OSTEOARTHRITIS

The (bionic) revolution in the management of osteoarthritis: challenges and perspectives

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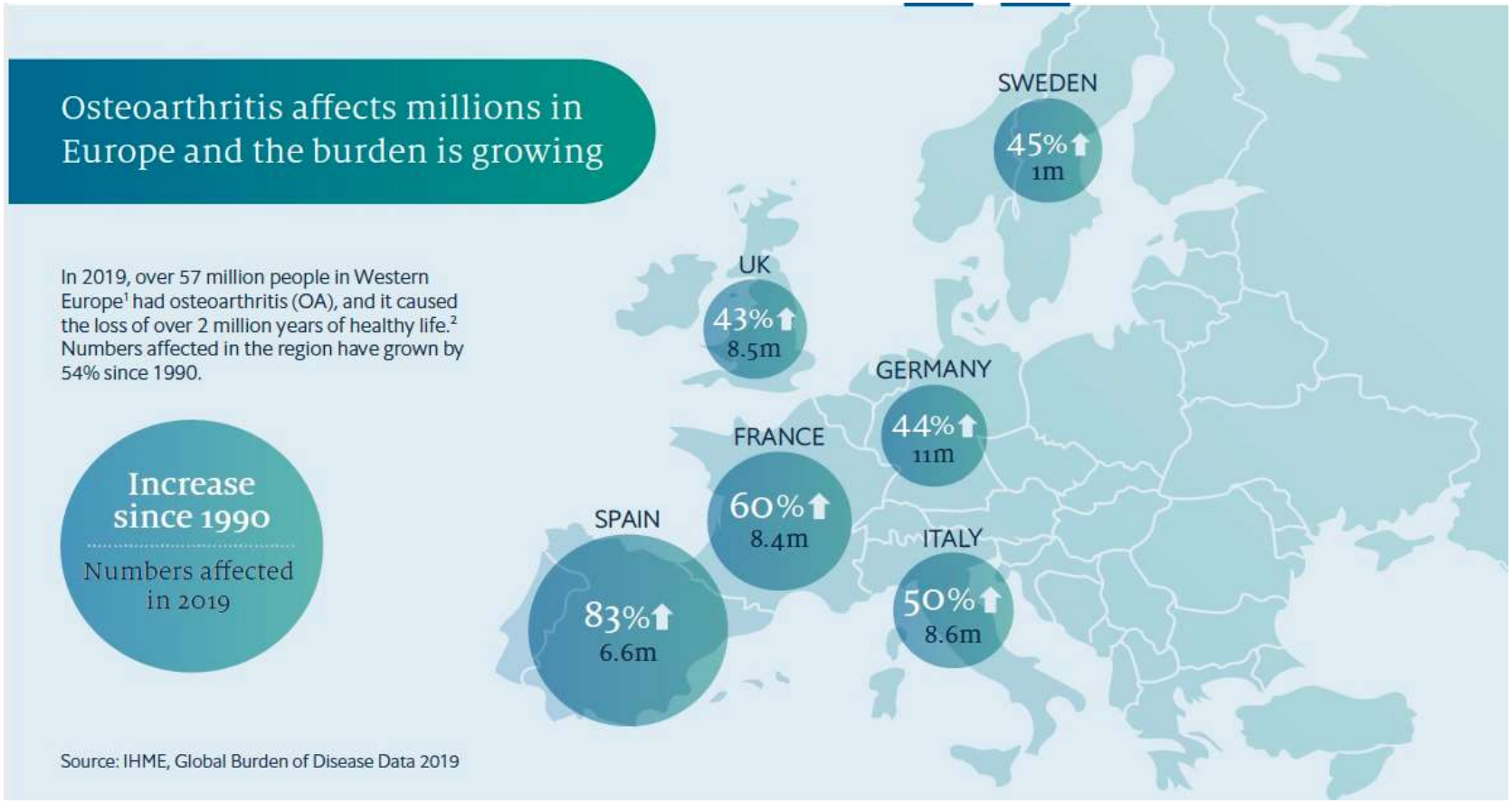
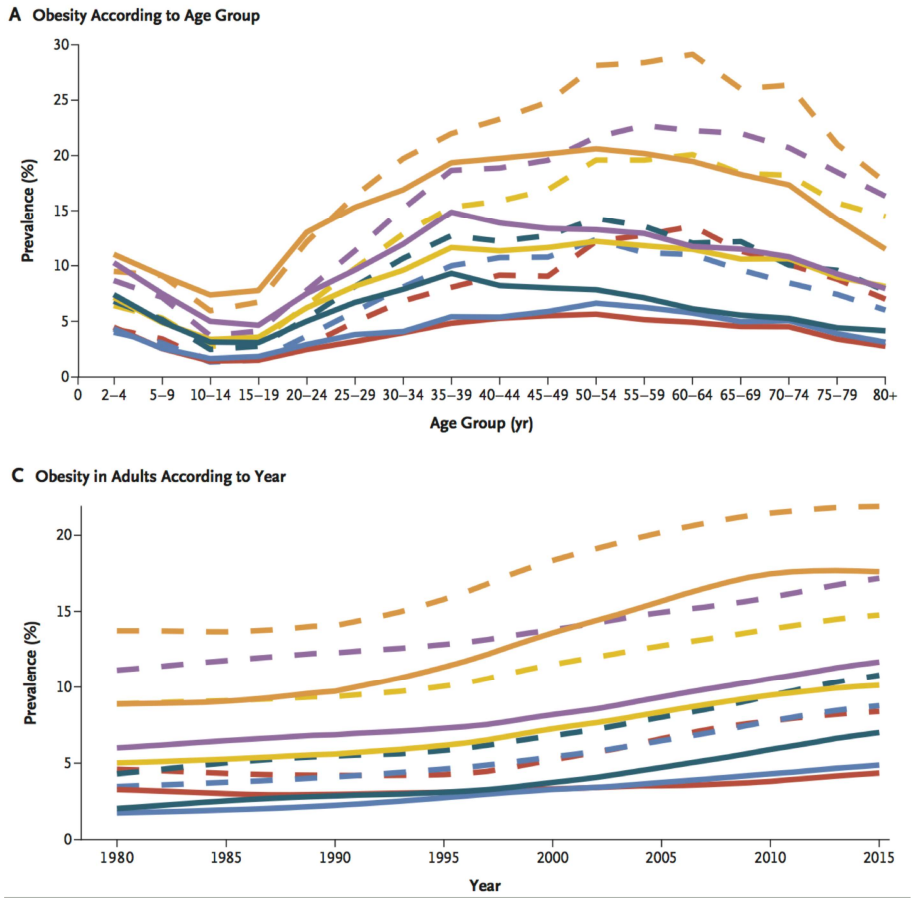
Epidemiology OA



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

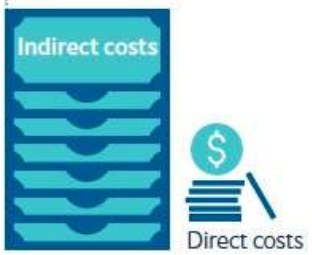
Up to **7.2bn**

Indirect healthcare costs

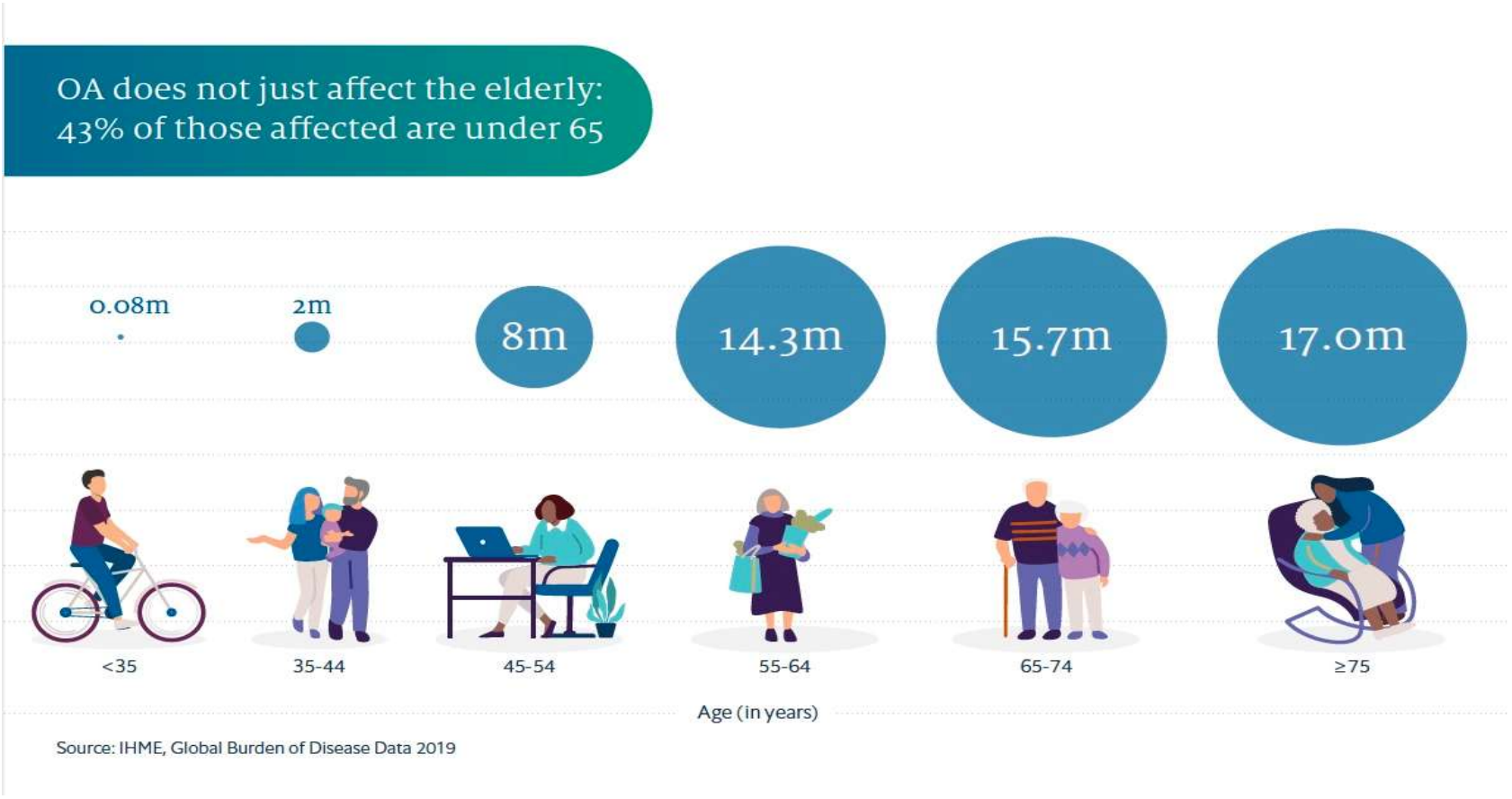
Up to **4.6bn**

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%

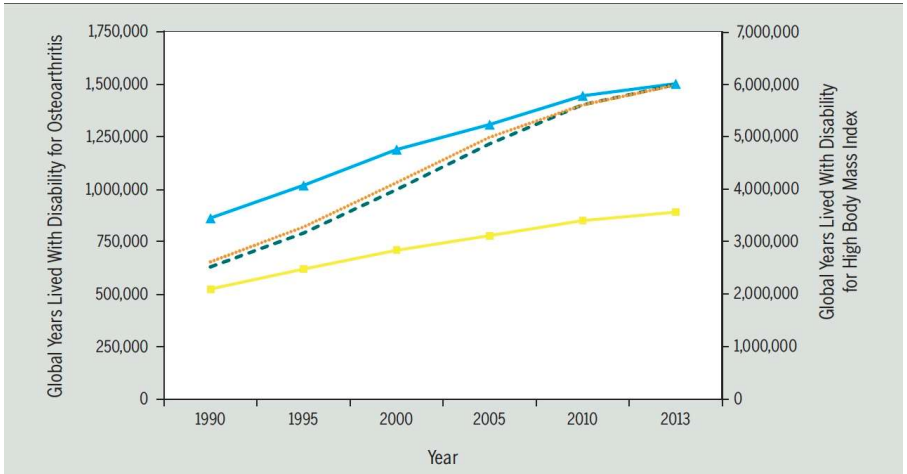
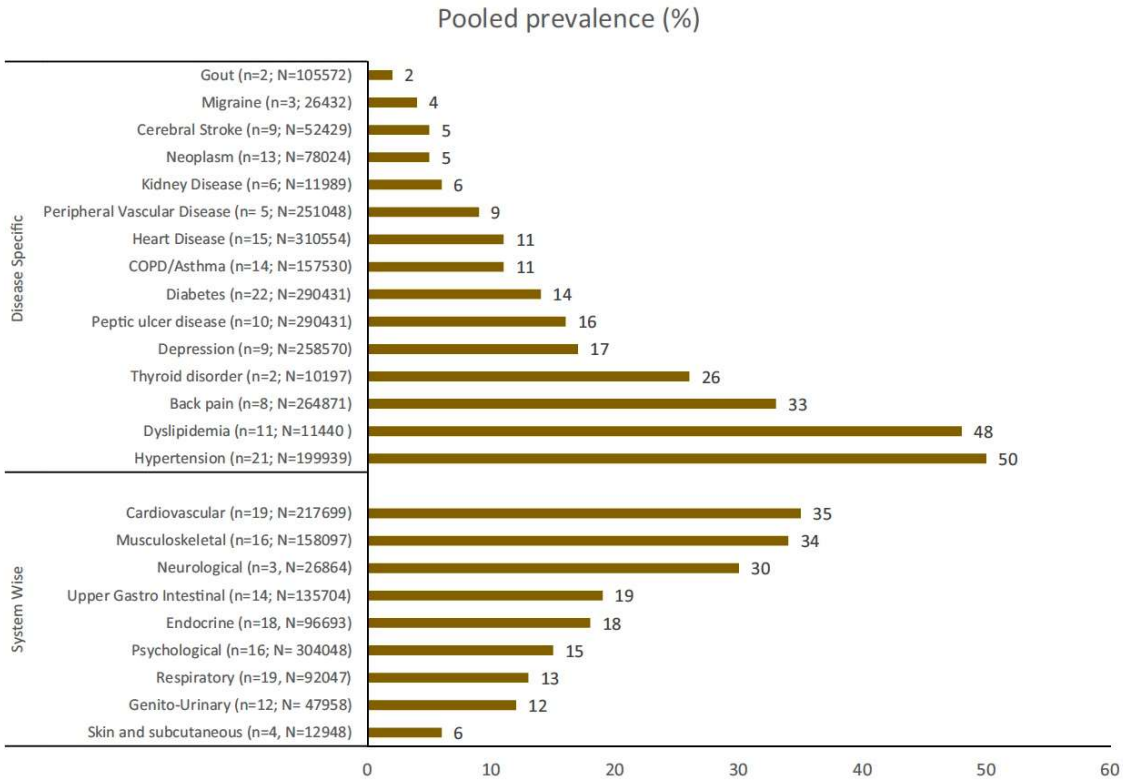


FIGURE 1. Growth in the global burden of osteoarthritis and global burden of high body mass index from 1990 to 2013 for males and females aged 15 to 49 years. Solid lines represent global years lived with disability for osteoarthritis (triangles indicate data for females and squares indicate data for 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 and comorbidities**
  - Meta-analysis Observational studies
  - RR X 1.2 versus non-OA
  - Most frequent:
    - Stroke
    - Gastric Ulcer
    - Metabolic syndrome

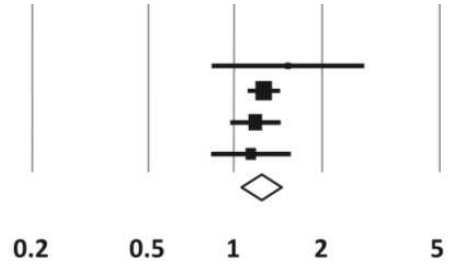


Swain et al. ACR 2020

Epidemiology OA

- **OA and mortality**
  - Meta-analysis
  - All causes and CV mortality with 3 OA sites (hand, knee, hip)
  - No increased risk of any cause mortality in OA patients (global)
  - Significant association between OA and mortality (after removing hand OA)
  - Higher CVD mortality HR 1.21 (CI: 1.10-1.34)

CV MORTALITY (any joint OA)					
Kluzek. 2015 (hand + knee [pooled]) **	1.50	0.82	2.74	1.317	0.188
Barbour. 2015	1.24	1.09	1.41	3.276	0.001
Castano Betancourt. 2013 (hip and/or knee)	1.16	0.95	1.42	1.447	0.148
PRO.V.A. study	1.12	0.83	1.55	0.711	0.477
Overall *(I^2=0% [p=0.79])*	1.21	1.10	1.34	3.747	<0.001



Veronese N. Seminar in Arthritis and Rheumatism 2016

Diagnosis OA

- **Symptoms**
  - Mechanical pain, often insidious and highly variable
  - Short morning stiffness
  - Limitation of function/motion
  - Others: depression, sleep disturbance, decrease QoL
  - **No correlation exists between the joint symptoms and the structural alterations on X-ray +++**

Diagnosis OA

OA has a significant impact on people's quality of life and daily activities

Most people with OA have joint pain, and this impacts their ability to function normally. People who have more severe pain have more limitations to their activities[3] and worse mental health[4] and quality of life.[5]

91%

say OA limits their ability to do normal activities[3]

84%

have joint pain or tenderness[3]

Up to **60%**

have moderate to severe pain[6]

49%

report that OA affects their work[3]

37%

report that OA limits their social lives[3]

Imaging OA

- **X-ray**
  - Exclude other diagnosis (Paget, neuroalgodystrophy…)
  - Not mandatory for diagnosis OA
  - Assess OA severity (KL grading)
  - Normal with early OA
  - No correlation with joint symptoms +++

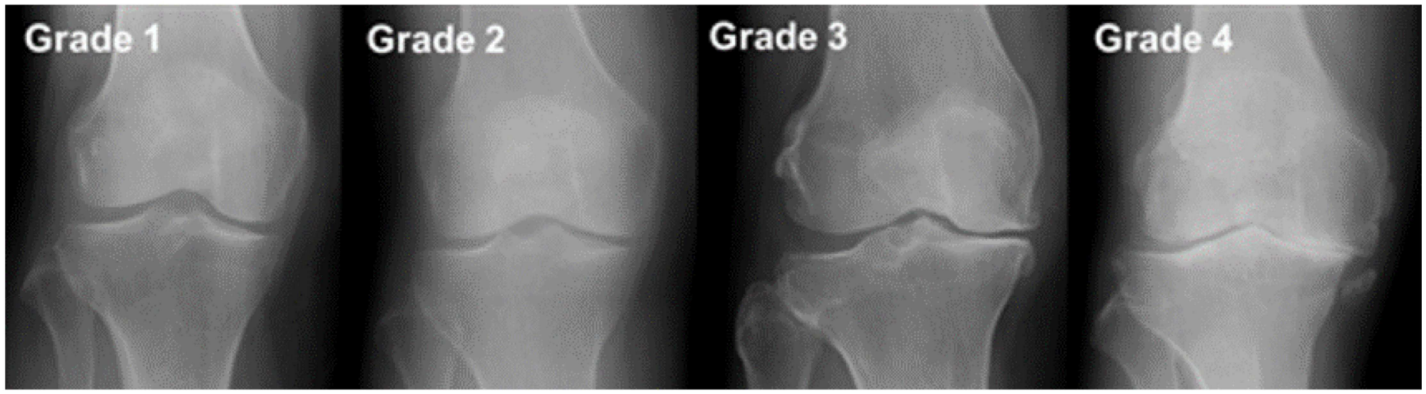
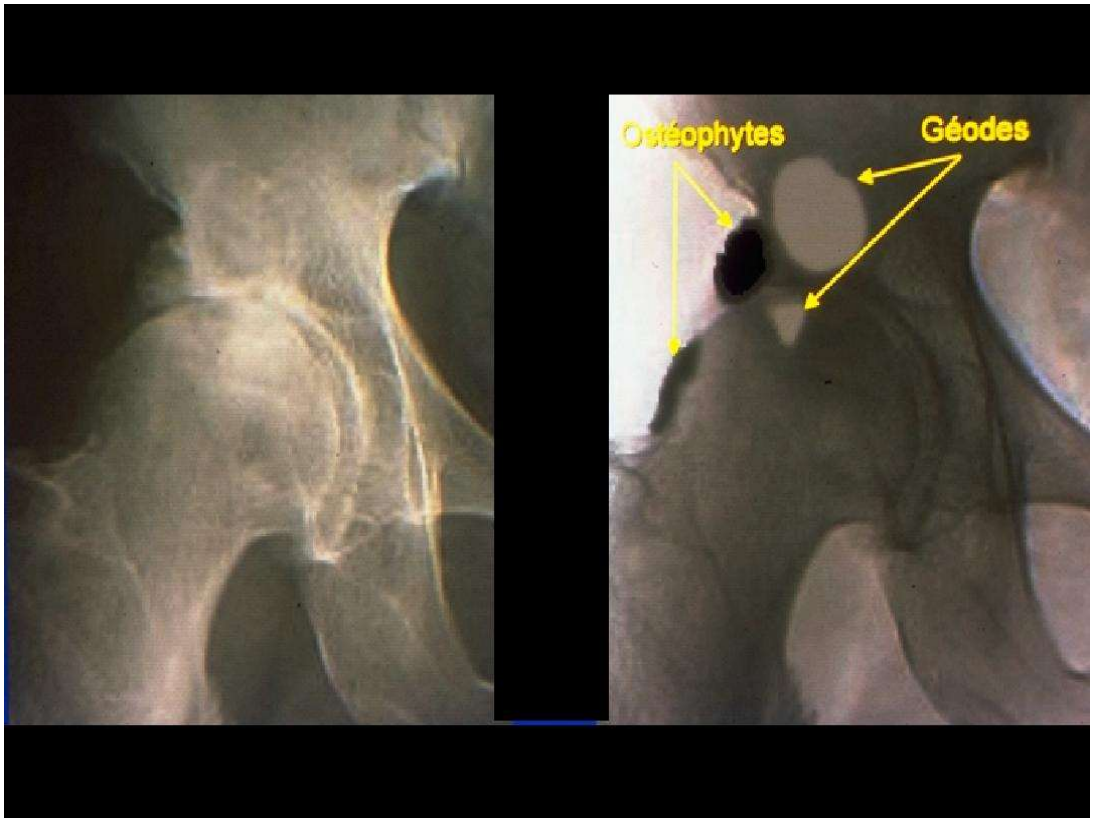


Figure 1. Kellgren-Lawrence classification.

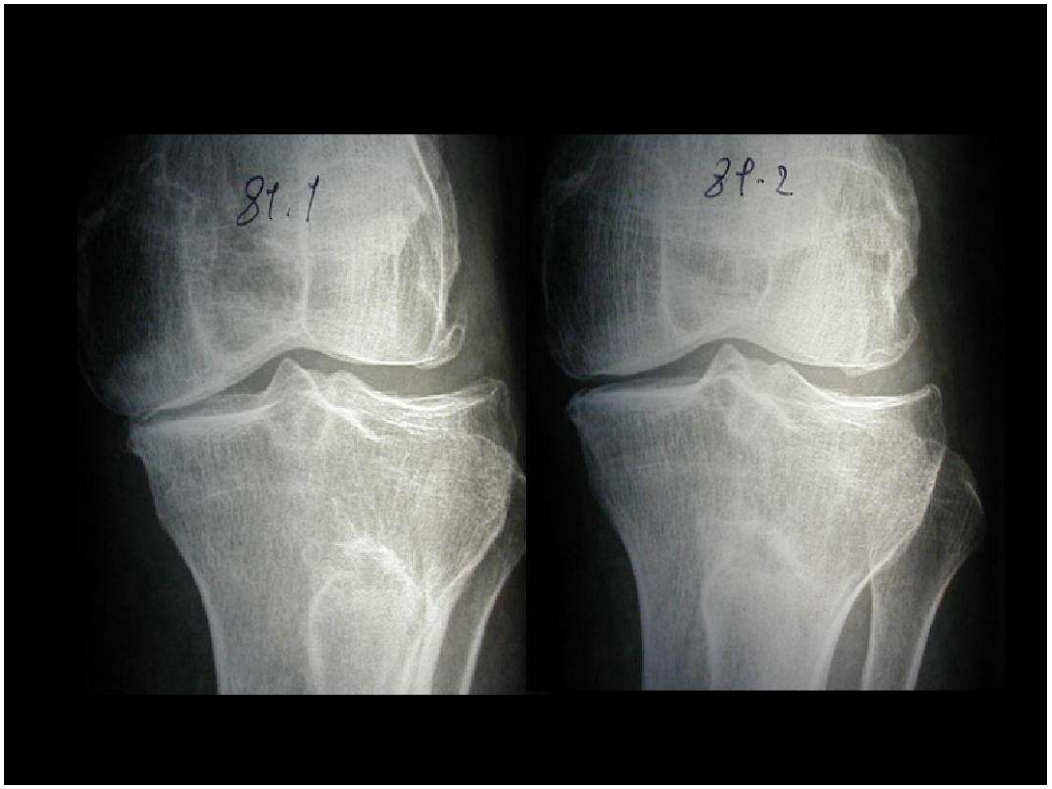
Clinical subsets OA

- **Hip OA**



Clinical subsets OA

- **Knee OA**

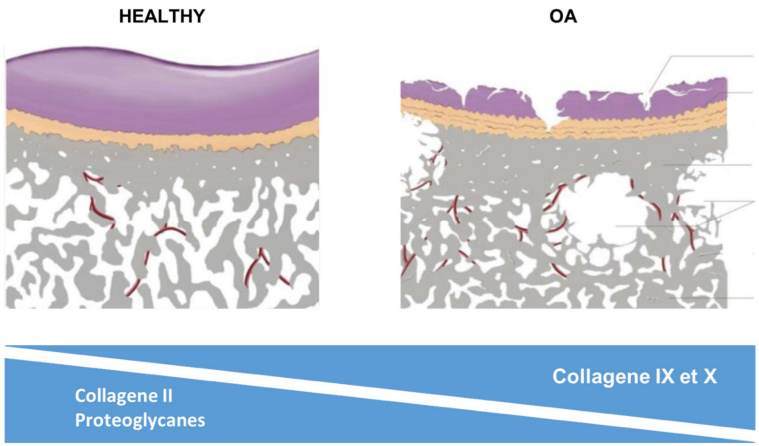


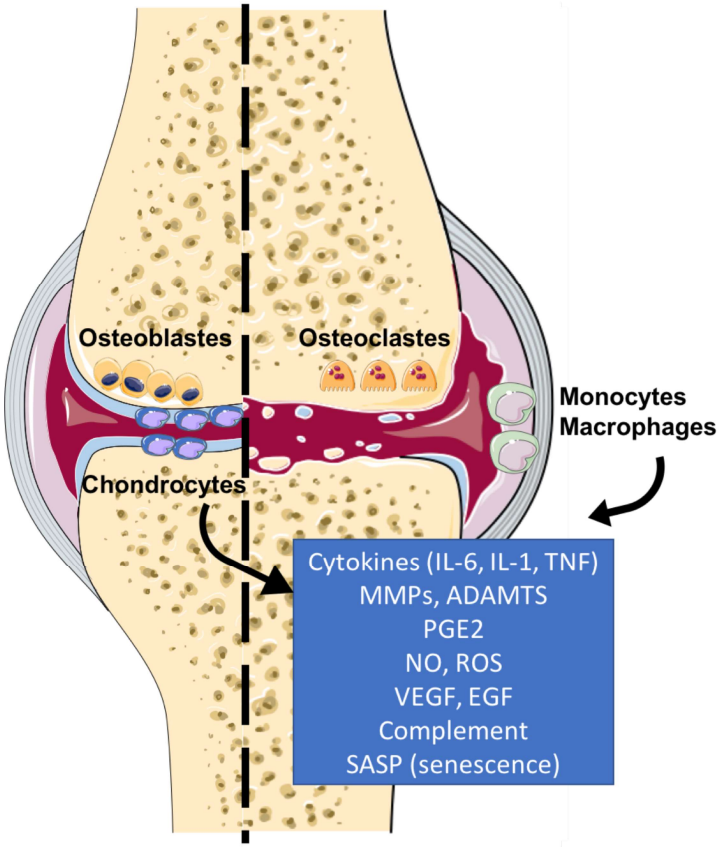
Clinical subsets OA

- **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**

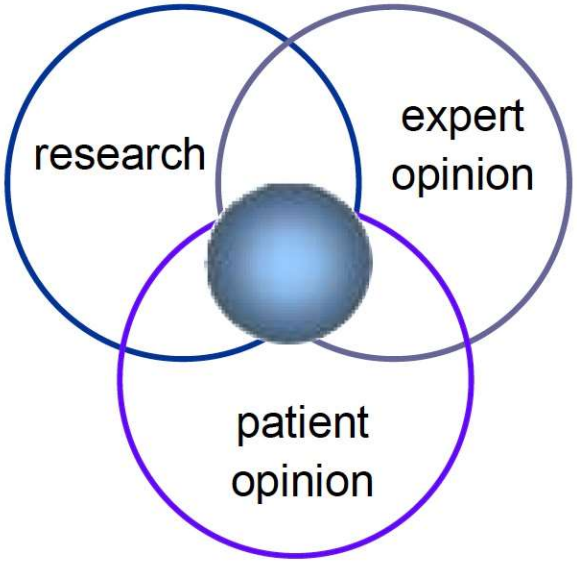
Therapeutic resources in OA

- **RCT, open studies**
- **EBM, experts advices**
- **International Recommendations (OARSI, EULAR, ACR, AAOS)**

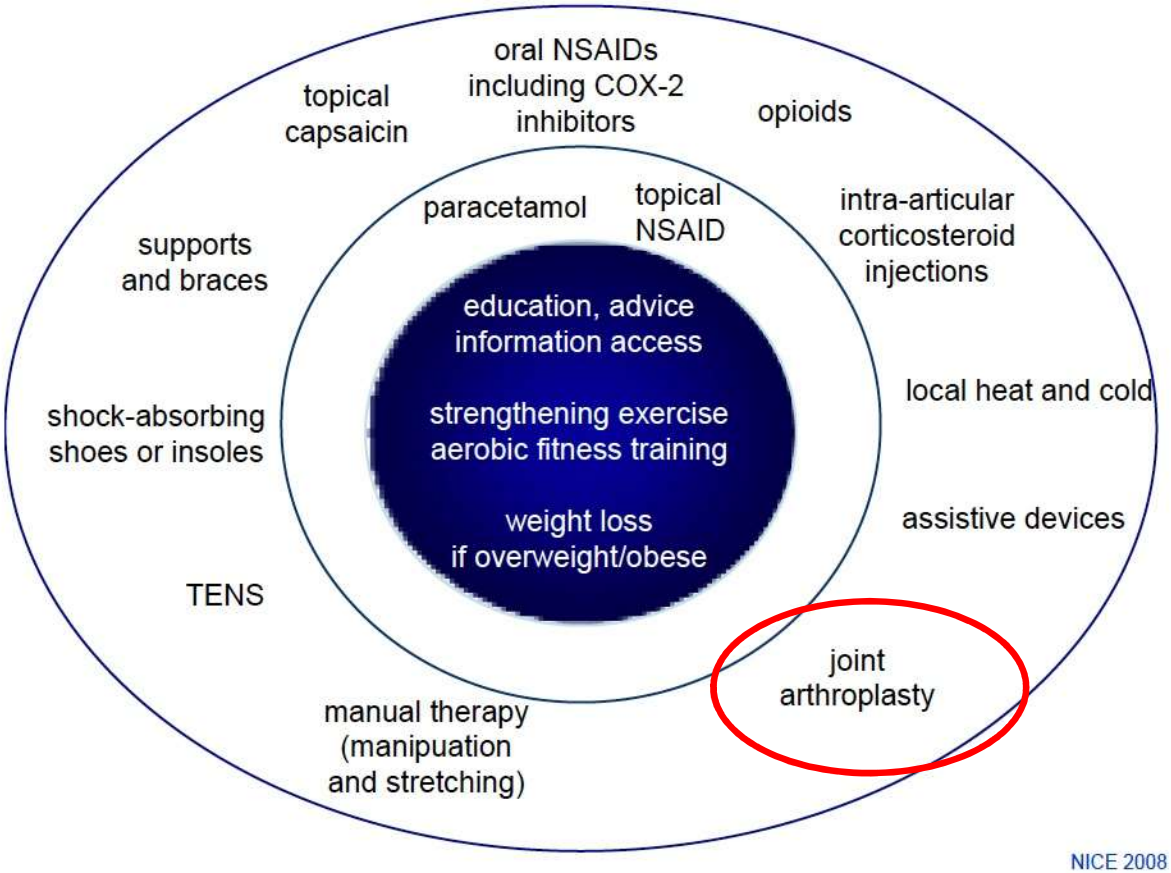
→ Non-pharmacological therapies

→ Pharmacological therapies

→ Surgery



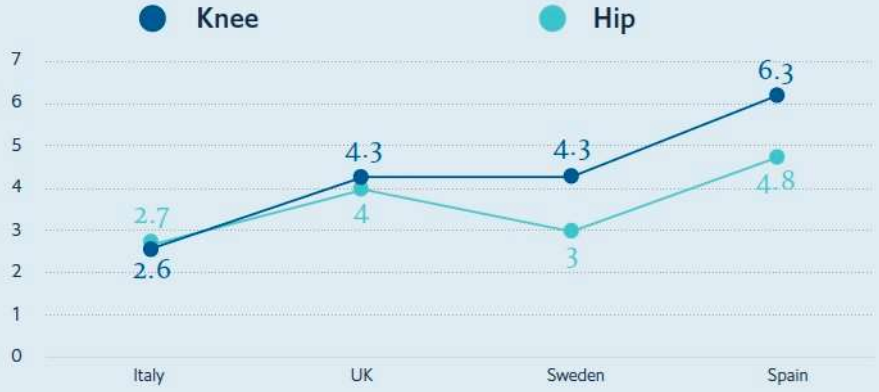
Therapeutic resources in OA



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).

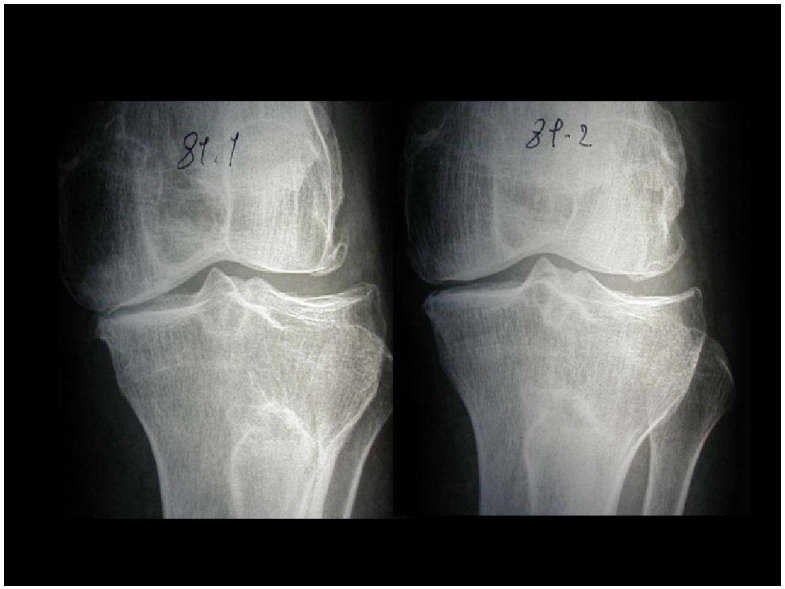
Surgical intervention

- **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

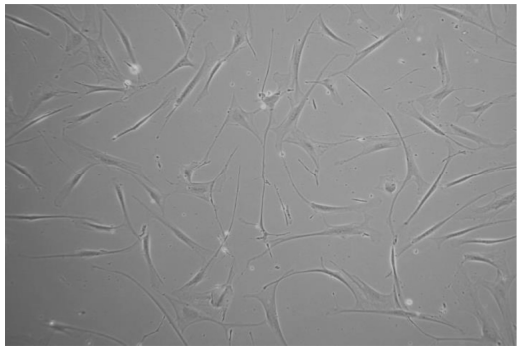


FIND NEW THERAPY
WITH VARIOUS TARGETS

MSC ???

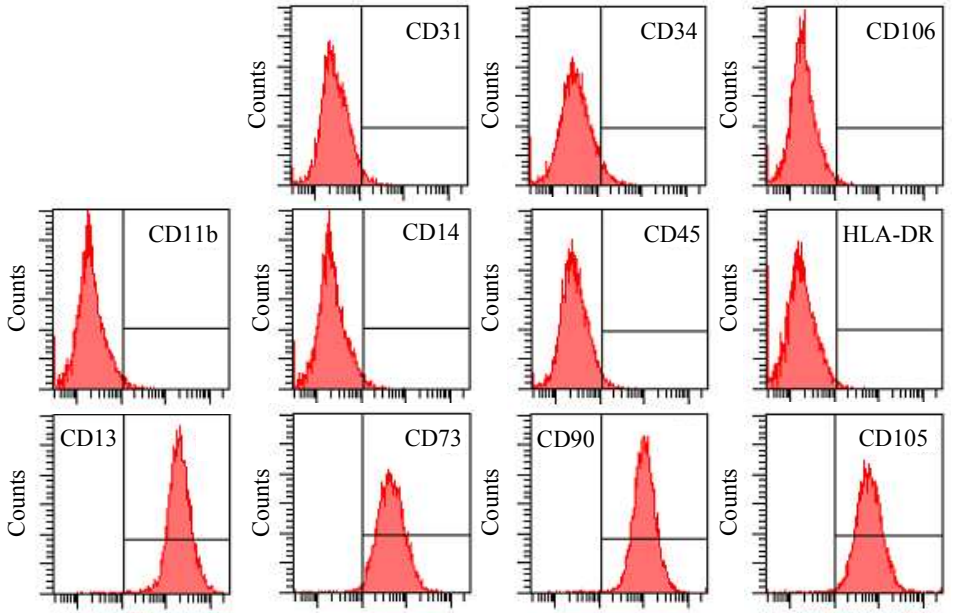
Characteristics of Mesenchymal Stem Cells (MSC)

- **Adherent to plastic**



(High expansion *in vitro)*

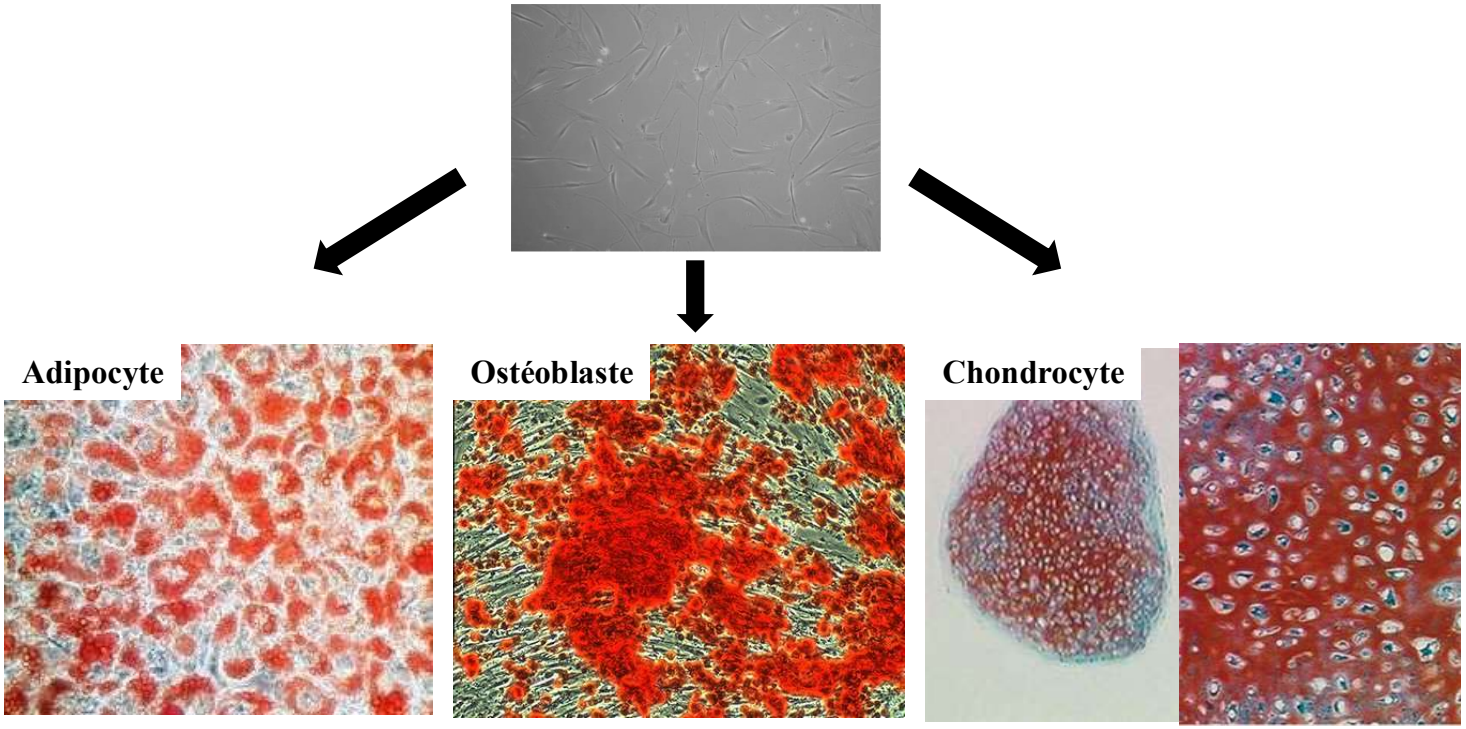
- **Immunophenotype** → No specific marker



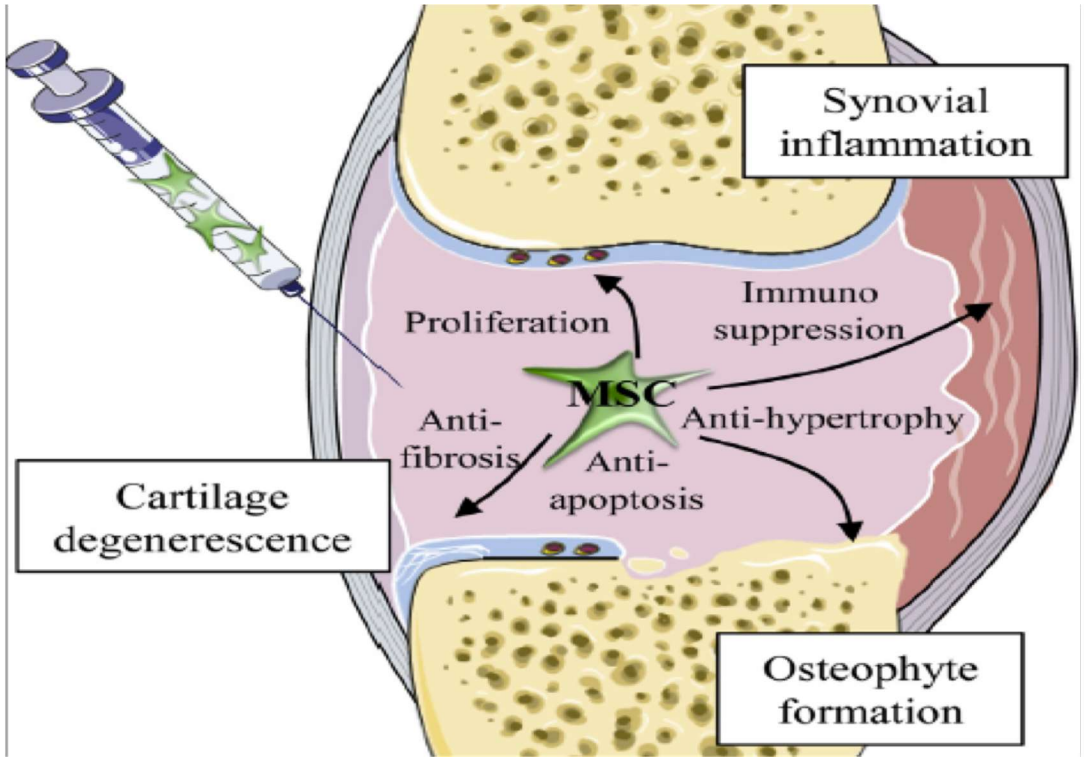
- **CD73⁺, CD90⁺, CD105⁺**, (CD13⁺)
- CD11b⁻, CD14⁻, CD19⁻, CD34⁻, **CD45⁻**, HLA-DR⁻, (CD31⁻, CD106⁻)

Characteristics of Mesenchymal Stem Cells (MSC)

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



Why MSC make senses in OA ?



Maumus M, Biochimie. 2013

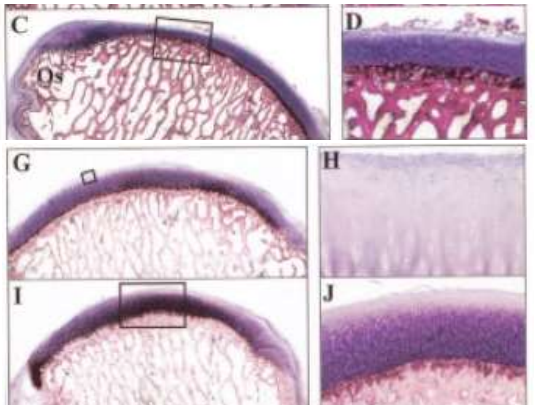
Cell therapy : futures options ?

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

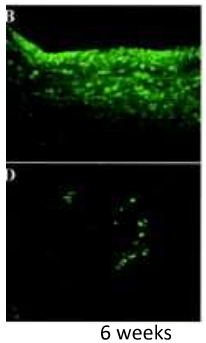
Chondroprotection

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

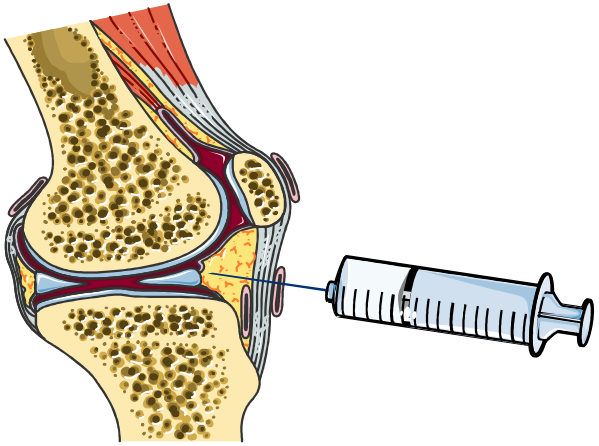
ADIPOA clinical trial

ADIPOA

lipoaspiration

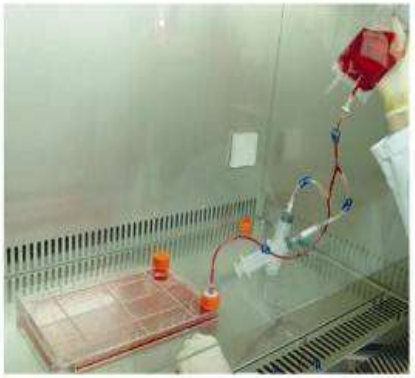
ADSC
isolation/expansion
GMP conditions
Cell viability
Release
criteria/toxicology

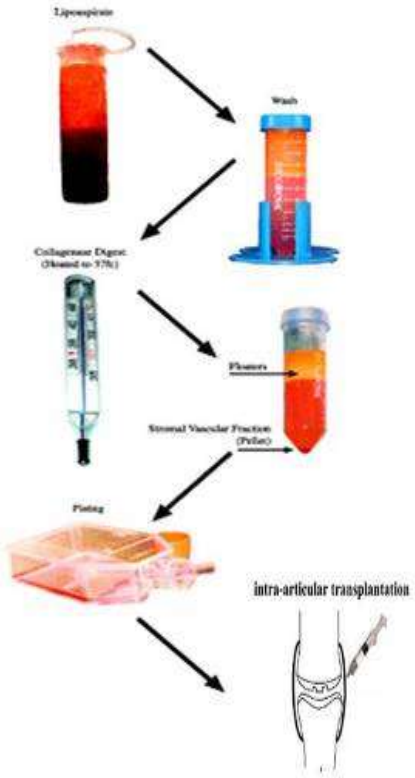
Intra-articular injections
Syringe, different doses



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

ADIPOA clinical trial: cell production





Quality controls:

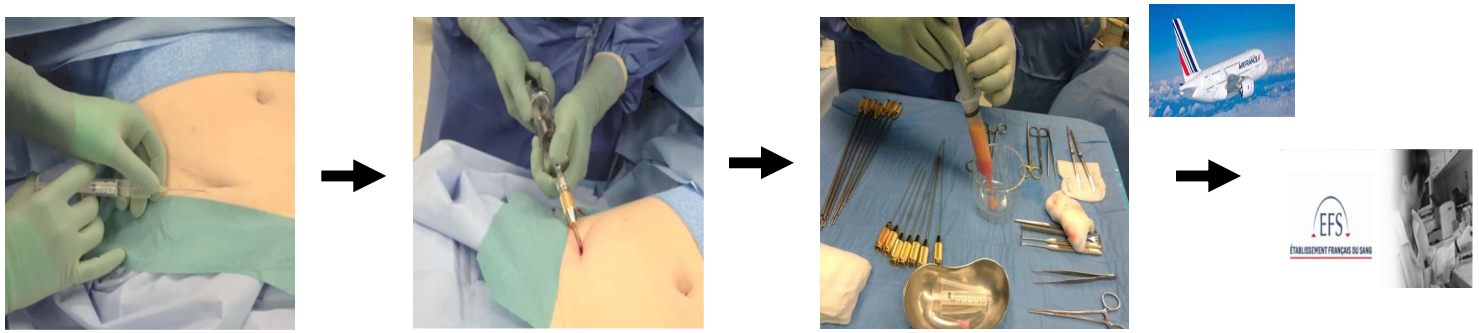
- Sterility test day 8
- Endotoxin test day 11
- Mycoplasma test day 11
- Karyotype performed on 20 cultures. All are normal.

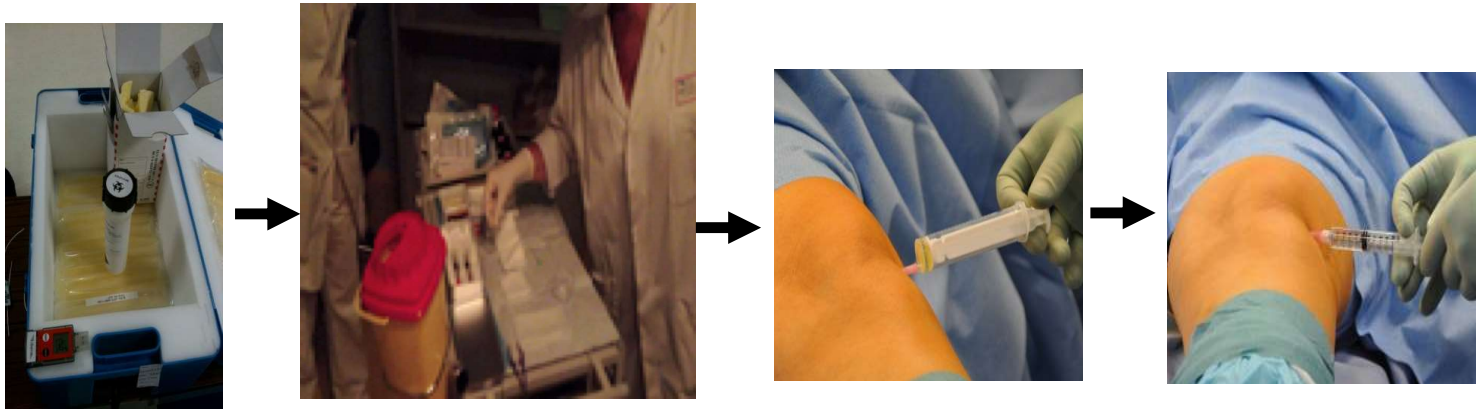
Release criteria:

- Cell viability >80%,
- CD45+ / CD14+ cells < 5%,
- CD90+ or CD73+cells > 80%
- Absence of expression of hTERT and Oct-4 at the end of the primary culture to assess genotype stability.

ADIPOA clinical trial: fat harvesting

ADIPOA

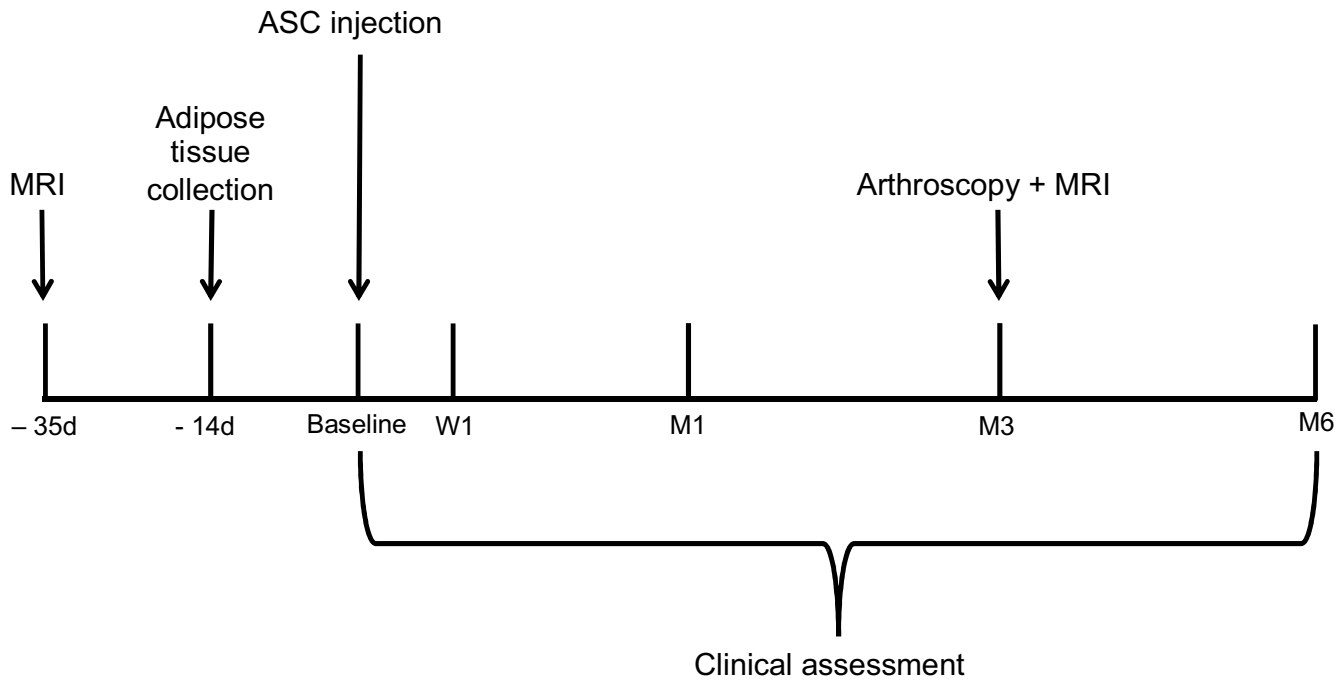




ADIPOA clinical trial: design

Adipose derived Stromal Cells for OsteoArthritis treatment.

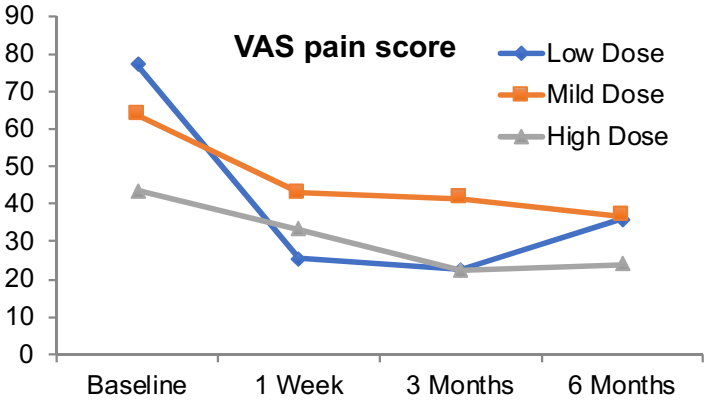
A phase 1 study, bi-centric (Mtp, Wurzburg), dose escalating study with autologous ASC in severe knee OA (>3 K/L)



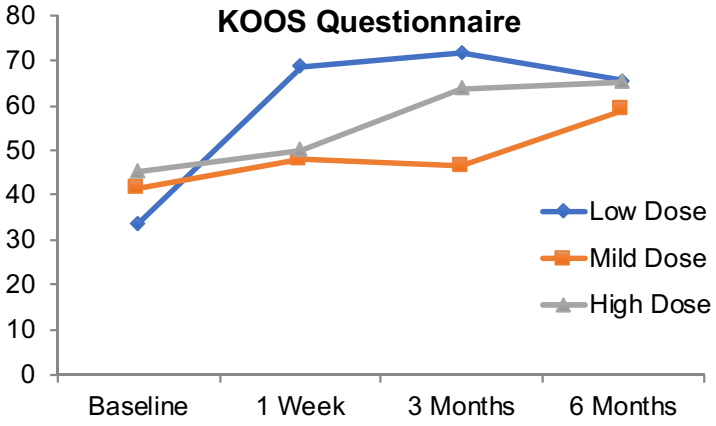
Pers YM et al. SCTM 2016

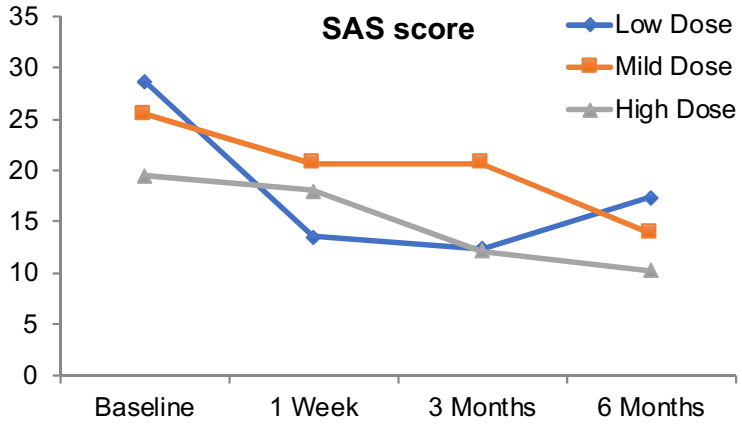
ADIPOA clinical trial

- **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**



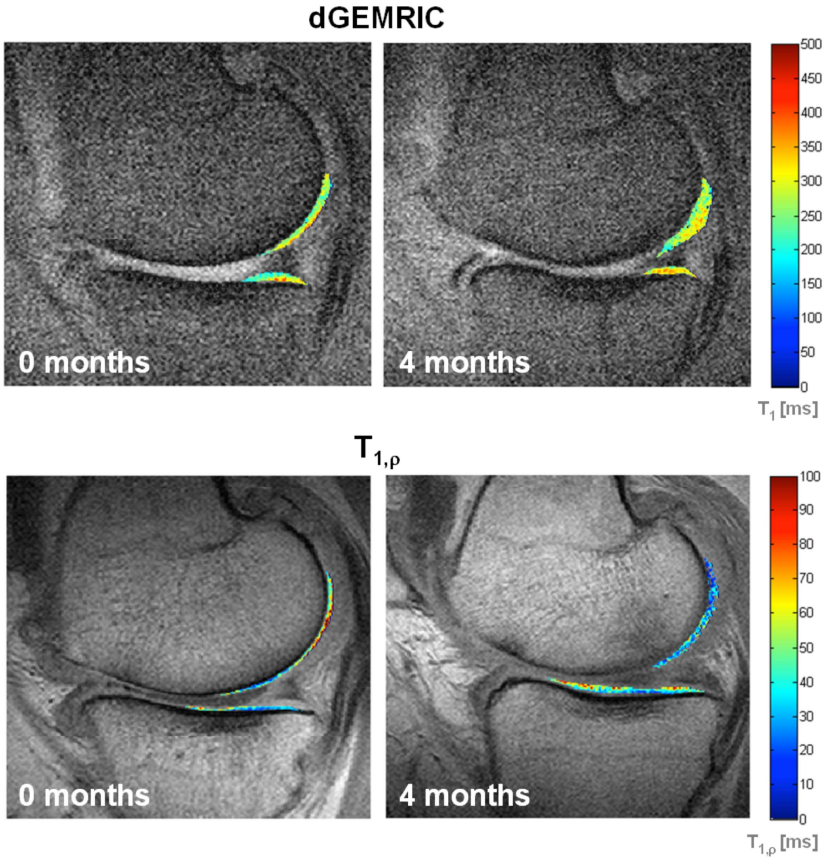
ADIPOA





Pers YM et al. SCTM 2016

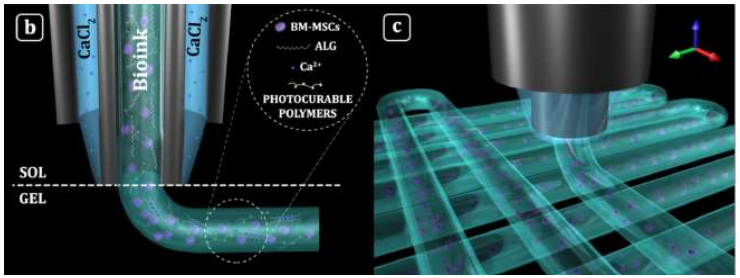
ADIPOA clinical trial: structural assessment



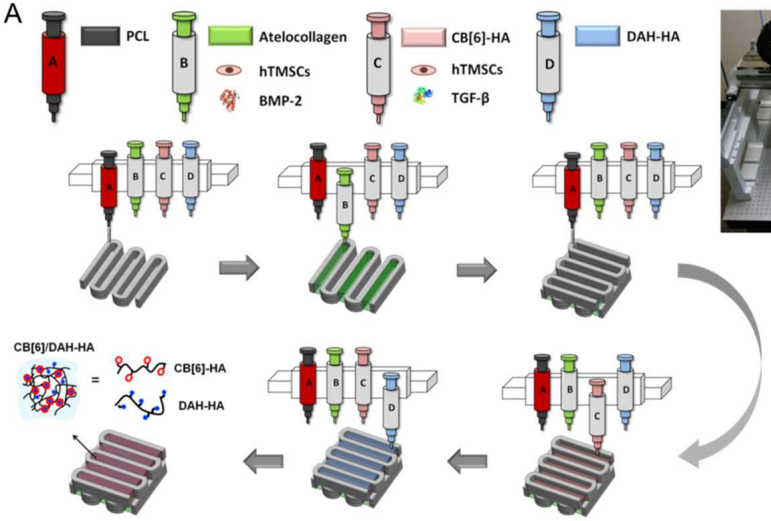
- dGEMRIC index increase in 3 out of 6 selected patients
- Suggest a possible structural effect

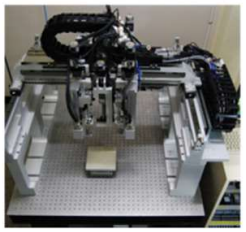
Pers YM et al. SCTM 2016

Perspectives: bio-printing for cartilage engineering



Costantini, 2016, Biofabrication





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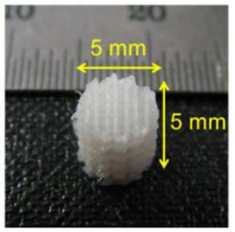

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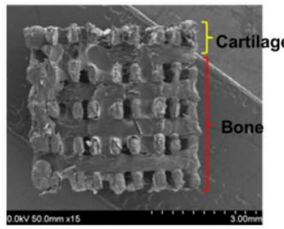
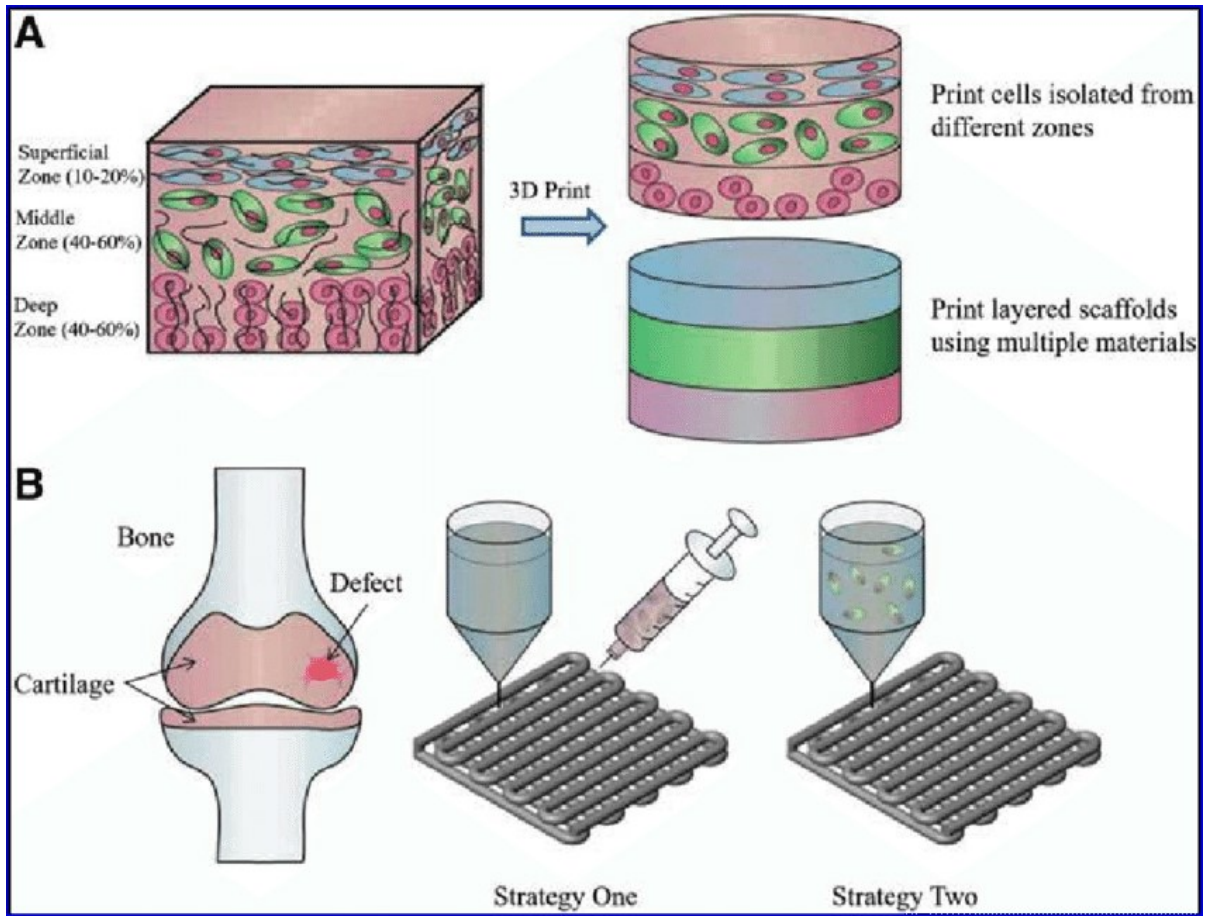


Multi head tissue/organ building system for regeneration of osteochondral defects

Shim, 2016, Biofabrication

Perspectives: bio-printing for cartilage engineering



Perspectives: bio-printing for cartilage engineering

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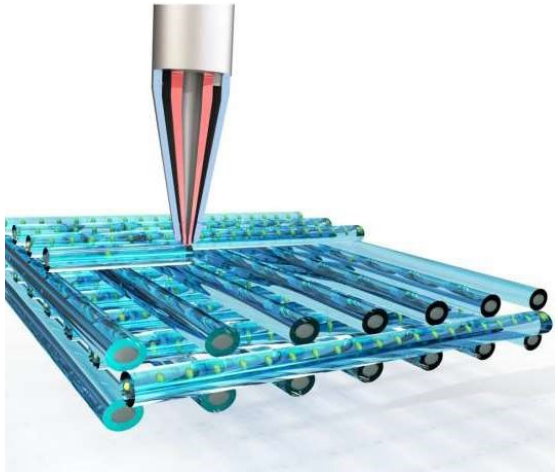
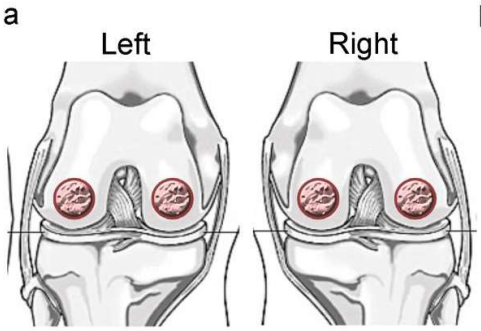
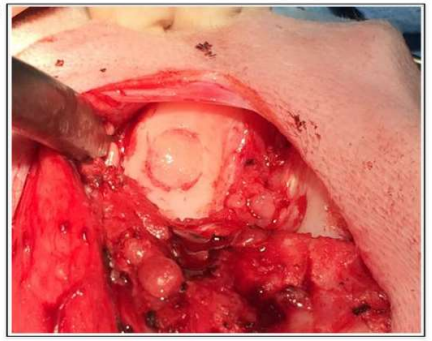
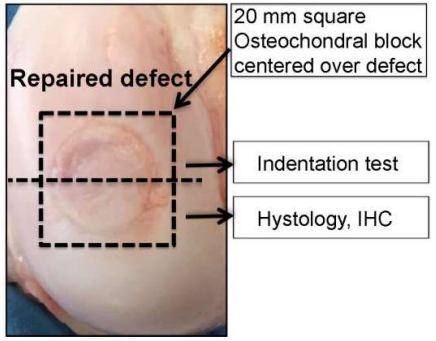


"Biopen"



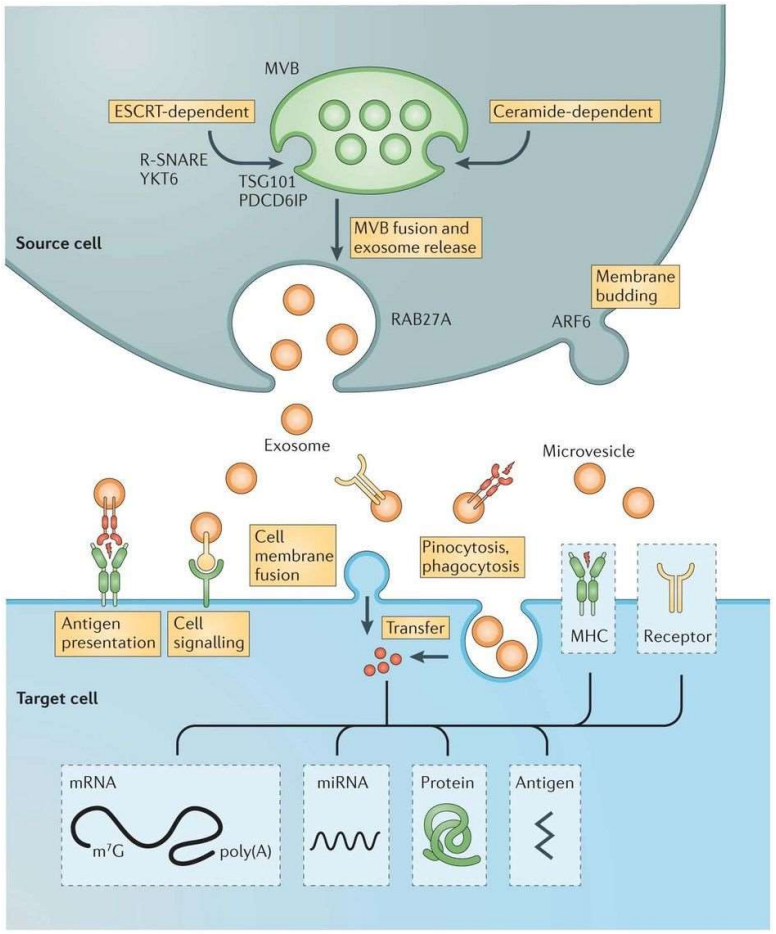




Extracellular vesicles (EVs) derived from MSC: a future option ?

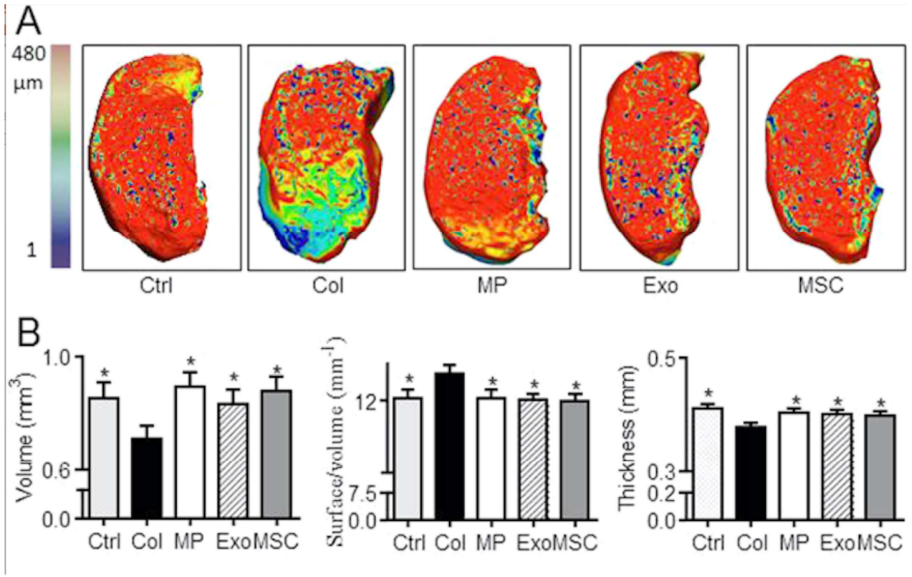
Vesicle types	Characteristics			
	Origin	Size	Markers	Contents
Exosomes	Endolysosomal pathway; intra-luminal budding of multivesicular bodies and fusion of multivesicular body with cell membrane	40–120 nm	Tetraspanins (such as TSPAN29 and TSPAN30), ESCRT components, PDCD6IP, TSG101, flotillin, MFGE8	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

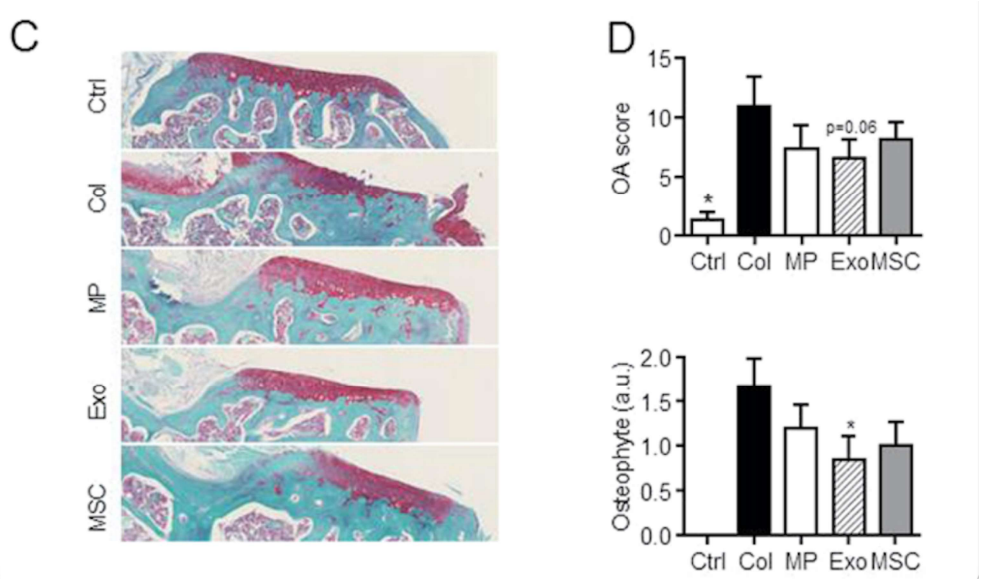
ESCRT, endosomal sorting complex required for transport, MFGE8, milk fat globule-EGF factor 8 protein; PDCD6IP, programmed cell death 6 interacting protein (also known as ALIX); TSG101, tumour susceptibility gene 101 protein; TSPAN29, tetraspanin 29.



Nature Reviews | Drug Discovery

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

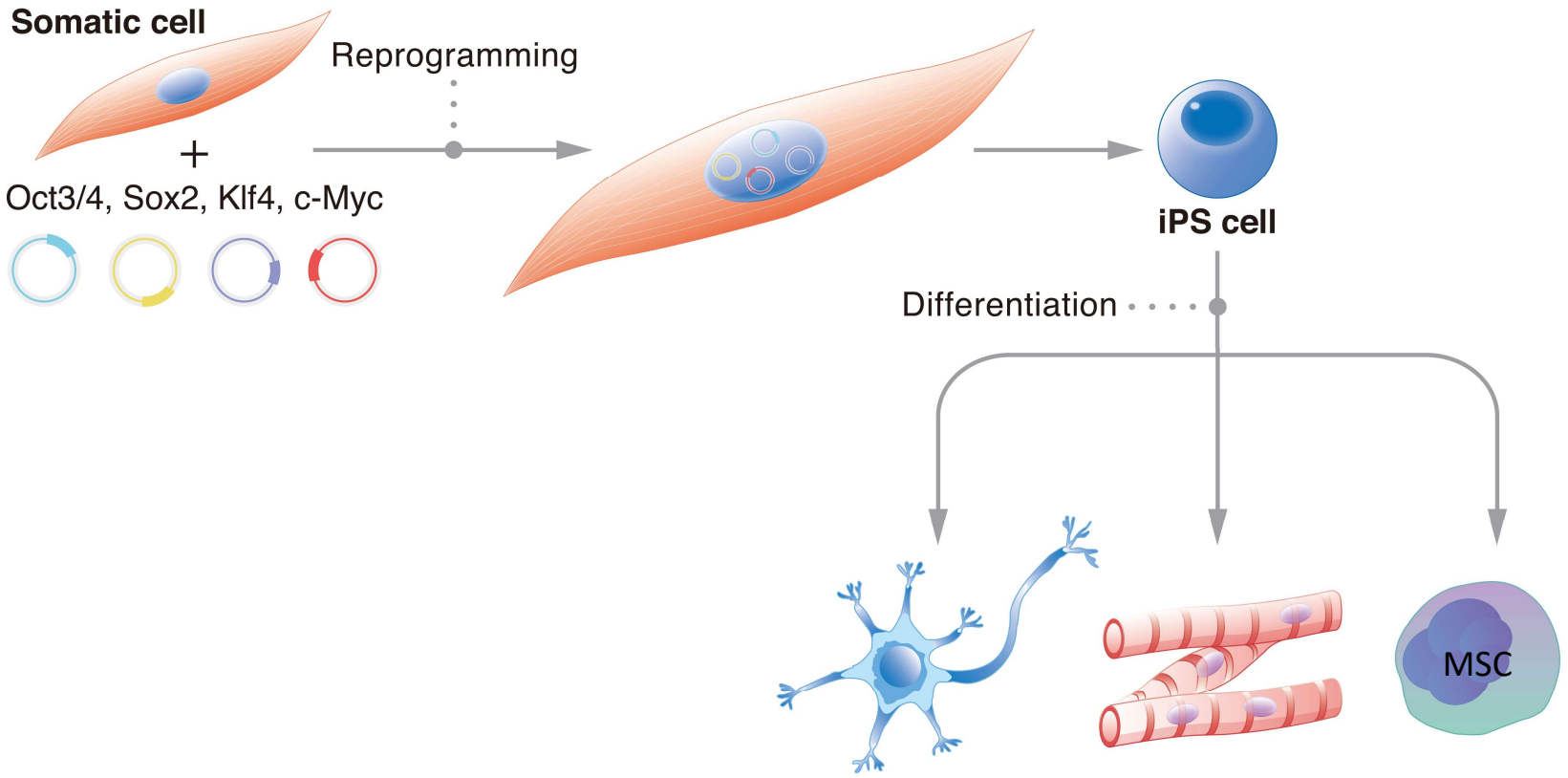




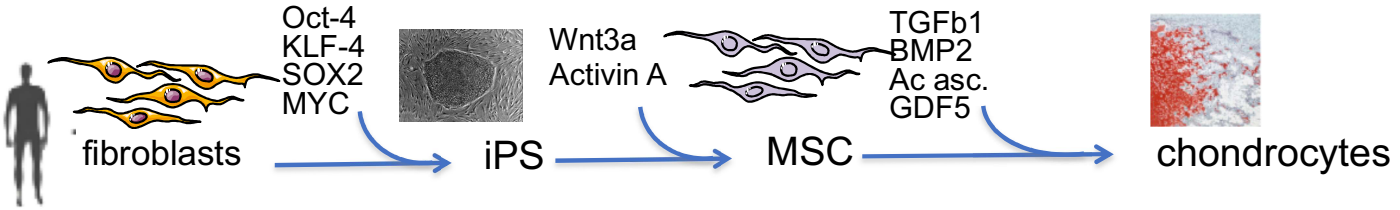
BM-MSC-derived MPs and Exos protected mice from osteoarthritic damages in the collagenase-induced OA model.

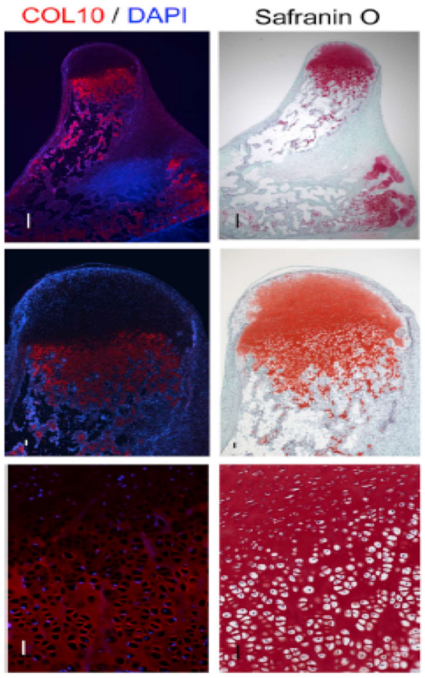
Cosenza S et al. Sci Report 2017

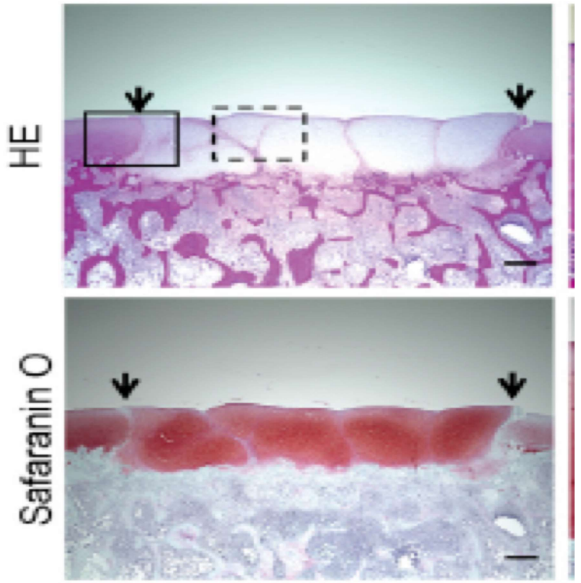
Reprogramming and iPS



Cell source for cartilage engineering







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

Bionic in OA : 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**…

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

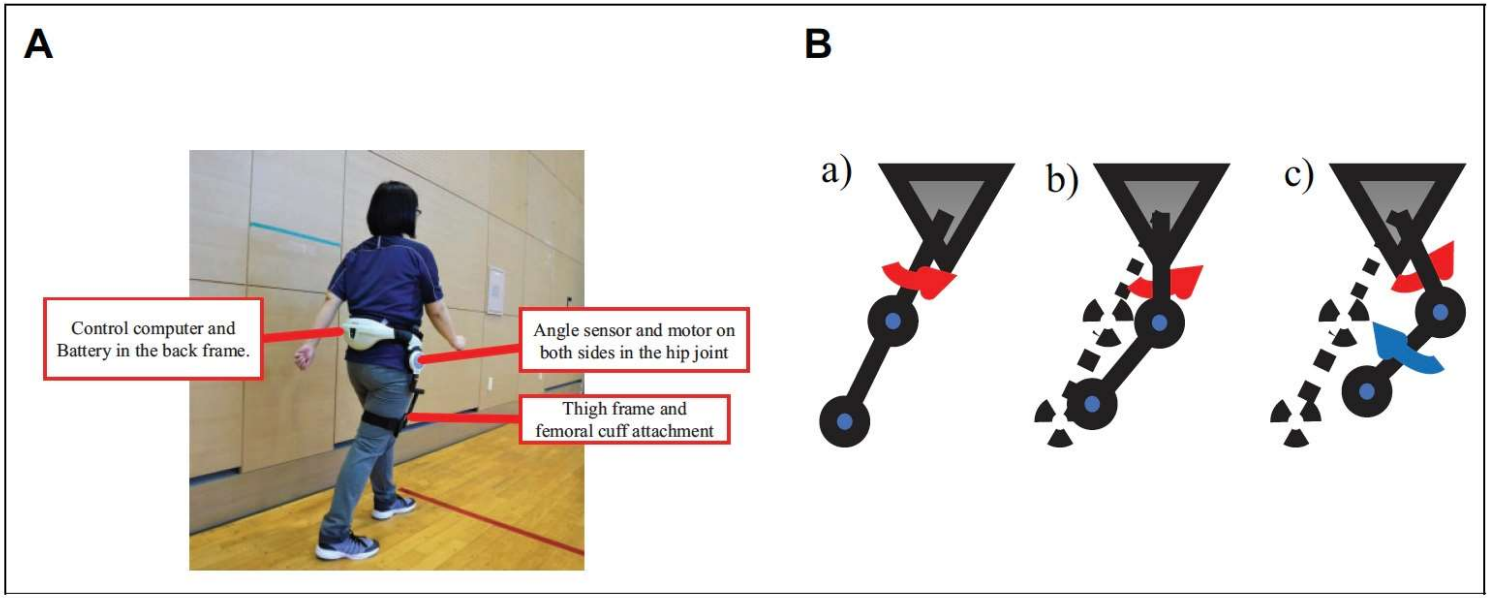


Figure 1. A, Gait training with the Honda Walking Assist (HWA)® device. B, The mechanism of knee flexion during the swing phase due to hip assistance using the HWA device. The HWA assistance has the effect of lifting the thigh (red arrow) during the swing phase (b and c), thereby promoting knee flexion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

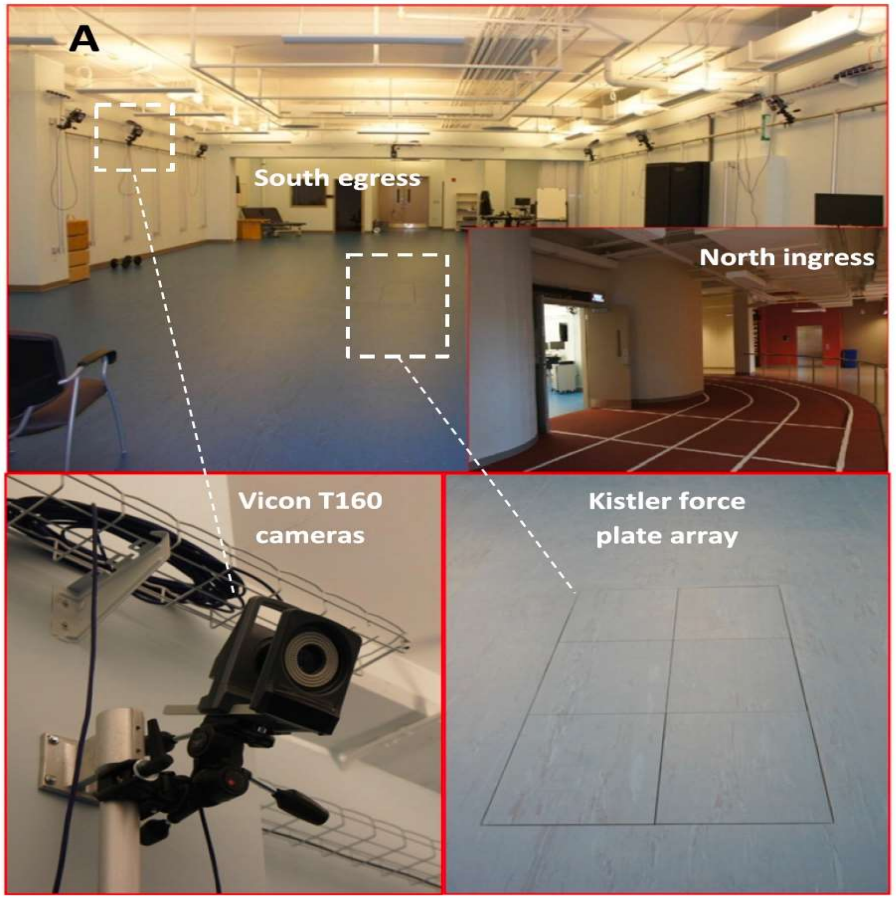
Exoskeleton

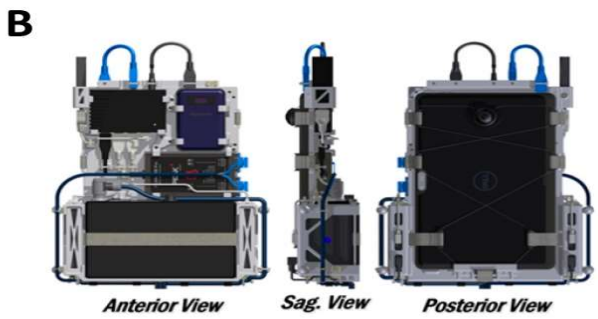
- PA and exercise is central to conservative management of knee OA
- Difficult for patients with KOA to regularly maintain

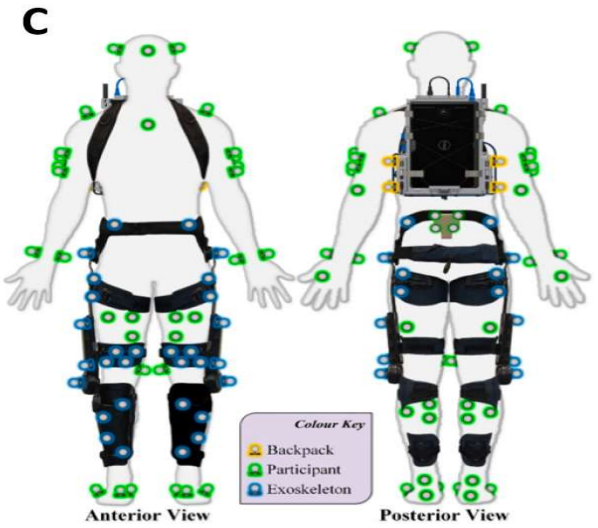
- To quantify how a lower-extremity robotic exoskeleton (dermoskeleton) modifies the external knee moments during over-ground walking
- Pilot study with healthy adults

McGibbon et al. Knee 2017

Exoskeleton







McGibbon et al. Knee 2017

Exoskeleton

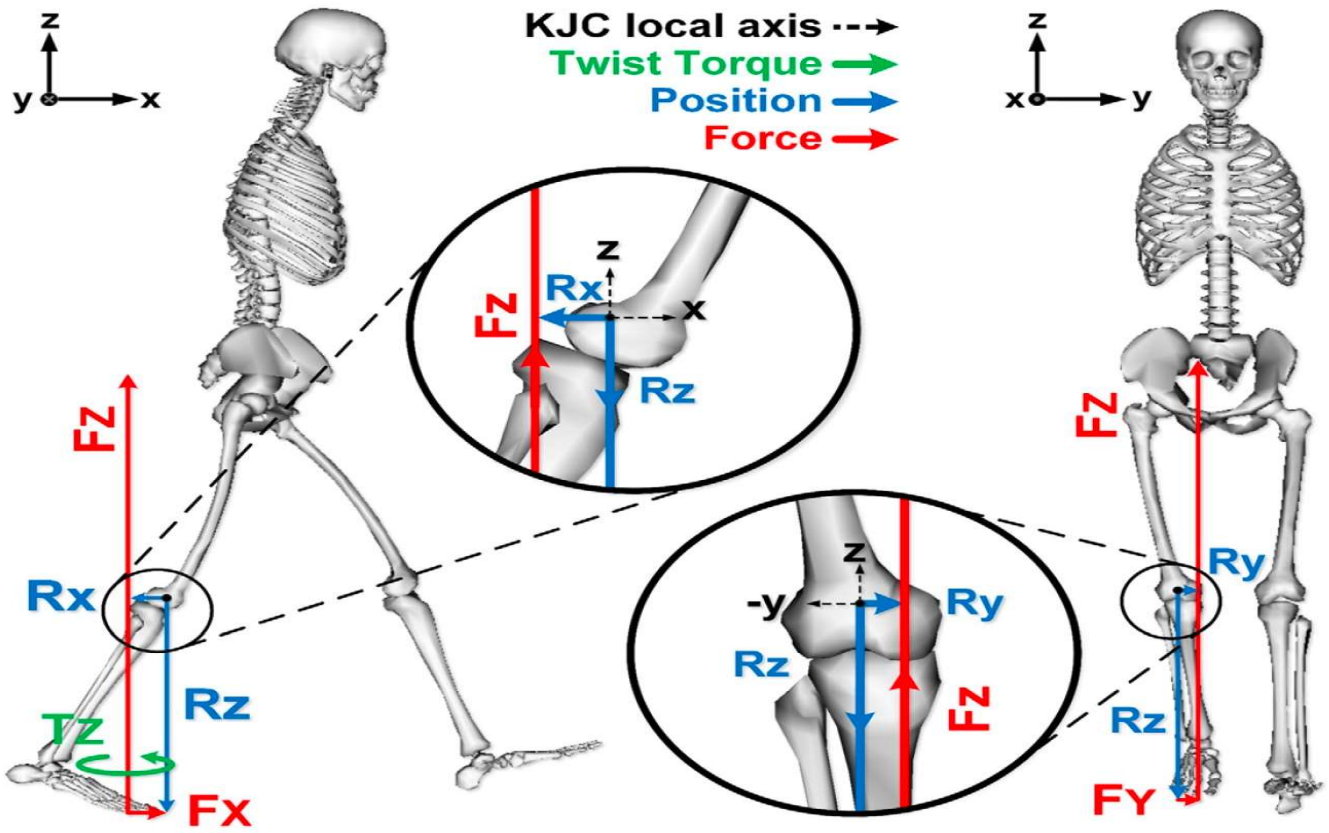
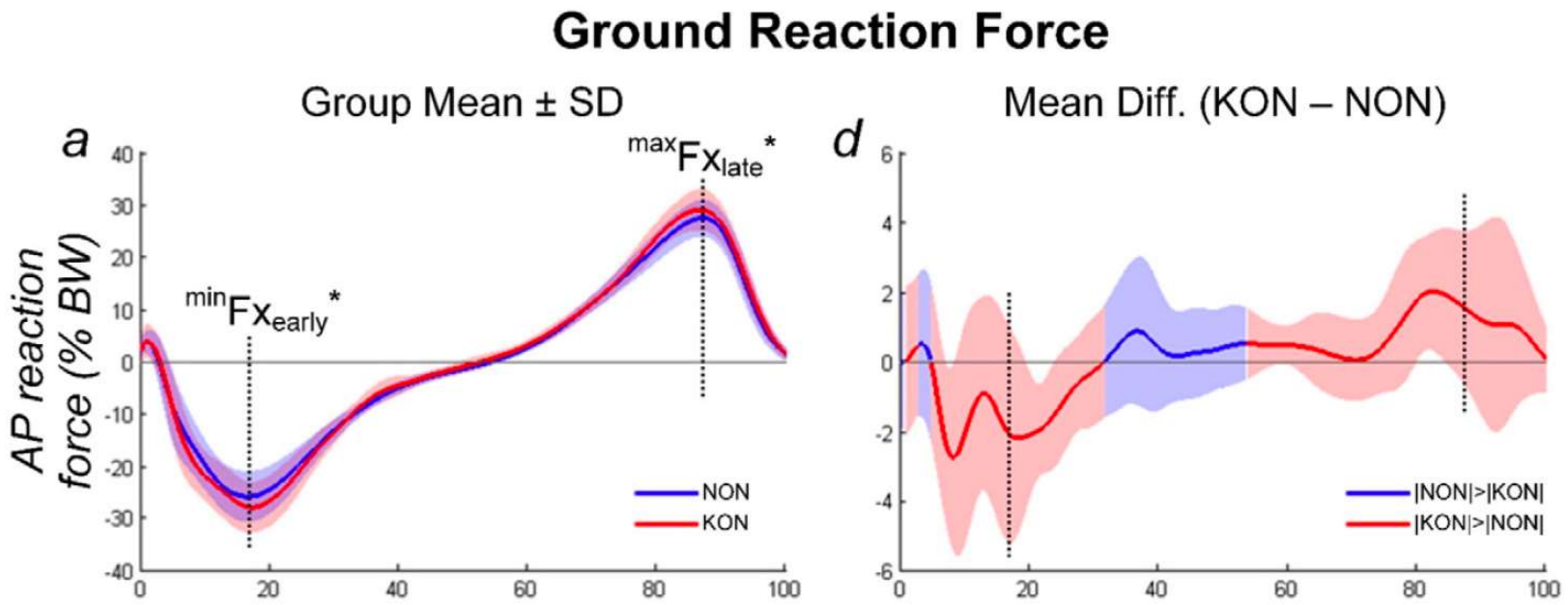


Figure 2. Illustration of the external knee moments calculated by the quasi-static model in laboratory coordinates.

McGibbon et al. Knee 2017

Exoskeleton

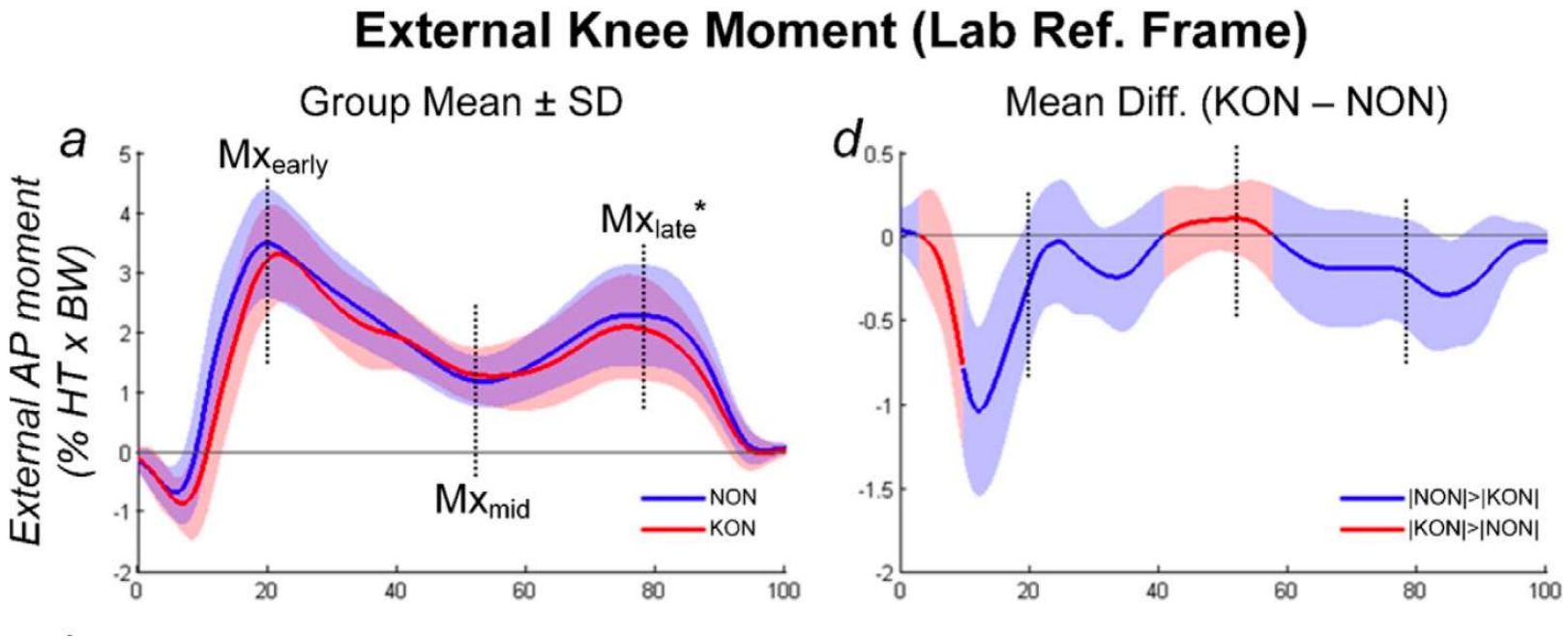
- Users took shorter and wider steps when walking with the dermoskeleton
- Ground reaction forces increased due to the added mass



McGibbon et al. Knee 2017

Exoskeleton

- Knee adduction moment significantly reduced in late stance phase of gait



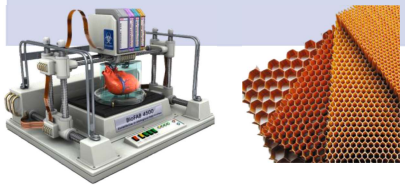
McGibbon et al. Knee 2017

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)

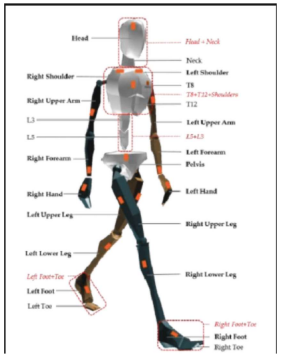
- Grail (virtual reality)

Grail (Laboratoire d'analyse du mouvement en immersion)

- MRI (ESAOTE)

IRM Gscan (Imagerie dynamique)

- XSENS-Awinda



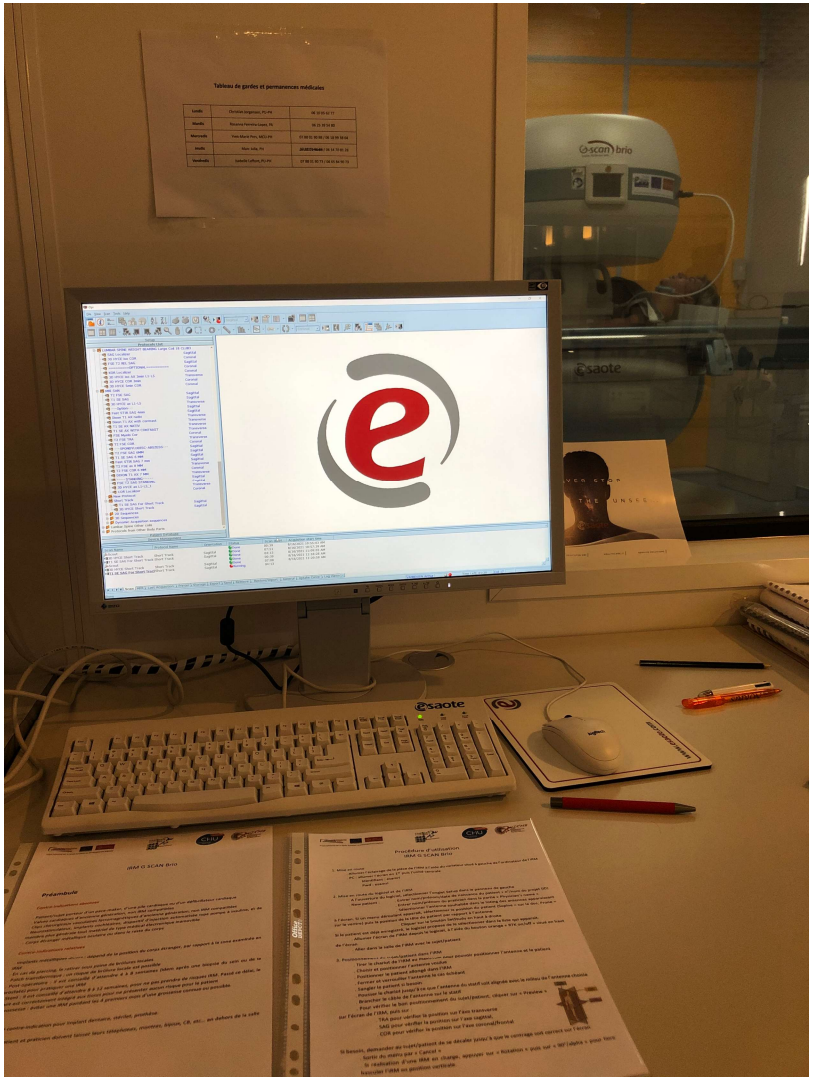
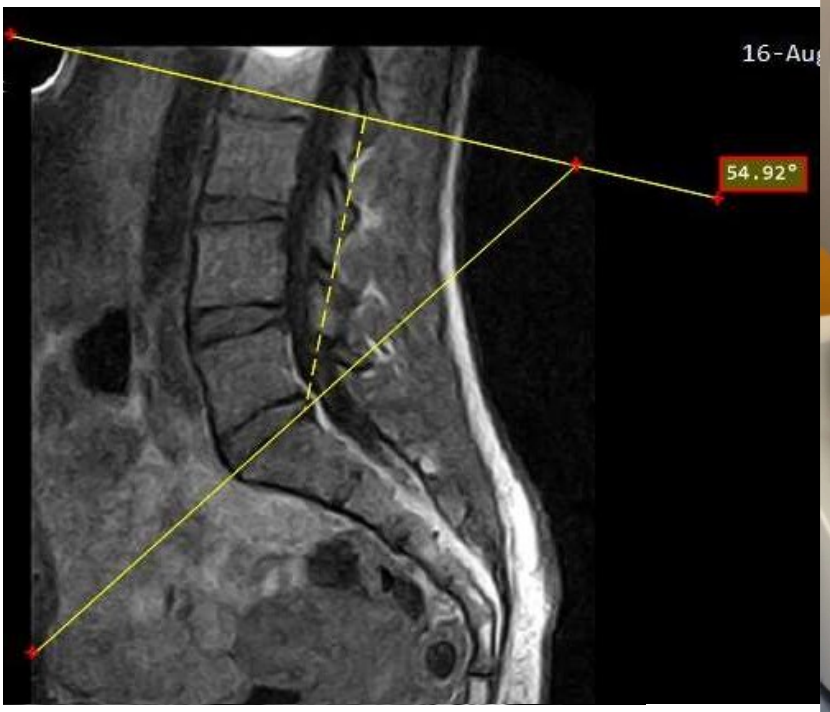


Tableau de gardes et permanences médicales
esaote
IRM G SCAN Brio
Préambule
Procédure d'utilisation
IRM G SCAN Brio


esaote
NEVER STOP
SEEING THE UNSEEN.

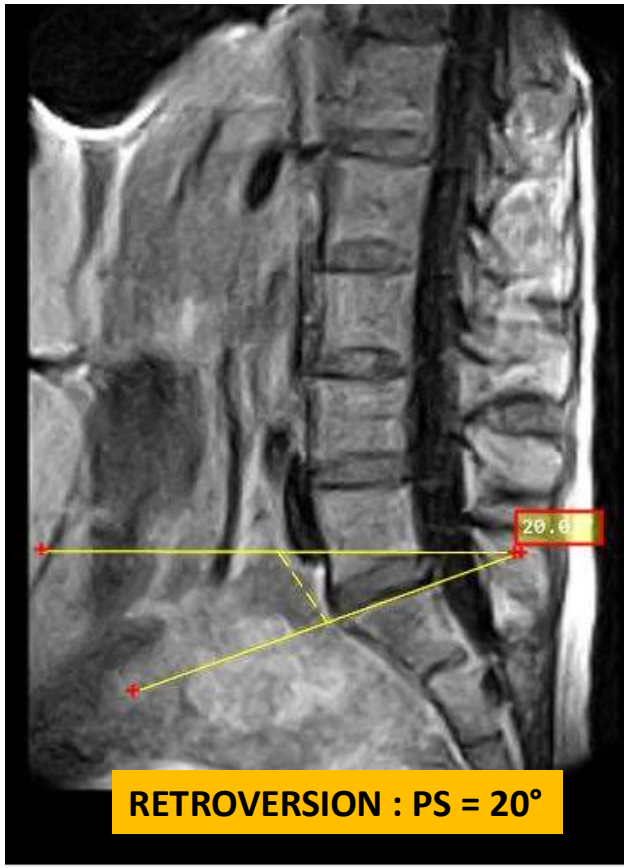
RACHIS

INFLUENCE DE LA POSITION DEBOUT SUR L'ÉQUILIBRE SAGITTAL DU RACHIS



RACHIS

MOBILITE PELVIENNE LORS DE L'ANTE/RETROVERSION DU BASSIN EN CHARGE



GENOU

MOBILITE MENISCALE LORS DE LA FLEXION DU GENOU MENISQUE EXT

GENOU

MOBILITE MENISCALE LORS DE LA FLEXION DU GENOU MENISQUE INT

APPLICATION EXPLORATOIRE GENOU

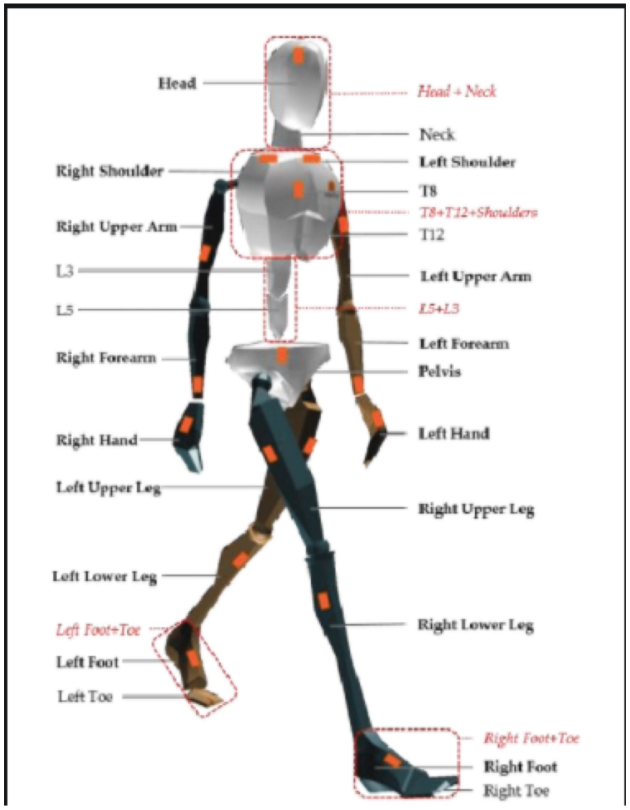
Mise en tension LCA et Course fémoro-patellaire

CARTIGEN platform

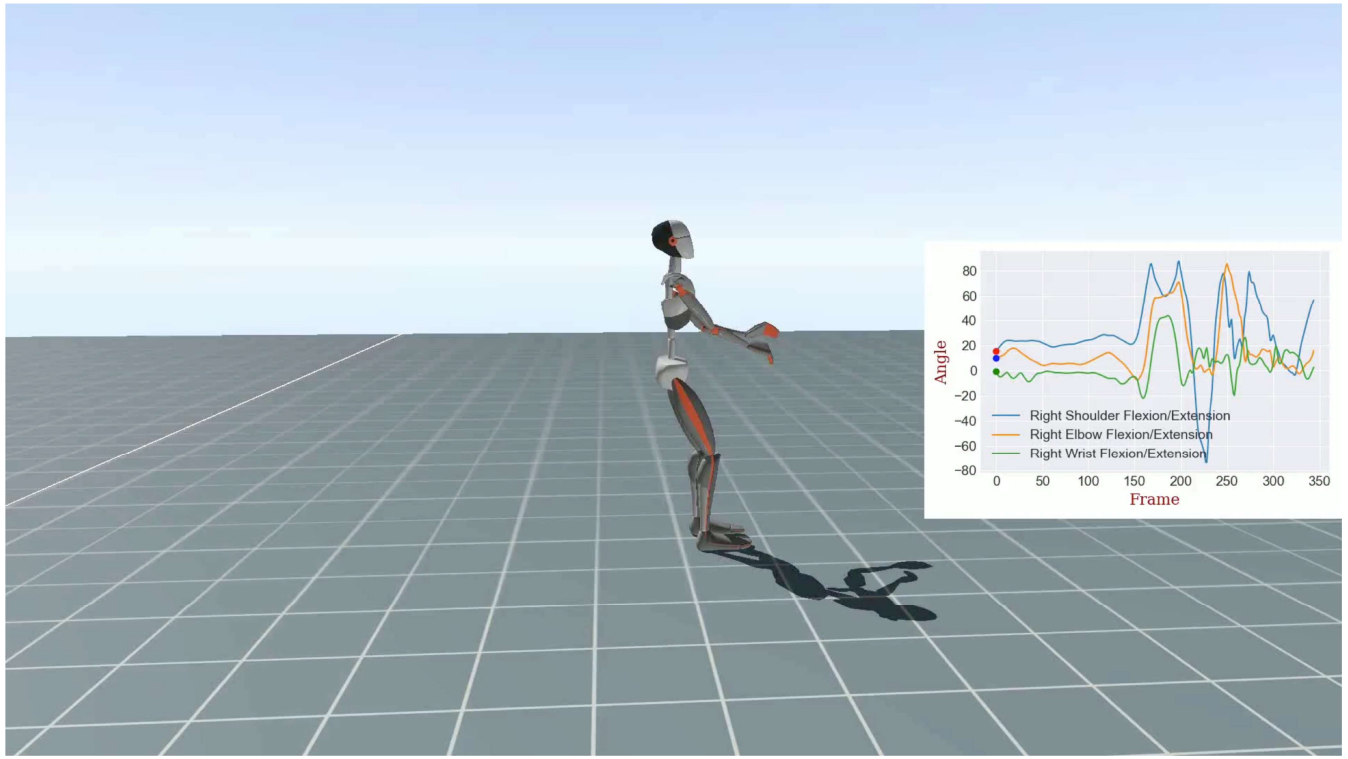
- **Equipment:**
  - Isokinetic
  - MRI
  - Grail (virtual reality)
  - XSENS-Awinda

CARTIGEN
To Restore Mobility

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



GLOBAL KINETIC
Sport medicine Volley ball



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

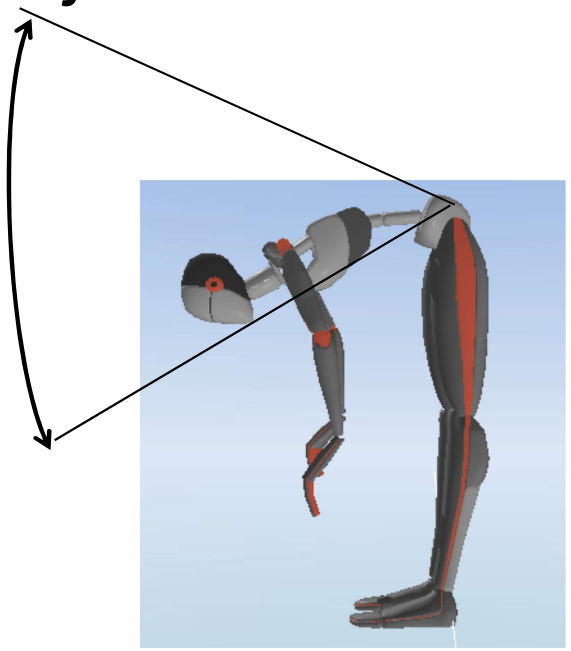
Exclusion criteria: history of lumbar fracture or pelvic surgery, severe scoliosis, neurological or inflammatory pathology.

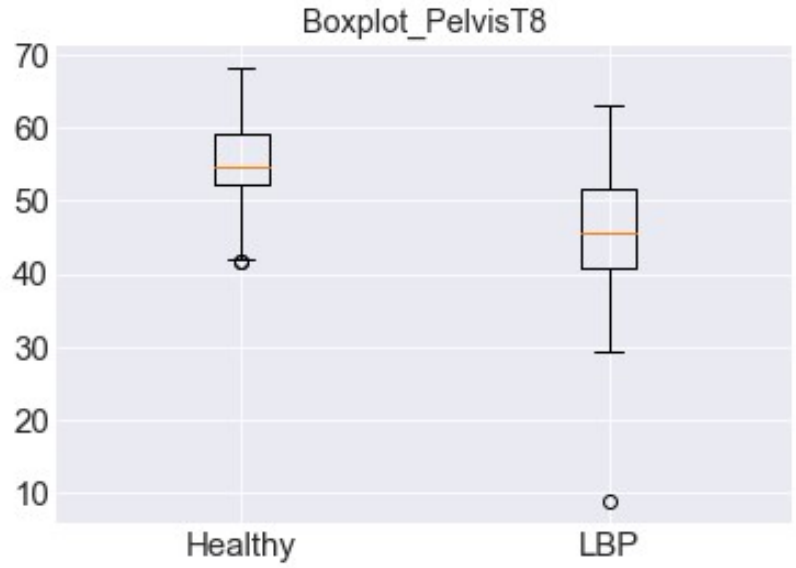
Matched with sex, age (+/- 5 years) and BMI (+/-1)

Spine OA study

Results

1. ROM lumbar flexion



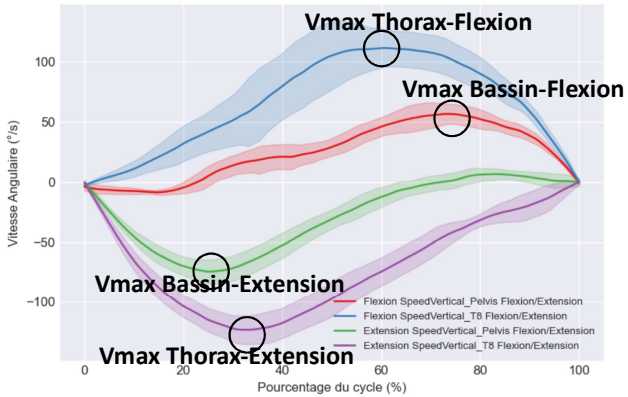


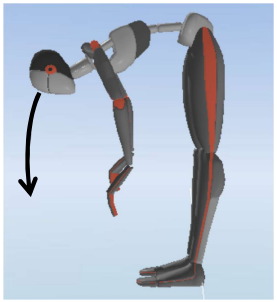
ROM < 10° LBP

Spine OA study

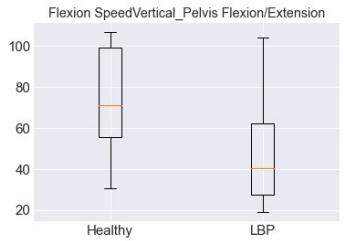
Results

2. Maximal speed

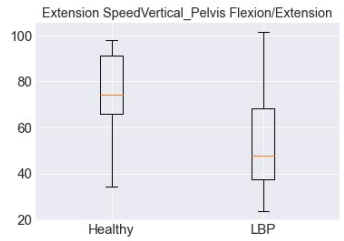


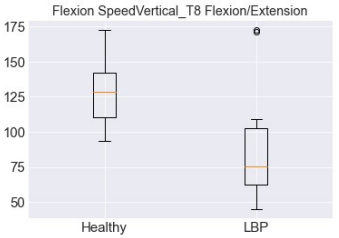


FLEXION **Extension**

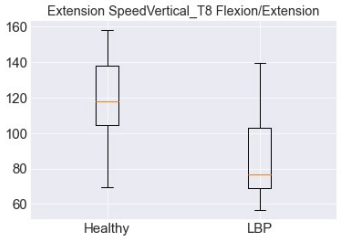


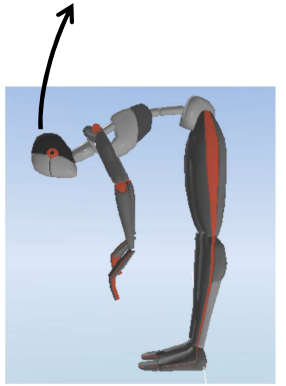
Bassin





Thorax





Speed : Healthy > 1.5 x LBP

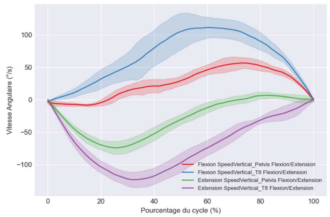
Spine OA study

Results

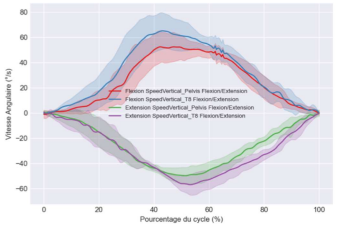
3. Fluidity analysis

Speed profiles

Healthy

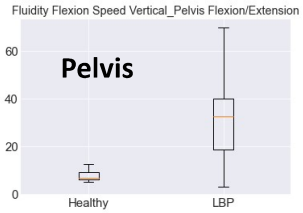


LBP

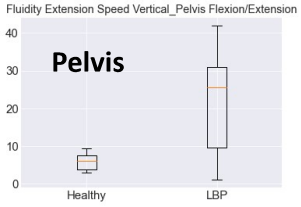


Amount of saccade (acceleration/deceleration)

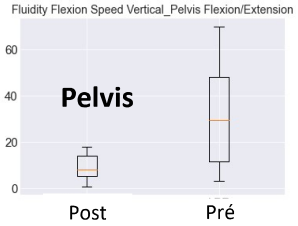
Flexion

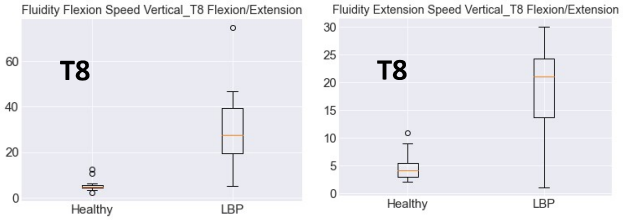


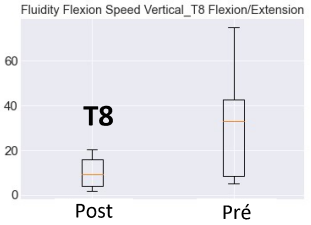
Extension



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

Ma et al. Bioactive Materials 2021

Bio prothesis

Bioactive Materials 6 (2021) 3437–3448

Contents lists available at ScienceDirect

Bioactive Materials

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

Check for updates

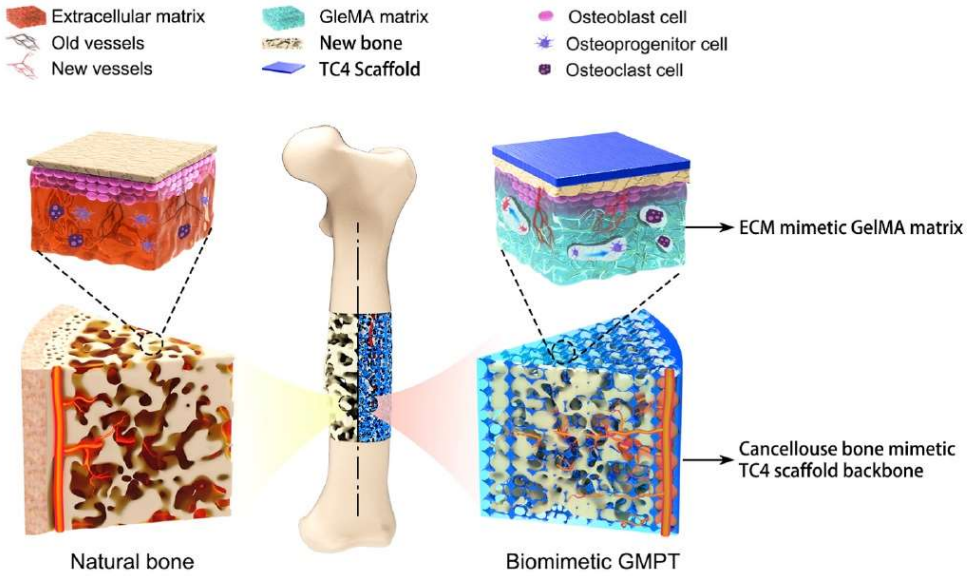
Biomimetic Ti–6Al–4V alloy/gelatin methacrylate hybrid scaffold with enhanced osteogenic and angiogenic capabilities for large bone defect restoration

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,*]

Ma et al. Bioactive Materials 2021

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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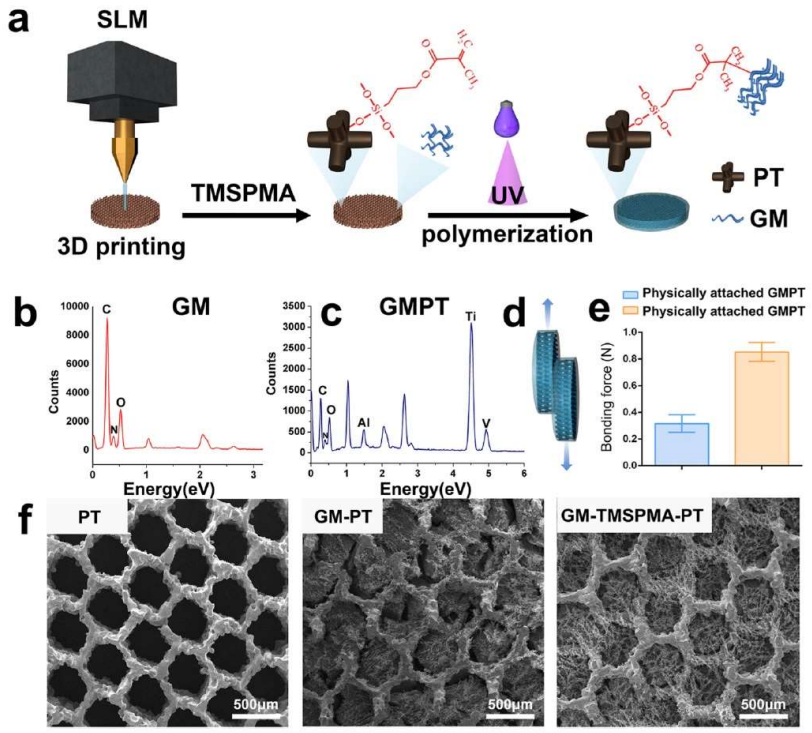
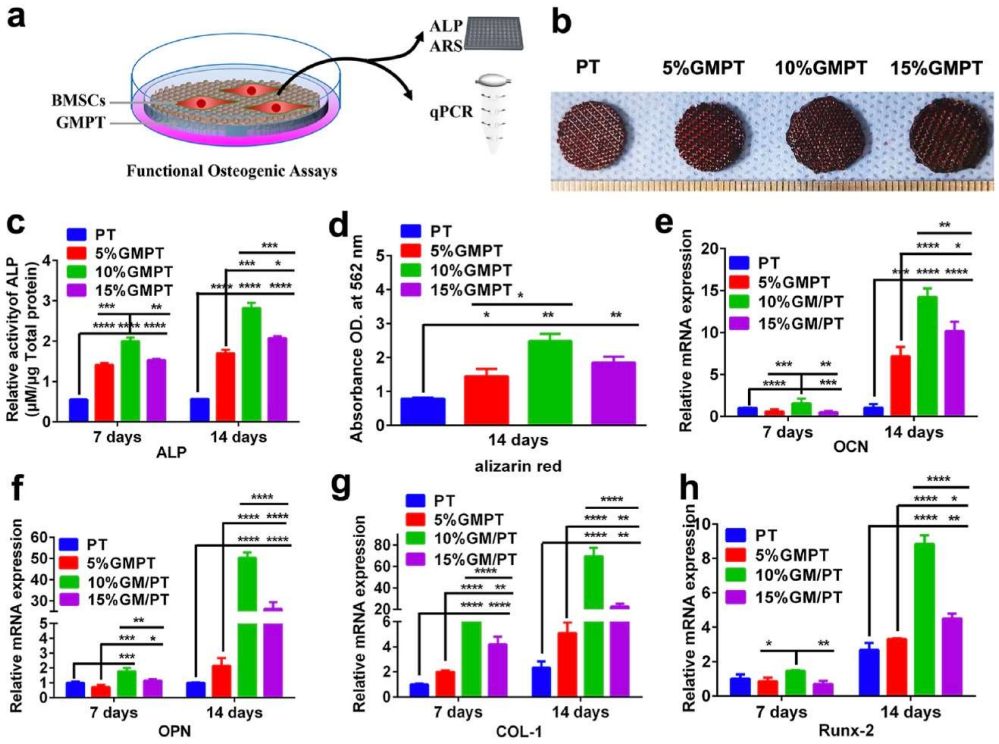
Bio prothesis

- GMPT demonstrates better osteogenic and angiogenic capabilities than PT





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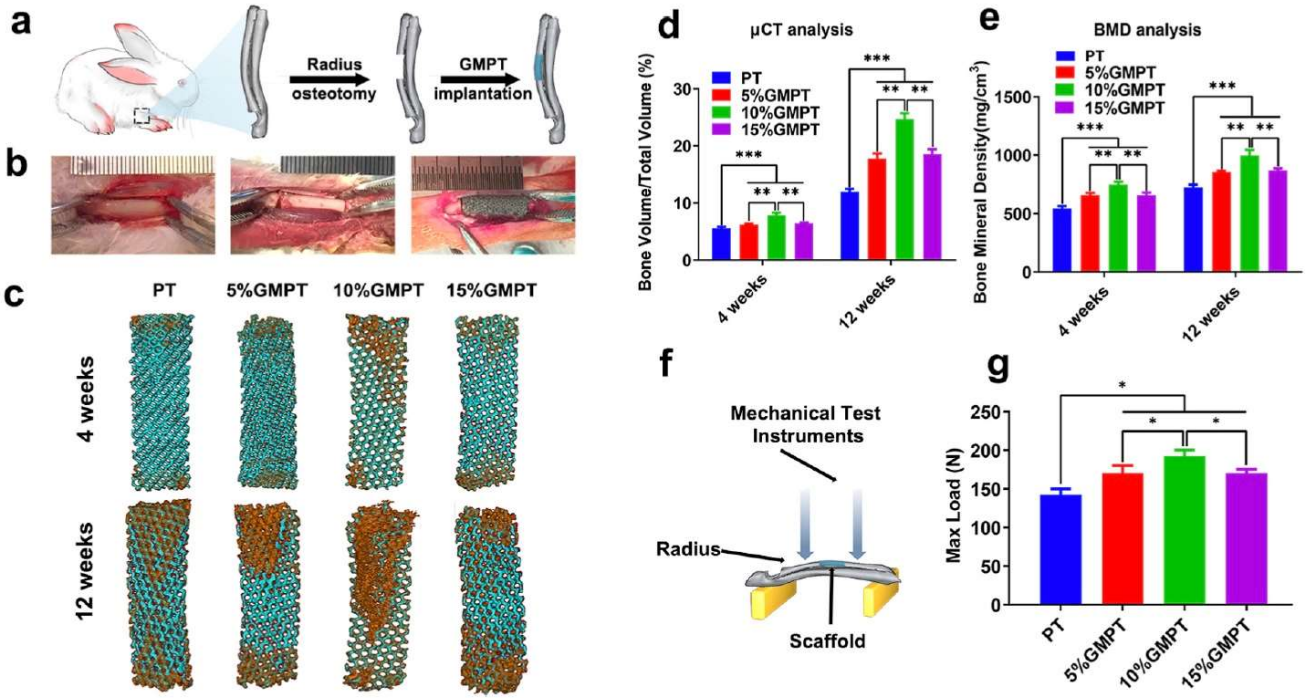
Bio prothesis

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



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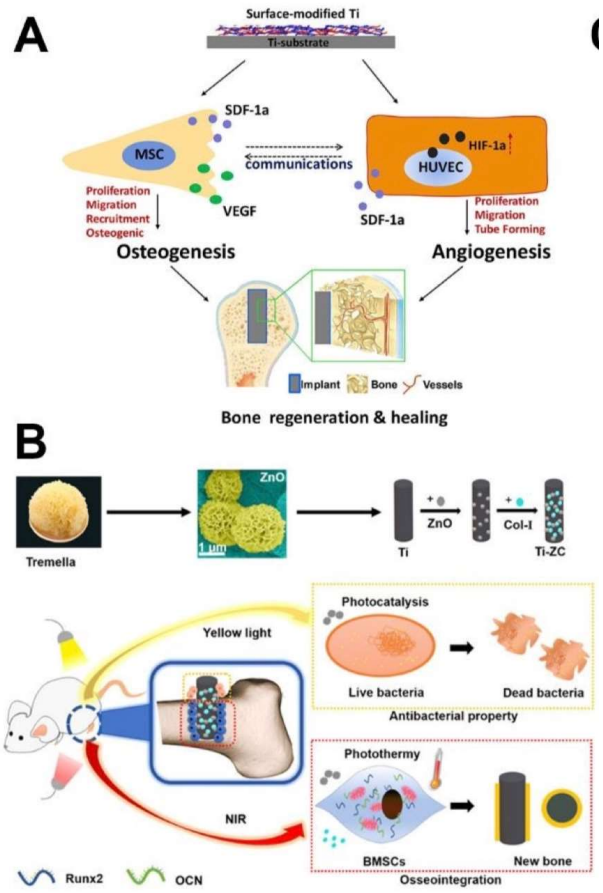
Bio prothesis = avoid infections



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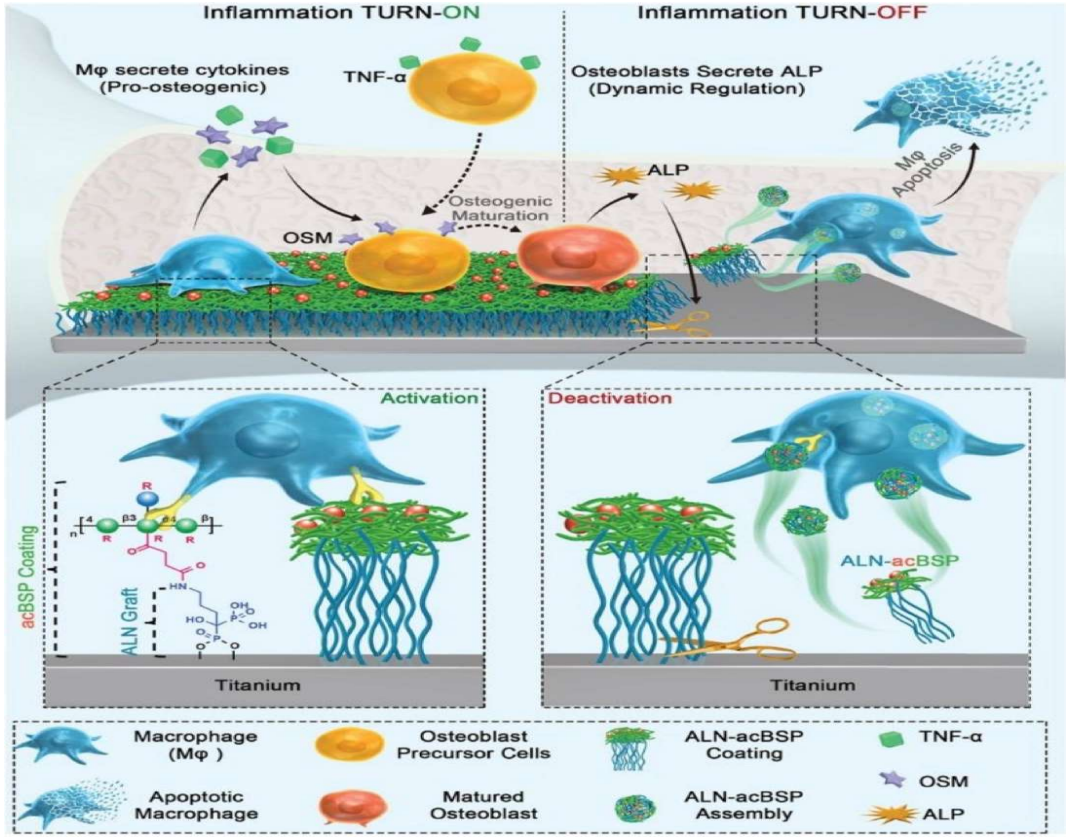
Bio prothesis = promote bone better integration



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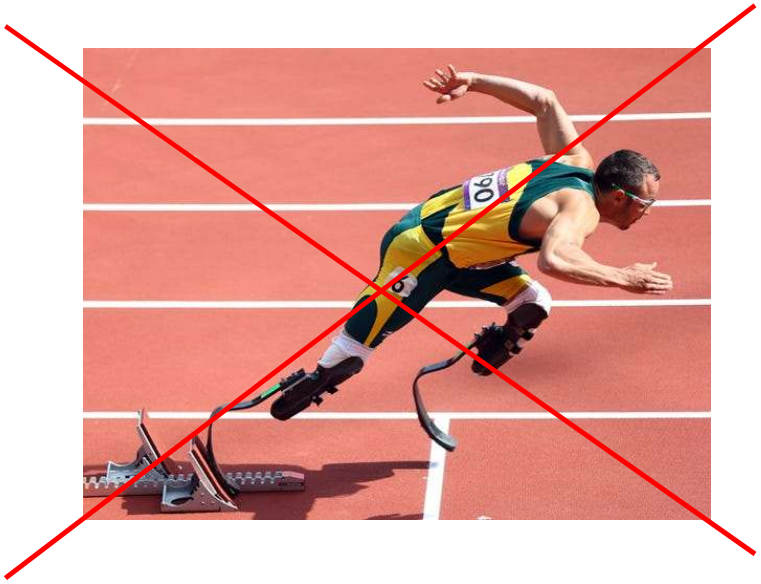
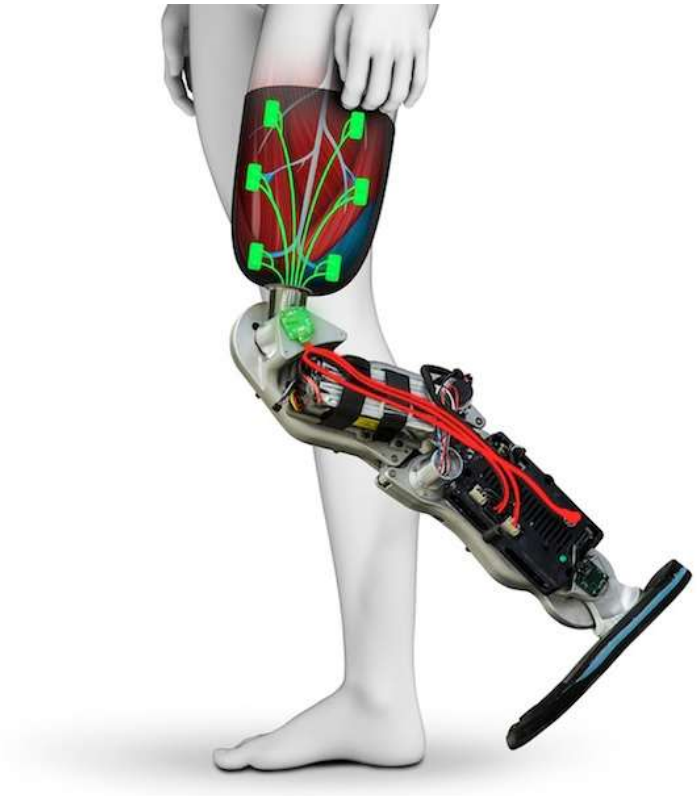
Bionic in OA : perspectives ?

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

The bionic leg

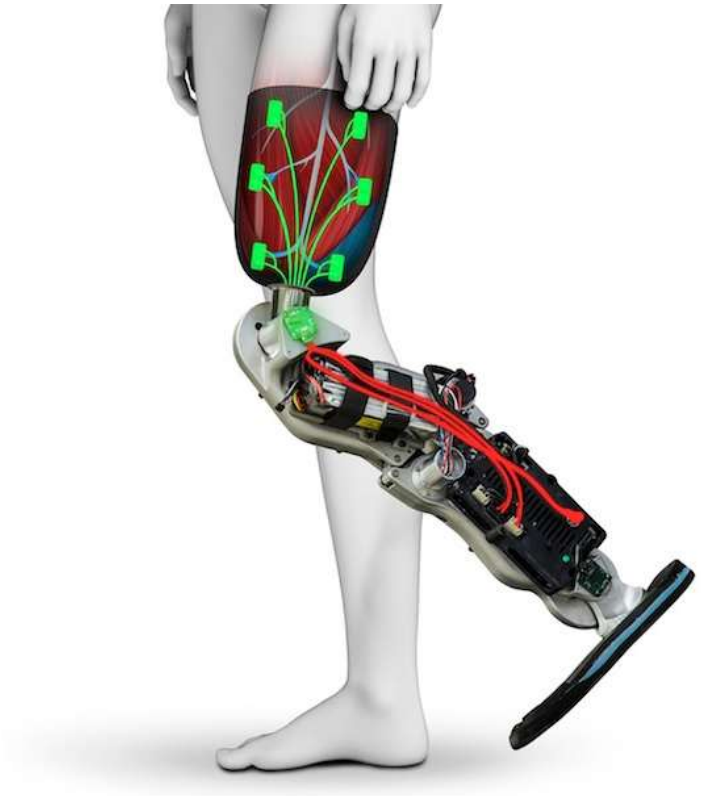


No electronics or sensors or magnets, just a simply-shaped spring that stores energy and uses it



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

QUESTIONS ????

Acknowledgements

- **CARTIGEN Engineer** : Gilles DUSFOUR
- CARTIGEN steering committee: I Laffont, D Mottet, S Perrey, M Julia, C Jorgensen, AL Bonnefont, A Dupeyron, S Kremer
- Team “Rachis”: A Glintzbeck, I Tavares, A Dupeyron
- Sport medicine : M Julia
- Other ongoing projects
  - Knee OA : A. Rakotozafiarison
  - Ankle OA: M Hechiche, P Aboukrat