Bojanic [2], Kendrick To [2] and Wasim Khan [2,*]



Joint Bone Spine 89 (2022) 105404

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Recommendations and metaanalyses

Safety and efficacy of adipose-derived mesenchymal stem cells for knee osteoarthritis: A systematic review and m-analysis

Mohamed Gadelkarim [a,b,1,*], Aya Abd Elmegeed [c,1], Ahmed Hafez Allam [d,1], Ahmed K. Awad [e], Mostafa Ahmed Shehata [b,f], Asmaa AbouEl-Enein [g], Mohamed Eid Alsadek [h], Mohammad Abo Deeb [i], Ahmed M. Afifi [j]

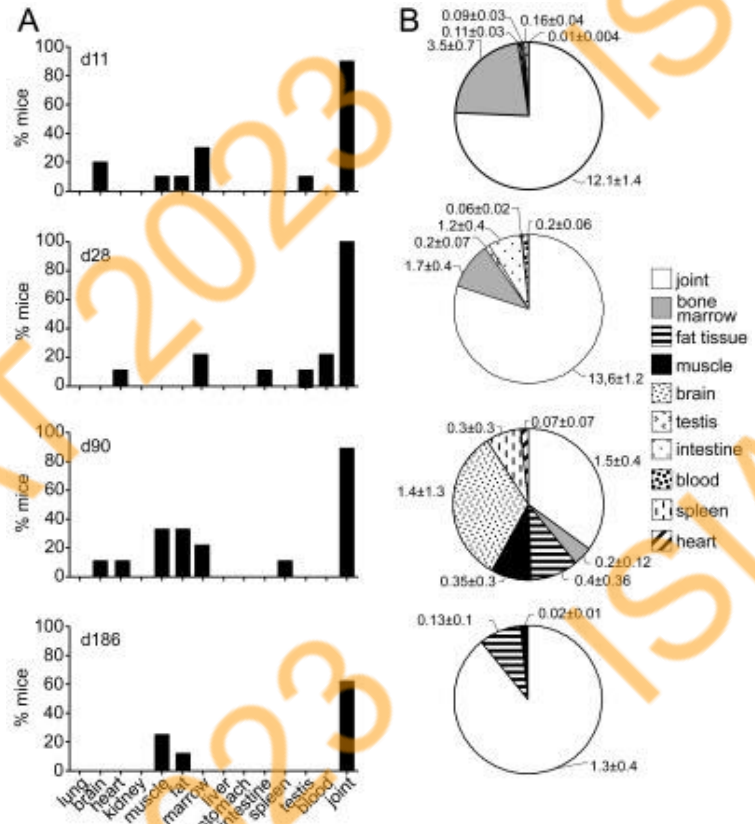
suppl. Informations

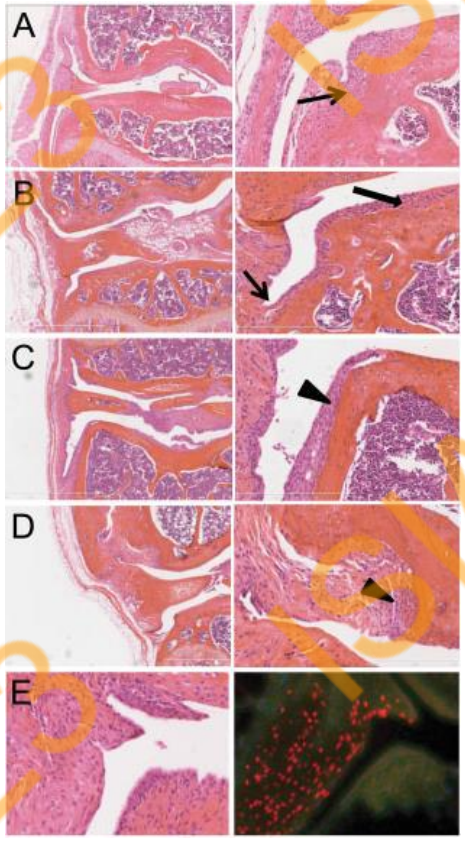
Conclusion: In the present single-arm meta-analysis, ADMSCs were associated with significant reduction in pain and improvement in QOL and knee functions in patients with knee OA. However, double arm analyses did not confirm these positive findings, which may be returned to the small sample size of included patients. Therefore, to introduce ADMSCs into clinical practice and establish guidelines for their use, more randomized controlled clinical trials with large sample sizes and long-term follow-ups are needed.

→ Heterogeneity in the current literature
Risk of bias not negligible

Agarwal et al. Cells 2021
Gadelkarim et al. JBS 2022

ASC distribution after IA injection -> reduced lifespan





ADIPOA

Maumus M et al. *Arthritis and rheumatology*. 2013

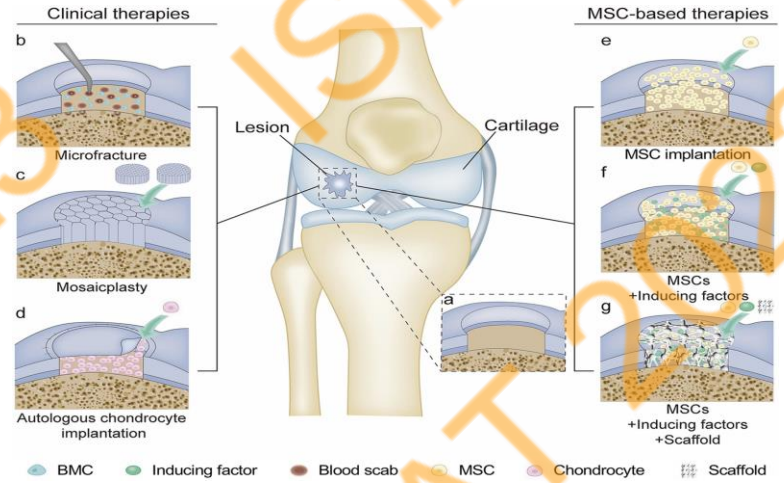
15% of ASCs are detected at 1 month

1,3% at 6 months.

ASCs are localised in synovial membrane

MSC based therapies for cartilage repair

- Several advantages
  - produce various ECM for the recovery of cartilage functions
  - release cytokines, growth factors, and chemokines to drive endogenous MSCs
  - combination of MSCs with the engineered scaffold
- Large cartilage lesions: surgery and tissue engineering



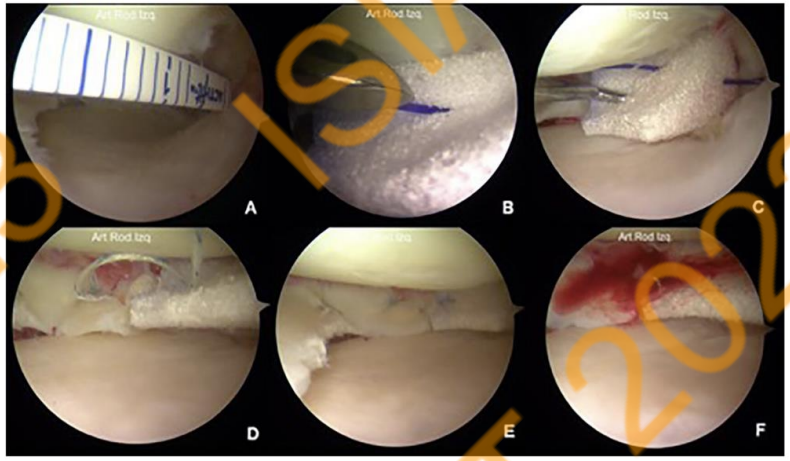
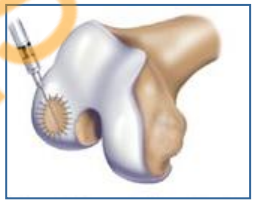


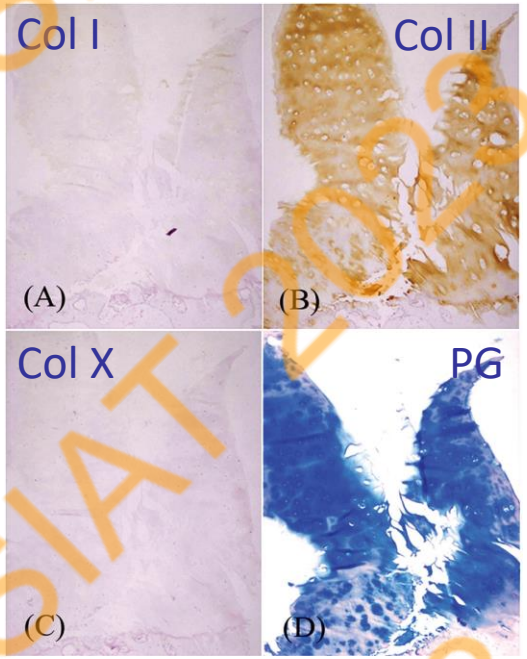
Figure 3. Surgical technique of medial meniscus substitution in the posterior horn with polyurethane implant enriched with MSCs. (**A**) Defect size is estimation with a flexible ruler. (**B**, **C**) Once the implant is trimmed in

Zhu C et al. Am J Transl Res 2021

MSC implant > chondrocyte implant ?



BM-MSCs efficacy compared to autologous chondrocyte implantation ?



MSCs are as efficient as chondrocytes for cartilage repair (n=36)

- Improvement of patient QoL and activities in sports
- Hyalin cartilage formation (1 year)
- Less graft hypertrophy

MSCs can be used as an alternative to chondrocytes for cartilage repair

- reduced costs, better rate of cartilage cell proliferation
- only one surgery
- minimize morbidity at the donor site

Nejadnik *et al,* Am J. Sports Med, 2010

Large experience of MSC implants in OA

Mesenchymal Stem Cell Implantation in Knee Osteoarthritis

Midterm Outcomes and Survival Analysis in 467 Patients

Yong Sang Kim,* MD, Dong Suk Suh,* MD, Dae Hyun Tak,* MD, Pill Ku Chung,* MD, and Yong Gon Koh,*† MD

Investigation performed at Yonsei Sarang Hospital, Seoul, Republic of Korea

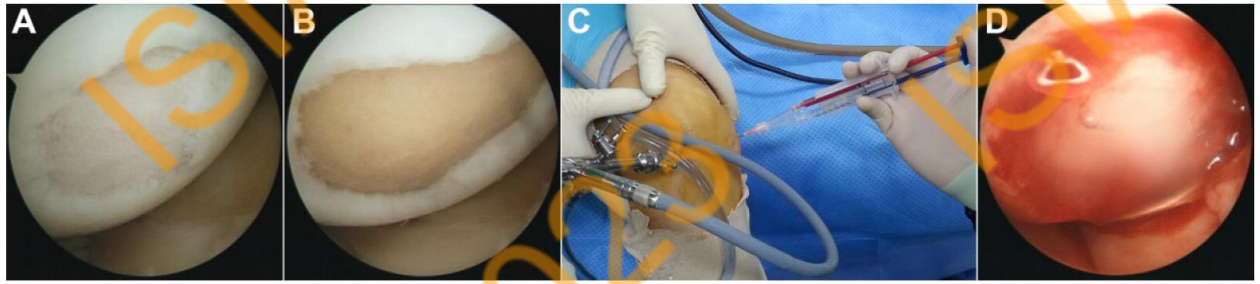


Figure 1. Arthroscopic implantation of mesenchymal stem cells loaded in fibrin glue. (A) An articular cartilage lesion in the medial femoral condyle was noticed. (B) An accurate debridement of all unstable and damaged cartilage in the lesion was performed. (C)

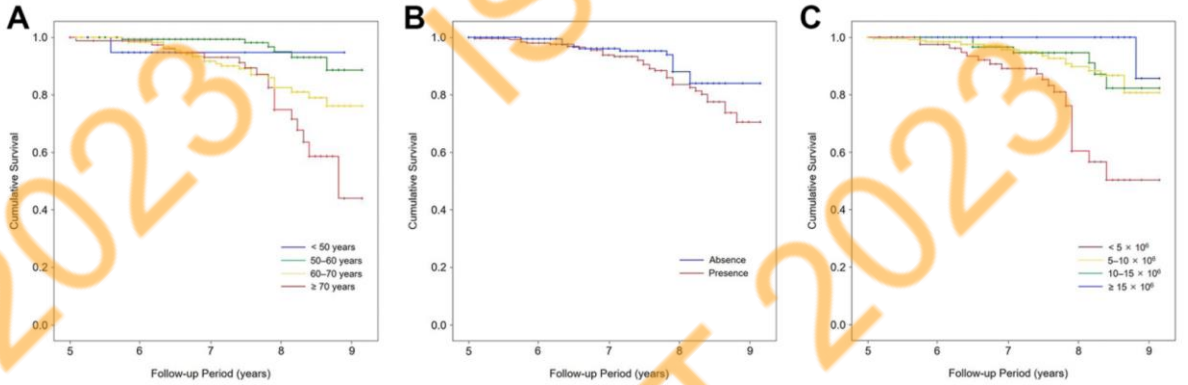


Figure 3. Kaplan-Meier survival curves. Survival rate of groups divided according to (A) age, (B) presence of bipolar kissing lesion, and (C) number of mesenchymal stem cells.

TABLE 2
Comparison of Preoperative and Postoperative Clinical and Radiological Outcomes[a]

		Postoperative			
	Preoperative	1 y	3 y	5 y	9 y
IKDC score	39.2 ± 7.2	66.6 ± 9.6[b]	67.2 ± 9.9[b,c]	66.1 ± 9.7[b,c,d]	62.8 ± 8.5[b,c,d,e]
Tegner score	2.3 ± 1.0	3.4 ± 0.9[b]	3.5 ± 0.9[b,c]	3.4 ± 0.9[c,d]	3.2 ± 0.9[b,c,d,e]
KL grade					
Grade 1	189 (39.1)	184 (38.1)	173 (35.8)	164 (34.0)[b,c]	159 (32.9)[b,c,d]
Grade 2	294 (60.9)	299 (61.9)	310 (64.2)	305 (63.1)[b,c]	293 (60.7)[b,c,d]
Grade 3				12 (2.5)[b,c,d]	26 (5.4)[b,c,d,e]
Grade 4				2 (0.4)[b,c,d]	5 (1.0)[b,c,d,e]

Kim et al. The Orthopaedic Journal of Sports Medicine 2020

Limited evidence of MSC implants in OA

Knee Surgery, Sports Traumatology, Arthroscopy
https://doi.org/10.1007/s00167-023-07575-w

KNEE

Mesenchymal stem cell implantation provides short-term clinical improvement and satisfactory cartilage restoration in patients with knee osteoarthritis but the evidence is limited: a systematic review performed by the early-osteoarthritis group of ESSKA-European knee associates section

Hamid Rahmatullah Bin Abd Razak[1] · Katia Corona[2] · Trifon Totlis[3,4] · Li Yi Tammy Chan[5] · Jose Filipe Salreta[6] · Obeida Sleiman[7] · Michele Vasso[8] · Mike H. Baums[7]

Received: 2 February 2023 / Accepted: 5 September 2023

Study	LoE	Country	Study design	QoE score/total
Kim et al. Am J Sports Med [18]	3	South Korea	RE	MINORS 17/24
Kim et al. Osteoarthritis Cartilage [15]	2	South Korea	PRO	MINORS 13/16
Park YB et al. Stem Cells Transl Med [25]	2	South Korea	PRO	MINORS 12/16
Kim et al. Knee Surg Sports Traumatol Arthrosc [16]	1	South Korea	RCT	MJS 5/8
Kim et al. Orthop J Sports Med [19]	4	South Korea	RE	MINORS 14/16
Song et al. Regen Ther [29]	4	South Korea	RE	MINORS 12/16
Song et al. World J Stem Cells [30]	4	South Korea	RE	MINORS 12/16
Kim et al. Orthop J Sports Med [20]	4	South Korea	RE	MINORS 14/16
Yang et al. Knee Surg Sports Traumatol Arthrosc [36]	3	South Korea	RE	MINORS 20/24

MINORS methodological index for non-randomised studies, *MJS* modified jadad scale, *PRO* prospective cohort study, *RCT* randomized control trial, *RE* retrospective cohort study

Abstract

Purpose Implantation of mesenchymal stem cells (MSCs) is a potential cell-based modality for cartilage repair. Currently, its clinical use largely surrounds focal cartilage defect repair and intra-articular injections in knee osteoarthritis. The MSCs' implantation efficacy as a treatment option for osteoarthritis remains contentious. This systematic review aims to evaluate studies that focused on MSCs implantation in patients with knee OA to provide a summary of this treatment option outcomes.

Methods A systematic search was performed in PubMed (Medline), Scopus, Cinahl, and the Cochrane Library. Original studies investigating outcomes of MSCs implantations in patients with knee OA were included. Data on clinical outcomes using subjective scores, radiological outcomes, and second-look arthroscopy gradings were extracted.

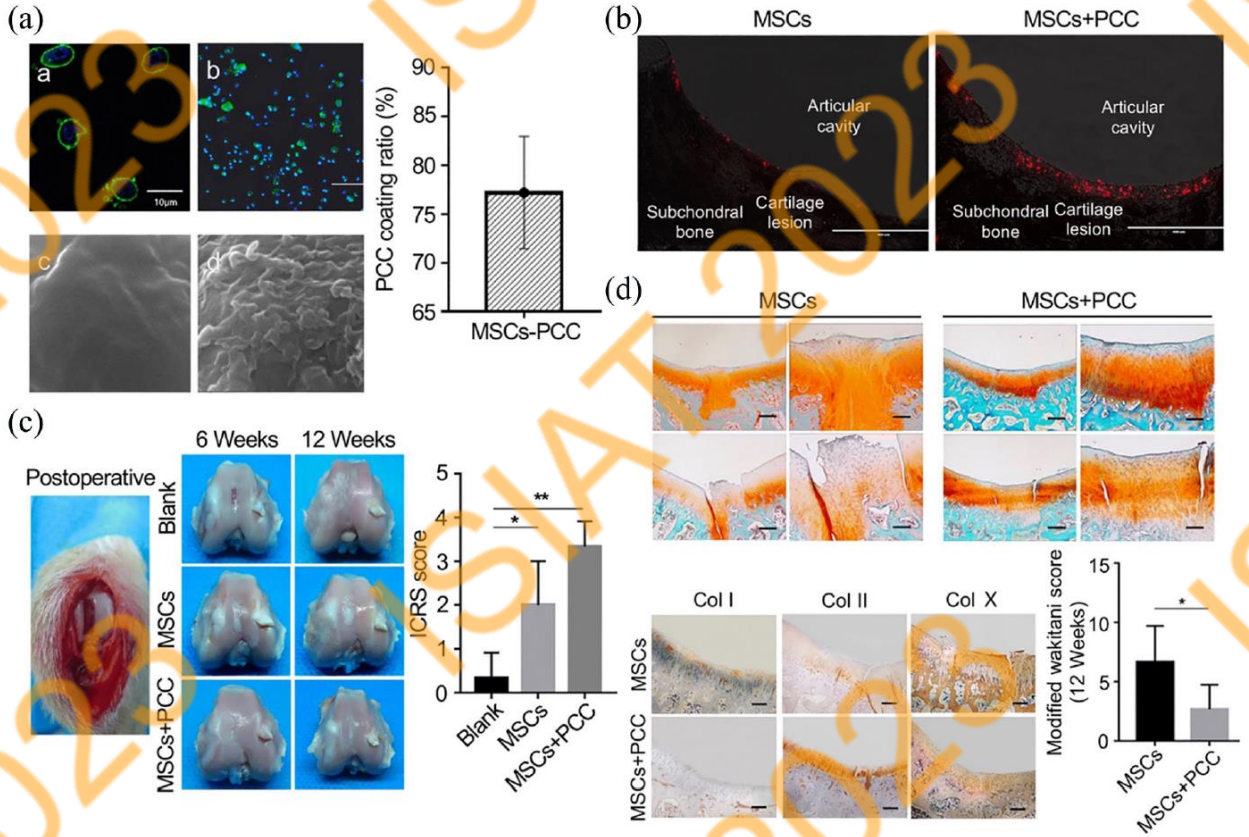
Results Nine studies were included in this review. In all included studies, clinical outcome scores revealed significantly improved functionality and better postoperative pain scores at 2–3 years follow-up. Improved cartilage volume and quality at the lesion site was observed in five studies that included a postoperative magnetic resonance imaging assessment and studies that performed second-look arthroscopy. No major complications or tumorigenesis occurred. Outcomes were consistent in both single MSCs implantation and concurrent HTO with MSCs implantation in cases with excessive varus deformity.

Conclusion According to the available literature, MSCs implantation in patients with mild to moderate knee osteoarthritis is safe and provides short-term clinical improvement and satisfactory cartilage restoration, either as a standalone procedure or combined with HTO in cases with axial deformity. However, the evidence is limited due to the high heterogeneity among studies and the insufficient number of studies including a control group and mid-term outcomes.

Level of evidence IV.

Bin Abd Razak et al. Knee surgery Sports Traumatology, Arthroscopy 2023

Implant MSC with scaffold > implant MSC ?



- Pericellular Col I coating (PCC) for BM-MSCs enhance the quality of cartilage regeneration

Xia H et al .Stem Cell Res Ther 2018

Choose the appropriate scaffold

- Biodegradable
- Biocompatible
- Support chondrogenesis and osteochondral tissue
- Mechanical properties
  - → Physical loading
  - → Space for tissue regeneration
- Porous structure (nutrients vs adhesion)
- Low immunogenicity
- Antimicrobial activity

Zhao X et al. Frontiers in Bioengineering and Biotechnology 2021

Choose the appropriate scaffold

NATURAL polymer

TABLE 1 | Characteristics of the outlined natural polymers for CTE.

Biomaterials	Characteristics	Advantages	Disadvantages	References
Chitosan	Originating from chitin; Linear natural carbohydrate biopolymer; Free amine groups in its backbone chain; Slower degradation rate	Biodegradability; Biocompatibility; Non-antigenicity; Adsorption capabilities; Antimicrobial activity; Promoting chondrogenesis	Low solubility; Low mechanical strength	Keller et al. (2017), Giuliani (2019), Sultankulov et al. (2019)
Collagen	Important part of natural cartilage organic materials; One of the most abundant proteins in humans and a major component of extracellular matrix	Biocompatibility; Low immunogenicity; Biodegradability; Promoting chondrogenesis; Facilitation of cell ingrowth and remodeling; Easy processing	Low solubility; Low mechanical strength; Rapid biodegradation rate	Lee et al. (2001), Kuroda et al. (2007), Turk et al. (2018), Li L. et al. (2019), Marques et al. (2019)
Silk	Extracted from Bombyx mori cocoon; A biocompatible material found as the core of a structural protein fiber;	Excellent mechanical properties; Biocompatibility Controlled biodegradability; Lower infection risk; Easy processing;	Delayed hypersensitivity; Initiator of immune reactions;	Zhang et al. (2010), Wang et al. (2011), Ma et al. (2018), Bharadwaz and Jayasuriya (2020)
Alginate	Produced from the cell wall of brown algae; Polysaccharide with negative charge; A cell-friendly gelation	Low immunogenicity; Biocompatibility; High abundance resources; Low prices; Regulation of the inflammatory chemokines; Good chondrogenic potential	Low biodegradability; Poor adhesion	Cho et al. (2009), Arlov et al. (2014), Park and Lee (2014), Filardo et al. (2018), Li L. et al. (2019)
Hyaluronic acid	A disaccharide unit; Abundant in the human body, present in the ECM of the skin, cartilage, and lenses	Biocompatibility; High hydrophilicity; Nontoxicity; Elasticity;	Low mechanical properties; Rapid enzymatic degradation	Collins and Birkinshaw (2013), Gupta et al. (2019), Li L. et al. (2019), Zheng et al. (2019)

- **Positive:** biocompatibility, biodegradability, favour cell interactions, cell adhesion
- **Negative:** mechanical properties, shape difficulty

SYNTHETIC polymer

TABLE 2 | Characteristics of the outlined synthetic polymers for CTE.

Biomaterials	Symbol	Characteristics	Advantages	Disadvantages	References
Poly(glycolic acid)	PGA	Linear, crystalline hydrophobic polyester; Semicrystalline polymer; Insoluble in most organic solvents	Biocompatibility; Availability; Easy processing; Composited with other biomaterials	Release of acidic degradation products; Poor cell adhesion; Fast biodegradability; Low mechanical properties	Klein et al. (2005), Zwingmann et al. (2007), Nakao et al. (2017), Birru et al. (2018)
Poly(lactic acid)	PLA	Polyesterification reaction production of lactic acid; Lower crystallinity and hydrophilicity than PGA; Four different forms	Biocompatibility, controllable biodegradability; Low toxicity and viscosity; Favorable mechanical properties; Thermostability; Thermoplasticity	Poor cell adhesion	Li et al. (2006), Zwingmann et al. (2007), Lopes et al. (2012), Revati et al. (2017), Smieszek et al. (2019), Szyszka et al. (2019), Marycz et al. (2020)
Poly(ethylene glycol)	PEG	An amphiphilic polymer that cannot be recognized by the immune system	Biocompatibility; Biodegradability; Non-immunogenic; Promoting chondrogenesis; Great flexibility; Low polydispersity	Poor cell adhesion	Karim et al. (2016), Ding and Li (2017), Cheng et al. (2018), Cheng H. et al. (2019), Li et al. (2018), Wang et al. (2019)
Poly-ε-caprolactone	PCL	Semi-crystalline; A synthetic polyester polymer	Biocompatibility; Biodegradability; Elasticity; Excellent mechanical properties; Thermoplastic	Poor hydrophilicity; Poor cell adhesion	Ousema et al. (2012), Sousa et al. (2014), Theodoridis et al. (2019), Venkatesan et al. (2020)

- **Positive:** low degradation, extended lifespan, better mechanical features, easily design shape
- **Negative:** acid degradation, weaker cell interactions, risk of local pH increase, cell adhesion

Zhao X et al. Frontiers in Bioengineering and Biotechnology 2021

Repair of focal defects with MSC+scaffold: Animals models

International Journal of *Molecular Sciences*

MDPI

Review

Bone Marrow-Derived Mesenchymal Stem Cell Implants for the Treatment of Focal Chondral Defects of the Knee in Animal Models: A Systematic Review and Meta-Analysis

Ernest Lee [1,†], Ilias Ektor Epanomeritakis [2,†], Victor Lu [3] and Wasim Khan [4,*]

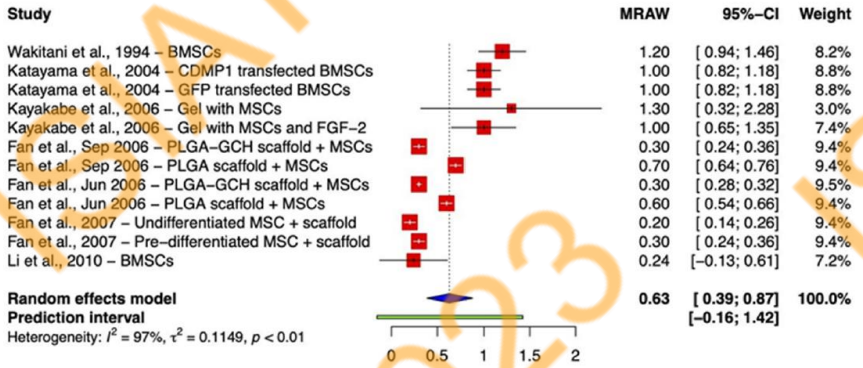


Figure 2. Forest plot on the mean histological integration score after receiving BMSC implant therapy, where 0/2 points = both edges integrated, 1/2 = one edge integrated, and 2/2 = no integration. (Abbreviations: BMSC, bone marrow-derived mesenchymal stem cell; CDMP1, cartilage-derived morphogenetic protein 1; GFP, green fluorescent protein; FGF-2, fibroblast growth factor-2; PLGA, poly-(lactic-co-glycolic acid); GCH, gelatin/chondroitin/hyaluronate; CI, Confidence Intervals) [22,24–28,30].

- High-quality integration was achieved
- Subgroup analysis showed better integration outcomes for studies using PLGA
- Limits:
  - Cell source
  - Implant composition
  - MSC characteristics

Lee E et al. IJMS 2023

Repair of focal defects with MSC+scaffold: **Humans**

Table 2 Application of MSC seeded onto different types of scaffolds into patients with damaged articular cartilage

Technique	n; Sex; Age (years) (mean ± SD)	Follow-up period (months)	Finding	Ref.
BM-MSC in type I collagen gel	1; M (31)	12	Hyaline-like cartilage	[49]
BM-MSC within type I collagen gel on a collagen scaffold seeded on PLA scaffold	3; 2 M, 1F (32–45)	18	Coverage of chondral defect	[73]
BMDC suspended in collagen or seeded on HA scaffold	48; 27 M, 21F (28 ± 9)	24–35	Coverage of chondral defect and hypertrophic cartilage	[57]
BMDC seeded on HA scaffold supplemented with platelet-rich fibrin	20; 12 M, 8F (28 ± 9)	29 ± 4	Proteoglycan and type II collagen	[58]
BMDC seeded on HA scaffold supplemented with platelet-rich fibrin	81; 47 M, 34F (30 ± 8)	59 ± 26	Hyaline-like cartilage	[74]
BM-MSC within platelet-rich fibrin glue	5; 4 M, 1F (25)	12	Coverage of chondral defect	[75]
BM-MSC covered by periosteum	72; 38 M, 34F (44 ± 11)	24	Aggrecan and type II collagen	[76]
BMDC with batroxobin covered by type I/III collagen matrix	15; 10 M, 5F (48)	24–38	Coverage of chondral defect	[77]
BM-MSC seeded on type I collagen scaffold supplemented with fibrin glue	2; 2 M (24–25)	30–31	Partial coverage of chondral defect	[78]
Peripheral blood-derived MSC with HA	5; 1 M, 4F (39 ± 11)	10–26	Partial coverage of chondral defect	[79]
BMDC within fibrin glue and coverage with collagen and collagen membrane	1; M; 37 yrs	24	Partial coverage of chondral defect	[80]
BMDC in fibrin glue and coverage with a PGA + HA membrane	9; 5 M, 4F (48 ± 9)	20–24	Hyaline-like cartilage	[81]
BMDC in collagen/platelet paste or seeded on HA or seeded on HA scaffold supplemented with platelet gel	49; 27 M, 22F (28 ± 9)	48	Coverage of chondral defect in 45%	[59]
Peripheral blood-derived MSC and HA	49; 17 M, 32F (37 ± 7)	24	Partial coverage of chondral defect	[18]

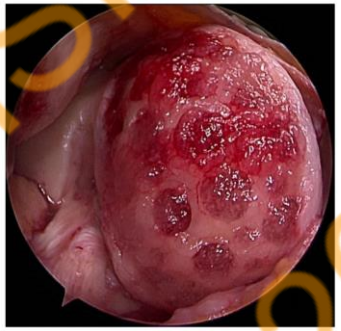
BM-MSC bone marrow-derived mesenchymal stem cells, *PLA* polylactic acid, *HA* hyaluronic acid, *PGA* polyglycolic acid

- Heterogeneous integration
- Few studies available

Yamagata et al. Inflammation and Regeneration 2018

Repair of focal defects with MSC+scaffold: Humans

- CARTISTEM (Medipost)
- Retrospective study
- Large lesion (> 4 cm^2)
- Located in medial femoral condyle
- Excluded other compartment lesions
- hUC-MSC + HA (+/- meniscectomy)
- 85 patients
  - ➢ Significant improvement in all PRO scores
  - ➢ MRI follow-up show repaired cartilage hypertrophy without correlation with PRO



Clinical and Magnetic Resonance Imaging Outcomes After Human Cord Blood–Derived Mesenchymal Stem Cell Implantation for Chondral Defects of the Knee

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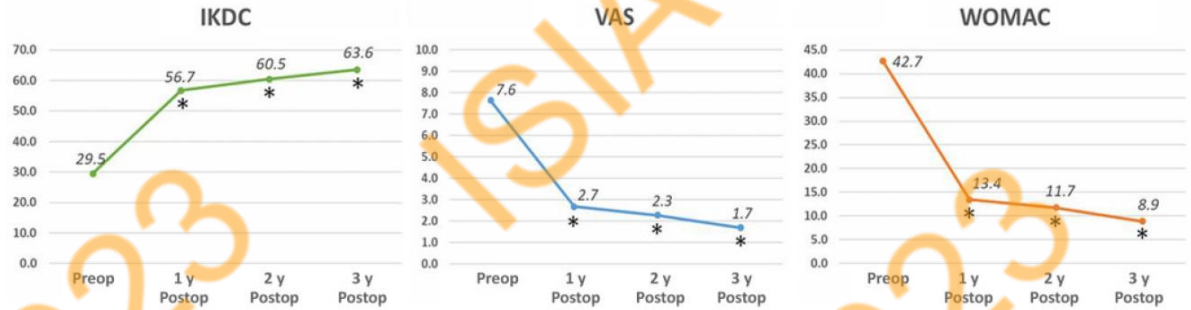
Investigation performed at Nowon Eulji Medical Center, Seoul, Republic of Korea



Song et al. The Orthopaedic Journal of Sports Medicine 2023

Conclusions: no definitive answer !!!

- We know…
  - Positive pre-clinical data
  - Numerous published phase I/II
  - Excellent tolerance
  - Cost issues
  - Risk of bias
  - Standardisation of cell manufacturing

- We don't know…
  - Tissue repair ?
  - Dose ? Frequency of delivery ?
  - Type of scaffolds ? 3D printing
  - The targeted population ?
  - A potency test ? Priming cells ?
  - Phase II/III studies ?

ADIPOA-2

→ Limitation = cell integration / indications

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