OSTEOARTHRITIS

The revolution 2.0 in the management of osteoarthritis: challenges and perspectives

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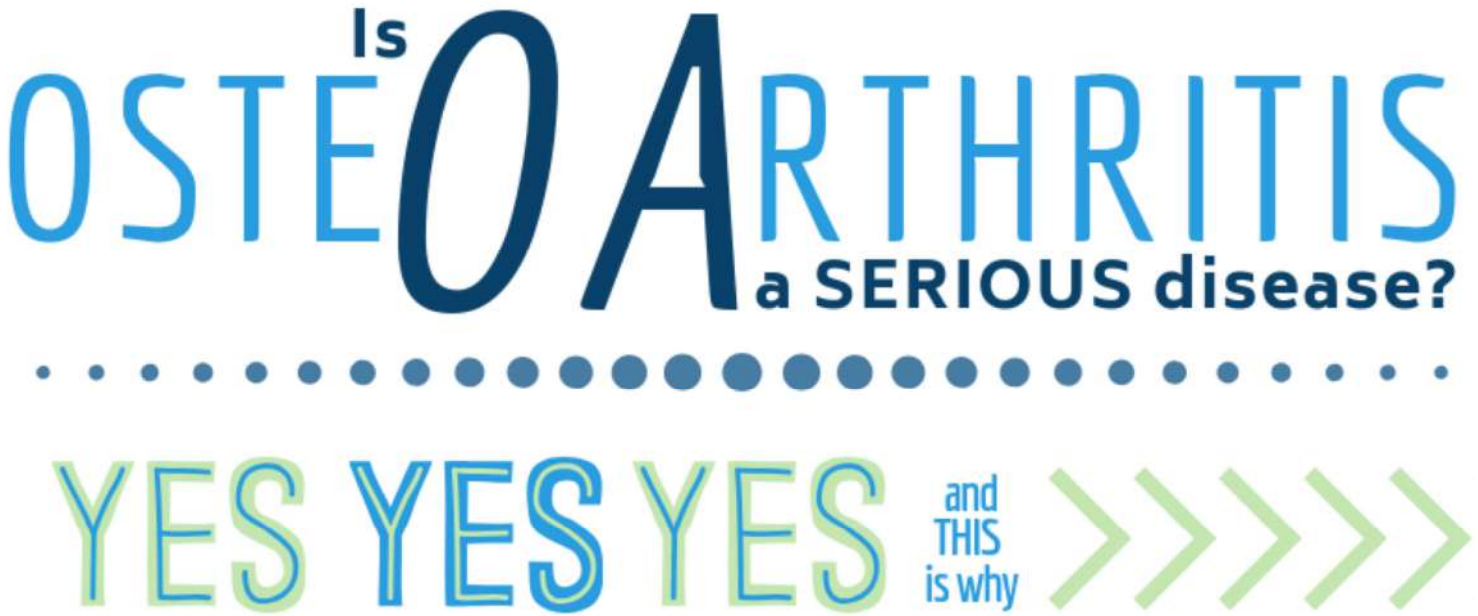
Disclosures

- 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

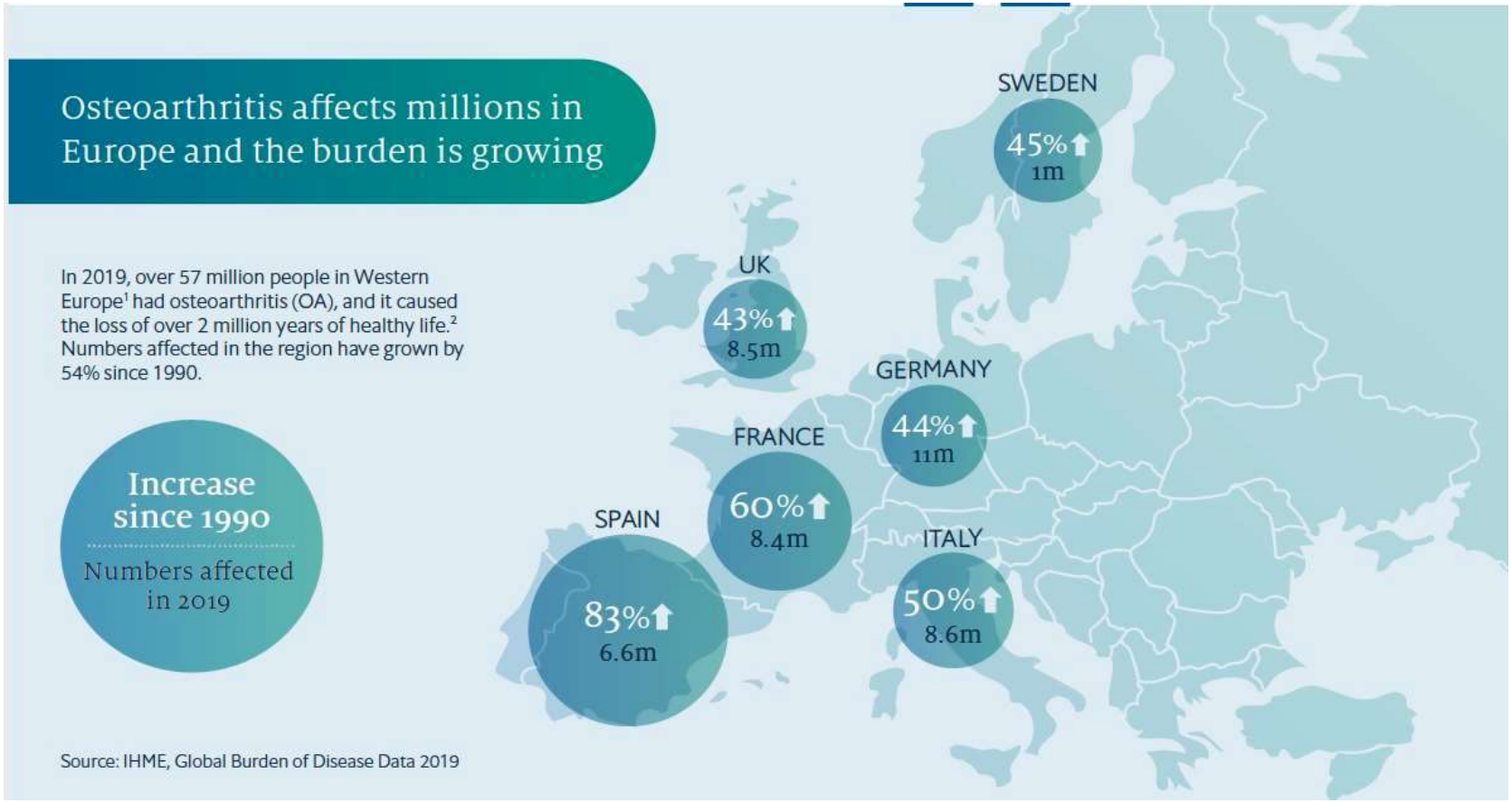
OA is COMMON & GROWING

Affects
240 million
people worldwide

2X more women than men

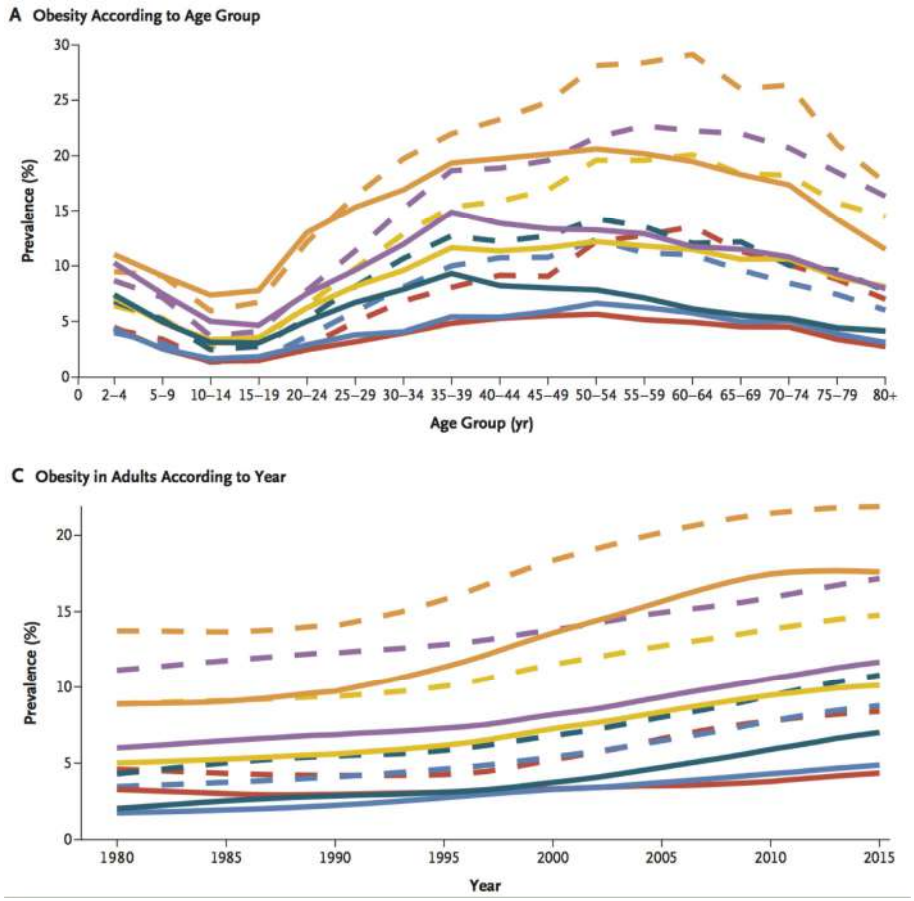
Bijlsma JWJ et al. Lancet 2011

Epidemiology OA



Epidemiology OA

- 17% whole population
- Incidence
  - ➢ Knee OA: 240/100.000 PA
  - ➢ Hand OA: 100/100.000 PA
  - ➢ Hip OA: 88/100.000 PA
- **Overweight +++**
  - ➢ RR 1.9 (hand OA + weight-bearing joints)
  - ➢ High risk joint replacement (X 5)



Bijlsma JWJ et al. Lancet 2011
The GBD 2015 collaboration. N Engl J Med 2017;377:13-27

Epidemiology OA

OA causes lost productivity and costs Europe billions of Euros each year

- In addition to the substantial direct healthcare costs, OA also impacts economies by causing absenteeism, presenteeism and early retirement, necessitating income support or disability allowance payments. People with OA may also need formal and informal care.
- European countries have reported annual OA-related costs in the billions:[7]

Direct healthcare costs

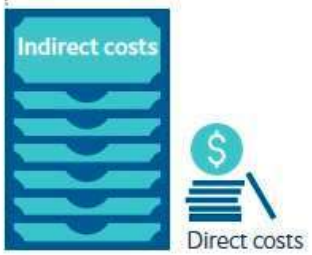
Up to **7.2bn**

Indirect healthcare costs

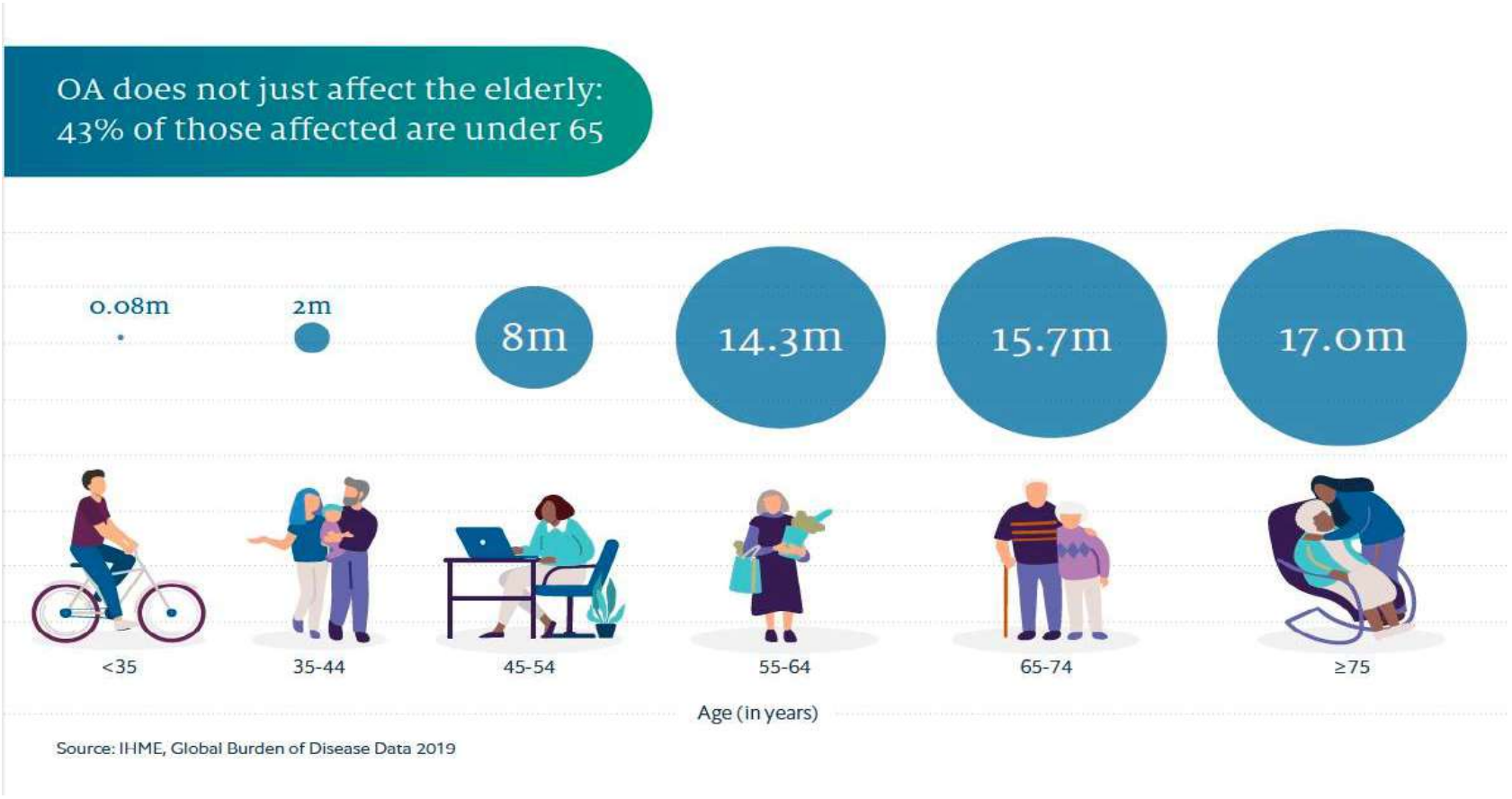
Up to **4.6bn**

Indirect costs are likely to be underestimated and could be as much as

4X direct costs.



Epidemiology OA



Epidemiology OA

- **Major public health problem in young people (< 50 years old)**
  - Risk factors: overweight/obesity/trauma
  - 7-13% knee (<45 YO)
  - Peak at 50 for the knee
  - Disability increases in 20 years (X2)
  - Parallel to obesity
  - Increasing TKR and THR
    - + 76%
    - + 30-60%

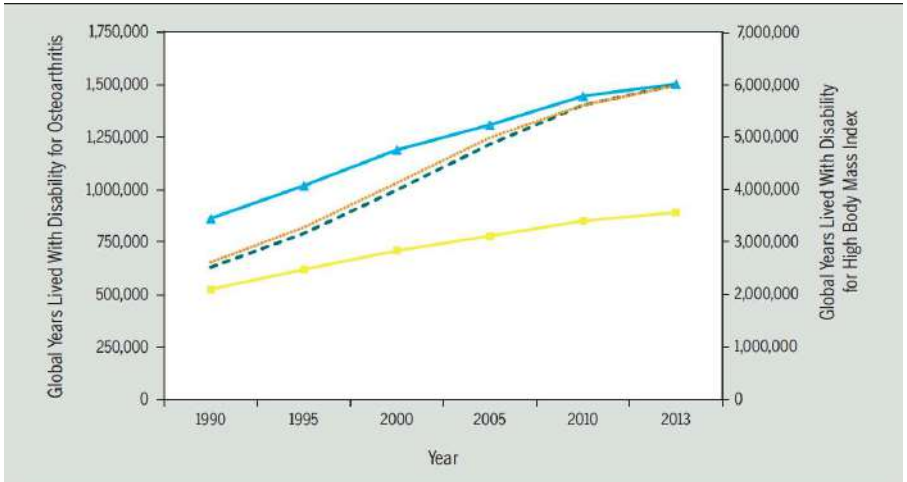


FIGURE 1. Growth in the global burden of osteoarthritis and global burden of high body mass index from 1990 to 2013 for males and females aged 15 to 49 years. Solid lines represent global years lived with disability for osteoarthritis (triangles indicate data for females and squares indicate data for males). The dotted line represents global years lived with disability for high body mass index for females, and the dashed line represents global years lived with disability for high body mass index for males. The graph was plotted using Global Burden of Disease Study data.[57]

Pereira D. O&Cart 2011
Ackerman J. Orthop Sports Phys Therapy *2017*

Epidemiology OA

OA limits LIFE

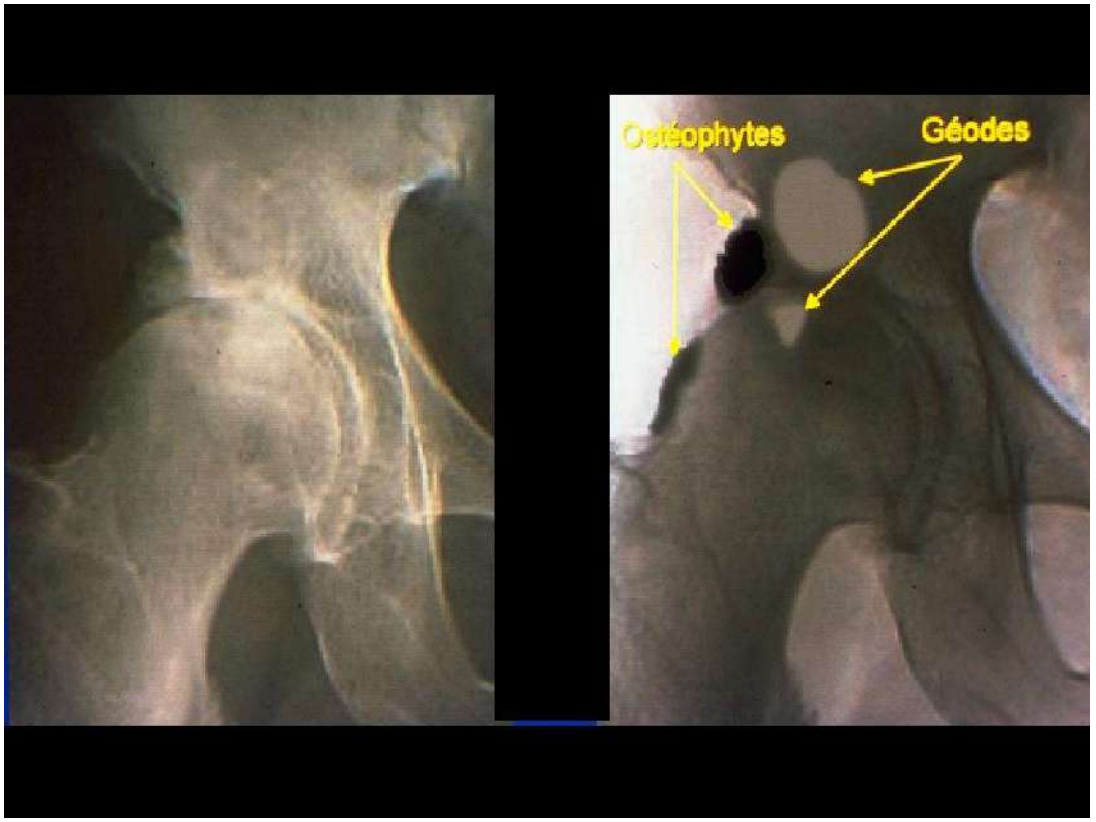
25% cannot do normal activities

80% are limited with movement

Risk of cardiovascular disease, diabetes, hypertension & death

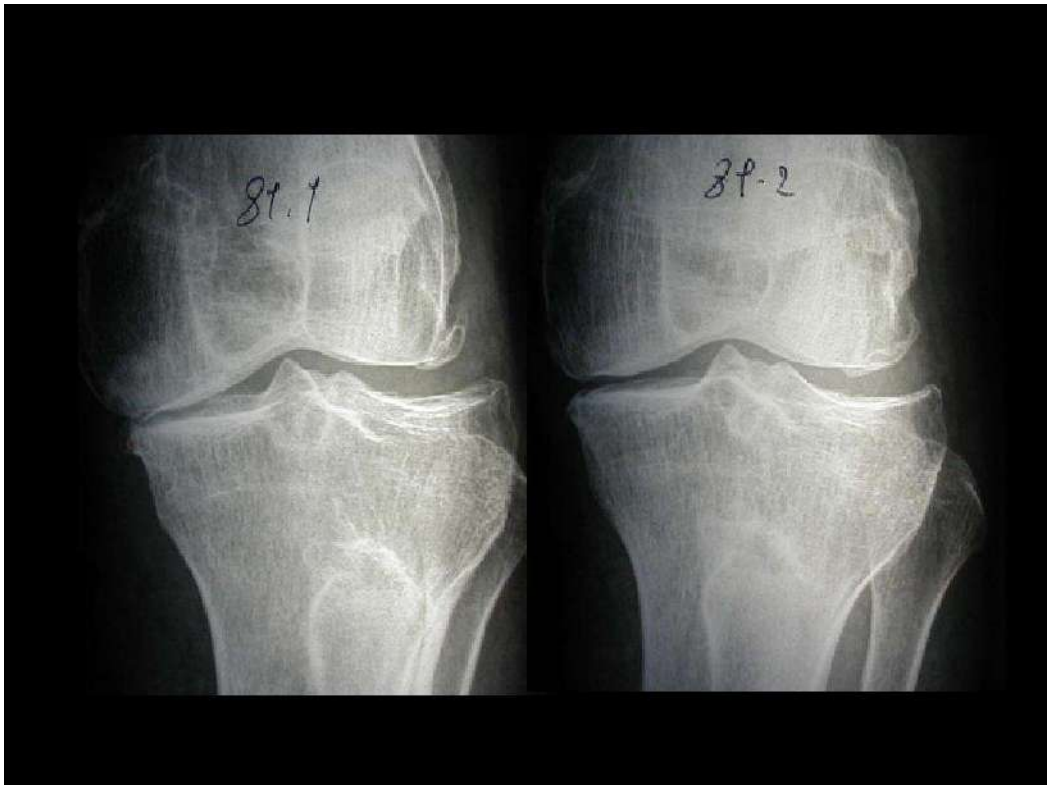
Clinical subsets OA

- **Hip OA**



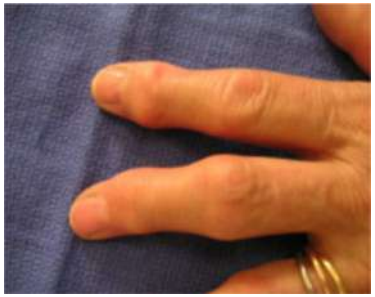
Clinical subsets OA

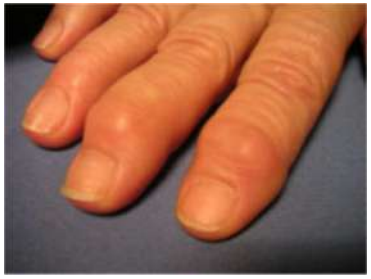
- **Knee OA**

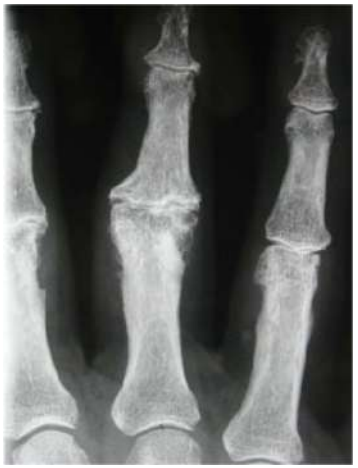


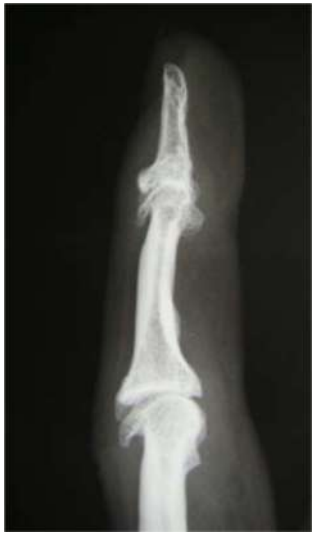
Clinical subsets OA

- **Hand OA**



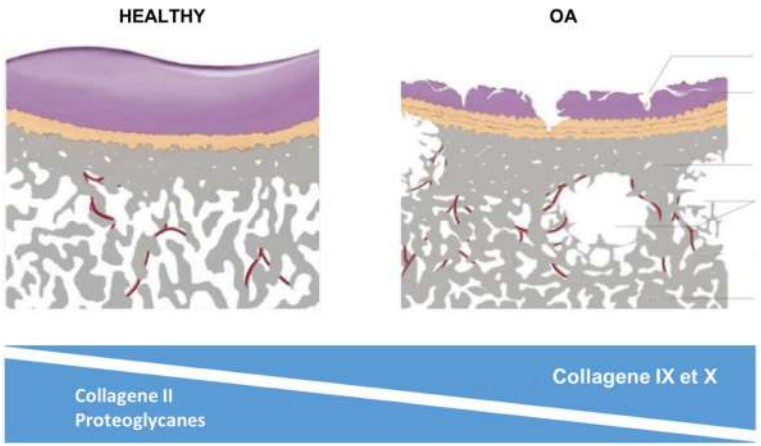


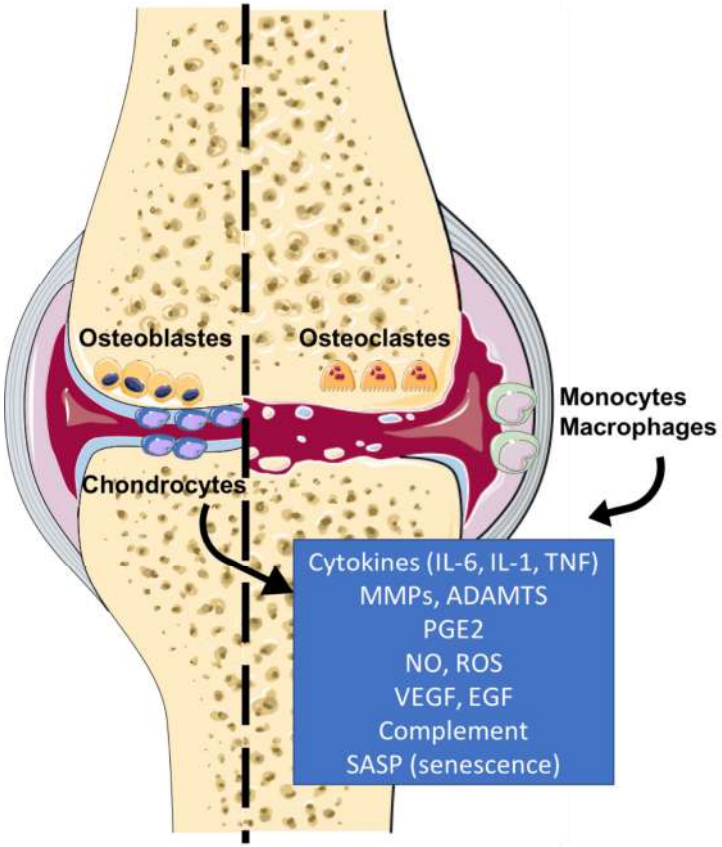




Pathophysiology in OA

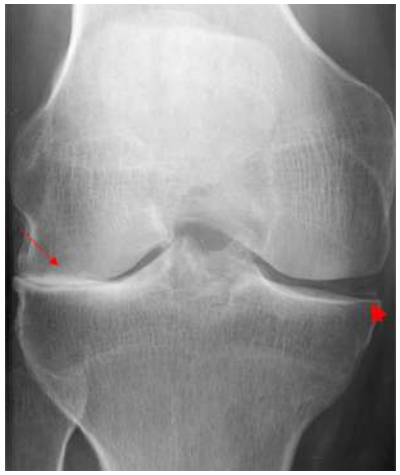
- **All the components of the joint are involved in the process:**
  - Cartilage ≈ chondrocytes + ECM
  - Subchondral bone ≈ OC/OB
  - Synovial ≈ inflammation
  - Muscles, ligaments





Treatment objectives

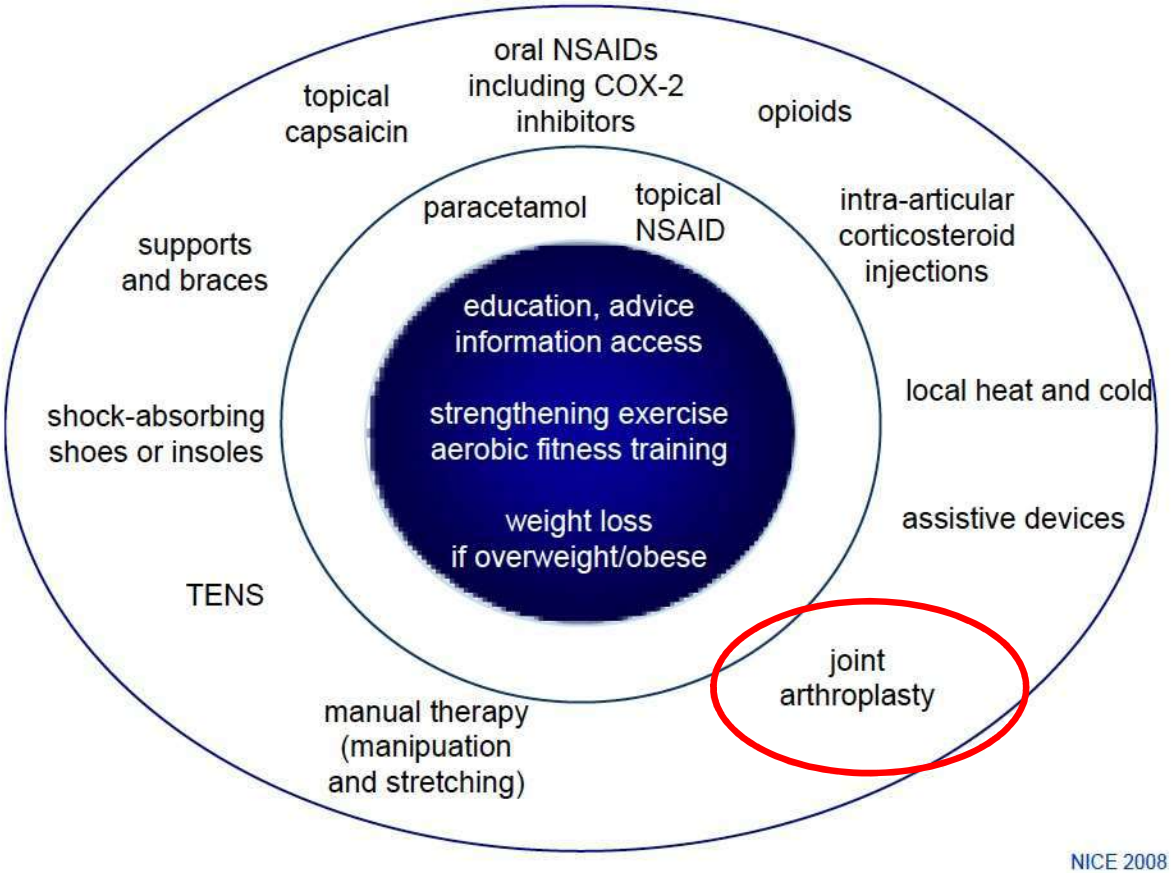
- **Reduce pain**
- **Improve function**
- **Maintain physical activity**
- **Education**
- **Slow down cartilage degradation**



- NB: DMOAD (disease modifying OA drug): structural modulation

→ **No drugs meet this definition**

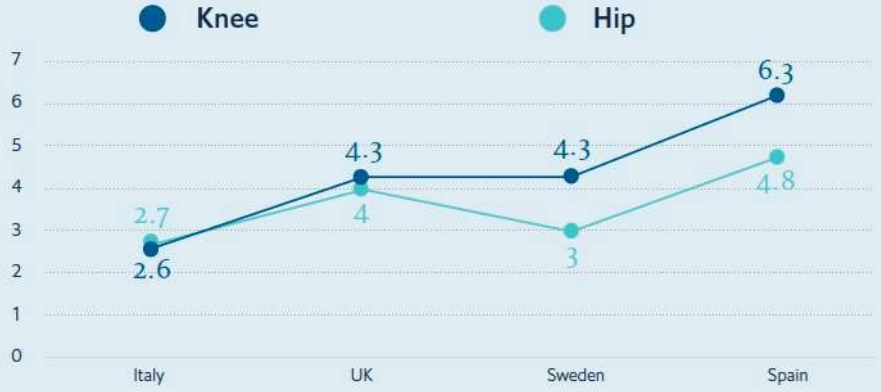
Therapeutic resources in OA



Epidemiology OA

Waiting times for joint replacement surgery can be long

Average waiting times for joint replacement surgery were up to six months in our focus countries pre-covid-19,[12] and are being lengthened by the pandemic. Not everyone with OA may be suitable for surgery or want to have it.



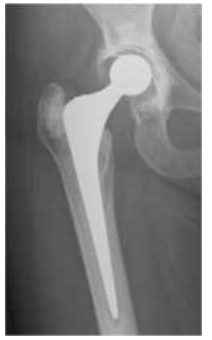
10-20%

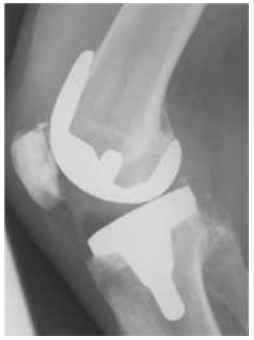
still have pain after joint replacement[13]

Source: OECD 2019 data (2018 for UK).

Surgical intervention

- **Total hip arthroplasty (THA) and total knee arthroplasty (TKA)**
  - Patients with persistent pain, stiffness and reduced function AND refractory to non-surgical treatments AND impact on their quality of life
  - Evidence based on numerous uncontrolled observational studies
  - Appropriate rehabilitation and domestic support in the first weeks
  - Recovery from TKA is slower
  - THA is more effective than TKA in restoring function to normal
  - Over 95% of joint replacements continue to function well into the second decade after surgery, and most provide lifelong pain-free function.
  - Approximately 20% patients are not satisfied

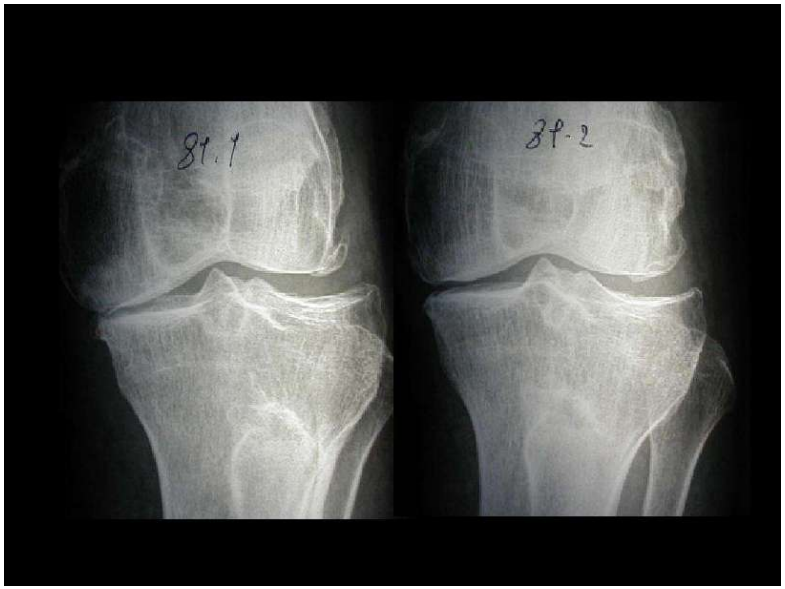




Martel-Pelletier J. Nat Rev Disease Primers 2016

Unmet need in OA

- **3 unmet medical needs**
  - Efficient disease modifying treatment
  - More effective symptomatic treatment: NSAIDs improve less than 50% WOMAC scores
  - Safer treatment: NSAIDs carry significant GI and CV risk

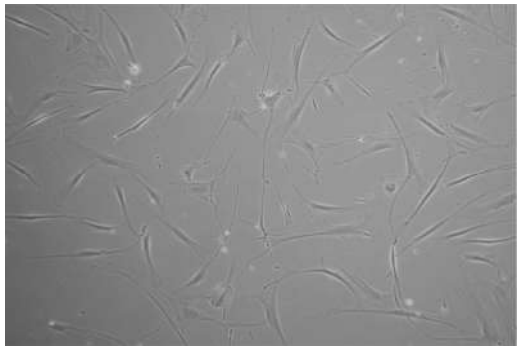


FIND NEW THERAPY
WITH VARIOUS TARGETS

MSC ???

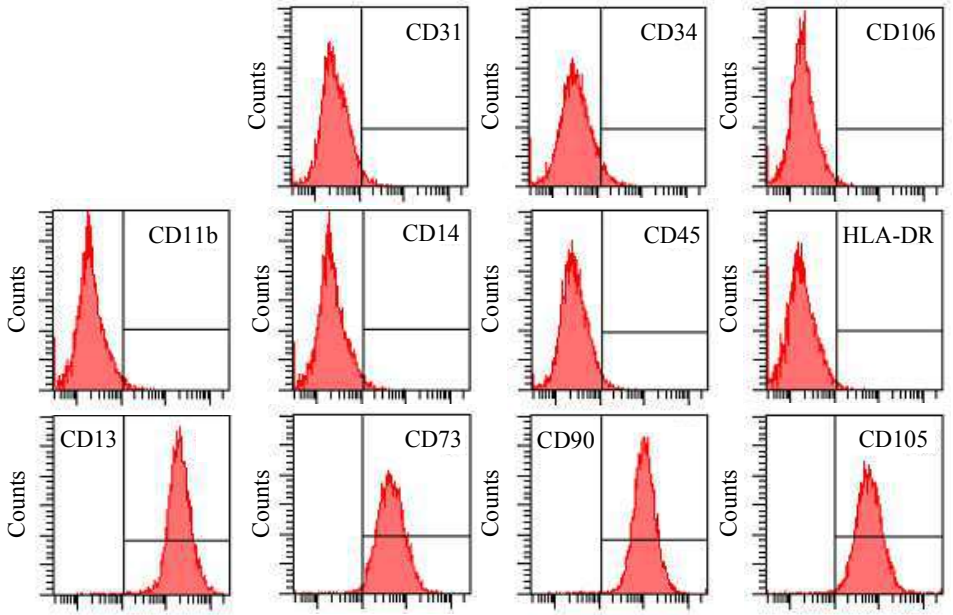
Characteristics of Mesenchymal Stem Cells (MSC)

- **Adherent to plastic**



(High expansion *in vitro)*

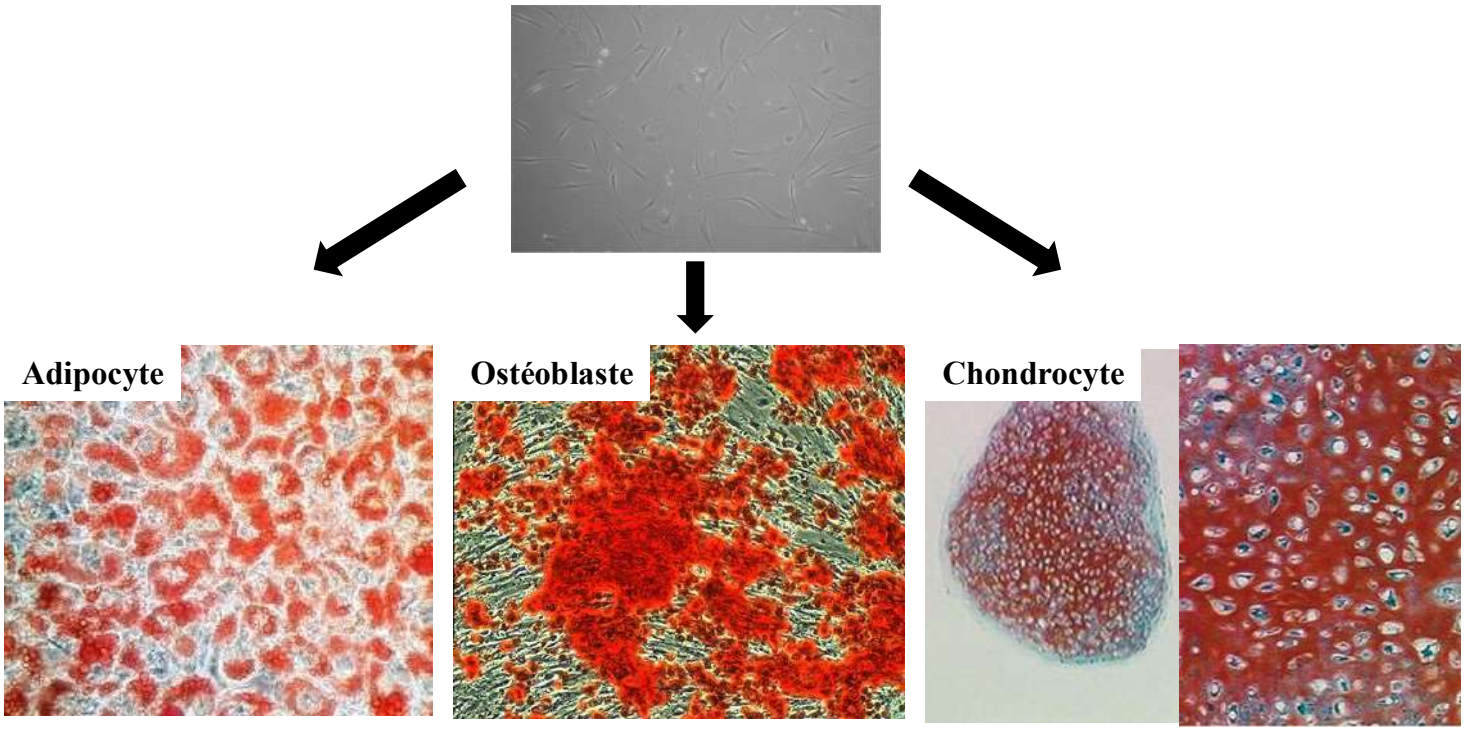
- **Immunophenotype** → No specific marker



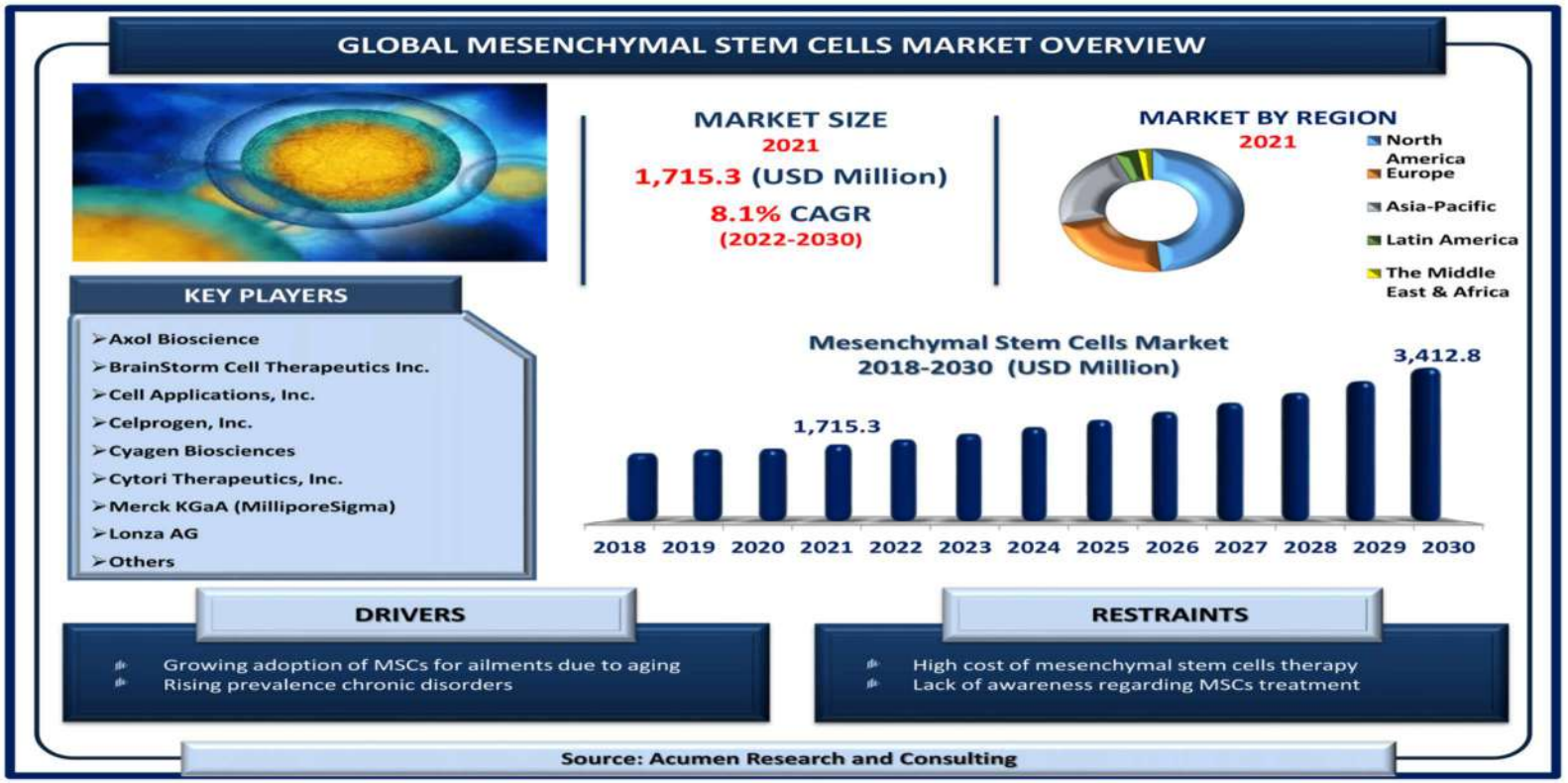
- **CD73⁺, CD90⁺, CD105⁺**, (CD13⁺)
- CD11b⁻, CD14⁻, CD19⁻, CD34⁻, **CD45⁻**, HLA-DR⁻, (CD31⁻, CD106⁻)

Characteristics of Mesenchymal Stem Cells (MSC)

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



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



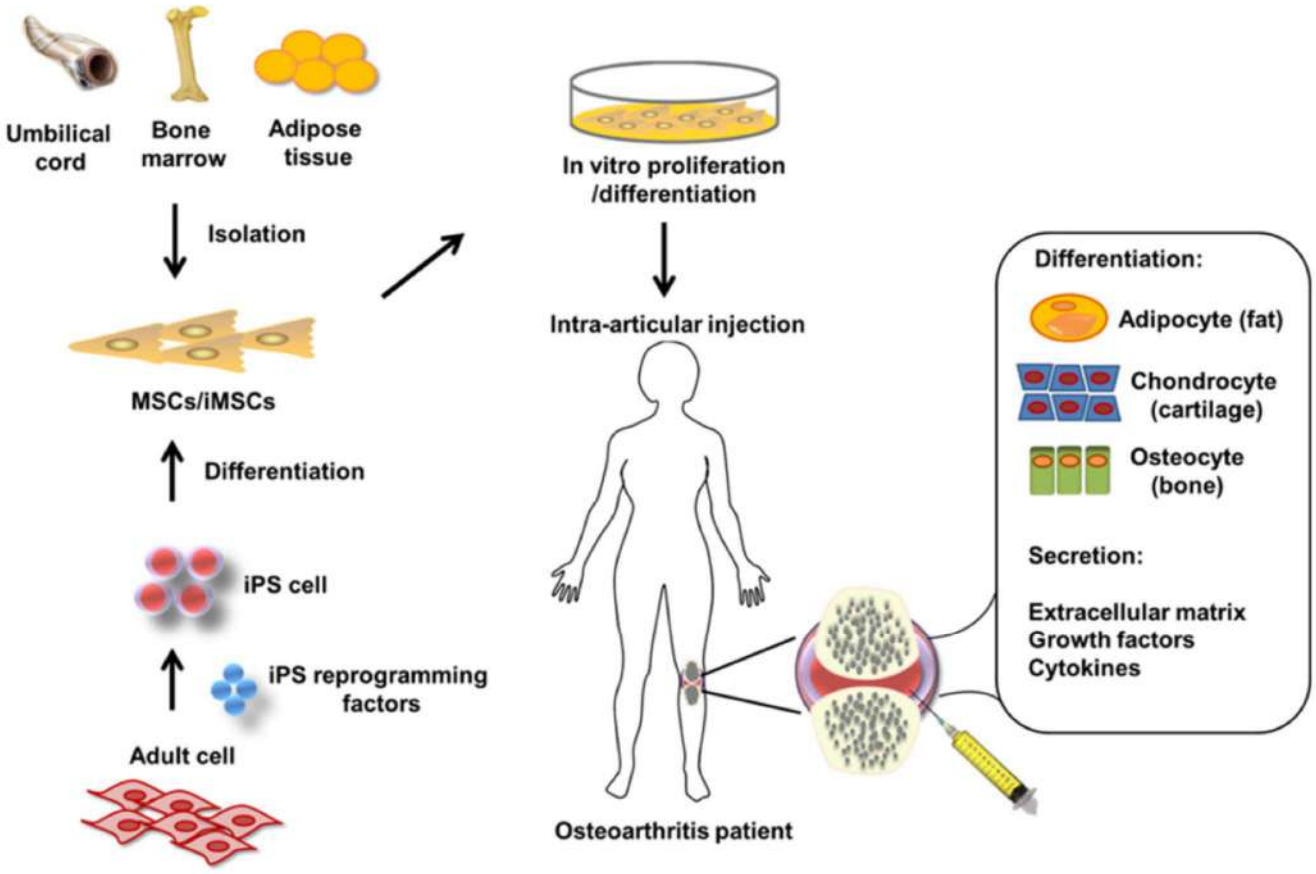
Mesenchymal Stem Cells Market Size - Global Industry, Share, Analysis, Trends and Forecast 2022 – 2030. Healthcare and Pharmaceuticals. https://www.acumenresearchandconsulting.com/mesenchymal-stem-cells-market. Published 2022

Cell therapy : futures options ?

- **Stem cell therapy**
  - Regenerative cartilage
- **Cartilage engineering**
  - Focal defects
- **EVs**
  - Substitute to cell therapy
- **iPS**
  - In vitro model
  - Infinite source

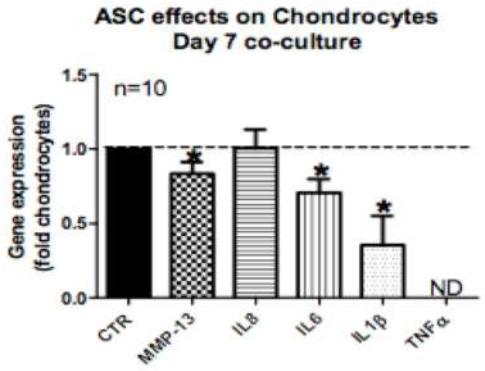
Why stem cell therapy makes sense in OA ?

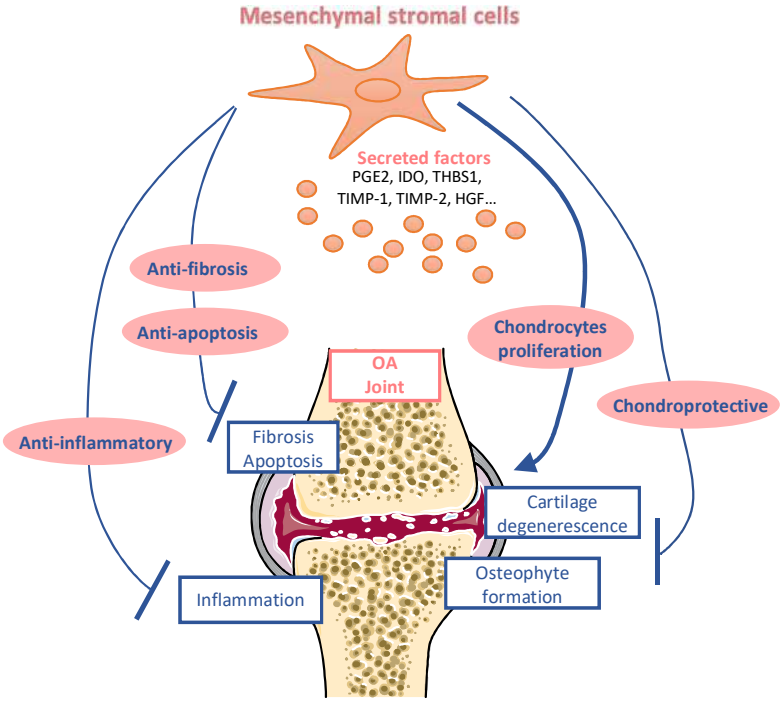
- MSC > Chondrocytes
- Sources available
- Cell differentiation
- Allo > autologous

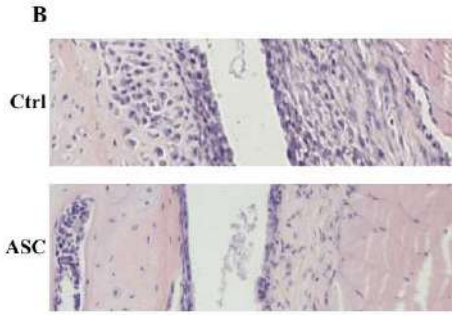


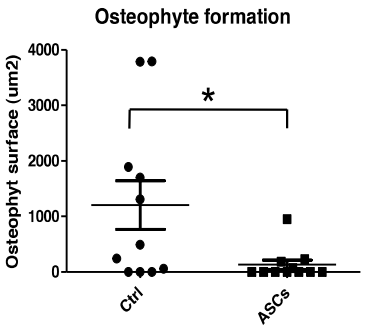
Zhu C et al. Am J Transl Res 2021

Why stem cell therapy makes sense in OA ?



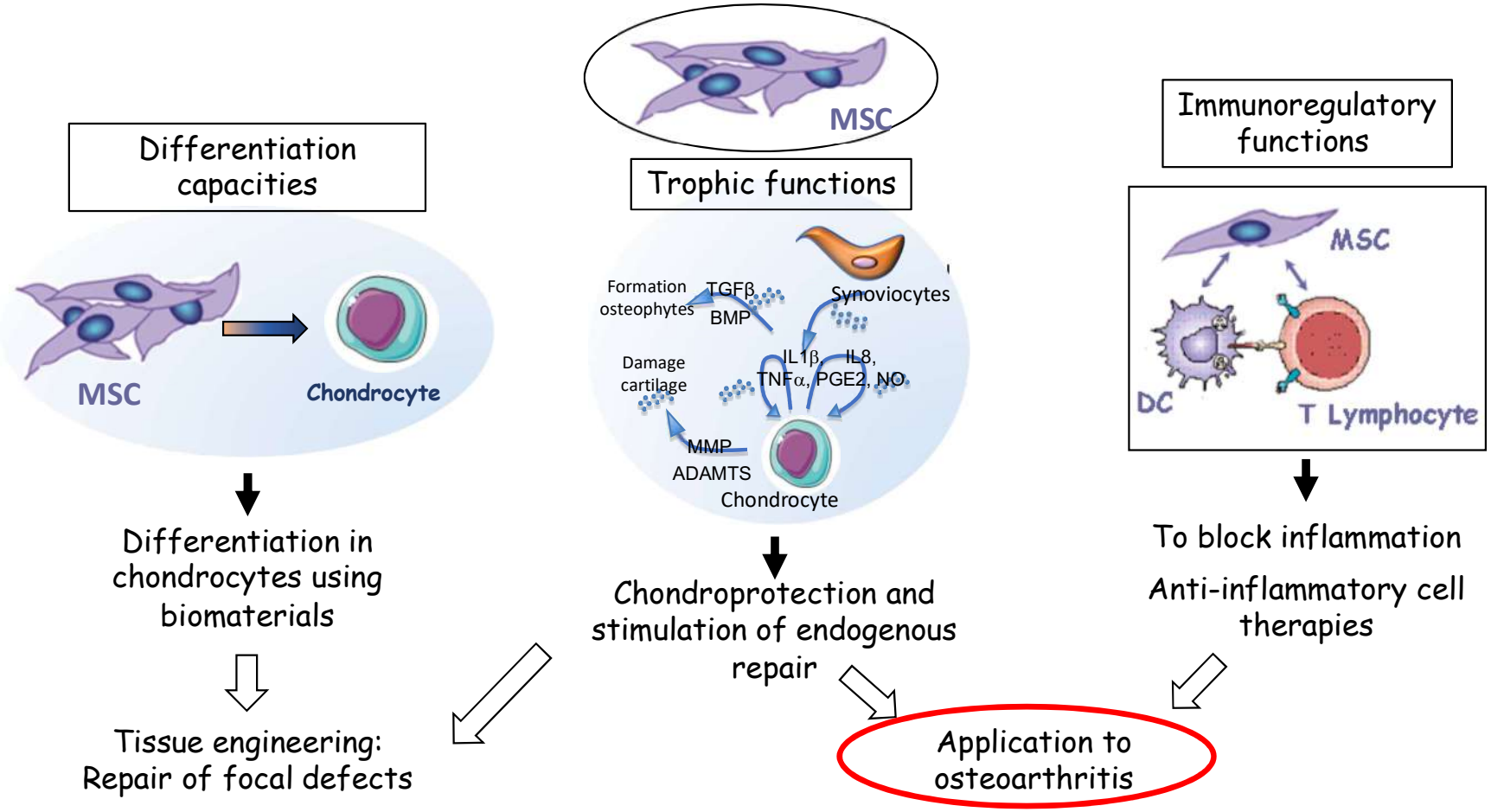






Maumus M, Pers YM et al. Med Sciences 2019
Ter Huurne and Van Lent P et al. Arthritis and Rheumatol. 2012
Manferdini et al. Arthritis and Rheumatol. 2013

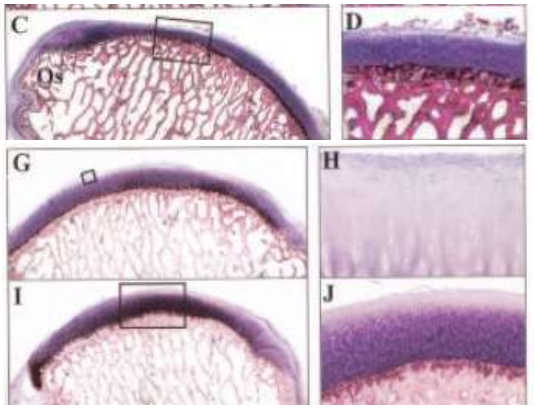
When MSC may be useful for cartilage damage ?



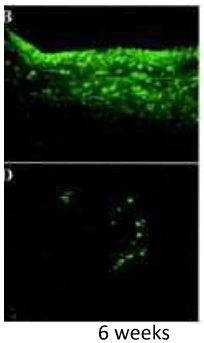
Chondroprotection

Pre-clinical data

- OA in goat model
- ACL resection + menisectomy
- IA injection of 10^7 GFP$^+$ BM-MSC + HA at 6 weeks



Murphy et al., Arthr Rheum 2003



6 weeks

- Meniscus regeneration for 4/6 goats

(less fibrillation, less PG loss, best cartilage integrity)

- Few GFP$^+$ MSC in cartilage

Majority of BM-MSC injection effects is not due to cell integration on cartilage but to their trophic activity

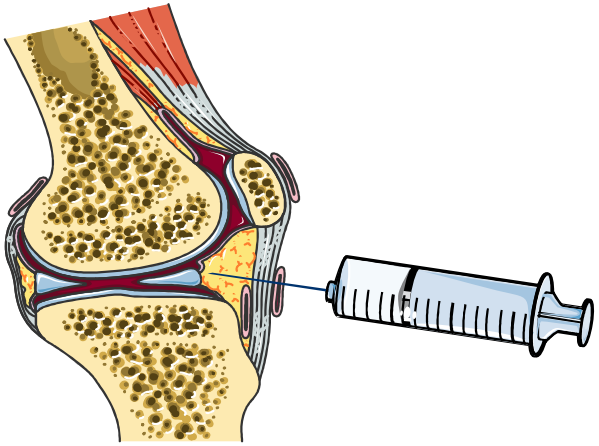
ADIPOA clinical trial

ADIPOA

lipoaspiration

ADSC
isolation/expansion
GMP conditions
Cell viability
Release
criteria/toxicology

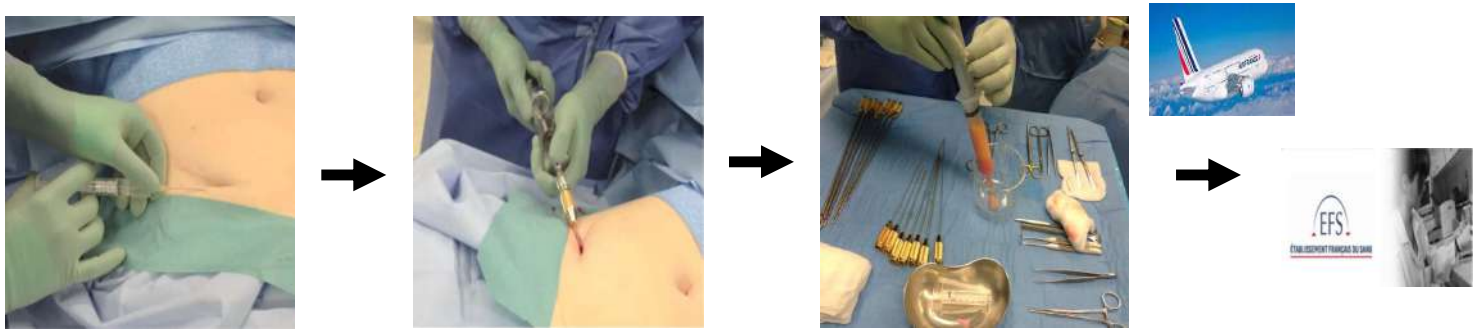
Intra-articular injections
Syringe, different doses

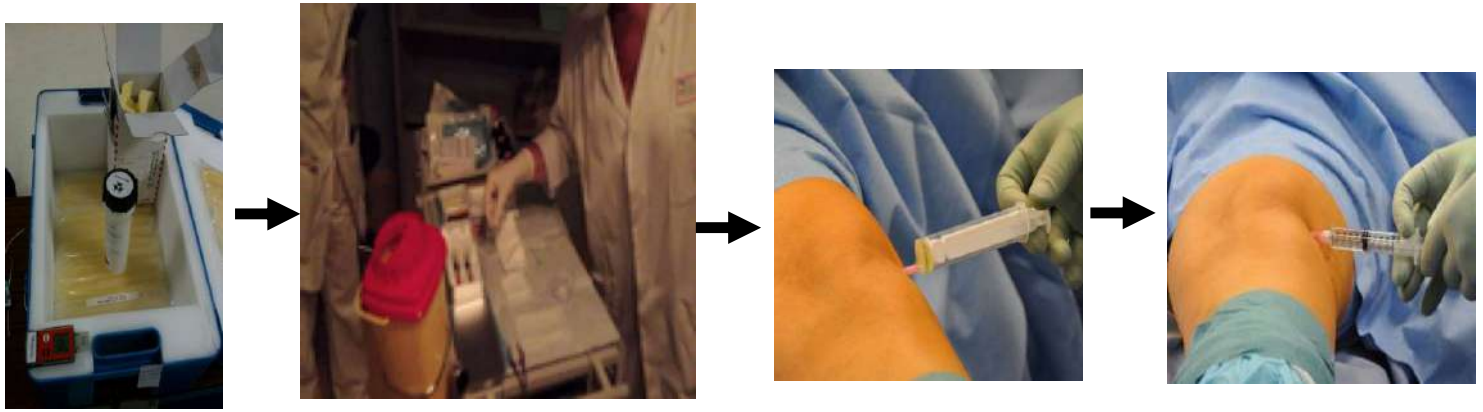


Evaluation: phase 1 trial
safety, dose response
clinical evaluation (WOMAC…)
MRI Gemric,

ADIPOA clinical trial: fat harvesting

ADIPOA



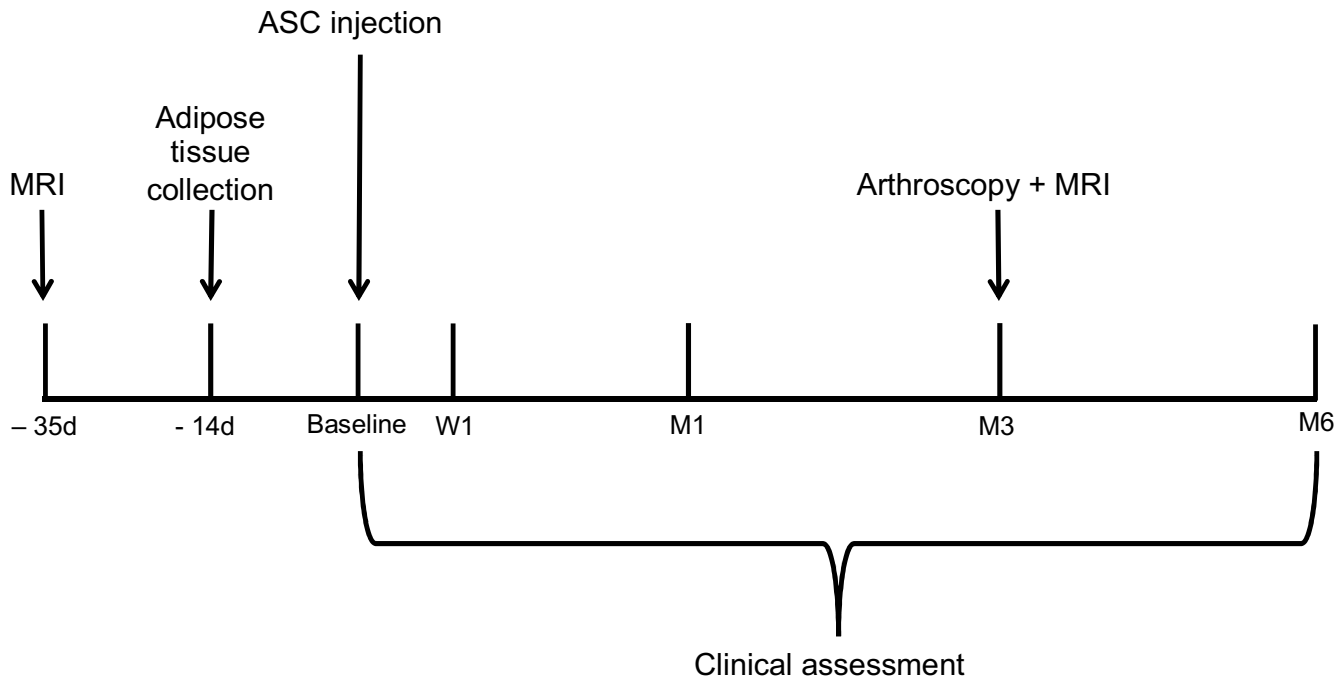


ADIPOA clinical trial: design

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)

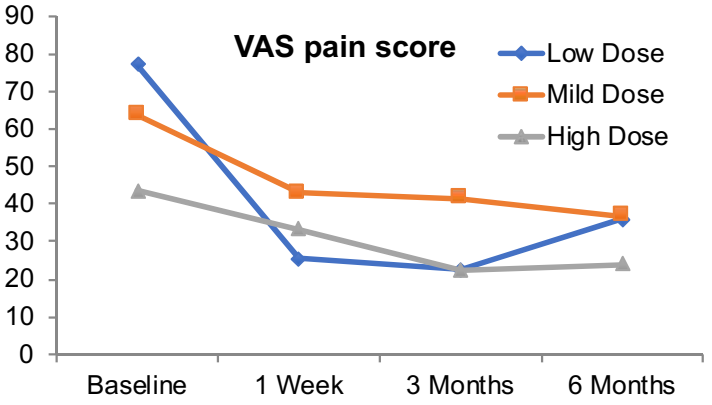
ADIPOA



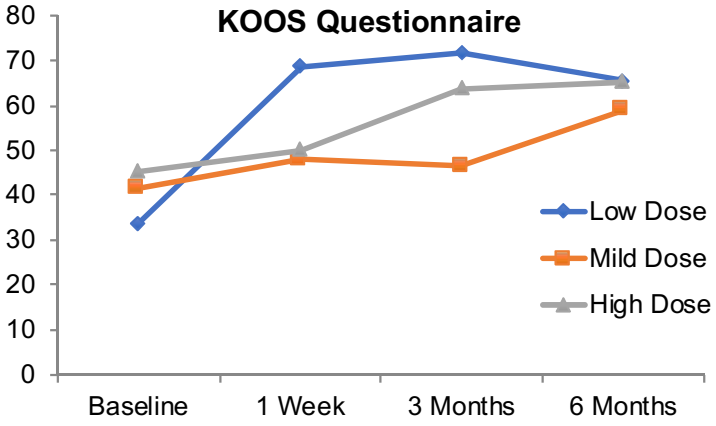
Pers YM et al. SCTM 2016

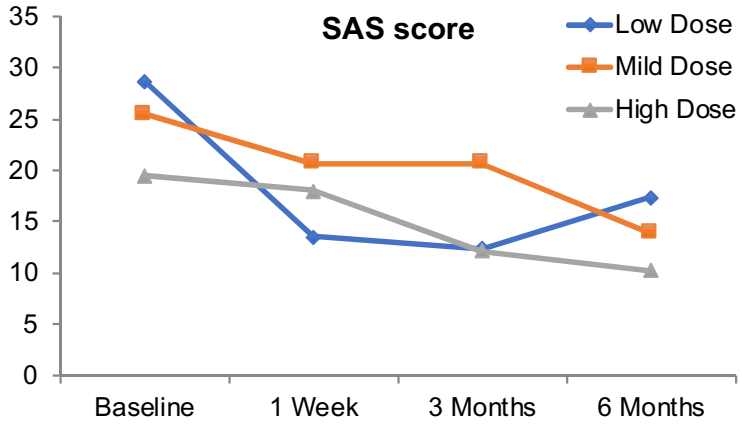
ADIPOA clinical trial

- **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

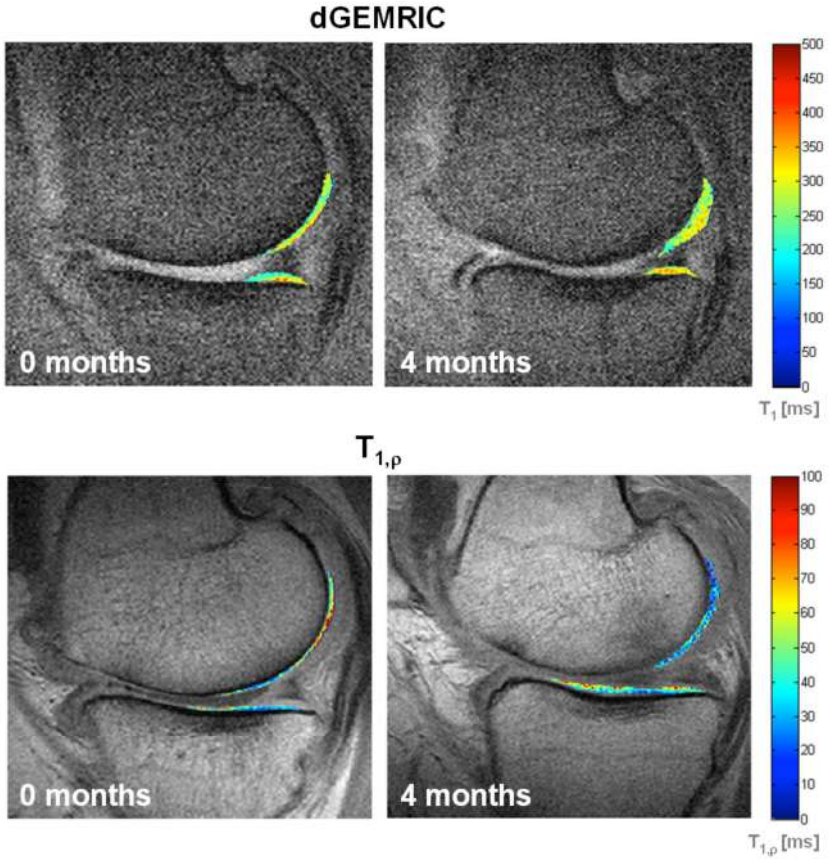




Pers YM et al. SCTM 2016

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

ADSC with a control group

STEM CELLS TRANSLATIONAL MEDICINE

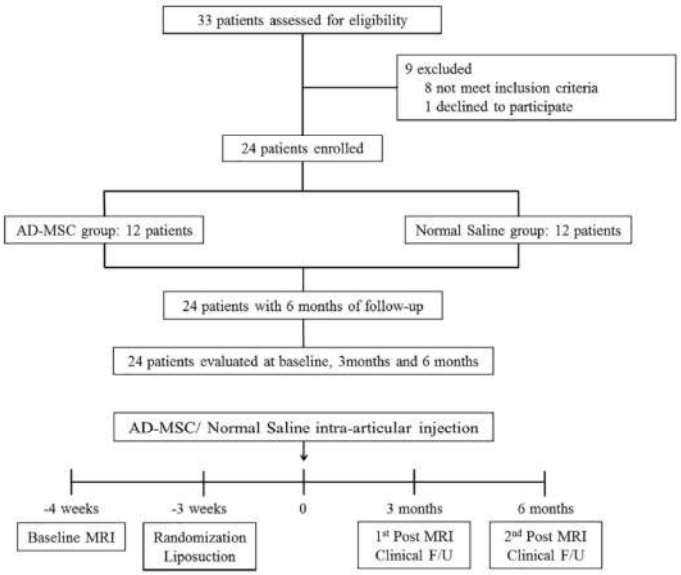
HUMAN CLINICAL ARTICLE

Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial

[a]Department of Orthopaedic Surgery, College of Medicine, Gangnam Severance Hospital, Yonsei University, Seoul, South Korea;

WOO-SUK LEE,[a] HWAN JIN KIM,[b,c] KANG-IL KIM,[b,c] GI BEOM KIM,[b,c] WOOK JIN[d]

Key Words. Knee • Osteoarthritis • Adipose-derived mesenchymal stem cell • Intra-articular injection



Wok-Sue Lee et al. Stem Cells Translational Medicine 2019

ADSC with a control group

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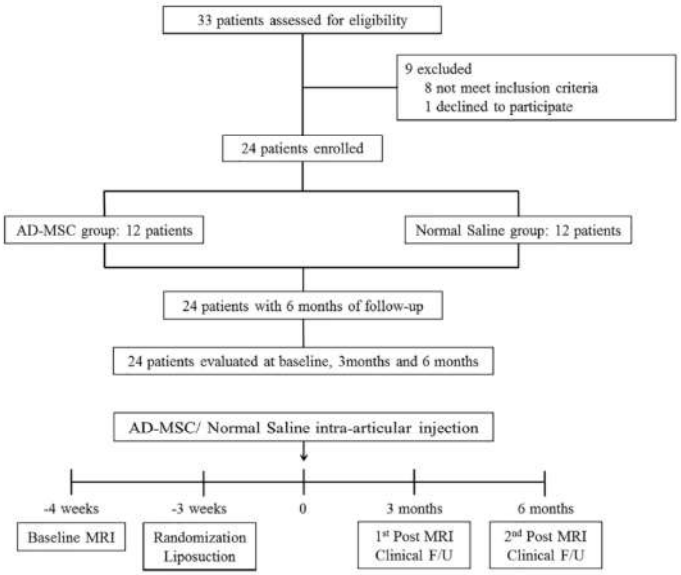
Key Words. Knee • Osteoarthritis • Adipose-derived mesenchymal stem cell • Intra-articular injection



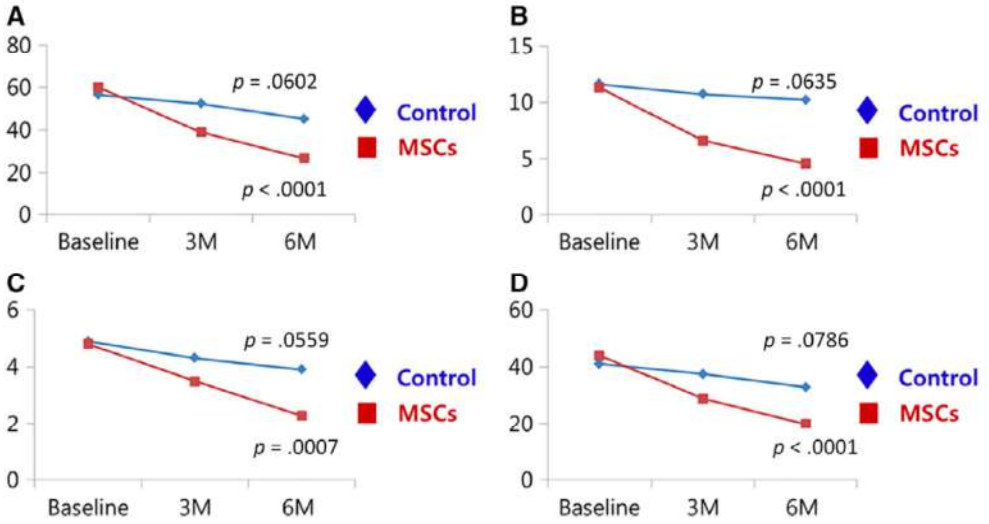


Figure 2. Changes in the WOMAC score during the 6-month period after intra-articular injection in the MSC group and control gro
Patients with injection of AD-MSC showed significant improvement in the WOMAC score. Patients in the control group did not sig

Wok-Sue Lee et al. Stem Cells Translational Medicine 2019

Meta-analysis MSC clinical results in OA

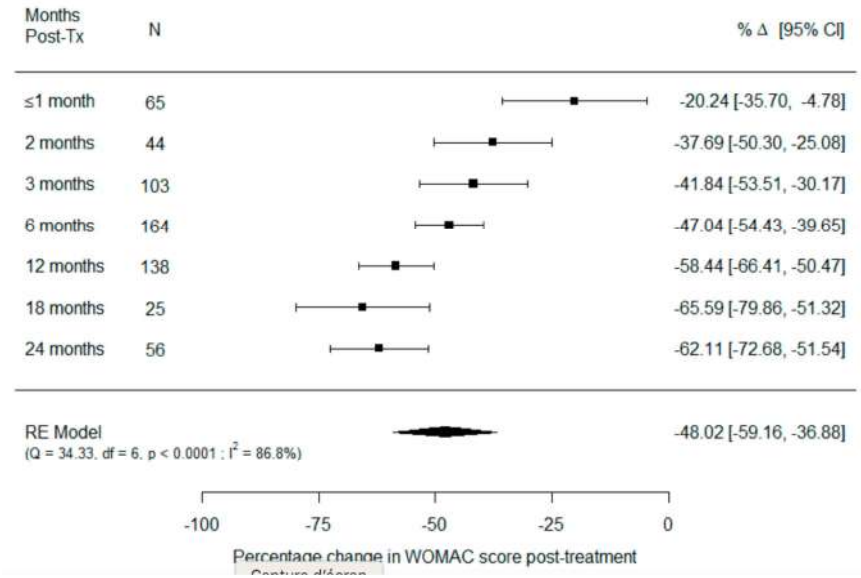
cells

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

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journal homepage: www.elsevier.com

ELSEVIER

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

The first (recent) phase III study

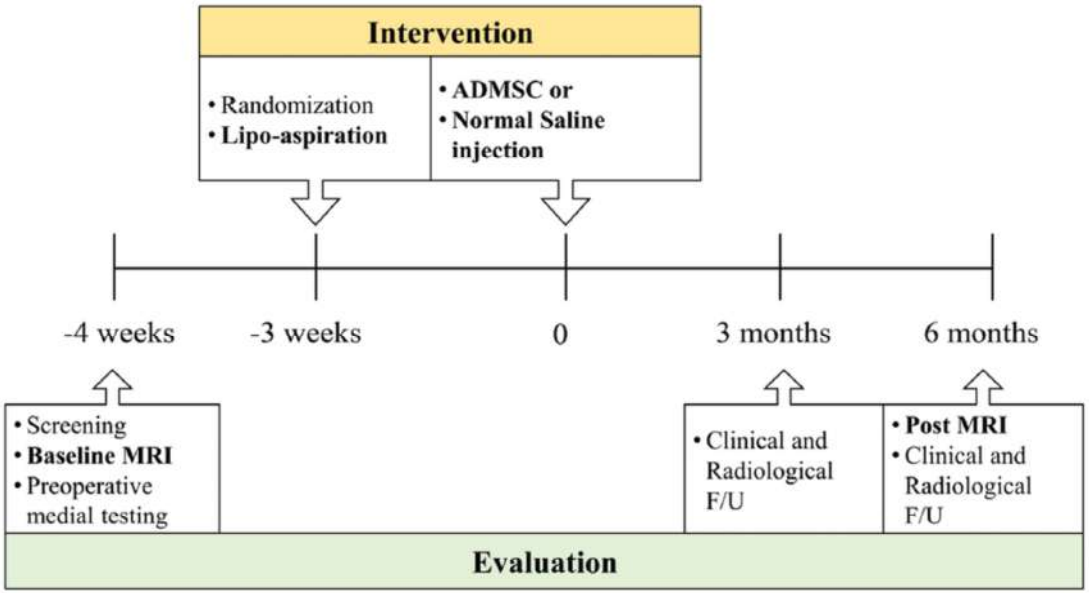
Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis

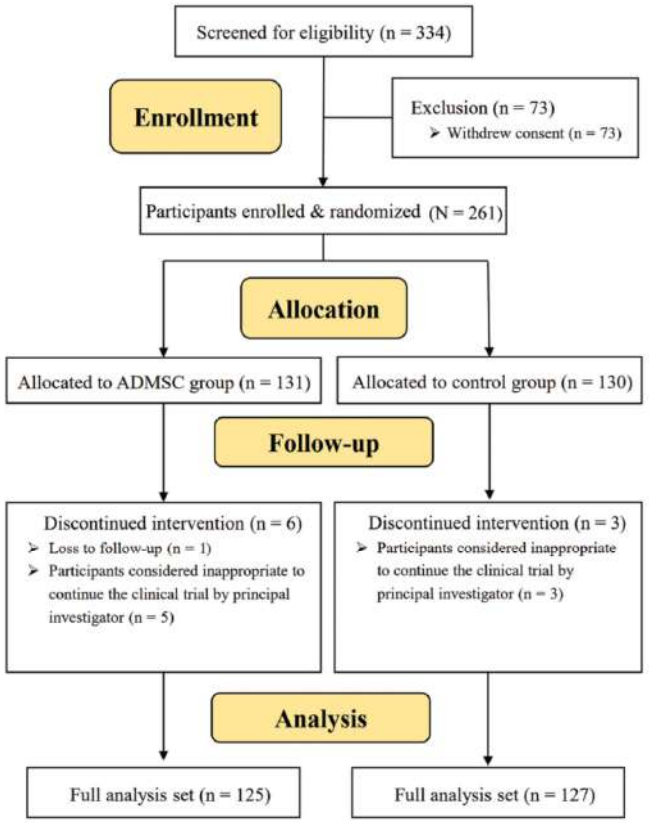
A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial

Kang-Il Kim, MD, PhD, Myung Chul Lee, MD, PhD, Ju Hong Lee, MD, PhD, Young-Wan Moon, MD, PhD, Woo-Suk Lee, MD, PhD, Han-Jun Lee, MD, PhD, Sun-Chul Hwang, MD, PhD, Yong In, MD, PhD, Oog-Jin Shon, MD, PhD, Ki-Cheor Bae, MD, PhD, Sang-Jun Song, MD, PhD, and Kwan Kyu Park, MD, PhD
Investigation performed at Kyung Hee University Hospital at Gangdong, Seoul, Korea

Kang-Il Kim et al. The American Journal of Sports Medicine 2023;51(9):2243–2253

The first (recent) phase III study





Kang-Il Kim et al. The American Journal of Sports Medicine 2023;51(9):2243–2253

The first (recent) phase III study

TABLE 1
Demographics and Baseline Characteristics: Full Analysis Set[a]

	ADMSC (n = 125)	Control (n = 127)
Age, y	63.7 ± 7.1	63.8 ± 7.1
Sex, male:female, No.	39:86	26:101
Body mass index, kg/m^2	26.3 ± 3.2	25.9 ± 3.1
Smoking, No. (%)	7 (5.6)	5 (3.9)
Duration of osteoarthritis diagnosis, mo	84.1 ± 68.1	85.7 ± 66.5
Symptom duration, mo	113.1 ± 79.1	108.3 ± 84.6
Radiologic data		
K-L grade 1:2:3:4, No.	0:0:125:0	0:0:127:0
HKA angle, deg[b]	−3.8 ± 5.3	−3.3 ± 4.7
Joint space width, mm	3.5 ± 1.3	3.6 ± 1.5
Clinical data		
100-mm VAS for pain	57.7 ± 17.1	60.9 ± 16.6
WOMAC index		
Pain	10.7 ± 3.3	11.3 ± 3.2
Stiffness	4.5 ± 1.3	4.9 ± 1.5
Function	39.8 ± 9.4	41.8 ± 10.3
Total	55.0 ± 13.4	58.0 ± 14.4
KOOS		
Symptoms	55.7 ± 15.9	51.7 ± 15.9
Pain	50.1 ± 13.9	46.9 ± 16.2
Activities of Daily Living	53.7 ± 14.8	50.2 ± 17.0
Sport and Recreation	23.6 ± 18.3	21.5 ±19.0
Quality of Life	32.9 ± 14.3	31.8 ± 16.1
SF-36		
PCS	38.0 ± 5.9	37.9 ±6.2
MCS	46.6 ± 10.1	45.9 ± 9.6
IKDC subjective score	38.5 ± 11.7	37.0 ± 13.1

Kang-Il Kim et al. The American Journal of Sports Medicine 2023;51(9):2243–2253

The first (recent) phase III study

TABLE 2
Mean Improvements in Primary Outcomes From Baseline to the Follow-up Visits: Full Analysis Set[a]

Outcome: LMM[b] or Time	ADMSC (n = 125)[c]	Control (n = 127)[c]	95% CI of the Difference	*P* Value
Δ 100-mm VAS on pain				
LMM	11.8 (2.9)[b]		6.4-17.4	**<.001**
3 months	22.2 ± 24.6	13.2 ± 23.7	0.6-12.7	**.030**
6 months	25.2 ± 24.6	15.5 ± 23.7	3.0-15.3	**.004**
Δ WOMAC				
Δ Pain subscore				
LMM	2.0 (0.5)[b]		1.0-3.0	**<.001**
3 months	3.8 ± 4.1	2.7 ± 3.8	0.1-2.1	**.027**
6 months	4.3 ± 4.0	2.7 ± 4.4	0.6-2.7	**.003**
Δ Stiffness subscore				
LMM	0.8 (0.2)[b]		0.3-1.2	**<.001**
3 months	1.4 ± 1.8	1.3 ± 1.6	-0.3-0.5	.620
6 months	1.8 ± 1.9	1.3 ± 1.9	0.1-1.0	**.017**
Δ Function subscore				
LMM	6.1 (1.7)[b]		2.8-9.4	**<.001**
3 months	13.3 ± 13.6	9.7 ± 12.1	0.4-6.8	**.030**
6 months	15.7 ± 13.4	10.3 ± 14.1	2.0-8.9	**.002**
Δ Total score				
LMM	8.9 (2.3)[b]		4.3-13.4	**<.001**
3 months	19.1 ± 18.7	13.5 ± 17.2	0.35-9.2	**.024**
6 months	21.7 ± 18.6	14.3 ± 19.2	2.8-12.4	**.002**

Kang-Il Kim et al. The American Journal of Sports Medicine 2023;51(9):2243–2253

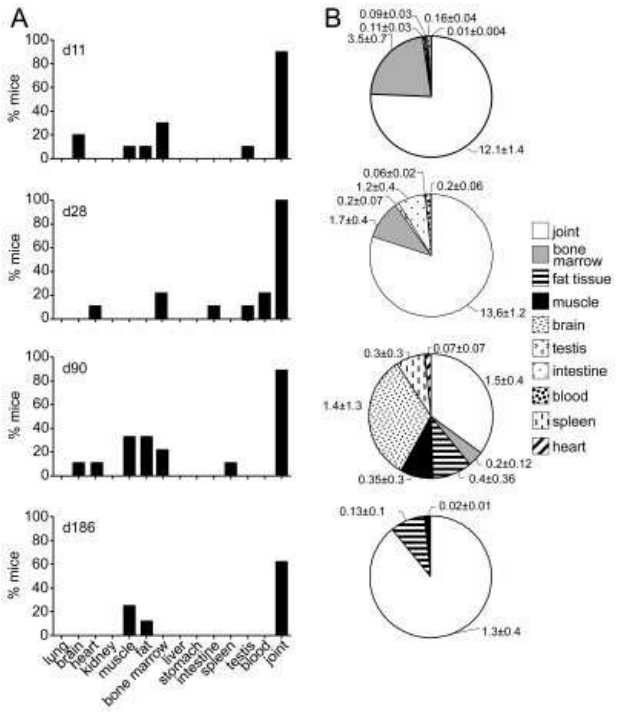
The first (recent) phase III study

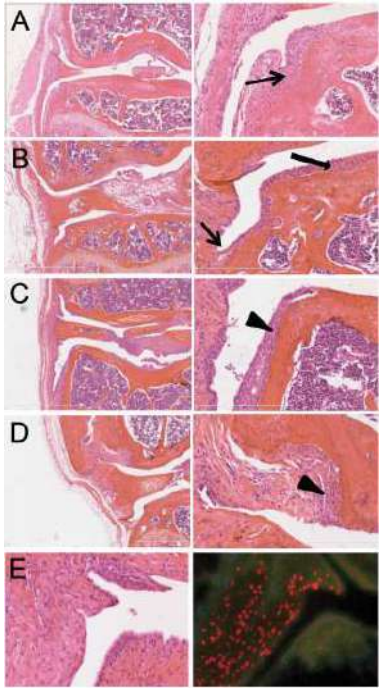
TABLE 4
Treatment-Emergent Adverse Events in the Safety Set[a]

	ADMSC (n = 125)	Control (n = 127)	*P* Value
Patient summary			
Patients with TEAE	48 (38.4)	41 (32.3)	.310
Patients with SAE	1 (0.8)	3 (2.4)	.622
Patients with fatal SAE	0	0	>.999
Procedure-related joint pain	3 (2.4)	1 (0.8)	.337
Procedure-related joint swelling	3 (2.4)	0	.198
Event summary			
Total TEAEs	72	65	
Severity by NCI-CTCAE scale			
Grade 1	50	36	
Grade 2	22	29	
Grade 3	0	0	
Grade 4	0	0	
Grade 5	0	0	
Relationship between the treatment and TEAEs			
Certain	0	0	
Probable/likely	8	2	
Possible	17	2	
Unlikely	42	58	
Conditional/unclassified	3	0	
Unassessable/unclassifiable	1	0	
Not applicable	1	3	
Result of TEAEs			
Recovered/resolved	54	43	
Recovering/resolving	16	21	
Not recovered/not resolved	2	1	
Recovered or resolved with sequelae	0	0	
Death	0	0	
Unknown	0	0	

Kang-Il Kim et al. The American Journal of Sports Medicine 2023;51(9):2243–2253

ASC distribution after IA injection -> reduced lifespan





ADIPOA

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

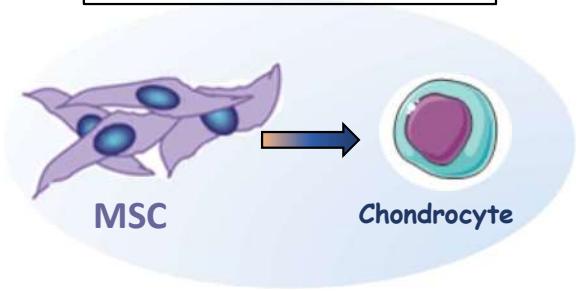
15% of ASCs are detected at 1 month

1,3% at 6 months.

ASCs are localised in synovial membrane

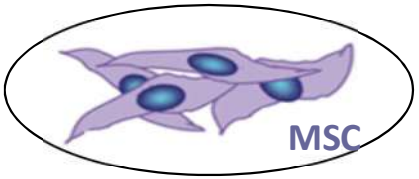
When MSC may be useful for cartilage damage ?

Differentiation capacities

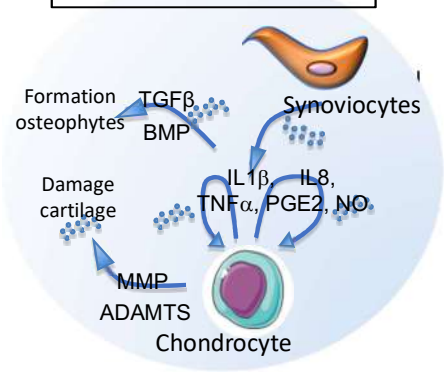


Differentiation in chondrocytes using biomaterials

Tissue engineering: Repair of focal defects

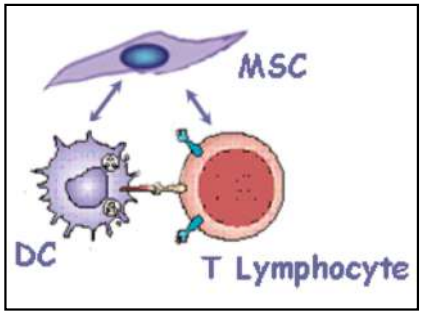


Trophic functions



Chondroprotection and stimulation of endogenous repair

Immunoregulatory functions



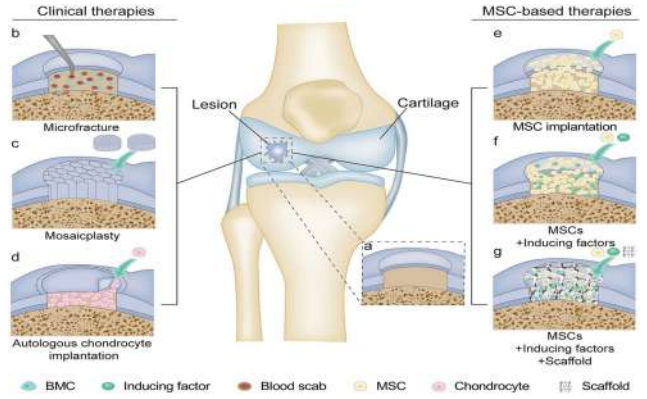
To block inflammation

Anti-inflammatory cell therapies

Application to osteoarthritis

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



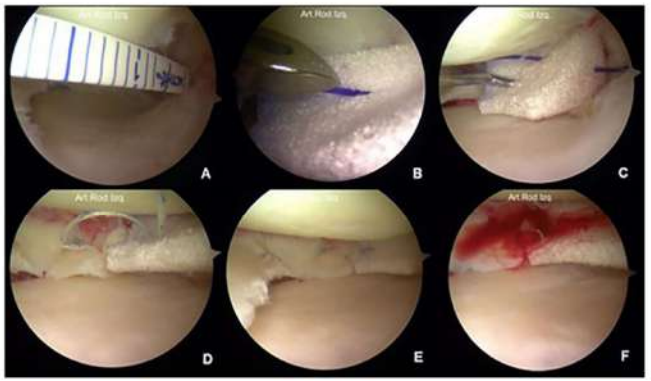
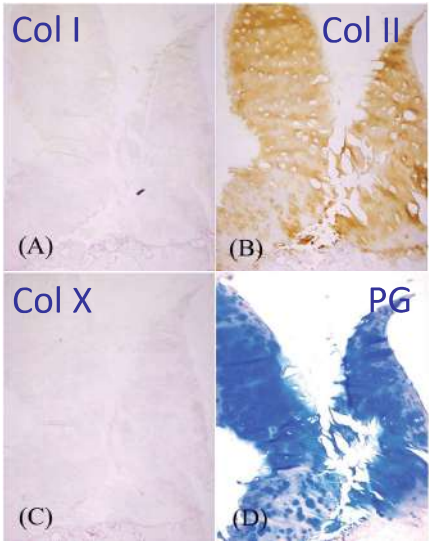


Figure 3. Surgical technique of medial meniscus substitution in the posterior horn with polyurethane implant enriched with MSCs. (**A**) Defect size is estimation with a flexible ruler. (**B**, **C**) Once the implant is trimmed in

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

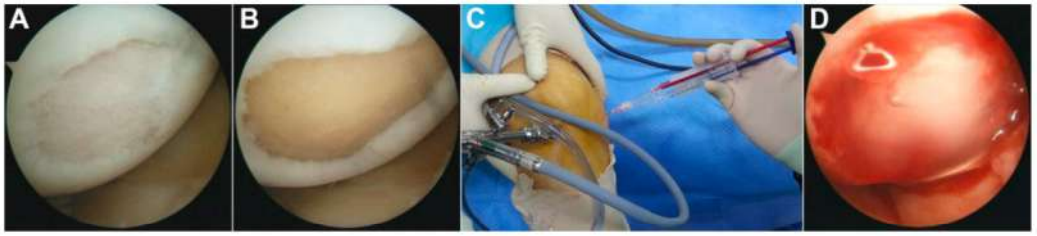


Figure 1. Arthroscopic implantation of mesenchymal stem cells loaded in fibrin glue. (A) An articular cartilage lesion in the medial femoral condyle was noticed. (B) An accurate debridement of all unstable and damaged cartilage in the lesion was performed. (C)

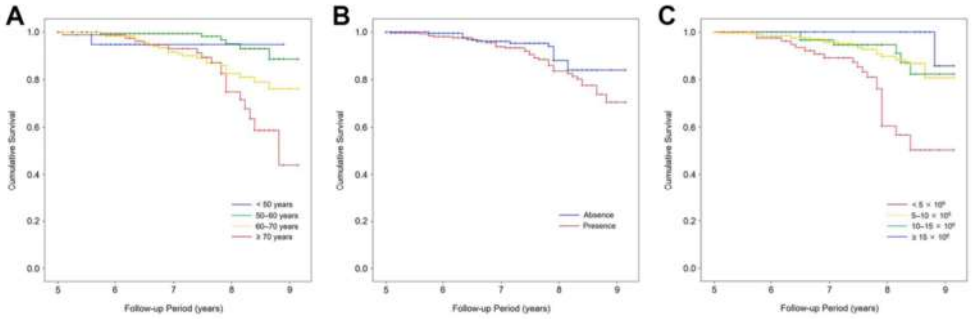


Figure 3. Kaplan-Meier survival curves. Survival rate of groups divided according to (A) age, (B) presence of bipolar kissing lesion, and (C) number of mesenchymal stem cells.

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.

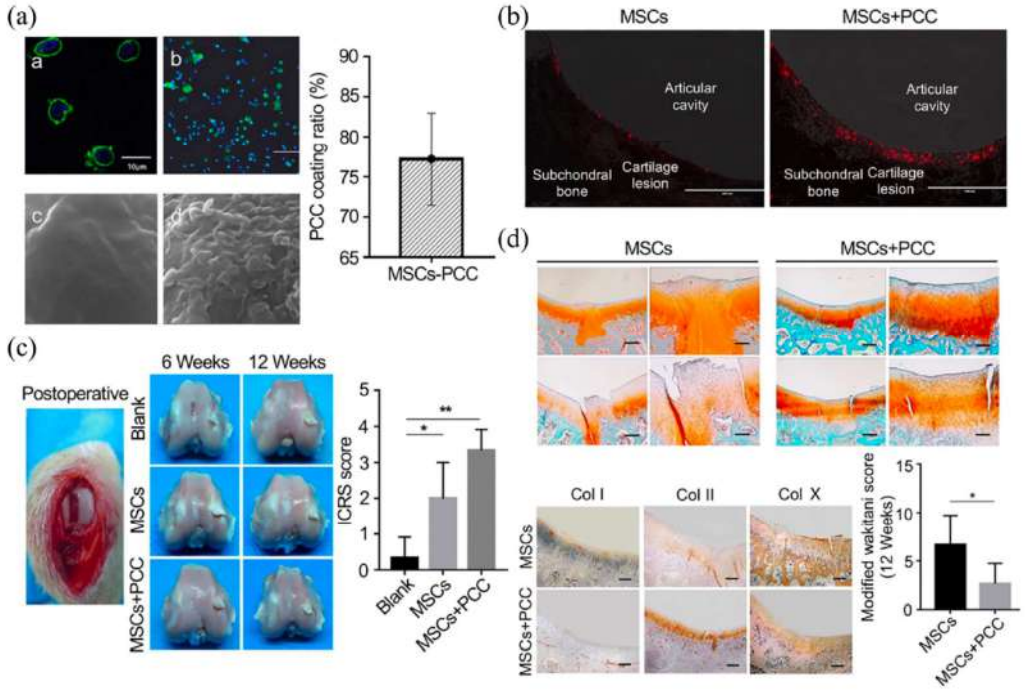
Results Nine studies were included in this review. In all included studies, clinical outcome scores revealed significantly improved functionality and better postoperative pain scores at 2–3 years follow-up. Improved cartilage volume and quality at the lesion site was observed in five studies that included 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
- 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

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,*]

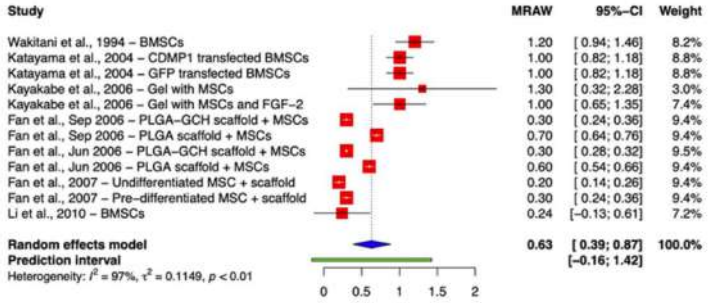


Figure 2. Forest plot on the mean histological integration score after receiving BMSC implant therapy, where 0/2 points = both edges integrated, 1/2 = one edge integrated, and 2/2 = no integration. (Abbreviations: BMSC, bone marrow-derived mesenchymal stem cell; CDMP1, cartilage-derived morphogenetic 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]

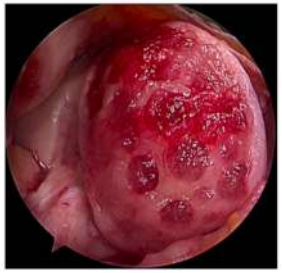
BM-MSC bone marrow-derived mesenchymal stem cells, *PLA* polylactic acid, *HA* hyaluronic acid, *PGA* polyglycolic acid

- Heterogeneous integration
- Few studies available

Yamagata et al. Inflammation and Regeneration 2018

Repair of focal defects with MSC+scaffold : Humans

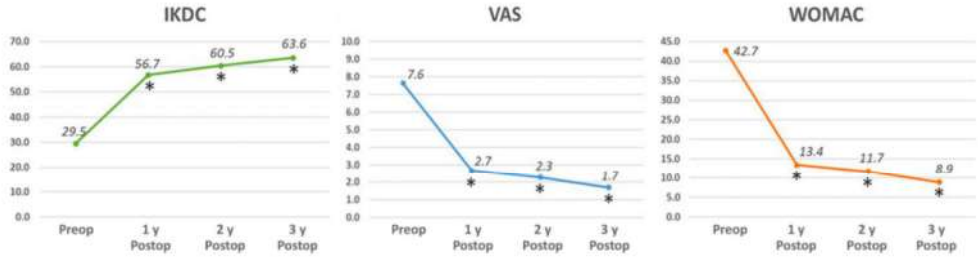
- CARTISTEM (Medipost)
- Retrospective study
- Large lesion (> 4 cm^2)
- Located in medial femoral condyle
- Excluded other compartment lesions
- hUC-MSC + HA (+/- meniscectomy)
- 85 patients
  - ➢ Significant improvement in all PRO scores
  - ➢ MRI follow-up show repaired cartilage hypertrophy without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



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

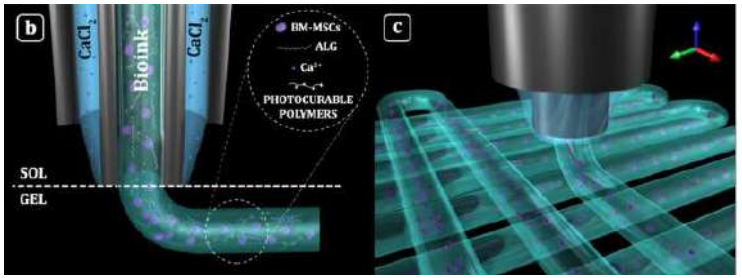
Jun-Seob Song,* MD, Ki-Taek Hong,* MD, Na-Min Kim,* MD, Byung-Hun Hwangbo,† MD, Bong-Seok Yang,‡ MD, Brian N. Victoroff,§ MD, and Nam-Hong Choi,†|| MD

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

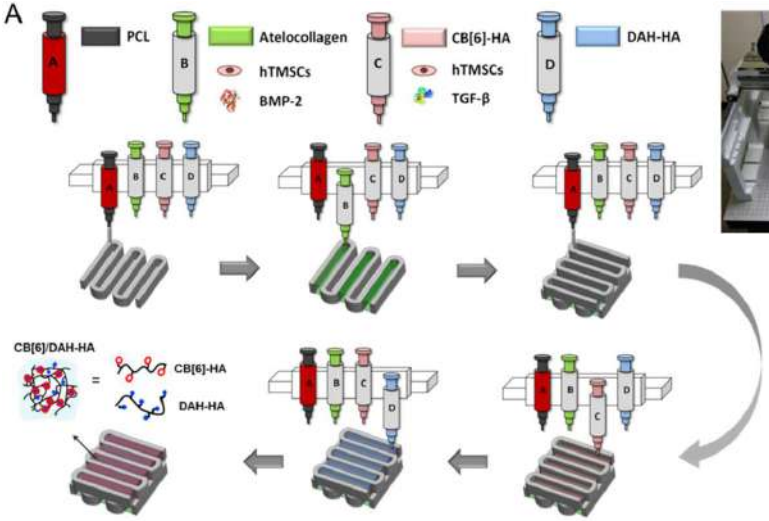


Song et al. The Orthopaedic Journal of Sports Medicine 2023

Perspectives: bio-printing for cartilage engineering



Costantini, 2016, Biofabrication



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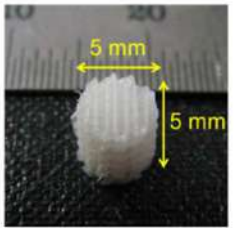

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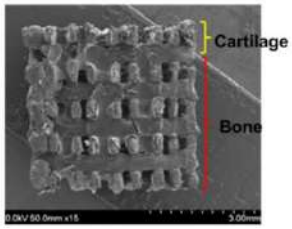
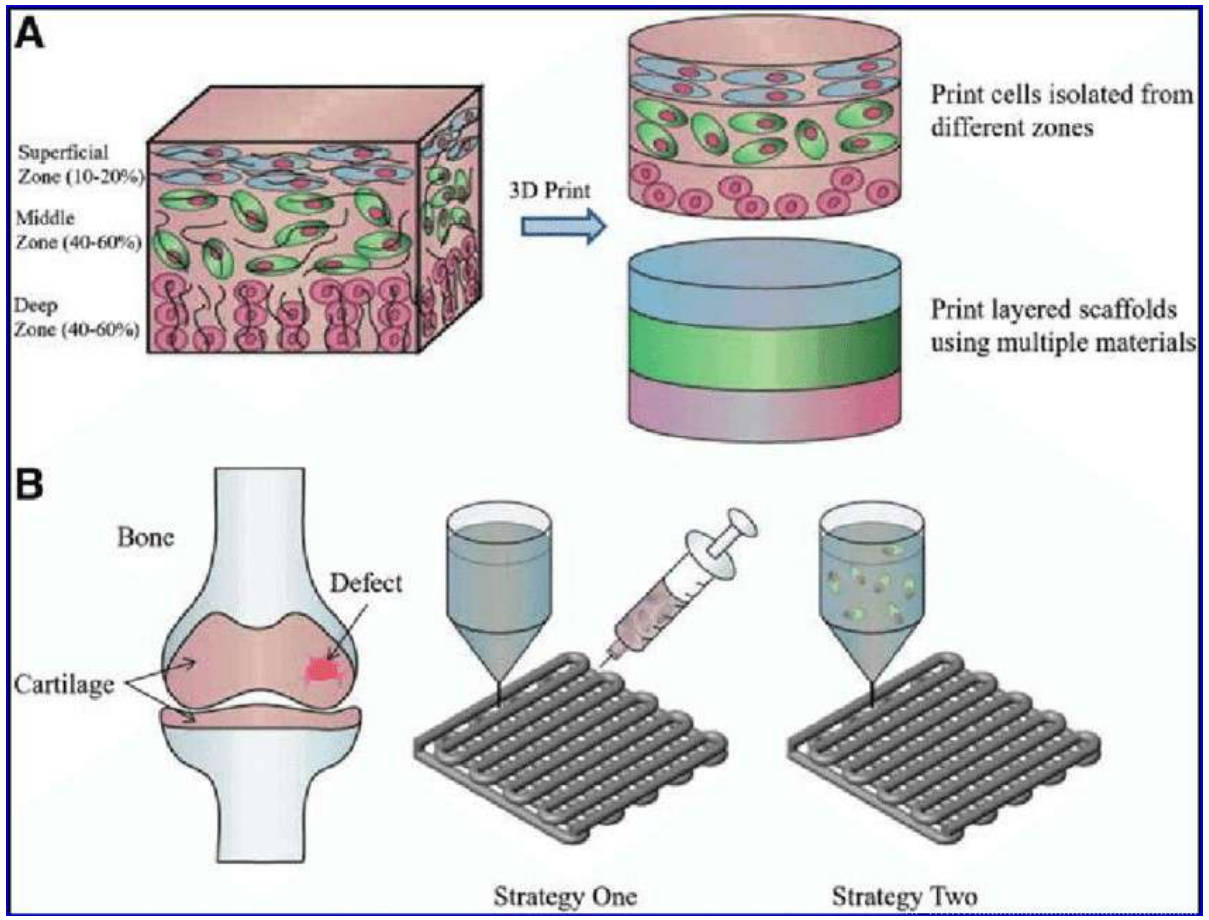


Multi head tissue/organ building system for regeneration of osteochondral defects

Shim, 2016, Biofabrication

Perspectives: bio-printing for cartilage engineering



Perspectives: bio-printing for cartilage engineering

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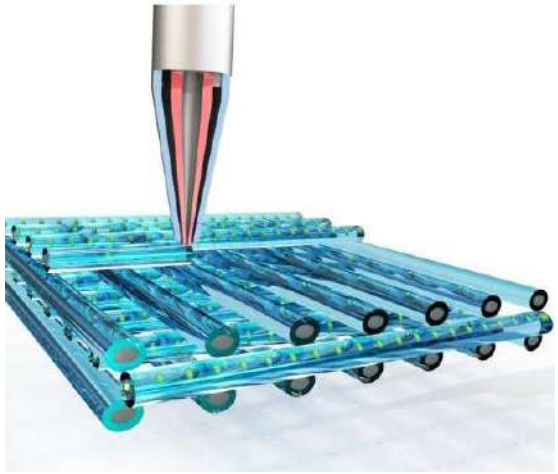
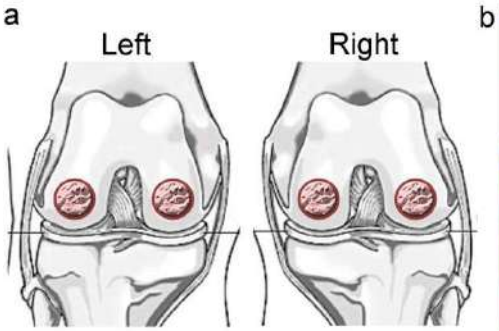
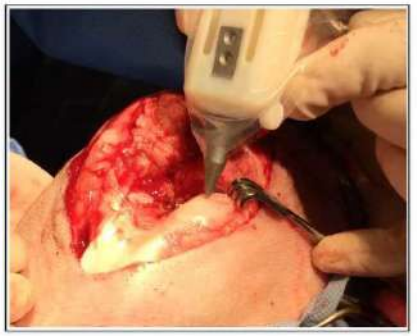
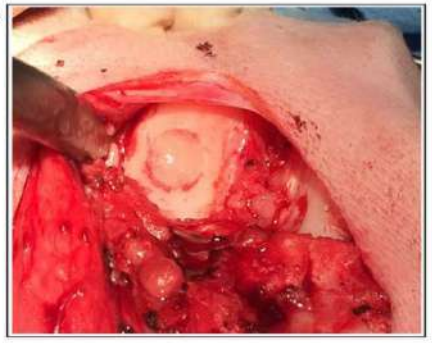
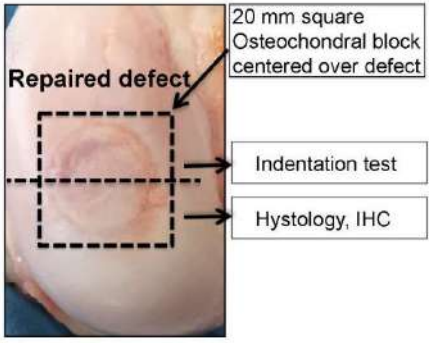


"Biopen"





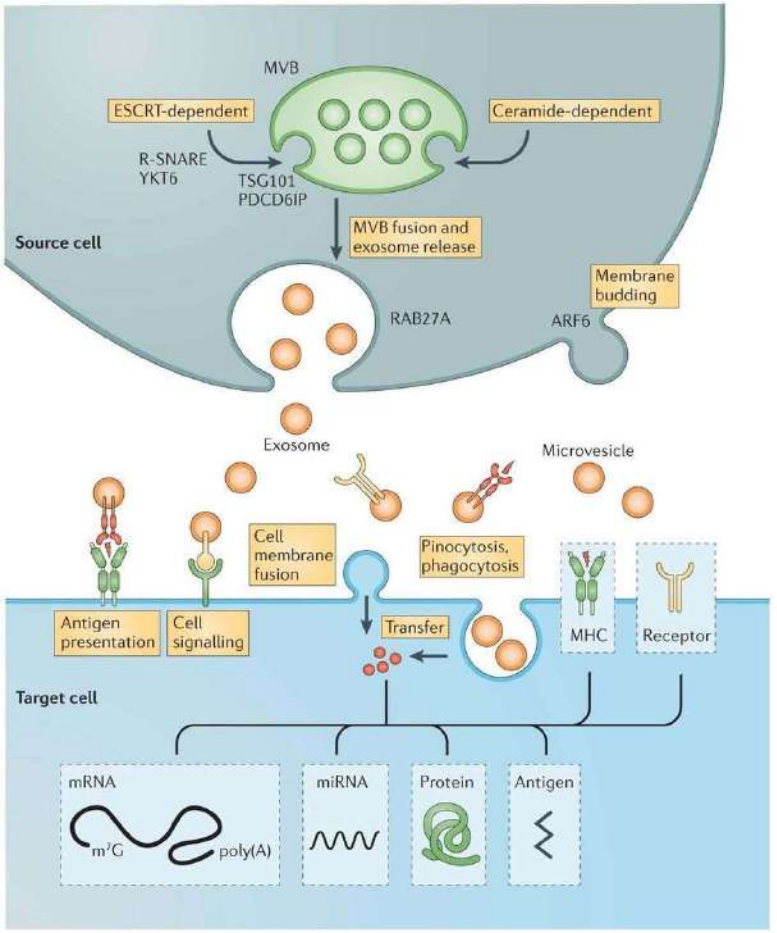




Extracellular vesicles (EVs) derived from MSC: a future option ?

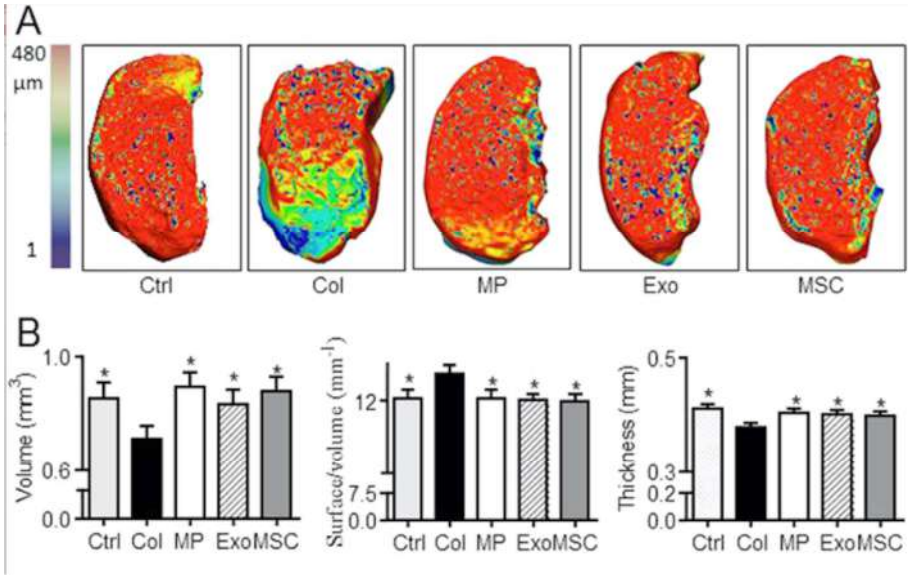
Vesicle types	Characteristics			
	Origin	Size	Markers	Contents
Exosomes	Endolysosomal pathway; intra-luminal budding of multivesicular bodies and fusion of multivesicular body with cell membrane	40–120 nm	Tetraspanins (such as TSPAN29 and TSPAN30), ESCRT components, PDCD6IP, TSG101, flotillin, MFGE8	mRNA, microRNA (miRNA) and other non-coding RNAs; cytoplasmic and membrane proteins including receptors and major histocompatibility complex (MHC) molecules
Microvesicles	Cell surface; outward budding of cell membrane	50–1,000 nm	Integrins, selectins, CD40 ligand	mRNA, miRNA, non-coding RNAs, cytoplasmic proteins and membrane proteins, including receptors
Apoptotic bodies	Cell surface; outward blebbing of apoptotic cell membrane	500–2,000 nm	Extensive amounts of phosphatidyl-serine	Nuclear fractions, cell organelles

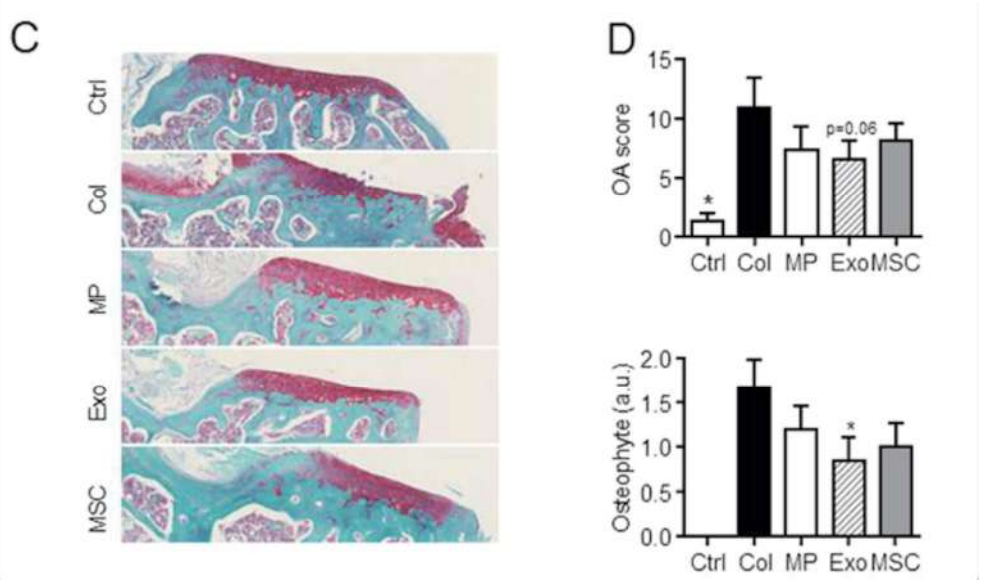
ESCRT, endosomal sorting complex required for transport, MFGE8, milk fat globule-EGF factor 8 protein; PDCD6IP, programmed cell death 6 interacting protein (also known as ALIX); TSG101, tumour susceptibility gene 101 protein; TSPAN29, tetraspanin 29.



Nature Reviews | Drug Discovery

Extracellular vesicles (EVs) derived from MSC: a future option ?

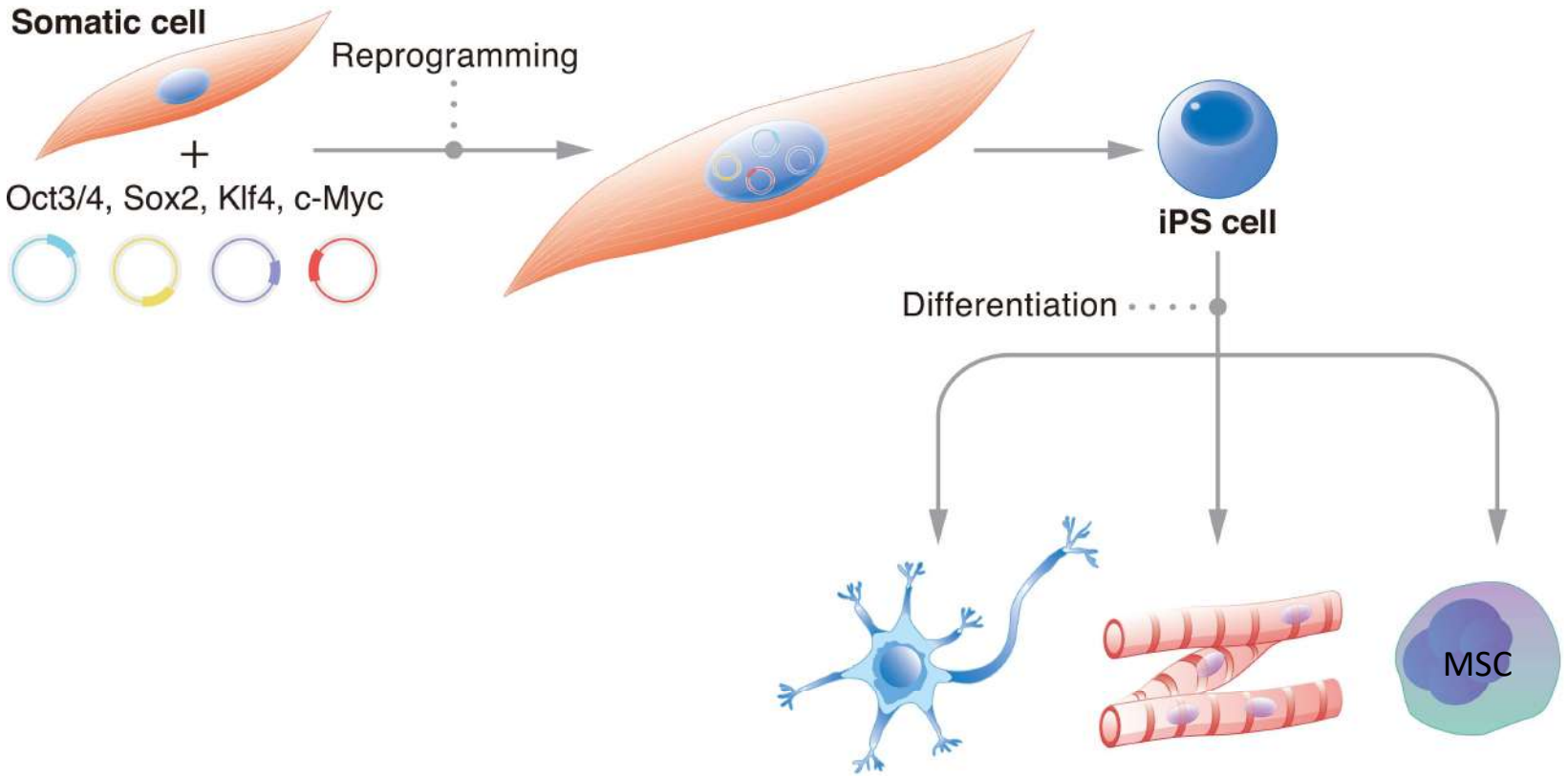




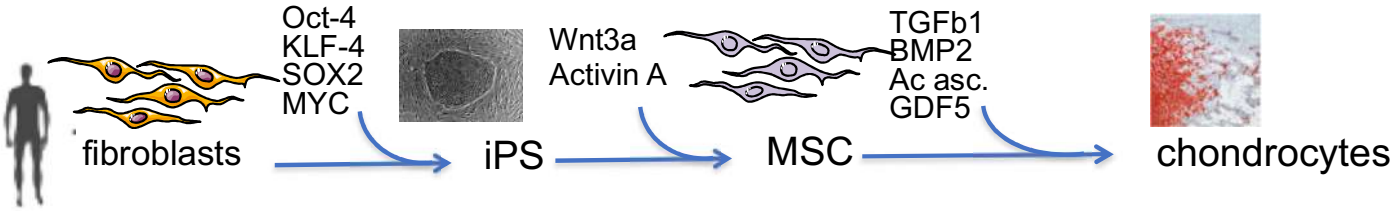
BM-MSC-derived MPs and Exos protected mice from osteoarthritic damages in the collagenase-induced OA model.

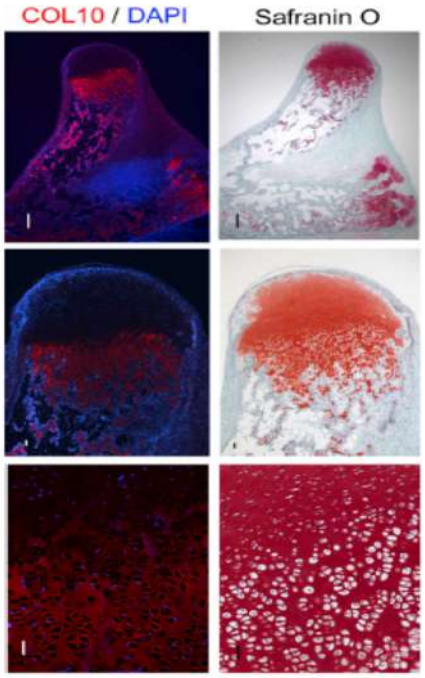
Cosenza S et al. Sci Report 2017

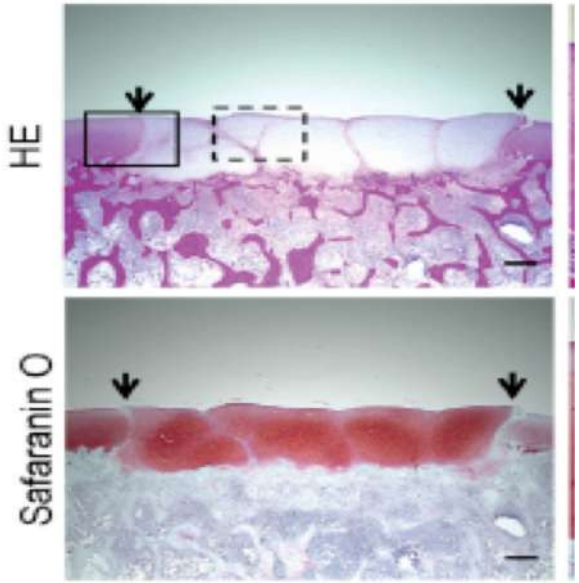
Reprogramming and iPS



Cell source for cartilage engineering







Takei Y et al. Sci Rep. 2020 Jul 30;10(1):12794

Bionic in OA : challenges ?

- **Exoskeleton**
  - Help rehabilitation or restore mobility with less pain
- **Bio prothesis (TKR, THR)**
  - Promote better bone integration
  - Avoid infections
  - Longer-life
- **The bionic leg**…

Exoskeleton

- Military context

Exoskeleton

- Honda Walking Assist (HWA) is a hip-wearable exoskeleton robot for gait training that assists in hip flexion and extension movements

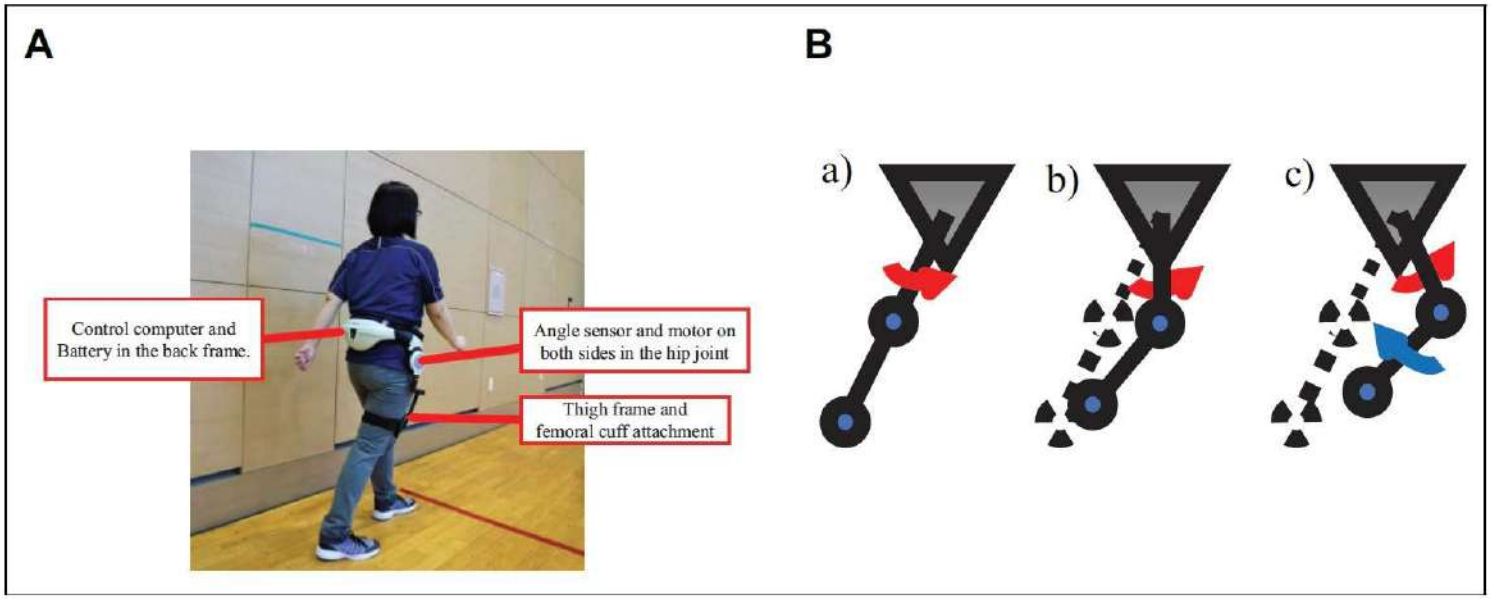


Figure 1. A, Gait training with the Honda Walking Assist (HWA)® device. B, The mechanism of knee flexion during the swing phase due to hip assistance using the HWA device. The HWA assistance has the effect of lifting the thigh (red arrow) during the swing phase (b and c), thereby promoting knee flexion (blue arrow).

Koseki K et al. Geriatric Orthopaedic Surgery 2021

Exoskeleton

- To evaluate the effects of walking exercises with HWA in patients who underwent total knee arthroplasty (TKA)

Table 1. Preoperative Baseline Characteristics of the Patients.[a]

Characteristics		Honda group, 10 patients (11 knees)	Control group, 11 patients (11 knees)	P value
Age		71.8 ± 6.2	75.9 ± 6.9	.467
Sex	Male/Female	0/10	1/10	1.000
Weight	(kg)	64.9 ± 10.3	59.5 ± 10.3	.988
Height	(cm)	148.7 ± 7.2	147.4 ± 7.8	.855
BMI	(kg/m^2)	29.4 ± 5.0	27.4 ± 4.6	.785
Disease	OA/RA	9/1	10/1	1.000
TKA operated side	Right/Left	6/5	4/7	.670
Contrateral side TKA		3	3	1.000
WOMAC-p score		45.9 ± 19.3	60.9 ± 21.9	.631
WOMAC-f score		65.5 ± 22.2	69.4 ± 12.9	.064
Physical therapy time during intervention period (Including HWA training)	(h)	34.1 ± 6.5	35.5 ± 8.9	.674

Abbreviations: BMI, body mass index; OA, osteoarthritis; RA, rheumatoid arthritis; TKA, total knee arthroplasty; WOMAC-P, Western Ontario and McMaster Universities Osteoarthritis Index subscales of pain scores; WOMAC-f, Western Ontario and McMaster Universities Osteoarthritis Index subscales of physical function scores.

[a]Values are expressed as numbers or as mean ± SD.

Koseki K et al. Geriatric Orthopaedic Surgery 2021

Exoskeleton

- A significant difference between preoperative and week 2
  - Self-selected walking speed (SWS)
  - Maximum walking speed (MWS)

Table 3. Walking Ability in the HWA and Control Groups.

			Honda Mean ± SD	Control Mean ± SD	p value[a]	d[b]
SWS	(m/s)	Preoperative	1.04 ± 0.22	1.09 ± 0.20	.586	0.24
		Week2	0.96 ± 0.17	0.70 ± 0.29	.022	1.09
		Week4	1.13 ± 0.25	1.00 ± 0.26	.260	0.51
		Week8	1.19 ± 0.23	1.04 ± 0.19	.107	0.71
MWS	(m/s)	Preoperative	1.30 ± 0.32	1.36 ± 0.20	.583	0.23
		Week2	1.20 ± 0.21	0.90 ± 0.35	.025	1.04
		Week4	1.40 ± 0.33	1.23 ± 0.25	.403	0.58
		Week8	1.46 ± 0.29	1.44 ± 0.21	.813	0.08

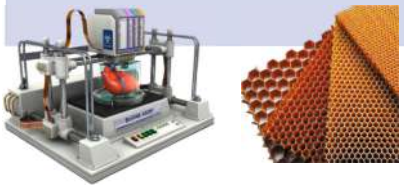
Koseki K et al. Geriatric Orthopaedic Surgery 2021

CARTIGEN platform

- Occitanie funding: innovative regional platform
- Coordination: Pr C. Jorgensen
- Organization:

CARTIGEN
To Restore
Mobility

Mobility	Tissue Engineering	Robotic
• Analysis and modelling movement for better management • I. Laffont	• Development of new therapies based on tissular Engineering and 3D bioprinting • D. Noel	• Bionic, exoskeleton • A. Khedar



CARTIGEN platform

- Isokinetic

Contrex (Appareil isocinétique)

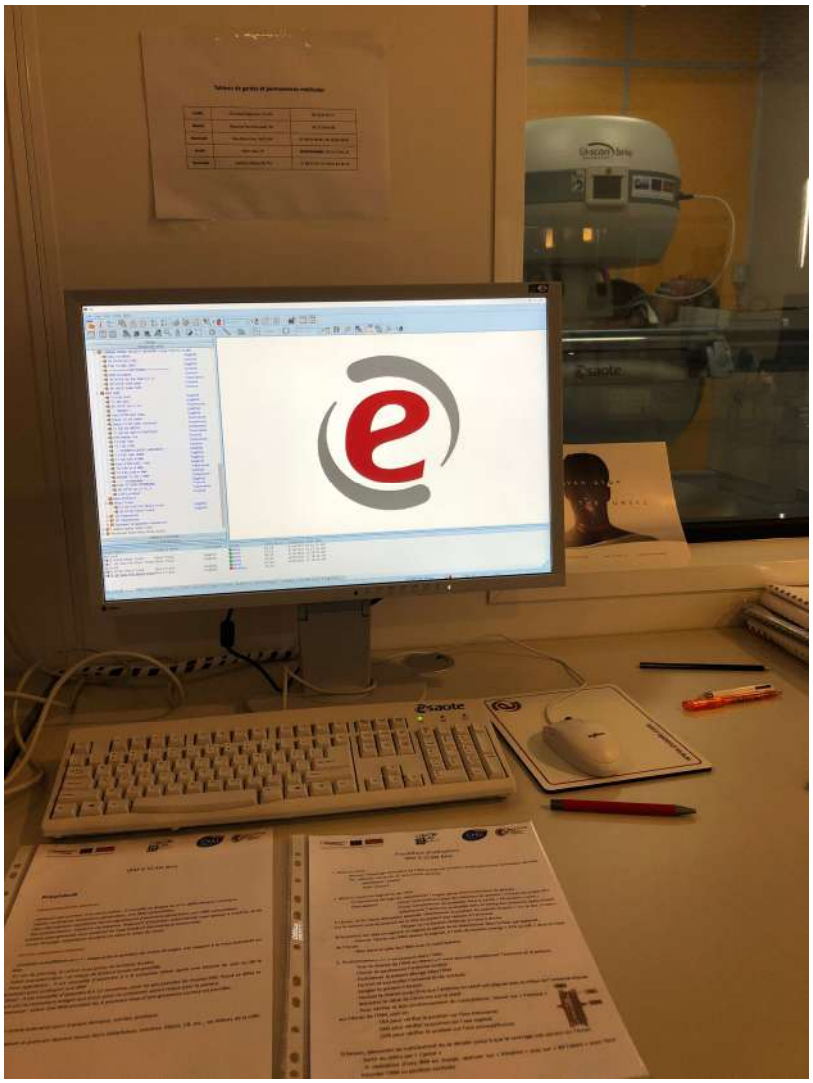
- Grail (virtual reality)

Grail (Laboratoire d'analyse du mouvement en immersion)

- MRI (ESAOTE)

IRM Gscan (Imagerie dynamique)

- XSENS-Awinda



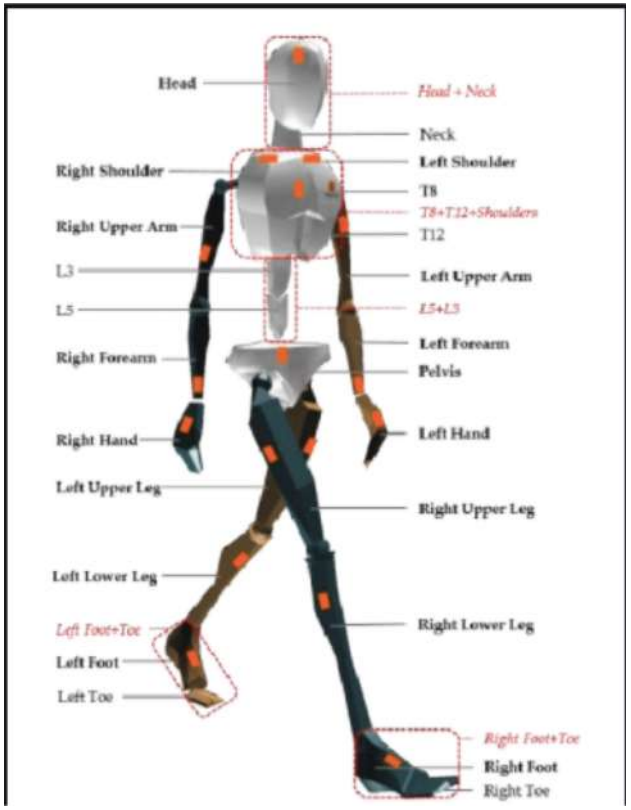

NEVER STOP
SEEING THE UNSEEN.

CARTIGEN platform

- **Equipment:**
  - Isokinetic
  - MRI
  - Grail (virtual reality)
  - XSENS-Awinda

CARTIGEN
To Restore
Mobility

- **17 inertial sensors** allowing to estimate the orientation, speed and acceleration of the different members of the body



Spine OA study

Objectives

→To provide an **objective measure** of motor behavior compared to subjective questionnaires

→ To Facilitate clinical assessment (future important **therapeutic goal** for follow-up

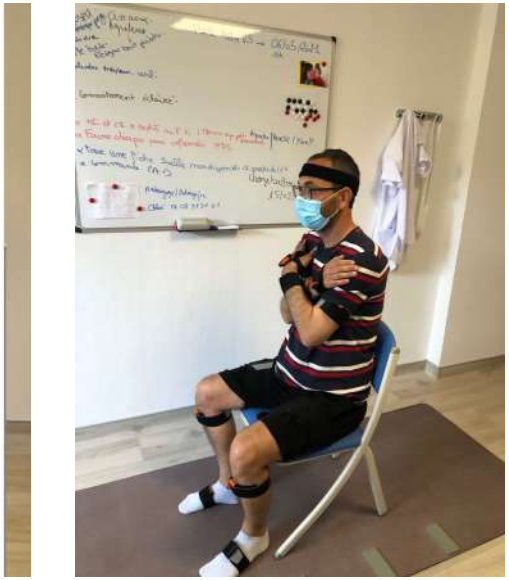
Spine OA study

Methodology

7 Movements

Simple movements : flexion / extension

More complex movements : right-left rotation / picking up an object / standing-sitting / walking



Spine OA study

Methodology

Exploratory study

Recruitment: 15 patients with LBP and 15 healthy subjects

Inclusion criteria: Common LBP evolving for at least 3 months between 18 and 65 years old with a BMI between 18 and 30

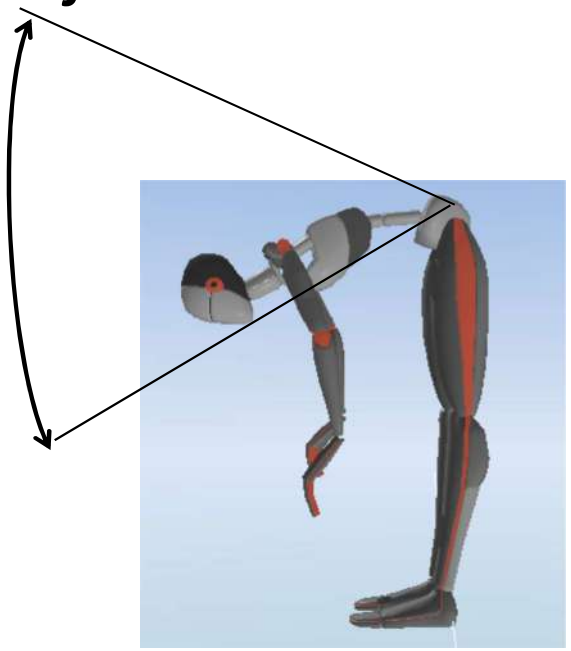
Exclusion criteria: history of lumbar fracture or pelvic surgery, severe scoliosis, neurological or inflammatory pathology.

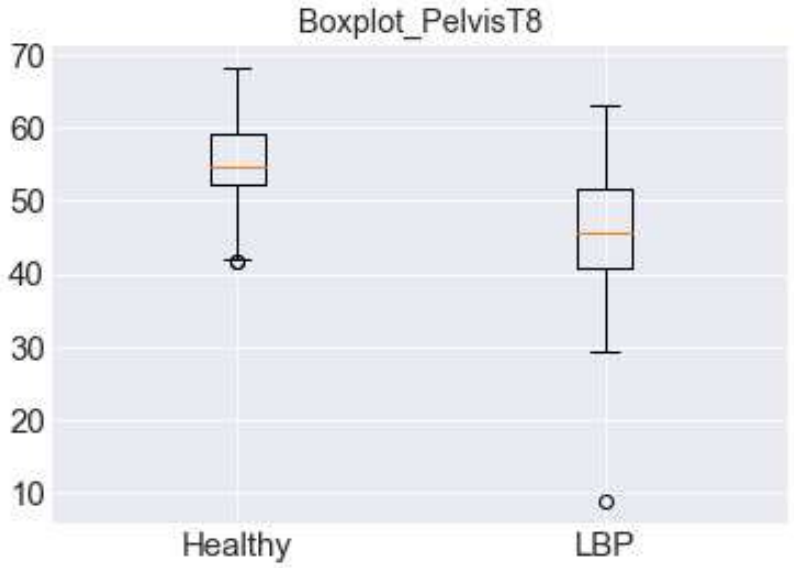
Matched with sex, age (+/- 5 years) and BMI (+/-1)

Spine OA study

Results

1. ROM lumbar flexion



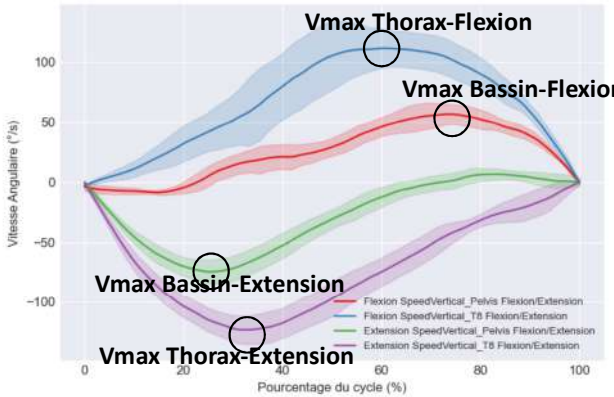


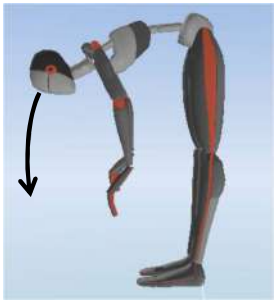
ROM < 10° LBP

Spine OA study

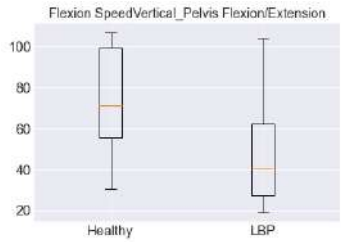
Results

2. Maximal speed

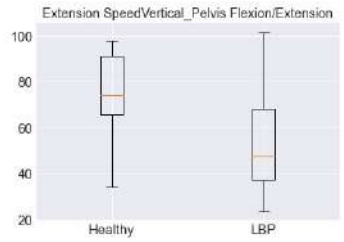


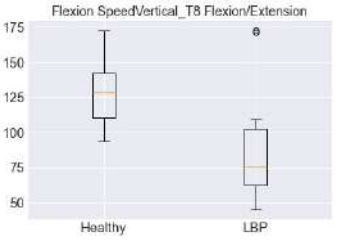


FLEXION **Extension**

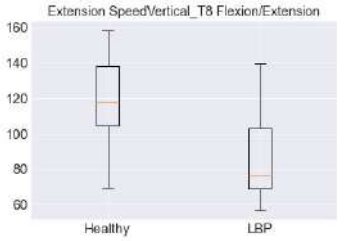


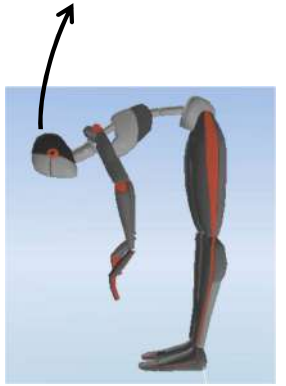
Bassin





Thorax





Speed : Healthy > 1.5 x LBP

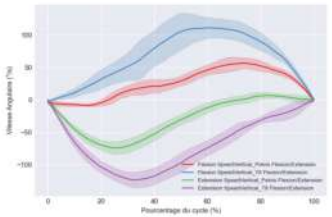
Spine OA study

Results

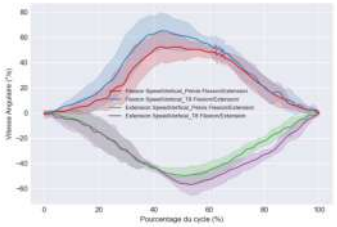
3. Fluidity analysis

Speed profiles

Healthy

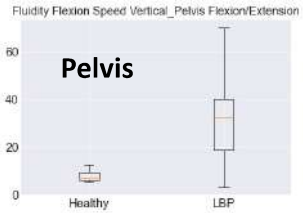


LBP

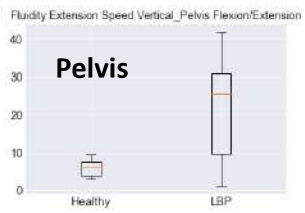


Amount of saccade (acceleration/deceleration)

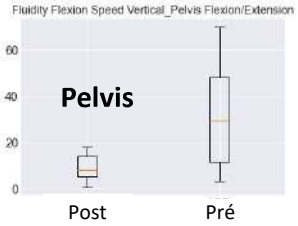
Flexion

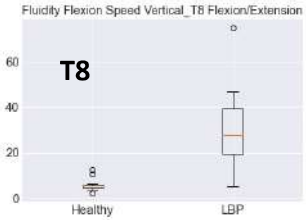


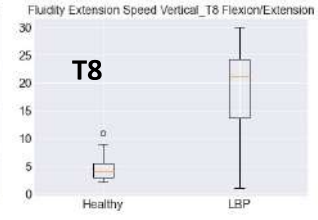
Extension

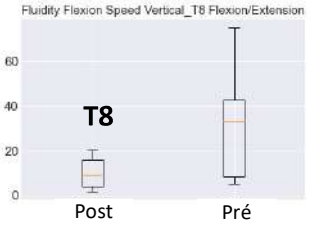


Flexion









3-4 X more fluid after Rehabilitation

Spine OA study

Conclusions

→ Confirm some parameters described in the literature

→ Identify new indicators such as fluidity

→ Correlate the kinematic results with the results of the questionnaires

Bionic in OA : perspectives ?

- **Exoskeleton**
  - Help rehabilitation or restore mobility with less pain
- **Bio prothesis (TKR, THR)**
  - Promote better bone integration
  - Avoid infections
  - Longer-life
- **The bionic leg…**

Bio prothesis

- **Bio prothesis (TKR, THR)**
  - Promote better bone integration
  - Avoid infections
  - Longer-life

Bio prothesis

- Titanium-based scaffolds are widely used implant materials for bone defect treatment
- Insufficient bone integration
  - Unmatched biomechanics
  - Poor bioactivities of conventional titanium based implants

- Critical to develop novel titanium-based scaffolds

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Bio prothesis

Bioactive Materials 6 (2021) 3437–3448

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.sciencedirect.com/journal/bioactive-materials

Biomimetic Ti–6Al–4V alloy/gelatin methacrylate hybrid scaffold with enhanced osteogenic and angiogenic capabilities for large bone defect restoration

Limin Ma [a,1], Xiaolan Wang [a,c,1], Ye Zhou [b,1], Xiongfa Ji [a], Shi Cheng [a], Dong Bian [a], Lei Fan [c], Lei Zhou [c,***], Chengyun Ning [c,**], Yu Zhang [a,*]

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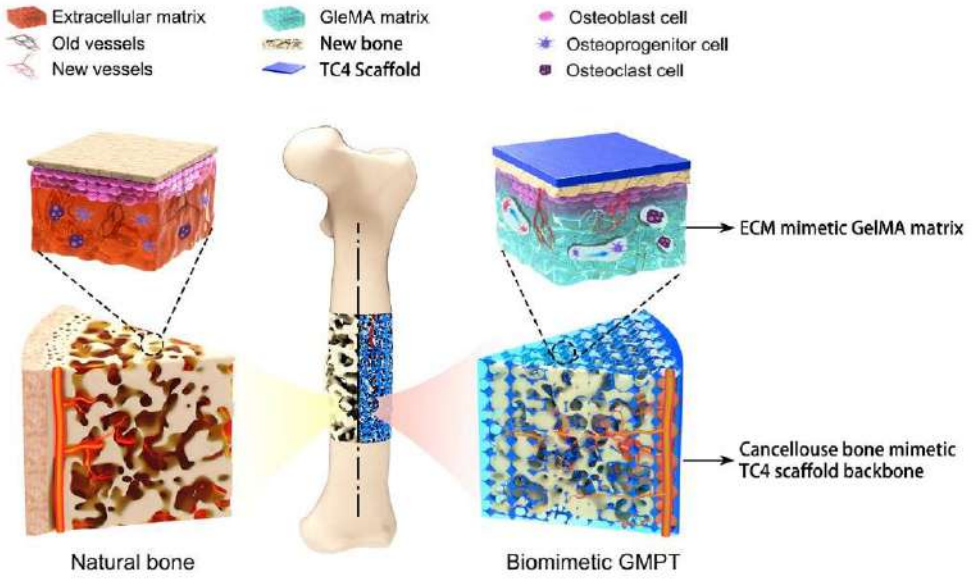
Bio prothesis

- Ti–6Al–4V alloy (TC4)/gelatin methacrylate (GelMA) hybrid scaffold with dual bionic features (GMPT) for bone defect repair
- Goal: mimics microstructure, mechanical properties and environment



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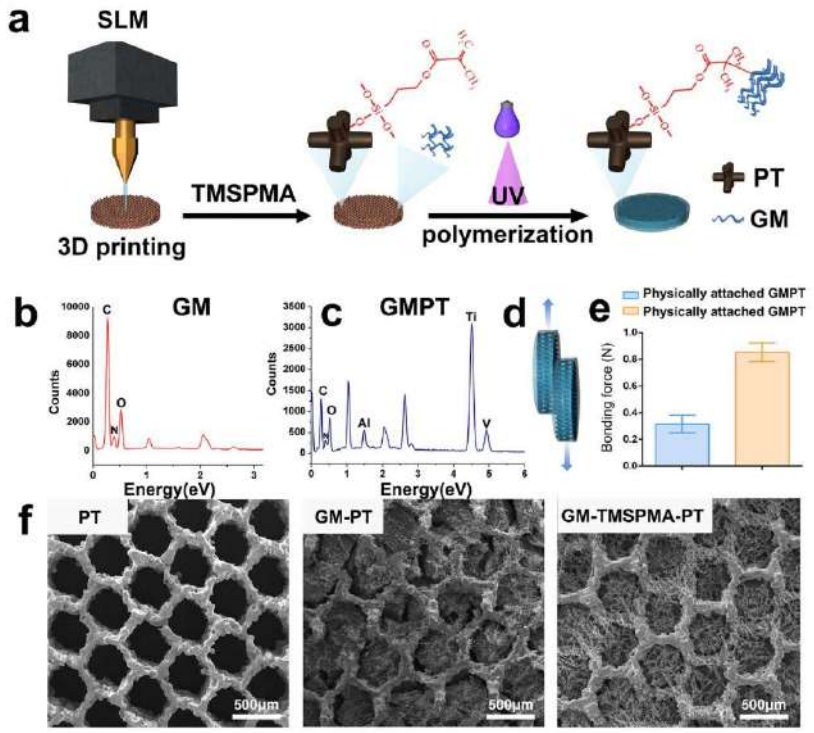
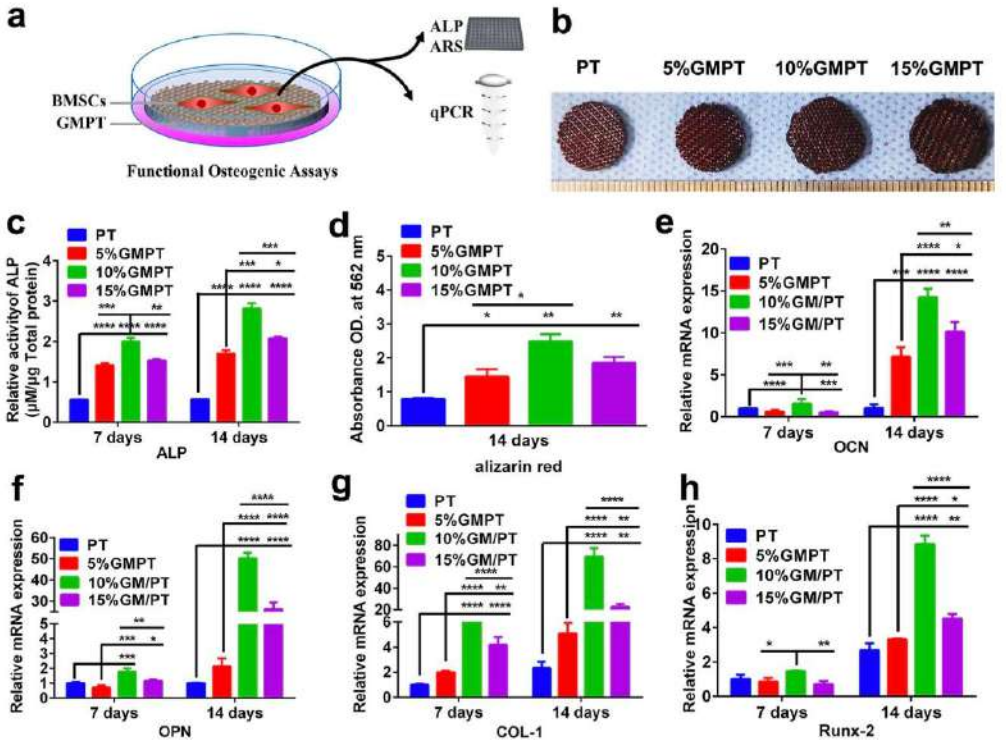
Bio prothesis

- GMPT demonstrates better osteogenic and angiogenic capabilities than PT





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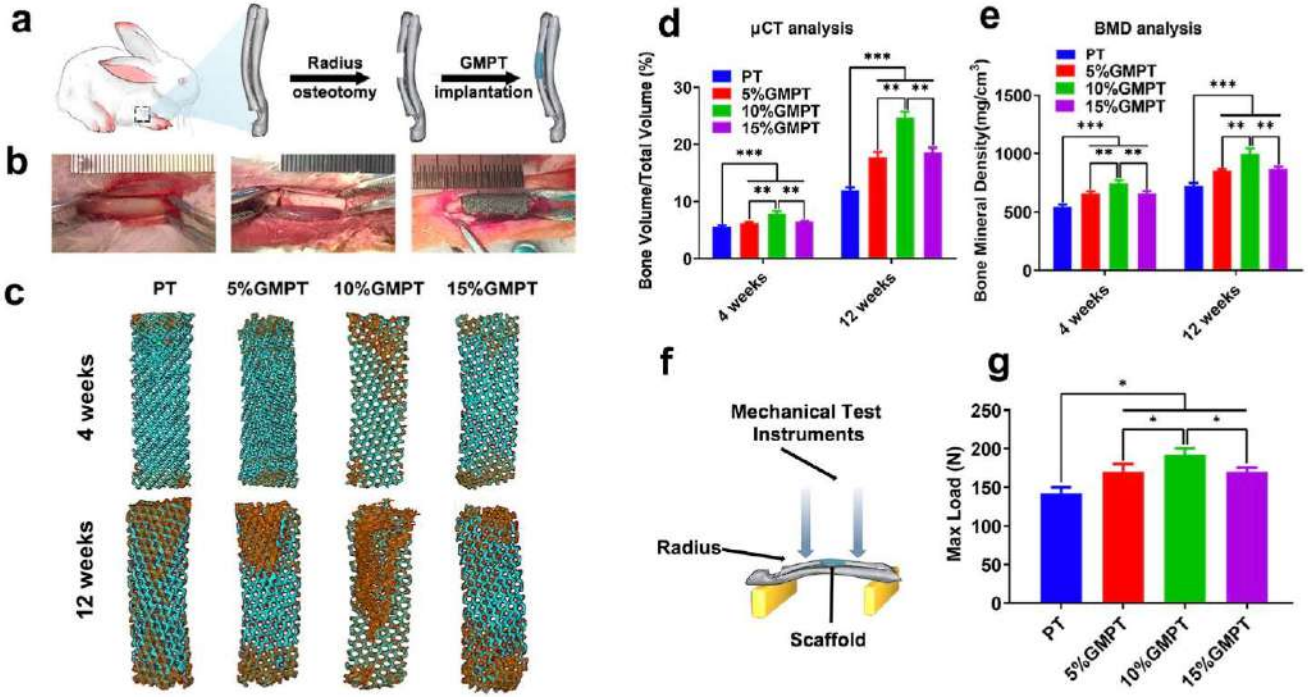
Bio prothesis

- GMPT in vitro and rabbit radius bone defect experimental results
- RNA-Seq analysis via the Pi3K/Akt/mTOR pathway



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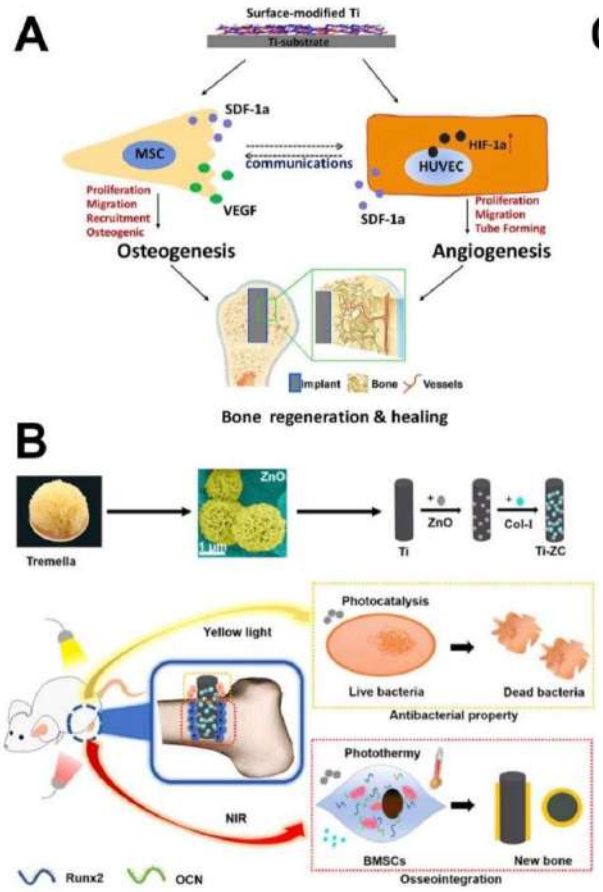
Bio prothesis = avoid infections



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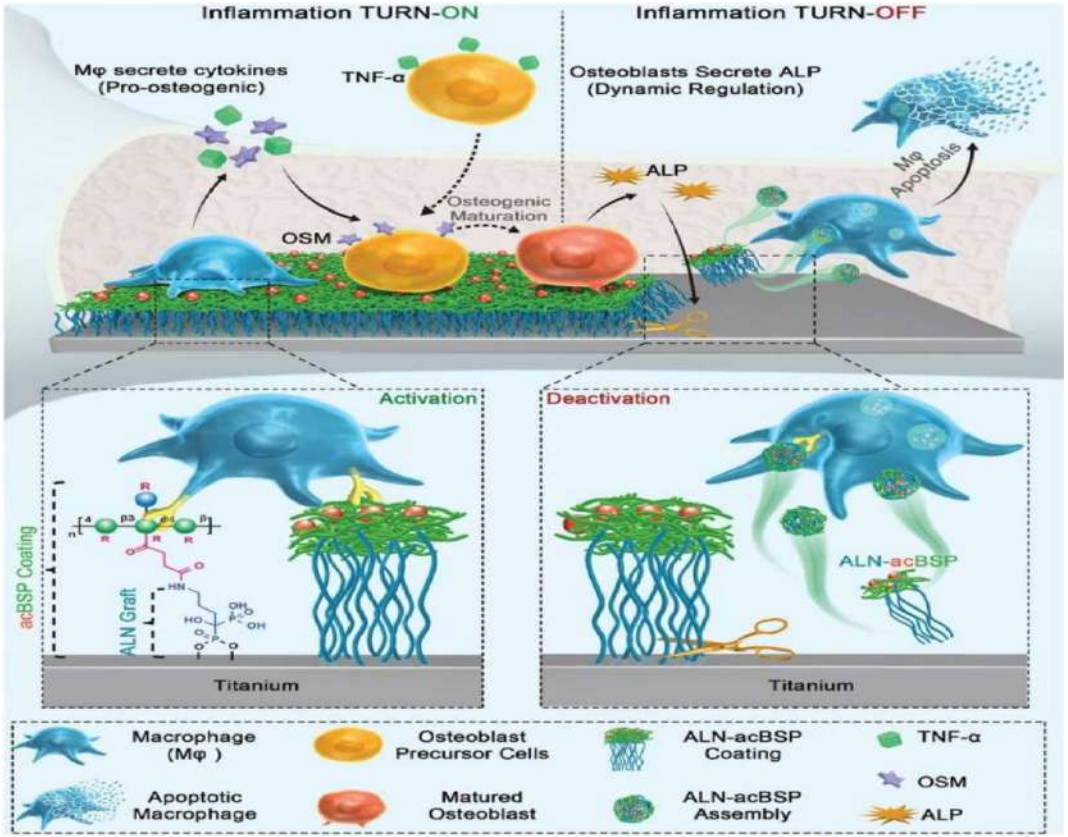
Bio prothesis = promote bone better integration



Zhu et al. Mat Advances 2021

Bionic in OA : perspectives ?

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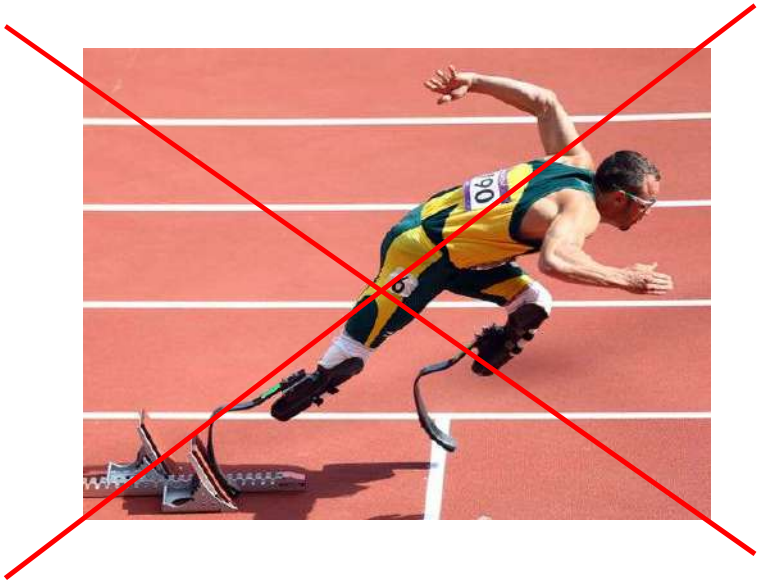
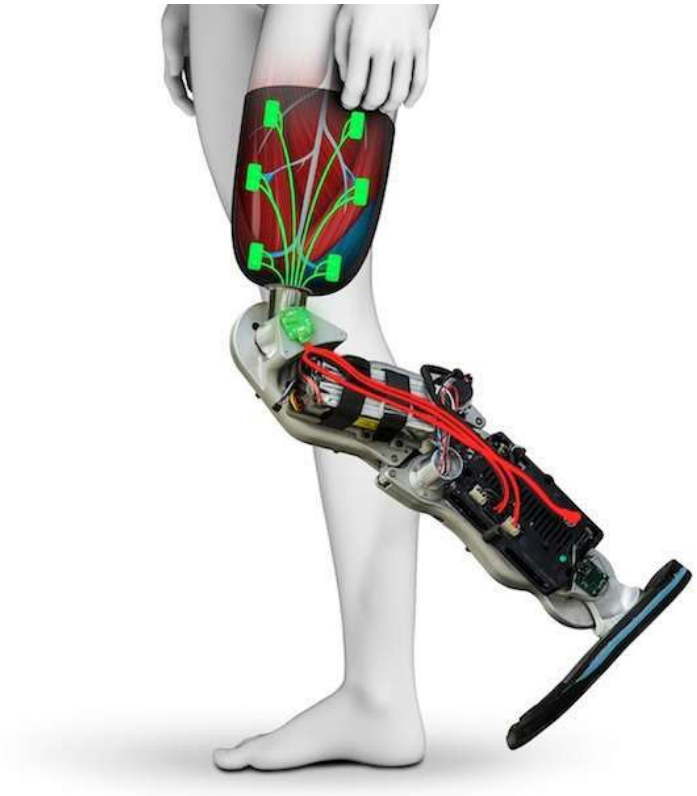
The bionic leg

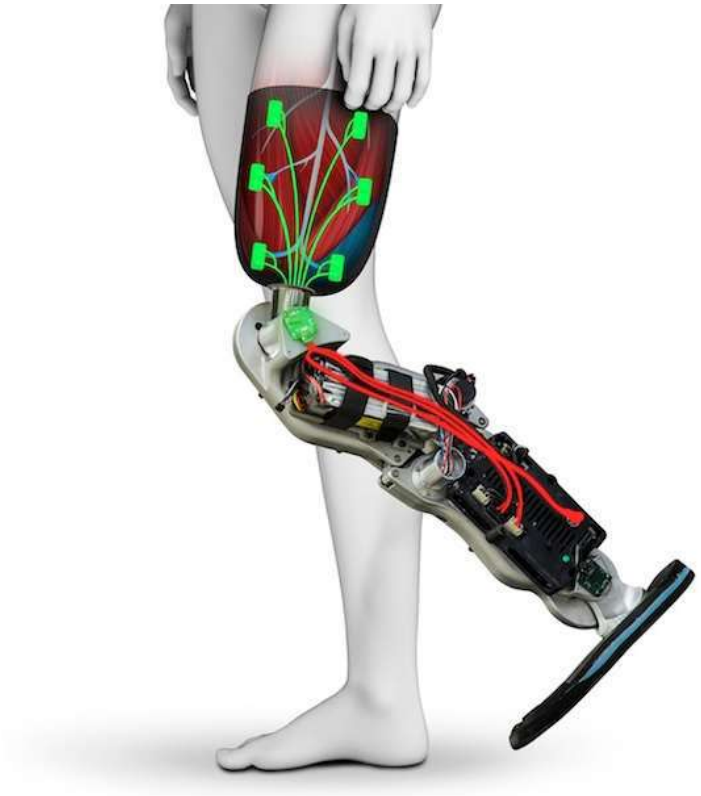


No electronics or sensors or magnets, just a simply-shaped spring that stores energy and uses it



The bionic leg

https://www.youtube.com/watch?v=kaFiwC1xh2Y



Conclusions

- Epidemiology in expansion: young people +++
- Prevention for post-traumatic OA +++
- Find new biomarkers (mobility) less subjective than pain
- Personalized medicine
- Non-pharmacological approaches: bionic to strongly reinforce rehabilitation and exercise/physical activity
- Joint surgery more accurate, more “biologic”, less complications
- Find futures therapies with a structural benefit

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  - Knee OA
  - Ankle OA

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