stem cell therapy in osteoarthritis in 2018

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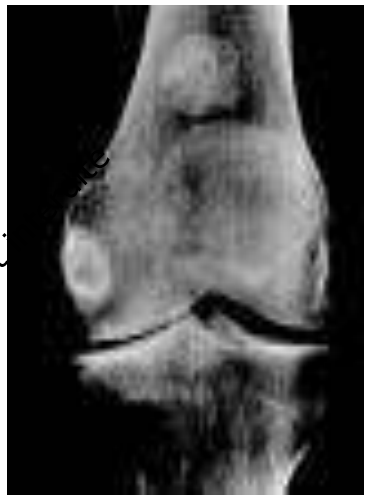
Unmet medical needs in OA

- **Osteoarthritis unmet medical needs** :
  - efficient disease-modifying treatment.
  - more effective symptomatic treatment: NSAIDs improve less than 50% WOMAC scores.
  - safer treatment. Traditional NSAIDs carry significant GI risk & COX-2 inhibitors CV risk.
- **Biologics: anti-IL1b, anti-NGFR**
- **Cell Therapy:**



- Clinicaltrials.gov lists 62 registered trials of knee OA in 2018 including bone marrow-derived mesenchymal stem cells (BMSCs), umbilical cord-derived (UCMSCs), adipose-derived (ADSCs), synovium-derived (SMSCs).
- Cupistem (Anterogen) was approved by the Korean Food and Drug Administration (FDA)
- Invossa (TissueGene), allogenic chondrocytes irradiated expressing TGFB1

Mesenchymal stem cell therapy

Self renewal

migration

differentiation

Secreted factors:
Anti inflammatory
Growth factors
Metabolism : glycolysis
Prevent apoptosis
Prevent fibrosis

Cartilage

muscle

osseux

adipeux

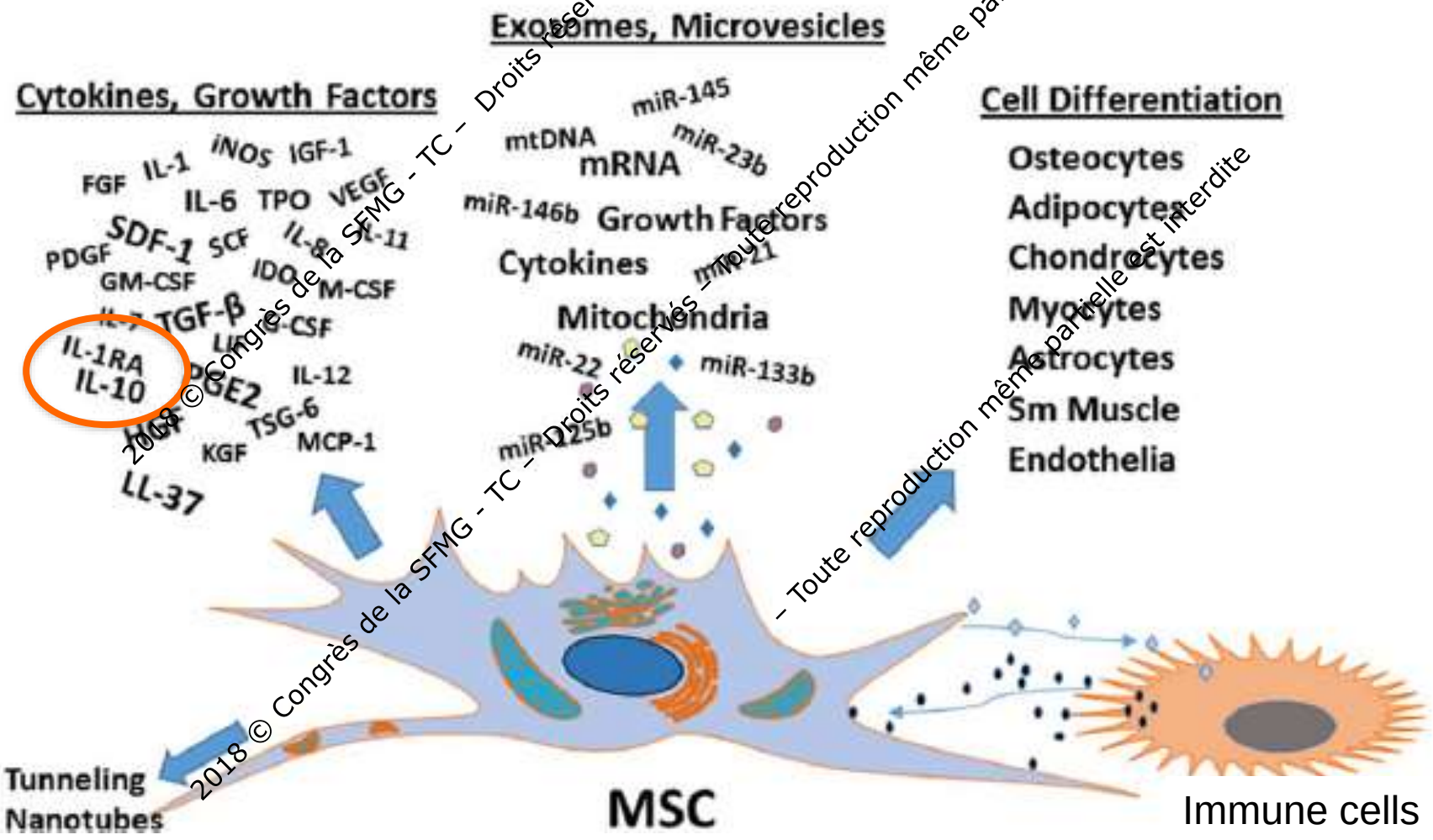
cardiomyocytes

MV, Exosomes : miR

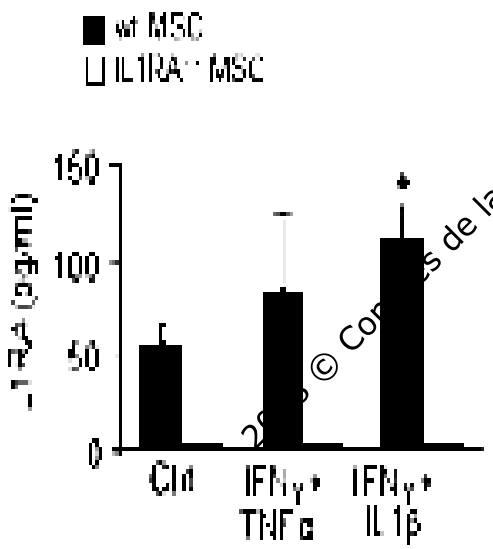
Nanotubes: mitochondria

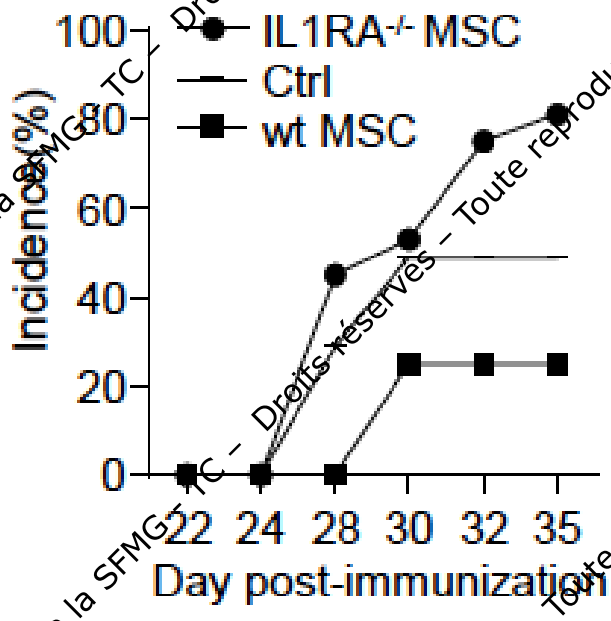
tissue regeneration

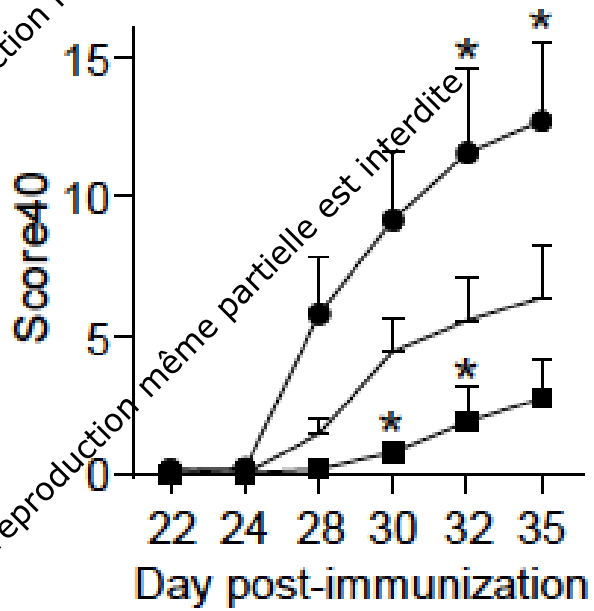
Biological properties of MSC



IL1RA critical for MSC arthritis prevention

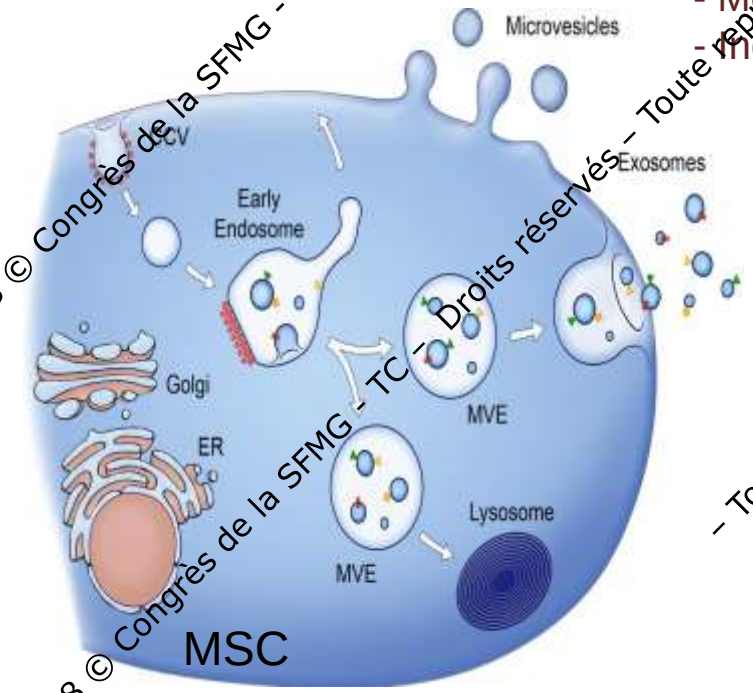






Luz-Crawford et al, Stem cells 2015

Therapeutic potential of extracellular vesicles-derived MSC in OA?



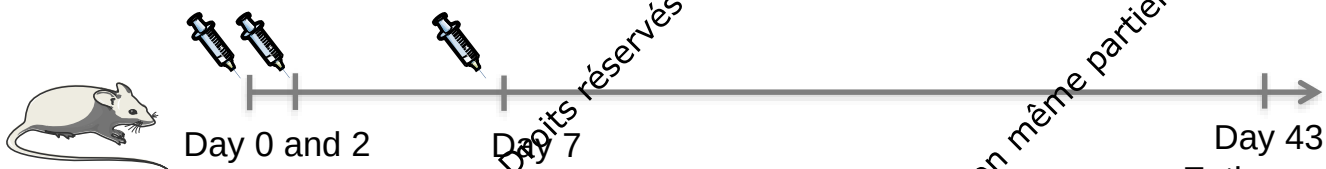
microvesicules

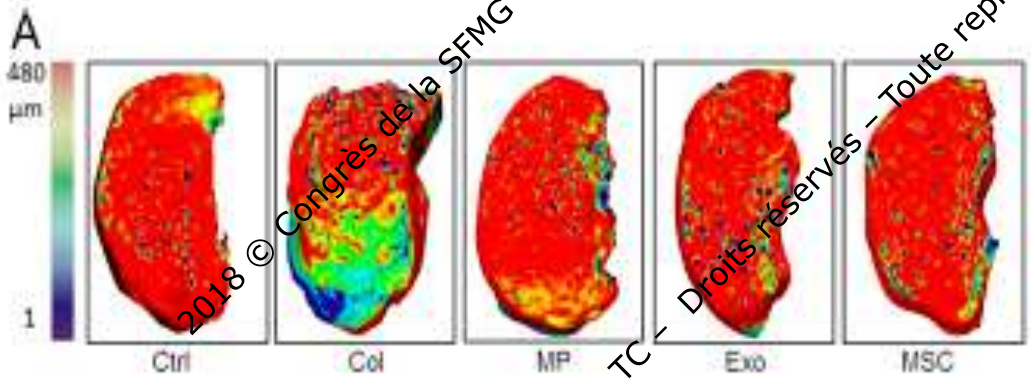
- 150-500nm
- Membrane budding
- Induced release

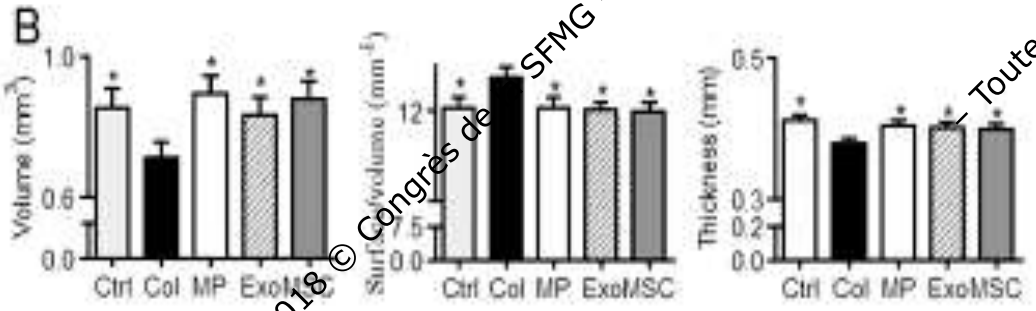
exosomes

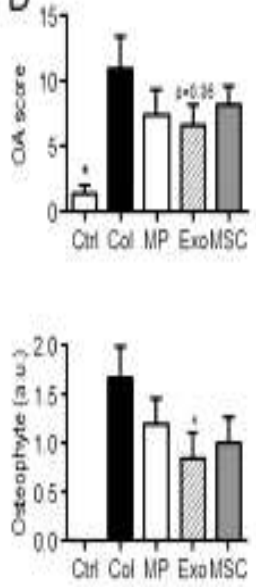
- 50-150nm
- Endosomal compartment
- Constitutive release

Therapeutic potential of extracellular vesicles-derived MSC in OA







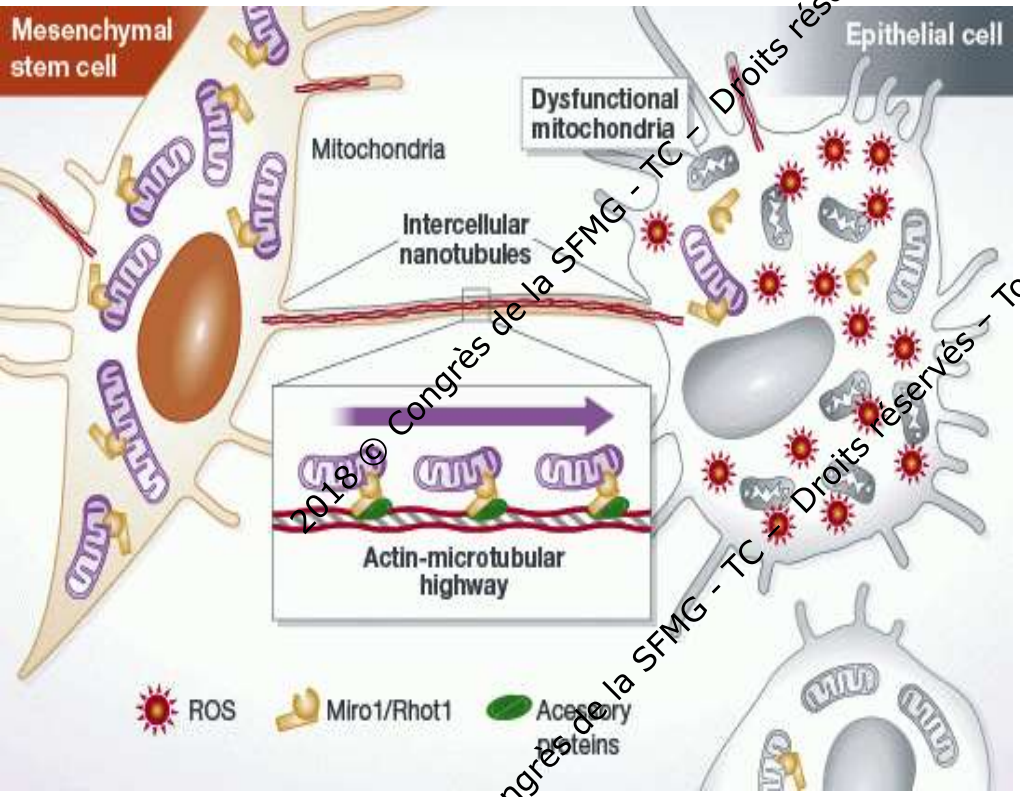


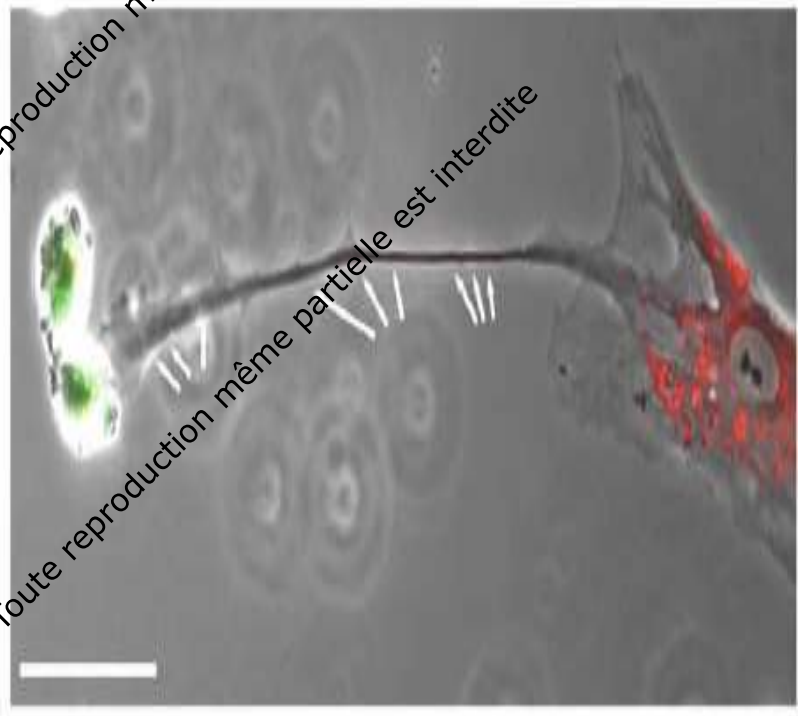
SCIENTIFIC REPORTS

OPEN

Mesenchymal stem cells derived exosomes and microparticles protect cartilage and bone from degradation in osteoarthritis

stem cells transfer of mitochondria to target cells

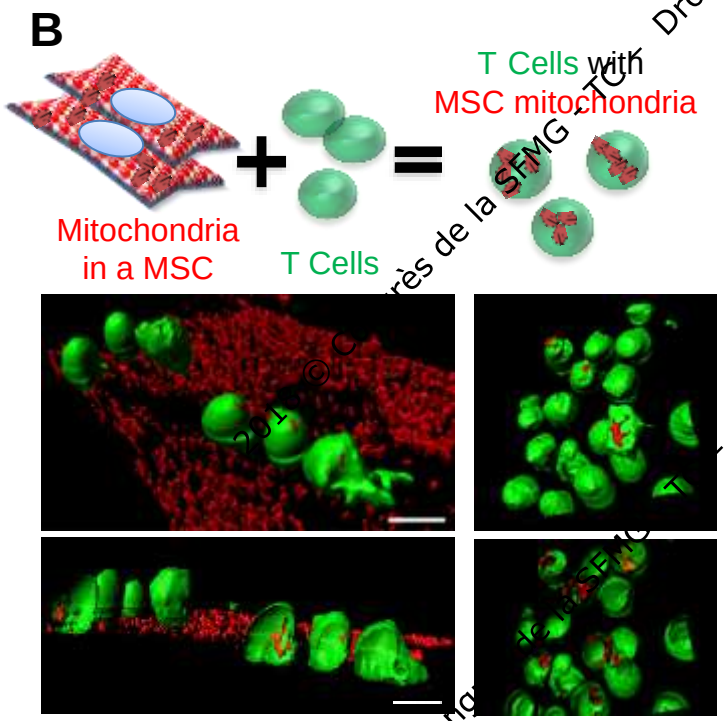


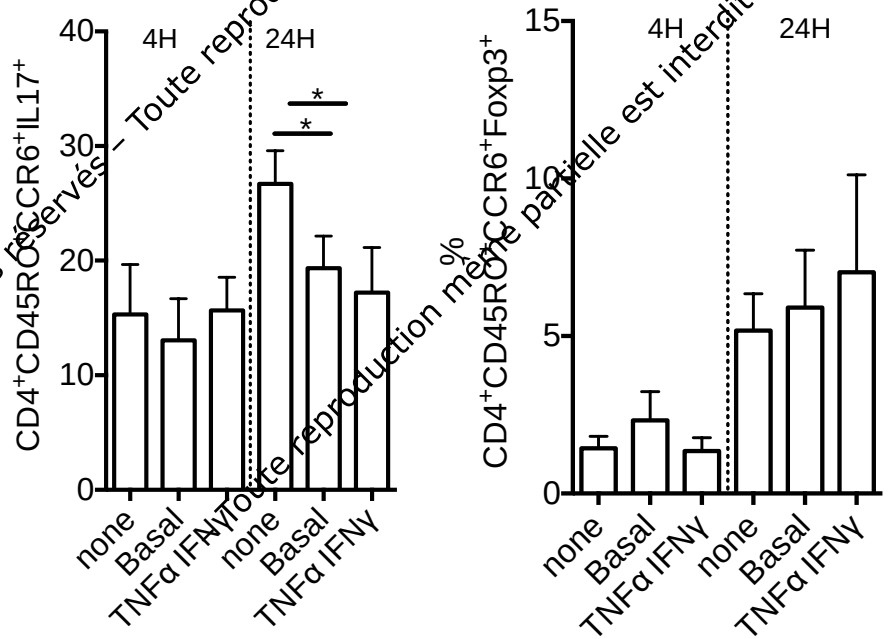


Caicedo et al, Scientific Rep 2015, Vignais et al 2017

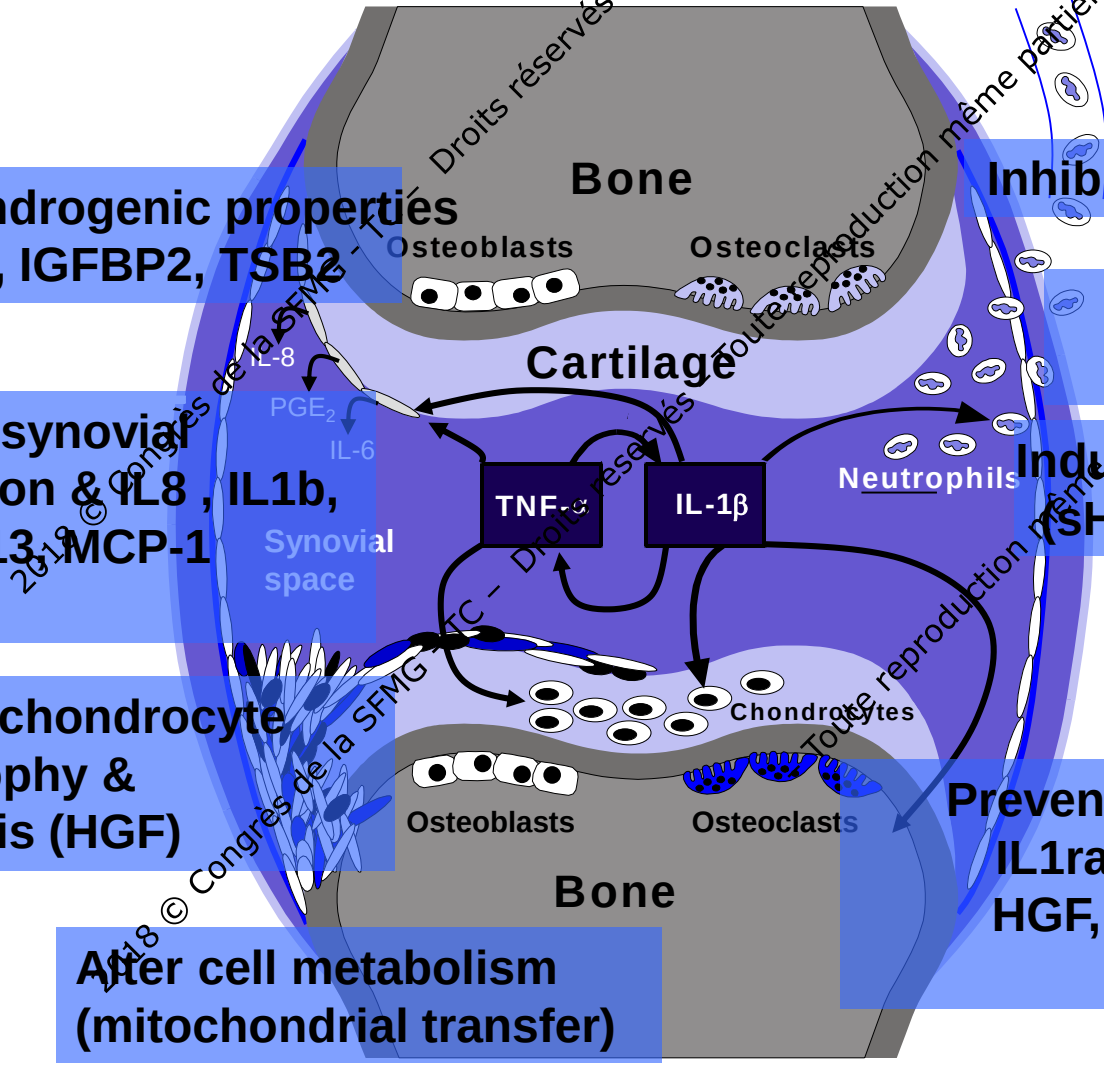
Islam, M.N. et al. Nat. Med. 18, 759–765 (2012).

stem cells transfer of mitochondria to Th17 cells





MSC based therapeutic applications in arthritis & osteoarthritis



Chondrogenic properties
IGF2, IGFBP2, TSB2

Inhibit Th17 (IL1RA, PGE2)

M2 polarization (IL1RA)

Induce Treg (HLAG5)

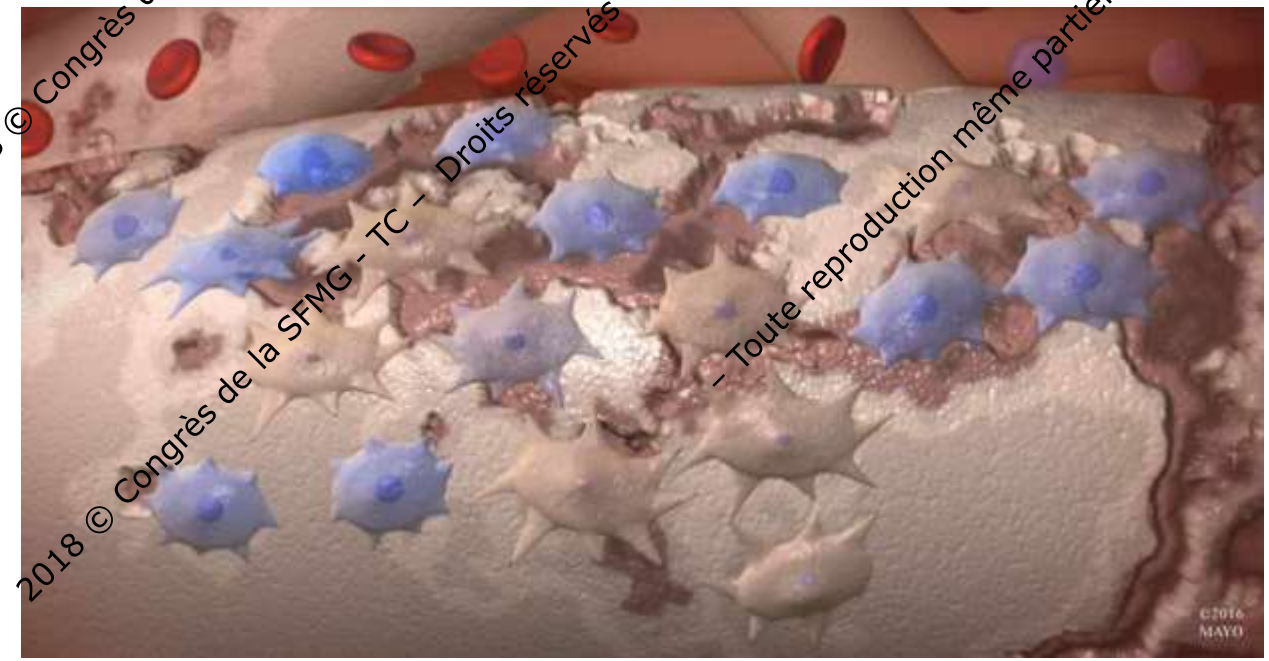
Decrease synovial Proliferation & IL8 , IL1b, IL6, MMP13, MCP-1 release

Prevent chondrocyte hypertrophy & apoptosis (HGF)

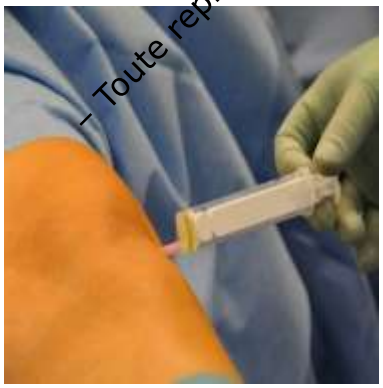
Prevent Inflammation : IL1ra, TGFb, TSG6 HGF, activin 1, IDO

After cell metabolism (mitochondrial transfer)

Clinical Transposition

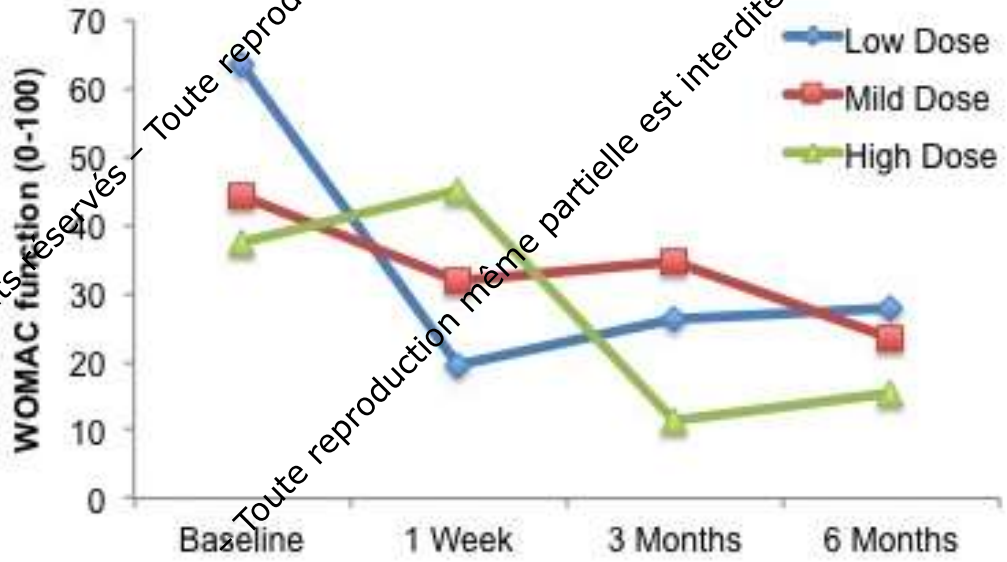


Clinical Procedure



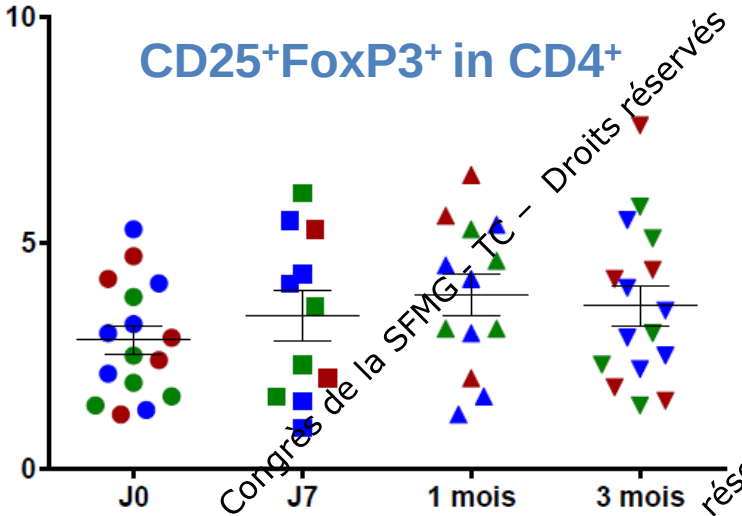
Clinical assessment months 6

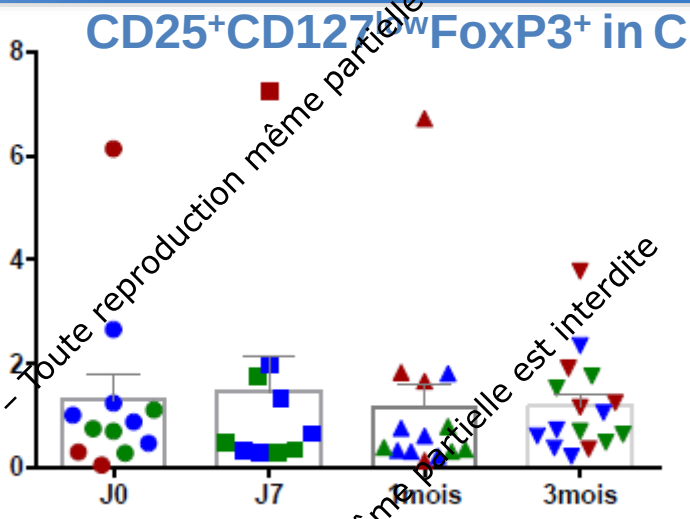
- n= 18
- Age: 61,83(±7,13) years
- mean duration OA was 10,8 (±6) years
- mean stage KL : 62,5% stage IV and 37,5% stage III
- initial WOMAC score : 68,05 (±18,07)
- mean initial VAS score : 50,18 (±12,52)
- Randomized controlled trial ongoing ADIPOA2

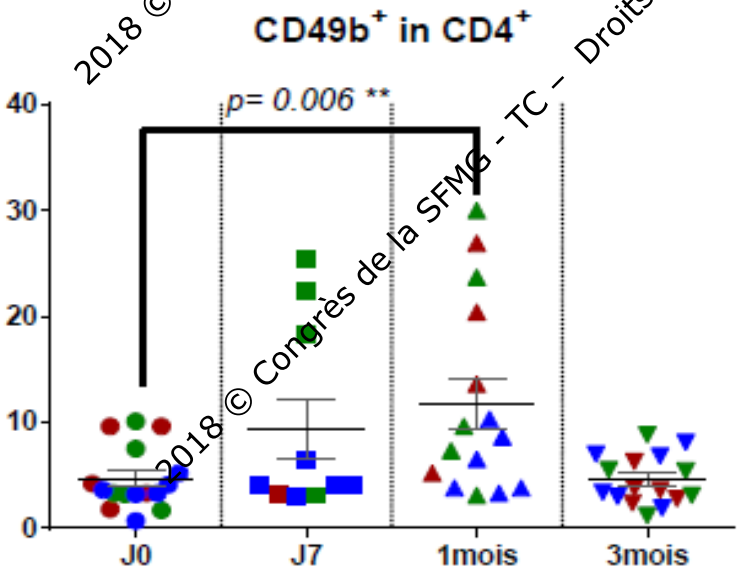


Pers et al, Stem cell Trans Med, 2016

Systemic immune impact of intra-articular ASC injection







Group 1 : 2x10⁶ ASC
Group 2 : 10x10⁶ ASC
Group 3 : 50x10⁶ ASC

ADIPOA2 phase 2 trial

- A phase IIb, multi-centre, prospective, randomized, **double-blind study**, comparing culture-expanded autologous ASC with placebo
- **3 arms to a total of 153 patients** and followed up for 25 months (1 month before and 24 months after knee injection)
- Duration of recruitment for each centre: 12 months

Treatment group	Dose	Frequency	Number of patients
Group 1	**2.10^6 ADSC**	**Single injection**	**51**
Group 2	**10.10^6 ADSC**	**Single injection**	**51**
Group 3	**Vehicle**	**Single injection**	**51**

Allogenic or autologous cells?

Allogenic proces

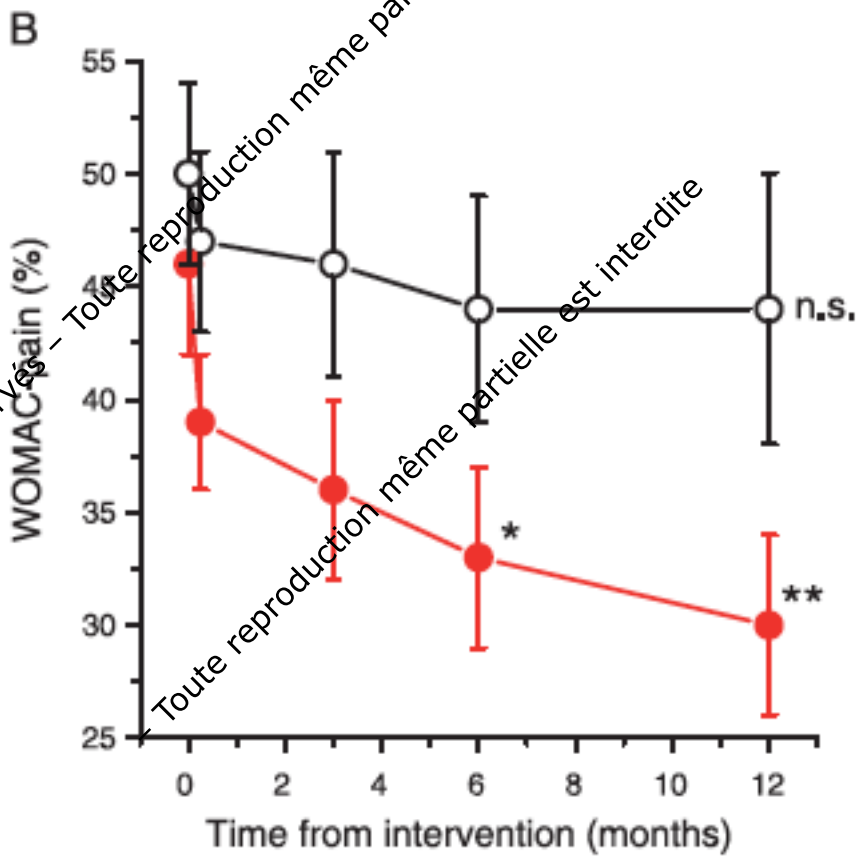
- biodistribution
- Anti-HLA response
- Reduction in cost production
- « on the shelf » product
- May be encapsulated
- May be genetically modified

autologous proces

- Safety
- Time for expansion
- cost
- Possible repeated administration

phase 2 clinical trial of Bone marrow allogenic stromal cell in knee OA

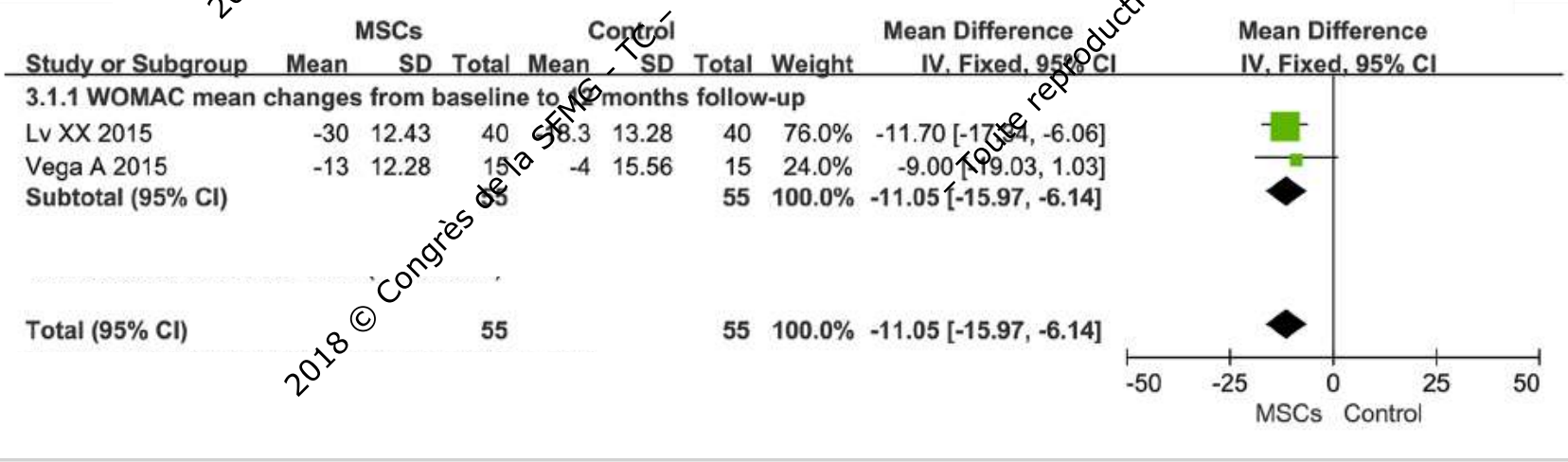
- Allogenic BM-MSC from 3 donors
- 30 patients OA grade II-IV randomized and followed 12 months
- Prospective, placebo controlled study, patients received single intra-articular injection:
  - **Group A 40 10^6 BM-MSC**
  - Group B HA (Durolane)
- Primary endpoint : efficacy month 12 on pain, WOMAC compared to baseline
- Secondary endpoints: SF12, MRI
- WOMAC improved of 34% (vs 12%)
- Global patients assessment : 77% improved compared to 38% in HA group at one year



Vega A, Transplantation 2015;99: 1681–1690

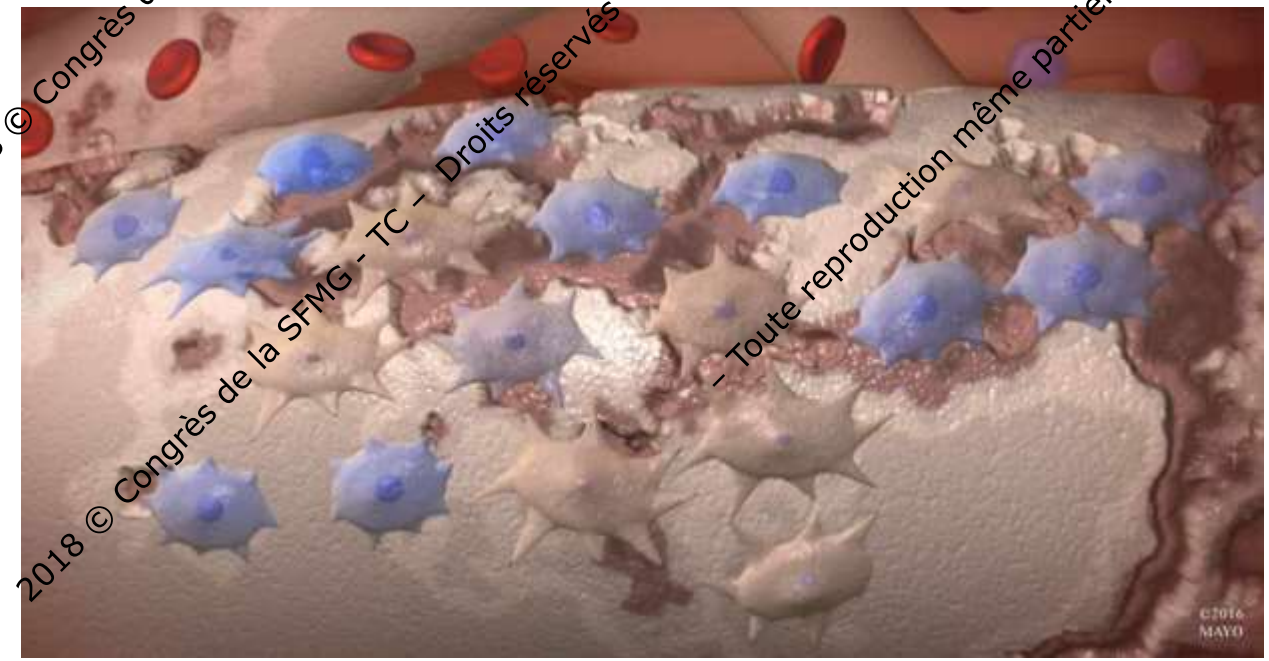
3 Metaanalysis confirm reproducible clinical impact. Imaging impact still pending

Studies	Intervention	time	Nb patients	WOMAC initial	WOMAC after injection	Δ score WOMAC
Orozco et al, 2013	Auto_BM	1 an	12	24 ± 14	6 ± 6	18 ± 13
Jo et al, 2014	Auto_ASC	6 m	12	56 ± 19	34 ± 23	22
Vega et al, 2016	Allo_BM	1 an	15	46 ± 15	30 ± 16	16 ± 23
Pers et al, 2016	Auto_ASC	6 m	12	44 ± 4	22 ± 1	21 ± 13



Pers et al Stem Cell Trans Med 2016, Yubo et al Plone One 2017

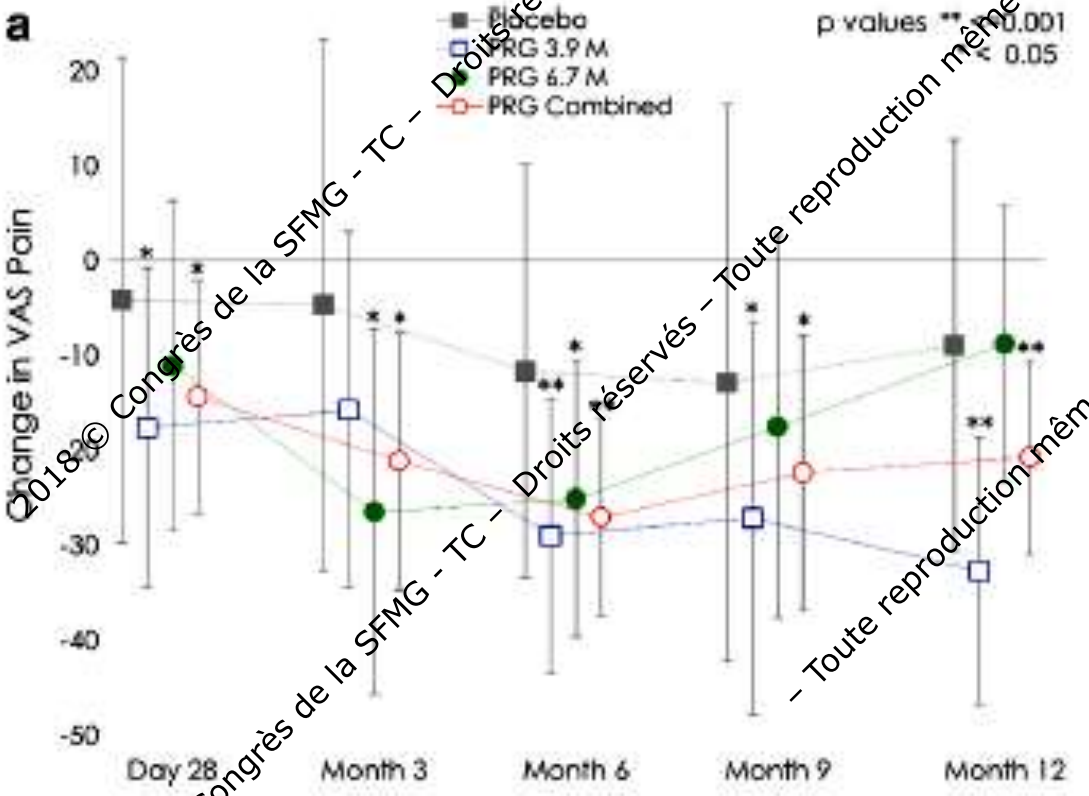
Improve MSC based cell therapy



How to improve ?

- Patients selection : synovitis, early stage
- *regenerative rehabilitation* defined as the integration of principles and approaches from rehabilitation medicine *(Moritz CT, Ped Phy Therapy, 2016)*
- Dose: range from 10^6 to 180 10^6 !
- number of injections
- Stimulate the MSC or combine cells

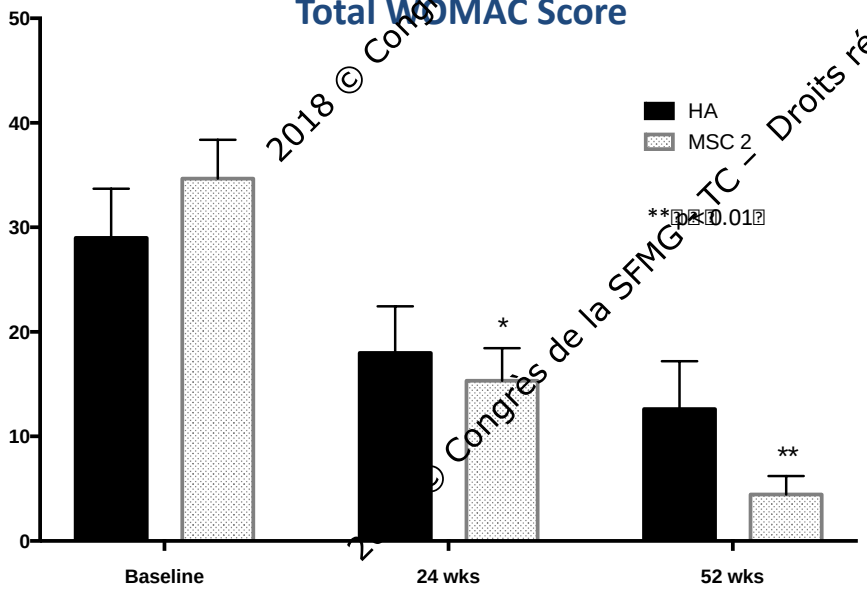
12 months results of STEP Trial (Progenza, Regeneus Ltd)

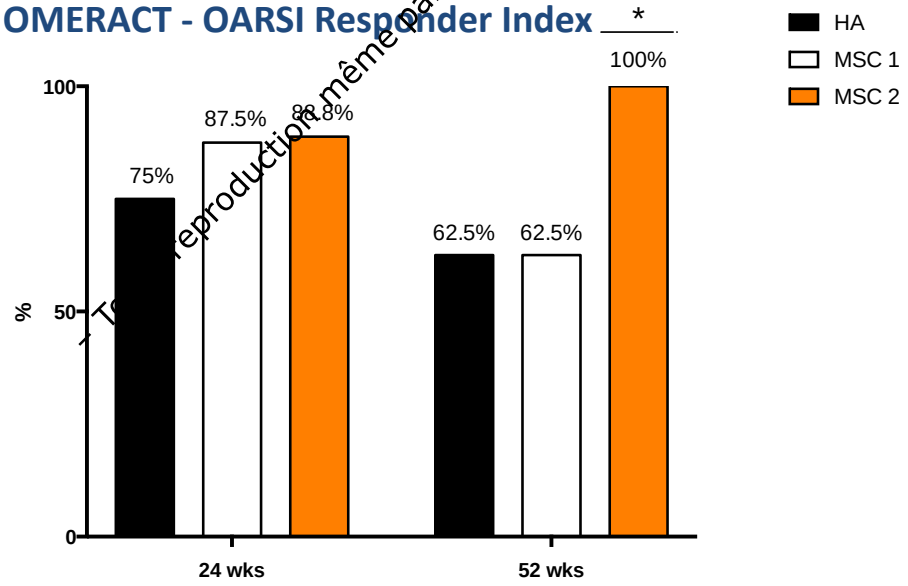


Kuah et al. J Transl Med (2018) 16:49

double injection of MSC in knee osteoarthritis.

- Sequential dose in knee OA (injection ($20x10^6$ UCMSC) baseline + second inj. month 6)
- Follow-up: 12 months
- 27 patients in 3 arms : 1 inj, 2 inj or HA. *Clinical trial NCT02580695*
- Second MSC treatment well tolerated
- Sequential dose of MSC superior to HA at 6 & 12 mo. *(Womac A-C, VAS & SF-36 physical)*

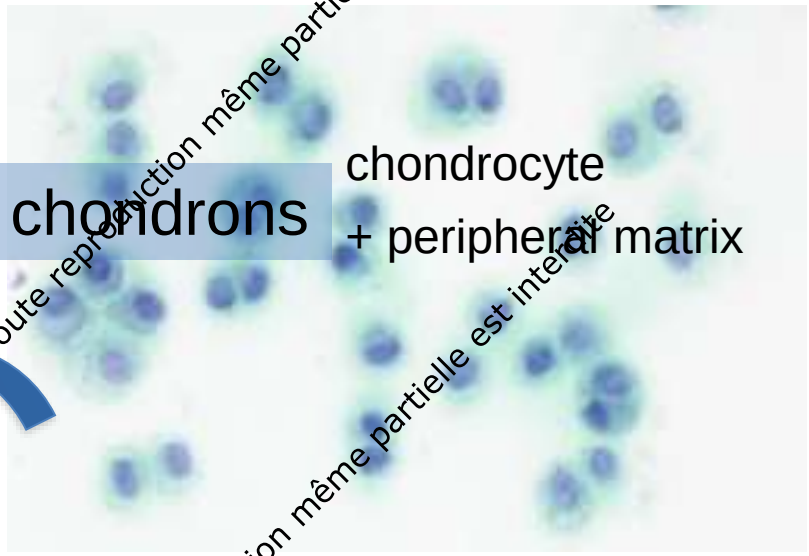


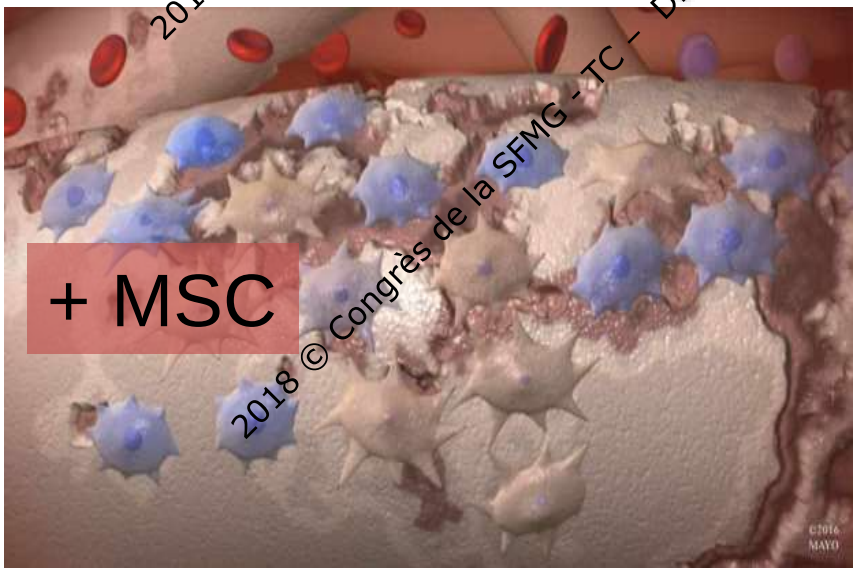


Espinoza F et al., submitted, 2018

Chondrons combined with MSC for cartilage defect

- Chondrons = chondrocytes with their native pericellular matrix
- May be combined with allogenic MSC to enhance chondrogenic potential of autologous chondrons

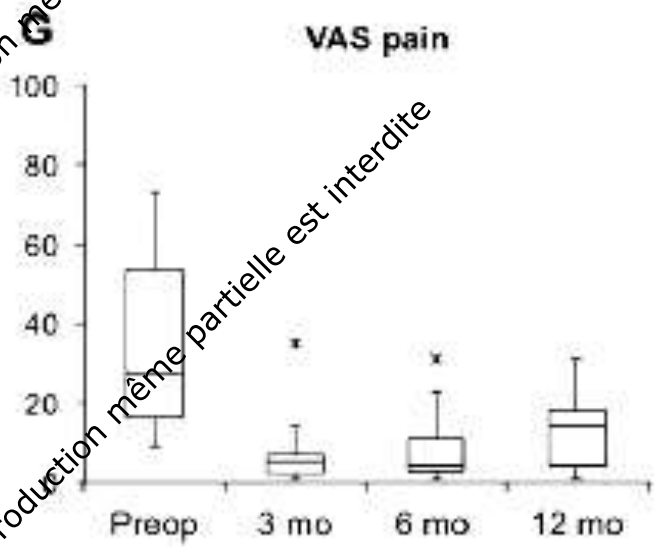




Vonk, Osteoarthritis & cartilage 2014
De Windt T, Stem Cells 2017

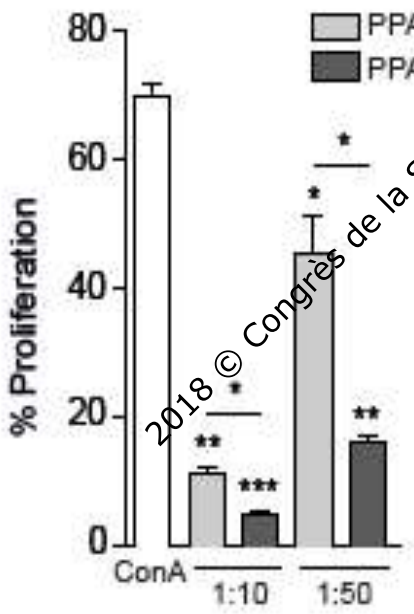
Chondrons combined with MSC for cartilage defect

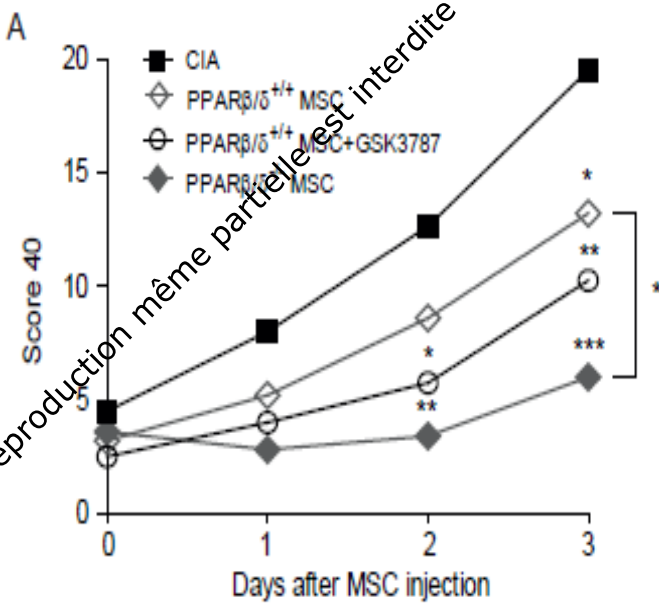
- phase I trial applied allogeneic MSCs + autologous Chondrons
- 10 patients with symptomatic isolated cartilage defect
- femoral condyle/trochlea defect size 2-8cm2
- Results : At 12 months, all patients showed statistically significant improvement in clinical outcome KOOS, VAS.
- Magnetic resonance imaging showed completely filled defects



De Windt T, STEM CELLS 2017;35:256–264

Can we improve MSC potency?





PPAR-β/δ ^{low} MSC have a stronger anti-inflammatory effect

Luz-Crawford et al, Ann Rheum Dis 2016

perspectives

- Efficacy of MSC derived cell therapy in knee OA confirmed months 12 and 24 in large metaanalysis
- 2 doses improves results month 12
- Safe
- Characterize the cells, develop potency assay
- Use of allogenic cells “on the shelf”
- Improve potency of MSC in the process
- Propose recommendations to conduct phase 3 trials: clinical & imaging endpoints. Patient inclusion criteria.
- Improving cell technology (iPS derived MSC, CRISPR/CAS)

National Network for MSC-based therapy since 2012 ….

Research Infrastructure

5 Cell Therapy Units for large scale production

- Besançon
- Créteil
- Clamart
- Grenoble
- Toulouse

1 Center for MSC Qualification

- Clonogenic potential CFU
- Phenotypic Analyses
- Stemness and differentiation potential
- Caryotype analyses

3 Preclinical platforms in various animal models

- Toulouse, Grenoble, Montpellier

2 Platforms for patient immunomonitoring

- Immunological effect of MSC in clinics
- Biomarkers

What services are available?

- **GMP production of ATMPs**
  - Manufacturing of stem cell clinical batches
- **Qualification of MSCs for clinical uses**
  - Safety and potency tests
- **Cell Therapy Consultancy Services**
  - Protocol methodology
  - Study design
  - Operational feasibility of non clinical and clinical projects
- **Expertise in pre-clinical and translational research**
  - Proof-of-concept
  - Biodistribution/tolerance
  - Tumorigenicity
  - Immunomonitoring

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