Thérapies cellulaires Applications cliniques ostéo-articulaires

Pr Yves-Marie PERS

PU-PH

Immunologie clinique et Thérapeutique ostéo-articulaire

Département de Rhumatologie - CHU Montpellier

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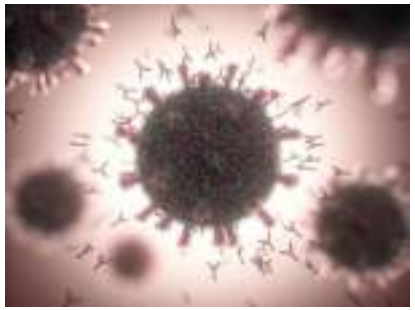
Disclosures

- Funding: Chugai, Amgen, Novartis
- Expert committee: Pfizer, Abbvie, Novartis, IBSA
- Conferences: Medac, BMS, Abbvie, UCB

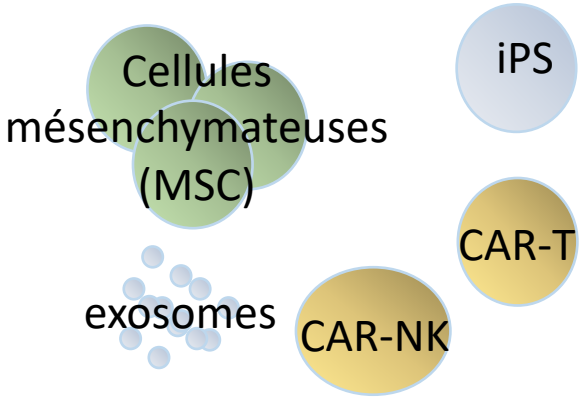
Biologic therapy in 2024

Chimie → **Anticorps monoclonaux** → **Thérapie cellulaire** → **Thérapies nucleotidiques**



- Maladies autoimmunes
- Lymphome (anti-CD20 …)
- oncologie : (anti-PDL1 …)
- COVID

Phase 3
AMM : rituximab, Pembrolizumab ...



Maladies ostéoarticulaires, fistules digestives, dermatologie
lymphome, carcinome, maladies autoimmunes …

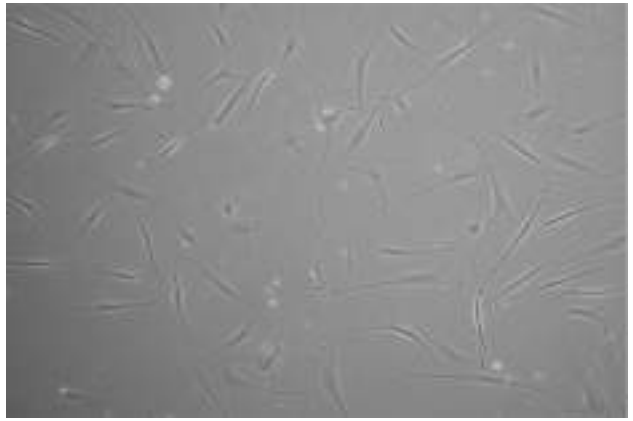
Phase 2-3 : RESPINE, ADIPOA2, iPSPINE
AMM : CAR-T KYMRIAH ® (Novartis),
MSC : Alofisel® (Takeda)

Vaccination COVID
Oncologie
Maladies rares

AMM COVID

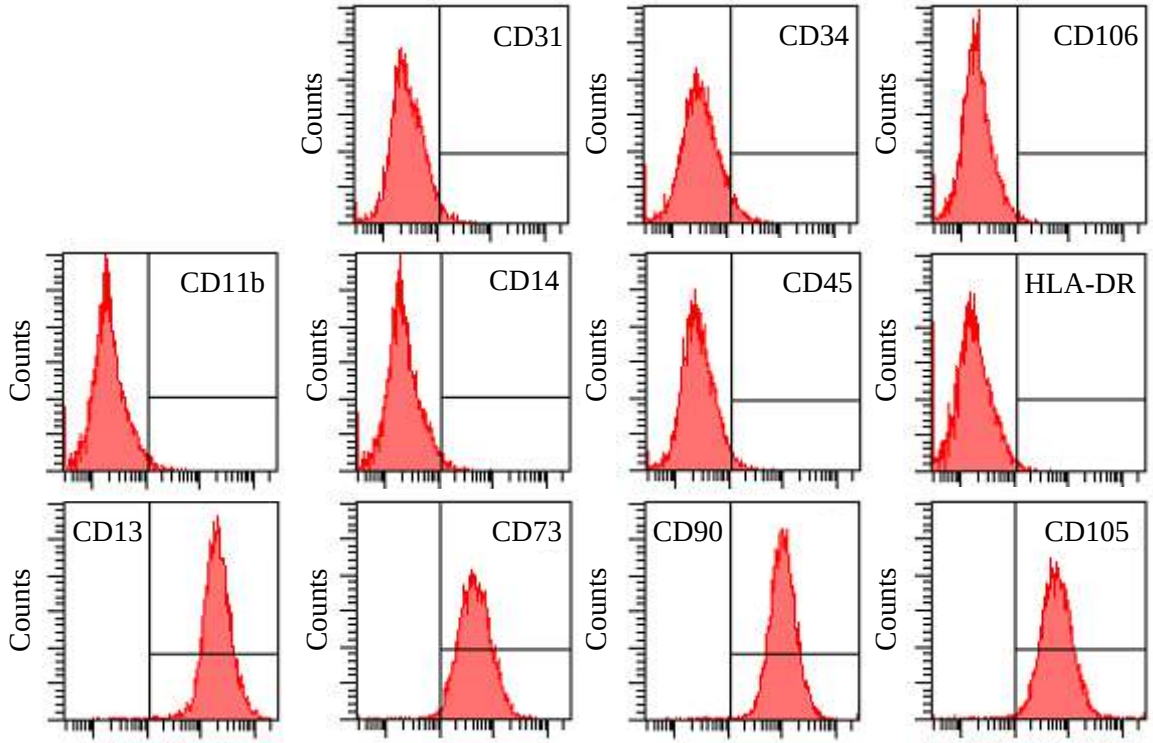
Characteristics of Mesenchymal Stem Cells (MSC)

- **Adherent to plastic**



(High expansion *in vitro)*

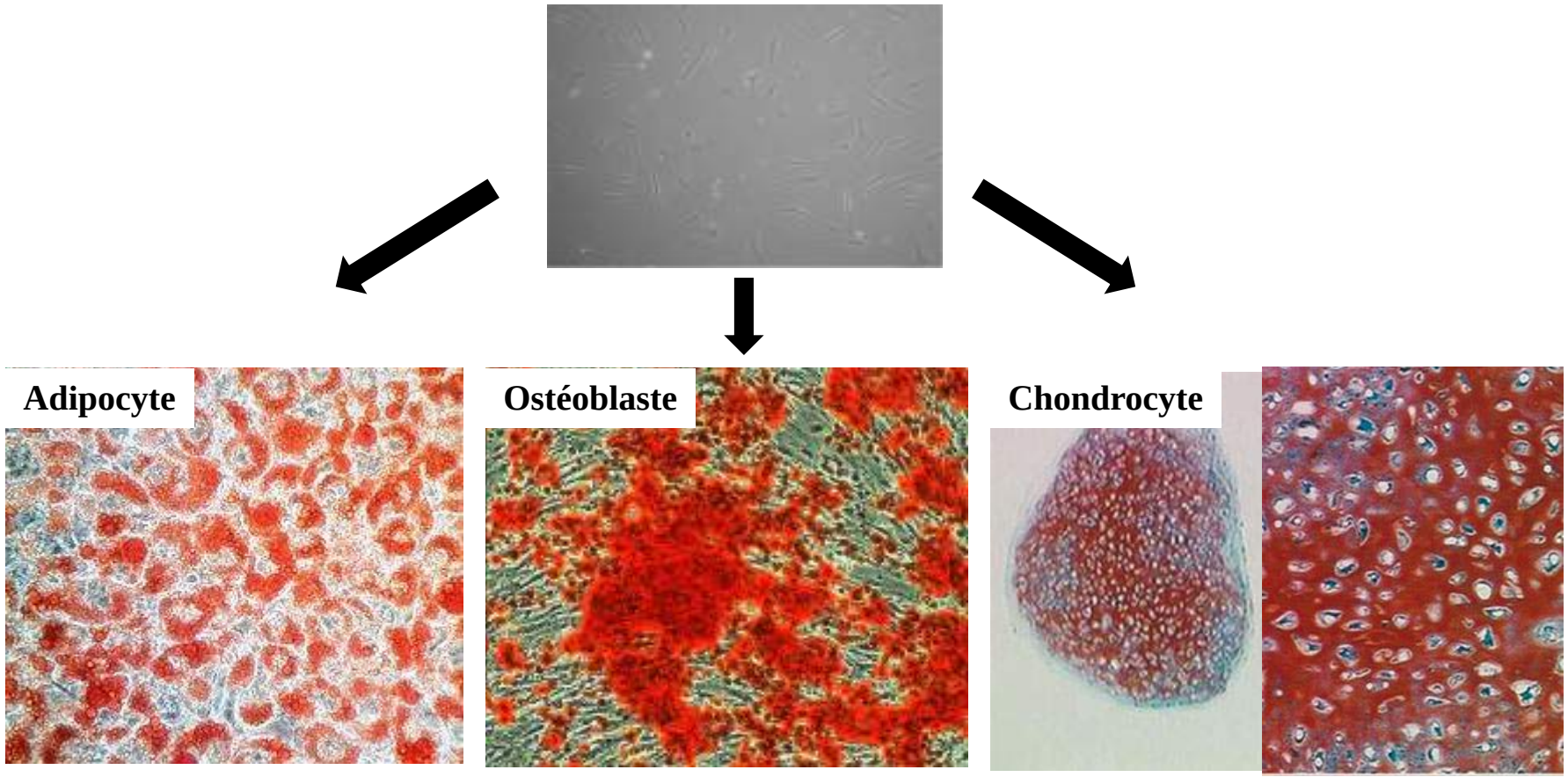
- **Immunophenotype** → No specific marker



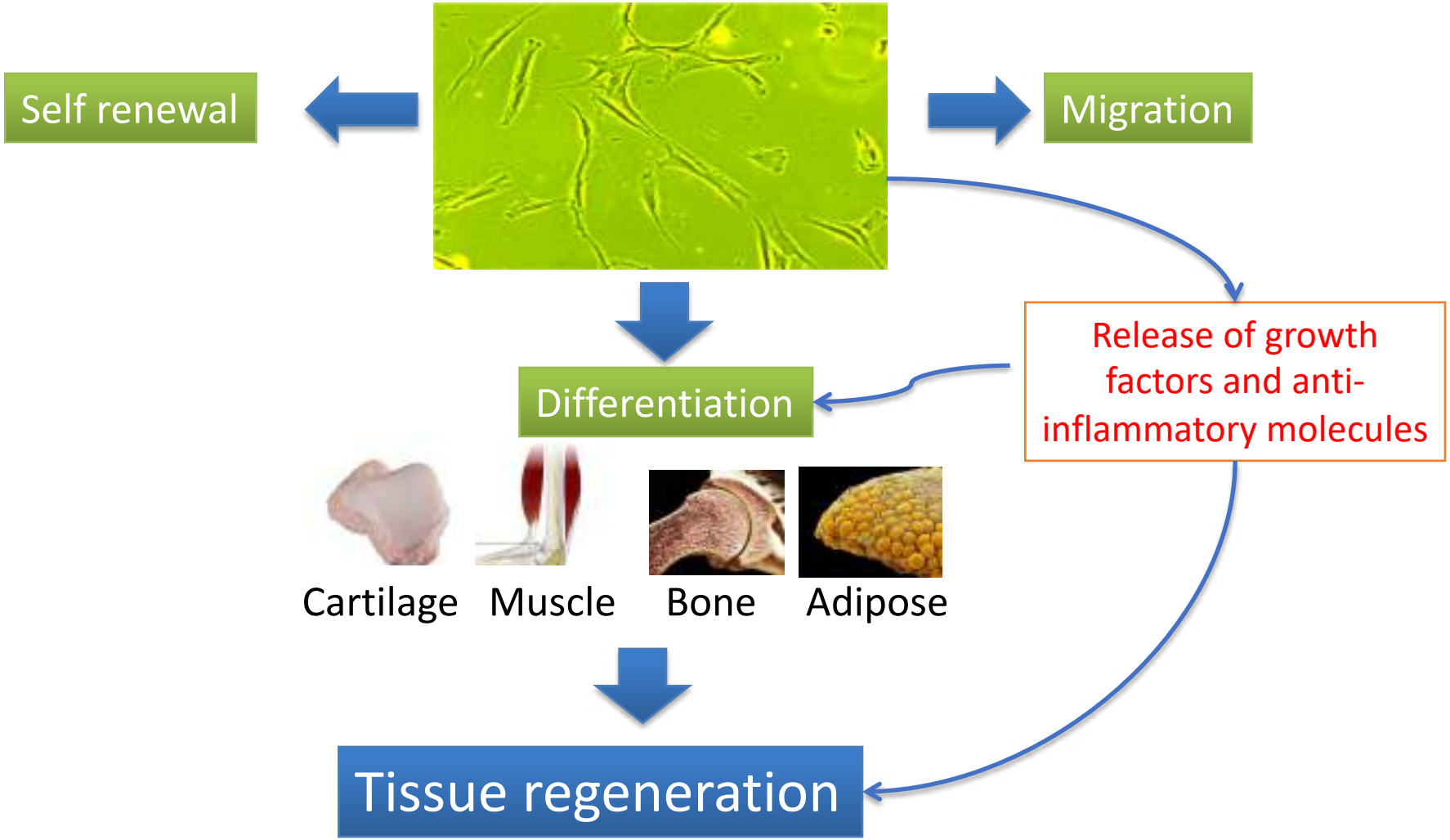
- **CD73⁺, CD90⁺, CD105⁺**, (CD13⁺)
- CD11b⁻, CD14⁻, CD19⁻, CD34⁻, **CD45⁻**, HLA-DR⁻, (CD31⁻, CD106⁻)

Characteristics of Mesenchymal Stem Cells (MSC)

- **Multipotency**: ability to differentiate into adipocytes (adipose tissue), osteoblasts (bone) and chondrocytes (cartilage)



Functions of MSC



Therapeutic applications of MSC

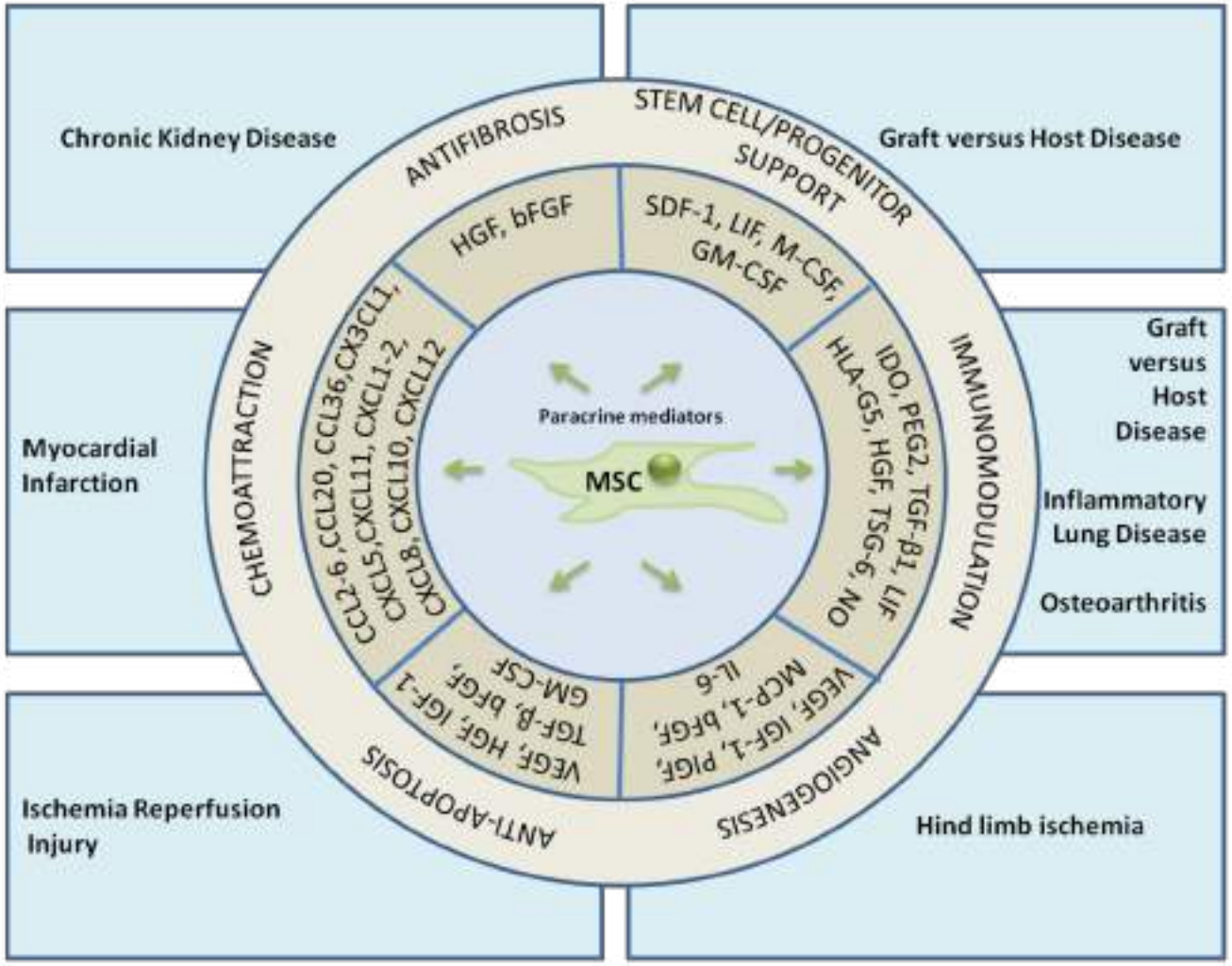
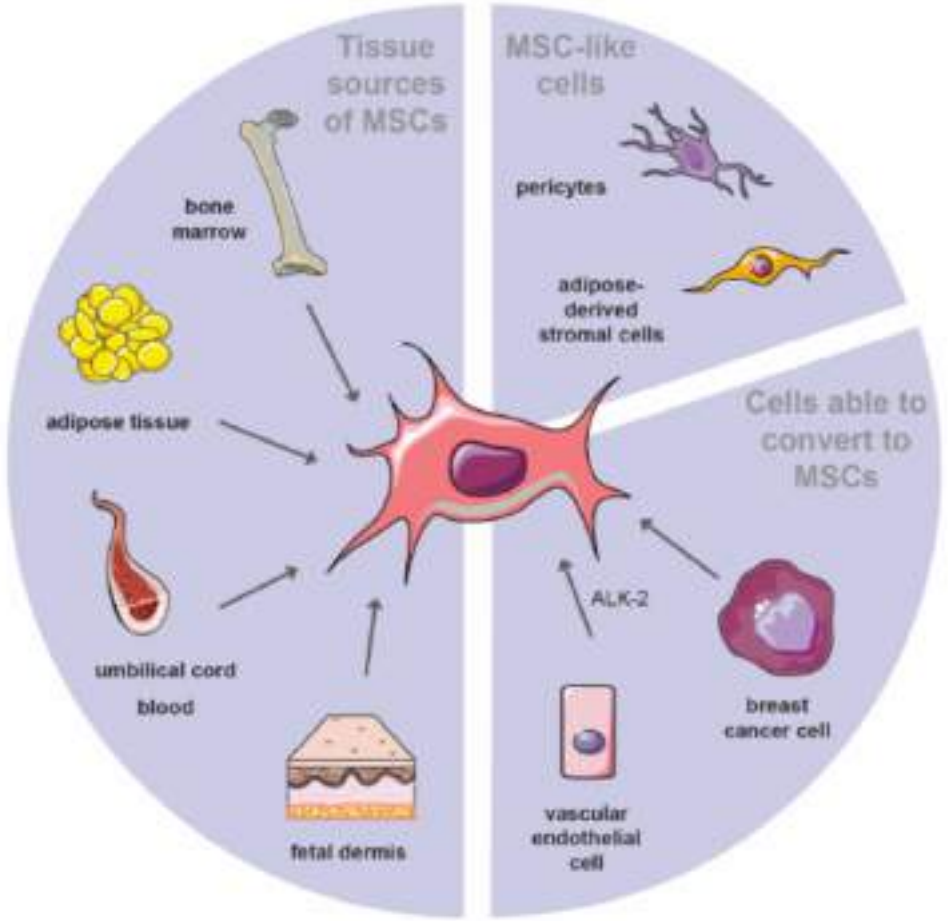
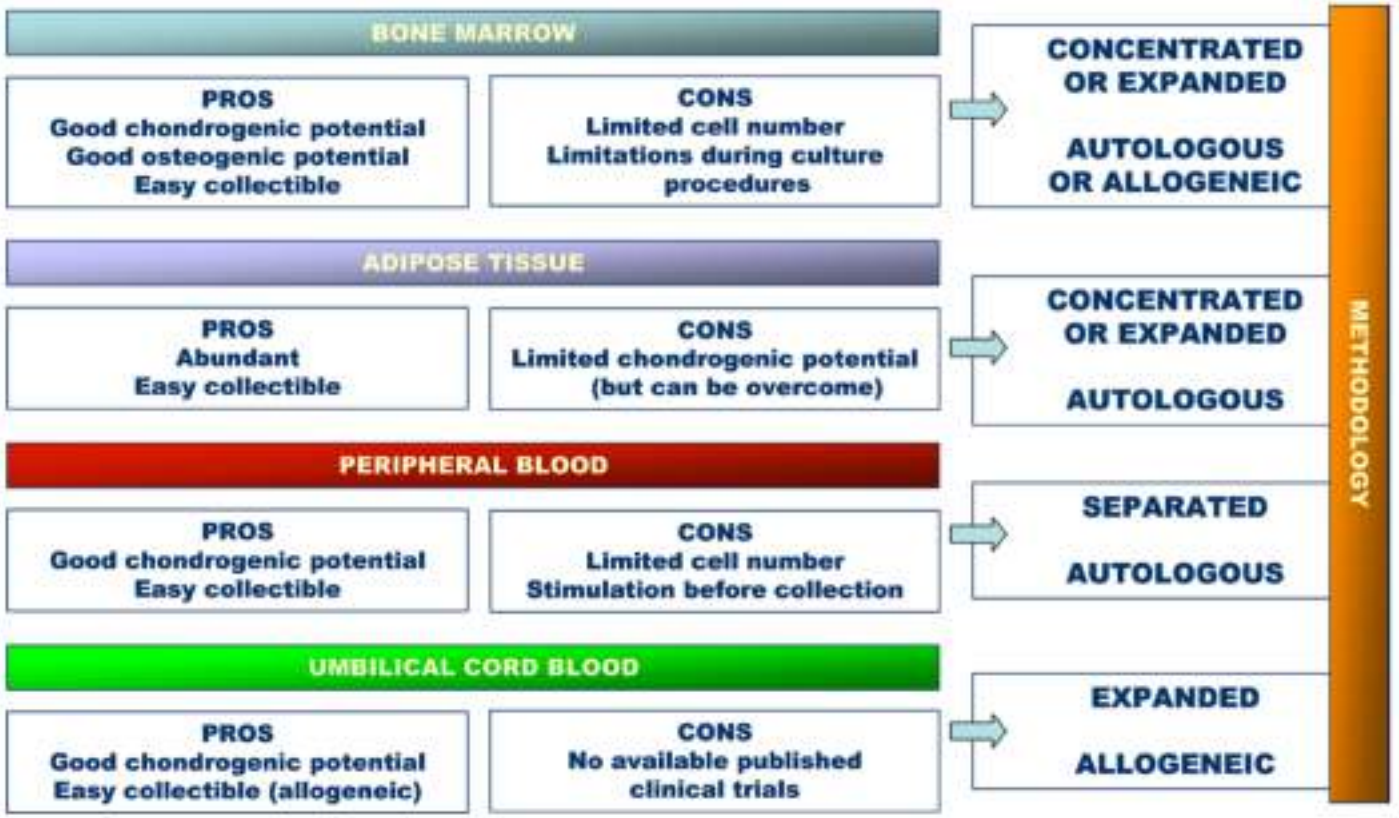


Figure 2. MSC paracrine-mediated mechanisms of action and their therapeutic relevance

Courtesy Barry F et al. The Biology and Therapeutic Applications of Mesenchymal cells. Volume 2. Chapter 29.

Therapeutic applications of MSC

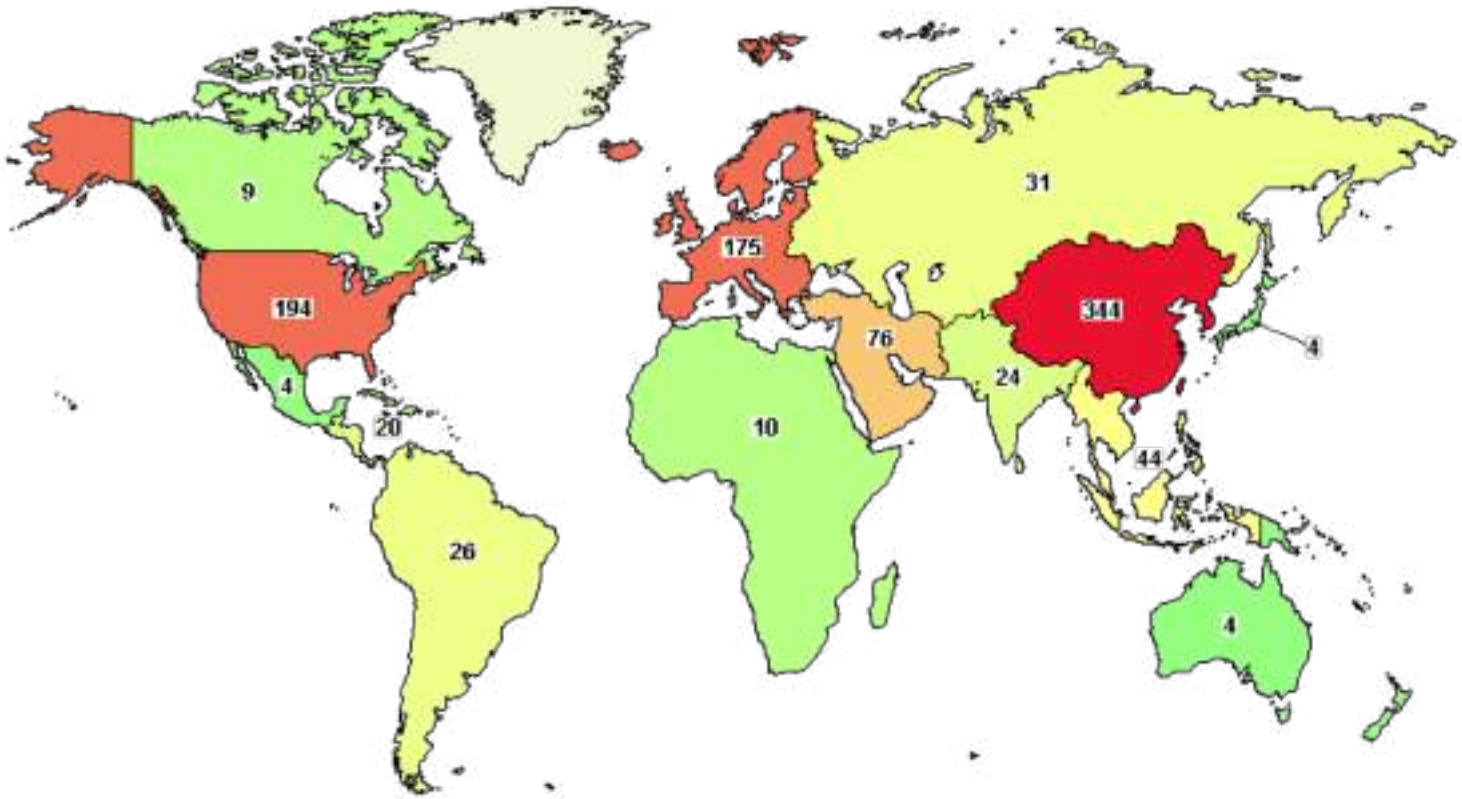




De Girolamo L. Knee Surg Sports Traumatol Arthrosc 2016

Therapeutic applications of MSC

- Registered Clinical trials of MSC based therapy on ClinicalTrials.gov (2023)
- Répartition par pays et continent



Therapeutic applications of MSC

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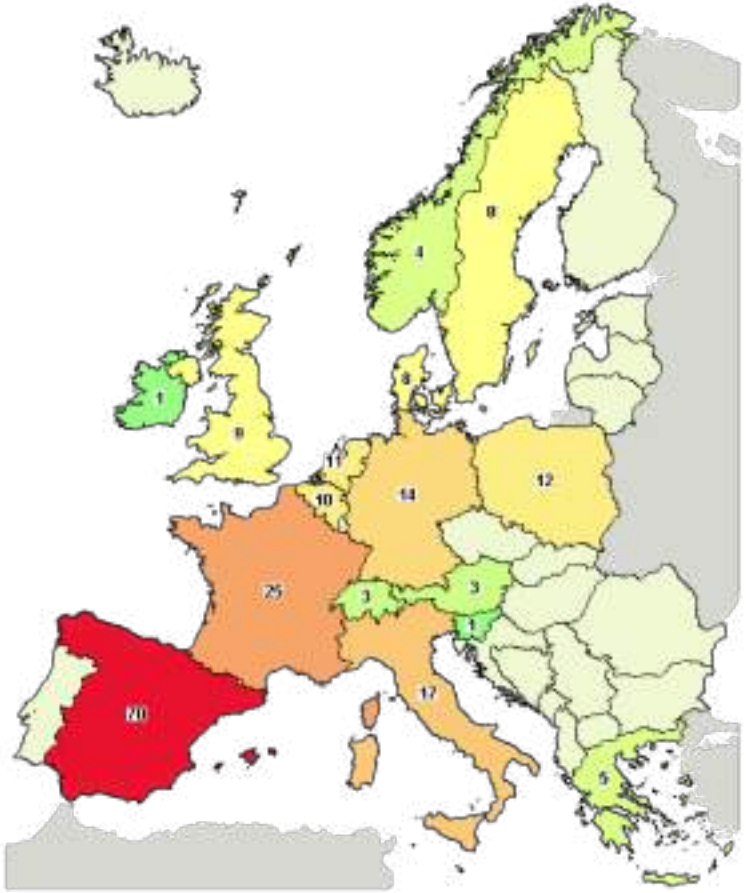
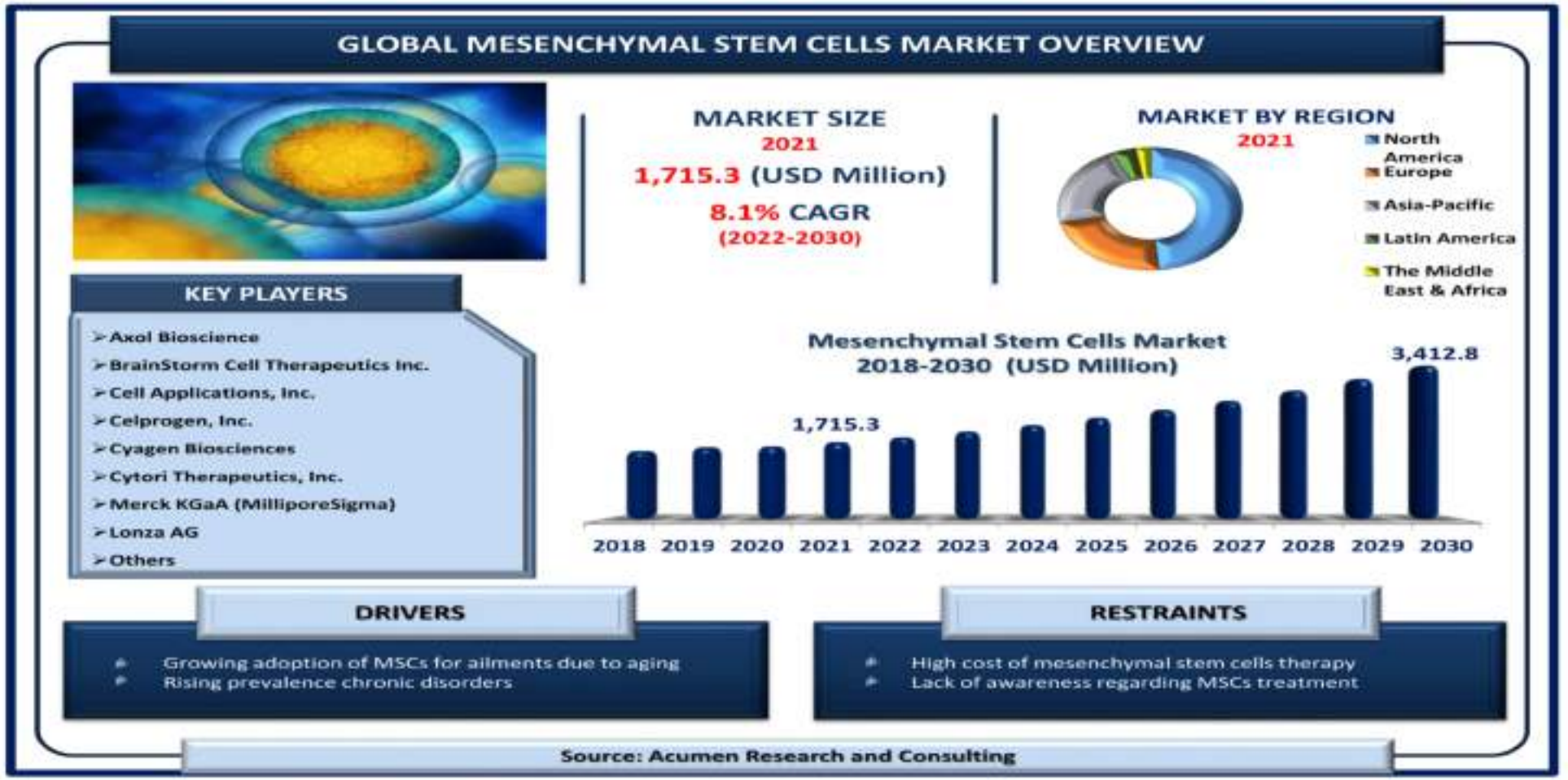


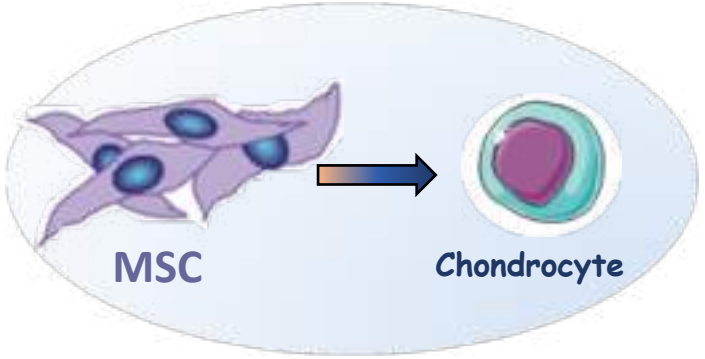
Global mesenchymal stem cell market expected to double in less than 10 years !



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

Clinical applications of MSC in rheumatology

Differentiation capacities



Differentiation in chondrocytes using biomaterials

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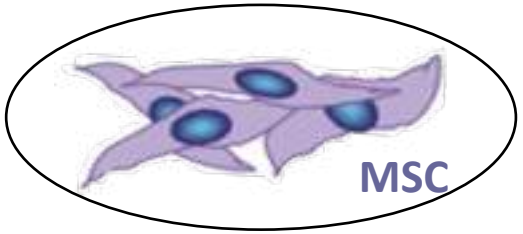
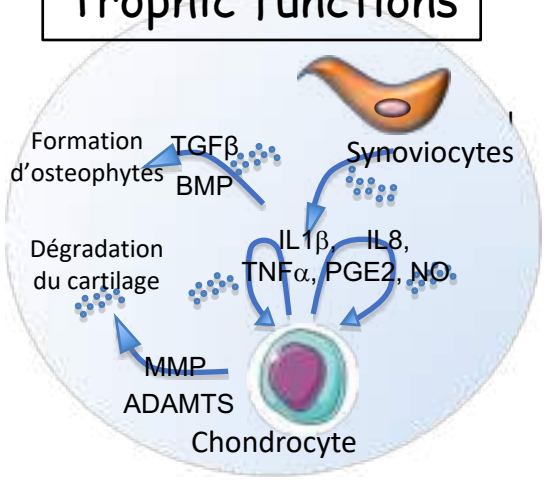
Tissue engineering: Repair of focal defects



Trophic functions



Chondroprotection and stimulation of endogenous repair

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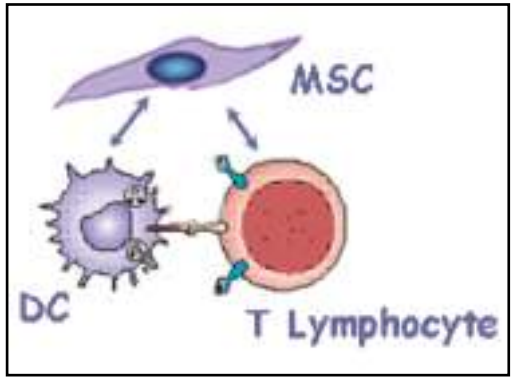
Application to OA / DDD

Immunoregulatory functions



To block inflammation

Anti-inflammatory cell therapies

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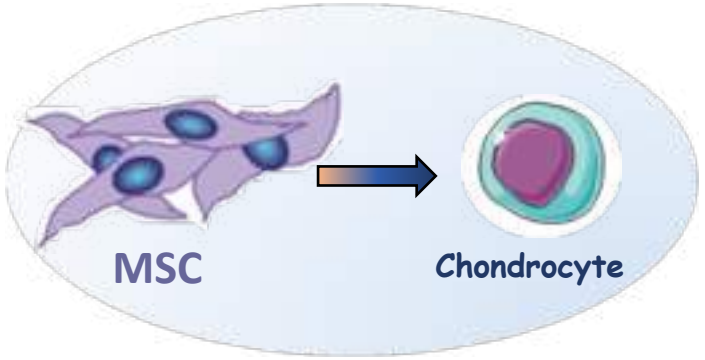
Application to rheumatoid arthritis

Clinical applications of MSC in rheumatology

Differentiation capacities



Differentiation in chondrocytes using biomaterials

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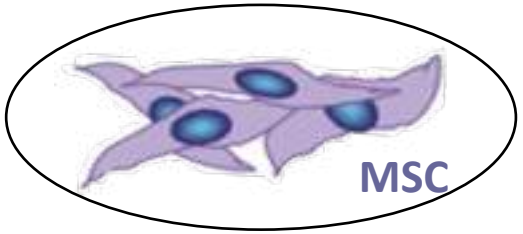
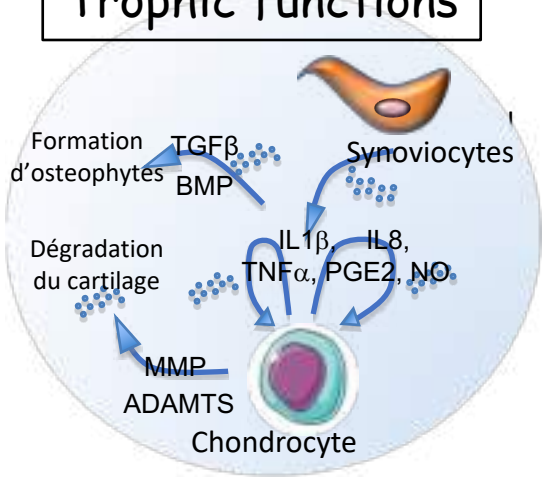


Trophic functions



Chondroprotection and stimulation of endogenous repair

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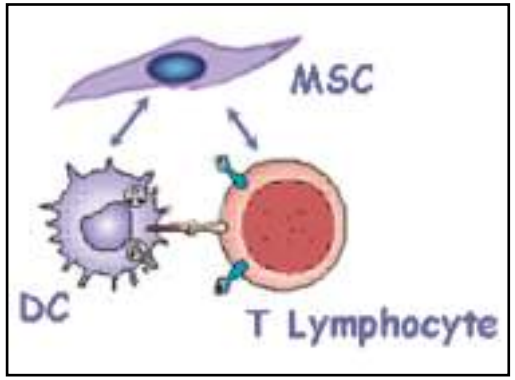
Application to OA / DDD

Immunoregulatory functions



To block inflammation

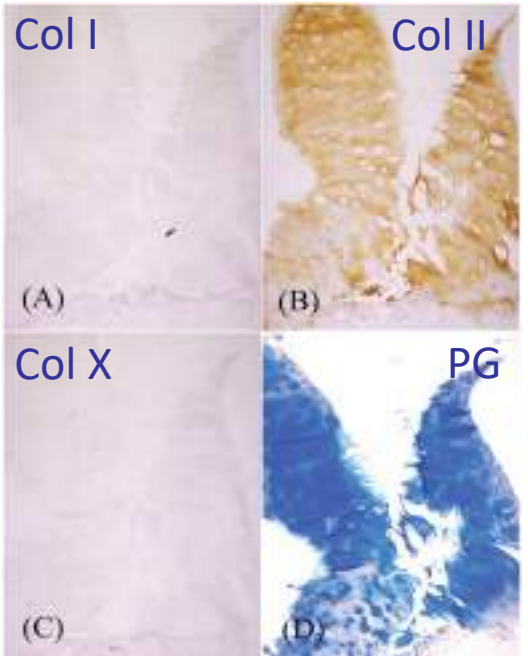
Anti-inflammatory cell therapies

⇩

Application to rheumatoid arthritis

MSC implant > chondrocyte implant ?

BM-MSCs efficacy compared to autologous chondrocyte implantation ?



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

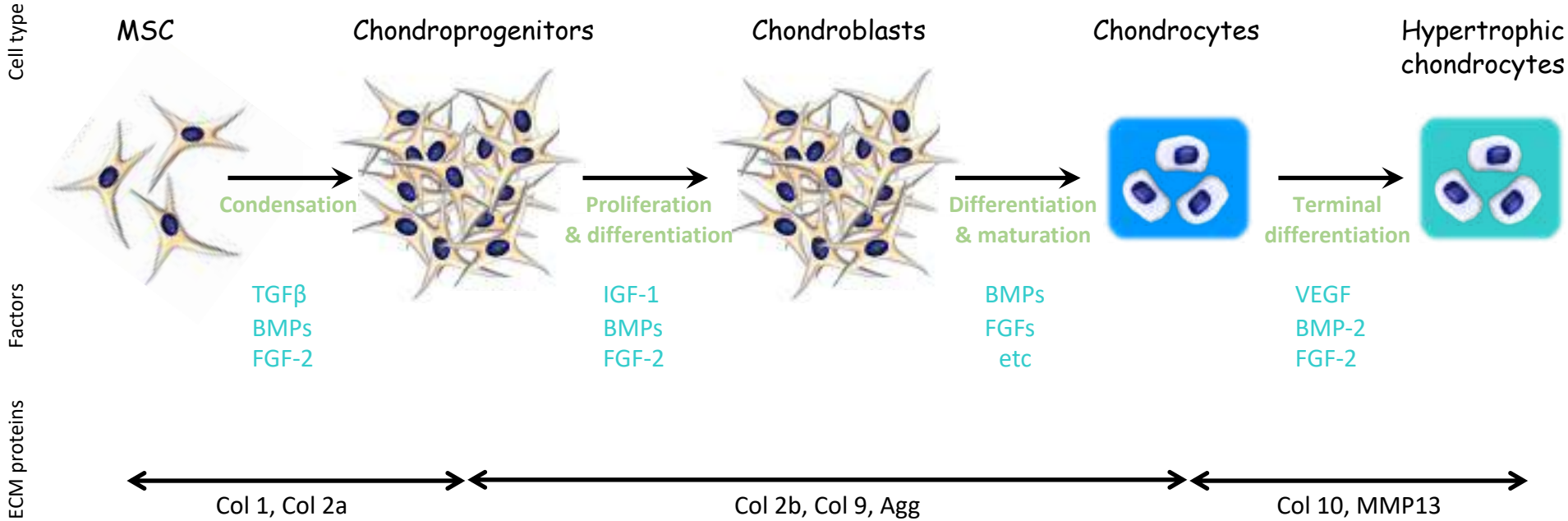
- Improvement of patient QoL and activities in sports
- Hyalin cartilage formation (1 year)
- Less graft hypertrophy

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

MSC chondrogenesis



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

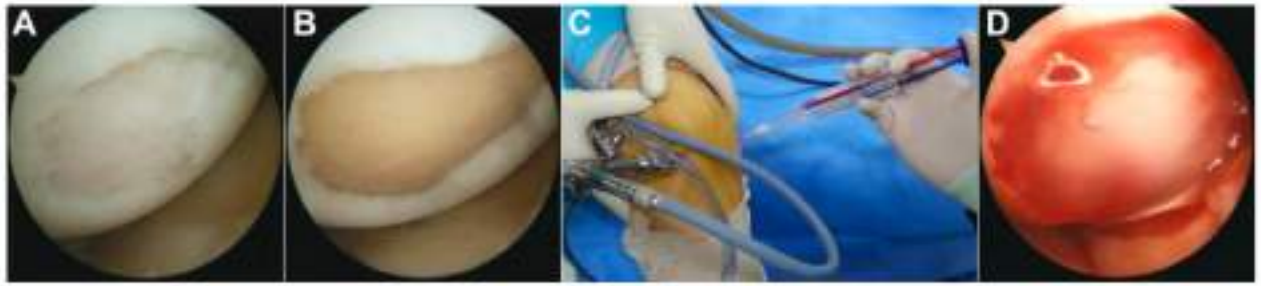


Figure 1. Arthroscopic implantation of mesenchymal stem cells loaded in fibrin glue. (A) An articular cartilage lesion in the medial femoral condyle was noticed. (B) An accurate debridement of all unstable and damaged cartilage in the lesion was performed. (C)

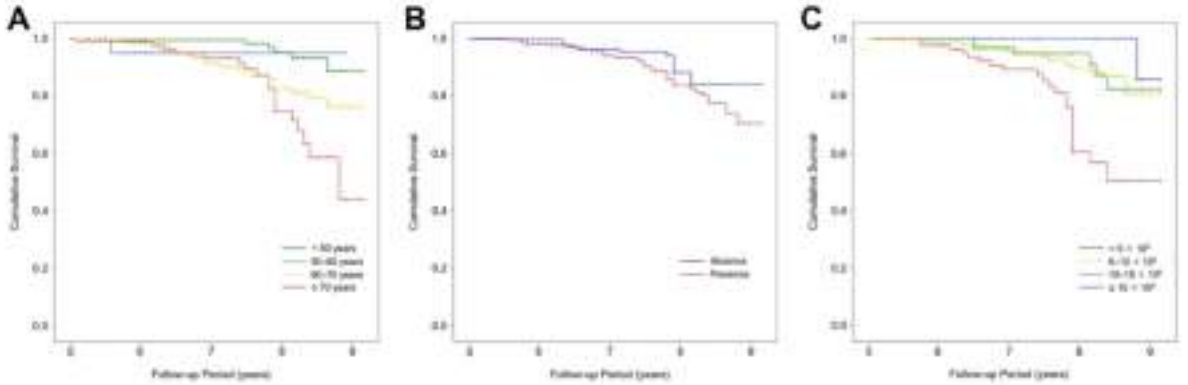


Figure 3. Kaplan-Meier survival curves. Survival rate of groups divided according to (A) age, (B) presence of bipolar kissing lesion, and (C) number of mesenchymal stem cells.

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[b,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.

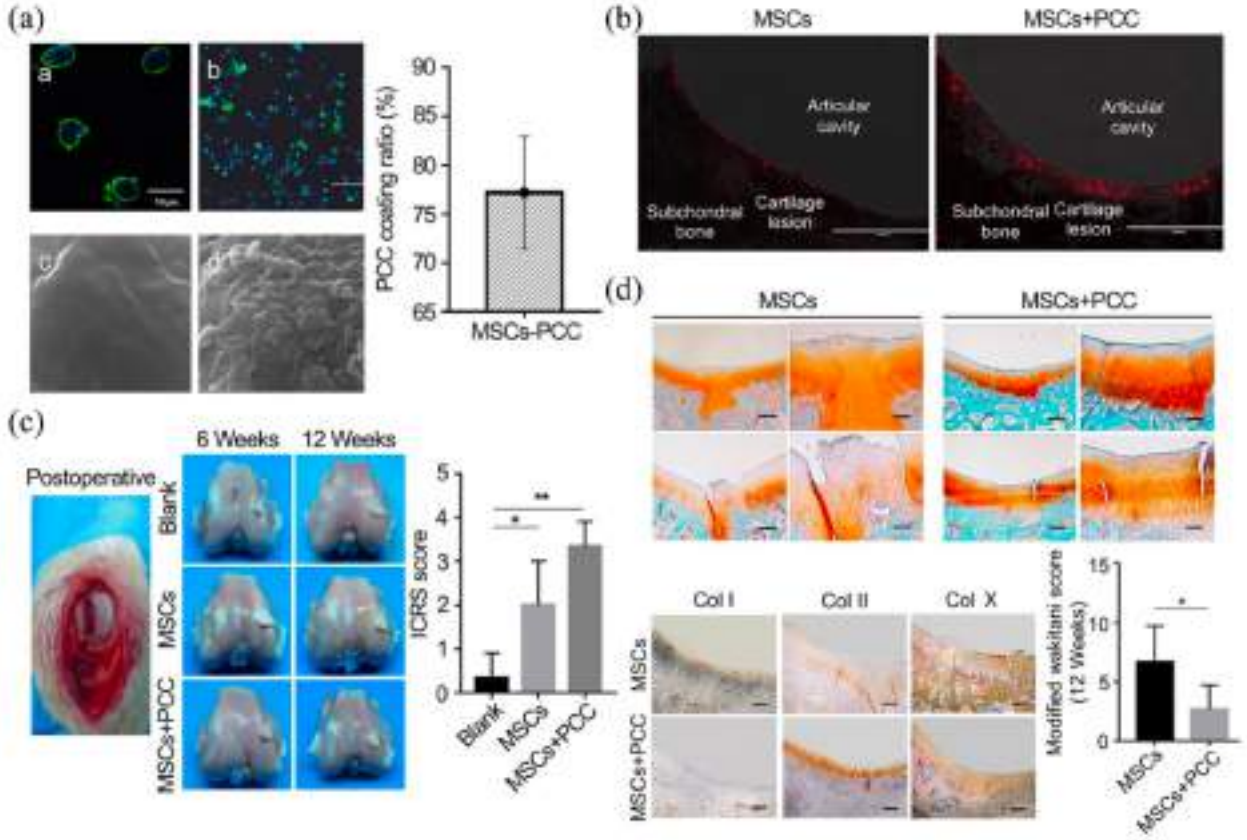
Results Nine studies were included in this review. In all included studies, clinical outcome scores revealed significantly improved functionality and better postoperative pain scores at 2–3 years follow-up. Improved cartilage volume and quality at the lesion site was observed in five studies that included 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
  Mechanical properties → Space for tissue regeneration
- Porous structure (nutrients vs adhesion)
- Low immunogenicity
- Antimicrobial activity

Zhao X et al. Frontiers in Bioengineering and Biotechnology 2021

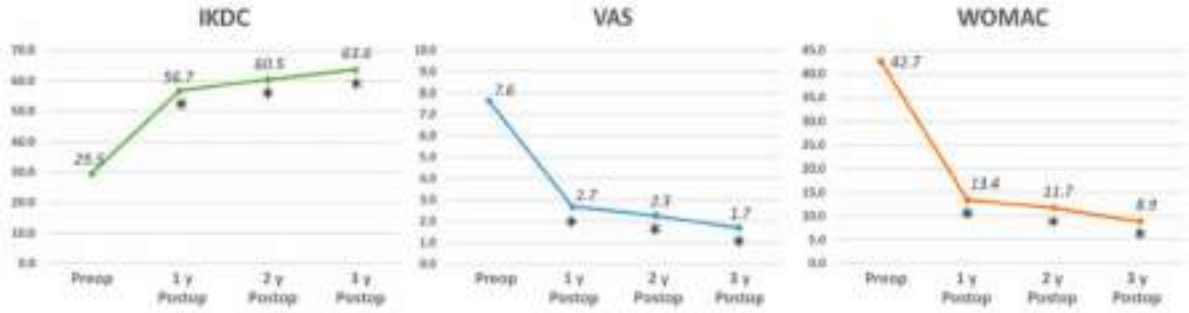
Repair of focal defects with MSC+scaffold : Humans

- 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

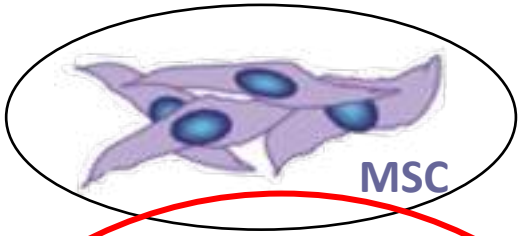
Jun-Seob Song,* MD, Ki-Taek Hong,* MD, Na-Min Kim,* MD, Byung-Hun Hwangbo,† MD, Bong-Seok Yang,‡ MD, Brian N. Victoroff,§ MD, and Nam-Hong Choi,†|| MD

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

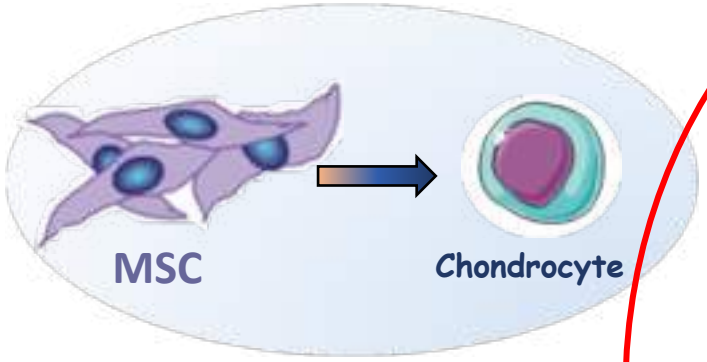


Song et al. The Orthopaedic Journal of Sports Medicine 2023

Clinical applications of MSC in rheumatology



Differentiation capacities



Differentiation in chondrocytes using biomaterials

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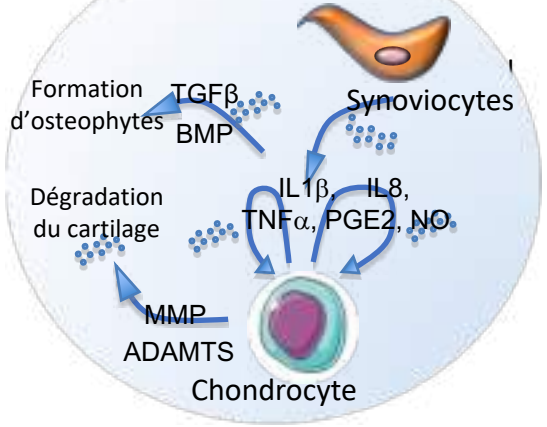
Tissue engineering: Repair of focal defects

Trophic functions



Chondroprotection and stimulation of endogenous repair

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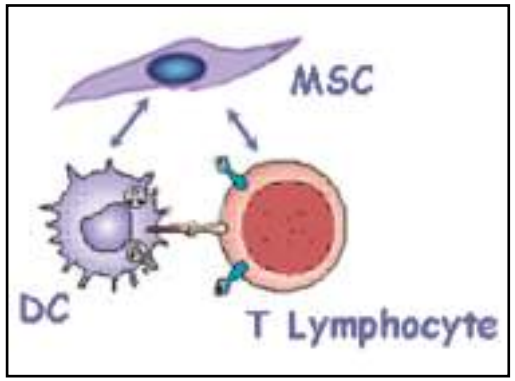
Application to OA / DDD

Immunoregulatory functions



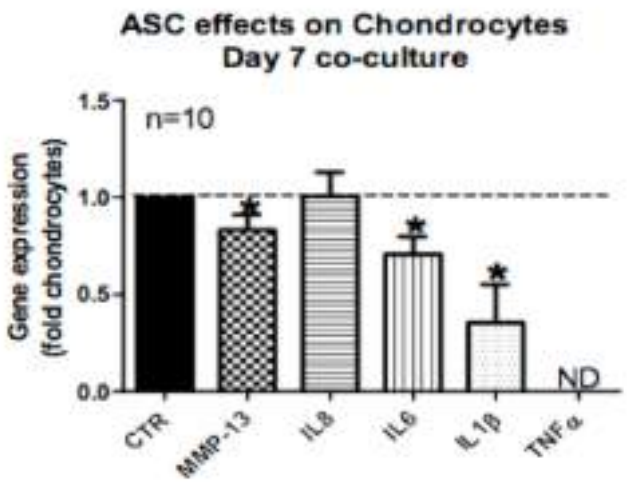
To block inflammation

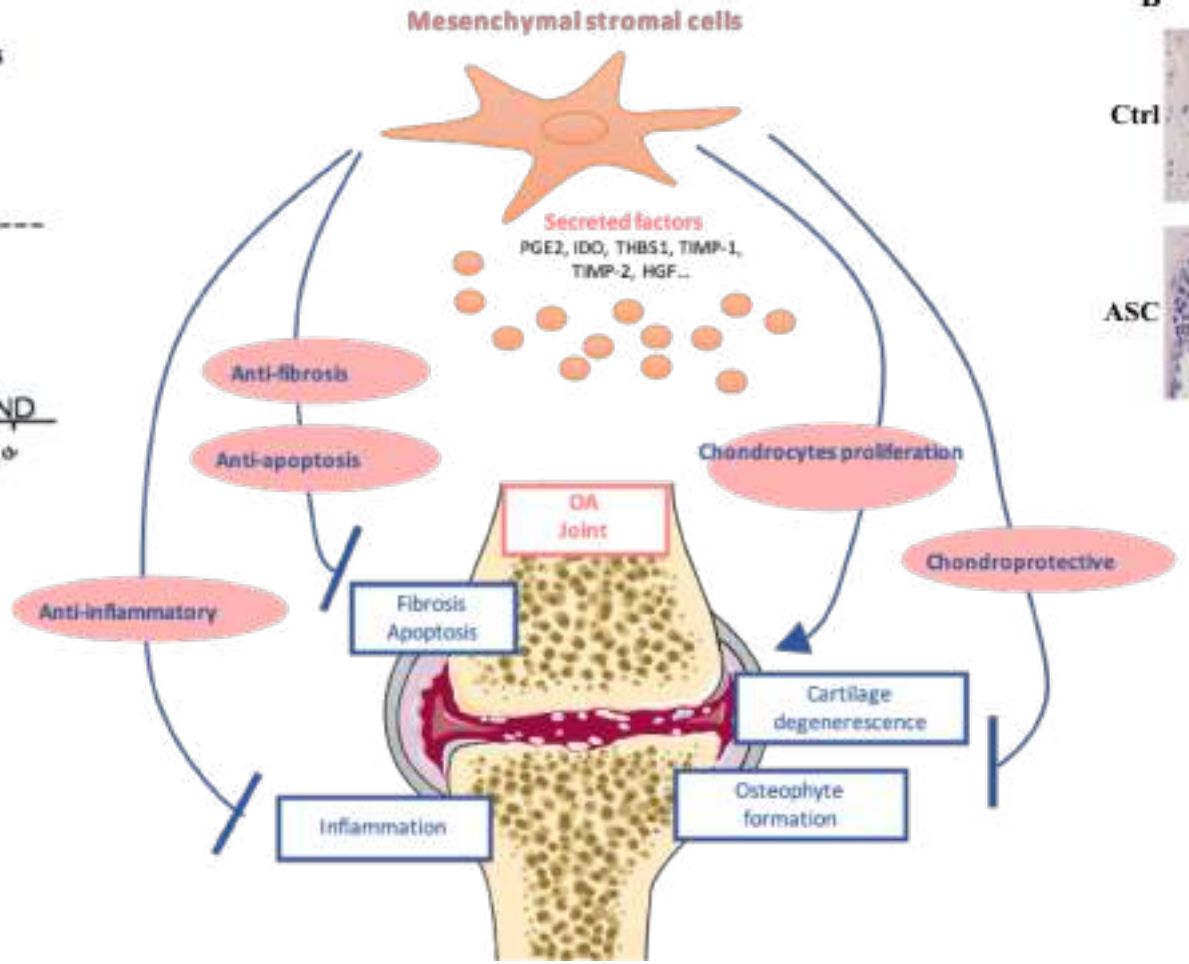
Anti-inflammatory cell therapies

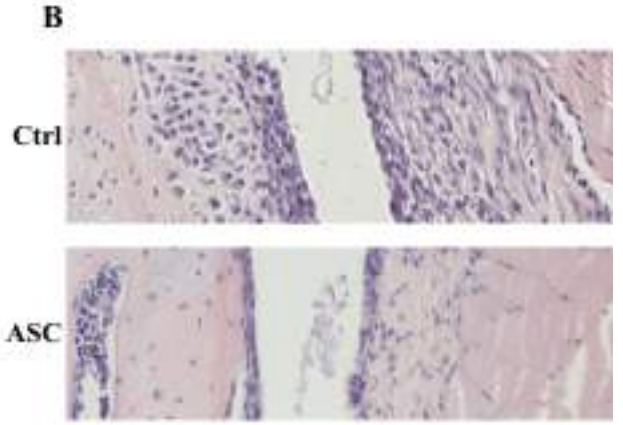
⇩

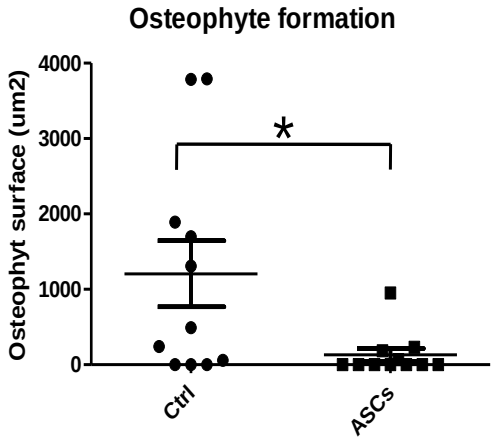
Application to rheumatoid arthritis

Why MSC therapy make sense in OA ?









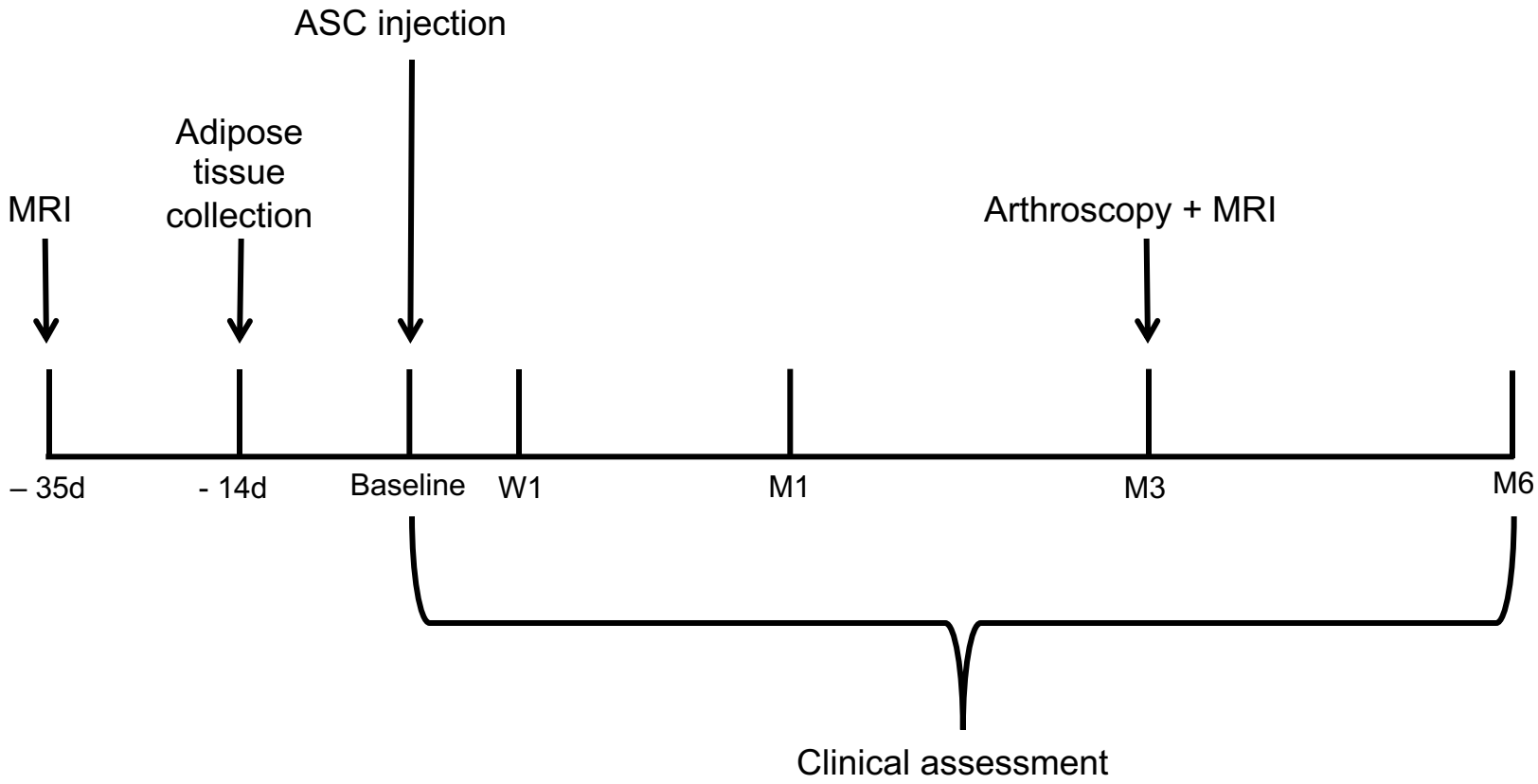
Maumus M, Pers YM et al. Med Sciences 2019
Ter Huurne and Van Lent P et al. Arthritis and Rheumatol. 2012
Manferdini et al. Arthritis and Rheumatol. 2013

ADIPOA clinical trial: design

Adipose derived Stromal Cells for OsteoArthritis treatment.

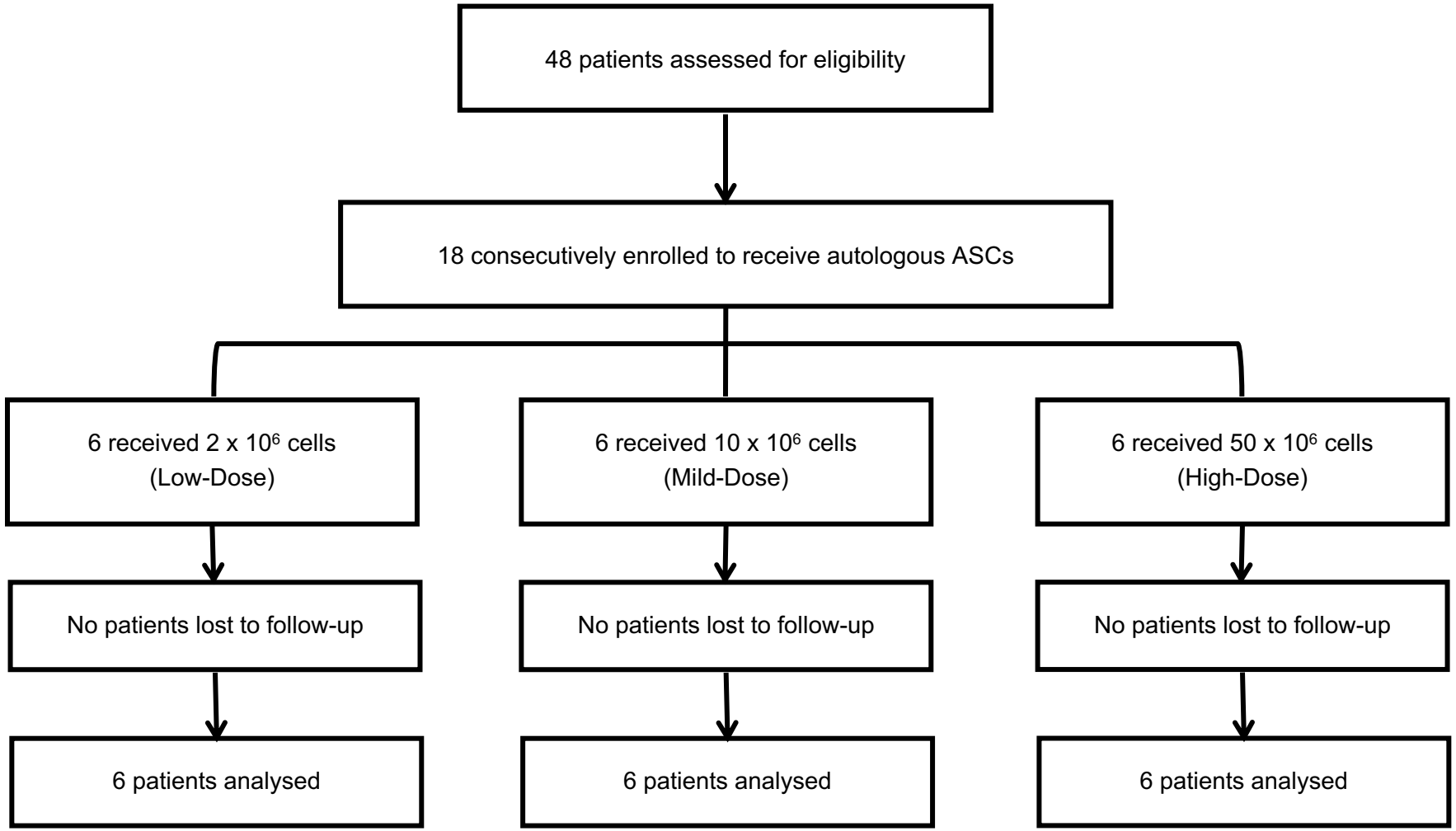
A phase 1 study, bi-centric (Mtp, Wurzburg), dose escalating study with autologous ASC in severe knee OA (>3 K/L)

ADIPOA



Pers YM et al. SCTM 2016

ADIPOA clinical trial: design

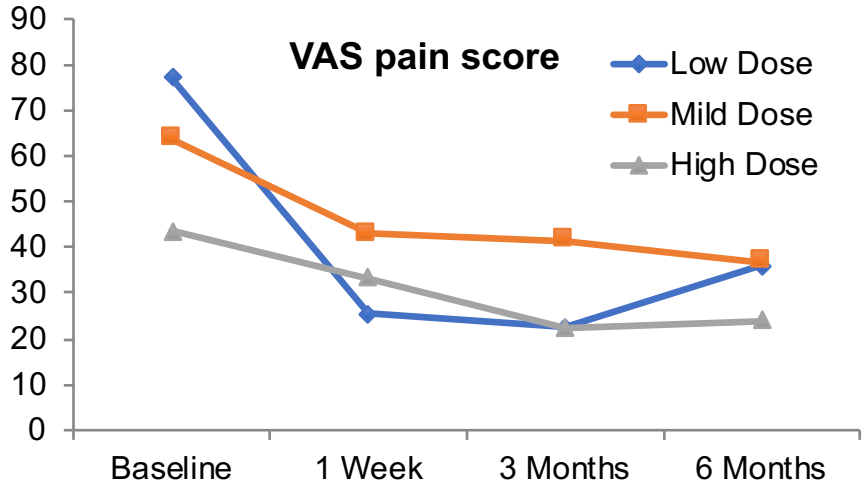


ADIPOA

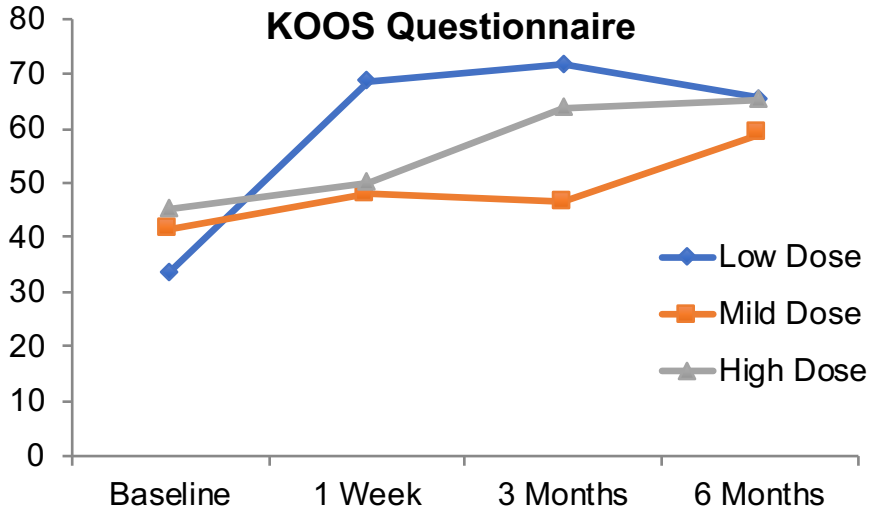
Pers YM et al. SCTM 2016

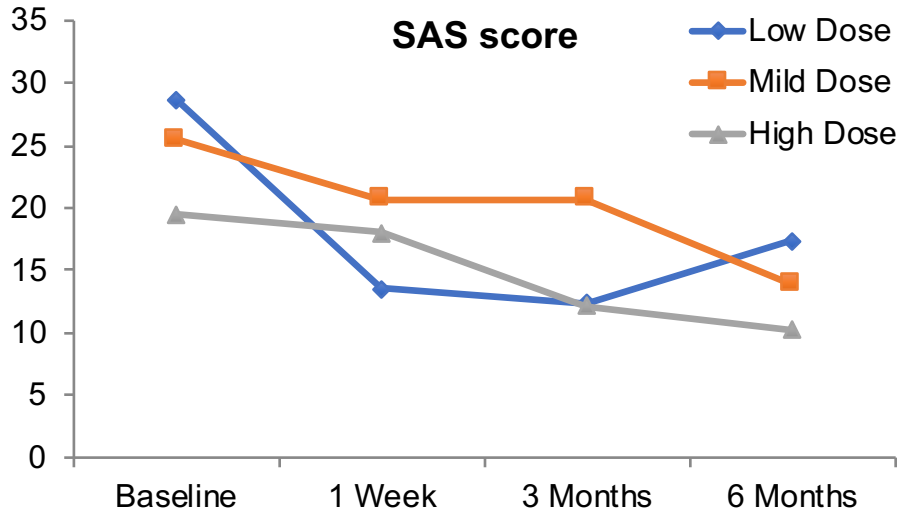
ADIPOA clinical trial

- Safe procedure: 4 local skin reaction in the first month
- Only 2 patients underwent surgery TKA after one year follow-up and 55% after 4 years



ADIPOA

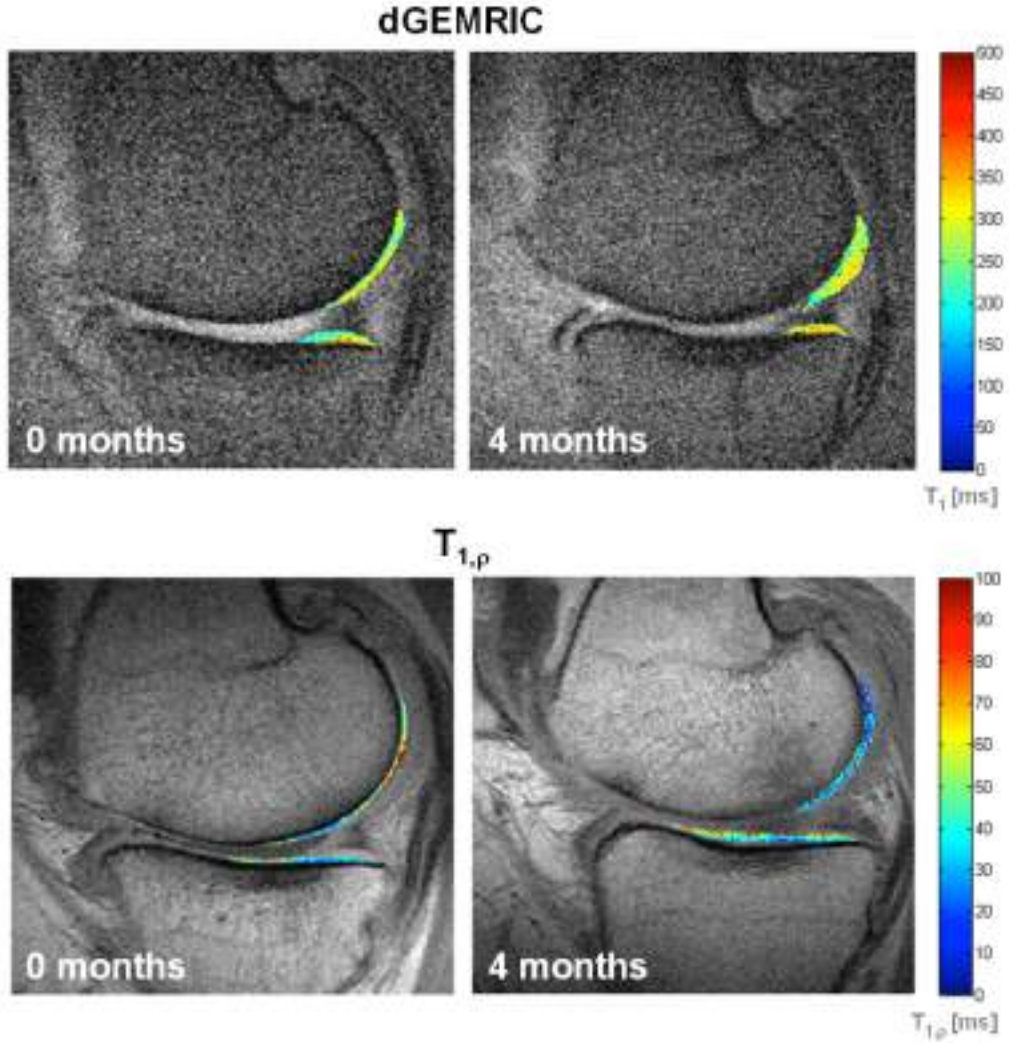




Pers YM et al. SCTM 2016

ADIPOA clinical trial: structural assessment

ADIPOA



- dGEMRIC index increase in 3 out of 6 selected patients
- Suggest a possible structural effect

Pers YM et al. SCTM 2016